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Influence of Metronidazole Particle Properties on Granules Prepared in a High-Shear Mixer-Granulator

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ABSTRACT Metronidazole is a good example of high-dose drug substance with poor granulating and tableting properties. Tablets are generally produced by liquid granulation; however, the technological process failure is quite frequent. In order to verify how the metronidazole particle characteristics can influence granule properties, three metronidazole batches differing for crystal habit, mean particle size, BET surface area and wettability were selected, primarily designed according to their different elongation ratio: needle-shaped, stick-shaped, and isodimensional. In the presence of lactose monohydrate and pregelatinized maize starch, respectively as diluent and binder, they were included in a formula for wet granulation in a high-shear mixer-granulator. In order to render the process comparable as far as possible, all parameters and experimental conditions were maintained constant. Four granule batches were obtained: granules from placebo (G-placebo), granules from needle-shaped crystals (G-needle-shaped), granules from stick-shaped crystals (G-stick-shaped), and granules from isodimensional crystals (G-isodimensional). Different granule properties were considered, in particular concerning porosity, friability, loss on drying (LOD), and flowability. In order to study their tabletability and compressibility, the different granules obtained were then compressed in a rotary press. The best tabletability was obtained with the isodimensional batch, while the poorest was exhibited by the stick-shaped one. Differences in tabletability are in good accordance with compressibility results: to a better tabletability corresponds an important granule ability to undergo a volume reduction as a result of an applied pressure. In particular, it was proposed that the greatest compressibility of the G-isodimensional must be related to the greatest granule porosity percentage.

KEYWORDS Metronidazole, Crystal habit, Elongation ratio, Wet granulation, High-shear mixer-granulator, Tabletability, Compressibility

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INTRODUCTION

There are several factors that influence granule properties and they can be coarsely splitted into process parameters and ingredients characteristics (Holm, 1997). Particularly, regarding this last, there are several evidences that

materials used in the granulation process could modify the granule properties (Khankari & Hontz, 1997). Among the product variables, which are generally considered as influencing granulation process, the main parameters are: particle size and particle size distribution, particle-specific surface area, solubility in liquid binder, wettability, and packing properties (Faure et al., 2001).

Metronidazole (MTZ) (Martindale, 1996) is an antimicrobial drug, orally administered in the unit dose of 250 mg. Because of its very poor compression properties, tablets cannot be obtained by direct compression and they must be rather produced by the wet granulation technology. During some preliminary studies (unreported results), the authors observed that granule properties were not always satisfactory, because they were occasionally friable and thus leading to tablets of poor crushing strength. The objective of this study is to verify if the metronidazole particle characteristics could influence granule properties, regardless of the excipients characteristics and process parameters. For this scope, three metronidazole batches of different particle characteristics were used to produce granules that, in turn, were compared to a placebo batch.

MATERIALS AND METHODS

Materials

Metronidazole (MTZ) USP was kindly supplied by Pharmacia (Ascoli, Italy). For the metronidazole crystallization, solvents of analytical grade such as ethyl acetate (Panreach Quimica, Barcellona, Spain) and butanol (Carlo Erba Reagenti, Milan, Italy) were used. The excipients used in the formulation were pregelatinized maize starch (Lycatab PGS®; Roquette Frères, Lestrem, France) and lactose α-monohydrate and magnesium stearate (A.C.E.F., Fiorenzuola d'Arda, Piacenza, Italy).

Crystallization Methods

For the crystallization of metronidazole, the "salting-in" method was performed using an appropriate amount of the drug dissolved in a given volume of suitable solvent at 40.0 ± 0.5°C. This solution was spontaneously left to cool at 10°C under continuous stirring, by means of an external ethanol cooling system circulating in a refrigerator (Cryostat F4-Q, Haake Q, Karlsruhe, Germany). The crystals were recovered upon filtration under vacuum, allowed to dry for 24 hr in a ventilated oven at room temperature and stored at 25.0 ± 0.5°C in the presence of P_2O_5.

Crystal physical Characterization

Crystal morphology was characterized by using a scanning electron microscope (SEM) (Stereoscan 360, Cambridge Instruments, Cambridge, UK). Samples were mounted on a metal stub with a double-sided adhesive tape and then recovered under vacuum with a 200 Å-thick gold layer using a metallizator (Balzer MED 010, Linchestein). Particle size was determined by counting the Ferret's diameter of 500 particles under SEM. The elongation ratio was determined by the ratio of maximum and minimum Ferret's diameters of 500 particles.

The specific surface area of the powders was measured in triplicate using the BET gas adsorption method. Powders were stored under vacuum for 3 hr at 25°C and then analyzed by using a Gemini 2360 BET surface area analyzer (Micromeritics, Norcross).

The particle wettability was determined by the capillary rise wetting method, based on the Washburn's equation. The theoretical basis of this method was reported by Lazghab et al. (2005). An appropriate amount of MTZ crystals was put in a glass cylinder (12 cm in length and 1 cm of internal diameter) closed on one end with a sintered glass filter. A reproducible bed porosity was obtained by packing the crystals contained into the tube. The tube was joined to a balance (1/100000 precision). The solvent was placed in a container posed under the tube, and brought in contact with the filter. The tube was weighed every second as long as saturation of the particle bed was obtained, which was indicated by no more increase of the mass. The rate of the liquid penetration through the powder bed was used to calculate the contact angle (Lazghab et al., 2005).

