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The spray drying of acetazolamide as method to modify crystal properties and to improve compression behaviour

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Abstract

Acetazolamide shows a very poor compression ability and tablets must usually be produced through a wet granulation process. However, the possibility to obtain pure acetazolamide for direct compression could be interesting for industrial application. With the scope to obtain a material for direct compression, three different crystallisation methods were chosen, with respect to acetazolamide solvent solubility. (a) Acetazolamide was dissolved in an ammonia solution and then spray dried. It was possible to characterise the spherical particles as a mixture of two polymorphic forms, I and II by Powder X-ray diffraction study. (b) Pure form I was obtained by slowly cooling to room temperature a boiling water solution. (c) Pure form II, the marketed form, was obtained by neutralisation of an ammonia solution. Their compression behaviour was investigated firstly by a rotary press. Whilst pure polymorphic forms I and II could not be compressed, the spray dried particles showed very good compression properties. In fact, tablets were obtained only by spray dried particles, which show very good properties under compression and the absence of capping tendency. On the other hand, it was impossible to obtain tablets from polymorphic forms I and II, whatever compression pressures were used. In order to explain their densification mechanism, a single-punch tablet machine, equipped for the measurement of the upper punch displacement in the die, was used. From calculated Heckel's parameters, it was demonstrated that the spray dried material shows a greater particle rearrangement in the initial stage of compression due to its spherical habit and minor wrinkledness of particle surface. The crystalline structure due to the presence of polymorphic forms I and II concur to lowering the intrinsic elasticity of the material. This fact avoids the risk of the rupturing the interpaticulate bonds, which are formed during the compression, concurring to the consolidation of the tablet.

Keywords: Acetazolamide; Spray drying; Polymorphism; Compression behaviour; Densification behaviour

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1. Introduction

Acetazolamide (AAA), an inhibitor of carbonic anhydrase, with weak diuretic activity, is used mainly in the management of glaucoma. Other indications include epilepsy and high-altitude disorders. In all treatments, the usual unit dose is 250 mg by mouth (Martindale, 1996). In view of the high dosage tablets must be produced usually through a wet granulation process because of the very poor compression properties of acetazolamide. The possibility of compressing it directly could be very interesting for industrial application. For this reason, we tried to obtain a direct compressible acetazolamide, and the spray drying method proved the best way.

Spray drying converts a liquid into a powder in a one-step process, producing fine, and dustless or agglomerated powders, usually approximately spherical with a narrow size range and generally hollow. The hollow nature imparts a low bulk density to the powders (Broadhead et al., 1992). Spray drying can also modify the crystallinity content of the material.

Particle size, crystal habit, crystallinity content, polymorphism and crystal moisture are the most common elements, to which a change in compression properties are attributed. Habit, which is the description of the outer appearance of a crystal, can be modified by crystallising the material in different conditions (e.g. needles, plates, etc.) York, 1983). Shell (1963) demonstrated the effect of crystal habit on tablet properties. Crystal form can affect considerably the compression behaviour of a drug. For example, Summers et al. (1976) pointed out the influence of the crystal form on the plastic-elastic deformation of the material, while, in a previous paper, we demonstrated the better compression properties of the orthorhombic paracetamol over that of the monoclinic form (Di Martino et al., 1996). The molecular structure of orthorhombic paracetamol is characterised by the presence of molecular parallel planes, which confer a greater plasticity on the material under compression (Joiris et al., 1998). Atoms and molecules can be ordered in a three-dimensional structure forming a crystalline state, as opposed to a disordered state, referred to as amorphous. An amorphous form or a form with a low crystallinity could be obtained for example by grinding or by rapid solvent evaporation (spray drying, freeze drying). This corresponds to a mechanical activated state, which is characterised by higher crystal disorder and higher energy content, and by better compression properties (Hüttenrauch et al., 1985). The presence of moisture in pharmaceutical powders can also play a significant role on the consolidation mechanism. For example, Garr and Rubinstein (1992) demonstrated the influence of moisture content in the consolidation properties of paracetamol, while Sebhatu et al. (1997) pointed out its effect on the compressional behaviour of spray dried lactose.

All these particle characteristics could influence the compression process at different stages. According to Train (1956), the densification process of powders can be divided into several stages, slippage and rearrangement of particles occur during the die filling and the initial stage of compression; elastic deformation is a reversible phenomenon hindering tablet formation, whereas brittle fracture and plastic deformation of particles are irreversible and promote tablet formation.

The aims of this work were to recrystallise acetazolamide in order to obtain a material for direct compression, and then to explain the reasons for its compression behaviour.

