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Improved compression properties of propyphenazone spherical crystals

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Abstract

Spherical propyphenazone crystals were produced by an agglomeration technique using a three solvents system. After selecting the best propyphenazone solvent (ethyl alcohol), non-solvent (demineralized water) and bridging liquid (isopropyl acetate), several of their ratios were tested by a Sheffé ternary diagram. Micromeritic properties of agglomerates such as flowability, were improved and their compression behavior was investigated and compared to that of raw crystals. By compression and densification studies, along with tablet SEM analysis, we have been able to explain the compression mechanism of propyphenazone spherical crystals and have shown that their better tablet/ability can be due to the small size of individual particles in the agglomerates

Keywords: Propyphenazone; Spherical crystallization; Compression behavior; Brittle fracture

1. Introduction

Direct tableting of pharmaceutical materials is desirable to reduce the cost of production (Shangraw, 1989). However, compressing a high-dosed drug directly requires good micromeritic properties, such as flowability, and a good and reproducible compression behavior. The spherical crystallization technique has been investigated to improve the flowability and compression properties of propyphenazone. This is a derivative of phenazone which is used as an antipyretic and analgesic in doses of 250–600 mg (Martindale, 1996).

The spherical crystallization technique has already been successfully applied to improve the micromeritic properties of acebutolol hydrochloride (Kawashima et al., 1994b). In the most common case, this technique is reputed to improve the

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wettability and dissolution rate of different drugs (Kawashima et al., 1986; Sano et al., 1992; Guillaume et al., 1993; Di Martino et al., 1999). Some drugs have also been recrystallized by the spherical agglomeration technique using polymeric materials to modify their release (Akbuga, 1989; Ribardiere et al., 1996).

There are two main methods for spherical crystallization: spherical agglomeration (SA method) and emulsion solvent diffusion (ESD method) (Kawashima, 1994a). In the SA method, a quasi-saturated solution of the drug, in a solvent in which it is very soluble, is poured into a poor solvent of the drug. Provided that the good and the poor solvents are freely miscible and interaction (binding force) between the solvents is stronger than drug interaction with the good solvent, crystals precipitate immediately. A suitable amount of a third solvent, which is not miscible with the poor solvent and which preferentially wets the precipitated crystals, is added to the system while stirring. This third solvent, which is called a 'bridging liquid', can collect the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension between the interface of solid and liquid (Kawashima and Takenaka, 1984). The SA method has been applied to several drugs (Guillaume et al. 1993; Di Martino et al., 1999). When interaction between the drug and the good solvent is stronger than that of the good and poor solvents, the good solvent drug solution is dispersed in the poor solvent, producing quasi-emulsion droplets, even if the solvents are normally miscible. This is due to an increase in the interfacial tension between good and poor solvent. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor-solvent phase. The counter-diffusion of the poor solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplet containing the poor solvent. This process is known as the emulsion solvent diffusion (ESD) process (Sano et al., 1992). In a particular case, this process was used for norfloxacin using an ammonia diffusion system (ADS) (Puechagut et al., 1998). In our case, the SA method was used. The aim of our study was to improve the compression properties of propyphenazone in direct compression by the spherical crystallization technique and to explain its compression behavior.

2. Materials and methods

2.1. Agglomeration of propyphenazone crystals

Propyphenazone solubility was measured spectrophotometrically (Cary 1E UV-VIS, Varian, Italy) in different solvents at room temperature at 246 or 275 nm, according to the solvents used. Ethyl alcohol 96% (v/v) was chosen as the best solvent and propyphenazone solubility in this solvent was also measured at 40°C. An excess of crystals was maintained in ethyl alcohol at this temperature under continuous stirring, the suspension was filtered through a 0.45 μm membrane filter (Millipore, France) and immediately diluted for spectrophotometric determinations.

Twenty grams of propyphenazone (A.C.E.F., Italy) was dissolved in 25 ml of ethyl alcohol 96% (v/v) (PRS, Panreac, Spain) at a temperature of 40°C. The solution was poured into 62.5 ml of demineralized water maintained at room temperature under continuous stirring at 500 rpm with a paddle device. Ten milliliters of isopropyl acetate 99% (Aldrich Chemical, USA), acting as a bridging liquid, was then added. After 10 min, 2.5 ml of isopropyl acetate was again added and the stirring was prolonged for 5 min more. Spherical crystals were then formed. They were filtered from the liquid and dried in an oven at 50°C for 12 h. The sieved 425–1400 μm fraction was recovered to exclude the biggest particles.