Liquid Granulation and Properties of Wet Granules

Liquid granulation was performed in a high-shear mixer-granulator (Romaco, Lucca, Italy), equipped with a vertical bowl of 2.6 L capacity and equipped with a 3-blade impeller that rotates at an interval

speed of 50–1500 rpm and with a vertical chopper that rotates at a fixed speed of 6000 rpm. A total of 1.6 L of the powder mixture was added to the mixer-granulator. Through a spraying nozzle, placed at the top on the bowl cover, the binder liquid was added. A peristaltic pump ensured the liquid constant feeding. The power consumption profile was recorded for each formulation until the overwetting point (past formation) and is expressed versus the granulating liquid amount. Granulation conditions are described in Table 1. The granule sieved fractions were weighed and expressed as percentage. The granule composition is summarized in Table 2. First, a placebo batch (G-placebo), composed of 90% w/w of lactose α-monohydrate and 10% w/w of pregelatinized maize starch was produced; 16.5 mL of water were used for each 100 g of solid part. Three medicated batches were then obtained by replacing the 75% of lactose by the MTZ (Table 2) and they were the G-needle-shaped produced from the needle-shaped crystals obtained by crystallization from water, the G-stick-shaped produced from the stick-shaped crystals obtained by crystallization from ethyl acetate, and the G-isodimensional produced from isodimensional crystals obtained by crystallization from butanol. High metronidazole content was used in order to render the effect of particle characteristics on formulation more evident.

The degree of liquid saturation (DLS) of wet granules was determined according to Saleh et al. (2005). It was defined as the portion of the overall intra-particle space occupied by the granulating liquid, and it was calculated according to Eq. (1).

$$DLS = \frac{c+1}{\left[\left(\frac{m_d}{m_w - m_d}\right) - c\right]} \times \frac{\rho_g}{\rho_l \chi} \qquad (1)$$

where c is the mass fraction of the dry material, d is the mean particle size of the examined granule population, m_w and m_d are masses of wet and oven-dried samples, respectively, ρ_g is the granule apparent density, and ρ_l is the density of granulating liquid. χ is the intra-particle void fraction calculated by Eq. (2).

$$\chi = 1 - \frac{\rho_g}{\rho_s} \qquad (2)$$

where ρ_s is true density of dry powder, experimentally measured by using an helium pycnometer, and ρ_g is

TABLE 1 **Experimental Conditions Used During the Liquid Granulation in the High-Shear Mixer-Granulator**

	Time (s)	Impeller speed (rpm)	Heating	Chopper	Vacuum
Dry mixing	420	300	No	No	No
Liquid addition	200	600	No	No	No
Granulation	640	850	No	Yes (6000 rpm)	No
Drying (phase I)	300	120	No	No	Yes
Drying (phase II)	900	120	Yes (40°C)	No	Yes

TABLE 2 **Granule Formulation and Wetting Agent Amount**

	Placebo	G-needle-shaped	G-stick-shaped	G-isodimensional
Metronidazole (% w/w)	No	75	75	75
Diluent (% w/w) Lactose α-monohydrate	90	15	15	15
Binding agent (% w/w) Lycatab PGS®	10	10	10	10
Wetting agent (mL/100 g) Demineralized water	16.5	16.5	16.5	16.5

the granule apparent density, calculated according to Eq. (3).

$$\rho_g = \frac{6}{n\pi d^3}\left[m_d - \frac{c}{c-1}(m_w - m_d)\right] \qquad (3)$$

where n is the number of particles in the analyzed sample.

Determination of Technological Properties of Granules

The particle size distribution was determined by sieving granules between 50–1000 μm. The analysis was repeated three times. For any subsequent characterization, the 180–600 μm fractions were selected. The loss on drying percentage (LOD%) was determined by a thermal balance (Scaltec, SMO 01, Germany), by heating an appropriate amount of granules at 120°C until constant weight. Results are the mean of four measurements. True particle densities were measured by using a helium pychnometer (Accupyc 1330, Micromeritics, England) with a cell of 10 cm^3. Results are the mean of 10 measurements. The porosity was determined by an Autopore 9220 mercury porosimetry (Micromeritics, Norcross). Results are the mean of 10 measurements. The friability was determined three times with a standard rolling-drum apparatus (Tecnogalenica, Milano, Italy). The friability index is expressed as the ratio of broken granule mass after 200 rotations and the initial granule mass. Carr index (Carr, 1965a,b) was determined from initial and tapped powder volumes (Tecnogalenica, Milano, Italy).

The compression study was performed on a high tech mini rotary press (Ronchi, Piccola 10, Italy) equipped with a computerized control system to detect and analyze force-signals (pressing and ejection force) and with 10 flat 11.28 mm-diameter punches. The magnesium stearate addition as lubricant directly in the granules was avoided in order to exclude any influence on results; hence, a discontinuous compression procedure was chosen and samples were manually introduced in only one die. Die and punches were prelubricated with a 1% magnesium stearate suspension in ethanol 96% (v/v). The powder mass was always constant in order to obtain 334 mg tablets. A simple formula was chosen, composed by 250 mg of metronidazole according to the therapeutic dosage, 50 mg of lactose and 34 mg of pregelatinized maize starch. The force at the upper punch was progressively increased and recorded. Results for each compression force were the mean of five measurements.

