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Monitoring crystal modifications in systems containing ibuprofen

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Summary

Qualitative and quantitative crystal analysis, including differential scanning calorimetry, X-ray powder diffraction and scanning electron microscopy were performed at different stages of ibuprofen tablet manufacture obtained at three levels of compaction. Melting points and enthalpy of fusion were carefully monitored and compared using statistical techniques (ANOVA and one degree of freedom procedures). Drug-disintegrant interactions were investigated using a fractional factorial design. Wetting and compaction affected the crystal surface as measured by a 0.2–8.6 kJ/mol decrease in the heat of fusion, and a shift of 2–3°C in the melting point. The differences were too small to suggest the existence of enantiotropically or monotropically related polymorphs. The results, however, indicated a lattice modification of ibuprofen during processing which we think occurred at the surface. The initial dissolution rates appeared to be inversely related to the amounts of ibuprofen in the formulation and the fastest drug release was obtained for a 1:3 intragranular ratio.

Introduction

Fundamental investigations, especially in the field of compaction and wet granulation, have long established that pharmaceutical processing can modify some characteristics of raw materials in such a way that can be detrimental to the overall performance of the final drug product (Chan and Decker, 1985; Lefevbre et al., 1986). Monitoring crystal changes has become essential in order to optimize many formulations (Halebian, 1975). For example, sulfanilamide crystal habit was altered as a function of increased compression forces or exposure to liquids (Cruaud et al., 1981) and physical interactions between ibuprofen and excipients can induce eutectic behavior (Gordon et al., 1984; Mura et al., 1987). The latter does not necessarily mean adverse incompatibility but may explain handling difficulties. Many pharmaceutical manipulations will affect the crystal habit of drug substances and these modifications may have adverse consequences on the formulation (Cruaud et al., 1981) or the drug bioavailability (Aguiar et al., 1967).

Crystal properties of ibuprofen are known to influence its pharmaceutical processing (Hiestand

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et al., 1981; Romero et al., 1991). This aspect of ibuprofen formulation is well documented and it is generally recognized that the drug undergoes changes due to processing (Franz, 1986). For example, eutectic behavior has been proposed with some pharmaceutical excipients (Gordon et al., 1984) and although never experimentally proven, surface sintering has been suggested as a theory for rearrangement of the crystal lattice during compression (Alhec and Zografi, 1991). For ibuprofen, nevertheless, very little has been published to support evidence of the crystal modifications. Thus, the mechanisms and consequences of such alterations have yet to be identified for this particular compound.

The objectives of this work were to elucidate the mechanisms of crystal distortion by which ibuprofen is modified during its processing and to investigate these effects on the biopharmaceutical properties of a model formulation.

Experimental

Materials

Ibuprofen USP grade was obtained from the Ethyl Co. (lot no. LH-6-72). Wet granulations containing Fast Flo Lactose (Sheffield lot no. 59009), Povidone (PVP, GAF lot no. G-30223A) and Explotab (Edward Mendell lot no. 1336) were prepared using purified water. Granule lubrication was achieved using magnesium stearate (Fisher Scientific Co.). The potassium monobasic phosphate and sodium hydroxide used for dissolution medium and buffers were obtained from Fisher Scientific. All chemicals were of analytical grade. Ibuprofen standards for spectrophotometry and differential scanning calorimetry (DSC) were provided by the Standard Division of USP Rockville, MD.

Methods

The experimental design consisted of analyzing ibuprofen alter dry mixing with excipients, wet massing and tableting. The model formulation, defined in Table 1 was prepared using five process steps presented in Table 2 The percentages of active in the formulations were 57, 67, and 77%. In addition, systems containing 3% extragranular disintegrant were formulated and tested for comparison purposes. Mixtures of ibuprofen, the diluent, the binder (6%), and the appropriate amount of disintegrant were dry mixed for 10 min. The powder was wet granulated in a planetary mixer (Kitchen Aid, model KS-A, Hobart) until the end-point, determined by power consumption, was reached. Flow rate of the granulation liquid remained constant throughout the entire experiment. Granules were dried on a tray at 40°C for 12 h and later mixed with lubricant in a V-blender for 10 min. Lubricated granules were then compressed into 350 mg