On the other hand, propyphenazone unagglomerated crystals were obtained by cooling after filtration a quasi-saturated ethanolic solution from 40°C to room temperature. Except for the SEM analysis, crystals were gently ground before use. Their mean size diameter was determined by counting Feret's diameter of 400 particles with a Galileo optical microscope.

2.2. Physical characterization of propyphenazone crystals

Particle shapes of propyphenazone unagglomerated and spherical crystals were observed using a scanning electron microscope (Cambridge S 360, United Kingdom). SEM analysis was also performed on propyphenazone tablets. Tablets, obtained at a compression pressure of about 200 MPa, were broken in two parts by a tablet strength tester (Erweka, TBH 30, Germany) along the diameter. Samples were mounted on a metal stub with double side adhesive tape and then covered under vacuum with a gold layer of 200 Å thickness using a metallizator (Balzer MED 010, Linchestein).

A DSC study was used to detect possible polymorphic transition during the crystallization process. Samples were analyzed using a DSC (Pyris 1, Perkin Elmer, USA) equipped with an ethanol cooling system circulating in a refrigerator (Cryostat F4-Q, Haake Q, Germany). A dry purge of nitrogen gas (20 ml/min) was used for all runs. The DSC was calibrated for temperature and heat flow using a pure sample of indium and zinc standards. Sample mass was ≈ 3–4 mg and aluminium closed pans were used. Each run was performed from 20 to 120°C at a heating rate of 10°C/min. An X-ray diffraction study was also carried out to exclude any polymorphic transition during propyphenazone crystallization. A Philips PW 1730 (Holland) was used as an X-ray generator for Cu Ka radiation ($\lambda = 1.54178$ Å). The experimental X-ray powder patterns were recorded on a PH 8203. The goniometer was a PH 1373 and the channel control a PH 1390. The data were collected in the continuous scan mode using a step size of 0.01 2θ. The scanned range was 2°θ to 40°θ.

2.3. Micromeritic properties

Apparent particle densities of agglomerated and unagglomerated crystals were measured using a helium pycnometer (Ultrapycnometer 1000, Quantachrome, New York, USA) with a cell of 60 cm^3. Results are the mean of 20 measurements. Carr's index (Carr, 1965a,b) was determined from powder volumes at the initial stage and after 1250 lappings to constant volume (Tecnogalenica, Italy). The angle of repose of agglomerated and unagglomerated crystals was measured by pouring the powder onto a 10 mm diameter plate.

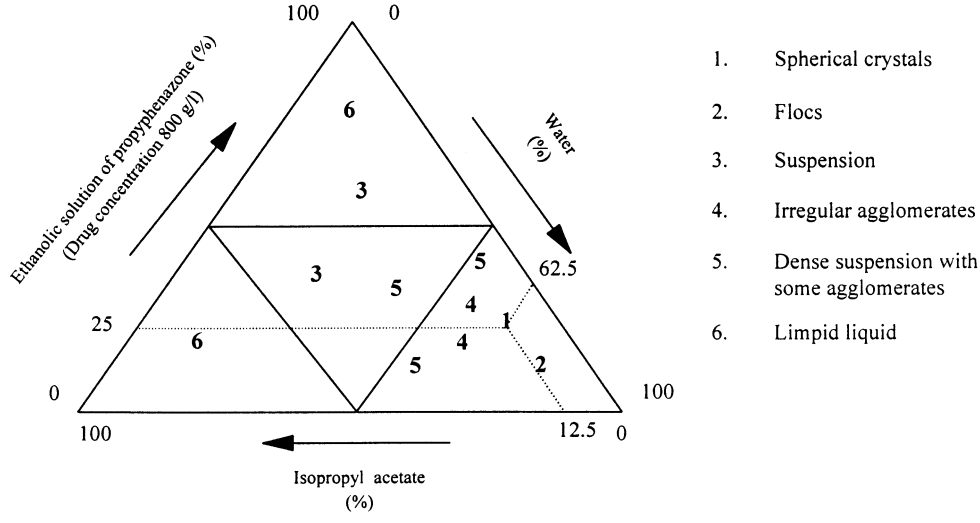

Fig. 1. Ternary diagram built from an incomplete Scheffé (1958) system. In this diagram results of different studies and the area for agglomerate obtention are indicated.

