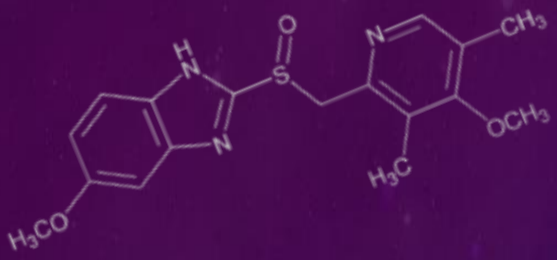
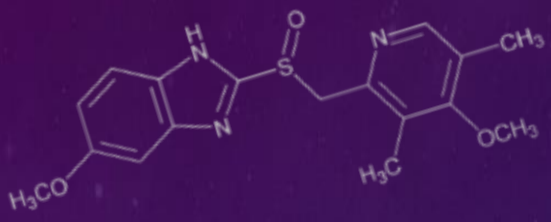
Desarrollo de Formulaciones Pediátricas de Omeprazol

Khadija Rouaz El Hajoui





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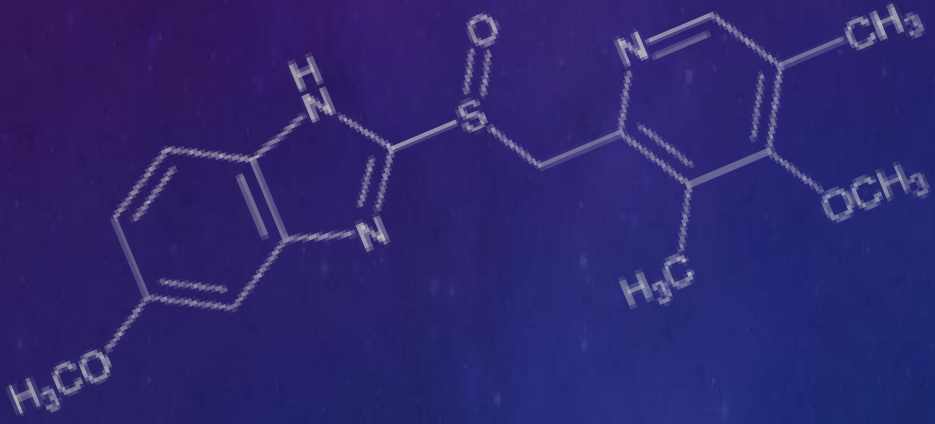

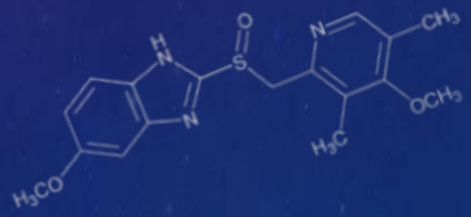

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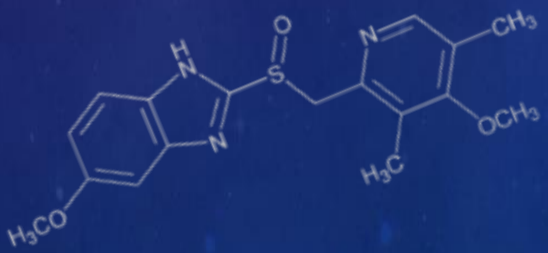

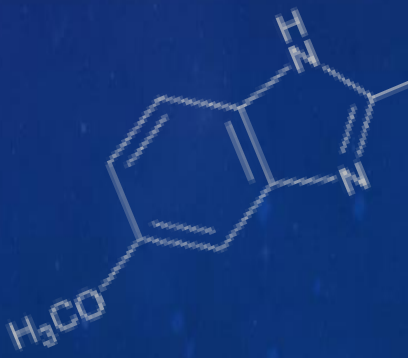

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FACULTAD DE FARMACIA Y CIENCIAS DE LA ALIMENTACIÓN

Departamento de Farmacia y Tecnología Farmacéutica, y Fisicoquímica

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FACULTAD DE FARMACIA Y CIENCIAS DE LA ALIMENTACIÓN

PROGRAMA DE DOCTORADO EN
INVESTIGACIÓN, DESARROLLO Y CONTROL DE MEDICAMENTOS

DESARROLLO DE FORMULACIONES PEDIÁTRICAS DE OMEPRAZOL

Memoria presentada por Khadija Rouaz El Hajoui, para optar al título de doctor por la Universidad de Barcelona

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KHADIJA ROUAZ EL HAJOUI

2024

A mi abuelo, Si Sellam, quién ha sido y será paz, luz y esperanza en mi vida,

a mis queridas hermanas, Hassna y Kholoud,

y a mi marido, Ayoub

من لم يعش حياته في طلب العلم، كان في بحر الجهل غريق.

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Podemos decir que agradecer, por definición, es un acto conclusivo de algo y se hace con la intención de dar cuenta de aquellos para con los cuales tenemos la responsabilidad de cifrar mediante las siguientes palabras su contribución en el proceso de esta tesis. Se trata de un acto aglutinador de varios matices y, quizá el más importante, sea el de que mis agradecimientos sirvan para reconocer el valor de las personas que me han acompañado y que el lector que no los conozca pueda hacerse una idea de lo que han supuesto para mí.

He recibido apoyo de muchas personas y todas ellas son importantes. Ahora bien, sí me gustaría empezar a mencionarlas siguiendo un orden, empezando por el círculo nuclear para luego pasar al círculo de relaciones extensas.

En primer lugar, al más cercano y lejano a la vez, a quien nunca podrá leer estas líneas porque ya no está. A mi abuelo materno quien con sus enunciados descriptivos sobre mis ganas de estudiar, aprender y saber supo convertirse en un faro de luz e instaurar en mí que es posible hacerme un camino profesional y académico en esta vida. A él por saber celebrar mis primeros logros como estudiante con sencillez, naturalidad y mucha elegancia. Supo estar y hacerme de espejo de tal forma que me permitió verme realizada en su propia mirada orgullosa de tenerme como nieta.

En segundo lugar, a dos chicas jóvenes y prometedoras, a mis pequeñas hermanas. Una se llama Kholoud y la otra Hassna. Son lo que sus nombres árabes significan. A ellas les agradezco su presencia constante y su escucha, aunque a veces desatenta por el cansancio de repetirles día tras otro lo mismo de la tesis, pero nunca falta de interés e ilusión. Han sabido ayudarme, en la medida de lo posible, con determinadas tareas cuando más lo he requerido y, sobre todo, han cumplido con convertirse en contenedores para evacuar mis angustias y volver a ubicarme en el proyecto de mi tesis doctoral.

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En tercer lugar, me gustaría aludir a aquellas personas que sin ser de la familia también han sabido estar como si lo fueran. La relación con ellas empieza a construirse desde lo profesional que también une, pero con el paso del tiempo, va adquiriendo distintas tonalidades altamente satisfactorias.

A mis directoras de tesis, la Dra. Encarna García Montoya y la Dra. Pilar Pérez Lozano. En muchas ocasiones me he sentido, yo y mi tesis en desarrollo, como si fuéramos varios instrumentos sonando sin harmonía debido a los diferentes obstáculos acontecidos durante el proceso. Ante semejante caos estaban ellas para reconducir, orientar e instaurar un nuevo orden a seguir. En definitiva, ejerciendo de directoras de orquestra. ¡Menuda tarea es la de dirigir, cualquier cosa!

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RESUMEN

El omeprazol es un inhibidor de la bomba de protones ampliamente utilizado para tratar enfermedades gastrointestinales en población pediátrica. Sin embargo, los medicamentos comercializados de omeprazol están diseñados para adultos en forma de cápsulas duras gastro-resistentes. En este contexto, los servicios de farmacia hospitalaria recurren a las formulaciones magistrales de omeprazol para suplir esta carencia. Ahora bien, estos preparados a menudo no cumplen los requisitos de estabilidad química primordiales para garantizar la efectividad de este API. Por ende, esta tesis doctoral propone el desarrollo de nuevas formulaciones pediátricas de omeprazol que sean gastro-resistentes y presenten un perfil de liberación adecuado.

Tras la revisión exhaustiva de las formulaciones magistrales y preparados oficinales de omeprazol, comúnmente empleados en niños, se identifica que el principal reto para estas formulaciones es la falta de gastro-resistencia. Por lo tanto, se inicia esta investigación con el desarrollo de pellets entéricos de omeprazol de 0,6 – 0,5 mm de diámetro, mediante la aplicación de un diseño factorial completo. A nivel de resultados, se consigue un recubrimiento óptimo empleando solo dispersiones de recubrimiento acuosas. El microanálisis EDS de la composición elemental de los pellets inertes del experimento 4 muestra una homogeneidad de las capas de recubrimiento, en la evaluación de contenido del omeprazol se consigue un porcentaje del 100%, en el ensayo de gastro-resistencia un porcentaje del 95% y una liberación superior al 80%, cumpliendo las especificaciones de la Ph. Eur. (*European Pharmacopoeia*) y de la USP-NF (*United States Pharmacopeia – National Formulary*) para el omeprazol. Las características morfológicas y propiedades de gastro-resistencia de los pellets obtenidos permiten su uso en formas farmacéuticas pediátricas, siendo una posible alternativa a las formulaciones magistrales de omeprazol empleadas actualmente en población pediátrica.

El siguiente paso en la investigación implica el uso de los pellets entéricos desarrollados para obtener dos formas farmacéuticas pediátricas de administración oral. Por una parte, se aplica la tecnología de impresión 3D por extrusión de semisólidos para elaborar gominolas medicinales personalizadas que sirvan como forma farmacéutica innovadora de omeprazol para uso pediátrico. Se compara la impresión 3D de hidrogeles con omeprazol dispersado (F1) con hidrogeles cargados con pellets de omeprazol gastro-resistentes (F2). La gastro-resistencia y los perfiles de disolución de las dos formulaciones se estudian con diferentes métodos para una mejor comparación y para subrayar la importancia de la metodología del ensayo. Ambas fórmulas presentan una reología

adecuada, buena imprimibilidad y cumplen los ensayos de uniformidad de contenido y masa. Sin embargo, solo las formas farmacéuticas impresas en 3D con pellets entéricos de omeprazol de las dosis semisólidas masticables (F2) destacan como una estrategia eficaz para abordar el reto de desarrollar una formulación pediátrica con una elevada gastro-resistencia y un perfil de liberación adecuado.

Por otra parte, se propone un diseño de experimentos para desarrollar una suspensión de omeprazol gastro-resistente destinada a la población pediátrica. Se emplea un diseño factorial completo que abarca tres factores principales (Aerosil® R972, alcohol cetostearílico y Span 80), cada uno evaluado en dos niveles. Tras la optimización, se formula la suspensión F10 y se somete a un estudio de estabilidad de un mes. Los resultados del ensayo de disolución no alcanzan los estándares deseados, logrando solo una liberación del 22%. Como consecuencia, se idean ocho suspensiones adicionales utilizando vehículos oleosos hidrófilos y otros excipientes para mejorar el perfil de disolución. La suspensión F17 se destaca al exhibir una liberación superior al 75% en 30 minutos, un tiempo de sedimentación lento y una resuspensión fácil. Los resultados sugieren que la formulación óptima para la administración de pellets entéricos de omeprazol en suspensión consiste en Labrafil M 1944 CS, Span 80 y Aerosil® 200.

ABSTRACT

This doctoral thesis proposes the development of new paediatric formulations of gastro-resistant omeprazole with an adequate release profile, given that it is a widely used API in the paediatric population to treat gastrointestinal disorders. The main challenge in omeprazole compounding formulas, commonly used in children, is the lack of gastro-resistance. Therefore, research begins with the development of 0,6 – 0,5 mm diameter omeprazole enteric pellets, applying a full factorial design. Optimal coating is achieved by employing aqueous coating dispersions. EDS microanalysis of the elemental composition of the inert pellets of experiment 4 shows homogeneity of the coating layers. In the evaluation of omeprazole content, a percentage of 100% is achieved, while in the gastro-resistance test a percentage of 95% is achieved, with a release of more than 80%, meeting the specifications of the Ph. Eur. and the USP-NF.

The developed omeprazole enteric pellets are utilized to create two paediatric oral dosage forms. Firstly, semi-solid extrusion 3D printing technology is employed to produce customized medicated gummies, offering an innovative paediatric delivery method for omeprazole. Hydrogels with dispersed omeprazole (F1) are compared to those loaded with gastro-resistant omeprazole pellets (F2). While both formulations meet quality standards in terms of rheology, printability, and uniformity, only F2 effectively address the challenge of achieving high gastro-resistance and optimal release.

Additionally, a design of experiments is proposed to develop a paediatric suspension of gastro-resistant omeprazole. Utilizing a full factorial design with three key factors (Aerosil® R972, ketostearyl alcohol and Span 80) at two levels each, the F10 suspension is optimized and subjected to a stability study. However, dissolution tests reveal only a 22% release rate, prompting the development of eight additional suspensions using hydrophilic oil vehicles and other excipients to enhance dissolution profiles. Among these, the F17 suspension stands out, achieving over 75% release within 30 minutes, with prolonged settling time and easy resuspension. Overall, the results suggest that the optimal formulation for administering omeprazole enteric pellets in suspension includes Labrafil M 1944 CS, Span 80 and Aerosil® 200.

ÍNDICE

1 INTRODUCCIÓN

1.1 Farmacología de la población pediátrica: Situación actual

La población pediátrica representa un 25 % de la población mundial total; un porcentaje que corresponde a dos mil millones de niños en el mundo [1]. Esta población constituye un grupo heterogéneo y en proceso de maduración fisiológica. Comprende los grupos de edad: prematuros, neonatos (0 – 27 días), lactantes y niños pequeños (28 días – 23 meses), niños (2 – 11 años) y adolescentes (12 – 18 años) (ver Figura 1) [2,3]. Así pues, son necesarias formas galénicas adaptadas a cada grupo de edad que permitan un ajuste posológico adecuado. El crecimiento y el desarrollo continuo del niño va a condicionar la respuesta de los medicamentos; por una parte, debido a los cambios en la composición corporal (agua extracelular, proteínas plasmáticas) y por otra, a la inmadurez de muchas enzimas implicadas en su metabolismo (principalmente, en el hígado). Los cambios en la ontogenia de la maduración de los órganos y los sistemas no son lineales y regulares, si bien los cambios más importantes van a producirse a los 12 – 18 meses de vida [4,5].

Resulta habitual en el ámbito médico escuchar que un "niño no es un adulto en miniatura". En efecto, existen unas diferencias fisiológicas, farmacocinéticas y farmacodinámicas, así como unas enfermedades exclusivamente pediátricas. A esto, debe añadirse que los grupos de edad que abarca la infancia (de 0 a 18 años) no son comparables entre sí, lo que justifica que los estudios realizados en adultos no pueden predecir la respuesta farmacológica en los niños. La heterogeneidad que caracteriza la población pediátrica implica una gran variabilidad en cuanto al peso, la superficie corporal, el tamaño de los órganos y los compartimentos, la maduración de los procesos de eliminación y la ontogenia de los mecanismos efectores de la respuesta a los fármacos (receptores, vías de señalización), entre otros factores [4,6].

Prematuros (Desde el día del nacimiento hasta la fecha prevista del parto)

- Número reducido de pacientes con gran heterogeneidad
- Sistema nervioso central inmaduro
- Aclaramiento renal y hepático incipientes
- Estados únicos de enfermedades neonatales
- Estratificación por peso y edad (gestacional y gestacional)
- Bajo volumen sanguíneo total

Neonatos (Nacimiento – 27 días)

- Contenido de agua y grasa corporal diferentes
- Alta relación entre área de superficie corporal y peso
- Barrera hematoencefálica inmadura
- Aclaramiento renal y hepáticas incipientes
- Absorción oral menos predecible

Lactantes y niños pequeños (28 días – 23 meses)

- Maduración rápida del sistema nervioso central
- Desarrollo del sistema inmunológico
- Crecimiento corporal total
- Maduración del sistema hepático y renal
- Considerable variabilidad interindividual en la maduración

Niños (2 – 11 años)

- Maduración del aclaramiento de fármacos (renal y hepático)
- Desarrollo psicomotor
- Crecimiento físico
- Inicio de la pubertad
- Desarrollo neurocognitivo

Adolescentes (12 – 18 años)

- Maduración sexual
- Cambios hormonales
- Crecimiento rápido
- Desarrollo neurocognitivo
- La falta de cumplimiento es un problema singular
- El límite de edad superior varía entre regiones

Figura 1. Grupos de edad pediátrica y sus principales características.

Fuente: [2,3,7].

Actualmente, sigue existiendo una situación de orfandad terapéutica en la edad pediátrica, que viene condicionada, en gran medida, por la falta de formas farmacéuticas adaptadas a las necesidades terapéuticas de los niños. Una elevada proporción de patologías

pediátricas que requieren tratamiento farmacológico, son tratadas con medicamentos que no están recomendados o no se especifica su uso en dicha población [4,8].

Por otro lado, más del 40% de las preparaciones de uso hospitalario están destinadas a los niños, pero casi el 60% de ellas no tienen adaptadas sus fichas técnicas para uso pediátrico. Ello obliga al recurso de la formulación magistral con frecuencia. La formulación magistral en pediatría representa un intento realista de suplir la falta de medicamentos adaptados y apetecibles para estos pacientes. Esta tradicional forma de elaboración de medicamentos tiene una importancia capital en esta área, con las ventajas siguientes, entre otras [4]:

- Posibilita el administrar medicamentos útiles que han dejado de comercializarse por razones extracientíficas.
- Permite personalizar un tratamiento a las necesidades del paciente: (I) utilizando excipientes tolerados por el niño, (II) asociando en la misma fórmula diversos principios activos o (III) dosificando dosis terapéuticas no registradas pero adaptadas al niño en función de su peso, edad y peculiar farmacocinética.
- Facilita la graduación de dosis de un principio activo (API).
- Conlleva una pauta de dosificación exacta, con lo que no sobran medicamentos y se evitan caducidades y automedicación.
- En ocasiones, es la única forma de prescribir fármacos para muchas denominadas “enfermedades raras” y “enfermedades olvidadas”.
- En enfermedades cutáneas, la formulación tópica permite elegir los excipientes adecuados a cada estadio de la enfermedad para un mismo API.
- No siempre resulta adecuado manipular formas farmacéuticas destinadas a adultos para adaptarlas a los niños debido a las siguientes razones: (I) la molturación de comprimidos para la elaboración de preparados líquidos puede conllevar a una desnaturalización del API debido al calor generado, (II) los excipientes destinados a adultos no siempre resultan convenientes en pediatría, y (III) la estabilidad del preparado obtenido puede desconocerse, generando componentes que podrían tener una elevada toxicidad (por ejemplo, una solución de hidroclorotiazida, elaborada manipulando formas farmacéuticas sólidas de este API, puede degradarse a formaldehído que resulta un producto muy tóxico).

1.2 Regulación de los medicamentos pediátricos

Las diferencias y características de la población pediátrica y la situación actual de la farmacología pediátrica confirman la necesidad de realizar ensayos clínicos en esta población y fomentar la investigación en medicamentos pediátricos para cubrir sus necesidades especiales con opciones seguras y de calidad. Por ello, tanto los Estados Unidos de América como la Unión Europea han implementado varias disposiciones legales con el objetivo de motivar, atraer o incluso obligar a las compañías farmacéuticas a llevar a cabo ensayos pediátricos [9].

Por una parte, la Regulación Europea de Medicamentos Pediátricos se destaca por sus tres iniciativas principales para asegurar la seguridad y eficacia de los medicamentos en niños: la adopción de incentivos para la industria farmacéutica, la implementación de un Plan de Investigación Pediátrica (PIP) que abarque todas las edades y la creación de un Comité Pediátrico (PDCO). Las compañías farmacéuticas se encuentran en la obligación de presentar un PIP para nuevas indicaciones, vías de administración o formulaciones de productos ya patentados, así como para el desarrollo de nuevos medicamentos. En caso de proporcionar la información requerida después de llevar a cabo los estudios conforme al PIP, la empresa recibe una extensión de seis meses en el Certificado de Protección Complementaria [9–11]. Además, la Regulación busca estimular la investigación para establecer la seguridad y eficacia de medicamentos ya utilizados en niños, pero con escasos datos de respaldo. A través de la Autorización de Uso Pediátrico de Comercialización (PUMA), si se realizan estudios basados en indicaciones y formulaciones pediátricas de acuerdo con el PIP acordado, el solicitante puede obtener la aprobación PUMA con una exclusividad de mercado de 10 años [12,13].

Por otra parte, el enfoque estadounidense para la autorización pediátrica se caracteriza por ser pragmático y flexible. Se solicita a las compañías farmacéuticas que completen un Plan de Desarrollo Pediátrico (equivalente al PIP en la UE) proporcionando datos suficientes de la población adulta. En situaciones en las que un medicamento se utiliza fuera de indicación en pediatría durante un período prolongado, las autoridades estadounidenses otorgan una autorización pediátrica basada en el número de niños ya tratados, la eficacia y los datos de seguridad disponibles de la población pediátrica, la duración del uso del producto fuera de indicación y la base de datos de seguridad en adultos. Esta flexibilidad es crucial, especialmente cuando se aborda la investigación

clínica de medicamentos fuera de patente, que suele ser complicada y plantea desafíos éticos debido a la renuencia de las empresas a proporcionar el medicamento fuera de indicación para la investigación, dada la reducida rentabilidad de estos productos [9,13].

A pesar de los esfuerzos regulatorios y la creciente comprensión por parte de la comunidad científica acerca de las diferencias entre la población pediátrica y adulta, el desarrollo de medicamentos pediátricos sigue siendo un reto considerable. Este obstáculo se atribuye a limitaciones que influyen de manera significativa en la progresión de medicamentos diseñados específicamente para niños, impactando así en los tratamientos destinados a abordar diversas patologías pediátricas. Por lo tanto, factores como el reducido tamaño de la población pediátrica, la variabilidad fisiológica y la carencia de datos históricos contribuyen a la incertidumbre en cuanto a la seguridad y eficacia de los medicamentos. Asimismo, la adaptación de formulaciones adecuadas para niños, junto con los elevados costos de investigación y la menor rentabilidad del mercado pediátrico, plantean desafíos adicionales [9,14,15]. Estas limitaciones subrayan la necesidad de un enfoque colaborativo integral para superar los complejos obstáculos asociados al desarrollo de medicamentos pediátricos.

Cabe mencionar que las limitaciones en la investigación y en el desarrollo de medicamentos pediátricos generalmente tienen un impacto directo en la adherencia a los medicamentos, también conocida como cumplimiento terapéutico, que es crucial para garantizar la eficacia de los mismos. Se entiende como adherencia o cumplimiento terapéutico el grado en que los pacientes toman los medicamentos prescritos por el médico; generalmente se representa como el porcentaje de las dosis prescritas a las realmente tomadas por el paciente durante un periodo de tiempo concreto. Un cumplimiento subóptimo puede comprometer el control de las enfermedades, reducir la efectividad del tratamiento y generar consecuencias negativas para la salud a largo plazo. Los pacientes con enfermedades agudas suelen presentar un porcentaje de adherencia más alto que los pacientes con enfermedades crónicas [16,17].

Por todo lo anterior, el enfoque de la investigación actual en medicamentos pediátricos se ha desplazado gradualmente hacia el desarrollo de medicamentos para satisfacer las necesidades de los niños; se presta atención a las formas farmacéuticas y a la exploración de nuevas tecnologías relacionadas con las preparaciones, los envases innovadores y los dispositivos novedosos de administración de medicamentos. Este enfoque busca no solo

superar las limitaciones inherentes al desarrollo de medicamentos pediátricos, sino también mejorar la experiencia del paciente pediátrico y sus cuidadores, promoviendo así una mejor adherencia al tratamiento [16].

1.3 Principios generales sobre las enfermedades del ácido gástrico

La enfermedad por reflujo gastroesofágico (ERGE), la ulceración gastroduodenal, la dispepsia no ulcerosa, la gastropatía por antiinflamatorios no esteroideos (AINE) y el síndrome de Zollinger-Ellison son entidades, todas diferentes, pero englobadas conjuntamente bajo la denominación de enfermedades relacionadas con el ácido. Su etiología es diversa, pero en todas subyace un desequilibrio entre los agentes irritativos locales y los mecanismos protectores del epitelio digestivo superior. Entre los primeros destaca la secreción ácida gástrica y, además, la infección por *Helicobacter pylori* (*H. pylori*), los ácidos biliares, la pepsina, o la frecuente presencia de productos químicos exógenos (AINE, etanol, etc.). Para una persona sana, la integridad de la mucosa queda asegurada por mecanismos protectores específicos de reparación y por la existencia de una vascularización particularmente rica, todo lo cual viene regulado esencialmente por mediadores como el óxido nítrico y los eicosanoides PGE 2 y PGI 2 [18,19].

Las lesiones de la mucosa digestiva solo se producen en los segmentos expuestos al ácido gástrico. Aunque estas lesiones pueden tener diversas causas, la reducción de la secreción gástrica se destaca como la principal opción terapéutica para abordar estos problemas. Una vez establecida la lesión, los medicamentos antisecretores aceleran el proceso de cicatrización. Este efecto se atribuye tanto a la necesidad de mantener niveles elevados de pH para la correcta realización de los fenómenos restitutivos del epitelio como a la mejora indirecta de la efectividad de los antibióticos empleados en terapia erradicadoras de *H. pylori*.

La secreción ácida se controla por un conjunto de mediadores endógenos que modulan la actividad de la célula parietal. Entre estos mediadores, destacan la acetilcolina, liberada por las terminales nerviosas vagales posganglionicas intramurales, actuando de forma nerocrina; la gastrina, producida por las células G antrales y liberada en el torrente circulatorio, con acción hormonal; y la histamina, almacenada por los mastocitos y células ECL (del inglés, *enterochromaffin-like cells*), siendo liberada en el fluido intersticial y actuando de forma paracrina. Cada una de estas sustancias ejerce su efecto

sobre receptores específicos localizados en la membrana de la célula parietal, los cuales están asociados a proteínas G. Se han identificado diversos sinergismos entre las acciones de la histamina, la acetilcolina y la gastrina (ver Figura 2). Además de estos tres secretagogos, otros mediadores como la somatostatina y las prostaglandinas desempeñan un papel determinante en la regulación de la producción de H^+[18–21].

En todos los casos el paso final en el proceso de secreción ácida exige la activación de una H^+ /K^+-ATPasa. Esta enzima intercambia H^+ por K^+ en una proporción de 1:1. Contiene dos subunidades: α, donde actúan los inhibidores de la bomba de protones, y β. En condiciones basales, la H^+ /K^+-ATPasa se sitúa en las membranas de las tubulovesículas situadas en el citoplasma celular; como estas vesículas no contienen K^+ ni su membrana es permeable a este, la enzima no es funcionante. Cuando se estimula la célula parietal, la membrana de las tubulovesículas pasa a integrarse en la membrana canalicular localizada en la porción apical de la célula. Con ello parte de la estructura molecular de la enzima se ve expuesta a los iones K^+ del medio extracelular lo cual, unido a un incremento asociado en la permeabilidad de la membrana a este ion, activa a la H^+ /K^+-ATPasa que comienza a secretar protones (ver Figura 2) [18–21].

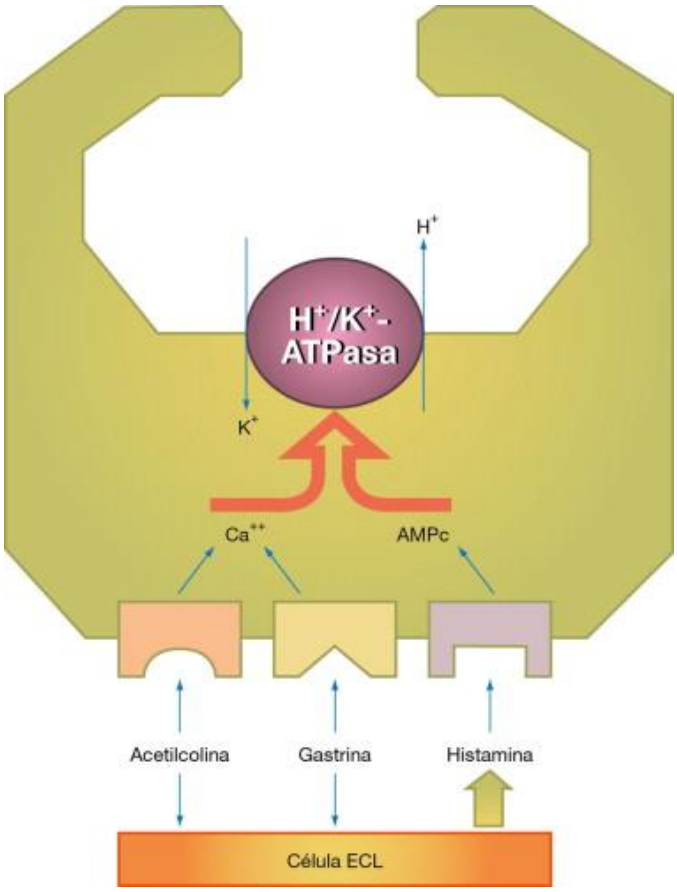

Figura 2. Mecanismos de secreción del ácido clorhídrico en la célula parietal del estómago.

Fuente: [21].

1.3.1 Posibilidades de actuación farmacológica: inhibición o neutralización de la secreción gástrica

El tratamiento de las lesiones mucosas está centrado en la inhibición de la producción del ácido clorhídrico con los inhibidores de la bomba de protones (IBP). Por su inferior capacidad inhibidora, las indicaciones de los antagonistas H_2 son ahora muy limitadas, mientras que otras posibilidades representadas por los anticolinérgicos selectivos M_1 (pirenzepina y telenzepina) o los antagonistas de gastrina (proglumida, loxiglumida, benzotrip) no tienen relevancia clínica. Aunque por su mecanismo de acción representan una alternativa a los IBP, los protectores de la mucosa tienen un papel secundario.

En función de los mecanismos, la acción farmacológica se clasifica de la siguiente manera: (I) inhibidores de la secreción ácida (IBP, antihistamínicos H_2); (II) neutralizantes de la secreción ácida (antiácidos); (III) protectores de la mucosa (sales de

bismuto coloidal, sucralfato, análogos de las prostaglandinas) y, (IV) tratamiento erradicador de *H. pylori*.

Conviene hacer una revisión del grupo de los inhibidores de la bomba de protones, concretamente del omeprazol (principio activo utilizado en la investigación doctoral). En este contexto, se presenta, en este mismo apartado de "Introducción", el artículo de revisión titulado "*Formulation of Omeprazole in the Pediatric Population: A Review*", el cual se centra en el uso del omeprazol en la población pediátrica y en proporcionar una visión general de los aspectos fisicoquímicos, farmacocinéticos y farmacológicos asociados con este API (ver páginas 150 – 164).

1.1 Técnicas de formulación galénica

En la Tabla 1 se muestran de forma resumida las diferentes técnicas de formulación galénica seguidas para conseguir una formulación óptima para la incorporación de omeprazol para medicamentos pediátricos.

Tabla 1. Técnicas de formulación galénica usadas en la presente tesis doctoral.

TÉCNICA GALÉNICA	DESCRIPCIÓN	APLICACIÓN	REFERENCIAS
GRANULACIÓN POR VÍA HÚMEDA	Implica la adición de un aglutinante dispersado en un líquido, generalmente agua, sobre las sustancias a granular. El método de granulación húmeda consta de las fases de mezclado, amasado, granulación, desecación y granulación final.	Estudios de preformulación	[22–25]
MATRICES INERTES: GRANULADO MATRICIAL	Las matrices inertes, también conocidas como matrices plásticas o insolubles, son redes sólidas porosas compuestas de sustancias no tóxicas ni digeribles, eliminadas intactas con las heces. Los excipientes empleados deben formar una red no desintegrable, ser insolubles en el tracto gastrointestinal, compatibles con fármacos y no tóxicos. La liberación del fármaco se produce por difusión a través de los poros de la matriz, influenciada por la concentración del fármaco, la solubilidad, aditivos y naturaleza de los líquidos de granulación, así como por el tamaño de partícula del excipiente y la forma del sistema matricial.	Estudios de preformulación	[26,27]

TÉCNICA GALÉNICA	DESCRIPCIÓN	APLICACIÓN	REFERENCIAS
GELIFICACIÓN IÓNICA	Consiste en encapsular APIS mediante la interacción entre un polímero y un polianión o policatión, formando un gel insoluble. Se utiliza alginato debido a sus propiedades de modulación de liberación y biodegradabilidad.	Estudios de preformulación	[28–31]
SALIFICACIÓN	Evita el uso de disolventes volátiles al emplear acetona como disolvente orgánico, emulsionado con una fase acuosa saturada de sal. El polímero y el APU se disuelven en el disolvente orgánico, seguido por la adición de la solución acuosa del coadyuvante con sal. Tras agitación, se forma una emulsión de fase oleosa externa A/O, seguida de la inversión de fases con agua, resultando en una dispersión de microesferas.	Estudios de preformulación	[32,33]
RECUBRIMIENTO DE PELLETS INERTES EN LECHO FLUIDO	Es una técnica fundamental en la industria farmacéutica, empleando el proceso de fluidización para suspender partículas sólidas mediante un flujo de aire. Ofrece diversas aplicaciones, como la estratificación de fármacos y la liberación modificada, aunque tiene desafíos como la limitación en el régimen de velocidad y la selección de tamaño y dureza de partículas. A pesar de ello, presenta ventajas como una mezcla eficiente, flexibilidad en el proceso y bajos costos de mantenimiento. Existen tres tipos de equipos de lecho fluido: *Bottom spray*, T*op spray* y *Tangencial spray*. El método de *Bottom spray*, también conocido como sistema Wurster, es preferido para el recubrimiento exitoso y la liberación modificada debido a su eficiencia y calidad superior. Permite una aplicación homogénea de recubrimiento y es adecuado para la estratificación de fármacos en dosis bajas a medias. La boquilla de pulverización se sitúa en el fondo de la cámara, permitiendo que las partículas se humedezcan y formen la película mientras se secan por el aire caliente, siguiendo una trayectoria controlada en la cámara.	Publicación 4	[34–40]

TÉCNICA GALÉNICA	DESCRIPCIÓN	APLICACIÓN	REFERENCIAS
IMPRESIÓN 3D DE FÁRMACOS: EXTRUSIÓN DE SEMISÓLIDOS	La producción de productos farmacéuticos impresos en 3D ha crecido significativamente, ofreciendo dosificaciones personalizadas y dispositivos de administración. La impresión 3D ofrece ventajas competitivas para productos complejos y personalizados, mejorando la seguridad y accesibilidad de los medicamentos. La tecnología de impresión 3D abarca varias categorías, destacando la extrusión de semisólidos (SSE, del inglés *Semi-Solid Extrusion*), que es particularmente útil en la bioimpresión y ampliamente utilizada en diversas áreas de investigación. La SSE deposita materiales semisólidos en capas que solidifican para crear objetos finales.	Publicación 5	[41–52]
ELABORACIÓN DE SUSPENSIONES	Las formas líquidas son preferidas en pediatría por su facilidad de dosificación. Las suspensiones son un sistema disperso heterogéneo constituido de un sólido insoluble, dispersado en un líquido. Siguen la fórmula patrón siguiente: API, humectante, viscosizante (si procede), floculante (si procede) y medio dispersante. En la preformulación, se consideran factores como la solubilidad del Api y la estabilidad química, mientras que durante el desarrollo se evalúa la viscosidad del vehículo, la sedimentación y la redispersión de las partículas para garantizar la estabilidad y la administración adecuada.	Publicación 6	[4,24,53–57]

A continuación, se expondrán los artículos de revisión publicados a lo largo de la presente tesis doctoral. Previamente a cada publicación, se proporcionará un breve resumen en castellano e inglés.

1.5 Publicación 1: Excipients in the paediatric population: A review

Citación	**Rouaz, K.**; Chiclana-Rodríguez, B.; Nardi-Ricart, A.; Suñé-Pou, M.; Mercadé-Frutos, D.; Suñé-Negre, J.M.; Pérez-Lozano, P.; García-Montoya, E. Excipients in the Paediatric Population: A Review. Pharmaceutics 2021, 13, 387. https://doi.org/10.3390/pharmaceutics13030387
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Resumen:

Este estudio teórico pretende revisar críticamente el uso de excipientes en la población pediátrica. Este estudio se basa en las normas y recomendaciones de las agencias reguladoras de medicamentos europeas y americanas. Por un lado, esta revisión describe los excipientes más frecuentemente utilizados en formulaciones de medicamentos pediátricos, identificando los compuestos que la literatura científica ha marcado como potencialmente nocivos en cuanto a los efectos secundarios generados tras su exposición. Por otro lado, esta revisión también destaca la importancia de llevar a cabo controles de seguridad de los excipientes, que en la mayoría de los casos están ligados a estudios de toxicidad. En la compilación de bases de datos para la población pediátrica se espera que un excipiente se centre en la seguridad y la toxicidad, como en la base de datos STEP (del inglés, *Safety and Toxicity of Excipients for Paediatrics*). Por último, se estudia una forma farmacéutica que parece prometedora para la población infantil, las ODT (del inglés, *Orally Disintegrating Tablets*).

Abstract:

This theoretical study seeks to critically review the use of excipients in the paediatric population. This study is based on the rules and recommendations of European and American drug regulatory agencies. On the one hand, this review describes the most frequent excipients used in paediatric medicine formulations, identifying the compounds that scientific literature has marked as potentially harmful regarding the side effects generated after exposure. On the other hand, this review also highlights the importance of carrying out safety -checks on the excipients, which, in most cases, are linked to toxicity studies. An excipient in the compilation of paediatric population databases is expected to target safety and toxicity, as in the STEP (Safety and Toxicity of Excipients for Paediatrics) database. Finally, a promising pharmaceutical form for child population, ODT (Orally Disintegrating Tablets), will be studied.

pharmaceutics

MDPI

Review

Excipients in the Paediatric Population: A Review

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Abstract: This theoretical study seeks to critically review the use of excipients in the paediatric population. This study is based on the rules and recommendations of European and American drug regulatory agencies. On the one hand, this review describes the most frequent excipients used in paediatric medicine formulations, identifying the compounds that scientific literature has marked as potentially harmful regarding the side effects generated after exposure. On the other hand, this review also highlights the importance of carrying out safety -checks on the excipients, which, in most cases, are linked to toxicity studies. An excipient in the compilation of paediatric population databases is expected to target safety and toxicity, as in the STEP database. Finally, a promising pharmaceutical form for child population, ODT (Orally Disintegrating Tablets), will be studied.

Keywords: excipients; paediatrics; security; toxicology; STEP and ODT

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1. Introduction

The scientific literature suggests that most commercialized drugs are not suitable to be used on the paediatric population, as they are presented in an inappropriate pharmaceutical dosage or form, or because of the excipients they contain. In the face of this reality, compounding is the alternative for paediatric patients. Auxiliary substances or excipients should be used in the development of a compounding formula in order to allow the drug to be administered in an easily and personalized manner. By doing so, the active ingredient will be formulated in a stable, effective, and safe form [1].

The process of formulating excipients in paediatrics is a complicated task that requires various considerations to be accounted for in order to for them to be appropriate; variables such as an acceptable taste, age, dosage forms, among others, must be taken into account when selecting safe excipients. Furthermore, children's rapid growth and development are associated with changes in various organs, body composition, protein bonds, active transport mechanisms and metabolic pathways, which must also be taken into account [2]. In addition to being a complicated task, it is also a critical step in the development of paediatric formulations, as some acceptable excipients in formulations for adult patients are not suitable for paediatric use.

It is thus of particular relevance to carry out an assessment of the safety of excipients prior to their use in paediatrics. Indeed, Georg Schmitt [3] advocates for non-clinical safety studies being carried out in juvenile animals to assess excipient toxicity or sensibility and also to establish safe exposures in paediatric age groups. He specifically recommends that excipient toxicity studies also be carried out, as they provide a detailed assessment

of clinical risk. He further suggests that even excipients with significant toxic potential for children may be acceptable after a rigorous assessment of the risk they pose is made. Another factor to be considered for toxicological studies is the extent to which the target disease may be alleviated by the formulation of that medicine. Thus, pharmaceutical companies should filter the demands for safety assessments by selecting those that will contribute to a potential therapeutic benefit, while helping to develop a reference list of excipients generally considered safe for use in paediatric formulations. In this way, the clinical decision-making process will be made easier.

This theoretical study's main objective is to critically review the use of excipients in paediatrics with an emphasis on the issue of safety, mainly on the basis of toxicological studies. This will enable information to be obtained that will allow decisions to be made regarding the masterful preparation of formulations. This study also seeks to investigate the development of databases and initiatives in order to record corroborated information on excipients for paediatric use, thus serving as a guide for clinical professionals.

To do this, databases such as Web of Science, PubMed, SciFinder and SciFindern Search, as well as books related to the subject, were consulted. Please note that most of the selected literature is from the last two decades. Subsequently, six tables were created to provide details on the data obtained:

- Table 1. Toxicity database.
- Table A1. Most important characteristics of the excipients discussed in this review (in alphabetical order).
- Table A2. Examples of solid and semi-solid medicines used in Spain for the paediatric population: List of excipients and relevant characteristics of the pharmaceutical form (PF) (performed consultation of CIMA database, September 2020).
- Table A3. Examples of liquid medicines used in paediatrics: List of excipients and relevant characteristics of (PF).
- Table A4. Examples of FDA-registered drugs used in paediatrics (FDA database and DAILYMED October 2020).
- Table A5. Examples of liquid formulations for paediatric use in research articles.

Table 1. Toxicity databases and public resources.

Name	Website	Creator
ACToR —Aggregated Computational Toxicology Resource	www.actor.epa.gov/actor/home.xhtml (accessed on 15 November 2020)	US Environmental Protection Agency's (EPA) National Center for Computational Toxicology (NCCT)
STEP—Safety and Toxicity of Excipients for Paediatrics *	www.eupfi.org/step-database-info/ (accessed on 15 November 2020)	European Paediatric Formulation Initiative
TOXNET—Toxicology Data Network	www.nlm.nih.gov/toxnet/index.html (accessed on 15 November 2020)	Specialized Information Services (SIS) USA
Vitic	www.lhasalimited.org/products/vitic.htm (accessed on 2 November 2020)	Lhasa Limited

* The purposes of the STEP database can be consulted in the Appendix A.

2. Paediatric Regulatory Context

Changes in physical, metabolic and psychological processes that occur during children's growth, from birth to adulthood, suggest that children should not be considered as young adults, and nor should they be grouped as a single group. Rather, the pharmaceutical development of paediatric drugs should focus on several acceptable dosage forms that are able to meet the needs of most children in different age groups. This can be achieved by developing dosage forms which facilitate the administration of a dose range which would vary according to the child's age and/or other important parameters [4].

Before there were regulations for the development of paediatric drugs, children were known as "therapeutic orphans". They lost the advances of conventional medicine, since the vast majority of advances were aimed at the adult population, and there were not many approved medicines for children. Children were treated with approved drugs following successful studies on adults, but with few or no trials on the paediatric population (off-label use). The large number of subsequent issues with clinical trials on children, as well as the need for drug authorization in the paediatric population, among other reasons, were the driving factors for the creation of a legislative and regulatory framework for clinical studies in paediatrics. The US pioneered these in the late 1980s, and with the adoption of these paediatric regulatory initiatives, significant improvements were made [4].

It was only in 1997 that European regulators agreed to strengthen legislation on the use of new medicines in children. In 2000, European health ministers asked the European Commission to make proposals for a legislation to ensure that new paediatric medicines placed on the market were tailored to the specific needs of children. In 2004, after a major debate, a regulatory bill was issued, which took into account lessons learned from paediatric regulation that the US was already addressing [5]. On 26 January 2007, the Paediatric Regulation entered into force in the European Union, and focused mainly on regulating the development of paediatric formulations for children between 0 and 18 years of age, but also sought to:

- Ensure that these medicines were of good quality.
- Verify that paediatric medicines were produced following ethical and legitimate research, that children were not subjected to unnecessary trials.
- Improve the accessibility and availability of information on drug use in the paediatric population.
- Such regulations led to the establishment of the Paediatric Committee (PDCO), whose main function was to regulate the studies that companies should conduct in children as part of a Paediatric Research Plan (PRP) [6].
- The Paediatric Regulation consists of [7]:
- Regulation (EC) 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use; and
- Regulation (EC) 1902/2006, an amending regulation in which changes were made to the original text in relation to the European Commission's decision-making procedures.

In October 2017, the European Commission published a ten-year report on the implementation of the Paediatric Regulation. The report showed an increase in medicines for children in most therapeutic areas over the past ten years, especially in rheumatology and infectious diseases. However, in rare diseases, progression was lower. A report on the first five years was also published in June 2013, which concluded that paediatric development had become a more integral part of the overall development of medicines in the European Union [4,8].

The European Guideline on pharmaceutical development of medicines for paediatric used [4] offers several tips for paediatric drug formulation.

Excipients in a paediatric formulation should be chosen appropriately, avoiding any excipients that are potentially toxic or unsuitable for children. Choosing the right excipients in the development of a new paediatric drug is one of the most important aspects, as it requires special safety considerations. In general, the following aspects should be taken into account when selecting an appropriate excipient for a paediatric medicinal product [4]:

- Excipient function in formulation and possible alternatives.
- Safety profile of the excipient for children in target age groups, based on a unique and daily exposure.
- Expected duration of treatment: short term (a single dose for a few days) or long term (weeks and/or months).
- Severity of the condition to be treated and therapeutic alternatives.
- Patient acceptability, including palatability.

- Allergies and sensitization. Children suffer from sensitization problems more commonly than adults. Applicants should avoid, when possible, excipients with known potential to cause sensitization or allergies.

If the use of any excipient in the formulation that produces or may pose any risk to the child cannot be avoided, the added value of the chosen pharmaceutical form of dosing (and the route of administration) should be balanced with the possible use of another. However, security issues can only become apparent when the product is used on a larger scale.

Furthermore, the first joint paediatric regulatory action was taken by the ICH (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use), an organization working on harmonizing drug regulation requirements between the EU, Japan and the US. In July 2000 Guideline E11 (R1) was published: Clinical investigation of medicinal products in the paediatric population, with the final version in August 2017 [9].

The objectives of this guide were to encourage and facilitate the development of paediatric medicines at the international level, as well as to provide a summary of critical problems in the development of these medicines and new approaches to their safe, efficient and ethical clinical study. ICH E11 became an important tool in the design of paediatric clinical research worldwide, providing guidelines (rather than proscribing practice) [9,10].

The WHO launched the initiative Making Medicines Child Size in 2008 to issue a list of essential medicines for children, betting on quality paediatric development and adequate access of these medicines to the entire paediatric population, in particular underdeveloped countries [11]. The most current one is the 7th edition, which was published in 2019 (WHO model list of essential medicines for children) [12].

In the early 1980s, the FDA (Food and Drug Administration) began taking steps to provide incentives to the pharmaceutical industry for the development of paediatric drugs. In 1994, the Paediatric Labelling Rule was issued, requiring the authorization of a new paediatric drug to be supported by safety and efficacy data to support its use. However, that rule was not mandatory and was unsuccessful. For this reason, the US-FDA proposed in 1998 Paediatric rule which proposed to guarantee the above-mentioned objectives, both at and after the approval of the new drug [13].

It should also be noted that the FDA (Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients) published a document that provides guidance on the development of safety profiles to support the use of new excipients as components of drugs or biological products, which could be applied in paediatric experiments [14,15].

Examples of Databases and Initiatives for the Registration of Information on Excipients Used in the Paediatric Population

It is certainly necessary to take into account the safety of excipients used in paediatric products, as the toxicity of these excipients may differ from that of adults [16]. Under this assumption, it is essential to develop methodologies that provide an integrated assessment of exposure to potentially toxic excipients contained in medicines. Therefore, in 2007, members of pharmaceutical industries, hospitals and academics interested in improving drug formulations in paediatrics founded the European Paediatric Formulation Initiative (EUPFI). The latter sought to address safety problems linked to excipients used in children [17], as well as the development of platforms for the systematic evaluation of excipients in new-borns [18].

EuPFI is currently a consortium of 10 pharmaceutical companies, 5 universities, 1 hospital and, exclusively, the European Medicines Agency (EMA) as an observer. The goals and objectives of this consortium are summarized in [19]:

1. Identify the problems and challenges associated with the development of paediatric formulation and consider ways to obtain better medicines and dosage forms clinically relevant to children.
2. Promote early pharmaceutical consideration for the development of paediatric medicines.

3. Identify potential information and knowledge gaps in the development of paediatric formulations.
4. Improve the availability of information from paediatric formulations.

The scientific literature shows that excipients commonly used in adult medicines have been associated with high toxicological risks and safety problems in children [20]. Following the United States Paediatric Formulation Initiative (USPFI) and Global Paediatric Research (GRIP), the Paediatric Excipient Safety and Toxicity Database (STEP) was created to address the need for effortless access to information about the excipients' safety and toxicity [21]. The STEP database is presented as a resource of information to facilitate access to data on the use and acceptability of excipients in children, thus allowing a rapid evaluation of the risks due to the use of certain excipients in the paediatric population and an improvement in the scientific decision making [2,22]. Furthermore, the STEP database provides comprehensive and comparative information on the safe use and acceptability of excipients in paediatrics. For the reasons listed above, the STEP database stands out with respect to other existing public resources (such as TOXNET) or databases (such as Vitic or ACToR) that organize their informational content in free text format, thus preventing data from being filtered as needed (see Table 1) [23].

In general, the above purposes go in line with increasing the number of excipients registered in the database to be useful in practical research. Therefore, the following selection criteria were considered for excipients of interest [2]:

1. Excipients known to be toxic/have general safety issues.
2. Frequency of appearance as contaminants or toxics in paediatrics (where applicable).
3. Evidence in the toxicity literature in paediatrics. The above criteria were applied to identify excipients for inclusion in the STEP database. Excipients were short-listed/prioritized through surveys within EU and US PFI members.

According to the above criteria, in the development of databases on the safety and toxicity of excipients in the paediatric population, the following are prioritized, as they are most likely to cause damage and side effects in this population [2]:

1. Propylene glycol (PG)
2. Ethanol
3. Polysorbate 80
4. Benzyl alcohol
5. Parabens (propyl, methyl, ethyl and butyl)
6. Benzalkonium chloride
7. Aspartame
8. Sorbitol
9. Benzoic acid
10. Sodium benzoate

In 2014, the first version of the STEP database was launched for the systematic evaluation of its integrity, quality, configurability, usability, and maintainability under the daily practices of the different and diverse professionals who use it. After launch, a validation study of the tool was initiated with the following objectives [2]:

1. Validate the STEP Version 1 database against the potential needs of end users to ensure that the STEP database meets users' expectations.
2. Evaluate the functionality and usability of data application by
    a. Ensuring proper ease of use (navigation), understanding and user satisfaction.
    b. Characterizing how easy it is to perform a task using the database.
    c. Identifying problems in interaction with systems.
3. Evaluate the impact of this database on the development of paediatric medicines.
4. Establish viable recommendations to further improve the functionality of the system and increase its beneficial effects on the development of paediatric medicines.

The results of the validation study identified different database usage issues, which are grouped into three areas: I. Content and presentation of results; II. Adequacy of the database to the characteristics of different users, navigation features; and III. Search. Many of the problems observed might have happened due to assuming that users would have sufficient knowledge, therefore some elements were not clearly exposed for the new user to understand. Furthermore, users with limited computer skills may also find the registration process confusing. These issues involved changes and improvements to STEP design and functionality, making it a more efficient database when deriving from a Version 2 [21].

To perform an adequate risk/benefit assessment of the current medication standard, it is necessary to compare the daily amount of excipients in the most vulnerable patient with clinically established safety levels for the same age group. The SEEN project is an example of this, as it developed a retrospective cohort study, with neonatal patients (age 5 or younger) treated with multiple medicines. Preparations were recorded with ethanol, propylene glycol, benzyl alcohol, parabens, aspartame, glycerol, sorbitol and polysorbate-80 and cumulative amounts [24] were calculated.

The results obtained demonstrated limited knowledge about the acceptability of different dosage forms, flavours and, more importantly, the safety of formulation excipients in relation to the age and stage of development of children [24].

3. Excipients: Functions and Main Adverse Effects

Paediatric formulations need excipients to maintain their quality and promote the acceptability of childhood patients [25]. However, just because they are necessary does not mean that they are toxicity-free products; in fact, a study by Georgi and collaborators [26,27] confirms that many of the medicines used in paediatrics contain some toxic or potentially toxic excipient for the paediatric population, with this data being present in two-thirds of new-borns in 21 European countries. Thus, excipients used in paediatric formulations require a thorough assessment of short-term and long-term safety prior to their use in these formulations [28]. A classification of the main excipients will then be developed according to the role they play in the formulation, mentioning the possible adverse effects on the paediatric population. Furthermore, a summary appendix (Appendix B (Table A1)) of the excipients discussed in this paper will be prepared.

3.1. Diluents

Lactose, starch and microcrystalline cellulose are often used as diluents, as they are generally safe in the adult population.

3.1.1. Lactose

Lactose, which is a mandatory excipient, is recommended not to be used in patients with lactose intolerance and is contraindicated in patients with galactosemia [1]. It may cause hypersensitivity reactions in children and new-borns. Infants with lactose intolerance do not properly metabolize lactose, due to the deficiency of the enzyme lactase, thus causing the accumulation of lactic acid, hydrogen and carbon dioxide. Symptoms such as severe abdominal pain, flatulence, bloating or swelling and diarrhoea may, therefore, appear, as well as systemic symptoms such as muscle, joint pain and eczema [28]. It should be noted that children may sometimes have very severe and prolonged reactions to lactose that can lead to additional complications, such as dehydration, bacterial proliferation and metabolic acidosis [1,28].

Starch, dehydrated calcium hydrogen phosphate, erythritol and cellulose powder are alternatives to lactose in paediatric formulations. They have lactose-like flow properties and produce tablets that can disaggregate in a time less than lactose [28].

3.1.2. Starch

Starch is one of the most commonly used excipients and, in addition to being a diluent, it has binder and disintegrating properties. Due to its properties, starch should be preserved

in a dry environment, as it can be an excellent growing medium for microorganisms in case of moisture, which may cause microbiological contaminations. In addition, it may give proliferation of carcinogenic aflatoxins, if contaminated by two species of fungi closely enhanced by each other: Aspergillus flavus and Aspergillus parasiticus [29].

3.1.3. Microcrystalline Cellulose

Microcrystalline cellulose is a partially depolymerized purified cellulose that is presented as a white, odourless and tasteless crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications. It is considered a relatively non-toxic and non-irritating material. It is not absorbed systemically after oral administration and therefore has little toxic potential [29,30].

Microcrystalline cellulose is used in pharmaceutical products, mainly as a binder and thinner in tablet and oral capsule formulations. In addition to its use as a binder and thinner, it also has some lubricating and disintegrating properties that make it useful for forming tablets [30].

3.2. Solvents

Some of the most common solvents are water, ethyl alcohol, propylene glycol (PG), glycerol and polyethylene glycol [28,29].

3.2.1. Water

Water is the most commonly used agent in paediatric formulations, as liquid preparations are easier to administrate and allow a more accurate dose adjustment [1,29]. Water is an ideal medium for the proliferation of microorganisms (bacteria and fungi) despite their purification, which is why antimicrobial agents have to be added.

In paediatric oral formulations, the total volume of fluid is of vital importance for the taste and ability to adequately measure the volume to be administered: in children under 5 years of age a volume of less than 5 mL should be administered and, in children under 10 years of age, a volume of less than 10 mL [29] should be administered.

3.2.2. Ethyl Alcohol (Ethanol)

Ethanol is one of the excipients of concern to international health regulatory agencies, as it causes neurotoxicity and cardiovascular problems in the paediatric population; it is a potentially harmful excipient in neonates. For this reason, permissible maximum limits have been set and, in some countries, non-alcoholic medicines are to be established. It is a very permeable excipient with regard to the blood–brain barrier, and the one most commonly used in oral medicinal products, reaching 63% of cases [26]. It is rapidly absorbed into the gastrointestinal tract and is primarily metabolized in the liver to acetaldehyde, which is oxidized to acetate [29].

Indeed, Macrel and Bernando's review of liquid formulations in Brazil has furthered our understanding of the high use of ethanol. These researchers demonstrated that ethanol is used in various concentrations and functions: as solvent (main function), co-saver, flavouring agent, preservative and as an extraction solvent in herbal medicines [26,27]. It also has antimicrobial properties and increases the permeability of many preparations [29].

The use of ethanol as an excipient carries potential hazards and adverse effects, which are already observed at a dose of 100 mg/dL. These effects include hypoglycaemia, acidosis and hydro-electrolytic alterations. Very high intake can lead to stupor, coma, respiratory depression and cardiovascular collapse. Hypoglycaemic seizures may also occur in children [29,31]. For all these side effects, any alcohol should be avoided in paediatric forms. However, it is still used in many liquid preparations, because it is the only solvent that allows the solubilization of certain active substances [29].

In both the United States and the European Union, guidance on maximum ethanol limits in medicinal formulations is increasing [17]. According to the World Health Orga-

nization and a regulation existing in the United States, the maximum alcohol content in paediatric formulations should not exceed the limits specified in Table A1 [29,31,32].

It should be noted that ethanol was also able to interact with many active substances of other medicines that the child is taking [29] and, therefore, possible interactions must be studied prior to concomitant administration. Furthermore, new contributions in the scientific literature on excipients, including ethanol, is expected to help health professionals predict the risks of using a particular excipient, especially in the paediatric population. For example, the guideline excipients in the label and package leaflet of medicinal products for human use alerts on the risk of the use of ethanol and proposes changes on its use.

3.2.3. Propylene Glycol (PG)

PG is used as a solvent to stabilize substances that are not water soluble, in parenteral and non-parenteral formulations. It also has moisturizing, antimicrobial properties and can be used as plasticizer. It is rapidly absorbed through the gastrointestinal tract and damaged skin and metabolized in the liver to lactic acid and pyruvic acid [29].

Exposure to high doses of PG may affect the Central Nervous System, especially in new-borns and children under 4 years of age [29]. Due to children's physiological and metabolic immaturity, PG can accumulate rapidly causing toxicity [33]. In new-borns, its half-life is very long, almost seventeen hours, compared to that of adults, which is about five hours [29]. The GRAS (Generally Recognized as Safe) classification of excipients typically does not consider the differences in physiological and metabolic maturation between the paediatric and adult populations [33], a fact that justifies some important adverse reactions presented by PG in the paediatric population [29]:

- Hyperosmolar syndrome in burnt children with topical arsenic sulfadiazine ointment containing PG.
- Precipitation of irreversible deafness in pretermits who received a multivitamin complex containing PG.
- Parenterally it is possible to observe haemolysis, seizures, respiratory depression, hypertension.
- Contact dermatitis is topically observed.

In the 1980s, cases of biochemical abnormalities, including hyperosmolarity, lactic acidosis and elevated levels of creatinine and bilirubin, were documented after exposure to 3 g/day of PG and for at least 5 consecutive days. Clinical symptoms, including seizures and bradycardia episodes [33], then appeared. In 2011, the U.S. FDA reported health problems in premature new-borns associated with the use of Kaletra® (lopinavir/ritonavir) solution; liquid preparation containing high amounts of PG and ethanol [33,34].

Exposure to PG in new-borns and children under 4 years of age remains common, despite historical and contemporary reports dealing with toxic adverse effects of this excipient. Thus, the study of Allegaert J. [33] in terms of the PG research project in new-borns is of great interest, as it provides scientific evidence on the tolerance and plasma clearance of this excipient, including differences in elimination pathways (renal pathway compared to the hepatic pathway).

3.2.4. Glycerol

Glycerol, a mandatory excipient (E-422), is used as solvent, sweetener, viscosizer and preservative.

When used at high concentrations (more than 40%), it can cause mucositis in the stomach, as well as diarrhoea and electrolyte disturbances due to its hygroscopic and osmotic properties. Therefore, a maximum amount of 10 g/dose [1,29] has been established.

In the adult population glycerol has few adverse effects. However, cases of neurological toxicity have been reported in the paediatric population [29].

3.2.5. Polyethylene Glycol (PEG)

PEG is a polar and water-soluble substance used as a co-solvent, suspensor and viscosity agent. The PEG 400 is the most used in liquid formulations. It may cause some laxative effect when taken orally, with the maximum daily dose established in adults at 10 mg/kg/day [1].

PEG has low oral bioavailability and renal elimination. Due to its properties, significant adverse effects such as diarrhoea and nephrotoxicity have been reported, so the maximum recommended daily dose is 10 mg/kg body weight [1]. It can also cause some laxative effect when taken orally. When new-borns and infants are exposed to high doses of PEG, gastrointestinal disorders, adverse effects typical of alcoholic solvents may occur [1,28].

3.3. Coating Agents

Phthalates

Phthalates play a primary role as a coating agent (film-forming, plasticizer) in medicinal formulations.

Exposure of pregnant women to phthalates has been associated with abnormalities in the development of the foetus, such as cleft palate and skeletal malformations; abnormalities that can end in stillbirth. It was observed that they have a high potential to produce toxicity in the development of experimental animals, as well as in their reproduction [28].

Due to these risks of certain phthalates to health, in March 2012, the CDER published a guide to orient the pharmaceutical industry on the use of phthalates: "Limiting the use of certain phthalates as excipients in CDER regulated products". This guidance document recommends limiting the use of certain phthalates, such as dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) [28].

3.4. Preservatives

Preservatives are a group of excipients that prevent microbial growth and, consequently, the degradation of the active substance and the possible alteration of the organoleptic characteristics of the final formula [35].

The American Academy of Paediatrics does not recommend the use of preservatives in reparations for patients under 3 years of age due to the lack of physiological and metabolic maturation of these patients. This lack of maturation may lead to the accumulation of preservatives in the liver, a fact that increases the risk of cardiovascular collapse, in addition to producing non-specific reactions or even allergies [1,35]. It should be noted that preservatives are not contraindicated in children under 3 years of age, but should only be used in imperative cases [1].

3.4.1. Sodium Benzoate

Sodium benzoate is a preservative widely used in pharmaceutical and cosmetic formulations, at concentrations between 0.02% and 0.05% [29]. Its maximum activity occurs in weakly acidic pH 4.5 solutions and is inactive at pH values greater than 5 [35].

As side effects, it can cause contact hives and other allergies. In premature children, its use is contraindicated, as it presents a risk of metabolic acidosis and jaundice [29,35].

One of the large prospective studies conducted by Nellis and collaborators [36,37] in hospitalized neonates in Europe described the administration of eight potentially harmful excipients of interest (EOI) (parabens, polysorbate 80, propylene glycol, benzoates, sodium saccharine, sorbitol, ethanol and benzalkonium chloride) and identified risk factors resulting from exposure. Neonates appear to lack the ability to conjugate benzoates with glycine, leading to the accumulation of benzoic acid that can cause metabolic acidosis and neurotoxicity [26,27].

The ESNEE (European Study of Neonatal Exposure to Excipients) clinical study [38] showed that sodium benzoate was found in 10 medicines given to new-borns, despite being a highly toxic excipient to them. Preservatives such as parabens (and their sodium

salts) and propyl para-hydroxy-benzoate were also found in 24 paediatric medications, and ethanol in 8.

3.4.2. Benzyl Alcohol

Benzyl alcohol presents antibacterial properties. For that reason, it is used as a preservative in a lot of medicines. Its activity depends on the pH; being at it is maximum at a low pH (between 2.5–4.5). It is used at the concentration of 0.01–0.15% in oral preparations [35].

In adults, it is metabolized to benzoic acid, which is conjugated in the liver with glycine. As a result, the acid hippuric formed is excreted in urine. However, in new-borns, this conversion of the benzoic acid into hippuric acid is very diminished, because of the lack of liver maturation. That justifies fatal intoxication cases in new-borns who had their umbilical catheters cleaned with benzoic acid. Consequently, cases of metabolic acidosis and respiratory depression occurred. Additionally, other adverse effects have been described, like intraventricular bleeding, cerebral palsy and developmental delay. In some cases, there have been reactions of hypersensitivity, allergy and contact dermatitis [29,39–41].

In the 1990s, Svinning and collaborators [42] conducted a review of the medical records of babies who weighed less than 1250 g at birth and were admitted to the neonatal intensive care unit. The main objective of this study was to assess the impact of the toxicity of benzyl alcohol, following discontinuation of the use of solutions to wash intravascular catheters containing benzyl alcohol. A significant decrease in mortality rate and incidence of Grade III/IV intraventricular haemorrhage was observed among infants weighing less than 1000 g at birth who were not exposed to benzyl alcohol (as opposed to those who were).

The maximum dose of benzoic acid (and other benzoates, calculated as benzoic acid) recommended by WHO is 5 mg/kg body weight per day in adults, a dose that, in children, logically, should be much lower [29,35]. As the effects on new-borns are severely toxic, the U.S. FDA has recommended the exclusion of benzyl alcohol from medications, intravenous fluids, and heparin washing solutions for them [36]. The EMA states that any medicine containing benzyl alcohol "should not be given to premature babies and new-borns" [42,43]. In fact, currently, any exposure to benzyl alcohol is contraindicated in children under 3 years of age [44].

3.4.3. Benzalkonium Chloride

Benzalkonium chloride is a quaternary ammonium used in ophthalmic preparations at a concentration of 0.01–0.02% (*v/v*). Generally, it is non-irritating or sensitizing and is well tolerated in skin solutions.

As a side effect, it can cause bronchoconstriction in asthmatic patients, if used in nebulization solutions. Furthermore, cases of ototoxicity may occur in otic preparations, hypersensitivity in topical skin preparations and respiratory failure in infants who ingest this excipient, with this side effect being the most severe [29].

3.4.4. Thiomersal

Thiomersal is a preservative widely used in vaccines and topical preparations, such as eye drops. Its toxicity is similar to mercury: in fact, it contains a mercury atom in its molecular structure. The concentration used depends on the medicinal product: in injectable preparations 0.01% is used and in ophthalmic solutions between 0.001% and 0.15% [30].

Several allergic hypersensitivity reactions (e.g., erythema, vesicles) have been reported. Therefore, health authorities have recommended their withdrawal from vaccines at risk of toxicity. Recently, thiomersal has also been implicated in the onset of autism spectrum disorders in children who received aluminium salt vaccines as an adjuvant. Accordingly, various countries (including Spain) no longer market paediatric vaccines with this component [29]. The use of single-dose vials is recommended in many cases to prevent the use of preservatives such as thiomersal or sulphites such as sodium metabisulphite [28].

3.4.5. Parabens

Parabens are the most commonly used preservatives (also in cosmetics and foods), due to their wide antimicrobial spectrum and their effectiveness over a very wide pH range (between 4 and 8) [29,35].

Parabens are of mandatory declaration. They are used at concentrations between 0.01 and 0.2% [45], although it is most common to use a mixture in proportion 10:1 (0.2% methylparaben + 0.02% propylparaben). The maximum recommended daily dose is 10 mg/kg body weight [35].

They may produce a cross-hypersensitivity reaction in patients allergic to aspirin. This is because the main metabolite of parabens is hydroxyparabenzoic acid, structurally very similar to aspirin [29].

Recent pharmacovigilance studies have highlighted certain questions about the purported safety (non-teratogenic or carcinogenic) of parabens [29]. Alternatives should therefore be found, especially in paediatric formulations. Antimicrobials are not necessary for parenteral formulations. The absence of parabens and benzoates in 85% of parenteral prescriptions suggests that administration of these excipients can be largely avoided [36].

3.5. Antioxidants

Antioxidants are a group of chemical compounds used to prevent oxidation of the active substances in formulations [29].

3.5.1. Sulphites

Sulphites are antioxidants widely used in different formulations; sodium sulphite, sodium bisulfite, sodium metabisulphite and potassium metasulfite [29] are the most common.

Regulatory agencies (e.g., FDA, EMA) consider excipient sulphites safe. However, they present risks and possible fatal side effects derived of their use. One of the most common cases occurs in asthmatic patients, who may develop severe bronchospasm if they take medicines containing sulphites in their formulation [29].

The antioxidants constitute a group of compound chemists used to avoid the oxidation of the active principles in the formulations [29].

It should be noted that a large number of people are sensitive to sulphites and may experience a variety of symptoms, including dermatological, gastrointestinal and respiratory symptoms. However, reactions that develop in the respiratory tract explain most cases of sensitivity to sulphites. It is important to note that several individuals experience a variety of symptoms after exposure to sulphites; therefore, skin, intestinal and respiratory reactions can occur simultaneously and in various combinations and severity. People with sensitive skin who regularly use cosmetics or topical medications containing sulphites have chronic skin symptoms, especially on the hands, perineum and face. Sensitivity to sulphites is a very real problem that significantly affects the health of many people, especially asthmatics. Sensitivity to sulphites should be considered when people show adverse reactions to a variety of exposures, without an obvious pattern, particularly when those people experience worsening asthma symptoms after consumption of foods such as dried fruits and wines, or adverse skin reactions, after the use of cosmetics or medicinal creams [46].

3.5.2. Propyl Gallate

Propyl gallate is an antioxidant used to prevent the breakdown of fatty acids. It is used at a concentration of 0.1% and also has a synergistic effect with other antioxidants. In neonates it can cause dermatitis, skin allergy and methemoglobinemia [29].

3.6. Sweeteners

The use of sweeteners varies between routes of administration and, like preservatives, are not necessary in parenteral administrations [36,37]. They have been linked to photosensitivity reactions, diarrhoea and poor absorption of nutrients [36,47].

The most commonly used sweeteners in pharmaceutical formulations are sucrose, sorbitol, mannitol, aspartame and sucralose.

3.6.1. Sucrose

Sucrose is a natural disaccharide that is hydrolysed in the gut into two monosaccharides: glucose and fructose.

In children with type I diabetes, the use of sucrose should be avoided. Very high concentrations (up to 35% are used for liquid formulations such as syrups). When the patient needs prolonged treatment with these preparations, he or she is at risk of dental damage. It has also been described that administration at very high doses on a daily basis may be carcinogenic [29].

3.6.2. Sorbitol

Sorbitol is a monosaccharide that is not absorbed into the digestive tract and is therefore considered safe in paediatric patients, although it is laxative at high doses. It is also used as a diluent as well as capsule plasticizer [29].

Sorbitol is another example of an excipient that causes gastrointestinal disorders, such as abdominal pain, swelling, flatulence, vomiting and osmotic diarrhoea. Because sorbitol is metabolized to fructose, it should be avoided on children with fructose intolerance and hypoglycaemia. In isolated cases it can cause liver damage leading to coma and even death [28–30].

In infants the accumulation of sorbitol can lead to diabetic complications such as retinopathy and cataracts. Therefore, the amount of sorbitol is limited to 0.3 mg/kg in paediatric formulations [28].

3.6.3. Mannitol

Mannitol is used as a sweetener and as a diluent. It has been linked to severe anaphylactic reactions in paediatrics [29]. As in the case of sorbitol, it is not absorbed into the digestive tract, so it has laxative properties at high doses.

3.6.4. Aspartame

Aspartame is an artificial sweetener that has 180 and 200 times more sweetener power than sucrose. Because of this, it is the most used sweetener in the pharmaceutical and food industry. It is a disaccharide made of an aspartic acid and a methyl phenylalanine ester. It is an excipient of mandatory declaration and its maximum dose has been set at 40 mg/kg body weight [29,35].

Phenylalanine is very harmful for patients with phenylketonuria, as well as for pregnant mothers who carry a foetus of such metabolopathy. The use of aspartame in patients with phenylketonuria should be avoided. The adverse effects of aspartame that have been described are: neurological (neurotoxicity, epilepsy, headache, panic attack and hallucinations), hypersensitivity reactions (vascular and granulomatous panniculitis) and cross-reaction with sulphonamides [29].

3.6.5. Saccharine

Saccharine is also an artificial sweetener 300–600 times stronger that sucrose, but if not used properly it can leave a residual bitter taste. Your daily dose should not exceed 2.5 mg/kg body weight. It is recommended to limit the daily dose in children and pregnant women [29,48].

Currently, controversy about its safety remains present, as in adults it has been linked to bladder cancer when used at very high doses. Adverse effects of saccharine include hives, itching, photosensibilization, eczema, as well as nausea and diarrhoea [29].

3.6.6. Sucralose

Sucralose has a sweetener power between 100 and 300 times higher than sucrose. Its maximum daily dose is 15 mg/kg in weight.

Sucralose is a non-toxic compound and is also not irritating, but it is not considered totally inert. It can increase the expression of cell flow transport protein glycoprotein P and two cytochrome P450 isoforms, which are essential substances in the drug purification process.

Furthermore, sucralose alters the composition of the microbiome of the digestive tract, which ends up causing the reduction of the proportion of beneficial bacteria. In addition, if cooked at high temperatures, chloropropanol can form, which is a toxic compound. It can also alter the patient's levels of glucose, insulin and glucagon-like peptide type 1 (GLP-1) [29].

