



Research paper

Exploration of moisture activated dry granulation for the development of gastroretentive tablets aided by SeDeM diagram

María Ximena Origoni^{a,b}, Anna Nardi-Ricart^c, Marc Suñé-Pou^{c,d}, Pilar Pérez-Lozano^{c,d,*},
Miquel Romero-Obón^c, Josep Maria Suñé- Negre^{c,d}, Ana Teresa Ochoa-Andrade^b,
Encarna García- Montoya^{c,d}

^a Graduate Program in Chemistry, Facultad de Química, Universidad de la República, Gral. Flores 2124, 11800 Montevideo, Uruguay

^b Pharmaceutical Technology, Department of Pharmaceutical Sciences, Facultad de Química, Universidad de la República, Gral. Flores 2124, 11800 Montevideo, Uruguay

^c Department of Pharmacy and Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII, 27-31, 08028 Barcelona, Spain

^d Pharmacotherapy, Pharmacogenetics and Pharmaceutical Technology Research Group Bellvitge Biomedical Research Institute (IDIBELL), Av. Gran Via de l'Hospitalet, 199-203, 08090 Barcelona, Spain



ARTICLE INFO

Keywords:

Moisture activated dry granulation
Gastroretentive tablet
QbD
SeDeM
Multiple linear regression analysis
Principal component analysis

ABSTRACT

Moisture activated dry granulation (MADG) is an attractive granulation process. However, only a few works have explored modified drug release achieved by MADG, and to the best of the authors knowledge, none of them have explored gastroretention. The aim of this study was to explore the applicability of MADG process for developing gastroretentive placebo tablets, aided by SeDeM diagram. Floating and swelling capacities have been identified as critical quality attributes (CQAs). After a formulation screening step, the type and concentration of floating matrix formers and of binders were identified as the most relevant critical material attributes (CMAs) to investigate in ten formulations. A multiple linear regression analysis (MLRA) was applied against the factors that were varied to find the design space. An optimized product based on principal component analysis (PCA) results and MLRA was prepared and characterized. The granulate was also assessed by SeDeM.

In conclusion, granulates lead to floating tablets with short floating lag time (<2 min), long floating duration (>4 h), and showing good swelling characteristics. The results obtained so far are promising enough to consider MADG as an advantageous granulation method to obtain gastroretentive tablets or even other controlled delivery systems requiring a relatively high content of absorbent materials in their composition.

1. Introduction

Moisture activated dry granulation (MADG) is an attractive granulation process. It offers advantages regarding energy saving, time efficiency, suitability for continuous processing [1] and formulation versatility, including controlled release polymeric matrix type products [2,3]. However, only a few works have been published exploring modified drug release achieved by MADG [2,4–6], and to the best of the authors knowledge, none of them have explored gastroretention. Briefly, in MADG, a small amount of water is used to activate agglomeration within a powder mixture which includes a binder, followed by the addition and blending of ingredients that absorb and distribute the

moisture, so no heat is required to dry the granules. The result is a uniform, free-flowing, and compactible granulate [7], with a typical particle size of 150–500 µm [8]. Therefore, MADG presents fewer critical process variables than conventional wet and dry granulation processes, a relevant characteristic which facilitates the implementation of quality by design (QbD) [9], as well as process scale up and validation.

Gastroretentive delivery systems are useful vehicles when prolonged gastric residence of the dosage form can improve the bioavailability of the active substance. Active pharmaceutical ingredients (APIs) which benefit from this formulation strategy are those that are locally active in the stomach, have a narrow absorption window in gastrointestinal tract [10], are unstable in the intestinal environment or exhibit low solubility

* Corresponding author at: Department of Pharmacy and Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII, 27-31, 08028 Barcelona, Spain.

E-mail address: perezlo@ub.edu (P. Pérez-Lozano).

<https://doi.org/10.1016/j.ejpb.2024.114456>

Received 19 April 2024; Received in revised form 26 July 2024; Accepted 12 August 2024

Available online 15 August 2024

0939-6411/© 2024 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

at high pH regions [11,12]. Amongst the various gastroretentive strategies, floating systems are the most prominent and have been among the most explored since their earliest appearance in the 1970s [13,14]. In several cases, the combination of different strategies such as floating and swelling (expandable) systems, have succeeded in achieving even more significant gastric residence time [13].

SeDeM diagram is a relatively new methodology that allows to evaluate if a solid (powder or granulate) is suitable for direct compression, as its main application. It comprises the study of a series of parameters that once analyzed provide the pharmacotechnical information required to decide the most convenient manufacturing process and formulation for a tablet. In addition to the original SeDeM which includes 12 factors, reduced SeDeMs with less parameters to assess are recently proving to be of value in development as well [15]. Definitely, SeDeM is a highly valuable tool available for the development of oral solid dosage forms and for the characterization of granules or mixtures before compressing [16–21]. The aim of the present work was to explore the applicability of an energy and time efficient granulation process such as MADG for the development of gastroretentive tablets, aided by SeDeM diagram.

2. Materials and methods

2.1. Materials

The excipients used in the present work were as follows: fine grade lactose monohydrate (Pharmatose 200 M, DFE Pharma, New Zealand), povidone K15 (PVP K15, ISP, USA), copovidone (Kollidon VA 64, BASF, Germany), fine grade copovidone (Kollidon VA 64 Fine, BASF, Germany), hydroxypropyl methylcellulose (Metolose 90SH-4000, Shin-Etsu, Japan), amorphous silica (Syloid 244FP, Grace, Germany) and magnesium stearate (Tablube, Nitika, India). Sodium alginate (Manucol LKX) was kindly gifted by FMC Corporation, Scotland. Sodium bicarbonate (food grade, Droguería Paysandú, Uruguay), povidone K30 (PVP K30, DIU, Uruguay) and colorant FD&C blue N°2 were locally purchased.

2.2. Methods

The target matrix tablet of the present development study was designed to function as a floating and, to some extent, expandable delivery vehicle. It was designed bearing in mind that medium and high API loads (drug substance content over 35% of the tablet weight) require in most cases, a previous granulation step, so MADG was the granulation method used to obtain the granulate.

Since the present study was designed to explore MADG ability to overcome the difficulties in processing the components of a gastroretentive formulation, no model drug was introduced at this stage. The work focused also on how each type of excipient required to produce an expandable floating system could play the traditional roles of binder, absorbent and/or moisture distributor defined in MADG [6,7], in order to contribute to further establish the versatility of this sustainable granulation process.

2.2.1. Quality target product profile (QTPP) and critical quality attributes (CQAs)

Quality by Design (QbD) is acknowledged as a highly recommended approach to apply to pharmaceutical development to give special emphasis on good product and process understanding. The first steps applied for the QbD approach [22] were to define the QTPP and identify potential CQAs based on prior knowledge. Those elements of QTPP which depend mainly on a particular API to load in the tablet, such as method of administration, stability, and API identification, assay and in vitro release were not included. Therefore, QTPP was defined according to the following elements: dosage form and design, route of administration, hypothetical drug load (using an API surrogate in this study),

and relevant gastroretentive tablet quality attributes.

Floating and swelling capacities and microbial limits, among other attributes, have been identified as CQAs (Table 1). Although microbiological quality is critical for product safety, it can be effectively controlled at the laboratory scale, and thus, this CQA will not be further discussed during the present study, although it must be considered in the control strategy for the final product.

2.2.2. Preliminary formulation and process design

The gastroretentive tablets were planned to be obtained by compression of granulates produced by MADG. The excipients required were hydrogelling polymers to form the matrix, fillers, binders, gas-forming agents, absorbents, coloring agent (to assist process and performance visualization) and water. Before compression, the granulate needed to be mixed with a lubricant.

