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RESEARCH PAPER

Properties of Ibuprofen Crystallized Under Various Conditions: A Comparative Study

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ABSTRACT

Different crystal forms of the analgesic drug ibuprofen were prepared and characterized in this study. Various conditions were used for the crystallization: crystallization was carried out using the solvent change method, the temperature change method, and the solvent evaporation method. Crystals were grown from different solvents. Different crystal forms with different properties were observed: cubic, needle-shaped, and plate-shaped crystals were obtained. Spherical agglomeration occurs when crystallization is carried out in acetonitrile or methanol. Flowability of these spherical crystals is increased. All crystals were determined as isomorphic by differential scanning calorimetry and x-ray analysis—which queries doubtful results of recent publications. Properties like dissolution behavior and properties influencing the manufacturing of dosage forms—like flowability—differ. Thus the choice of the optimal preparation method influencing the crystal habit is important in manufacturing the drug ibuprofen.

Key Words: *Crystal habit; Crystallization techniques; Habit modification; Ibuprofen*

INTRODUCTION

Most drugs appear in different crystal forms. Many drug substances form different crystal lattices with different internal packing arrangements of molecules; thus polymorphic forms exist. However, there exist also drugs whose crystals only have differences in their outer appearance; these drugs

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form different habits without differences in the crystal lattice. This results in isomorphic crystals. Crystals can be modified by crystallizing the drug in different ways which affect the physical and physicochemical properties, such as melting point, solubility, true density, dissolution profile, flowability, and tabletability. The existence of polymorphic forms has to be evaluated in drug development, as transformation of a primary formed unstable polymorphic crystal into a stable form can cause problems in manufacturing or storage of drugs. So either the stable polymorph has to be found and used, or if a dosage form with a metastable crystal form is manufactured, its stability has to be proved. Problems caused by polymorphic changes of drug substances are described by several authors: polymorphic changes of thiamine hydrochloride affecting the mechanical properties, such as crushing strength and disintegration time of the tablets during granulation and tabletting, are described in Ref. [1]. Thus bioavailability can be affected, as also shown by the following example: in 1998 several lots of capsules of the drug ritonavir failed the dissolution test. A polymorphic form, which was hitherto unknown, with greatly reduced solubility was formed.[2] But dissolution rate and processing properties such as flowability cannot only differ for various polymorphic forms, but also for various habits of the same drug.[3] Thus the optimization of crystal properties through modification of surface or habit without the formation of a polymorphic form should be preferred in drug development. Beside differences concerning the individual crystal, differences in crystal agglomeration can also occur. Flowability and compressibility of a drug can be improved using the spherical crystallization technique. In Ref. [4], spherical crystallization is defined as an agglomeration technique that transforms crystals directly into a compacted spherical form during the crystallization process. Spherical crystallization is carried out by pouring a drug solution into an emulsion consisting of a liquid that can wet the drug crystals incorporated in a liquid that is a non-solvent of the drug. Precipitated crystals gather in the wetting liquid. Another method for spherical agglomeration is the ''quasi-emulsion solvent diffusion method'' with a two-solvent system[5]: a drug solution is poured into a non-solvent that is not miscible with the drug solution. An emulsion is formed, crystallization of the drug starts on the surface of the droplets, and the solvent diffuses into the non-solvent. Spherical crystallization can also occur by phase separation, as described in Ref. [6]. Thus properties of a drug can be affected by choosing a suitable polymorphic form, by choosing a suitable crystal habit, and by using special crystallization techniques. In this study different crystal habits are prepared in order to optimize drug powder properties.

Ibuprofen is a common analgesic drug. Because of its hydrophobic properties, it shows low solubility in water. Flowability and compressibility are bad, thus in most cases for production of solid dosage forms a granulation step is necessary. Ibuprofen can form different crystal forms with different properties. In Ref. [7], five ibuprofen raw materials obtained from different suppliers were compared. All crystals were isomorphic. However, differences concerning the crystal habit, the crystal size, and the surface area that affect the granulation process (different liquid requirements in wet granulation) and the coating process were described. Nikolakakis et al.[8] describe the effect of different solvents and the presence of a methacrylic polymer on the habit of ibuprofen prepared by a temperature change method. Crystallization was carried out with different cooling rates using different alcohols and acetone in the presence of different methacrylic polymers. Especially the solvent and the cooling rate have an effect on the micromeritic properties due to interactions with hydrophobic faces of the growing crystals. The polymer has a smaller effect. The polarity of the solvent affects the crystal habit, as the use of methanol results in the most symmetrical and smooth crystals while the use of a low polarity solvent (acetone) results in elongated crystals. A further study[9] describes differences in crystal habit of ibuprofen crystallized by a cooling process from different alcohols and hexane. During the cooling process ibuprofen powder is added as nuclei. While ibuprofen crystallized from methanol and ethanol shows a polyhedral crystal habit, crystallization from hexane results in needlelike crystals. The crystal habit influences the mechanical properties of the drug. If ibuprofen is crystallized from ethanol and methanol, the powder flow is increased. If hexane is used, the crystals show the worst powder flow and produce the softest tablets. While Refs. [8] and [9] describe no polymorphic forms, different crystal forms of ibuprofen analyzed as polymorphic forms have been

