Dissolution Rate Enhancement by *in Situ* Micronization of Poorly Water-Soluble Drugs

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Purpose. The purpose of this study was to evaluate a novel *in situ* micronization method avoiding any milling techniques to produce nano- or microsized drug particles by controlled crystallization to enhance the dissolution rate of poorly water-soluble drugs.

Methods. Ibuprofen, itraconazole, and ketoconazole microcrystals were prepared by the association of the previously molecularly dispersed drug using a rapid solvent change process. The drug was precipitated in the presence of stabilizing agents, such as hydrocolloids. The obtained dispersion was spray-dried. Particle size, morphology, dissolution rate, specific surface area, and wettability were analyzed. Physicochemical properties were characterized using differential scanning calorimetry and X-ray diffractometry.

Results. The obtained dispersions showed a homogeneous particle size distribution. Drugs are obtained in a mean particle size of approximately 2 μm and below. A high specific surface area was created and *in situ* stabilized. Different stabilizers showed differences in protecting the precipitated drug from crystal growth. The surface was hydrophilized because of the adsorbed stabilizer. Thus, a drug powder with markedly enhanced dissolution rate was obtained.

Conclusions. *In situ* micronization is a suitable method for the production of micro-sized drugs. This technique can be performed continuously or discontinuously and uses only common technical equipment. Compared to milled products drug properties are optimized as all particle surfaces are naturally grown, the particle size is more uniformly distributed and the powder is less cohesive.

KEY WORDS: micronization; inhibition of crystal growth; dissolution rate enhancement; poorly water-soluble drug; controlled crystallization.

INTRODUCTION

The poor water solubility of many drugs—especially several newly developed substances—is a challenge in pharmaceutical research. Because of their low bioavailability, several potential drugs have to be delayed or abandoned in pharmacological screenings because of their lipophilicity (1). Their dissolution rate is the limiting factor in most case because drugs with high lipophilicity can permeate biomembranes quickly. Thus, the research on strategies for drug dissolution enhancement is of high interest. According to the Noyes-Whitney equation, the administration of a drug in a reduced particle size is a very promising way to improve drug bioavailability of poorly soluble substances (2). The common way for reducing the particle size is the disruption of previously formed larger particles by milling techniques such as jet-milling, milling in a pearl-ball-mill, or high-pressure homogenization. However, these methods have several disadvantages resulting from the mechanical disruption process. The micronization process using mills is extremely inefficient (3) because of the high-energy input that can alter the surface properties as a thermodynamically activated surface is created (4,5). Even a small amount of activated material at the surface affects the drug substance properties, such as the blending characteristics (6) or flow properties (7). When the partially amorphous surface recrystallizes, the physical properties of the drug change. The conversion of crystalline solid surfaces into partially amorphous solid surfaces leads to a "dynamic nature" of the micronized drug (8). The newly created surfaces are not naturally grown because the cleavage plane is the crystal face with the smallest attachment energy (9). Thus, this surface will dominate the size-reduced particles and the milled powder is characterized by their surface properties. In most cases the surface shows poor wetting properties; therefore, because of agglomeration, the increase in the dissolution rate is not as high as calculated from the increase in surface area. Nanosuspensions (DissoCubes®) are milled by high-pressure homogenizers (10,11). The high pressures used cause changes in the crystal structure, and as a result, the amorphous fraction in the particle increases (12). Thus milling affects several physical properties of the drug, such as powder flow, agglomeration behavior, or electrostatic behavior. Beside these effects, the chemical reactivity or degradation also can be affected by milling (13,14). Even the particle size can change during storage after micronization because of stress relaxation processes (15). Beside these problematic properties, a further disadvantage especially of jet-milling processes, is a broad size distribution (16). Because of abrasion, the product can be afflicted with metallic impurities that can affect the chemical stability as a result of catalytic activity.

