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RESEARCH PAPER

Ibuprofen Agglomerates Preparation by Phase Separation

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ABSTRACT

The compression ability and dissolution rate of ibuprofen are poor. There are many processes to optimize these properties through adapted formulations. However, it would be more satisfactory to obtain directly during the crystallization step crystalline particles that can be directly compressed and quickly dissolved. This was the aim of this work. Ibuprofen spherical agglomerates were obtained using a very simple method based on the difference of solubility of ibuprofen in ethanol and in water. By cooling down an ibuprofen-saturated solution in an ethanol/water 50/50 mixture from 60°C to room temperature under stirring, a phase separation occurs. Ibuprofen crystallizes in separated water droplets. After separation by sieving and drying, spherical agglomerates were obtained. A study of the physical properties of ibuprofen agglomerates was carried out using electron scanning microscopy and X-ray powder diffraction. The compression ability was tested using an instrumented tablet machine, and the dissolution rate was measured using continuous flow cells. An improvement in compression and dissolution properties of the spherical agglomerates produced was observed. The process of crystallization in a separated dispersed phase could be envisaged each time a drug exhibits opposite solubilities in two miscible solvents.

INTRODUCTION

Ibuprofen is a drug widely used for its analgesic and anti-inflammatory properties. There are many marketed oral dosage forms, either tablets or hard gelatin capsules. Most usually, ibuprofen is supplied as a fine powder that exhibits poor technological and dissolution properties. The therapeutic dose is relatively high: 200 mg for an analgesic effect, 400mg for an anti-inflammatory one. It is the reason why dosage forms often contain several ex-

cipients and why the tablets are often prepared using a granulation process. We tried to improve flow properties, compression ability, and the dissolution rate of ibuprofen.

Several processes are described in the literature of studies to improve these properties. In some of them, an adjuvant is used, allowing better behavior. It is the case of several ''paracetamols for direct compression.'' However, it seems more advisable to crystallize directly pure drug particles that exhibit good properties owing to a special crystallization process. Agglomeration techniques are, at present, the most widely used.

There are two types of agglomeration techniques in the liquid phase. For the first type, into a suspension of small monocrystals, a second liquid (nonmiscible to the first one) in which the crystals are not soluble, but which can wet them, is added into the suspension under stirring. The spherical droplets gather the crystals inside them and give, after separation and drying, spherical agglomerates (Fig. 1a). Similar to this simple process is ''spherical crystallization,'' which is, as defined by Kawashima, Okumura, and Takenaka (1), ''an agglomeration technique which transforms crystals directly into a compacted spherical form during the crystallization process.'' Spherical crystals are composed of a great number of elementary crystallites in disordered disposition, which is a favorable factor for compression due to the isotropic texture created inside these polycrystalline particles.

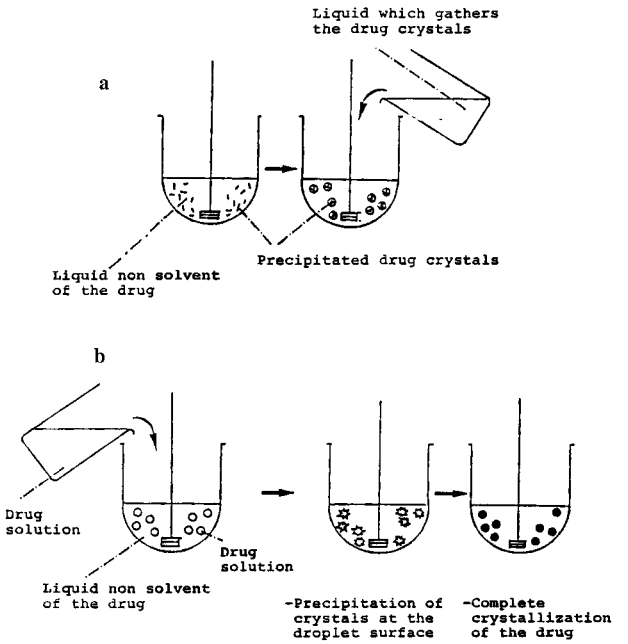

Figure 1. (a) Principle of the agglomeration in liquid phase; (b) principle of ''quasi emulsion solvent diffusion'' method.