Results were expressed as tabletability, that is, the capacity of different materials to be transformed into tablets of specified strength under the effect of compression pressure (Joiris et al., 1998) and as compressibility, which is the ability of a material to undergo a reduction in volume as a result of an applied pressure (Joiris et al., 1998).

Thickness and diameter of intact ejected tablets were measured with a manual micrometer (Mitutoyo, Japan) immediately after ejection. Tablet porosity was calculated from tablet dimensions, mass, and powder density. Crushing force was measured immediately after compression with a tablet strength tester (Erweka, type TBH30, Germany). Tensile strength Q (Fell & Newton, 1970) was calculated according to Eq. (4):

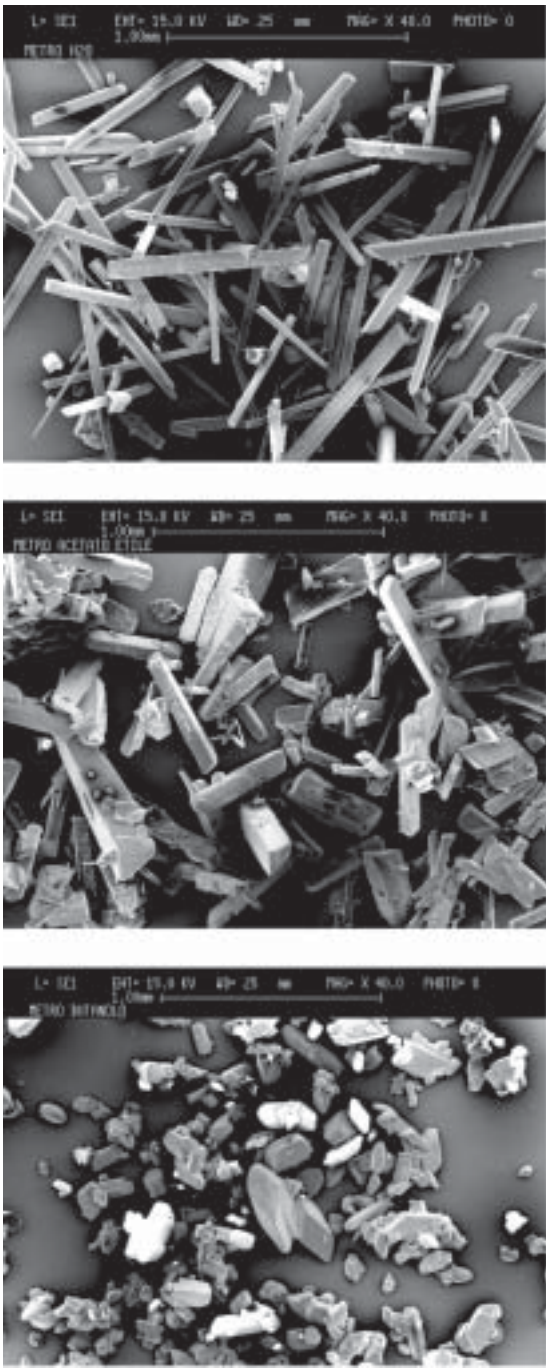
$$Q = \frac{2H}{\pi dt} \qquad (4)$$

where H is the tablet crushing strength, d the diameter, and t the thickness of the tablet.

RESULTS AND DISCUSSION

Crystallization From Different Solvents and Batch Selection

Metronidazole was crystallized in three different solvents by the salting-in method. The shape of the different types of crystals is depicted in Fig. 1. The physical characteristics of the particles are indicated in Table 3. Crystals were arbitrarily classified according to three different crystal habits, which is the depiction of the outer appearance of crystals (York, 1983), taking into account their elongation ratio, expressed as the ratio of maximum and minimum Ferret's diameters measured on 500 particles. The three different crystal habits are defined as follows: "needle-shaped" with an elongation ratio greater than 10, "stick-shaped" with an elongation ratio in the range of 10:3 and "isodimensional" with an elongation ratio lower than 3. Crystals obtained from water are classified as needle-shaped because of the important elongation ratio (about 16:17). Crystals from ethyl acetate appear as



(a)

(b)

(c)

FIGURE 1 **SEM Photomicrigraphs of Metronidazole Crystals Used for Preparing Granule Batches (Magnification: 40×).**

stick-shaped crystals of large particle size distribution, with an elongation ratio of approximately 5.0. Crystals obtained from butanol are isodimensional, the elongation ratio being 1.70. All batches did not show tendency to the agglomeration. All types of crystals show the same crystalline structure and the existence of different crystalline forms was excluded by X-ray powder diffractometry (unreported data). The mean particle size and the agglomeration tendency were reported in Table 3.

Some additional properties of the selected samples, such as density, specific surface area, flowability, and wettability were measured (Table 3). True density, measured by helium pychnometry, was practically the same for all the batches. In fact, this parameter is more frequently influenced by the crystalline structure rather than by the outer appearance of crystals. Highly significant are the differences in specific surface area that, obviously, reflects the particle size: it is higher for isodimensional particles, because of the lower mean particle diameter. Compressibility index (or Carr index, CI), which is expressive of the attitude of a powder to reduce its volume under tapping and consequently, of the powder flowability, is higher for the stick-shaped particles than the isodimensional and the needle-shaped particles. Water wettability is expressed as the contact angle at the solid/liquid interface: lower the contact angle, greater water wettability. Among the three types of crystals, the contact angle is highest for isodimensional particles crystallized from butanol and decreases by increasing the elongation ratio. These results can be explained by a lower hydrophilic surface area of isodimensional crystals, with respect to crystals of higher elongation ratio. In any case, no great differences are shown by the three samples and the results indicate a good affinity of the particles for the granulating liquid.

