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Research paper

Dissolution improvement of four poorly water soluble drugs by cogrinding with commonly used excipients

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Abstract

The rate of the dissolution of four poorly soluble drugs (EMD 57033, albendazole, danazol and felodipine) was improved by cogrinding them with various excipients (lactose monohydrate, corn starch, polyvinylpyrrolidone, hydroxypropylmethyl cellulose and sodium lauryl sulphate) using a jet-milling technique. Solid state characterization studies by X-ray diffraction and differential scanning calorimetry verified the maintenance of the crystalline state of the active substances after milling. In vitro dissolution of the coground mixtures in biorelevant media was much faster than from micronised drug in the corresponding physical mixtures for all four compounds. Supersaturated solutions were generated in some cases (EMD 50733 and felodipine), but this phenomenon appeared to be drug- and excipient-specific. Cogrinding with lactose monohydrate resulted in fast dissolution with unstable supersaturation for EMD 57033. Cogrinding the same drug with PVP or HPMC produced a more sustained supersaturation. SLS accelerated the dissolution of EMD 50733 but inhibited supersaturation. The results suggest that the cogrinding with selected excipients is a powerful tool to accelerate the dissolution of poorly soluble drugs without converting the drug to the amorphous form or changing the particle size.

Keywords: Albendazole; Cogrinding; Danazol; Dissolution rate enhancement; Felodipine; Jet-milling; Particle size reduction; Poorly soluble drugs; Solubility; Supersaturation

1. Introduction

During the last decade the trend in drug discovery has been to produce more and more compounds that exhibit high lipophilicity and poor water solubility [1]. Such physicochemical characteristics lead to problematic biopharmaceutical properties, which in turn diminish the likelihood of success in the clinic [2]. Many approaches have been developed to improve solubility and to enhance the dissolution rate of poorly soluble drugs, including both modifications to the drug substance itself and the creation of specific formulations. Physical modifications often aim to increase the surface area, solubility and wettability of the powder particles and therefore typically focus on particle size reduction or generation of amorphous states [3,4].

Classically, particle size reduction is performed by milling and a wide variety of apparatus is available. The increase in bioavailability after micronisation of drugs, which is most often performed by jet-milling, is well known and the technique has been applied to a variety of poorly soluble compounds (e.g. [5–12]). By contrast, there is little literature describing the use of cogrinding as a processing method. To date, large quantities of water-soluble polymers have typically been used as the cogrinding excipient [13,14]. An example is polyvinylpyrrolidone (PVP), which has been used to concomitantly increase the dissolution rate and suppress any recrystallization [15,16]. Cogrinding or comelting with surfactants such as sodium lauryl sulphate (SLS) or sodium desoxycholate [17] or sugars [18]

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has also been investigated, but in these cases amorphous states of the drugs were generated.

This paper describes the preparation of coground formulations of four poorly soluble drugs, two with medium and two with higher lipophilicity, by jet-milling with generally accepted excipients. The main focus of the present research was to identify excipient/processing combinations which can optimize the dissolution rate of poorly soluble drugs, while maintaining the crystalline structure of the drug to circumvent the stability issues often associated with the amorphous form. The drugs selected for study were EMD 57033, an investigational calcium-sensitizing agent [19], albendazole, danazol, and felodipine. Lactose monohydrate, corn starch, PVP, hydroxypropylmethyl cellulose (HPMC) and SLS were used as excipients.

2. Materials and methods

2.1. Chemicals

EMD 57033 was a development candidate from Merck KGaA (Darmstadt, Germany). The drug was synthesized by alkaline hydrolysis of its chemically modified prodrug EMD 82571 (lot 02/HH/31). Danazol was acquired from BMP GmbH (Hamburg, Germany); albendazole and felodipine were purchased from Sigma (Steinheim, Germany). The chemical structures of the drug substances are given in Fig. 1. SLS, corn starch, lactose monohydrate, HPMC 2910/5 and Povidone 25 (PVP) were all provided by Merck KGaA (Darmstadt, Germany). Sodium taurocholate was obtained from Prodotti Chimici E Alimentari S.P.A. (Basaluzzo, Italy). Egg-phosphatidylcholine, Lipoid E PC, was purchased from Lipoid GmbH (Ludwigshafen, Germany). All other chemicals used were of HPLC grade or analytical grade.