2. Materials and methods

2.1. Acetazolamide crystals obtention

Acetazolamide USP was purchased from Sigma–Aldrich Chemical (Steinheim, Germany). The acetazolamide solubility in ammonia solution 0.1 N (R.P. Normapur A.R., Prolabo, Fontenay/Bois, France) was determined by equilibrating the liquid phase with an excess of acetazolamide at 25.0 ± 0.5°C under stirring. A 24-h period is necessary to reach the equilibrium. The saturated solution was filtered through a 0.45-μm filter (Millipore, Molsheim, France). After an appropriate dilution, the concentration of the filtrate was determined spectrophotometrically (Cary 1E UV–VIS, Varian, Leinì, Italy) at 265.4 nm. The solubility is of 18.13 g l^{-1}.

The crystallisation of acetazolamide was carried out following three different methods chosen by considering that acetazolamide is soluble only in boiling water and in alkaline solutions.

1. Neutralisation of an alkaline diluted solution. Acetazolamide crystals (16.67 g) were dissolved in 1000 ml of an ammonia solution 0.1 N (R.P. Normapur A.R., Prolabo, Fontenay/Bois, France) and then recrystallised by neutralisation with a hydrochloridric solution (0.1 N) (R.P. Normapur A.R., Prolabo, Fontenay/Bois, France). Crystals were filtered, washed with demineralised water and dried in a ventilated oven at 50°C for 12 h. By this method, the polymorphic form II was obtained.
2. Slow cooling of a water solution. Acetazolamide crystals (20 g) were dissolved in 950 ml of boiling demineralised water and the solution was then cooled down slowly to room temperature according to Griesser et al. (1997). Crystals were filtered and dried in a ventilated oven at 50°C for 12 h. By this method, the polymorphic form I was obtained.
3. Solvent vaporation (spray drying). Acetazolamide crystals (16.67 g) were dissolved in 1000 ml of an ammonia solution 0.1 N and then spray-dried. Laboratory scale spray-drying was carried out using a spray dryer (Mini Spray Dryer, Buchi, B-191, Flawil, Switzerland), in accordance with the manufacturer's documentary advice, and the operating conditions were maintained at the following settings, inlet temperature 160°C; outlet temperature 150°C; pump flow rate 20°C min^{-1}. By this method, the spray dried crystals were a mixture of two polymorphic forms I and II, as will be explained in Section 3. Because of the small particle size of spray dried crystals, form I and II crystals were ground in a mortar to obtain samples with crystals of approximately the same dimensions. Forms I and II were stable to grinding as was confirmed by X-ray diffraction data.

2.2. Physical characterisation of acetazolamide samples

Before and after grinding, particle shapes of acetazolamide crystals were observed using an electron scanning microscope (Stereoscan 360, Cambridge Instruments, Cambridge, UK). SEM analysis was also performed for acetazolamide tablets obtained from spray dried material. Tablets, obtained at a compression pressure of about 250 MPa, were broken in two parts by a hardness tablet tester (Erweka, TBH 30, Heusenstamm, Germany) along the cross-section. Samples were mounted on a metal stub with double-sided adhesive tape and then recovered under vacuum with a gold layer of 200 Å thickness using a metallisator (Balzer MED 010, Linchestein). Particle size was determined on ground particles by counting the Ferret's diameter of 500 particles using electron scanning microscopy.

The powder X-ray diffraction study was carried out to characterise crystal acetazolamide obtained with different methods. A Philips PW 1730 (Holland) was used as X-ray generator for Cu Kα radiation ($\lambda = 1.54178$ Å). The experimental X-ray powder patterns were recorded on a Philips PH 8203. The goniometer supply was a Philips PW 1373 and the channel control a Philips PW 1390. The data were collected in the continuous scan mode using a step size of 0.01°2θ. The scanned range was 2–45° (2θ). The powder X-ray diffraction study was also used to determine the relative content of two polymorphic forms in the spray dried crystals.

Different percentages of form II (1, 5, 10, 15, 30, 60, 80, 90%) were added to form I and mixed to obtain a homogeneous mixture. One characteristic reflection for each form was chosen in a place, where no reflections for the other form existed. The height of the peak for form II ($2\theta =$ 10.1) was measured versus that for form I ($2\theta =$ 13.9). A linear regression was found, which was used to calculate approximately the content of form II versus form I ($R = 0.99378$; S.D. = 4.67618) (Di Martino et al., 1996). The stability check of spray dried crystals was carried out by X-ray analysis. Spectra of compressed and uncompressed crystals were compared, after 3 months at room conditions, to that of the sample at zero time.

