ELSEVIER

International Journal of Pharmaceutics 170 (1998) 51–61

international journal of pharmaceutics

Ground and native crystals: comparison of compression capacity and dissolution rate

P. Longuemard [a], M. Jbilou [a], A.-M. Guyot-Hermann [a,*], J.-C. Guyot [b]

[a] *Laboratoire de Pharmacie Galénique, Université de Lille II, Faculté de Pharmacie, Rue Laguesse, B.P. 83, 59006 Lille, France*
[b] *Laboratoire de Pharmacotechnie Industrielle, Université de Lille II, Faculté de Pharmacie, Rue Laguesse, B.P. 83, 59006 Lille, France*

Received 10 July 1997; received in revised form 11 March 1998; accepted 13 March 1998

Abstract

Some authors such as Hüttenrauch have suggested that the trauma to crystals during grinding may induce defects in these crystals causing disorder in the crystal lattice. This decrease in crystallinity should improve compression capacity and dissolution rate, independently of any particle-size considerations. We have tried to study this hypothesis, using two types of crystals: aspirin and lactose α-monohydrate. For precise and significant comparison, native and ground crystals must have the same particle size. Fine native crystals were separated by sieving from a recrystallized batch. Fine ground crystals were prepared by grinding the separated coarser crystals. Very fine crystals adsorbed on the crystal surface were removed by pneumatic sieving (Alpine®). These two types of crystals were then studied as regards their morphology, crystalline state, compression capacity, and dissolution properties. From this study, it seems that no significant compression capacity improvement is to be observed when native and ground crystals of the same particle size are compared. A slight increase in the dissolution rate of ground aspirin crystals might be ascribed to surface defects improving crystal wetting. Disorder seems to occur only at the crystal surfaces.

Keywords: Aspirin; Compression; Dissolution; Grinding ; Lactose

1. Introduction

The amorphous and crystalline states are two extreme states of solid substances. In an amorphous product molecules are in an irregular arrangement within the particles. The lack of long-range order which characterizes crystalline state confers on the particles a good compression ability due to the plasticity and isotropy of force transmission through such a structure. Unfortunately, the great instability of amorphous forms

* Corresponding author. Tel.: + 33 3 20964029; fax: + 33 3 20959009.

0378-5173/98/$19.00
PII S0378-5173(98)00120-3

makes their use difficult. On the other hand, the perfect crystalline state is characterized by a three-dimensional long-range order which confers on the particle a high degree of order. Depending on the crystalline structure of the substance, direct compression may be absolutely impossible. This is the case of the usually marketed monoclinic paracetamol. However, molecules exist in a high energy state in amorphous particles which induces faster dissolution than from crystallized particles. Between these two extreme states, there are, in fact, a lot of different degrees of order.

A lower degree of order can result from several causes: fast recrystallization, the presence of impurities and too harsh treatment. Hüttenrauch advanced, 20 years ago, that grinding, drying and tabletting could induce defects in the crystalline network: these defects would decrease the degree of order and could give to the particle a certain 'viscoelasticity' (Hancock and Zografi, 1997). Consequently, compression and dissolution properties could be improved (Hüttenrauch and Keiner, 1979a,b, Hüttenrauch, 1983): this is the 'Activation Theory' of Hüttenrauch.

Other authors such as Hersey and Krycer (1981) and Morita et al. (1984) confirmed the importance of grinding on crystalline network deformations. Grant and York (1986) and Vachon and Grant (1987) pointed out that the pharmaceutical processing of a solid causes defects in the crystal lattice which contribute to the disorder. They studied the thermodynamic consequences of this phenomenon.

To verify this hypothesis, we carried out an experiment on aspirin and lactose crystals, which were either native crystals or ground crystals of the same particle size.

2. Materials and methods

2.1. Materials

Aspirin was from Rhône Poulenc-Cooper (Melun, France). Lactose EFK was from the Société du Sucre de Lait HMS, (Sains du Nord, France).