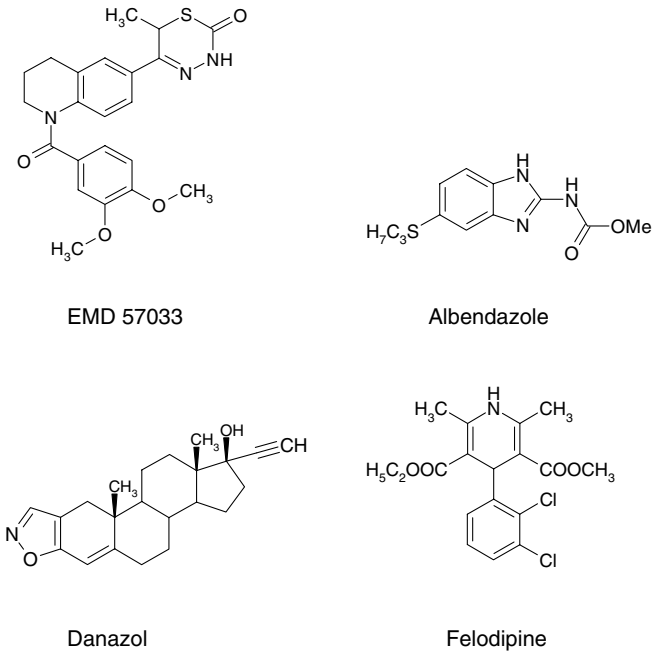

Fig. 1. Chemical structures of EMD 50733, albendazole, danazol and felodipine.

2.2. Solubility determination

The solubility of each drug substance was determined in SLS solutions at various concentrations, in water and in FaSSIF (Fasted State Simulated Intestinal Fluid) using a standardized shake flask method at 37 °C. After shaking for 48 h, the supernatant was then filtered through a 0.22 μm membrane filter and the filtrate was assayed per HPLC.

2.3. Preparation of physical mixtures

Physical mixtures were prepared by physically blending the active (10%) and excipients, and then manually filling the blend into Coni-Snap Supro A hard gelatine capsules (Capsugel, Belgium).

2.4. Preparation of micronised drugs and coground mixtures

Micronised drug substances and coground mixtures were prepared by milling the drug by itself or in a physical mixture with various excipients using an Alpine 50 AS jet-mill (Hosokawa Alpine AG, Germany) operating at 5 bar air pressure and a feed rate of 0.5–1.0 g/min. The milled powder was then manually filled into Coni-Snap Supro A hard gelatine capsules, after blending with lactose monohydrate, if necessary, to obtain a concentration of the active substance of 10%. Homogeneity of the mixtures was investigated by quantitative HPLC determination of the drug content after accurate weighing of an aliquot of powder, dissolving and diluting with mobile phase.

2.5. Particle size measurement

Particle size was determined by laser light diffraction. The equipment consisted of a Malvern Mastersizer 2000 (Malvern Instruments, Germany) including a Scirocco 2000 module for dry measurement purposes operating at 3.0 bar air pressure for dispersion with evaluation of data by Malvern software version 4.0 using the Fraunhofer approximation as the evaluation algorithm [20]. It had been previously established that a sufficient dispersion of particles but no milling occurs at 3 bar air pressure.

2.6. HPLC analysis

The system consisted of a Merck Hitachi pump L-6200A, a Merck Column Thermostat T-6300 operating at 36 °C, a Merck Hitachi Interface D-6000A, a Merck Hitachi UV–vis Detector L-4250 and a Merck Hitachi Autosampler AS-4000A. Data acquisition and evaluation was

performed with Merck Hitachi D-7000 Chromatography Data Station Software version 4.0. Using a LiChrospher 60 RP select B 125-3 (5 μm) column and a mobile phase consisting of 65% of pure water and 35% of acetonitrile at a flow rate of 1 ml/min, EMD 57033 was eluted at approximately 5 min. The detection wavelength was set at 321 nm. The same column and flow rate was used to detect felodipine at a wavelength of 362 nm and a retention time of about 4 min using a mobile phase consisting of pure water and acetonitrile at a ratio of 1:1. Using a LiChrospher 100 RP-18 125-4 (5 μm) column and a mobile phase consisting of 40% of pure water and 60% of acetonitrile at a flow rate of 1.25 ml/min, danazol was eluted at approximately 4 min. The detection wavelength was set at 285 nm. The same column and a mobile phase consisting of 40% of ammonium dihydrogenphosphate solution (10 mM) and 60% of methanol at a flow rate of 1.3 ml/min were used to elute albendazole at about 5 min (detection wavelength 254 nm).

2.7. X-ray diffraction studies

Powder X-ray patterns were recorded using a Bruker AXS diffractometer (Bruker AXS GmbH, Germany) with a PSD-50M detector and EVA Application Software version 6. Measurements were performed with a Cu Kα radiation source at 40 kV voltage, 30 mA current and a maximum scanning speed of 2°/min.

2.8. Differential scanning calorimetry

DSC curves were obtained by a Differential Scanning Calorimeter (DSC 821^e, Mettler-Toledo, Switzerland) at a heating rate of 5 K/min from 25 to 250 °C under nitrogen.