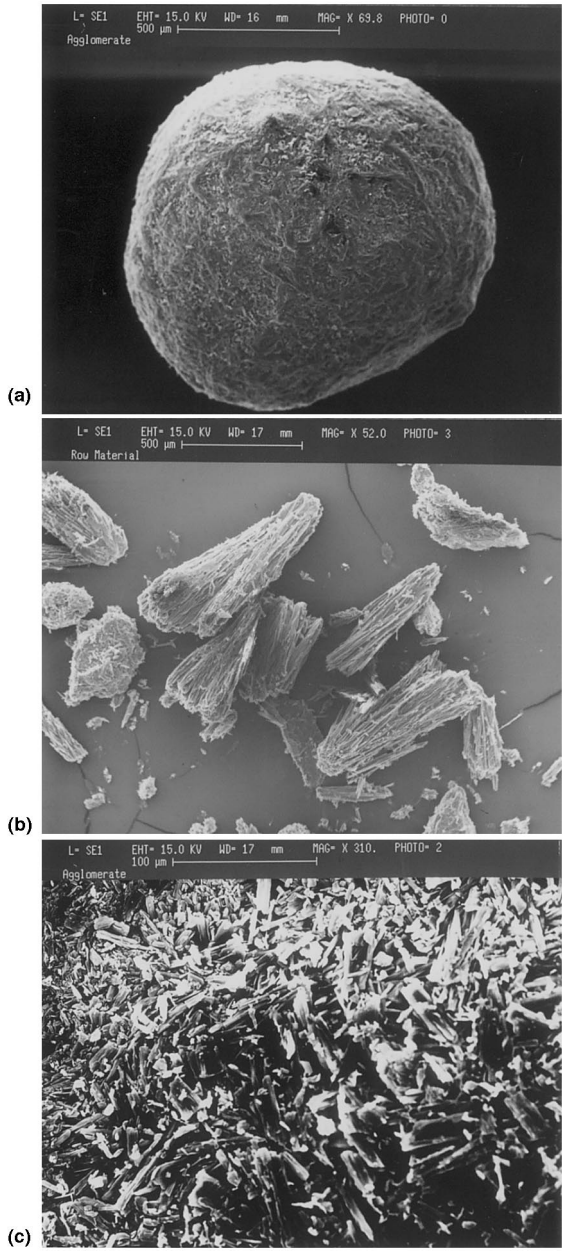

Fig. 2. Scanning electron microscopy of propyphenazone crystals: (a) single spherical crystal; (b) crystals obtained by cooling from 50°C to room temperature in an ethanolic solution; (c) surface of spherical crystal.

2.4. Determination of residual solvent concentration

The determination of residual water on propyphenazone crystals was made according to the titrimetric method of Karl Fischer (Metrhom, Automat E 547) after calibration with all-sodium tartrate (AG, Merk, Germany) and dissolution of crystals in methanol (J.T. Baker, Holland). The Fischer reagent solutions were from Riedel-de-Haen (Ref: 36116 and 36117, Germany). The determination of ethanol and isopropyl acetate was performed by gas phase chromatography on a Shimadzu GC-14B chromatograph (Japan) fitted with a flame ionization detector and a CR-6A Shimadzu integrator. The packed column was Porapack Super Q (Alltech, France), mesh range 80/100, length 1.80 m, diameter 3.175 mm. Carrier gas was anhydrous nitrogen. The temperatures were fixed as follows: column: 150°C; injector: 190°C; detector: 210°C. For assays, 500 mg of propyphenazone crystals were dissolved in 5 ml of 2-propanol (RP Normapur, Prolabo, France), 5 µl were injected into the chromatograph. Standard solutions (five concentrations from 100 to 1000 ppm) were injected to validate the method (linearity, specificity, repeatability). The calibration curves showed a good linearity ($R = 0.99994$ for ethanol, $R = 0.99984$ for isopropyl acetate).

2.5. Compression behavior of agglomerated and unagglomerated crystals

The compression study of propyphenazone agglomerated and unagglomerated crystals was carried out on a high tech mini rotary press (Ronchi, Piccola 10, Italy) equipped with a computerized control system to detect and analyze force-signals (pressing force and ejection force) and with 10 flat 6 mm-diameter punches. Because the sample quantities were small, they were introduced manually in only one die. Die and punches were prelubricated with a 1% magnesium stearate suspension (A.C.E.F., Italy) in ethanol 96% (v/v) (PRS, Panreac, Spain). The powder mass was 80 mg. The die table speed was 7 rpm. The compression pressures were progressively increased and the force at the upper punch was recorded. Results for each compression force were the mean of five measurements.

