https://doi.org/10.31925/farmacia.2022.6.13 **ORIGINAL ARTICLE**

EVALUATION OF THE GRANULOMETRY IMPACT OF THE COMPRESSION MIXTURE IN THE FORMULATION DEVELOPMENT OF TABLETS

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Abstract

The aim of this research was the preformulation and preliminary formulation studies of oral gastro-resistant tablets containing 500 mg mesalazine. Increased compliance of the patients, superior chemical stability and modified release modulation, enhanced by the local effect on the mucosa were elected as arguments for choosing this type of formulation. The impact and dependence relationship between the sizes of the obtained granules were evaluated through technical parameters, together with dissolution studies. Wet granulation of mesalazine and starch showed that the third formulation (F3) generates the highest amount (64.19%) of granules in the range 1000 - 300 μm. Oblong tablets (pilot batches) were obtained and the cores were coated with an enteric acrylic agent. The results of the dissolution studies for the F2.2 formulation demonstrate the importance and the impact of the pre-compression phase on the dissolution process of the active substance.

Rezumat

Lucrarea de față s-a concentrat pe studiul de preformulare și formulare preliminară a comprimatelor gastrorezistente orale care conțin 500 mg mesalazină. Ca argumente pentru alegerea acestui tip de formulare au fost alese complianța crescută a pacienților, stabilitatea chimică superioară și modularea eliberării modificate, augmentate de efectul local asupra mucoasei. Impactul și dependența dintre dimensiunile granulelor obținute au fost evaluate prin parametri tehnici, împreună cu studii de dizolvare. Granularea umedă a mesalazinei și amidonului a arătat că a treia formulare (F3) generează cea mai mare cantitate (64,19%) de granule în intervalul 1000 - 300 μm. S-au obținut tablete alungite (loturi pilot), iar nucleele au fost acoperite cu un agent acrilic enteric. Rezultatele studiilor de dizolvare pentru formularea F2.2 demonstrează importanța și impactul fazei de precomprimare asupra procesului de dizolvare a substanței active.

Keywords: pharmaceutical development, particle size distribution, compression process, mesalazine, granules

Introduction

There is a constant requirement in understanding the functional properties of the raw material used in the pharmaceutical development, thus including their manufacturability, together with the necessity of developing analysis methods for such properties [5]. Since the tablet is the dominating dosage form, the tabletting behaviour, such as the ability of particulate solids into tablets, is an important manufacturing property of drugs in particulate form. To any formulation scientist, a way to control materials critical properties for their readiness is mandatory.

In the light of the particle engineering, tablet structure and strength are discussed in terms of a relationship between the properties of the particulate material and the properties of the formed tablet. The powder controlling properties, related to the fracture toughness and the tensile strength of the tablets, are the compression mechanics of the particles and their dimensions. In addition, the structure and strength of a tablet may change after its formation, both from a short-term and a long-term perspective [1, 21].

The granulometry of the compression mixture greatly influences the technological process of compression by reducing the compression speed (with an impact on productivity) and the need to use equipment with special technical equipment such as the specially designed pre-compression stage of punches and molds, respectively the quality of the finished product. The existence of a mixture of granules and powders greatly affects the appearance of the pharmaceutical form by the appearance of tablets with broken edges, broken or exfoliated tablets and difficulties in coating with film agent [12, 14].

The granulation of one or more substances used in oral solid dosage forms represents a process of improving or solving some problems such as lack of free flow, masking of specific properties (unpleasant taste) or

limiting the interaction with other substances in the mixture for various reasons (inactivation, modification of properties). The application of the granulation step for certain ingredients in the mixture of a solid dosage forms requires a thorough study, because many technical problems may appear in the following stages of the technological flow such as separating the granules from the mixture in the homogenization step with other powdery substances as a result of the different density and diameter of the granules [7].