Excipient selection required to consider the role of each substance in the gastroretentive tablet and how it could properly work in MADG process, as some excipient characteristics, such as particle size distribution or water absorption capacity, may interfere in MADG processing steps [6,23].

For example, the matrix agent percentage in a floating tablet may often vary between 20 and 50% and typical candidates for this role, such as hydroxypropyl methylcellulose or sodium alginate show great water absorption capacity. Therefore, such a great amount of polymer could impair water function as binder activator if it is used in its totality in the intragranular mix, since water is usually used in small quantities (2–4%) in MADG. In the present work instead, these polymers are partly tried as absorbents in the moisture distribution step. Regarding binders, they can be used singly or in multiple combinations to achieve the desired effects or address specific concerns [7]. In fact, the required balance between distribution ability and agglomeration efficiency of binders may not always be easy to accomplish using only one agent in the MADG process. The use of combinations of binders could widen opportunities to improve granulation performance. Fine grade lactose monohydrate, a soluble non-directly compressible excipient, was chosen as a surrogate for a water-soluble API and as a filler in the tablets. This milled type of lactose generally recommended for wet granulation and necessarily present in high proportion in the formulations of the present study, is known to present poor flow values [24]. Therefore, granulation is justified to render the particulate beds apt for compression, and the selected excipient is an appropriate choice as non-directly compressible API surrogate and filler. It was also taken into account that according to Ullah et al. [7], the primary factors to be considered in MADG formulation are API solubility, particle-size distribution, and API loading. The rationale behind the decision to design the tablet for soluble APIs, belonging to classes I or III of the Biopharmaceuticals Classification System (BCS) [25], was that the eventual presence of a relatively high content of a soluble ingredient could be even more challenging to the integrity of a floating matrix. Undoubtedly, aspects regarding active ingredient release will depend on each API to be formulated in the final floating tablets, and their compositions will require further optimization for proper *in vitro/in vivo* performance. However, major changes in physico-mechanical attributes of granules and tablets are not expected, while minor changes in pharmacotechnical behavior generated by the inclusion of an API should be promptly identified by SeDeM diagram, helping to further optimized the final formulation. As a result, success in achieving placebo floating tablets by MADG could draw attention to this sustainable process and promote its use in modified release dosage forms.

The manufacturing process was designed in preliminary studies. A formulation screening step was used to rapidly explore the ability of the selected binders and matrix formers/absorbents to be processed by MADG in order to produce floating tablets. The ranges of concentrations proposed for these components and the gas-forming agent were set in relation to basic knowledge of the product and feasibility at the commercial manufacturing scale. The screening was also improved by two

Table 1

QTPP and respective CQAs determined for placebo floating gastroretentive tablet (development phase without API added to the formulation).

QTPP Element		Target	CQA	Justification
Dosage form		Tablet	N/A	N/A
Dosage design		Floating and expandable matrix tablet	N/A	N/A
Route of administration		Oral	N/A	N/A
Drug load (hypothetical, use of API surrogate)		Not less than 35% of the tablet weight	N/A	N/A
Tablet quality attributes	Appearance	Circular, convex tablet, 12 mm in diameter.	No	N/A
	Weight variation	Relative standard deviation (RSD) <5%	Yes	May affect dose
	Floating capacity	Floating duration (FD) not less than 4 h and floating lag time (FLT) less or equal to 4 min in 0.1 N HCl pH 1.2.	Yes	May affect retention time in stomach
	Swelling capacity	High percentage of swollen tablet after 60 and 120 min (diameter not less than 14 mm after 60 min) in 0.1 N HCl pH 1.2.	Yes	May affect retention in stomach
	Microbial limits	Meets relevant pharmacopeia criteria.	Yes	Not studied at this phase*

N/A: not applicable.

* Not studied at this phase, but this CQA will be considered in the control strategy for the final product.

experimental runs representing the extremes of a design of experiment which finally was not completed. This prior exploration of the factor-level combinations of a DoE, usually recommended before embarking on the random order used for executing a design, provided information about the process that led to discard the full completion of the DoE, while helping in the rationale use of resources [26].

The outcome of this experimental screening would be the foundations in future studies to set the conditions for a DoE aimed to define the space design and optimize floating tablets obtained by MADG containing active ingredients.

2.2.3. Initial risk assessment

An initial risk assessment was performed based on prior knowledge. Risk assessment is considered useful in pharmaceutical development because the products and their manufacturing processes can be complex and generally involve multiple relevant factors [27]. The designed manufacturing process and its parameters were kept constant throughout the formulation development. Therefore, to identify possible variables affecting CQAs, only formulation factors (e.g. material attributes) were considered. An Ishikawa diagram was used to identify potential critical material attributes (CMAs) that could explain the variability in the key responses [26]. After deciding to reduce the number of variables in the study and thus, keep the selected gas-forming agent concentration unchanged, the type and concentration of floating matrix formers and of binders remained as the most relevant CMAs to investigate.

2.2.4. Preparation of granulates and tablets

The compositions of all the formulated tablets are shown in Table 2.

Table 2

Formulations of placebo floating gastroretentive tablets.

Trial	Component (%) [*]						
	Lactose	HPMC 4 M	Copovidone	Povidone K15	Povidone K30	Sodium alginate	Water
A1	43.10	27.00	4.00	4.00	—	7.00	3.00
A2	60.10	10.00	4.00	4.00	—	7.00	3.00
A3	36.10	30.00	5.00	3.00	—	10.00	4.00
A4	56.10	20.00	5.00	3.00	—	—	4.00
A5	54.10	20.00	7.50	2.50	—	—	4.00
A6	54.10	20.00	5.00	5.00	—	—	4.00
A7	54.10	20.00	—	10.00	—	—	4.00
A8	54.10	20.00	—	5.00	5.00	—	4.00
A9	55.10	20.00	4.50	4.50	—	—	4.00
A10	55.10	20.00	4.50 ^{**}	4.50	—	—	4.00
Excipient function	Filler	Hydrogelling agent and absorbent		Binder		Hydrogelling agent	

— Excipient not added at this formulation.

* The amounts of sodium bicarbonate (10.00%), colorant (0.15%), amorphous silica [absorbent] (1.00%) and magnesium stearate (0.75%) were kept constant in all the formulations.

** Finer grade copovidone is used.

Manufacturing process: batches of 300 g were processed as follows. All solid materials were previously sifted through a 0.5 mm sieve. Binder, colorant and equivalent parts of the hydrogelling agent (sodium alginate when present in the composition plus part of hydroxypropyl methylcellulose (HPMC 4 M)) and of the filler were premixed for 2 min in a tumbling mixer (Turbula, Willy A. Bachofen, Muttentz, Switzerland) at 145 rpm. Afterwards, the premix, sodium bicarbonate, another part of the cellulose polymer and the rest of the filler were mixed for 15 min in the tumbling mixer at 145 rpm. The mixture was loaded into a high-speed mixer (HR7628 food processor, Philips, Amsterdam, The Netherlands). Impeller speed was kept constant during the whole process at the lowest setting of the mixer (approximately 1500 rpm). Water was sprayed into the powder bed at a rate of 3.6 g/minute for 2.5–3.3 min as a flat fan spray pattern, while mixing. Mixing continued for 30 additional seconds. Afterwards, the first absorbent (rest of the hydroxypropyl methylcellulose) was gradually incorporated over a period of 2 min. The addition of the second absorbent (amorphous silica) took 30 to 45 s and mixing was continued for another 45 to 60 s. Granulates were screened through a 0.7 mm sieve. The granulate plus magnesium stearate were mixed for 3 min in the tumbling mixer at 145 rpm. Finally, each blend was compressed into tablets in a rotary tablet press (RL 15, Kilian, Germany) at 20 kN, using 12 mm flat round tooling.