TABLE 1

Formulations used in the study

Ingredients	Amount (%)								
	Formulation A			Formulation B			Formulation C		
Ibuprofen	57	57	57	67	67	67	77	77	77
Fast Flo Lactose	36	36	36	26	26	26	16	16	16
PVP	6	6	6	6	6	6	6	6	6
Mg stearate	1	1	1	1	1	1	1	1	1
Na starch glycolate [a]	1	2	3	1	2	3	1	2	3
Intragranular ratio	1	1:2	1:3	1	1:2	1:3	1	1:2	1:3
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

[a] All systems contained 1% of intragranular disintegrant. The total amount of disintegrant is reported as a percentage (in weight) of the overall formulation.

tablets using 3/8 concave punches using an instrumented F3 single punch press. Three compaction pressures were investigated: low, intermediate and high (averaging 1, 10 and 30 kN, respectively).

At the end of each manufacturing step I and III–V (Table 2), samples were withdrawn and analyzed by X-ray powder diffraction and scanning electron microscopy (SEM) photographs. Thermal analysis (DSC) was performed on all samples (Kim et al., 1985) using a Perkin Elmer, series 7 instrumented unit, calibrated with indium and interfaced with a P 7500 E computer. For whole tablets, the electron microscopy photographs were shot from 35 and 80° angles on pressed and side surfaces, on horizontal and vertical cross-section of tablets embedded and prepared according to a method described by Hess (1978).

Crystal packing

The unit cell of ibuprofen crystal was analyzed using the molecular modeling software (Macromodel 3.0). The coordinates of single X-ray reflection data was obtained from the literature (McConnell, 1974) and the molecular arrangement of a crystal lattice, simulated on this program.

Comparative analysis

In an effort to mimic the effect of processing, ibuprofen and physical mixtures of the formulation were ground thoroughly for 10 min in a mortar or melted at a temperature above 80°C and recrystallized upon cooling at room temperature. DSC was further performed on the samples and their thermal profiles compared to those of pure and formulated ibuprofen. Additionally, the hygroscopicity of ibuprofen was measured after storage at 35°C and 85% relative humidity (RH). Karl Fisher analysis was performed at regular time intervals on 100 mg samples exposed to humidity.

Biopharmaceutical properties

The dissolution apparatus used a paddle rotating at 50 rpm in a USP phosphate buffer at pH 7.4 and a temperature of 37°C. This method using a six-vessel dissolution apparatus (Vankel) had been shown to discriminate between various ibuprofen formulations (Romero et al., 1988). An ultraviolet spectrophotometer was used to determine the concentration of ibuprofen at 264 nm in the dissolution fluid. For low ibuprofen concentrations, the percentage dissolved was also calculated from measurements obtained at 220 nm.

Statistical analysis

All results were analyzed statistically using an analysis of variance at the 99% confidence level to determine differences between enthalpy of fusion and melting ranges. Sums of squares were calculated to perform one degree of freedom comparisons using orthogonal contrasts. These tests allowed the investigation of the effect of compaction on the thermal parameters. A restricted fractional factorial design was used to test the effects of drug/disintegrant interactions. The independent variables were amounts of active and the concentration of extragranular disintegrant. These factors had three levels but in the interpretation of the data greatest weight was placed on any effects on dissolution.

TABLE 2

Experimental methodology

Processing	Steps	Analysis
Dry mixing (V-blender) 10 min (ibuprofen, lactose, Explotab, PVP)	I	DSC, SEM, X-ray
Wet granulation (monitored by power consumption)	II	
12 h tray drying at 40°C	III	DSC, SEM, X-ray
Mixing (V-blender) 10 min (granules, Explotab, lubricant)	IV	DSC, SEM, X-ray
Compaction (tablets)	V	DSC, SEM, X-ray dissolution, hardness

DSC, differential scanning calorimetry; SEM, scanning electron microscopy; X-ray, X-ray diffraction.