The separation in this step leads to the appearance of unsubstantied dosage forms with large variations in the number of active substances and failure to meet the criterion of uniformity of the content. Thus, the separation of the granules from the mixture, in the compression step, is a result of the vibrations of the compression equipment or the technological type of feeding (for example the feeding by suction force of the compression mixture) [8]. The most problems appear in the compression phase, and their solutions are difficult and require documentation of the impact on the quality of the finished product, as the validated technological processes have a significant impact on the critical process parameters (compression force and compression speed) and are requiring the revalidation of the process as well [4, 11, 14, 15]. Therefore, the diameter of the granules must be carefully selected following technological studies and adequately documented in order to prevent further technological problems, especially in the current production phase with the aim of marketing the product [4, 9, 11].

The current study aimed to evaluate the impact and the dependence relationship between the size of the granules in the compression mixture and the hardness of the tablet, height, friability, diameter and aspect, respectively the technological variations of the technical parameters, together with dissolution studies [15].

Materials and Methods

The raw materials used in the present study were: micronized mesalazine – MSZ (API, Minapharm Pharmaceuticals, Egypt), and excipients: Starch 1500 (pregelatinized corn starch – Colorcon Hungary), Kollidon 30 (polyvinylpyrrolidone – BASF Germany), Vivapur 102 (microcrystalline cellulose, JTS Pharma – Germany), Ac-di-Sol (croscarmellose Sodium, Dupont – France), Aerosil 200 (anhydrous colloidal silicon dioxide, Evonik Industries AG – USA), Tabletosse 80 (lactose monohydrate, 80 mesh, Meggle – Germany), Talcum (Luzenac Inc. – USA) and Magnesium stearate (Mosselman S.A. – Belgium). All the components were of pharmaceutical grade and complied with the relevant monographs of the European Pharmacopoeia, 9th edition [23]. Also purified water [23] was used in the process.

For the manufacturing steps, the following equipment was used: laboratory batches weighing (Mettler Toledo scale with 2 decimals,); compression machine with eccentric, mono-punch, high speed granulator Micromix Huettlin with 2.5 L vessel, Microlab Huttlin Bosch Germany fluidized bed drying equipment, granulometry analytic-sieve-machine (Retsch AS200 GmbH & Co., Haan, Germany) or a sieve machine with 3 mm square mesh or 1 mm round mesh Frewitt Coniwitt Switzerland (for 4 minutes, interval 10 seconds, amplitude 1.00 m/g, tested quantity 100.00 g), mill system for calibration Erweka AR403 Germany, homogenizer Servolift USA with a 20 L bin. After the completion of the wet granulation step, the granule was calibrated using a granulometry analytic-sieve-machine (Retsch AS200 GmbH & Co., Haan, Germany) or a sieve machine with 3 mm square mesh or 1 mm round mesh Frewitt Coniwitt. The final moisture content of the granule was determined on a 5 g sample at 105ºC using a thermobalance. For the second and the third formulation, the drying process was performed through a Microlab Germany fluidized bed drying equipment. The dried granule was calibrated using 1 mm square mesh sieve.

The in-process and at the end control was performed using the following laboratory equipment: Thermo-scale Mettler Toledo Switzerland Halogen Moisture Analyzer HR73 to determine the degree of drying of the granule (test parameters: 105°C, amount sample: 5 g granules), Erweka Germany TAR Friability Tester (Friability/Abrasion Tester) (test parameters: 10 cores, speed 100 revolutions in 3 minutes [22]), hardness, diameter and height tester – Erweka Germany TBH 210.

Tablet formulation

The qualitative and quantitative compositions of the tested formulas are depicted in Table I. Batches of mesalazine were prepared by manual and automatic wet granulation method. The accurate weighed API was put into the high-speed granulating apparatus Micromix (F2) and Pilotmix (F3), and the previously binder solution was slowly added, until a uniform granule was formed. The wet granulation step for formulation F1 was done manually (the binder was added in small portions under manual mixing). The homogenization of binder was performed using an IKA blender. After the completion of the wet granulation step, the granule was calibrated using a 2 mm or 3 mm square mesh sieve, and the drying process was carried out slowly in open air for 24 hours (the granules were arranged in a thin layer), for the first formulation manufacturing process (F1). A slightly modification was performed for the drying process of the second (F2) and third formulation (F3), by resorting to a bed-fluid dryer at laboratory or pilot scale. The technological parameters are presented in Table II. The final moisture content of the granule was determined on a 5 g sample at 105°C using a thermobalance. The dried granule was calibrated using 1 mm square mesh sieve.