2.9. Dissolution testing

Release from the capsules was determined in a calibrated USP XXVIII apparatus 2 (paddle method) in 900 ml medium using a PharmaTest dissolution tester (Type PTWS, PharmaTest, Germany) operating at 75 rpm and 37 °C. Helix sinkers (11/31, 8/23, Sotex GmbH, Germany) were used to prevent floating of the capsules. Samples were taken according to USP guidelines by withdrawal of 3 ml without replacement at each pull point. Each sample was immediately filtered through a 0.22 μm membrane filter and appropriately diluted with HPLC mobile phase prior to analysis.

2.10. Statistical evaluation and presentation

Results from solubility determination and in vitro dissolution studies are presented as mean values with standard deviations. Particle size distributions are summarized by the characteristic volume-based *d*-values that correspond to 10%, 50% and 90% of the total particle population, respectively.

3. Results and discussion

3.1. Solubility studies

Table 1 summarizes the experimentally determined solubility of the drug substances in pure water, FaSSIF and SLS solutions of various concentrations. The CMC of SLS solutions is known to be approximately 8.2 mmol/l (0.236%) [21–23]. To avoid the time-consuming and rather expensive preparation of FaSSIF for dissolution studies, synthetic surfactants like SLS may be acceptable to reflect FaSSIF. Similar solubility in SLS and FaSSIF identifies the concentration of SLS which might be used to replace FaSSIF in dissolution studies. Such a substitution has to be additionally justified by verifying that dissolution profiles in the two media are homomorphic. It is strongly emphasized that the substitution of biorelevant media by surfactant solutions is drug-specific: both the type and concentration of surfactant required to match results in FaSSIF must be determined on a case by case basis. For example, results in Table 1 indicate that the concentration of SLS needed to produce the same increase in solubility observed with FaSSIF varies by more than a factor of 2 between EMD 50733 and albendazole.

Subsequent sections describe results with coground and physical blends on a drug by drug basis.

3.2. EMD 57033

With an aqueous solubility of 5 μg/ml (at 37 °C) and a log *P* value of 2.7, EMD 57033 is considered to be a poorly soluble drug [24]. Although FaSSIF increases the solubility of EMD 57033 by 40%, a dose of 30 mg exhibits a dose:solubility ratio in FaSSIF of more than 4200 ml. The dissolution rate of EMD 57033 is therefore anticipated to limit its absorption from the gastrointestinal tract.

Table 2 summarizes the effect of individual and combined excipients on the dissolution of EMD 57033 from cogrinds and the dissolution curves for various EMD 57033/excipient combinations are shown in Fig. 2. A comparison of selected combinations in Figs. 2a (FaSSIF) and 2b (SLS 0.12%) illustrates that dissolution experiments in FaSSIF and 0.12% SLS solution result in homomorphic profiles and these media are therefore interchangeable for

Table 1
Solubility of EMD 57033, danazol, albendazole and felodipine in various media at 37 °C in μg/ml (mean ± SD)

	EMD 57033	Danazol	Albendazole	Felodipine
Water	4.9 ± 0.1	0.5 ± 0.1	1.3 ± 0.1	1.0 ± 0.2
FaSSIF	6.9 ± 0.2	8.1 ± 0.1	2.1 ± 0.1	51.8 ± 2.0
0.12% SLS	7.0 ± 0.1	0.6 ± 0.1	1.4 ± 0.1	n.d.
0.24% SLS	15.5 ± 1.4	13.5 ± 0.1	1.9 ± 0.1	n.d.
0.32% SLS	84 ± 2.4	74 ± 0.8	4.9 ± 0.2	n.d.
0.36% SLS	123 ± 4	104 ± 1	7.1 ± 0.1	n.d.
0.50% SLS	253 ± 8	204 ± 4	12.9 ± 0.1	n.d.

n.d. – not determined.

Table 2
Dissolution behaviour of coground EMD 57033 in 0.12% SLS solution

Components in coground mixture	Supersaturation occurred	Maximum level (compared to saturation limit) (%)	Initial dissolution rate	Stability of supersaturation
Lactose	Yes	220	Rapid	Unstable
Lactose/corn starch	Yes	250	Rapid	Unstable
HPMC	Yes	280	Slow	Stable
HPMC/lactose	Yes	280	Rapid	Stable
PVP	Yes	230	Slow	Stable
PVP/lactose	Yes	260	Rapid	Stable
SLS	No	100	Rapid	–
SLS/lactose	No	100	Rapid	–
SLS/polymer	No	100	Rapid	–
SLS/polymer/lactose	No	100	Rapid	–

