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# Ibuprofen crystals with optimized properties

Norbert Rasenack, Bernd W. Müller *

*Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University Kiel, Gutenbergstr. 76, 24118 Kiel, Germany*

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**Abstract**

The common analgesic drug ibuprofen shows bad dissolution and tableting behavior due to its hydrophobic structure. Additionally its high cohaesivity results in low flowability. Because of the bad compaction behavior ibuprofen has to be granulated usually before tableting. Another problem in manufacturing is the high tendency for sticking to the punches. A crystal form with optimized properties of ibuprofen was prepared and characterized in this study. Crystallization was carried out using the solvent change technique in the presence of different water-soluble additives. These additives were only present during the crystallization process and removed after precipitation by a washing process. A nearly pure ibuprofen powder was received, as GC-analysis showed. Plate-shaped crystals with increased powder dissolution, increased flowability and good tableting behavior were obtained. All crystals were determined as isomorphic by DSC and X-ray analysis. Thus the improvement of the substance characteristics of ibuprofen is reached by changes in the outer appearance of the crystals and in surface modifications. Due to the fact that ibuprofen molecules can form hydrogen bonds, additives that can interact with these hydrogen bonds during the crystallization process can modify the properties of the resulting crystals. 

*Keywords:* Ibuprofen; Dissolution; Flowability; Tableting behavior; Crystallization techniques; Crystallization in the presence of additives

## 1. Introduction

Ibuprofen is widely used as an analgesic and antirheumatic drug. The common crystal form shows disadvantages concerning the properties affecting the manufacturing properties. Powder flow is bad because of a high cohesivity and adhesivity. Because of the bad compaction behavior ibuprofen has to be granulated in most cases before tableting. Another problem in manufacturing is the high tendency for sticking to the punches. Beside these disadvantageous properties ibuprofen shows bad dissolution behavior because of its hydrophobic structure. However, a rapid drug release is preferable, especially for analgesic drugs.

* Corresponding author. Tel.: +49-431-880-1333; fax: +49-431-880-1352

*E-mail address:* bwmueller@pharmazie.uni-kiel.de (B.W. Müller).

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The properties of a drug can be affected by choosing a suitable polymorphic form, by choosing a suitable crystal habit, by using special crystallization techniques, and by using a suitable preparation with excipients. In the literature several methods for improving the properties of ibuprofen are described. Usually a preparation with excipients is used to optimize the substance properties. A coprecipitation with Eudragit® S100 is described by Khan et al. (1994). Kachrimanis et al. (1998) also describe spherical crystal agglomerates obtained by crystallization by the solvent change technique in the presence of Eudragit® S100. A powder with a drug-load of 90% (m/m) is obtained. Flowability and compressibility were improved because of the Eudragit® S100 the drug release is sustained. Another way to obtain a drug powder with improved flowability is the spherical crystallization technique as described by Kawashima et al. (1982). Spherical crystallization is defined as an agglomeration technique that transforms crystals directly into a compacted spherical form during the crystallization process. Gordon and Chowhan (1990) describe crystals of naproxen that were modified by the spherical crystallization technique. An improvement of the flow characteristics and the compressibility of drug raw material was observed. However, an increase in drug dissolution cannot be achieved by this method. Another agglomeration technique is the non-solvent-shock-agglomeration (Möller and Korsatko, 1999). Melted ibuprofen is agglomerated in a non-solvent. Beside differences in crystal agglomeration, differences concerning the individual crystal can also occur. Ibuprofen is able to form different crystal forms with different properties. The shape of a crystal affects its tabletability. As the shape of ibuprofen crystals depends on the solvent, powder flow and compactability can be improved by the choice of a suitable solvent (Gordon and Amin, 1984). Also hydrogen bonding affects the crystal shape (Shankland et al., 1996). In the ibuprofen single crystal unit cell four ibuprofen molecules are attached with two hydrogen bonds as described by Romero et al. (1993). The two remaining carboxylic-groups are available for binding to neighboring unit cells. Thus in the crystal structure of ibuprofen the hydrophilic structures are mutually bonded which results in a hydrophobic crystal structure. The most important faces in the ibuprofen crystal are the (001) and (100) faces. While the (001) face is dominant in crystals grown from solvents other than alcohols, the (100) face is dominant in ibuprofen grown from ethanol or methanol (Bunyan et al., 1991). The (100) face is the slowest growing one and, therefore, dominates the morphology (Shankland et al., 1996). This surface can either be polar or non-polar. Due to the fact that at the polar surface the carboxylic groups are projected out, they can interact freely with polar molecules as no periodic bond chains are disrupted by adsorption of polar molecules. Thus, the growth rate is controlled by the non-polar surface variant. However, strong hydrogen bonding and difficult displacement of the solvent can change the growth rate as the growth kinetics is transferred to the polar surface (Bunyan et al., 1991). Nikolakakis et al. (2000) 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 affect the micromeritic of the growing crystals. The polymer has a smaller effect. Garekani et al. (2001) describe differences in crystal habit of ibuprofen that is 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 show 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 produced the softest tablets. The importance of the crystal structure for processing properties is described by Romero et al. (1991). 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 are described. In a screening of several crystallization methods (solvent change, temperature change, solvent evaporation) using different solvents Rasenack and Müller (2002a) describe different crystal habits for ibuprofen. Differences concerning the flowability were observed, but no improvement of dissolution rate was reached. Einig et al. (2000) describe a pharmaceutical mixture containing the common crystal form of ibuprofen [90% (m/m)], a nonionic surfactant (0.5%) and other excipients such as diluents, disintegrants and binding agents normally used in tablet production. The drug release in powder dissolution according to the USP 25 method was 100% after 5 min because of the dissolution enhancing effect of the surfactants. Another way of improving drug dissolution is the forming of an inclusion complex with a cyclodextrin as described by Mura et al. (1998). A disadvantage of formulations with cyclodextrins is the low drug-load.

The aim of this study was to find a crystal form of ibuprofen that is isomorphic with the common crystal form but shows optimized properties as pure drug powder. Crystallization was carried out by the solvent change technique in the presence of different additives. These additives were removed from the product, so a pure drug powder was obtained. Modified substance properties, which were affected by the additives, were investigated.