Because of the disadvantages of milling processes, techniques were developed that produce the drug directly in the optimal particle size. However, the preparation and stabilization of small particles is not easy because of their tendency to grow. Thus, several examples of inorganic clusters prepared for example in electrochemical cells exist, but stable dispersions of organic substances (beside polymer-lattices) are scarce. Because of the high surface that must be created, the established methods need high amounts of stabilizing excipients leading to amorphous products. The most important examples are the so-called hydrosols developed by Gaβmann *et al.* (17). Hydrosols are colloidal aqueous suspensions containing drug nanoparticles of poorly water-soluble drugs for intravenous administration. They are prepared by a precipitation process as the drug solution is mixed with a relatively high volume of water (96–98% water after mixing) in the presence of stabilizing agents such as poloxamer and modified gelatins, which act as "short term stabilizers" (17). After precipitation, the amorphous hydrosol is stable for approximately 60 min because of the stabilizers and the high amount of nonsolvent. After this time, the drug crystallizes. Because the clouding correlates with the particle size, crystallization and particle growth can be observed by a steep increase of absorbance at a wavelength where the drug substance does not absorb. Thus, for durable stabilizing the amorphous nanosized drug, the hydrosol is immediately spray-dried with ex-

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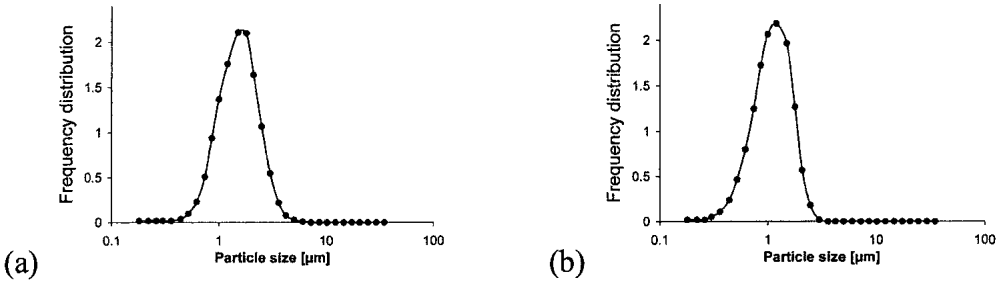

Fig. 1. Particle size distribution in dispersion 60 min after precipitation (HPMC solution). (a) ibuprofen; (b) ketoconazole.

cipients such as lactose or mannitol before crystallization occurs. Before use, the preparations are reconstituted with water. Hydrosols contain the drug in a particle size of approximately 200 nm and are thus suitable for parenteral application. An example is cyclosporin, which can be formed as a hydrosol (ratio drug: gelatin = 1: 20). According to this principle, colloidal dispersions of β-carotene are produced. Amorphous carotenoid nanoparticles contain high amounts of stabilizing agents, such as gelatin, and softening agents, such as sugar. Because the amount of β-carotene is approximately 10–15% (18,19), these preparations can be called embeddings. Because of the high amount of stabilizer and the immediately spray-drying, the product is amorphous. Micronized drugs can also be prepared using supercritical carbon dioxide (20,21). The drug is precipitated in the supercritical fluid. A disadvantage of this technique is the high machine expenditure.

The aim of this study was to prepare crystalline micro sized drug particles of poorly water-soluble drugs use in oral administration forms to enhance the dissolution rate. Because the drug powders are prepared directly in the micronized state during the particle formation without any further size-reduction, this technique can be described as an *in situ* micronization technique. The molecularly dispersed drug is transformed to particles in the desired size and stabilized in the formed dispersion. Because they are model drugs with a poor solubility in water, ibuprofen, itraconazole, and ketoconazole were used. The first aim was to find a stabilizing agent that was able to stabilize the associated drug in small particle size against crystal growth. Furthermore, the use of an effective stabilizer is important to obtain a drug powder with a drug load as high as possible. By the use of a suitable stabilizer, the crystal germs can be stabilized. To find a stabilizer with high affinity to the newly created high surface, several potential stabilizing agents were compared. The resulting product showed a high drug load and contained the drug in crystalline form.