Table I

Qualitative and quantitative details for tested formulas

Raw material	Formulation code		
	F1	F2	F3
	mg/tablet		
Mesalazine	500.00	500.00	500.00
Starch 1500	37.50	-	7.50
Kollidon 30	20.65	22.50	22.50
Ac-di-Sol	22.50	-	-
Vivapur 102	154.35	-	-
Aerosil 200	7.50	7.50	7.50
Magnesium stearate	7.50	7.50	7.50
Tabletosse 80	-	197.50	190.00
Talcum	-	15.00	15.00
Purified water	*q.s.*		
Total amount for tablets (mg)	750.00		

Table II

Technological parameters for the bed-fluid drying step

Parameter	Value		
	F2.1	F2.2	F3
Heat			
In air flow (m^3/h)	40	80	150
In air temperature (ºC)	65	60	60
Dryer load			
In air flow (m^3/h)	48	250 - 450	150 - 450
In air temperature (ºC)	60		
Drying			
In air flow (m^3/h)	25 - 40	300 - 450	100 - 450
In air temperature (ºC)	50 - 60	52-60	
Filter shake interval (s)	60	40	

Subsequently, Aerosil 200 was uncluttered by passing it in a mixture with a part of Vivapur 102 (for F1) and a part of Tabletosse 80, respectively (for F2 and F3) through a 1 mm square mesh sieve. The sorted granules, the rest of Vivapur 102, Starch 1500 and Ac-di-Sol are added on the top of the previously formed mixture. All components are homogenized until a visible homogenous mixture is obtained. Slightly modifications are required for the last two formulation, in this manufacturing step, respectively the calibrated granules among with Aerosil 200 and a part of the Tabletosse 80, the rest of the Tabletosse 80, Starch 1500 and talcum were homogenized. All components of F1 are manually homogenized until a visibly homogeneous mixture is obtained. At the end, we added the magnesium stearate and homogenized for 1 - 1.5 minutes. For F2 and F3 the blending step was performed using a Servolift blending bin.

The granule obtained with F1 was sorted into 3 size fractions defined in Table IV. Each granular fraction was embedded in a compression mixture to highlight the technical aspects of the compression step. It is to mention that slightly different manufacturing steps were performed for the second formulation, by using a compression equipment set with a pre-compression stage, that allowed an arrangement of the components and a good elimination of the air between the particles of the mixture. The compression machine was equipped with flat 12 mm diameter punches, but also featured multiple technological variations regarding the press mechanism.

All compression blends for F1 and F2.1 were performed and run under similar conditions and the compression step was performed on the same machine, Riva Minipress MII. For F2.2 and F3 formulation the compression step was done using Fette 102i compacting machine. In Table III, the information related to the compression stage is reproduced.

Table III

Compression stage technological parameters

Technological parameters	F1.1	F1.2	F1.3	F2.1	F2.2	F3
Compression force (kN)	12.50	12.50	14.00	11.00	20.30	19.70 - 20.30
Punches type (mm)	12 biconvex				12 flat	
Pre-compression stage	No				Yes	
Compression speed (tablet/ min)	40	40	40	40	20,000	23,000

Particle size distribution

The determination was made using a system of over-lapping/alpine sieves mounted in descending order of mesh size on a Retsch AS200 apparatus. The sieves used are with wire mesh with a diameter of: 1 mm, 0.8 mm, 0.4 mm, 0.2 mm and 0.05 mm. Determination of the particle size distribution was performed with the Retsch AS200 device with the following test conditions: time 4 minutes, interval 10 seconds, amplitude 1.00 m/g, tested quantity 100.00 g. For the first formulation, the dry and calibrated granules were subjected to a granule sorting stage using a system composed of 4 alpine sieves (for 5 minutes) with the diameter described in Table IV.