The water loss of all samples was determined after maintaining them 1 week at 20°C under vacuum, and by drying in presence of P_2O_5 as desiccator (ACEF, Fiorenzuola d'Arda, Italy). True densities of three samples were measured by using a helium pycnometer (Ultrapycnometer 1000, Quantachrome, USA) with a cell of 60 cm^3. Results are the mean of ten measurements. The apparent densities at the initial stage and at constant volume (1250 tapping) were determined by measuring the volumes of 100 g of powder.

2.3. Compression behaviour of acetazolamide samples

The compression study of all the acetazolamide samples was performed using a rotary press (High-Tech-Mini, Ronchi, Cinisello Balsamo, Italy) equipped with a computerised control system for detection and analysis of force-signals (pressing force and ejection force). This press is equipped with ten flat punches of 6 mm of diameter. Because of the small quantities of samples, they were introduced manually in only one die. Die and punches were prelubricated with 1% w/v Mg stearate (FU-USP grade, ACEF, Fiorenzuola d'Arda, Italy) slurry in 96% v/v ethyl alcohol (analytical grade, PRS, Panreac, Montcada i Reixac, Spain). Powder mass was 100 mg. The die table speed was 7 rpm. The compression forces were increased progressively and the force at the upper punch was recorded. Results for each compression force are the mean of five measurements.

2.4. Densification study

For the densification study, powders were compressed with an instrumented Frogerais OA single-punch tablet machine (Frogerais, Vitry, France) equipped with 11.3 mm flat-faced punches, by introducing 470 mg samples manually into the prelubricated die. The lubrication was obtained by introducing to the hopper a mixture of Avicel PH 102 (FMC Europe NV, Brussels, Belgium) and 1% w/w Mg stearate and by compressing this mixture before each sample, according to Lefebvre et al. (1989). Five replicates cycles were performed for both substances, corresponding to maximal punch pressure of about 150 MPa. For a single compression cycle, both the compression pressures on the upper and lower punches and the displacement of the upper punch were measured and recorded at a frequency of 400 Hz. Correction of the displacement transducer data for machine looseness and punch deformation was carried out according to Juslin and Paronen (1980).

The densification behaviour of powders was studied using Heckel's equation (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 of yield pressure (P_Y). The constant A is the sum of two densification terms,

$$A = \ln(1/1 - D_0) + B \quad (2)$$

Were $\ln (1/1 - D_0)$ is related to the initial die filling, and B is the densification due to the slippage and rearrangement of both primary and fragmented particles. Constants A and B can be expressed as relative densities using,

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

$$D_B = D_A - D_0 \quad (4)$$

To make a clearer distinction between densification due to the movements of the original particles and that due to the brittle fracture, Doelker (1994) proposed modifying the definition of D_0 (and subsequently that of D_B) by using a relative precompression density D'_0 term, which also includes the initial rearrangement of particles. In this condition, Eqs. (2) and (4) become respectively,

$$A = \ln(1/1D'_0) + B' \quad (5)$$

$$D'_B = D_A - D'_0 \quad (6)$$

Where D'_B is this time only the representative of the densification due to fragmentation. D'_0 corresponds to the relative density of the powder at the moment when the last recorded applied pressure is still nil. In this study, Heckel's profiles were generated by 'the continuous method' (Heckel,

1961) from single compression cycles. All samples were 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, and data ranging from 50 to 100 MPa for linear regression analysis. Each value is a mean of five measurements.

The immediate apparent elastic recovery was calculated according to Armstrong and Haines-Nutt (1974),

$$\text{Immediate apparent elastic recovery (\%)} = [(t_2 - t_1)/t_1]\,100 \quad (7)$$

Where t_1 is the minimal thickness of the powder in the die when the upper punch displacement was maximal and t_2 is the powder thickness at the end of compression, before tablet ejection (when the last pressure was recorded).

2.5. Powder bed and tablet characterisation

Thickness and diameter of intact ejected tables were measured with a manual micrometer with an accuracy of 0.01 mm (Mitutoyo, Kanagawa, 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 hardness tester (Erweka, TBH 30, Heusenstamm, Germany). Tensile strength Q was calculated according to Eq. (8) (Fell and Newton, 1970),

$$Q = \frac{2H}{\pi dt} \quad (8)$$

where H is the tablet crushing strength, d the diameter, and t the thickness of the tablet. Powder bed porosity was calculated from die dimensions, upper punch displacement, powder mass, and true density.