reported in recent publications.[10,11] Variations in the physicochemical properties were observed. In Ref. [10], the existence of polymorphic forms is derived from differences in melting point and from differences in infrared (IR) spectroscopy. The data of melting points are not recorded by differential scanning calorimetry but by an ordinary melting point apparatus. Statistical data are not given. Differences in IR are reported for wavenumbers of 1600–1800 and 3000 cm^{-1}. But this area of the spectrum (valence oscillation) is characteristic for the chemical composition of the molecule. Therefore no differences should be observed at these wavenumbers. Different crystal forms show differences in the fingerprint (deformation oscillation). But in Ref. [10] there are no differences in the fingerprint described. Thus the analytical data presented are not comprehensible. The same inconsistency is established in Ref. [11]. Small differences in melting point are interpreted as polymorphic forms, without giving a standard deviation. X-ray diffractograms are identical in the area of high peaks, but the authors explain differences at the low peaks (>30 2θ) as an indication for polymorphism. The different ibuprofen crystals prepared by Khan and Jiabi[11] show similar dissolution profiles if dissolution is carried out in phosphate buffer pH 6.8. However, in distilled water very different dissolution results are proposed. The crystals precipitated in ethanol and acetone show the smallest particle sizes and have the highest dissolution rates. While the pH value is constant if a buffer is used, in this dissolution medium the pH decreases during dissolution due to the acid ibuprofen dissolving. Thus even crystal forms which are rapidly dissolved (75% after 200 min) are not completely dissolved after 500 min (also 75% after 500 min).

The purpose of this study was to evaluate the existence of polymorphic ibuprofen crystals employing the solvent change technique, the temperature change technique, and the solvent evaporation method as various crystallization techniques using several solvents. Another aim was to optimize the crystal properties of ibuprofen by searching for a crystallization condition which leads to thermodynamically stable ibuprofen crystals with better properties than the common crystal form. Different ibuprofen crystals were prepared under various conditions, using different crystallization procedures and different solvents.

MATERIALS AND METHODS

Materials

Ibuprofen was supplied by BASF AG (Ludwigshafen, Germany). Organic solvents were of analytical grade or higher. Sodium hydroxide and hydrochloric acid were obtained from Merck KG (Darmstadt, Germany). Water was used in double-distilled quality.

Crystallization Procedures

In the first step ibuprofen was dissolved. The concentration was below the saturation concentration to avoid any crystals remaining that would affect the crystallization process. Crystallizations by the solvent change and the temperature change method were carried out using a double-walled glass vessel with thermostat.

Solvent Change

A suitable amount of the drug was dissolved in 100 mL of the solvent. After precipitation was reached by adding 450 mL of water (20°C) (respectively hydrochloric acid in the case of precipitation by changing the pH value) continuously over 120 min under stirring conditions, the crystals were collected by filtration under vacuum conditions. They were dried in a desiccator under vacuum. In the case of precipitation with hydrochloric acid the crystals were washed with cold water in order to remove the NaCl.

The solvents used were methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, propylene glycol, and a solution of sodium hydroxide in water (pH 10).

Temperature Change

A suitable amount of the drug was dissolved in the solvent at 40°C. Precipitation was reached by cooling to 5°C during 120 min under stirring conditions. The obtained crystals were collected by filtration under vacuum conditions and dried in a desiccator under vacuum.

The solvents used were methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, diethyl ether, dichloromethane, and hexane.

Solvent Evaporation

A suitable amount of the drug was dissolved in the solvent. Solvent was removed under vacuum conditions at 40°C using a rotatory evaporator (Labo-rota SM300, Resona Technics, Gossau, Switzerland). After collecting the crystals, agglomerates were mechanically disagglomerated.

The solvents used were methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, diethyl ether, dichloromethane, and hexane.

Characterizing Methods

Dissolution Studies: Powder Dissolution

Powder dissolution was performed according to the USP XXIV rotating paddle method in 900 mL of pH 7.4 phosphate buffer using an Erweka DT6 dissolution apparatus (Erweka, Heusenstamm, Germany). The dissolution medium was vacuum-degassed. The stirring speed employed was 100 rpm, and the temperature was maintained at 25 ± 0.5°C. Quantification of the dissolved amount of ibuprofen was carried out spectrophotometrically at 221 nm (Lambda40 UV VIS Spectrometer, Perkin Elmer, Connecticut, USA). All samples were analyzed in triplicate.

Dissolution Studies: Intrinsic Dissolution

In powder dissolution the specific surface area, crystal habit, wettability, and differences in agglomeration tendency all affect the dissolved amount. In intrinsic dissolution the surface is equal for all samples, so differences in crystal lattice and wettability can be detected. Intrinsic dissolution was carried out according to USP25. Two hundred milligrams of drug powder were compressed at 30 kN for 90 sec. Changes in crystal were excluded by x-ray analysis. During dissolution the compact was fixed in a sample holder, so that only one side of the compact had contact with the dissolution medium. Dissolution was carried out in 900 mL of pH 7.4 phosphate buffer using an Erweka DT6 (Erweka, Heusenstamm, Germany). The dissolution medium was vacuum-degassed. The stirring speed employed was 100 rpm, and the temperature was maintained at 25 ± 0.5°C. The dissolved amount of ibuprofen was maintained at 221 nm (Lambda40 UV VIS Spectrometer, Perkin Elmer, Connecticut, USA).