Results and Discussion

Crystal packing

The single crystal unit cell for the racemate includes four molecules: two *R*-(−) and two *S*-(+) isomers attached with two central hydrogen bonds between the carboxylic groups of dextrorotatory and levorotatory molecules (Fig. 1). In addition, Fig. 2 shows the juxtaposition of eight crystal unit cells. Six hydrogen bonds between cells could be identified. Each intermolecular interaction was shared between four other cells as favored by the preferential positioning of *R*-(−) and *S*-(+) molecules. Each unit has been cleared of the molecules not involved in the intercellular interactions. The resulting effect is the delimitation of a plane, on which intermolecular distances are most likely to be affected during tangential stress. Thus, this eight-cell system may explain the weakness of the ibuprofen crystal during processing.

The mass fraction of water obtained by the Karl-Fisher technique, averaged 0.063 ± 0.001 and 0.55 ± 0.004% (mean ± SD) before and after exposure to humidity, respectively. This analysis confirmed that although the moisture increased 10-fold alter exposure to 85% RH for 76 h, it did not exceed 0.55%, possibly concentrating at the surface since ibuprofen does not include crystallization water. This moisture was defined by Alhec and Zografi (1991) as plasticization or molecular mobility.

Thermal analysis

Thermal analysis indicated that only compaction or grinding of the physical mixture affected both the melting point and the heat of fusion of ibuprofen (Table 3). All parameters were compared at the 99% confidence level. Furthermore, the enthalpy of fusion decreased progressively from 25.7 to as low as 18.1 kJ/mol

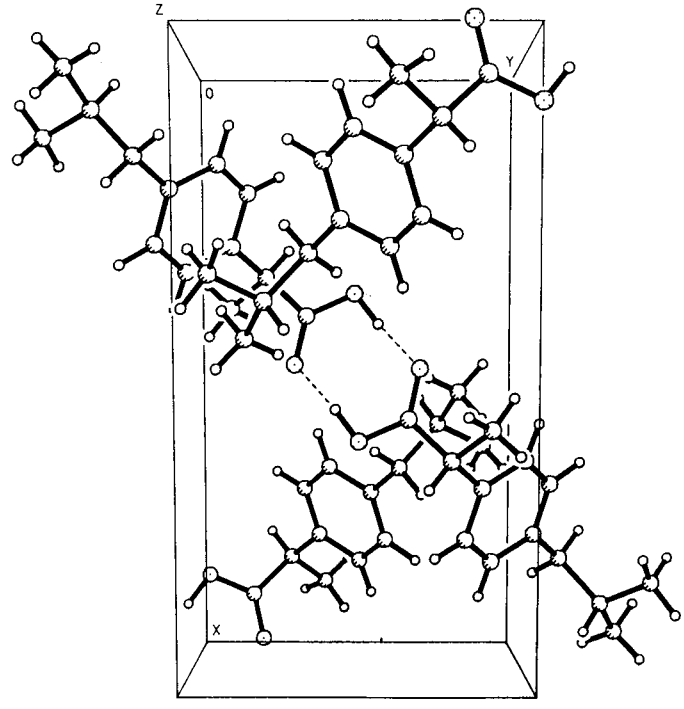

Fig. 1. Unit cell of ibuprofen racemate, molecular arrangement and crystal packing: there are two molecules of *R*-(+) and two of *S*-(−) within the crystal cell; the dashed lines correspond to hydrogen bonds.

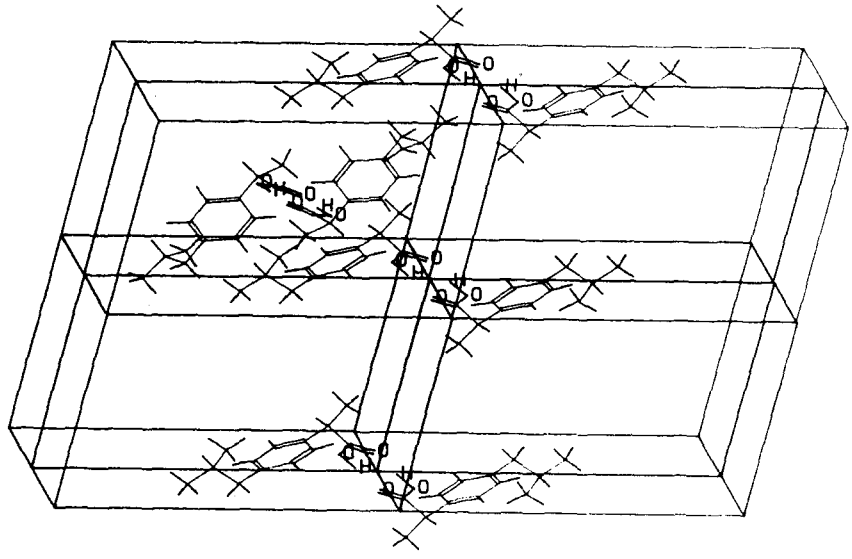

Fig. 2. Details of the crystal packing show preferential intermolecular interactions in one direction indicating the weakness of the plane most likely to rupture during compression.