3. Results and discussion

3.1. Physical characterisation of acetazolamide crystals

Scanning electron photomicrographs (Fig. 1) show acetazolamide crystals obtained from various crystallisation methods, before and after grinding. The polymorphic form I (Fig. 1a), obtained by slow cooling of water solution, shows a typical acicular shape, while in the polymorphic form II (Fig. 1b), obtained by neutralisation of an alkaline diluted solution, acicular bigger crystals exist together with little irregular particles. Crystals obtained by spray drying (Fig. 1c) appear like spherical particles. Their surface is sufficiently smooth and the particles not to form aggregates. In Fig. 1, scanning electron photomicrographs also show form I and II particles ground before compression study (spray dried particles were not grounded). As a consequence of grinding, particles assume an irregular shape, although some form I crystals keep their acicular appearance.

In Table 1, physical properties of acetazolamide crystals are reported. Their particle mean diameters are rather similar. A higher particle mean diameter with a higher standard deviation value can be observed for form I. The water loss is close for all three samples, that of spray dried being intermediate. Apparent density and tapped density are also indicated. True density of spray dried crystals is intermediate between that of modification I and II. X-ray diffraction patterns for forms I and II are in accordance with Griesser et al. (1997) while the spray dried crystals are a mixture of plymorphic forms I and II (Fig. 2). Because diffractogram baselines are very flat for all three samples, the presence of a large amorphous phase can be excluded also for the spray dried material. Supposing then the spray dried crystals are exclusively constituted of forms I and II, and admitting the volume additivity for a biphasic solid, it is possible to estimate the proportion of the two phases from pycnometric data, according to the following equation,

$$f_1 = [d_1\ (d_t - d_2)]/[d_t(d_1 - d_2)] \quad (9)$$

where f_1 is the amount of form I in the spray dried, and d_1, d_2, d_t are the true density, respectively, of form I, form II, and spray dried. A proportion of 40% of form I and 60% of form II is obtained from the true density values of Table 1. The content of form II in the spray dried was quantified as about 12% by powder X-ray diffraction. This result was very reproducible, being

approximately the same for all batches. In a first analysis, those results appeared very different, but in a more careful analysis of X-ray diffraction data, this can be explained. The calculation of form II content was based on the linear regression analysis established from physical mixtures of two forms, and considering their two mean peaks, the 13.9 and 10.1 (2θ), respectively, for forms I and II. Nevertheless, for the spray dried, a higher form II content is noted than form I, when large angles are considered (greater than 30° 2θ). This fact can be explained by a phase segregation in the spray dried, the form I being on the particle surface, while the form II is on its core. Actually, the X-ray beam is able to penetrate only the particle surface at the small angles, while it can

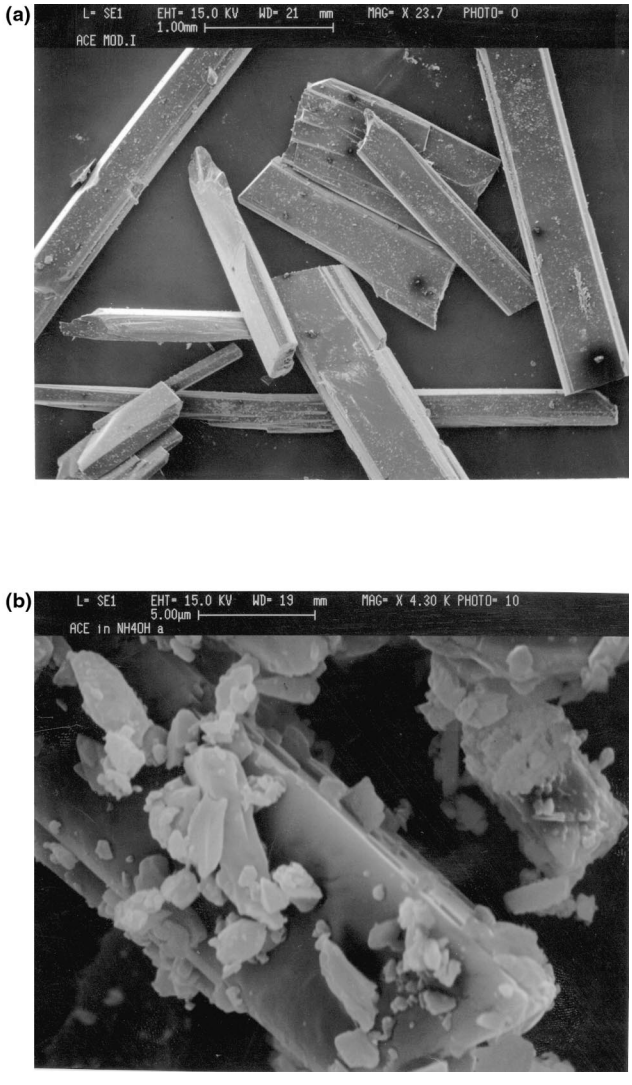

Fig. 1. Scanning electron microscopy of acetazolamide crystals, (a) form I recrystallised according to Griesser et al. (1997) (unground particles); (b) form II recrystallised by the neutralisation method (unground particles); (c) spherical particles recrystallised by the spray drying method; (d) form I ground particles; (e) form II ground particles.