MATERIALS AND METHODS

Materials

Ibuprofen 50 was provided by BASF AG (Ludwigshafen, Germany), and itraconazole and ketoconazole were supplied by Janssen Pharmaceutica (Beerse, Belgium). For comparison of the analytical data, drugs were used as obtained and called "common crystals." Acetone and isopropyl alcohol (Merck KG, Darmstadt, Germany) were of analytical grade. Water was used in double-distilled quality. The stabilizing agents used were agar (Merck KG), calcium caseinate (Lactonat®EC, Lactoprot, Kaltenkirchen, Germany), dextran 200 (Sigma, Deisenhofen, Germany), gelatin A (Merck KG), hydoxyethylcellulose HEC (Natrosol®Pharm G, Natrosol®HHX, Hercules, Wilmington, DE, USA), hydroxyethylstarch (HES 130, HES 450, Fresenius Kabi, Bad Homburg, Germany), hydroxypropylcellulose HPC (Klucel® GF, Klucel® LF, Herculesmethylcellulose MC (Tylose® M 4000, Clariant, Frankfurt, Germany), methylhydroxyethylcellulose MHEC (Tylopur® MH 50, Tylopur® MH 4000, Clariant), hydroxypropylmethylcellulose (HPMC; Metolose® 60 SH 15, 4000, 10,000, Shin Etsu, Tokyo, Japan), sodium carboxymethylcellulose NaCMC (Tylopur® C 30), sodium alginate (Sigma), pectin (pectin Classic AU 204, low viscosity, Herstreith & Fox KG, Neuenburg, Germany), polyvinylalcohol (average molecular weight 30,000–70,000; Sigma), and polyvinylpyrrolidone (Kollidon®30, BASF AG).

Crystallization Procedure

Crystallization was conducted using the solvent change method by instantaneously mixing two liquids in the presence of a stabilizing agent as described by Rasenack and Müller (22). In the first step, the drug was dissolved in an organic solvent that is miscible with water. The chosen concentration depends on the solubility of the drug (ibuprofen: 5 g/100 mL isopropyl alcohol; itraconazole: 0.75 g/500 mL acetone; ketoconazole: 0.5 g/100 mL acetone). The stabilizing agents were dissolved in water. By batch-wise mixing the two liquids (20

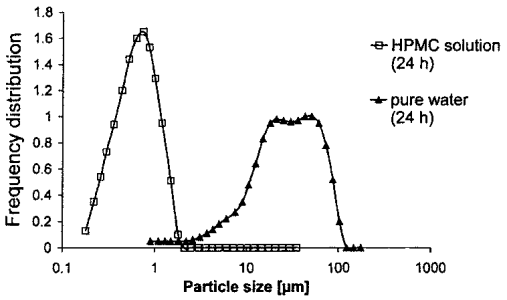

Fig. 2. Particle size distribution of itraconazole 24 h after precipitation with pure water respectively. HPMC solution.

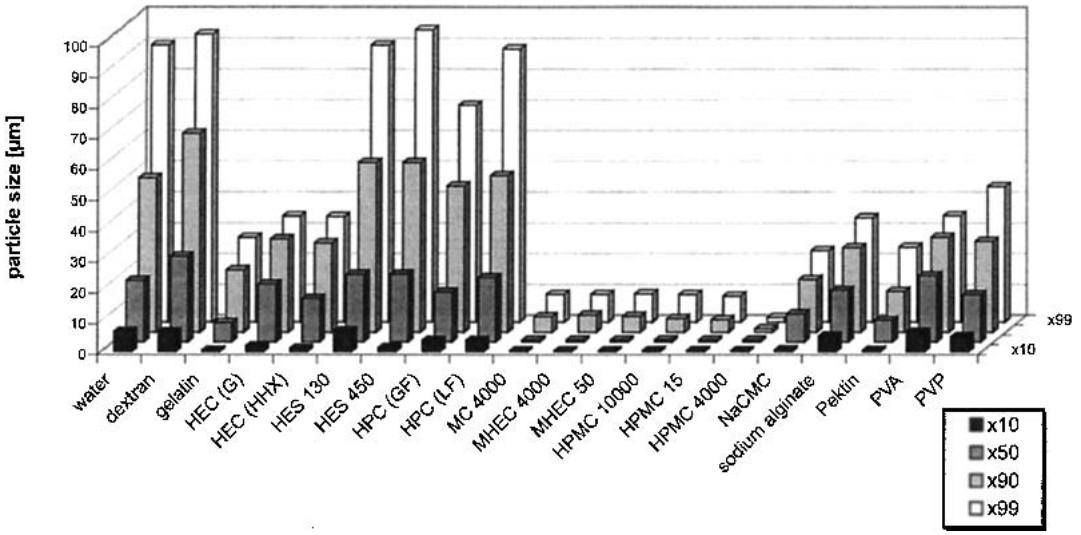

Fig. 3. Particle size of itraconazole (dispersion 24 h after precipitation) [concentration of stabilizer in water = 0.025% (m/m)].

