https://doi.org/10.31925/farmacia.2022.5.23 **ORIGINAL ARTICLE**

DETERMINATION OF THE IMPACT OF THE COMPRESSION FORCE BY EVALUATING THE MECHANICAL AND RELEASE PROPERTIES OF MESALAZINE TABLETS

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Abstract

Drug delivery to the targeted site of action in the human body is always affected by the excipients used and almost in the same manner by some processing variables like changes in the compression force. The aim of this study was to investigate the impact of the changes in compression forces during tablet manufacturing on the mechanical and release properties of mesalazine matrix tablets. For the mechanical properties, hardness and friability were used as assessment properties, while dissolution test was undertaken in order to ascertain the release properties. Data were analysed using One-way ANOVA at $p < 0.05$. The tablet hardness and friability were typically compression pressure-dependent with a significant difference in tablet hardness and friability with the increase in compression pressure ($p < 0.001$). The release properties of mesalazine tablets were not significantly influenced by compression pressure but rather by the polymer and the material properties of the drug.

Rezumat

Cedarea țintită a substanței medicamentoase din forma farmaceutică este aproape întotdeauna influențată de prezența excipienților, dar și de variabile ce intervin în procesul de obținere al acestora, cum ar fi forța de comprimare. Scopul studiului a fost de a investiga impactul modificărilor forței de comprimare în procesul de comprimare asupra proprităților mecanice și de cedare a mesalazinei din comprimate. Pentru proprietățile mecanice, au fost investigate rezistența comprimatului la rupere și friabilitatea, iar în cazul proprietăților de cedare, au fost efectuate teste de dizolvare. Datele au fost analizate prin intermediul analizei unifactoriale de varianță ANOVA, stabilind $p < 0,05$ ca având semnificație statistică. Rezistența la rupere și friabilitatea depind într-o manieră proporțională de forța de comprimare ($p < 0,001$). Forța de comprimare nu a influențat proprietățile de cedare ale mesalazinei din comprimate, acestea fiind modificate de matrița polimerică și de componentele materiale ale comprimatelor.

Keywords: mesalazine, fluidbed, compression pressure, mechanical properties, release properties

Introduction

Since the discovery of the compressed tablet, performed by Thomas Brockedon almost 175 years ago [23], it has been the most popular dosage form, especially because of the many advantages among which we can state: accurate dose, ease of handling and administration, good stability, easy of manufacturing in a large scale, cost effectiveness, good patients' acceptance [24].

The main goal of the design and manufacturing process of compressed tablets is to release and deliver orally the correct amount of drug in the right form, at or over the accurate time period and in the desired physiological location, but keeping its chemical integrity sheltered. In some cases, not only the manufacturing process, but the chemical properties and the complete chemical make-up of the tablets can affect in different manner the efficacy of the drug being administered.

Some of the manufacturing processes that can affect the tablet quality are tabletting machine force compression and speed [14, 17, 20, 26, 27]. Thus, in order to ensure a tablet production with good bioavailability, the assessment of tablet properties is a powerful tool of the quality control.

Tablet production is a mechanical stress process involving a scale of steps. The first is related with the filling of the die where some rearrangement takes place. The powder becomes more packed with no inter-particulate void space for any relative particle movement. As the compression force increases, stress begins to built-up at the particle contact point in the die and the material begins to deform. This step is irreversible, because even the removal of the compression force takes place, the particles have deformed upon the elastic limit of the material. A crumbled tablet results if the force cannot exceed the elastic limit of

the particle. In tablet compression, materials have a dependant compression limit, and below this limit, materials will not form a coherent compact pharmaceutical form, as beyond this limit, materials form a coherent tablet with increased strength as the compression force increases. When there is an exceeded critical compression force limit, tablet strength reduces and lamination and capping may develop [27].

The compressive force applied by a rotary or eccentric compression machine strongly influences the mechanical properties of a tablet, such as: hardness, friability, height, disintegration or dissolution and they are widely used parameters to control the tablet manufacturing process [1]. Tablet hardness is a surrogate measure for compression force during manufacture, often because the tablet machine is unable to measure the compression force. Modern compression equipment is adequately designed for better adjustment of tablet properties by setting a pre-compression force (which helps to deaerate the compression mixture) and uniformizing the feed flow with the help of an automated feed unit [11, 28]. The compression force felt by the mixture is a set of mechanical and technical factors – adjustment of the equipment. Broadly speaking, the equipment measures the strength exerted by the dosage mixture on the compression effect, the increase in density by reducing the initial volume. Further, inconsistent tablet properties are issued due to non-uniform compression forces and thus the efficacy of the dosage form can be affected [15]. Marais *et al*. showed that the magnitude of the compression force influences tablet hardness and disintegration time. A rise in compression force produces an increase or decrease in the disintegration time, depending on the formulation and also increases tablet hardness [16].

The present study will measure the effect of changes in compression force during tablet manufacturing on the mechanical and release properties of mesalazine tablets, determined by appropriate methods, for tablets obtained from a compression mixture containing powdery substances and granules. The tablets are obtained by granulating the active substance with a type of pre-gelatinized starch (Starch 1500), then mixing the granules with a directly compressible mixture of excipients. Two types of polymeric agents are used to ensure a modified release profile [2, 9, 21, 22].