Table 1
Solubility of aspirin in 38% alcohol

Temperature (°C)	Solubility (g/l)
20	17.6
40	65.2
56	206.1
68	553.1

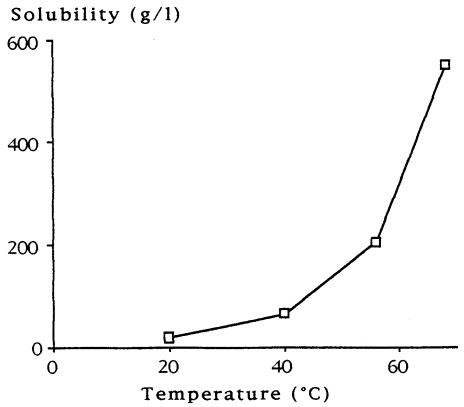

Fig. 1. Solubility curve of aspirin in 38% alcohol.

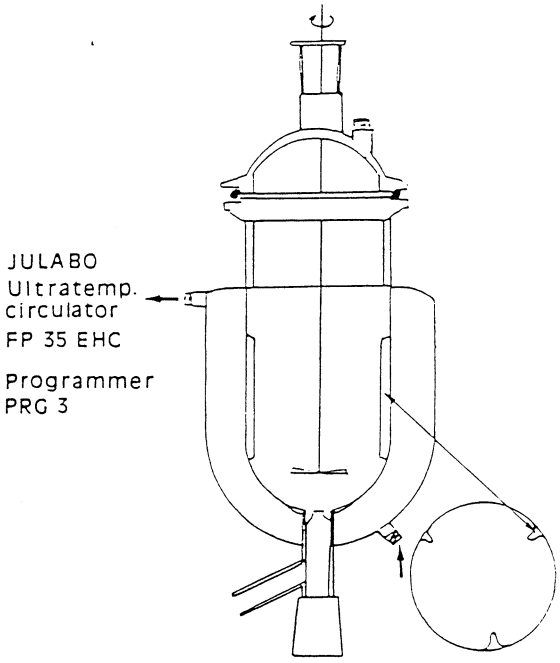

Fig. 2. The crystallizer.

Table 2
Conditions of recrystallization process for aspirin and lactose crystals

	Aspirin	Lactose
Recrystallization medium (500 ml)	38% alcohol	Water
Mass of powder to dissolve	160 g	320 g
Dissolution temperature	60°C	60°C
Rotation speed of the helix	600 rpm	200 rpm from 60 to 45°C, 100 rpm from 45 to 20°C
Cooling down and seeding	From 60 to 20°C within 75 min (no seeding)	In three steps: (1) from 60 to 45°C within 140 min; (2) seeding with 500 mg of lactose; (3) cooling down to 20°C

For a rigorous study, it was necessary to standardize crystal production. The native and ground crystals to be compared were prepared from the same crystallization batch, and the fine particles which adhered to the surface of the crystals were withdrawn, because they could falsify results.

2.2. Preparation of crystals

2.2.1. Determination of solubility curve

This was the first step in determining supersaturation which produced a high yield, without any excess of crystals in suspension during cooling down, to prevent uneasy rotation of the helix in the crystallizer.

The selected solvents were 38% alcohol for aspirin and water for lactose.

Solubility was determined by successive additions of aspirin or lactose crystals into 50 ml of solvent maintained at different temperatures, up to the point when they no longer dissolved. A graph of solubility against temperature was plotted (e.g. aspirin in 38% alcohol in Table 1 and Fig. 1).

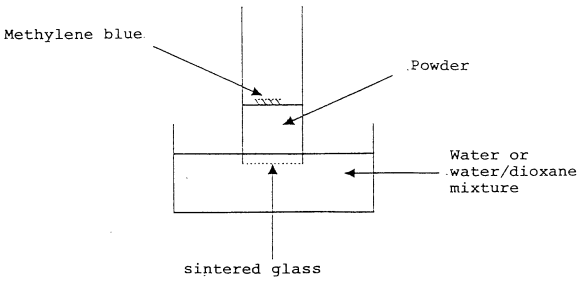

Fig. 3. Powder bed hydrophilicity measurement device.