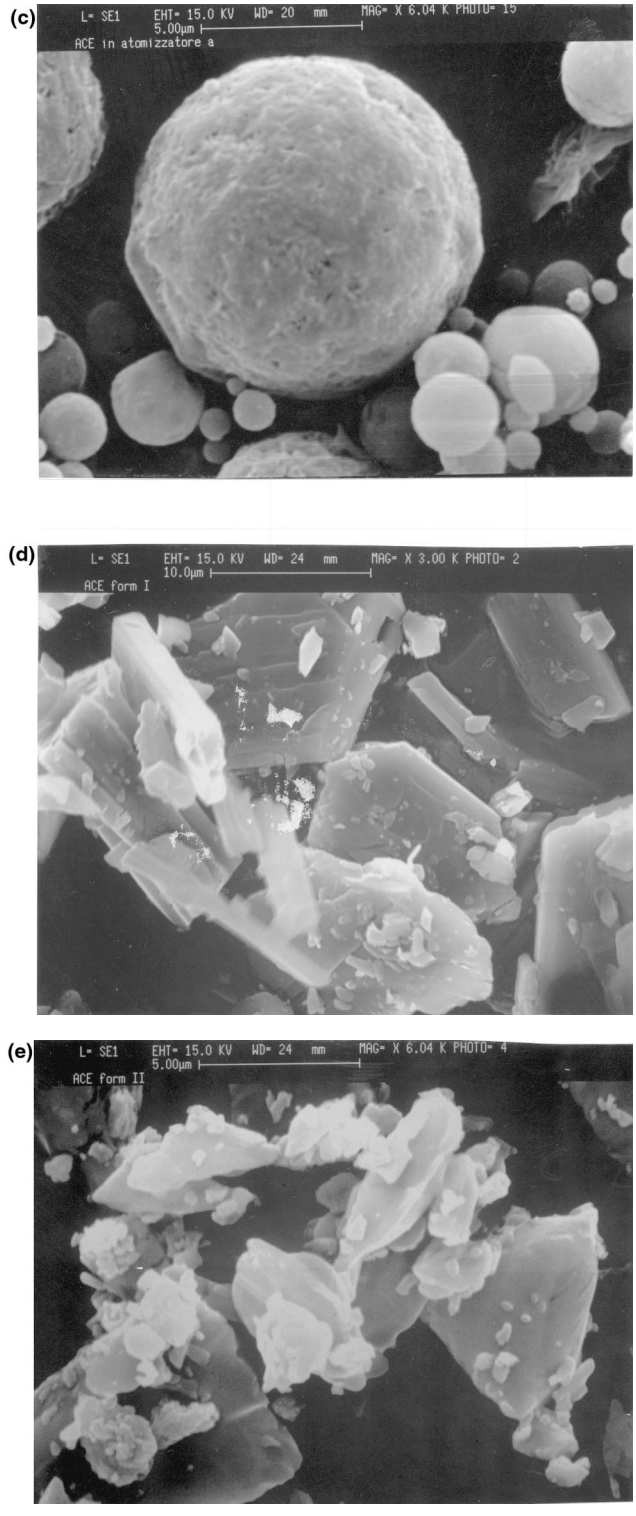

Fig. 1. (*Continued*)

Table 1
Physical properties of acetazolamide particles after grinding used in the compression study

	Particle shape	Particle mean diameter[a] (normal distribution)	Water loss (%)[b]	True density (g cm^{-3})[c]	Apparent density (g cm^{-3})[d]	Tapped density (g cm^{-3})[e]
Spray dried particles (unground)	Spherical	9.66 μm (4.30)	0.29	1.7356 (0.00216)	0.262	0.423
Crystals of form I (ground)	Irregular	11.50 μm (10.92)	0.36	1.7664 (0.00042)	0.288	0.514
Crystals of form II (ground)	Irregular	6.90 μm (6.97)	0.17	1.7160 (0.00117)	0.203	0.390

[a] Determined by counting Feret's diameter of 500 particles by S.E.M. S.D. are reported.
[b] Determined by maintaining at constant weight at 20°C under vacuum in presence of P_2O_5 as desiccator.
[c] Determined by using a helium pycnometer. Results are the mean of ten measurements. 95% confidence intervals are reported.
[d] Determined by measuring the volume of 100 g of powder.
[e] Determined by measuring the volume of 100 g of powder after the nth tapping to constant volume.