Materials and Methods

The materials used in this investigation were micronized mesalazine (Minapharm Pharmaceuticals, Egypt), starch 1500 (pre-gelatinized corn starch), carbopol 971 powder (Fluka AG, Buchs, Switzerland), Methocel K100LV (hydroxypropyl methylcellulose), Methocel K15M, Vivapur 102 (microcrystalline cellulose) (Dow, Michigan, USA), Aerosil 200 (anhydrous colloidal silicon dioxide) (Colorcon GmbH, Germany), Surelease E-7-19040 Clear (ethylcellulose aquaeous dispersion, Colorcon, USA), Kollidon 30 (polyvinylpyrrolidone), talcum and magnesium stearate (Faci, Italy). All other solvents and chemicals were of analytical grade.

Tablet formulation

Batches of mesalazine were prepared by direct compression method. All the ingredients mentioned in Table I were blended to form a uniform powder mix and compressed at pressures between 8.9 and 17.5 kN with a Fette Compacting 102i rotary machine with 8 punches ϕ 12 mm biconvex.

Table I

Qualitative and quantitative details for tested formulas

Raw material name	Formula 1 (F1)	Formula 2 (F2)	Formula 3 (F3)
	mg/tablet		
Mesalazine	500.00	500.00	500.00
Starch 1500	37.50	-	-
Carbopol 971 powder	-	35.70	-
Surelease E-7-19040 Clear	-	112.50	-
Kollidon 30	-	-	22.50
Methocel K100LV	75.00	-	-
Methocel K15M	-	-	175
Vivapur 102	107.50	79.30	22.50
Aerosil 200	15.00	7.50	7.50
Talcum	7.50	7.50	15.00
Magnesium stearate	7.50	7.50	7.50
Purified water	q.s.		
Total amount for tablets	750.00		

Preliminary test were performed in order to determine the compatibility of mesalazine with different excipients through differential scanning calorimetry. Thermal analysis by differential scanning calorimetry (DSC) was carried out using a thermal analyser (Netzsch DSC 200F3) to investigate the compatibility between mesalazine and different excipients. The DSC thermograms of pure drug, individual excipients, and

drug–excipient mixtures (1:1 w/w) were recorded. For each measurement a sample of approximately 7 mg was placed in an aluminium pan and scanned in the temperature range 30 - 350°C. A heating rate of 10°C/min was used, and the thermal analysis was performed under dynamic nitrogen atmosphere (Table II). The test was conducted in three steps with the purpose of obtaining possible interactions between the API and the used excipients.

Table II

Conditions for testing the thermostability of raw materials

Stage	Temperature (°C)	Heating speed (°K/min)	Time (min)	No. collected points/ min.	No. collected points/°K
Start	30	-	-	-	-
Dynamic stage	400	10	37	100	10
End (safety temperature)	410	-	-	-	-

Uniformity of weight

Twenty tablets from each batch were weighed individually and the average weight and standard deviation was calculated.

Dimensions

The thickness and diameter of twenty tablets from each batch were measured using a micrometer screw gauge and the average thickness and diameter with their standard deviation were calculated.

Hardness

Hardness was determined by using a Tablet Hardness Tester (Erweka TBH 210, Germany). Mean of three determinations were taken.

Friability

Friability was calculated as the percentage lost in weight of 10 tablets placed in a Tablet Friability Apparatus (Erweka TAR Friability Tester, Germany) which was operated for 3 min at 100 revolutions *per* minute. Mean of three determinations were taken [29].

Dissolution test

The release characteristics of mesalazine were performed according to the USP dissolution II paddle method [30] using a USP Dissolution Apparatus Erweka ZT320, Germany, operated at 100 rpm. The dissolution medium was 900 mL of pH = 7.5 buffer medium at 37 ± 0.5°C. Five mL samples were withdrawn at specified time intervals and immediately replaced with 5 mL of fresh dissolution medium. The withdrawn sample was analysed spectrophotometrically at 330 nm using Jenway UV-780 print UV-Spec.

In order to obtain the uniformity of the granules coating process, the surface structure of the granules was studied by a scanning electron microscope (JEOL, JSM840A Scanning Microscope, Japanese Electron Optics Limited, Japan).

The raw materials weighed for the wet granulation stage were prepared as follows. 3.4 kg mesalazine was placed in the vessel of Huetlin Bosch Pilotmix 30T high speed granulator. The granular agent was obtained from 0.25 kg Starch 1500 gradually added over the purified water. The homogenization of binder was performed using an IKA blender. The technological parameters for the binder preparation step are shown in Table III.

Table III

Technological parameters for binder preparation

Technological parameters	Data
Mixer speed (rpm)	400 - 600
Time (minutes)	40

The wet granulation step was performed using a Huetlin Bosch Pilotmix 30T high speed granulator, Germany. The technological parameters used for the wet granulation step are presented in Table IV.

Table IV

Technological parameters for the wet granulation

Technological parameters	Data
Adding the binder	
Mixer speed (rpm)	60
Binder flow (kg/minute)	0.10
Granulation	
Mixer speed (rpm)	70
Chopper speed (rpm)	600 - 900
Torque (N)	18

The wet calibration was performed using a 3 mm square mesh and Frewitt Coniwitt A150 equipment, Italy. The technological parameters involved 30 rpm speed for this step granulation.

The obtained granules were dried using a fluid bed dryer Unilab Huetlin Bosch, Germany, to 60°C. For the drying of the granules, the technological parameters shown in Table V have been established and set.