The difference between aspirin solubility at 56°C and 20°C would make it possible to obtain nearly 100 g of aspirin crystals from the saturated solution during cooling down from 56°C to 20°C. Thus, for a good yield, we chose saturation at 60°C in alcohol at 38% (solubility 320 g/l).

For lactose, we selected saturation at 60°C in water (solubility 700 g/l).

2.2.2. Crystallization

Recrystallization medium (500 ml) was introduced into the crystallizer, the dimensions of which were established by Veesler (1991) (Fig. 2). A Julabo thermostat/cryostat and a PRG3 programmer were used to regulate heating and cooling. Stirring was started at the same time as heating. When the temperature reached 60°C the mass of either aspirin or lactose corresponding to saturation was added. After complete dissolution of the crystals, the cooling cycle was started.

The various conditions of the recrystallization process are summarized in Table 2.

Crystals were separated from the solution through filtration under vacuum. A quantity of solvent equivalent to about 10% of the weight of the crystals was added to the crystals to wash them. The crystals were then placed in a thin layer at room atmospheric conditions for 24 h and then in a ventilated oven at 80°C for 2 h.

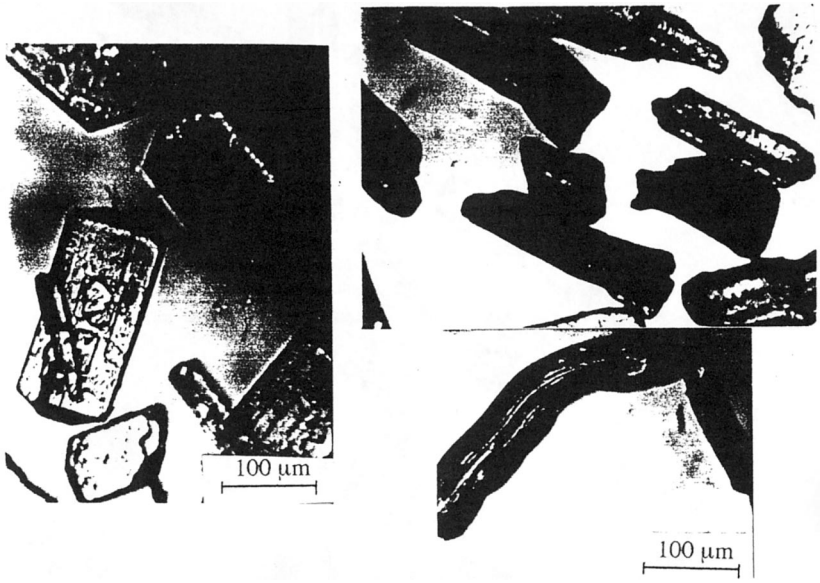

Fig. 4. Appearance of aspirin crystals under optical microscope. Left: native crystals; right: ground crystals.

Fig. 5. Appearance of lactose crystals under optical microscope. Left: native crystals; right: ground crystals.

2.2.2.1. Separation of native crystals. The crystallization of aspirin is different to that of lactose.

The size of lactose crystals is smaller than that of aspirin whatever the crystallization conditions were tried. This is why we selected for this study the 100/200 μm size fraction for aspirin crystals and the 50/100 μm size fraction for lactose crystals. These particle size fractions were separated by sieving.

2.2.2.2. Preparation of ground crystals. Crystals with coarse particle size (over 500 μm for aspirin,

Table 3
Compresssion characteristics of aspirin crystals

Native crystals			Ground crystals		
Y1 (daN)	CS (daN)	CI	Y1 (daN)	CS (daN)	CI
2077	4.2	202	2384	3.9	164
1913	4.4	230	2063	3.7	179
1843	4.4	239	1954	4.0	205
1823	3.7	236	1610	3.9	242
1616	4.3	266	1579	3.7	234
1587	3.7	233	1360	3.1	228
1045	3.4	325	1135	2.8	247
981	3.1	316	918	2.9	316
881	3.1	352	899	2.5	278
854	3.8	445	787	2.3	292
778	3.3	424	764	2.4	314
774	3.6	465	692	2.1	304
680	3.1	456	582	1.9	326
580	2.9	500			
561	3.0	535			

Y1, force on upper punch; CS, crushing strength; CI, cohesion index.