Table IV

Sorted granule size for formulation tests (for F1)

Formulation code	**F1.1**	**F1.2**	**F1.3**
Granule size	< 0.9 mm and > 0.71	< 0.71 mm and > 0.5	< 0.5 mm and > 0.2

Dissolution test

For the dissolution of mesalazine from the obtained finished products as a result of the development study of the intended generic product - modified release tablets with mesalazine, a UV-Vis method was adopted from the USP, Mesalamine Extended-Release Capsules monograph [24]. The experimental conditions for the dissolution test (operational parameters) are shown in Table V.

Table V

Dissolution test parameters

Apparatus	USP 2 (paddles)
Rotations number	100 rpm
Dissolution medium	pH = 7.5 buffer
Average dissolution volume	900 mL
Dissolution medium temperature	37 ± 0.5°C
Period	Maximum 12 hours

For the test solution, after the expiration of the dissolution time, 5 mL of sample solution from each dissolution vessel were withdrawn and filtered. 0.5 mL of this solution were added to a 10 mL volumetric flask with dissolution medium. The absorbance of the reference solution and the sample solutions were measured in a 1 cm cuvette at a wavelength of 330 nm with a suitable spectrophotometer, using the dissolution medium as a blank.

Results and Discussion

In order to obtain gastro-resistant tablets containing 500 mg MSZ, several excipients were selected. The compatibility of the API with these excipients was tested using DSC and the results were presented in a previous research [3]. No interactions were revealed between mesalazine and Vivapur 102, magnesium stearate, Aerosil 200, Kollidon 30, talc and lactose. In this regard, formulations containing MSZ, starch, croscarmellose sodium, magnesium stearate, colloidal silicium dioxide, lactose and talcum were agreed.

The final humidity of the MSZ granule is presented in Table VI.

Table VI

The humidity of the MSZ granules

Formulation code	**F1**	**F2**	**F3**
Humidity (%w/w)	0.54	0.38	0.39

MSZ has poor flow capacity, rendering inefficient the process of direct compacting. The granulation of the API offers the possibility to significantly modify this inconvenient. It also prevents the components of the powder mixture from being separated; it improves the compression properties of the mixture by reducing the proportion of air between the particles and reduces the compressive force needed for tableting [19].

The granulating agent created a strong bond between the active substance particles, resulting hard granules with higher strength. Mixture 1.1 presented a good free flow, but with a high risk of separation of the granular phase, due to the different density of the granules compared to the powder phase – composed of the excipients added in the formulation phase. The tablets obtained with the formula 1.1 presented a strong different appearance from that of product 1.3, they have a densely pigmented and glossy appearance. The compression mixture 1.3 containing small-sized granules (between < 0.5 mm and > 0.2 mm) presented a low compression capacity and a much-reduced resistance compared to formula 1.1 which contains large-sized granules. Therefore, the size of the granules influences the intergranular adhesion of the mixture and the technical properties of the finished product. The reduced height of the tablets in Formula 1.1 is due to the large size sorted mesalazine granules. They show high packing capacity and good adhesion between the particles of the compression mixture. However, the use of a rotary compression machine with the possibility of applying a precompression force can significantly adjust this difference.

The obtained tablets were pharmaco-technically tested, and the results are presented in Table VII.