Table V

Technological parameters for drying

Technological parameters	Data
Heat	
Air flow rate (m^3/h)	400
Inlet air (^oC)	70
Feed the fluidbed	
Air flow rate (m^3/h)	400 - 500
Inlet air (^oC)	60
Drying	
Air flow rate (m^3/h)	170 - 400
Inlet air (^oC)	60

The dry granules were calibrated using a 2 mm square mesh and Frewitt Coniwitt A150 equipment, Italy, at a speed of 30 rpm.

The efficiency of the granulation step was calculated, and the quantitative formula of the tested series was recalculated. The raw materials weighed for the homogenization stage were prepared as follows: Vivapur 102 and Aerosil 200 were standardized by sieving on a 0.70 mm square mesh sieve to result Mixture 1. Magnesium stearate and Talcum have been standardized by sieving on a 0.70 mm square mesh sieve to result Mixture 2. The order of addition to the mixer vessel was calibrated dry granule, Methocel K100LV, Mixture 1 and Mixture 2.

The homogenization step of the raw materials was performed in a 20 L vessel attached to a Servolift Laboratory type homogenization equipment, Germany. For the homogenization step, the technological parameters shown in Table VI were established and set. The mixture was lubricated with magnesium stearate under similar conditions for 1 minute.

Table VI

Technological parameters for the homogenization step

Technological parameters	Data
Speed (rpm)	20
Time (minute)	8
Rotation direction: only right	

The resulting mixture was compressed using a Fette Compacting 102i rotary machine (Fette Gompacting GmbH, Germany) with 8 punches ϕ 12 mm biconvex (Table VII).

Table VII

Technological parameters for compression step of formulas F1, F2 and F3

Technological parameters	Data		
	F1	**F2**	**F3**
Feeding speed (rpm)	60		
Compression speed (tablet/h)	Maximum 9000		
Precompression and compression depth (mm)	2.00		
Precompression force (kN)	2.1	2.9	2.8
Compression force (kN)	8.9	10.2	17.5
Filling depth (mm)	12.85	13.35	12.97
Punches height in precompression (mm)	5.10	4.80	4.80
Punches height in compression (mm)	4.00	3.90	3.80

In order to obtain similar properties, more alike with the reference product (Pentasa® 500 mg, modified released tablets, Ferring Pharmaceuticals), for the second formulation, a coating agent whose base was represented by a 15% aqueous dispersion with ethyl cellulose (Surelease E-7-19040 clear) was used. This dispersion was added over purified water and subjected to a homogenization process until it became visibly uniform. The coating process of the previously formed granules was carried out using a fluidized bed coating system Microlab Huttlin (Syntegon, Germany) with bottom spraying. For the third formulation, we aimed at obtaining a hydrophilic matrix type system, with possible trends between mesalazine and Kollidon 30 granules. After the completion of the wet granulation stage, the granule was calibrated using a 2 mm square mesh sieve, and the drying process was carried out slowly in open air for 24 hours (the granule was placed in a thin layer on a sheet of paper). The final moisture content of the granule was 0.55%, determined on a 5 g sample at 105°C, using a thermobalance. The dry granule was calibrated using a sieve with a square mesh of 1 mm. Aerosil 200 was subjected to a de-agglomeration operation by passing it mixed with croscarmellose sodium through a 1 mm square mesh sieve. We added mesalazine granule, hydroxy-propylmethylcellulose and talc to the previously formed mixture. All components were homogenized manually until a visibly homogeneous mixture was obtained. At the end, magnesium stearate is added and homogenized for 1 - 1.5 minutes.

Results and Discussion

The DSC thermograms registered in the preliminary studies are presented in Figures 1, 2, 3, 4, 5, 6, 7 and 8.

The preliminary conclusions were encouraging, as there were not recorded any major interferences between the API ant the selected excipient, so they are reliable for the formulation step.

The binder for wet granulation required a long period of time for the starch solubilisation, and the solution obtained required the application of an adequate spray pressure in order to generate small granulation cores. Wet granulation using Starch 1500 based binder encountered viscosity problems due to the gelling tendency.

The wet granule did not show superior resistance, because in the drying stage the initial air flow of 400 m^3/h destroyed part of the granule. The final moisture of the granule was 0.26%, determined on a sample of 5 g at 105°C, using a thermobalance.

The compression mixture showed satisfactory free flow and reacted to the settings of the set technological parameters. The compression stage proceeded without difficulties and within the proposed limits.

The results of the pharmaco-technical tests performed on the obtained tablets are presented in Table VIII.

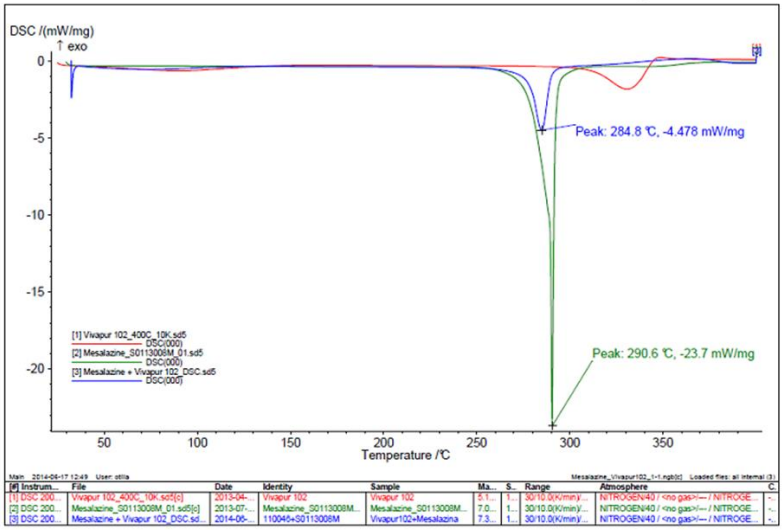

Figure 1.
The DSC curve for the preliminary compatibility study between API and Vivapur 102 (1:1)