Table 4
Compression characteristics of lactose crystals

Native crystals			Ground crystals		
Y1 (daN)	CS (daN)	CI	Y1 (daN)	CS (daN)	CI
2491	7.5	301	2564	9.0	351
2187	6.2	284	1937	6.5	336
1805	4.2	233	1677	4.8	286
1380	3.5	254	1550	4.4	284
1180	2.6	220	1372	4.0	292
1063	2.3	216	1311	3.5	267
924	2.1	227	934	2.6	278
899	1.7	189	473	1.1	233
563	1.0	178	287	0.6	No sens

Y1, force on upper punch; CS, crushing strength; CI, cohesion index.

over 200 μm for lactose) were separated by sieving and ground using a Radiola R.A.3200 grinder mill for 30 s.

The 100/200 μm sieved fraction of aspirin crystals and the 50/100 μm sieved fraction of lactose crystals were then separated.

To withdraw all the fine particles adsorbed on the crystal surfaces, pneumatic sieving (Alpine) on a 50 μm sieve was carried out. A control by microscopy confirmed that the crystal surfaces were clean.

2.3. Physical study of crystals

2.3.1. Microscopy

After observation under an optical microscope, the morphology of the crystal surface was studied using a Jeol CX 100 scanning electron microscope, fitted with an ASID 4-D device.

2.3.2. The specific surface area

It was estimated by the BET method with krypton (ASAP 2000, Micromeritics)

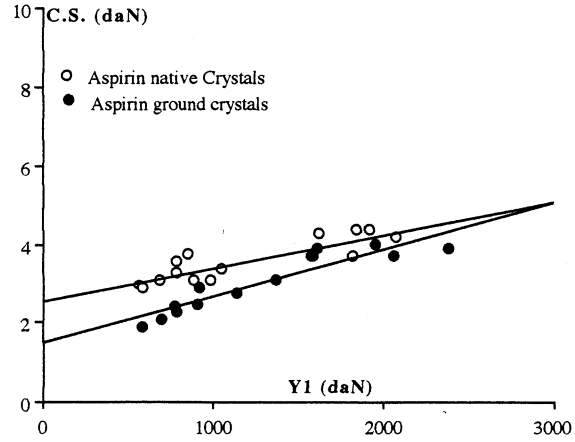

Fig. 6. Compression characteristics of native and ground crystals of aspirin.

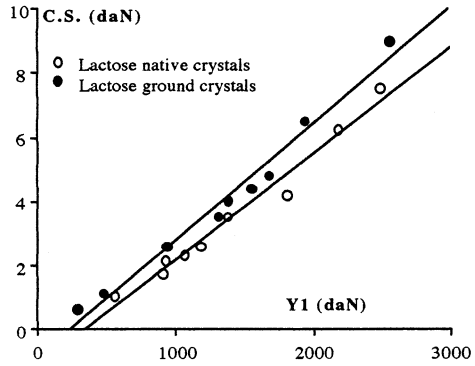

Fig. 7. Compression characteristics of native and ground crystals of lactose.

2.3.3. Differential scanning calorimetry

A differential scanning calorimetry study, using a Mettler TA 3000 DSC 20 device, made it possible to determine the melting temperature, the melting enthalpy and the molecular purity of the crystals.

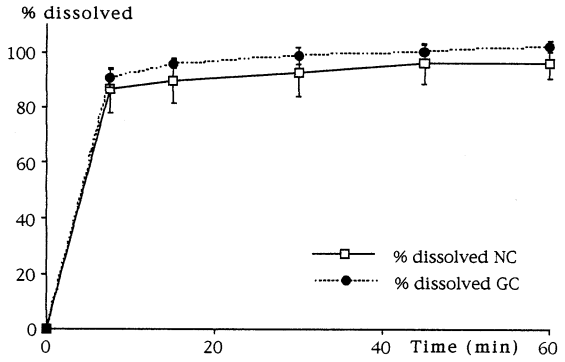

Fig. 8. Dissolution curves of native and ground aspirin crystals.