Liquid Granulation and Technological Characterization of Granules

Four different granule batches were produced (Table 2): the placebo (G-placebo) with no drug, the needle-shaped (G-needle-shaped) produced with crystals obtained from water, the stick-shaped (G-stick-shaped) produced with crystals obtained from ethyl acetate, and the isodimensional (G-isodimensional) produced with crystals obtained from butanol. It must be noted that the same granulation procedure was always applied (Table 1), in order to avoid differences in process variables.

The excipients for wet granulation were selected in order to minimize their effect on granule properties, which should be related as much as possible on the MTZ powder characteristics. In order to highlight differences in tabletability among the different types of granules, lactose α-monohydrate was used as diluent for its very poor tabletability properties. In this case, the possibility to highlight differences in tabletability

TABLE 3 Physical Properties of Metronidazole Crystals Prepared by the Salting-in Method and Expressed According to the Crystallization Solvents

	Crystals from water	Crystals from ethyl acetate	Crystals from butanol
Crystal habit	Needle-shaped	Stick-shaped	Isodimensional/Polyhedral
Agglomeration tendency	No	No	No
Elongation ratio (μm)	16.72 ± 7.91	5.02 ± 2.82	1.70 ± 0.81
Mean particle size (μm)	379 ± 240	250 ± 100	240 ± 30
Apparent particle density (g/cm^3)	1.4418 ± 0.0006	1.4457 ± 0.0009	1.4448 ± 0.0006
BET surface (m^2/g)	0.78 ± 0.08	0.56 ± 0.07	1.35 ± 0.09
Initial density (g/cm^3)	0.65 ± 0.21	0.98 ± 0.12	0.60 ± 0.08
Tapped density (g/cm^3)	0.88 ± 0.35	1.13 ± 0.37	0.81 ± 0.89
Carr index	26.09	13.27	26.19
Contact angle (θ)	26.58 ± 1.38	30.21 ± 2.08	31.55 ± 1.23

among the granules was not compromised. In fact, the alternative use of a diluent with better compression properties, such as microcrystalline cellulose for instance, should have masked the influence of the drug properties on granules characteristics. Lycatab PGS® was used as a binder for similar reasons. In fact, it has been shown to have minor performance in comparison with other common binders, in granule strength and granule tabletability (Becker, 1997).

During the study of a wet granulation process, the main problem is related to the determination of the appropriate binder liquid amount. In order to determine the appropriate amount of granulating liquid, the power consumption method was used according to Leuenberger (1982). The granulating liquid was progressively added at constant feeding, while each batch was processed in the high-shear mixer-granulator. The power consumption of the impeller was recorded by the software Labtech® Realtime Vision Version 3.0 (1998) and expressed versus the granulating liquid amount. In Fig. 2, the power consumption profile (PCP) of the four granule batches is reported. The length of the stage III (the steady flow stage), which is considered as the most appropriate for the granulation, is approximately the same for the four batches.

Additionally, in order to find a same granulating liquid amount, appropriate for all the formulations, different granulations were performed by changing the amount of granulating liquid. The experiments were performed with amounts ranging between 14 and 18 mL/100 g of powdered mass which corresponds to the steady flow stage for all the batches. The mean diameter of dried granules was determined and expressed versus the amount of liquid added and results are given in Fig. 3. The mean particle size increases by increasing the granulating liquid. The amount of 16.5 mL/100 g was chosen because it gave granules with appropriate and narrow size distribution (lower standard deviation). In Fig. 4, it is reported the normal particle size distribution of the batches obtained with a 16.5% of water as binder liquid. In consequence of differences in mean particle size and BET surface, one should expect greater differences in the amount of granulating liquid requested for granulation (Johansen & Schæfer, 2001). Probably, the initial differences in properties of different crystals are leveled out by a particle size reduction of the most fragiles caused by the forces exerted by the three blade impeller. It must be considered that a high-speed granulation process, such that occurring in a high-shear mixer-granulator, proceeds by means of several stages: dry mixing, liquid-solid mixing, granulation and drying. During dry mixing and solid-liquid mixing, the high strength exerted by the impeller and particle-particle frictions should promote the grinding of the most fragile particles. Moreover, during the solid-liquid mixing, depending on particle surface area in contact with fluid and water solubility of the component mix, some very small particles can be dissolved in the liquid. These are probably the reasons of the greater granule densification of both G-needle-shaped and G-stick-shaped. Additionally, the lower porosity % of the G-stick-shaped can be explained by the particle packing properties (Table 3) that favors densification during the granulation. The degree of liquid saturation (DLS%) reflects mainly the particle wettability. The DLS% of the