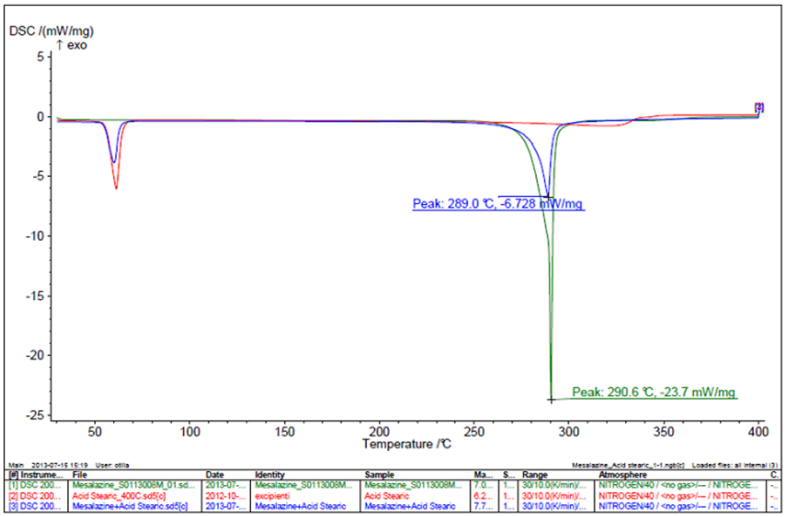

Figure 2.
The DSC curve for the preliminary compatibility study between API and magnesium stearate (1:1)

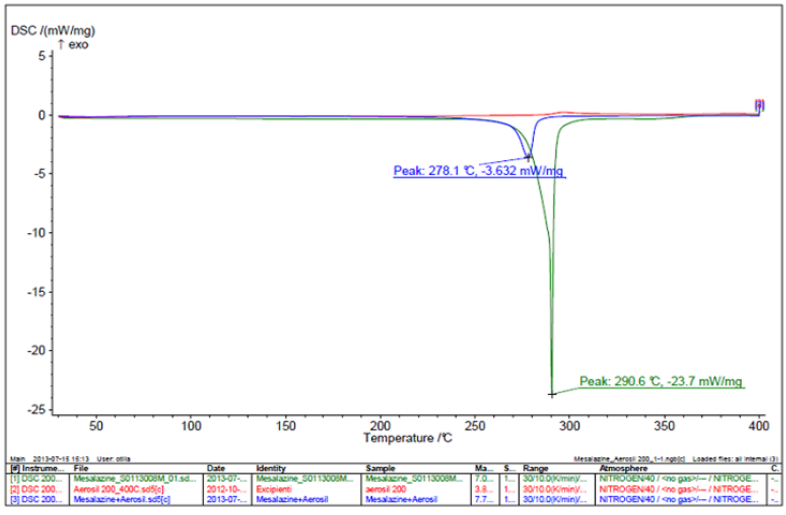

Figure 3.
The DSC curve for the preliminary compatibility study between API and Aerosil 200 (1:1)

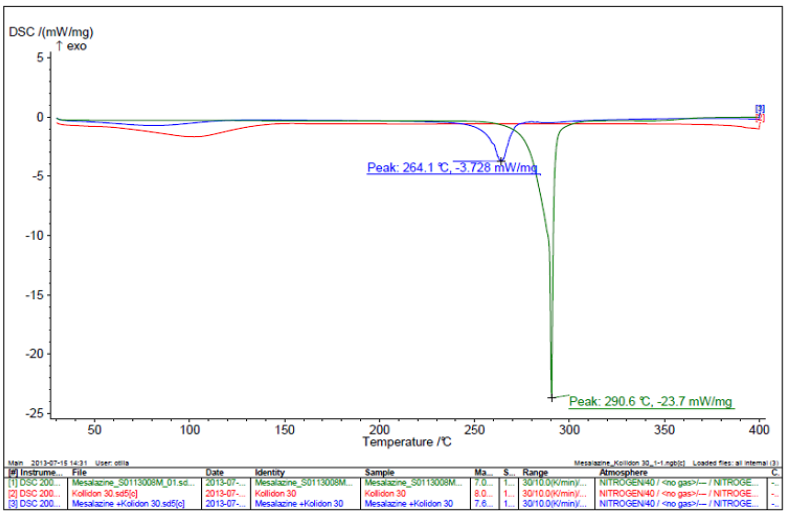

Figure 4.
The DSC curve for the preliminary compatibility study between API and Vivapur 102:Kollidon 30 (1:1)