3.7. Surfactants

Polysorbates

Polysorbates are partial esters of sorbitol fatty acids and their copolymerized anhydrous with ethylene oxide. They are used as dispersant agents, emulgents, non-ionic sanitary surfactants, solubilizers, and moisturizers, among other things.

In general, they are considered non-toxic and non-irritating. However, they have been associated with serious side effects, including deaths in under-weight neonates who received vitamin E preparations with this substance [25]. In addition, polysorbate 80 has been associated with increased mortality in new-borns [42].

3.8. Colorants

Colorants are excipients used to facilitate the identification of the formula by parents and patients. The most commonly used dyes are whip dyes, quinolones, triphenylmethane and xanthines.

Tartrazine (yellow number 5) has been implicated in anaphylactic reactions, edema, asthma, bronchospasm, eosinophils, angioedema and hives in patients with sensitivity to it. It appears to cause histamine degranulation of mast cells [29]. As a result, most global regulatory agencies restrict the use of dyes such as tartrazine, because azo dyes have been linked to hypersensitivity and ADHD reactions in children. These dyes can be replaced by plant dyes such as annatto, malt beta-carotene and turmeric and should not be used at all in paediatric formulations [28].

3.9. Excipients not Recommended in Paediatrics and Paediatric Formulations

To investigate the exposure of children to excipients not recommended at an early age, a compilation of paediatric formulations (nationally and internationally) was made (see Appendices C–F). As will be seen below, most of these formulations contain some excipient not recommended in paediatrics:

In Appendix C, there is a summary table (Table A2) of examples of solid and semi-solid medicines used in the paediatric population, marketed in Spain. Additionally, a list of excipients and relevant characteristics of the pharmaceutical form (PF) is shown (performed consultation of CIMA database, September 2020). It clearly shows that the reason such excipients are not recommended for the paediatric population is because of the adverse effects they may cause, which include:

- Approximately 100% of the formulations shown here carry at least one excipient not recommended for the paediatric population.
- Benzalkonium chloride, methyl para hydroxybenzoate and propyl para hydroxybenzoate are some of the most commonly used preservatives in solid and semi-solid formulations for paediatric use, even though they are considered to be potentially toxic in neonates.
- Sucrose, aspartame and mannitol are used as sweetener. 100% of the oral solid formulations collected in Table A4 carry at least one excipient of these: 40% of formulations carry mannitol and aspartame; 20% carry the 3 excipients; 20% sucrose and aspartame and the remaining 20% only sucrose.
- Propylene glycol is another excipient commonly used in solid formulations as a solvent, moisturizer and preservative. Caution should be exercised in children under 4 years of age and neonates, as propylene glycols, at high doses, may cause alterations in the Central Nervous System, in addition to other side effects discussed in the previous sections of this paper.
- Microcrystalline cellulose, methylcellulose and ethyl cellulose are one of the most commonly used excipients in solid formulations. They have no major side effects, but in high amounts they can cause a laxative effect.
- Most of the solid formulations collected in Table A2 use flavourings such as grape essence, lemon flavouring, caramel cream aroma or orange essence, in order to achieve a better palatability. The main drawback of their incorporation into paediatric formulations is that they usually have a complex and poorly known composition [49].
- Lanolin is an excipient used in pastes and ointments, which are frequently used in the paediatric population. This excipient may cause skin hypersensitivity reactions, which is why caution should be exercised in patients with known sensitivity issues [50].

Appendix D (Table A3) lists marketed liquid formulations suitable for the paediatric population. Liquid formulations are the most common in paediatrics because of their easy administration. The need for at least one liquid formulation of any drug indicated in the paediatric population is becoming increasingly noticeable. Not all active principles are soluble or stable in water. Therefore, excipients are used in liquid formulations to improve the solubility of certain active principles and/or increase their stability. The problem is that most excipients found in adult formulations should not be used in paediatrics. However, as shown in Table A3, there are a wide variety of marketed formulations indicated in paediatrics that contain these non-recommended excipients:

- Ethanol, sorbitol and propylene glycol, despite being contraindicated in paediatrics, especially ethanol, are still included in some paediatric formulations.
- The addition of non-recommended sweeteners, such as sucrose, sucralose or sodium saccharine, is also seen in these paediatric formulations.
- The addition of preservatives in paediatric formulations should be avoided as much as possible, and if necessary, in the least amount. Parabens are among the safest preservatives in paediatrics, yet others that are not recommended are still used (e.g., Table A3: sodium benzoate, benzoic acid and benzyl alcohol). Benzalkonium chloride, despite not being recommended for asthmatic patients, is used for the formulation of most eye drops, nasal drops and gothic drops.

Appendix E (Table A4) and Appendix F (Table A5) provide examples of FDA-registered drugs (liquids and solids) and liquid formulations in paediatric use research, respectively. Like the other examples provided, these medicinal products and liquid formulations contain at least one excipient not recommended for the paediatric population, such as propylene glycol, polysorbates, methyl or propyl para hydroxybenzoate, benzyl alcohol, benzoic acid, ethanol or sucralose, among others.

- Excipients not recommended for paediatric population are most commonly used in oral solutions and suspensions (referred to in Tables A4 and A5, propylene glycol, benzoic acid, polyethylene glycol, polysorbate 80 and sodium benzoate).
- Like the other examples, there is also frequent use of sweeteners (fructose, sucrose, sucralose, aspartame and sodium saccharine).
- Benzalkonium chloride is one of the most commonly used preservatives in ophthalmic and nasal drops, as shown in Table A4. It is usually a safe excipient, but can cause serious adverse effects, such as bronchoconstriction in asthmatic patients, ototoxicity in erotic preparations or respiratory failure in infants who ingest this excipient, this adverse effect being the most severe.

4. Promising Pharmaceutical Form in the Paediatric Population: ODT and 3D Drug Printing

The development of Orally Disintegrating Tablets (ODT) has received greater interest among researchers and the pharmaceutical industry over the past decade. ODT tablets are designed to dissolve quickly upon contact with saliva, in the absence of additional water, compared to traditional tablets [51].

ODT tablets offer several advantages, combining the properties of solid and liquid formulations. They are quickly ingested when inserted into the tongue, eliminating the need to chew the tablet, swallow it intact or take it with water. Currently, they are a widely accepted form of dosing, especially for patients who have difficulty swallowing (paediatric and geriatric), and for the treatment of patients where therapeutic compliance is difficult [51,52].

As a result of the rapid disintegration of ODT tablets, the active substance comes into contact with taste buds, so a key aspect to consider in these formulations is palatability. It is necessary to mask the taste of bitter active ingredients in order to develop successful formulations. In the past, sweeteners and aromas were used as methods of flavour masking in dispersible or rapidly disaggregation tablets. However, these additives were not a sufficient means to completely mask the taste. Currently, with scientific and technological advances, different dosing alternatives are available to mask the taste, such as freeze-deriding, microencapsulation, fluid bed coating or coating in supercritical fluids [51].

It should be mentioned that there is an innovative tool for pharmaceutical pre-formulation of ODT tablets. This tool makes it possible to predict whether a disintegrating excipient or a mixture of excipient powder + active substance is suitable for obtaining an oral dispersible tablet by direct compression or not: the new model SeDeM-ODT [53].

The SeDeM-ODT model (based on the SeDeM expert system) indicates the ability of a powder to be compressed, providing the Good Compressibility and oral dispersibility Index (IGCB). This index is composed of six main factors which indicate whether a powder mixture has the ability to be compressed by direct compression. Furthermore, it indicates whether the tablets are suitable for formulation as oral dispersible tablets. Thus, the SeDeM-ODT model facilitates the selection of excipients with the appropriate properties to produce ODT tablets using direct compression technologies [53].

Figure 1 will detail several special features and advantages of ODT tablets [52,54].

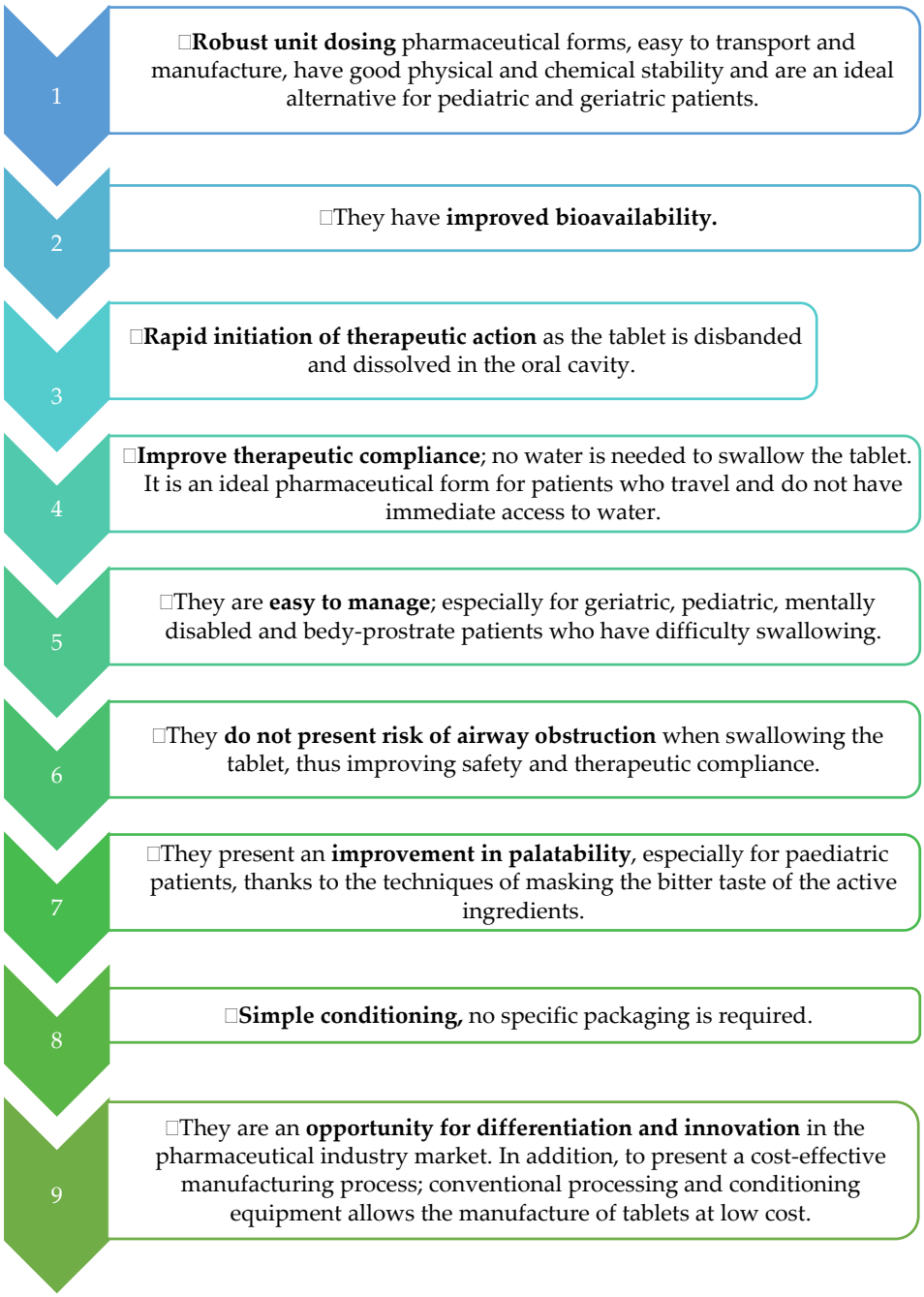

Figure 1. Characteristics and advantages of ODT tablets.

Figure 2 specifies the most noteworthy drawbacks of ODT tablets [54].

On the other hand, the technical disadvantages associated with the manufacturing process of ODT tablets could be solved by three-dimensional drug printing technology. Generally speaking, this technology is supported by the following processes: a program capable of generating a file is required with the necessary information for printing the drug. This same program (also present on the computer that will control the printer) must be able to read the instructions contained in the generated file and convert it into precise commands for the 3D printer to generate the part [55].

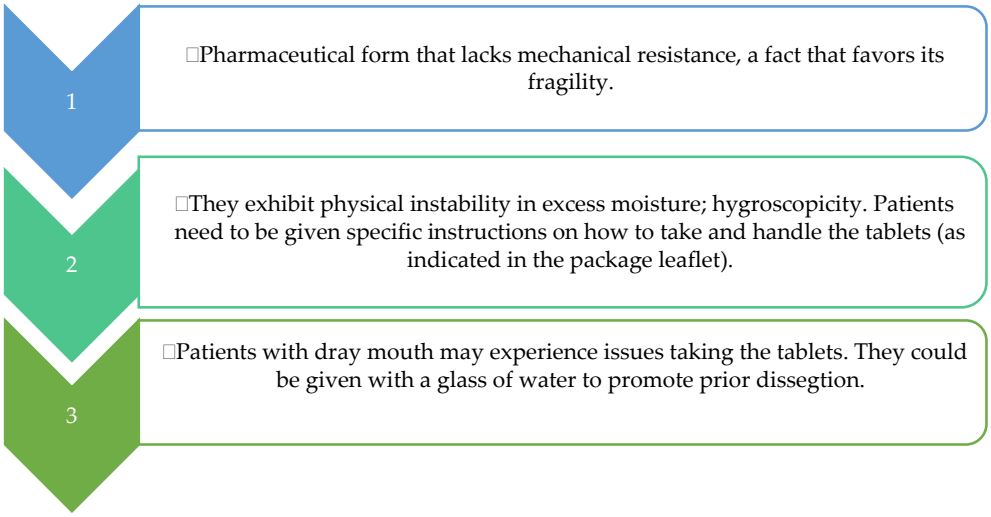

Figure 2. Disadvantages of ODT tablets.

The response to drugs may be different among patients, due to inter-individual variability, caused by both genetic and environmental factors. Accordingly, "patient-specific" or "tailor-made" dosage concepts could be an alternative to mass production in the traditional pharmaceutical industry. In this approach, 3D printing has proven to be a manufacturing technique with great potential, as it allows the creation of three-dimensional objects, layer by layer, with total freedom of form and design. Thus, obtaining customized pharmaceutical forms is one of the main objectives of 3D printing in the pharmaceutical sector [55].

Paediatric patients are one of the population groups with the greatest need for personalized dosing adapted to their requirements (age, weight, pathological status, etc.). However, most 3D printed drugs are solid oral formulations, which are not suitable for this population group. Medicinal gummies developed through 3D printing (tailor-made to the patient) could be a form of oral dosing suitable for paediatric patients, due to their striking appearance and pleasant organoleptic characteristics [55].

New advances in obtaining medicines and medical devices, using 3D printing technology, have generated novel perspectives in the processes of obtaining these products. At present; however, several issues are perceived that will need to be resolved as the perfection and implementation of this technique progresses, in order to make it a common process of obtaining medicines and medical devices.

5. Conclusions

The critical study suggests that excipients are often used at higher concentrations than recommended in international paediatric guidelines, and with inappropriate labelling, increasing the potential risks associated with the various excipients discussed [26].

Indeed, the pharmacokinetic and pharmacodynamic profiles of the child population vary substantially, with paediatric safety profiles related to the age and development of excipients often differing from those of adults [48]. The most toxic excipients in neonates are known to be sodium benzoate, propylene glycol, methyl para hydroxybenzoate, propyl, sodium saccharine, benzyl alcohol, benzalkonium chloride, polysorbate 80 and ethanol [56]. However, these excipients are used in formulations according to the study conducted.

European new-borns receive several potentially harmful pharmaceutical excipients: parabens, polysorbate 80, propylene glycol, benzoates, sodium saccharine, sorbitol, ethanol and benzalkonium chloride. According to the study conducted by Nellis and collaborators [36], there are regional variations in the neonatal administration of these potentially harmful excipients. This suggests the possibility of reducing exposure to parabens, polysorbate 80, propylene glycol and sodium saccharine by replacing it with products without these excipients. However, a joint effort by the regulatory authorities on medicines, in

particular the paediatric committees, will be necessary. Current therapeutic options for the paediatric population justify further toxicokinetic and drug safety studies so that they are tailored to the special needs of the paediatric population.

In general, there is little information regarding excipients in paediatrics. It is of the utmost importance to develop new research related to the safety and toxicity of excipients to reduce the prevalence of adverse effects in paediatric populations. Gallon formulators can formulate safer, more stable and higher quality products. Furthermore, the possible adverse effects of the active ingredients and the excipients used in the paediatric population should be reconsidered—since excipients that are safe in adults—may have potentially toxic effects in children.

Finally, the development of databases such as STEP is relevant and beneficial for the development and use of drugs in paediatrics. Additionally, the SEEN project is relevant both nationally and internationally, as it reveals the current status of excipients and takes into account the frequency and quantity (in terms of medicines given to new-borns and young children).

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Appendix A. Purposes of the STEP Database

More specifically, the purposes of the STEP database are [22] to:

1. Serve as a public base for evidence regarding the safety and toxicity of excipients in order to allow the pharmaceutical industry, academics, pharmacists, physicians and regulators to make informed decisions.
2. Improve prospects of identifying potential security issues in the early stages of the development process when excipients are selected.
3. Help highlight any relationships between exposure and evidence of clinically significant toxicity in the paediatric age group in general, or in paediatric subpopulations.
4. Identify possible differences in expression, types or patterns of toxicity in children compared to adults. Provide a basis for assessing the need to generate new data for paediatric medicines (e.g., bridge studies, juvenile toxicity studies, etc.), in order to clarify what kind of new data, knowledge gaps or studies may be needed.
5. Support companies with their regulatory presentations with easily available information.
6. Support and improve research activities by providing a platform to share unreleased data and available data with corporate entities.

Appendix B

Table A1. Most important characteristics of the excipients discussed in this paper (in alphabetical order).

Excipient	Functions	DAI *	Recommendations	Adverse Effects	References
Aspartame	Artificial Sweetener	40 mg/kg	- Contraindicated in patients with phenylketonuria	- Neurological involvement: neurotoxicity, epilepsy, headache, panic attack, hallucinations - Hypersensitivity reactions: vascular, granulomatous panniculitis - Cross reaction with sulfamides	[29,35]
Benzalkonium chloride	Preservative	NA	- Caution in asthmatic patients	- Bronchoconstriction - Ototoxicity - Hypersensitivity	[29]
Benzyl alcohol	Preservative	5 mg/kg	- Contraindicated in children under 3 years of age by immature their metabolism	In new-borns and children under 3 years of age cause: - Metabolic acidosis and respiratory depression - Intraventricular haemorrhage - Cerebral palsy and developmental delay - Hypersensitivity reactions	[29,35,36,39–44]
Ethyl alcohol	Solvent and preservative	6 mg/kg/dose (<6 years)	Paediatric formulations should not exceed the following limits of ethanol: - In children over 12 years of age: less than 10% (*v/v*) - In children 6–12 years old: less than 5% (*v/v*) - In children under 6 years of age: less than 0.5 (*v/v*)	- Hypoglycaemia, acidosis and hydroelectrolytic alterations - Stupor, coma respiratory and CNS depression, cardiovascular toxicity	[17,26,27,29,31,32]

Table A1. *Cont.*

Excipient	Functions	DAI *	Recommendations	Adverse Effects	References
Glycerol	Solvent, sweetener, viscosizer and preservative	10 g/dose	- Caution in paediatric population - Do not exceed the safe daily dose (1.0–1.5 g/kg body weight)	- Mucositis in the stomach - Diarrhoea and electrolyte disturbances	[1,29]
Lactose	Diluent	NA	- Caution in patients with lactose intolerance - Contraindicated in galactosemia	Symptoms of lactose intolerance: severe abdominal pain, flatulence, bloating or swelling and diarrhoea. - Systemic symptoms such as muscle and joint pain and eczema - In children it can cause dehydration, bacterial proliferation and metabolic acidosis	[1,28]
Parabens	Preservative	10 mg/kg	- It is recommended to avoid its use in neonates	- Cross hypersensitivity reactions in patients allergic to acetylsalicylic acid - Hyperbilirubinemia in new-borns	[29,35,36]
Phthalates	Coating agents (plasticizers)	NA	- Not recommended for use in pregnant women or children under 3 years of age	- Anomalies in the development of the foetus: cleft palate and skeletal malformations. May lead to stillbirth	[28]
Polyethylene glycol	Solvent, suspensor and viscosity agent	10 mg/kg	- Caution in new-borns and infants	- Nephrotoxicity - Gastrointestinal disorders - Laxative effect	[1,28]

Table A1. *Cont.*

Excipient	Functions	DAI *	Recommendations	Adverse Effects	References
Polysorbates	Dispersing, emulgent, surfactants, solubilizing and moisturizing agents	NA	- Caution in new-borns	- Serious adverse effects: deaths in low-weight neonates who received vitamin E preparations with polysorbates. - Polysorbate 80: increased mortality in new-borns	[25,42]
Propyl gallate	Antioxidant	NA	- Caution in new-borns	- In neonates it can cause dermatitis, skin allergy and methemoglobinemia	[29]
Propylene glycol	Solvent, moisturizing and preservative	- Neonates: 1 mg/kg - Under 5 years: 50 mg/kg - Adults: 500 mg/kg	- It is recommended to avoid in children under 4 years of age because of lack of metabolic maturation	- CNS depression - Laxative effect from high osmolality after oral administration	[29,33,34]
Saccharine	Sweetener	2.5 mg/kg	- It is recommended to limit the daily dose in pregnant women and children	- Urticaria, itching and eczema - Photosensitization - GI disturbances: Nausea and diarrhoea	[29,48]
Sorbitol	Sweetener and diluent	- Children 0–2 years 5 mg/kg - Over 2 years: 140 mg/kg	- Contraindicated in patients with fructose intolerance - Not recommended for use in patients with hypoglycaemia	- Gastrointestinal disorders - It can cause hepatic damage with comma and even death	[28–30]
Starch	Diluent and added	NA	- Conservation in dry environment - Well tolerated by children	- In case of moisture, carcinogenic aflatoxins may occur	[29]

Table A1. *Cont.*

Excipient	Functions	DAI *	Recommendations	Adverse Effects	References
Sucralose	Sweetener	15 mg/kg	- Caution in patients with metabolic disorders	Alters the composition of the digestive tract microbiome - At high temperatures chloropropanol may form - May alter glucose, insulin and GLP-1 *2 levels	[29]
Sucrose	Sweetener	NA	- Not recommended for use in children with type I diabetes	- Dental damage - At very high doses on a daily basis I could be carcinogenic	[29]
Sulphites	Antioxidant	NA	- Avoid in asthmatic patients	- Hypersensitivity and bronchospasm reactions	[29]
Tartrazine, quinolines, triphenylmethane, xanthines	Colorants	NA	- It is recommended not to use them in paediatric formulations	- Hypersensitivity reactions in patients' sensitive to tartrazine - Azo colorants: cross-sensitivity reactions with acetylsalicylic acid Erythromycin: photosensitization reactions	[28,29]
Thiomersal	Preservative	NA	- Avoid use in vaccines as a preservative due to its side effects	- Hypersensitivity reactions - Autism spectrum disorders	[28,29]

* ADI: Admissible Daily Intake; *2 GLP-1: Glucagon Like Peptide; NA: Not Available.

Appendix C

Table A2. Examples of solid and semisolid medicines used in Spain for paediatric population: List of excipients and relevant characteristics of FF (Performed consultation of CIMA database, September 2020).

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
SOLID PREPARATIONS	POWDERS	Example 1: Amoxicillin Normon 250 mg/5 mL EFG Oral Suspension Powder	Saccharose, Glucose, Methyl parahydroxybenzoate (E-218), Propyl parahydroxybenzoate (E-216), Anhydrous sodium citrate, Colloidal silica and Orange essence	Amoxicillin	- Powders are administered after prior dissolution. - They are little employees in the paediatric population; present the drawback that it is difficult to mask the bad taste. - Risk of accidental aspirations. - They are usually used in master formulation and for the administration of antacids.	[29,57,58]
		Example 2: Azithromycin Sandoz 200 mg/5 mL EFG Oral Suspension Powder	Sucrose, Xanthan gum (E415), Hydroxypropyl cellulose, Anhydrous trisodium phosphate, Colloidal anhydrous silica (E551), Aspartame (E951), Aroma of caramel cream and Titanium dioxide (E171)	Azithromycin		
	GRANULATED	Example 1: Paediatric Gelocatil 325 mg Granules	Calcium carbonate, Sodium hydrogen carbonate, Citric acid anhydrous, Anhydrous sodium citrate, Aspartame (E-951), Sucrose, Mannitol (E-421), Amorphous silica, Glycerol die-stearate type 1, Croscarmellose sodium, Sodium glycolate starch type A (potato starch) gluten-free, Ethyl cellulose, Hydroxypropyl methylcellulose and Polyethylene glycol 400	Paracetamol	- Granules are more stable and fluid than powders. - The most used are effervescent granules, which in the presence of water react by releasing carbon dioxide, which protects the stomach and partly anesthetizes taste buds. - They should be completely dissolved prior to administration in order to reduce bicarbonate intake. - Children are often pleased by their resemblance to certain refreshing drinks.	[29,59]

Table A2. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
SOLID PREPARATIONS	ORAL DISPERSIBLE TABLETS (ODT)	Example 1: Apiretal 325 mg oral dispersible tablets	Ethyl cellulose, Microcrystalline cellulose, Crospovidone, Aspartame (E-951), Colloidal silica, Mannitol, Talco, Magnesium stearate and Grape essence	Paracetamol	As advantages of oral dispersible tablets, the following stand out: - They combine the advantages of liquid forms and solid oral forms. - An exact dose may be given compared to liquids. - They have a pleasant taste, thus facilitating therapeutic compliance in the paediatric population. - No need to swallow the tablet or drink water; dissolves rapidly in saliva, being an appropriate choice for patients with swallowing problems, such as children or geriatric patients. - They are safe and effective and can be bio-equivalent with respect to conventional tablets. - They have rapid absorption and, therefore, a rapid introduction of the therapeutic effect. Disadvantages include: - The lack of mechanical resistance presented by traditional tablets. - The possibility of physical instability in excess moisture. - ODTs require special conditioning to ensure their stability.	[54,60,61]
		Example 2: Junifen 200 mg lemon-flavored oral dispersible tablets	Ethyl cellulose, Precipitated silicon dioxide, Hypromellose, Mannitol, Aspartame (E-951), Croscarmellose sodium, Magnesium stearate and Lemon flavouring	Ibuprofen		

Table A2. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
SOLID PREPARATIONS	SUPPOSITORIES	Example 1: Febectal Infants 150 mg Suppositories	Colloidal anhydrous silica, Solid semi-synthetic glycerides	Paracetamol	As advantages, the following stand out: - Generally, they avoid gastric intolerance problems. - They are of interest when the medicine is inactive orally, the patient is unconscious or are children who refuse to swallow the medication. - They avoid inactivation by the effect of first liver step. Disadvantages include: - Reproducible behaviour can only be obtained if absorbed into an area two centimetres from the end of the rectum. - Absorption of the active substance may be erratic. - As it avoids the effect of first liver step, it can increase the possibility of poisoning. - In certain cultures, it is a form that is not well accepted socially.	[29,62]

Table A2. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
SEMI-SOLID PREPARATIONS	GELS	Example 1: Fenistil 1 mg/g Gel	Benzalkonium chloride, Disodium edetate, Carbomer, Sodium hydroxide, Propylene glycol amd Purified water	Dimethindene maleate	- It is a semi-soft transparent colloid, with a large proportion of liquids. - Low penetration power. - Many incompatibilities with active substances. - It is easy to apply, pleasant and soothing for its refreshing properties.	[29,63]
SEMI-SOLID PREPARATIONS	CREAMS	Example 1: Perme-Cure 5% Cream	Butylhydroxytoluene (E-321), Castor Oil, Deionized water, Steareth-2, Ceteareth-2-Phosphate, Sosa to the 20 %, Vitamin E acetate, Phenonip, Citric acid, Disodium edetate and Scent	Permethrin cis:trans (25:75)	As advantages, the following stand out: - Comfortable and easy application. - Provide a controlled release of the active substance. - They act as emollients and moisturizers, due to their composition	[64]
	OINTMENTS	Example 1: Oftacilox 3 mg/g Ophthalmic Ointment	Liquid paraffin and White Vaseline	Ciprofloxacin	- Ointments are forms of external use intended to be administered by gentle friction on a surface of the body, to achieve a local action or with the aim of penetrating the drug through it. - In many cases, the topical route is a route of absorption comparable to oral or other, so the dosage and duration of treatment must be very well specified. New-borns and infants have a very increased skin-to-weight ratio. Coupled with the fact that at this age the skin is very permeable, it makes them especially vulnerable to toxic frames by ointments.	[29,65]

Table A2. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
	PASTES	Example 1: Anti-congestive Cusi (Paste Lassar)	Lanolin (wool fat), Liquid Vaseline and Stringy Vaseline	- Zinc oxide - Corn starch	- This is a suspended ointment. - They are used when you want to locate the action of the active substance to a specific area, as they are irritating and staining.	[29,66]
SEMI-SOLID PREPARATIONS	NON-CREAM EMULSIONS	Example 1: Lactisona 10 mg/mL Skin Emulsion	Carbomer 940, 1,3-dimethylol-5,5-dimethyl hydantoin, Dihydro-acetic acid, Pyrrolidone sodium carboxylate, Lactic acid, Sodium hydroxide, Stearyl alcohol, Glycerol stearate, Cetyl alcohol, Isopropyl palmitate, Mineral oil, Myristyl lactate, Fragrance and Water	Hydrocortisone	- Emulsions are a dispersed system, stabilized by the addition of an adequate emulsifier, two immiscible phases, where both the internal and external phases are liquid. - The emulsions enable fat-soluble and water-soluble active ingredients to come into contact with the skin simultaneously, encompassing each of them in the phase of the emulsion for which they have the greatest affinity. - Patients or users of topical application preparations often prefer emulsion vehicles to those of any kind.	[50,67]

Appendix D

Table A3. Examples of liquid medicines used in paediatrics: List of excipients and relevant characteristics of Pharmaceutical Form.

	Pharmaceutical Form		Excipients	API	Pharmaceutical Form Characteristics	References
LIQUID PREPARATIONS	ORAL SOLUTIONS	Example 1: Diazepam 2 mg/5 mL Solution without sugar	Sodium Docusate, Aluminium silicate and Magnesium, Propylene glycol, Raspberry Flavour, Sodium Saccharine, Precool Erythrosine (E127), Sorbic Acid (E200), Propyl para hydroxybenzoate, Methyl para hydroxybenzoate, Sorbitol, Liquid (Non-Crystalized) (E420) and Glycerol (E422)	Diazepam	As advantages, the following stand out: - Release of the active substance(s) much faster than in solid forms. - The dosages are correctly expressed in milligrams, micrograms and U/mL, allowing them to be adapted to the child's weight. - Easy and comfortable dosing, as it is in volume (spoons, drops, etc.) - Less irritation effect if it is an aggressive medicine, at the gastric level, as it is dampened by dilution. - Solutions, suspensions or emulsions are obtained, depending on the size of the particles of the internal phase. As disadvantages they present: - Greater ease and possibility of contamination than solid pharmaceutical forms, which forces the addition of preservatives.	[29,49,68–70]
		Example 2: Paracetamol Level 100 mg/mL Oral Solution	Citric acid, Sodium hydroxide, Sucrose, Propylene glycol, Macrogol, Strawberry Essence, Cochineal Red A (Ponceau 4R) (E-124), Hydrochloric Acid 5 N and Purified Water	Paracetamol		
		Example 3: Diazepam Intensol™ Oral Solution 5 mg/mL * *Do not use in children under 6 months of age*	Alcohol, Yellow D&C 10, Polyethylene glycol, Succinic Acid and Water	Diazepam		[71,72]
		Example 4: Prednisolone 10 mg/mL Oral Solution	Sodium Methyl para hydroxybenzoate, Sodium Propyl para hydroxybenzoate, Glycerol, Sodium Saccharine, Sodium Edetate, Sodium Aqueous solutions of medicinal substances that areDihydrate, Orange flavour (contains propylene glycol), Sodium hydroxide and Purified Water	Prednisolone		

Table A3. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
LIQUID PREPARATIONS	ORAL SOLUTIONS	Example 5: Ozalin	Citric acid monohydrate, Gamma-cyclodextrin, Sucralose, Orange flavour (contains 70–80% ethanol), Sodium hydroxide, injectable water	Midazolam	*See "Pharmaceutical Form Characteristics (Oral Solutions)" section of the previous page*	[73–75]
		Example 6: Flumil 20 mg/mL Oral Solution	Para-Hydroxybenzoate Methyl (E218), Sodium Benzoate (E211), Sodium Edetate, Carmellose Sodium, Sodium saccharine, Sodium Cyclamate, Sucralose, Raspberry Aroma, Sodium Hydroxide and Purified Water	Acetyl cysteine		
		Example 7: Paediatric Lanacordin 0.05 mg/mL * *Including newborns and premature*	Sucrose, Ethanol, Tartrazine (E-102), Anhydrous Sodium Phosphate, Citric Acid (E-330), Methyl Hydroxybenzoate, Lime Essential Oil, Propylene glycol (E-1520) and Purified Water	Digoxin		
LIQUID PREPARATIONS	ORAL SUSPENSIONS	Example 1: Paracetamol 120 mg/5 mL Oral Suspension	Propylene glycol, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Xanthan Gum, 70% Sorbitol Solution, Sucrose, Mango flavour and Purified Water	Paracetamol	As advantages, the following stand out: - Suspensions are the ideal pharmaceutical forms for the administration of non-water-soluble active ingredients. - The fact that the active substance is insoluble, allows an extension of the time of action in the body. - It is easier to mask the taste than in syrups and elixirs (more pleasant for children). - Good relative bioavailability.	[76,77]
		Example 2: Junior Parapaed 120 mg/5 mL Oral Suspension	Ethanol, Polysorbate 80, Glycerol, Magnesium and Aluminium silicate, Liquid maltitol syrup, Sodium saccharine (E954), xanthan gum, cherry flavour, sodium benzoate, Citric acid monohydrate and purified water	Paracetamol		

Table A3. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
LIQUID PREPARATIONS	ORAL SUSPENSIONS	Example 3: Mycostatin 100.000 UI/mL Oral Suspension	Sucrose, 96% ethanol, Carmellose sodium, Cinnamic aldehyde, Mint Essence, Cherry Aroma, Anhydrous Disodium Hydrogen phosphate, Glycerol (E-422), Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, Sodium Hydroxide, Hydrochloric Acid and Purified Water	Nystatin	Disadvantages include: - Sediment formation. - Difficulty removing the viscosity of the vehicle. - Less stability than solid shapes, solutions and emulsions. - The use of very fine particle size causes the formation of sediments that are very difficult to re-suspend. *It is important to shake the suspension for at least 10 s before use*	[78,79]
		Example 4: Paediatric Algidrin 20 mg/mL Oral Suspension ** Do not give to children under 3 months of age*	Microcrystalline cellulose, Carboxymethylcellulose sodium, Sorbitol (E-420), Maltitol (E-965), Beta-cyclodextrin, Sodium Saccharine, Sucralose (E-955), Forest Fruit Aroma, Allura AC Red Colouring (E-129), Methyl para hydroxybenzoate, Ethyl para hydroxybenzoate, Propyl para hydroxybenzoate and Purified Water	Ibuprofen (Lysine)		
LIQUID PREPARA-TIONS	ORAL SUSPEN-SIONS	Example 5: Paediatric Septrin 8 mg/40 mg/mL Oral Suspension ** Suitable for infants from 6 weeks of age*	Sorbitol, Glycerol (E-422), Dispersible Cellulose, Carmellose Sodium, Polysorbate 80, Methyl para hydroxybenzoate, Sodium Benzoate, Sodium Saccharine, Banana flavour (Propylene Glycol E-1520, Sodium Citrates E-331), Ethanol 96°, Vanilla flavour (Benzyl Alcohol, Caramel Colour E-150d, Propylene Glycol E-1520, Glycerol E-422, Water), Purified Water.	- Trimetho-prim - Sulfametho-xazole	*See "Pharmaceutical Form Characteristics (Oral Suspension)" section of the previous page*	[80]

Table A3. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
LIQUID PREPARATIONS	ELIXIRS	Example 1: Paracetamol Elixir Pediátrico 120 mg/5 mL	Ethanol 96° (10% *v*/*v*), Propylene glycol, Inverted Syrup, Amaranth Solution (E123), Glycerol, Glycerine, Chloroform and Concentrated Raspberry Juice	Paracetamol	- Hydro alcoholic solution sweetened with low sugar. - It has high alcohol content, which will have to be considered at certain ages, as it can create addition or generate other side effects: drowsiness and various dangers arising.	[29,81,82]
		Example 2: Lanoxin Elixir * *Fit for premature neonates*	Methyl Hydroxybenzoate, Sucrose, Sodium Phosphate Anhydrous, Citric Acid Monohydrate, Quinine Yellow, Ethanol (96%), Propylene Glycol, Lime flavour and Purified Water	Digoxin		
	SYRUPS	Example 1: Daleron Syrup 120 mg/5 mL	Sorbitol, Glycerol, Xanthan Gum, Maltitol, Microcrystalline Cellulose, Croscarmellose Sodium, Sodium Benzoate, Citric Acid, Pineapple flavour, Riboflavin and Purified Water	Paracetamol	- Syrups are liquid solutions with sweetening, flavouring and viscosizing properties. They are almost saturated aqueous solutions of sucrose (64%). They have the following drawbacks: - Alterations that require the incorporation of preservatives and specify	[29,83,84]
		Example 2: Loratadine 5 mg/mL Syrup Oral Solution	Propylene glycol, Glycerol, Sodium Benzoate, Citric Acid Monohydrate, Sucrose, Peach flavour and Purified Water	Loratadine		

Table A3. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
LIQUID PREPARA-TIONS	SYRUPS	Example 3: Polaramine 0.4 mg/mL Syrup ** Not suitable for children under 2 years old*	Ethanol, Sucrose, Sodium Citrate, Sodium Chloride, Sorbitol, Methyl paraben, Propyl paraben, Menthol, Apricot flavour, Orange flavour, Ponceau 4R Colouring (E-124) and Purified Water	Dexchlorpheni-ramine maleate	See "Pharmaceutical Form Characteristics (Syrups)" section of the previous page	[85,86]
		Example 4: Paediatric Mucosan 3 mg/mL Syrup	Hydroxyethyl cellulose, Sucralose, Benzoic Acid (E-210), Wild Berry Aroma, Vanilla Aroma and Purified Water	Ambroxol hydrochloride		
LIQUID PREPARATIONS	ORAL DROPS IN SOLUTION	Example 1: Romillary 15 mg/mL Oral drops in Solution * Not recommended for use in children under 2 years of age	Propylene glycol, anhydrous ethanol, Flavourings: coriander oil, orange essential oil and lemon tetraroma, macrogol glycerol ricinolate (chromophore EL), Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, sodium saccharine, citric acid monohydrate, sodium hydroxide and purified water	Hydrobromide dextromethorphan	- Oral liquid medicinal products may be placed on the market in the form of drops for children of different ages. - The main benefits of drops are low dosing volume, facilitating swallowing and dosing flexibility. As disadvantages, the following stand out: the variation of the droplet size and errors in the count, which would result in an incorrect dosage. This can cause serious problems in those medicines with a narrow therapeutic margin.	[87–90]
		Example 2: Alerlisin 10 mg/mL Oral Drops in Solution ** Do not use in children under 2 years of age*	Glycerol, Propylene glycol (E-1520), Sodium Saccharine, Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, Sodium Acetate, Glacial Acetic Acid and Purified Water	Cetirizine hydrochloride		

Table A3. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
LIQUIDPREPARA-TIONS	ORAL DROPS IN SOLUTION	Example 3: Paediatric Cleboril 62.5 g Oral Drops in Solution	Benzoic acid (E-210), Sodium hydroxide and purified water	Clebopride malate	See "Pharmaceutical Form Characteristics (Oral Drops in Solution)" section of the previous page	[91–93]
		Example 4: Fluor Lacer 1.4 mg/mL Oral Drops * Indicated for tooth decay prophylaxis in children 1–6 years old	Sodium Saccharine, Propylene glycol, Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, Disodium edetate, Cochineal Red Colouring (E-124), Strawberry Aroma and Purified Water	Sodium Fluoride		
		Example 5: Hydropolivit Oral Drops in Solution ** Recommended for children over 2 years old*	Propylene glycol, Polysorbate 80, Sorbitol 70% (E-420), Glycerol (E-422), Sodium Saccharine, Sodium Edetate, Monothioglycerol, Methyl para hydroxybenzoate, Butylhydroxyanisole (E-320), Banana Essence, Vanilla Essence, Sodium Hydroxide and Purified Water	-Retinol palmitate Cholecalciferol Alpha-tocopherol acetate Riboflavin Pyridoxine hydrochloride Ascorbic acid Biotin Nicotinamide		
LIQUID PREPARATIONS	ORAL DROPS INSUSPENSION	Example 1: Zamene 22.75 mg/mL Oral Drops in Suspension * Special interest in paediatrics. Not recommended in children under 2 months of age.	Aluminium and Magnesium silicate, Carboxymethylcellulose sodium, Benzyl alcohol, 70% Sorbitol, Polysorbate 80, Acetic Acid and Purified Water	Deflazacort	They have the same characteristics as oral drops in solution	[94,95]

Table A3. *Cont.*

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
		Example 2: Dezacor 22.75 mg/mL Oral Drops in Suspension * Special interest in paediatrics. Not recommended in children under 2 months of age.	Sorbitol solution 70%, Carboxymethylcellulose sodium, Aluminium silicate and magnesium, Polysorbate 80, Benzyl Alcohol, Sucralose, Tropical Fruit Aroma, Citric Acid Monohydrate, Sodium Hydroxide and Purified Water	Deflazacort		
	OPHTHALMIC DROPS OR COLLYRIUMS	Example 1: Atropine BP 1.0% (*w*/*v*)/Vistatropin 1.0% (*w*/*v*) Eye drops in solution	Benzalkonium chloride in solution and purified water	Atropine sulphate	- Sterile solutions aimed at exercising their action in the conjunctiva. - May cause systemic side effects, especially observed after instillation of mydriatic eye drops.	[29,68,96,97]
		Example 2: Chibroxin 3 mg/mL Collyrium in solution	Sodium Acetate, Benzalkonium Chloride, Disodium Edetate, Concentrated Hydrochloric Acid, Sodium Chloride and Water for Injections	Norfloxacin		
LIQUID PREPARATIONS	NASAL DROPS	Example 1: Rhinovin® Children's 0.5 mg/mL Nasal Drops in Solution ** Do not use in children under 6 years of age*	Dihydrogen phosphate of sodium dihydrate, disodium phosphate dodecahydrate, disodium Edetate, Benzalkonium Chloride, Sorbitol (E420), Hypromellose, Sodium Chloride and Purified Water	Xylometazoline hydrochloride	- Aqueous solutions of medicinal substances that are instilled through the nose and act on the nasal mucosa. - Oils are contraindicated in their formulation, because the ciliary function has to be maintained. - It can be an excellent route of systemic administration, in addition to use as a topical route (there are promising studies with insulin and other substances).	[29,68,98,99]

Table A3. *Cont.*

Pharmaceutical Form		Excipients	API	Pharmaceutical Form Characteristics	References
	Example 2: Utabon Children 0.25 mg/mL Nasal Drops in Solution * *Do not use in children under 6 years of age*	Benzalkonium chloride, anhydrous disodium hydrogen phosphate, Sodium dihydrogen phosphate dihydrate, glycine (E-640), Sorbitol (E-420) and Purified water	Oxymetazoline hydrochloride		
OTIC DROPS	Example 1: Otic cetraxal 3 mg/mL Otic drops en Solución * *Indicated in adults and child*	Lactic acid, Povidone, Anhydrous Glucose, Propylene glycol, Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, Hydrochloric Acid and Purified Water	Ciprofloxacin	- Liquid preparations to apply to the middle and outer ear. - The active substances are usually antiseptics, local anaesthetics and antibiotics.	[29,100,101]
	Example 2: Otix Otic Drops in Solution * Do not administer in children under 2 years of age	Benzalkonium Chloride, Sulphuric acid, Sodium Chloride, Sodium Hydroxide, Tribasic Sodium Citrate, Polysorbate 80, Citric Acid and Purified Water	- Dexamethasone sodium phosphate - Trimethoprim - Polymyxin B sulphate	Excipients have to be suitable to achieve a pH of 5–6.	
LIQUID PREPARATIONS	OTIC DROPS	Example 3: Ciproxin Simple 3 mg/mL Otic Drops in Solution * Not recommended for children under 1 year old	Benzalkonium Chloride, Sodium Acetate Trihydrate, Glacial Acetic Acid, Mannitol (E-421), Disodium Edetate, Hydrochloric Acid and/or Sodium Hydroxide and Purified Water	Ciprofloxacin hydrochloride	See "Pharmaceutical Form Characteristics (Otic Drops)" section of the previous page	[102]
PARENTERAL PREPARATIONS FOR INJECTION	INTRAVENOUS	Example 1: Digoxin Kern Pharma 0.25 mg/mL solution for injection * including premature neonates	Ethanol, Propylene Glycol, Citric Acid Anhydrous, Bi-sodium Anhydrous Phosphate and Bi-distillate Water.	Digoxin	- The intravenous line is the one of choice in new-borns and in emergencies. It achieves a quick effect and are easy to dos. - Risk of infection and can be painful at times and cause difficult-to-resolve injuries.	[29,103]

Appendix E

Table A4. Examples of FDA-registered drugs used in paediatrics (FDA and DAILYMED database consultation October 2020).

Pharmaceutical Form			Excipients	Active Principle	Age	References
LIQUID PREPARATIONS	ORAL SOLUTIONS	Abilify Solution Oral	Disodium edetate, fructose (200 mg per mL), glycerine, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose (400 mg per mL), and purified water. The Oral solution is flavoured with natural orange cream and other natural flavours	Aripiprazole	6 to 18 years	[104]
		Demerol Solution Oral	Benzoic acid, flavour, liquid glucose, purified water, saccharin sodium	Meperidine hydrochloride	Adult and paediatric patients	[105]
		Diazepam Oral Solution (Lannett Company)	Polyethylene glycol, propylene glycol, non-crystallizing sorbitol solution, sodium citrate anhydrous, bitterness modifier flavour, anhydrous citric acid, peppermint flavour, mint flavour, FD&C Network No. 40 aluminium lake, D&C Yellow No. 10 aluminium lake and purified water	Diazepam (5 mg/5 mL)	Children from 6 months	[106]
	ORAL SUSPENSIONS	Adzenys ER (Extend release)	Purified water, sorbitol, propylene glycol, xanthan gum, natural orange flavour, methacrylic acid and methyl methacrylate copolymer, sodium polystyrene sulfonate, vegetable oil, triethyl citrate, methylparaben, citric acid, sucralose, propylparaben, orange colour (FD&C Yellow No. 6), and polyethylene glycol	Amphetamine	6 to 17 years	[107]
		Children's Tylenol® Cold + Cough + Sore Throat Oral Suspension	Anhydrous citric acid, D&C network No. 33, FD&C network No. 40, flavours, glycerine, microcrystalline cellulose and sodium carboxymethyl cellulose, purified water, sodium benzoate, sorbitol solution, sucralose, xanthan gum	Acetaminophen 160 mg Dextromethorphan hydrobromide 5 mg	4 to 11 years	[108]
	ORAL SUSPENSIONS	Dyanavel XR (Extend release)	Anhydrous citric acid, bubble-gum flavour, glycerine, methylparaben, modified food starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulphate, sodium polystyrene sulfonate, sucralose, triacetin and xanthan gum	Amphetamine	Children from 6 years	[109]
	SYRUPS	Midazolam hydrochloride syrup	Anhydrous Citric Acid, D&C Network No. 33, edetate disodium, glycerine, sodium benzoate, sorbitol, Water, Hydrochloric Acid, Sodium Citrate	Midazolam hydrochloride	Children from 6 months	[110]

Table A4. *Cont.*

Pharmaceutical Form			Excipients	Active Principle	Age	References
LIQUID PREPARATIONS	OTIC DROPS	Ciprofloxacin and dexamethasone suspension/drops	Benzalkonium chloride, boric acid, edetate disodium, acetic acid, sodium acetate, sodium chloride, sodium hydroxide, tyloxapol, water, hydrochloric acid, hydroxyethyl cellulose (3000 cps at 1%)	- Ciprofloxacin hydrochloride - Dexamethasone	Children from 6 months	[111]
	OPHTHALMIC DROPS OR COLLYRIUMS	ALLERGY EYE DROPS-ketotifen fumarate solution/drops	Benzalkonium chloride 0.01%, glycerine, purified water. may contain hydrochloric acid and/or sodium hydroxide (to adjust PH).	Ketotifen (0.025 %) (equivalent to ketotifen fumarate 0.035 %)	Children from 3 years. Children under 3 years of age: consult to doctor	[112]
	NASAL DROPS	LITTLE REMEDIES DECONGESTANT NASAL DROPS phenylephrine hydrochloride liquid	Benzalkonium chloride, glycerine, polyethylene glycol, potassium phosphate monobasic, purified water, Sodium EDTA, sodium phosphate dibasic	Phenylephrine hydrochloride 1.25 mg/mL	Children	[113]
	ORAL DROPS	BIO-G-TUSS PAEDIATRIC DROPS (solution)	Citric acid, grape flavour, glycerine, methylparaben, polyethylene glycol, propylparaben, purified water, Sodium citrate, sucralose	- Dextromethorphan HBr (7.5 mg/mL) - Guaifenesin (88 mg/mL) - Phenylephrine HCl (2.5 mg/mL)	Children	[114]
SOLI PREPARATIONS	CHEWABLE TABLET	Children's Motrin—Ibuprofen Tablet, Chewable	Acesulfame potassium, ammonium glycyrrhizin, aspartame, carnauba wax, croscarmellose sodium, hypromellose, magnesium stearate, mannitol, natural and artificial flavours, silicon dioxide, sodium lauryl sulphate, soybean oil, succinic acid	Ibuprofen 100 mg	2 to 11 years	[115]
		Acetaminophen Children's	Citric acid, crospovidone, D&C network No. 27 aluminium lake, D&C network No. 30 aluminium lake, dextrates hydrated, ethyl cellulose, flavours, magnesium stearate, mannitol, polyethylene, stearic acid, sucralose	Acetaminophen 80 mg	2 to 6 years	[116]
	TABLETS	Diazepam Tablet	Anhydrous lactose, magnesium stearate, cellulose microcrystalline, FD&C blue n. 1	Diazepam 10 mg	Children from 6 months	[117]
		Dexamethasone 1.5 mg tablet	Lactose monohydrate, magnesium stearate, maltodextrin, corn starch, sucrose	Dexamethasone 1.5 mg	It depends on the pathology	[118]

Appendix F

Table A5. Liquid formulations for paediatric use in Research Articles.

Formula	Pharmaceutical Form	Excipients	Active Principle (Dose)	Age	Stability (Stability in Use)	References
Organic solvent-based formulation of lorazepam (Oral Solution)	Oral solution	PEG 400 (10% *v/v*), Propylene glycol (3% *m/v*), Glycerol (87% *v/v*) and Orange essence (0.1%)	Lorazepam (1 mg/mL)	Children 1 month to 12 years old	12 months at 4 °C (Stability in use: 4 weeks)	[119]
Oral solution of amlodipine besylate for children	Oral solution	Sucrose jarabe (32% *m/v*), Methylparaben (solution 15% *m/v*) (0.3% *m/v*) and Purified water (75%)	Amlodipine Besylate (0.5 mg/mL)	Paediatric Population (children and teenagers)	12 months at 4 °C (Stability in use: 18 weeks)	[120]
Oral tizanidine hydrochloride, Formulation for hospital use	Oral solution	CMC (carboxymethyl cellulose) (0.5%), Potassic sorbate (0.15%), Sucralose (0.10%), Citric acid and Purified water	Tizanidine Hydrochloride (1 g/mL)	Paediatric Population	70 days at 15–30 °C, 2–8 °C and 40 °C	[121]
Paediatric oral formulation of clonidine hydrochloride	Oral solution	Sucrose syrup (20% *v/v*), Raspberry essence (0.05%), Methyl paraben solution 15% (1% *m/v*), Citric acid monohydrate (1% *m/v*), Disodium hydrogen phosphate (1.8% *m/v*) and Purified water	Clonidine HCL (50 µg/mL)	Paediatric Population	9 months at room temperature, protected from light	[122]
Oral liquid formulation of clonidine hydrochloride for paediatric patients	Oral solution	Potassic sorbate, Sucrose and Monohydrate citric acid	Clonidine hydrochloride (20 µg/mL)	Paediatric Patients (all ages)	90 days at 5 °C (cooling) (Stability in use: 42 days at 5 °C)	[123]
Paediatric oral formulations of sodium dichloroacetate	Oral solution	Vehicle Mascagni (% *w/v*): Sucralose (0.02%), Hydroxyethyl cellulose (0.2%), Citric acid (0.09%), Sodium citrate (0.09%) and Potassium sorbate (0.18%)	Sodium dichloroacetate (DCA) (9.5% *w/v*)	Paediatric Patients	3 months at 4 °C and 25 °C (Stability in use: 1 month to 4 °C)	[124]
Furosemide solutions for personalized paediatric administration	Oral solution (extemporaneous)	Solution I: Buffer carbonate-bicarbonate (pH) (10 mL) Excipient for syrup (cps 100 mL) (ACOFARMA): sucrose, water, sorbitol, glycerine, aroma, citric acid, methyl paraben, potassium sorbate, sodium phosphate and colorant. Solution II: Buffer carbonate-bicarbonate (pH) (10 mL) -Excipient for syrup—without sugars (cps 100 mL) (ACOFARMA): sodium saccharine, xanthan gum, water, sorbitol, glycerine, aroma, citric acid, sodium citrate, methyl paraben, propyl paraben, potassium sorbate, sodium phosphate and colorant.	Furosemide (2 mg/mL)	Paediatrics	60 days at 4 and 25 °C	[125]
Formulation comprising acetaminophen, especially for paediatrics (PATENT)	Oral solution (nano-emulsion)	NF glyceryl mono linoleate (5–30%, preferably 8-26% *w/v*), PEG-35 castor oil (30–60%, preferably 39–46% *w/v*), NF diethylene glycol mono ethyl ether (20–45%, preferably 24–40% *w/v*) and Water	Paracetamol (5–18% *w/v*)	Paediatrics	NA	[126]

Table A5. *Cont.*

Formula	Pharmaceutical Form	Excipients	Active Principle (Dose)	Age	Stability (Stability in Use)	References
Paediatric formulations of ursodeoxycholic acid from oral administration	Oral suspension	Glycerol (20%), Methyl cellulose 1000 (1% *v/v*) and Purified water	Ursodeoxycholic acid (UDCA) (1.5 mg/mL)	Paediatric Population	30 days at 25 °C or in fridge	[127]
Oral paediatric formulation of hydrochlorothiazide	Oral suspension	Glycerol (20%), Methyl cellulose 1000 (1% *v/v*), Citric acid (pH corrector) and Water	Hydrochlorothiazide (2 mg/mL)	Paediatric Population in general	3 weeks at 5 °C and protected from light	[128]
Oral suspension of clindamycin HCL with ion exchange resin for paediatric use	Oral suspension	Glycerine (30% *w/v*), Sucralose (3%), Aroma of maple syrup (7%), Grape aroma (10%), Cremophor RH 40 (15%), Xanthan gum (0.2%) and Deionized water (cps 5 mL)	Clindamycin HCL resin (Amberlite IRP 69) (5.5% *w/v*)	Paediatric Population	1 month at 25 °C	[129,130]
Isoniazid suspension formulated with cationic resin for paediatric use	Oral suspension	Sorbitol solution 70% USP (4.9 mL/ 5 mL), USP monohydrate citric acid (50 mg/5 mL) and USP potassic sorbate (5 mg/5 mL)	Isoniazid resin/Kyron T-134 100 mg/5 mL/200 mg/ 5 mL	Paediatric Population	3 months at 40 °C (accelerated stability study)	[131]
Paediatric xylometazoline nasal spray formulation	Nasal Spray	Sodium colatum (105 mg/10 mL), PEG 400 (1.35 mL/10 mL), Sodium carboxy methyl cellulose (10 mg/10 mL), Glycerine (0.15 mL/10 mL), Methyl paraben (3.3 mg/10 mL), Sodium chloride and Purified water (cps 10 mL)	Xylometazoline HCl (5 mg/10 mL)	Paediatric Population	12 months at 25 °C	[132]

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1.6 Publicación 2: Pharmaceutical Forms and Excipients in the Paediatric Population

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Debido al considerable impacto de la **Publicación 1**, la editorial Vide Leaf decidió realizar una reedición completa de artículo, incorporándolo como un **Capítulo de Libro** de acceso abierto. En esta versión revisada, añadió y amplio en un nuevo apartado dedicado a las formas farmacéuticas prometedoras en la población pediátrica: los comprimidos ODT o las gominolas elaboradas por impresión 3D de fármacos.

Resumen:

Este estudio teórico pretende revisar críticamente el uso de excipientes en la población pediátrica. Este estudio se basa en las normas y recomendaciones de las agencias reguladoras de medicamentos europeas y americanas. Por un lado, esta revisión describe los excipientes más frecuentemente utilizados en formulaciones de medicamentos pediátricos, identificando los compuestos que la literatura científica ha marcado como potencialmente nocivos en cuanto a los efectos secundarios generados tras su exposición. Por otro lado, esta revisión también destaca la importancia de llevar a cabo controles de seguridad de los excipientes, que en la mayoría de los casos están ligados a estudios de toxicidad. En la compilación de bases de datos para la población pediátrica se espera que un excipiente se centre en la seguridad y la toxicidad, como en la base de datos STEP. Por último, se estudian formas farmacéuticas que parecen prometedoras para la población infantil: los comprimidos ODT y las gominolas elaboradas por impresión 3D de fármacos.

Abstract:

This theoretical study seeks to critically review the use of excipients in the paediatric population. This study is based on the rules and recommendations of European and American drug regulatory agencies. On the one hand, this review describes the most frequent excipients used in paediatric medicine formulations, identifying the compounds that scientific literature has marked as potentially harmful regarding the side effects generated after exposure. On the other hand, this review also highlights the importance of carrying out safety -checks on the excipients, which, in most cases, are linked to toxicity studies. An excipient in the compilation of paediatric population databases is expected to target safety and toxicity, as in the STEP database. Finally, promising pharmaceutical forms suitable for the paediatric population, such as ODT and gummies fabricated via 3D printing, are currently under investigation.

Book Chapter

Pharmaceutical Forms and Excipients in the Paediatric Population

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Abstract

This theoretical study seeks to critically review the use of excipients in the paediatric population. This study is based on the rules and recommendations of European and American drug

regulatory agencies. On the one hand, this review describes the most frequent excipients used in paediatric medicine formulations, identifying the compounds that scientific literature has marked as potentially harmful regarding the side effects generated after exposure. On the other hand, this review also highlights the importance of carrying out safety -checks on the excipients, which, in most cases, are linked to toxicity studies. An excipient in the compilation of paediatric population databases is expected to target safety and toxicity, as in the STEP database. Finally, a promising pharmaceutical form for child population, ODT (Orally Disintegrating Tablets), will be studied.

Keywords

Excipients; Paediatrics; Security; Toxicology; STEP and ODT

Introduction

The scientific literature suggests that most commercialized drugs are not suitable to be used on the paediatric population, as they are presented in an inappropriate pharmaceutical dosage or form, or because of the excipients they contain. In the face of this reality, compounding is the alternative for paediatric patients. Auxiliary substances or excipients should be used in the development of a compounding formula in order to allow the drug to be administered in an easily and personalized manner. By doing so, the active ingredient will be formulated in a stable, effective, and safe form [1].

The process of formulating excipients in paediatrics is a complicated task that requires various considerations to be accounted for in order to for them to be appropriate; variables such as an acceptable taste, age, dosage forms, among others, must be taken into account when selecting safe excipients. Furthermore, children's rapid growth and development are associated with changes in various organs, body composition, protein bonds, active transport mechanisms and metabolic pathways, which must also be taken into account [2]. In addition to being a complicated task, it is also a critical step in the development of paediatric formulations, as some acceptable

excipients in formulations for adult patients are not suitable for paediatric use.

It is thus of particular relevance to carry out an assessment of the safety of excipients prior to their use in paediatrics. Indeed, Georg Schmitt [3] advocates for non-clinical safety studies being carried out in juvenile animals to assess excipient toxicity or sensibility and also to establish safe exposures in paediatric age groups. He specifically recommends that excipient toxicity studies also be carried out, as they provide a detailed assessment of clinical risk. He further suggests that even excipients with significant toxic potential for children may be acceptable after a rigorous assessment of the risk they pose is made. Another factor to be considered for toxicological studies is the extent to which the target disease may be alleviated by the formulation of that medicine. Thus, pharmaceutical companies should filter the demands for safety assessments by selecting those that will contribute to a potential therapeutic benefit, while helping to develop a reference list of excipients generally considered safe for use in paediatric formulations. In this way, the clinical decision-making process will be made easier.

This theoretical study's main objective is to critically review the use of excipients in paediatrics with an emphasis on the issue of safety, mainly on the basis of toxicological studies. This will enable information to be obtained that will allow decisions to be made regarding the masterful preparation of formulations. This study also seeks to investigate the development of databases and initiatives in order to record corroborated information on excipients for paediatric use, thus serving as a guide for clinical professionals.

To do this, databases such as Web of Science, PubMed, SciFinder and SciFindern Search, as well as books related to the subject, were consulted. Please note that most of the selected literature is from the last two decades. Subsequently, six tables were created to provide details on the data obtained:

- Table 1. Toxicity database.
- Table A1. Most important characteristics of the excipients discussed in this review (in alphabetical order).
- Table A2. Examples of solid and semi-solid medicines used in Spain for the paediatric population: List of excipients and relevant characteristics of the pharmaceutical form (PF) (performed consultation of CIMA database, September 2020).
- Table A3. Examples of liquid medicines used in paediatrics: List of excipients and relevant characteristics of (PF).
- Table A4. Examples of FDA-registered drugs used in paediatrics (FDA database and DAILYMED October 2020).
- Table A5. Examples of liquid formulations for paediatric use in research articles.

Table 1: Toxicity databases and public resources.

Name	Website	Creator
ACToR — Aggregated Computational Toxicology Resource	www.actor.epa.gov/actor/home.xhtml (accessed on 15 Nov 2020)	US Environmental Protection Agency's (EPA) National Center for Computational Toxicology (NCCT)
STEP—Safety and Toxicity of Excipients for Paediatrics *	www.eupfi.org/step-database-info/ (accessed on 15 Nov 2020)	European Paediatric Formulation Initiative
TOXNET—Toxicology Data Network	www.nlm.nih.gov/toxnet/index.html (accessed on 15 Nov 2020)	Specialized Information Services (SIS) USA
Vitic	www.lhasalimited.org/products/vitic.htm (accessed on 02 Nov 2020)	Lhasa Limited

* The purposes of the STEP database can be consulted in the Appendix A.

Paediatric Regulatory Context

Changes in physical, metabolic and psychological processes that occur during children's growth, from birth to adulthood, suggest that children should not be considered as young adults, and nor should they be grouped as a single group. Rather, the

pharmaceutical development of paediatric drugs should focus on several acceptable dosage forms that are able to meet the needs of most children in different age groups. This can be achieved by developing dosage forms which facilitate the administration of a dose range which would vary according to the child's age and/or other important parameters [4].

Before there were regulations for the development of paediatric drugs, children were known as "therapeutic orphans". They lost the advances of conventional medicine, since the vast majority of advances were aimed at the adult population, and there were not many approved medicines for children. Children were treated with approved drugs following successful studies on adults, but with few or no trials on the paediatric population (off-label use). The large number of subsequent issues with clinical trials on children, as well as the need for drug authorization in the paediatric population, among other reasons, were the driving factors for the creation of a legislative and regulatory framework for clinical studies in paediatrics. The US pioneered these in the late 1980s, and with the adoption of these paediatric regulatory initiatives, significant improvements were made [4].

It was only in 1997 that European regulators agreed to strengthen legislation on the use of new medicines in children. In 2000, European health ministers asked the European Commission to make proposals for a legislation to ensure that new paediatric medicines placed on the market were tailored to the specific needs of children. In 2004, after a major debate, a regulatory bill was issued, which took into account lessons learned from paediatric regulation that the US was already addressing [5]. On 26 January 2007, the Paediatric Regulation entered into force in the European Union, and focused mainly on regulating the development of paediatric formulations for children between 0 and 18 years of age, but also sought to:

- Ensure that these medicines were of good quality.
- Verify that paediatric medicines were produced following ethical and legitimate research, that children were not subjected to unnecessary trials.

- Improve the accessibility and availability of information on drug use in the paediatric population.
- Such regulations led to the establishment of the Paediatric Committee (PDCO), whose main function was to regulate the studies that companies should conduct in children as part of a Paediatric Research Plan (PRP) [6].
- The Paediatric Regulation consists of [7]:
- Regulation (EC) 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use; and
- Regulation (EC) 1902/2006, an amending regulation in which changes were made to the original text in relation to the European Commission's decision-making procedures.

In October 2017, the European Commission published a ten-year report on the implementation of the Paediatric Regulation. The report showed an increase in medicines for children in most therapeutic areas over the past ten years, especially in rheumatology and infectious diseases. However, in rare diseases, progression was lower. A report on the first five years was also published in June 2013, which concluded that paediatric development had become a more integral part of the overall development of medicines in the European Union [4,8].
The European Guideline on pharmaceutical development of medicines for paediatric used [4] offers several tips for paediatric drug formulation.

Excipients in a paediatric formulation should be chosen appropriately, avoiding any excipients that are potentially toxic or unsuitable for children. Choosing the right excipients in the development of a new paediatric drug is one of the most important aspects, as it requires special safety considerations. In general, the following aspects should be taken into account when selecting an appropriate excipient for a paediatric medicinal product [4]:

- Excipient function in formulation and possible alternatives.
- Safety profile of the excipient for children in target age groups, based on a unique and daily exposure.
- Expected duration of treatment: short term (a single dose for a few days) or long term (weeks and/or months).

- Severity of the condition to be treated and therapeutic alternatives.
- Patient acceptability, including palatability.
- Allergies and sensitization. Children suffer from sensitization problems more commonly than adults. Applicants should avoid, when possible, excipients with known potential to cause sensitization or allergies.

If the use of any excipient in the formulation that produces or may pose any risk to the child cannot be avoided, the added value of the chosen pharmaceutical form of dosing (and the route of administration) should be balanced with the possible use of another. However, security issues can only become apparent when the product is used on a larger scale.

Furthermore, the first joint paediatric regulatory action was taken by the ICH (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use), an organization working on harmonizing drug regulation requirements between the EU, Japan and the US. In July 2000 Guideline E11 (R1) was published: Clinical investigation of medicinal products in the paediatric population, with the final version in August 2017 [9].

The objectives of this guide were to encourage and facilitate the development of paediatric medicines at the international level, as well as to provide a summary of critical problems in the development of these medicines and new approaches to their safe, efficient and ethical clinical study. ICH E11 became an important tool in the design of paediatric clinical research worldwide, providing guidelines (rather than proscribing practice) [9,10].

The WHO launched the initiative Making Medicines Child Size in 2008 to issue a list of essential medicines for children, betting on quality paediatric development and adequate access of these medicines to the entire paediatric population, in particular underdeveloped countries [11]. The most current one is the 7th edition, which was published in 2019 (WHO model list of essential medicines for children) [12].

In the early 1980s, the FDA (Food and Drug Administration) began taking steps to provide incentives to the pharmaceutical industry for the development of paediatric drugs. In 1994, the Paediatric Labelling Rule was issued, requiring the authorization of a new paediatric drug to be supported by safety and efficacy data to support its use. However, that rule was not mandatory and was unsuccessful. For this reason, the US-FDA proposed in 1998 Paediatric rule which proposed to guarantee the above-mentioned objectives, both at and after the approval of the new drug [13].

It should also be noted that the FDA (Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients) published a document that provides guidance on the development of safety profiles to support the use of new excipients as components of drugs or biological products, which could be applied in paediatric experiments [14,15].

Examples of Databases and Initiatives for the Registration of Information on Excipients Used in the Paediatric Population

It is certainly necessary to take into account the safety of excipients used in paediatric products, as the toxicity of these excipients may differ from that of adults [16]. Under this assumption, it is essential to develop methodologies that provide an integrated assessment of exposure to potentially toxic excipients contained in medicines. Therefore, in 2007, members of pharmaceutical industries, hospitals and academics interested in improving drug formulations in paediatrics founded the European Paediatric Formulation Initiative (EUPFI). The latter sought to address safety problems linked to excipients used in children [17], as well as the development of platforms for the systematic evaluation of excipients in new-borns [18].

EuPFI is currently a consortium of 10 pharmaceutical companies, 5 universities, 1 hospital and, exclusively, the European Medicines Agency (EMA) as an observer. The goals and objectives of this consortium are summarized in [19]:

1. Identify the problems and challenges associated with the development of paediatric formulation and consider ways to obtain better medicines and dosage forms clinically relevant to children.
2. Promote early pharmaceutical consideration for the development of paediatric medicines.
3. Identify potential information and knowledge gaps in the development of paediatric formulations.
4. Improve the availability of information from paediatric formulations.

The scientific literature shows that excipients commonly used in adult medicines have been associated with high toxicological risks and safety problems in children [20]. Following the United States Paediatric Formulation Initiative (USPFI) and Global Paediatric Research (GRIP), the Paediatric Excipient Safety and Toxicity Database (STEP) was created to address the need for effortless access to information about the excipients' safety and toxicity [21]. The STEP database is presented as a resource of information to facilitate access to data on the use and acceptability of excipients in children, thus allowing a rapid evaluation of the risks due to the use of certain excipients in the paediatric population and an improvement in the scientific decision making [2,22]. Furthermore, the STEP database provides comprehensive and comparative information on the safe use and acceptability of excipients in paediatrics. For the reasons listed above, the STEP database stands out with respect to other existing public resources (such as TOXNET) or databases (such as Vitic or ACToR) that organize their informational content in free text format, thus preventing data from being filtered as needed (see Table 1) [23].

In general, the above purposes go in line with increasing the number of excipients registered in the database to be useful in practical research. Therefore, the following selection criteria were considered for excipients of interest [2]:

1. Excipients known to be toxic/have general safety issues.
2. Frequency of appearance as contaminants or toxics in paediatrics (where applicable).

3. Evidence in the toxicity literature in paediatrics. The above criteria were applied to identify excipients for inclusion in the STEP database. Excipients were shortlisted/prioritized through surveys within EU and US PFI members.

According to the above criteria, in the development of databases on the safety and toxicity of excipients in the paediatric population, the following are prioritized, as they are most likely to cause damage and side effects in this population [2]:

1. Propylene glycol (PG)
2. Ethanol
3. Polysorbate 80
4. Benzyl alcohol
5. Parabens (propyl, methyl, ethyl and butyl)
6. Benzalkonium chloride
7. Aspartame
8. Sorbitol
9. Benzoic acid
10. Sodium benzoate

In 2014, the first version of the STEP database was launched for the systematic evaluation of its integrity, quality, configurability, usability, and maintainability under the daily practices of the different and diverse professionals who use it. After launch, a validation study of the tool was initiated with the following objectives [2]:

1. Validate the STEP Version 1 database against the potential needs of end users to ensure that the STEP database meets users' expectations.
2. Evaluate the functionality and usability of data application by
    a. Ensuring proper ease of use (navigation), understanding and user satisfaction.
    b. Characterizing how easy it is to perform a task using the database.
    c. Identifying problems in interaction with systems.
3. Evaluate the impact of this database on the development of paediatric medicines.

4. Establish viable recommendations to further improve the functionality of the system and increase its beneficial effects on the development of paediatric medicines.

The results of the validation study identified different database usage issues, which are grouped into three areas: I. Content and presentation of results; II. Adequacy of the database to the characteristics of different users, navigation features; and III. Search. Many of the problems observed might have happened due to assuming that users would have sufficient knowledge, therefore some elements were not clearly exposed for the new user to understand. Furthermore, users with limited computer skills may also find the registration process confusing. These issues involved changes and improvements to STEP design and functionality, making it a more efficient database when deriving from a Version 2 [21].

To perform an adequate risk/benefit assessment of the current medication standard, it is necessary to compare the daily amount of excipients in the most vulnerable patient with clinically established safety levels for the same age group. The SEEN project is an example of this, as it developed a retrospective cohort study, with neonatal patients (age 5 or younger) treated with multiple medicines. Preparations were recorded with ethanol, propylene glycol, benzyl alcohol, parabens, aspartame, glycerol, sorbitol and polysorbate-80 and cumulative amounts [24] were calculated.

The results obtained demonstrated limited knowledge about the acceptability of different dosage forms, flavours and, more importantly, the safety of formulation excipients in relation to the age and stage of development of children [24].