2.2.5. Characterization of granulates

Granulates were characterized by studying their particle size distribution, bulk and tapped density and moisture content.

Particle size distributions (USP 786, May 2023) were determined by sieve analysis (AS 200 control, Retsch, Haan, Germany). DIN-ISO 3310/1 standard sieve series was 75, 90, 125, 180, 250, 355 and 500 µm. The

mean particle size, 10th, 50th and 90th percentiles, and span (relation between 3 fractions [percentile 90th – percentile 10th] /percentile 50th) were calculated.

Bulk density was determined according to United States Pharmacopeia (USP 616, May 2024), and Carr index and Hausner ratio were calculated, too. In tapped density test, mechanical vibration of the graduated cylinder (100 mL) at 1.5 mm of amplitude of oscillation was used to achieve tapping.

The moisture content was determined on a halogen moisture analyzer (Mettler Toledo HR 73, USA) and the percentage of moisture content was calculated from the weight loss of the sample on heating at 105 ± 1 °C.

The tests were performed in duplicate and average results were reported for all of the characterizations.

2.2.6. Characterization of tablets

Appearance and dimensions, hardness, friability, weight variation, and floating and swelling capacity of tablets were studied. The tests were performed in duplicate and average results were reported for all the characterizations.

2.2.6.1. Dimensions, tensile strength, and friability. Diameter, thickness and hardness (USP 1217, May 2019) of randomly selected tablets ($n = 6$) were measured with a caliper and a hardness tester (TBH 125, Erweka, Heusenstamm, Germany), respectively. The results were used to calculate tensile strength by the following formula [28]: $2 \cdot H / \pi \cdot D \cdot T$; where H is hardness, D is diameter and T is overall thickness. Friability was determined according to the (USP 1216, Aug 2023) at 25 ± 1 rpm during 4 min in a friability tester (Senova, CS-4, Shanghai, China).

2.2.6.2. Weight variation. Tablets ($n = 20$) were randomly weighed on a scale (Kern, PLJ 600 3NM, Balingen, Germany) and RSD of weights were calculated.

2.2.6.3. In vitro floating and swelling properties. A dissolution tester (VK 7000 10–1700, Vankel, New Jersey, USA) USP apparatus 2 was employed in floating and swelling tests. One tablet was introduced into each dissolution vessel containing 500 mL of 0.1 N HCl, pH 1.2 maintained at 37 ± 1 °C. Swelling and floating lag time evaluations were conducted at 50 rpm [29,30], while floating duration test was run with no stirring [31]. The time for the tablet to reach the upper portion of the vessel (floating lag time) and the time taken to constantly float on the medium (floating duration) were determined by visual observation. At predetermined intervals during the swelling tests (15, 30, 60, 120 and 240 min), the swollen tablets were removed from the solution and immediately wiped with a filter paper to remove surface droplets. The extent of swelling was determined by the percentage of weight gain of swollen tablet. The total time of 4 h in swelling and floating studies was considered appropriate, since as discussed by Diós et al. [31], during fasting, interdigestive series of electrical events may cycle the gastric content to the duodenum in every 2–3 h. Nevertheless, the diameter of swollen tablet was also considered a determining factor to ensure the ability of gastroretention [11]. Thus, the diameters of swollen tablets were measured with a caliper at 60 min.

2.2.7. Data analysis

A principal component analysis (PCA) was used for data analysis of granulates and tablets. As Altan et al. stated analysis methods that take the correlation structure into account such as PCA can provide effective analyses [32]. Ten samples (A1–A10) and seven variables were considered to perform PCA. The variables included were as follows: mean particle size (X_m), tapped density (DensTp), Carr index (IC), Hausner ratio (IH) from granulate and, swelling at 60 min (Swell60), swelling at 120 min (Swell120) and floating lag time (FLT) from tablets. All data analyses were performed using R language [33] and FactoMinR package

[34].

Moreover, the construction of a design space was attempted with the results from the previous ten formulations (A1–A10) against the factors that were experimentally varied (Table 2) by multiple linear regression analysis (MLRA). The same seven variables from PCA were considered to perform MLRA. The analysis will allow generating the equations that ascertain the interaction effects of CMAs on CQAs in the studied interval and determining their surface of response. Furthermore, the obtained contour plots will enable to identify areas in which the values of each response meet the goals stated in the QTPP. Minitab Statistical Software (21 ed) was the software used for this analysis.

2.2.8. Final product

A 300 g batch of optimized product (A11, formula described in section 3.4) based on results of the previous formulations, PCA results and MLRA was prepared. The granulate and the tablet were fully characterized as previously described. The granulate was also assessed based on a reduced and adapted SeDeM expert system. The various parameters involved were determined for the granulate, according to reported methods [19–21]. Each parameter was determined (in triplicate or duplicate, depending on the parameter) and mean values were used in calculation of SeDeM diagram radii values (r).

Finally, formula A11 was scaled up to 1000 g in a high shear mixer MAV-10 (SAR Labortecnic, Barcelona, Spain), and prior to compression it was characterized by the SeDeM method (full and reduced), to corroborate its compressibility. Also, for corroborating results at the new scale, FLT was assessed in the tablets.

3. Results and discussion

3.1. Characterization of granulates and tablets

The MADG granulates presented particle size distributions in the expected range and Hausner ratio values which ranged from poor (1.38) to excellent flow character (1.10) [35], as it is shown in Table 3. Granulate A6 presents relatively high X_m and low span, suggesting a more uniform binder activation and granule growth during the moisture distribution stage. However, the purpose of the MADG process is not to make large particles, but rather to generate only enough particle size enlargement to ensure satisfactory granulation flow and compactability without segregation, not generally requiring further size reduction [7]. Regarding moisture content of granulates, it ranged between 3.8 and 5.4% after matrix formers/absorbents were used to redistribute moisture within each batch, producing relatively dry granules suitable for compression.

Tablets with appropriate aspect and high mechanical strength (tensile strength values ranged between 2.6 and 4.5 MPa [28], and friability weight loss was at most 0.2%) were obtained from all the granulates (Table 4). The results of relative standard deviation of tablet weight were less than or equal to 3%, excepting assay A3 (7.5%), which is the formulation including the largest concentration of hydrogelling polymers. This result agrees with the assumption about the criticality of the total amount of polymer in the formulation, even when it is used divided between the initial dry blend and the moisture distribution stage, as the presence of water is limited in the MADG process. All tablets remained constantly floating (FD) in the acidic medium for at least 4 h, so the duration of floating was not a discriminatory parameter between formulations. On the other hand, the flotation delay time of the tablets ranged from 51 s to more than 5 min. Therefore, this attribute appeared as one of the most discriminatory tablet properties for comparison purposes among formulas.

3.2. PCA

Regarding the PCA analysis of the results obtained, the first two dimensions of the PCA explained 84% of the variance of the experimental

Table 3

Result data of mean values of attributes of granulates.