Table 1
Micromeritic properties for agglomerates and unagglomerated particles of propyphenazone

Sample	Particle shape	Granulometric size (μm)	Angle of repose (°)	True density (g/ml)[c]	Carr index (%)[d]
Unagglomerated particles	Needle	38.4 ± 15.44[a]	38.0	1.1382 (0.00025)	27.55
Agglomerates	Spherical	425–1400[b]	30.8	1.1407 (0.00037)	6.89

[a] Determined by counting 400 of Feret's diameter of 400 particles. Standard deviation is also indicated.
[b] Fraction was recovered by sieving method.
[c] Results are determined by helium pycnometry from the mean of 20 measurements. In parenthesis 95% confidence intervals are indicated.
[d] Determined from Carr's equation: $[(V_0 - V_t)/V_0] \times 100$, where V_0 is the volume of the powder bed at initial stage and V_t the volume after nth tapping.

For the densification study, powders were compressed on an instrumented Frogerais OA single punch tablet machine (Frogerais, France) equipped with 11.3 mm flat-faced punches, by introducing 320 mg samples manually into the prelubricated die, according to Lefebvre et al. (1989). Five cycles were performed for both substances, corresponding to maximal punch pressure of about 150 MPa. For a single compression cycle, both compression pressures on the upper and lower punches and the displacement of the upper punch were measured and recorded at a frequency of 4000 Hz. Correction of displacement transducer data for machine looseness and punch deformation were carried out according to Juslin and Paronen, 1980). Pressure transmission through powder bed in the die was estimated by comparing the maximal compression pressures on the upper and lower punches. Transmission coefficient corresponds to the ratio of lower punch and upper punch values.

2.6. Densification study

The densification behavior of powders was studied using Heckel's equation (Heckel, 1961)

$$\ln 1/(1 - D) = KP + A \quad (1)$$

where D is the relative density of the compressed powder bed at applied pressure P. K is the slope of the straight linear portion of the Heckel plot and the reciprocal of K is the mean yield pressure (P_Y). The constant A is the sum of two densification terms:

$$A = \ln[1/(1 - D'_0)] + B' \quad (2)$$

According to Doelker (1994), D'_0 corresponds to the relative density of the powder at the moment when the last recorded applied pressure is still nil, and B' is the densification due to particle fragmentation. Constants A and B' can be expressed as relative densities using:

$$D_A = 1 - e^{-A} \quad (3)$$

$$D'_B = D_A - D'_0 \quad (4)$$

Heckel's profiles were established from single compression cycles of tablets compressed approximately at 150 MPa. Parameters P_Y, D_A, D'_0, D'_B were calculated using a precompression pressure value of 1.5 MPa. Several methods were described to select a linear region of the Heckel function in order to determine Heckel constants. According

Table 2
Residual solvent contents in propyphenazone crystals. Results are the mean of three determinations; 95% confidence intervals are reported

Water[a]	0.504%–0.103%
Ethanol[b]	81 ppm ± 4 ppm
Isopropyl acetate[b]	79 ppm ± 3 ppm

[a] Determined according to the titrimetric method of Karl Fisher.
[b] Determined by gas phase chromatography.

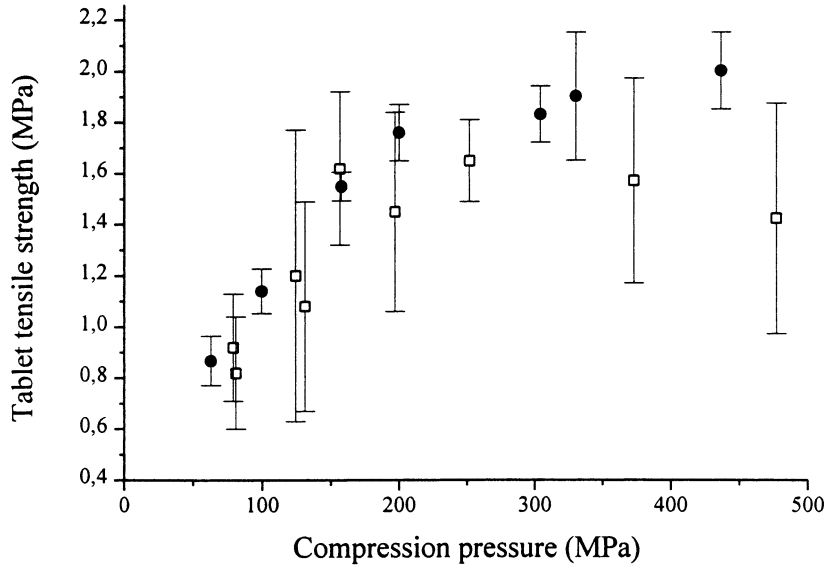

Fig. 3. Tensile strength–pressure profiles of propyphenazone samples. Tablet tensile strength is quoted as a function of maximal upper punch pressure. Each point is the mean of five measurements. Ninety-five percent confidence intervals are also shown. Spherical crystals (●); unagglomerated particles (□).