Scanning Electron Microscopy (SEM)

Scanning electron micrographs of crystals were taken using a scanning electron microscope (Philips XL 20, Philips, Eindhoven, Netherlands). Samples were fixed on an aluminum stub with conductive double-sided adhesive tape (Leit-Tabs, Plannet GmbH, Wetzlar, Germany) and coated with gold in an argon atmosphere (50 Pa) at 50 mA for 50 sec (Sputter Coater, Bal-Tec AG, Lichtenstein).

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (DSC7, Perkin Elmer, Connecticut, USA) was used. The equipment was calibrated using indium and zinc. Samples were heated at 10°C/min in aluminum pans under nitrogen atmosphere. The onsets of the melting points and enthalpies of fusion were calculated by the software (Pyris, Perkin Elmer, Connecticut, USA).

X-ray Diffractometry

Powder x-ray diffraction (PXRD) patterns were collected in transmission using an x-ray diffractometer (Stoe, PSD supply unit, Darmstadt, Germany) with Cu $K_{\alpha 1}$ radiation (monochromator: germanium) generated at 30 mA and 40 kV. Powder was packed into the rotating sample holder between two films (PETP).

Relative Crystallinity

To quantify possible disorder in crystal structure, the relative crystallinity was determined. Crystalline substances show sharp peaks, but amorphous substances only show a "halo." Partially amorphous substances show both. So by comparing the intensity of the PXRD patterns the relative crystallinity can be determined. By mixing the drug powder with an internal standard as described for example in Refs. [12,13], a quantification can be carried out eliminating the effects caused by differences in sample density or sample preparation. In this study magnesium oxide (Merck KG, Darmstadt, Germany; approximately 20%, accurately weighted and mixed in an IKA-Reagenzglasschüttler VF2, IKA Labortechnik, Staufen, Germany) is used. The PXRD patterns of ibuprofen and magnesium oxide are clearly different (Fig. 1). The intensity of the ibuprofen peaks at 16.545 2θ, 20.067 2θ, and 22.192 2θ, and in the case of magnesium oxide