Excipients: Functions and Main Adverse Effects

Paediatric formulations need excipients to maintain their quality and promote the acceptability of childhood patients [25]. However, just because they are necessary does not mean that they are toxicity-free products; in fact, a study by Georgi and

collaborators [26,27] confirms that many of the medicines used in paediatrics contain some toxic or potentially toxic excipient for the paediatric population, with this data being present in two-thirds of new-borns in 21 European countries. Thus, excipients used in paediatric formulations require a thorough assessment of short-term and long-term safety prior to their use in these formulations [28]. A classification of the main excipients will then be developed according to the role they play in the formulation, mentioning the possible adverse effects on the paediatric population. Furthermore, a summary appendix (**Appendix B (Table A1))** of the excipients discussed in this paper will be prepared.

Diluents

Lactose, starch and microcrystalline cellulose are often used as diluents, as they are generally safe in the adult population.

Lactose

Lactose, which is a mandatory excipient, is recommended not to be used in patients with lactose intolerance and is contraindicated in patients with galactosemia [1]. It may cause hypersensitivity reactions in children and new-borns. Infants with lactose intolerance do not properly metabolize lactose, due to the deficiency of the enzyme lactase, thus causing the accumulation of lactic acid, hydrogen and carbon dioxide. Symptoms such as severe abdominal pain, flatulence, bloating or swelling and diarrhoea may, therefore, appear, as well as systemic symptoms such as muscle, joint pain and eczema [28]. It should be noted that children may sometimes have very severe and prolonged reactions to lactose that can lead to additional complications, such as dehydration, bacterial proliferation and metabolic acidosis [1,28].

Starch, dehydrated calcium hydrogen phosphate, erythritol and cellulose powder are alternatives to lactose in paediatric formulations. They have lactose-like flow properties and produce tablets that can disaggregate in a time less than lactose [28].

Starch

Starch is one of the most commonly used excipients and, in addition to being a diluent, it has binder and disintegrating properties. Due to its properties, starch should be preserved in a dry environment, as it can be an excellent growing medium for microorganisms in case of moisture, which may cause microbiological contaminations. In addition, it may give proliferation of carcinogenic aflatoxins, if contaminated by two species of fungi closely enhanced by each other: Aspergillus flavus and Aspergillus parasiticus [29].

Microcrystalline Cellulose

Microcrystalline cellulose is a partially depolymerized purified cellulose that is presented as a white, odourless and tasteless crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications. It is considered a relatively non-toxic and non-irritating material. It is not absorbed systemically after oral administration and therefore has little toxic potential [29,30].

Microcrystalline cellulose is used in pharmaceutical products, mainly as a binder and thinner in tablet and oral capsule formulations. In addition to its use as a binder and thinner, it also has some lubricating and disintegrating properties that make it useful for forming tablets [30].

Solvents

Some of the most common solvents are water, ethyl alcohol, propylene glycol (PG), glycerol and polyethylene glycol [28,29].

Water

Water is the most commonly used agent in paediatric formulations, as liquid preparations are easier to administrate and allow a more accurate dose adjustment [1,29]. Water is an ideal

medium for the proliferation of microorganisms (bacteria and fungi) despite their purification, which is why antimicrobial agents have to be added.

In paediatric oral formulations, the total volume of fluid is of vital importance for the taste and ability to adequately measure the volume to be administered: in children under 5 years of age a volume of less than 5 mL should be administered and, in children under 10 years of age, a volume of less than 10 mL [29] should be administered.

Ethyl Alcohol (Ethanol)

Ethanol is one of the excipients of concern to international health regulatory agencies, as it causes neurotoxicity and cardiovascular problems in the paediatric population; it is a potentially harmful excipient in neonates. For this reason, permissible maximum limits have been set and, in some countries, non-alcoholic medicines are to be established. It is a very permeable excipient with regard to the blood–brain barrier, and the one most commonly used in oral medicinal products, reaching 63% of cases [26]. It is rapidly absorbed into the gastrointestinal tract and is primarily metabolized in the liver to acetaldehyde, which is oxidized to acetate [29].

Indeed, Macrel and Bernando's review of liquid formulations in Brazil has furthered our understanding of the high use of ethanol. These researchers demonstrated that ethanol is used in various concentrations and functions: as solvent (main function), co-saver, flavouring agent, preservative and as an extraction solvent in herbal medicines [26,27]. It also has antimicrobial properties and increases the permeability of many preparations [29].

The use of ethanol as an excipient carries potential hazards and adverse effects, which are already observed at a dose of 100 mg/dL. These effects include hypoglycaemia, acidosis and hydro-electrolytic alterations. Very high intake can lead to stupor, coma, respiratory depression and cardiovascular collapse. Hypoglycaemic seizures may also occur in children [29,31]. For all these side effects, any alcohol should be avoided in paediatric

forms. However, it is still used in many liquid preparations, because it is the only solvent that allows the solubilization of certain active substances [29].

In both the United States and the European Union, guidance on maximum ethanol limits in medicinal formulations is increasing [17]. According to the World Health Organization and a regulation existing in the United States, the maximum alcohol content in paediatric formulations should not exceed the limits specified in Table A1 [29,31,32].

It should be noted that ethanol was also able to interact with many active substances of other medicines that the child is taking [29] and, therefore, possible interactions must be studied prior to concomitant administration. Furthermore, new contributions in the scientific literature on excipients, including ethanol, is expected to help health professionals predict the risks of using a particular excipient, especially in the paediatric population. For example, the guideline excipients in the label and package leaflet of medicinal products for human use alerts on the risk of the use of ethanol and proposes changes on its use.

Propylene Glycol (PG)

PG is used as a solvent to stabilize substances that are not water soluble, in parenteral and non-parenteral formulations. It also has moisturizing, antimicrobial properties and can be used as plasticizer. It is rapidly absorbed through the gastrointestinal tract and damaged skin and metabolized in the liver to lactic acid and pyruvic acid [29].

Exposure to high doses of PG may affect the Central Nervous System, especially in new-borns and children under 4 years of age [29]. Due to children's physiological and metabolic immaturity, PG can accumulate rapidly causing toxicity [33]. In new-borns, its half-life is very long, almost seventeen hours, compared to that of adults, which is about five hours [29]. The GRAS (Generally Recognized as Safe) classification of excipients typically does not consider the differences in physiological and metabolic maturation between the paediatric

and adult populations [33], a fact that justifies some important adverse reactions presented by PG in the paediatric population [29]:

- Hyperosmolar syndrome in burnt children with topical arsenic sulfadiazine ointment containing PG.
- Precipitation of irreversible deafness in pretermits who received a multivitamin complex containing PG.
- Parenterally it is possible to observe haemolysis, seizures, respiratory depression, hypertension.
- Contact dermatitis is topically observed.

In the 1980s, cases of biochemical abnormalities, including hyperosmolarity, lactic acidosis and elevated levels of creatinine and bilirubin, were documented after exposure to 3 g/day of PG and for at least 5 consecutive days. Clinical symptoms, including seizures and bradycardia episodes [33], then appeared. In 2011, the U.S. FDA reported health problems in premature new-borns associated with the use of Kaletra® (lopinavir/ritonavir) solution; liquid preparation containing high amounts of PG and ethanol [33,34].

Exposure to PG in new-borns and children under 4 years of age remains common, despite historical and contemporary reports dealing with toxic adverse effects of this excipient. Thus, the study of Allegaert J. [33] in terms of the PG research project in new-borns is of great interest, as it provides scientific evidence on the tolerance and plasma clearance of this excipient, including differences in elimination pathways (renal pathway compared to the hepatic pathway).

Glycerol

Glycerol, a mandatory excipient (E-422), is used as solvent, sweetener, viscosizer and preservative. When used at high concentrations (more than 40%), it can cause mucositis in the stomach, as well as diarrhoea and electrolyte disturbances due to its hygroscopic and osmotic properties. Therefore, a maximum amount of 10 g/dose [1,29] has been established.

In the adult population glycerol has few adverse effects. However, cases of neurological toxicity have been reported in the paediatric population [29].

Polyethylene Glycol (PEG)

PEG is a polar and water-soluble substance used as a co-solvent, suspensor and viscosity agent. The PEG 400 is the most used in liquid formulations. It may cause some laxative effect when taken orally, with the maximum daily dose established in adults at 10 mg/kg/day [1].

PEG has low oral bioavailability and renal elimination. Due to its properties, significant adverse effects such as diarrhoea and nephrotoxicity have been reported, so the maximum recommended daily dose is 10 mg/kg body weight [1]. It can also cause some laxative effect when taken orally. When new-borns and infants are exposed to high doses of PEG, gastrointestinal disorders, adverse effects typical of alcoholic solvents may occur [1,28].

Coating Agents

Phthalates

Phthalates play a primary role as a coating agent (film-forming, plasticizer) in medicinal formulations. Exposure of pregnant women to phthalates has been associated with abnormalities in the development of the foetus, such as cleft palate and skeletal malformations; abnormalities that can end in stillbirth. It was observed that they have a high potential to produce toxicity in the development of experimental animals, as well as in their reproduction [28].

Due to these risks of certain phthalates to health, in March 2012, the CDER published a guide to orient the pharmaceutical industry on the use of phthalates: “Limiting the use of certain phthalates as excipients in CDER regulated products”. This guidance document recommends limiting the use of certain phthalates, such as dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) [28].

Preservatives

Preservatives are a group of excipients that prevent microbial growth and, consequently, the degradation of the active substance and the possible alteration of the organoleptic characteristics of the final formula [35].

The American Academy of Paediatrics does not recommend the use of preservatives in reparations for patients under 3 years of age due to the lack of physiological and metabolic maturation of these patients. This lack of maturation may lead to the accumulation of preservatives in the liver, a fact that increases the risk of cardiovascular collapse, in addition to producing non-specific reactions or even allergies [1,35]. It should be noted that preservatives are not contraindicated in children under 3 years of age, but should only be used in imperative cases [1].

Sodium Benzoate

Sodium benzoate is a preservative widely used in pharmaceutical and cosmetic formulations, at concentrations between 0.02% and 0.05% [29]. Its maximum activity occurs in weakly acidic pH 4.5 solutions and is inactive at pH values greater than 5 [35].

As side effects, it can cause contact hives and other allergies. In premature children, its use is contraindicated, as it presents a risk of metabolic acidosis and jaundice [29,35].

One of the large prospective studies conducted by Nellis and collaborators [36,37] in hospitalized neonates in Europe described the administration of eight potentially harmful excipients of interest (EOI) (parabens, polysorbate 80, propylene glycol, benzoates, sodium saccharine, sorbitol, ethanol and benzalkonium chloride) and identified risk factors resulting from exposure. Neonates appear to lack the ability to conjugate benzoates with glycine, leading to the accumulation of benzoic acid that can cause metabolic acidosis and neurotoxicity [26,27].

The ESNEE (European Study of Neonatal Exposure to Excipients) clinical study [38] showed that sodium benzoate was found in 10 medicines given to new-borns, despite being a highly toxic excipient to them. Preservatives such as parabens (and their sodium salts) and propyl para-hydroxy-benzoate were also found in 24 paediatric medications, and ethanol in 8.

Benzyl Alcohol

Benzyl alcohol presents antibacterial properties. For that reason, it is used as a preservative in a lot of medicines. Its activity depends on the pH; being at it is maximum at a low pH (between 2.5–4.5). It is used at the concentration of 0.01–0.15% in oral preparations [35].

In adults, it is metabolized to benzoic acid, which is conjugated in the liver with glycine. As a result, the acid hippuric formed is excreted in urine. However, in new-borns, this conversion of the benzoic acid into hippuric acid is very diminished, because of the lack of liver maturation. That justifies fatal intoxication cases in new-borns who had their umbilical catheters cleaned with benzoic acid. Consequently, cases of metabolic acidosis and respiratory depression occurred. Additionally, other adverse effects have been described, like intraventricular bleeding, cerebral palsy and developmental delay. In some cases, there have been reactions of hypersensitivity, allergy and contact dermatitis [29,39–41].

In the 1990s, Svinning and collaborators [42] conducted a review of the medical records of babies who weighed less than 1250 g at birth and were admitted to the neonatal intensive care unit. The main objective of this study was to assess the impact of the toxicity of benzyl alcohol, following discontinuation of the use of solutions to wash intravascular catheters containing benzyl alcohol. A significant decrease in mortality rate and incidence of Grade III/IV intraventricular haemorrhage was observed among infants weighing less than 1000 g at birth who were not exposed to benzyl alcohol (as opposed to those who were).

The maximum dose of benzoic acid (and other benzoates, calculated as benzoic acid) recommended by WHO is 5 mg/kg body weight per day in adults, a dose that, in children, logically, should be much lower [29,35]. As the effects on new-borns are severely toxic, the U.S. FDA has recommended the exclusion of benzyl alcohol from medications, intravenous fluids, and heparin washing solutions for them [36]. The EMA states that any medicine containing benzyl alcohol "should not be given to premature babies and new-borns" [42,43]. In fact, currently, any exposure to benzyl alcohol is contraindicated in children under 3 years of age [44].

Benzalkonium Chloride

Benzalkonium chloride is a quaternary ammonium used in ophthalmic preparations at a concentration of 0.01–0.02% (*v/v*). Generally, it is non-irritating or sensitizing and is well tolerated in skin solutions.

As a side effect, it can cause bronchoconstriction in asthmatic patients, if used in nebulization solutions. Furthermore, cases of ototoxicity may occur in otic preparations, hypersensitivity in topical skin preparations and respiratory failure in infants who ingest this excipient, with this side effect being the most severe [29].

Thiomersal

Thiomersal is a preservative widely used in vaccines and topical preparations, such as eye drops. Its toxicity is similar to mercury: in fact, it contains a mercury atom in its molecular structure. The concentration used depends on the medicinal product: in injectable preparations 0.01% is used and in ophthalmic solutions between 0.001% and 0.15% [30].

Several allergic hypersensitivity reactions (e.g., erythema, vesicles) have been reported. Therefore, health authorities have recommended their withdrawal from vaccines at risk of toxicity. Recently, thiomersal has also been implicated in the onset of autism spectrum disorders in children who received aluminium

salt vaccines as an adjuvant. Accordingly, various countries (including Spain) no longer market paediatric vaccines with this component [29]. The use of single-dose vials is recommended in many cases to prevent the use of preservatives such as thiomersal or sulphites such as sodium metabisulphite [28].

Parabens

Parabens are the most commonly used preservatives (also in cosmetics and foods), due to their wide antimicrobial spectrum and their effectiveness over a very wide pH range (between 4 and 8) [29,35].

Parabens are of mandatory declaration. They are used at concentrations between 0.01 and 0.2% [45], although it is most common to use a mixture in proportion 10:1 (0.2% methylparaben + 0.02% propylparaben). The maximum recommended daily dose is 10 mg/kg body weight [35].

They may produce a cross-hypersensitivity reaction in patients allergic to aspirin. This is because the main metabolite of parabens is hydroxyparabenzoic acid, structurally very similar to aspirin [29].

Recent pharmacovigilance studies have highlighted certain questions about the purported safety (non-teratogenic or carcinogenic) of parabens [29]. Alternatives should therefore be found, especially in paediatric formulations. Antimicrobials are not necessary for parenteral formulations. The absence of parabens and benzoates in 85% of parenteral prescriptions suggests that administration of these excipients can be largely avoided [36].

Antioxidants

Antioxidants are a group of chemical compounds used to prevent oxidation of the active substances in formulations [29].

Sulphites

Sulphites are antioxidants widely used in different formulations; sodium sulphite, sodium bisulfite, sodium metabisulphite and potassium metasulfite [29] are the most common.

Regulatory agencies (e.g., FDA, EMA) consider excipient sulphites safe. However, they present risks and possible fatal side effects derived of their use. One of the most common cases occurs in asthmatic patients, who may develop severe bronchospasm if they take medicines containing sulphites in their formulation [29].

The antioxidants constitute a group of compound chemists used to avoid the oxidation of the active principles in the formulations [29].

It should be noted that a large number of people are sensitive to sulphites and may experience a variety of symptoms, including dermatological, gastrointestinal and respiratory symptoms. However, reactions that develop in the respiratory tract explain most cases of sensitivity to sulphites. It is important to note that several individuals experience a variety of symptoms after exposure to sulphites; therefore, skin, intestinal and respiratory reactions can occur simultaneously and in various combinations and severity. People with sensitive skin who regularly use cosmetics or topical medications containing sulphites have chronic skin symptoms, especially on the hands, perineum and face. Sensitivity to sulphites is a very real problem that significantly affects the health of many people, especially asthmatics. Sensitivity to sulphites should be considered when people show adverse reactions to a variety of exposures, without an obvious pattern, particularly when those people experience worsening asthma symptoms after consumption of foods such as dried fruits and wines, or adverse skin reactions, after the use of cosmetics or medicinal creams [46].

Propyl Gallate

Propyl gallate is an antioxidant used to prevent the breakdown of fatty acids. It is used at a concentration of 0.1% and also has a synergistic effect with other antioxidants. In neonates it can cause dermatitis, skin allergy and methemoglobinemia [29].

Sweeteners

The use of sweeteners varies between routes of administration and, like preservatives, are not necessary in parenteral administrations [36,37]. They have been linked to photosensitivity reactions, diarrhoea and poor absorption of nutrients [36,47].

The most commonly used sweeteners in pharmaceutical formulations are sucrose, sorbitol, mannitol, aspartame and sucralose.

Sucrose

Sucrose is a natural disaccharide that is hydrolysed in the gut into two monosaccharides: glucose and fructose. In children with type I diabetes, the use of sucrose should be avoided. Very high concentrations (up to 35% are used for liquid formulations such as syrups). When the patient needs prolonged treatment with these preparations, he or she is at risk of dental damage. It has also been described that administration at very high doses on a daily basis may be carcinogenic [29]

Sorbitol

Sorbitol is a monosaccharide that is not absorbed into the digestive tract and is therefore considered safe in paediatric patients, although it is laxative at high doses. It is also used as a diluent as well as capsule plasticizer [29].

Sorbitol is another example of an excipient that causes gastrointestinal disorders, such as abdominal pain, swelling, flatulence, vomiting and osmotic diarrhoea. Because sorbitol is

metabolized to fructose, it should be avoided on children with fructose intolerance and hypoglycaemia. In isolated cases it can cause liver damage leading to coma and even death [28–30].

In infants the accumulation of sorbitol can lead to diabetic complications such as retinopathy and cataracts. Therefore, the amount of sorbitol is limited to 0.3 mg/kg in paediatric formulations [28].

Mannitol

Mannitol is used as a sweetener and as a diluent. It has been linked to severe anaphylactic reactions in paediatrics [29]. As in the case of sorbitol, it is not absorbed into the digestive tract, so it has laxative properties at high doses.

Aspartame

Aspartame is an artificial sweetener that has 180 and 200 times more sweetener power than sucrose. Because of this, it is the most used sweetener in the pharmaceutical and food industry. It is a disaccharide made of an aspartic acid and a methyl phenylalanine ester. It is an excipient of mandatory declaration and its maximum dose has been set at 40 mg/kg body weight [29,35].

Phenylalanine is very harmful for patients with phenylketonuria, as well as for pregnant mothers who carry a foetus of such metabolopathy. The use of aspartame in patients with phenylketonuria should be avoided. The adverse effects of aspartame that have been described are: neurological (neurotoxicity, epilepsy, headache, panic attack and hallucinations), hypersensitivity reactions (vascular and granulomatous panniculitis) and cross-reaction with sulphonamides [29].

Saccharine

Saccharine is also an artificial sweetener 300–600 times stronger that sucrose, but if not used properly it can leave a

residual bitter taste. Your daily dose should not exceed 2.5 mg/kg body weight. It is recommended to limit the daily dose in children and pregnant women [29,48].

Currently, controversy about its safety remains present, as in adults it has been linked to bladder cancer when used at very high doses. Adverse effects of saccharine include hives, itching, photosensibilization, eczema, as well as nausea and diarrhoea [29].

Sucralose

Sucralose has a sweetener power between 100 and 300 times higher than sucrose. Its maximum daily dose is 15 mg/kg in weight.

Sucralose is a non-toxic compound and is also not irritating, but it is not considered totally inert. It can increase the expression of cell flow transport protein glycoprotein P and two cytochrome P450 isoforms, which are essential substances in the drug purification process.

Furthermore, sucralose alters the composition of the microbiome of the digestive tract, which ends up causing the reduction of the proportion of beneficial bacteria. In addition, if cooked at high temperatures, chloropropanol can form, which is a toxic compound. It can also alter the patient's levels of glucose, insulin and glucagon-like peptide type 1 (GLP-1) [29].

Surfactants

Polysorbates

Polysorbates are partial esters of sorbitol fatty acids and their copolymerized anhydrous with ethylene oxide. They are used as dispersant agents, emulgents, non-ionic sanitary surfactants, solubilizers, and moisturizers, among other things.

In general, they are considered non-toxic and non-irritating. However, they have been associated with serious side effects, including deaths in under-weight neonates who received vitamin

E preparations with this substance [25]. In addition, polysorbate 80 has been associated with increased mortality in new-borns [42].

Colorants

Colorants are excipients used to facilitate the identification of the formula by parents and patients. The most commonly used dyes are whip dyes, quinolones, triphenylmethane and xanthines.

Tartrazine (yellow number 5) has been implicated in anaphylactic reactions, edema, asthma, bronchospasm, eosinophils, angioedema and hives in patients with sensitivity to it. It appears to cause histamine degranulation of mast cells [29]. As a result, most global regulatory agencies restrict the use of dyes such as tartrazine, because azo dyes have been linked to hypersensitivity and ADHD reactions in children. These dyes can be replaced by plant dyes such as annatto, malt beta-carotene and turmeric and should not be used at all in paediatric formulations [28].

Excipients not Recommended in Paediatrics and Paediatric Formulations

To investigate the exposure of children to excipients not recommended at an early age, a compilation of paediatric formulations (nationally and internationally) was made (see Appendixes C–F). As will be seen below, most of these formulations contain some excipient not recommended in paediatrics:

In Appendix C, there is a summary table (Table A2) of examples of solid and semi-solid medicines used in the paediatric population, marketed in Spain. Additionally, a list of excipients and relevant characteristics of the pharmaceutical form (PF) is shown (performed consultation of CIMA database, September 2020). It clearly shows that the reason such excipients are not recommended for the paediatric population is because of the adverse effects they may cause, which include:

- Approximately 100% of the formulations shown here carry at least one excipient not recommended for the paediatric population.
- Benzalkonium chloride, methyl para hydroxybenzoate and propyl para hydroxybenzoate are some of the most commonly used preservatives in solid and semi-solid formulations for paediatric use, even though they are considered to be potentially toxic in neonates.
- Sucrose, aspartame and mannitol are used as sweetener. 100% of the oral solid formulations collected in Table A4 carry at least one excipient of these: 40% of formulations carry mannitol and aspartame; 20% carry the 3 excipients; 20% sucrose and aspartame and the remaining 20% only sucrose.
- Propylene glycol is another excipient commonly used in solid formulations as a solvent, moisturizer and preservative. Caution should be exercised in children under 4 years of age and neonates, as propylene glycols, at high doses, may cause alterations in the Central Nervous System, in addition to other side effects discussed in the previous sections of this paper.
- Microcrystalline cellulose, methylcellulose and ethyl cellulose are one of the most commonly used excipients in solid formulations. They have no major side effects, but in high amounts they can cause a laxative effect.
- Most of the solid formulations collected in Table A2 use flavourings such as grape essence, lemon flavouring, caramel cream aroma or orange essence, in order to achieve a better palatability. The main drawback of their incorporation into paediatric formulations is that they usually have a complex and poorly known composition [49].
- Lanolin is an excipient used in pastes and ointments, which are frequently used in the paediatric population. This excipient may cause skin hypersensitivity reactions, which is why caution should be exercised in patients with known sensitivity issues [50].

Appendix D (Table A3) lists marketed liquid formulations suitable for the paediatric population. Liquid formulations are the most common in paediatrics because of their easy administration. The need for at least one liquid formulation of

any drug indicated in the paediatric population is becoming increasingly noticeable. Not all active principles are soluble or stable in water. Therefore, excipients are used in liquid formulations to improve the solubility of certain active principles and/or increase their stability. The problem is that most excipients found in adult formulations should not be used in paediatrics. However, as shown in Table A3, there are a wide variety of marketed formulations indicated in paediatrics that contain these non-recommended excipients:

- Ethanol, sorbitol and propylene glycol, despite being contraindicated in paediatrics, especially ethanol, are still included in some paediatric formulations.
- The addition of non-recommended sweeteners, such as sucrose, sucralose or sodium saccharine, is also seen in these paediatric formulations.
- The addition of preservatives in paediatric formulations should be avoided as much as possible, and if necessary, in the least amount. Parabens are among the safest preservatives in paediatrics, yet others that are not recommended are still used (e.g., Table A3: sodium benzoate, benzoic acid and benzyl alcohol). Benzalkonium chloride, despite not being recommended for asthmatic patients, is used for the formulation of most eye drops, nasal drops and otic drops.

Appendix E (Table A4) and Appendix F (Table A5) provide examples of FDA-registered drugs (liquids and solids) and liquid formulations in paediatric use research, respectively. Like the other examples provided, these medicinal products and liquid formulations contain at least one excipient not recommended for the paediatric population, such as propylene glycol, polysorbates, methyl or propyl para hydroxybenzoate, benzyl alcohol, benzoic acid, ethanol or sucralose, among others.

- Excipients not recommended for paediatric population are most commonly used in oral solutions and suspensions (referred to in Tables A6 and Table A5, propylene glycol, benzoic acid, polyethylene glycol, polysorbate 80 and sodium benzoate).
- Like the other examples, there is also frequent use of sweeteners (fructose, sucrose, sucralose, aspartame and sodium saccharine).

- Benzalkonium chloride is one of the most commonly used preservatives in ophthalmic and nasal drops, as shown in Table A4. It is usually a safe excipient, but can cause serious adverse effects, such as bronchoconstriction in asthmatic patients, ototoxicity in otic preparations or respiratory failure in infants who ingest this excipient, this adverse effect being the most severe.

Promising Pharmaceutical Form in the Paediatric Population: ODT and 3D Drug Printing

ODT Tablets

The development of Orally Disintegrating Tablets (ODT) has received greater interest among researchers and the pharmaceutical industry over the past decade. ODT tablets are designed to dissolve quickly upon contact with saliva, in the absence of additional water, compared to traditional tablets [51].

ODT tablets offer several advantages, combining the properties of solid and liquid formulations. They are quickly ingested when inserted into the tongue, eliminating the need to chew the tablet, swallow it intact or take it with water. Currently, they are a widely accepted form of dosing, especially for patients who have difficulty swallowing (paediatric and geriatric), and for the treatment of patients where therapeutic compliance is difficult [51,52].

As a result of the rapid disintegration of ODT tablets, the active substance comes into contact with taste buds, so a key aspect to consider in these formulations is palatability. It is necessary to mask the taste of bitter active ingredients in order to develop successful formulations. In the past, sweeteners and aromas were used as methods of flavour masking in dispersible or rapidly disaggregation tablets. However, these additives were not a sufficient means to completely mask the taste. Currently, with scientific and technological advances, different dosing alternatives are available to mask the taste, such as freeze-

deriding, microencapsulation, fluid bed coating or coating in supercritical fluids [51].

It should be mentioned that there is an innovative tool for pharmaceutical pre-formulation of ODT tablets. This tool makes it possible to predict whether a disintegrating excipient or a mixture of excipient powder + active substance is suitable for obtaining an oral dispersible tablet by direct compression or not: the new model SeDeM-ODT [53].

The SeDeM-ODT model (based on the SeDeM expert system) indicates the ability of a powder to be compressed, providing the Good Compressibility and oral dispersibility Index (IGCB). This index is composed of six main factors which indicate whether a powder mixture has the ability to be compressed by direct compression. Furthermore, it indicates whether the tablets are suitable for formulation as oral dispersible tablets. Thus, the SeDeM-ODT model facilitates the selection of excipients with the appropriate properties to produce ODT tablets using direct compression technologies [53]. Figure 1 will detail several special features and advantages of ODT tablets [52,54].

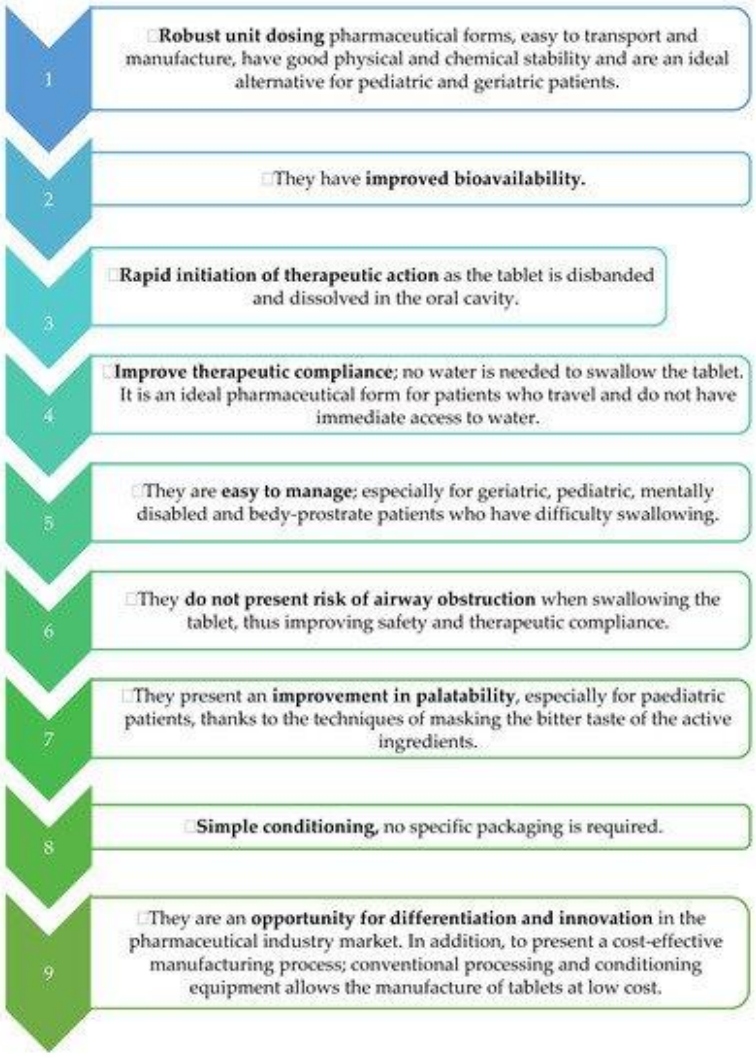

Figure 1: Characteristics and advantages of ODT tablets.

Figure 2 specifies the most noteworthy drawbacks of ODT tablets [54].

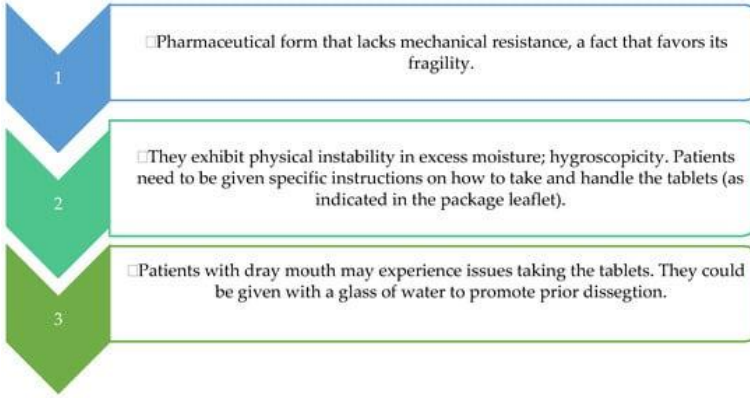

Figure 2: Disadvantages of ODT tablets.

3D Drug Printing

On the other hand, the technical disadvantages associated with the manufacturing process of ODT tablets could be solved by three-dimensional drug printing technology. Generally speaking, this technology is supported by the following processes: a program capable of generating a file is required with the necessary information for printing the drug. This same program (also present on the computer that will control the printer) must be able to read the instructions contained in the generated file and convert it into precise commands for the 3D printer to generate the part [55].

The response to drugs may be different among patients, due to inter-individual variability, caused by both genetic and environmental factors. Accordingly, "patient-specific" or "tailor-made" dosage concepts could be an alternative to mass production in the traditional pharmaceutical industry. In this approach, 3D printing has proven to be a manufacturing technique with great potential, as it allows the creation of three-dimensional objects, layer by layer, with total freedom of form and design. Thus, obtaining customized pharmaceutical forms is one of the main objectives of 3D printing in the pharmaceutical sector [55].

Paediatric patients are one of the population groups with the greatest need for personalized dosing adapted to their requirements (age, weight, pathological status, etc.). However, most 3D printed drugs are solid oral formulations, which are not suitable for this population group. Medicinal gummies developed through 3D printing (tailor-made to the patient) could be a form of oral dosing suitable for paediatric patients, due to their striking appearance and pleasant organoleptic characteristics [55].

New advances in obtaining medicines and medical devices, using 3D printing technology, have generated novel perspectives in the processes of obtaining these products. As seen in the table A6, among the several 3DP techniques, only Fused Deposition Modelling (FDM), Semi-Solid Extrusion (SSE), Binder Jetting (BJ) and Selective Laser Sintering (SLS), have been specifically used to date in the fabrication of drug dosages for paediatric population. FDM is one of the most commonly explored additive manufacturing methods due to the low cost of printers, print quality and ability to use drug-loaded filaments through hot-melt extrusion (HME) [56]. However, only solid dosages can be produced through this technology and often are not suitable for oral administration in kids due to swallowing difficult or the associated risk of choking [55]. A wider-used extrusion-based 3DP technique for children dosing is SSE –where instead of a solid thermoplastic filament, a gel or paste is extruded through the nozzle-, since more appetizing and visually-attractive chewable dosages can be obtained [55–60]. Apart from that, orally disintegrating tablets suitable for children can be manufactured via BJ and SLS. Both methods are powder-based technologies where particle union for the construction of the 3D structure is driven by a focused laser (SLS) [61,62] or by means of spraying a binding solution (BJ) [63,64].

Regardless of the method chosen, the use of 3D printing technology allows the production of small batches of medicines, each with tailored dosages, release characteristics, sizes and shapes may finally leading to the concept of personalized medicines becoming a reality. Nevertheless, further developments are still required to ensure that commercial 3D

printers fit Good Manufacturing Practices (GMP) as well as deeper characterization of the fabrication processes and the materials related (API stability, nonpharmaceutical-grade excipients used...) is needed also to conform to such regulations [56,65].

At present, however, several issues are perceived that will need to be resolved as the perfection and implementation of this technique progresses in order to make it a common process of obtaining medicines and medical devices.

Conclusions

The critical study suggests that excipients are often used at higher concentrations than recommended in international paediatric guidelines, and with inappropriate labelling, increasing the potential risks associated with the various excipients discussed [26].

Indeed, the pharmacokinetic and pharmacodynamic profiles of the child population vary substantially, with paediatric safety profiles related to the age and development of excipients often differing from those of adults [48]. The most toxic excipients in neonates are known to be sodium benzoate, propylene glycol, methyl para hydroxybenzoate, propyl, sodium saccharine, benzyl alcohol, benzalkonium chloride, polysorbate 80 and ethanol [66]. However, these excipients are used in formulations according to the study conducted.

European new-borns receive several potentially harmful pharmaceutical excipients: parabens, polysorbate 80, propylene glycol, benzoates, sodium saccharine, sorbitol, ethanol and benzalkonium chloride. According to the study conducted by Nellis and collaborators [36], there are regional variations in the neonatal administration of these potentially harmful excipients. This suggests the possibility of reducing exposure to parabens, polysorbate 80, propylene glycol and sodium saccharine by replacing it with products without these excipients. However, a joint effort by the regulatory authorities on medicines, in particular the paediatric committees, will be necessary. Current

therapeutic options for the paediatric population justify further toxicokinetic and drug safety studies so that they are tailored to the special needs of the paediatric population.

In general, there is little information regarding excipients in paediatrics. It is of the utmost importance to develop new research related to the safety and toxicity of excipients to reduce the prevalence of adverse effects in paediatric populations. Gallon formulators can formulate safer, more stable and higher quality products. Furthermore, the possible adverse effects of the active ingredients and the excipients used in the paediatric population should be reconsidered—since excipients that are safe in adults—may have potentially toxic effects in children.

Finally, the development of databases such as STEP is relevant and beneficial for the development and use of drugs in paediatrics. Additionally, the SEEN project is relevant both nationally and internationally, as it reveals the current status of excipients and takes into account the frequency and quantity (in terms of medicines given to new-borns and young children).

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Appendix A. Purposes of the STEP Database

More specifically, the purposes of the STEP database are [22] to:

1. Serve as a public base for evidence regarding the safety and toxicity of excipients in order to allow the pharmaceutical industry, academics, pharmacists, physicians and regulators to make informed decisions.
2. Improve prospects of identifying potential security issues in the early stages of the development process when excipients are selected.
3. Help highlight any relationships between exposure and evidence of clinically significant toxicity in the paediatric age group in general, or in paediatric subpopulations.
4. Identify possible differences in expression, types or patterns of toxicity in children compared to adults. Provide a basis for assessing the need to generate new data for paediatric medicines (e.g., bridge studies, juvenile toxicity studies, etc.), in order to clarify what kind of new data, knowledge gaps or studies may be needed.
5. Support companies with their regulatory presentations with easily available information.
6. Support and improve research activities by providing a platform to share unreleased data and available data with corporate entities.

Appendix B

Table A1: Most important characteristics of the excipients discussed in this paper (in alphabetical order).

Excipient	Functions	DAI *	Recommendations	Adverse Effects	References
Aspartame	Artificial Sweetener	40 mg/kg	Contraindicated in patients with phenylketonuria	Neurological involvement: neurotoxicity, epilepsy, headache, panic attack, hallucinations Hypersensitivity reactions: vascular, granulomatous panniculitis Cross reaction with sulfamides	[29,35]
Benzalkonium chloride	Preservative	NA	Caution in asthmatic patients	Bronchoconstriction Ototoxicity Hypersensitivity	[29]
Benzyl alcohol	Preservative	5 mg/kg	Contraindicated in children under 3 years of age by immature their metabolism	In new-borns and children under 3 years of age cause: Metabolic acidosis and respiratory depression Intraventricular haemorrhage Cerebral palsy and developmental delay Hypersensitivity reactions	[29,35,36,39–44]
Ethyl alcohol	Solvent and preservative	6 mg/kg/dose (<6 years)	Paediatric formulations should not exceed the following limits of ethanol: In children over 12 years of age: less than 10% (*v/v*) In children 6–12 years old: less than 5% (*v/v*) In children under 6 years of age: less than 0.5 (*v/v*)	Hypoglycaemia, acidosis and hydroelectrolytic alterations Stupor, coma respiratory and CNS depression, cardiovascular toxicity	[17,26,27,29,31,32]
Glycerol	Solvent, sweetener, viscosizer and preservative	10 g/dose	Caution in paediatric population Do not exceed the safe daily dose (1.0–1.5 g/kg body weight)	Mucositis in the stomach Diarrhoea and electrolyte disturbances	[1,29]
Lactose	Diluent	NA	Caution in patients with lactose intolerance Contraindicated in galactosemia	Symptoms of lactose intolerance: severe abdominal pain, flatulence, bloating or swelling and diarrhoea. Systemic symptoms such as muscle and joint pain and eczema In children it can cause dehydration, bacterial proliferation and metabolic acidosis	[1,28]
Parabens	Preservative	10 mg/kg	It is recommended to avoid its use in neonates	Cross hypersensitivity reactions in patients allergic to acetylsalicylic acid Hyperbilirubinemia in new-borns	[29,35,36]
Phthalates	Coating agents (plasticizers)	NA	Not recommended for use in pregnant women or children under 3 years of age	Anomalies in the development of the foetus: cleft palate and skeletal malformations. May lead to stillbirth	[28]
Polyethylene glycol	Solvent, suspensor and	10 mg/kg	Caution in new-borns and	Nephrotoxicity	[1,28]

	viscosity agent		infants	Gastrointestinal disorders Laxative effect	
Polysorbates	Dispersing, emulgent, surfactants, solubilizing and moisturizing agents	NA	Caution in new-borns	Serious adverse effects: deaths in low-weight neonates who received vitamin E preparations with polysorbates. Polysorbate 80: increased mortality in new-borns	[25,42]
Propyl gallate	Antioxidant	NA	Caution in new-borns	In neonates it can cause dermatitis, skin allergy and methemoglobinemia	[29]
Propylene glycol	Solvent, moisturizing and preservative	Neonates: 1 mg/kg Under 5 years: 50 mg/kg Adults: 500 mg/kg	It is recommended to avoid in children under 4 years of age because of lack of metabolic maturation	CNS depression Laxative effect from high osmolality after oral administration	[29,33,34]
Saccharine	Sweetener	2.5 mg/kg	It is recommended to limit the daily dose in pregnant women and children	Urticaria, itching and eczema Photosensitization GI disturbances: Nausea and diarrhoea	[29,48]
Sorbitol	Sweetener and diluent	Children 0–2 years 5: mg/kg Over 2 years: 140 mg/kg	Contraindicated in patients with fructose intolerance Not recommended for use in patients with hypoglycaemia	Gastrointestinal disorders It can cause hepatic damage with comma and even death	[28–30]
Starch	Diluent and added	NA	Conservation in dry environment Well tolerated by children	In case of moisture, carcinogenic aflatoxins may occur	[29]
Sucralose	Sweetener	15 mg/kg	Caution in patients with metabolic disorders	Alters the composition of the digestive tract microbiome At high temperatures chloropropanol may form May alter glucose, insulin and GLP-1 *[2] levels	[29]
Sucrose	Sweetener	NA	Not recommended for use in children with type I diabetes	Dental damage At very high doses on a daily basis I could be carcinogenic	[29]
Sulphites	Antioxidant	NA	Avoid in asthmatic patients	Hypersensitivity and bronchospasm reactions	[29]
Tartrazine, quinolines, triphenylmethane, xanthines	Colorants	NA	It is recommended not to use them in paediatric formulations	Hypersensitivity reactions in patients' sensitive to tartrazine Azo colorants: cross-sensitivity reactions with acetylsalicylic acid Erythromycin: photosensitization reactions	[28,29]
Thiomersal	Preservative	NA	Avoid use in vaccines as a preservative due to its side effects	Hypersensitivity reactions Autism spectrum disorders	[28,29]

* ADI: Admissible Daily Intake; *[2] GLP-1: Glucagon Like Peptide; NA: Not Available.

Appendix C

Table A2: Examples of solid and semisolid medicines used in Spain for paediatric population: List of excipients and relevant characteristics of FF (Performed consultation of CIMA database, September 2020).

Pharmaceutical Form			Excipients	API	Pharmaceutical Form Characteristics	References
SOLID PREPARATIONS	POWDERS	Example 1: Amoxicillin Normon 250 mg/5 mL EFG Oral Suspension Powder	Saccharose, Glucose, Methyl parahydroxybenzoate (E-218), Propyl parahydroxybenzoate (E-216), Anhydrous sodium citrate, Colloidal silica and Orange essence	Amoxicillin	Powders are administered after prior dissolution. They are little employees in the paediatric population; present the drawback that it is difficult to mask the bad taste. Risk of accidental aspirations. They are usually used in master formulation and for the administration of antacids.	[29,67,68]
		Example 2: Azithromycin Sandoz 200 mg/5 mL EFG Oral Suspension Powder	Sucrose, Xanthan gum (E415), Hydroxypropyl cellulose, Anhydrous trisodium phosphate, Colloidal anhydrous silica (E551), Aspartame (E951), Aroma of caramel cream and Titanium dioxide (E171)	Azithromycin		
	GRANULATED	Example 1: Paediatric Gelocatil 325 mg Granules	Calcium carbonate, Sodium hydrogen carbonate, Citric acid anhydrous, Anhydrous sodium citrate, Aspartame (E-951), Sucrose, Mannitol (E-421), Amorphous silica, Glycerol die-stearate type 1, Croscarmellose sodium, Sodium glycolate starch type A (potato starch) gluten-free, Ethyl cellulose, Hydroxypropyl methylcellulose and Polyethylene glycol 400	Paracetamol	Granules are more stable and fluid than powders. The most used are effervescent granules, which in the presence of water react by releasing carbon dioxide, which protects the stomach and partly anesthetizes taste buds. They should be completely dissolved prior to administration in order to reduce bicarbonate intake. Children are often pleased by their resemblance to certain refreshing drinks.	[29,69]
SOLID PREPARATIONS	ORAL DISPERSIBLE TABLETS (ODT)	Example 1: Apiretal 325 mg oral dispersible tablets	Ethyl cellulose, Microcrystalline cellulose, Crospovidone, Aspartame (E-951), Colloidal silica, Mannitol, Talco, Magnesium stearate and Grape essence	Paracetamol	As advantages of oral dispersible tablets, the following stand out: They combine the advantages of liquid forms and solid oral forms. An exact dose may be given compared to liquids. They have a pleasant taste, thus facilitating therapeutic compliance in the paediatric population. No need to swallow the tablet or drink water; dissolves rapidly in saliva, being an appropriate choice for patients with swallowing problems, such as children or geriatric patients. They are safe and effective and can be bio-equivalent with respect to conventional tablets. They have rapid absorption and, therefore, a rapid introduction of the therapeutic effect. Disadvantages include: The lack of mechanical resistance presented by traditional tablets. The possibility of physical instability in excess moisture. ODTs require special conditioning to ensure their stability.	[54,70,71]
		Example 2: Junifen 200 mg lemon-flavored oral dispersible tablets	Ethyl cellulose, Precipitated silicon dioxide, Hypromellose, Mannitol, Aspartame (E-951), Croscarmellose sodium, Magnesium stearate and Lemon flavouring	Ibuprofen		

SOLID PREPARATIONS	SUPPOSITORIES	Example 1: Febectal Infants 150 mg Suppositories	Colloidal anhydrous silica, Solid semi-synthetic glycerides	Paracetamol	As advantages, the following stand out: Generally, they avoid gastric intolerance problems. They are of interest when the medicine is inactive orally, the patient is unconscious or are children who refuse to swallow the medication. They avoid inactivation by the effect of first liver step. Disadvantages include: Reproducible behaviour can only be obtained if absorbed into an area two centimetres from the end of the rectum. Absorption of the active substance may be erratic. As it avoids the effect of first liver step, it can increase the possibility of poisoning. In certain cultures, it is a form that is not well accepted socially.	[29,72]
SEMI-SOLID PREPARATIONS	GELS	Example 1: Fenistil 1 mg/g Gel	Benzalkonium chloride, Disodium edetate, Carbomer, Sodium hydroxide, Propylene glycol amd Purified water	Dimethindene maleate	It is a semi-soft transparent colloid, with a large proportion of liquids. Low penetration power. Many incompatibilities with active substances. It is easy to apply, pleasant and soothing for its refreshing properties.	[29,73]
SEMI-SOLID PREPARATIONS	CREAMS	Example 1: Perme-Cure 5% Cream	Butylhydroxytoluene (E-321), Castor Oil, Deionized water, Steareth-2, Ceteareth-2-Phosphate, Sosa to the 20 %, Vitamin E acetate, Phenonip, Citric acid, Disodium edetate and Scent	Permethrin cis:trans (25:75)	As advantages, the following stand out: Comfortable and easy application. Provide a controlled release of the active substance. They act as emollients and moisturizers, due to their composition	[74]
	OINTMENTS	Example 1: Oftacilox 3 mg/g Ophthalmic Ointment	Liquid paraffin and White Vaseline	Ciprofloxacin	Ointments are forms of external use intended to be administered by gentle friction on a surface of the body, to achieve a local action or with the aim of penetrating the drug through it. In many cases, the topical route is a route of absorption comparable to oral or other, so the dosage and duration of treatment must be very well specified. New-borns and infants have a very increased skin-to-weight ratio. Coupled with the fact that at this age the skin is very permeable, it makes them especially vulnerable to toxic frames by ointments.	[29, 75]
	PASTES	Example 1: Anti-congestive Cusi (Paste Lassar)	Lanolin (wool fat), Liquid Vaseline and Stringy Vaseline	Zinc oxide Corn starch	This is a suspended ointment. They are used when you want to locate the action of the active substance to a specific area, as they are irritating and staining.	[29, 76]

SEMI-SOLID PREPARATIONS	NON-CREAM EMULSIONS	Example 1: Lactisona 10 mg/mL Skin Emulsion	Carbomer 940, 1,3-dimethylol-5,5-dimethyl hydantoin, Dihydro-acetic acid, Pyrrolidone sodium carboxylate, Lactic acid, Sodium hydroxide, Stearyl alcohol, Glycerol stearate, Cetyl alcohol, Isopropyl palmitate, Mineral oil, Myristyl lactate, Fragrance and Water	Hydrocortisone	Emulsions are a dispersed system, stabilized by the addition of an adequate emulsifier, two immiscible phases, where both the internal and external phases are liquid. The emulsions enable fat-soluble and water-soluble active ingredients to come into contact with the skin simultaneously, encompassing each of them in the phase of the emulsion for which they have the greatest affinity. Patients or users of topical application preparations often prefer emulsion vehicles to those of any kind.	[50, 77]

Appendix D

Table A3: Examples of liquid medicines used in paediatrics: List of excipients and relevant characteristics of Pharmaceutical Form.

Pharmaceutical Form			**Excipients**	**API**	**Pharmaceutical Form Characteristics**	**References**
LIQUID PREPARATIONS	ORAL SOLUTIONS	Example 1: Diazepam 2mg/5mL Solution without sugar	Sodium Docusate, Aluminium silicate and Magnesium, Propylene glycol, Raspberry Flavour, Sodium Saccharine, Precool Erythrosine (E127), Sorbic Acid (E200), Propyl para hydroxybenzoate, Methyl para hydroxybenzoate, Sorbitol, Liquid (Non-Crystalized) (E420) and Glycerol (E422)	Diazepam	As advantages, the following stand out: Release of the active substance(s) much faster than in solid forms. The dosages are correctly expressed in milligrams, micrograms and U/mL, allowing them to be adapted to the child's weight. Easy and comfortable dosing, as it is in volume (spoons, drops, etc.) Less irritation effect if it is an aggressive medicine, at the gastric level, as it is dampened by dilution. Solutions, suspensions or emulsions are obtained, depending on the size of the particles of the internal phase. As disadvantages they present:	[29,49,78–80]
		Example 2: Paracetamol Level 100 mg/mL Oral Solution	Citric acid, Sodium hydroxide, Sucrose, Propylene glycol, Macrogol, Strawberry Essence, Cochineal Red A (Ponceau 4R) (E-124), Hydrochloric Acid 5 N and Purified Water	Paracetamol		
		Example 3: Diazepam Intensol™ Oral Solution 5 mg/mL * *Do not use in children under 6 months of age*	Alcohol, Yellow D&C 10, Polyethylene glycol, Succinic Acid and Water	Diazepam	Greater ease and possibility of contamination than solid pharmaceutical forms, which forces the addition of preservatives.	[81,82]
		Example 4: Prednisolone 10mg/mL Oral Solution	Sodium Methyl para hydroxybenzoate, Sodium Propyl para hydroxybenzoate, Glycerol, Sodium Saccharine, Sodium Edetate, Sodium Aqueous solutions of	Prednisolone		

			medicinal substances that areDihydrate, Orange flavour (contains propylene glycol), Sodium hydroxide and Purified Water			
LIQUID PREPARATIONS	ORAL SOLUTIONS	Example 5: Ozalin	Citric acid monohydrate, Gamma-cyclodextrin, Sucralose, Orange flavour (contains 70–80% ethanol), Sodium hydroxide, injectable water	Midazolam	*See "Pharmaceutical Form Characteristics (Oral Solutions)" section of the previous page*	[83–85]
		Example 6: Flumil 20 mg/mL Oral Solution	Para-Hydroxybenzoate Methyl (E218), Sodium Benzoate (E211), Sodium Edetate, Carmellose Sodium, Sodium saccharine, Sodium Cyclamate, Sucralose, Raspberry Aroma, Sodium Hydroxide and Purified Water	Acetyl cysteine		
		Example 7: Paediatric Lanacordin 0.05 mg/mL * *Including newborns and premature*	Sucrose, Ethanol, Tartrazine (E-102), Anhydrous Sodium Phosphate, Citric Acid (E-330), Methyl Hydroxybenzoate, Lime Essential Oil, Propylene glycol (E-1520) and Purified Water	Digoxin		
LIQUID PREPARATIONS	ORAL SUSPENSIONS	Example 1: Paracetamol 120 mg/5 mL Oral Suspension	Propylene glycol, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Xanthan Gum, 70% Sorbitol Solution, Sucrose, Mango flavour and Purified Water	Paracetamol	As **advantages**, the following stand out: Suspensions are the ideal pharmaceutical forms for the administration of non-water-soluble active ingredients. The fact that the active substance is insoluble, allows an extension of the time of action in the body. It is easier to mask the taste than in syrups and elixirs (more pleasant for children). Good relative bioavailability.	[86,87]
		Example 2: Junior Parapaed 120 mg/5 mL Oral Suspension	Ethanol, Polysorbate 80, Glycerol, Magnesium and Aluminium silicate, Liquid maltitol syrup, Sodium saccharine (E954), xanthan gum, cherry flavour, sodium benzoate, Citric acid monohydrate and purified water	Paracetamol		
LIQUID PREPARATIONS	ORAL SUSPENSIONS	Example 3: Mycostatin 100.000 UI/mL Oral Suspension	Sucrose, 96% ethanol, Carmellose sodium, Cinnamic aldehyde, Mint Essence, Cherry Aroma, Anhydrous Disodium Hydrogen phosphate, Glycerol (E-422), Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, Sodium Hydroxide, Hydrochloric Acid and Purified Water	Nystatin	Disadvantages include: Sediment formation. Difficulty removing the viscosity of the vehicle. Less stability than solid shapes, solutions and emulsions. The use of very fine particle size causes the formation of sediments that are very difficult to re-suspend. *It is important to shake the suspension for at least 10 s before use.*	[88,89]
		Example 4: Paediatric Algidrin 20 mg/mL Oral Suspension * *Do not give to children under 3 months of age*	Microcrystalline cellulose, Carboxymethylcellulose sodium, Sorbitol (E-420), Maltitol (E-965), Beta-cyclodextrin, Sodium Saccharine, Sucralose (E-955), Forest Fruit Aroma, Allura AC Red Colouring (E-129), Methyl para hydroxybenzoate, Ethyl para hydroxybenzoate, Propyl para hydroxybenzoate and Purified Water	Ibuprofen (Lysine)		
LIQUID PREPARA-TIONS	ORAL SUSPEN-SIONS	Example 5: Paediatric Septrin 8 mg/40 mg/mL	Sorbitol, Glycerol (E-422), Dispersible Cellulose, Carmellose Sodium, Polysorbate	Trimetho-prim	*See "Pharmaceutical Form Characteristics (Oral*	[90]

		Oral Suspension ** Suitable for infants from 6 weeks of age*	80, Methyl para hydroxybenzoate, Sodium Benzoate, Sodium Saccharine, Banana flavour (Propylene Glycol E-1520, Sodium Citrates E-331), Ethanol 96°, Vanilla flavour (Benzyl Alcohol, Caramel Colour E-150d, Propylene Glycol E-1520, Glycerol E-422, Water), Purified Water.	Sulfametho-xazole	*Suspension)" section of the previous page*	
LIQUID PREPARATIONS	ELIXIRS	Example 1: Paracetamol Elixir Pediátrico 120 mg/5 mL	Ethanol 96° (10% *v*/*v*), Propylene glycol, Inverted Syrup, Amaranth Solution (E123), Glycerol, Glycerine, Chloroform and Concentrated Raspberry Juice	Paracetamol	Hydro alcoholic solution sweetened with low sugar. It has high alcohol content, which will have to be considered at certain ages, as it can create addition or generate other side effects: drowsiness and various dangers arising.	[29,91,92]
		Example 2: Lanoxin Elixir ** Fit for premature neonates*	Methyl Hydroxybenzoate, Sucrose, Sodium Phosphate Anhydrous, Citric Acid Monohydrate, Quinine Yellow, Ethanol (96%), Propylene Glycol, Lime flavour and Purified Water	Digoxin		
	SYRUPS	Example 1: Daleron Syrup 120 mg/5 mL	Sorbitol, Glycerol, Xanthan Gum, Maltitol, Microcrystalline Cellulose, Croscarmellose Sodium, Sodium Benzoate, Citric Acid, Pineapple flavour, Riboflavin and Purified Water	Paracetamol	Syrups are liquid solutions with sweetening, flavouring and viscosizing properties. They are almost saturated aqueous solutions of sucrose (64%). They have the following drawbacks: Alterations that require the incorporation of preservatives and specify	[29,93,94]
		Example 2: Loratadine 5 mg/mL Syrup Oral Solution	Propylene glycol, Glycerol, Sodium Benzoate, Citric Acid Monohydrate, Sucrose, Peach flavour and Purified Water	Loratadine		
LIQUID PREPARA-TIONS	SYRUPS	Example 3: Polaramine 0.4 mg/mL Syrup ** Not suitable for children under 2 years old*	Ethanol, Sucrose, Sodium Citrate, Sodium Chloride, Sorbitol, Methyl paraben, Propyl paraben, Menthol, Apricot flavour, Orange flavour, Ponceau 4R Colouring (E-124) and Purified Water	Dexchlorpheni-ramine maleate	*See "Pharmaceutical Form Characteristics (Syrups)" section of the previous page*	[95,96]
		Example 4: Paediatric Mucosan 3 mg/mL Syrup	Hydroxyethyl cellulose, Sucralose, Benzoic Acid (E-210), Wild Berry Aroma, Vanilla Aroma and Purified Water	Ambroxol hydrochloride		
LIQUID PREPARATIONS	ORAL DROPS IN SOLUTION	Example 1: Romillary 15 mg/mL Oral drops in Solution ** Not recommended for use in children under 2 years of age*	Propylene glycol, anhydrous ethanol, Flavourings: coriander oil, orange essential oil and lemon tetraroma, macrogol glycerol ricinolate (chromophore EL), Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, sodium saccharine, citric acid monohydrate, sodium hydroxide and purified water	Hydrobromide dextromethorphan	Oral liquid medicinal products may be placed on the market in the form of drops for children of different ages. The main benefits of drops are low dosing volume, facilitating swallowing and dosing flexibility. As disadvantages, the following stand out: the variation of the droplet size and errors in the count, which would result in an incorrect dosage. This can cause serious problems in those medicines with a narrow therapeutic margin.	[97–100]
		Example 2: Alerlisin 10 mg/mL Oral Drops in Solution ** Do not use in children under 2 years of age*	Glycerol, Propylene glycol (E-1520), Sodium Saccharine, Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, Sodium Acetate, Glacial Acetic Acid and Purified Water	Cetirizine hydrochloride		

LIQUID PREPARA-TIONS	ORAL DROPS IN SOLUTION	Example 3: Paediatric Cleboril 62.5 g Oral Drops in Solution	Benzoic acid (E-210), Sodium hydroxide and purified water	Clebopride malate	*See "Pharmaceutical Form Characteristics (Oral Drops in Solution)" section of the previous page*	[101–103]
		Example 4: Fluor Lacer 1.4 mg/mL Oral Drops * *Indicated for tooth decay prophylaxis in children 1-6 years old*	Sodium Saccharine, Propylene glycol, Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, Disodium edetate, Cochineal Red Colouring (E-124), Strawberry Aroma and Purified Water	Sodium Fluoride		
		Example 5: Hydropolivit Oral Drops in Solution * *Recommended for children over 2 years old*	Propylene glycol, Polysorbate 80, Sorbitol 70% (E-420), Glycerol (E-422), Sodium Saccharine, Sodium Edetate, Monothioglycerol, Methyl para hydroxybenzoate, Butylhydroxyanisole (E-320), Banana Essence, Vanilla Essence, Sodium Hydroxide and Purified Water	-Retinol palmitate Cholecalciferol Alpha-tocopherol acetate Riboflavin Pyridoxine hydrochloride Ascorbic acid Biotin Nicotinamide		
LIQUID PREPARATIONS	ORAL DROPS IN SUSPENSION	Example 1: Zamene 22.75 mg/mL Oral Drops in Suspension * *Special interest in paediatrics.* *Not recommended in children under 2 months of age.*	Aluminium and Magnesium silicate, Carboxymethylcellulose sodium, Benzyl alcohol, 70% Sorbitol, Polysorbate 80, Acetic Acid and Purified Water	Deflazacort	They have the same characteristics as oral drops in solution	[104,105]
		Example 2: Dezacor 22.75 mg/mL Oral Drops in Suspension * *Special interest in paediatrics.* *Not recommended in children under 2 months of age.*	Sorbitol solution 70%, Carboxymethylcellulose sodium, Aluminium silicate and magnesium, Polysorbate 80, Benzyl Alcohol, Sucralose, Tropical Fruit Aroma, Citric Acid Monohydrate, Sodium Hydroxide and Purified Water	Deflazacort		
	OPHTHALMIC DROPS OR COLLYRIUMS	Example 1: Atropine BP 1.0% (*w*/*v*)/Vistatropin 1.0% (*w*/*v*) Eye drops in solution	Benzalkonium chloride in solution and purified water	Atropine sulphate	Sterile solutions aimed at exercising their action in the conjunctiva. May cause systemic side effects, especially observed after instillation of mydriatic eye drops.	[29,78,106, 107]
		Example 2: Chibroxin 3 mg/mL Collyrium in solution	Sodium Acetate, Benzalkonium Chloride, Disodium Edetate, Concentrated Hydrochloric Acid, Sodium Chloride and Water for Injections	Norfloxacin		

LIQUID PREPARATIONS	NASAL DROPS	Example 1: Rhinovin® Children's 0.5 mg/mL Nasal Drops in Solution * *Do not use in children under 6 years of age*	Dihydrogen phosphate of sodium dihydrate, disodium phosphate dodecahydrate, disodium Edetate, Benzalkonium Chloride, Sorbitol (E420), Hypromellose, Sodium Chloride and Purified Water	Xylometazoline hydrochloride	Aqueous solutions of medicinal substances that are instilled through the nose and act on the nasal mucosa. Oils are contraindicated in their formulation, because the ciliary function has to be maintained. It can be an excellent route of systemic administration, in addition to use as a topical route (there are promising studies with insulin and other substances).	[29,78,108, 109]
		Example 2: Utabon Children 0.25 mg/mL Nasal Drops in Solution * *Do not use in children under 6 years of age*	Benzalkonium chloride, anhydrous disodium hydrogen phosphate, Sodium dihydrogen phosphate dihydrate, glycine (E-640), Sorbitol (E-420) and Purified water	Oxymetazoline hydrochloride		
	OTIC DROPS	Example 1: Otic cetraxal 3 mg/mL Otic drops en Solución * *Indicated in adults and child*	Lactic acid, Povidone, Anhydrous Glucose, Propylene glycol, Methyl para hydroxybenzoate, Propyl para hydroxybenzoate, Hydrochloric Acid and Purified Water	Ciprofloxacin	Liquid preparations to apply to the middle and outer ear. The active substances are usually antiseptics, local anaesthetics and antibiotics. Excipients have to be suitable to achieve a pH of 5–6.	[29,110,111]
		Example 2: Otix Otic Drops in Solution * *Do not administer in children under 2 years of age*	Benzalkonium Chloride, Sulphuric acid, Sodium Chloride, Sodium Hydroxide, Tribasic Sodium Citrate, Polysorbate 80, Citric Acid and Purified Water	Dexamethasone sodium phosphate Trimethoprim Polymyxin B sulphate		
LIQUID PREPARATIONS	OTIC DROPS	Example 3: Ciproxin Simple 3 mg/mL Otic Drops in Solution * Not recommended for children under 1 year old	Benzalkonium Chloride, Sodium Acetate Trihydrate, Glacial Acetic Acid, Mannitol (E-421), Disodium Edetate, Hydrochloric Acid and/or Sodium Hydroxide and Purified Water	Ciprofloxacin hydrochloride	*See "Pharmaceutical Form Characteristics (Otic Drops)" section of the previous page*	[112]
PARENTERAL PREPARATIONS FOR INJECTION	INTRAVENOUS	Example 1: Digoxin Kern Pharma 0.25 mg/mL solution for injection * including premature neonates	Ethanol, Propylene Glycol, Citric Acid Anhydrous, Bi-sodium Anhydrous Phosphate and Bi-distillate Water.	Digoxin	The intravenous line is the one of choice in new-borns and in emergencies. It achieves a quick effect and are easy to dos. Risk of infection and can be painful at times and cause difficult-to-resolve injuries.	[29,113]

Appendix E

Table A4: Examples of FDA-registered drugs used in paediatrics (FDA and DAILYMED database consultation October 2020).

Pharmaceutical Form			Excipients	Active Principle	Age	References
LIQUID PREPARATIONS	ORAL SOLUTIONS	Abilify Solution Oral	Disodium edetate, fructose (200 mg per mL), glycerine, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose (400 mg per mL), and purified water. The Oral solution is flavoured with natural orange cream and other natural flavours	Aripiprazole	6 to 18 years	[114]
		Demerol Solution Oral	Benzoic acid, flavour, liquid glucose, purified water, saccharin sodium	Meperidine hydrochloride	Adult and paediatric patients	[115]
		Diazepam Oral Solution (Lannett Company)	Polyethylene glycol, propylene glycol, non-crystallizing sorbitol solution, sodium citrate anhydrous, bitterness modifier flavour, anhydrous citric acid, peppermint flavour, mint flavour, FD&C Network No. 40 aluminium lake, D&C Yellow No. 10 aluminium lake and purified water	Diazepam (5 mg/5 mL)	Children from 6 months	[116]
	ORAL SUSPENSIONS	Adzenys ER (Extend release)	Purified water, sorbitol, propylene glycol, xanthan gum, natural orange flavour, methacrylic acid and methyl methacrylate copolymer, sodium polystyrene sulfonate, vegetable oil, triethyl citrate, methylparaben, citric acid, sucralose, propylparaben, orange colour (FD&C Yellow No. 6), and polyethylene glycol	Amphetamine	6 to 17 years	[117]
		Children's Tylenol® Cold + Cough + Sore Throat Oral Suspension	Anhydrous citric acid, D&C network No. 33, FD&C network No. 40, flavours, glycerine, microcrystalline cellulose and sodium carboxymethyl cellulose, purified water, sodium benzoate, sorbitol solution, sucralose, xanthan gum	Acetaminophen 160 mg Dextromethorphan hydrobromide 5 mg	4 to 11 years	[118]
	ORAL SUSPENSIONS	Dyanavel XR (Extend release)	Anhydrous citric acid, bubble-gum flavour, glycerine, methylparaben, modified food starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulphate, sodium polystyrene sulfonate, sucralose, triacetin and xanthan gum	Amphetamine	Children from 6 years	[119]
	SYRUPS	Midazolam hydrochloride syrup	Anhydrous Citric Acid, D&C Network No. 33, edetate disodium, glycerine, sodium benzoate, sorbitol, Water, Hydrochloric Acid, Sodium Citrate	Midazolam hydrochloride	Children from 6 months	[120]
LIQUID PREPARATIONS	OTIC DROPS	Ciprofloxacin and dexamethasone suspension/drops	Benzalkonium chloride, boric acid, edetate disodium, acetic acid, sodium acetate, sodium chloride, sodium hydroxide, tyloxapol, water, hydrochloric acid, hydroxyethyl cellulose (3000 cps at 1%)	Ciprofloxacin hydrochloride Dexamethasone	Children from 6 months	[121]
	OPHTHALMIC DROPS OR COLLYRIUMS	ALLERGY EYE DROPS- ketotifen fumarate solution/ drops	Benzalkonium chloride 0.01%, glycerine, purified water. may contain hydrochloric acid and/or sodium hydroxide (to adjust PH).	Ketotifen (0.025 %) (equivalent to ketotifen fumarate 0.035 %)	Children from 3 years. Children under 3 years of age: consult to doctor	[122]
	NASAL	LITTLE	Benzalkonium chloride, glycerine, polyethylene glycol,	Phenylephrine	Children	[123]

	DROPS	REMEDIES DECONGESTANT NASAL DROPS phenylephrine hydrochloride liquid	potassium phosphate monobasic, purified water, Sodium EDTA, sodium phosphate dibasic	hydrochloride 1.25 mg/ml		
	ORAL DROPS	BIO-G-TUSS PAEDIATRIC DROPS (solution)	Citric acid, grape flavour, glycerine, methylparaben, polyethylene glycol, propylparaben, purified water, Sodium citrate, sucralose	Dextromethorphan HBr (7.5 mg/mL) Guaifenesin (88 mg/mL) Phenylephrine HCl (2.5 mg/mL)	Children	[124]
SOLID PREPARATIONS	CHEWABLE TABLET	Children's Motrin—Ibuprofen Tablet, Chewable	Acesulfame potassium, ammonium glycyrrhizin, aspartame, carnauba wax, croscarmellose sodium, hypromellose, magnesium stearate, mannitol, natural and artificial flavours, silicon dioxide, sodium lauryl sulphate, soybean oil, succinic acid	Ibuprofen 100 mg	2 to 11 years	[125]
		Acetaminophen Children's	Citric acid, crospovidone, D&C network No. 27 aluminium lake, D&C network No. 30 aluminium lake, dextrates hydrated, ethyl cellulose, flavours, magnesium stearate, mannitol, polyethylene, stearic acid, sucralose	Acetaminophen 80 mg	2 to 6 years	[126]
	TABLETS	Diazepam Tablet	Anhydrous lactose, magnesium stearate, cellulose microcrystalline, FD&C blue n. 1	Diazepam 10 mg	Children from 6 months	[127]
	TABLETS	Dexamethasone 1.5 mg tablet	Lactose monohydrate, magnesium stearate, maltodextrin, corn starch, sucrose	Dexamethasone 1.5 mg	It depends on the pathology	[128]

Appendix F

Table A5: Liquid formulations for paediatric use in Research Articles.