The second type of method of agglomeration is the ''quasi emulsion solvent diffusion method,'' which was also described by Kawashima and coworkers (2). An emulsion of small droplets of a concentrated drug solution is carried out in a liquid phase in which the drug is not soluble. At the droplet surface, the drug precipitates, and the external phase slowly diffuses into the droplets, causing total drug crystallization inside the droplets, which gives the crystalline agglomerates formed their spherical shape (Fig. 1b).

We tried to prepare spherical crystals of ibuprofen according to Kawashima et al.'s process (1). Therefore, in a first step, a choice of three adequate solvents was undertaken. These solvents must be as follows: the first one must be a good solvent of the drug; the second solvent must be a liquid in which the drug is insoluble; and the third solvent must be a liquid in which the drug is insoluble, but which can wet the drug crystals. The ibuprofen chemical formula is nearly that of fatty acids, so this drug exhibits very extreme solubilities, and it was not possible to find the three types of solvents. This is the reason why we excluded the spherical crystallization process.

On the other hand, due to its chemical formula, the melting point of ibuprofen is very low (76°C). Consequently, it would be difficult to eliminate residual solvents from the ibuprofen particles without melting them. We then researched by recrystallization in different nontoxic solvents, a possible satisfactory crystal habit, favorable to direct compression and allowing a fast dissolution rate.

MATERIALS

The ibuprofen was from Cooper-Melun (France) and Laporte Organics Francis, Caronno Pertusella (Italy). The ethanol was normapur (Prolabo, France). Different mixtures of ethanol with water were prepared in different proportions. The acetone was normapur (Prolabo, France), and the tetrahydrofuran was extra pure (Scharlau, Barcelona, Spain).

METHODS

Preparation of Crystalline Particles

Preparation Trials in a Device for the Solubility Measurement

A solvent must be selected first. For this, the solubility in different solvents must be studied. The solubility must

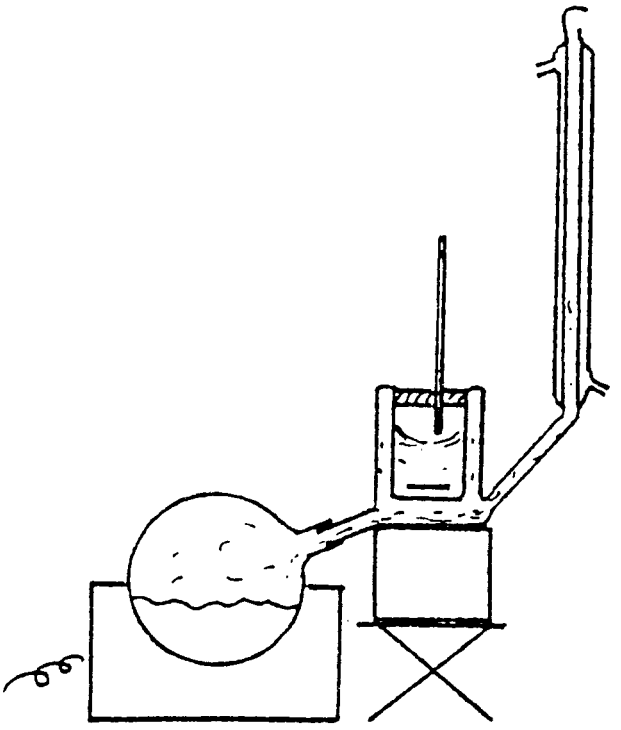

Figure 2. Device used for solubility determination.

be sufficiently high at relatively low temperatures to give satisfactory yield without degradation by too high a temperature. In addition, the difference between the solubilities at the selected saturation temperature and at room temperature must not be too high to avoid a too massive crystallization, which will hinder the particle dispersion under stirring.

The device used was a vapor jacketed Pyrex cell; inside the cell, the temperature is kept constant with the circulating vapor of cyclopentane, the boiling point of which is 49°C (Fig. 2). The solubility of ibuprofen in each solvent was determined by successive additions of ibuprofen crystals to the solvent in the cell to the point at which they no longer dissolve. This method allows observation of the crystal habits of particles that crystallize during the cooling of the liquid medium under stirring.