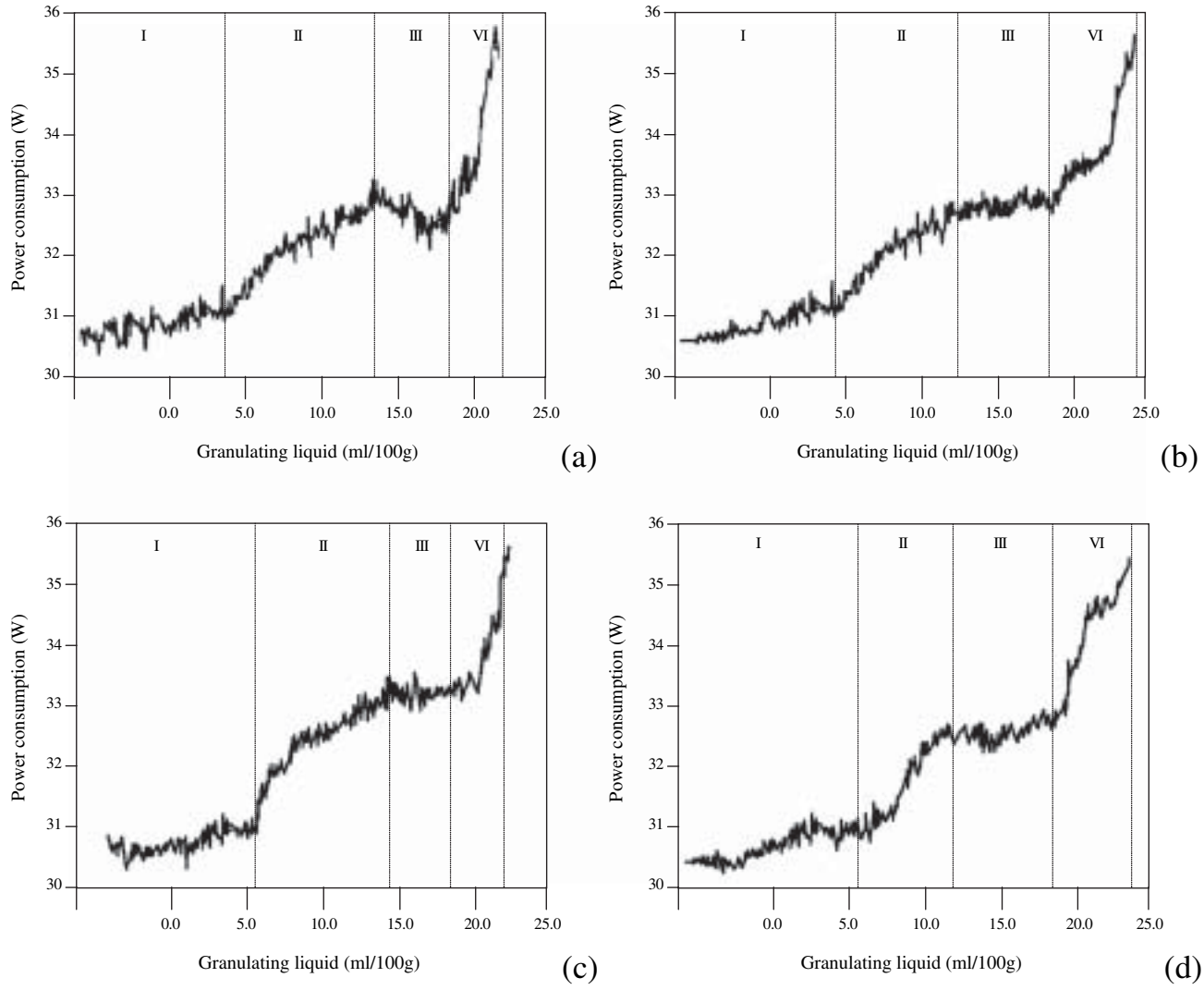


FIGURE 2 **Power Consumption Profile (PCP) According to Leuenberger (1982). (a) G-placebo; (b) G-needle-shaped; (c) G-stick-shaped; (d) G-isodimentional.**

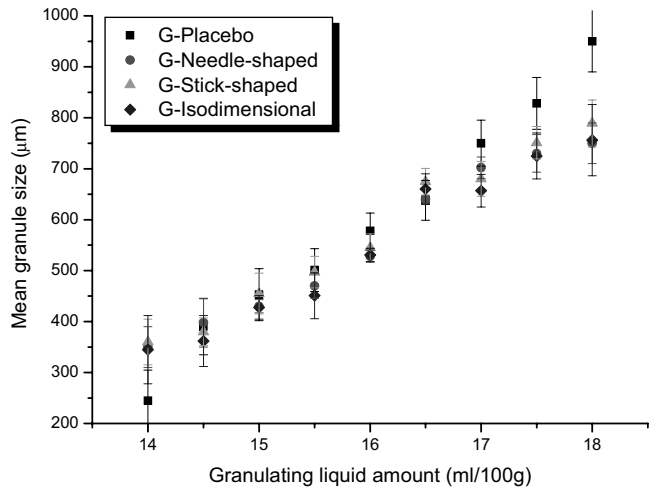


FIGURE 3 **Mean Granule Size Expressed Versus the Granulating Liquid Amount. The Range of the Granulating Liquid Amount has Been Determined by the PCP Experiments.**