Formula	Pharmaceutical Form	Excipients	Active Principle (Dose)	Age	Stability (Stability in Use)	References
Organic solvent-based formulation of lorazepam (Oral Solution)	Oral solution	PEG 400 (10% *v/v*), Propylene glycol (3% *m/v*), Glycerol (87% *v/v*) and Orange essence (0.1%)	Lorazepam (1mg/mL)	Children 1 month to 12 years old	12 months at 4 °C (Stability in use: 4 weeks)	[129]
Oral solution of amlodipine besylate for children	Oral solution	Sucrose jarabe (32% *m/v*), Methylparaben (solution 15% *m/v*) (0.3% *m/v*) and Purified water (75%)	Amlodipine Besylate (0.5 mg/mL)	Paediatric Population (children and teenagers)	12 months at 4 °C (Stability in use: 18 weeks)	[130]
Oral tizanidine hydrochloride, Formulation for hospital use	Oral solution	CMC (carboxymethyl cellulose) (0.5%), Potassic sorbate (0.15%), Sucralose (0.10%), Citric acid and Purified water	Tizanidine Hydrochloride (1 g/mL)	Paediatric Population	70 days at 15–30 °C, 2–8 °C and 40 °C	[131]
Paediatric oral formulation of clonidine hydrochloride	Oral solution	Sucrose syrup (20% *v/v*), Raspberry essence (0.05%), Methyl paraben solution 15% (1% *m/v*), Citric acid monohydrate (1% *m/v*), Disodium hydrogen phosphate (1.8% *m/v*) and Purified water	Clonidine HCL (50 µg/mL)	Paediatric Population	9 months at room temperature, protected from light	[132]
Oral liquid formulation of clonidine hydrochloride for paediatric patients	Oral solution	Potassic sorbate, Sucrose and Monohydrate citric acid	Clonidine hydrochloride (20 µg/mL)	Paediatric Patients (all ages)	90 days at 5 °C (cooling) (Stability in use: 42 days at 5 °C)	[133]
Paediatric oral formulations	Oral solution	Vehicle Mascagni (% *w/v*): Sucralose (0.02%),	Sodium dichloroacetate	Paediatric	3 months at 4 °C and 25	[134]

of sodium dichloroacetate		Hydroxyethyl cellulose (0.2%), Citric acid (0.09%), Sodium citrate (0.09%) and Potassium sorbate (0.18%)	(DCA) (9.5% *w/v*)	Patients	°C (Stability in use: 1 month to 4 °C)	
Furosemide solutions for personalized paediatric administration	Oral solution (extemporaneous)	Solution I: Buffer carbonate-bicarbonate (pH) (10 mL) Excipient for syrup (cps 100 mL) (ACOFARMA): sucrose, water, sorbitol, glycerine, aroma, citric acid, methyl paraben, potassium sorbate, sodium phosphate and colorant. Solution II: Buffer carbonate-bicarbonate (pH) (10 mL) -Excipient for syrup—without sugars (cps 100 mL) (ACOFARMA): sodium saccharine, xanthan gum, water, sorbitol, glycerine, aroma, citric acid, sodium citrate, methyl paraben, propyl paraben, potassium sorbate, sodium phosphate and colorant.	Furosemide (2 mg/mL)	Paediatrics	60 days at 4 and 25 °C	[135]
Formulation comprising acetaminophen, especially for paediatrics (PATENT)	Oral solution (nano-emulsion)	NF glyceryl mono linoleate (5–30%, preferably 8-26% *w/v*), PEG-35 castor oil (30–60%, preferably 39–46% *w/v*), NF diethylene glycol mono ethyl ether (20–45%, preferably 24–40% *w/v*) and Water	Paracetamol (5–18% *w/v*)	Paediatrics	NA	[136]
Paediatric formulations of ursodeoxycholic acid from oral administration	Oral suspension	Glycerol (20%), Methyl cellulose 1000 (1% *v/v*) and Purified water	Ursodeoxycholic acid (UDCA) (1.5 mg/mL)	Paediatric Population	30 days at 25 °C or in fridge	[137]
Oral paediatric formulation of hydrochlorothiazide	Oral suspension	Glycerol (20%), Methyl cellulose 1000 (1% *v/v*), Citric acid (pH corrector) and Water	Hydrochlorothiazide (2 mg/mL)	Paediatric Population in general	3 weeks at 5 °C and protected from light	[138]
Oral suspension of clindamycin HCL with ion exchange resin for paediatric use	Oral suspension	Glycerine (30% *w/v*), Sucralose (3%), Aroma of maple syrup (7%), Grape aroma (10%), Cremophor RH 40 (15%), Xanthan gum (0.2%) and Deionized water (cps 5 mL)	Clindamycin HCL resin (Amberlite IRP 69) (5.5% *w/v*)	Paediatric Population	1 month at 25 °C	[139,140]
Isoniazid suspension formulated with cationic resin for paediatric use	Oral suspension	Sorbitol solution 70% USP (4.9 mL/ 5 mL), USP monohydrate citric acid (50 mg/5 mL) and USP potassic sorbate (5 mg/5 mL)	Isoniazid resin/Kyron T-134 100 mg/5 mL/200 mg/5 mL	Paediatric Population	3 months at 40 °C (accelerated stability study)	[141]
Omeprazole nano-particles suspension	Oral suspension (nanoparticles)	Eudragit® RS100, Eudragit® L100-55, acetone, peanut oil, polysorbate 80, sodium bicarbonate	Omeprazole	Paediatric Population	NA	[142]
Omeprazole oily suspension	Oral suspension	Sesame oil (37.5 %), Compritol® 888 ATO (1.54 %), Soy lecithin (4 %), Calcium carbonate (14.5 %), Aspartame (0.1 %), Labrafac® (42 %), Vanilla flavour (0.11 %), Caramel flavour (0,05 %)	Omeprazole (2 mg/mL)	Paediatric Population	28 days at 4 ºC (the formulation packed in topaz coloured glass bottles to isolate light)	[143]
Glibenclamide oral liquid paediatric formulations for the treatment of permanent neonatal diabetes mellitus	Oral suspension	CMC sodium (0.80 %), glycerin (5 %), sorbitol 70% solution (25 %), sodium saccharine (0.20 %), anhydrous citric acid (0.10 %), propylene glycol (0.60 %), methylparaben (0.13 %), propylparaben (0.01 %) and distilled water as solvent (q.s.)	Glibenclamide (2.5 mg/mL)	Paediatric Population	90 days at ≤ 40 °C.	[144]
Omeprazole-based delayed-release liquid oral dosage form	Syrup	Kollidon® 30 (10 % w/w), Sorbitol (60 % w/w), Disodium hydrogen phosphate dihydrate, Avicel RC-591 (2 % w/w), water	Omeprazole (20 mg/100 mL)	Paediatric Population	10 days at 25 ºC/50 %	[145]

Paediatric xylometazoline nasal spray formulation	Nasal Spray	Sodium colatum (105 mg/10 mL), PEG 400 (1.35 mL/10 mL), Sodium carboxy methyl cellulose (10 mg/10 mL), Glycerine (0.15 mL/10 mL), Methyl paraben (3.3 mg/10 mL), Sodium chloride and Purified water (cps 10 mL)	Xylometazoline HCl (5 mg/10 mL)	Paediatric Population	12 months at 25 °C	[146]

Appendix G

Table A6: 3D printing formulations for paediatric use in Research Articles.

3D Printing Technology	Pharmaceutical Form	Excipients	Active Principle (Dose)	Pharmaceutical form characteristics	References
Binder Jetting	ORALLY DISINTEGRATING TABLETS	Microcrystalline cellulose, mannitol, aerosil 200 (colloidal silicone dioxide), polyvinylpyrrolidone, glycerine, polysorbate 20, sucralose	Levetiracetam	Colourful cartoon paediatric preparations with high accuracy and reproducibility.	[73]
	ORALLY DISINTEGRATING TABLETS	Hydroxypropyl cellulose, polyoxyethylene, microcrystalline cellulose, lactose, polyvinylpyrrolidone, sodium croscarmellose	Theophylline, metoprolol	Disk-shaped tablets with drug doses digitally regulated.	[74]
Fused Deposition Modelling (FDM)	SUPPOSITORY	Polyvinyl alcohol, Glyceryl distearate, polyethylene glycol	Ibuprofen, domperidone,	3D printed PVA-based suppository shells incorporating a pharmaceutical ionic liquid for personalized therapy.	[147]
	CHEWABLE SOLID TABLETS	Polyethylene glycol, Hypromellose acetate succinate	Indomethacin	Palatable paediatric dosage forms with Starmix® designs, high reproducibility, and content uniformity.	[148]
	TABLETS	Polyvinyl alcohol, sorbitol	Baclofen	Customized oval minitablets for paediatric population.	[149]
Selective Laser Sintering (SLS)	ORALLY DISINTEGRATING TABLETS	Vinylpyrrolidone-vinyl acetate copolymer (Kollidon®), mannitol	Ondansetron	Disk-shaped tablets with improved taste masking.	[71]
	ORALLY DISINTEGRATING TABLETS	Polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat®), ethyl cellulose	Paracetamol, ibuprofen	Minitablets with high flexibility and control over the drug content and release properties.	[72]
Semi-solid Extrusion (SSE)	SUPPOSITORY	Coconut oil, Lauroyl Macrogol-32 glycerides (Gelucire® 44/14, Gelucire® 44/16)	Tacrolimus	Self-supported lipid-based suppositories with different sizes without the need for moulds.	[150]
	ORALLY DISINTEGRATING TABLETS	Polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat®)	Levetiracetam	Disk-shaped tablets with drug doses digitally regulated.	[151]
	ORALLY DISINTEGRATING FILM	Hydroxypropyl cellulose, propylene glycol	Warfarin	Films imprinted with a QR code containing information about the dosage form.	[152]
	CHEWABLE SOLID TABLETS	Bitter chocolate, corn syrup	Paracetamol, ibuprofen	Dosage form with customized shapes for the administration hydrophilic and lipophilic active compounds.	[67]
Semi-solid Extrusion (SSE)	CHEWABLE GEL TABLETS	Sucrose, pectin, maltodextrin	Isoleucine	Chewable preparations for maple syrup urine disease (MSUD) treatment. First-time preparation and administration in a clinical setting.	[68]
	CHEWABLE GEL TABLETS	Gelatine, locust bean gum, glycerol	Paracetamol, ibuprofen	Drug-loaded ink directly extruded in Lego™-like moulded chewable bricks.	[69]

	CHEWABLE GEL TABLETS	Gelatine, corn starch, carrageenan, xanthan gum	Ranitidine	Gummy customized dosages with appetising visual appearance, easy handling, and ready intake.	[65]
	CHEWABLE GEL TABLETS	gelatine, HPMC, corn syrup	Lamotrigine	Soft dosage formulation with various shapes and colours.	[70]

1.7 Publicación 3: Formulation of Omeprazole in the Pediatric Population: A Review

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Resumen:

Este estudio sistemático propuso revisar críticamente el uso de omeprazol en la población pediátrica. Aunque este fármaco es ampliamente reconocido y utilizado, su aplicación en esta población presenta desafíos debido a problemas relacionados con su formulación y administración. En primer lugar, se buscó proporcionar una visión general de los aspectos fisicoquímicos, farmacocinéticos y farmacológicos del omeprazol, así como abordar las preocupaciones sobre las formulaciones preparadas extemporáneamente, centrándose especialmente en los problemas de inestabilidad. Además, se realizó una revisión exhaustiva de las formulaciones pediátricas publicadas que contienen este principio activo (API), con el objetivo de explorar los enfoques adoptados por los investigadores para resolver dichos problemas y determinar si se tuvieron en cuenta las consideraciones de estabilidad. En conclusión, esta investigación bibliográfica resalta la falta de consideración de la necesaria gastro-resistencia en las formulaciones (que no se suele tener en cuenta por los investigadores), así como la influencia significativa de factores específicos, como el pH y la humedad en la estabilidad del omeprazol.

Abstract:

This systematic study aimed to critically review the use of omeprazole in the paediatric population. This drug is well known and widely used but remains difficult to use in this population due to formulation and administration issues. On the one hand, this study aimed to provide an overview of the physicochemical, pharmacokinetic and pharmacological aspects of omeprazole and the issues related to extemporaneously prepared formulations, especially instability issues. On the other hand, a review of published paediatric formulations containing this active pharmaceutical ingredient (API) was also carried out to explore how researchers have tried to solve these problems and whether they have considered stability issues. In conclusion, it seemed clear from this bibliographic research that the necessary gastro-resistance is not always accounted for in formulations and that stability is highly dependent on specific factors, such as pH and humidity.

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Review Article

Formulation of Omeprazole in the Pediatric Population: A Review

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Abstract

This systematic study aimed to critically review the use of omeprazole in the Pediatric population. This drug is well known and widely used but remains difficult to use in this population due to formulation and administration issues. On the one hand, this study aimed to provide an overview of the physicochemical, pharmacokinetic and pharmacological aspects of omeprazole and the issues related to extemporaneously prepared formulations, especially instability issues. On the other hand, a review of published Pediatric formulations containing this active pharmaceutical ingredient (API) was also carried out to explore how researchers have tried to solve these problems and whether they have considered stability issues. In conclusion, it seemed clear from our investigation that the necessary gastro-resistance is not always accounted for in formulations and that stability is highly dependent on specific factors, such as pH and humidity.

Keywords: Omeprazole, Pediatrics, Pharmacokinetics, Pharmacology and Stability

INTRODUCTION

Currently, children are still considered to be therapeutic orphans due to the lack of pharmaceutical options that are adapted to the needs of pediatric patients. These patients constitute a heteromorphic population that is characterized by constant changes throughout the maturation process. Therefore, a large number of pediatric pathologies are treated with drugs that have not been studied for their potential therapeutic use in the pediatric population. However, in recent decades, there has been a great amount of interest in the development of oral medicines for pediatric use, both for rare and common diseases [1,2]. According to the European Medicines Agency (EMA) [3,4], pediatric investigation plans should include measures to adapt the formulation of the medicinal product to be age-appropriate for the different subsets of the pediatric population. There are several aspects to consider when deciding whether the pharmaceutical design of a pediatric medicinal product is appropriate, including the following:

- The minimum age, relevant developmental physiology and age characteristics of children in the target age groups
- The condition to be treated and its characteristics in the pediatric population
- The appropriate dose (considering the pharmacodynamic response curve and/or therapeutic margin) and dosage regimen (i.e., dose calculation, dose titration, dose flexibility, etc.)
- The maximum duration of therapy and dosing frequency
- The setting where the product is likely to be used (e.g., hospitals, community pharmacies, etc.)
- The stability of the compound formulations

In addition, all studies on pediatric medicinal products must be in line with the WHO criteria, as well as the WHO's "Make medicines child-sized" campaign and 2009 "Better Medicines for Children" initiative, to ensure that medicines for children are appropriate, safe and effective [5,6]. At the same time, the EMA also emphasizes the development of pediatric medicines that meet the abovementioned requirements, which can be found in the pediatric regulation section of the EMA website [7] and pediatric investigation plans [8].

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Typically, the lack of marketed pediatric medicines affects hospital pharmacy services, where magistral formulations are used to meet the needs of special patients (i.e., pediatric,

geriatric or swallowing-impaired patients). Regarding pediatric patients, oral liquid formulations are often the most suitable preparations because they allow for safe and easy dosage adjustment (according to body weight or body surface area, etc.) and avoid the need to swallow tablets or capsules. Obviously, liquid preparations that are formulated in hospital pharmacies must also be tested for quality and stability as medicinal and commercially available products. However, in practice, reliance is placed on official published information (i.e., information from the National Formulary, drug regulatory agencies, web-based bibliographies, etc.) because hospital centers do not have the capacity or resources to carry out stability or exhaustive quality controls as in the pharmaceutical industry. Thus, this lack of stability and quality studies limits the use of many medicines in special patients [2,9].

According to data provided by the Hospital Materno Infantil del Vall de Hebrón (Barcelona, Spain), omeprazole is one of the most widely used active pharmaceutical ingredients in magistral formulations for the treatment of gastrointestinal diseases in the pediatric population, a fact that has been corroborated by other international hospitals, including hospitals in Thailand [10], Morocco [11] and France [12]. In addition, omeprazole formulations that are used for pediatric patients must meet the quality and safety requirements of the EMA, FDA and WHO [2,9] which is very difficult due to the chemical instability problems that are associated with omeprazole. For this reason, it is important to develop pediatric formulations of omeprazole that address these stability issues.

This study explored the characteristics of omeprazole that limit the development of adequate pediatric formulations. Additionally, a review of published pediatric formulations containing this API (from PubMed, SciFinder^{n}, Scopus and Web of Science) was conducted to see how researchers have tried to overcome the issues with omeprazole and how they have demonstrated its stability [5-8]. Finally, it was clear from the review of published studies that the administration of omeprazole in children is an important issue; although there have been studies on administration in pediatric patients, the appropriate doses are not well established and the drug information does not provide recommendations for use in the pediatric population [9].

PHARMACOLOGICAL CHARACTERISTICS AND MECHANISM OF ACTION OF OMEPRAZOLE

Omeprazole is a proton pump inhibitor (PPI) and is one of the most widely used antisecretory drugs due to its good efficacy and the lack of significant adverse effects [13,14]. It selectively and irreversibly inhibits the H^+/K^+-ATPase or proton pump, which is the final step in the acid secretory pathway. Its inhibitory capacity is independent from the stimulus that triggers acid production, i.e., it reduces both basal and stimulated gastric secretion [15-17].

Omeprazole is a substituted benzyl imidazole derivative and a racemic mixture of two enantiomers. It should be noted that omeprazole is a prodrug that is activated in acidic media. As a lipophilic weak base (pKa of 4,0), it is electrically uncharged and highly lipid soluble at approximately pH 7, which is why it can easily cross cell membranes [15,18]. It accumulates selectively in the acidic environments of the canaliculi of stimulated parietal cells. Once it reaches parietal cells, it crosses the cell membranes via passive diffusion. In the secretory canaliculi of these cells, omeprazole is in its active achiral form and is exposed to a pH of less than 2,0 (about 1). It is ionized through a protonation process, which transforms it into a sulphonamide (i.e., a stable molecule at acidic pH levels and not lipophilic). Its positive charge prevents it from crossing parietal cell membranes, leading to the accumulation and concentration of the drug in the canaliculi [18]. This accumulation is essential as it allows for a prolonged therapeutic effect despite the drug having a short plasma half-life (**Figure 1**) [15]. This sulphonamide reacts by forming covalent bonds with the sulfhydryl (thiol) groups of the cysteine radicals on the extracellular surfaces of its alpha-subunits and the H^+/K^+-ATPase, thereby irreversibly inhibiting the activity of this enzyme. Therefore, the reactivation of the secretory activity is only possible after the resynthesize of the inhibited enzyme, which has a half-life of about 18 h [18]. This need for de novo enzyme genesis enables a prolonged inhibitory effect on acid secretion [15,16,19].

Omeprazole was originally approved by the FDA in 1989 for the treatment of gastric acid-related disorders, such as gastro-esophageal reflux, peptic ulcer disease and other conditions that are characterized by excessive gastric acid secretion. Omeprazole is generally effective and well tolerated, which has promoted its common use in children and adults. It was the first clinically useful drug of its kind and its formulation was followed by the formulation of many other proton pump inhibitor drugs [13,19,21]. The most commonly used PPI drugs are omeprazole, lansoprazole, pantoprazole (in sodium salt form), rabeprazole and esomeprazole (which is an optical isomer of omeprazole) [13,17]. Omeprazole is a white or off-white crystalline powder, which melts at 155 ºC with decomposition, has a weak basic character and is freely soluble in lipids, ethanol and methanol, slightly soluble in acetone and isopropanol and very slightly soluble in water. Its stability is pH-dependent as it degrades rapidly in acidic media but remains practically stable in alkaline conditions [19,22-24].

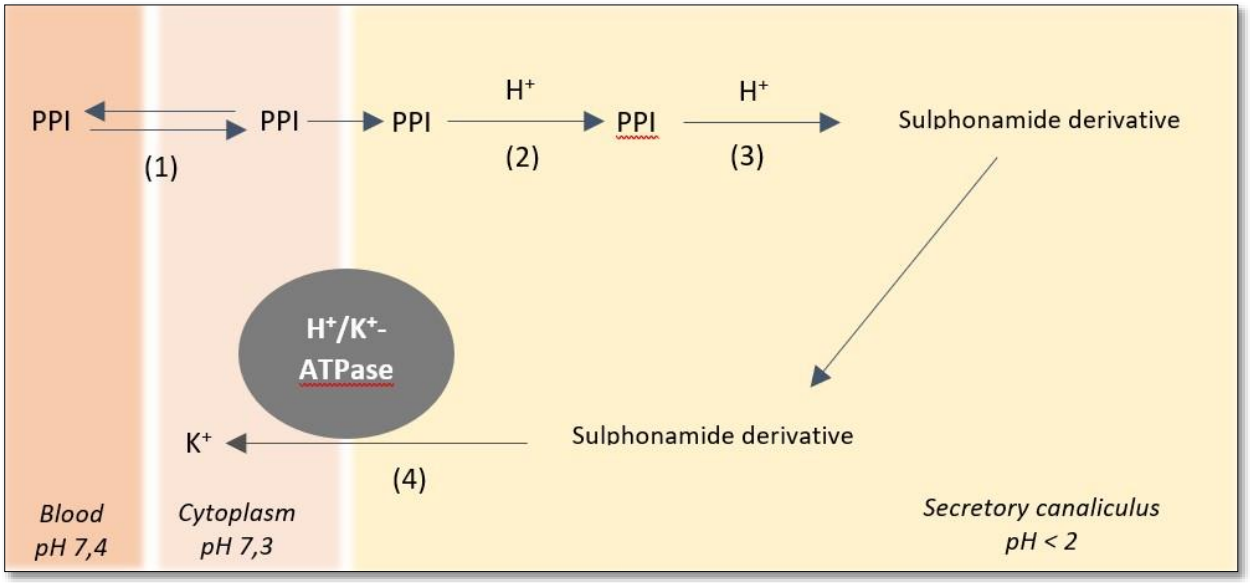

Figure 1. The mechanism of action of proton pump inhibitors (PPIs) on acid secretion via parietal cells [20]. PPI drugs reach parietal cells that are carried by blood, diffuse into cytoplasm (1) and are protonated in the acidic environments of the secretory canaliculi (2) whereby they lose their ability to cross biological barriers and become trapped. Then, by the action of these same acidic environments, their chemical structure is modified and they become a sulphonamide derivative (3). This tetracyclic compound reacts rapidly and forms covalent bonds with the sulfhydryl groups in the luminal sector of the H^+/K^+-ATPase, thereby forming the so-called inhibitor complex (4). Based on data from: Esplugues JV, Martí-Cabrera M, Flórez J. Farmacología de la secreción gastrointestinal y de la ulceración mucosa digestiva. Elsevier España SL, editor. Farmacología Humana [Internet]. 6th ed. 2014; p. 708-22. (cited 2022 Jun 5). Available from: https://www.clinicalkey.com/student/content/book/3-s2.0-B9788445823163000449

PHARMACOKINETIC CHARACTERISTICS OF OMEPRAZOLE

In adults, omeprazole is administered orally in the form of capsules that contain enteric-coated (pH-sensitive) mini-granules or pellets in order to prevent ionization by acidic gastric environments and promote absorption in the duodenum (which increases its bioavailability by up to 50%). There are also buffered release forms of omeprazole and preparations for intravenous administration [13,15].

The absorption of omeprazole depends on the different formulations and therefore, its oral bioavailability is also varied. It should be noted that its bioavailability is the same whether administered orally or via a nasogastric tube [18,25].

After absorption in the small intestine, omeprazole passes from the blood into the parietal cells of the stomach and then into the canaliculi, where it exerts its therapeutic action [15]. It is metabolized in the liver by the cytochrome P450 enzyme complex, which is an enzyme that is absent in approximately 3% of white people and 20% of Asian people, hence why there may be more cases of intoxication when using the drug in the usual doses [15,26]. The CYP2C19 and CYP3A4 isoenzymes are responsible for most of its metabolism; therefore, changes in the maturation of this enzyme complex may affect the pharmacokinetic parameters of omeprazole. Cytochrome P450 activity is low at birth, reaches adult levels in early life and then increases and surpasses adult levels during childhood before recovering to adult levels after puberty [16]. Parietal cell immaturity and achlorhydria during the first 20-30 months of life are also maturation-dependent factors for the two isoenzymes that may prevent the transformation of omeprazole into its active form and, consequently, its accumulation in the intracellular canaliculi of parietal cells. Gastric emptying and intestinal transit are other age-varying factors that may affect the bioavailability of omeprazole in the pediatric population [16,27,28]. Thus, in order to determine the most appropriate dose for different age groups, safety and efficacy studies must be conducted.

As a consequence of the particular mechanism of action of omeprazole, the level of acid inhibition that is produced does not correlate with the plasma concentration but instead with the area under the plasma concentration versus time curve. This is because omeprazole forms covalent bonds with the proton pump stimulating enzyme, which means that the therapeutic effect of a single dose of the drug is maintained for more than 24 h even though its plasma half-life is 60 min [24]. The administration of food delays absorption and decreases the area under the plasma concentration versus time curve. Therefore, omeprazole should be administered on an empty stomach, preferably first thing in the morning, regardless of the time elapsed between the administration of the drug and the subsequent ingestion of food [13,18].

The initial bioavailability of omeprazole is low, so its maximum effect is not reached with the first dose but instead after 5-7 days of repeated administration. This gradual build-up could be due to the fact that gastric secretion is inhibited after the first few doses, leading to a decrease in the gastric degradation of successive doses. Alternatively, it may be due

to reduced first-pass metabolism. Omeprazole is more than 90% bound to plasma proteins (mainly albumin and α1-acid glycoprotein), so its volume of distribution is low (0,3-0,4 L/kg). It can cross the blood–brain and placental barriers [13,15].

CLINICAL TRIALS ON THE PHARMACOKINETICS OF OMEPRAZOLE IN PEDIATRICS

The pharmacokinetics of omeprazole has been studied in children but mainly in those older than 2 years, so studies on younger children are still needed [29]. In a multicenter study by Andersson [30], the pharmacokinetics of orally administered omeprazole was evaluated in children from different age groups (1-16 years). The authors concluded that the pharmacokinetic parameters were mainly in the same range as those for adults, with the exception of the 1-6-year age group in which increased metabolic activity was observed. These results suggested an increase in metabolic activity as age decreased until the second year of life. This increased metabolic capacity in children aged 1-6 years is probably the main factor that explains the higher omeprazole dose requirements for young children compared to older children and adults.

In a subsequent study, also by Andersson et al., the pharmacokinetics of intravenously administered omeprazole was evaluated in new-born and infants requiring acid suppression [31]. The half-life and clearance of omeprazole in neonates (≤ 10 days) was found to be longer and lower than those in children aged 4,5-17 months. These values for the half-life and plasma clearance (expressed per body weight) could be explained by the low CYP2C19 and CYP3A4 enzyme activity that is present at birth. It is worth mentioning that these values were also close to the values of slow metabolizers with respect to the CYP2C19 enzyme. It was concluded that the new-born had a lower omeprazole metabolization rate than the other infants in the study, suggesting that their CYP2C19 and CYP3A4 enzymes were not yet fully mature.

It is worth highlighting that omeprazole is widely used for the treatment of gastric acid-mediated disorders. However, its pharmacokinetic and chemical instability does not allow for the synthesis of simple aqueous dosage formulations for the treatment of special patients (i.e., pediatric, geriatric or swallowing-impaired patients). Therefore, Karami [32] conducted a randomized parallel pilot study involving 34 pediatric patients with acid peptic disorder, who were treated with omeprazole. An omeprazole suspension was prepared by adding omeprazole powder to 8,4% sodium bicarbonate to obtain a final concentration of 2 mg/ml of omeprazole. Patients received either the suspension or granules. After oral administration, blood samples were collected and analyzed for omeprazole levels using a validated HPLC method. No significant differences were observed between the two dosage forms, both 2 h before and after the last dose. These results demonstrated that omeprazole suspensions are a suitable substitute for granules in the pediatric population [32].

In another prospective randomized clinical trial involving critically ill children who were at risk of gastrointestinal bleeding, Solana et al. studied the effects of two doses of intravenously administered omeprazole on gastric pH and the incidence of gastrointestinal bleeding. It was established that therapeutic efficacy was achieved when the gastric pH was above 4 and there was an absence of clinically significant gastrointestinal bleeding [33]. Between 24 and 48 h, a 1 mg/kg dose maintained gastric pH above 4 for a greater amount of time. The plasma levels of omeprazole were found to be higher after the 1 mg/kg dose. However, no correlations were found between omeprazole plasma levels and gastric pH levels. No toxic adverse effects were detected and there was no clinically significant bleeding [33].

Hassall [34] conducted an open multicenter study involving 57 children aged from 1 to 16 years old to determine the efficacy, safety and tolerability of omeprazole as a treatment for erosive esophagitis among this group of patients. For the curative dose of omeprazole, the investigators used a dose that corresponded to the treatment of acid reflux of less than 6% in a 24-hour intra-esophageal pH study. The dose correlated with the degree of esophagitis but not with age or underlying diseases. Of the 57 patients who completed the study, two thirds had grade 3 or 4 (0-4 scale) chronic esophagitis and about half had a neurological impairment or repaired esophageal atresia. It was concluded that omeprazole was well tolerated, effective and safe when used as a treatment for erosive esophagitis and gastro-esophageal reflux symptoms in children, including those for whom anti-reflux surgery or other treatment had failed. Reflux symptoms improved dramatically in almost all patients, including uncured patients. Additionally, the doses per Kg of omeprazole that were needed to cure erosive esophagitis in children were found to be higher than those needed in adults: 0,7-3,5 mg/kg/day in 44% of patients and 1,4 mg/kg/day in another 28% of patients.

A study by Strauss [35] investigated the effect of omeprazole on refractory histological esophagitis in pediatric patients. In total, 18 patients with histological esophagitis and recurrent symptoms who had been treated with H_2-receptor antagonists and prokinetic agents were prospectively treated with omeprazole. It was well tolerated in most patients and no short-term adverse reactions were observed. In patients with only histological evidence of esophagitis, omeprazole doses of approximately 0,5 ± 1,0 mg/kg/day were useful in controlling symptoms and improving esophageal histology. Those doses were similar to those used in adults with erosive esophagitis. Omeprazole did not produce prolonged symptomatic remission in children with recurrent esophagitis, even after the documented healing of esophagitis. No advantages were found for using omeprazole in patients whose symptoms were previously controlled by H_2-receptor antagonists. It was concluded that the treatment of symptoms

with omeprazole could be advisable for patients without erosive esophagitis. However, the long-term progression of histological esophagitis could not be determined.

ADVERSE EFFECTS OF OMEPRAZOLE

The introduction PPIs in 1989 marked a turning point in the treatment of heartburn-related disorders. Due to their novel and effective mechanism of action and low side effects, these drugs rapidly displaced others (e.g., H2 antagonists), leading to an exponential increase in their prescription. However, this widespread use of PPIs has led to evidence of some previously undescribed adverse effects, particularly in the long term. Below is a summary table (**Table 1**) describing the adverse effects associated with the use of PPIs and investigated in recent decades.

Table 1. Adverse effects of omeprazole.

Adverse effect	Study	Conclusion	Reference	Year
Association between PPI use and risk of pneumonia in children	Self-controlled case series study	An increased risk of pneumonia was observed both immediately before and immediately after starting PPI treatment. This pattern of association could probably be explained by the underlying risk of pneumonia due to factors that were transiently present around the time PPI treatment initiation. In this case, it was concluded that the obtained results did not support a causal relationship between PPI use and pneumonia risk	[36]	2022
Association between PPI use and the risk of depression and anxiety	Cohort study	PPI use was associated with an increased risk of depression and anxiety in children	[37]	2022
Increased risk of renal, liver and cardiovascular disease, dementia, enteroendocrine tumors in the gastrointestinal tract, susceptibility to respiratory and gastrointestinal infections, and impaired nutrient absorption	Review	The risks and benefits of long-term PPI use should be carefully considered, especially in young patients whose treatment with these drugs could last for many years	[38]	2021
Association between PPI use and the risk of asthma in children	Cohort study	PPI use was associated with an increased risk of asthma in children compared to non-use	[39]	2021
Myocardial infarction, stroke, miscarriage, spontaneous abortion, proliferative changes, chills, heart failure, thrombosis and dementia	Review (72 articles)	The use of omeprazole should be monitored in patients with cardiac disorders using concomitant antiplatelet agents and patients with new transplants using mycophenolic acid to avoid serious adverse reactions.	[40]	2018
Effect of long-term omeprazole therapy on the numbers of antral G and D cells in children	Review	Omeprazole therapy was associated with a significant increase in the number of G cells and the ratio of G to D cells in children	[41]	2001
Increased risk of acute gastroenteritis and pneumonia in children treated with gastric acidity inhibitors	Multicenter prospective study: 186 subjects	The number of subjects presenting with acute gastroenteritis and community-acquired pneumonia was significantly higher in patients who were treated with GA inhibitors compared to the healthy controls during the 4-month follow-up period	[42]	2006
Effects of PPI use on duodenal bacteriology, carbohydrate absorption and bowel habits	Review	Conventional treatment for duodenal ulcers with a PPI significantly increased the bacterial colonization of the duodenum and intestinal transit speed	[43]	1996

Although most researchers claim that more studies are needed, it seems clear that the most common side effects of omeprazole therapy are asthma [39], pneumonia [36,42] and acute gastroenteritis [42].

PEDIATRIC OMEPRAZOLE FORMULATIONS

It is important to note that there have not been many published studies concerning pediatric formulations of omeprazole, even though it is one of the most commonly prescribed APIs in the pediatric population.

With respect to the stability of omeprazole as a raw material, it is a substance that can be degraded by several factors, which have to be considered when developing formulations. Some of these factors are discussed in **Table 2** [44-47]. It is clear that the formulation of this drug is not straightforward.

In order to facilitate our understanding of the current state of the subject, two summary tables (**Tables 3 & 4**) were drawn up following the literature search. Table 3 shows a list of published omeprazole formulations that are suitable for the pediatric population, although they are in the early stages of development. Most have undergone tentative quality controls to demonstrate the chemical validity of the product; however, most of the stability studies that have been carried out to demonstrate how long the proposed formulation is stable have not considered the gastro-resistance test. As mentioned previously, omeprazole is sensitive to acidic environments

and needs to be protected from these environments so that it can pass through the cells of the intestine into the blood.

Table 2. External factors that affect omeprazole stability.

Factor	Effect of factor on the stability of omeprazole	Reference
pH	Depends on the pH of the solution. At 20ºC, the half-life of the product is 15 minutes at pH 4 and only 1.8 minutes at pH 2. At pH 7, the half-life is about 30 hours while at pH 9, it is more than one week. At 37°C, the half-life is about 10 hours at pH 7, while at alkaline pH levels in a 0.1 N sodium hydroxide solution, it is about one year.	[44-47]
Temperature	Omeprazole is virtually stable at elevated temperatures (37ºC to 50ºC). A slight discoloration has been observed in samples stored at elevated temperatures.	
Ultraviolet Light	After exposure to artificial light (xenon lamp: 280-830 nm; approximately 830 W/m2; 150 000 lux) for 48 hours, omeprazole was degraded by 20% in one study. The main degradation product was 5-methoxy-2-mercaptobenzimidazole, which is one of the starting products in the synthesis of omeprazole. When samples were protected by amber-colored glass, the stability of omeprazole increased considerably.	
Humidity	It is recommended to store omeprazole in airtight packaging to avoid the action of external factors (humidity, oxygen, etc.). If omeprazole is not protected from humidity, it changes from its initial white color to a brownish color and may even turn black in the case of exposure to extreme humidity. Omeprazole specialties that are repackaged using heat-sealing systems that do not adequately protect against moisture have a stability time of 7 days when stored under ambient conditions.	

This is a key point in the development of omeprazole formulations. In **Table 3**, the formulations are grouped according to their pharmaceutical form: suspensions, syrups, mucoadhesive tablets, mucoadhesive films and suppositories. All of the formulations were considered to be good alternatives to the extemporaneous oral omeprazole preparations that are produced as officinal or compounding formulas in hospitals, most of which are made by manipulating commercial omeprazole drugs (capsules with pellets or mini-granules) or using omeprazole powder in sodium bicarbonate solutions. If these proposed alternatives are confirmed, they could improve the therapeutic efficacy and facilitate the administration of this active pharmaceutical ingredient in the pediatric population.

Further examples of stability studies on the liquid compounding formulas and extemporaneous preparations of omeprazole that are used in the pediatric population are presented in **Table 3**. Among the presented examples, the following parameters were generally studied: the shelf life of the preparations and the optimal storage temperature. It was observed that most preparations are best stored refrigerated rather than at ambient temperatures. It is noteworthy that only three of the studies (examples 3, 5 and 6 in **Table 4**) found that the solution turned yellow after 7 days, which is quite common when working with omeprazole [48-50]. More specifically, it is interesting to note that the recapitulated examples studied the stability of omeprazole suspensions at different concentrations [48,51]. In example 3, it was concluded that suspensions comprising sodium bicarbonate and 0,6-4 mg/mL of omeprazole could be stored at 4ºC in the dark for up to 28 days [48]. Other parameters, such as viscosity (example 3) and pH (examples 5 and 6), were also studied [48-50]. None of the examples studied the gastro-resistance required for omeprazole in depth or how the preparation of an alkaline liquid affects the protection of omeprazole once it reaches the stomach. For example, if the patient is able to drink, a common practice is to administer pellets with an acidic drink (e.g., fruit juice) to avoid the action of gastric juice with a pH of less than 5.3 [18]. This practice is also not discussed in the various studies collected.

Table 3. Examples of pediatric omeprazole formulations.

Pharmaceutical Form			Excipients	Controls	Stability	Reference	Year
Liquid Preparations	Suspensions	Example 1: 2% omeprazole oily suspension	Sesame oil (37.5%; carrier) Compritol® (1.54%; viscous agent) Soy lecithin (0.1%; emulsifying and stabilizing agent) Calcium carbonate (14.5%; protective antacid)	Very good palatability (beige color, pleasant smell with vanilla and caramel aromas, sweet taste and creamy texture) Good content uniformity (by shaking before use) Good release profile	Store in a refrigerated and amber-colored container	[52,53]	2012 - 2015

			Aspartame (0.11%; sweetener) Labrafac (42%; omeprazole suspension vehicle) Vanilla and caramel flavorings (0.05%)				
Liquid Preparations	Suspensions	Example 2: Enteric-coated omeprazole nanoparticle suspension (0.5 mg/mL)	Eudragit® RS 100 (extended-release polymer with a nanoparticle matrix) Eudragit® L 100-55 (pH-sensitive gastro-resistant polymer) Acetone (solvent) Peanut oil (to promote the formation and loading of the API into nanoparticles) Polysorbate 80 (surfactant) Sodium bicarbonate (pH regulator) NaOH solution 0.03 M (alkaline excipient)	The release of enteric omeprazole nanoparticles is pH-dependent	Storage and stability conditions are not specified	[54]	2020
Liquid Preparations	Syrups	Example 3: Delayed-release liquid in oral dosage form based on omeprazole (2 mg/mL)	Excipient Coating (by fluid bed) Microcrystalline cellulose pellets (diameter of 200–300 µm) Eudragit® L100-55 (enterosoluble polymer) Eudragit® E100 (gastrosoluble polymer) Povidone (binder) Talc (10 µm of micronized talc; binder) Ascorbic acid palmitate (antioxidant) Hydrogen phosphate (antioxidant) Disodium hydrogen phosphate dihydrate (pH regulator) Silicon (silicon emulsion) Silicon (30% simethicone emulsion; anti-foaming agent) Titanium dioxide (opacifier) Tryethyl-2-acetylcitrate (plasticizer) -Glyceryl monostearate (hydrophobic excipient to increase the strength of the polymer against water) Aluminum oxide (excipient with anti-electrostatic properties) Excipient Syrup Sorbitol (syrup vehicle; sweetener and stabilizer) Microcrystalline cellulose and sodium carboxymethylcellulose (viscous agents) Polyvinylpyrrolidone (syrup vehicle; suspending agent; sweetener and stabilizer) Sodium carbonate anhydrous and disodium hydrogen phosphate dihydrate (pH neutralizers)	Delayed-release properties -Multi-layered diameter of less than 500 µm (to avoid swallowing problems)	Stable after 10 days at room temperature	[55]	2019
Solid Preparations	Bucoadhesive Tablets	Example 4: Adhesive buccal	Sodium alginate (bio-adhesive polymer)	Physicochemical properties, including bio-adhesive strength	Storage and stability conditions are not specified	[56]	2000

		omeprazole tablets (20 mg)	Hydroxypropyl methyl cellulose (bio-adhesive polymer) Carbopol and polycarbophil (cross-linking agents; anionic and water swellable polymers) Monosodium potassium phosphate, monobasic sodium phosphate, dibasic sodium phosphate and magnesium oxide (alkaline excipients)	23% of the administered omeprazole dose is absorbed into the oral cavity within 15 minutes	Stable in human saliva for 4 hours		
Solid Preparations	Oral Films	Example 5: Pediatric omeprazole: L-arginine films (ratio 1:2)	Carrageenan (gel base and stabilizing agent) Sodium alginate (bio-adhesive polymer) Metolose® (viscous agents) Polyethylene glycol 400 (plasticizer) L-arginine (pH stabilizer) Ethanol and water (solvents)	Good molecularly dispersion within the Metolose® film matrix	Storage and stability conditions are not specified	[57]	2014
Solid Preparations	Oral Films	Example 6: Paediatric omeprazole oral films	Metolose® (mucoadhesive polymer) Polyethylene glycol 400 (plasticizer) L-arginine (stabilizer) Gelatine (gelling and film-forming agent) Beta- and gamma-cyclodextrin (stabilizers and release modulators) Ethanol (solvent) Potassium dihydrogen phosphate and sodium hydroxide (pH regulators)	No controls specified	Stable at room temperature for 28 days More stable at room temperature than at 40°C Short and long-term stability improves with increased pH levels	[58]	2018
Solid Preparations	Alginate Microspheres	Example 7: Alginate microspheres as vehicles for omeprazole/SBA-15	Tetraethyl orthosilicate (type SBA-15; mesoporous silicate) Sodium alginate (matrix-forming agent for gel microspheres) Pluronic® 12 3 (surfactant) Granular anhydrous calcium chloride (aqueous solution; cross-linking agent) Deionized water (solvent)	Uniform size distribution and drug content Drug dosage ranges from 1% to nearly 7% w/w Homogeneous and reproducible release kinetics All formulations demonstrate enteric properties, except one	Storage and stability conditions are not specified	[59]	2015
Solid Preparations	Suppositories	Example 8: Omeprazole suppositories for children	L-arginine base (stabilizer) Witepsol® H15 (melting wax; base of suppository)	No controls specified	Omeprazole content is stable at 90-110% for 1 year when stored in the dark at room temperature A long-term stability study showed no signs of discoloration	[60]	2020

Table 4. Examples of stability studies on the liquid compounding formulas and extemporaneous preparations of omeprazole that are used in pediatrics.

Formula		Composition	Study and Storage Conditions Results: Stability	Reference	Year
Liquid Preparations	Example 1: Oral liquid omeprazole suspension for pediatric patients (2 mg/mL)	Formulation A: Oral liquid omeprazole suspension (2 mg/mL) using crushed omeprazole granules Formulation B: Oral liquid omeprazole suspension (2 mg/mL) using an omeprazole base with a complete vehicle, including wetting agents, suspending agents, sweeteners, antioxidants and flavorings	Formulations A and B can be stored for at least 150 and 90 days, respectively, under refrigerated conditions (4 ºC) Formulation A can be stored at room temperature (25 ºC) for 14 days, while Formulation B is not recommended to be stored at room temperature for more than 1 day	[61]	2020

	Example 2: Omeprazole suspension from the contents of 20 mg omeprazole capsules (2 mg/mL)	Formulation: A 2 mg/mL omeprazole suspension was prepared by emptying 10 omeprazole capsules (20 mg) and mixing with 1 g of methylcellulose. Then, a sodium bicarbonate solution (8.4%) was added and homogenized to 100 mL with the same solution	Self life is 32 days at room temperature and 54 days when refrigerated (2-8ºC)	[62]	2018
Liquid Preparations	Example 3: Omeprazole and sodium bicarbonate suspension (2 mg/mL)	Formulation A: A commercial preparation of 20 mg of omeprazole and sodium bicarbonate suspended at initial omeprazole concentrations of 0,6 and 2 mg/mL Formulation B: A commercial preparation of 40 mg of omeprazole and sodium bicarbonate suspended at initial omeprazole concentrations of 1,2, 2, 3 and 4 mg/mL Stability of omeprazole was quantified using HPLC Viscosities of refrigerated suspensions were measured after 0, 1 and 7 days	Suspensions were stored at 4ºC in the dark (refrigerated) or at 22-25ºC (room temperature) in the light for one week (samples were also stored refrigerated for 1 month) Suspensions of 0,6-4 mg of omeprazole per mL can be stored at 4 °C in the dark for up to 28 days No viscosity variations over 7 days Samples contained 90% of their initial omeprazole content after 7 days despite turning yellow	[48]	2006
Liquid Preparations	Example 4: Commercial omeprazole and sodium bicarbonate powder suspension	Formulation: An omeprazole/sodium bicarbonate suspension (2 mg/mL) Samples were stored refrigerated and analyzed by HPLC immediately after preparation and after 7, 15, 30 and 45 days The stability of a 1 mg/kg dose was determined with an estimated volume of simulated gastric fluid for a hypothetical 12.7 kg pediatric patient in triplicate over 2 hours at 37 ºC	The suspension was stable for at least 45 days when stored at 3-5 ºC A partial dose of 12.7 mg was stable following exposure to simulated gastric fluid for 2 hours at 37 ºC	[63]	2007
Liquid Preparations	Example 5: Omeprazole suspension from commercial 20 mg capsules (2 mg/mL)	Formulation A: Oral liquid omeprazole suspension (2 mg/mL) using the contents of Probitor® (20 mg omeprazole) capsules Formulation B: Oral liquid omeprazole suspension (2 mg/mL) from adding omeprazole powder to 8.4% sodium bicarbonate solution	Samples were stored in 100 mL amber glass bottles under refrigeration (2–8 ºC) or at room temperature (21 ± 2 ºC) One of each sample was shaken and the other was not shaken, then the pH was measured and color changes were determined using a visual scale Omeprazole concentrations were measured using tandem mass spectrometry with liquid chromatography Formulation A was stable for 45 days in a refrigerator when shaken regularly (without shaking, API decreased rapidly for 7 days) Color changes were observed in the samples pH remained constant	[49]	2008
Liquid Preparations	Example 6: Omeprazole suspension (2 mg/mL)	Formulation: Omeprazole base (0.2%), sodium bicarbonate (8,4%), Xanthan gum 1% aqueous solution (50 mL), vanilla essence (0.1-0.2%), saccharin sodium (0.1-0.3%) and purified water (qsp 100 mL)	The pH ranges studies were 1.2, 2.2 and 4.5 10 mL of the suspension, equivalent to 20 mg of omeprazole, was added to each of the pH media and observed for 2 hours 10 mL of a placebo was also added to a 1.2 pH medium and observed for 2 hours At pH 1.2, a change in color from clear to slightly yellow was observed after less than 1 minute, which intensified after 5 minutes At pH 2.2 and 4.5, the samples were no longer completely transparent and began to show slight color changes after 5 minutes The placebo medium did not change color	[50]	2021

			The 2 mg/mL omeprazole suspension was instable in acidic media (the color changes indicated the degradation of the omeprazole)		
Liquid Preparations	Example7: Omeprazole suspension (2 mg/mL)	Three oral suspensions of omeprazole were prepared using omeprazole powder at three concentrations (2, 5 and 10 mg/ml) and Oral Mix Dry Alka, SF (OMSF®), which contains calcium carbonate as a pH neutralizing agent, was used as the suspension vehicle	The concentration of omeprazole was determined after 0, 7, 14, 28, 42, 56 and 70 days using HPLC with photodiode array detection (HPLC-PDA) The pH, homogeneity, color, odor and microbial levels were also determined Omeprazole was stable in the OMSF® vehicle for 70 days Preparations were stable at 4ºC for 70 days The pH decreased from 9.0 to 7.7 during the study, which was an acceptable change The microbiological study was correct None of the samples showed any changes in color, odor or appearance over 70 days	[51]	2022

DISCUSSION

Omeprazole is widely used for the treatment of gastric disorders in the pediatric population. However, as previously mentioned in this review, the main problem with this active pharmaceutical ingredient (API) is its degradation in acidic environments [32,58]. This point is crucial because gastro-resistant excipients are not recommended for the pediatric population unless their use is completely justified [2]. Furthermore, omeprazole doses are not well established for pediatric population and the drug information does not include any recommendations for children [9]. Thus, hospitals do not have any guidelines for the administration of this medicine in pediatric patients.

Regarding the instability of omeprazole in acidic media, formulators are used to ensure the release of the API in the small intestine, thereby protecting omeprazole from gastric pH levels. One alternative that healthcare professionals apply to administer omeprazole to the pediatric population is the use of nasogastric tubes, which deliver the API directly to the small intestine [18,25]. Another common practice is the administration of omeprazole powder with sodium bicarbonate to promote alkaline pH levels [63]. However, this strategy seems to degrade the API (i.e., the solutions turn yellow) and the release of omeprazole in the small intestine has not been demonstrated. The third most widely used strategy is the preparation of liquid formulations that incorporate gastro-resistant pellets from commercialized capsules in acidic drinks (i.e., fruit juices). The acid pH levels of those drinks prevent the release of omeprazole in the liquid formulation. However, none of these preparations and strategies have shown the same quality or stability parameters as commercial products. Indeed, there is a lack of information about their stability [2,9]. There have only been a few studies describing the stability of some of these preparations. For example, there have been studies demonstrating that alkali solutions with gastro-resistant pellets are stable for 7-32 days [48,49,61,62] or 28 days [58] at room temperature.

In this study, a review of articles describing pediatric formulations of omeprazole was performed. Examples of various dosages and forms that are suitable for use in the pediatric population were collected, including suspensions, syrups, oral tablets, mucoadhesive films and suppositories. These examples could be good alternatives to the current officinal or extemporaneous preparations of omeprazole. Nevertheless, most of these works did not demonstrate the gastro-resistance of the proposed formulations (the only work that did discuss this point was the study by Del Gaudio et al. [59]). Furthermore, the stability problems were not fully resolved in these studies. Indeed, most of the proposed preparations had to be stored refrigerated [52,53,63] and were only stable for 2-4 weeks. The formulation that demonstrated the longest stability (1 year) was the suppository developed by Bestebreurtje [60]. Thus, more research is needed to solve the gastro-resistance and stability issues of omeprazole formulations.

In recent years, multiparticulate and orally disintegrating tablet (ODT) formulations have attracted interest, along with liquid formulations [64]. However, the aim is to develop final dosage forms without compromising the pharmaceutical efficacy of the drug [64]. Another interesting approach is the development of microspheres [59] or nanoparticles [54] that can encapsulate the API. However, studies on these drug delivery vehicles have not demonstrated the gastro-resistance of the developed formulations. Currently, new technologies (such as additive manufacturing (AM), commonly known as 3D printing (3DP)) are opening new frontiers in pharmaceutical applications. For example, 3DP is a tool that enables the manufacture of formulations with intricate structure designs, customized dosing and drug combinations and controlled release. Hence, 3DP allows for the customization of medicines, which could revolutionize pharmaceutical practice and provide personalized medicines for the pediatric population [65].

CONCLUSION

Omeprazole is a drug that has demonstrated its efficacy and security in adult patients over the last 30 years. However, the safe administration of omeprazole in children has not yet been fully resolved; although it has been studied at the clinical level and its therapeutic usefulness for the pediatric population has been validated. Nevertheless, the problems of its stability in acidic media and the need to adapt the dose according to the weight of the patient are barriers to its routine use. Different extemporaneous preparations are normally used but they do not solve the stability issue, as reported in this review. Clearly, much more investment and effort are required to assess all of the critical points during the development stage and more clinical trials are needed, including trials involving the pediatric population.

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2 OBJETIVOS

La presente tesis plantea como objetivo principal:

1. El desarrollo de una nueva formulación pediátrica de omeprazol, de calidad y estable.

Para completar este objetivo, se plantean los objetivos específicos siguientes:

2. Realizar una revisión sobre el uso de excipientes en la población pediátrica, basándose en las normas y recomendaciones de las agencias regulatorias del medicamento, tanto la EMA como la FDA.
3. Realizar una revisión sobre el estado de arte de la aplicabilidad de las formulaciones de comprimidos buco-dispersables (ODT, del inglés *Orally Disintegrating Tablets*) en población pediátrica. Así como, del uso de la impresión 3D (fabricación aditiva) para desarrollar formas farmacéuticas adaptadas a las necesidades del paciente pediátrico en un camino hacia la medicina personalizada.
4. Estudiar la estabilidad de algunas de las formulaciones pediátricas que actualmente se utilizan a nivel hospitalario para administrar omeprazol en pacientes pediátricos, como punto de partida para los siguientes objetivos.
5. Investigación de las características químicas, físicas y galénicas del omeprazol para poder desarrollar una formulación pediátrica de calidad.
6. Aplicación de la técnica de recubrimiento de pellets inertes de celulosa microcristalina para el desarrollo de pellets entéricos de omeprazol que se adapten a las necesidades del paciente pediátrico.
7. Aplicación de la tecnología de impresión 3D por extrusión de semisólidos para desarrollar *drugmies* (gominolas medicinales) a medida del paciente pediátrico.

3 RESULTADOS: PUBLICACIONES

En esta sección se expondrán los artículos científicos publicados a lo largo de la presente tesis doctoral. Previamente a cada publicación, se proporcionará un breve resumen en castellano e inglés.

3.1 Publicación 4: Optimisation of the Manufacturing Process of Organic-Solvent-Free Omeprazole Enteric Pellets for the Paediatric Population: Full Factorial Design

Citación	**Rouaz-El-Hajoui, K.**; García-Montoya, E.; López-Urbano, A.; Romero-Obon, M.; Chiclana-Rodríguez, B.; Fraschi-Nieto, A.; Nardi-Ricart, A.; Suñé-Pou, M.; Suñé-Negre, J.M.; Pérez-Lozano, P. Optimisation of the Manufacturing Process of Organic-Solvent-Free Omeprazole Enteric Pellets for the Paediatric Population: Full Factorial Design. Pharmaceutics 2023, 15, 2587. https://doi.org/10.3390/ pharmaceutics15112587
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Resumen:

Las formulaciones líquidas son ampliamente utilizadas en la población pediátrica. Sin embargo, con ciertos principios activos (API), como el omeprazol, asegurar la calidad y estabilidad resulta desafiante. El omeprazol, en particular se utiliza como un ejemplo modelo debido a la falta de una formulación pediátrica que cumpla los requisitos de gastro-resistencia, lo que continúa siendo un reto. En este estudio experimental, se propone el desarrollo de pellets entéricos, utilizando dispersiones acuosas de recubrimiento en lugar de disolventes orgánicos comúnmente empleados en los recubrimientos de lecho fluido. Se emplea el método de diseño de experimentos como herramienta estadística para crear y analizar los experimentos. Específicamente, se utiliza un diseño factorial completo aleatorizado, con incrementos medios de peso, tanto de la capa protectora como de la entérica, como factores, cada uno con dos niveles asignados.

Así, el diseño de experimentos utilizado es 2^2 + 1 punto central. En conjunto, los pellets entéricos obtenidos pueden ofrecer una alternativa a las formulaciones magistrales actuales de omeprazol utilizadas en la población pediátrica (que no cumplen con las especificaciones necesarias de gastro-resistencia) para garantizar la eficacia terapéutica de este principio activo.

Abstract:

Liquid formulations are mostly used in the paediatric population. However, with certain active pharmaceutical ingredients (APIs), it is very difficult to guarantee quality and stability; this is the case, for example, with omeprazole. Omeprazole is used as a model drug due to the lack of a paediatric formulation meeting gastro-resistance requirements, which remains a challenge today. In this experimental study, the development of enteric polymer-coated pellets is proposed. It is proposed to use aqueous coating dispersions without the use of organic solvents, which are commonly used in fluidised bed coatings. To do this, the design of experiments method is used as a statistical tool for experiment creation and the subsequent analysis of the responses. This study uses a randomised full factorial design. The mean weight increases of the protective layer and the enteric coating are chosen as factors. Each factor is assigned two levels. Therefore, the design of the used experiments is a 2^2 + 1 central point. Overall, the obtained pellets can be an alternative to the compounding formulas of omeprazole that are currently used in the paediatric population, which do not meet the gastro-resistance specifications necessary to guarantee the therapeutic efficacy of this active ingredient.

pharmaceutics

MDPI

Article

Optimisation of the Manufacturing Process of Organic-Solvent-Free Omeprazole Enteric Pellets for the Paediatric Population: Full Factorial Design

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Abstract: Liquid formulations are mostly used in the paediatric population. However, with certain active pharmaceutical ingredients (APIs), it is very difficult to guarantee quality and stability; this is the case, for example, with omeprazole. Omeprazole is used as a model drug due to the lack of a paediatric formulation meeting gastro-resistance requirements, which remains a challenge today. In this experimental study, the development of enteric polymer-coated pellets is proposed. It is proposed to use aqueous coating dispersions without the use of organic solvents, which are commonly used in fluidised bed coatings. To do this, the design of experiments method is used as a statistical tool for experiment creation and the subsequent analysis of the responses. In particular, this study uses a randomised full factorial design. The mean weight increases of the protective layer and the enteric coating are chosen as factors. Each factor is assigned two levels. Therefore, the design of the used experiments is a 2^2 + 1 central point. Overall, the obtained pellets can be an alternative to the compounding formulas of omeprazole that are currently used in the paediatric population, which do not meet the gastro-resistance specifications necessary to guarantee the therapeutic efficacy of this active ingredient.

Keywords: omeprazole; pellets; enteric coating; design of experiments and paediatric population

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1. Introduction

Administering drugs in the paediatric population remains difficult due to the lack of pharmaceutical forms adapted to the needs of paediatric patients. One setting in which this difficulty is evident is hospital pharmacy services, which resort to classical formulation techniques to try to overcome the lack of marketed paediatric medicines. Oral liquid preparations are used as they are the most suitable for such patients; they avoid the need to swallow tablets or capsules and allow simple dosage adjustment according to body weight or body surface area. Generally, these preparations are not subjected to the same quality, safety, and stability tests as marketed medicines and medical devices due to the inability and lack of hospital facility resources to perform these controls. As a result, many medicines are limited with regard to their use in paediatric patients [1,2].

Omeprazole (OME) is a drug with a very evident lack of a paediatric dosage form that meets the stability, safety, and quality requirements demanded by drug regulatory agencies

(FDA, EMA, and WHO). OME-compounding formulas used in paediatrics do not conform to their physicochemical, pharmacokinetic, and pharmacodynamic characteristics, and, therefore, the therapeutic effectiveness is directly affected [3–5]. OME is a selective and irreversible proton pump inhibitor (PPI) active substance (API). It is widely used in children and adults to treat peptic ulcers, dyspepsia, gastro-oesophageal and laryngopharyngeal reflux, and Zollinger–Ellison syndrome because of its good tolerability and few adverse effects. It is a substituted benzylimidazole derivative in the form of a racemic mixture of two enantiomers. It is a prodrug that is active in acidic media and that reduces acid production in the stomach, relieves symptoms, and promotes gastrointestinal tract healing. Its stability is directly dependent on pH; it remains practically stable in alkaline conditions but degrades rapidly in acidic conditions. It is absorbed in the small intestine; thus, it must be protected from the acidic environment of the stomach. Otherwise, it will not reach its therapeutic target [6–10].

In general, most galenic development is performed non-systematically; to study the effects of a specific factor on a selected response, the levels of each factor are changed separately while keeping all other factors constant. This experimental methodology involves many experiments and is usually influenced by the experience of the researcher and overall is neither an efficient nor cost-effective strategy [11,12]. In this situation, FFD has several advantages over a traditional experimental methodology, such as the provision of the maximum amount of information with the minimum number of experiments, the possibility of increasing the number of factors studied or their levels, and considering possible interactions between factors, simple modelling results, and a thorough search for the optimal response, among others [13,14].

Developing a paediatric dosage form of OME remains a challenge today, as alkaline liquid dispersions are often prepared, which do not ensure the protection of the OME in the gastric environment. Therefore, this experimental study proposes developing very small enteric polymer-coated pellets which can be used to formulate liquid pharmaceutical dosage forms adapted to paediatric patients. OME enteric pellets have been produced using the fluid bed coating technique using three different layers. To determine the optimal conditions of the coating process, the design of experiment (DOE) method was applied, particularly, the full factorial design (FFD) of factors with two levels each and a central point. Our aim was to study the effects of several factors on one or more responses and to find a mathematical model relating the response to the factors [13,15]. As the quality of pharmaceutical products is a prerequisite in any manufacturing process, this study followed the criteria of the quality by design (QbD) method described in the guidelines of the International Conference on Harmonisation (ICH Q8 R2) [16].

2. Materials and Methods

2.1. Materials

Micronized omeprazole (CAS no. 73590-58-6) was received from Esteve Química, Barcelona, Spain. Lactose monohydrate (CAS no. 10039-26-6), sodium lauryl sulphate (CAS no. 151-21-3), titanium dioxide (CAS no. 13463-67-7), and Talc (CAS no. 14807-96-6) were purchased from Fagron Ibérica SAU, Terrassa, Spain. Vivapur® MCC spheres were purchased from JRS Pharma GmbH & Co. KG, Rosenberg, Germany. Hydroxypropyl methyl cellulose (CAS no. 9004-65-3) and hydroxypropyl cellulose (CAS no. 9004-64-2) were purchased from Shin-Estu Chemical Co., Ltd., Tokyo, Japan. Eudragit® L-30 D-55 was purchased from Evonik Corp., Barcelona, Spain. Triethyl citrate (CAS no. 77-93-0), disodium dihydrogen phosphate (CAS no. 7558-79-4), sodium dihydrogen phosphate (CAS no. 7558-80-7), sodium tetraborate decahydrate (CAS no. 1303-96-4), tribasic sodium phosphate dodecahydrate (CAS no. 10101-89-0), sodium hydroxide (CAS no. 1310-73-2), disodium hydrogen phosphate 12-hydrate (CAS no. 10039-32-4), hydrochloric acid 5 M (CAS no. 7647-01-0), and ethanol 96% (CAS no. 64-17-5) were purchased from PanReac Química S.L.U., Barcelona, Spain.

The water used for the analysis was of MilliQ grade. All used solvents were of analytical grade.

2.2. Methods

2.2.1. Full Factorial Design (FFD)

A randomised full factorial design 2^2 + 1 centre point was used, i.e., 2 factors were studied at 2 levels to optimise the coating process of microcrystalline cellulose inert pellets (MCC). Our aim was to study and identify the relationships between the factors studied and the responses obtained, thus creating a design space that allows the working conditions to be adjusted and optimised. The statistical programme Minitab 21.0 was used for the creation and analysis of the experimental design. The associations between the factors studied, their interactions, and the responses obtained were mathematically described.

Inert MCC pellets (200 µm in diameter) were coated with three different layers: active ingredient, protective, and enteric. The studied factors were the average weight increase in the pellets after the second (Factor A) and third (Factor B) coatings. For the protective layer, two values of weight increase were set (2% and 6%), as well as for the enteric layer (50% and 100%). A central point was also studied. The scheme of the experiments is shown in Table 1 (which appears in the next paragraph). The protective coating was applied to avoid possible interactions between the OME and the used enteric polymer, Eudragit® L-30 D-55 [17,18]. As these interactions could lead to the degradation of the OME, the weight increase in the protective layer was chosen as a critical factor. Enteric coating, the most critical and relevant for achieving gastro-resistance in the OME, was the second factor in the FFD. The percentages of weight increase were set at the discretion of the researcher.

Table 1. Design of experiments: randomised full factorial design 2^2 + 1 central point.

Statistical Order	Running Order	Block	Factor A	Factor B
4	1	1	+	+
5	2	1	0	0
2	3	1	+	-
3	4	1	-	+
1	5	1	-	-

The evaluation of the omeprazole content, the percentage of gastro-resistance, and the percentage of release were selected as the responses. Assays were performed according to the guidelines of the European Pharmacopoeia (Ph. Eur.) and the United States Pharmacopeia and the National Formulary (USP-NF).

2.2.2. Preparation of Omeprazole Enteric Pellets

Inert MCC pellets were coated in a fluidised bed (*Glatt AG*) equipped with a bottom spray coating process on a Würster column. They were coated with three successive coating layers: (1) a drug layer, (2) a protective layer, to avoid possible interactions between the first layer and the third layer, and (3) an enteric polymer layer, to protect the omeprazole from the acidic gastric environment. Coating formulations were developed using exclusively aqueous vehicles, thus avoiding the use of organic solvents, which are not recommended in paediatric formulations due to their potential side effects. The non-use of organic solvents and the completion of the coating process in only 3 steps are advantages over other studies on developing enteric formulations of OME for paediatric populations, such as the study by Federica Ronchi et al. [19]. In this study, organic solvents were used to prepare the coating dispersions, and the process was carried out in 5 steps.

The first coating dispersion was prepared by dissolving disodium phosphate dodecahydrate, lactose monohydrate, and lauryl sulphate in water (in the listed order). Then, omeprazole was dispersed in the above solution and added to a previously prepared aqueous solution of Hypromellose and hydroxypropyl cellulose. The pH was adjusted to 7.5 with a 0.1 N NaOH solution. The second coating solution was prepared by dissolving

Hypromellose in water. The third coating dispersion was prepared by dissolving triethyl citrate and a 1 N NaOH solution in Eudragit® L-30 D-55. At the same time, a dispersion of titanium dioxide and talc in water was prepared. This dispersion was added to the solution and kept under constant stirring until complete homogenisation. Coating dispersions 1 and 3 were passed through a 200 µm sieve before coating to avoid possible lumps that could clog the gun. Furthermore, they were kept under continuous and gentle stirring (mechanical stirrer: Heidolph, model Hei-TORQUE CORE) during the whole coating process to avoid the sedimentation of the insoluble components.

Table 2 specifies the composition of the 3 coating layers and the function of each excipient in the formulation [20].

Table 2. Formulations of the coating layers.

Component	Functions	First Coating Layer	Second Coating Layer	Third Coating Layer
Omeprazole, micronised	API	9.50%	---	---
Hypromellose (Grade 606)	Film-forming agent	1.64%	3.40	---
Hydroxypropyl cellulose	Film-forming agent and binder	1.87%	---	---
Disodium phosphate · 12 H_2O	Buffering agent	0.50%	---	---
Lactose monohydrate	Filler, carrier, and dispersant agent	2.50%	---	---
Sodium lauryl sulphate	Witting and dispersing agent	0.15%	---	---
Eudragit® L-30 D-55	Enteric polymer	---	---	74.56%
Triethyl citrate	Plasticising and film-forming agent	---	---	2.67%
Sodium hydroxide 1 N	pH regulator	---	---	7.23%
Titanium dioxide	Adjuvant of the film-forming agent, opacifier, and pigment blocker	---	---	0.77%
Talc	Opacifying agent	---	---	5.03%

The coating process was carried out in a dark room to avoid the possible degradation of omeprazole by light. The first and second coating layers were successively deposited on the inert MCC pellets to minimise degradation. In the first coating layer, the dispersion was applied until an average pellet weight increase of 25 ± 3% was achieved. Layers 2 and 3 were applied until the average weight increases specified in the FFD were achieved (see Table 3). Before coating with the third layer, the obtained pellets were sieved to avoid possible agglomerates (600 µm sieve). The pellets obtained were sorted by passing them through a 600 µm sieve (agglomerates) and then a 380 µm sieve (fines). Pellets that passed through the 600 µm mesh and were retained in the 380 µm mesh were considered correct. The working conditions for the three coating layers are detailed in the Supplementary Data.

Table 3. Average pellet weight increases according to the FFD.

Experiment	Second Coating Layer: Average Pellet Weight Increase	Third Coating Layer: Average Pellet Weight Increase
1	6%	100%
2	4%	75%
3	6%	50%
4	2%	100%
5	2%	50%

2.2.3. Characterisation: API and Coated Pellets

Determination of Particle Size Distribution (PSD)

The particle size distribution of micronised omeprazole was determined following the general method "2.9.31. Particle size analysis by laser light diffraction" of the Eur. Ph. [21] using a Mastersizer 2000 (Malvern), with the dry basis SCIROCCO 2000 module. The sample was placed in the Scirocco accessory tray, and the method described in Table 4 was followed.

Table 4. Method of determining the PSD of micronised omeprazole.

Material	Polystyrene Latex
Refractive index	1.59
Control of particle distribution	
– Vibration	50%
– Pressure	2 Bar
Measurement cycles	
– Measurement time	6 s
– Measurement snaps	6000
– Background time	6 s
– Aliquot measures	1

The PSD of the pellets obtained from the best-performing FFD experiment was also determined. As the omeprazole pellets were larger than 75 µm, we decided to use the sieving method to determine their PSD, following the general method "2.9.38. Particle Size Distribution. Estimation by analytical sieving" of the Eur. Ph. [22]. Theoretically, omeprazole pellets have a PSD of 510 µm, so 4 sieves with different spacings (0.60, 0.5, 0.40, and 0.30) were used. The sieve cascade was placed on a vibrating sieve shaker (CISA). On the top sieve, 10 ± 0.05 (SD) g of omeprazole pellets was placed and kept under vibration at power 10 for 10 min. The sieves and the base were weighed with the fraction of omeprazole pellets retained. The test was carried out in triplicate.

Determination of Flow Properties of OME Enteric Pellets

The angle of repose and sliding velocity measurements were conducted to determine the flow properties of omeprazole enteric pellets. Additionally, the Hausner ratio was measured. The tests were performed in accordance with the recommendations outlined in the European Pharmacopoeia monographs "2.9.16. Flowability" [23] and "2.9.36. Powder flow" [24].

An ANORSA funnel with reference X5992 and a sheet of millimetre paper were utilised to measure the angle of repose. The funnel was secured in a metal support clamp, with the centre of the millimetre paper positioned just below the lower mouth of the funnel, 7 cm from the paper. The funnel was covered with a piece of paper and filled with the omeprazole enteric pellets. Subsequently, the paper was removed, and the pellets were allowed to fall onto the millimetre paper. If they did not fall out easily, the funnel was gently tapped with a metal spatula until all pellets slid out. The test was conducted in triplicate.

On the other hand, the sliding speed test was carried out using an ANORSA funnel with the reference X7705. For this test, 100 g of omeprazole enteric pellets was weighed, and the mouth of the funnel was covered with paper. The funnel was then filled with the sample, and the paper covering the mouth of the funnel was removed. The time taken for the entire sample to slide down the funnel was recorded. The test was conducted in triplicate.

Determination of Coating Uniformity

A morphological evaluation of the coating uniformity of the enteric layer (outer layer) and protective and API layers (inner layers) was carried out using scanning electron microscopy (SEM). A J-6510 scanning electron microscope was used, with a GATAN ALTO-1000 freezing unit and a backscattered electron detector (EDS). Coated pellets were cut with a scalpel under a magnifying glass and mounted on microscope specimen holders to observe the different coating layers. The samples were coated with a conductive carbon wire and observed after 24 h. They were observed at different magnifications between 120x and 220x. X-ray microanalysis was performed using an EDS detector to determine the elemental composition of each layer.

Determination of API via Infrared Radiation

A sample of micronised omeprazole was analysed using an IR spectrometer (Thermo Nicolet, Avatar 320 FT-IR, Caldic, Chicago, IL, USA). This determination was used to identify the API. A plot of the results shows the spectrum of the substance, expressing the frequency values in cm^{-2}.

Differential Scanning Calorimetry (DSC)

The samples of micronised OME and coated pellets were thermally analysed using a differential scanning calorimeter (DSC). The analysed OME enteric pellets were obtained from the best-performing experimental design of the 5 specified in the FFD. Thermograms were obtained using a DSC-822e (Mettler-Toledo, Oakland, CA, USA) under a nitrogen flow rate of 50 mL/min. The samples were crimped in an aluminium sample dish and heated at a rate of 10 °C/min from 30 to 300 °C. Also, the melting point of API was determined.

Determination via X-ray Diffraction (XRD)

XRD analysis was performed using an X'Pert Pro MPD X-ray diffractometer (PANalytical, Malvern, UK). The samples of micronised OME and OME enteric pellets from the best-performing FFD experiment (intact and grounded) were encapsulated between polyester films with thicknesses of 3.6 micrometres. The measurements were carried out from 2 to 60°2θ, with a step size of 0.026°2θ and a measuring time of 300 s per step.

2.2.4. Evaluation of Omeprazole Content

The technical procedures of European Pharmacopoeia were used as a reference to assess whether the individual omeprazole contents were within the limits set with reference to the average content of coated pellet samples. Ph. Eur. monograph "2.9.6. Uniformity of contents of single-dose preparations" was employed to determine content uniformity [25]. As enteric pellets do not have a specific test, the procedure suitable to tablets was chosen. In this standard, preparation complies with the test if each content is between 85% and 115% of the average content. To assess the omeprazole content of the coated pellets, pellets equivalent to 20 mg OME were weighed and transferred to a 50 mL volumetric flask. Then, 10 mL of ethanol 96° was added, and the flask was sonicated for about 15 min. Next, 20 mL of 0.1 M sodium borate solution was added and sonicated for 15 min. Finally, the solution was tempered and made up to volume with a 0.1 M sodium borate solution. An aliquot was filtered, and the amount of dissolved omeprazole was determined via UV-vis HPLC (Agilent 1100 series, Waldbronn, Germany). The test was performed in triplicate.

2.2.5. Gastro-Resistance Trial

The gastro-resistance of OME enteric pellets was determined with a USP apparatus II (Erweka DT 700, Langen, Germany). USP-NF monograph "Omeprazole delayed-release capsules" was used to determine gastro-resistance [26]. For this assay, USP-NF tolerances state that no more than 15% of the amount of omeprazole should be dissolved within 2 h. Each dose, containing coated pellets equivalent to 20 mg of omeprazole, was placed in a vessel containing 0.1 N hydrochloric acid (500 mL) and maintained at 37 ± 0.5 °C with a shaking speed of 100 rpm. Six samples from each FFD experiment were analysed. After 2 h, the medium containing OME enteric pellets was filtered through a sieve with an aperture of NMT 0.2 mm. The samples were collected in a sieve and rinsed with water. With approximately 10 mL of ethanol 96°, OME enteric pellets were carefully transferred to a 50 mL volumetric flask and sonicated for 15 min. After that, 20 mL of 0.1 M sodium borate solution was added and sonicated again for 15 min. Finally, the solution was tempered and made up to volume with 0.1 M sodium borate solution. An aliquot was filtered, and the amount of dissolved omeprazole was determined via UV-vis HPLC (Agilent 1100 series, Waldbronn, Germany).

2.2.6. Dissolution Trial

The drug release profiles of OME enteric pellets were determined using a USP apparatus II (Erweka DT 700, Langen, Germany). The dissolution method from the USP-NF monograph for "Omeprazole delayed-release capsules" was used [26]. According to the USP-NF tolerances, no less than 75% of the omeprazole should dissolve within 30 min. Each dose, which contained OME enteric pellets equivalent to 20 mg OME, was placed in an apparatus II vessel containing 0.1 N hydrochloric acid (500 mL) and maintained at 37 ± 0.5 °C with a stirring speed of 100 rpm. After 2 h, 400 mL of 0.235 M dibasic sodium phosphate was added to the 500 mL of 0.1 N hydrochloric acid in the vessel. The pH was adjusted to 6.8 ± 0.5 using 2 N hydrochloric acid or 2 N sodium hydroxide as necessary. The samples were taken at 15, 30, and 45 min and filtered before determining the amount of dissolved omeprazole using UV-vis HPLC (Agilent 1100 Series, Waldbronn, Germany). The dissolution assay was performed in triplicate for each FFD experiment.