Crystallization on a Wider Scale

The crystallizer, the dimensions of which are shown in Fig. 3, was a cylindrical vessel with a hemispherical bottom. Stirring was ensured using a Raynerie Turbo test 33/300 type fitted with a turbine-type agitator. Into the

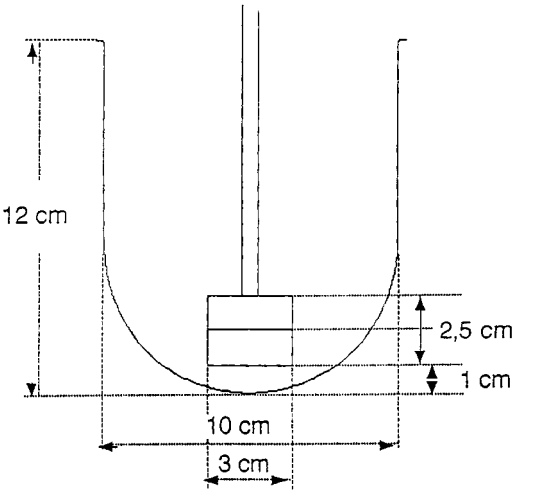

Figure 3. Crystallizer used for ibuprofen agglomerate preparation.

crystallizer, 300 ml of 50% alcohol were introduced at 60°C, and 45 g of ibuprofen were dissolved in it; then, the solution was left to cool at 25°C under stirring at 300 rpm for 30 min. Crystalline particles were separated from the solution through filtration under vacuum. A quantity of solvent equivalent to about 10% of the weight of the crystals was used to wash them. Then, crystals were placed in a thin layer in an oven at 60°C for 3 hr.

Physical Study of Crystalline Particles

Crystals were observed under an optical microscope using a Wild Leitz M 20 microscope. The morphology of the dried crystals was investigated by means of a Jeol CX 100 scanning electron microscope. The specific surface area was estimated by the BET method using krypton (ASAP 2000 device, Micromeritics). X-ray powder diffraction was carried out using an X-ray generator device (Siemens) fitted with a Guinier de Wolff camera (CuKα radiation, $\gamma = 1.54178$ Å).

Flow properties were evaluated according to the European Pharmacopoeia (3). The compression ability was investigated on an instrumented single-punch tablet machine (Frogerais OA) using the 1 CP method of Guyot (4). The crushing strength was determined using a Schleuniger tablet hardness tester 6D.

The dissolution rate was determined in continuous flow cells (5) in 800 ml of the buffered solution at pH 7.2 and 37°C according to the USP XXIII recommendations

Table 1

Solubilities and Habits of Ibuprofen Crystals

Solvent	Solubility (g/100 ml)	Habit	Elongation (Length/Width)	Transparence
THF	300	Needles	5	+
Acetone	233	Needles	8	+
Ethanol	230	Needles	7	+
Alcohol 50%	25	Crystal agglomerates	1.2	No
Water	Nearly insoluble	No crystal		

concerning ibuprofen tablets (6). Sample mass was 200 mg. The delivery of the pump was 50 ml/min. The dissolution medium was assayed for ibuprofen concentration spectrophotometrically by measuring absorption at 221 nm. The results are expressed as a percentage of dissolved drug. To express the dissolution data more rigorously, results were expressed in relation to either the sample mass or the surface area unity.

RESULTS

Preparation of Crystalline Particles

The solubilities and the crystal habits of ibuprofen obtained from different solvents are reported in Table 1. The most interesting crystalline particles seemed to be those prepared from 50% alcohol.

As can be seen in Fig. 4, the marketed ibuprofen crystals A are small acicular crystals; marketed crystals B are smooth, rounded particles that exhibit a surface with a partially melted aspect. The crystals obtained from 50% alcohol exhibit a nearly spherical shape, which could improve flow properties. On the other hand, as can be seen in Fig. 4, these particles are crystal agglomerates, which is a favorable factor for compression ability, due to a certain isotropy of the particle texture. In order to select the best preparation conditions, we studied the influence of the alcoholic degree and of the rotation speed of stirring.

Influence of the Percentage of Alcohol

The preparation process was the same described in the Method section. The rotation speed was fixed at 300 rpm. The solvent was 25%, 30%, 40%, 50%, and 60% alcohol. The most interesting results are reported in Table 2.