mL of drug solution + 80 mL of nonsolvent in the case of ibuprofen and ketoconazole, respectively, 50 mL of drug solution + 80 mL of nonsolvent in the case of itraconazole) a dispersion is formed. The nonsolvent was poured rapidly from a beaker into the drug solution under stirring conditions using a magnetic stirrer. The stability of the dispersion depends on the stabilizer that is used. For each drug, several stabilizers and different concentrations were tested by measuring the particle size at different times after precipitation. A solution of HPMC (ibuprofen: 0.1%; itraconazole: 0.025%; ketoconazole: 0.05%) was used for preparing the micronized drugs. After spray-drying the prepared dispersion during its stability (Büchi 190 Mini Spray-dryer, Büchi Labortechnik AG, Flawil, Switzerland; $temperature_{inlet}$: 128°C; $temperature_{outlet}$: 55°C; air flow 600 Nl/h; 0.5-mm noozle; aspirator stream 40 m^3/h) a micro- respectively nanosized drug powder was obtained (drug content: ibuprofen 92.6%; itraconazole 79.0%; ketoconazole 71.4%). In this study, the spray-drying process was not used to form particles as if solutions are spray-dried but only to dry previously formed particles. Because of the small particles, a high stream of volume was used to obtain a higher yield. Furthermore, a cone was inserted between the bottom of the cyclone and the collecting vessel. Passing through the gap of approximately 1.5 mm, the powder can deposit in the collecting vessel. Swirling up and swirling out of the collecting vessel is reduced.

Product Characterization

Particle Size

The volume particle size distribution was measured using a laser diffractometer (Helos, Sympatec GmbH, Clausthal Zellerfeld, Germany). The dispersions were diluted with water and measured in a cuvette. The spray-dried drug powder was previously suspended in water. Particle size distribution is characterized by the X10 (10% below this size), the X50, X90, and the X99-value.

Powder Dissolution

Dissolution studies were performed assuring sink-conditions according to the paddle method (USP) using an Erweka DT6 dissolution apparatus (Erweka, Heusenstamm, Germany). The stirring speed used was 100 rpm, and the temperature was maintained at 37°C ± 0.5°C. The dissolution medium (900 mL) was phosphate buffer pH 7.4 (USP 25) in the case of ibuprofen and simulated intestinal fluid in the case

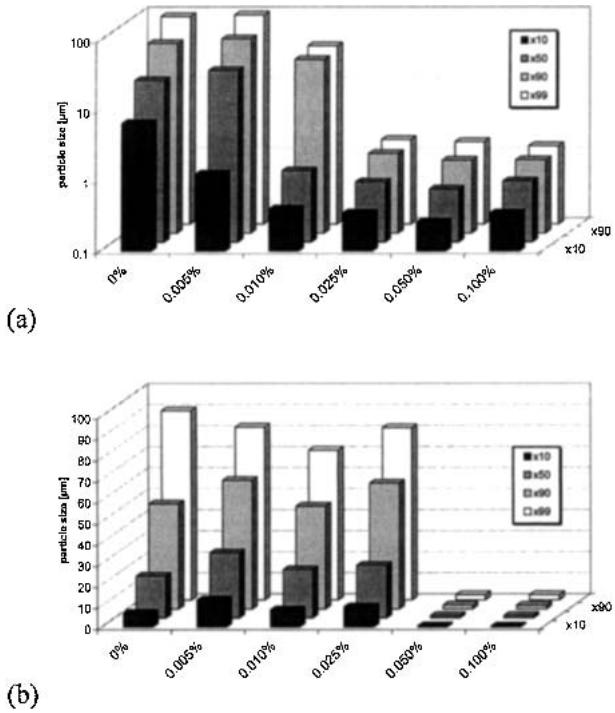

Fig. 4. Influence of different concentrations of HPMC4000 on particle size in dispersion. (a) itraconazole 24 h after precipitation; (b) ketoconazole 120 min after precipitation [concentration in precipitating liquid in & (m/m)].