during the tablet manufacture. If the assumption that a pure equilibrium exists at the melting point (T_m) is valid, then the changes are probably indicative of enthalpic modifications (weaker intermolecular interactions) at the crystal surface before compression. If ΔH^f is the enthalpy of fusion of the sample, we defined $\Delta\Delta H^f$, the enthalpy change, as the difference between the enthalpy of fusion of pure ibuprofen and the enthalpy of ibuprofen systems in the melting temperature range of ibuprofen.

Mixing with excipients and processing are the combination factors responsible for the enthalpy change. All values of the enthalpy of fusion were significantly affected by processing as determined by an F test (see Table 4). The magnitude of the change depended on the stage of processing. The orthogonal contrasts L_1–L_3 were found statistically significant. Compression had an effect on the enthalpy of fusion and ibuprofen in lower strength formulations appeared to be less sensitive than in higher strength tablets. The heat of fusion for ibuprofen was less affected in granules than in tablets.

TABLE 3

Thermal analysis of ibuprofen

System	Melting point (°C) mean ± (SD)	Enthalpy (ΔH) (kJ/mol) mean ± (SD)	Entropy (ΔS) ($J\ g^{-1}\ K^{-1}$)
Ibuprofen pure	77.7 ± (0.6)	25.7 ± (0.5)	0.35
Ibuprofen ground	76.8 ± (0.2)	23.7 ± (0.9)	0.33
Ibuprofen melted [a]	76.9 ± (0.4)	23.0 ± (0.9)	0.11
Ibuprofen RH [b]	77.2 ± (0.3)	25.6 ± (0.1)	0.35
Physical mixture	77.4	21.0	0.29
Physical mixture ground	75.3	18.1	0.25
Granules	77.3 ± (0.2)	21.9 ± (1.3)	0.30
Tablets	75.2 ± (0.9)	18.2 ± (1.7)	0.25

[a] Ibuprofen melted and recrystallized at room temperature.
[b] Ibuprofen exposed to 85% humidity for 76 h.

TABLE 4

Analysis of variance (enthalpy of fusion) and one degree of freedom orthogonal comparisons

Source	Degree of freedom (DF)	F_{test}	$F_{0.01,1,42}$
Among formulation	9	13.6 [a]	7.3
Compaction vs no compaction contrast L_1	1	9.5 [a]	7.3
Low compaction forces vs high compaction forces contrast L_2	1	42.9 [a]	7.3
Low ibuprofen strength vs high ibuprofen contrast L_3	1	19.8 [a]	7.3
Within formulation	42	–	–

[a] Significant difference at 99% confidence interval.

X-ray crystallography

In Fig. 3 the X-ray diffraction patterns of pure ibuprofen dry granules and ground tablets indicated crystal changes of ibuprofen during pharmaceutical manipulations: dilution with excipients only decreased the intensity of the diffractogram. Wet granulation, however, induced a slight rearrangement of the crystal lattice. At low angles of the spectrum, the 12.2 deflection peak completely disappeared. No further changes were visible on the X-ray diffraction pattern after compaction.