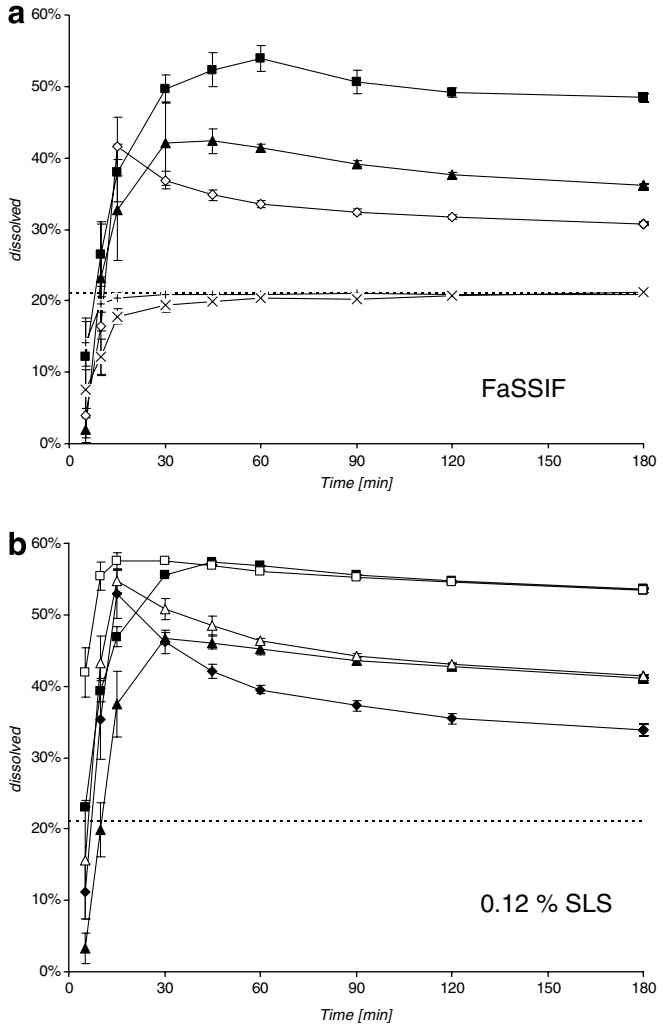

Fig. 2. Dissolution profiles of 30 mg EMD 57033 in (a) FaSSIF and (b) 0.12% SLS solution ($n = 3$, ±SD). (×) indicates micronised drug in a physical mixture with lactose monohydrate. (◇) indicates a coground mixture with lactose monohydrate. (■) indicates a binary coground mixture with HPMC (1:1). (▲) indicates a binary coground mixture with PVP (1:1). (+) indicates a tertiary coground mixture with SLS/lactose monohydrate (1:8). (□) indicates a tertiary coground mixture with HPMC/lactose monohydrate (1:8). (△) indicates a tertiary coground mixture with PVP/lactose monohydrate (1:8). (◆) indicates a tertiary coground mixture with corn starch/lactose monohydrate (2:7). Dotted line indicates the EMD 57033 solubility limit in the medium.

EMD 57033. Fig. 2a shows that cogrinding EMD 57033 with lactose monohydrate, PVP or HPMC results in generation of supersaturated solutions, whereas cogrinding with SLS or simply micronising the drug does not. Whereas cogrinding with lactose monohydrate led to an unstable supersaturation, cogrinding of EMD 57033 with HPMC or PVP led to slower but more sustained (at least in vitro) supersaturation. Cogrinding with both polymer (HPMC or PVP) and lactose monohydrate appeared to result in an additive effect, increasing the dissolution rate (lactose) and sustaining supersaturation (polymer).

At the surface of a drug crystal, the concentration of drug results from a balance of dissolution of the solid drug and deposition of crystals from the surrounding solution. Presence of a polymer at the surface slows down the process of crystallization by slowing down diffusion of the drug molecules to the solid surface and by reducing the surface area available for nucleation on the particle surface. On the other hand, presence of a polymer at the dissolving surface restricts access of water molecules to the crystal surface [25–27], thus slowing dissolution. In the EMD 57033 dissolution studies, cogrinding with lactose monohydrate increased the rate of dissolution but the disaccharide could not prevent precipitation. The polymers, PVP and HPMC, were able to substantially decrease the rate of recrystallization but the diffusion barrier resulted in a lower rate of dissolution than observed for the lactose monohydrate cogrind.

Interestingly, cogrinding with SLS prevented supersaturation, even though the dissolution rate itself was increased. This finding was irrespective of the quantity of SLS coground (2–30% investigated, not all results shown) and the other excipients in the formulation (HPMC, PVP, lactose and combinations thereof, results not shown).

With respect to processing considerations, the homogeneity of the coground mixtures was extremely high. Cogrinding can thus be considered a suitable process to improve the content uniformity, especially for low dose formulations of high potency compounds. A decrease in air pressure during jet-milling (from 5 bar to either 3 or 2 bar) still resulted in a supersaturation of the respective formulations, but at a lower level (not shown).

The particle size distribution of the coground compound and its coground mixture was in most cases unchanged (see Table 3). The high $d(0.90)$ value measured for the HPMC coground product is attributable to the inability of the dry milling process to reduce the HPMC particle size and should not be interpreted as a change in the particle size of the active drug.