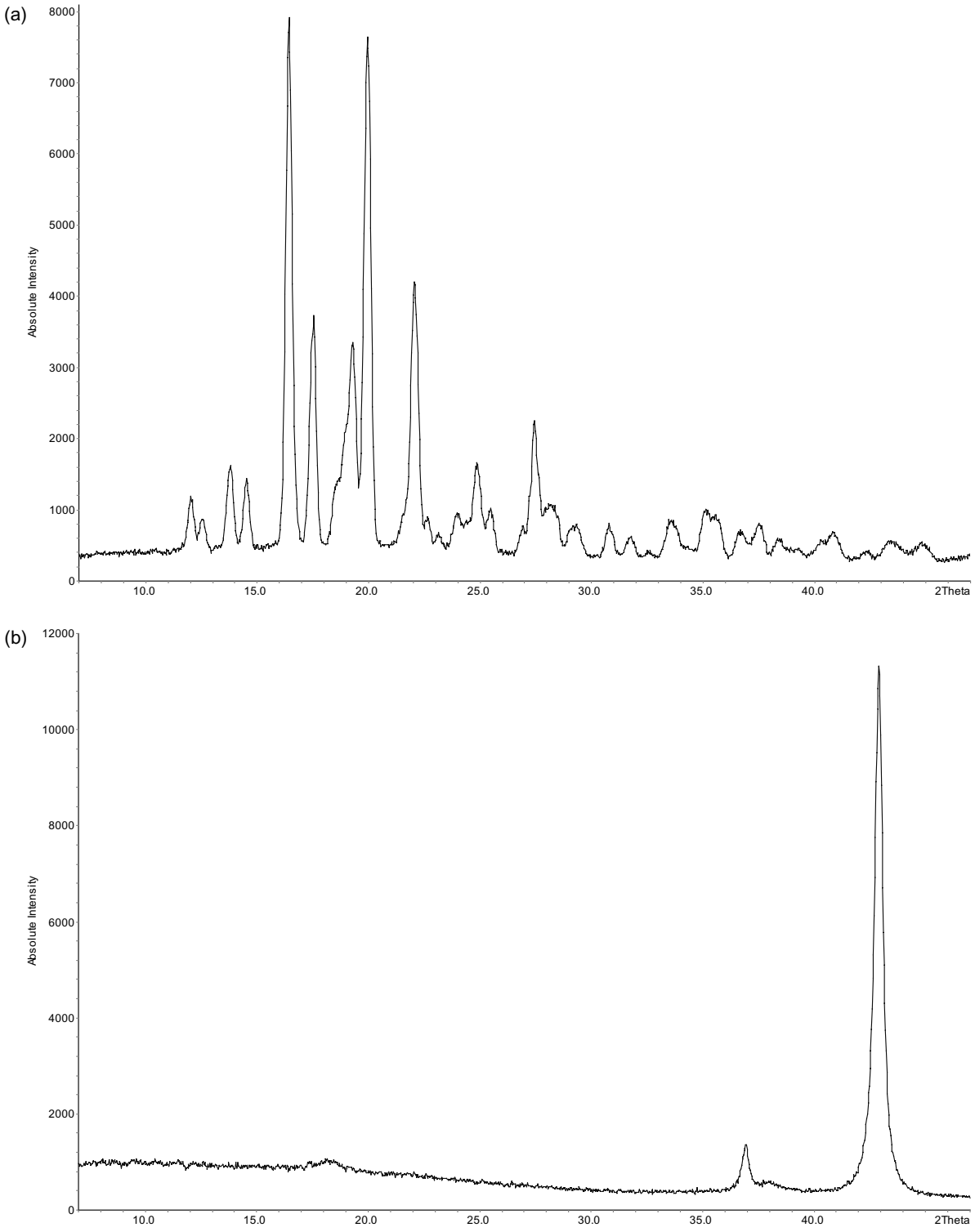

Figure 1. X-ray diffraction patterns: (a) ibuprofen, (b) magnesium oxide, (c) physical mixture of ibuprofen with magnesium oxide.

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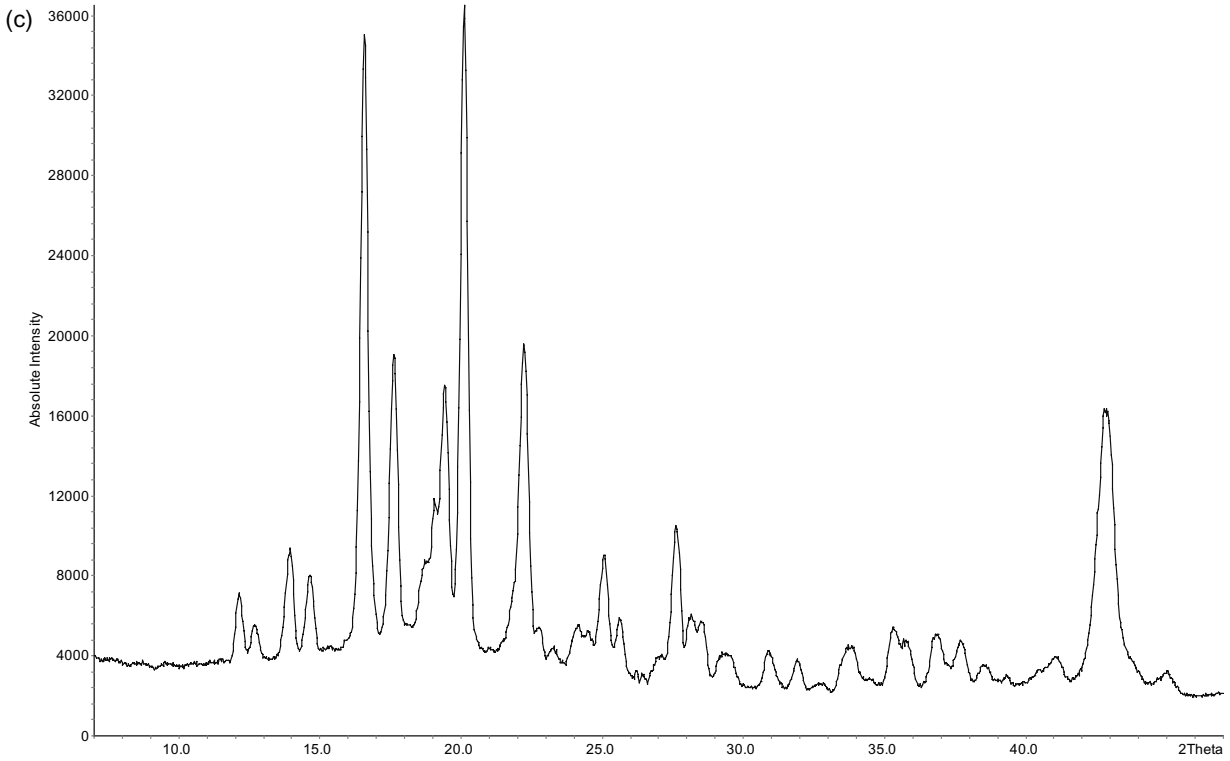

Figure 1. Continued.

at 42.782 2θ, was calculated using the computer program WinXPow (Stoe, Darmstadt, Germany). Relative crystallinity was determined using Eq. (1):

$$\text{relative crystallinity} = \frac{\text{weight (MgO)} \times \sum \text{intensity ibuprofen}}{\text{weight (ibuprofen)} \times \text{intensity MgO}} \quad (1)$$

Infrared Spectroscopy

Infrared spectra were recorded using a Bruker IFS 66 IR spectrometer (Bruker Inc., Karlsruhe, Germany). Compacts with KBr (KBr for infrared spectroscopy, Merck KG, Darmstadt, Germany) were used.