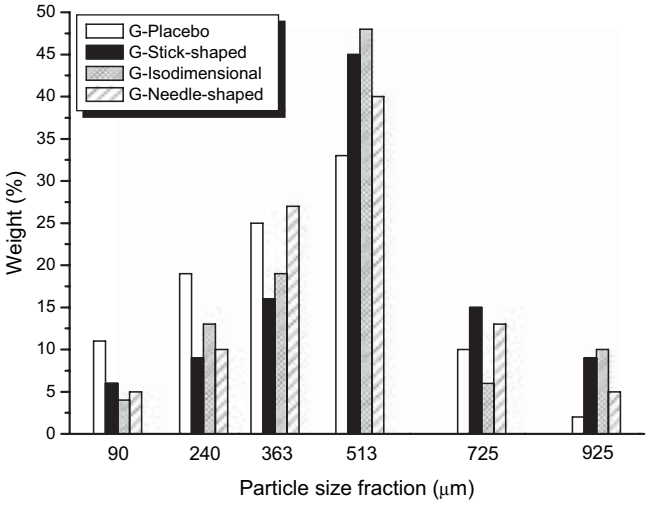


FIGURE 4 **Normal Particle Size Distribution of Different Granule Batches. Results Were Obtained From Granulometric Sieving Analysis.**

G-needle-shaped sample is the highest one. This fact can be explained by the greater crystal wettability that favors the contact between the particles and the wetting liquid and it is magnified by the particle size reduction exerted by the impeller occurring during the granulation. The final granule porosity is the consequence of the densification occurring by the particle size reduction.

On the contrary, the G-isodimensional exhibits the lowest DLS% and is in accordance with the lower particle wettability and with the greater resistance of the particles to grinding. The higher porosity reflects these evidences and the particle packing properties (Table 3). The G-placebo exhibits the highest final granule porosity and this fact can be explained by the lower DLS%.

Granule final water content ranges approximately in the same interval (2.5–3%).

Granule Compression Properties

The initial and tapped granule densities and Carr's Indexes are reported in the Table 4. The initial bulk density is ranked in the order: G-isodimensional > G-needle-shaped > G-stick-shaped > G-placebo. Also G-needle-shaped shows a higher initial bulk density than G-placebo and G-stick-shaped. All the granules show very good compressibility, as indicated by the Carr's index. The best compressibility is exhibited by the G-placebo, thanks to the presence of a large amount of small granules that permits a better filling of the voids and, thus, densification.

Granules, compressed in a rotary press, exhibit a very different tabletability (Fig. 5a). The best compression behavior is exhibited by the G-isodimensional batch. It displays very good tabletability along the entire compression pressure range, whereas tablet tensile strength proportionally increases by increasing of compression pressure. Only a slight decrease in the slope is observed after a compression pressure of 110 MPa and tablet capping was never observed. Far lower tabletability was exhibited by the G-placebo; however, it always exhibits better tabletability than the G-stick-shaped and better tabletability than the G-needle-shaped up to about 150 MPa. At the compression pressure of about 95 MPa, the G-placebo tabletability reaches a limit value and any further increase in compression pressure enables to increase tablet tensile strength. For compression pressures higher than 150 MPa, G-needle-shaped overcomes the placebo tabletability, where the poorest property is always exhibited by the G-stick-shaped batch. Differences in tabletability can be related to differences in compressibility (Fig. 5b). The G-isodimensional batch exhibits a very high tendency to reduce its volume: tablet porosity decreases linearly with an increase in compression pressure, up to about 110 MPa, reaching a limit value of 6%. Quite good compressibility can also be observed for G-needle-shaped batch: 7% tablet porosity was reached, however only at higher compression pressures (160 MPa). In the range 40–110 MPa, this batch exhibits similar compressibility to that of placebo formula, although tablet tensile strength and porosity of this last one reach limit values. It is possible to affirm that the main reason for differences in tabletability is attributed to compressibility. In Figs. 6 and 7, SEM microphotographs of tablets obtained at a compression pressure of about 100 MPa are presented. Particularly in Fig. 6, photographs refer to the tablet surface, while in Fig. 7 photographs show the internal tablet section, when broken in two parts in the tablet

TABLE 4 **Technological Properties of Metronidazole Granules**

	G-placebo	G-needle-shaped	G-stick-shaped	G-isodimensional
Apparent particle density (g/cm^3)	1.4734 ± 0.0024	1.4372 ± 0.0007	1.4550 ± 0.0016	1.4248 ± 0.0023
DLS (%)[(a)]	35.10 ± 2.50	45.55 ± 2.37	41.48 ± 1.62	40.29 ± 1.78
Porosity (%)	52.33 ± 5.37	40.24 ± 4.67	38.75 ± 1.28	46.71 ± 3.25
Friability index (%)	47.87 ± 3.67	28.24 ± 0.71	30.28 ± 1.23	27.37 ± 0.93
LOD (%)	2.35 ± 1.28	3.24 ± 0.79	3.89 ± 0.45	3.32 ± 0.27
Initial density (g/cm^3)	1.56 ± 0.13	1.62 ± 0.15	1.60 ± 021	1.76 ± 0.09
Tapped density (g/cm^3)	1.64 ± 0.73	1.76 ± 0.21	1.79 ± 0.52	1.94 ± 0.64
Carr index	4.69	11.35	10.16	8.82

[(a)]The DLS refers to the wet granules just before drying.