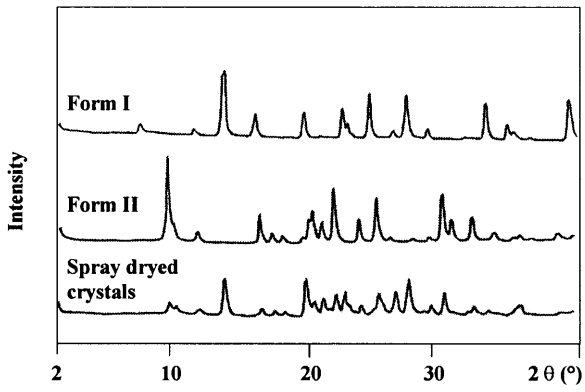

Fig. 2. X-ray diffraction patterns of acetazolamide polymorphic pure forms I and II and spray dried crystals.

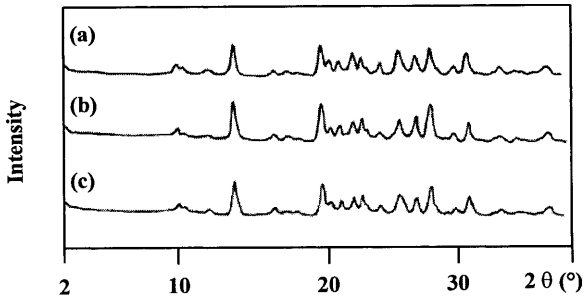

Fig. 3. Physical stability of spray dried crystals realised by X-ray diffraction, (a), after recrystallisation; (b), uncompressed crystals after 3 months; (c), compressed crystals after 3 months.

Table 2
Compression study and 95% confidence intervals for spray dried acetazolamide particles carried out on a rotary press

Compression pressures (MPa)	Tablet tensile strength (MPa)	Tablet porosity (%)[a]
186	1.06 ± 0.56	23.28 ± 1.04
224	1.61 ± 0.58	20.97 ± 0.96
306	1.69 ± 0.07	17.68 ± 0.86
400	2.00 ± 0.32	13.87 ± 0.91

[a] Determined from ejected tablets.

penetrate the entire particle at the large ones. So, the phase proportions calculated from density data are congruent, with the powder X-ray diffraction study evidencing the granule structure.

Spray dried acetazolamide exhibits a very good physical stability after 3 months also under compression (Fig. 3).

3.2. Compression behaviour of acetazolamide crystals

All acetazolamide samples were compressed on the rotary press. Although low compression speeds were used, no tablets were recovered for either of the polymorphic pure forms I and II. In Table 2, only compression behaviour results for spray dried acetazolamide are reported. It is possible to observe a decrease of tablet porosity and an increase of tablet tensile strength proportional to the increase of compression pressures, without capping occurring. This is an important result because the possibility to improve tablet/ability of acetazolamide is proved.

3.3. Compression behaviour of acetazolamide crystal

With the scope to explain differences in the compression mechanism of the three different materials a densification study was carried out.

Table 3 shows powder bed porosities at the initial stage of compression (corresponding to an applied precompression pressure of 1.5 MPa). This porosity is clearly lower for spray dried particles (35.2%) than that of polymorphic forms I and II (respectively, 51.7 and 44.5%). This is also related to the fact that at the initial stage (under 50 MPa), the particle rearrangement is greater for the spray dried sample as it can be noted by the higher D'_0 value (Table 4, Fig. 4.) This fact could be due either to the minor wrinkledness of the particle surface or to their spherical morphology which affords a better filling of interparticular voids. In this stage, we exclude the influence of particular size, that would instead involve a decrease in D'_0. Form I porosity value is higher than that of form II probably because of the presence of some acicular crystals that incorrectly fill the die.

The Heckel's D'_B value of form II (0.174) is clearly higher that of form I (0.06) (Table 3). Because the D'_0 values are rather close, this fact

Table 3
Porosity values and 95% confidence intervals for the acetazolamide samples, obtained from a single-punch tablet machine

Porosity	Spray dried particles (%)	Crystals of form I (%)	Crystals of form II (%)
Initial[a]	35.2 ± 0.5	51.7 ± 0.3	44.5 ± 0.4
Minimal[b]	7.7 ± 0.4	8.0 ± 0.2	4.6 ± 0.6
Final[c]	9.7 ± 0.4	10.5 ± 0.3	10.0 ± 0.4
Tablet[d]	11.6 ± 0.4		

[a] Calculated from die dimensions at the initial stage of compression, when a precompression pressure of 1.5 MPa was applied.
[b] Calculated at the maximum upper punch displacement.
[c] Calculated at the end of compression, when the last compression pressure was recorded.
[d] Calculated from dimensions of recovered tablets.