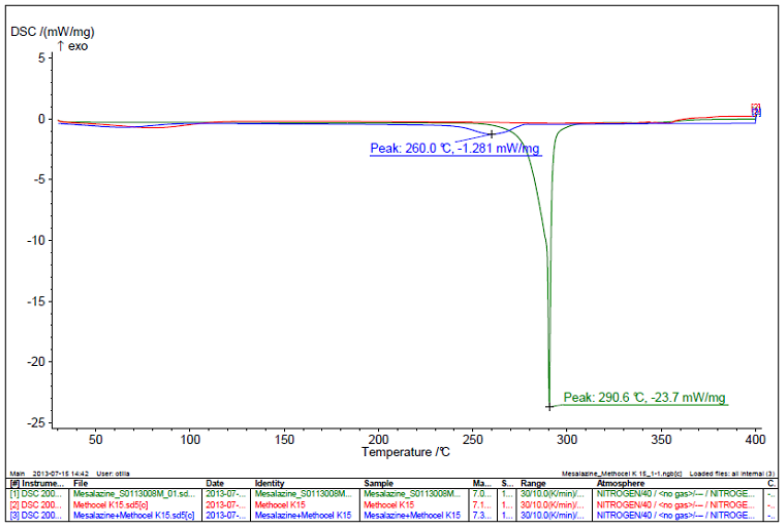

Figure 5.
The DSC curve for the preliminary compatibility study between API and Vivapur 102:Methocel K 15 M (1:1)

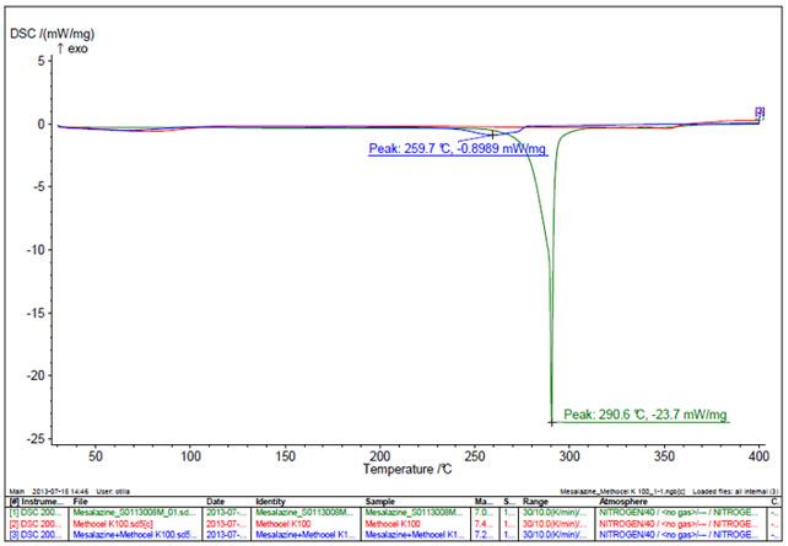

Figure 6.
The DSC curve for the preliminary compatibility study between API and Vivapur 102:Methocel K100 (1:1)

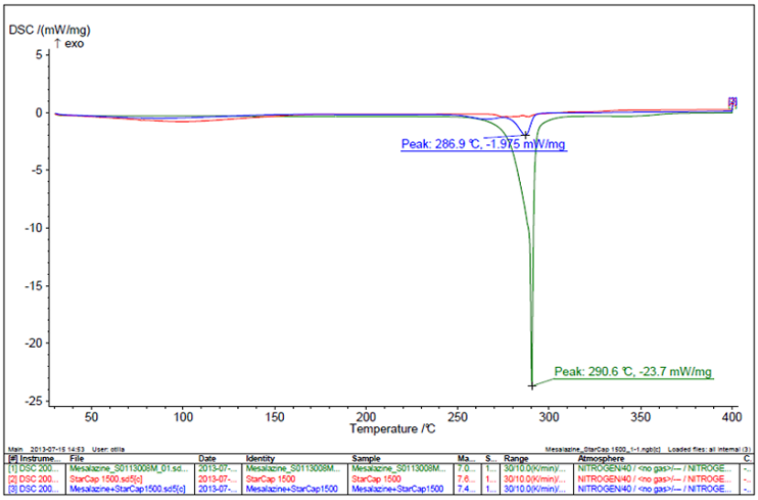

Figure 7.
The DSC curve for the preliminary compatibility study between API and Vivapur 102:Starch 1500 (1:1)

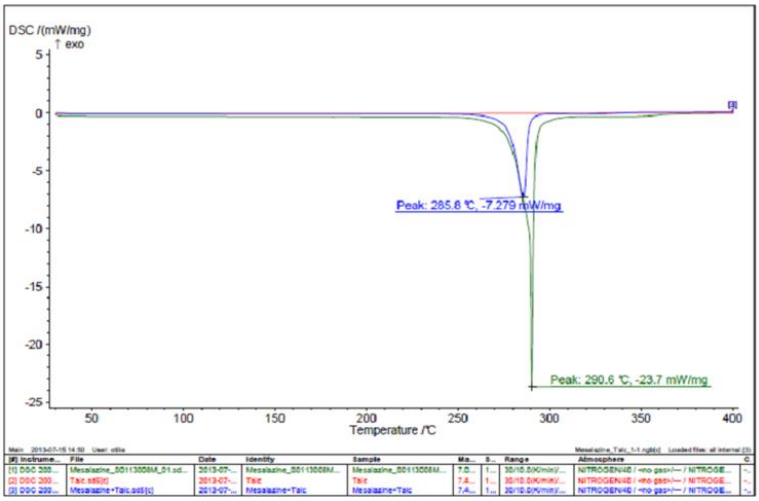

Figure 8.
The DSC curve for the preliminary compatibility study between API and Vivapur 102:Talcum (1:1)