3. Results and Discussion

3.1. Characterisation: Micronised OME and OME Enteric Pellets

3.1.1. Particle Size Distribution

The PSD determination of raw material indicated that 10% of omeprazole particles are smaller than 1.299 µm, 50% are smaller than 4.872 µm, and 90% are smaller than 12.913 µm. It is confirmed that the omeprazole used in this study was micronised (see Figure S1 of supplementary data). OME enteric pellets obtained from FFD experiment 4 showed the best gastro-resistance and release results. Therefore, they were chosen for characterisation. The PSD of these pellets indicates that 70% ± 0.68 (SD) have a mean diameter between 0.6 and 0.5 mm. Thus, the theoretical size of the OME enteric pellets is confirmed (see Table 5). The Supplementary Data show the PSD of micronised omeprazole (see Figure S1).

Table 5. PSD of OME enteric pellets obtained from FFD experiment 4.

Sieve Light (mm)	Sieve Tare (g) ± SD	Sieve Weight + Retained Sample (g) ± SD	Retained Fraction (g) ± SD	Retained Fraction (%) ± SD
0.60	458.42 ± 0.03	458.42 ± 0.03	0.00	0.00
0.50	433.48 ± 0.05	440.66 ± 0.04	7.18 ± 0.04	70.47 ± 0.68
0.40	381.84 ± 0.05	384.73 ± 0.07	2.89 ± 0.07	28.38 ± 0.59
0.30	407.77 ± 0.11	407.85 ± 0.11	0.08 ± 0.01	0.79 ± 0.09
Base	378.41 ± 0.01	378.41 ± 0.0.1	0.00	0.00

3.1.2. Determination of Flow Properties of OME Enteric Pellets

Tests to determine the flow properties of the selected pellets, chosen as the final tests, are outlined in Table 6. An average sliding velocity of 6.05 s ± 0.15 (SD), an average angle of repose of 27.39° ± 0.84 (SD), and a Hausner ratio of 1.086 were obtained. According to the "2.9.36. Powder Flow" [24] monograph of the Ph. Eur., the enteric omeprazole pellets from experiment 4 exhibit excellent flow properties. This is evident as the angle of repose falls within the range of 25–30°, the Hausner ratio falls within the range of 1.00–1.11, and the sliding velocity is notably rapid.

Table 6. Flow properties of OME enteric pellets obtained from FFD experiment 4.

Angle of Repose (°) ± SD	Bulk Density (g/mL) ± SD	Tapped Density (g/mL) ± SD	Sliding Velocity ± SD	Hausner Ratio
27.39 ± 0.84	0.81 ± 0.03	0.87 ± 0.01	6.05 ± 0.15	1.09

3.1.3. Determination of Coating Uniformity

Regarding the microscopic observation of OME enteric pellets via SEM, Figure 1 shows the resulting images from secondary electron (SEI) and backscattered electron (BEC) detection. The figure also shows images obtained from the XR microanalysis (EDS) of the elemental composition of pellet coating layers. Thus, the inert core, active layer, and enteric layer are identified. Small imperfections such as roughness, porosity and cracks are identified on the surfaces. These coating imperfections are in line with the results obtained in the gastro-resistance test, in which 95% of the total APIs was recovered and 5% was degraded. The degraded percentage of APIs is due to small parts of the coated pellet surface that were not fully coated by enteric polymer. It is also worth mentioning that these imperfections could be due to the lack of precision when cutting the pellets, which was not easy due to their size. Figure 2 shows the results of EDS mapping, which corroborate the above observations: the inert CCM core is clearly differentiated from the API layer and enteric layer. The protective layer, being so thin and containing only carbon, hydrogen, and oxygen in its elemental composition, could not be differentiated. The obtained images show a remarkable surface homogeneity. Figure 2G shows sulphur, an element that is only part of the chemical structure of omeprazole, homogeneously distributed around the inert core (MCC spheres). This indicates a homogeneous distribution of omeprazole in the obtained coated pellets. Figure 2E,F,H shows magnesium, silicon, and titanium homogeneously distributed in the outermost layer. These elements are part of the chemical structure of excipients in the enteric coating. Figure 2D shows how sodium is distributed in the API and enteric layers, as this element is part of the elemental composition of excipients in both layers ($Na_2PO_4 \cdot 12H_2O$ in the API layer and NaOH in the enteric layer).

3.1.4. Infrared Radiation, Differential Scanning Calorimetry, and X-ray Diffraction

The IR spectrum of micronised omeprazole demonstrates characteristic stretches, which confirms the identity of the API used in the experiments. Figure S1 of the Supplementary Data shows the obtained spectrum. In summary, the observed characteristic stretches in the IR spectrum are the following: (I) the absorption band for C=C stretching vibrations of the benzene ring is observed at 3062 cm^{-1}; (II) C-H stretching vibrations are observed at 2903.4 cm^{-1}; (III) C-N stretching vibrations of the pyridine ring are observed in the range of 1158.54–1310.92 cm^{-1}; (IV) N-H bending vibrations of the pyridine ring are observed in the range of 1510.14–1627.12 cm^{-1}, and the absorption band for S=O stretching vibrations of the sulfone group is observed in the range of 1012.25–1111.94 cm^{-1}.

DSC and X-ray analysis were used to investigate the micronised omeprazole's physical state. The DSC thermograms revealed that the raw OME material melted at approximately 158.42 °C, a value that aligns with the literature and affirms the crystalline nature of the raw API. In the case of OME enteric pellets, the first phase of melting was attributed to triethyl citrate at 60.08 °C, a value in agreement with the documented melting point of this excipient

in the scientific literature [27]. Subsequently, the thermograms exhibited the melting of micronised omeprazole at 143.08 °C, accompanied by two endothermic bands associated with decomposition processes (with peaks at 149.22 °C and 157.95 °C). A third band (with a peak at 206.95 °C) was indicative of the decomposition of Eudragit® L30 D-55 [28,29]. The X-ray diffractogram of micronised omeprazole exhibited its characteristic peaks related to a crystalline structure. The diffractogram of the OME enteric pellets (ground or intact) revealed crystalline excipients, such as titanium dioxide (Antase) and talc. Additionally, amorphous, or partially crystalline, excipients were observed. The peaks of the crystalline phases of omeprazole (using the diffractogram of micronised OME as a reference) were clearly visible. Figure 3 shows the diffractograms and thermograms obtained for both omeprazole and coated pellets. The Supplementary Data show the individual thermograms and diffractograms for each sample.

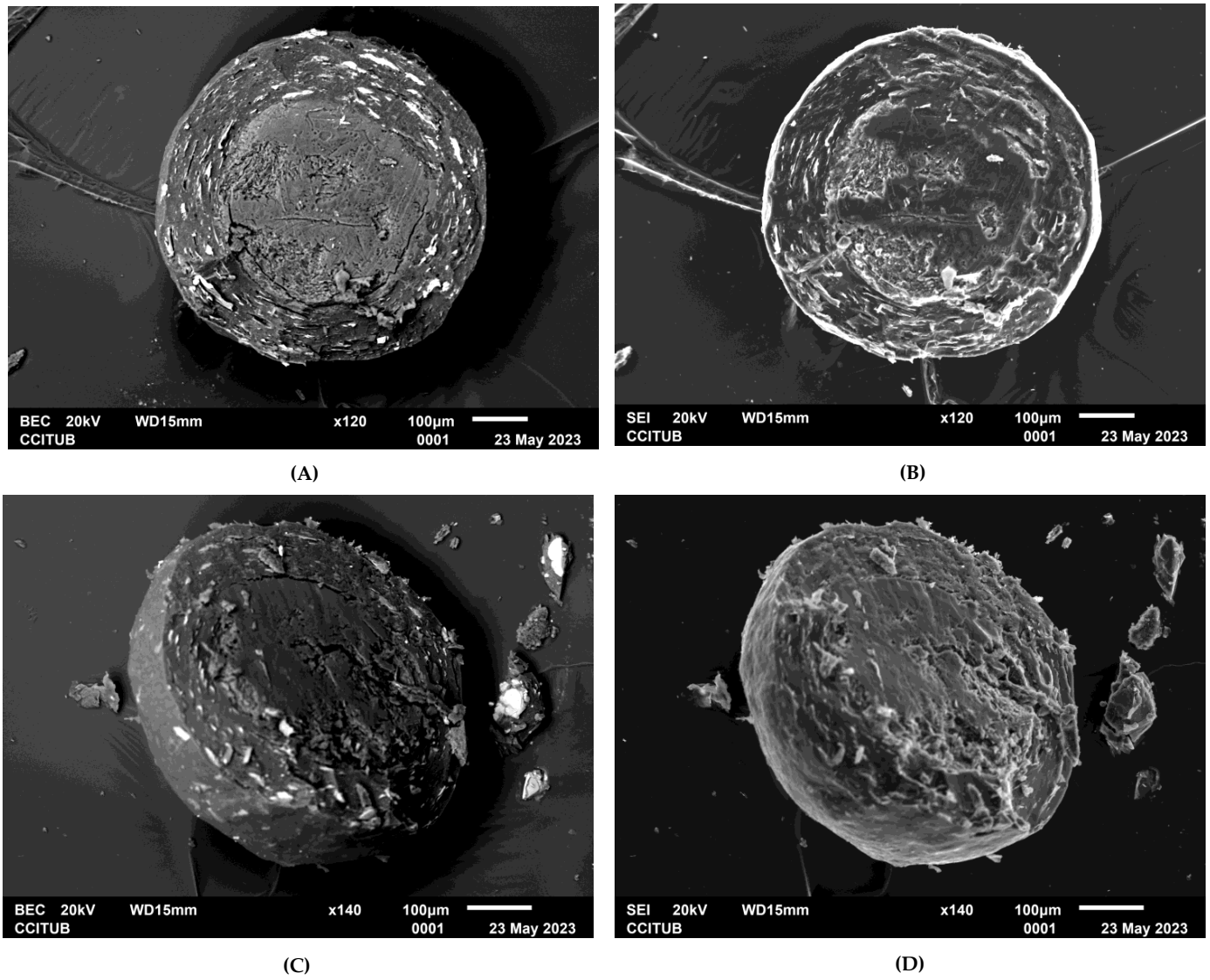

Figure 1. Micrographs of the cross-sectioned enteric pellets of OME obtained via SEM. Images (**A**) and (**B**) were obtained at 120x and (**C**) and (**D**) at 140x.

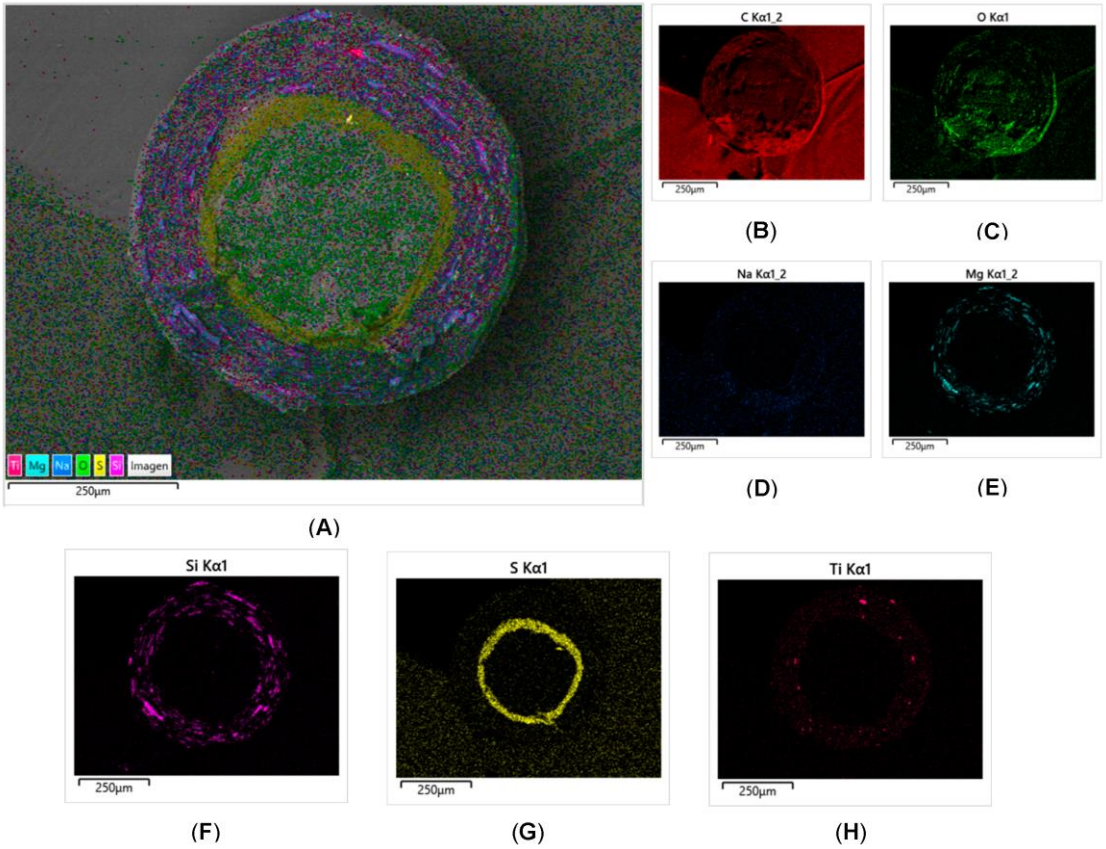

Figure 2. Energy-dispersive X-ray spectroscopy (EDS) micrographs of omeprazole enteric pellets. Subfigure (**A**) presents the results of EDS mapping, illustrating the various components of the coating layers: Ti (pink), Mg (navy blue), sodium (blue), O (green), S (yellow), and Si (purple). Subfigures (**B**–**H**) depict the distribution of each component within the pellets. Notably, (**G**) showcases the homogeneous distribution of sulphur, an element exclusive to the chemical structure of omeprazole, surrounding the inert core.

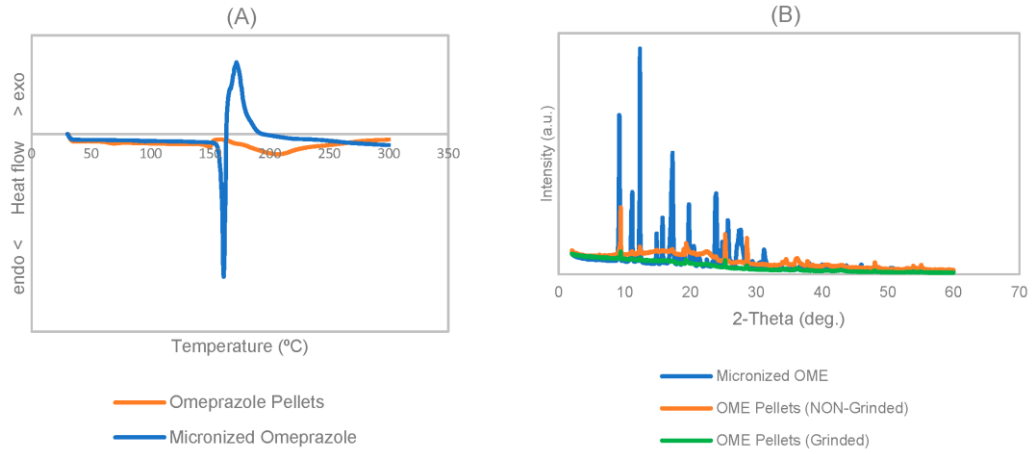

Figure 3. Drug characterisation: (**A**) DSC and (**B**) XRD.

3.2. Experimental Responses of the FFD

3.2.1. Evaluation of Omeprazole Content

The evaluation of the OME content tests was satisfactory: the average API content in OME enteric pellets of the three coating layers of the different experiments was 100% (see

Table 7). Therefore, content uniformity complied with the specifications of the Ph. Eur. [25], as the obtained values are within the range of 85–115%.

Table 7. Evaluation of OME content in coated pellets.

Experiment	Theoretical Dose (mg) ± SD	Actual Dose (mg) ± SD	Dose Accuracy (% (*w*/*w*)) ± SD
Experiment 1	24.67 ± 0.18	24.72 ± 5.49	100.20 ± 1.13
Experiment 2	28.64 ± 3.93	28.67 ± 8.23	100.10 ± 1.41
Experiment 3	27.24 ± 5.32	27.26 ± 7.22	100.07 ± 1.43
Experiment 4	25.19 ± 3.88	25.23 ± 15.40	100.16 ± 2.36
Experiment 5	27.07 ± 10.25	27.06 ± 12.28	99.96 ± 0.40

3.2.2. Gastro-Resistance Trial

The degradation of omeprazole in acidic media makes gastro-resistance testing in this medium a prerequisite for demonstrating the stability of the API.

Table 8 shows the results of gastro-resistance tests performed with the coated pellets obtained from the DoE. The results of experiments 1 and 4 were the most satisfactory, as in both experiments, the USP specification was met, since after the gastro-resistance test, an API percentage higher than 85% is recovered. Experiment 4 is the most optimal, with an average API percentage after the gastro-resistance test of 95%. In experiments 1 and 4, the average weight increase of the enteric coating was 100%, which is the average weight increase necessary to avoid API degradation and comply with the specifications. The reason for the high average weight increase used is that the chosen inert pellets that were used in the experiments are very small (200 µm in diameter). It is necessary to apply a higher amount of the enteric coating to cover the entire surface area of the pellets effectively when dealing with such small particles.

Table 8. Gastro-resistance of coated pellets.

Experiment	Dose Accuracy after Gastro-Resistance Test (% (*w*/*w*)) ± SD	Amount of API Degraded after Gastro-Resistance Test (%) ± SD
1	87.06 ± 1.06	12.94 ± 1.06
2	78.06 ± 1.88	21.93 ± 2.01
3	80.64 ± 1.34	19.36 ± 1.34
4	95.13 ± 1.29	4.87 ± 1.30
5	79.93 ± 1.59	20.07 ± 1.56

The results obtained in experiments 2, 3, and 5 confirm that with a 50% and 75% increase in the weight of the enteric coating, a level of gastro-resistance exceeding 85% is not achieved. These findings suggest that it is possible that not the entire specific surface area of the pellets is covered with the enteric coating, thus leading to API degradation in an acidic environment. This could explain the behaviours observed in experiments 2, 3, and 5. Additionally, it is important to note that the difficulty in pellet recovery (filtration + transfer to a volumetric flask) after the gastro-resistance test, due to the small size of the pellets, could contribute to the observed losses in the API. Since the results of experiments 1 and 4 confirmed that a 100% increase in the enteric coating weight is required to achieve the necessary gastro-resistance, we concluded that a 100% increase in the weight of the enteric coating is essential in these circumstances to ensure adequate gastro-resistance.

3.2.3. Dissolution Trial

Dissolution testing serves as an important tool in the biopharmaceutical characterisation of a product at different dosage stages, from drug development to the quality control and quality assurance of the final product [30]. Therefore, dissolution assays are of great interest in drug development, allowing the simulation of the in vitro behaviour of investigational dosage forms. Dissolution tests were performed on the OME enteric pellets obtained

from the DoE. The results of the dissolution profiles are displayed in Figure 4, where experiments 1 and 4 are the fastest-releasing experiments. Both experiments 1 and 4 complied with the USP-NF specifications [26]. After 30 min, they achieved an API percentage of more than 75%, particularly 80.95% ± 2.34 (SD) in experiment 1 and 82.61% ± 1.67 (SD) in experiment 4. On the other hand, experiments 3 and 5 exhibit lower release rates at 67% ± 1.30 (SD) and 65% ± 4.00 (SD), respectively. These two experiments feature a 50% enteric coating. As revealed in the gastro-resistance test (refer to Table 7, Section 3.2.2), this level of enteric coating does not provide complete resistance to the 0.1 N hydrochloric acid medium. Consequently, it can be inferred that the reduced release is attributed to a portion of the API undergoing degradation during the initial phase of the dissolution test. In experiment 2, a slightly higher release rate of 70% ± 1.37 (SD) is achieved.

It is important to emphasise that while a thicker coating typically leads to longer dissolution times, our experimental results reveal a different scenario. Experiments 1 and 4, featuring a 100% weight increase and exhibit a faster dissolution profile compared to experiment 2, with a 75% weight increase, and experiments 3 and 5, with a 50% weight increase. This can be attributed to several factors: Even when formulations are identical, minor variations in coating uniformity and the response to the gastric environment can explain the observed differences in the dissolution rates. Although these differences may be subtle, they hold significant implications for the efficacy of the final product. Furthermore, it is worth noting that the limited degradation of the API during the initial phase of the dissolution test, combined with the physicochemical characteristics of omeprazole, represents a primary factor preventing the 100% release in any experiment.

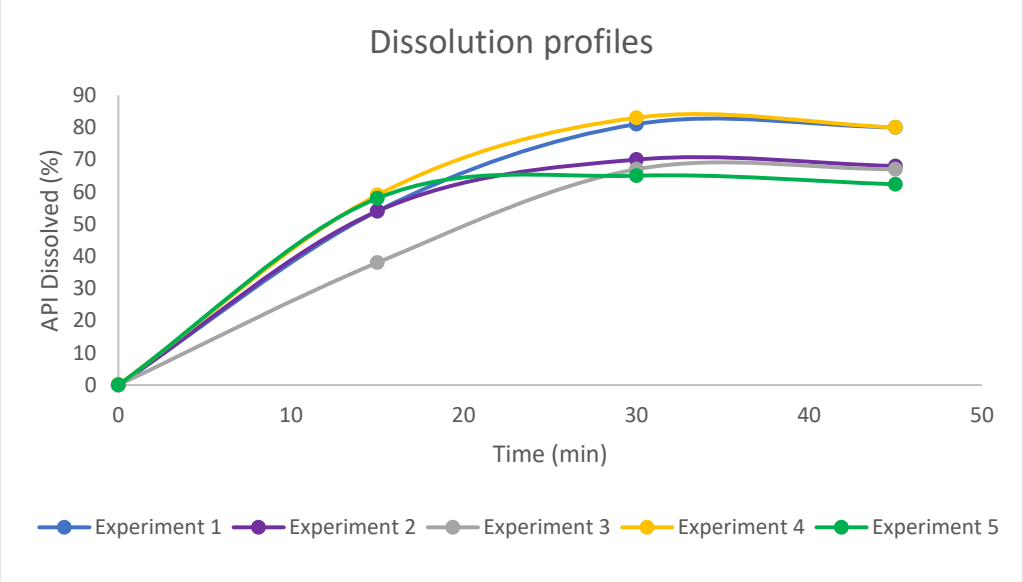

Figure 4. Dissolution profiles of FFD coated pellets.

3.3. Statistical Analysis of the Full Factorial Design

After the regression analysis of the DoE data provided by Minitab, we observed that the evaluation of the omeprazole content depends on both factors, with a *p*-value regression of 0.028 and an R^2 of 97.3%, and the dissolution depends only on Factor B (average percentage increase of the enteric layer), with a *p*-value regression of 0.066 and an R^2 of 72%. For gastro-resistance, no model was found that describes its association with the factors studied. The experiment designs did not include replicates, which influenced the statistical analysis results, making them not highly robust. Replicates would provide the possibility to evaluate the existing interactions, and the number of data would allow more precision in determining the model. Therefore, we decided to use statistical analysis in a qualitative way: contour plots to optimise the development process of omeprazole enteric

pellets. Figures 5–7 show the Pareto and contour plots for each response studied in relation to Factors A and B. In the Pareto diagrams, the factors that exceed the standard line by 85% are the factors that significantly influence each response. In this case, the alpha value used was 0.15, as this avoided discarding data that could have significance in the model studied, allowing for a conservative assessment of the data. The contour plots are also presented, showing the most optimal working areas.

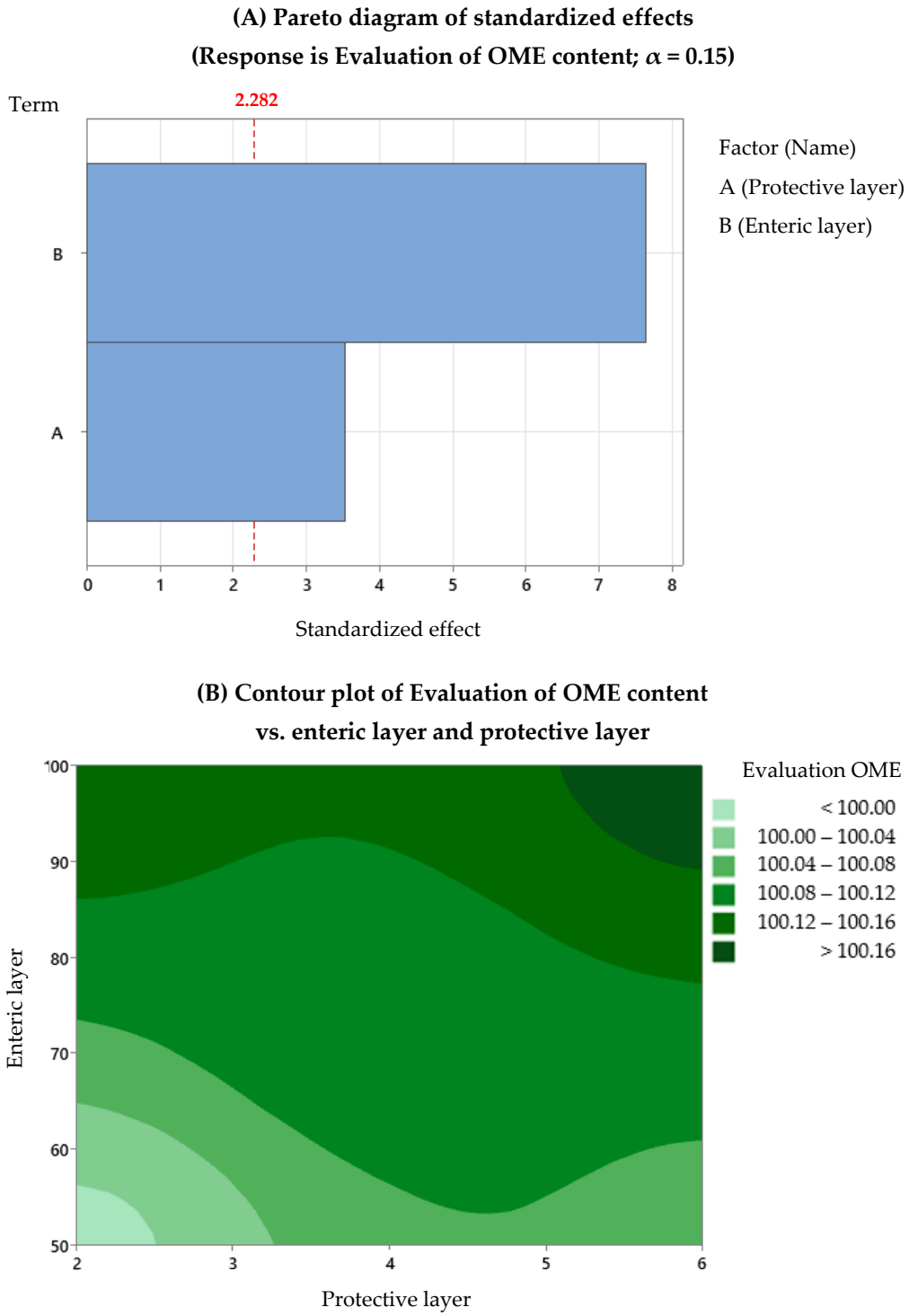

Figure 5. Evaluation of omeprazole content: (**A**) Pareto diagrams and (**B**) contour plots.

Regarding the evaluation of the omeprazole content response, the optimal working zone corresponds to a percentage increase in the weight of 100% of the enteric layer.

However, regarding the protective layer, no differences are observed between using 2% and 6%; all conducted experiments give an omeprazole content higher than 100% (as shown in Figure 5A,B).

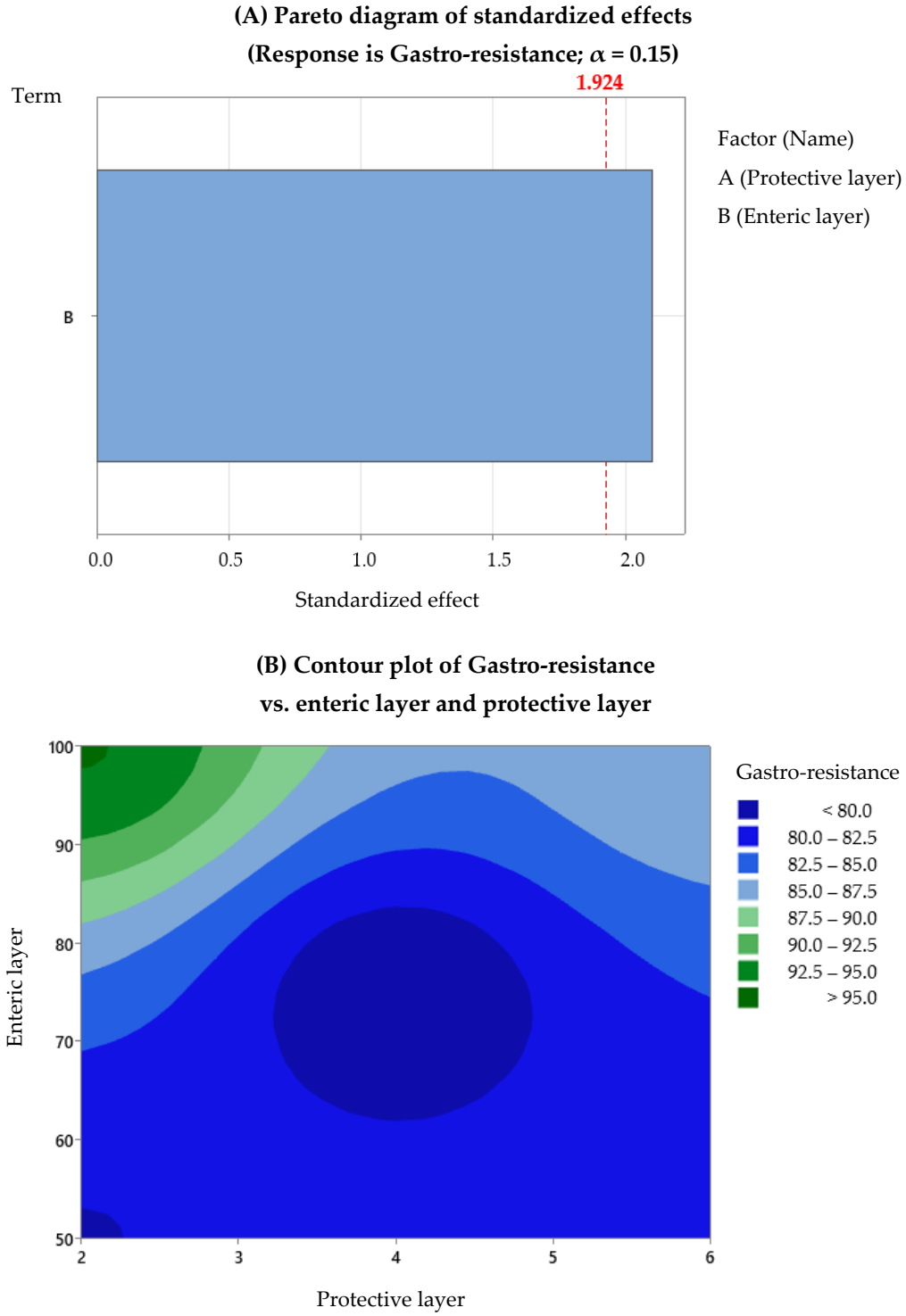

Figure 6. Gastro-resistance: (**A**) Pareto diagrams and (**B**) contour plots.

Regarding the gastro-resistance response, according to the Pareto diagram, only Factor B, which represents the enteric coating, is statistically significant for this response (Figure 6A). The contour plot indicates that a combination of 100% of the enteric coating and 2–3% of the protective coating would result in achieving 95% gastro-resistance (Figure 6B). This suggests that the enteric coating has a significant effect on the abil-

ity of the pellets to resist degradation in the stomach and ensures that the API is not released prematurely.

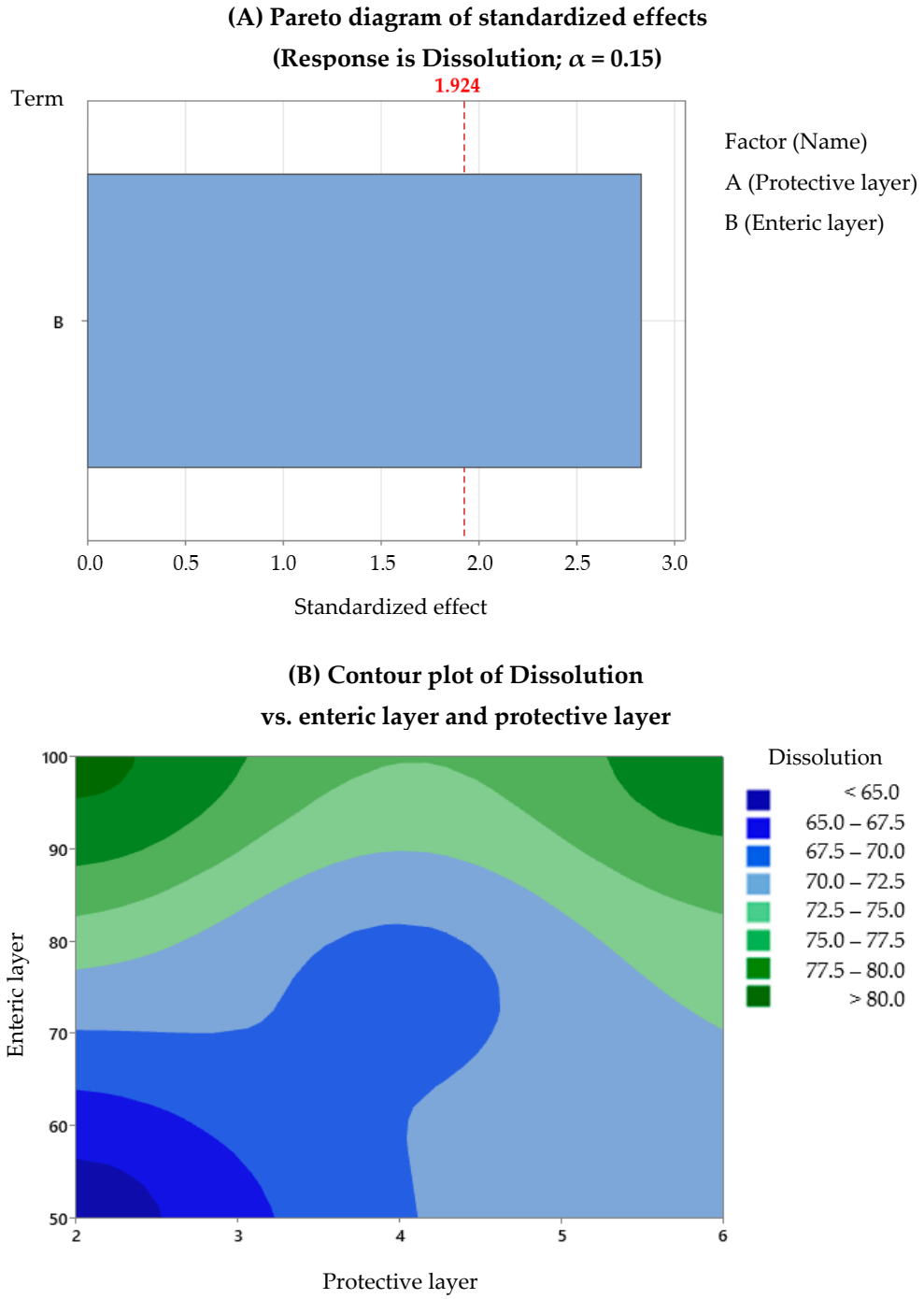

Figure 7. Dissolution: (**A**) Pareto diagrams and (**B**) contour plots. Factor A is not observed in graph (**A**) because the response is solely influenced by Factor B.

As for the dissolution response, only the protective layer is significant according to the Pareto diagram (Figure 7A). Based on the contour plot, the dissolution response would be compliant with the desired specifications when the enteric coating percentage is higher than 85% and/or when the percentage of the protective layer falls between 2% and 6% (Figure 7B). This combination of enteric layer and protective layer percentages ensures that the drug is released effectively, achieving the desired dissolution profile.

With a 100% average weight increase in the enteric layer and a 2% and/or 6% increase in the protective layer, the best gastro-resistance and dissolution characteristics were achieved. These conditions correspond to experiments 1 and 4 (see Table 3). Although promising results have been obtained in these two experiments, more in-depth research and further experimental studies will be necessary to confirm and verify the findings and explore potential interactions between the factors and studied responses with a more accurate statistical model.

4. Conclusions

This study has shown the development of 0.6–0.5 mm diameter omeprazole enteric pellets by applying a full factorial design. The results showed that an optimal coating was achieved using only aqueous coating dispersions, without the use of organic solvents, which has not been published before as far as the authors are aware of. This is of great importance in the paediatric population, as the use of organic solvents in this population is not recommended due to the possible side effects they may cause. We know that due to their morphological characteristics and gastro-resistance properties, OME enteric pellets can be used in pharmaceutical forms for paediatric use as a possible alternative to the compounding formulas of omeprazole currently used in the paediatric population, which must meet the gastro-resistance and quality specifications required to guarantee the therapeutic efficacy of this API. After experimentation, batch 4 is shown to be suitable, which corresponds to the conditions of 2% of the second coating layer and 100% of the third coating layer. The EDS microanalysis of the elemental composition of the inert pellets of experiment 4 of the FFD demonstrated a homogeneity of the coating layers. In the evaluation of the omeprazole content, a percentage of 100% was achieved. In the gastro-resistance test, 95% was not achieved, and in the dissolution test, a release rate of more than 80% was achieved in under 15 min. With these results, Ph. Eur. and USP-NF specifications for omeprazole have been met. Despite the conservative assessment of the statistical analysis results of the FFD, due to its lack of robustness, the proposal of this design is a good strategy to describe the optimal workspace for the two studied factors. Furthermore, the design can also be used to guide further research to optimise the overall coating process.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharmaceutics15112587/s1, Table S1. Working conditions for the 3 coating layers of pellets; Figure S1. PSD of omeprazole raw material; Figure S2. IR spectrum of micronised omeprazole; Figure S3. DSC thermogram of micronized omeprazole; Figure S4. DSC thermogram of omeprazole enteric pellets; Figure S5. X-ray powder diffraction diagram for NON grinded sample of omeprazole enteric pellets; Figure S6. X-ray powder diffraction diagram for grinded sample of omeprazole enteric pellets.

Author Contributions: Conceptualisation, K.R.-E.-H., P.P.-L. and E.G.-M.; methodology, K.R.-E.-H., J.M.S.-N., A.F.-N., B.C.-R. and A.L.-U.; investigation, K.R.-E.-H.; writing—original draft preparation, K.R.-E.-H.; formal analysis, K.R.-E.-H. and P.P.-L.; writing—review and editing, K.R.-E.-H. and E.G.-M.; validation, P.P.-L. and E.G.-M.; visualisation, M.S.-P. and A.N.-R.; supervision, M.R.-O., P.P.-L. and E.G.-M.; project administration, J.M.S.-N. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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Supplementary Materials: Optimisation of the Manufacturing Process of Organic Solvent-Free Omeprazole Enteric Pellets for the Paediatric Population: Full Factorial Design

Khadija Rouaz-El-Hajoui, Encarnación García-Montoya, Andrea López-Urbano, Miquel Romero-Obon, Blanca Chiclana-Rodríguez, Alex Fraschi-Nieto, Anna Nardi-Ricart, Marc Suñé-Pou, Josep María Suñé-Negre and Pilar Pérez-Lozano

1. Coating parameters

Table S1. Working conditions for the 3 coating layers.

Working Conditions	First Coating Layer	Second Coating Layer	Third Coating Layer
Inlet air temperature	50–60 °C	60–65 °C	55–70 °C
Exhaust air temperature	35–45 °C	30–40 °C	35–45 °C
Product temperature	35–45 °C	35–45 °C	35–45 °C
Würster gun pressure	1.3–2 Bar	1.3–2 Bar	1.3–2 Bar
Pump speed	4–8 rpm	2–4 rpm	5–12 rpm
Compound air outlet position	45–90	60–90	60–90

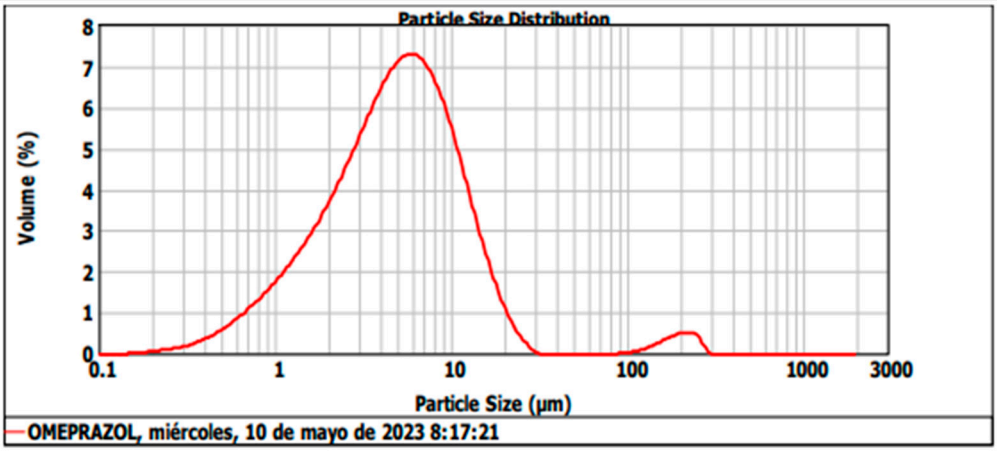
2. Particle size distribution

MASTERSIZER 2000

Result Analysis Report

Sample Name: OMEPRAZOL	**SOP Name:** OMEPARAZOL SCIROCCO	**Measured:** miércoles, 10 de mayo de 2023 8:17:21	
Sample Source & type:	**Measured by:** User	**Analysed:** miércoles, 10 de mayo de 2023 8:17:22	
Sample bulk lot ref: Tesi khadija	**Result Source:** Measurement		
Particle Name: Polystyrene latex	**Accessory Name:** Scirocco 2000	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 1.590	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 2.44 %
Dispersant Name:	**Dispersant RI:** 1.000	**Weighted Residual:** 0.332 %	**Result Emulation:** Off
Concentration: 0.0002 %Vol	**Span :** 2.384	**Uniformity:** 1.47	**Result units:** Volume
Specific Surface Area: 2.13 m²/g	**Surface Weighted Mean D[3,2]:** 2.814 um	**Vol. Weighted Mean D[4,3]:** 9.745 um	

d(0.1): 1.299 um **d(0.5):** 4.872 um **d(0.9):** 12.913 um



Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %
0.010	0.00	0.115	0.00	0.915	5.55	7.287	69.03	51.371	97.98	320.535	100.00
0.011	0.00	0.130	0.00	1.034	6.89	8.233	74.47	58.041	97.98	362.148	100.00
0.014	0.00	0.147	0.00	1.168	8.45	9.302	79.49	65.575	97.98	409.163	100.00
0.018	0.00	0.166	0.01	1.320	10.24	10.510	83.96	70.000	97.98	462.281	100.00
0.021	0.00	0.187	0.04	1.491	12.28	11.874	87.77	74.089	97.98	522.296	100.00
0.027	0.00	0.211	0.08	1.684	14.59	13.416	90.90	83.707	97.98	590.102	100.00
0.030	0.00	0.239	0.14	1.903	17.21	15.157	93.35	94.574	97.98	666.711	100.00
0.034	0.00	0.270	0.23	2.150	20.16	17.125	95.17	98.000	97.98	753.265	100.00
0.038	0.00	0.305	0.35	2.429	23.47	19.348	96.44	106.852	98.00	851.056	100.00
0.043	0.00	0.345	0.51	2.745	27.17	21.860	97.26	120.724	98.05	961.542	100.00
0.049	0.00	0.389	0.73	3.101	31.29	24.698	97.73	136.397	98.16	1086.372	100.00
0.055	0.00	0.440	1.04	3.503	35.83	27.904	97.96	154.104	98.34	1227.408	100.00
0.062	0.00	0.497	1.44	3.958	40.78	31.527	97.98	174.110	98.61	1386.753	100.00
0.070	0.00	0.561	1.97	4.472	46.09	35.620	97.98	196.714	98.98	1566.785	100.00
0.080	0.00	0.634	2.62	5.053	51.69	40.000	97.98	222.251	99.38	1770.189	100.00
0.090	0.00	0.717	3.43	5.709	57.48	40.244	97.98	251.105	99.79	2000.000	100.00
0.102	0.00	0.810	4.40	6.450	63.31	45.469	97.98	283.704	100.00		

Figure S1. PSD of raw material.

3. IR spectrum of the API

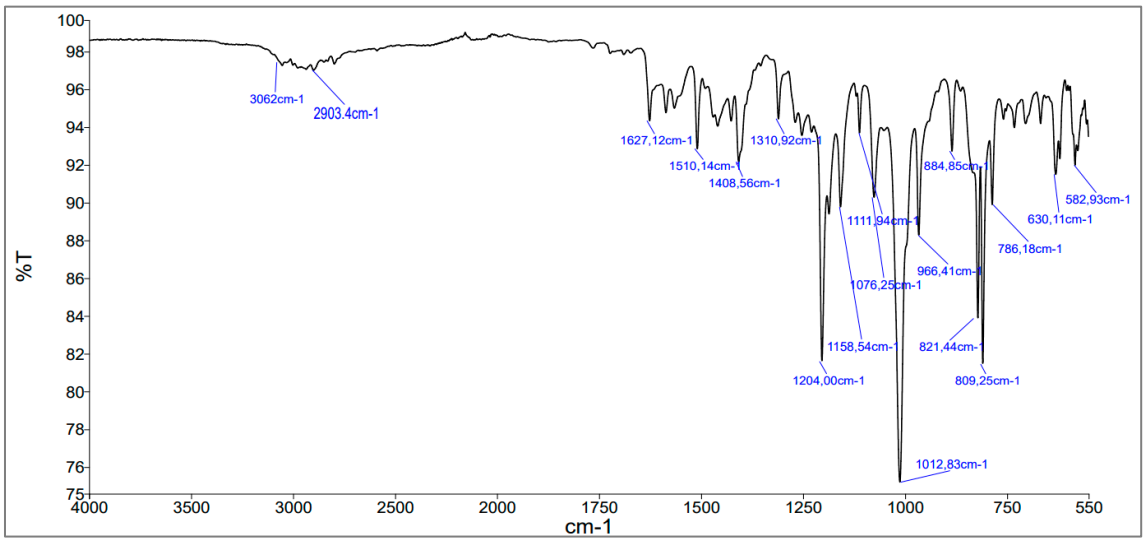


Figure S2. IR spectrum of micronised omeprazole.

4. Differential Scanning Calorimetry analysis

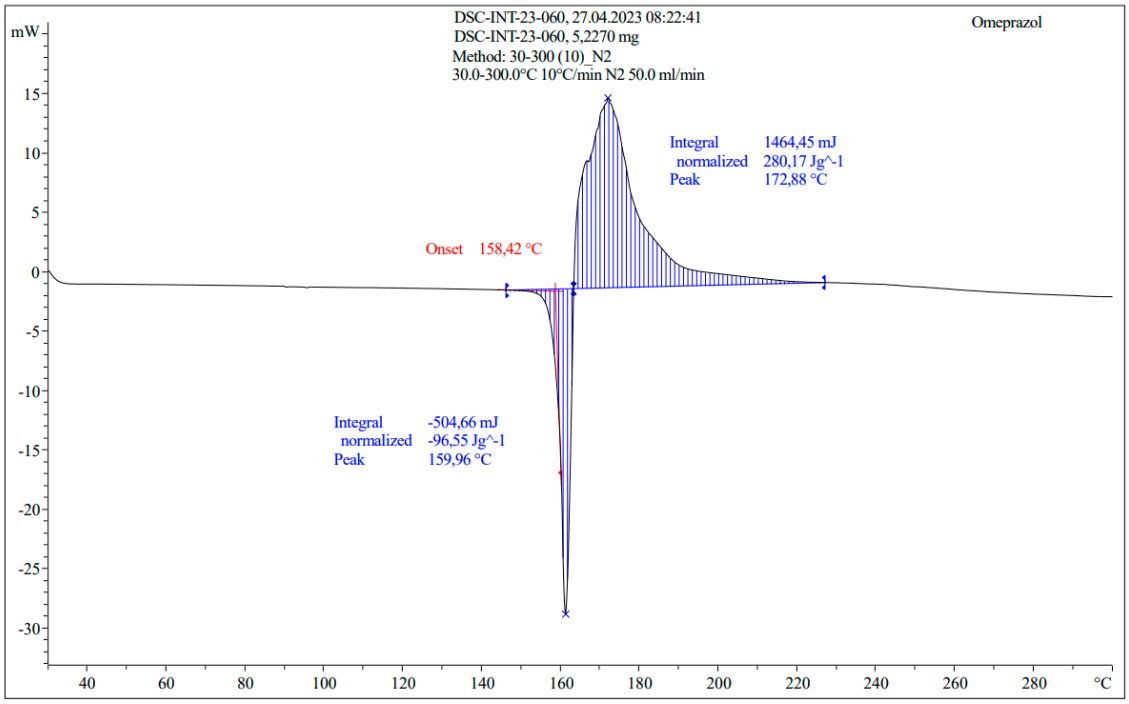


Figure S3. DSC thermogram of micronized omeprazole.

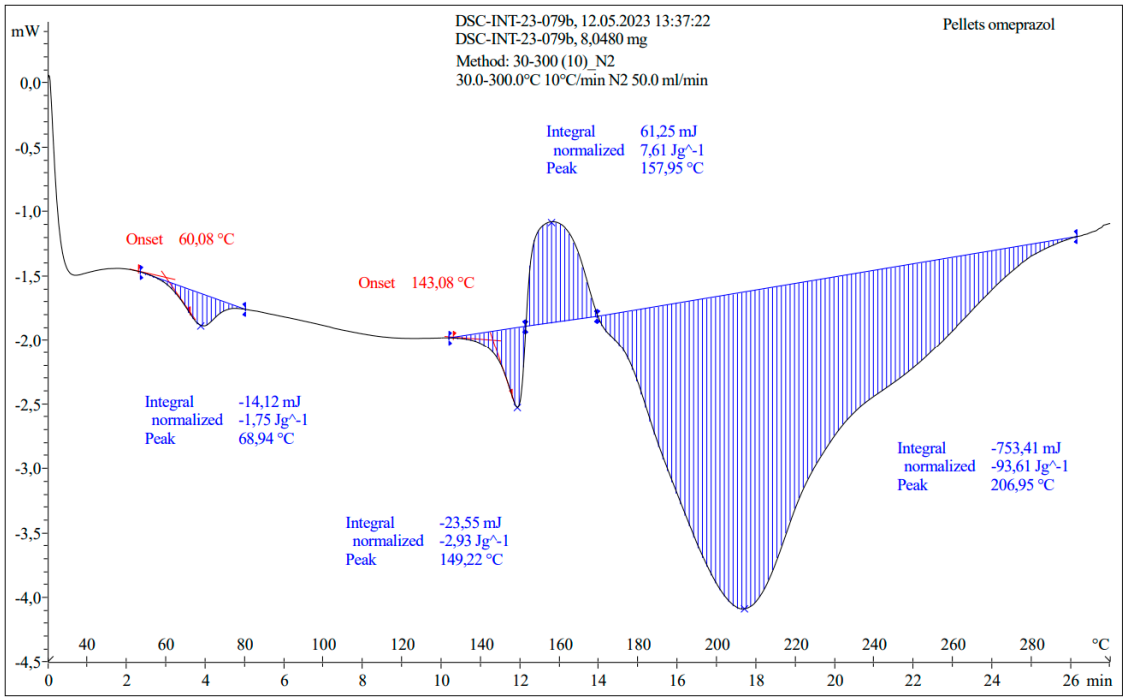


Figure S4. DSC thermogram of omeprazole enteric pellets.

5. X-Ray Diffraction analysis

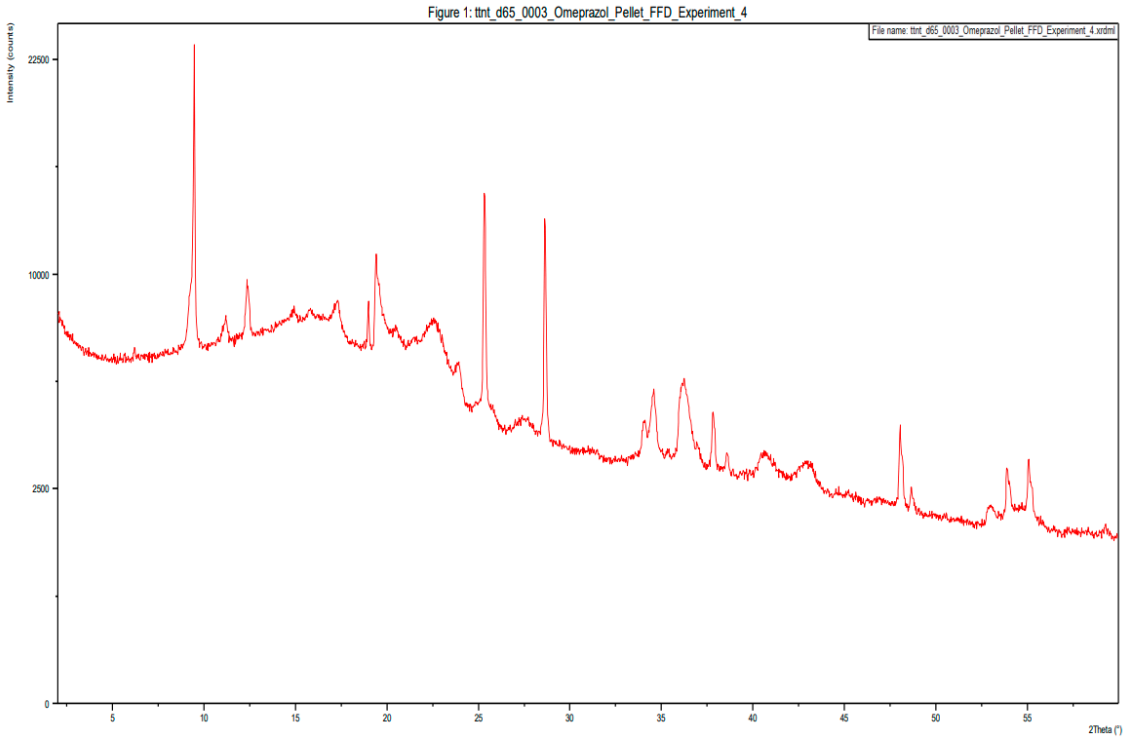


Figure S5. X-ray powder diffraction diagram for NON grinded sample of omeprazole enteric pellets.

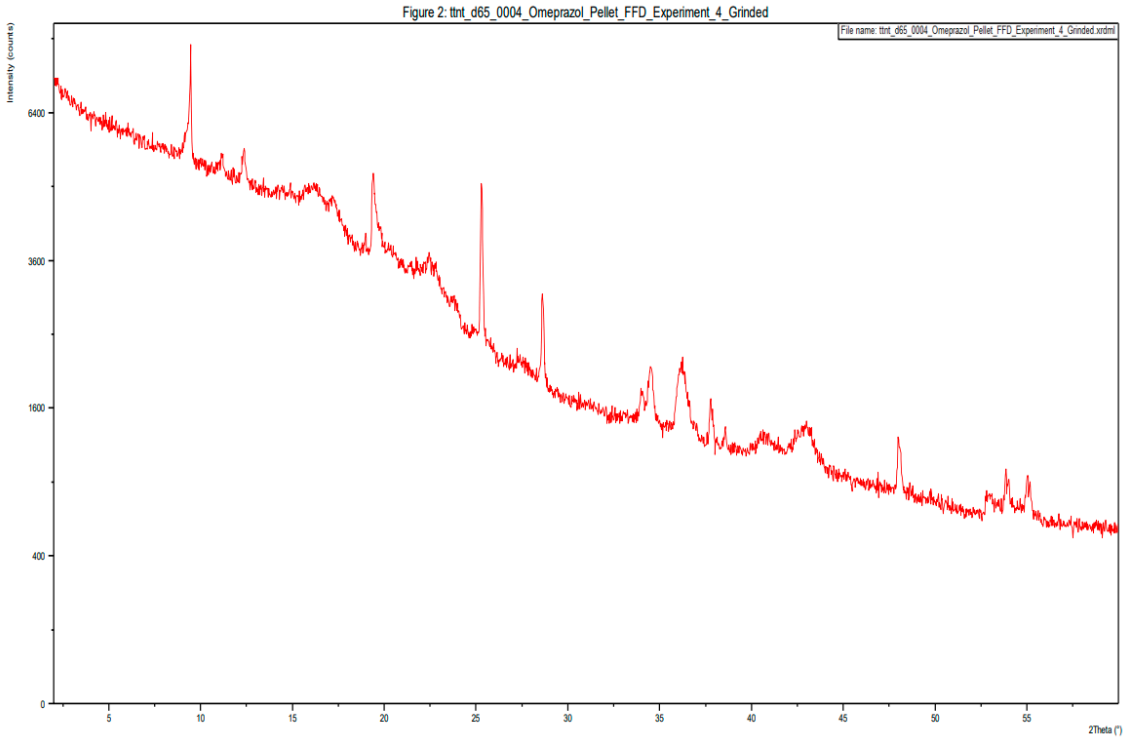


Figure S6. X-ray powder diffraction diagram for grinded sample of omeprazole enteric pellets.

3.2 Publicación 5: Pellets and gummies. Seeking a 3D printed gastro-resistant omeprazole dosage for paediatric administration

Citación	**Rouaz-El Hajoui K**, Herrada-Manchón H, Rodríguez-González D, Fernández MA, Aguilar E, Suñé-Pou M, Nardi-Ricart A, Pérez-Lozano P, García-Montoya E. Pellets and gummies: Seeking a 3D printed gastro-resistant omeprazole dosage for paediatric administration. Int J Pharm. 2023 Aug 25;643:123289. doi: 10.1016/j.ijpharm.2023.123289. Epub 2023 Aug 2. PMID: 37536640.
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Resumen:

La producción de productos farmacéuticos impresos en 3D ha prosperado en los últimos años, y permite generar medicamentos personalizados en pequeños lotes. Esto es especialmente útil para pacientes que necesitan dosis o formulaciones específicas, como los niños. Habitualmente los servicios de farmacia hospitalaria buscan alternativas a las dosis orales sólidas convencionales, optando por formulaciones orales líquidas. Sin embargo, garantizar la calidad y la estabilidad, especialmente en el caso de API sensibles al pH como el omeprazol, sigue siendo un difícil reto. Este artículo presenta la aplicación de la tecnología de impresión 3D por extrusión de semisólidos para desarrollar gominolas (gummies) medicinales a medida del paciente, con un aspecto llamativo, que sirvan como forma farmacéutica innovadora de omeprazol para uso pediátrico. El estudio compara la impresión 3D de hidrogeles con omeprazol dispersado (F1) con hidrogeles cargados con pellets de omeprazol gastro-resistentes (F2). La gastro-resistencia y los perfiles de disolución se estudian con diferentes métodos para una mejor comparación y para subrayar la importancia de la metodología del ensayo. Ambas fórmulas desarrolladas para

la impresión 3D presentan una reología adecuada, buena imprimibilidad y cumplen las normas de uniformidad de contenido y masa. Sin embargo, solo las formas farmacéuticas impresas en 3D con pellets entéricos de omeprazol de las dosis semisólidas masticables (F2) destacan como una estrategia eficaz para abordar el reto de desarrollar una formulación pediátrica con una elevada gastro-resistencia y un perfil de liberación adecuado.

Abstract:

The production of 3D printed pharmaceuticals has thrived in recent years, as it allows the generation of customised medications in small batches. This is particularly helpful for patients who need specific doses or formulations, such as children. Compounding pharmacies seek alternatives to conventional solid oral doses, opting for oral liquid formulations. However, ensuring quality and stability, especially for pH-sensitive APIs like omeprazole, remains a challenge. This paper presents the application of semi-solid extrusion 3D printing technology to develop patient-tailored medicinal gummies, with an eye-catching appearance, serving as an innovative omeprazole pharmaceutical form for paediatric use. The study compares 3D printing hydrogels with dissolved omeprazole to hydrogels loaded with gastro-resistant omeprazole pellets, a ground-breaking approach. Gastro-resistance and dissolution profiles were studied using different methods for better comparison and to emphasize the significance of the assay's methodology. Both developed formulas exhibit proper rheology, good printability, and meet content and mass uniformity standards. However, the high gastro-resistance and suitable release profile of 3D printed chewable semi-solid doses with enteric pellets highlight this as an effective strategy to address the challenge of paediatric medication.

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Pellets and gummies: Seeking a 3D printed gastro-resistant omeprazole dosage for paediatric administration

Khadija Rouaz-El Hajoui [a,1], Helena Herrada-Manchón [c,1], David Rodríguez-González [c,d], Manuel Alejandro Fernández [c], Enrique Aguilar [d], Marc Suñé-Pou [a,b], Anna Nardi-Ricart [a], Pilar Pérez-Lozano [a,b,*], Encarna García-Montoya [a,b]

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ABSTRACT

The production of 3D printed pharmaceuticals has thrived in recent years, as it allows the generation of customised medications in small batches. This is particularly helpful for patients who need specific doses or formulations, such as children. Compounding pharmacies seek alternatives to conventional solid oral doses, opting for oral liquid formulations. However, ensuring quality and stability, especially for pH-sensitive APIs like omeprazole, remains a challenge. This paper presents the application of semi-solid extrusion 3D printing technology to develop patient-tailored medicinal gummies, with an eye-catching appearances, serving as an innovative omeprazole pharmaceutical form for paediatric use. The study compares 3D printing hydrogels with dissolved omeprazole to hydrogels loaded with gastro-resistant omeprazole pellets, a ground-breaking approach.. Gastro-resistance and dissolution profiles were studied using different methods for better comparison and to emphasize the significance of the assay's methodology. Both developed formulas exhibit proper rheology, good printability, and meet content and mass uniformity standards. However, the high gastro-resistance and suitable release profile of 3D printed chewable semi-solid doses with enteric pellets highlight this as an effective strategy to address the challenge of paediatric medication.

1. Introduction

In recent years, the production of 3D printed pharmaceuticals —which refer to medications that are manufactured using 3D printing technology— has thrived. This involves the use of 3D printers to create a wide variety of products, from customized drug dosages to complex drug delivery devices, by depositing successive layers of inks —mixtures of the active pharmaceutical ingredient (API) with a carrier material (excipients)—, according to a selected digital design. The versatility of 3D printing in terms of technologies and materials has made it a focal point of research for personalized medication. Numerous researchers have shared their findings in solid oral dosage forms, focusing on controlled release of active pharmaceutical ingredients (Algahtani et al., 2020; Chen et al., 2021; Cui et al., 2020), printing pills with multiple active ingredients (or polypills) (Haring et al., 2018; Khaled et al., 2015a, 2015b; Pereira et al., 2020), and designing medications tailored to meet specific patient needs, including those with visual impairments (Awad et al., 2020). Additionally, 3D printing enables the production of customized medications in small batches, which is particularly beneficial for patients requiring specific doses or formulations, as children (Januskaite et al., 2020; Scoutaris et al., 2018; Wang et al., 2021). Consequently, instead of relying on a limited selection of standardised commercial products, medications can be printed with the exact dosage and formulation needed by the patient. As a result, processes such as splitting, crushing and dissolving tablets or administering intravenous fluids orally are unnecessary, and risks associated with these

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manipulations —cross-contamination, inaccurate dosing and altered absorption— are avoided (Crawford et al., 2018; Parodi et al., 2015; van Kampen et al., 2022).

At the same time, the need for other administration options for patients who are unable to take medications in solid oral dosages, such as tablets or capsules, has prompted compounding pharmacies to choose alternatives. Regarding paediatric patients, oral liquid formulations are often the most suitable preparations because they allow for safe and easy dosage adjustment (according to body weight, body surface area, etc.) (Batchelor and Marriott, 2015). Consequently, liquid preparations compounded in hospital pharmacies must also be tested for quality and stability as medicinal and commercially available products. However, in practise, reliance is placed on official published information (that is, information from the National Formulary, drug regulatory agencies, web-based bibliographies, etc.) due to the lack of capacity or resources to perform exhaustive controls as in the pharmaceutical industry (Ramírez et al., 2018; Rouaz et al., 2021a).

One of the most widely used API in pharmaceutical compounding for the paediatric population is omeprazole (Chen et al., 2022; Tiengkate et al., 2022; Yang et al., 2022). Omeprazole is an effective and well tolerated proton pump inhibitor (PPI), used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, laryngopharyngeal reflux, and Zollinger–Ellison syndrome (Ramírez et al., 2018; Tiengkate et al., 2022). Helping to relieve symptoms and promote healing of the gastrointestinal tract by means of reducing the production of acid in the stomach, omeprazole was the first clinically useful PPI drug, and its discovery was followed by the formulation of many others in the same family (Flórez et al., 2014; Sachs et al., 2006; Strand et al., 2017). Compounded omeprazole formulations must meet the quality and safety requirements, which are currently very difficult to achieve because of the chemical instability problems of this API. Omeprazole is a white or off-white crystalline powder, which melts at 155 °C with decomposition, has a weak basic character and is freely soluble in lipids, ethanol and methanol, slightly soluble in acetone and isopropanol, and very slightly soluble in water. Its stability is pH dependent, as it degrades rapidly in acidic medium, but remains practically stable under alkaline conditions (European Directorate for the Quality of Medicines & HealthCare (EDQM), n.d.; Strand et al., 2017; The United States Pharmacopeial Convention (USP), n.d.).The development of paediatric formulations with this active substance is limited not only by its physicochemical characteristics, by also but its pharmacokinetic and pharmacodynamic characteristics. As its absorption site is the proximal small intestine, omeprazole must be protected from gastric acid and ensure that it passes through the stomach intact, a fact that is usually not assessed in available compounded oral liquid forms (Shin and Kim, 2013). In this context, further research into new pharmaceutical technologies is needed to offer customised, safe, and high-quality medicines to this population.

As 3D printing of active ingredients is opening new frontiers in drug development, the incorporation of omeprazole in semi-solid printable formulations is herein presented as an alternative in the production patient-specific drug dosages. Semi-solid extrusion (SSE) 3D printing allows the creation of patient-tailored medicinal gummies (Han et al., 2022; Tagami et al., 2021; Zhu et al., 2022), coined by these authors as ‘drugmies’: oral dosages with eye-catching appearance and good organoleptic properties, which can improve treatment adherence and reduce psychological impact of the disease, particularly in children (Herrada-Manchón et al., 2020). Thus, this paper presents the application of this technique in the development of a pharmaceutical form for paediatric use and a comparison of results between 3D printing hydrogels with dissolved omeprazole or hydrogels loaded with gastro-resistant purposely made omeprazole pellets, an alternative that, to the best of our knowledge, has never been explored before.

2. Materials and methods

2.1. Materials

Omeprazole (CAS no. 73590–58-6) and gelatin (CAS no. 9000–70-8) were purchased from Merck KGaA, Darmstadt, Germany. Micronized omeprazole for pellet coating was given from Esteve Química, Barcelona, Spain. Xanthan gum (CAS no.11138–66-2), Lactose monohydrate (CAS no. 10039–26-6), sodium lauryl sulphate (CAS no. 151–21-3), titanium dioxide (CAS no. 13463–67-7), Talc (CAS no. 14807–96-6) and purified water (CAS no.7732–18-5) were purchased from Fagron Ibérica SAU, Terrassa, Spain. Carboxymethyl Cellulose (CAS no. 9004–32-4) and glycerol (CAS no. 56–81-5) were purchased from Guinama S.L.U, Valencia, Spain. Carrageenan (Gelification Iota®) was acquired through Guzmán Gastronomía SL, Barcelona, Spain. Lemon essence (Aroma de limón, Dr. Oetker Ibérica, Barcelona, Spain), lemon juice (Limón exprimido Hacendado, JR Sabater S.A., Murcia, Spain), liquid sweetener (Edulcorante de mesa líquido Hacendado, Jesús Navarro S.A., Alicante, Spain), sodium bicarbonate (Bicarbonato sódico Hacendado, Jesús Navarro S.A., Alicante, Spain) and food coloring (Colorante alimentario Vahiné®, McCormik España, Sabadell, Spain) were purchased from a local convenience store. Vivapur® MCC spheres were purchased from JRS Pharma Gmbh & Co. KG, Rosenberg, Germany. Hydroxypropyl methyl cellulose (CAS no. 9004–65-3) and hydroxypropyl cellulose (CAS no. 9004–64-2) were purchased from Shin-Estu Chemical Co., Ltd., Tokyo, Japan. Eudragit® L-30 D-55 was purchased from Evonik Corp., Barcelona, Spain. Triethyl citrate (CAS no. 77–93-0), disodium dihydrogen phosphate (CAS no. 7558–79-4), sodium dihydrogen phosphate (CAS no. 7558–80-7), sodium tetraborate decahydrate (CAS no. 1303–96-4), tribasic sodium phosphate dodecahydrate (CAS no. 10101–89-0), sodium hydroxide (CAS no. 1310–73-2), disodium hydrogen phosphate 12-hydrate (CAS no. 10039–32-4), hydrochloric acid 5 M (CAS no. 7647–01-0) and ethanol 96 % (CAS no. 64–17-5) were purchased from PanReac Química S.L.U., Barcelona, Spain.

2.2. Preparation of omeprazole pellets

Inert microcrystalline cellulose pellets (200 μm in diameter) were transferred to a fluid bed (Glatt AG) equipped with a bottom spray coating process on a Würster column. The pellets were coated with three successive coating layers: (i) a drug layer, (ii) a protective layer, to avoid possible interactions between the first layer and the third layer, and (iii) an enteric polymer layer to protect the omeprazole from the acidic gastric environment.

The first coating dispersion was prepared by dissolving disodium phosphate dodecahydrate, lactose monohydrate and lauryl sulphate in water (in that order). Omeprazole was then dispersed in the above solution and added to a previously prepared aqueous solution of hypromellose and hydroxypropyl cellulose. The pH was adjusted to 7.5 with a 0.1 N NaOH solution. The second coating solution was prepared by dissolving hypromellose in water. Finally, the third coating dispersion was prepared by dissolving triethyl citrate and 1 N NaOH solution in Eudragit® L-30 D-55. At the same time, a dispersion of titanium dioxide and talc was prepared in water. This dispersion was added to the solution and kept under constant stirring until it was completely homogenised. First and third coating dispersions were passed through a 200 μm sieve before coating to avoid possible lumps that could clog the gun. Furthermore, they were kept under continuous and soft agitation (mechanical stirrer: Heidolph, Hei-TORQUE CORE Model) during the whole coating process, to avoid sedimentation of the insoluble components.

The coating process was carried out in a dark room to avoid the potential degradation of omeprazole by light. The first and second coating layers were successively deposited on the inert microcrystalline cellulose pellets in a successive step to minimise such degradation. In the first coating layer, the dispersion was applied until an average increase in pellet weight of 27 % was achieved and, in the second layer, the

solution was applied until an average increase of 2 % was achieved. Before coating with the third layer, the pellets obtained were sieved to avoid possible agglomerates (600 μm sieve). In the last coating layer, the dispersion was applied until an average pellet weight increase of 110 % was achieved. The pellets obtained were sorted by passing them through an 800 μm mesh (agglomerates) and then through a 450 μm mesh (fines). Pellets that passed through the 800 μm mesh and were retained by the 450 μm mesh were considered correct. The working conditions used for the three coating layers are detailed in Table 1:

2.3. Preparation of pharmaceutical inks

Pharmaceutical inks (F1 and F2) were prepared from two different novel ink compositions (Table 2), thoroughly designed to promote omeprazole stability, material extrudability and content homogeneity. Ink formulation steps differed regarding the colloid's composition, in order to comply with the material physicochemical specifications and achieve proper gel-forming effect of the excipients. For F1, solid excipients (carboxymethyl cellulose, carrageenan and xanthan gum) and omeprazole were weighed and mixed in a recipient. Glycerol was added to the solid mixture to improve carboxymethyl cellulose wetting and avoid further lump formation. In parallel, sodium bicarbonate was dissolved into the liquid excipients, also weighed and mixed in a separate recipient. The addition of sodium bicarbonate allowed to reach basic pH values and promote omeprazole stability within the hydrogel. In a final step, the liquid phase was gradually added on top of the solid blend, manually mixing until the final viscous paste was acquired. For the formulation of the ink with loaded pellets (F2), carrageenan and xanthan gum were weighed and mixed in a recipient. Gelatine was also weighed in a separate recipient, was hydrated with water and lemon juice and subsequently melted in a water bath at 40 °C. The remaining liquid excipients were weighed and introduced in the melted gelatine blending, which later was gradually introduced on top of the carrageenan-xanthan gum mixture. Omeprazole pellets were added and integrated in a last step, mixing the blend until a paste with a visible homogeneous pellet content was achieved. In this case, lemon juice was added as a flavouring and acidifying agent to ensure pellet stability, since the Eudragit protective coat remains functional at pH values lower than 5. Once formulated, the pH of the inks was measured using a food-grade pH meter (Foodcare HI981032, Hanna Instruments Inc., Rhode Island, USA) to ensure the stability of the API in each composition. The pH values for F1 ranged between 8.4 and 8.5, while for F2, they ranged between 2.9 and 3.0.