SEM

In order to complement results of the thermal analysis, qualitative observations were performed

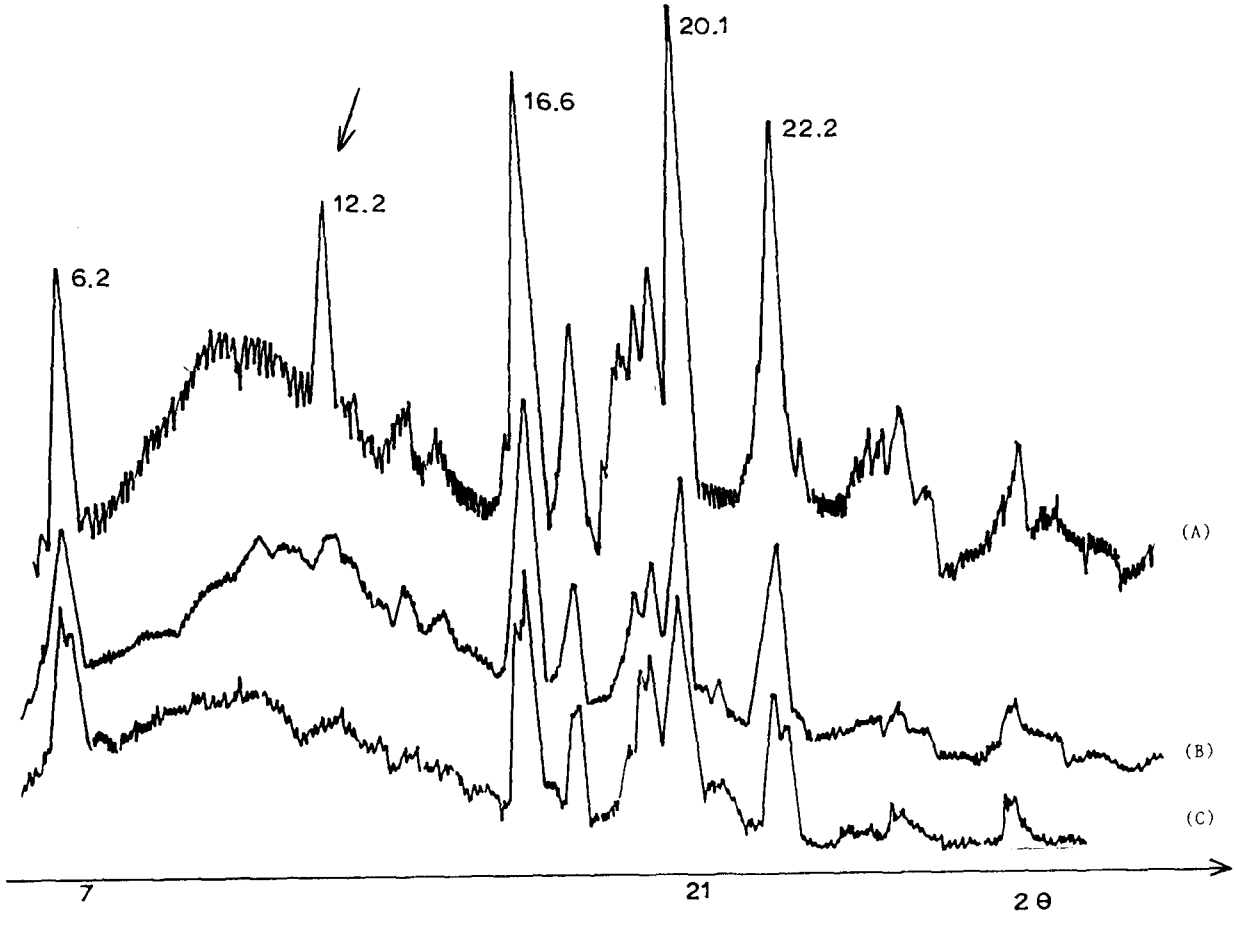

Fig. 3. X-ray diffraction patterns of (A) pure ibuprofen, (B) granulations and (C) tablets.

by SEM. Morphological changes from pure to formulated ibuprofen were visible at the $\times 1000$ magnification as shown on Fig. 4. On the tablets, the crystals are visible but the particle boundaries are not detectable (indicating sintering or fusion at the surface). Thus, an ibuprofen network appeared to result from sintering of the ibuprofen crystals during processing. Cross-sections of