Table 4
Heckel parameters and immediate elastic recovery for the acetazolamide samples. 95% confidence intervals are also indicated

	Spray dried particles	Crystals of form I	Crystals of form II
P_Y	145.4 ± 2.4	99.2 ± 5.0	93.3 ± 1.7
D'_0	0.648 ± 0.005	0.483 ± 0.003	0.555 ± 0.004
D_A	0.755 ± 0.002	0.543 ± 0.002	0.728 ± 0.002
D'_B	0.108 ± 0.005	0.060 ± 0.005	0.174 ± 0.005
Immediate elastic recovery (%)	2.24 ± 0.08	2.82 ± 0.06	6.07 ± 0.31

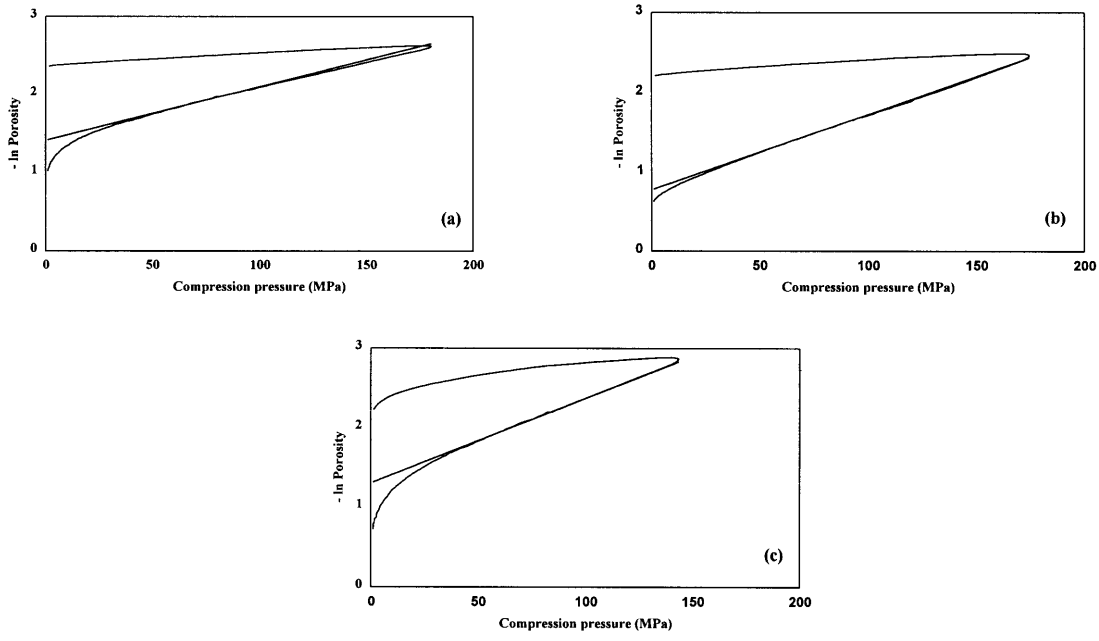

Fig. 4. Heckel's plots for acetazolamide samples, (a) spray dried crystals; (b) form I; (c) form II. These are obtained from a single compression cycle. Straight lines correspond to linear regression analysis of data ranging from 50 to 100 MPa.

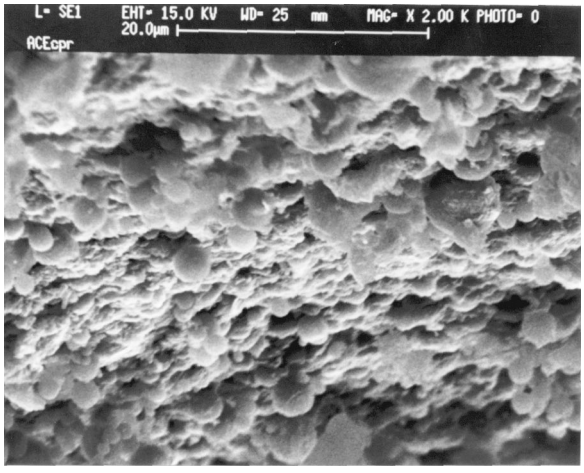

Fig. 5. SEM microphotograph of tablet cross section of spray dried crystals. Tablet was obtained at a compression pressure of about 250 MPa.

cannot be correlated to a difference in the particles rearrangement, but rather to a greater tendency to fragmentation in form II (D_A values). The fragmentation tendency could be correlated to the differences in brittleness of the materials. The D'_B value for the spray dried sample (0.108) is intermediate to that of forms I (0.06) and II (0.174), which could correspond to the fact that the spray dried form is a mixture of both polymorphic forms.