## 2. Materials and methods

### 2.1. Materials

Ibuprofen 50 was supplied by BASF AG (Ludwigshafen, Germany). These common ibuprofen crystals are employed as 'control' in this study. Isopropyl alcohol (Merck KG, Darmstadt, Germany) was of analytical grade. Water was used in double-distilled quality. All employed additives are of pharmaceutical quality. A list of additives used in this study is given in Table 1. The additives are divided in three groups referring to the characteristics of the obtained ibuprofen crystals.

Excipients for tablet production were microcrystalline cellulose (Avicel® PH 102, FMC Corp. Philadelphia, USA), sodiumcarboxymethylcellulose (AcDiSol®, FMC Corp. Philadelphia, USA), colloidal silicium dioxide (Aerosil®, Degussa, Frankfurt, Germany), and magnesium stearate (Merck KG).

### 2.2. Methods

#### 2.2.1. Crystallization procedure

Crystallization was carried out using the solvent change method as described by Rasenack et al. (2001) in the presence of water-soluble additives using a double-walled glass vessel with thermostat. In the first step ibuprofen was dissolved in isopropyl alcohol at 40 °C (80 g/100 ml). The concentration was below the saturation concentration to avoid any crystals remaining that would

Table 1
Surfactants and hydrophilic substances used as additives in crystallization process

| Surfactants with PEG chain | Surfactants without PEG chain | Hydrophilic additives |
|---|---|---|
| Polyoxyethylene-sorbitane-fatty acid-ester (polysorbates, Tween®; ICI, Frankfurt, Germany) | Sucrosemonolaurate (Sisterna B.V., Roosendaal, Netherlands) | Trehalose (Sigma, Deisenhofen, Germany) |
| Polyoxyethylene alcohols (Brij®; ICI) | Sucrosemonopalmitate (Sisterna B.V.) | Dextran 200 (Sigma) |
| Polyoxyethylene-glycerylmonoisostearate (Tagat®I; Goldschmidt, Essen, Germany) | Sucrosemonostearate (Sisterna B.V.) | Hydroxypropyl cellulose (Klucel®; Hercules Inc., Wilmington, USA) |
| Polyoxyethylen 40 hydrogenated castor oil (Cremophor® RH 40; BASF) | Sodiumlaurate (Merck KG) | Hydroxyethyl starch (Fresenius, Bad Homburg, Germany) |
| Poloxamer 188 (Pluronic® F68; BASF) | Sodiumstearate (Merck KG) | Polyvinyl alcohol (Sigma), Polyvinylpyrrolidone (Kollidon®25; BASF) |

affect the crystallization process. If possible, the additive (8 g) was dissolved in the isopropyl alcohol. Due to their tendency to form a gel at higher concentrations only 3.2 g of the sodium salts of fatty acids were used. Additives that are not soluble in organic solvents were dissolved in the water. Precipitation was reached by adding 410 ml of water (5 °C) continuously over 70 min under stirring conditions. Temperature was lowered from 40 to 20 °C continuously using a thermostat (Lauda Compact-Kältethermostat RKP20-D, Messgerätewerk Lauda, Lauda-Königshofen, Germany). The obtained crystals were collected by filtration under vacuum conditions. They were washed with ice-cold water (5 × 50 ml) and dried in a desiccator under vacuum conditions.

### 2.2.2. Characterizing methods

*2.2.2.1. Dissolution studies: powder dissolution in phosphate buffer.* Powder dissolution and dissolution from tablets were performed according to the USP 25 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.

*2.2.2.2. Dissolution studies: powder dissolution in simulated gastric fluids.* Dissolution studies of selected ibuprofen samples were carried out in simulated gastric fluid as a second dissolution medium using the same technical parameters as described above. This consists of 0.25% sodium dodecyl sulfate and 0.2% sodium chloride and is adjusted with hydrochloric acid to pH 1.2 ± 0.1. Surface tension is lowered by SDS in an attempt to mimic in vivo conditions as described by Pedersen et al. (2000). Another aim of using a dissolution medium containing a surfactant is to exclude the improvement of dissolution rate effected by surfactants remaining on the crystals.

*2.2.2.3. 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 und wettability can be detected. Intrinsic dissolution was carried out using the 'rotating disk' method (USP 25). Drug powder (200 mg) were compressed at 30 kN for 90 s. Changes in polymorphic modifications were excluded by X-ray-analysis. During dissolution the compact was fixed in a sample holder, so that only one side of the compact was in 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 was 100 rpm, and the temperature was maintained at 25 ± 0.5 °C. The dissolved amount of ibuprofen was quantified at 221 nm (Lambda40 UV VIS Spectrometer, Perkin Elmer).

*2.2.2.4. Scanning electron microscopy (SEM).* Scanning electron-micrographs of crystals were obtained using a Philips XL 20 (Philips, Eindhoven, Netherlands). Samples were fixed on an aluminium 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 s (Sputter Coater, Bal-Tec AG, Lichtenstein).

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

*2.2.2.6. 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 Kα 1 radiation (monochromator: Germanium) generated at 30 mA and 40 kV. Powder was packed into the rotating sample holder between two films (PETP).

*2.2.2.7. Relative crystallinity.* To quantify possible disorder in crystal structure, the relative crystallinity was determined. Crystalline substances show sharp peaks, whereas 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 by Saleki-Gerhardt et al. (1994), Cordes (1997) 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; approximately 20%, accurately weighted and mixed in an IKA-test tube shaker VF2, IKA Labortechnik, Staufen, Germany) is used. PXRD patterns of ibuprofen and magnesium oxide are distinctly different: the main peaks of ibuprofen are below 30 2θ; in this area magnesium oxide does not show any peaks. The main peak of magnesium oxide (42.8 2θ) appears in an area where ibuprofen shows no peaks. Intensity of the ibuprofen peaks at 16.5 2θ, 20.1 2θ, and 22.2 2θ and in the case of magnesium oxide at 42.8 2θ were calculated using the computer program WINXPOW (Stoe). Relative crystallinity was determined using Eq. (1).

$$\text{relcryst.} = \frac{\text{weight}_{(MgO)} \times \sum \text{intensity}_{ibuprofen}}{\text{weight}_{(ibuprofen)} \times \text{intensity}_{MgO}} \quad (1)$$

Eq. (1): Calculation of the relative crystallinity.