The particle sizes of crystalline particles obtained from 25% and 30% alcohol are very coarse and very irregular. These particles were not studied further. The 50% alcohol was the best recrystallization solvent.

Influence of the Rotation Speed of the Stirring

The preparation process was the same in 50% alcohol, but the rotation speeds were 200, 300, and 600 rpm (Table 3). Particles obtained at 200 rpm were too gross and too irregular. At 600 rpm, particles were very irregular and friable. The most appropriate rotation speed seemed to be 300 rpm.

Crystalline State of Ibuprofen Particles

Using thermogravimetry, no mass loss was observed that could be indicative of solvate formation. Powder X-ray diffraction patterns of the three types of ibuprofen are reported in Fig. 5. No polymorphism can be detected: the crystalline form is the same. As can be seen, the ibuprofen agglomerates, as well as the marketed A crystals, are very crystalline. As for marketed B crystals, very low crystallinity can be observed.

Technological and Dissolution Properties of Ibuprofen Agglomerates

Flow Properties

The flow properties were dramatically improved. The marketed ibuprofen samples exhibited no flow; ibuprofen agglomerates we prepared exhibited a flow time of 4 to 5 sec.

Compression Ability

The results of the comparison between ibuprofen agglomerates and marketed Ibuprofen are given in Table 4 and Fig. 6. Y_1 and Y_2 are the maximum forces measured on the upper and lower punches during compression. Y_2/Y_1 is indicative of the force transmission through the powder bed. The compression capacity was estimated by the cohesion index, that is, the ratio of the force necessary for the crushing of the tablet against the force Y_1, mea-