During the single compression cycle of forms I and II, higher particulate deformation can be observed for form II (minimal porosity 4.6%) compared with form I (minimal porosity 8%) (Table 3). Nevertheless, at the end of the compression cycle, during the recovery of the upper punch, the porosity values become the same for both (10% for form II and 10.5% for form I) owing to the higher immediate elastic recovery for form II (form II 6.07%; from I 2.82%) (Table 4). Fig. 4 clearly shows that the minimal porosities, and thus, maximal apparent density reached at the end of densification, are very different for forms I and II. The maximal one is higher for from II, which involves higher elastic recovery, but the final one is very constant for forms I and II. So, differences in the apparent elastic recovery are dependent on the difference in apparent density of the materials. The constancy of final porosity may indicate that the intrinsic compressibility of forms I and II are very close. In fact, when the compression pressure exceeds 50 MPa, the particle deformation of both forms becomes comparable and the P_Y values are similar (form I, 99.2; form II, 93.3).

Spray dried minimal porosity (Table 3), is intermediate between that of form I and II, but its final porosity is the lower one due to its lower immediate elastic recovery (Table 4). The P_Y value, which corresponds to the deformation during the second stage of compression, is far higher for the spray dried sample (145.4) than that of forms I (99.2) and II (93.3), showing that spray dried particles are less deformed in this pressure range. Besides, S.E.M. analysis of tablets obtained by spray dried crystals shows that they are unbroken under compression (Fig. 5), indicating a very low brittle fracture tendency under compression. It must be noted that, conversely to forms I and II, the spray dried crystals do not show any capping tendency.

If we try to make a conclusion from these observations, we can analyse different aspects. The spherical particle shape of spray dried particles affecting the rearrangement in the initial stage of compression with the constitution of a powder bed with a lower porosity can probably act favourably on the proximity of the particles during the second stage of compression and their interaction for the constitution of interparticulate bonds. The complex crystalline structure of the spray dried material due to the contemporary presence of the two polymorphic forms I and II undoubtedly affects the second stage of the compression and the intrinsic compressibility of the material primarily by lowering its elasticity tendency. On the other hand, if we consider that crystals of form I show greater plastic deformation (P_Y, 99.2) than spray dried particles (P_Y, 145.4) and an immediate elastic recovery not far different to this of spray dried particles (respectively, 2.82 and 2.24%), we could expect a good compression behaviour, but this does not occur. Deformability tendency and low elastic recovery of form I are not sufficient to favourise particle interaction and

the constitution of interparticulate bonds of sufficient strength. In conclusion, we can schematise the improved tablet/ability of the spray dried acetazolamide in this sense, spherical habit and minor wrinkledness of particle surface concur to particle rearrangement at the initial stage of compression. The lower powder bed porosity allows an intimate interaction of the particles during the subsequent compression stage. The crystalline structure due to the presence of polymorphic forms I and II concur to lowering the intrinsic elasticity of the material. This fact avoids the risk of the rupturing of the interparticulate bonds, which are formed during the compression concurring to the consolidation of the tablet.

4. Conclusions

The spray dried acetazolamide crystals are composed of two different crystalline forms, the polymorphic forms I and II, as was shown by X-ray diffraction study and pycnometry. Form I is located preferentially on the crystal surface, while form II is in the core. Firstly, compression behaviour of spray dried acetazolamide was studded by a rotary press and compared with that of pure polymorphic forms I and II; both pure polymorphs, although showing some differences, are not compressible, giving capped tablets although compression pressures were used. On the contrary, spray dried crystals, although being a mixture of the two polymorphic forms, have good compression properties, withouth capping occurring. From a densification study, we tried to explain the compression mechanism of three samples. Spherical habit and minor wrinkledness of particle surface concur to particle rearrangement at the initial stage of compression. The lower powder bed porosity allows an intimate interaction of the particles during the subsequent compression stage. The crystalline structure due to the presence of polymorphic forms I and II concur to lowering the intrinsic elasticity to the material. This fact avoids the risk of the rupting of the interpaticulate bonds, which are formed during the compression concurring to the consolidation of the tablet.

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