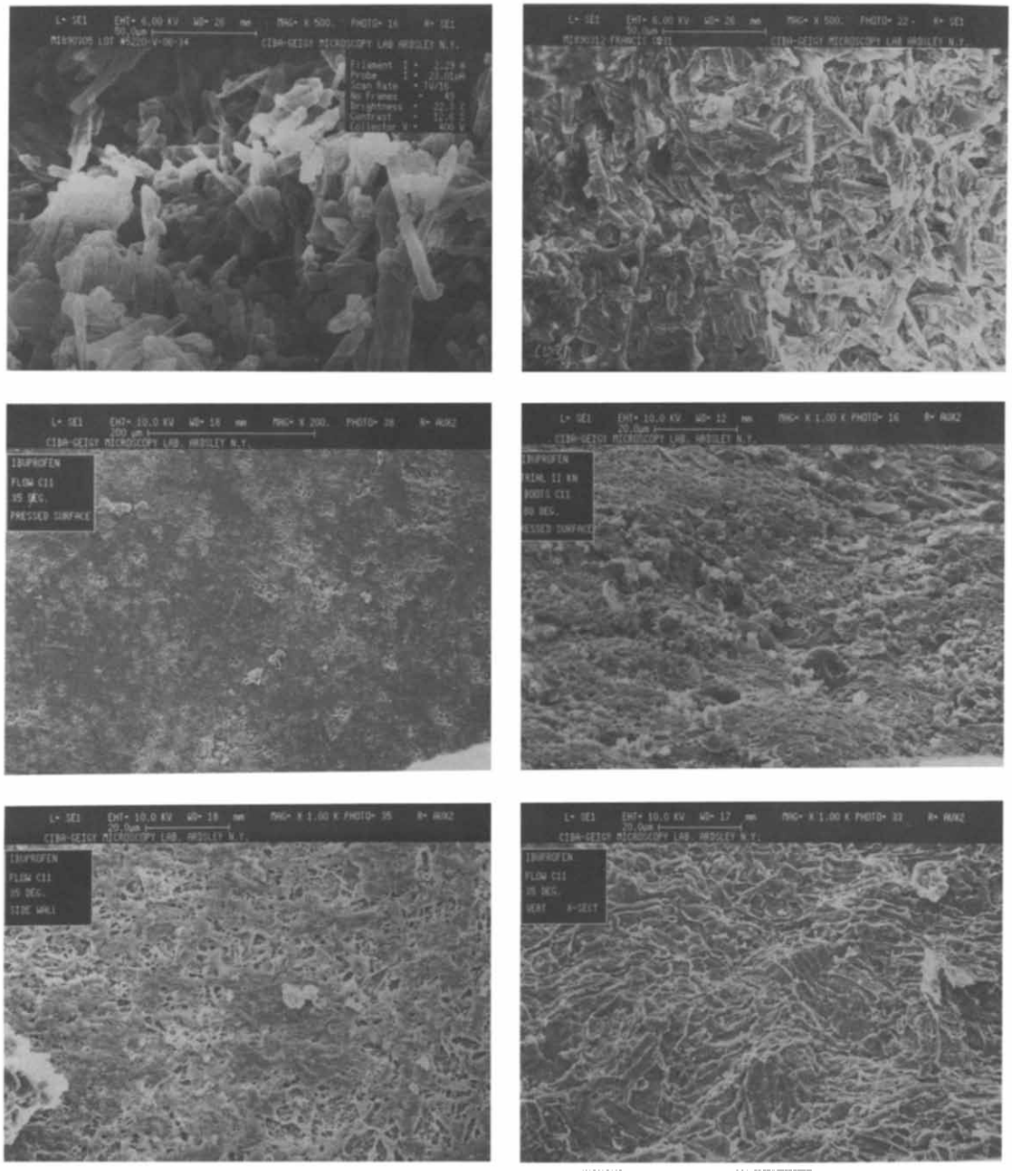

Fig. 4. Identification of the ibuprofen network. Electron microscopy photographs of: (A) pure ibuprofen, (B) granules (wet massing). (C) Tablets (C1, C2) pressed surface, (C3) side walls, (C4) vertical cross-section.

tablets showed a film of PVP (light membrane) covering packs of ibuprofen crystals (dark). Some starch glycolate particles are also visible. The observation of SEM photographs gave an estimate of the the crystal modification suggested by thermal analysis (Hess, 1978). We think that the process of wet granulation induced the lattice fragilization and upon compaction, further crystal disruption occurred with a possible consolidation of the hydrophobic matrix. The disintegration and dissolution analysis confirmed that the ibuprofen network was hydrophobic. When two ibuprofen particles are in contact, within a formulation, thermal properties have already been disturbed; upon compaction, enough mechanical energy is provided to induce sintering of the crystalline envelopes of ibuprofen as visualized on these SEM photographs.