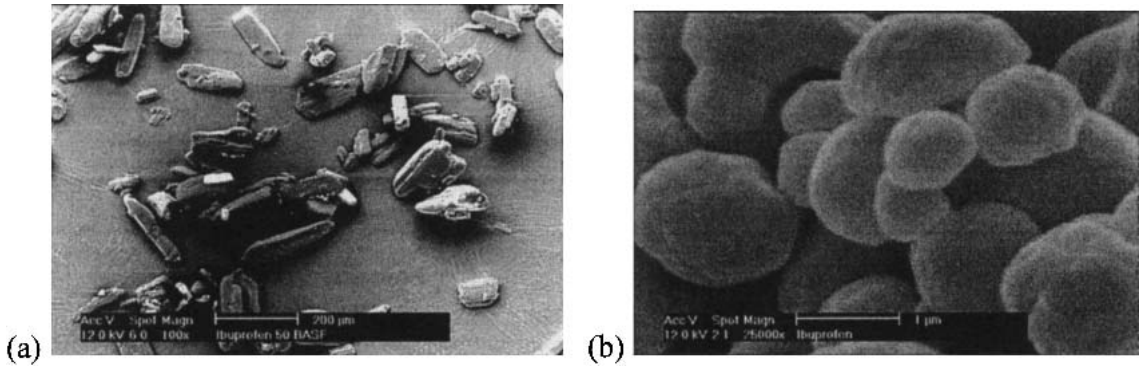

Fig. 5. Scanning electron micrograph of ibuprofen. (a) common crystals; (b) micronized drug.

of itraconazole and ketoconazole. This dissolution medium consisted of 0.25% sodium dodecyl sulfate and 0.2% sodium chloride (all Merck KG). Surface tension was lowered by sodium dodecyl sulphate in an attempt to mimic *in vivo* conditions as described by Pedersen *et al.* (23). Because of their physiologic relevance for dissolution testing of poorly water-soluble drugs the addition of a surfactant is generally to be preferred to e.g., hydroalcoholic mediums (24). Quantification of the dissolved amount of drug was conducted spectrophotometrically at 221 nm (ibuprofen), 262 nm (itraconazole), 226 nm (ketoconazole) (Lambda40 UV VIS Spectrometer, Perkin Elmer, Wilten, CT, USA). All samples were analyzed in triplicate.

Scanning Electron Microscopy

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

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, GA, USA) was used.

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 under vacuum. The contact angle between the disc and a single drop of water (25 μL) was determined 10 s and 180 s after the droplet was put onto the disc. Determination was repeated 20 times.

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 aluminium pans under nitrogen atmosphere. The onsets of the melting points and enthalpies of fusion were calculated by the software (Pyris, Perkin Elmer, CT, USA).

X-Ray Diffractometry

Powder X-ray diffraction patterns were collected in transmission using an X-ray diffractometer with a rotating anode (Stoe and Cie GmbH, Darmstadt, Germany) with Cu Kα1 radiation (monochromator: graphite) generated at 200 mA and 40 kV. Powder was packed into the rotating sample holder between two films (PETP).

RESULTS AND DISCUSSION

When a hydrophobic substance is precipitated, a hydrophobic surface is formed. The energy of the system increases. Thus a stabilizing agent—provided that it has any affinity to