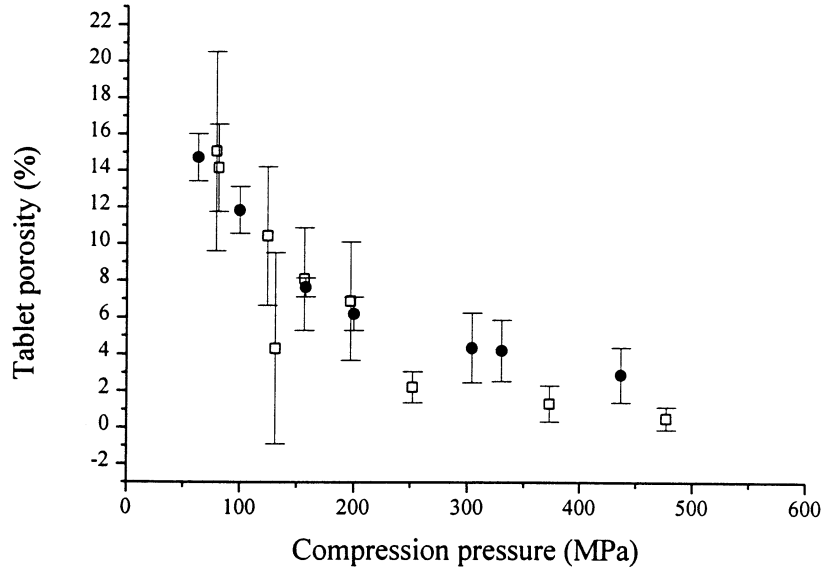

Fig. 4. Compressibility of propyphenazone samples. Tablet porosity is quoted as a function of maximal upper punch pressure. Each point is the mean of five measurements. Ninety-five percent confidence intervals are also shown. Spherical crystals (●); unagglomerated particles (□).

to Paronen and Ilkka (1996), we selected a range of measurement points where the linear regression coefficient was as high as possible. This corresponds for both samples to the 50 to 100 MPa range, with coefficient values superior to 0.998. Each value is a mean of five measurements. Elas-

tic recovery was calculated according to Armstrong and Haines-Nutt (1974):

$$\text{Elastic recovery } (\%) = [(t_1 - t_2)/t_1] \times 100 \quad (5)$$

where t_1 is the minimal thickness of the powder bed in the die and t_2 is the tablet thickness measured immediately after ejection.

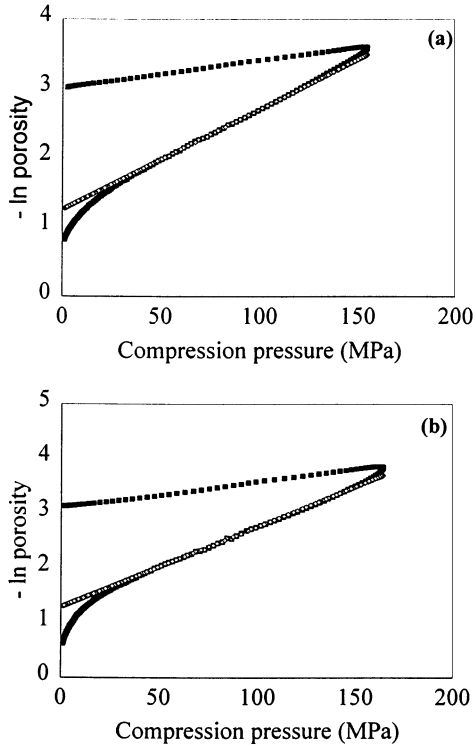

Fig. 5. Typical Heckel's plots for two propyphenazone samples, obtained from a single compression cycle. Straight lines correspond to linear regression analysis of data ranging from 50 to 100 MPa. (a) Unagglomerated crystals, (b) spherical crystals.