Table 3
Particle size distribution of EMD 57033, pure and in coground formulations

	$d(0.10)$ (μm)	$d(0.50)$ (μm)	$d(0.90)$ (μm)
EMD 57033, micronised	0.7	2.2	6.9
EMD 57033/lactose	0.6	2.9	7.5
EMD 57033/HPMC	0.8	4.4	45.0
EMD 57033/PVP	0.6	3.1	7.3
EMD 57033/SLS/lactose	0.7	2.1	4.6

Temporary supersaturation during dissolution experiments is often caused by generation of amorphous drug [17,28]. However, X-ray analysis indicated that EMD 57033 remained fully crystalline after processing (Fig. 3). Using DSC, the crystalline melting peak of EMD 57033 (onset approx. 155 °C) was overlapped by an exotherm from lactose monohydrate, thus a quantitative assessment of the extent of crystallinity of the drug was not possible with this technique (results not shown).

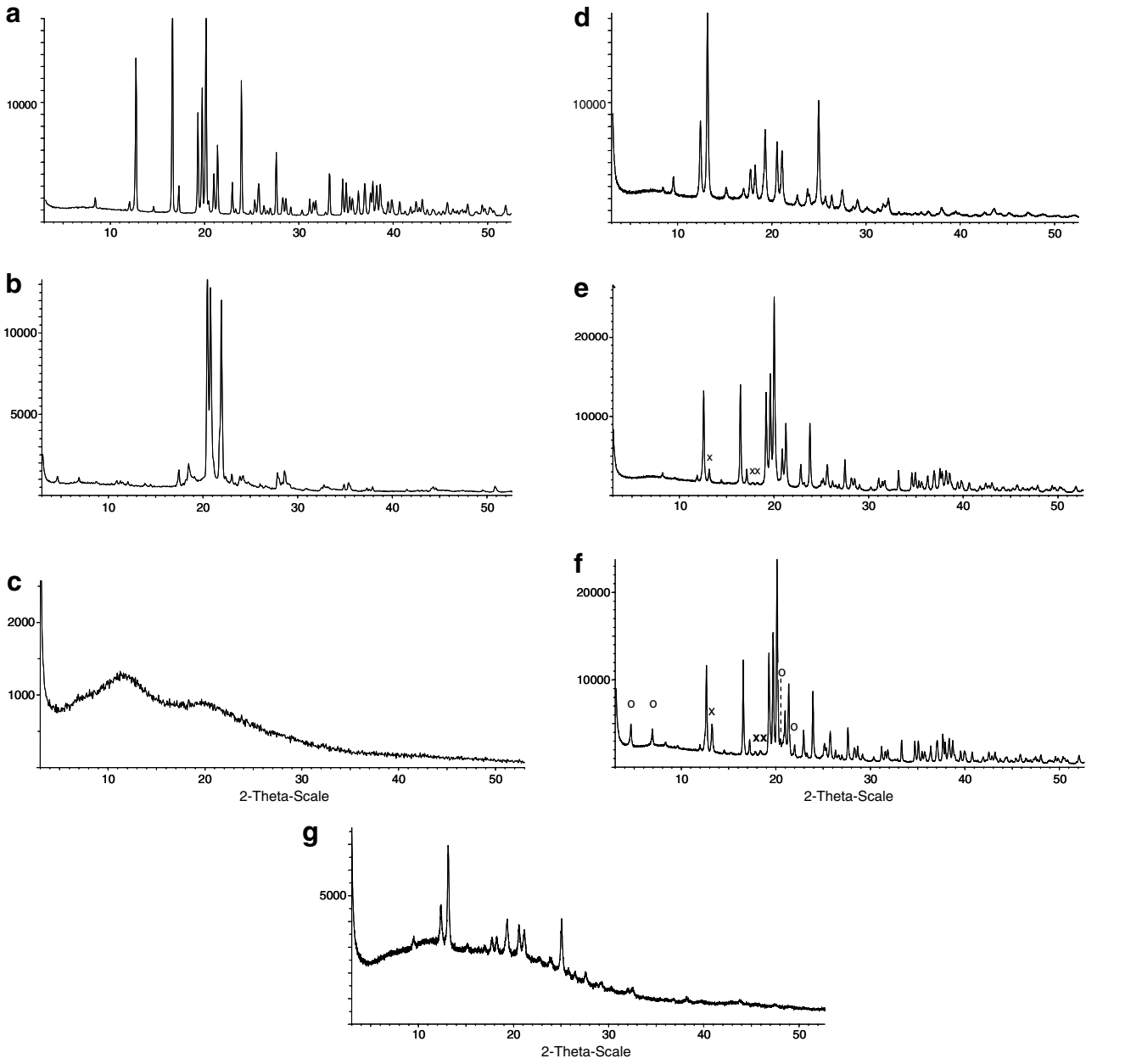

Fig. 3. X-ray analysis of pure lactose monohydrate (a), SLS (b), PVP (c), micronised EMD 57033 (d) and coground mixtures of the drug with lactose monohydrate (1:9, e), SLS and lactose monohydrate (1:1:8, f) and PVP (1:1, g). Crystalline peaks of the active in lactose monohydrate mixtures are marked by X, those of SLS by O.