*2.2.2.8. Method for analyzing tableting behavior.* The compressions were carried out using a Fette Exacta 11 (Wilhelm Fette Inc., Schwarzenbek, Germany) single punch press, equipped with flat punches of 12 mm diameter. Data (punch force, displacement, time) were recorded (piezoelectric, resp. inductive). For measuring the mechanical properties (crushing strength) of the compacts a Pharma Test PTB300 (Frankfurt, Germany) was used. To compare different tableting behavior a punch force–displacement-profile of the pure drug and powder mixtures was recorded. By mathematical calculation based on characteristic data (Table 2) of the compression process and the resulting compact a factor ('$T$-factor') for comparing the tableting properties was obtained (Rasenack and Müller, 2002b). The $T$-factor (J cm$^4$) is calculated using Eq. (2). A high value shows good tabletability. The equation is suitable for comparing different powders at the same machine parameters: the values of the most important parameters do not seem to be transferable when using different adjustments. For comparability the same experimental set-ups (same adjustment of upper and lower punch, same true volume of each substance compressed) are, therefore, required.

Table 2
Readings used for the calculation

| Factor | Unit | |
|---|---|---|
| Plastic deformation | % | Percentage of the plastic energy |
| Total energy | N m | Plastic and elastic energy |
| Crushing strength $F_c$ | N | Stability of the comprimate |
| $F_{\max}$ | kN | Upper punch force (maximum) |
| $S_{F_{\max}}$ (up) | mm | Displacement of upper punch in $F_{\max}$ |
| $e$ | cm$^3$ | Volume (true) tableted |

$$T = plastic\ \ def \times energy_{total} \times \frac{F_c}{F_{\max}} \times s_{F_{\max}\ (up)} \times e \quad (2)$$

Eq. (2): Calculation of the $T$-factor.

To obtain comparable data, constant true volumes were poured manually into the previously cleaned die. The amount of powder required was calculated from the true density. Each powder was tableted ten times. The relative standard deviation of the calculated $T$-factors was lower than 5%.

*2.2.2.9. 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.

*2.2.2.10. Particle size measurement.* Particle size measurement was carried out using a laserdiffractometer (Helos KFS Rodos, Sympatec GmbH, Clausthal Zellerfeld, Germany).

*2.2.2.11. True density.* True density was determined using the helium gaspycnometer AccuPyc 1330 (Micromeritics Instrument Corporation).

*2.2.2.12. Flowability.* Flowability was quantified using avalanche analysis to quantify powder flowability (AeroFlow—TSI Modell 3250, TSI, Aachen, Germany). The powder sample is put in a cylindrical drum that slowly rotates about its horizontal axis at a constant rate. When the incline angle of the powder's surface becomes too great for its molecular structure to support, the powder collapses down toward the bottom. This event is referred to as an 'avalanche'. The time interval between avalanches and the amplitude of the avalanche is recorded. Before measurement the powder was disagglomerated through a sieve (710). Sixty mililitre of each powder were used; measurement was carried out over 300 s with 1 UpM. Factors characterizing the flowability are the mean time between avalanches, the scatter and the maximum time. A high mean time and a high maximum time show cohesivity; irregular flow characteristics result in a high scatter.

*2.2.2.13. Contact angle.* The contact angle was measured by the sessile drop technique using a goniometer (G1, Krüss GmbH, Hamburg, Germany). A compressed disc of the powder (200 mg) was made at 30 kN for 90 s. The contact angle between the disc and water (saturated with ibuprofen) was determined 10 and 180 s after the droplet was put onto the disk.

*2.2.2.14. Moisture sorption behavior.* The moisture sorption behavior (adsorption and desorption) was analyzed using a VTI MB 300G (VTI Corporation, Hialeah, Florida, USA) at 25 °C over the humidity range 0–95% RH (steps of 5% RH). Sample sizes of approximately 75 mg were used.

*2.2.2.15. Quantification of remaining additives.* Ibuprofen that was crystallized in the presence of sucrosemonolaurate and dextran was analyzed for remaining additives. Sucrosemonolaurate was quantified after saponification to lauric acid and derivatization with *N*-methyl-*N*-trimethylsilyl-trifluoracetamid by GC (HP 5890, Hewlett Packard Comp., Palo Alto, California, USA; carrier gas: helium; capillar-column: DB5, 30 m × 0.25 cm × 0.25 μm, Fisons Instruments, Manchester, UK; detector: FID; internal standard methyl heptadecanoate). Quantification limit was 50 mg/kg (= 0.05 ppm). Dextran was quantified enzymatically (testkit D-Glucose, Roche Diagnostics, Mannheim, Germany) as glucose after saponification (in view of the glucose from sucrosemonolaurate).

*2.2.2.16. Tablet production.* The tablet production was carried out using a Fette Exacta 1 (Wilhelm Fette Inc.) single punch press, equipped with flat punches of 9 mm diameter. Tablets containing 200 mg of ibuprofen were produced. The punch force was adjusted in order to receive tablets with a crushing strength of approximately 50 N. The tablets produced for analyzing the dissolution were prepared using 85% ibuprofen (control/crystallized with sucrosemonolaurate/crystallized with sucrosemonolaurate and dextran 200), 7% microcrystalline cellulose (Avicel®PH102), 7% sodiumcarboxymethylcellulose (AcDiSol®), 0.5% colloidal silicium dioxide (Aerosil®) and 0.5% magnesium stearate. This powder mixture was tableted directly. However, the composition was not optimal for all crystal forms, but for evaluating the dissolution behavior the same powder mixture had to be tableted for all ibuprofen crystals.