Table VII

Results of the performed pharmaco-technical tests

Parameters	Results					
	F1.1	**F1.2**	**F1.3**	**F2.1**	**F2.2**	**F3**
Appearance	Round tablet, biconvex, light grey tablets with intense pale pink to pale brown marbling		Round tablet, biconvex, grey to light pink tablets	Round tablet, biconvex, light grey tablets with intense pale pink to pale brown marbling	Round tablet, plates, but with edges, light grey tablets with intense pale pink to pale brown marbling	
High (mm)	5.49	6.02	6.43	5.25	4.87	4.83
Diameter (mm)	12.3	12.2	12.05	12.6	12.6	12.06
Hardness (N)	276.1	110.3	62.4	314	170	171
Friability (%)	0.1	0.65	0.57	0.35	0.1	0.08
Average mass (mg/tablet)	750.48	751.02	748.32	749.67	753.48	754.11

The impact of granulometry on tablet height was measured and expressed graphically in Figure 1 (the values on the horizontal axis represent the diameter of the sieve meshes in μm). Using granules obtained in the same conditions, but sorting the granulometric fractions, it has been imposed a low variability in the granulation process (manual granulation), making possible the study of a technological relationship between the triad granules diameter – compression force – tablets high. The three studied sort of F1 for the evaluation of the granulometry put at the glance the fact that the granules diameter couldn't perform great variation in the release profile as the previous tested formulas presented in another study [3].

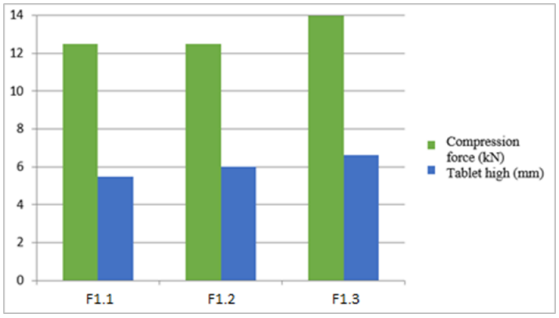

Figure 1.

Graphic representation of the granulometric influence on tablet height and compression force (F1)

The granulation of mesalazine with the help of high shear mixer and fluid bed equipment (F2) leads to homogeneous and dense granules that are easily compressed, and the resulting tablets showed high resistance to breaking due to the high degree of compaction. The compression mixture is free flowing, but in steps with central cone formation. The compression machine was equipped with flat 12 mm diameter punches, but also presented multiple technological variations regarding the press mechanism, a fact that conducted to the recording of very large differences between F2.1 and F2.2. The large differences recorded on a qualitatively and quantitatively identical formula can be justified by the variations of the compression equipment used (found comparatively in Table III), respectively the tested series size and the equipment used for the granulation and homogenization stages. Regarding the hardness of the tablets related to the compression force between Formulas 2.1 and 2.2 there are very large differences, differences explained by the technological variations earlier presented (Figure 2) (the values on the horizontal axis represent the diameter of the sieve meshes in μm).

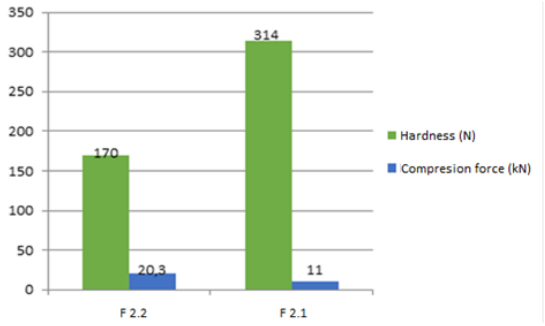

Figure 2.

Graphic representation of the granulometric influence on tablet height and compression force (F2)

The use of the wetting agent in the homogenization (pulverization) phase (for F2 and F3) greatly increased the dissolution capacity of the tablet, as it allowed the gelatinization of this excipient, compared to F1, in which gelatinization is stopped by introducing it into the granulation phase. The particle size distribution of F2 and F3 is similar, following the same steps (Figure 3).

Notable differences are recorded for the granulometric distribution of Formula 2.1, these differences are generated by the size of the series used, respectively the specifics of small-scale equipment. The strength of the granules obtained by the spray technology of the binder ensures its uniform dispersion and uniform packing of mesalazine in the granules, and the large amount of active substance used increases the condensing capacity of the granules.