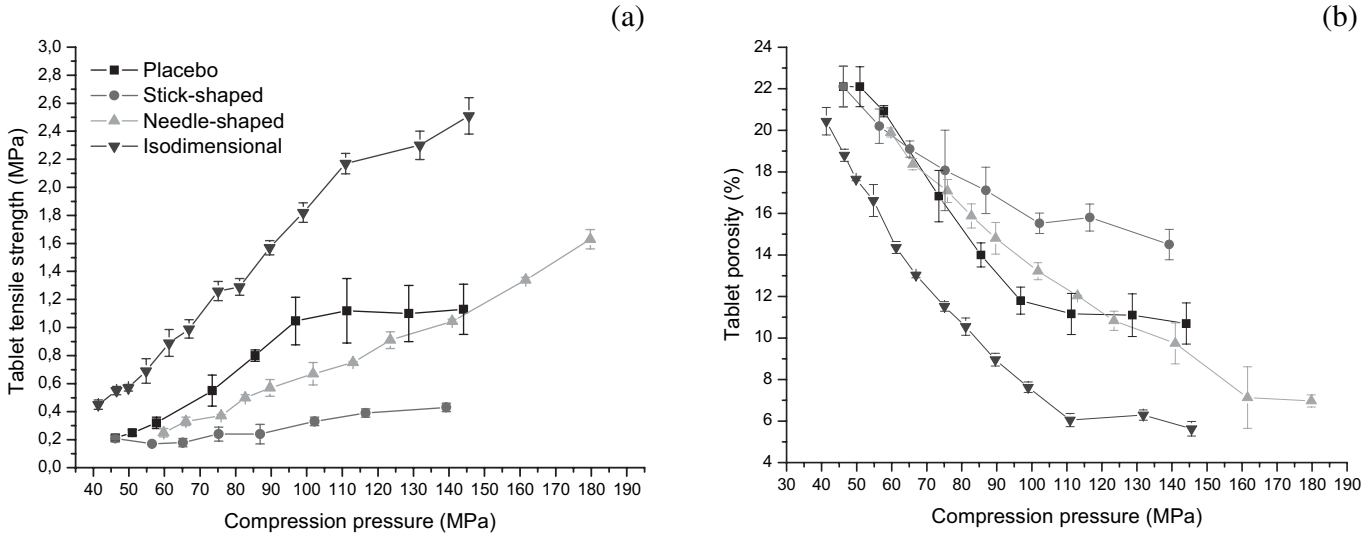


FIGURE 5 **Compression Behavior of Granule Samples. Each Point is the Mean of Five Measurements, Whose Error Bars are Given as: (a) Tabletability is Expressed as Tablet Tensile Strength Versus Maximal Compression Pressure; (b) Compressibility is Expressed as Tablet Porosity Versus Maximal Compression Pressure.**

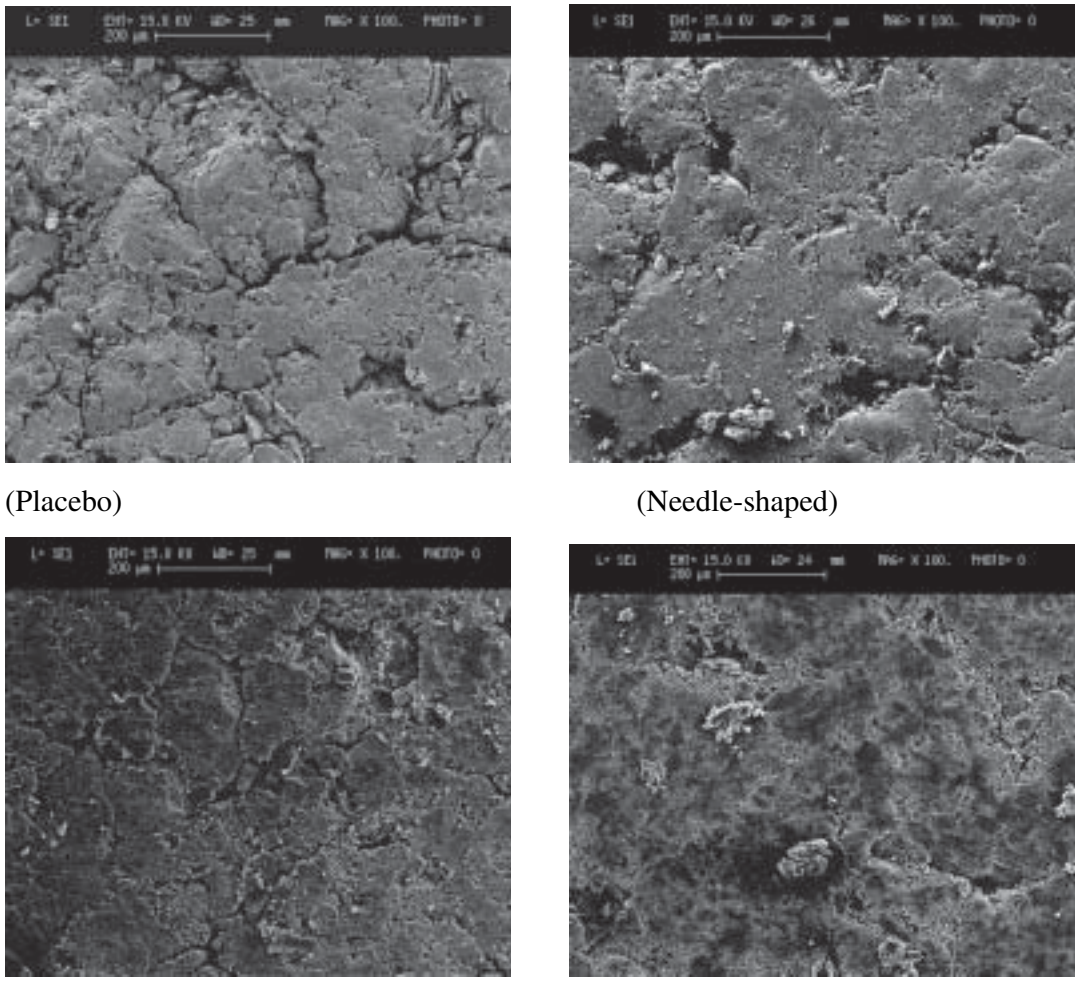
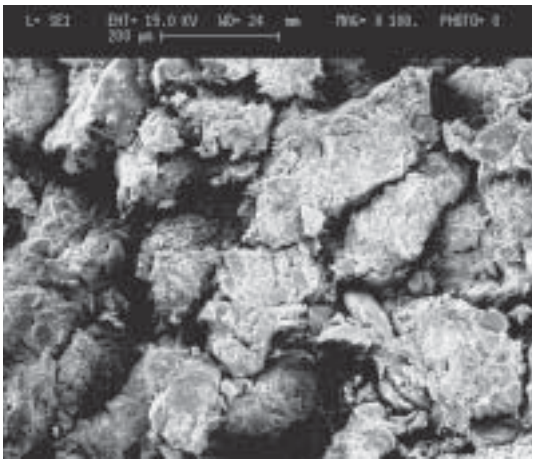
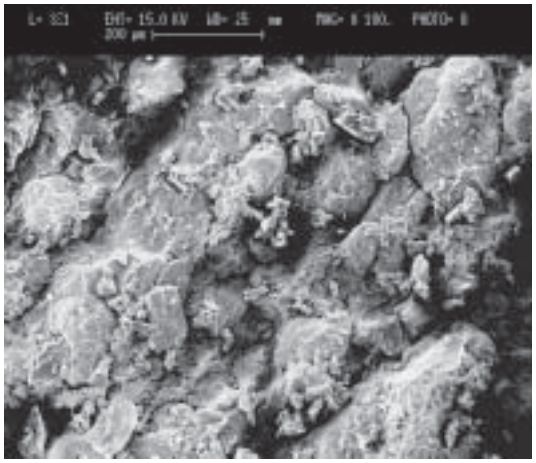