3.3. Albendazole

The poorly soluble albendazole shows an aqueous solubility of 1.3 μg/ml at 37 °C. With a log *P* value of 2.7, the drug has a lipophilicity comparable to that of EMD 57033. The dissolution rate of albendazole is known to limit its absorption from the gastrointestinal tract. FaSSIF increases the solubility of albendazole by 60%, indicating modest solubilisation by bile salt micelles. Similar behaviour was observed in SLS solutions, but sink conditions cannot be expected at SLS concentrations below 1%. Amounts of powder blends and cogrinds corresponding to 9 mg albendazole were used for dissolution experiments, as this resulted in a dose:solubility ratio similar to that for 30 mg EMD 57033.

Fig. 4 compares the dissolution behaviour of several coground mixtures of albendazole with its micronised form in physical mixture in 0.25% SLS solution (in which albendazole solubility matches that in FaSSIF). The physical mixture of micronised albendazole with lactose dissolved slowly and failed to approach the solubility limit within the experimental period, while the coground mixtures reached maximum dissolution within 10 min. Despite the similarity in physicochemical properties of albendazole and EMD 57033, no supersaturation occurred.

The quantitative composition of the physical mixture and the corresponding coground mixture was identical and the particle size of pure albendazole ($d(0.90) \approx 3.2$ μm) was at least as small as in the coground mixtures (e.g. with lactose $d(0.90) \approx 6.7$ μm).

3.4. Danazol

With an aqueous solubility of 0.5 μg/ml (at 37 °C) and no groups ionisable within the physiological pH range, danazol can be considered to have poor and pH-independent solubility. The log *P* value of danazol was reported as 4.53 [29], much higher than that of EMD 57033 and albendazole. FaSSIF increases the solubility of danazol by a factor of 16, to 8 μg/ml, indicating that the lipophilic danazol is solubilised well in the bile salt/lecithin mixed micelles. Amounts of powder blends and cogrinds corresponding to 36 mg danazol were used for dissolution experiments, as this resulted in a dose:solubility ratio of 4.4 l, similar to that for 30 mg EMD 57033.

Fig. 5 compares selected cogrinds of danazol with the equivalent physical blends containing either unprocessed or milled drug in FaSSIF. The physical mixture of raw danazol (micronised grade, $d(0.90) \approx 8.6$ μm) with lactose monohydrate dissolved slowly. The dissolution rate was slightly enhanced after particle size reduction of danazol ($d(0.90) \approx 3.5$ μm). Cogrinds, by contrast, accelerated the dissolution. However, no supersaturation was observed. The superior dissolution rates of the cogrinds were not due to particle size reduction in the cogrinding process; the particle diameter ($d(0.90) \geqslant 5.8$ μm) was unchanged. X-ray analysis indicated that danazol remained fully crystalline after cogrinding (Fig. 6). Similar to EMD 57033, DSC results were inconclusive due to overlap of endotherms beyond 200 °C.

3.5. Felodipine

Felodipine is neutral and exhibits an aqueous solubility of approximately 1 μg/ml at 37 °C. With a log *P* value of 4.8 [30], the drug has a lipophilicity comparable to danazol. FaSSIF increases the solubility of felodipine by a factor of 52, indicating that the drug is solubilised well by mixed

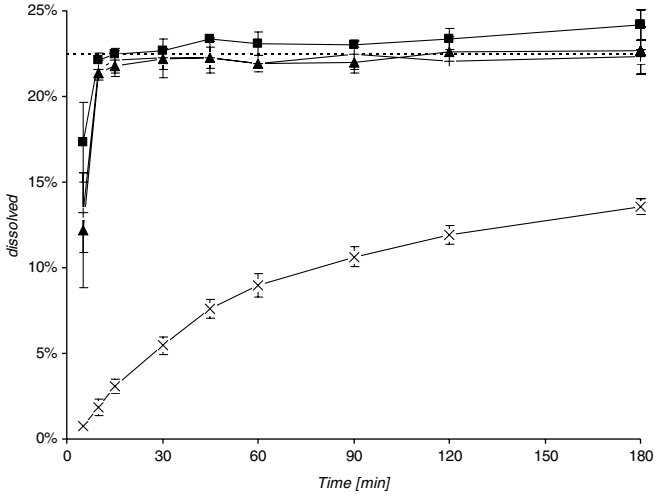

Fig. 4. Dissolution profiles of 9 mg albendazole in 0.25% SLS solution ($n = 3$, ±SD), micronised in physical mixture with lactose monohydrate (×) and in coground mixtures with lactose (■), PVP (▲) and SLS/lactose (1:8, +). The binary coground mixture with PVP (1:1) was physically blended with lactose monohydrate. Dotted line indicates the albendazole solubility limit in the medium.