Table 3
Heckel parameters, elastic recovery and 95% confidence intervals for the two propyphenazone samples

	Unagglomerated crystals	Spherical crystals
P_Y	68.7 ± 4.0	69.3 ± 5.2
D'_0	0.575 ± 0.006	0.498 ± 0.008
D_A	0.714 ± 0.001	0.728 ± 0.003
D'_B	0.139 ± 0.007	0.230 ± 0.010
Elastic recovery (%)	4.62 ± 0.27	4.63 ± 0.42

2.7. Tablet characterization

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 and Newton, 1970) was calculated according to Eq. (6):

$$Q = 2H/\pi dt \quad (6)$$

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

3. Results and discussion

3.1. Agglomerate obtention

The study started with the choice of the best solvent for propyphenazone. Ethyl alcohol 96% (v/v) was selected because in this solvent the drug was very soluble (800 g/l at 40°C). In this way, it was possible to obtain a very concentrated drug solution which increases the densification of the material during the crystallization process. The concentration of the solution at 40°C corresponds to a quasi-saturated solution. The crystallization of propyphenazone from ethyl alcohol by cooling down, gave typical needle-shaped crystals. The addition of the solution to the non-solvent phase (water) caused propyphenazone precipitation and a weak tendency to particle agglomeration was observed. The addition of the bridging liquid (isopropyl acetate) favored the transfer of the drug to this emulsified phase in which crystal agglomerates densified and developed spherically. To find the best percentage of the three liquids, a ternary diagram was built (Sheffé, 1958). The model chosen was an experimental design according to Sheffé (third degree incomplete model). Experiments were carried out according to Di

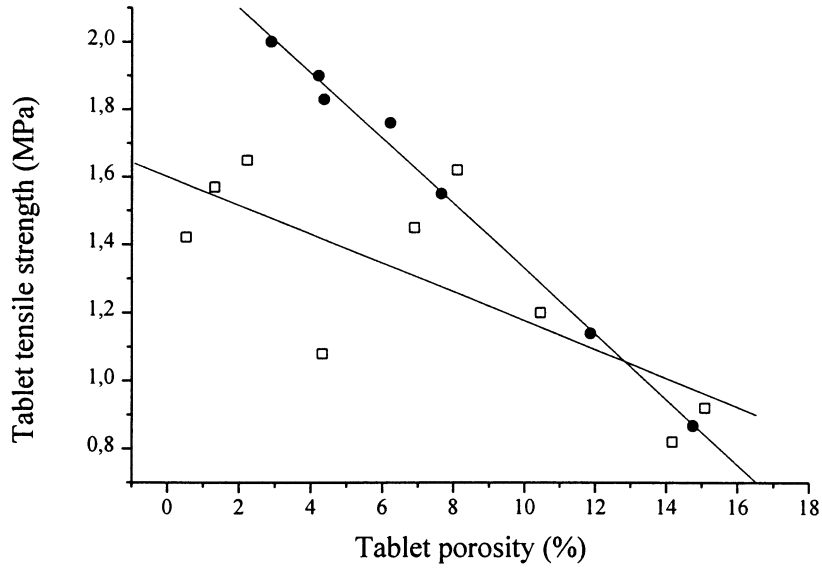

Fig. 6. Compactibility of propyphenazone samples. Tablet tensile strength is quoted as a function of tablet porosity. Spherical crystals (●); unagglomerated particles (□).

Martino et al. (1999). The results of our experiments are reported in Fig. 1. It must be noted that ethyl alcohol is miscible with water in any proportion and isopropyl acetate is miscible with 23 parts of water, giving an emulsion in a large area of the ternary diagram. After location of the agglomerate formation zone, different stirring rates were tested. An optimum was found at 500 rpm. A lower stirring rate of 250 rpm reduced the possibility of agglomerate obtention, while a higher stirring rate of 700 rpm destroyed the agglomerates.

3.2. Physical characterization of propyphenazone crystals

Fig. 2 shows a typical shape of agglomerated (Fig. 2a) and unagglomerated crystals (Fig. 2b). The spherical single particle is formed by very small needle-shaped crystals, which are closely compacted into a spherical form, as is clearly evident when the crystal surface is enlarged (Fig. 2c). DSC thermograms for propyphenazone agglomerated and unagglomerated particles make it possible to exclude polymorphic transitions during crystallization. This result is confirmed by the X-ray diffraction study. Micromeritic properties of propyphenazone agglomerated and unagglomerated crystals are given in Table 1. Flowability of the agglomerates is greatly improved, as is exhibited by their angle of repose that is lower than that of unagglomerated particles. The apparent particle density of agglomerates is slightly higher than that of unagglomerated crystals. Carr's index is very different for the samples, as it is very high for unagglomerated crystals. As will be pointed out later, this has important consequences on the initial compression stage.