For aspirin, measurements must be carried out from a relatively high temperature (100°C) and at a relatively fast heating rate (10°C/min) to avoid degradation before melting. The capsule was closed by a lid which was perforated to determine temperature and enthalpy melting. The experiment was carried out under an anhydrous nitrogen flow.

For lactose, we considered the enthalpy of desolvation to be indicative of the degree of crystallinity of the substance, since bound water gives crystallinity to the crystal. The heating run at 10°C/min was carried out in a capsule without a lid, under an anhydrous nitrogen flow to make it easier for water to escape. The starting temperature was 50°C.

Table 5
Dissolution rate of the two types of crystals

Time (min)	Native crystals			Ground crystals		
	Dissolved (%)	S.D.	CV	Dissolved (%)	S.D.	CV
7.5	86.31	8.09	9.37	90.47	3.27	3.61
15	89.69	8.06	8.98	95.79	1.41	1.47
30	92.9	8.89	9.57	98.97	3.16	3.19
45	95.89	7.30	7.61	100.38	2.58	2.57
60	96.20	5.88	6.11	102.41	1.98	1.93

S.D., standard deviation; CV, coefficient of variation.

2.3.4. Powder X-ray diffraction

A Siemens X-ray generator fitted with a Guinier de Wolff camera (Nonius) (CuKα radiation, $\lambda = 1.54178$ A) was used.

2.3.5. Powder bed hydrophilicity

The wetting of the crystals was investigated using the very simple method of determining powder bed hydrophilicity (Lefebvre et al., 1988). The sample mass was 2 g. The powder was put on the sintered glass of an Alhin tube, partially plunged (1 mm) into water (Fig. 3). We noted the time it took for the water capillary to rise up to the powder surface. Some methylene blue crystals at the top of the powder displayed this critical time more clearly. The faster the rising time, the greater the wettability of the powder.

Pure water cannot wet crystals of aspirin, thus mixtures of dioxane–water were used in different proportions: 20:80, 15:85 and 12.5:87.5 (v/v).

Table 6
Wetting of aspirin crystals by dioxane–water mixtures (measured as time for the rising up of dioxane–water mixtures)

Dioxane–water (v/v)	Native crystals	Ground crystals
20:80	3 min 48 s	26 s
15:85	10 min 38 s	1 min 21 s
12.5:87.5	20 min 37 s	1 min 51 s

Table 7
Wetting of lactose crystals by water (measured as time for the rising up of water)

	Native crystals	Ground crystals
	18 s	10 s
Pure water	20 s	11 s

Table 8
BET specific surface area (m^2/g) of crystals

	Native crystals	Ground crystals
Aspirin	0.0745	0.1331
Lactose	0.1950	0.2259

2.3.6. Compression study

Compression capacity was investigated on an instrumented Frogerais OA single punch tablet machine, using the 1 CP method of Guyot (Guillaume et al., 1992, Guyot et al., 1992).

To evaluate compression capacity we noted for each tablet the force Y1 at the level of the upper punch as well as the crushing strength, and we calculated the cohesion index which is the ratio of the crushing strength against the compression force Y1, multiplied by 10^5 for reading convenience. The higher the cohesion index, the better the compression ability.

Crushing strength was determined using a Shleuniger tablet hardness tester 6D.

2.3.7. Dissolution study

Dissolution rate was determined only for aspirin, using continuous flow cells (Merle et al., 1977), on a sample mass of 400 mg in 800 ml of 0.1 N HCl at 37°C. The amount of aspirin dissolved after 7.5, 15, 30, 45 and 60 min was determined spectrophotometrically at 270 nm.

3. Results and discussion

3.1. Morphological aspects

A clear alteration could be seen in the aspirin crystals under an optical microscope: the transparent native crystals had become opaque and some slightly curved crytals were also seen (Fig. 4). Opacity is an indication of defects in the crystal.

Native crystals of lactose are relatively transparent whereas ground crystals are nearly opaque (Fig. 5).

3.2. Compression study

Results are reported in Tables 3 and 4. The crushing strength is plotted against Y1 force in Figs. 6 and 7 for aspirin and lactose, respectively.