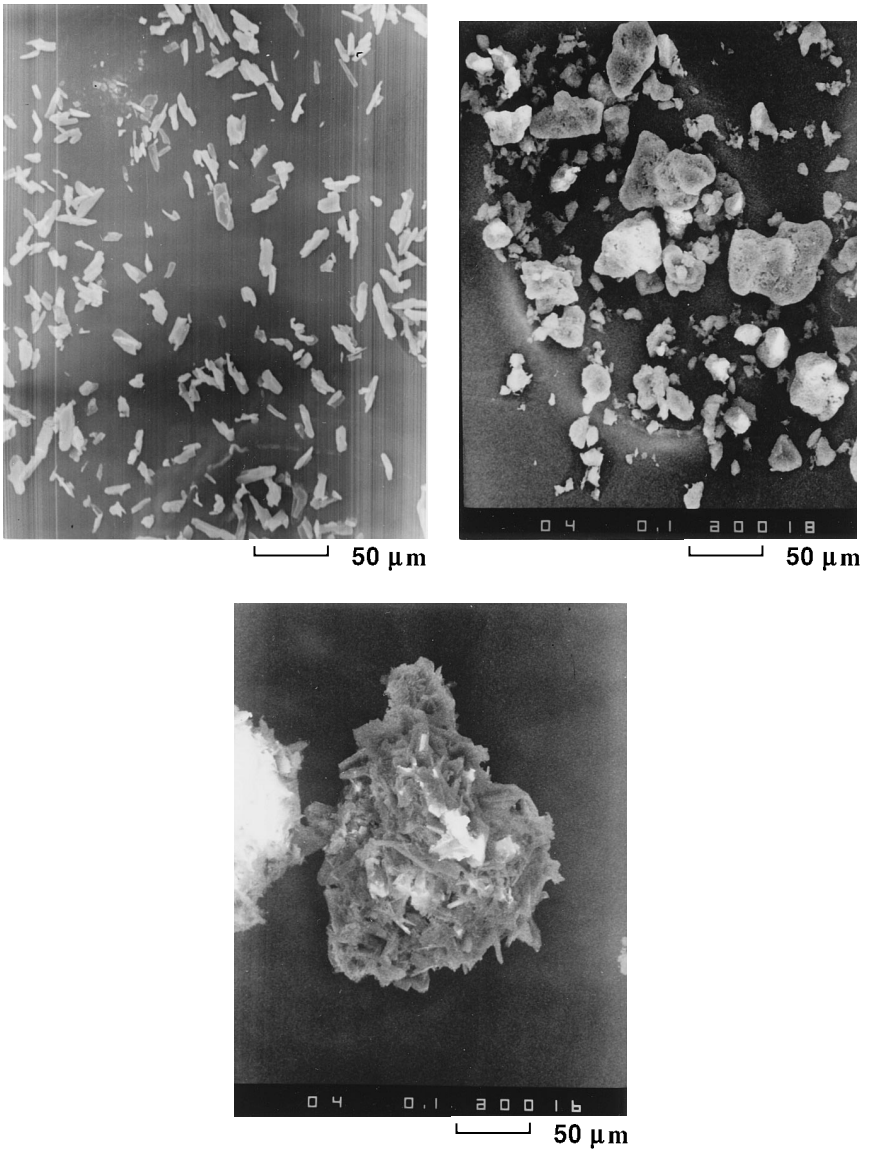

Figure 4. Aspect of ibuprofen particles (electron scanning microphotographs; ⊢—⊣ 200µm).

Table 2

Influence of Alcohol Percentage on Habit and Flow Properties of Ibuprofen Crystalline Particles

	40%	50%	60%
Elongation (length/width)	1.50	1.20	1.33
Mean diameter	>800 µm	350 µm	<200 µm
Flow time	>12 sec	4–5 sec	No flow

Table 3

Dimensions of Ibuprofen Crystalline Particles Prepared at Different Stirring Rotation Speeds

	200 rpm	300 rpm	600 rpm
Elongation (length/width)	1.45	1.2	1.25
Mean diameter	>900 μm	350 μm	<300 μm

sured during compression, muliplied by 10^5 for convenience (7).

The compression ability improvement brought to the ibuprofen by the agglomerate form is clear. Sticking and capping appear for a higher compression force as far as the agglomerates are concerned: above 2257 daN for agglomerates, 1329 for B crystals, and 920 for A crystals. The crushing strength of compacts is higher for agglomerates, up to 5.8 daN, whereas 5.1 and 4.0 are obtained as a maximum with B and A crystals, respectively.

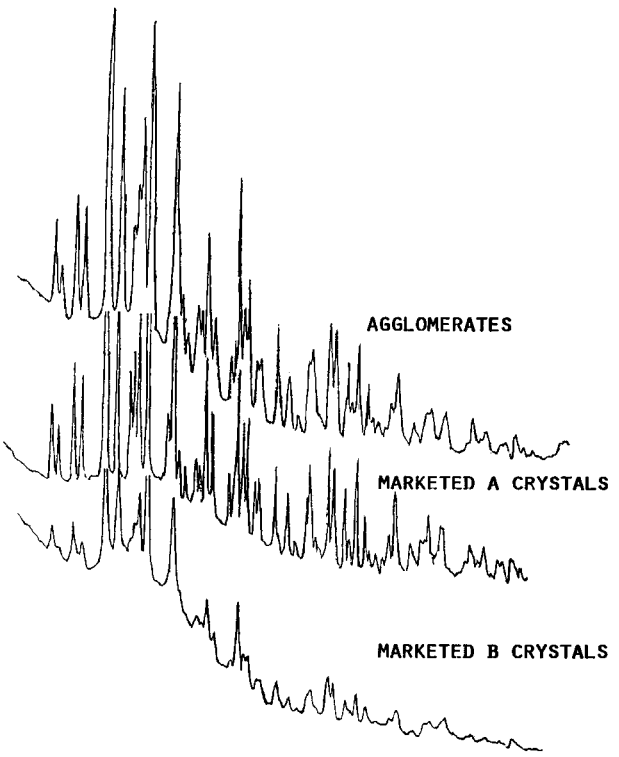

Figure 5. Powder x-ray diffraction patterns of the three types of ibuprofen particles.

Finally, when we consider the slope of the curve of crushing strength against compression force (Fig. 6), a decrease can be observed as far as A and B crystals are concerned, as early as when the lower compression forces are applied; as far as agglomerates are concerned, the slope increases up to a compression force of 649 daN, giving 5.0 daN crushing strength, which is indicative of much better compression behavior.

After these trials, better technological properties for ibuprofen agglomerates seem to be noted.