## 3. Results and discussion

The properties of ibuprofen crystals that were obtained by the crystallization technique employed in this study differ significantly from the common crystal form. A macroscopically visible difference is the optimized flowability. Ibuprofen crystallized in the presence of additives shows an increased flowability. Especially crystals grown in the pre-

sence of hydrophilic additives, sucrose esters or sodium salts of fatty acids are free flowing drug powders that only show little cohesivity or adhesivity.

The outer appearance of the crystals differs (Fig. 1). However, all crystals are isomorphic as DSC (same melting point, same heat of fusion) and X-ray analysis show. Also the relative crystallinity is the same for all crystals (rel. cryst. = 0.62, S.D. = 0.02), and the true density is 1.11 g/cm$^3$ (S.D. = 0.01) for all samples. The common crystal form of ibuprofen is a needle-shaped habit with a rough

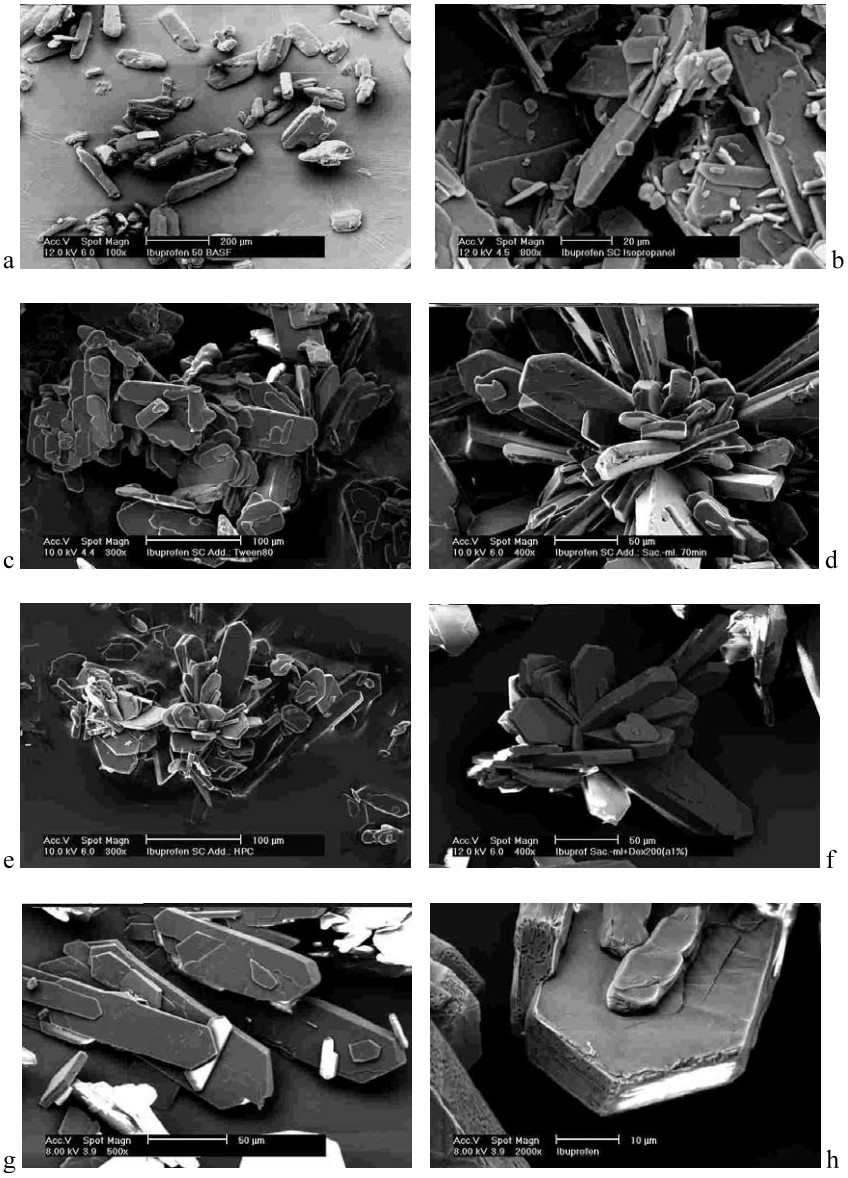


Fig. 1. SEM photographs of the ibuprofen crystals. (a) Control; (b) crystallized without additives; (c) crystallized in the presence of polysorbate 80; (d) crystallized in the presence of sucrosemonolaurate; (e) crystallized in the presence of hydroxypropyl cellulose; (f) crystallized in the presence of sucrosemonolaurate and dextran 200; (g, h) crystallized in the presence of sucrosemonolaurate and hydroxypropyl cellulose.

Table 3
Flowability of ibuprofen

| | *Tablettose®* | Control | Without additives | Tween®80 | Sucrose-monolaurate | Dextran | Sucrose-monolaurate+dextran |
|---|---|---|---|---|---|---|---|
| Mean (s) | *2.3* | 4.9 | 4.4 | 3.0 | 3.0 | 3.0 | 3.1 |
| Scatter (s) | *0.8* | 2.3 | 1.9 | 1.3 | 0.9 | 1.1 | 1.0 |
| Max (s) | *4.2* | 12.0 | 8.4 | 6.6 | 5.4 | 5.2 | 5.0 |

surface (Fig. 1a). Crystals that were prepared by the solvent change technique are plate-shaped. However, within ibuprofen that was crystallized in the presence of different additives differences can be observed. The crystals grown without additives (Fig. 1b) are formed irregularly. Differences in crystal morphology of the crystals grown in the presence of additives are discernible (Fig. 1): All crystals are elongated thin plates, but the form of the edges varies: well-formed crystals with a triangular top are obtained in the presence of surfactants without a PEG chain (Fig. 1d) and hydrophilic additives (Fig. 1e). The combination of both of them results in geometrically exact crystals having symmetrical tops (Fig. 1f–h). Crystals are either single or adjacented at their tops forming hedgehog-like structures. In contrast to this, crystals that are formed in the presence of surfactants with a PEG chain (Fig. 1c) are agglomerated with their whole surfaces to each other. The crystal edges are not symmetrically shaped. The observed crystal morphology indicates that additives with hydroxyl groups affect the growing crystal in a special manner.