For aspirin, two slightly overlapping clouds of points are observed for Y1 force less than 1500 daN. The native crystals seemed to be slightly better but this difference was not significant. The

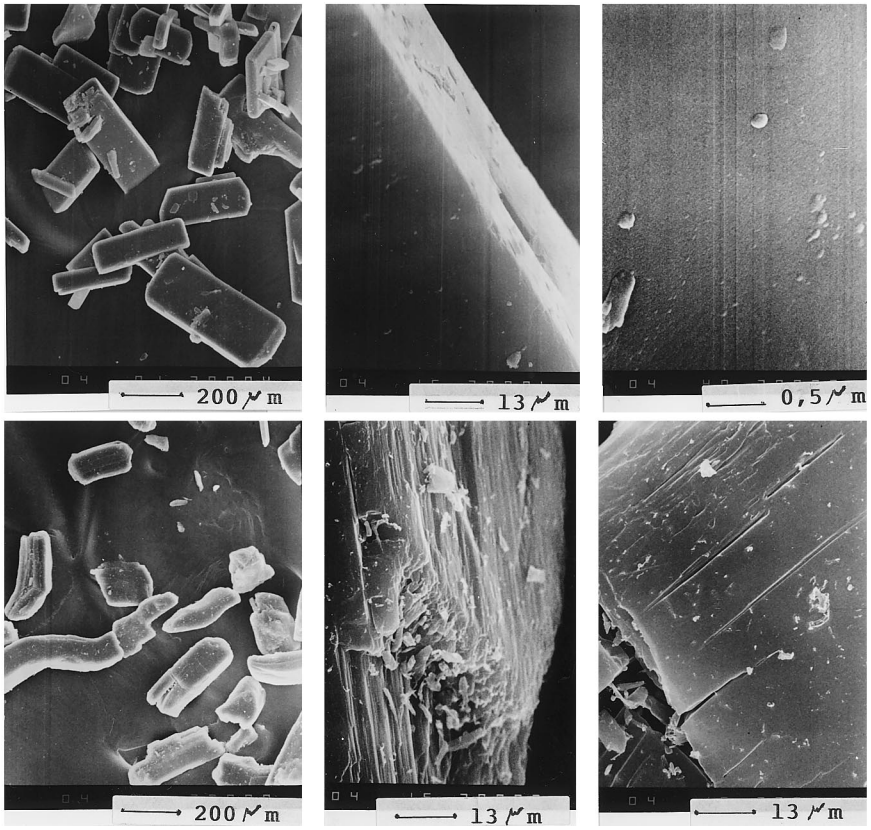

Fig. 9. SEM photographs of aspirin crystals. (On top: native crystals. On botton: ground crystals.)

results for lasctose were more regular. A slight tendency to better results could be observed for ground crystals, but the difference was not significant. It is clear that ground crystals are not significantly better than native ones, contrary to what would be expected from Hüttenrauch's theory.

3.3. Dissolution study of aspirin crystals

Data are given in Table 5 and Fig. 8. The dissolution rates of the two types of crystals are similar. However, it can be noted that the standard deviation is smaller as far as ground crystals are concerned. Ground crystals could be more wettable than native ones. Their dissolution reproducibility is better. The better wettability of ground crystals can be clearly vizualized in the dissolution cell in which ground crystals disperse more easily than native ones. These results could be indicative of a variation in crystal surface states, but not in the internal structure of the crystals. Further experiments concord with this hypothesis.

3.4. Experiments demonstrating crystal surface modifications

3.4.1. Powder bed hydrophilicity

In Table 6, we can observe a clear improvement in the wettability of aspirin crystals due to the grinding treatment.

The results for lactose crystals follow the same trend as those for aspirin. Data confirm that surface modification occurs during grinding (Table 7).