Table VIII
Results of the pharmaco-technical tests performed using F1

Parameters	Results (± SD)
Appearance	Round tablets, biconvex, light gray tablets and pale pink to pale brown marbles
High (mm)	5.31 ± 1.63
Diameter (mm)	11.82 ±1.56
Hardness (N)	118 ± 1.10
Friability (%)	0.62 ± 0.92
Uniformity of wieght (mg/tablet)	746.91 ± 1.79

In order to obtain a formulation with good mechanical properties, but with the main goal of observing the dependencies, respectively the pharmaco-technical variations, technological tests were performed [19]. The technological parameters used and set are depicted in Table IX.

Through the six technological tests performed with F1, the dependence of two technological parameters was demonstrated, by decreasing the distance between the punches in the compression phase there is an increase of the force necessary for compression (inverse relative proportionality). Figure 9 shows the dependence of the 2 technological parameters.

It was observed and defined the inverse proportionality relations for the following pharmaco-technical parameters: height, diameter, friability and hardness compared to the compression force. The pharmaco-technical characteristics obtained for the six technological tests performed on the same formula are represented in Figure 10.

Table IX

Technological parameters for compression tests performed with Formula 1

Technological parameters	Data					
	1.1	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**
Feeding speed (rpm)	60					
Compression speed (tablet/h)	Maximum 9000					
Pre-compression and compression depth (mm)	2.00					
Pre-compression force (kN)	2.1	2.9	2.8	2.7	2.8	2.8
Compression force (kN)	8.9	10,2	11.3	12.7	14.9	17.5
Filling depth (mm)	12.85	12.85	12.85	12.85	12.90	12.95
Punches height in pre-compression (mm)	5.10	4.80	4.80	4.80	4.80	4.80
Punches height in compression (mm)	4.00	3.90	3.80	3.70	3.60	3.50

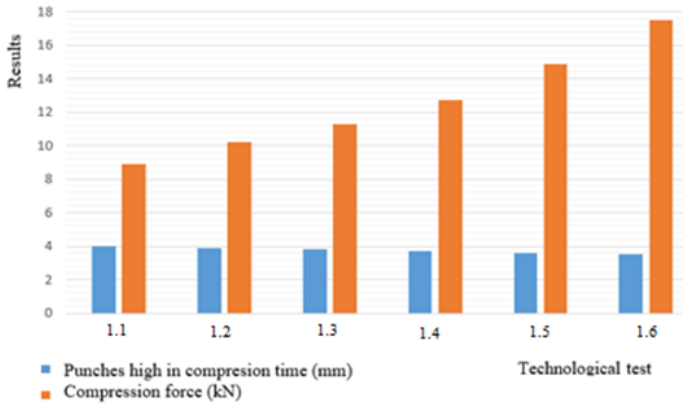

Figure 9.

Dependence of the compression force and punches height in compression tests for F1

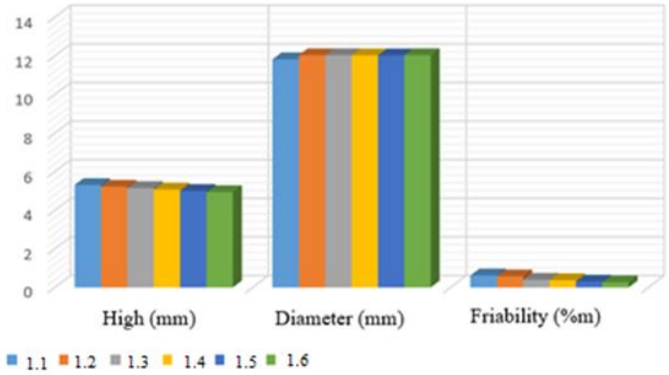

Figure 10.

Graphic representation of pharmaco-technical datasets of F1

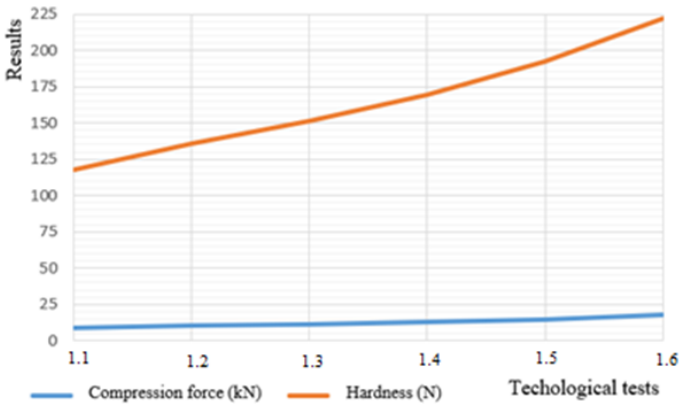

Figure 11.

Graphic representation of direct proportionality relationship

The present study adequately documented the relationship of direct proportionality between the tensile strength/hardness of tablets and the compressive strength applied. The use of a single compression mixture, obtained through well-controlled and properly measured technological processes, reduced the technological variables making it possible to carefully study the compression process. Figure 11 shows the direct proportionality relationship.

Taking into consideration the results obtained for F1, the tests were performed also for F3, and the results are presented in the Table X.