Attribute / Formula	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
Mean size (μm) Xm	122	150	107	148	153	167	172	139	141	155
10th percentile (μm)	16	19	15	16	18	22	20	15	16	17
50th percentile (μm)	86	95	73	80	88	105	99	73	83	87
90th percentile (μm)	240	342	185	410	412	421	475	359	329	423
Span	2.6	3.4	2.3	4.9	4.5	3.8	4.6	4.7	3.8	4.6
Moisture content (%)	4.9	4.9	5.4	3.8	4.5	4.0	4.5	4.7	4.6	4.5
Bulk density (g/mL)	0.59	0.47	0.47	0.46	0.52	0.50	0.52	0.57	0.55	0.51
Tapped density (g/mL)	0.65	0.60	0.53	0.64	0.65	0.62	0.71	0.71	0.70	0.65
Carr index (%)	9	21	12	28	20	20	27	20	21	22
Hausner ratio	1.10	1.27	1.14	1.38	1.25	1.25	1.37	1.26	1.26	1.28

Table 4

Result data of mean values of attributes of tablets.

Attribute / Formula	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
Relative standard deviation of weight (%)	1.3	0.7	7.5	2.0	0.8	1.1	3.2	1.4	0.6	0.8
Tensile strength (MPa)	3.3	3.4	3.9	3.0	2.6	3.0	3.5	3.3	3.4	4.2
Friability (%)	0.1	0.1	0.0	0.2	0.1	0.2	0.1	0.1	0.1	0.1
Swelling at 15 min (%)	26.59	25.05	28.12	26.57	22.90	28.27	27.58	23.23	28.76	35.58
Swelling at 60 min (%)	48.14	59.18	65.58	26.16	31.81	45.53	38.05	39.77	29.47	50.70
Swelling at 120 min (%)	54.38	95.91	85.07	28.91	37.08	61.71	53.64	59.12	41.07	56.34
FLT (sec)	179	313	155	53	56	55	77	104	51	73
FD (min)	>240	>240	>240	>240	>240	>240	>240	>240	>240	>240
Diameter at 60 min (mm)	18	13	13	15	14	14	13	13	15	13

data. As shown in Fig. 1, the first principal component (Dim1) was responsible for 63% of the total variance in the data set and the second (Dim2) was responsible for 21%. The first dimension is positively correlated to Xm, DensTp, IC and IH, while negatively correlated to Swell60, Swell120 and FLT. Xm and Swell120 are also positively correlated with Dim 2. The correlation matrix was performed to confirm the correlations among variables in PCA, and the following correlations were found: Xm is positively correlated with IC and IH. IC and IH show a

perfect positive correlation ($r = 1.00$, $p < 0.00$) as expected, DensTp is negatively correlated with Swell60, and both swelling times are positively correlated to each other and to FLT.

PCA revealed the following trends about correlations between factors of the formulation (Fig. 2). The presence of sodium alginate mainly influenced floating lag time and swelling of the tablets. The alginate-containing formulations (A1, A2 and A3) presented the greatest percentage of swelling after 120 min, but also the longest floating lag periods (over 2.5 min), which could be due to the insolubility of alginates in the acidic stomach conditions as already reported [14]. The rest of the assays (A4 to A10) presented higher density and mean granule size, lower swelling capacity and FLT, while IC and IH varied from intermediate to high values. These tablets included only hydroxypropyl methylcellulose as floating matrix former and showed FLT under 2 min. Among these granulates, formulations with higher binder concentration, and including at least 5% of povidone K15 either alone or in the presence

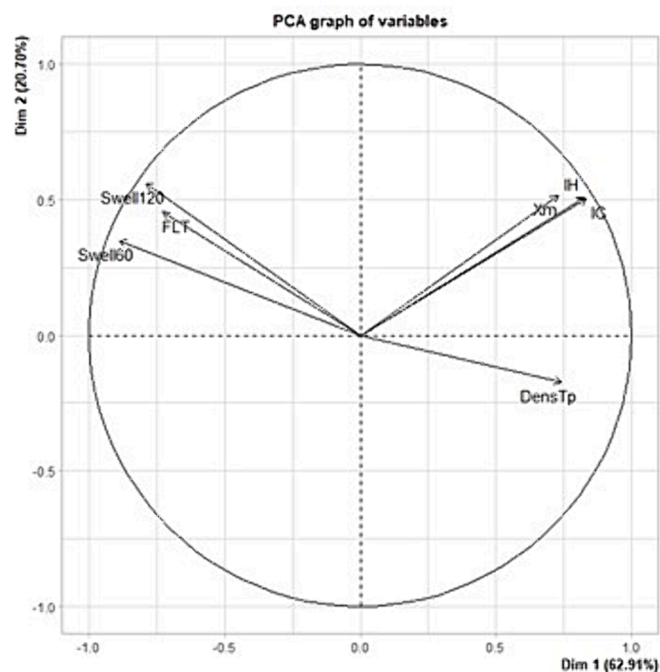


Fig. 1. Loading plot representing the variables direction in the first and second dimensions of PCA. Length of arrows mean influence. Same direction implies correlation. Same direction and sense means positive correlation and same direction and opposite sense indicates negative correlation between variables. Angles close to 90 degrees indicate independence between variables.

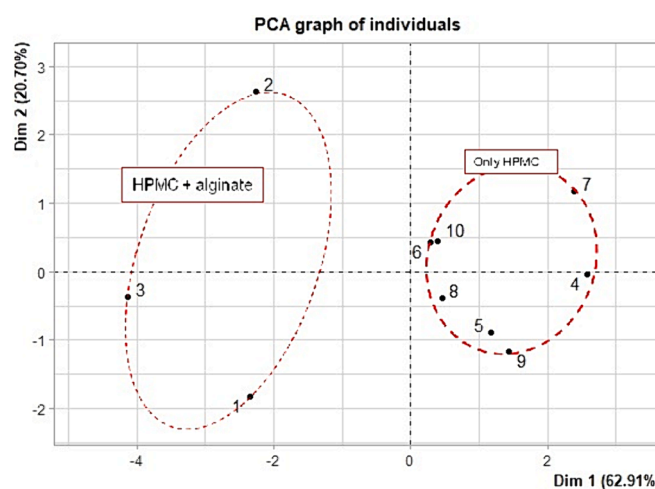


Fig. 2. Score plot representing the formulations in the first and second dimensions of PCA. Relative distance and position mean similarity in formulations. In this figure, two clusters are shown corresponding to only HPMC (right) or HPMC+alginate (left).

of copovidone (A6 and A7), produced lower percentage of fines (fraction below 75 μm). However, the use of a finer grade of copovidone (A10) did not result in a reduction of granulate fines as would be expected on account of an increased contact surface between the binder and the filler particles [36] or the eventually easier activation with moisture of the smaller binder spheres.

3.3. MLRA

With respect to the MLRA applied to the results of all the trials (A1-A10), a full statistical analysis was performed for the studied responses. Among all the responses, two CQAs were the most relevant and significant and are discussed below: FLT and Swell120.

3.3.1. FLT modeling and contour plots

When considering FLT as response, proportions of copovidone, alginate and HPMC showed statistical significance ($p < 0.001$). Due to non-linearity, the alginate proportion is considered as quadratic term also, providing a significant goodness of fit with $R^2 = 95.04\%$. See [supplementary material S1 \(Figure S1.1\)](#), for the graph and details of the statistical analysis.

The resulting equation (Eq. (1)) for FLT is the following:

$$\begin{aligned} \text{FLT}(\text{sec}) = & 926 - 158 * \% \text{COPOV} - 42.2 * \% \text{HPMC} + 62.5 * \% \text{ALGINATE} \\ & - 4.89 * (\% \text{ALGINATE})^2 + 7.67 * \% \text{HPMC} * \% \text{COPOV} \end{aligned} \quad (1)$$

Contour diagrams for FLT ([Fig. 3](#)) show optimal response (lower FLT) when %Alginate decreases and %HPMC increases within the studied range, keeping %Copovidone as minor contributor. There is interaction between the CMAs %Copovidone and %HPMC, and non-linearity linked to the amount of alginate. (See [supplementary material S1 \(Figure S1.2\)](#). Both are included in the final model, interaction and quadratic term showing the best goodness of fit and high significant value ($p < 0.001$).