Effect of processing

The decrease in T_m averaged a statistically significant 2–3°C upon compaction. ΔT_m was not proportional to the compression as indicated by paired *t*-tests (Fig. 5). The reported values of compaction are arithmetic means of upper punch compression forces recorded on the instrumented press. The enthalpy change, $\Delta\Delta H^f$, was defined as the difference between the heat of fusion of pure ibuprofen and the energy of fusion of the formulated ibuprofen. $\Delta\Delta H^f$ was indicative of the extent of some crystal modifications observed during processing. The effects of compaction and

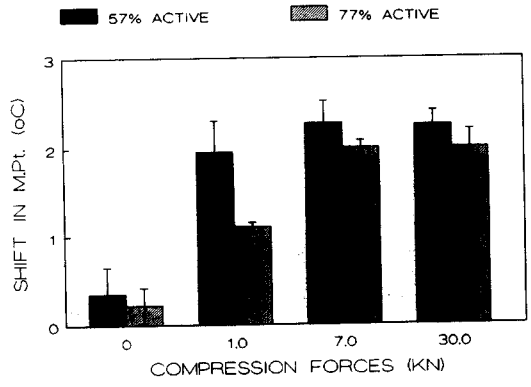

Fig. 5. Effect of tabletting on the melting point.

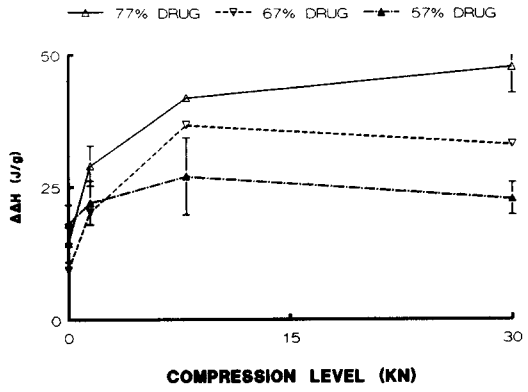

Fig. 6. Effect of tabletting on the enthalpy parameter.

low ibuprofen strength on the thermodynamic parameter have been found statistically significant (Table 4). In Fig. 6 for all strengths studied

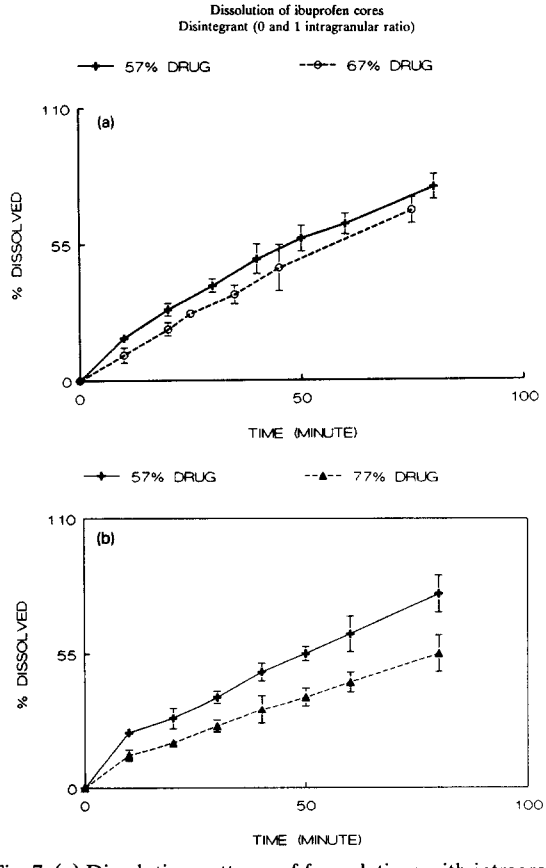

Fig. 7. (a) Dissolution patterns of formulations with intragranular disintegrant (disintegrant level 1%; 100% intragranular). (b) Dissolution patterns of formulations with extragranular disintegrant (disintegrant level 3%; 0% intragranular).