Specific Surface Area

The specific surface area was determined using the gas adsorption method. Calculation is based on the BET equation. A Surface Area Analyzer Gemini-2360 (Micromeritics Instrument Corporation, Norcross, USA) was employed.

True Density

True density was determined using the helium gas pycnometer AccuPyc 1330 (Micromeritics Instrument Corporation, Norcross, USA).

Angle of Response

For characterizing the flowability the angle of response was determined by pouring the drug powder through a funnel. Height h and radius r of the powder cone were measured to calculate the angle of response as $\tan\alpha = h/r$. A small value for α represents a good flowing powder.

RESULTS AND DISCUSSION

By variations in crystallization conditions different crystal forms of ibuprofen were obtained. In Fig. 2 the common ibuprofen crystal (BASF = control) is shown, in Figs. 3–5 exemplary SEM pictures of crystallized samples are shown. If crystallization was carried out using the solvent change

Figure 2. Ibuprofen control.

method from polar organic solvents like alcohols, acetone, or propylene glycol, plate-shaped crystals were observed (e.g., Fig. 3a). Crystals which were precipitated by changing the pH show a needlelike habit (Fig. 3b). Special effects were observed when methanol or acetonitrile were used in the solvent change crystallization technique. In case of methanol, spherical agglomerates and single platelike crystals were obtained. If crystallization is carried out from acetonitrile, only spherical agglomerates were observed. During the precipitation process a phase separation seems to occur as the solvent, saturated with ibuprofen, shows a miscibility gap with the solvent–water mixture, corresponding to the ''quasi-emulsion solvent diffusion method'' as described in Ref. [5]. Crystallization occurs on emulsion droplets, and this leads to spherical agglomerates (Fig. 3c). If ibuprofen was crystallized by a cooling process, plate-shaped crystals were observed when alcohols were used as solvent (e.g., Fig. 4a). Crystals from acetone (in contrast to the solvent change method), diethyl ether, and hexane were needlelike (e.g., Fig. 4b). Temperature change crystallization in dichloromethane led to more cubic crystals (Fig. 4c). In case of acetonitrile, spherical agglomerates were observed. The solvent evaporation method resulted in agglomerated crystals. Plate-shaped crystals prepared from alcohols (Fig. 5a) and needle-shaped crystals prepared from non-polar solvents like diethyl ether (Fig. 5b) were observed. As a result of the different crystal habit, the prepared ibuprofen crystals show significant differences in the specific surface area (Table 1). Especially the very voluminous powders obtained by

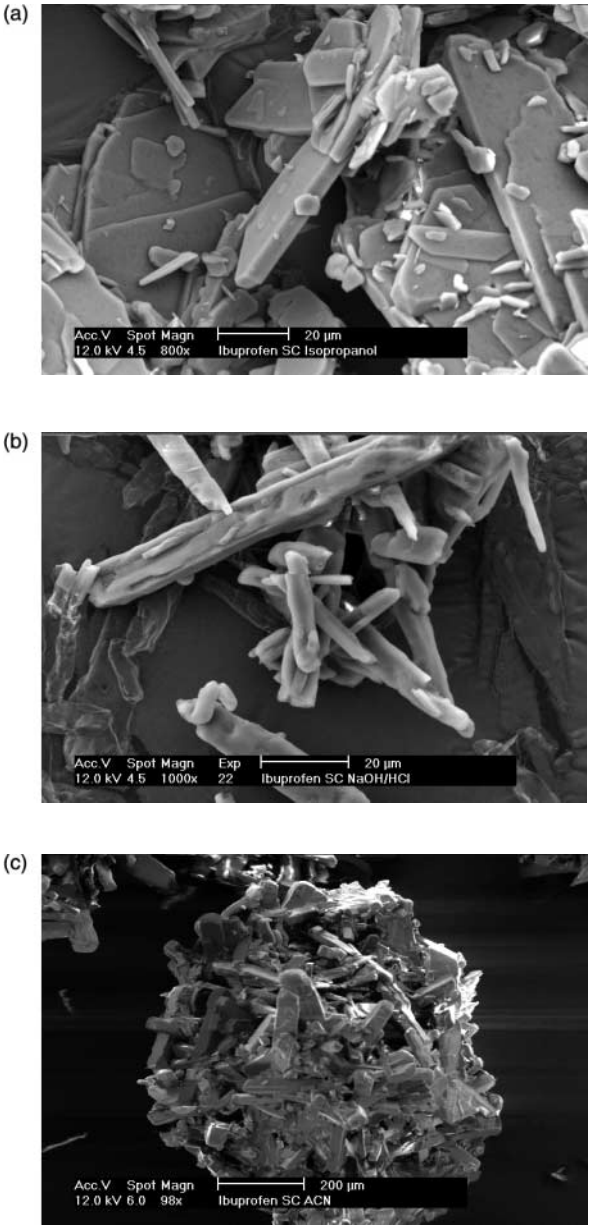

Figure 3. SEM photographs of ibuprofen crystals prepared by solvent change method: (a) isopropyl alcohol, (b) NaOH, (c) acetonitrile.

