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

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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.

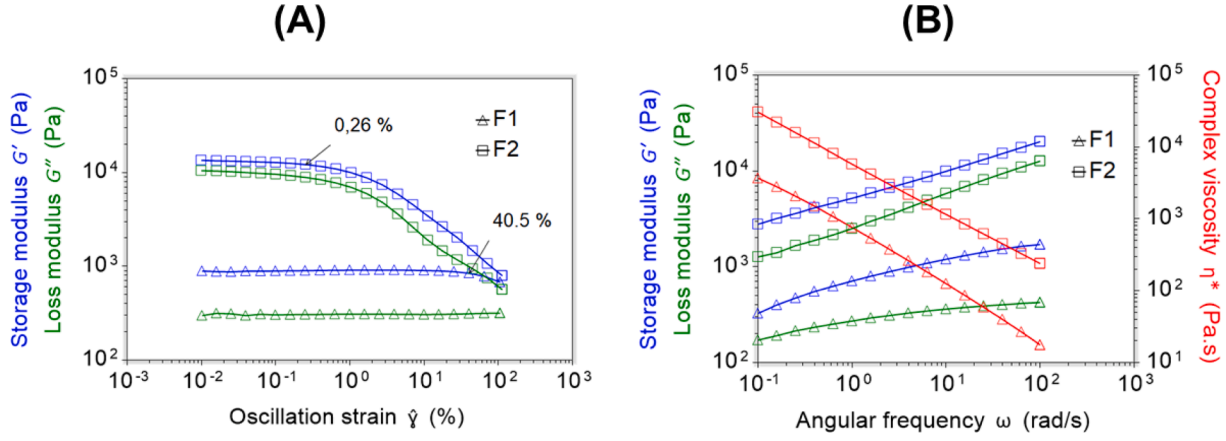

Fig. 1. (A) Amplitude sweeps from 0.01 to 100 % strain. (B) Frequency sweeps from 0.1 to 100 rad/s.

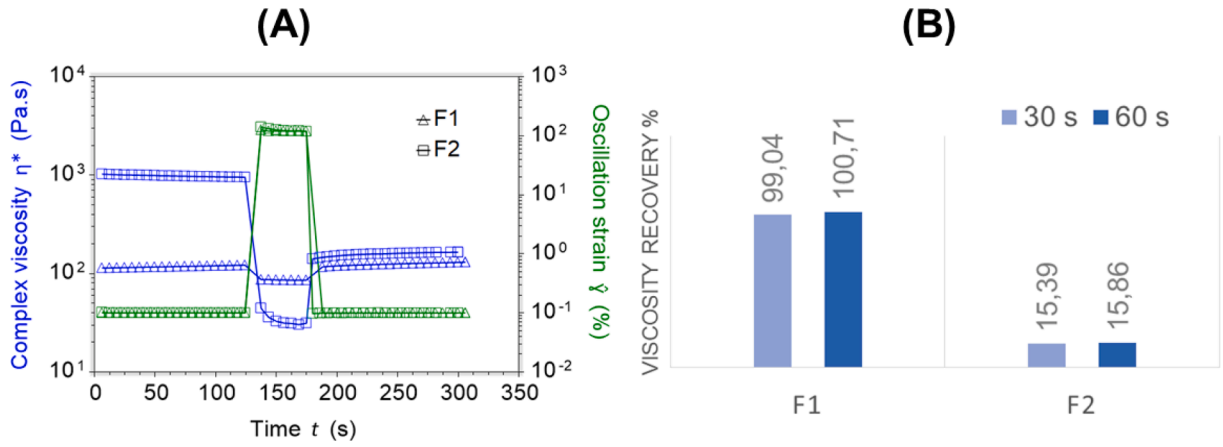

Fig. 2. Stepped Dynamic Method (SDM) tests and viscosity recovery % obtained.

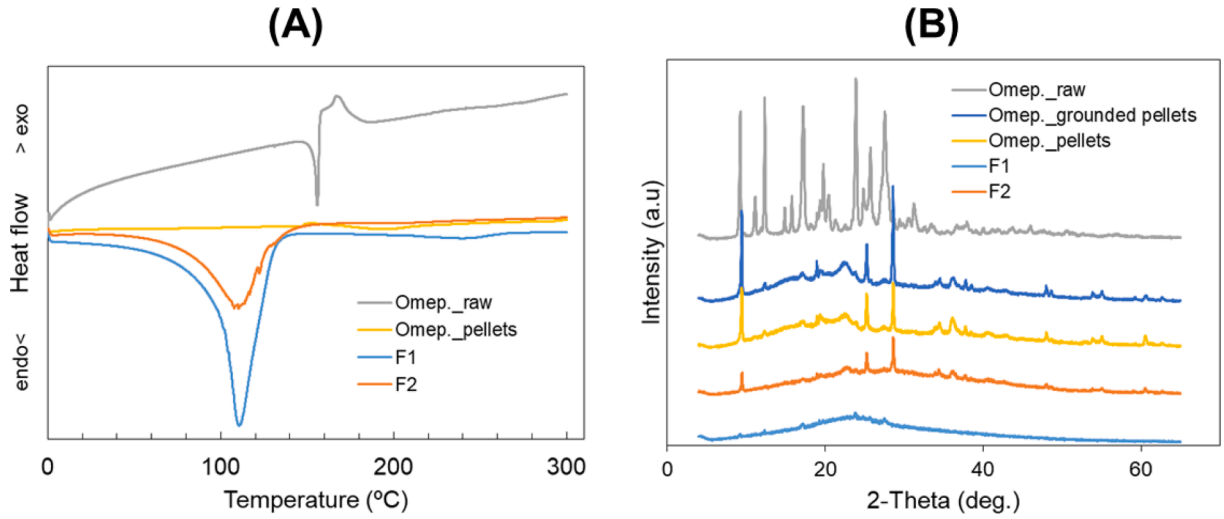

Fig. 3. Drug characterization results: (A) DSC, (B) XRD.