In correlation to the crystal structures observed by SEM, there exist differences in the powder flow as shown for characteristic samples in Table 3. The common crystal form is cohesive: the mean between two avalanches is 5 s, with a high scatter (2.3 s) and a maximum time of 12 s. This shows an irregular flow characteristic. When the crystal habit is changed from the needle-shaped crystals to the thin plates, flowability increases. Ibuprofen that is crystallized without any additives is not such cohesive as the common crystal form. If crystallization is carried out in the presence of additives, the flowability increases significantly, especially if surfactants without a PEG chain or hydrophilic additives like dextran or a combination of these are used. Each group of the additives is represented in Table 3 with data for polysorbate 80, sucrosemonolaurate, dextran and a combination of sucrosemonolaurate with dextran. Especially when comparing the data with the data obtained for preagglomerated lactose, the importance for processing parameters becomes evident. The flowability correlates with the observations by SEM: The well-formed crystals that are mainly agglomerated at the top have the best flowing properties; ibuprofen crystallized without additives the worst. Polysorbate-modified powder takes an intermediate position.

Also in the tabletability of the pure drug powders, there exist differences: the ibuprofen powders with an optimized flowability show a better tabletability, represented by a higher $T$-factor (Table 4). If the powder is filled more homogenously into the die, the punch force is more effectively used; the resulting compacts show a higher crushing strength. The prepared ibuprofen samples can be divided into four groups: In the presence of surfactants with a PEG chain no increase in tabletability is observed. Samples crystallized in the presence of hydrophilic additives or surfactants without a PEG chain show an increased tabletability which can be further improved by their combination. In Table 5 characteristic data for ibuprofen compacts (common crystal form and ibuprofen crystallized in the presence of sucrosemonolaurate and dextran) are compared. At nearly the same maximal punch force the total energy (=area under the punch force–displacement curve) is significantly higher for the plate-shaped crystals. The elastic recovery is lower, thus more energy is put into the drug powder during the tableting process, resulting in compacts that are much more stable. Depending on the alignment of the crystals in the die, the

Table 4
Tabletability of ibuprofen

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Ibuprofen crystallized in the presence of surfactants with PEG chain* | | | | | | | |
| | Control | Without additives | Tween® 80 | Brij® 98 | Tagat® I | Cremophor® RH40 | Poloxamer 188 |
| *T*-Factor (J cm$^4$) | 0.33 | 0.39 | 0.37 | 0.34 | 0.30 | 0.31 | 0.30 |
| *Ibuprofen crystallized in the presence of surfactants without PEG chain* | | | | | | | |
| | Sucrosemonolaurate | Sucrosemonopalmitate | Sucrosemonostearate | Sodiumlaurate | Sodiumstearate | | |
| *T*-Factor (J cm$^4$) | 0.46 | 0.44 | 0.41 | 0.45 | 0.43 | | |
| *Ibuprofen crystallized in the presence of hydrophilic additives* | | | | | | | |
| | Trehalose | Dextran | Hydroxypropyl-cellulose | Hydroxyethylstarch | Polyvinylalcohol | Polyvinylpyrrolidone | |
| *T*-Factor (J cm$^4$) | 0.49 | 0.45 | 0.43 | 0.41 | 0.50 | 0.49 | |
| *Ibuprofen crystallized in the presence of sucrosemonolaurate and hydrophilic additives* | | | | | | | |
| | +Trehalose | +Dextran | +Hydroxypropyl-cellulose | +Hydroxyethyl-starch | +PVA | +PVP | |
| *T*-Factor (J cm$^4$) | 0.51 | 0.53 | 0.54 | 0.52 | 0.50 | 0.50 | |

Results: mean of ten measurements; S.D. $< 5\%$.

Table 5
Comparison of ibuprofen compacts: characteristic data (pure drug powder)

| | Control | Crystallized in the presence of sucrosemonolaurate and dextran |
|---|---|---|
| Flowability | Cohesive | Free flowing, not cohesive |
| Sticking to the punches | Adhesive | Not adhesive |
| Elastic recovery (%) | 24 | 19 |
| $F_{max}$ (kN) | 16 | 15 |
| Total energy (J) | 4.2 | 4.9 |
| Crushing strength (N) | 32 | 55 |

Same true volumes of pure ibuprofen were tableted ten times with same machine adjustments.

contact area between the particles can vary. Another difference concerns the affinity of the ibuprofen powder to the punches. The common crystals stick to the punches. A sticking to the punches was not observed for ibuprofen (not even for pure drug powder without any lubricants) that was crystallized in the presence of sucrose esters, sodium salts of fatty acids, hydrophilic polymers or a combination of these additives (Table 5). This indicates that differences concerning the surface structure of the crystals occur during the employed crystallization process. The common ibuprofen crystals have a rough surface, which may cause a higher tendency for sticking to the punches. Fig. 2a shows the irregular surface of the ibuprofen tablet (control). An irregular structure with holes caused by pulled out substances that are sticking to the punch can be observed. In contrast, if tablets are prepared with ibuprofen that is crystallized in the presence of sucrosemonolaurate and dextran, the tablet surface is much more regular and smooth (Fig. 2b). These ibuprofen crystals can be directly tableted to tablets with a drug-load of 85%.

All these differences described above concern the handling and processability of the drug powder. Beside these there exist differences concerning the drug release: the powder dissolution shows differences depending on the crystallization process. By changing the crystal habit, the drug powder dissolves only a little bit faster than the control (Fig. 3a). A further increase in dissolution behavior is observed if ibuprofen is crystallized in