3.3. Determination of residual solvent concentration

The results of residual solvent concentration in propyphenazone crystals are reported in Table 2. According to the European Pharmacopoeia (Third edition, addendum 1999), ethanol and isopropyl acetate are class 3 solvents (solvents with low toxic potential), thus the limits of 5000 ppm are acceptable without justification. The results obtained for ethanol and isopropyl acetate are largely below the tolerated limits; the porous structure means that solvents can escape easily during the drying phase.

3.4. Compression behavior of agglomerated and unagglomerated crystals

Tablettability is the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compression pressure. The tensile strength/pressure profiles of propyphenazone agglomerated and unagglomerated crystals are shown in Fig. 3. The tablet tensile strength of spherical crystals is always higher than that of unagglomerated particles. At low compression pressures (50–100 MPa), a no great difference is exhibited between the samples. Even with an increase in compression forces (150–250 MPa), the tablet tensile strength of unagglomerated crystals is always lower than that of agglomerated particles and no increase over 250 MPa could be registered whereas the tensile strength of agglomerates continues to increase proportionally with compression pressures. A great variability in tensile strength of tablets obtained by unagglomerated powder has to be pointed out as it is clearly evident from confidence intervals data in Fig. 3.

To account for the improved performance of spherical propyphenazone crystals, other com-

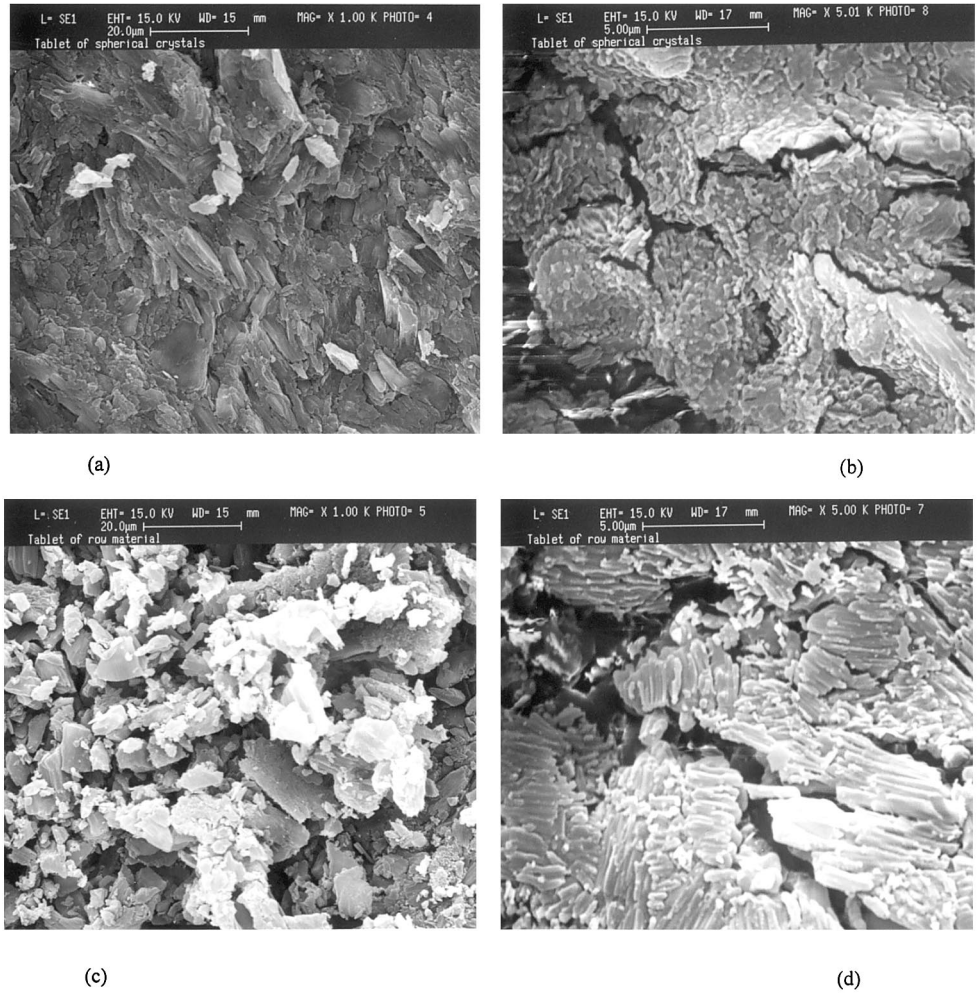

Fig. 7. SEM microphotographs of the tablet cross section. Tablets were obtained at a compression pressure of about 200 MPa. (a–b) tablet of spherical crystals; (c–d) tablet of unagglomerated particles.

pression properties, i.e. compressibility and compactibility, were investigated. The compressibility of a material is its ability to be reduced in volume as a result of an applied pressure. The gradual change in tablet porosity as a function of the increase in compression forces is shown in Fig. 4. In this case, no great difference is to be noted between the two samples, indicating that both crystal samples exhibit similar compressibility. As for tablet/ability, compressibility results were more dispersed for unagglomerated crystals, resulting in greater confidence intervals.