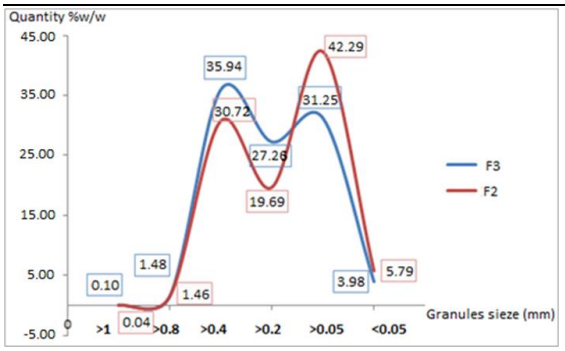

Figure 3.
Graphical representation of the particle size distribution for the granule obtained in formulations F2.2 and F3

Figure 4 shows a comparison of the particle size distribution obtained with formulas 2.2 and 3 under similar technological conditions and with formula 2.1 under different technological conditions, but using small-scale equipment that respects the principles of those used on a larger scale (pilot – Formulas 2.2 and 3 or industrial).

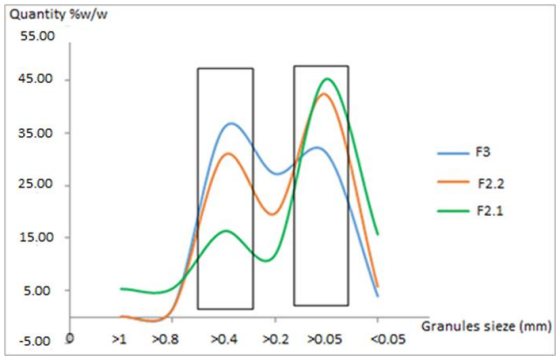

Figure 4.
Comparative graphic representation of the particle size distribution for the granules obtained in formulation tests 2.1, 2.2 and 3

The dissolution profile of the new developed MSZ generic was compared to that of Pentasa® 500 mg gastro-resistant tablets, in order to preliminary assess therapeutic equivalence [6]. This immediate release of the API would suggest that the generic product could start to produce a therapeutic effect in a shorter amount of time compared to the original. After 15 minutes there is almost complete dissolution of the active substance in the generic product tablets.
The granulometry of the F1.1 granules (diameter between 710 - 900 μm) didn't significatively influenced the dissolution test of MSZ. In the first 15 min, a medium growth of 7% is observed [13]. But the identified variations are negligible for a prolonged release form. Very large differences between the yield profile of Formulas 2.1 and 2.2 are a cumulative result of technological factors and the area difference for the tablets of the 2 formulas, a difference of 71.64 mm^2 [16, 17].

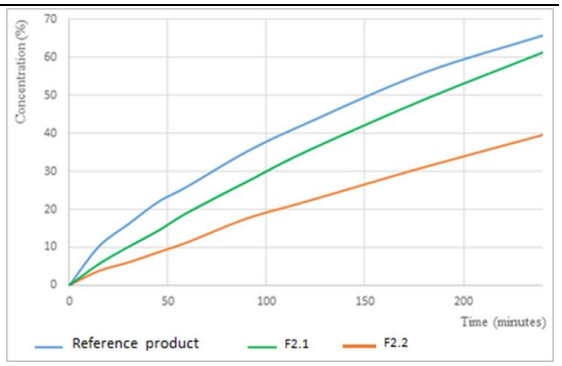

Figure 5.
The dissolution profile of the tested formula F2 and reference product

An increase in the concentration of dissolved mesalazine is observed, the increase is visible after the interval of 300 minutes when the difference between the two profiles is 26.02%, and towards the end of the test it reaches 9.93% (at 540 minutes). The surface difference between the 2 profiles (reference product and F 2.2) is considerable; this is an expression of the different release mode for the active substance in 2 different formulations, also directly influenced by the technological process because in F2.1 was used an eccentric compression machine without pre-compression force. In pre-compression, a placement of the layers of the granulation mixture is carried out with the aim of good compaction and deaeration. In this case, technical defects such as lamination or core microcracks are also avoided. A reduction of spaces in the tablet (in the form of voids or microcracks) in formula F2.2 significantly slowed down the process of dissolution and release of the active substance in the tablet. By using a wetting agent in the homogenization stage (powdering), the release capacity of the tablet is increased (Figure 6).