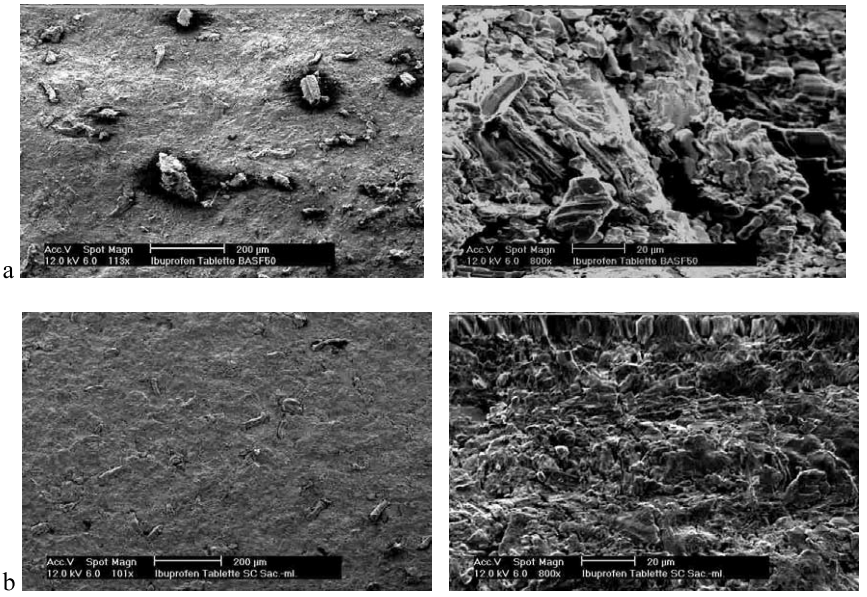


Fig. 2. SEM-photograph of ibuprofen tablet surface. (a) Ibuprofen control; (b) ibuprofen crystallized in the presence of sucrosemonolaurate and dextran.

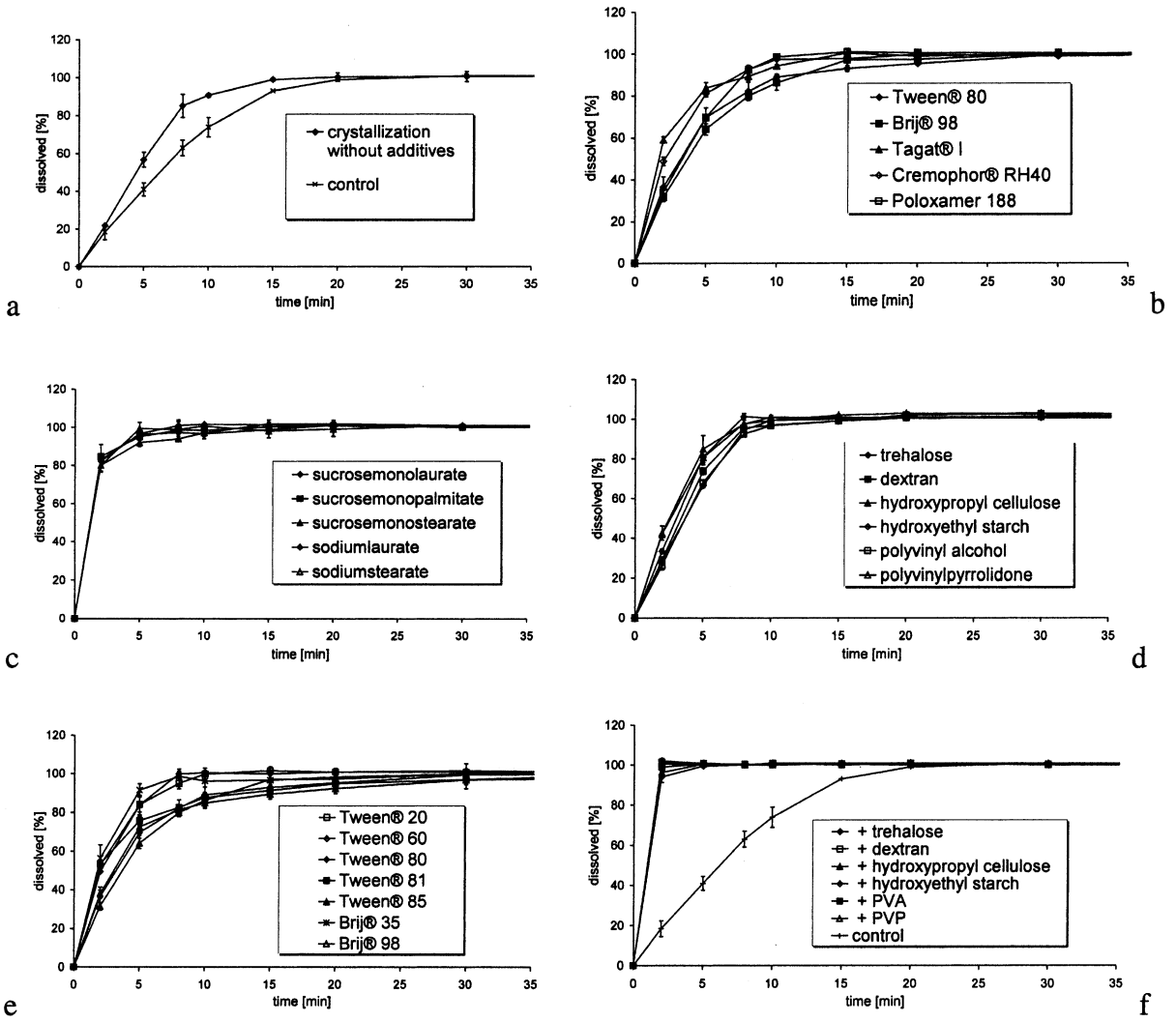


Fig. 3. Dissolution profiles of ibuprofen. (a) Common crystal form and crystallized without additives; (b) crystallized in the presence of surfactants with PEG chain; (c) crystallized in the presence of surfactants without PEG chain; (d) crystallized in the presence of hydrophilic additives; (e) crystallized in the presence of different types of surfactants with PEG chain; (f) crystallized in the presence of sucrosemonolaurate and different hydrophilic additives.