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

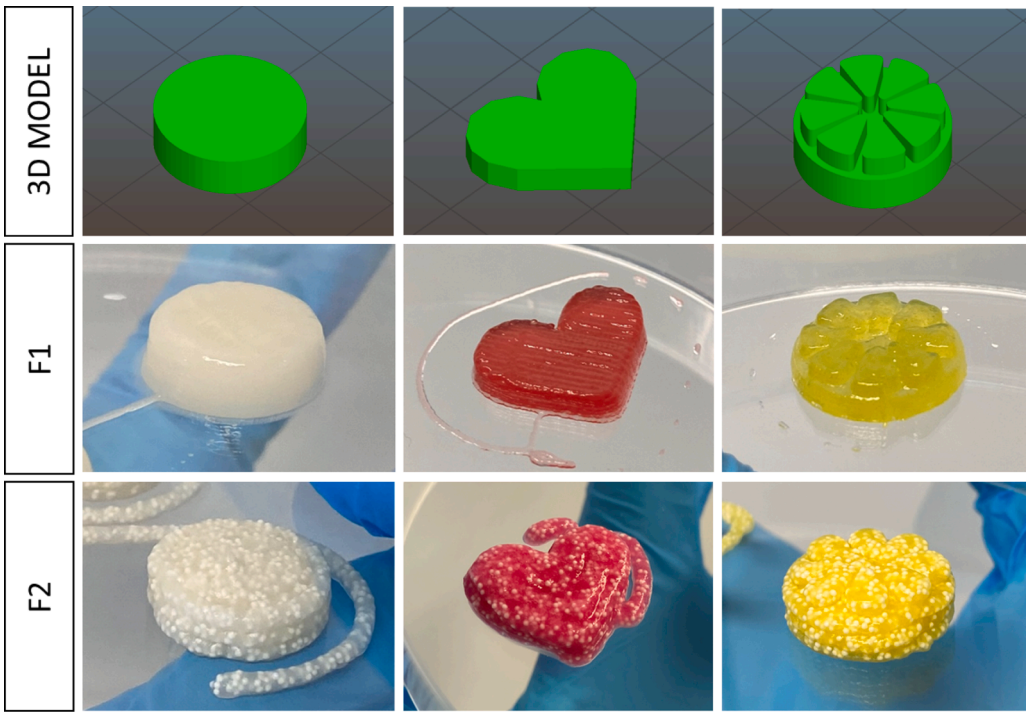

Fig. 4. 3D models and drugmies printed with F1 and F2.

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.

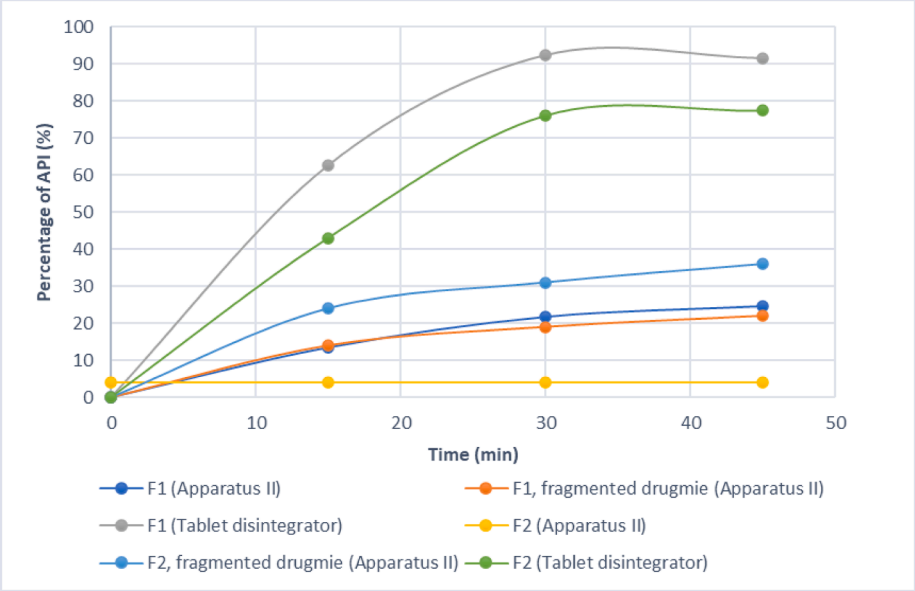

Fig. 7. Drug dissolution profiles of drugmies dosages printed with F1 and F2 formulas.

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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