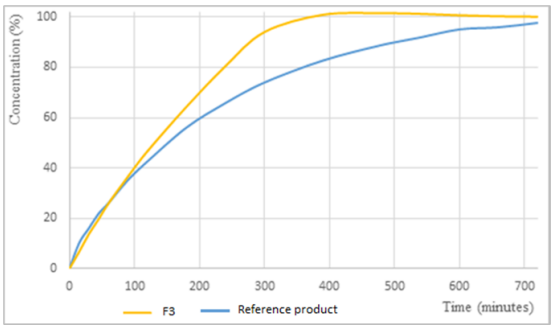

Figure 6.
The dissolution profile of the tested formula F3 and reference product

In a previous study [2], wet granulation of mesalazine and starch [20] showed that the fourth (LM04 – 500 mg MSZ, 66 mg starch, 484 mg purified water) formulation generates the highest amount (69.1%) of granules in the range of 1000 - 300 μm. Oblong tablets (pilot batches) were produced and the cores

were coated with an enteric coating acrylic agent in order to achieve gastro-resistance. Batch LM04 showed steadier characteristics. However, the tablet hardness was low, an inconvenient for the coating process. The augmentation of the compression force did not improve the results. A change in the formulation was needed in order to optimize the tableting process. Similar results as presented in this study was obtained by Muthumanikandar RV *et al*., who prepared colon targeted drug delivery system of mesalamine tablets by wet and dry granulation methods, coated by using Eudragit S100 and triple coat by Eudragit E100 and S100. Both formulations scarcely released mesalamine in pH 7.2 medium at 10% coating level. Triple coating of F01, F02 batches had a release of 99.03%, 87.28% of drug release in pH 7.2. The batch tablets coated with 7.5% of coating showed drug release of about 1.52%, 1.49% in 0.1 N HCl for 2 h [10]. Which failed to comply with the USP standards of < 1% in 0.1 N HCl. By using hot melt extrusion technique, other researchers found that the samples have shown appreciably enhanced drug release compared to mesalamine alone in the simulated gastric fluid within 90 min. Presence of Eudragit EPO increased drug release of M1 E1, M1 E2 and M1 E3 relatively more compared to the presence of Kollidon VA-64 – polyethylene glycol (samples prepared with Kollidon VA-64 + PEG6000, in different proportions 15:15, 30:10 and 30:15, mg) [18].

Conclusions

The size of the granules significantly influences the compression process and the quality of the product obtained. Therefore, it is necessary to apply high compression forces in order to obtain resistant tablets to be handled and packed properly.

Formula F1 with subsets of data (F1.1, F1.2 and F1.3) demonstrates the relationship between the granulometry of the compression blend and the pharmaco-technical parameters such as hardness and friability. In the case of F1.3, the friability is more than 5 times higher than F1.1; even if the compression force applied was higher than 1.5 kN. By applying higher compression forces in order to correct some deficiencies of the applied technology or the used formula, we cannot obtain satisfactory qualitative results for the finished product. The technological stages of wet granulation or compaction, as the case may be, apply to substances or mixtures of substances that do not have a good free-flowing capacity; the stage that will correct this technical problem, but which has multiple implications for the quality of the final tablet.

The use of the precompression force greatly strengthens the quality of the tablets obtained by good compaction of the mixtures, respectively its deaeration. These elements define the structure of the core obtained by substantially reducing gaps and microcracks. The results of the dissolution test of formula F2.2 demonstrate the importance and impact of the precompression phase on the dissolution process of the active substance. In many cases, the precompression phase affects the quality of the dissolution process for API, and correction is possible by introducing wetting agents into the formulation. This principle was also used in the case of formula F3.

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Conflict of interest

The authors declare no conflict of interest.

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