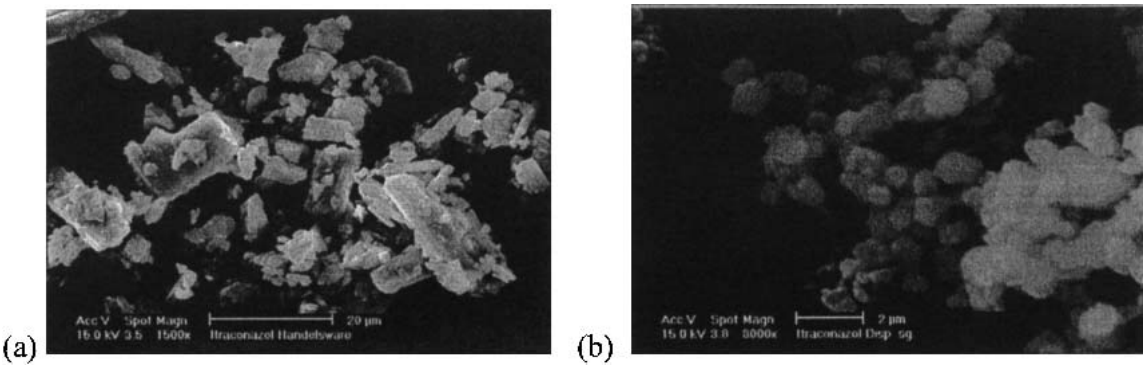

Fig. 6. Scanning electron micrograph of itraconazole. (a) common crystals; (b) micronized drug.

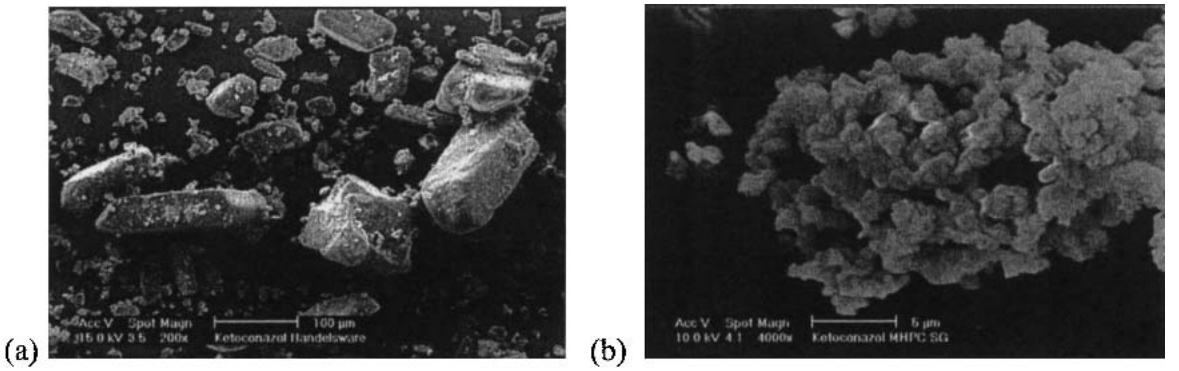

Fig. 7. Scanning electron micrograph of ketoconazole. (a) common crystals; (b) micronized drug.

the surface—covers the newly formed surface spontaneously. Thereby, the surface energy and consequently the enthalpy of the system is lowered. The small particles that normally would agglomerate because of their hydrophobic surface are sterically stabilized against crystal growth by a layer of protective polymer (25).

Characterizing the Precipitated Dispersion

The analgesic drug ibuprofen and the antifungal drugs itraconazole and ketoconazole show a mean particle size of approximately 2 μm and below if precipitated in the presence of a stabilizing agent. The particle size distributions of the formed dispersions are shown in Figs. 1 and 2. In all cases a tight particle size distribution is received. The effect of the stabilizing agent (HPMC) on the particle size of itraconazole is obvious (Fig. 2): 24 h after precipitation itraconazole with pure water, a broad particle size distribution with a mean particle size (X50) of 30 μm is formed. In contrast, a tight particle size distribution with a mean particle size (X50) of 600 nm is formed if the drug is precipitated in the presence of HPMC. Thus, HPMC can stop the molecular association and the crystal growth by forming a protective layer around the nucleation germs. The stability of the dispersion depends on the stabilizer that is used. When comparing the particle size distribution obtained in the presence of different stabilizing agents, differences are detected (Fig. 3); particularly, cellulose ethers with alkyl-substituents (MC, MHEC, HPMC) are able to protect a particle growth. Additives with a mainly hydrophilic molecule structure, such as dextran, hydroxyethylstarch, or polar substituted cellulose ethers, do not stabilize the formed drug particles in that way. This shows that the additive must be able to interact with the newly formed surface. As e.g., HPMC shows surface activity (26), it can be adsorbed onto the newly created surface of the precipitated drug to lower the interfacial tension; particularly, cellulose ethers containing methoxyl or hydroxypropyl groups are adsorbed onto hydrophobic solid surfaces as described for hydrophobic silicon dioxide (27). A dependency of the resulting particle size on the viscosity of the precipitating liquid (determined using an Ubbelohde-viscometer) cannot be found. The effect of different concentrations on the resulting particle size of precipitated itraconazole (dispersion 24 h after precipitation) is shown in Fig. 4a. A minimum necessary amount of stabilizer (0.025% in the precipitating liquid) was found. Below this concentration, a particle growth occurs. However, the use of a higher amount of HPMC does not result in smaller itraconazole particles. A protective layer around the particles seems to be important. A similar relationship can be observed in the case of ketoconazole (Fig. 4b). Here two groups of particle size distributions can be observed: Below a minimal concentration of the stabilizer, large crystals with a mean particle size (X50) of 25 μm are obtained. If the minimum effective amount is used, a tight particle size distribution with a mean particle size of 1.2 μm is obtained. Because of the higher solubility of ketoconazole compared with itraconazole, the particle growth of ketoconazole is more rapid and thus the two groups of preparations can be sharply distinguished. Itraconazole that is not stabilized effectively grows slowly, thus different particle sizes (Fig. 4a) are observed in the case of using different amounts of stabilizer as a result of the fact that particle growth has not yet finished.