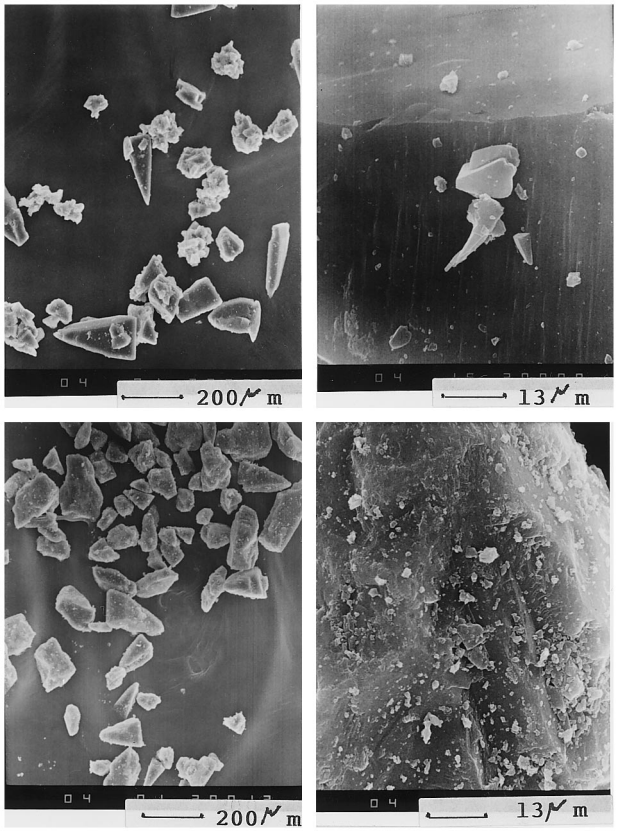

Fig. 10. SEM photographs of lactose crystals. (On top: native crystals. On bottom: ground crystals.)

3.4.2. Specific surface area of crystals

Results of BET specific surface area with krypton conformed with the hypothesis of surface defects (Table 8). It is noteworthy that no difference was observed when nitrogen was used instead of krypton. Consequently, the surface irregularities produced by grinding are very superficial: only one or very few molecular layers.

3.4.3. Scanning electron microscopy (SEM)

On the SEM photographs (Figs. 9 and 10) we can clearly see that native crystals exhibit neat outlines, whereas ground crystals are more tortuous. In addition, for aspirin, splits parallel to the great axis of the crystal can be seen. These probably correspond to the sliding plane of the aspirin structure (Hesse, 1978).

3.5. Experiments showing the absence of internal modifications

3.5.1. Powder X-ray diffraction

No significant modification in powder X-ray diffraction patterns was observed; in fact, the definition of the reflections of the ground crystals are even slightly better on the film. Recording of the film does not allow individualization of the near neighbour reflections, which can lead to erroneous interpretation. By film observation, the crystallinity of the two crystal types can be held to be similar.

3.5.2. Differential scanning calorimetry analysis

Results are reported in Table 9. Melting enthalpies of native and ground aspirin crystals are similar. It was the same as far as desolvation enthalpies of lactose were concerned. Conse-

Table 9
Differential scanning calorimetry results from the two types of crystals

Aspirin			Lactose		
	Native crystals	Ground crystals		Native crystals	Ground crystals
Melting temperature (°C)	135.1 135.4	139.5 139.5	Desolvation temperature (°C)	147.5	146.6
Melting enthalpy (J/G)	172 168	174 171	Desolvation enthalpy (J/G)	106	111
Molecular purity (%)	96.5	97.9			

quently, crystallinity (i.e. the degree of order of ground and native crystals) seems to be the same.

Note that the differences in melting temperature of the aspirin crystals were initially surprising. An explanation may be that the coarse and fine crystals from the same crystallization batch could contain different amounts of impurities. At the beginning of the crystallization process, the first fine crystals collect many impurities. Some of them grow more than others and peripheral layers contain fewer impurities. Fragments of these coarse particles will contain fewer impurities than finer native particles of the same particle size (Fig. 11). This phenomenon, which was sometimes observed in the crystallization process, was studied by Roberts et al. (1990): "the impurities have a tendency to concentrate in the precipitating solid in the early stages of nucleation and growth".

Molecular purity analysis by differential scanning calorimetry confirms the higher purity of ground crystals.