Table X

Composition and codification of metronidazole gel formulations

Parameters	Results (±SD)
Appereance	Round, biconvex tablets of light gray colour and diffuse marbling of pale pink to pale brown colour
High (mm)	6.02 ± 1.94
Diameter (mm)	12.03 ± 1.22
Hardness (N)	164.1 ± 1.32
Friability (%)	0.1 ± 0.54
Uniformity of weight(mg/tablet)	751.8 ± 1.18

As the results emphasize, compression pressure has no effect on the diameter of the tablets, expected fact due to the plastic deformation taking place as the powder bed in the die is in a confined region. The radial force is exerted on the die wall which makes the tablet to assume the diameter of the die as the axial pressure increases. Tablet thickness reduces as compression pressure increases. This is expected as increase compression pressure which tends to displace gas from a powder bed due to particle rearrangement, leading to a reduction in the height of the powder bed in the die, thereby leading to volume reduction [27]. Our study has been able to establish that by maintaining all other manufacturing processes constant and having compression pressure as the only variable, there was a great influence on the hardness of the tablet for the three formulations. ANOVA analysis revealed a significant difference in the tablet hardness with an increase in the compression pressure ($p < 0.001$). This is the conclusion also obtained by Femi-Oyewo MN *et al.* and Haresh TM *et al.* [6, 8]. This could be due to gas displacement from the powder bed in the die as compression pressure increases bringing particles in close contact. The friability values were observed to decrease as pressure increases in all the formulations. This decrease could have been due to the formation of more solid bonds which led to the formation of tablets with increasing hardness and more resistance to fracture and abrasion [1, 18]. According to Odeku OA *et al.* [18], convectional tablets which loose less than 1% of their weight during the friability test are generally considered acceptable.

For the second formulation, we used Surelease, known as a pseudo-latex coating material which is plasticized aqueous dispersion of EC with 25% (w/w) solid content. Surelease E-7-19010 which was used in this study consists of EC, oleic acid and medium chain triglycerides as plasticizers, in ammonium hydroxide solution. Surelease has been utilized as film coating material [25] and also as a granulation liquid [7]. In order to observe the uniformity of the coating layer of the mesalazine granules (using Carbopol 971, with Surelease E-7-19040 clear), microscopic studies were carried out (for F2). The results of microscopic studies revealed a reduced degree of coverage for some areas of the granules (crystalline areas), as it can be depicted in Figure 12.

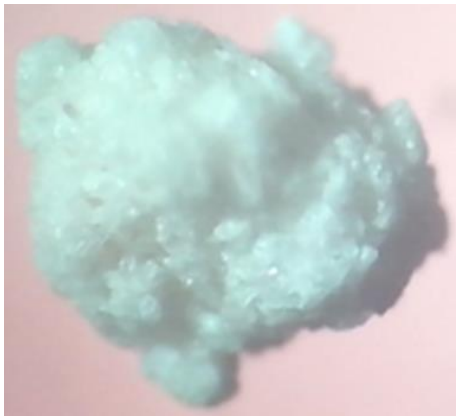

Figure 12.
Optical image of the granules obtained by using Surelease E-7-19040 (1000x)

An alternative technological method to the technological process of coating the dry granules obtained by calibrating using a rotisieve consists in the pellet spheronization technique. This technique guarantees obtaining dense granules with regular and well-formed external surfaces that can be uniformly covered with a yield profile modelling agent.

Another inconvenience of the technological process applied to F2 is given by the risk of separation of the compression mixture due to the large dimensions of some coated granules as a result of the appearance of intergranular adhesion effects. This risk cannot be completely eliminated, but it can be greatly reduced by permanently adjusting the fluidbed filming process.

The dissolution profile of F1 (Figure 13) showed a strong similarity between F1 and the used reference product. During the dissolution process, the lack of the

disaggregation mechanism of the tablets was observed; they only had a dissolution effect. The ingredients of the formulation, together with the technological process of wet granulation and compression, do not ensure a mechanism for transferring the solvent to the core of the tablet and finally disaggregating the tablet. Another observation that reinforces this conclusion is given by the way a tablet is destroyed during the hardness test, the tablets break into 2 roughly equal parts.