Heckel's profiles were then analysed to obtain more details on the compressibility of these substances. Typical Heckel cycles of unagglomerated and spherical crystals are depicted in Fig. 5, and characteristic values of P_Y, D_A, D'_0, D'_B and elastic recovery are reported in Table 3. During early compression stage, below 50 MPa, both profiles are clearly different, with a more pronounced curvature of the spherical crystal cycles. This corresponds to different D'_0 values, the compression of spherical crystals beginning at lower relative density, while the initial rearrangement phase without pressure increase is longer for unagglomerated material. Also the D'_B value is greater for spherical crystals, indicating a greater brittle fracture tendency of this material during the early stage of compression. It must be kept in mind that spherical agglomerates are composed of very fine individual crystals, which are certainly released and possibly further fragmented at this stage.

However, over 50 MPa, both profiles are superimposable, showing comparable P_Y and D_A values. So, it seems that plastic deformation of propyphenazone crystals and their fragments is similar in the medium to high pressure range whatever the nature of the initial material is. Moreover, elastic recovery is comparable for both materials, resulting in the formation of tablets of similar porosity for both crystal types, even when their internal structure differs. Elastic recovery is relatively high for a brittle material, but it must be noted that tablets survive the decompression phase and show no sign of capping.

The same transmission coefficient (0.897) was observed for both propyphenazone samples, indicating a similar pressure transmission through powder bed. It should be noted that the die was lubricated with magnesium stearate, and that transmission coefficients could be different with other lubrication conditions.

Compactibility is the ability of a material to produce tablets with sufficient strength under the effect of densification (Joiris et al., 1998) and it is an important property of compressed materials. Indeed, even if particles come into close contact during compression, permanent inter-particle bonds have to be formed to obtain sufficiently strong tablets. Fig. 6 shows the relashionship between tablet porosity and the tensile strength of agglomerates and unagglomerated propyphenazone crystals. In this case the better compactibility of agglomerates is evident in particular at lower porosity (between 10 and 2.5%), where the crushing strength for agglomerates is always higher. In this case linear regression fit was generated for both materials. The slope for agglomerates is higher (-0.096) than that for unagglomerated crystals (-0.042). Once again, it should be noted that mean strength values corresponding to compressed spherical crystals are regularly arranged along the regression line, while unagglomerated crystal values are much more dispersed, indicating the greater variability of this material under compression. The root mean square values are are 0.223 and 0.037, respectively for unagglomerated particles and agglomerates. Surprisingly, compactibility studies based on tablet strength–porosity relationship are scarcely used in compression literature. In a previous study, we compared the compactibility of two different fraction sizes of orthorhombic paracetamol (Joiris et al., 1998) and we observed that the compactibility of small size fraction was higher. The same observation was reported for sodium chloride by Eriksson and Alderborn (1995). Likewise, in the case of propyphenazone, our results suggest that spherical crystals could behave like small particles, which can result from the breakage of agglomerates by the punch during compression. To verify this hypothesis, SEM micrographs were performed on the vertical cross-section of tablets broken in the strength tester. Fig. 7 shows the SEM of tablets of spherical and unagglomerated crystals. Their principal differ-

ences concern particle size. Actually, agglomerates are broken during compaction leaving very small single particles whose agglomerates were originally composed. As a consequence of compaction, consolidation implies an increase in mechanical strength resulting from particle–particle interaction. It is possible to assume an increase in particle–particle interaction due to the small size and distances of particles.

4. Conclusion

Spherical crystallization has been revealed as an interesting technique to improve the compression properties of propyphenazone. The improvement in flowability contributes to making the filling of the die easier and more precise and thus gives more reproducible results. This fact, added to an increase in tablet/ability and compactibility properties, helps to obtain a material for direct compression. These properties are probably due to the characteristics of agglomerated crystals which consist of an agglomeration of very small particles, favorable to compression.

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