With both inks, printer compatible syringes (BD 3 ml Syringe Luer-Lok™ Tip; Benton, Dickinson and Company, Belgium) were filled after formulation and stored in the fridge at 4 °C until use.

Table 1
Coating parameters.

Working conditions	First coating layer	Second coating layer	Third coating layer
Inlet air temperature	50 – 60 °C	60 – 65 °C	55 – 70 °C
Exhaust air temperature	35 – 45 °C	30 – 40 °C	35 – 45 °C
Product temperature	35 – 45 °C	35 – 45 °C	35 – 45 °C
Coating dispersion temperature	Room temperature	Room temperature	Room temperature
Inlet air relative humidity	25 – 45 °C	25 – 45 °C	25 – 45 °C
Exhaust air relative humidity	20 –40 °C	20 – 40 °C	20 – 40 °C
Pause time	120 s	120 s	120 s
Shaking time	5 s	5 s	5 s
Würster gun pressure	1.3 – 2 Bar	1.3 – 2 Bar	1.3 – 2 Bar
Pump speed	4 – 8 rpm	2 – 4 rpm	5 – 12 rpm
Compound air outlet position	45 – 90	60 – 90	60 – 90

Table 2
Detailed composition of the inks.

	F1	F2
Omeprazole powder	1.0 %	–
Omeprazole pellets		22.5 %
Carboxymethyl Cellulose	3.0 %	–
Gelatine	–	8.0 %
Carrageenan	2.0 %	2.0 %
Xanthan gum	0.5 %	0.5 %
Sodium bicarbonate	2.5 %	–
Glycerol	15.0 %	–
Liquid sweetener	1.0 %	6.5 %
Essence	0.5 %	0.5 %
Lemon juice	–	20.0 %
Purified water	74.5 %	40.0 %

To avoid possible disturbances in the detection of the API that could be caused by the food colouring, this ingredient was not included in the batches of inks formulated for quantification, dissolution and gastro-resistance tests. In the remaining tests, 0.5 wt% of food colouring was included in the formulas, an amount that was subtracted from the total water content.

2.4. Rheological analysis

Rheological characterization of ink samples was carried out with a controlled stress rheometer (Discovery HR-2, DHR, TA Instruments, USA) equipped with cross-hatched parallel plates (25 mm diameter, 500 mm gap) and a controlled convection/radiant heating oven for stable temperature control (Environmental Test Chamber, ETC, TA Instruments, USA).

Linear viscoelastic behaviour and viscosity recovery were studied using small-amplitude oscillatory shear (SAOS) tests. For each test, the set temperature was equal to the printing temperature needed for each pharmaceutical ink (37 °C for F1 and 20 °C for F2). As a previous step to obtain mechanical spectra or frequency sweeps, the linear viscoelastic region (LVR) was determined by means of amplitude sweeps in a strain interval of 0.01 to 100 % and at a fixed frequency of 1 Hz. Frequency sweep analysis was performed with angular frequency ranging from 0.1 to 100 rad/s at constant deformation (within the LVR). A 120 s conditioning step was added to ensure the sample equilibration and temperature. Stepped Dynamic Method (SDM) tests were performed to evaluate thixotropy and measure complex viscosity (η*) under low deformation (0.1 % strain), high deformation (120 % strain, out of the LVR of the inks to destroy the internal structure of the samples), and again under low deformation. Complex viscosity recovery was determined as the percentage of viscosity obtained during the first 30 s and the last 60 s in the third step (after high deformation) based on the mean average viscosity obtained in the last 30 s of the first step.

2.5. Drug characterization

2.5.1. Differential scanning calorimetry (DSC)

Samples of pure omeprazole, omeprazole pellets and drug-loaded inks (F1 and F2) were thermally analysed using differential scanning calorimeter (DSC). Thermograms were obtained using a DSC822e Differential Scanning Calorimeter (Mettler-Toledo, USA), under a nitrogen gas flow of 50 ml/min. The samples were crimped on an aluminium sample pan and heated at a rate of 5 °C/min from 0 to 300 °C. Additionally, an omeprazole sample was also measured at a rate of 20 °C/min to corroborate the detection of the melting point.

2.5.2. X-ray diffraction (XRD)

XRD analysis was performed using an X'Pert Pro MPD X-ray diffractometer (PANalytical, UK). Samples of pure omeprazole, omeprazole pellets (intact and grounded), and drug-loaded inks (F1 and F2) were filled into a zero-background sample holder (ZBH), compressing

them to obtain smooth and uniform surfaces. Measurements were carried out from 5 to 65 ° 2θ, at a constant scanning speed of 0.02 °/s.

2.6. Printing process

Drugmies were manufactured using a syringe-based extrusion 3D printer (bIDO-I, Idonial Technological Centre, Spain). 3D models (.STL files) were created using AUTODESK® TINKERCAD™, a free web app for 3D design. Open-source slicing software (Slic3r) was used to convert stereolithography (.stl) format files to.gcode extension files, the printer-readable format.

Differences in the composition of both formulas derived in different printing configurations for each of them. For printing dosages with F1, stainless steel, blunt end dispenser tips (Fisnar, United Kingdom) with 0.51 mm inner diameter (21G) were used as printing nozzles, allowing the fabrication of structures with 0.5 mm of layer height and a printing speed of 15 mm/s. Before the printing process, the F1 syringes were tempered by introducing them in a 37 °C bath for 30 min. The print head temperature was set at 37 °C to keep the ink fluid enough to be extruded through the nozzle and correctly draw the paths made by the printer. The print bed temperature was adjusted to 15 °C to ensure ink temperature-induced gelification in situ. Regarding the composition F2, on account of the high pellet content and their diameter, a 1.60 mm (14G) nozzle was selected for printing. In this case, conical plastic nozzles (Fisnar, United Kingdom) were chosen to facilitate ink flow. The layer height was established at 1.5 mm and the printing speed was reduced to 5 mm/s to ensure precise deposition working with a thicker ink filament. The speeds were modified from the parameter settings of the employed slicing program. The travel speed was kept at 15 mm/s to prevent material dripping between layers or figures. Printing temperatures selected were 20 °C for the extruder and 15 °C for the printing bed. An extended list of printing parameters is included in Supplementary Data.

The figures were printed in batches of 3 units for F1 and 2 units for F2, due to the limited printer's syringe capacity (3 ml). Each figure was individually printed, completing each element before automatically moving on to the next until the ink cartridge was finished. Flat glass pieces or disposable Petri dishes were used as printing supports to remove the figures easily from the printing bed, facilitate cleaning tasks, and reduce waiting time between printing processes.

2.7. Evaluation of mass uniformity and visual analysis

The visual appearance and mass uniformity of printed figures was analysed to assess the organoleptic characteristics and check the accuracy in the 3D model reproduction and design reproducibility. 20 drugmies of three different 3D models (disk, heart and lemon slice) were printed with both compositions and evaluated. Different and random cartridges (syringes) were chosen within the same batch to print each of the figures. Each drugmie was weighed individually using a digital precision balance (FH-200, GRAM, Spain) to evaluate the mass uniformity regardless of the 3D design and formulation chosen for 3D printing. To do so, and making an approach to European Pharmacopoeia technical procedures, the average mass was determined, and the individual mass deviations were checked to ensure that none deviated by more than 5 % from the average weight (weight compliance limits).

2.8. Evaluation of omeprazole content

The technical procedures of the European Pharmacopoeia were taken as a reference to assess whether the individual omeprazole contents were within the limits set with reference to the average content of the printed drugmies samples. Specifically, Ph. Eur. monograph "Uniformity of content of single-dose preparations" method was employed to determine the uniformity of content (European Directorate for the Quality of Medicines & HealthCare (EDQM), 2013). As chewable tablets do not have a specific test, the procedure suitable to tablets was chosen. In this standard, the preparation complies with the test if each individual content is between 85 % and 115 % of the average content. To assess the omeprazole content of the drugmies, each unit was weighed and transferred to a 50 ml volumetric flask. 10 ml of ethanol was added, and flask was sonicated for about 15 min until the gummy dosage was broken. 20 ml of 0.1 M sodium borate solution was added and sonicated again for 15 min. After that, to dissolve the excipients and extract the highest possible omeprazole fraction, the flask was stirred at 40 ± 2 °C for 30 min. Finally, the solution was tempered, made up to volume with 0.1 M sodium borate solution, and the previous filtered determination of the amount of dissolved omeprazole was made through DAD HPLC (Agilent 1100 Series, Germany). The test was carried out in triplicate.

2.9. Gastro-resistance test

Gastro-resistance of the printed drugmies was determined with a USP apparatus II (Erweka DT 700, Germany). The gastro-resistance method from USP monograph for omeprazole delayed-release capsules was used, as no specific assay has been established for chewable doses (The United States Pharmacopeial Convention (USP), 2023). For this assay, USP tolerances state that not more than 15 % of the amount of omeprazole must be dissolved in 2 h. Each dose, containing approximately 10 mg of omeprazole, was placed in a vessel containing 0.1 N hydrochloric acid medium (500 ml), maintained at 37 ± 0.5 °C with a stirring speed of 100 rpm. Six units of each omeprazole formulation were analysed. As the drugmies are chewable tablets, the gastro-resistance assay was repeated by fragmenting the drugmies into 8 pieces before pouring them into the vessel to better replicate a chewed tablet.

In the same way, due to the lack of the recommended dissolution equipment for chewable doses, the gastro-resistance test was also performed in the tablet disintegrator as described in Section 2.9.1 of the European Pharmacopoeia 11. 2nd Edition (Ph. Eur. 2022). It was decided to use the tablet disintegrator because the movement performed by the apparatus will be better adapted to the dose under study. To do so, a type A tablet disintegrator machine (according to European Pharmacopoeia) was used in which the gastro-resistance of the drugmies is studied in 0.1 M hydrochloric acid medium for 2 h. Three units of each omeprazole formulation were analysed. After 2 h, the medium containing the omeprazole drugmies was filtered through a sieve with an aperture of NMT 0.2 mm. The drugmies were collected in the sieve and rinsed with water. With approximately 10 ml of alcohol, the drugmies were carefully transferred to a 50 ml volumetric flask and sonicated until the drugmies were broken up. After that, 20 ml of 0.1 M sodium borate solution was added, and the solution was again sonicated and stirred in order dissolve the excipients that form the drugmie matrix and recover as much API as possible. Finally, the solution was tempered and made up to volume with 0.1 M sodium borate solution before the determination of the amount of dissolved omeprazole in a filtered sample through DAD HPLC (Agilent 1100 Series, Germany).

2.10. Dissolution profile

The drug release profiles of the printed drugmies were determined with a USP apparatus II (Erweka DT 700, Germany). The dissolution method from USP monograph for "omeprazole delayed-release capsules" was used, as no specific assay has been established for chewable doses (The United States Pharmacopeial Convention (USP), 2023). For this assay, USP tolerances state that not less than 75 % of the amount of omeprazole must be dissolved in 45 min. Each dose, containing approximately 10 mg of omeprazole, was placed in a vessel of the apparatus II containing alkaline dissolution medium pH 6.8 (500 ml), kept at 37 ± 0.5 °C with a stirring speed of 100 rpm. Six units of each omeprazole formulation were analysed. Similar to the gastro-resistance test, in addition, the dissolution assay was repeated by fragmenting the tablets into 8 pieces before pouring them into the vessel to better

replicate a chewed tablet.

For the same reasons stated in the previous section, it was decided to also carry out the dissolution test in the tablet disintegrator as described in Section 2.9.1 of the European Pharmacopoeia 11.2nd Edition (Ph. Eur. 2022). To do so, a type A tablet disintegrator machine was used in which the dissolution time of 3 units of each omeprazole formulation was studied using a medium pH 6.8 (500 ml), at 37 ± 0.5 °C. In the three studies, the samples were taken at 5, 15, 30 and 45 min and filtered before determining the amount of omeprazole dissolved by DAD HPLC (Agilent 1100 Series, Germany).

3. Results and discussion

3.1. Rheological characterisation and printability assessment of inks

Measurement of the strain amplitude dependence of the storage and loss moduli (G', G") is a good first step taken in characterising the viscoelasticity of a fluid. The LVR ends in a critical strain value (γ_c) from which the behaviour of the ink is non-linear and the storage module decreases. Below these values, the material behaves solid-like with the structure intact, while increasing the strain above the γ_c disrupts the network structure. Furthermore, the extension of the LVR is inversely related to the solid nature of the sample: the smaller the length, the greater the solid behaviour (Herrada-Manchón et al., 2023). Fig. 1A shows the amplitude sweeps for both compositions, with G'>G" values that reflects highly structured materials for the two inks. F1 ink showed a larger LVR and a more viscous behaviour, with a critical strain of 40.55 %. On the contrary, the critical strain of F2 was 0.26 %, denoting a greater solid character and corresponding to its higher solid content derived from the presence of pellets in its composition.

After the ink's linear viscoelastic region was defined by an amplitude sweep, their structure was further characterized using a frequency sweep at a strain below the critical strain. In a frequency sweep, measurements are made over a range of oscillation frequencies at a constant oscillation amplitude and temperature. This test helps to better understand the internal structure of the material and the time-dependent behaviour. For example, high frequencies represent short-term behaviour such as that caused by a mixing or extrusion process, while low frequencies represent long-term behaviour, such as settling (Liu et al., 2019). Fig. 1B shows how, for both compositions, the complex viscosity decreases as the angular frequency increases, verifying their suitability for being extruded in a 3D printing process. Naturally, the viscosity values of F2 were considerably higher, since the composition of this ink was thoroughly selected to ensure the proper carrying of the pellet content, avoid its aggregation or sedimentation, and to prevent filter-pressing phenomena —retention of particles in the nozzle at such a level that only fluid phase is deposited— caused by the extrusion process.

Thixotropy is a time-dependent shear-thinning property used to characterize the structure change reversibility and can be quantitatively measured through a Stepped Dynamic Method (SDM), an oscillatory procedure suitable for high viscosity samples that may suffer wall slip in lineal creep-recovery tests (Chen, 2020). With this three-step method, the fluid attains the state of rest in the first step, suffers structural destruction in step two, and regenerates the structure in step three.

The tests performed revealed higher recovery values for F1, reaching almost its initial value 30 s after applying high strain %. By contrast, F2 showed a slow recovery viscosity, hindering the correct deposition of the ink while printing (Fig. 2). To prevent and overcome this issue, the printing speed was reduced from 15 mm/s to 5 mm/s in the infill and perimeter parameter settings of Slic3r when using composition F2. This adjustment allowed the ink to settle properly and regain its self-supporting properties, enabling flawless printing of subsequent layers. On the other hand, the travel speed was kept at 15 mm/s to ensure the printer's nozzle moved swiftly between layers or figures, thus avoiding accidental depositions or dripping.

3.2. Drug characterization

DSC and X-ray analysis were employed to investigate the physical state of the drug in the final formulations (Fig. 3). The DSC thermographs show that omeprazole raw material melted around 157.5 °C, a value that matched the bibliography and confirmed the crystalline state of the raw API. In the case of the drug-loaded inks, the determination of the melting point of omeprazole was not possible, which indicates that the drug may be forming a solid solution with the hydrogels excipients and is existing in an amorphous state within the ink matrices. In both formulations, only a broad endothermic transition was observed between 40—150 °C for F1 and 20—170 °C for F2, corresponding to the loss of moisture in the hydrogels. Furthermore, enteric omeprazole pellets were also analysed, showing a water-loss between 50 and 90 °C, and two endothermic bands associated with decomposition processes (see Supplementary Data). Detailed individual thermographs can be consulted in Supplementary Data.

Similar results were achieved by means of the XRD analysis. The X-ray diffractogram of omeprazole showed its characteristic peaks of crystalline structure. By contrast, the complete absence of sharp peaks in the diffractogram of the F1 formulation suggested that the drug was in its amorphous state in this composition (Palekar et al., 2019). Finally, F2 ink and omeprazole pellets (either ground or intact samples) showed similar structural behaviours, with only a residual degree of crystallinity remaining.

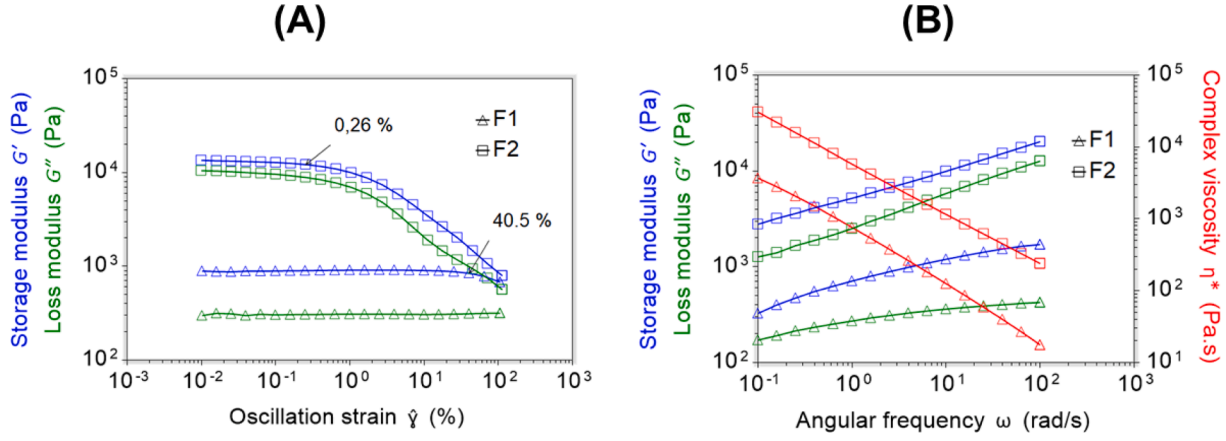

Fig. 1. (A) Amplitude sweeps from 0.01 to 100 % strain. (B) Frequency sweeps from 0.1 to 100 rad/s.

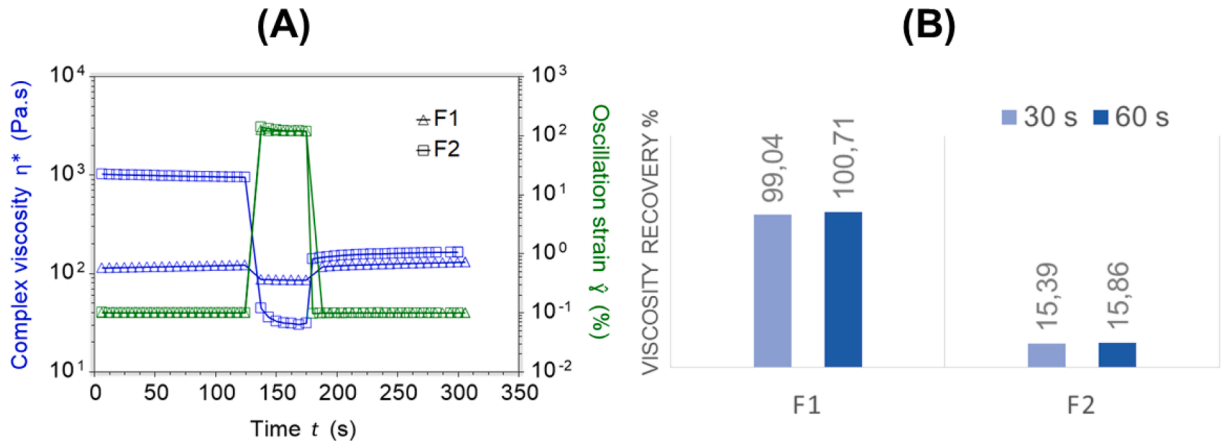

Fig. 2. Stepped Dynamic Method (SDM) tests and viscosity recovery % obtained.

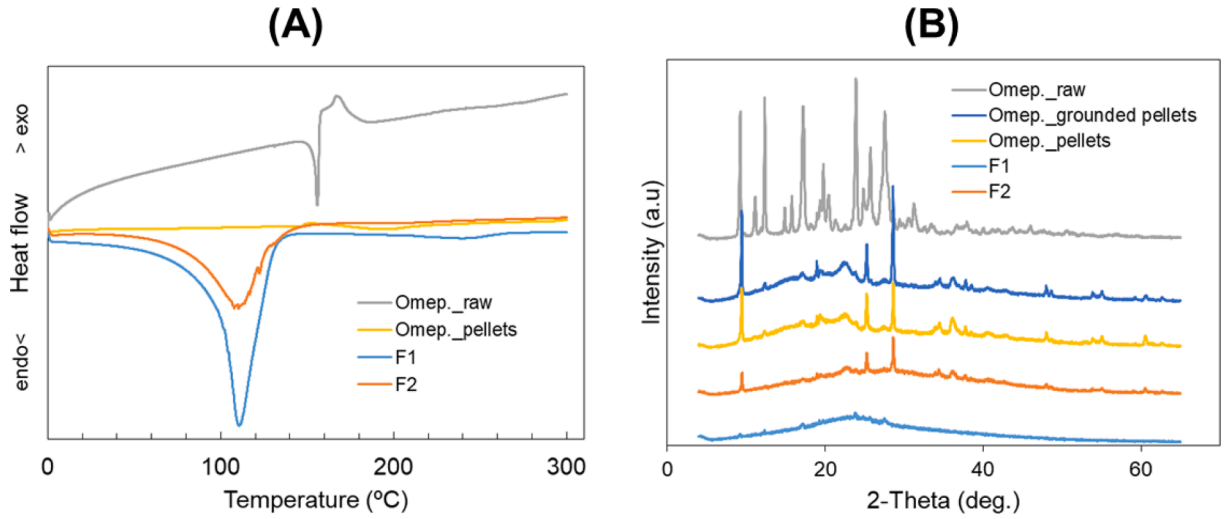

Fig. 3. Drug characterization results: (A) DSC, (B) XRD.

3.3. Printing process, visual analysis and mass uniformity of drugmies

The temperature regulation system enabled the management of inks viscosity and the induction of an in situ gelification so as to help with the design execution. The proper configuration of the printing parameters allowed the successful fabrication of gummy oral dosages that reproduced de 3D models with high fidelity (Fig. 4). As expected, F1 models were more detailed, as the use of a narrower nozzle allowed the printing of thinner layers and, by extension, drugmies had a better resolution. For F2, thicker lines were obtained, but the results comfortably meet the expectations. In these drugmies, the pellets were clearly visible, verifying their physical integrity throughout the fabrication process. By contrast, in F1 printed dosages, no particles, spots or heterogeneously coloured parts were seen in any case, also confirming both the suitability of the formula and its elaboration process. All the printed drugmies had a pleasant smell, a shiny colour, and a tasty appearance, requirements that must be fulfilled when focussing on some more demanding population sectors, such as children. Moreover, the use of pellets offers the possibility of further masking the unpleasant taste of the active ingredients.

After printing, the drugmies were placed in the refrigerator for 15 min to allow homogenous gelification. After that time, all the compositions and models tested were manipulable and easy to handle (Fig. 5). However, for F1 doses, due to the quick melting of the composition with body warmth, long-lasting handling (greater than5 min) is not recommended to avoid drugmie damage and possible loss of API content.

The mass of each 3D printed gummy dose was measured to determine the upper and lower mass limits according to the standard for each selected model. All the weights fell within these limits and met the acceptance criteria since none of the individual masses differed from the average mass by more than 5 % (see Supplementary Data). As a result, the gummy doses had a uniform mass regardless of the 3D model or formula used (Table 3). In this vein, it is demonstrated that drug dosages can be printed to meet patient dose requirements, while design versatility can improve patient acceptance of medication and treatment adherence.

3.4. Evaluation of omeprazole content

In the formulation process of F1 ink, omeprazole was directly added with the rest of the excipients, causing a homogenous distribution within the whole hydrogel matrix. On the contrary, in the F2 formulation the API was only present in the enteric granules and, consequently, the adequacy of its dose derived from the content of granules in the hydrogel. Although the differences in the composition and formulation process between the two inks were notable, the omeprazole was successfully evaluated in both cases using the same extraction process. Thus, the dosage precision showed satisfactory results, as the obtained values were above 90 %, specifically 103 % for F1 and 106 % for F2

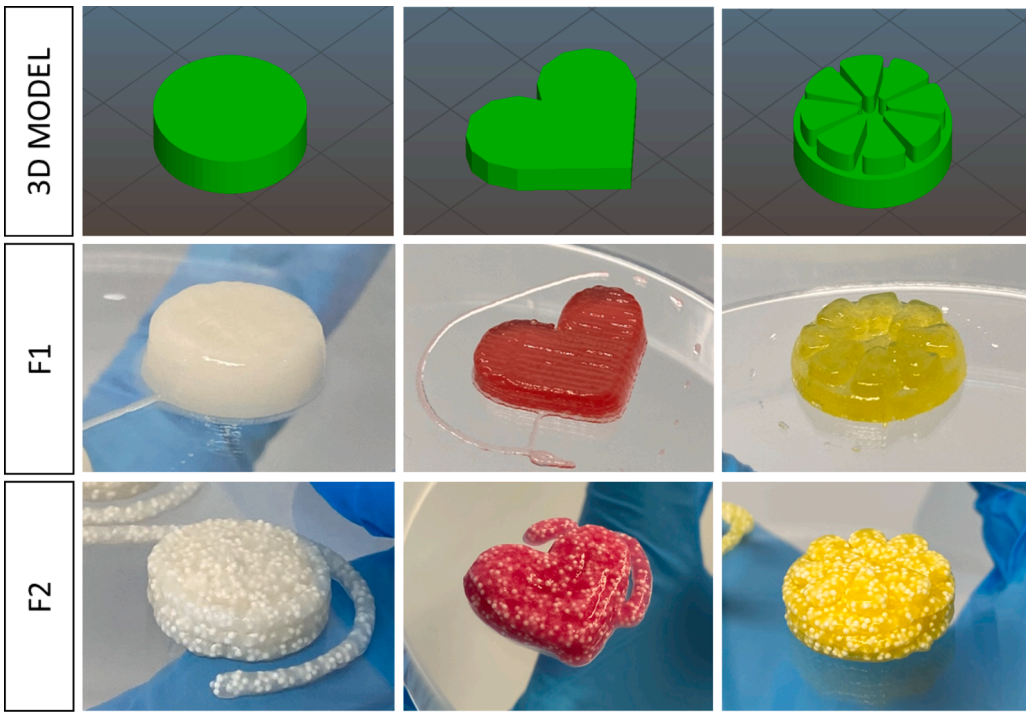

Fig. 4. 3D models and drugmies printed with F1 and F2.

Fig. 5. Handling of different 3D printed drugmies.

Table 3
Printed dosage mass uniformity.

	3D Model	Mean weight (g) ± SD	Weight compliance limits (g)
F1	Disk	0.759 ± 0.018	0.721 – 0.797
	Heart	0.653 ± 0.014	0.620 – 0.686
	Lemon slice	0.802 ± 0.019	0.762 – 0.842
F2	Disk	0.901 ± 0.017	0.856 – 0.946
	Heart	0.860 ± 0.023	0.817 – 0.903
	Lemon slice	1.267 ± 0.030	1.204 – 1.331

Table 4
Evaluation of omeprazole content of F1 and F2.

Formula	Theoretical dose (mg) ± SD	Measured dose (mg) ± SD	Dose accuracy (%) ± SD
F1	6.94 ± 0.25	7.17 ± 0.41	103.29 ± 2.30
F2	10.86 ± 0.80	11.53 ± 0.97	106.08 ± 1.43

(Table 4). As a result, the uniformity of the content of the two batches of drugmies complied with the standards, since the measured content was within the 85–115 % range marked by the general monograph (see Supplementary Data).

3.5. Gastro-resistance test

As mentioned above, omeprazole is rapidly degraded in the acidic environment of the stomach (Burnett and Balkin, 2006; Palekar et al., 2019). Therefore, it is necessary to assess the level of protection and stability of both formulations in this environment by means of gastro-resistance tests.

Fig. 6 shows the evolution of F1 drugmies throughout the assay. As can be seen, the drugmies gradually turned brown with time, a fact directly associated with the degradation of omeprazole in acidic medium (Burnett and Balkin, 2006; Graudins et al., 2008; Rouaz et al., 2021b). When performing the gastro-resistance test by fragmenting the drugmies before pouring them into the apparatus II vessel, the identical results were obtained for F1 as when performing the test without fragmenting them, i.e., the F1 drugmies were shown not to be gastro-resistant. The colour changes observed were also the same: the acidic medium turned yellowish within moments after pouring the drugmies and at the end of the test the recovered pieces had a brownish colour. After UV–vis HPLC analysis of the samples tested in apparatus II and in the tablet disintegrator, it was confirmed that the entire omeprazole content was degraded. Thereby, this composition did not meet the specifications for gastro-resistance (see Supplementary Data).

Regarding formulation F2, the results of the gastro-resistance test performed on the tablet disintegrator were positive as UV–vis HPLC analysis of the samples tested confirmed that only 18 % of the API was degraded in acidic medium (0.1 M hydrochloric acid for 2 h). By contrast, the results of the non-sliced samples tested in apparatus II concluded that the 64 % of the omeprazole was degraded after the assay. However, when the fragmented drugs were tested using this apparatus, similar results were obtained as in the tablet disintegrator test, with a gastro-resistance percentage of 86%. In this case, the USP specification was met, as less than 15% of omeprazole degraded after being subjected to acidic medium for 2 h. These results confirm that the fragmentation of the drugmies better simulates the behaviour of a chewable tablet than testing the drugmies in one piece.

The clear explanation for these results lies in the methodology of the tests and the inherent properties of the devices used. It underscores the significance of carefully selecting appropriate protocols for conducting such crucial assays. Tablet disintegrators work by raising and lowering a ‘basket’ in and out the test medium, applying a mechanical breakdown of the dosage comparable to mastication process, which allows easy the release and recovery of the pellets out of the hydrogel matrix. Similarly, in the case of diced drugmies added in apparatus II, the pellets were also easily extracted and recovered, as the fragmentation process enhances the release of the pellets into the media. In that way, it is worth mentioning that the API extraction process needed and used for the apparatus II whole samples was way more aggressive. In this case, to recover the whole pellet content, the drugmies were sonicated for 30 min and kept in stirring for 60 min at 45 – 50 °C, while the drugmies fragmented drugmies or those tested in the tablet disintegrator only needed half the time of sonication and stirring. Consequently, it is reasonable to consider that some omeprazole might have been degraded in the final extraction process, and these modifications in the extraction process were likely the primary reasons for the discrepancy in the results between the devices.

In conclusion, while not all the tests fully met the chosen USP specifications as a reference, mainly due to the challenges in the extraction process, this study demonstrated that incorporating enteric omeprazole pellets in 3D printed drugmies represents a significant improvement compared to using raw omeprazole. This approach offers an alternative oral dosage form that addresses the lack of gastro-resistance observed in compounded oral suspensions, which is a prominent issue in current pediatric formulations of omeprazole (Boscolo et al., 2020; Shin and Kim, 2013). Despite the extraction difficulties, the use of enteric omeprazole pellets in 3D printed drugmies holds promise as a potential solution for enhancing the effectiveness of paediatric medication delivery.

3.6. Dissolution test and drug release profiles

Dissolution assays are commonly used in drug development to simulate the *in vitro* behaviour of pharmaceutical doses with the aim of predicting bioavailability and therapeutic efficacy. In that way, printed dosages of each formulation were studied using an apparatus II and a tablet disintegrator (Fig. 7).

The dissolution tests conducted on apparatus II showed that the F1 formulation exhibited an API release of 25% after 45 min for non-fragmented dosages, while the F2 formulation showed almost zero API release in the same timeframe when using entire dosages. However, an improvement in the F2 dissolution profile was observed when the dissolution test was performed with fragmented drugmies in apparatus II, achieving a 36% release (compared to 4% without fragmentation). This enhancement can be attributed to the release of pellets into the dissolution medium when drugmies are fragmented, facilitating their dissolution. On the other hand, no significant improvement was observed for the F1 formulation, with both non-fragmented and fragmented drugmies exhibiting similar release percentages of 25% and 22%, respectively.

In contrast, when using the tablet disintegrator, both formulations showed an API release of over 76% in 30 min. Thus, the dissolution test performed on the disintegrator complied with the USP monograph specifications for “omeprazole delayed-release capsules” for both formulas, as more than 75% of the API dissolved within 45 min.

4. Conclusions

The search of stable, safe, and gastro-resistant omeprazole formulations suitable for paediatric patients is still a challenge. However, after the experiments conducted in the present work, the use of enteric pellets

Fig. 6. Appearance of the F1 drugmies during the 2 h gastro-resistance test: starting with the image on the right, the drugmies at 0 min, 15 min, 30 min and 120 min are shown.

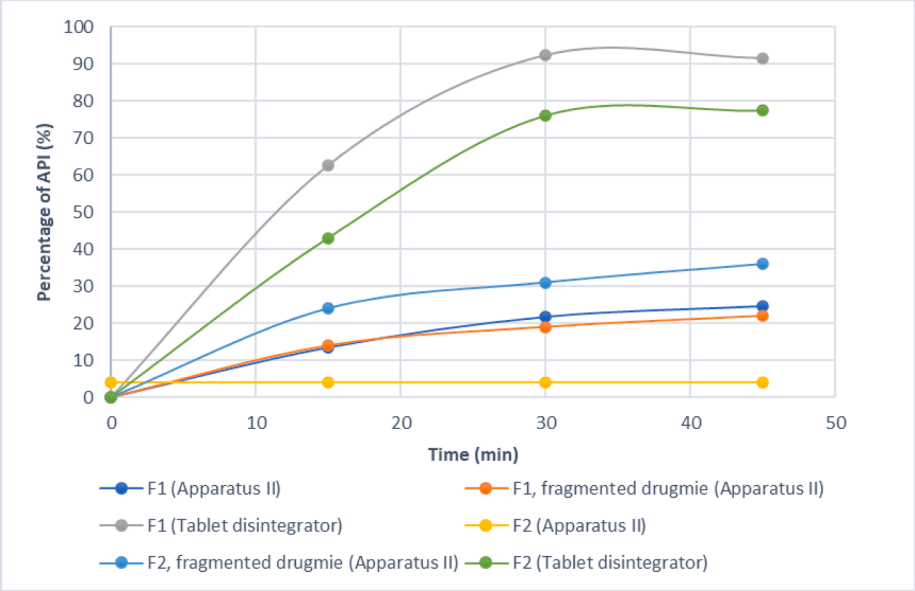

Fig. 7. Drug dissolution profiles of drugmies dosages printed with F1 and F2 formulas.

in 3D printing of chewable semi-solid doses is presented an innovative and effective strategy to solve this gap in current children medication. The proper rheology and the good printability, the content and mass uniformity, the adequate release profile and the high gastro-resistance are the main attributes determined for the F2 composition successfully explored. By contrast, although the required specifications for F1 were also met in most of the assays, the total degradation of the API during the gastro-resistance test remarked the importance of this test to assess the viability of every pH-sensitive API used in a new pharmaceutical form. Furthermore, the gastro-resistance and dissolution test results underscore the significance of the chosen methods and their impact on the release behaviour of omeprazole formulations.Also noteworthy is the fact that this study opens a new and interesting line of research that combines ground-breaking and classical pharmaceutical technologies developments: the semi-solid 3D printing and the fluid bed pellet coating. In that way, this work seeks to be another step in the path to the future production of patient-tailored, appealing and eye-catching drug doses, which may help paediatric patients cope with or overcome a disease while reducing its psychological impact.

CRediT authorship contribution statement

Khadija Rouaz El Hajoui: Investigation, Writing – original draft, Formal analysis, Methodology. **Helena Herrada-Manchón:** Investigation, Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Project administration, Funding acquisition. **David Rodríguez-González:** Investigation, Formal analysis, Methodology. **Manuel Alejandro Fernández:** Project administration, Funding acquisition. **Enrique Aguilar:** Writing – review & editing, Funding acquisition, Resources. **Marc Suñé-Pou:** Writing – review & editing, Visualization. **Anna Nardi Ricart:** Validation, Visualization. **Pilar Pérez-Lozano:** Conceptualization, Validation, Formal analysis, Supervision, Writing – review & editing. **Encarna García-Montoya:** Conceptualization, Supervision, Project administration, Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2023.123289.

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Supplementary Data

Pellets and gummies: seeking a 3D printed gastro-resistant omeprazole dosage for paediatric administration

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1. Printing parameters

Table S1. Extended list of most relevant printing parameters set.

	F1			F2		
3D model	Disk	Heart	Lemon Slice	Disk	Heart	Lemon Slice
STL file name	Disk15mm.stl	Heart.stl	Lemon.stl	Disk15mm.stl	Heartpellets.stl	Lemonpellets.stl
Extrusion multiplier	1	1	1	1	1	1
First layer speed (%)	95	95	95	100	100	100
Nozzle diameter (mm)	0.51	0.51	0.51	1.60	1.60	1.60
Fill angle (°)	45	45	45	45	45	45
Fill density* (%)	70	80	60	80	70	70
Pattern	Rectilinear	Rectilinear	Rectilinear	Concentric	Concentric	Concentric
Perimeters	2	2	2	2	2	2
Perimeter speed (mm/s)	15	15	15	5	5	5
Solid infill speed (mm/s)	15	15	15	5	5	5
Travel speed (mm/s)	15	15	15	5	5	5
Top solid layer	1	1	1	1	1	1
Bottom solid layer	1	1	1	1	1	1
First layer height (mm)	0.5	0.5	0.50	1.5	1.5	1.5
Layer height (mm)	0.5	0.5	0.5	1.5	1.5	1.5

*** Fill density %** was adjusted for each configuration of parameters after Slic3r previsualization to ensure a proper execution, minimizing gaps in the deposition.

2. Mass uniformity assay of 3D printed gummy oral dosages.

Table S2. Individual weights of printed figures and mass uniformity assay calculated values.

F1											
Disk				Heart				Lemon Slice			
Figure	**Mass (g)**	**Figure**	**Mass (g)**	**Figure**	**Mass (g)**	**Figure**	**Mass (g)**	**Figure**	**Mass (g)**	**Figure**	**Mass (g)**
1	0.759	11	0.754	1	0.672	11	0.663	1	0.818	11	0.775
2	0.767	12	0.752	2	0.635	12	0.654	2	0.807	12	0.775
3	0.750	13	0.750	3	0.649	13	0.647	3	0.780	13	0.817
4	0.734	14	0.792	4	0.664	14	0.622	4	0.828	14	0.803
5	0.772	15	0.802	5	0.659	15	0.640	5	0.811	15	0.793
6	0.759	16	0.782	6	0.677	16	0.650	6	0.802	16	0.768
7	0.765	17	0.762	7	0.651	17	0.634	7	0.828	17	0.817
8	0.727	18	0.756	8	0.659	18	0.638	8	0.776	18	0.815
9	0.760	19	0.750	9	0.664	19	0.650	9	0.807	19	0.795
10	0.758	20	0.738	10	0.671	20	0.660	10	0.826	20	0.794
Standard deviation	**Average mass (X)**	**Upper limit ((X) + 5 %)**	**Lower limit ((X) - 5 %)**	**Standard deviation**	**Average mass (X)**	**Upper limit ((X) + 5 %)**	**Lower limit ((X) - 5 %)**	**Standard deviation**	**Average mass (X)**	**Upper limit ((X) + 5 %)**	**Lower limit ((X) - 5 %)**
0.018	0.759	0.797	0.721	0.014	0.653	0.686	0.620	0.019	0.802	0.842	0.762
F2											
Disk				Heart				Lemon Slice			
Figure	**Mass (g)**	**Figure**	**Mass (g)**	**Figure**	**Mass (g)**	**Figure**	**Mass (g)**	**Figure**	**Mass (g)**	**Figure**	**Mass (g)**
1	0.909	11	0.904	1	0.865	11	0.832	1	1.301	11	1.225
2	0.911	12	0.891	2	0.828	12	0.853	2	1.257	12	1.242
3	0.918	13	0.858	3	0.854	13	0.879	3	1.285	13	1.288
4	0.930	14	0.909	4	0.872	14	0.864	4	1.288	14	1.252
5	0.900	15	0.904	5	0.825	15	0.817	5	1.326	15	1.212
6	0.906	16	0.858	6	0.885	16	0.871	6	1.290	16	1.245
7	0.898	17	0.912	7	0.857	17	0.846	7	1.288	17	1.229
8	0.895	18	0.897	8	0.887	18	0.892	8	1.275	18	1.257
9	0.907	19	0.904	9	0.874	19	0.862	9	1.287	19	1.285
10	0.912	20	0.891	10	0.890	20	0.839	10	1.228	20	1.288
Standard deviation	**Average mass (X)**	**Upper limit ((X) + 5 %)**	**Lower limit ((X) - 5 %)**	**Standard deviation**	**Average mass (X)**	**Upper limit ((X) + 5 %)**	**Lower limit ((X) - 5 %)**	**Standard deviation**	**Average mass (X)**	**Upper limit ((X) + 5 %)**	**Lower limit ((X) - 5 %)**
0.017	0.901	0.946	0.856	0.023	0.860	0.903	0.817	0.030	1.267	1.331	1.204

3. DSC Analysis

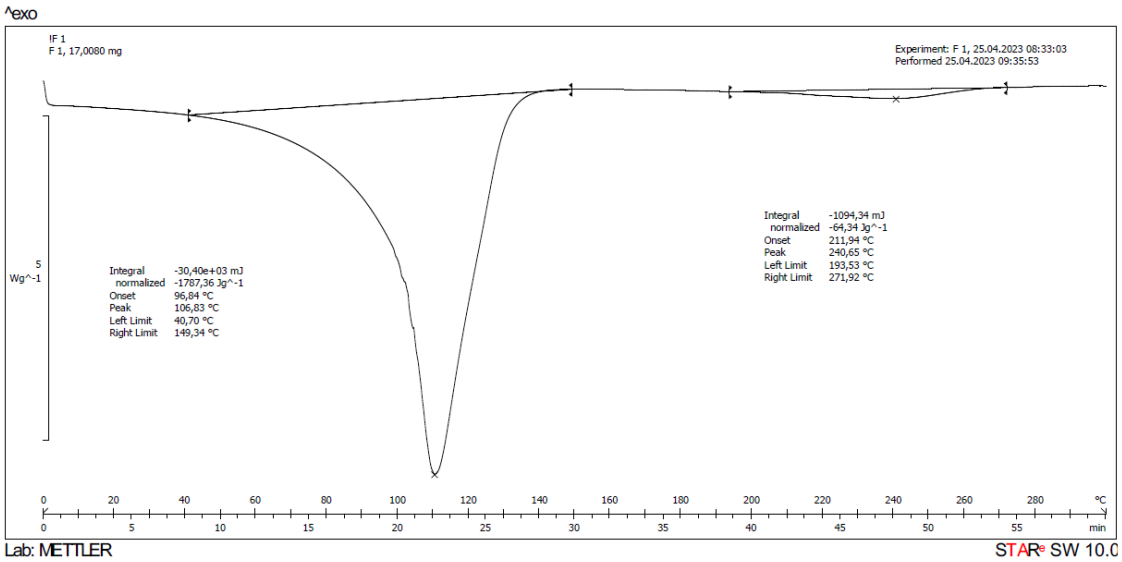


Figure S1. DSC thermogram of F1

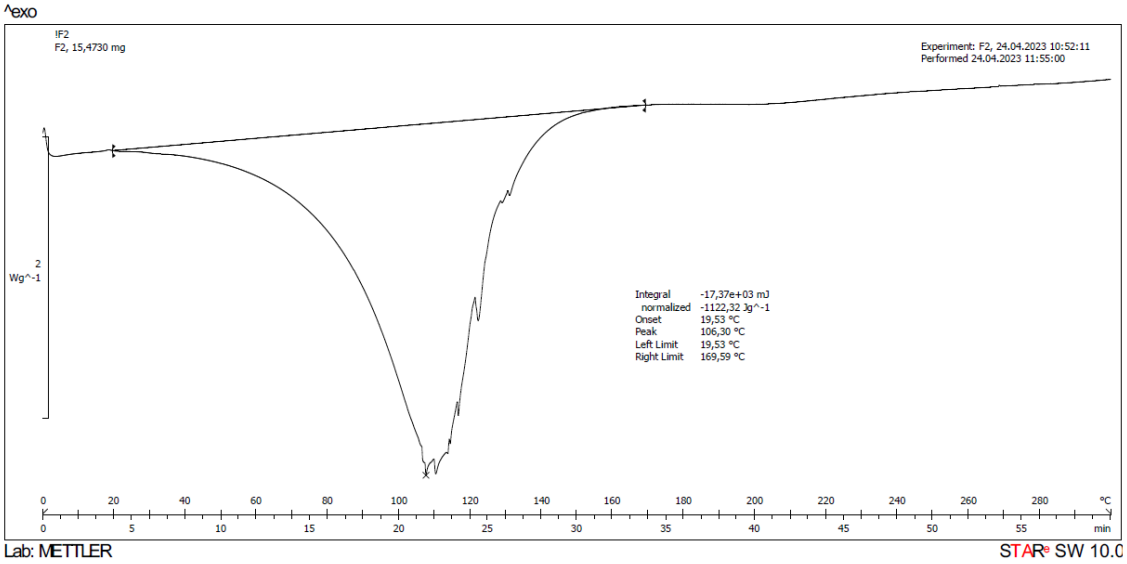


Figure S2. DSC thermogram of F2

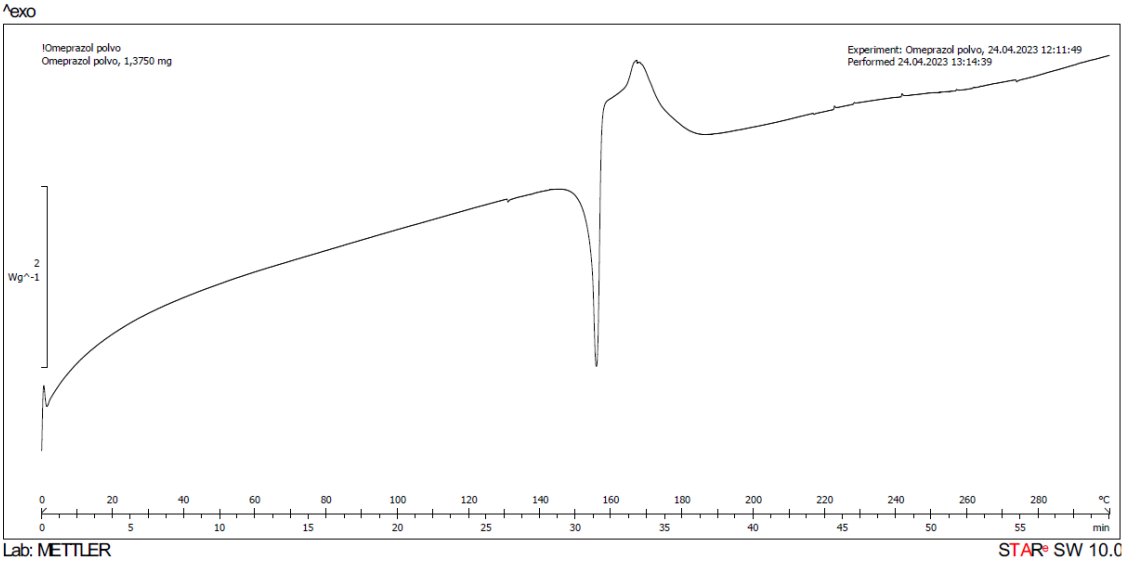


Figure S3. DSC thermogram of raw omeprazole at 5 ºC/min

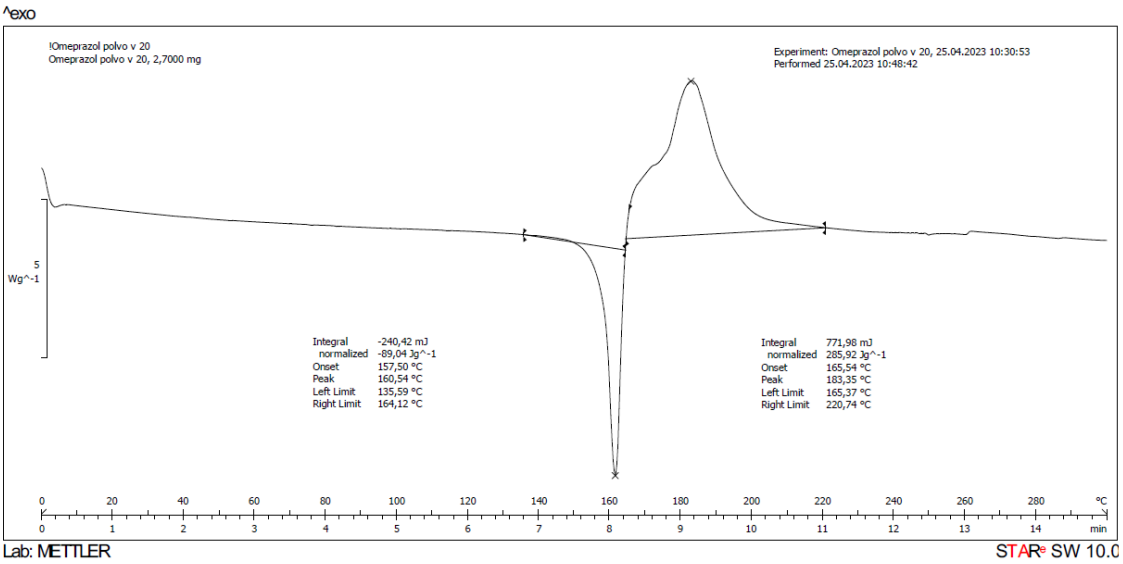


Figure S4. DSC thermogram of raw omeprazole at 20 ºC/min

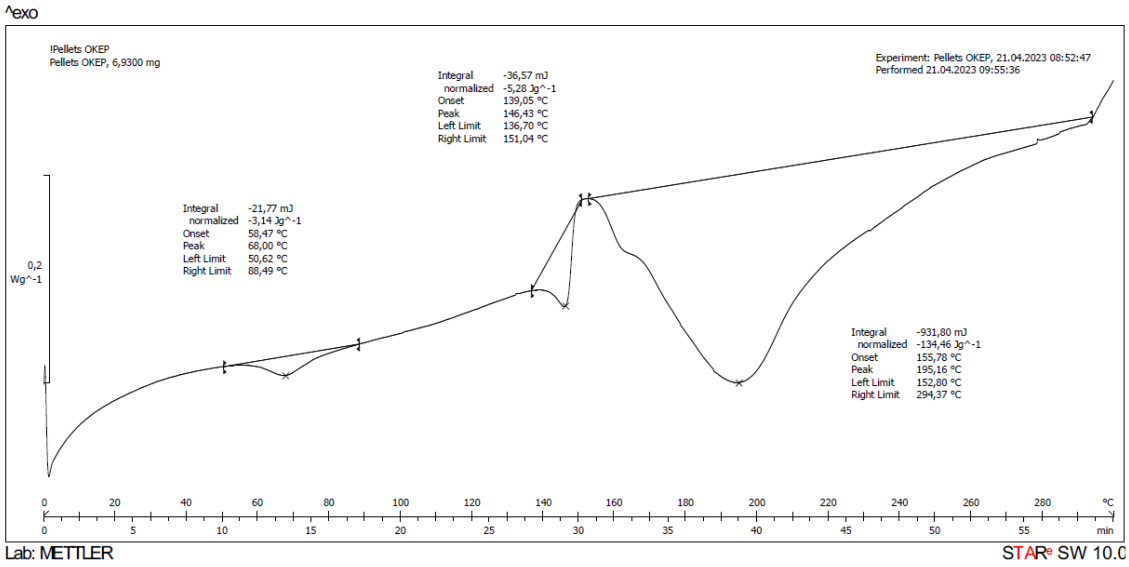


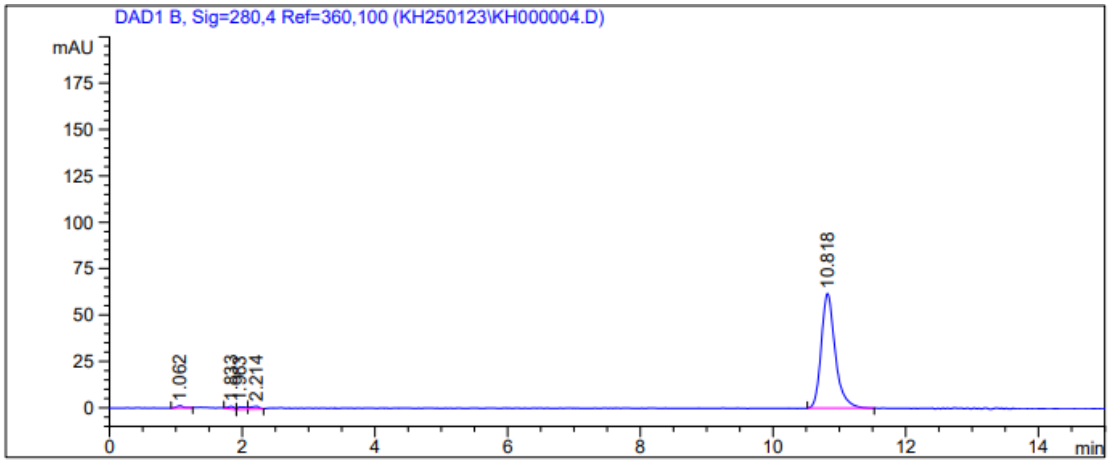
Figure S5. DSC thermogram of enteric omeprazole pellets

4. Evaluation of omeprazole content

Table S3. Evaluation of omeprazole content of F1 and F2.

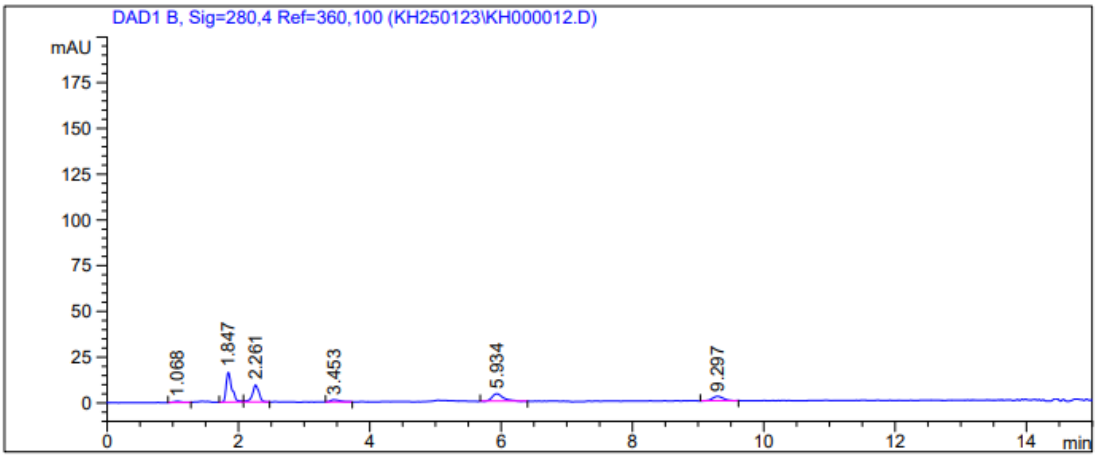
Formula	Samples	Drugmie weight (mg)	Problem Area	Theoretical concentration (µg/mL)	Actual concentration (µg/mL)	Percentage API dissolved
F1	Sample 1	665.46	817.64	133.09	133.94	100.64
	Sample 2	708.41	903.30	141.68	147.98	104.44
	Sample 3	708.79	906.76	141.76	148.54	104.79
F2	Sample 1	905.47	2962.98	230.09	248.70	108.09
	Sample 2	868.38	2776.87	221.40	233.08	105.28
	Sample 3	782.87	2502.67	199.60	210.06	105.24

5. Chromatograms of the F1 and F2 drugmies after evaluation of omeprazole content and gastro-resistance test



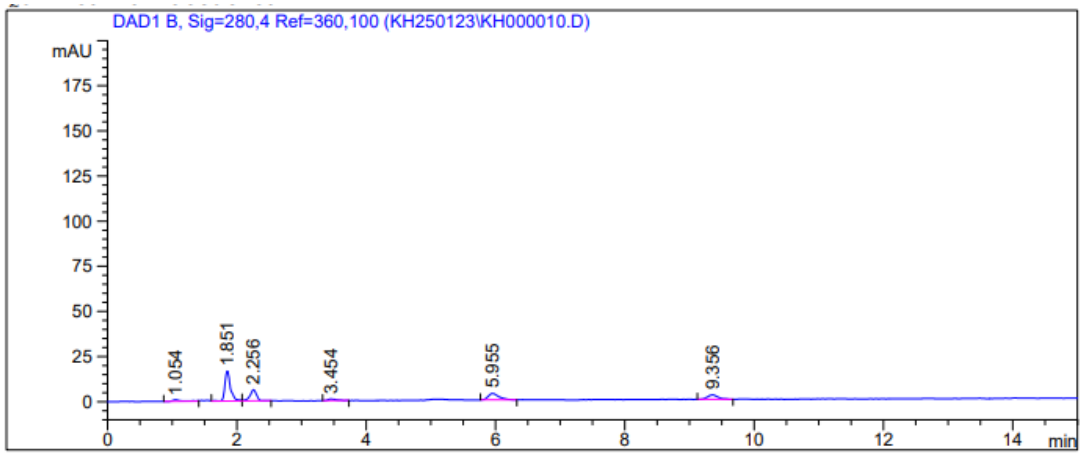

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 B, Sig=280,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   1.062 PB    0.1032    8.59671    1.17749   0.8716
   2   1.833 BP    0.1075    9.71527    1.42533   0.9850
   3   1.963 VV    0.1079   11.37364    1.38299   1.1532
   4   2.214 VV    0.1359   14.61819    1.49743   1.4821
   5  10.818 BB    0.2236  910.46832   61.90174  92.3106
   6  27.013 BP    0.3871   31.53718 9.80828e-1   3.1975

Totals :                   986.30930   68.36581
```

Figure S6. Chromatogram of an F1 drugmie sample after evaluation of omeprazole content.



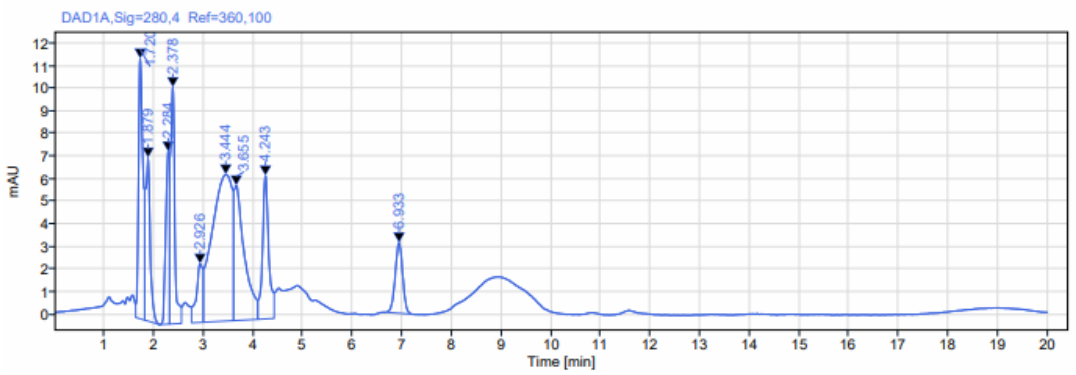

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=280,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   1.068 PB    0.1121    5.98698 7.26957e-1   0.9498
   2   1.847 VV    0.0905   98.77126   16.34285  15.6700
   3   2.261 VB    0.1082   64.20428    9.34354  10.1859
   4   3.453 BP    0.1428   11.12958    1.15088   1.7657
   5   5.934 BB    0.1773   48.71154    4.08005   7.7280
   6   9.297 PB    0.1802   29.52502    2.45621   4.6841
   7  20.596 BB    0.2360  165.71527   10.74232  26.2906
   8  25.255 PV    0.1580   18.68857    1.60358   2.9649
   9  25.698 VV    0.2932   95.81880    4.41542  15.2016
  10  26.266 VB    0.2512   91.77102    5.71997  14.5594

Totals :                  630.32233   56.58178
```

Figure S7. Chromatogram of a F1 drugmie sample after gastro-resistance test in Apparatus II.




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=280,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   1.054 PB    0.1605   10.39531 8.88651e-1   1.8374
   2   1.851 VV    0.0907  100.62999   16.60789  17.7870
   3   2.256 VB    0.1091   44.02029    6.32966   7.7809
   4   3.454 PB    0.1535    9.41367 9.19314e-1   1.6639
   5   5.955 BP    0.1717   42.81981    3.62671   7.5687
   6   9.356 BP    0.1746   28.59772    2.44210   5.0548
   7  20.642 BB    0.2327  146.58231    9.46481  25.9094
   8  25.340 PV    0.1890   15.92041    1.16830   2.8140
   9  25.716 VV    0.2781   62.98420    3.22102  11.1329
  10  26.311 VB    0.2316   61.85993    3.84746  10.9342
  11  28.829 PB    0.6332   42.52528 8.09117e-1   7.5166

Totals :                  565.74891   49.32503
```

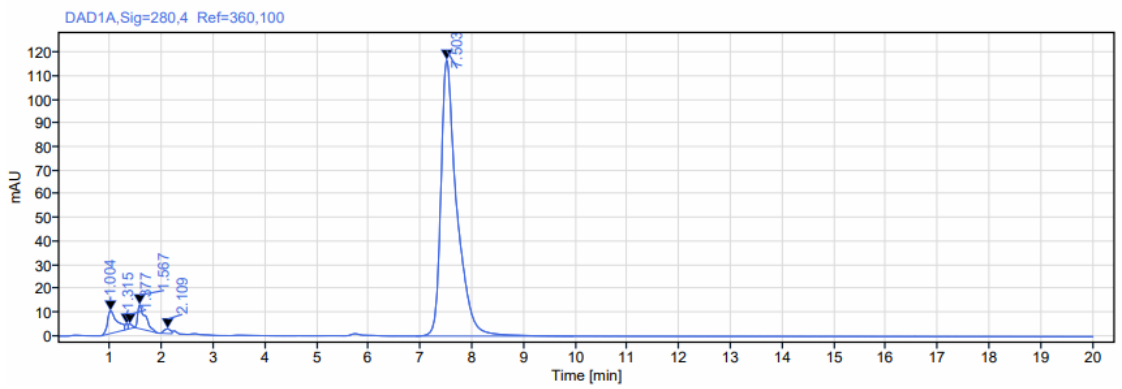
Figure S8. Chromatogram of an F1 drugmie sample after gastro-resistance test in the tablet disintegrator.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.720	VV	0.18	71.34	11.51	11.83	0.59768	940.2
1.879	VB	0.31	47.57	7.23	7.88	1.11281	712.8
2.284	BV	0.18	38.32	7.63	6.35	2.10296	892.1
2.378	VV	0.24	63.28	10.47	10.49	1.08401	506.5
2.926	VV	0.24	23.37	2.59	3.87	1.52171	908.4
3.444	VV	0.61	182.04	6.48	30.17	2.27960	999.6
3.655	VV	0.49	88.84	5.97	14.73	0.25344	995.3
4.243	VV	0.33	55.86	6.33	9.26	0.84578	846.1
6.933	BB	0.49	32.69	3.12	5.42	1.01300	725.4
		Sum	603.30				

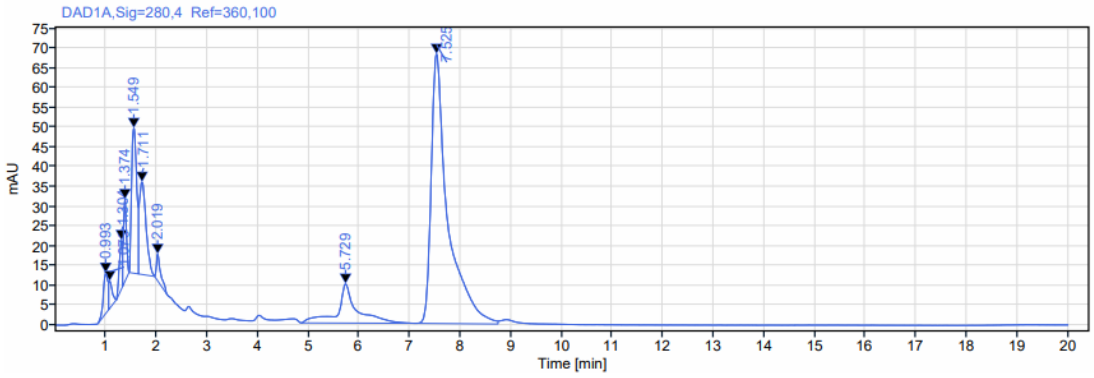
Figure S9. Chromatogram of an F1 fragmented drugmie sample after gastro-resistance test in Apparatus II.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.004	BV	0.45	119.90	9.52	4.34	0.44671	971.3
1.315	VV	0.07	8.99	2.29	0.33	1.35512	998.0
1.377	VB	0.13	9.80	1.95	0.35	0.62344	998.1
1.567	BB	0.44	103.14	10.12	3.73	0.29867	716.4
2.109	BV	0.24	17.44	2.02	0.63	1.20263	980.8
7.503	BB	3.05	2502.46	116.95	90.61	0.52779	998.1
		Sum	2761.74				

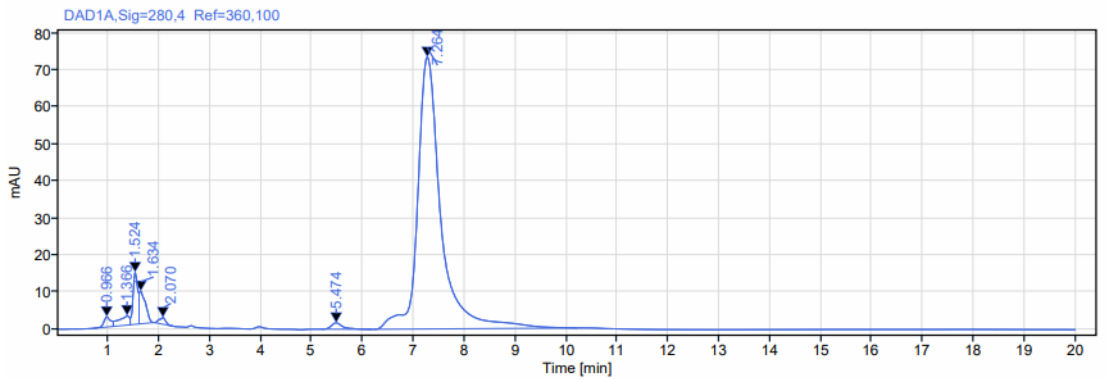
Figure S10. Chromatogram of an F2 drugmie sample after evaluation of omeprazole content.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
0.993	BV	0.20	62.92	10.23	2.45	1.14450	992.5
1.073	VB	0.15	31.89	6.87	1.24	0.37482	976.0
1.304	BV	0.12	51.06	12.31	1.99	2.40838	282.8
1.374	VB	0.13	84.57	20.72	3.30	0.95147	728.4
1.549	BV	0.19	259.04	36.66	10.10	0.74192	980.0
1.711	VB	0.32	217.71	23.36	8.49	0.60019	961.6
2.019	BB	0.25	39.65	6.70	1.55	0.36017	998.8
5.729	BB	2.26	264.28	9.89	10.30	0.75504	274.9
7.525	BV	1.62	1553.67	68.13	60.58	0.41949	999.2
		Sum	2564.81				

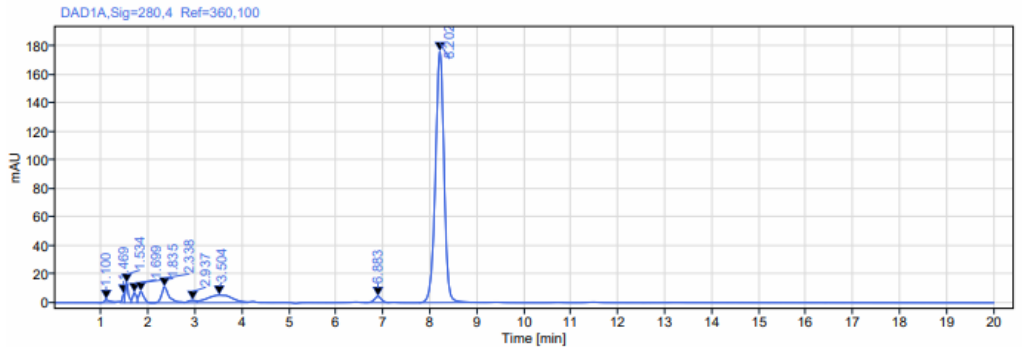
Figure S11. Chromatogram of an F2 drugmie sample after gastror-esistance test in Apparatus II.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
0.966	BV	0.37	25.50	2.75	0.98	0.72163	995.0
1.366	VV	0.33	36.98	2.57	1.41	3.88517	541.4
1.524	VV	0.17	90.88	14.03	3.48	0.80991	692.7
1.634	VB	0.29	74.71	8.81	2.86	0.26769	637.9
2.070	BB	0.41	15.83	1.83	0.61	1.27027	953.3
5.474	BB	0.98	26.67	1.72	1.02	0.66020	611.0
7.264	BB m	0.47	2344.44	73.52	89.65		999.4
		Sum	2615.01				

Figure S12. Chromatogram of an F2 drugmie sample after gastro-resistance test in the tablet disintegrator.

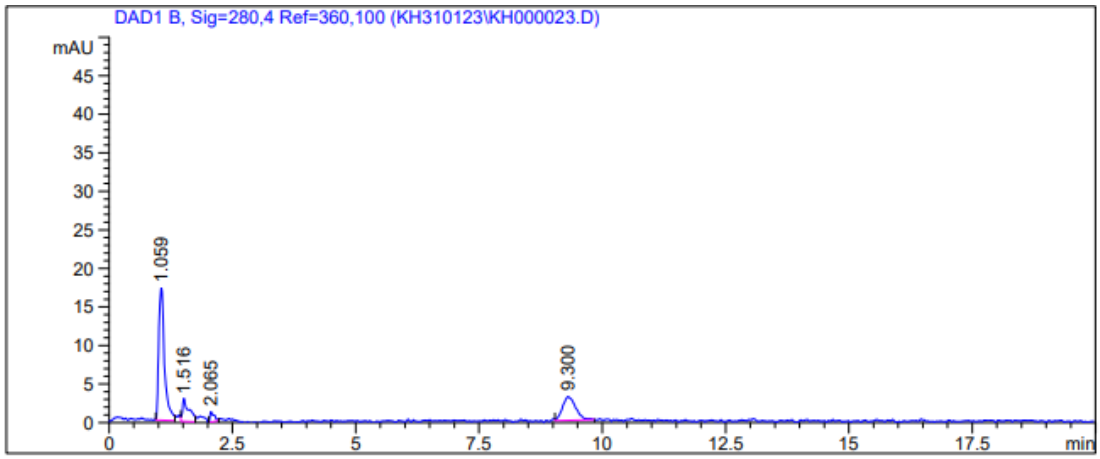


Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.100	BV	0.34	19.80	2.31	0.70	0.44687	997.2
1.469	VV	0.09	18.55	6.10	0.66	2.04261	985.6
1.534	VV	0.14	62.89	13.82	2.22	0.67025	973.2
1.699	VV	0.13	39.55	7.20	1.40	0.87170	977.2
1.835	VB	0.34	59.58	7.91	2.11	0.64953	913.2
2.338	BV	0.65	123.66	11.16	4.37	0.56605	525.4
2.937	VV	0.27	19.71	1.73	0.70	1.30568	979.6
3.504	VV	1.09	197.51	5.29	6.98	0.88253	727.8
6.883	VV	0.54	45.13	4.28	1.60	0.99000	410.0
8.202	BB	1.13	2242.90	176.12	79.27	1.05776	995.5
		Sum	2829.28				

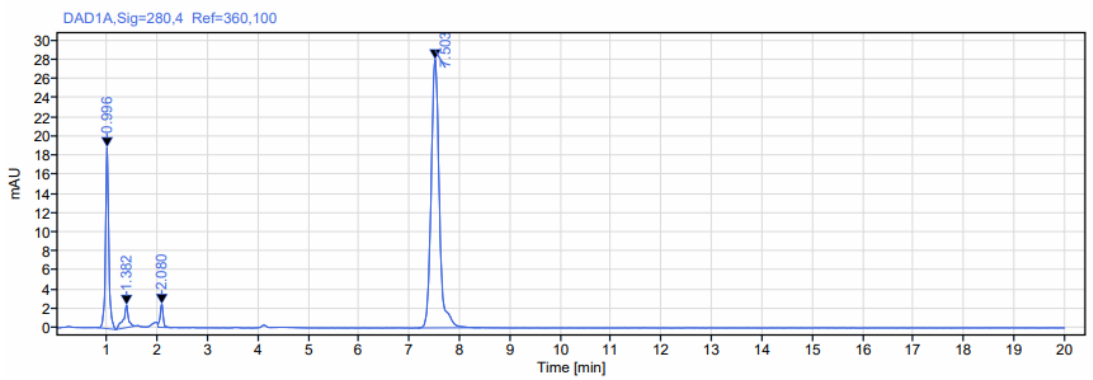
Figure S13. Chromatogram of an F2 fragmented drugmie sample after gastro-resistance test in Apparatus II.

6. Chromatograms of the F1 and F2 drugmies after dissolution test




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 B, Sig=280,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   1.059 BB    0.1242  138.88884   17.20132  60.0043
   2   1.516 VB    0.1203   27.05869    2.96936  11.6902
   3   2.065 PB    0.0831    8.37038    1.37341   3.6163
   4   9.300 BB    0.2398   57.14671    3.08983  24.6892

Totals :                   231.46462   24.63393
```

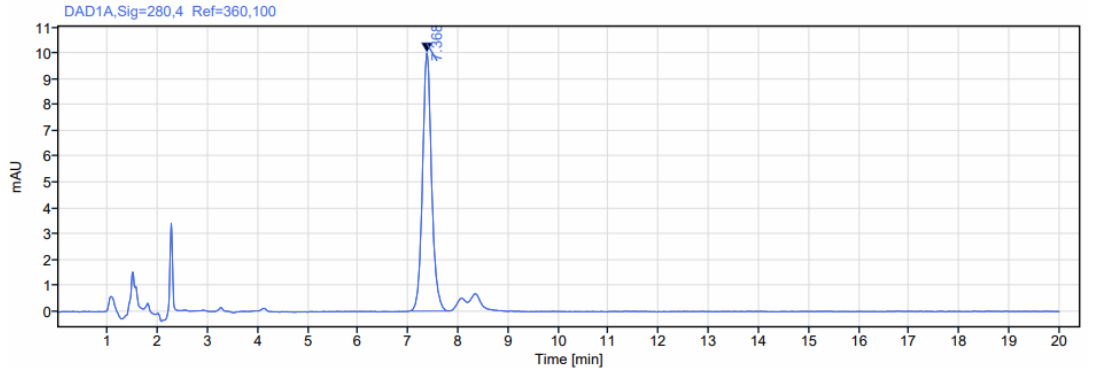
Figure S14. Chromatogram of an F1 drugmie sample after 45 minutes of dissolution test in Apparatus II.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
0.996	BB	0.37	84.46	18.92	19.85	0.88539	922.0
1.382	BB	0.39	15.96	2.34	3.75	1.57451	920.7
2.080	VB	0.26	10.29	2.41	2.42	1.09344	957.5
7.503	BB	1.25	314.73	28.03	73.98	0.86882	999.8
		Sum	425.44				

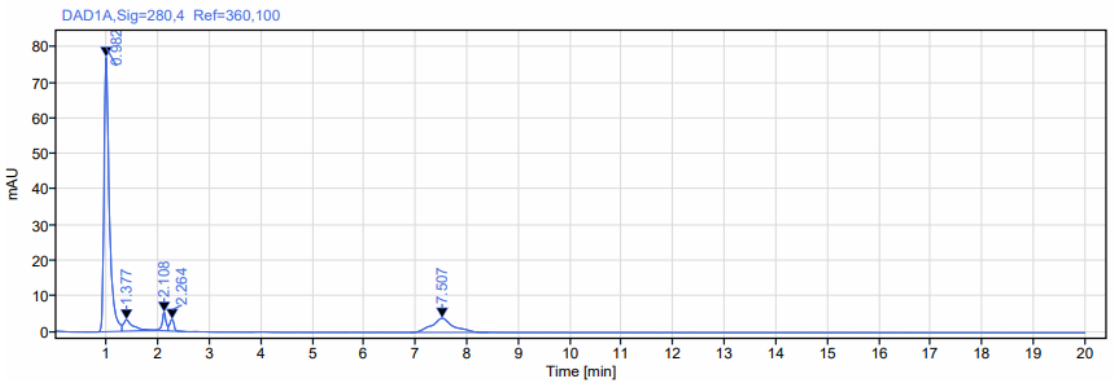
Figure S15. Chromatogram of an F1 drugmie sample after 45 minutes of dissolution test in the tablet disintegrator.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
7.368	BB	0.73	126.32	9.99	100.00	0.89305	999.2
		Sum	126.32				

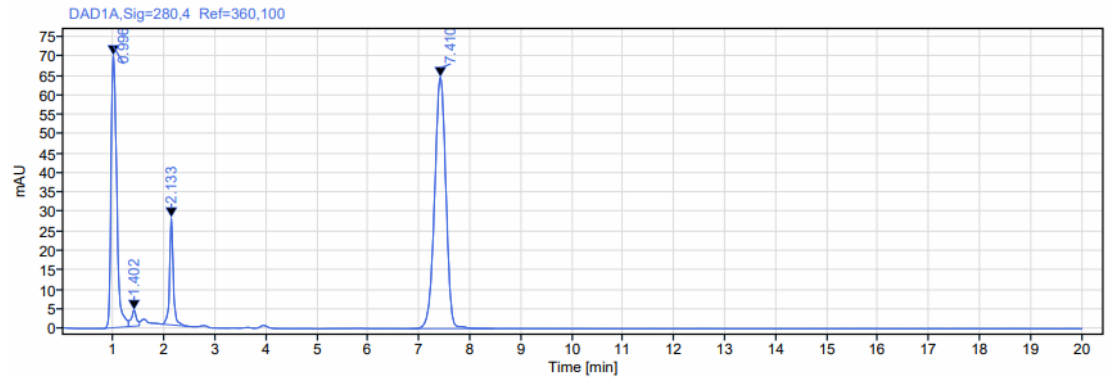
Figure S16. Chromatogram of an F1 fragmented drugmie sample after 45 minutes of dissolution test in Apparatus II.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
0.982	BV	0.47	556.77	77.06	73.38	0.58760	923.7
1.377	VB	0.64	40.91	3.14	5.39	0.41803	894.8
2.108	BV	0.26	26.30	5.13	3.47	0.98168	939.7
2.264	VB	0.34	19.17	3.26	2.53	1.24574	994.1
7.507	BB	1.51	115.60	3.99	15.24	0.89387	994.3
		Sum	758.74				

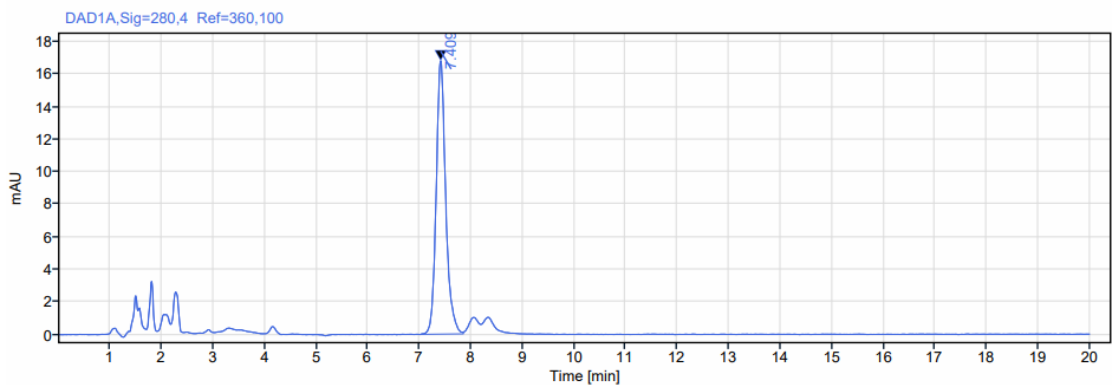
Figure S17*. Chromatogram of a F2 drugmie sample after 45 minutes of dissolution test in Apparatus II.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
0.996	BV	0.48	540.60	70.07	31.77	0.63526	504.0
1.402	VV	0.21	29.23	4.10	1.72	1.14594	877.9
2.133	BB	0.59	139.35	27.59	8.19	0.85380	971.3
7.410	BB	1.64	992.55	64.70	58.33	1.02851	999.6
		Sum	1701.72				

Figure S18*. Chromatogram of an F2 drugmie sample after 45 minutes of dissolution test in the tablet disintegrator.