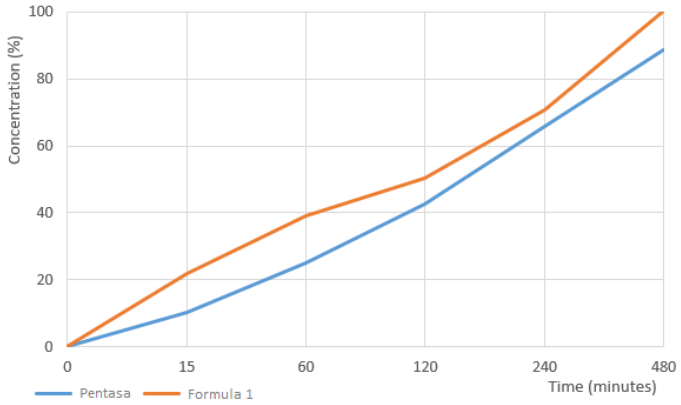

Figure 13.
Dissolution profile of the tested formula F1

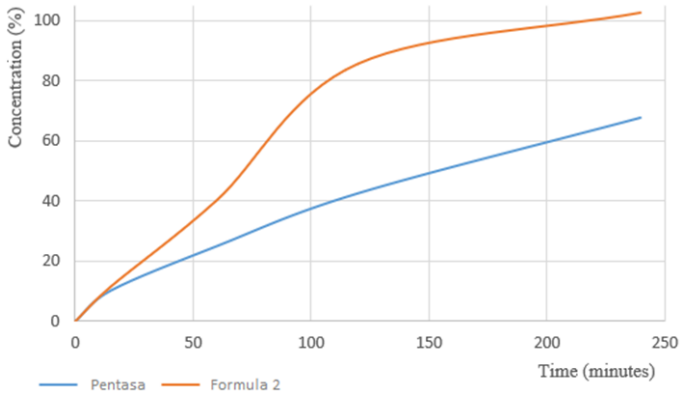

Figure 14.
Dissolution profile for Surelease E-7-19040 clear coating granules (F2)

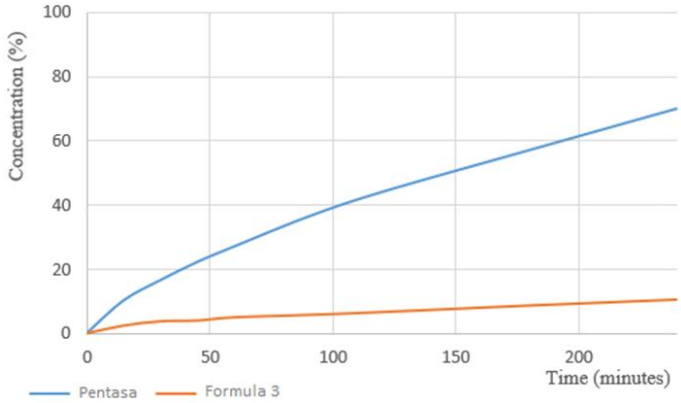

Figure 15.
Dissolution profile of the tested formula F3

The study on the F2 dissolution profile (Figure 14) indicates a pronounced dissolution of mesalazine from the tablets as a result of an incomplete coating of the granules obtained. This conclusion is reinforced by microscopic images of granules shot with Surelease E-7-19040 clear.

Formulation 3 compared to Formulation 1 contains a large amount of polymeric agent that shapes the

dissolution profile and a reduced amount for the cellulosic diluent, Vivapur 102 (Figure 15). In this case, the release of mesalazine is much delayed, and the gel matrix formed by hydrating the tablet reduced the rate of release of mesalazine from the tablet. The intense gelation of the tablet significantly limited the release surface of mesalazine as a result of the tablet sticking to the base of the dissolution vessel of the USP II device.

By surveilling the literature data, we acknowlege the study presented by Krishnakumar DL *et al* [13], whose tablets obtained with hydroxypropilmethyl-cellulose acetate succinate (HPMCAS) and sodium alginate in two coats (upper and lower) in different quantities were investigated. The mesalazine tablets coated by compressing 100 mg of HPMCAS in both upper and lower coats released almost 100% drug within 3 hours. But the tablets prepared with 150 mg HPMCASon the core tablets maintained good integrity during the dissolution test and prevented escape of mesalazine both in the acid and buffer stages. The amount of Mesalazine released from the tablets coated with higher proportion of HPMCAS alone was comparable to that released from the tablets coated with equal proportions of two pH sensitive polymers. Joshna B *et al*. [12] used natural polymers, as pectin and Xanthan gum and also synthetic polymer hydroxypropilmethylcellulose (HPMC E50 LV). Tablets were prepared by direct compression method using different polymers and both pre-compression and post-compression evaluations were conducted. Using the same polymers, compression coated mesalamine tablets were prepared by compression coating method using cellulose acetate phthalate as the enteric polymer. The tablets were also subjected to pre-compression and post-compression evaluation and all the values obtained were in acceptable limits. Dissolution studies were conducted in different media having pH 1.2, 6.8 and 7.4. The dissolution results showed the drug release of uncoated tablet of HPMC E50 LV was 108.42% at 480 minutes, Pectin was 100.53% at 300 minutes and Xanthan gum was 108.73% at 90 minutes. The drug release of coated tablets of HPMC E50 LV was 100.42% at 680 minutes, Pectin was 102.31% at 580 minutes and Xanthan gum was 100.42% at 300 minutes. Hence the study showed that the compression coated tablets of mesalamine using HPMC E50 LV showed delayed release of the drug in 680 minutes. While Elbary Ahmed *et al* obtained cumulative percentages of drug released at 6, 10 and 14 h, forward selected as dependent variables and restricted to 7.5 - 22.5% (Y1), 42.5 - 57.5 % (Y2), and 72.5 - 87.5% (Y3), respectively (in order to perform a Box-Behnken experimental design) [5].

The optimized formulation contained 5.72% Carbopol®, 9.77% Eudragit® RS and 1.45% croscarmellose sodium and provided a release profile which was very close to the targeted release profile, where the calculated values of f1 and f2 were 8.47 and 67.70, respectively, and followed zero-order release kinetics. Several authors [3, 4] have stated that compression pressure is a statistically significant factor regarding tablet hardness, but its effect on drug release was found to be minimal.

Conclusions

It can be concluded that compression pressure does not have a significant effect on release rate and mechanism, but the matrix forming polymer and the material properties are of great influence.

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Conflict of interest

The authors declare no conflict of interest.

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