3.3.2. Swell120 modeling and contour plot

When considering Swell120 as response, proportions of copovidone

and HPMC showed statistical significance ($p < 0.001$), providing a significant goodness of fit with $R^2 = 72.5\%$. (See [supplementary material S1 \(Figure S1.3\)](#)).

There is interaction between the CMAs copovidone and HPMC, and non-linearity linked to the amount of HPMC. (See [supplementary material S1 \(Figure S1.4\)](#). Both are included in the final model, interaction and quadratic term, showing the best goodness of fit and high significant value ($p < 0.001$).

The resulting equation (Eq. (2)) for Swell120 is the following:

$$\begin{aligned} \text{Swell120}(\text{min}) = & 417 - 51.2 * \% \text{COPOV} - 24.88 * \% \text{HPMC} \\ & + 0.344 * (\% \text{HPMC})^2 + 2.41 * \% \text{COPOV} * \% \text{HPMC} \end{aligned} \quad (2)$$

The contour plot with Swell120 as response vs the proportions of copovidone and HPMC shows optimal conditions (area striped in [Fig. 4](#)) at different combinations of copovidone and HPMC.

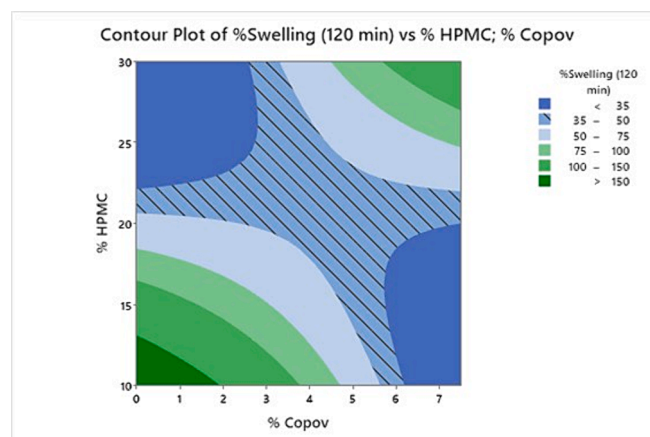


Fig. 4. Contour plot of Swell120 (%) versus %HPMC and %copovidone. The striped area represents the space to achieve a desirable 35–50 % of matrix swelling.

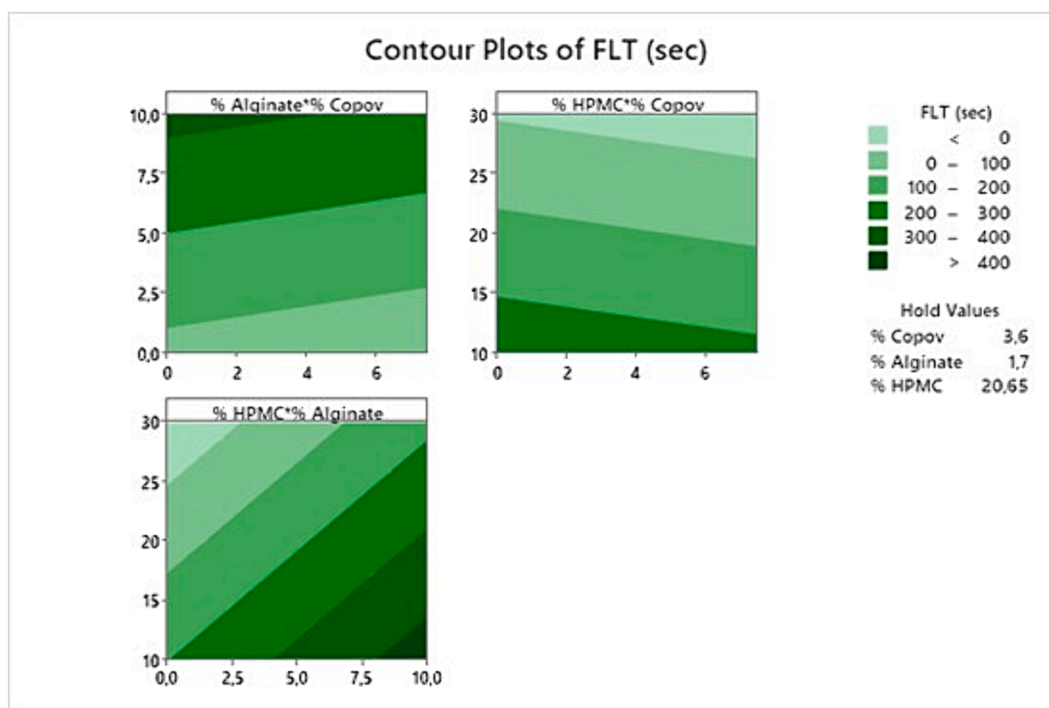


Fig. 3. Contour plot of FLT (sec) for the 3 significant parameters of the model. The light green area represents the space to achieve an appropriately low FLT. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In summary, results were indicative of a successful granulation process, even more considering that not directly compressible fillers and floating matrix formers capable of impairing moisture function were present over 70% w/w in all of the experimental runs. PCA trends evidenced the influence of the formulation factors on granulate attributes and tablet CQAs, which the MLRA could confirmed, and thus conducted the selections of excipients and their concentrations in the final product: hydroxypropyl methylcellulose was chosen over sodium alginate as hydrogelling agent, povidone K15 (present in at least 5%) was selected as one of the binders and finally, regular copovidone (present in 4.5–5.0%) was chosen over its finer grade as the other binder.

3.4. Final product

Graphical optimization was carried out by analysis of contour plots in pursuit of a design space (Fig. 5). As it is shown in Fig. 5, the optimal zones (for minimum FLT and Swell120 over 35%) overlap in the region marked with crossed lines. In summary, a space which could achieve for the entire experimental domain to get these two CQAs of floating tablets (FLT and Swell120) jointly within the specification limits emerged. As presented in the QTPP, quality targets aimed to achieve FLT under 4 min and sufficiently high percentage of tablet swelling which could provide tablet diameters over 14 mm after 60 min. Therefore, the identified region was delimited by FLT under 100 s and Swell120 over 35% which translate in tablet diameters of not less than 16 mm. The optimal interval to obtain the tablets complying with the QTPP is in the central area of the graph. And the two factors are dependent. The identified region restricted the desirable ranges of the factors as follows: if concentration of copovidone is less than 5% or greater than 6%, the percentage of HPMC should be over 22%. While if a concentration of copovidone between 5–6% is used, the percentage of HPMC can be decreased up to approximately 17%. Regarding the third factor, alginate should not be included or should be present only in a minor percentage.

Assays A6 and A9 presented the best attributes in the screening, showing suitable swelling and flowability, low FLT, as well as acceptable diameters of swollen tablets at 60 min. Based on their compositions and previously discussed PCA trends and linear regression models, a new assay (A11) was formulated and evaluated. A11 formulation is as follows: hydroxypropyl methylcellulose (18.00%), povidone K15 (5.00%), copovidone (5.00%), water (4.00%), lactose (56.10%), sodium bicarbonate (10.00%), colorant (0.15%), amorphous silica (1.00%) and magnesium stearate (0.75%). The decision to slightly reduce hydrogelling agent content from 20 to 18% aimed to formulate a tablet matrix

with the lowest possible percentage of absorbent agent to ease MADG processability, without risking the good floating and swelling attributes that the relatively high HPMC concentration assayed in the knowledge space had provided.