the use of propylene glycol or the neutralization technique (NaOH/HCl) have a high specific surface area. Similar high specific surfaces were determined for needle-shaped crystals prepared in hexane or diethyl ether. Surface area and crystal form of course affect the flowability (Table 2) of the ibuprofen powders, as crystals with a high surface area or a

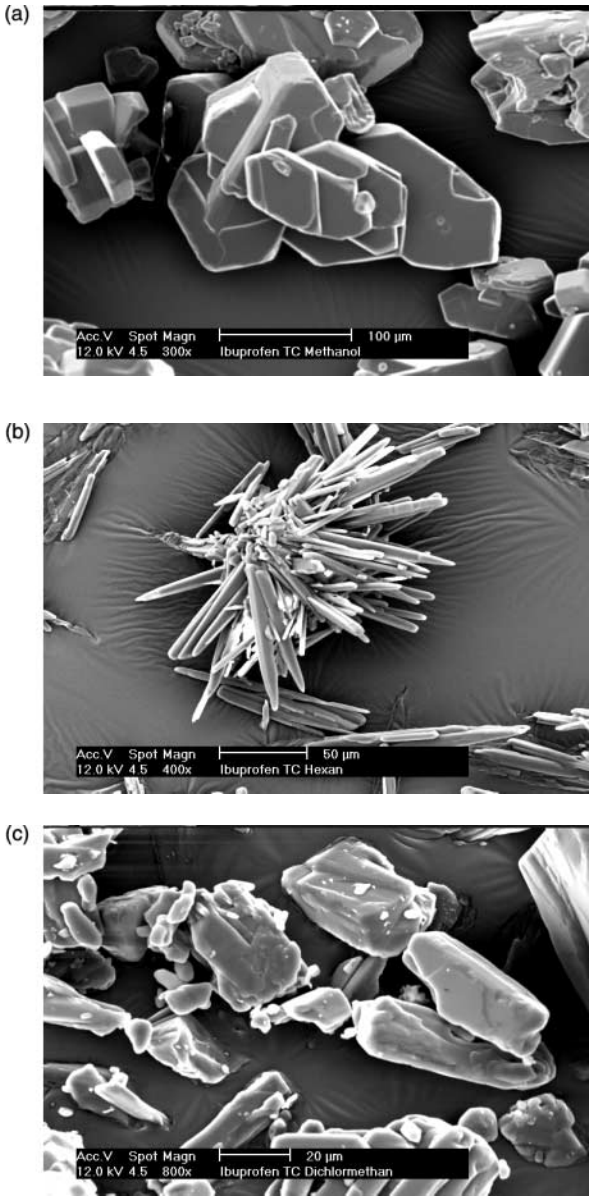

Figure 4. SEM photographs of ibuprofen crystals prepared by temperature change method: (a) methanol, (b) hexane, (c) dichloromethane.

marked needle-shaped habit are cohesive. Compared with the common ibuprofen crystals, an increase in powder flow can be achieved by optimizing the crystallization process: the flowability of spherical agglomerates prepared from acetonitrile is very good. Platelike crystals have an intermediate position. The observed differences do not result in a significant improvement of the dissolution profile.

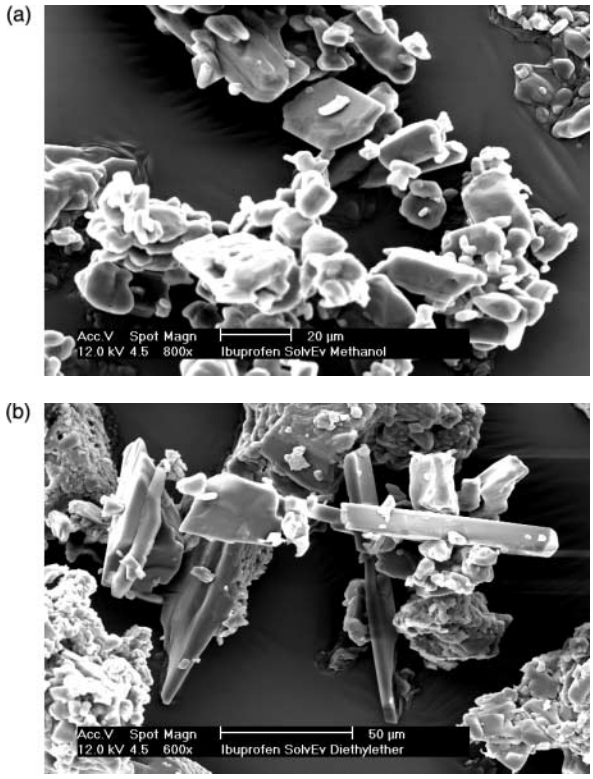

Figure 5. SEM photographs of ibuprofen crystals prepared by solvent evaporation method: (a) methanol, (b) diethyl ether.