the presence of surfactants with a PEG chain (Fig. 3b) or in the presence of hydrophilic additives (Fig. 3d). However, all these ibuprofen crystals show only a little improvement of the dissolution rate. The type of the hydrocarbon chain or the length of the PEG chain do not influence the dissolution profile in a significant way (Fig. 3e), but in tendency surfactants with a saturated hydrocarbon chain lead to an ibuprofen powder with a higher dissolution profile than those with an oleyl chain. A dramatic improvement in drug dissolution occurs if ibuprofen is crystallized in the presence of surfactants without a PEG chain (sucrose esters and sodium salts of fatty acids) (Fig. 3c). As a common property of surfactants these additives have a hydrophobic and a hydrophilic part of the molecule. The hydrophilic part has high hydrophilicity located in a small area, either in the form of a sugar with eight hydroxyl-groups or an anionic carboxylic-group. In contrast

to these structures, the surfactants with a PEG chain have a long hydrophilic chain where the hydrophilicity is not located in such a concentrated manner. Surfactants with PEG chains can form hydrogen bonds, but these are weaker than those of hydroxyl-groups. This results in different interactions with the growing ibuprofen crystals as additives with a high tendency to form hydrogen bonds can interact with the (100) face of the growing crystal. By strong hydrogen bonding the crystal growth rate is transferred to the polar (100) face variant (Bunyan et al., 1991). The geometric exactness and different types of adjacenting show that different additives affect the resulting crystals in different ways. A further improvement in dissolution rate can be achieved if ibuprofen is crystallized in the presence of a sucrose ester and hydrophilic additives, as shown in Fig. 3f. Differences in dissolution kinetics are made especially evident when comparing the slope in the sigma-minus-plot $[\ln(m_0-m)/t]$ as shown in Table 6 for the initial dissolution. To evaluate the effect on dissolution, the amount of drug released in minute 2 was analyzed statistically (Fig. 4): The main effect is attributable to sucrosemonolaurate, but also dextran and the combination have significant effects. Beside the hydrophilization caused by interactions, slight amounts of surfactant that remain in the product can be anchored in the crystal surface. The effect of dextran, for example, is lower; it can form hydrogen bonds, but due to its purely hydrophilic nature it cannot interact with ibuprofen in that way. If a combination is used, the effects increase.

Different dissolution behavior can be attributed to differences in the wettable surface. The specific surface area of the prepared ibuprofen crystals is

Table 6
Slope in sigma-minus-plot $\ln(m_0-m)$ vs. time (initial)

| Crystallization in the presence of | Slope (ln mg/min) |
|---|---|
| *Control* | *0.09* |
| Without additives | 0.13 |
| Polysorbate 80 | 0.25 |
| Dextran | 0.26 |
| Sucrosemonolaurate | 0.88 |
| Sucrosemonolaurate+dextran | 3.65 |

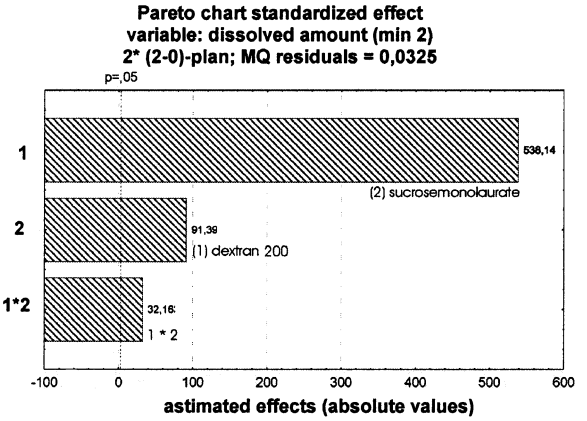


Fig. 4. Statistical evaluation (powder dissolution, 2 min).

different (Table 7), but there is no correlation between the dissolution profile and the total surface. Because of the hydrophobic crystal surface of ibuprofen, a distinction has to be drawn between the surface area and the wettable surface that is available to the dissolution medium. The crystals formed in the presence of surfactants with a PEG chain are bigger (X50 = 50 μm) and more agglomerated than in the presence of most of the hydrophilic additives (X50 = 45 μm). This correlates with the specific surface areas. If crystallization is carried out in the presence of sucrosemonolaurate and a hydrophilic additive, the formed specific surface is similar as in the case of crystallization with only the hydrophilic additive. Different supersaturation profiles during precipitation process can explain different crystal growth rates. The specific surface area of samples prepared in the presence of sucrosemonolaurate takes a mean position, but the dissolution rate is high. This indicates that other effects influencing the drug release rate exist.

Agglomeration tendency, flowability and dissolution behavior can be affected by crystal modification. Agglomeration and surface properties affect the distribution in the dissolution medium and thus the dissolution rate. The common ibuprofen crystals remain agglomerated on the surface of the dissolution medium because of a high flotation. In contrast to this, ibuprofen that was crystallized in the presence of sucrosemonolaurate and dextran 200 is spread finely over the

Table 7
Specific surface area of ibuprofen

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Ibuprofen crystallized in the presence of surfactants with PEG chain* | | | | | | | |
| | Control | Without additives | Tween® 80 | Brij® 98 | Tagat® I | Cremophor® RH40 | Poloxamer 188 |
| Spec. surface area ($m^2/g$) (±S.D.) | 0.112±0.013 | 0.297±0.039 | 0.181±0.019 | 0.189±0.017 | 0.182±0.012 | 0.179±0.019 | 0.195±0.019 |
| *Ibuprofen crystallized in the presence of surfactants without PEG chain* | | | | | | | |
| | Sucrosemonolaurate | Sucrosemonopalmitate | Sucrosemonostearate | Sodiumlaurate | Sodiumstearate | | |
| Spec. surface area ($m^2/g$) (±S.D.) | 0.234±0.015 | 0.258±0.017 | 0.274±0.018 | 0.211±0.015 | 0.239±0.014 | | |
| *Ibuprofen crystallized in the presence of hydrophilic additives* | | | | | | | |
| | Trehalose | Dextran | Hydroxypropyl-cellulose | Hydroxyethylstarch | Polyvinylalcohol | Polyvinylpyrrolidone | |
| Spec. surface area ($m^2/g$) (±S.D.) | 0.331±0.012 | 0.281±0.013 | 0.245±0.017 | 0.224±0.015 | 0.151±0.014 | 0.193±0.009 | |
| *Ibuprofen crystallized in the presence of sucrosemonolaurate and hydrophilic additives* | | | | | | | |
| | +Trehalose | +Dextran | +Hydroxypropyl-cellulose | +Hydroxyethyl-starch | +PVA | +PVP | |
| Spec. surface area ($m^2/g$) (±S.D.) | 0.311±0.019 | 0.314±0.017 | 0.279±0.009 | 0.314±0.019 | 0.172±0.011 | 0.207±0.011 | |

Results: mean of three measurements; S.D., standard deviation.