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
7.409	BB	0.82	215.61	16.81	100.00	0.83590	999.0
		Sum	215.61				

Figure S19*. Chromatogram of an F2 fragmented drugmie sample after 45 min of dissolution test in Apparatus II.

*For the analysis of the F2 dissolution test samples, the volume injected into the HPLC UV-vis is doubled, so that the area considered for the determination of the dissolved percentage of API is half of the detected value.

3.3 Publicación 6: Optimisation of the manufacturing process of a paediatric omeprazole enteric pellets suspension: Full Factorial Design

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Cuartil	---

Resumen:

En este estudio se propuso aplicar el diseño de experimentos (DoE) para desarrollar una suspensión de pellets entéricos de omeprazol destinada a la población pediátrica. Se empleó un diseño factorial completo que abarcó tres factores principales (Aerosil® R972, alcohol cetostearílico y Span 80), cada uno evaluado en dos niveles (2% y 6% para el factor A (Aerosil® R972) y 2% y 4% para los Factores B y C (alcohol cetostearílico y Span 80, respectivamente)). Tras la optimización, se formuló la suspensión F10 y se sometió a un estudio de estabilidad durante un mes. Los resultados del ensayo de disolución no alcanzaron los estándares deseados, logrando solo una liberación del 22%. Como consecuencia, se idearon ocho suspensiones adicionales utilizando vehículos oleosos hidrófilos (Labraphac Hydrophile WL 1219, Labrafil M2125 CS y Labrafil M 1944 CS) y excipientes (Gelucire 44/14 y Aerosil® 200) con el objetivo de mejorar el perfil de disolución. La suspensión F17 se destacó al exhibir una liberación de más del 75% en 30 minutos, un tiempo de sedimentación superior en comparación con todas las demás formulaciones y una resuspensión sin esfuerzo. Los resultados sugieren que la formulación óptima para la administración de pellets entéricos de omeprazol en suspensión consiste en Labrafil M 1944 CS, Span 80 y Aerosil® 200. Este estudio ha allanado el camino para el desarrollo de un vehículo oleoso en suspensión, abriendo nuevas vías de investigación para el diseño de formulaciones pediátricas de omeprazol que cumplan con los requisitos de gastro-resistencia.

Abstract:

The propose of the present study was to apply the design of experiments (DoE) to develop an omeprazole enteric pellets suspension for use in the paediatric population. This experimental study employed a Full Factorial Design for drug development, encompassing three factors (Aerosil® R972, cetostearyl alcohol, and Span 80) at two levels (2% and 6% for factor A (Aerosil® R972) and 2% and 4% for factors B and C (cetostearyl alcohol and Span 80, respectively)). Following the optimization, the suspension F10 was formulated and subjected to a stability study for one month. The dissolution test results were suboptimal, achieving only an 22% release. Subsequently, eight additional suspensions were devised using hydrophilic oily vehicles (Labraphac Hydrophile WL 1219, Labrafil M2125 CS and Labrafil M 1944 CS) and excipients (Gelucire 44/14 and Aerosil® 200) to enhance the dissolution profile. Suspension F17 showed over 75% within 30 minutes, displaying superior sedimentation time when compared to all other formulations, along with effortless resuspension. The findings suggest that the optimal vehicle for the administration of enteric omeprazole pellets in suspension is the formulation comprising Labrafil M 1944 CS, Span 80, and Aerosil® 200. This study has paved the way for an oily suspension vehicle, opening new avenues of research for developing paediatric omeprazole formulations that fulfil gastro-resistance requirements.

Optimisation of the manufacturing process of a paediatric omeprazole enteric pellets suspension: Full Factorial Design

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Abstract

Objective:

The propose of the present study was to apply the design of experiments (DoE) to develop an omeprazole enteric pellets suspension for use in the paediatric population.

Methodology:

This experimental study employed a Full Factorial Design for drug development, encompassing three factors (Aerosil® R972, cetostearyl alcohol, and Span 80) at two levels (2% and 6% for factor A (Aerosil® R972) and 2% and 4% for factors B and C (cetostearyl alcohol and Span 80, respectively)).

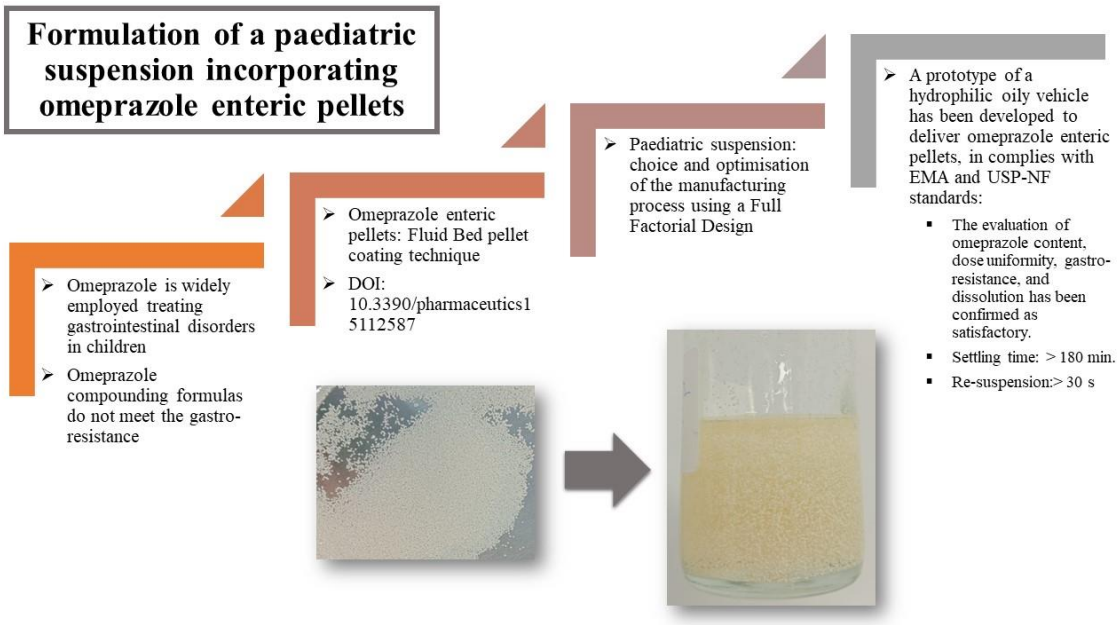
Results:

Following the statistical optimization, the suspension F10 was formulated and subjected to a stability study for one month. The dissolution test results were suboptimal, achieving only an 22% release. Subsequently, eight additional suspensions were devised using hydrophilic oily vehicles (Labraphac Hydrophile WL 1219, Labrafil M2125 CS and Labrafil M 1944 CS) and excipients (Gelucire 44/14 and Aerosil® 200) to enhance the dissolution profile. Suspension F17 showed over 75% within 30 minutes, displaying superior sedimentation time when compared to all other formulations, along with effortless resuspension.

Conclusion:

The findings suggest that the optimal vehicle for the administration of omeprazole enteric pellets in suspension is the formulation comprising Labrafil M 1944 CS, Span 80, and Aerosil® 200. This study has paved the way for an oily suspension vehicle, opening new avenues of research for developing paediatric omeprazole formulations that fulfil gastro-resistance requirements.

Graphical Abstract



Keywords: Omeprazole enteric pellets, Aerosil® 200, Span 80, Labrafil M 1944 CS, suspension, paediatric population.

1 Introduction

Liquid preparations for oral administration are widely used in paediatric patients due to their ease of administration and adjustability of dosage based on body weight or body surface area (1–3). Suspensions are among the most commonly used oral liquid formulations in paediatric population, particularly within hospital pharmacy services. These suspensions can be either ready-to-use or extemporaneous preparations. Frequently, hospital pharmacy departments counter the need to transform solid dosage forms into liquid preparations, due to the lack of paediatric-friendly dosage forms for specific active pharmaceutical ingredients (APIs) (2). Omeprazole (OME) is one such API lacking a paediatric formulation on the market. However, data from Hospital Materno Infantil del Vall de Hebrón (Barcelona, Spain), and other international hospitals in Thailand (4), France (5) and Morocco (6), indicate widespread use of omeprazole for treating gastric disorders in the paediatric population (7).

OME is a selective and irreversible proton pump inhibitor (PPI) widely used as antisecretory for its therapeutic efficacy and minimal adverse effects. It exerts action by reducing both basal and stimulated gastric secretion, irrespective of the stimulus triggering acid production. OME is used in adults and children for the treatment of various gastric disorders such as peptic ulcer, gastro-oesophageal reflux and other conditions characterised by excessive gastric acid secretion (8–11). OME is a crystalline powder, either white or off-white, with a melting and decomposition point at 155 ºC. It possesses weak basic properties and high solubility in lipids, ethanol, and methanol, with limited solubility in acetone, isopropanol and water. Although it is stable in alkaline environments, it degrades rapidly in acidic conditions (12–15). Consequently, in adults, OME is typically administered in oral capsules containing enteric minigranules or pellets to prevent its ionisation in acidic conditions and facilitate absorption in the small intestine.

Table 1 shows a formulation of Omeprazole 2 mg/mL suspension in xanthan gum (16) that represents one of the most used OME formulations in paediatric patients. Sodium bicarbonate is used to alkalinise the suspension vehicle and to promote OME stability. However, this approach exhibits limited effectiveness; upon administration, when the suspension encounters the acidic stomach environment, OME eventually degrades. Furthermore, as an aqueous suspension, the stability of OME is compromised due to its susceptibility to moisture (17,18).

In recent decades, drug development has tended to explore design and formulation techniques for APIs to reduce costs and manufacturing time, while ensuring the quality of the pharmaceutical properties of the final formulation. This optimizes the drug development stages, especially the pre-formulation stage. FFD is a systemic experimental methodology that offers several advantages over traditional trial-and-error experimentation. FFD enables the definition of optimal design space with minimal experiments, permitting the study of factors effects and their interactions on one or more responses. Thus, FFD stands as a powerful experimental design tool, providing a complete view of the behaviour of the system and allowing finding a mathematical model that links the studied response to the considered factors (19,20).

Hence, this study aims to apply the design of experiments (DoE) to the formulate a liquid dosage form of OME by studying its excipients and their proportion in the formulation. Specifically, this study seeks to

develop an omeprazole enteric pellets suspension for use in the paediatric population, applying a $2^3 + 1$ centre point FFD. The application of the FFD aims to assess the influence of each of excipient in the formulation and its role in the suspension's manufacturing process. Ultimately, the FFD methodology will define a design space for producing the omeprazole enteric pellets suspension.

2 Materials and methods

2.1 Materials

Micronized omeprazole (CAS no. 73590-58-6) was kindly donated by Esteve Química, Barcelona, Spain. Lactose monohydrate (CAS no. 10039-26-6), sodium lauryl sulphate (CAS no. 151-21-3), titanium dioxide (CAS no. 13463-67-7), Talc (CAS no. 14807-96-6) and cetostearyl alcohol (CAS no. 67762-27-0) were purchased from Fagron Ibérica SAU, Terrassa, Spain. Vivapur® MCC spheres were purchased from JRS Pharma GmbH & Co. KG, Rosenberg, Germany. Hydroxypropyl methyl cellulose (CAS no. 9004-65-3) and hydroxypropyl cellulose (CAS no. 9004-64-2) were purchased from Shin-Estu Chemical Co., Ltd., Tokyo, Japan. Eudragit® L-30 D-55, Aerosil® 200 (CAS no. 7631-86-9) and Aerosil® R972 (CAS no. 68611-44-9) were kindly donated by Evonik Corp., Barcelona, Spain. Sorbitan oleate (CAS no. 215-665-4) was purchased from Tokyo Chemical Industry CO., LTD. Medium-Chan Triglycerides (CAS no. 73398-61-5) was purchased from Guimama SLU. Labraphac Hydrophile WL 1219, Labrafil M2125 CS and Labrafil M1944 CS were kindly donated by Gattefossé, Barcelona, Spain. Gelucire® 44/14 (CAS no. 121548-04-7) was purchased from Gatteefossé, Barcelona, Spain. Triethyl citrate (CAS no. 77-93-0), disodium dihydrogen phosphate (CAS no. 7558-79-4), sodium dihydrogen phosphate (CAS no. 7558-80-7), sodium tetraborate decahydrate (CAS no. 1303-96-4), tribasic sodium phosphate dodecahydrate (CAS no. 10101-89-0), sodium hydroxide (CAS no. 1310-73-2), disodium hydrogen phosphate 12-hydrate (CAS no. 10039-32-4), hydrochloric acid 5 M (CAS no. 7647-01-0) and ethanol 96 % (CAS no. 64-17-5) were purchased from PanReac Química S.L.U., Barcelona, Spain.

The water used for analysis was MilliQ grade. All solvents used were analytical grade.

2.2 Methods

2.2.1 Full Factorial Design

In this study, a randomised Full Factorial Design (FFD) with a central point was applied to delineate a design space for the development of an omeprazole enteric pellets suspension. Pharmaceutical formulations typically consist of a blend of excipients and active pharmaceutical ingredient. Therefore, the impact of using three specific excipients in the production of the final suspension was studied. The selected excipients (factors) included Aerosil® R972 (Factor A), cetostearyl alcohol (Factor B) and Span 80 (Factor C). For each factor, two levels were designated: 2% and 6% for Factor A, and 2% and 4% for Factors B and C. The selection of both factors and their levels was made at the discretion of the researcher. The statistical program

Minitab 21.0 was utilized of the creation and analysis of the experimental design. **Table 2** show a schematic representation of the FFD experiments.

The responses considered in this study encompass sedimentation time, viscosity of the oil vehicle and coefficient of variation of the dosage uniformity. Additionally, the physicochemical characteristics of the final suspension, including its appearance, relative density and uniformity of the OME content, are carefully monitored.

Recognizing the pivotal role of drug and pharmaceutical quality in galenic development, this study adheres to the criteria of the Quality by Design (QbD) method outlined in the guidelines of the International Conference on Harmonisation (ICH Q8 R2) (21). Following with these criteria, the Design of Experiments (DoE) statistical tool was employed to mathematically describe the relationships among the studied factors, their interactions, and the values of the responses. This approach enables the optimization of the studied factors and the creation of an optimal design space under the most favourable conditions for producing the OME enteric pellets suspension.

2.2.2 Preparation of omeprazole enteric pellets

To prepare omeprazole enteric pellets, inert MCC spheres (microcrystalline cellulose inert pellets) underwent a three-layer coating process in a fluidised bed (*Glatt AG, Binzen, Germany*) equipped with a Würster column bottom spray coating process. The coating layers included: (1) an OME layer, (2) a protective layer to prevent interactions with the API and the enteric polymer, and (3) a layer of Eudragit® L-30 D-55 to shield the omeprazole from the acidic gastric environment. Detailed information on the coating process is provided in the study titled "Optimisation of the Manufacturing Process of Organic Solvent-Free Omeprazole Enteric Pellets for the Paediatric Population: Full Factorial Design"(22). **Figure 1** illustrates the OME enteric pellets utilized in the development of the suspensions.

2.2.3 Preparation of omeprazole enteric pellets suspension

Suspensions constitute a heterogeneous dispersed system comprising particles of an insoluble solid (dispersed phase) with a particle size exceeding 0.1 µm, dispersed in a liquid (dispersing medium). This type of liquid preparation adheres to the standard formula, including the API, wetting agent, viscosifier (if applicable), flocculant (if applicable) and dispersing medium. The present research aims to formulate a standard composition for producing an omeprazole enteric pellets suspension. Due to OME's instability in acidic media, an oily preparation based on Medium Chain Triglycerides (MCT) was chosen. MCTs are commonly employed in oral formulations for drugs unstable or insoluble in aqueous media, such as OME. Moreover, their safety profile and properties make MCTs a favourable alternative as an oily vehicle for paediatric OME formulations (23,24).

To optimise the oil vehicle for the OME enteric pellets suspension, a FFD was employed (refer to Section 2.2.1). Excipients Aerosil® R972, Span 80 and cetostearyl alcohol were selected for this purpose. Aerosil® R972, a hydrophobic colloidal silica, acted as a suspending agent, anti-caking agent, stabiliser and viscosifier, facilitating suspension and resuspension of the enteric OME pellets. Span 80, a non-ionic

surfactant, served as a wetting, dispersing and suspending agent, while cetostearyl alcohol provided viscosity-increasing properties (23).

The manufacturing process involved heating MCTs to 60 °C, adding Aerosil® R972 under mechanical agitation (*Heidolph, Schwabach, Germany*) until completely dissolved. Subsequently, lowering the temperature to 40°C, and adding cetostearyl alcohol. Once dissolved, Span 80 was introduced, and the mixture was tempered to room temperature with continuous stirring. Finally, a specified amount of OME enteric pellets (22) was added under magnetic stirring (*Multimix Heat D, Ovan, Barcelona, Spain*) to achieve a concentration of 2 mg OME per 1 mL. **Table 3** details the composition of the 9 FFD suspensions prepared.

2.2.4 Controls on suspensions: FFD responses

2.2.4.1 Organoleptic characteristics

For each omeprazole enteric pellets suspension, the final organoleptic characteristics are assessed, including appearance, colour, texture, and presence of agglomerates of omeprazole enteric pellets.

2.2.4.2 Sedimentation and resuspension time

Settling and resuspension times are critical for assessing suspension stability. Longer settling times and faster resuspension times improve stability. To determine settling time, vigorously shake the omeprazole enteric pellets suspension until uniform distribution, and then measure the time taken for the pellets to settle. Conversely, for resuspension time determination, allow the suspension to settle completely, and once all pellets have settled, measure the time it takes to achieve resuspension.

2.2.4.3 Suspension vehicle viscosity

The monograph "2.2.8. Viscosity" from the European Pharmacopoeia (version 11.2 online) (25) served as the guideline for determining the vehicle viscosity of the omeprazole enteric pellets suspension. To conduct the analysis, a sample amount (medium drop size) slated for examination was positioned at the center of the viscometer (CAP 2000+ Viscometer, Brookfield) and recorded. The viscosity reading was conducted under the following conditions: Spindle number 4; Hold time of 20 s; speed of 200 rpm; run time of 12 s; and sample temperature of 25 ºC. The viscosity readings were taken in triplicate.

2.2.4.4 Relative density of the suspension

The procedure outlined in the monograph "2.2.5. Relative density" from the European Pharmacopoeia (version 11.2 online) (26) was adhered to for determining the relative density of the omeprazole pellets suspension. An empty 10 mL flask was weighed, filled with the sample, and reweighed. The sample weight was divided by the volume of the sample (10 mL) to obtain the density (g/mL). The density reading was adjusted with the theoretical density of water at the reading temperature to calculate the relative density (g/mL). The determination was performed in triplicate.

2.2.4.5 Evaluation of omeprazole assay

To evaluate the omeprazole assay according to European Pharmacopoeia procedures, referencing monograph "2.9.6. Uniformity of content of single-dose preparations" (27), adhere to the specified range of 85% and 115% of the average content for individual content. Take 10 mL (form formulations F1 to F10) or 5 mL (for formulations F11 a F18) of the 2 mg/mL OME enteric pellets suspension using a syringe and weigh by difference. Transfer to a 50 mL (F1 to F10) or 100 mL (F11 to F18) volumetric flask, add 15 mL of ethanol, and sonicate for 15 min. Subsequently, introduce 20 mL of 0.1 M sodium borate solution and sonicate for an additional 15 min. Keep the mixture under magnetic stirring (*Multimix Heat D, Ovan, Barcelona, Spain*) for 15 minutes at a temperature of 35 – 40 ºC. Allow it to cool and adjust to volume with 0.1 M sodium borate solution. Finally, filter an aliquot and determine the amount of dissolved omeprazole using UV-vis HPLC (*Agilent 1100 series, Waldbronn, Germany*).

2.2.4.6 Dosage uniformity

To assess the dosage uniformity of the OME enteric pellets suspension according to the European Pharmacopoeia, specifically in the monograph "2.9.40. Uniformity of Dosage Units" (28), 10 units are individually analysed. The average value of the 10 samples must fall within the range of 85% to 115%, with an acceptance value of ≤ 15. A 5 mL sample is taken and weighed, then transferred to a 100 mL volumetric flask, add 15 mL of ethanol, and sonicate for 15 minutes. Subsequently, add 30 mL of 0.1 M sodium borate solution and sonicate again for 15 minutes. Keep the mixture under magnetic stirring (*Multimix Heat D, Ovan, Barcelona, Spain*) for 15 minutes at a temperature of 35-40 ºC. Allow it to cool and adjust the volume to the mark with 0.1 M sodium borate solution. Finally, filter an aliquot and determine the quantity of dissolved OME using UV-vis HPLC (*Agilent 1100 series, Waldbronn, Germany*).

2.2.4.7 Gastro-resistance test

No monograph addressing delayed-release omeprazole suspension is present in the the European and USP pharmacopoeias. Therefore, the gastro-resistance testing of the developed suspension will follow the USP-NF monograph for omeprazole delayed-release capsules (29). To comply with this monograph, no individual value should surpass 15% of the dissolved omeprazole during the gastro-resistance test. For this assay, take 10 mL (F1 to F10) or 5 mL (F11 to F18) of OME 2mg/mL enteric pellets suspension using a syringe and weighed by difference. Transfer the weighed sample to a beaker containing 500 mL of 0.1 N hydrochloric acid medium. The gastro-resistance test was conducted using a USP II apparatus (Erweka DT 700, Germany). Six samples were subjected to continuous agitation at a speed of 100 rpm for 2 hours at a temperature of 37 ± 0.5 ºC. After the test, retrieve the OME enteric pellets by filtering through a 0.2 mm sieve and rinse with deionised water. Transfer to a 100 mL volumetric flask, add 15 mL ethanol, and sonicate for 15 min. Add 30 mL of 0.1 M sodium borate solution and sonicate again for 15 minutes. Maintain under magnetic stirring (*Multimix Heat D, Ovan, Barcelona, Spain*) for 15 minutes at a temperature of 35 – 40 ºC. Allow it to warm and make up to volume with 0.1 M sodium borate solution. Filter an aliquot and determine the amount of dissolved omeprazole through UV-vis HPLC (*Agilent 1100 Series, Waldbronn, Germany*).

2.2.4.8 Dissolution test

The drug release profiles of OME enteric pellets were determined utilizing a USP apparatus II (Erweka DT 700, Langen, Germany), following the dissolution method outlined in the USP-NF monograph for "Omeprazole Delayed-Release capsules" (29). In accordance with the USP-NF tolerances, a minimum of 75% of the omeprazole should dissolve within 30 minutes. Each dose, containing OME enteric pellets equivalent to 20 mg (F10) or 10 mg (F11 to F17) of OME, was introduced into an apparatus II vessel containing 0.1 N hydrochloric acid (500 mL) at 37 ± 0.5 °C and stirred at 100 rpm. After 2 hours, 400 mL of 0.235 M dibasic sodium phosphate was added, and the pH was adjusted to 6.8 ± 0.5 using 2 N hydrochloric acid or 2 N sodium hydroxide. Samples were taken at 15, 30, and 45 minutes, filtered, and analysed for dissolved OME using UV-vis HPLC (*Agilent 1100 Series, Waldbronn, Germany*). Triplicate assays were conducted for each formulation.

2.2.5 Stability study of the final FFD suspension

To investigate the stability of the omeprazole enteric pellets within the prepared oily vehicle, a preliminary stability study was conducted on the selected final suspension of the FFD (suspension F10). The composition of this suspension was determined based on the results obtained from the design of experiments.

The stability assessment took place under temperature conditions of 25 ºC and 40 ºC. Additionally, it explored how the type of final packaging affects the stability; thus, opaque plastic and amber glass containers were employed. To prevent potential degradation of OME due to light exposure, samples were stored in light-protected cabinets. Samples were analysed at two time points: immediately after preparation and after one month. Prior to sampling, vigorous manual shaking for approximately 30 second was performed to ensure a homogeneous distribution of the pellets throughout the oil vehicle. At each analysis point, the appearance and colour of the oil vehicle and the omeprazole enteric pellets were scrutinized. Tests for omeprazole assay, gastro-resistance and dissolution tests were also conducted.

2.2.6 Formulations to improve the dissolution profile

Eight formulations were devised to enhance the dissolving capabilities, as illustrated in **Table 4**. Formulations F11 through F18 utilize hydrophilic oil vehicles in contrast to the F10 suspension. Labraphac Hydrophile WL 1219 serves as an oil vehicle in Formulations F11 and F12, replacing MCTs. With a higher hydrophilic content, this excipient aims to augment dissolving. Cetostearyl alcohol is the distinguishing factor between F11 and F12; F11 lacks it, while F12 includes it. Another hydrophilic substitute for MCTs, Labrafil M 1944 CS, functions as an oil vehicle in formulas F13, F14 and F15. The distinctions among F14, F13 and F15 lie in F14 containing cetostearyl alcohol and Gelucire® 44/14, F13 lacking contain cetostearyl alcohol, and F15 lacking both excipients. Gelucire® 44/14 is incorporated for its viscosity and wetting properties (Raymond C Rowe et al., 2009), facilitating the dispersion of the enteric OME pellets in the oil vehicle and enhancing content uniformity. Labrafil M 1944 CS replaces MCTs as a hydrophilic oil vehicle in formulations F16, F17 and F18. Gelucire® 44/14 is absent in F16 and F17 but present in F18. Cetostearyl

alcohol is omitted in F16, F17, and F18. All formulations include 2% Span 80. Aerosil® R972 is included in Formulations F11 to F17 at 5.70%. However, in F18, Aerosil® R972 is substituted with Aerosil® 200 at 4%. This substitution is implemented due to the hydrophobic properties of Aerosil® R972 (Raymond C Rowe et al., 2009), with the belief that replacing it with Aerosil® 200 (Colloidal Silicon Dioxide) will enhance the dissolution profile of the suspension.

For the preparation of suspensions, the oil vehicle was heated to 60 ºC. Aerosil® R972 (or Aerosil® 200 in the case of F18) was introduced and stirred until fully dissolved through mechanical agitation (*Heidolph, Schwabach, Germany*). Gelucire® 44/14 (included in F13, F14, and F18) was incorporated and stirred until completely dissolved using mechanical agitation. The mixture was then cooled to 40 °C with continuous stirring, and cetostearyl alcohol (included in F12 and F14) was added. After complete dissolution, Span 80 was introduced, and the mixture was tempered to room temperature under mechanical stirring. Finally, using magnetic stirring (*Multimix Heat D, Ovan, Barcelona, Spain*), a quantity of OME enteric pellets (22) was added to achieve a concentration of 2 mg OME per 1 mL in the suspensions.

After the preparation of the suspensions, the following parameters were assessed: appearance, viscosity of the excipient mixture, relative density, resuspension time, settling time, and dissolution test.

3 Results

3.1 Controls on suspensions: FFD responses

Table 5 presents the results of the controls conducted on the developed suspensions. Concerning organoleptic characteristics, suspensions F1 and F3 failed to meet the required organoleptic standards, showing pellet agglomerates and uneven distribution upon resuspension. In contrast, the remaining suspensions displayed favourable organoleptic characteristics, including a slightly yellowish colour. Upon shaking, the pellets were homogeneously distributed, devoid of agglomerates and adhering to the container's bottom.

The suspensions F1, F2, F5 and F8, with a 6% of Aerosil® R972 content, exhibited viscosities exceeding 200 mPa·s and longer settling times. Among them, F2 had the slowest settling time, while F6, with a 2% Aerosil® R792 content, had the fastest. Regarding relative density, it was consistent across all suspensions, with the highest was in F2 (0.998 g/mL) and the lowest was in F6 (0.963 g/mL).

In terms of omeprazole dose uniformity, significant variability was observed among samples of the same suspension. However, F2 exhibited uniformity in omeprazole content within the specifications outlined in the monograph "2.9.6. Uniformity of content of single-dose preparations" of the Ph. Eur. monograph (27), with a low coefficient of variation. The obtained percentage of OME obtained was 94.76 ± 3.64.

3.2 Statistical analysis of the FFD

Regression analysis of the DoE data was conducted using Minitab 21.0 statistical software. When performing linear regression of the FFD responses and their interactions, no significant p-values were

obtained ($\alpha = 0.05$). Therefore, the decision was made to conduct the statistical analysis without considering the interactions. It was noted that Factor B (percentage of cetostearyl alcohol) did not exert a significant influence on any response. Upon conducting the statistical analysis without considering Factor B and its interactions, it was concluded that Factor A (percentage of Aerosil® R972) significantly influenced all three responses: a p-value of 0.005 for the coefficient of variation of dosage uniformity, and 0.000 for settling time and the viscosity of the oil vehicle. Regarding the coefficient of coefficient of variation of dose uniformity, the influence of Factor C (percentage of Span 80) was also observed, with a p-value of 0.019. Another statistical analysis was performed, considering factors A and C, along with their interaction. In this analysis, it was confirmed that the percentage of Aerosil® R972 significantly influenced the studied responses. Additionally, for the response of the coefficient of variation of dose uniformity, it was observed that factors A and C, as well as their interaction (p-value of 0.036), had significant influences on this response. The R2 obtained in the analysis considering the interactions of factors A and C were very similar to the statistical analysis without considering them. Following the principle of parsimony, and among the possible models with equivalent R2, it is advisable to select the simplest one. Therefore, the final linear regression equations (refer to **Table 6)** were chosen to only consider Factor A (percentage of Aerosil® R972) and Factor C (percentage of Span 80).

Pareto diagrams illustrating the relationship between the studied factors studied and responses are presented below. Factors that surpass the standard line at the 95.0% confidence level are deemed to significantly impact the studied responses. It is evident from **Figures 2**, **3** and **4** that Aerosil® R972 has a substantial impact on all three responses. Notably, the coefficient of variation of dosage uniformity response is also affected by the percentage of Span 80.

Figures 2, **3** and **4** also present contour plots of the final statistical model, delineating the optimal working area. When the Aerosil® R972 percentage ranges from 5% to 6%, and Span 80 percentage is 2%, the highest values for oil vehicle viscosity and settling time, coupled with the lowest values for the coefficient of variation in dosage uniformity, are attained.

Optimisation, as depicted in **Figure 5**, reveals the optimum levels for Factor A to be 5.70% (w/w) and for Factor C to be 2.0% (w/w). At these levels, a composite desirability of 0.89 is achieved. Using this composition, the final suspension was prepared and underwent a one-month stability study.

3.3 Stability study of the final FFD suspension

A stability study was carried out on the suspension of omeprazole enteric pellets using the composition outlined in **Table 7**. The primary objective was to evaluate the gastro-resistance properties of the suspension and the impact of the oil vehicle on the OME enteric pellets. The resulting suspension displayed desirable organoleptic characteristics, featuring a slight yellowish colour in the oily vehicle and white omeprazole enteric pellets. Upon agitation, the pellets dispersed uniformly without agglomerates or adherence to the container's bottom.

After one month of stability, samples stored at 25 ºC and 40 ºC were analysed. **Table 8** shows the evaluation of OME assay, gastro-resistance test and dissolution test analyses. Samples stored at 25°C exhibited higher stability, with 93% content uniformity in glass containers compared to 87% in plastic containers. At 40°C, samples met the Ph. Eur. content evaluation specification, but had slightly lower percentages (90% in glass containers and 86% in plastic containers). Colour changes were observed in samples stored at higher temperatures: the omeprazole enteric pellets turned from white to pink, and the oily vehicle also took on a pink hue (initially, during the stability study, it was slightly yellowish). Gastro-resistance testing, at 25°C met the USP-NF specification, whereas samples stored at 40°C in glass containers did not. Dissolution testing revealed delayed release attributed to the suspension's oily nature; after the test were low at 22% at time 0 (see **Table 8**).

3.4 Formulations to improve the dissolution profile

Table 9 displays the outcomes of the evaluations conducted subsequent to the preparation of suspensions F11 – F 18. In terms of visual characteristics, all suspensions exhibited transparency and a slight yellowish tint, except for F18, which presented a subtle turbulence. Consequently, this formulation was omitted from further consideration. The viscosity of the oil vehicle ranged from 176 to 328 mPa-s, with F12 showcasing the lowest value and F14 the highest. Notably, formulations incorporating Gelucire® 44/14 (F13, F14, and F18) displayed a cloudy and less transparent appearance after a brief period. This effect was particularly pronounced in F18 after 24 hours, prompting its exclusion from further analysis.

The relative densities consistently hovered around 1 mg/mL for all formulations. Regarding resuspension time, only F14 and F18 exceeded 30 seconds, while others demonstrated easy resuspension in under 30 seconds. In terms of settling time, suspensions with Labraphac Hydrophile WL 1219 oil vehicle (F11 and F12) settled in 5 minutes, those with Labrafil M2125 CS (F13, F14, and F15) in 6 minutes, and suspensions with Labrafil M 1944 CS (F16 and F18) in 10 minutes. However, F17 exhibited a settling exceeding 180 minutes. This was attributed to the use of Aerosil® 200 instead of Aerosil® R972 in its composition, a change that significantly prolonged the settling time from 10 minutes to over 3 hours. This modification also positively influenced the dispersion of enteric OME pellets in the oil vehicle. Consequently, F17 was deemed the optimal suspension due to its superior organoleptic characteristics compared to the other formulations.

F17 was chosen as the final formulation, and its manufacturing process was reproduced to perform analytical tests assessing OME assay, dose uniformity, gastro-resistance, and dissolution. The results, as displayed in **Table 10**, were deemed satisfactory, meeting the specifications stipulated in the Ph. Eur. and the USP-NF for all conducted tests.

For the content assessment, an average OME content of 98% was achieved, falling within the 85-115% range specified by the Ph. Eur. (27). Dose uniformity reached a percentage of 110%, also meeting the criteria of the monograph "2.9.40. Uniformity of Dosage Units" in the Ph. Eur. (28). Regarding gastro-resistance, an average API percentage after the test of 97% was achieved, surpassing the USP-NF

specification (29), where no more than 15% of OME should degrade in 0.1 M hydrochloric acid medium for 2 hours.

In terms of the dissolution test, F17 exhibited a significant improvement compared to various prepared suspensions, including F10. Replacing medium-chain triglycerides (MCTs) with hydrophilic oily vehicles resulted in a positive impact on the dissolution profile, as evidenced by formulations F11 – F17 achieving release levels higher than 22%, surpassing that of F10. Conversely, the inclusion of cetostearyl alcohol had a detrimental effect on API dissolution, with formulation F12 exhibiting the lowest release at 37%. This was further supported by the slightly higher release observed in F11, which lacked cetostearyl alcohol. Additionally, the addition of Gelucire® 44/14 in formulations F13 and F14 led to slightly higher dissolution levels, indicating an improvement in the wetting of the omeprazole enteric pellets. Furthermore, formulations containing Span 80 and Aerosil® R972 in different oil vehicles (F11, F15, and F16) displayed higher release levels compared to F10. In F17, Labrafil M 1944 CS is utilized as the oil vehicle, while Aerosil® R972 is substituted with Aerosil® 200. These modifications lead to a substantial enhancement in the release of the enteric OME pellets, reaching a release rate of 79%.

4 Discussion

The main objective proposed in this study was to develop an oral liquid formulation of omeprazole suitable for paediatric use, meeting the gastro-resistance and release criteria outlined in Ph. Eur. and USP-NF. This objective was satisfactorily achieved through experimentation.

Omeprazole, being susceptible to degradation in acidic environments (8,9,15), necessitates an enteric coating to maintain its effectiveness. However, commonly used compounding formulas for paediatric patients, such as omeprazole 2mg/mL suspension in xanthan gum (16), often fail to meet the gastro-resistance requirements (7,18,30). This inadequacy prompted the exploration of an alternative approach utilizing omeprazole enteric pellets with morphological characteristics tailored to paediatric patient (22), aiming to develop an enteric suspension.

A full factorial design was employed, incorporating three factors at 2 levels plus a central point. These factors included the percentage of Aerosil® R972 (Factor A), cetostearyl alcohol (Factor B) and Span 80 (Factor C). Post-preparation, organoleptic assessments revealed significant discrepancies among the suspensions. For instance, suspensions F1 and F3 presented agglomerates and lacked transparency in the oily vehicles, indicating formulation issues. This underscores the importance of meticulous excipient selection and proportioning to ensure the quality of the final product (21,31–33).

A correlation is established between the viscosity of the oily vehicle and Aerosil® R972 content, with higher percentages leading to increased viscosity and prolonged sedimentation times, determinant for precise dosing. Furthermore, uniformity in relative density across all suspensions suggested formulation consistency, emphasizing the importance of fine-tuning composition for desired physical properties and optimal performance (34–36).

Regarding dose uniformity, suspension F2 exhibited optimal results, with a value of 95 ± 3 (SD). The remaining suspensions present standard deviations higher than 5, indicating a lack of dose uniformity. This underscores the suitability of a 6% Aerosil® R972 content for achieving desired organoleptic characteristics and dose uniformity within regulatory specifications.

Regression analysis revealed the significant influence of Aerosil® R972 and Span 80 percentages on the three responses examined (see **Table 6**), underlining their pivotal roles in suspension development. Pareto diagrams and contour plots helped define an optimal working zone for these factors, indicating that the ideal percentages are between 5% and 6% for Aerosil® R972 and 2% for Span 80 (refer to **Figures 2**, **3** and **4**).

Subsequent formulation adjustments led to the development of suspension F10, subjected to a preliminary stability study indicating room temperature as the optimal storage condition. This aligns with findings from previous stability studies on liquid omeprazole preparations. The developed suspension shows a notable improvement compared to the liquid omeprazol preparations utilized in paediatric patients (37–40), particularly in terms of gastro-resistance, achieving a percentage of 93% after a two-hours exposure to 0.1 M hydrochloric acid medium. Nevertheless, the release of omeprazole is constrained, with only 22% released at time 0. These outcomes are ascribed to the characteristics of the oily vehicle employed in the formulation, which impedes the release of the API.

Further optimization efforts involved the preparation of suspensions F11 to F18, incorporating hydrophilic oily vehicles and release-favouring excipients. Formulation F17 emerged as standout performer, demonstrating improved API release attributed to the inclusion of Labrafil M 1944 CS an Aerosil® 200, achieving 79%. These adjustments enabled compliance with the omeprazole dissolution test specifications according to the USP-NF (29). It is noteworthy that the results of this research emphasize the direct impact of the excipients used on both gastro-resistance and omeprazole release. Analyses of the F17 suspension showed satisfactory outcomes concerning omeprazole evaluation assay (98%), dose uniformity (average content within the range of 85 – 115%, meeting the acceptance value of 13.13) and gastro-resistance (96%), aligning with the specifications outlined in Ph. Eur. (27,28) and USP-NF (29) specifications for such tests (see **Table 10**).

5 Conclusions

The study successfully defined an optimal working area for producing a stable omeprazole enteric pellets suspension with consistent physicochemical properties, suitable for one-month storage at room temperature in topaz glass containers. Aerosil® R972 emerged as the excipient that significantly influenced the suspension's physicochemical attributes, particularly the viscosity of the oil vehicle and settling time. Within the 5% to 6% range, Aerosil® R972, yielded desired values for these parameters, facilitating accurate dosing. Samples of the F10 suspension stored at 25 ºC for one month met content uniformity and gastro-resistance specifications outlined by the Ph. Eur. and the USP-NF, respectively. However, the dissolution test presented a challenge, with only a 22% release. Consequently, eight supplementary suspensions were formulated, incorporating hydrophilic oil vehicles and excipients (Gelucire 44/14 and

Aerosil® 200) to enhance the dissolution. Remarkably, suspension F17 exhibited a release profile exceeding 75% within 30 minutes, demonstrating superior settling time and easy resuspension of the OME enteric pellets. Furthermore, the Ph. Eur. and USP-NF specifications were met for OME evaluation assay (98%), dosage uniformity (average content of 110%, meeting the acceptance value of 13.13) and gastro-resistance (96% API remaining after exposure to 0.1 M hydrochloric acid). Based on these results, the final composition of the prototype oily vehicle for administering enteric pellets of omeprazole to paediatric patients includes Labrafil M 1944 CS, Aerosil® 200, and Span 80. These findings highlight the need for further research to address the critical issue in current omeprazole compounding formulas for paediatric patients, crucial for enhancing effectiveness.

Supplementary information

The supplementary materials are enclosed within a separate document.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Tables

Table 1 Composition of 2 mg/mL OME Suspension in Xanthan Gum (16)

Components	Percentage (%)
Omeprazole base	0.2
Sodium bicarbonate	8.4
Xanthan gum (aqueous solution 1%)	50 mL
Vanilla essence	0.1 – 0.2
Sodium saccharin	0.1 – 0.3
Purified water q.s.	100 mL

Table 2 Design of Experiments: Randomised Full 2^3 Factorial Design with Central Point

Statistical order	Running order	Block	Factor A	Factor B	Factor C
4	1	1	6%	2%	4%
2	2	1	6%	2%	2%
3	3	1	2%	2%	4%
5	4	1	2%	4%	2%
6	5	1	6%	4%	2%
1	6	1	2%	2%	2%
9	7	1	4%	3%	3%
8	8	1	6%	4%	4%
7	9	1	2%	4%	4%

Table 3 Composition of the Developed FFD Suspensions

Suspension	Aerosil® R972	Cetostearyl alcohol	Span 80	Medium-Chain triglycerides
F1	6%	4%	2%	q.s. 100
F2	6%	2%	2%	q.s. 100
F3	2%	4%	2%	q.s. 100
F4	2%	2%	4%	q.s. 100
F5	6%	2%	4%	q.s. 100
F6	2%	2%	2%	q.s. 100
F7	3%	2%	2%	q.s. 100
F8	6%	4%	4%	q.s. 100
F9	2%	4%	4%	q.s. 100

Table 4 Composition for Suspensions F11 to F18

Components	F11 (% (w/w))	F12 (% (w/w))	F13 (% (w/w))	F14 (% (w/w))	F15 (% (w/w))	F16 (% (w/w))	F17 (% (w/w))	F18 (% (w/w))
Aerosil® R972	5.70	5.70	5.70	5.70	5.70	5.70	---	5.70
Span 80	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Cetostearyl alcohol	---	2.00	---	2.00	---	---	---	---
Gelucire® 44/14	---	---	5.00	5.00	---	---	---	5.00
Aerosil® 200	---	---	---	---	---	---	4.00	---
Labraphac Hydrophile WL 1219	88.77	86.77	---	---	---	---	---	---
Labrafil M2125 CS	---	---	83.77	81.77	88.77	---	---	---
Labrafil M 1944 CS	---	---	---	---	---	88.77	90.47	83.77
OME enteric pellets	3.53	3.53	3.53	3.53	3.53	3.53	3.53	3.53

Table 5 FFD responses: Controls for Suspensions F1 to F9. Presented Mean ± SD

Formula	Organoleptic characteristics	Viscosity of oil vehicle (mPa·s) ± SD	Relative density (g/mL) ± SD	Resuspension time (s)	Sedimentation time (s)	Dose accuracy (% (w/w)) ± SD
F1	Does not comply	289.53 ± 1.25	1.00 ± 0.00	> 30	300	106.69 ± 10.61
F2	Complies	273.23 ± 0.42	1.00 ± 0.00	< 30	360	94.76 ± 3.45
F3	Does not comply	49.93 ± 0.38	0.97 ± 0.01	> 30	100	88.20 ± 11.59
F4	Complies	45.17 ± 2.60	098 ± 0.02	< 30	111	84.74 ± 26.28
F5	Complies	284.67 ± 3.67	0.98 ± 0.02	< 30	300	108.66 ± 19.37
F6	Complies	36.60 ± 1.18	0.97 ± 0.01	< 30	83	99.30 ± 12.74
F7	Complies	96.03 ± 1.41	0.96 ± 0.02	< 30	185	102.75 ± 14.96
F8	Complies	218.43 ± 4.03	0.99 ± 0.01	> 30	300	80.08 ± 10.89
F9	Complies	47.97 ± 1.36	0.96 ± 0.02	< 30	111	100.78 ± 37.20

Table 6 Minitab Output for the Regression Equation of the FFD Responses and their Association with the Studied Factors. X1: Aerosil® R972; X2: Span 80

Regression equation	R^2 (adjusted)
CV (%) = – 16.18 + 2.30 X1 + 14.75 X2 – 1.714 X1*X2	93.64%
Sedimentation time (s) = – 8.2 + 53.44 X1	96.11%
Viscosity of oil vehicle (mPa·s) = 113.1 – 63.9 X1 + 14.91 X^2	96.83%

Table 7 Composition of the Final OME Enteric Pellets Suspension from the FFD (F10)

Component	Percentage (% (w/w))
Enteric pellets of omeprazol (*)	3.53
Aerosil® R972	5.70
Span 80	2.00
Cetostearyl alcohol	2.00
Medium-Chain Triglycerides	86.77
(*) Quantity of enteric pellets of OME equivalent to 0.20 g of OME	

Table 8 Stability Study Results for F10. Presented as Mean ± SD

Stability conditions	Evaluation of OME content (% ± SD)		Gastro-resistance essay (% ± SD)		Dissolution essay (% ± SD)	
	Glass packaging	Plastic packaging	Glass packaging	Plastic packaging	Glass packaging	Plastic packaging
Time 0	98.58 ± 2.56		95.50 ± 4.41		22.47 ± 12.13	
25 ºC, 1 month	92.93 ± 3.78	86.53 ± 2.05	89.75 ± 4.79	89.54 ± 0.11	18.11 ± 3.28	17.36 ± 2.41
40 ºC, 1 month	89.95 ± 6.58	85.56 ± 0.46	69.66 ± 3.55	85.67 ± 2.85	35.14 ± 4.32	29.73 ± 2.82

Table 9 Controls for Final Suspensions of Formulations F11 – F18. Presented as Mean ± SD

Formula	Organoleptic characteristics	Viscosity of oil vehicle (mPa·s) ± SD	Relative density (g/mL) ± SD	Resuspension time (s)	Sedimentation time (min)	Dissolution test (% (w/w)) ± SD
F11	Complies	192.60 ± 0.82	0.99 ± 0.03	< 30	5	42.98 ± 19.44
F12	Complies	176.33 ± 1.02	0.98 ± 0.02	< 30	5	36.67 ± 8.28
F13	Complies	215.33 ± 0.51	0.99 ± 0.01	> 30	6	47.88 ± 19.45
F14	Complies	323.47 ± 1.10	0.98 ± 0.02	> 30	6	56.16 ± 8.91
F15	Complies	327.73 ± 0.74	0.99 ± 0.02	< 30	6	48.80 ± 6.88
F16	Complies	295.20 ± 1.10	0.99 ± 0.01	< 30	10	57.19 ± 3.41
F17	Complies	263.60 ± 0.66	1.00 ± 0.00	< 30	> 180	79.19 ± 4.30
F18	Does not comply	320.30 ± 0.80	0.99 ± 0.03	> 30	10	Discarded formula

Table 10 Results of F17: (A) Evaluation of OME Content, (B) Dosage Uniformity, (C) Gastro-resistance Test and (D) Dissolution Test. Presented as Mean ± SD

(A) Evaluation of OME Content (% (w/w) ± SD)		
Theoretical Dose (mg) ± SD	**Actual Dose (mg) ± SD**	**Dose Accuracy (% (w/w)) ± SD**
10.48 ± 5.81	10.29 ± 3.35	98.30 ± 4.01
(B) Dosage Uniformity (% (w/w) ± SD)		
Theoretical Dose (mg) ± SD	**Actual Dose (mg) ± SD**	**Dose Accuracy (% (w/w)) ± SD**
9.30 ± 2.14	10.36 ± 2.66	109.97 ± 1.94
(C) Gastro-resistance test		
Theoretical Dose (mg) ± SD	**Actual Dose (mg) ± SD**	**Dose Accuracy after Gastro-Resistance Test (% (w/w)) ± SD**
10.91 ± 0.50	10.57 ± 0.40	96.96 ± 1.27
(D) Dissolution test		
Theoretical Dose (mg) ± SD	**Actual Dose (mg) ± SD**	**API Dissolved (% (w/w)) ± SD**
10.28 ± 1.52	7.96 ± 1.35	77.24 ± 5.02

Figures

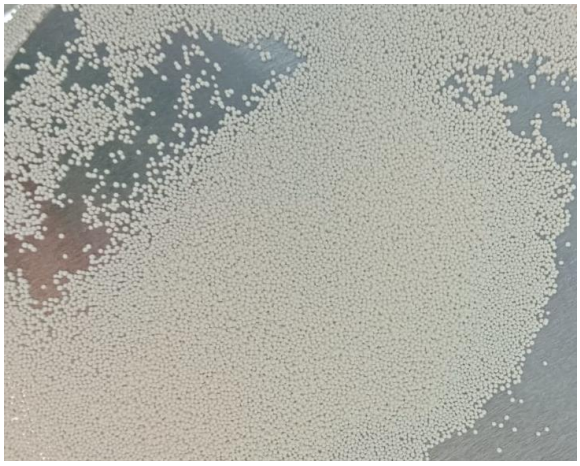

Fig. 1 Omeprazole Enteric Pellets after Coating Process

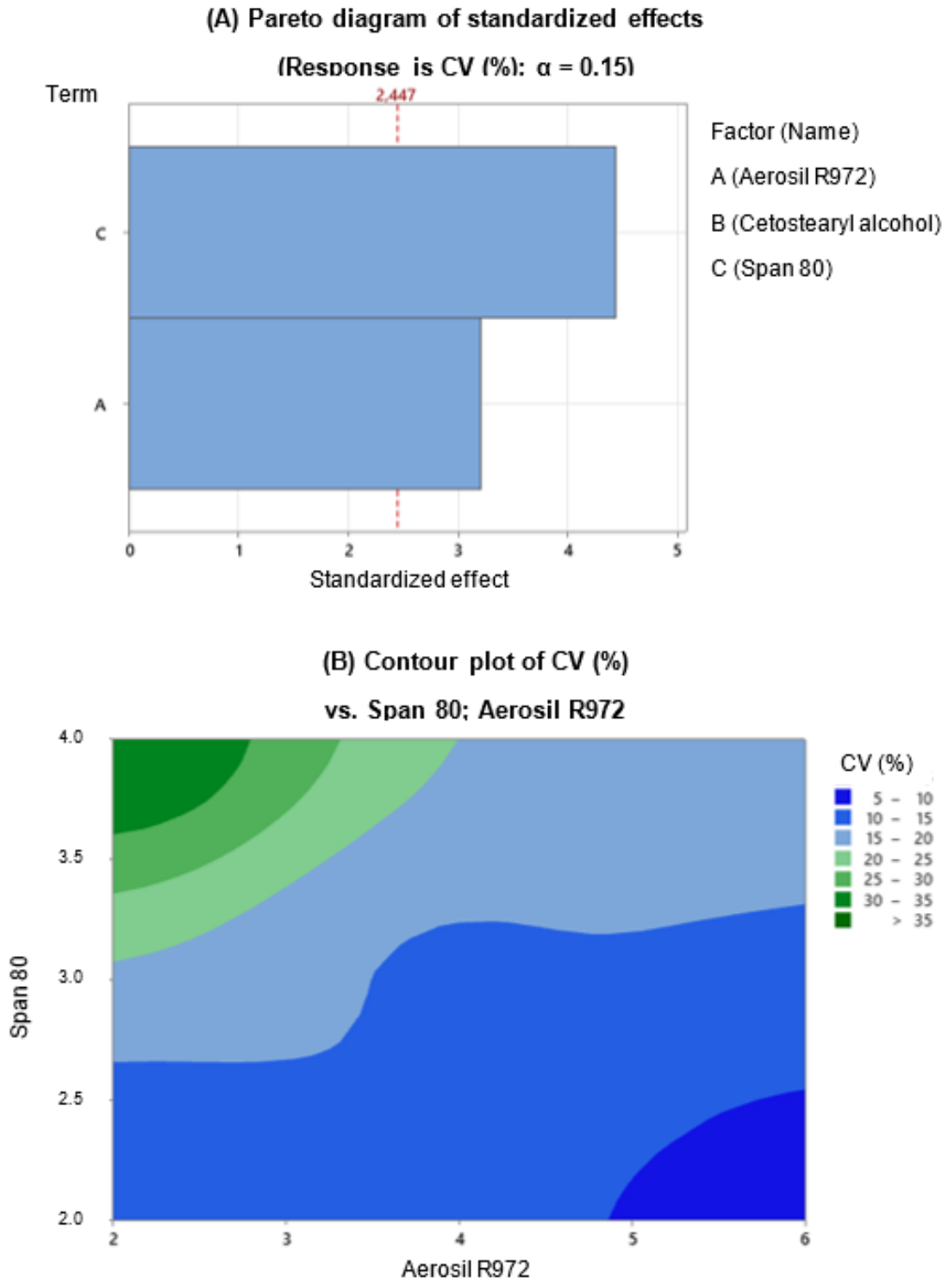

Fig. 2 Coefficient of Variation (%): (A) Pareto diagram and (B) Contour plots

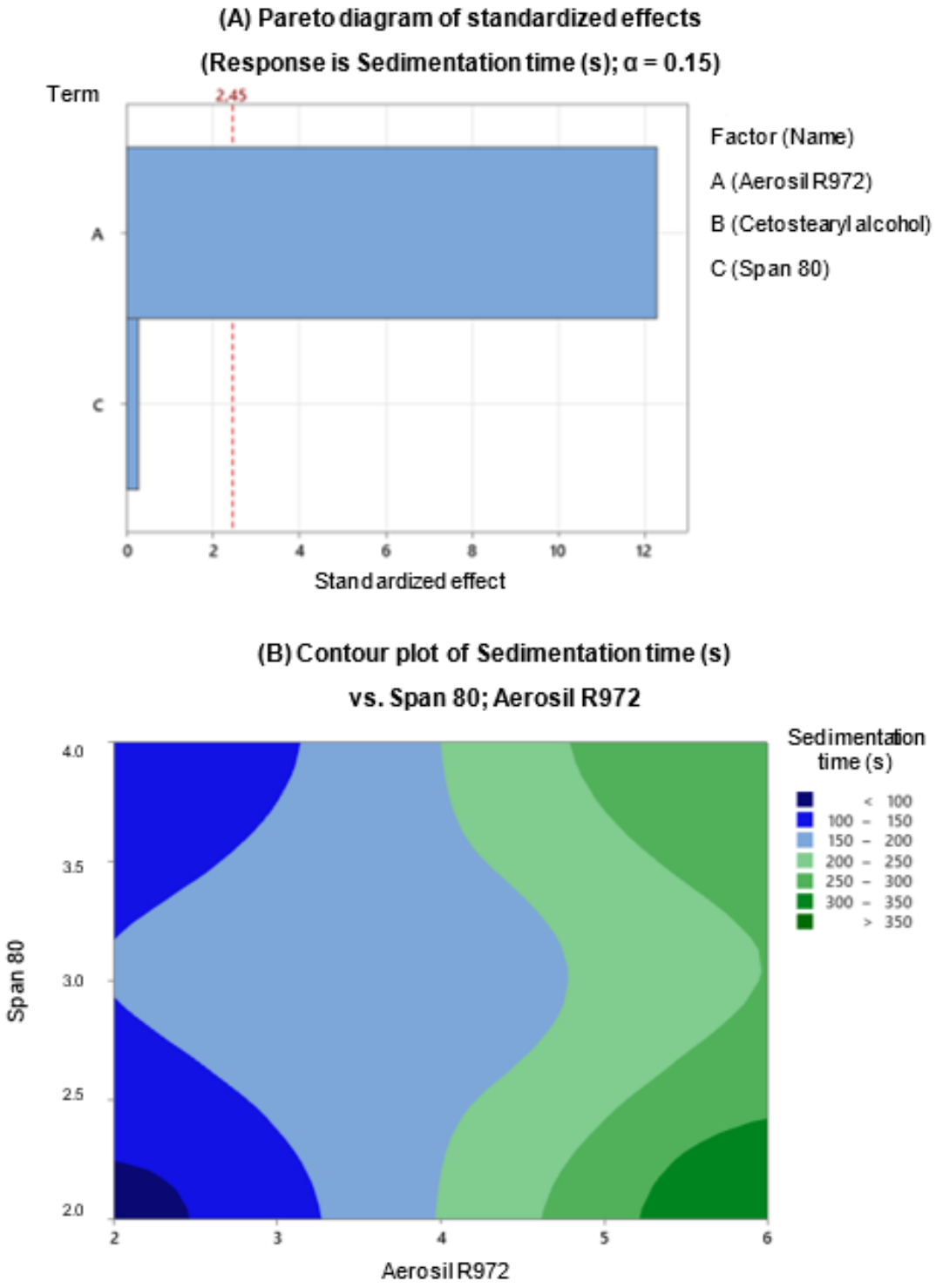

Fig. 3 Sedimentation time (s): (A) Pareto diagram and (B) Contour plots

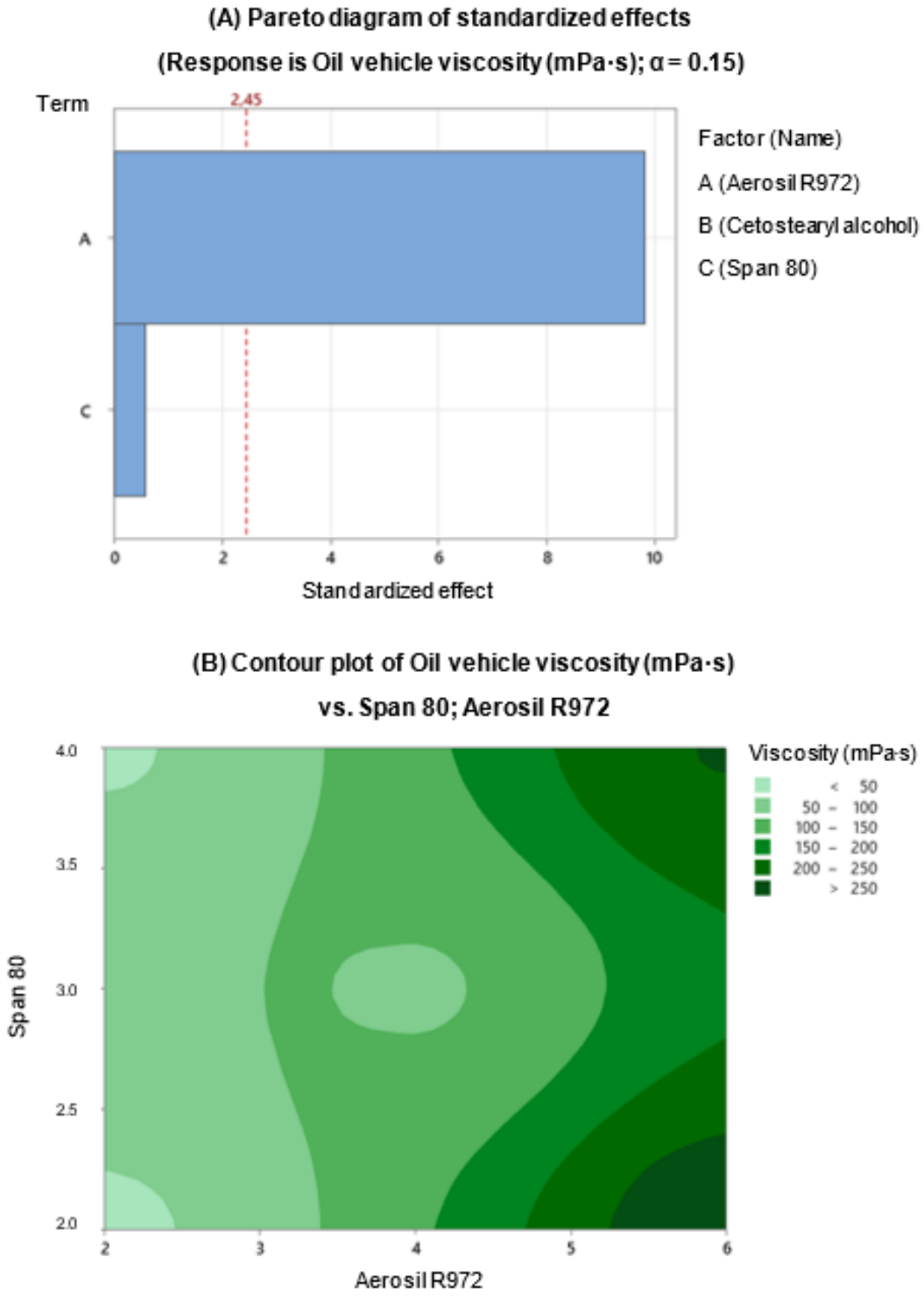

Fig. 4 Oil vehicle viscosity (mPa·s): (A) Pareto diagram and (B) Contour plots

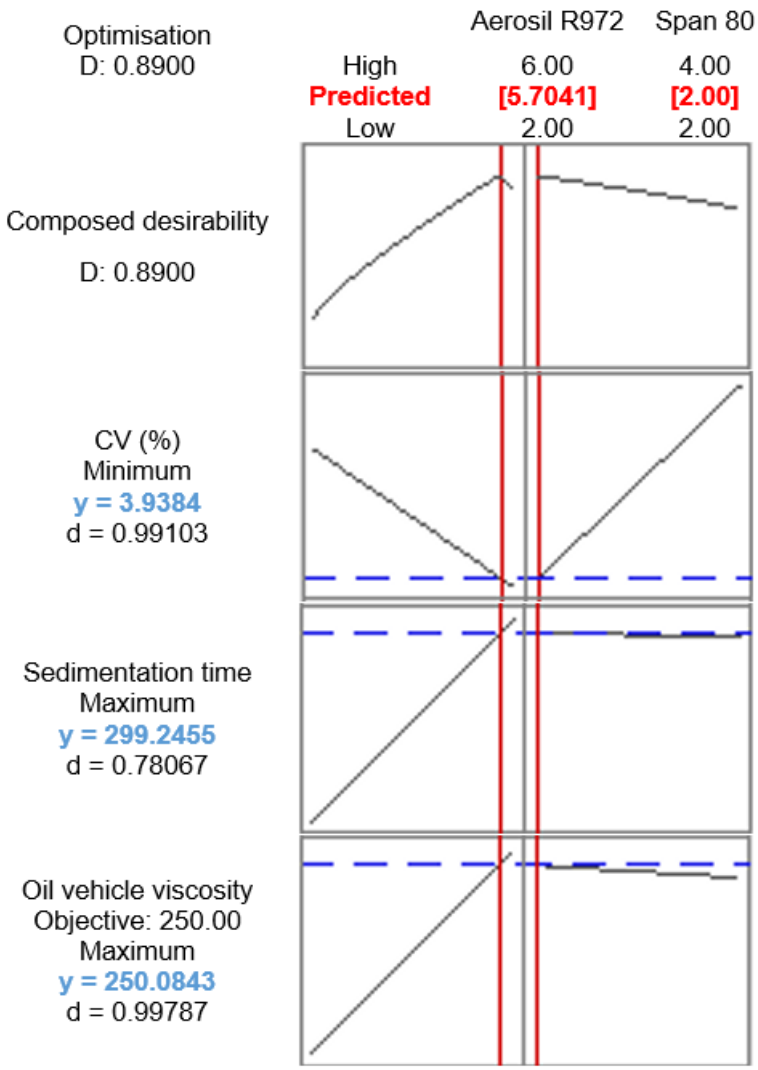

Fig. 5 Optimisation of the FFD Responses

Supplementary Data

Optimisation of the manufacturing process of a paediatric omeprazole enteric pellets suspension: Full Factorial Design