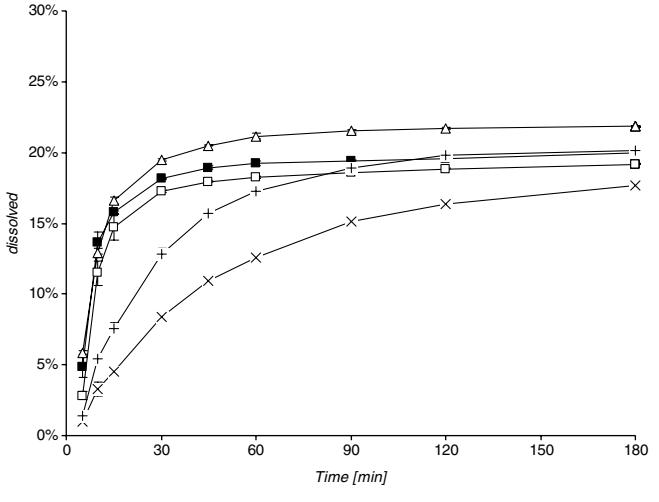

Fig. 5. Dissolution profiles of 36 mg danazol in FaSSIF ($n = 3$, ±SD). (×) indicates unprocessed danazol in physical mixture with lactose monohydrate. (+) indicates milled danazol in physical mixture with lactose monohydrate. (■) indicates a binary coground mixture with lactose monohydrate. (△) indicates a binary coground mixture with PVP (1:1), physically blended with lactose monohydrate. (□) indicates a tertiary coground mixture with corn starch/lactose monohydrate (2:7).

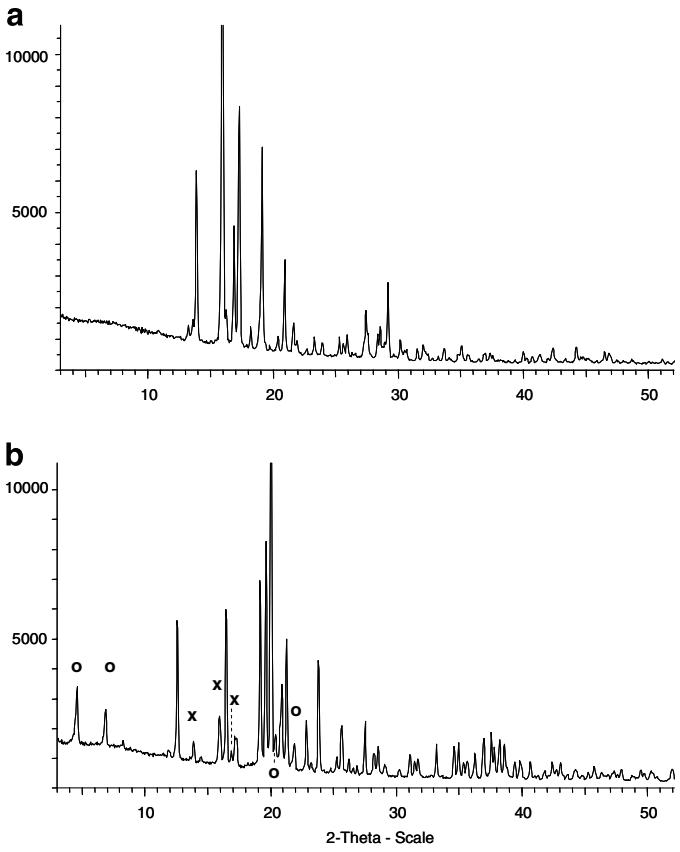

Fig. 6. X-ray analysis of milled danazol (a) and its coground mixture with SLS/lactose monohydrate (1:8, b). Crystalline peaks of the active are marked by X, those of SLS by O.

micelles. A similar dose:solubility ratio to 36 mg danazol can be achieved with 120 mg felodipine in a volume of 500 ml. However, clinically relevant doses of felodipine are much lower (e.g. 10 mg). In FaSSIF, the dose:solubility ratio is approximately 200 ml. Dissolution is therefore considered not to be limiting to absorption, provided micronised drug substance is used.