The results of the full characterization of the A11 (granulate and tablet) are shown in Table 5 a & b. Results shown in Table 6 confirm the validity of the generated mathematical models for FLT and Swell120 response prediction.

The results of the complete SeDeM diagram on the A11 granulate manufactured at a 1000 g scale in the MAV-10 high shear mixer are shown and discussed in the supplementary material S2. According to the results of the radii of the SeDeM diagram, the parametric profile is >5, which would imply that the characteristics of the studied product are acceptable enough to be directly compressed; in other words, the granulate obtained by MADG is a suitable product for compression. In this regard, attention should be drawn to the very good average of 6.87 obtained for the Dimension incidence factor derived from high bulk and tapped density, and to the even better average of 7.41 for Flowability/Powder flow incidence factor, since the good rheological characteristics will favor the compression process, achieving weight uniformity and homogeneous hardness of the tablets.

In order to compare the optimized formulation (A11) manufactured at different scales and mixers, the granulate A11 was characterized based on a reduced SeDeM expert system, which is reported in Table 7 and both reduced SeDeM diagrams were plotted in Fig. 6.

Two granulates with a similar SeDeM diagram reduced to the 8 parameters tested were obtained using different shear mixers (Philips and MAV-10), which demonstrated the robustness of the moisture activated dry granulation technology for processing the proposed formulation. Indeed, in both cases equivalent acceptance or qualification rates are obtained: parametric index of 0.50 (Philips) and 0.38 (MAV-10), parametric profile of 4.92 (Philips) and 5.04 (MAV) and good compression index of 4.43 (Philips) and 4.54 (MAV). According to the results of the radii of the SeDeM Diagram, the parametric profile is near to 5 in both cases, as well as the good compression index is close to 5, even with several SeDeM's parameters not included in the reduced model with only 8 parameters.

At first glance, certain characteristics of the granulate might not seem to meet the required acceptability criteria for compression, regardless of whether it is produced using Philips equipment or MAV equipment. However, previous studies conducted by Nofrerias et al. [37], Canadell-Heredia et al. [38] and Aguilar JE et al [39] demonstrated that appropriate tablets could still be achieved with lower Index of Good Compressibility (IGC) values, ranging between 3.5 and 4. As such, it is crucial not to dismiss the formulation outright and further explore its potential.

Thus, it is necessary to analyze the groups of individual factors classified by the type of incident considered to assess the real equivalence between both types of manufacturing technologies.

For the incidence factor relative to Dimensions (this factor affects the size and capacity to pile up), there is a mean of 4.83 for Philips and a mean of 6.87 for MAV. In both cases, high densities are obtained for both the bulk and tapped densities. A granulate high-density favors obtaining smaller tablets. However, the density obtained using Philips technology is 30% less than MAV technology, probably due to the greater granulation capacity of the latter (high shear mixer).

The Compressibility incidence factor evaluated with only two parameters, the inter-particle porosity and the Carr Index, presents a mean of 4.19 for Philips and a mean of 2.37 for MAV. There is a significant difference, since both parameters are calculated from the values of the bulk and tapped densities, which are different. For the product obtained with the Philips technology there is a medium density while for the product obtained with the MAV technology a high density is obtained.

The Flowability/Powder flow incidence factor is good in both cases, obtaining an average of 5.53 for Philips and an average of 6.96 for MAV, considering that only two parameters are evaluated: Hausner index and

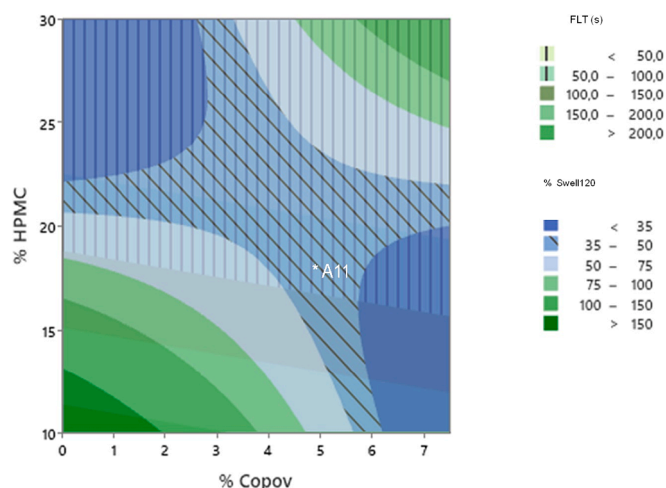


Fig. 5. Superimposed contour plots to delimit the formulation design space. The hold value assigned for % Alginate was 0 for the statistical study. Optimized formula A11 is drawn in the graph.

Table 5
Result data of mean values for the optimized formula (A11). (a) Attributes of granulate. (b) Attributes of tablets.

a)Attributes of granulate.											
Mean size (µm)	10 th percentile (µm)	50 th percentile (µm)	90 th percentile (µm)	Span	Moisture content (%)	Apparent density (g/mL)	Tapped density (g/mL)	Carr index (%)	Hausner ratio	Angle of repose (°)	
292.6	78.3	219.5	672.0	2.7	4.8	0.42	0.54	21	1.27	38	
b)Attributes of tablets.											
RSD weight (%)	Tensile strength (MPa)		Friability (%)	Swelling at 60 min (%)		Swelling at 120 min (%)		Diameter at 60 min (mm)		FLT (sec)	FD (min)
0.7	1.5		0.2	23.94		35.57		14		66	>240

angle of repose. The granules have good rheological characteristics, which will favor the compression process by making it possible to fill the matrix on a regular basis, thereby achieving a correct weight uniformity and homogeneous hardness of the tablets. The granules obtained using MAV technology have better flowability/powder flow characteristics, which can be correlated with the higher density that high shear mixer technology provides to the granules. The Lubricity/Stability incidence factor (which affects lubricity and future stability of the tablet) is only evaluated by a single test: loss on drying. In this case, while in the Philips batch there is a moderate loss on drying of 4.81%, in the case of the MAV batch 5.39% is obtained, which translated into radii in the SeDeM diagram is equivalent to 5.19 in the first case and 4.61 in the second case. Both results are within the specifications established for the granulate and can be considered equivalent.

The Lubricity /Dosage incidence factor presents a value of 5.10 for Philips and 3.35 for MAV. This difference is due to the presence of a percentage of around 20% of fine particles in the granulates obtained in MAV due to the technology used, which generates a greater amount of fine dust. Despite this, the proposed process gives rise to granulates with sufficiently good characteristics relative to granule size and homogeneity to allow correct compression thereof.

Finally, it can be visually observed that the two diagrams obtained are equivalent (Fig. 6), and it can be concluded that MADG process generated a granulate that could be subjected to a compression process without the addition of excipients to the final blend (except for the lubricant magnesium stearate, to produce appropriate tablets).

4. Conclusions

Floating tablets with appropriate physical attributes were obtained by MADG aided by SeDeM Diagram. The results agreed with the initial assumption about the criticality of the total amount of excipients with great water absorption capacity present in the formula, since the presence of water is limited in the MADG process. Nevertheless, tablets showing good floating capabilities (short floating lag time <2 min and which floated for >4 h), as well as good swelling characteristics could be produced by modulating the CMAs (type and concentration of floating matrix formers and of binders) in formulation design and by using a granulating process designed to partly employ the floating matrix formers as absorbents in the moisture distribution step. Moreover, SeDeM Diagram probed the suitability of these granulate formulations for compression.