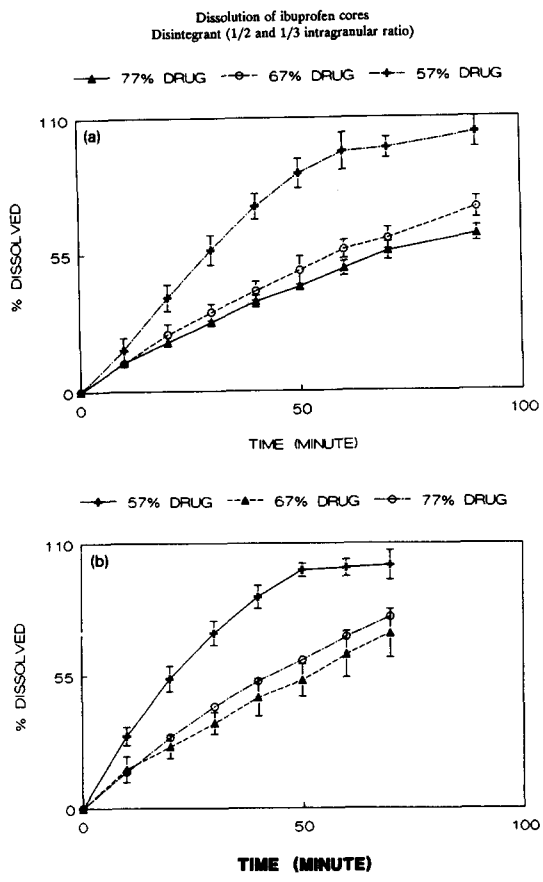

Fig. 8. (a) Dissolution patterns of formulations with 1:2 intragranular disintegrant (disintegrant level 2%; 50% intragranular). (b) Dissolution patterns of formulations with 1:3 intragranular disintegrant (disintegrant level 3%; 1/3 intragranular).

the enthalpy change increased and stabilized at a plateau value. Low concentrations of ibuprofen seemed to be less sensitive to mechanical stress. The latter, however, had the highest shift before tableting. These results suggest that excipients have a disruptive effect on the ibuprofen crystal and a protective effect upon compaction. Similar effects had been previously suggested in a study on the pharmaceutical processing of sulfanilamide (Cruaud et al., 1981).

TABLE 5

Crystal modifications and initial drug release rates

Ibuprofen concentration (%)	Enthalpy change ($\Delta\Delta H^f$) (J/g)	Release rate (mg/h)
A 57	27.2	10.8
B 67	36.0	0.66
C 77	41.9	0.63

Dissolution studies

The dissolution profiles of ibuprofen cores also exhibited similar trends, as seen in Figs 7 and 8. Low ibuprofen content led to cores with fast dissolution rates as compared to higher strength dosage forms. Although the data suggested that initial drug release rates might be related to the extent of the ibuprofen network (Table 5), any correlation was insignificant because of the limited number of points. Within the tablet, the crystal modification of ibuprofen created a surface hydrophobic network that seemed to be the limiting factor of drug release. The dissolution efficiency was optimal for the lowest amount of ibuprofen and the highest concentration of disintegrant (3%) in the 1:3 intragranular ratio. Formulation with 100% extra- or intragranular disintegrant had lower dissolution efficiencies than did formulation combining extra/intragranular disintegrant at the same concentration. This might be another piece of evidence for the existence of the hydrophobic network.

Conclusions

The crystal packing of ibuprofen occurs with preferential orientation in which a weak plane has been identified as probably responsible for the crystal modifications during compaction. Pharmaceutical processing does alter the crystal habit of ibuprofen (not its internal structure) in a stepwise manner. We identified three progressive mechanisms. Mixing with excipients induced the destabilization and fragilization of intermolecular interactions; wet granulation resulted in the distribution of water at the crystal surface (the amorphous region) (both mechanisms account for a drop of 4.1 kJ/mol in the enthalpy of fusion and predispose the ibuprofen to sintering); compaction brought the enthalpy decrease to another

6.2–8.6 kJ/mol and provides enough energy to initiate sintering as observed on the scanning electron microscope. In addition to lattice rearrangement, the resulting ibuprofen network is hydrophobic and could be the limiting factor of drug dissolution. As a consequence formulators must be cautious when increasing ibuprofen concentration in tablet formulations.

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