Characterizing the Spray-Dried Drug Powders

After spray-drying the prepared dispersions, drug powders are obtained (Fig. 5b, Fig. 6b, and Fig. 7b). The precipitated drugs are isomorphic with the common crystals, as X-ray and DSC analysis showed. The particle size distribution of the dispersions is fixed by the drying process. However, because of the fact that a suspension is spray-dried, the particle size is not affected by the spray-drying process. The common crystals of ibuprofen (Fig. 5a) are prepared by crystallization and show a relatively homogeneous particle size. However, the milled drugs itraconazole and ketoconazole show very heterogeneous particle sizes (Fig. 6a and Fig. 7a). The drug powders prepared in this study consist of uniform particles. Because of the small particle size, the drug is agglomerated. After redispersing the drug powder in water, the particle size

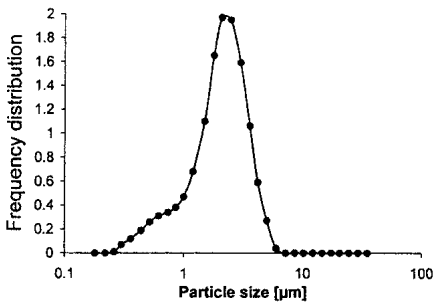

Fig. 8. Particle size distribution of micronized ketoconazole (dispersed in water).