All crystals obtained by the solvent change or temperature change technique show similar dissolution profiles (Figs. 6a and b). A higher specific surface area does not result in a faster dissolution. Thus the crystal surfaces are hydrophobic and have poor wettability. This correlates with the observation made during dissolution: after transferring the powder into the vessel, it remains as an agglomerate on the surface and is not finely spread over the surface of the dissolution medium or finely suspended in the dissolution medium. Because of the higher agglomeration, the crystals prepared by solvent evaporation show a slower dissolution (Fig. 6c). After 60 min, 80% of the drug is dissolved. Due to a high agglomeration, the remaining 20% is dissolved slowly (100% dissolution after approximately 120 min). Thus a prolonged dissolution process is obtained. The intrinsic dissolution rate is equal for all crystals. This attributes to the existence of only one crystal modification in all crystal forms. Different polymorphic forms would contain different free energy, their intrinsic dissolution rate would be

Table 1

Specific Surface Area of Ibuprofen

				Ibuprofen crystallized by solvent change method				
	Control	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Propylen Glycol	NaOH/HCl
Specific surface area (m^2/g) ($\pm$SD)	*0.112 ± 0.013*	0.362 ± 0.015	0.271 ± 0.006	0.297 ± 0.039	0.115 ± 0.011	0.331 ± 0.014	0.448 ± 0.013	0.557 ± 0.018
				Ibuprofen crystallized by temperature change method				
	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Diethyl Ether	Dichloromethane	Hexane
Specific surface area (m^2/g) ($\pm$SD)	0.164 ± 0.007	0.177 ± 0.031	0.287 ± 0.008	0.067 ± 0.010	0.241 ± 0.006	0.382 ± 0.094	0.192 ± 0.026	0.396 ± 0.048
				Ibuprofen crystallized by solvent evaporation method				
	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Diethyl Ether	Dichloromethane	Hexane
Specific surface area (m^2/g) ($\pm$SD)	0.212 ± 0.009	0.116 ± 0.011	0.118 ± 0.010	0.153 ± 0.006	0.201 ± 0.009	0.117 ± 0.012	0.250 ± 0.010	0.282 ± 0.015

Results: mean of three measurements; SD = standard deviation.

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Table 2

Angle of Response of Ibuprofen

			Ibuprofen crystallized by solvent change method					
	Control	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Propylen Glycol	NaOH/HCl
Angle of response (°) (±SD)	*60.5 ± 0.86*	40.5 ± 0.72	44.3 ± 0.91	37.7 ± 0.95	28.8 ± 0.51	41.0 ± 1.03	57.7 ± 1.43	58.0 ± 1.28
			Ibuprofen crystallized by temperature change method					
	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Diethyl Ether	Dichloromethane	Hexane
Angle of response (°) (±SD)	40.7 ± 1.14	49.7 ± 0.93	55.0 ± 0.87	29.0 ± 0.76	55.3 ± 0.91	58.5 ± 1.21	51.3 ± 0.99	58.7 ± 1.28
			Ibuprofen crystallized by solvent evaporation method					
	Methanol	Ethanol	Isopropyl Alcohol	Acetonitrile	Acetone	Diethyl Ether	Dichloromethane	Hexane
Angle of response (°) (±SD)	42.5 ± 1.05	47.3 ± 0.91	44.5 ± 1.21	43.5 ± 0.82	44.5 ± 0.87	48.3 ± 0.012	52.5 ± 1.01	50.0 ± 0.95

Results: mean of three measurements; SD = standard deviation.

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different. The results of the intrinsic dissolution rate correlate with the results obtained by thermoanalysis (same melting point, same heat of fusion). This is confirmed by x-ray analysis: all crystals show the same patterns. Relative crystallinity is equal for all samples (rel. cryst. = 0.62, SD = 0.02), thus a complete crystallization has occurred. Correlating with these results, true density is 1.11 g/cm^3 (SD = 0.01) for all crystals, and infrared spectrograms show an identical fingerprint area. Thus all crystals prepared are isomorphic. Consequently in this study, which used several different preparation conditions, no polymorphism for ibuprofen was observed and the data presented in Refs. [10] and [11] are refuted.

CONCLUSIONS

The crystal habit of ibuprofen was affected by different crystallization methods and different solvents. In contrast to statements in other studies, in this screening no polymorphic crystals were observed.