Table 8
Vapor sorption measurement

| | Control | Sucrosemonolaurate | Sucrosemonolaurate+dextran |
|---|---|---|---|
| Begin of water adsorption at RH (%) | >95 | 85 | 60 |
| Mass difference 0–95% RH (%) | 0.00 | 0.06 | 0.20 |
| Hysteresis at 75% RH (%) | 0.00 | 0.00 | 0.04 |

dissolution medium and suspended finely in it. However, ibuprofen that is crystallized with surfactants of the PEG-type is agglomerated and dissolves more slowly. Thus a better wettability caused by the residue of surfactants in the final product does not cause the effect. This is emphasized by the analysis on purity: the amount of sucrosemonolaurate was 0.08% (m/m) (S.D. = 0.02; four separately prepared samples analyzed) the content of dextran was below the quantification limit (<0.01%). Therefore, according to the pharmacopoeias, a pure drug powder was obtained. The most important effect influencing the dissolution profile is the distribution behavior. Intrinsic dissolution shows nearly the same results for all crystals, as agglomerating effects are excluded by carrying out the dissolution from a standardized compact. The contact angle of all samples does not differ (approximately 64°, 10 s after putting the droplet onto the compact; approximately 63° after 180 s). These results confirm that there are no high amounts of surfactants remaining in the drug powder. However, these methods are not very sensitive for detecting slight differences. Beside the determination of the contact angle a more sensitive method to analyze the affinity to water is the vapor sorption measurement (Table 8): the common ibuprofen crystals do not show any water adsorption, even at 95% RH no increase in mass can be observed. Ibuprofen crystallized in the presence of sucrosemonolaurate shows a slight water uptake, beginning at 85% RH. If ibuprofen is prepared in the presence of sucrosemonolaurate and dextran, the water uptake starts at 60% RH. Of course, the water uptake (+0.2%) is very low, but in comparison to other samples there is a significant difference. A hysteresis (difference between adsorption and desorption) is only observed at these ibuprofen crystals. This is an indication for a hydrophilization of the crystal surface. Differences in water uptake can also influence the tabletability.

Fig. 5 shows that differences in powder dissolution are also important for the drug release from tablets. Tablets, which are prepared using ibuprofen that was crystallized in the presence of sucrosemonolaurate and dextran, show a drug release of over 90% after 2 min, including the disintegration time (of approximately 40 s). Tablets (85% drug content) containing the common ibuprofen crystals are relatively faster in release than it could be expected from the results of powder dissolution. Because of the mass of a tablet, flotation effects are lower. To estimate the relevance of detected differences in drug dissolution, dissolution studies were carried out in simulated gastric fluid. This testing medium contains a surfactant (SDS), which results in a relatively faster dissolution of the common crystals. The effect of flotation is lower because of the higher wettability, and agglomerates are disagglomerated rapidly. No significant difference between the common crystals, the ibuprofen crystallized without additives, the ibuprofen crystallized in the presence of a surfactant with a PEG

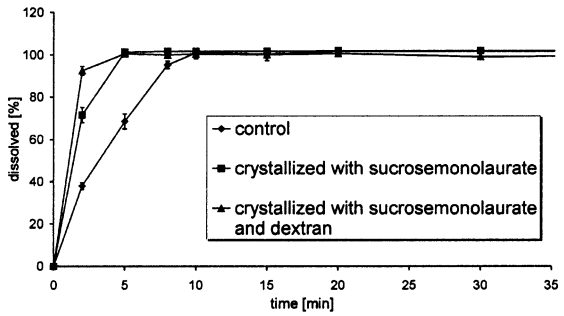


Fig. 5. Dissolution from tablets (including destintegration time).

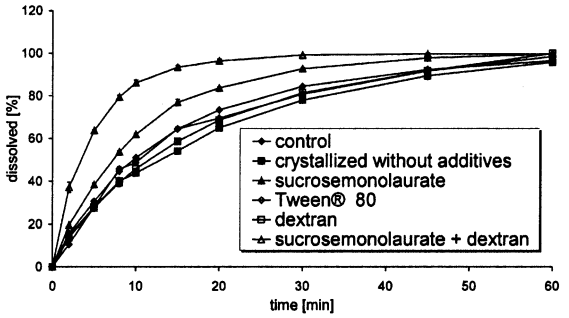


Fig. 6. Dissolution profile in simulated gastric fluid.

chain or a hydrophilic additive can be detected. Ibuprofen crystals precipitated in the presence of a sucrose ester and especially in the presence of sucrosemonolaurate and a hydrophilic additive show a significant increase in powder dissolution (see Fig. 6). In this dissolution study all hydrophobic surfaces can interact with the SDS in the medium, thus it can be excluded that little amounts of remaining additives are responsible for the increase in drug dissolution. Thus the modified crystals cause different dissolution kinetics. This effect occurs especially in the presence of sucrose esters or sodium salts of fatty acids and is intensified by addition of hydrophilic additives.

## 4. Conclusions

If crystallization is carried out in the presence of additives, special effects can occur that influence the crystal habit and the crystal surface. Thus the properties of the resulting drug powder can be affected, even if a pure drug results. Effects that are not obtainable by different crystallization processes without additives can be achieved. In ibuprofen crystals the hydrogen bonds play an important role. Additives that are able to interact strongly with the hydrogen bonds of ibuprofen are able to affect the growth rate of the dominant (100) surface transferring the growth rate to the polar variant of the surface as described by Bunyan et al. (1991). Especially the carboxylic-group of sodium salts of fatty acids or the sucrose esters (many hydroxyl-groups) are suitable for this strong interaction. Geometrically exactly shaped crystals are formed, which shows the influence on the crystallization process. The environment affects the external shape of the ibuprofen crystal, without changing the internal structure; all crystals were isomorphic. By the use of additives during the crystallization process, an improvement of handling properties and of dissolution properties can be reached.

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