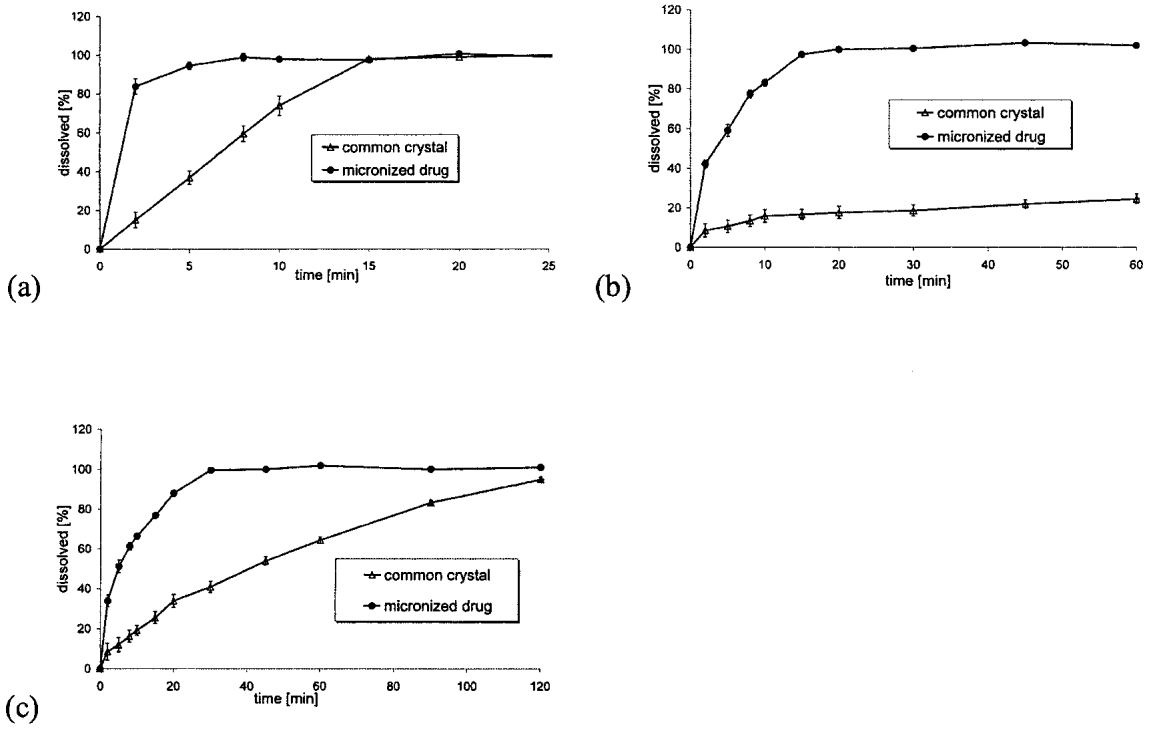

Fig. 9. Powder dissolution. (a) ibuprofen; (b) itraconazole; (c) ketoconazole.

distribution (Fig. 8) is nearly the same as in the dispersion that is spray-dried. Thus, the agglomerated crystals are deagglomerated. No electrostatic effects occur; thus, the powder flow is increased compared with milled itraconazole or ketoconazole. The dissolution rate of the micronized drugs is significantly increased compared with the common crystals (Fig. 9). Particularly, the common crystals of itraconazole only show a very slow dissolution because of the effect of aerophilization, which is often observed with milled drugs. Thus, the dissolution rate of a milled drug is lower than would be expected from the Noyes-Whitney equation. The crystals are not wettable (not even by the used simulated gastric juice containing a surfactant). Thus, they are agglomerated on the surface of the dissolution medium. The dramatic increase in drug dissolution rate can be explained by an increased specific surface area (Table I). This high surface area is hydrophilized, the contact angle is decreased because of adsorbed hydrophilic HPMC (Table II). The contact angles of the micronized drugs are nearly the same for ibuprofen, itraconazole, and ketoconazole and also nearly the same as for the pure cellulose ether. The adsorbed HPMC determines the surface properties of the resulting product. Thus by precipitating microcrystals in the presence of stabilizing protective additives, a high and hydrophilized surface area can be formed in a one process step without using any milling techniques.

CONCLUSIONS

By the method used in this study, small drug particles are prepared without size-reduction techniques. Micronized poorly water-soluble drugs can be prepared by controlled crystallization of primary molecularly dispersed substances. The precipitation technique in the presence of protective hydrophilic polymers followed by spray-drying results in a drug powder with a markedly enhanced drug dissolution rate. A high and hydrophilized surface area is created. To form a protective layer on the crystal surface, the polymer must have an affinity to the hydrophobic crystal surface. Compared with, e.g., solid dispersions or cyclodextrin encapsulations, the amount of drug in the preparation is relatively high. The production process can be conducted discontinuously or continuously using a static mixer and is possible as a one-process step and needs only common equipment. This technique offers a relatively easy way for production of micronized drugs that are characterized by a homogeneous particle size distribution. Critical effects resulting from milling processes are avoided.

Table I. Specific Surface Area [m^2/g] (±S.D.)

	Common crystal	Micronized drug
Ibuprofen	0.11 ± 0.01	2.00 ± 0.09
Itraconazole	0.21 ± 0.02	4.03 ± 0.10
Ketoconazole	0.18 ± 0.02	3.01 ± 0.09

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

Table II. Contact Angle [°] (±S.D.)

	Common crystal		Micronized drug	
	t_1 = 0 s	t_2 = 180 s	t_1 = 0 s	t_2 = 180 s
Ibuprofen	63.9 ± 1.5	62.3 ± 1.4	42.3 ± 1.6	33.0 ± 1.5
Itraconazole	48.2 ± 1.3	47.2 ± 1.0	39.1 ± 1.4	30.1 ± 1.3
Ketoconazole	44.6 ± 1.1	42.8 ± 1.3	38.2 ± 1.3	29.8 ± 1.1

Results: mean of 20 measurements; S.D. = standard deviation.

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