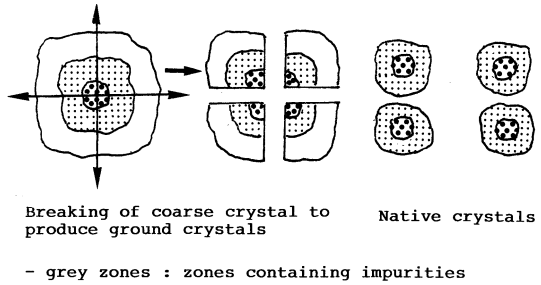

Fig. 11. Explanation of the lower impurity content of ground crystals.

4. Conclusion

Native and ground crystals of two pharmaceutical substances, aspirin and Lactose, were prepared from the same crystallization batch. Crystals had the same particle size and all fine adsorbed particles had been removed.

The compression and dissolution studies of these crystals show that no disorder was introduced into the crystalline network in any significant way. On the other hand, surface modifications seemed to occur during grinding, allowing for better wettability of crystalline surfaces.

The theory of Hüttenrauch, that crystalline defects created inside the crystalline particle are due to the energy produced during grinding, seems to be invalidated. Only the crystalline surface seems to be damaged.

Acknowledgements

The authors would very much like to thank Jean-Luc Dubois (Roussel Uclaf Romainville) for the specific surface area measurements, Loïc Brunet (CCME, Lille I University) for the SEM photographs, and Peter Miller (Roussel, Uclaf) for his very kind help in translating the manuscript into English.

References

Grant, D.J.W., York, P., 1986. Entropy of processing: a new quantity for comparing the solid state disorder of pharmaceutical materials. Int. J. Pharm. 30, 161–180.

Guillaume, F., Guyot-Hermann, A.M., Guyot, J.C., 1992. Elaboration and physical study of an oxodipine solid dispersion in order to formulate tablets. Drug Dev. Ind. Pharm. 18 (8), 811–827.

Guyot, J.C., Téte, L., Tak Tak, S.S., Delacourte, A., 1992. Practical interest of cohesion index for the technological formulation of tablets. In: Proceedings 6th International Conference, vol. III, pp. 246–254.

Hancock, B.C., Zografi, G., 1997. Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci. 86 (1), 1–12.

Hersey, J.A., Krycer, I., 1981. Detection of mechanical activation during the milling of lactose monohydrate. Int. J. Pharm. Tech. Prod. Manuf. 2 (2), 55–56.

Hesse, H., 1978. Tablets under the microscope. Pharm. Technol. 9, 37–58.

Hüttenrauch, R., 1983. Modification of starting materials to improve tabletting properties. Pharm. Ind. 45 (4), 435–440.

Hüttenrauch, R., Keiner, I., 1979a. Produce lattice defects by drying process. Int. J. Pharm. 2, 59–60.

Hüttenrauch, R., Keiner, I., 1979b. Influence of lattice defects upon mixing process. Powder Technol. 22, 289–290.

Lefebvre, C., Barthélémy, C., Guyot-Hermann, A.M., Guyot, J.C., 1988. An attempt at bringing to light a 'phase inversion' in a binary mixture of two dimensional rounded particles. Drug Dev. Ind. Pharm. 14 (15-17), 2443–2465.

Merle, C., Mangin, C., Guyot-Hermann, A.M., 1977. Essai d'un appareil de dissolution à flux continu. Bull. Soc. Pharm. Lille 2-3, 87–94.

Morita, M., Nakai, Y., Fukuoka, E., Nakajima, S.I., 1984. Physicochemical properties of crystalline lactose: Effect of crystallinity on mechanical and structural properties. Chem. Pharm. Bull. 32 (10), 4076–4083.

Roberts, K.J., Sherwood, J.N., Stewart, A., 1990. The nucleation of n. eicosane crystals from solution in n. dodecane, in the presence of homologous impurities. J. Crystal Growth 102, 419–426.

Vachon, M.G., Grant, D.J.W., 1987. Enthalpy–entropy compensation in pharmaceutical solids. Int. J. Pharm. 40, 1–14.

Veesler, S. 1991. Cristallisation de l'hydrargillite: cinétique et attrition. Thesis, Marseille III University.