Fig. 7 compares the dissolution of micronised felodipine with several cogrinds of felodipine at levels corresponding to (a) the same dose:solubility ratio (approx. 4400 ml) as used for the other drugs investigated and (b) its clinical dose (10 mg). The physical mixture of the micronised form with lactose dissolved slowly and did not reach the saturation limit within 90 min, even using the 10 mg dose. These observations highlight the fact that rapid and complete dissolution of a poorly soluble drug cannot be assumed just because the dose:solubility ratio is low. The coground mixtures optimized the dissolution of both strengths resulting in complete dissolution after just 10 min and a slight supersaturation for some combinations, clearly demonstrating the advantages of a coground formulation in terms of overcoming the wetting problems of felodipine.

As with the other drugs studied, the quantitative composition of the physical mixture and the corresponding coground mixture was identical and the particle size was not reduced by cogrinding ($d_{90} \sim 2.6$ μm micronised vs.

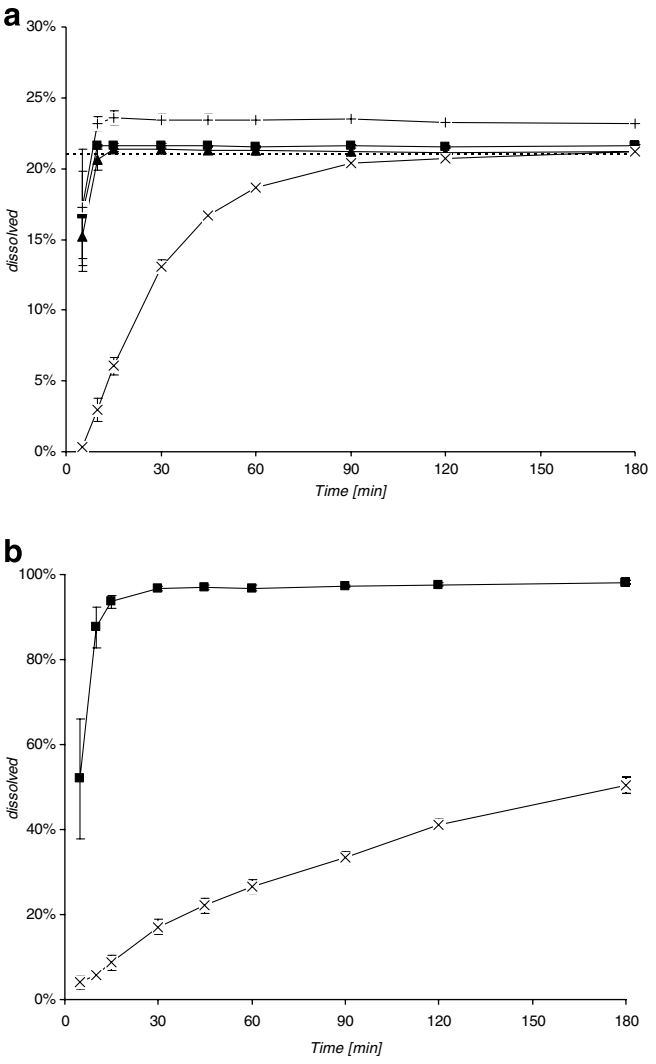

Fig. 7. Dissolution profiles of (a) 120 mg and (b) 10 mg felodipine in 500 ml FaSSIF ($n = 3$, ±SD). (×) indicates micronised active in physical mixture with lactose monohydrate. (■) indicates a binary coground mixture with lactose monohydrate. (▲) indicates a binary coground mixture with PVP (1:1), physically blended with lactose monohydrate. (+) indicates a tertiary coground mixture with SLS/lactose monohydrate (1:8). Dotted line (a) indicates the felodipine solubility limit in the medium.

e.g. 8.3 μm in lactose monohydrate cogrind). Further, cogrinding did not modify the crystalline structure of felodipine, as determined by X-ray analysis (results not shown).

3.6. General discussion

It was demonstrated for four drugs, all with a solubility of less than 5 μg/ml in water, that cogrinding in the dry state with commonly used excipients leads to pharmaceutical powder preparations with accelerated dissolution, while retaining substance crystallinity as well as excellent content uniformity. The effects appeared to be similar for drugs with log P values in the 2.5–4.5 range. Supersaturations occurred in some cases, but this appeared to be excipient and drug-dependent and no generalizations can be made with respect to supersaturation in terms of compound lipophilicity or sol-

ubility. The superior dissolution characteristics of coground mixtures, compared to micronising and then blending with excipients, were shown not to be caused by further reductions in particle size, nor is the drug converted into the amorphous state. Since drugs retained their crystalline form during cogrinding, the expectation is that the cogrind would be less susceptible than its amorphous counterparts to conversion of the physical form during storage.

4. Conclusion

Cogrinding is a powerful method to enhance the dissolution rate of poorly soluble drugs and in some cases can be used to produce supersaturated solutions. Bioavailability data in dogs for various formulations of EMD 57033, including the cogrinds that led to supersaturated solutions, will be published in a subsequent paper.

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