Future research should explore the addition of active ingredients belonging to BCS class I or III to study drug release from these delivery systems. However, the results obtained so far are promising enough to consider MADG as an advantageous granulation method to obtain gastroretentive tablets or even other controlled delivery systems requiring a relatively high content of absorbent materials and medium to high content of soluble API in their composition.

5. Funding

This work was supported by the Agència de Gestió d'Ajuts Universitaris I de Recerca (AGAUR) [2021SGR01068] .

CRedit authorship contribution statement

María Ximena Origoni: Writing – original draft, Methodology, Investigation, Formal analysis. **Anna Nardi-Ricart:** Validation, Investigation. **Marc Suñé-Pou:** Validation, Investigation. **Pilar Pérez-Lozano:** Writing – review & editing, Validation. **Miquel Romero-Obón:** Formal analysis, Data curation. **Josep Maria Suñé- Negre:** Writing – review & editing, Resources, Conceptualization. **Ana Teresa Ochoa-Andrade:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Encarna García- Montoya:** Writing – review & editing, Writing – original draft, Methodology,

Table 6
Formulation settings and observed and predicted values of responses used in A11 analysis.

HPMC (%)	Copovidone (%)	Alginate (%)	Response	Observed	Predicted	Residual*
18	5	0	FLT (sec)	66	67	1
			Swell120 (%)	35.6	40.2	4.6

* Residual: |Observed value – Predicted value|.

Table 7
Result data of reduced SeDeM for the optimized formula (A11). (1000 g batch in MAV mixer and 300 g batch in PHILLIPS).

INCIDENCE	Parameter	acronym	units	r Philips	r MAV	incidence mean Phillips	incidence mean MAV
Dimensions	Bulk density	Da	g/ml	4,25	6,34	4,83	6,87
	Tapped density	Dc	g/ml	5,4	7,40		
Compressibility	Inter-particle porosity	Ie	–	4,18	1,88	4,19	2,37
	Carr Index	IC	%	4,2	2,86		
Flowability / Powder flow	Hausner Index	IH	–	8,65	9,17	5,53	6,96
	Angle of repose	(α)	°	2,4	4,74		
Lubricity /Stability	Loss on Drying	%HR	%	5,19	4,61	5,19	4,61
Lubrify / Dosage	Homogeneity index	(I0)		5,1	3,35	5,10	3,35
				Phillips (300 g)		MAV (1000 g)	
PARAMETRIC INDEX				0,50		0,38	
IPP PARAMETRIC PROFILE (mean of the radius)				4,92		5,04	
GOOD COMPRESSION INDEX (IGC)				4,43		4,54	

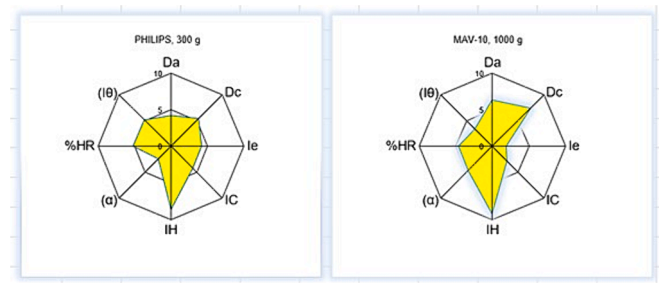


Fig. 6. Comparison of reduced SeDeM diagram of the optimized formula (A11) manufactured at different scales. Index of Good Compression (IGC) for Phillips = 3.12 and IGC for MAV-10 = 3.20.

Formal analysis.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpb.2024.114456>.

References

[1] S. Shanmugam, Granulation techniques and technologies: recent progresses, *Bioimpacts*. 5 (1) (2015) 55–63, <https://doi.org/10.15171/bj.2015.04>.
[2] A.M. Railkar, J.B. Schwartz, Use of a moisture granulation technique (MGT) to develop controlled-release dosage forms of acetaminophen, *Drug Dev. Ind. Pharm.* 27 (4) (2001) 337–343, <https://doi.org/10.1081/DDC-100103733>.
[3] I. Ullah, J. Wang, Moisture-activated dry granulation, *Pharm. Tech. Eur.* 23 (2011) 4–5.

[4] A.M. Railkar, J.B. Schwartz, The effects of formulation factors on the moist granulation technique for controlled-release tablets, *Drug Dev. Ind. Pharm.* 27 (9) (2001) 893–898, <https://doi.org/10.1081/DDC-100107669>.
[5] A.R.M. Bayomi, M.A. Al-Suwayeh, S.A. El-Helw, Excipient-excipient interaction in the design of sustained-release theophylline tablets: in vitro and in vivo evaluation, *Drug Dev. Ind. Pharm.* 27 (6) (2001) 499–506, <https://doi.org/10.1081/DDC-100105174>.
[6] A. Ochoa-Andrade, M. Fierro, M. Bauzán, M.X. Origoni, V. Trezza, Polysaccharide absorbents in moisture activated dry granulation, *SF J. Pharm. Anal. Chem.* 1 (2018) article 1010.
[7] G.J. Wiley, J. Wang, S. Kiang, I. Ullah, N.B. Jain, S.Y. Chang, Moisture-activated dry granulation - part I: a guide to excipient and equipment selection and formulation development, *Pharm. Technol.* 33 (2009) 62–70.
[8] I. Ullah, J. Wang, S.Y. Chang, H. Guo, S. Kiang, N.B. Jain, Moisture-activated dry granulation part II: the effects of formulation ingredients and manufacturing-process variables on granulation quality attributes, *Pharm. Technol.* 33 (2009) 42–51.
[9] B. Venkateswara Reddy, K. Navaneetha, K. Venkata Ramana Reddy, Process development and optimization for moisture activated dry granulation method for losartan potassium tablets, *Int. J. Pharmacy Pharm. Sci.* 6 (2014) 312–317.
[10] L. Hu, L. Li, X. Yang, W. Liu, J. Yang, Y. Jia, C. Shang, H. Xu, Floating matrix dosage form for dextromethorphan hydrobromide based on gas forming technique: in vitro and in vivo evaluation in healthy volunteers, *Eur. J. Pharm. Sci.* 42 (1–2) (2011) 99–105, <https://doi.org/10.1016/j.ejps.2010.10.010>.
[11] Y.C. Chen, H.O. Ho, T.Y. Lee, M.T. Sheu, Physical characterizations and sustained release profiling of gastroretentive drug delivery systems with improved floating and swelling capabilities, *Int. J. Pharm.* 441 (1–2) (2013) 162–169, <https://doi.org/10.1016/j.jipharm.2012.12.002>.
[12] P. Dorożyński, P. Kulinowski, A. Mendyk, R. Jachowicz, Gastroretentive drug delivery systems with L-dopa based on carrageenans and hydroxypropylmethylcellulose, *Int. J. Pharm.* 404 (1–2) (2011) 169–175, <https://doi.org/10.1016/j.jipharm.2010.11.032>.
[13] C.M. Lopes, C. Bettencourt, A. Rossi, F. Buttini, P. Barata, Overview on gastroretentive drug delivery systems for improving drug bioavailability, *Int. J. Pharm.* 510 (1) (2016) 144–158, <https://doi.org/10.1016/j.jipharm.2016.05.016>.
[14] L. Whitehead, J.T. Fell, J.H. Collett, J.L. Sharma, A. Smith, Floating dosage forms: an in vivo study demonstrating prolonged gastric retention, *J. Control. Release*. 55 (1) (1998) 3–12.
[15] Villca Pozo, F., Roig Carreras, M., Lucas Gómez, E., Pérez Lozano, P., García Montoya, E., Miñarro Carmona, M., Tico Grau, J.R., Suñé Negre, J.M. Formulation of matrix pellets by extrusion-spheronization and characterization using the SeDeM Diagram. 11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology (Poster Communication). Granada (Spain), 19–22 March 2018.
[16] J.E. Aguilar-Díaz, E. García-Montoya, P. Pérez-Lozano, J.M. Suñe-Negre, M. Miñarro, J.R. Tico, The use of the SeDeM diagram expert system to determine the suitability of diluents-disintegrants for direct compression and their use in formulation of ODT, *Eur J Pharm iopharm.* 73 (3) (2009) 414–423, <https://doi.org/10.1016/j.ejpb.2009.07.001>.
[17] J.E. Aguilar-Díaz, E. García-Montoya, J.M. Suñe-Negre, P. Pérez-Lozano, M. Miñarro, J.R. Tico, Predicting orally disintegrating tablets formulations of ibuprofen tablets: an application of the new SeDeM-ODT expert system, *Eur J Pharm Biopharm.* 80 (3) (2012) 638–648, <https://doi.org/10.1016/j.ejpb.2011.12.012>.