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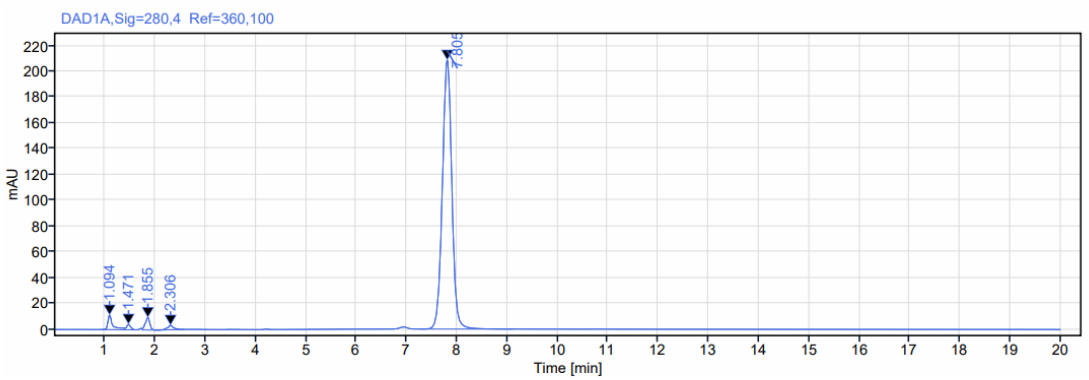
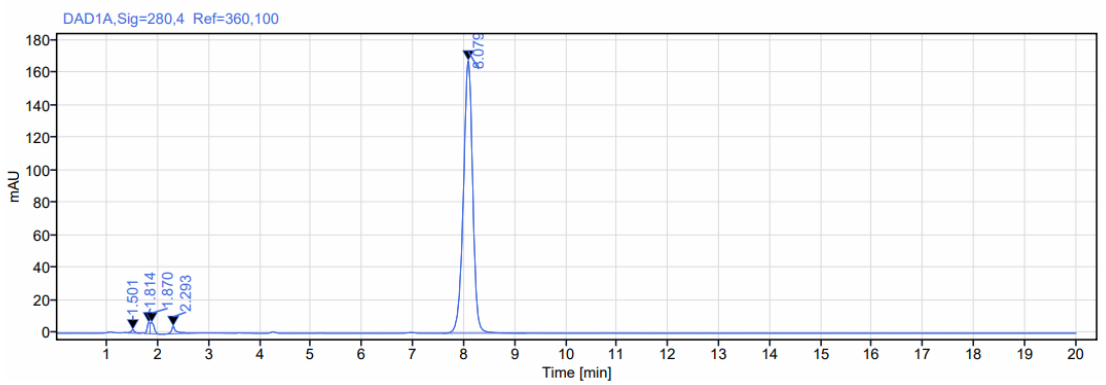
1. Chromatograms of the suspensions F10 and F17 after evaluation of omeprazole content



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.094	BV	0.47	76.90	11.24	2.63	0.44522	346.3
1.471	VB	0.21	24.29	4.27	0.83	0.86386	878.6
1.855	VB	0.29	60.50	9.60	2.07	1.25710	998.0
2.306	BB	0.54	29.82	3.52	1.02	0.96448	720.2
7.805	BB	1.83	2732.58	208.41	93.45	1.00419	993.5
		Sum	2924.10				

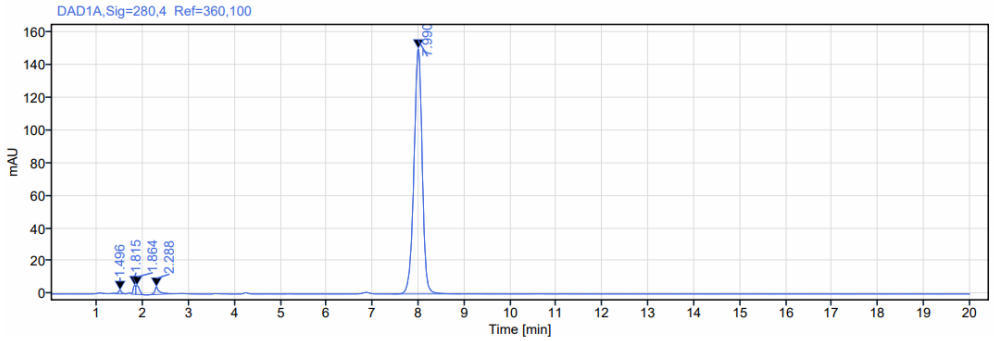
Fig. 1S Chromatogram of an F10 suspension sample following the evaluation of omeprazole content at the initial time (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.501	VB	0.24	10.59	2.00	0.48	1.09874	
1.814	VV	0.10	23.87	6.71	1.07	1.55435	
1.870	VB	0.20	36.02	6.87	1.62	0.52394	
2.293	BB	0.54	29.95	4.57	1.35	0.51511	
8.079	BB	1.64	2126.00	167.54	95.49	1.07622	
		Sum	2226.44				

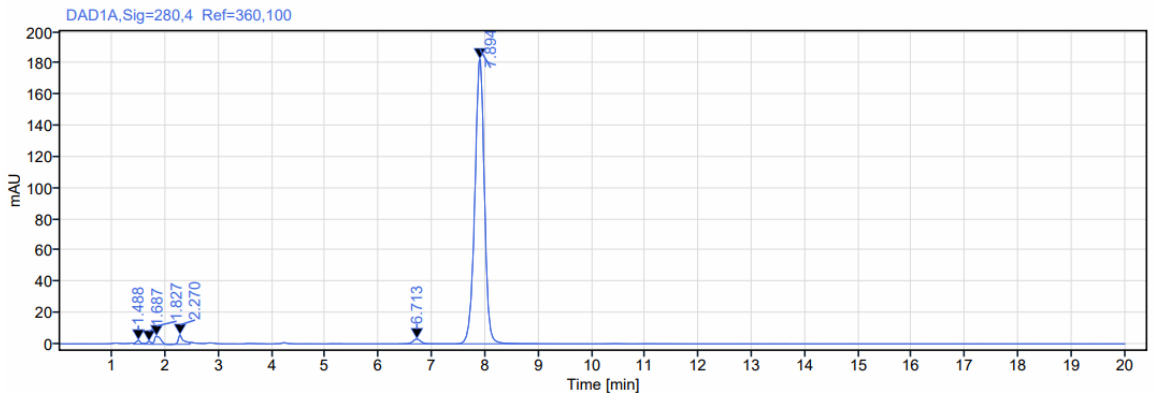
Fig. 2S Chromatogram illustrating an F10 suspension sample after the evaluation of omeprazole content, following one month of stability at 25 ºC in a topaz glass container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.496	VB	0.23	11.07	2.16	0.56	1.10536	
1.815	VV	0.10	19.50	5.39	0.99	1.65327	
1.864	VB	0.20	28.90	5.42	1.47	0.39544	
2.288	BB	0.52	31.68	4.55	1.61	0.52095	
7.990	BB	1.48	1875.47	149.82	95.37	1.07535	
		Sum	1966.61				

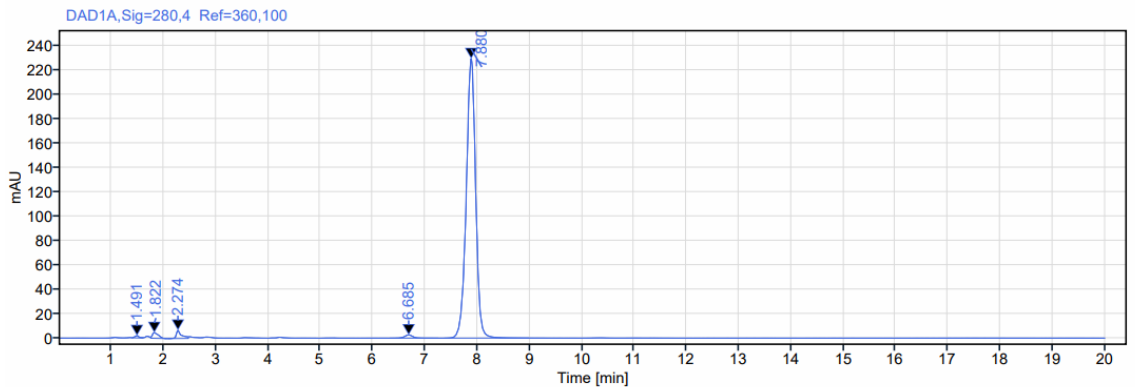
Fig. 3S Chromatogram illustrating an F10 suspension sample after the evaluation of omeprazole content, following one month of stability at 25 ºC in an opaque plastic container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.488	VV	0.22	15.13	2.45	0.62	0.87098	
1.687	VV	0.14	9.98	1.84	0.41	0.90906	
1.827	VB	0.32	42.09	5.29	1.74	0.43084	
2.270	BV	0.37	41.36	6.09	1.71	0.45937	
6.713	BB	1.02	33.26	3.09	1.37	0.97320	
7.894	BB	1.61	2283.48	182.92	94.15	1.06659	
		Sum	2425.31				

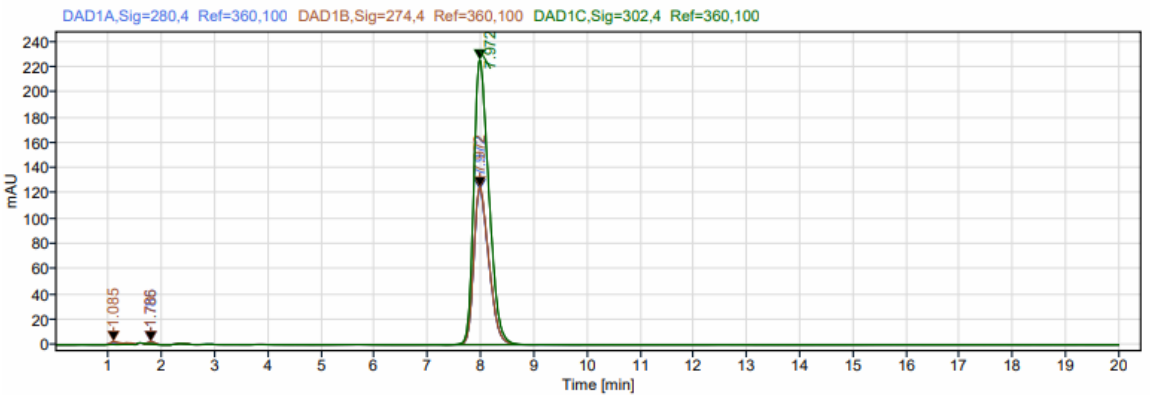
Fig. 4S Chromatogram illustrating an F10 suspension sample after the evaluation of omeprazole content, following one month of stability at 40 ºC in a topaz glass container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.491	BV	0.21	10.56	1.87	0.35	0.87179	
1.822	VB	0.31	37.25	4.66	1.25	0.46230	
2.274	BV	0.40	46.50	6.74	1.56	0.40482	
6.685	BB	0.93	28.40	2.62	0.95	0.95312	
7.880	BB	1.62	2862.14	229.02	95.89	1.06607	
		Sum	2984.84				

Fig. 5S Chromatogram illustrating an F10 suspension sample after the evaluation of omeprazole content, following one month of stability at 40 ºC in an opaque plastic container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.785	VB	0.36	19.45	1.84	0.79	0.85037	
7.972	BB	2.56	2434.44	122.73	99.21	0.63899	
		Sum	2453.89				

Signal: DAD1B,Sig=274,4 Ref=360,100

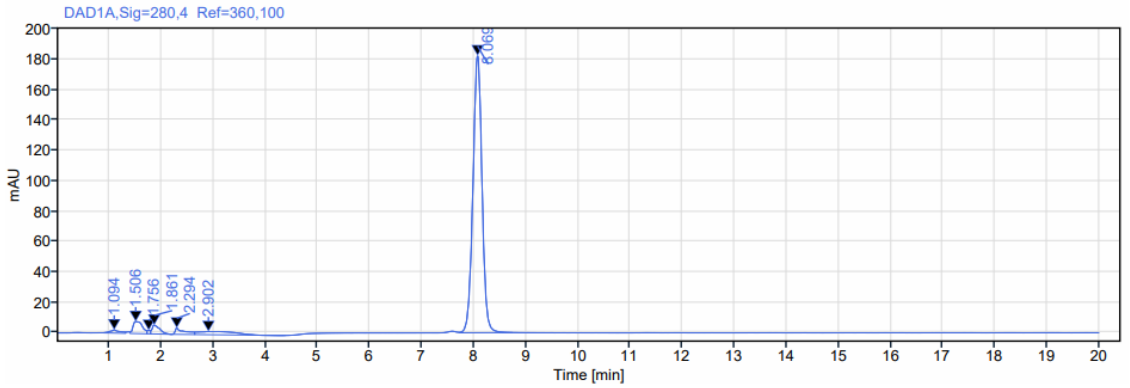
RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.085	BV	0.36	26.33	2.17	1.05	0.57428	
1.786	VB	0.36	21.20	2.03	0.84	0.81630	
7.972	BB	1.76	2470.18	124.82	98.11	0.64106	
		Sum	2517.70				

Signal: DAD1C,Sig=302,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
7.972	BB	1.76	4470.93	225.83	100.00	0.64135	
		Sum	4470.93				

Fig. 6S Chromatogram of an F17 suspension sample following the evaluation of omeprazole content at the initial time (injected volume: 20 µL)

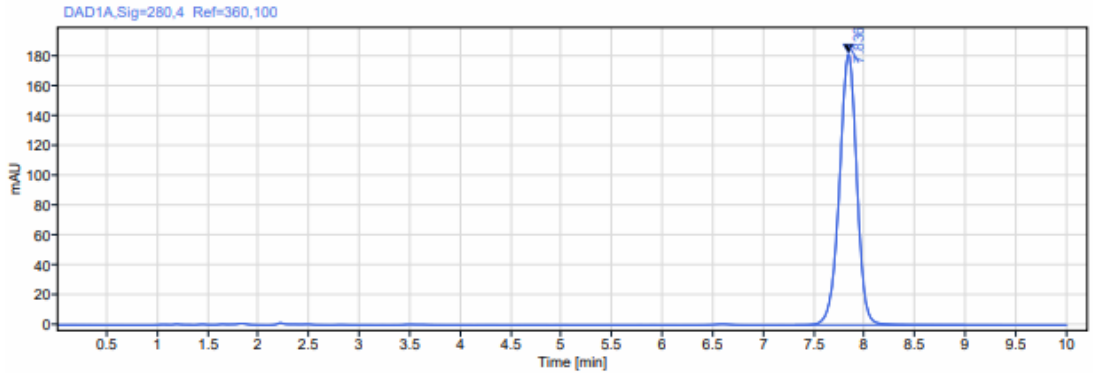
2. Chromatograms of the suspensions F10 and F17 after gastro-resistance test



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.094	BV	0.42	26.53	2.08	1.04	0.67887	998.5
1.506	VV	0.33	98.76	7.86	3.86	0.38649	974.0
1.756	VV	0.07	8.93	2.27	0.35	1.00923	997.8
1.861	VV	0.40	59.26	5.76	2.32	0.36632	477.4
2.294	VB	0.44	51.73	4.12	2.02	0.18010	424.5
2.902	BB	1.74	101.99	2.05	3.99	0.37956	991.4
8.069	VB	1.02	2208.72	182.32	86.42	1.00867	995.0
		Sum	2555.92				

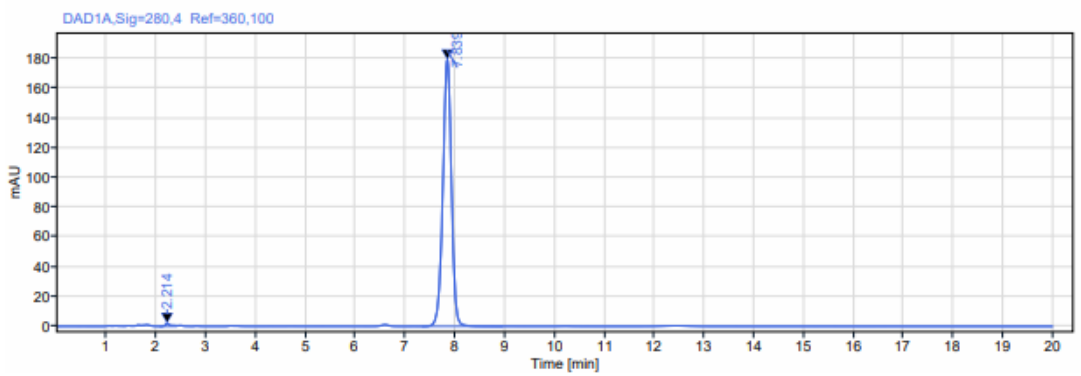
Fig. 7S Chromatogram of an F10 suspension sample after the gastro-resistance test at the initial time (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
7.836	BB	1.69	2176.76	181.76	100.00	1.05703	999.6
		Sum	2176.76				

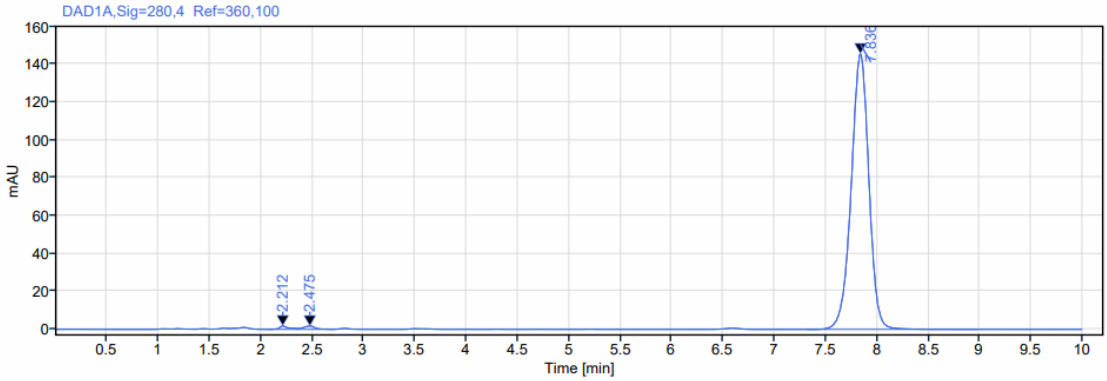
Fig. 8S Chromatogram illustrating an F10 suspension sample after the gastro-resistance test, following one month of stability at 25 ºC in a topaz glass container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
2.214	BV	0.34	15.16	2.11	0.70	0.44415	957.1
7.839	BB	1.63	2158.08	179.44	99.30	1.05145	999.7
		Sum	2173.24				

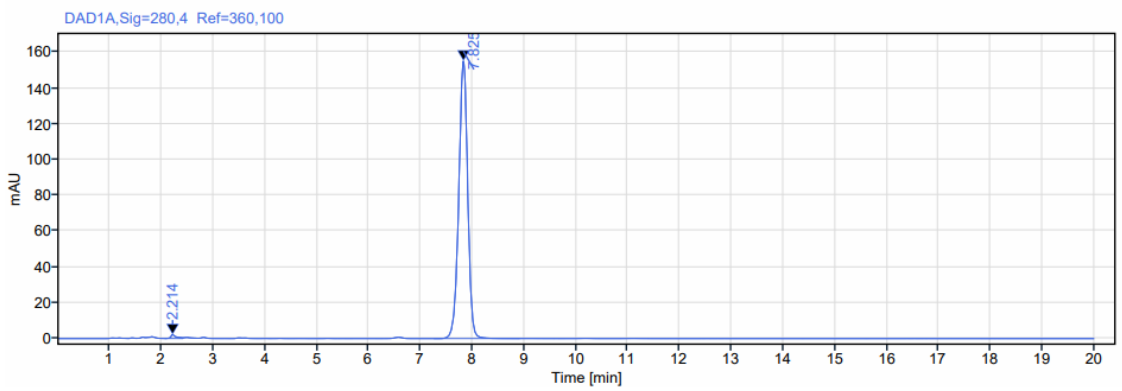
Fig. 9S Chromatogram illustrating an F10 suspension sample after the gastro-resistance test, following one month of stability at 25 ºC in an opaque plastic container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
2.212	BV	0.29	11.46	1.83	0.65	0.49824	897.2
2.475	VV	0.35	14.17	1.76	0.80	1.14009	805.7
7.836	BB	1.66	1742.45	145.52	98.55	1.05324	999.8
		Sum	1768.08				

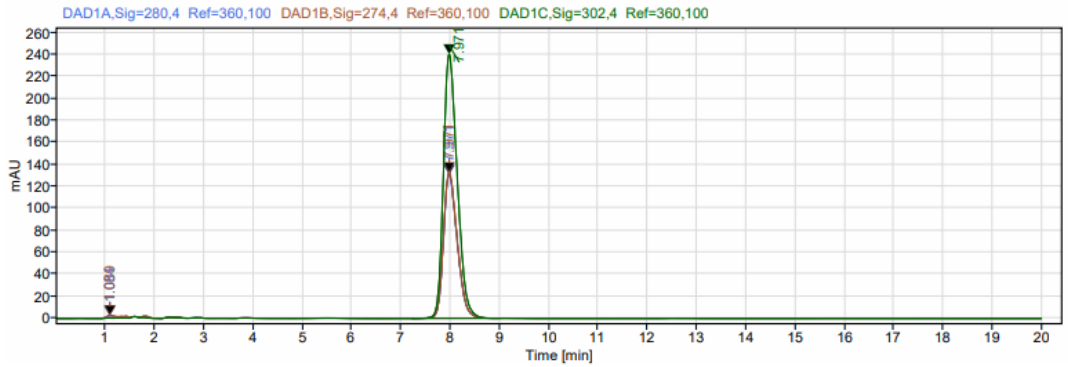
Fig. 10S Chromatogram illustrating an F10 suspension sample after the gastro-resistance test, following one month of stability at 40 ºC in a topaz glass container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
2.214	BV	0.35	15.63	2.18	0.83	0.42305	942.6
7.825	BB	1.66	1863.83	155.30	99.17	1.05596	999.8
		Sum	1879.46				

Fig. 11S Chromatogram illustrating an F10 suspension sample after the gastro-resistance test, following one month of stability at 40 ºC in an opaque plastic container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.084	BV	0.35	21.72	1.83	0.85	0.62372	
7.971	BB	1.72	2545.48	130.57	99.15	0.68162	
		Sum	2567.20				

Signal: DAD1B,Sig=274,4 Ref=360,100

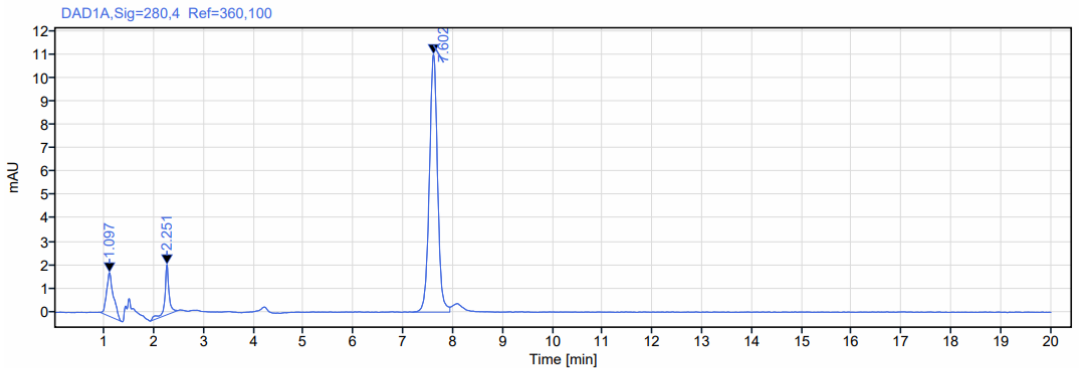
RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.089	BV	0.35	29.29	2.47	1.12	0.64250	
7.971	BB	1.81	2589.57	132.83	98.88	0.68169	
		Sum	2618.86				

Signal: DAD1C,Sig=302,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
7.971	BB	1.76	4686.57	240.29	100.00	0.68186	
		Sum	4686.57				

Fig. 12S Chromatogram illustrating an F17 suspension sample following the gastro-resistance test at the initial time (injected volume: 20 µL)

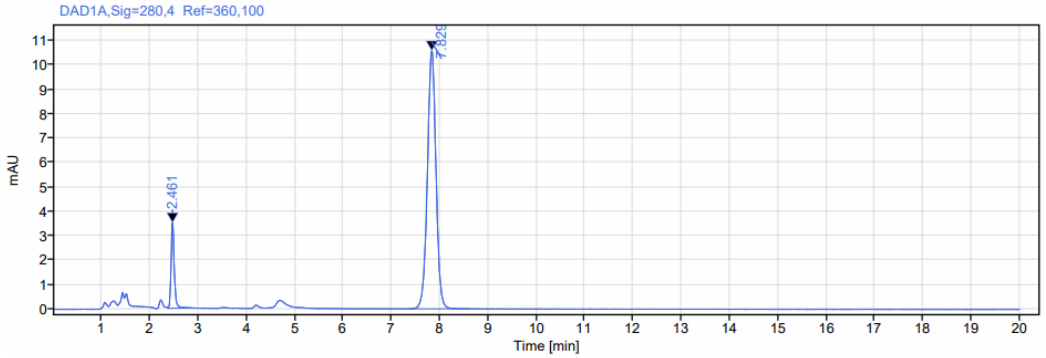
3. Chromatograms of the suspensions F10 and F17 after dissolution test



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
1.097	BB	0.43	17.71	1.86	11.31	0.67879	514.5
2.251	BB	0.55	12.74	2.13	8.14	1.07461	118.2
7.602	BV	0.75	126.10	10.99	80.55	0.98361	999.0
		Sum	156.55				

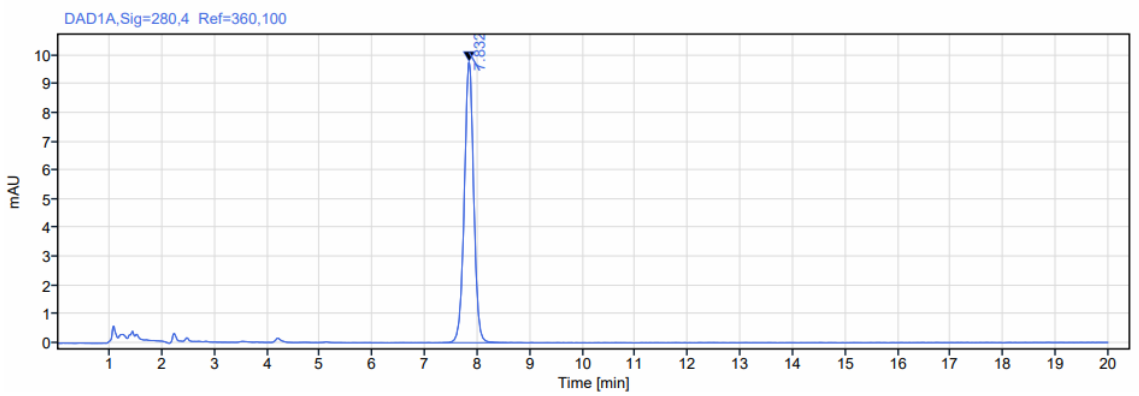
Fig. 13S Chromatogram illustrating an F10 suspension sample after a 45-minutes dissolution test at the initial time (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
2.461	VB	0.42	16.13	3.50	10.98	0.75942	998.9
7.829	BB	1.27	130.83	10.58	89.02	0.99623	1000.0
		Sum	146.96				

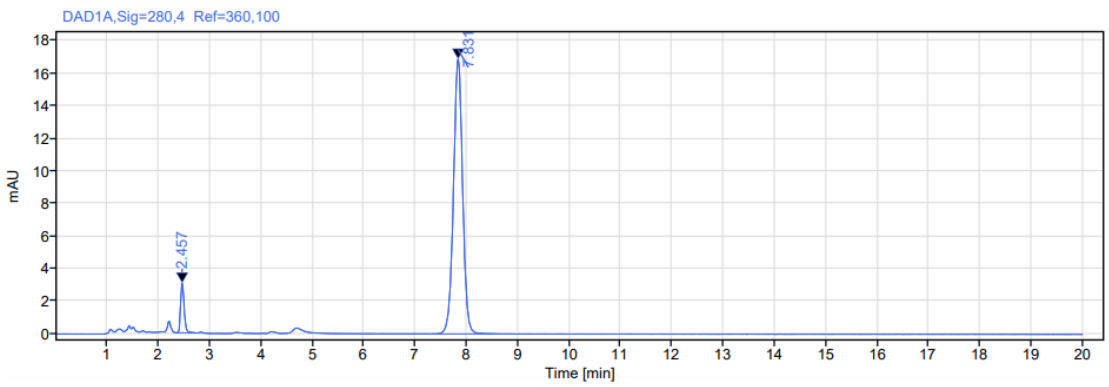
Fig. 14S Chromatogram illustrating an F10 suspension sample after a 45-minutes dissolution test, following one month of stability at 25 ºC in a topaz glass container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
7.832	BB	1.24	121.37	9.76	100.00	0.99074	1000.0
		Sum	121.37				

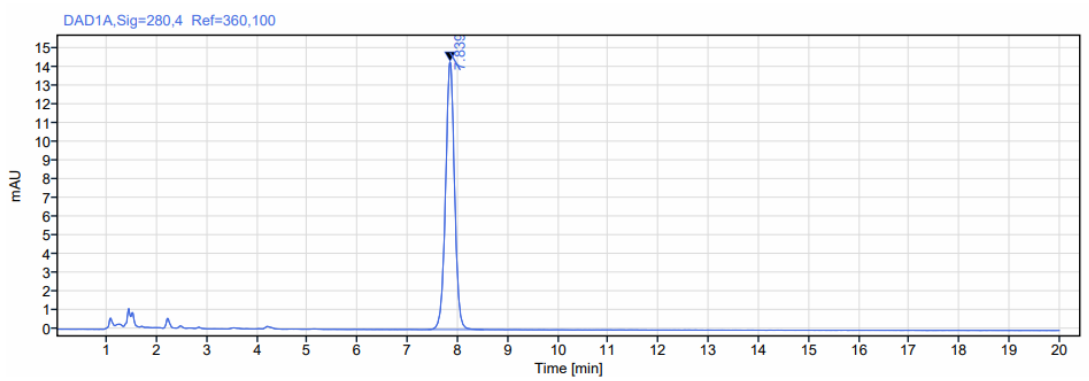
Fig. 15S Chromatogram illustrating an F10 suspension sample after a 45-minutes dissolution test, following one month of stability at 25 ºC in a topaz glass container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
2.457	BB	0.39	14.79	3.05	6.60	0.73734	997.8
7.831	BB	1.23	209.41	16.89	93.40	0.99446	1000.0
		Sum	224.19				

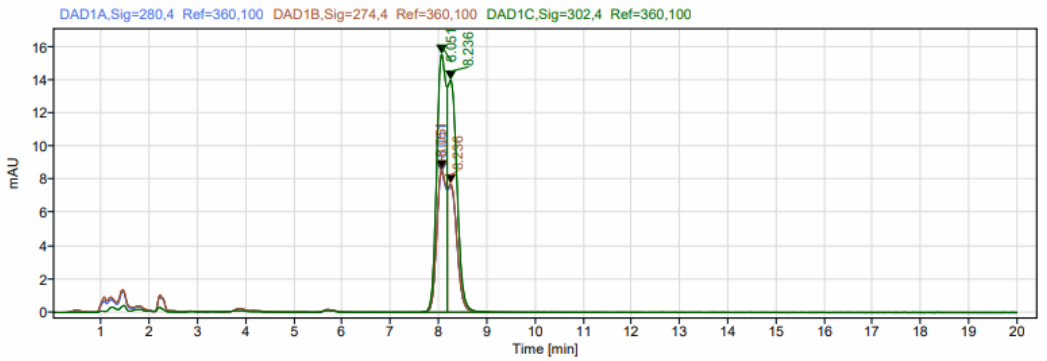
Fig. 16S Chromatogram illustrating an F10 suspension sample after a 45-minutes dissolution test, following one month of stability at 40 ºC in a topaz glass container (injected volume: 10 µL)



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
7.839	BB	1.11	178.06	14.30	100.00	0.99009	1000.0
		Sum	178.06				

Fig. 17S Chromatogram illustrating an F10 suspension sample after a 45-minutes dissolution test, following one month of stability at 40 ºC in an opaque plastic container (injected volume: 10 µL).



Signal: DAD1A,Sig=280,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
8.051	BB m	0.34	217.02	8.44	100.00		
		Sum	217.02				

Signal: DAD1B,Sig=274,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
8.051	BV	0.59	116.72	8.58	52.85	1.14119	
8.236	VB	0.94	104.13	7.72	47.15	0.41432	
		Sum	220.85				

Signal: DAD1C,Sig=302,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Peak Symmetry (classic)	Peak Purity
8.051	BV	0.55	210.84	15.53	52.75	1.13978	
8.236	VB	0.87	188.83	13.97	47.25	0.41504	
		Sum	399.68				

Fig. 18S Chromatogram illustrating an F17 suspension sample following the dissolution test at the initial time (injected volume: 20 µL)

4 DISCUSIÓN GENERAL

Este capítulo ofrece una discusión global de los principales resultados presentados anteriormente.

4.1 Uso de Excipientes en Población Pediátrica

La literatura científica resalta que muchos medicamentos comercializados no son adecuados para su uso en la población pediátrica, debido a su dosificación, forma farmacéutica o excipientes. En este contexto, la formulación magistral u oficinal surge como una alternativa para garantizar dosificaciones apropiadas y seguridad en la administración. La selección de excipientes para estas formulaciones requiere consideraciones minuciosas, incluyendo el sabor, así mismo la edad y las características fisiológicas en constante cambio del paciente pediátrico. La seguridad de los excipientes es esencial, lo que ha llevado a la defensa de estudios no clínicos en animales juveniles para evaluar riesgos potenciales en la población pediátrica [54,58]. La evaluación del riesgo clínico y el balance entre beneficio terapéutico y riesgo deben ser concluyentes en la selección de los excipientes. Este enfoque ayudará a garantizar la seguridad y eficacia de los medicamentos pediátricos, facilitando la toma de decisiones clínicas y mejorando el cuidado del paciente pediátrico [59].

El estudio y desarrollo de medicamentos pediátricos ha experimentado una notable evolución en las últimas décadas, con un enfoque más centrado en las necesidades específicas de la población pediátrica. Y la implementación de regulaciones tanto en Europa como en Estados Unidos ha sido fundamental para este proceso. La normativa europea, iniciada en 1997 y fortalecida con el Reglamento Pediátrico en 2007, ha garantizado un mayor acceso a medicamentos adaptados a los pacientes pediátricos, promoviendo la ética en la investigación y la disponibilidad de información [2]. La colaboración internacional, como la guía ICH E11, ha facilitado el diseño de estudios clínicos pediátricos a nivel global [60]. Además, iniciativas como la lista de medicamentos esenciales de la OMS para niños y las directrices de la FDA han contribuido a mejorar la calidad y seguridad de los medicamentos pediátricos [61–63]. Cabe mencionar que, a pesar de todos estos avances, persisten desafíos, como la necesidad de desarrollar más medicamentos para enfermedades raras y garantizar un acceso equitativo a nivel mundial [64,65]. En conjunto, las acciones regulatorias y colaborativas han transformado el panorama de la atención médica pediátrica, priorizando el bienestar y la salud de la población pediátrica.

Las discusiones sobre la seguridad de los excipientes en medicamentos pediátricos enfatizan la necesidad de evaluar exhaustivamente los riesgos asociados. Iniciativas como la *European Paediatric Formulation Initiative* (EUPFI) [66] y la base de datos STEP [58,67,68] han surgido para abordar esta necesidad, proporcionando acceso a información detallada sobre la seguridad y toxicidad de los excipientes en población infantil. Proyectos como el estudio SEEN (del inglés, *Safe Excipient Exposure in Neonates and Small Children*) [69] han contribuido a comprender mejor la exposición de los niños a los excipientes y sus posibles impactos en la seguridad y tolerabilidad de los medicamentos. En general, estas iniciativas subrayan la necesidad continua de evaluar y mejorar la seguridad de los excipientes en medicamentos pediátricos para garantizar un tratamiento óptimo y seguro para los pacientes pediátricos.

Por una parte, en la **Tabla A1** de la **Publicación 1** se resume las características principales de los excipientes más utilizados en formulaciones pediátricas, incluyendo su Ingesta Diaria Aceptable (IDA), recomendaciones de uso en población pediátrica y efectos adversos observados. Por otra parte, en las **Tablas A2**, **A3** y **A4** de la **Publicación 1**, se presentan varios ejemplos de formas líquidas, semisólidas y sólidas empleadas en población pediátrica.

El estudio de revisión realizado en la **Publicación 1** resalta el uso inadecuado y, a menudo excesivo, de excipientes en formulaciones pediátricas, aumentando los riesgos para los pacientes pediátricos [70]. Se evidencia la necesidad de una regulación más estricta y una supervisión rigurosa por parte de las autoridades reguladoras del medicamento. Es necesario realizar más estudios toxicocinéticos y de seguridad para adaptar los medicamentos a las necesidades pediátricas y reducir los posibles efectos adversos. Además, se requiere una mayor atención a los excipientes utilizados en la población infantil, así como una revisión de las prácticas de formulación para garantizar la seguridad y calidad de los medicamentos pediátricos.

4.2 Formas Farmacéuticas Prometedoras en Población Pediátrica

En la **Publicación 2**, **Capítulo de Libro**, se presentan en detalle las características de dos tecnologías farmacéuticas emergentes: los comprimidos ODT y la impresión 3D de medicamentos. Estas tecnologías ofrecen enfoques innovadores y prometedores para abordar las necesidades de dosificación en la población pediátrica. Aunque ambas tienen

el potencial de transformar la producción y administración de medicamentos pediátricos, también se enfrentan a desafíos técnicos y regulatorios. Durante el desarrollo de estos medicamentos, es necesario garantizar que los productos fabricados cumplan con los estándares de calidad y seguridad requeridos por las Buenas Prácticas de Fabricación o Normas de Correcta Fabricación (BPF o NCF) y otras regulaciones relacionadas. Asimismo, se necesitan más investigaciones y desarrollos para mejorar la eficiencia y la versatilidad de ambas tecnologías, así como para abordar cuestiones relacionadas con la estabilidad de los principios activos y la selección de materiales adecuados para la impresión 3D. Además, otro criterio a considerar es la adecuación de las instalaciones donde se han de elaborar los medicamentos impresos por 3D, ajustándolas a las NCF [71,72].

Por un lado, los comprimidos ODT han ganado popularidad debido a su capacidad para disolverse rápidamente en la saliva, proporcionando una forma conveniente de administrar medicamentos, especialmente para pacientes con dificultades para tragar, como son los pacientes pediátricos y geriátricos. La palatabilidad de este tipo de comprimidos es un aspecto clave a tener en cuenta, puesto que el principio activo entra en contacto con las papilas gustativas. Con los avances tecnológicos y científicos se dispone de diferentes alternativas de dosificación para enmascarar el sabor, como por ejemplo la liofilización, la microencapsulación o el recubrimiento en lecho fluido [73–75]. Además, herramientas como el diagrama SeDeM-ODT ofrecen una forma innovadora de predecir la idoneidad de los excipientes y las formulaciones para la producción de comprimidos ODT, lo que puede acelerar el proceso de desarrollo de medicamentos [76].

Por otro lado, la impresión 3D de medicamentos permite personalizar las dosis de acuerdo con las necesidades específicas de cada paciente. Esto es especialmente relevante en el caso de los pacientes pediátricos, que pueden requerir dosificaciones adaptadas a su edad, peso y condición médica. Aunque la mayoría de los medicamentos impresos en 3D son formulaciones sólidas, se están explorando opciones como las gominolas medicinales, que podrían ser más atractivas y fáciles de administrar para los niños [71]. Entre las diversas técnicas de impresión 3D, solo las técnicas *Fused deposition Modelling* (FDM), *Semi-Solid Extrusion* (SSE), *Binder Jetting* (BJ) y *Selective Lases Sintering* (SLS) se han utilizado específicamente en la fabricación de medicamentos destinados a la población pediátrica. La técnica SSE ofrece la posibilidad de crear dosis masticables visualmente

atractivo para los niños, mientras que las técnicas BJ y SLS permiten la fabricación de comprimides ODT [77–82]. Independientemente del método escogido, la tecnología de impresión 3D permite la producción de medicamentos en pequeños lotes, con dosis personalizadas, características de liberación y formas adaptadas a cada paciente, lo que podría hacer realidad los medicamentos personalizados [80].

4.3 Uso de Omeprazol en Población Pediátrica

El omeprazol se emplea ampliamente para el tratamiento de trastornos gástricos en la población pediátrica. Sin embargo, el principal problema de este principio activo es su degradación en ambientes ácidos. Este punto es de especial importancia porque los excipientes gastro-resistentes no se recomiendan para la población pediátrica a menos que su uso esté completamente justificado. Además, las dosis de omeprazol no están bien establecidas para la población pediátrica y la ficha técnica de los medicamentos comercializados no incluyen recomendaciones de uso para niños [83,84]. Así pues, los hospitales no disponen de directrices exactas para la administración de este API en pacientes pediátricos que contemplen estas limitaciones [54].

En cuanto a la inestabilidad del omeprazol en medios ácidos, se utilizan excipientes que aseguran la liberación del API en el intestino delgado, protegiéndolo así de los niveles de pH gástrico. Una alternativa que aplican los profesionales sanitarios para administrar omeprazol a la población pediátrica es el uso de sondas nasogástricas, que liberan el API directamente en el intestino delgado [85,86]. Otra práctica habitual es la administración de omeprazol en polvo con bicarbonato sódico para promover niveles alcalinos de pH [87]. Sin embargo, esta estrategia parece degradar el API, puesto que el aspecto de los preparados adquiere un color amarillento y, no se demuestra la liberación de omeprazol en el intestino delgado. La tercera estrategia más utilizada es la preparación de formulaciones líquidas que incorporan pellets gastro-resistentes procedentes de cápsulas comercializadas en bebidas ácidas (por ejemplo, zumos de frutas). Los niveles de pH ácido de esas bebidas impiden la liberación de omeprazol en la formulación líquida. Ahora bien, ninguna de estas preparaciones y estrategias ha mostrado los mismos parámetros de calidad o estabilidad que los productos comerciales para adultos. De hecho, se carece de información sobre su estabilidad [54]. Sólo se han realizado unos pocos estudios que describan la estabilidad de algunos de estos preparados. Por ejemplo, ha

habido estudios que demuestran que las soluciones alcalinas con pellets gastro-resistentes son estables durante 7-32 días [88–91] o 28 días a temperatura ambiente [84].

En la **Publicación 3**, se realiza una revisión de artículos que describen formulaciones pediátricas de omeprazol. Se recogen ejemplos de diversas dosificaciones y formas adecuadas para su uso en la población pediátrica, como suspensiones, jarabes, comprimidos orales, películas mucho-adhesivas y supositorios. Estos ejemplos podrían ser buenas alternativas a los actuales preparados oficinales o extemporáneos de omeprazol (ver **Tabla 3** y **Tabla 4** de la **Publicación 3**). Cabe mencionar que la mayoría de estos trabajos no demuestran la gastro-resistencia de las formulaciones propuestas. Además, los problemas de estabilidad no se resuelven completamente en estos estudios. De hecho, la mayoría de los preparados propuestos deben almacenarse refrigerados y sólo son estables durante 2 – 4 semanas [87,92,93]. La formulación que demuestra una mayor estabilidad (1 año) es el supositorio desarrollado por Bestebreurtje [94]. Explorado el estado actual de las formulaciones pediátricas de omeprazol, queda claro la necesidad de seguir investigando para resolver los problemas de gastro-resistencia y estabilidad de dichas formulaciones.

Así pues, puede deducirse del estudio que, en los últimos años, las formulaciones orales multiparticuladas y sólidas dispersables han ganado interés junto con las formulaciones líquidas. Pero, sigue siendo un reto la necesidad de formas de dosificación que no comprometan la eficacia farmacéutica del fármaco [95]. Otro enfoque interesante es el desarrollo de microesferas [96] o nanopartículas [97] que puedan encapsular el API. En este caso, faltan estudios sobre estos vehículos de administración de fármacos para demostrar la gastro-resistencia de las formulaciones desarrolladas. Actualmente, las nuevas tecnologías, como la fabricación aditiva, comúnmente conocida como impresión 3D (3DP, del inglés *3D Printing*) están abriendo nuevas fronteras en el desarrollo de medicamentos [98].

4.4 Desarrollo de Pellets Entéricos de Omeprazol para su Uso en Población Pediátrica

La administración de fármacos en los pacientes pediátricos presenta desafíos debido a la falta de formas farmacéuticas adaptadas a sus necesidades. Esto es especialmente evidente en entornos hospitalarios, donde la carencia de medicamentos pediátricos

comercializados de ciertos APIs conlleva la formulación personalizada de preparados orales líquidos. No obstante, estos preparados generalmente no cumplen totalmente con los estándares de estabilidad exigidos ya que carecen de estudios concretos [54,99].

El omeprazol es un API con una clara falta de una forma farmacéutica adecuada para la población pediátrica tras la revisión realizada (**Publicación 1** y **3**). Las fórmulas magistrales de omeprazol usadas en pediatría no cumplen con sus características fisicoquímicas y afectan su efectividad terapéutica. Este fármaco es ampliamente utilizado en niños y adultos para tratar afecciones gastrointestinales debido a su buena tolerabilidad y eficacia [100–102]. Sin embargo, su estabilidad depende del pH, lo que plantea desafíos en su administración pediátrica [19,103,104].

En la **Publicación 4**, se presenta un estudio experimental que aborda el reto de desarrollar una forma farmacéutica pediátrica de omeprazol, estable en medio gástrico. Por lo tanto, se propone la fabricación de pellets entéricos para formular preparados líquidos adaptados a pacientes pediátricos. El recubrimiento de los pellets inertes de celulosa microcristalina se realiza en lecho fluido en tres capas sucesivas para proteger el fármaco de la degradación gástrica y posibles interacciones no deseadas. Además, se utilizan pellets inertes con un tamaño más pequeño que los actualmente comercializados para favorecer su utilización posterior en otras formas farmacéuticas como suspensiones o gominolas elaboradas por técnicas de impresión 3D. En este estudio se evita el uso de solventes orgánicos, hecho de vital importancia en formulaciones pediátricas para evitar efectos secundarios. Se aplica un diseño de experimentos para determinar las condiciones óptimas del proceso de recubrimiento y establecer un modelo matemático que relacione los factores con las respuestas (ver apartado **2.2.** ***Methods*** de la **Publicación 4**). Asimismo, se siguen los criterios del método de calidad por diseño (QbD, del inglés *Quality by Design*) descrito en las directrices de la ICH Q8 R2 [105].

El espectro IR del omeprazol micronizado muestra bandas características que confirman la identidad del omeprazol micronizado utilizado en los experimentos. Se observan las vibraciones de estiramiento de los enlaces C=C del anillo bencílico en 3062 cm^{-1}, del enlace C-H en 2903,4 cm^{-1}, de los enlaces C-N y N-H del anillo piridínico en los intervalos 1158,54 – 1310,92 cm^{-1} y 1510,14 – 1627,12, respectivamente, y del grupo sulfona en el intervalo 1012,25 1111,94 cm^{-1} (ver **Figure S1** de la **Publicación 4**). Los resultados de los análisis por calorimetría diferencial de barrido (DSC, del inglés

Differential Scanning Calorimetry) revelan que el omeprazol micronizado muestra un punto de fusión acorde con su naturaleza cristalina (a 158,42 ºC), mientras que los pellets entéricos exhiben un punto de fusión inicial atribuido al trietilcitrato a 60,08 ºC [106], seguido de la fusión del API a 143,08 ºC y del Eudragit® L30 D-55 a 206,95 ºC [107,108]. En los difractogramas de rayos X, tanto para el omeprazol micronizado como para los pellets entéricos, se identifican los picos característicos de la estructura cristalina del API, así como señales correspondientes a excipientes cristalinos como el dióxido de titanio y el talco (ver **Figura 3** de la **Publicación 4**).

La determinación del tamaño de partícula (PSD, del inglés *Particle Size Determination*) del omeprazol micronizado indica que el 10% de las partículas de omeprazol son más pequeñas que 1,299 µm, el 50% son más pequeñas que 4,872 µm y el 90% son más pequeñas que 12,913 µm. Se confirma pues que el omeprazol utilizado en este estudio es micronizado. También, se determina el tamaño de partícula obtenidos del Experimento 4, puesto que mostraron los mejores resultados de gastro-resistencia y de liberación. El PSD de estos pellets indica que el 70% ± 0,68 (SD) tienen un diámetro medio entre 0,5 y 0,6 mm (ver **Tabla 5** de la **Publicación 4**). Con estos resultados se confirma que se cumple el tamaño teórico de los pellets entéricos de omeprazol desarrollados.

Según la monografía "*2.9.36. Powder Flow*" de la Ph. Eur. [109] los pellets entéricos de omeprazol del Experimento 4 exhiben excelentes propiedades de flujo. Esto se evidencia dado que el ángulo de reposo se encuentra dentro del rango de 25 – 30 º, el Índice de Hausner está dentro del rango de 1,00 – 1,11 y la velocidad de deslizamiento es notablemente rápida (ver **Tabla 6** de la **Publicación 4**).

La observación microscópica de los pellets entéricos de omeprazol del Experimento 4 mediante SEM, revela pequeñas imperfecciones como rugosidad, porosidad y grietas en las superficies del recubrimiento. Estas imperfecciones son coherentes con los resultados obtenidos en el ensayo de gastro-resistencia. Cabe mencionar que las imperfecciones en el recubrimiento podrían deberse a la falta de precisión al cortar los pellets, lo que no fue fácil debido a su tamaño. En el análisis de mapeo EDS (del inglés, *Energy Dispersive X-Ray Spectroscopy*) se identifica el núcleo inerte, la capa de principio activo y la capa entérica, mostrando una distribución homogénea de los componentes en los pellets recubiertos (ver **Figura 1** y **Figura 2** de la **Publicación 4**).

Respecto a las respuestas del diseño factorial completo llevado a cabo, la evaluación del contenido de omeprazol demuestra resultados satisfactorios en los 5 experimentos realizados, con un contenido medio de API del 100%, cumpliendo con las especificaciones de la Ph. Eur. [110] (ver **Tabla 7** de la **Publicación 4**). Los experimentos 1 y 4, con un incremento del 100% en el peso de la capa entérica, muestran una gastro-resistencia óptima, alcanzando porcentajes del 87% y del 95%, respectivamente. Estos resultados cumplen con las especificaciones de la USP, que requieren un porcentaje superior al 85% [111]. En contraste, los experimentos con un aumento menor en esta capa no logran proporcionar una protección adecuada contra la degradación del API en medio ácido (ver **Tabla 8** de la **Publicación 4**).

Los resultados de los ensayos de disolución resaltan la importancia de la gastro-resistencia en la eficacia de la liberación del omeprazol. Aunque se espera que un recubrimiento más grueso arrojaría en tiempos de disolución más largos, los experimentos 1 y 4, muestran una liberación más rápida en comparación con los experimentos 2, 3 y 5 (con incrementos de peso inferiores de la capa entérica). En los experimentos 1 y 4 se logran porcentajes de liberación del 80% y del 83%, respectivamente. Estos resultados cumplen con las especificaciones de la USP, que requieren una liberación superior al 75% en 60 minutos [111] (ver **Figura 4** de la **Publicación 4**). Esto puede atribuirse a variaciones en la uniformidad del recubrimiento y a la respuesta al entorno gástrico, hecho que resalta la importancia de un diseño de formulación preciso para garantizar la eficacia del producto final.

Por último, el análisis estadístico del diseño factorial completo revela que el contenido de omeprazol depende de ambos Factores A y B (el incremento de peso medio de la capa protectora y de la capa entérica, respectivamente), mientras que la disolución depende solamente del factor B. En cuanto al ensayo de gastro-resistencia, no se encuentra un modelo para describir la asociación entre la gastro-resistencia y los factores estudiados. Cabe mencionar que la falta de replicados en los diseños experimentales afectó a la robustez de los análisis estadísticos, no pudiéndose evaluar las interacciones existentes entre los factores de estudio. Por eso, se opta por realizar un análisis cualitativo de los resultados obtenidos utilizando los diagramas de Pareto y gráficos de contorno para optimizar el proceso de desarrollo de los pellets entéricos de omeprazol. Mediante estos últimos se describen las zonas óptimas de trabajo para cada respuesta estudiada en relación con los factores A y B. La zona óptima para la respuesta de evaluación de

contenido de omeprazol implica un aumento del 100% en el peso de la capa entérica, sin diferencias significativas observadas entre el uso del 2% o el 6% para la capa protectora (ver **Figura 5** de la **Publicación 4**). En cuanto a la respuesta de gastro-resistencia, solo el Factor B, que representa el recubrimiento entérico, es estadísticamente significativo según el diagrama de Pareto. El diagrama de contorno sugiere que combinar el 2 – 3% del factor A con el 100 del factor B lograría una gastro-resistencia del 95% (ver **Figura 6** de la **Publicación 4**). Respecto a la respuesta de disolución, el diagrama de Pareto muestra que solo el factor A presenta una influencia significativa, mientras que el diagrama de contorno muestra que se consiguen porcentajes de liberación dentro de las especificaciones de la USP cuando el porcentaje del factor A es del 2% y/o del 6% y el del factor B es superior al 85% (ver **Figura 6** de la **Publicación 4**).

4.5 Pellets y drugmies: Desarrollo de una dosificación gastro-resistente de omeprazol por impresión 3D

En los últimos años, la producción de medicamentos por impresión 3D ha aumentado, permitiendo la fabricación de dosificaciones personalizadas mediante la deposición de capas de tintas que contienen principios activos y excipientes [41–43]. Esta tecnología es especialmente beneficiosa para pacientes que requieren dosis específicas, como los pacientes pediátricos, y reduce los riesgos asociados con la manipulación de formas de dosificación estándar, utilizadas en adultos. Además, se pueden preparar medicamentos con una apariencia atractiva y propiedades organolépticas que mejoren la adherencia al tratamiento [49,81,112].

En la **Publicación 5** de la presente tesis se explora la tecnología de impresión 3D para abordar los desafíos que presenta el desarrollo de una formulación pediátrica de omeprazol, debido a su inestabilidad química y sus características farmacocinéticas. La incorporación de omeprazol en formulaciones semisólidas imprimibles para impresión 3D, específicamente utilizando la técnica de extrusión semisólida (SSE) para crear dosis personalizadas en forma de drugmies (gominolas). Se realiza una comparación entre la impresión 3D de hidrogeles con omeprazol dispersado e hidrogeles cargados con pellets entéricos de omeprazol (los obtenidos del **Experimento 4** de la **Publicación 4**). El uso de pellets en la técnica de SSE supone una alternativa novedosa en el campo de la impresión 3D.

En la **Publicación 5** se elaboran dos tipos de tintas farmacéuticas (F1 y F2) con el objetivo de mejorar la estabilidad del omeprazol, la capacidad de extrusión del material y la homogeneidad del contenido. La formulación de las tintas varía según la composición del coloide, empleando diferentes excipientes para cada tipo. Además, en la F1 se incorpora omeprazol en polvo, mientras que en la F2 se utilizan pellets entéricos de omeprazol (los desarrollados en la **Publicación 4**). Posteriormente, las tintas se envasan en jeringas compatibles con impresoras y se almacenan en refrigeración hasta su utilización (ver **Tabla 2** de la **Publicación 5**).

La caracterización reológica de las tintas es determinante para comprender su capacidad de impresión. Las barridas de amplitud proporcionan información sobre el comportamiento viscoelástico de las tintas, con los valores críticos de deformación indicando su transición de un comportamiento similar al sólido a uno no lineal [113]. Es importante destacar que las diferencias en la composición entre F1 y F2 dan lugar a perfiles reológicos distintos, con F2 mostrando un mayor carácter sólido debido a su contenido de pellets. Se realiza una caracterización adicional de la estructura de la tinta a través de barridas de frecuencia, que revela el comportamiento de la viscosidad compleja en un rango de frecuencias de oscilación. Ambas tintas exhiben una viscosidad adecuada para la extrusión en procesos de impresión 3D, aunque la F2 muestra valores de viscosidad más altos atribuidos a su composición adaptada para acomodar el contenido de pellets [114]. La tixotropía, una propiedad esencial para la capacidad de impresión de la tinta, se evalúa utilizando un Método Dinámico Escalonado. La F1 demuestra valores de recuperación más altos, indicando una regeneración estructural más rápida en comparación con F2 [115]. Esta discrepancia requiere ajustes en la velocidad de impresión, con F2 requiriendo una reducción para permitir el correcto ajuste de la tinta y la recuperación para la deposición de capas posteriores (ver **Figuras 1 y 2** de la **Publicación 5**).

Los resultados de los análisis DSC y XRD indican una transición del estado cristalino del omeprazol a un estado amorfo en las formulaciones de tinta, lo que sugiere una posible formación de solución sólida con los excipientes de hidrogel. Esta transición es crítica para la eficacia del fármaco, ya que el estado amorfo puede afectar la biodisponibilidad y la estabilidad del fármaco en el sistema de tinta [116]. La comparación de los difractogramas de rayos X entre las muestras de omeprazol y las formulaciones F1 y F2 respalda esta observación, mostrando una falta de picos característicos de cristalización

en las formulaciones de tinta, especialmente en la formulación F1. Este hallazgo sugiere que el proceso de formulación puede haber inducido la transición del omeprazol al estado amorfo, lo que podría tener implicaciones significativas en la eficacia del fármaco en la administración y liberación en contextos de impresión 3D (ver **Figura 3** de la **Publicación 5**).

La uniformidad de masa de las dosis impresas demuestra la capacidad de adaptarse a los requisitos del paciente, lo que podría mejorar la aceptación y adherencia al tratamiento. El estudio realizado subraya la importancia de la tecnología de impresión 3D en la fabricación de dosis de medicamentos personalizados y uniformes. Además, la versatilidad del diseño ofrece la posibilidad de mejorar la aceptabilidad de la medicación por parte de los pacientes pediátricos, lo que puede tener un impacto positivo en la adherencia al tratamiento (ver **Figuras 4 y 5** y **Tabla 3** de la **Publicación 5**). La capacidad de controlar la viscosidad de las tintas y la gelificación in situ durante el proceso de impresión garantiza la calidad y la integridad física de las dosis impresas. En conjunto, estos resultados reafirman el potencial de la impresión 3D en la fabricación de dosis de medicamentos personalizados y de alta calidad.

La homogeneidad en la distribución del omeprazol en la formulación F1 y la presencia de pellets entéricos en la formulación F2 plantean diferencias significativas en la forma en que se evalúa el contenido del fármaco. Sin embargo, los resultados satisfactorios de la evaluación del contenido de omeprazol en ambas formulaciones muestran la efectividad del proceso de extracción empleado. La precisión de la dosificación por encima del 90% indica la consistencia en la formulación de ambas tintas, indicando una distribución adecuada y uniforme del fármaco dentro de la matriz del hidrogel. Esto garantiza que las dosis impresas cumplan con los estándares de contenido establecidos, lo que es esencial para la eficacia terapéutica y la seguridad del medicamento (ver **Tabla 4** de la **Publicación 5**).

Referente al ensayo de gastro-resistencia, la formulación F2 muestra resultados positivos cuando se emplea el disgregador de comprimidos, con tan solo un 18% de degradación del API en medio ácido. No obstante, las pruebas en el aparato de disolución tipo II revelan una degradación del API del 64% debido a un proceso de extracción más agresivo. El mecanismo del disgregador de comprimidos simula el proceso de masticación, facilitando una recuperación del API más suave en comparación con los métodos más

agresivos empleados con el aparato II. Si bien ninguna de las formulaciones cumple completamente con las especificaciones de la USP-NF [111], el uso de pellets entéricos de omeprazol en medicamentos impresos en 3D representa una mejora con respecto al omeprazol en su forma original, abordando problemas observados en formulaciones magistrales pediátricas de omeprazol (ver **Figura 6** de la **Publicación 5**).

Respecto al ensayo de disolución, el análisis de los resultados revela diferencias significativas en los perfiles de liberación del API entre los aparatos utilizados. Mientras que el aparato II muestra una liberación baja para la formulación F1 y prácticamente nula para la formulación F2, el disgregador de comprimidos demuestra una rápida y sustancial disolución del API para ambas formulaciones, superior del 75% en 30 minutos. Esto sugiere la influencia del aparato en el comportamiento de disolución. Aunque el aparato II es comúnmente utilizado, los resultados deben interpretarse con cautela, especialmente para formulaciones de liberación retardada o con cinética de disolución compleja. El uso de aparatos alternativos, como el disgregador de comprimidos, puede ofrecer perspectivas complementarias y garantizar el cumplimiento de los estándares regulatorios. Se requieren más investigaciones para comprender los factores subyacentes que contribuyen a las diferencias observadas en los perfiles de disolución y optimizar las metodologías de prueba para predecir con precisión el rendimiento *in vivo* (ver **Figura 7** de la **Publicación 5**).

4.6 Desarrollo de una Suspensión de Pellets Entéricos de Omeprazol para su Uso en Población Pediátrica

Los preparados líquidos para administración oral, como se ha mencionado anteriormente, son los más utilizados en la población pediátrica debido a su facilidad de administración y ajuste de dosis según el peso o área de superficie corporal. Las suspensiones son formulaciones líquidas comúnmente utilizadas en pacientes pediátricos, especialmente en servicios de farmacia hospitalaria, debido a la falta de formas de dosificación pediátricas de ciertos principios activos, como el omeprazol.

En la **Publicación 6** se propone aplicar un diseño de experimentos para la formulación de una suspensión pediátrica usando los pellets entéricos de omeprazol del Experimento 4. Se emplea un diseño factorial completo con tres factores a 2 niveles (2^3) + 1 punto central para estudiar la influencia de los excipientes y su proporción en la formulación,

así como su papel en el proceso de fabricación de la suspensión. Se pretende definir un espacio de diseño para la fabricación de la suspensión de pellets entéricos de omeprazol. Dada la inestabilidad del omeprazol en medios acuosos, se opta por una preparación oleosa a base de triglicéridos de cadena media. Se evalúan diversas características de las suspensiones elaboradas, incluyendo las características organolépticas, el tiempo de sedimentación y resuspensión, la viscosidad del vehículo oleoso, la densidad relativa, el contenido de omeprazol, la gastro-resistencia y la disolución. Además, se realiza un estudio preliminar de estabilidad de la suspensión seleccionada como definitiva y una reformulación del prototipo del vehículo oleoso obtenido del DoE para mejorar la liberación de los pellets entéricos (ver detalles en el apartado de ***2.2. Methods*** de la **Publicación 6**).

Los controles de las suspensiones desarrolladas, de la F1 a la F9, resaltan diferencias notables en las características organolépticas. Mientras que las suspensiones F1 y F3 no cumplen con los estándares requeridos, sugiriendo problemas de formulación, las demás muestran resultados satisfactorios. Se establece una correlación entre la viscosidad del vehículo oleoso y el porcentaje de Aerosil® R972: las suspensiones con mayor contenido de este componente (6%) presentan una viscosidad elevada y tiempos de sedimentación más prolongados, lo que es determinante para una dosificación precisa. La consistencia en la densidad relativa de todas las suspensiones sugiere una uniformidad en la formulación, destacando la importancia de ajustar cuidadosamente la composición para alcanzar las propiedades físicas deseadas y un rendimiento óptimo [117–119].

Respecto a la uniformidad de dosis de omeprazol, la variabilidad entre las muestras resalta la necesidad de medidas rigurosas de control de calidad durante la producción. El contenido constante de omeprazol en la suspensión F2 evidencia la eficacia de los procesos de formulación y fabricación para mantener una dosificación uniforme. Esto confirma la idoneidad del contenido del 6% de Aerosil® R972 para lograr características organolépticas correctas y una uniformidad de dosis óptima dentro de los parámetros especificados (ver **Tabla 3** de la **Publicación 6**).

El análisis estadístico del diseño factorial completo destaca el impacto significativo del porcentaje de Aerosil® R972 (Factor A) y Span 80 (Factor C) en las propiedades de la suspensión. El Aerosil® R972 presenta un impacto directo en la viscosidad del vehículo oleoso, el tiempo de sedimentación y la uniformidad de dosis, mientras que el Span 80

afecta principalmente la uniformidad de dosis. Los diagramas de Pareto resaltan la influencia de ambos excipientes en las propiedades de las suspensiones. Los gráficos de contorno identifican un rango óptimo de formulación, sugiriendo un 5 – 6% de Aerosil® R972 y un 2% de Span 80 para lograr unas propiedades óptimas.

Mediante el programa estadístico Minitab, se realiza una optimización de las respuestas estudias, prediciendo las cantidades ideales del Factor A y C para conseguir unas propiedades correctas (ver **Figura 5** de la **Publicación 6**). Se elabora una suspensión, nombrada como F10, con las cantidades de excipientes obtenidas en la optimización y se somete a un estudio de estabilidad de 1 mes (ver **Tabla 7** de la **Publicación 6**). Dicho estudio sugiere que la temperatura ambiente es óptima para el almacenamiento, con mayor estabilidad y mínimos cambios de color de los pellets entéricos de omeprazol. Sin embargo, la gastro-resistencia y la liberación del API no han sido satisfactorios, motivo por el cual se planifica una nueva investigación para incorporar vehículos oleosos hidrofílicos y explorar el uso de otros excipientes.

Para la optimización de la disolución de la suspensión de pellets entéricos de omeprazol, se elaboran 8 suspensiones, de la F11 a la F18, incorporando vehículos oleosos hidrofílicos y explorando el uso de otros excipientes (ver **Tabla 9** de la **Publicación 6**). La formulación F17 destaca por sus características organolépticas superiores. Al reemplazar los triglicéridos de cadena media con Labrafil M 1944 CS como vehículo oleoso hidrofílico, y substituir el Aerosil® R972 por el Aerosil® 200, se logra una mejora significativa en la liberación de los pellets entéricos de omeprazol, alcanzando un 79% en 30. Estos cambios permiten cumplir con las especificaciones del ensayo de disolución del omeprazol según la USP- NF [111]. Los análisis de la suspensión F17 muestran resultados satisfactorios en cuanto a la evaluación de contenido del omeprazol (98%), la uniformidad de dosis (contenido medio dentro del intervalo del 85 – 115%) y la gastro-resistencia (96%), cumpliendo con las especificaciones de la Ph. Eur. [110,120] y la USP-NF [111] para dichos ensayos (ver **Tabla 10** de la **Publicación 6**).

Tras la investigación realizada, la composición final del prototipo de vehículo oleoso para administrar pellets entéricos de omeprazol a pacientes pediátricos incluye Labrafil M 1944 CS, Aerosil® 200 y Span 80.

A continuación, como resumen, se presenta un esquema global (Figura 3) relacionando las diferentes publicaciones de la tesis doctoral:

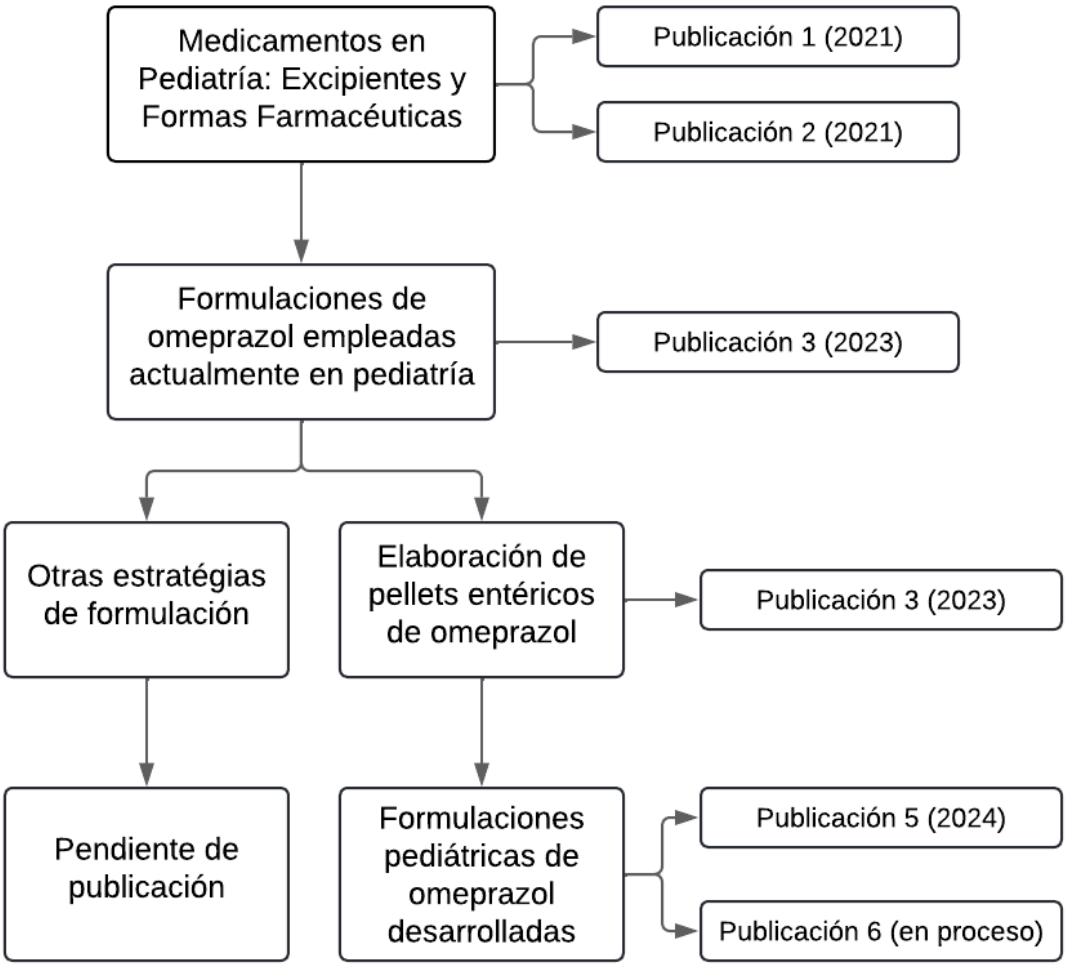


Figura 3. Esquema global de publicaciones de la presente tesis doctoral.

5 CONCLUSIONS

With the objectives stated in this doctoral thesis and after its development, the primary conclusion is as follows:

1. A suspension for administering omeprazole enteric pellets, featuring an average diameter of 0,5 – 0,6 mm, has been formulated with the following composition: Labrafil M 1944 CS (90,47%), Aerosil® 200 (4,00%), Span 80 (2,00%) and omeprazole enteric pellets (3,53%). This suspension presents a viable alternative to the existing paediatric compounding formulas of omeprazole, as it meets the specifications outlined in the Ph. Eur. and USP-NF regarding dissolution and gastro-resistance tests.

Among the specific conclusions drawn, the following stand out:

2. A thorough revision of excipients utilization in the paediatric population highlights a concerning trend: the frequent use of excipient at concentrations exceeding regulatory agencies limits, coupled with inadequate labelling practices. Furthermore, the significant disparities in pharmacokinetic and pharmacodynamic profiles between paediatric and adult populations underscore the necessity for ongoing research endeavours aimed at enhancing the safety profile of excipients and mitigating their potential adverse effects in paediatric patients.
3. Orally disintegrating tablet formulations and the utilization of 3D printing techniques, particularly semisolid extrusion, represent innovative and promising approaches for crafting dosage forms tailored to the needs of the paediatric patient.
4. The prevalent use of liquid compounding formulas of omeprazole in the paediatric population often gives rise to gastro-resistance issues, exemplified by omeprazole 2 mg/mL suspension containing xanthan gum.
5. Extensive bibliographic research into omeprazole, supplemented by characterization experiments, unequivocally underscores the imperative of applying enteric coating to omeprazole. This preventive measure is crucial for averting its degradation in the acidic medium of the stomach, particularly prior to its incorporation into liquid preparations intended for paediatric use.

6. Regarding the development of enteric pellets of omeprazole tailored to paediatric patients, the following conclusions have been drawn:
    - **A.** The development of omeprazole enteric pellets, ranging in diameter from 0,50 to 0,60 mm, has been successfully achieved using the method of coating inert pellets of microcrystalline cellulose in a fluidized bed.
    - **B.** The small size of the omeprazole enteric pellets allows for their convenient incorporation into suspensions and other pharmaceutical forms produced using 3D printing techniques, specifically semi-solid extrusion. This size also facilitates swallowing for paediatric patients, addressing challenges associated with swallowing solid pharmaceutical forms such as tablets or capsules, particularly for children under 6 years of age.
    - **C.** Optimal coating has been attained solely using aqueous dispersions, eliminating the need for organic solvents, which are not recommended for use in the paediatric population due to possible side effects.
    - **D.** The most suitable coating conditions involve a weight increase of either 2% or 6% for the protective layer and 100% for the enteric layer. These conditions have resulted in a uniformity of 100% in the omeprazole content, a 95% gastro-resistance percentage, and an 80% release of omeprazole within 15 minutes, meeting the specifications of the Ph. Eur. and the USP-NF. Additionally, EDS microanalysis of the different coating layers indicates that the coating process has been carried out uniformly.
7. Regarding the application of 3D printing technology through semi-solid extrusion to develop customized dosage forms for the paediatric population, the following conclusions have been drawn:
    - **A.** The application of the 3D printing technique through semi-solid extrusion has enabled to production of chewable and personalized gummies for paediatric patients, characterized by an attractive and eye-catching appearance, using omeprazole base (Formula 1) and omeprazole enteric pellets (Formula 2).
    - **B.** Both formulations have demonstrated appropriate rheology, good printability, and uniformity in dose and mass within the specifications established by Ph. Eur. and USP-NF.
    - **C.** While Formula 1 exhibited complete degradation of the API in the gastro-resistance test, Formula 2 achieved gastro-resistance levels of 82%.

D. Regarding the dissolution test, low release levels were observed for both formulations when using dissolution apparatus II. However, when utilizing the table disintegrator, release levels higher than 75% within 30 minutes were attained for both formulations.

E. This research integrates innovative pharmaceutical technologies with traditional methods, such as 3D printing and fluidized bed pellet coating, laying the groundwork to produce personalized drugs tailored to the needs of the paediatric population.

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