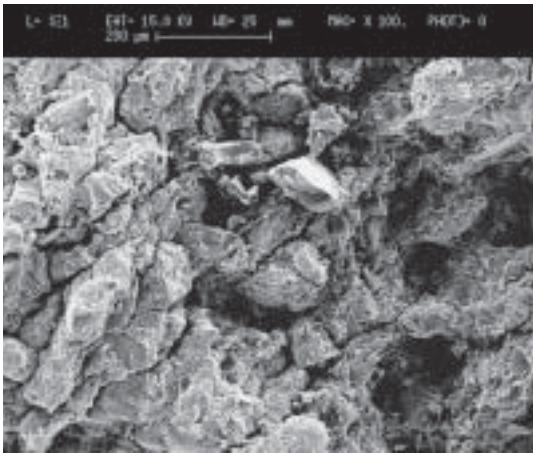
FIGURE 6 **SEM Microphotographs of Internal Section of Tablets Obtained From Different Granules at 100 MPa: (a) Tablet From G-placebo 100×, (b) Tablet From G-needle-shaped 100×, (c) Tablet From G-stick-shaped 100× (d) Tablet From G-isodimensional 100×.**



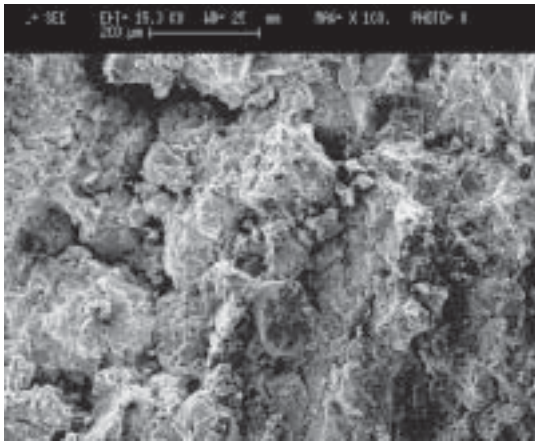
(Placebo)



(Needle-shaped)



(Stick-shaped)



(Isodimensional)

FIGURE 7 **SEM Microphotographs of Surface of Tablets Obtained From Different Granules at 100 MPa: (a) Tablet From G-placebo 100×, (b) Tablet From G-needle-shaped 100×, (c) Tablet From G-stick-shaped 100× (d) Tablet From G-isodimensional 100×.**

strength tester. In both cases, it can be observed that tablets obtained from G-isodimensional are less porous, than the other batches.

CONCLUSION

The metronidazole particle characteristics strongly affect the properties of granules produced by wet granulation process in a high-shear mixer-granulator. Among the particle characteristics, the crystal habit, the elongation ratio, the particle size distribution, and the wettability are the most significant. The granules that are produced from the different particles differ among them and the main parameter affected is the granule porosity percentage. Granules of higher porosity, such as those prepared from the isodimensional particles, exhibit a greater ability to densificate under the compression pressure and this fact is expressed as a greater tabletability. The fragile particles such as the needle-shaped that can be broken by the high-shear forces involved in the granulation process can densificate, giving granules of lower porosity that are unable to undergo further densification during compression.

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