- [18] J. Aguilar-Díaz, E. García-Montoya, P. Pérez-Lozano, J. Suñé-Negre, M. Miñarro, J. Ticó, SeDeM expert system a new innovator tool to develop pharmaceutical forms, *Drug Dev. Ind. Pharm.* 40 (2) (2014) 222–236, <https://doi.org/10.3109/03639045.2012.756007>.
- [19] P. Pérez, J.M. Suñé-Negre, M. Miñarro, M. Roig, R. Fuster, E. García-Montoya, C. Hernández, R. Ruhí, J.R. Ticó, A new expert system (SeDeM diagram) for control batch powder formulation and preformulation drug products, *Eur J Pharm Biopharm.* 64 (3) (2006) 351–359, <https://doi.org/10.1016/j.ejpb.2006.06.008>.
- [20] J.M. Suñé-Negre, P. Pérez-Lozano, M. Miñarro, M. Roig, R. Fuster, C. Hernández, R. Ruhí, E. García-Montoya, J. Ticó, Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation, *Eur. J. Pharm. Biopharm.* 69 (3) (2008) 1029–1039, <https://doi.org/10.1016/j.ejpb.2008.01.020>.
- [21] J.M. Suñé-Negre, P. Pérez-Lozano, M. Roig, R. Fuster, C. Hernández, R. Ruhí, E. García-Montoya, M. Miñarro, J.R. Ticó, Optimization of parameters of the SeDeM diagram expert system: hausner index (IH) and relative humidity (%RH), *Eur J Pharm Biopharm.* 79 (2) (2011) 464–472, <https://doi.org/10.1016/j.ejpb.2011.04.002>.
- [22] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Pharmaceutical Development: Q8 (R2), 2009. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf.
- [23] H. Takasaki, E. Yonemochi, R. Messerschmid, M. Ito, K. Wada, K. Terada, Importance of excipient wettability on tablet characteristics prepared by moisture activated dry granulation (MADG), *Int. J. Pharm.* 456 (1) (2013) 58–64.
- [24] I. Ilić, P. Kása, R. Dreu, K. Pintye-Hódi, S. Srčić, The compressibility and compactability of different types of lactose, *Drug Dev. Ind. Pharm.* 35 (10) (2009) 1271–1280, <https://doi.org/10.1080/03639040902932945>.
- [25] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Biopharmaceutics classification system-based biowaivers: M9, 2019. M9.Guideline.Step4.2019.1116.pdf (ich.org).
- [26] J. Bergum, L. Pfahler, E. Senderak, K.E. Vukovinsky, S. Sethuraman, S. Altan, Statistical considerations in design space development (Part I of III), *Pharm. Technol.* 34 (2010) 66–70.
- [27] P. Benjasirimongkol, S. Piriyaprasath, K. Moribe, P. Srimornsak, Use of risk assessment and plackett-burman design for developing resveratrol spray-dried emulsions: a quality-by-design approach, *AAPS PharmSciTech* 20 (1) (2019) 14, <https://doi.org/10.1208/s12249-018-1220-z>.
- [28] K.G. Pitt, M.G. Heasley, Determination of the tensile strength of elongated tablets, *Powder Technol.* 238 (2013) 169–175, <https://doi.org/10.1016/j.powtec.2011.12.060>.
- [29] Atishkumar S. Mundada, Design and development of sustained release floating beads of metronidazole using natural polymer, *SF Drug Del Res J* 1 (2017) article1.
- [30] M. Ibrahim, H.A. Sarhan, Y.W. Naguib, H. Abdelkader, Design, characterization and in vivo evaluation of modified release baclofen floating coated beads, *Int. J. Pharm.* 582 (2020) 119344, <https://doi.org/10.1016/j.ijpharm.2020.119344>.
- [31] R. Diós, S. Nagy, S. Pál, T. Pernecker, B. Kocsis, F. Budán, I. Horváth, K. Szigeti, K. Bölcskei, D. Máthé, A. Dévay, Preformulation studies and optimization of sodium alginate based floating drug delivery system for eradication of *Helicobacter pylori*, *Eur. J. Pharm. Biopharm.* 96 (2015) 196–206, <https://doi.org/10.1016/j.ejpb.2015.07.020>.
- [32] J. Bergum, L. Pfahler, E. Senderak, K.E. Vukovinsky, S. Sethuraman, S. Altan, Statistical considerations in design space development (Part II of III), *Pharm. Technol.* 34 (2010) 52–60.
- [33] R Core Team, 2021. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <http://www.r-project.org/>. (accessed 2023 Nov 24th).
- [34] S. Lê, J. Josse, F. Husson, FactoMineR: an R package for multivariate analysis, *J. Stat. Softw.* 25 (2008) 1–18, <https://doi.org/10.1016/j.envint.2008.06.007>.
- [35] United States Pharmacopeial Convention, [1174] Powder Flow, in: U.S. Pharmacopoeia-National Form. [USP 40 NF 35], Rockville, 2017: pp. 1602–1606.
- [36] R.S. Chaudhary, C. Patel, V. Sevak, M. Chan, Effect of Kollidon VA®64 particle size and morphology as directly compressible excipient on tablet compression properties, *Drug Dev. Ind. Pharm.* 44 (1) (2018) 19–29, <https://doi.org/10.1080/03639045.2017.1371735>.
- [37] I. Nofreñas, A. Nardi, M. Suñé-Pou, J. Boeckmans, J. Suñé-Negre, E. García-Montoya, P. Pérez-Lozano, J.R. Ticó-Grau, M. Miñarro-Carmona, Optimization of the cohesion index in the SeDeM diagram expert system and application of SeDeM diagram: an improved methodology to determine the cohesion index, *PLoS One* 13 (9) (2018) e0203846.
- [38] R. Canadell-Heredia, M. Suñé-Pou, A. Nardi-Ricart, P. Pérez-Lozano, J.M. Suñé-Negre, E. García-Montoya, Formulation and development of paediatric orally disintegrating carbamazepine tablets, *Saudi Pharm J. Now* 30 (11) (2022) 1612–1622.
- [39] Aguilar, J.E. (editor). *Formulation Tools for Pharmaceutical Development*. Woodhead Publishing Series in Biomedicine. Oxford. 2013. ISBN: 978-1907568992.