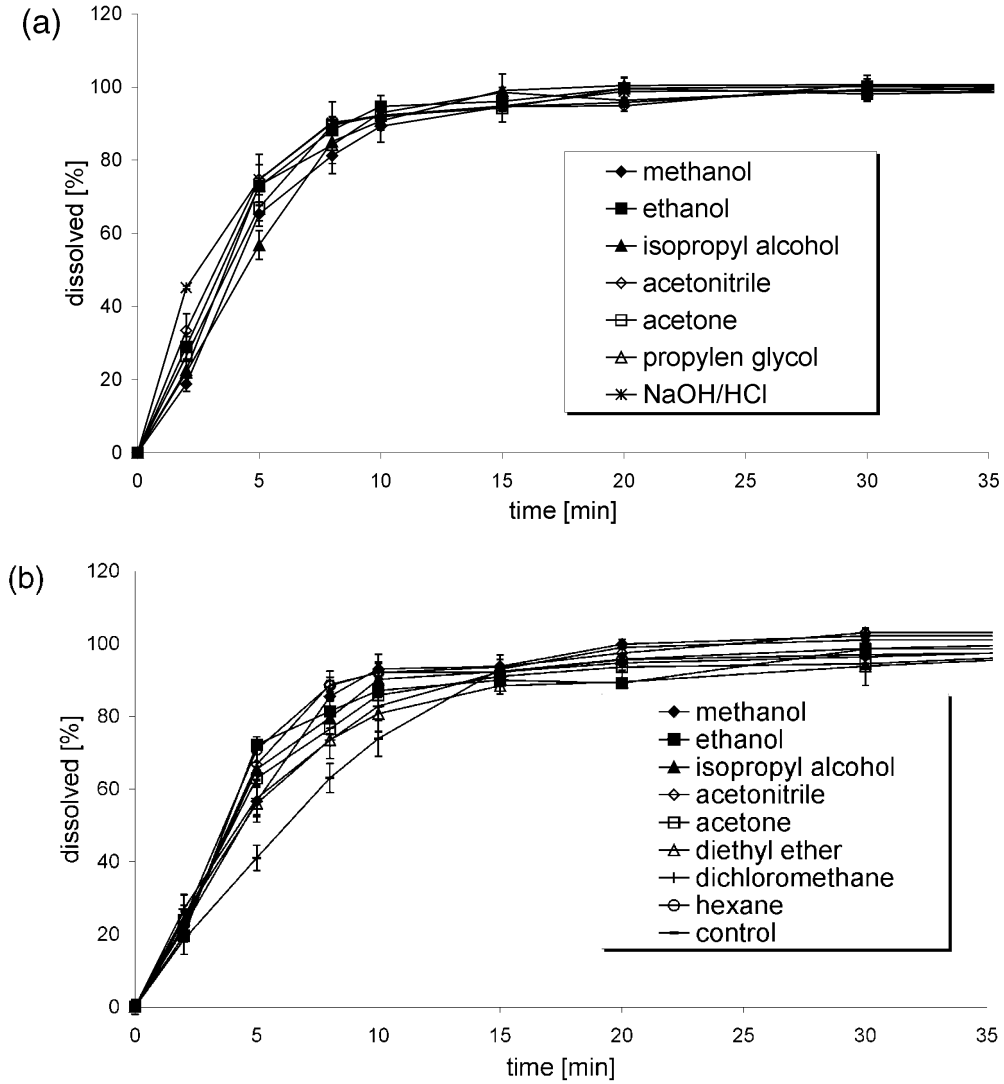

Figure 6. Dissolution profiles of ibuprofen crystallized by (a) solvent change technique, (b) temperature change technique, (c) solvent evaporation technique.

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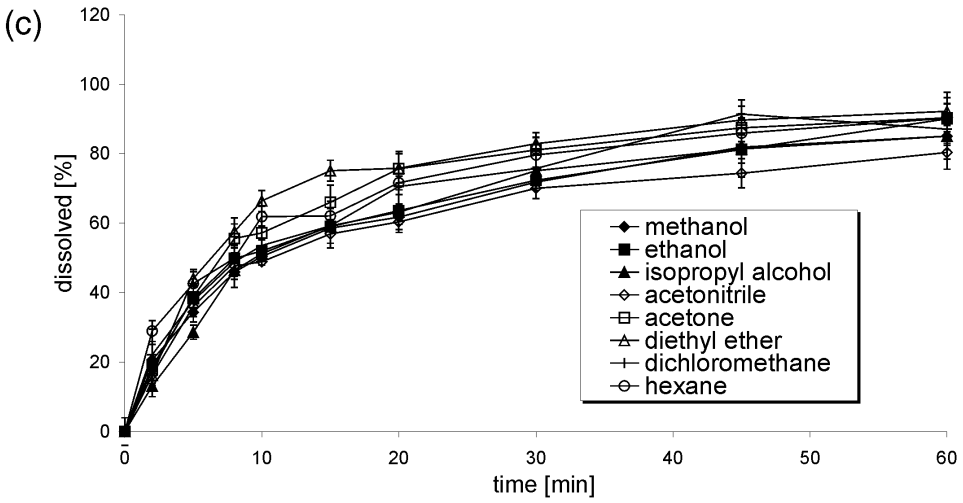

Figure 6. Continued.

Only the external shape of the growing ibuprofen crystal is affected by the environment, without changing the internal structure. Ibuprofen seems to form only one crystal modification. However, different crystal habits were prepared, affecting the properties of the substance. Plate-shaped and needle-shaped crystals can be distinguished. In some cases spherical agglomerates are obtained. Especially the powder flow can be improved by the choice of an optimal crystallization method. The common crystal form shows a poor flowability. This can be optimized by using plate-shaped crystals, or especially the spherical agglomerates obtained from acetonitrile. Differences in specific surface area also exist, but the dissolution rate was not affected significantly because of the hydrophobic crystal surface. Thus mainly differences concerning the handling properties were found, but in comparison to the commercially available ibuprofen no dramatic improvement was achieved by the crystallization methods employed.

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