Dissolution Study

Results of the dissolution study are reported in Tables 5 and 6 and in Figs. 7a and 7b. They are expressed either as a percentage of dissolved drug without consideration of shape and particle size or in relation to the original sample surface. The results of the measurements of the specific surface area of the crystalline particles were as follows:

Marketed crystals A: 0.1400 m^2/g
Marketed crystals B: 0.4971 m^2/g
Agglomerates: 0.2449 m^2/g

These results, at first, are surprising; however, explanations can be found. As far as native marketed crystals A are concerned, the apparent low specific surface area of these very small crystals could be explained by their flat shape, which can produce very dense aggregates. Indeed, the flat faces of the crystals adhere to each other during the measurement. We do not take this value into account. In spite of the very irregular surface of agglomerates, the smaller particle size of marketed B crystals gives them a higher specific surface area. From these results, we expressed the dissolution data in relation to the sample surface at time 0, that is, for 200 mg: 0.04898 m^2 for marketed crystals B and 0.09942 m^2 for agglomerates.

The dissolution is faster from ibuprofen agglomerates than from marketed B crystals, particularly when it is ex-

Table 4

Compression Characteristics of Ibuprofen

	Y_1 (daN)	Y_2	Y_2/Y_1	Crushing Strength (daN)	Cohesion Index
Marketed ibuprofen A	412	354	0.86	2.9	703
	442	385	0.87	3.0	679
	574	500	0.87	3.0	522
	748	662	0.89	4.0	534
	828	733	0.88	3.7	447
	920[a]	819	0.89	3.9	424
Marketed ibuprofen B	393	350	0.89	3.0	763
	533	489	0.92	3.7	694
	655	592	0.90	4.2	641
	1213	1137	0.94	4.8	395
	1260	1188	0.94	4.6	365
	1329[a]	1253	0.94	5.1	383
Ibuprofen agglomerate	502	449	0.89	3.5	697
	522	465	0.89	3.9	747
	649	582	0.90	5.0	770
	862	793	0.92	5.8	673
	1438	1370	0.95	4.9	340
	1503	1421	0.95	5.0	333
	2257[a]	2148	0.95	5.5	244

[a] Above this Y_1 value, capping occurs.

pressed more realistically as a function of the surface area. On the other hand, the better wettability of agglomerates is clear when we compare the variation coefficient of the dissolution of these two types of crystalline particles (Table 5).

As far as marketed A crystals are concerned, the dissolution rate is similar to that of agglomerates. However, it must be recalled that the particle size of the A crystals is much finer than that of agglomerates.

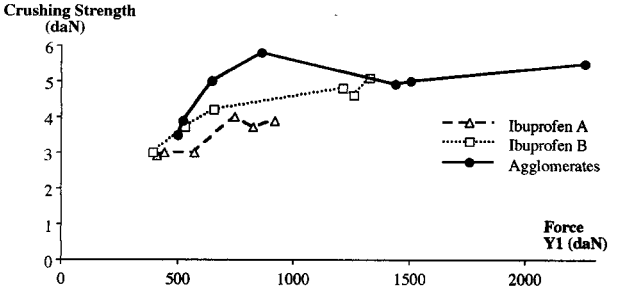

Figure 6. Compression characteristics (Crushing strength against compression force) or the ibuprofen particles (marketed A, marketed B, agglomerates).

DISCUSSION

A question may be raised: Why should agglomerates be obtained in 50% alcohol and not in other solvents tested? A hypothetical explanation is put forward next.

Ibuprofen is nearly insoluble in water and freely soluble in ethanol. The 50% alcohol is composed of water and pure ethanol. The solubility of ibuprofen in hot 50% alcohol is relatively high, but when cooling is started, this solubility decreases. The spherical shape of the agglomerates leads us to think that phase separation occurs. Ibuprofen precipitates inside the microdroplets of the separated dispersed phase, which could be a saturated solution of ibuprofen in ethanol. The ibuprofen precipitation is perhaps due to the diffusion of the external phase, which is more concentrated in water, into the ibuprofen saturated alcoholic solution, which composes the microdroplets. This process is nearly the quasi emulsion solvent diffusion of Kawashima et al. (2).

Table 5

Dissolution Rate of Ibuprofen from Native Marketed Crystals and Crystal Agglomerates

Time (min)	Marketed Crystals A			Marketed Crystals B			Agglomerates		
	Mean (%)	$\sigma_{(n-1)}$	CV (%)	Mean (%)	$\sigma_{(n-1)}$	CV (%)	Mean (%)	$\sigma_{(n-1)}$	CV (%)
7.5	72	3	4.2	59	10	17	75	3	4
15	80.1	5.4	6.7	66	9	13	81	1.5	2
30	89.3	4	4.5	74	8	11	85	3	3.5
45	94.4	4.4	4.7	77.5	6	8	91	2.5	3
60	97.0	3.7	3.8	77.5	6	8	95	2	2

Table 6

Dissolution Rate of Ibuprofen from Native Marketed Crystals and Crystal Agglomerates in Relation to the Sample Surface at Time 0

Time (min)	Marketed Crystals B (mg/m^2)	Agglomerates (mg/m^2)
7.5	1.187	3.062
15	1.328	3.307
30	1.489	3.470
45	1.589	3.716
60	1.589	3.819

This behavior would be the same as that advanced in a previous paper (8). At a certain temperature, a mixture of two solvents is homogeneous when these solvents are pure. In the presence of a third compound with a solubility that is higher in one of the two solvents, phase separation occurs. Precipitated crystals gather in the microdroplets and give spherical agglomerates.

CONCLUSION

Ibuprofen agglomerates were prepared in 50% alcohol. The spherical shape of agglomerates allows good flow properties. The compression properties are not in relation to the degree of crystallinity of the particles since

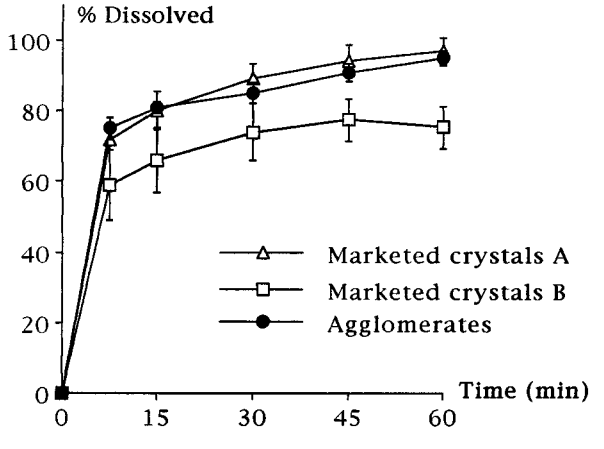

Figure 7a. Dissolution rate of Ibuprofen from marketed A crystals, marketed B crystals and agglomerates (expressed in mass percentages).

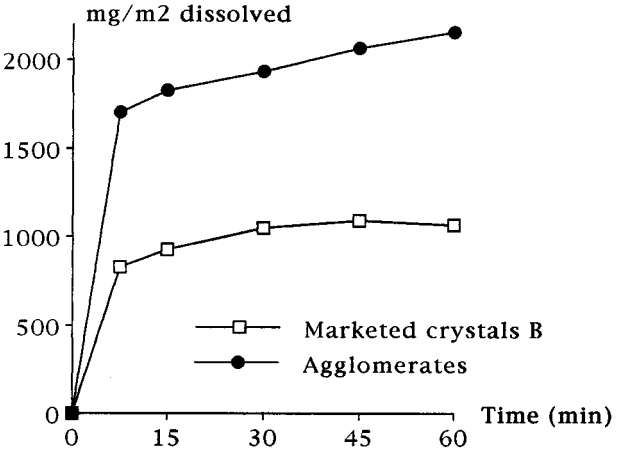

Figure 7b. Dissolution rate of ibuprofen marketed B crystals and agglomerates, expressed in relation of the sample surface at 0 time.

ibuprofen agglomerates, which are very crystalline, exhibit good compression capacity, whereas marketed B crystals (which are the least crystalline) are not the best. In fact, the isotropy of the agglomerate texture improves compression ability, allowing direct compression for tablet preparation. Then, to a minor degree, agglomerate porosity gives them good wettability and fast dissolution properties. Therefore, it seems that agglomerates are a good raw material. In addition, the residual solvents are not toxic.

The formation process of the ibuprofen agglomerates by phase separation could be envisaged each time a substance exhibits opposite solubilities in two miscible solvents.

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