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Research paper

Adsorption of pharmaceutical excipients onto microcrystals of siramesine hydrochloride: Effects on physicochemical properties

Anne Zimmermann [a,*], Anna Millqvist-Fureby [b], Michiel Ringkjøbing Elema [c], Tue Hansen [c,1], Anette Müllertz [a], Lars Hovgaard [a,2]

[a] Department of Pharmaceutics and Analytical Chemistry, University of Copenhagen, Copenhagen Ø, Denmark
[b] YKI, Institute for Surface Chemistry, Stockholm, Sweden
[c] H. Lundbeck A/S, Pharmaceutical Development, Valby, Denmark

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ABSTRACT

A common challenge in the development of new drug substances is poor dissolution characteristics caused by low aqueous solubility. In this study, microcrystals with optimized physicochemical properties were prepared by precipitation in the presence of excipients, which adsorbed to the particle surface and altered particle size, morphology, and dissolution rate. The poorly water-soluble drug siramesine hydrochloride was precipitated by the antisolvent method in the presence of each of various polymeric and surface active excipients. Powder dissolution studies of six of the resulting particle systems showed a significant increase in percent dissolved after 15 min compared to the starting material.

A quantitative determination of the amount of excipient adsorbed to the surface of the drug particles proved that only a very small amount of excipient was needed to exert a marked effect on particle properties. The adsorbed amount of excipient constituted less than 1.4% (w/w) of the total particle weight, and thus powders of very high drug loads were obtained. Sodium lauryl sulphate (SLS), hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose (HPC), which exhibited the greatest degree of adsorption, also had the greatest effect on the physicochemical properties of the particles. X-ray Photoelectron Spectroscopy (XPS) analysis of the surface composition and scanning electron microscopy studies on particle morphology suggested that the excipients adsorbed to specific faces of the crystals.

1. Introduction

An increasing number of active pharmaceutical ingredients (APIs) suffer from poor water solubility, which is associated with poor dissolution characteristics. Dissolution rate in the gastro-intestinal tract is the rate limiting factor for the absorption of many of these drugs, which therefore suffer from poor oral bioavailability [1].

Pharmaceutical excipients can be used to produce formulations with enhanced dissolution rate of APIs, e.g., complexation with cyclodextrins, solid dispersions, and lipid formulations [2–4]. In recent years, increased attention has been given to particulate systems where excipients are adsorbed directly onto drug particles to produce powders with optimized physicochemical properties. Precipitation of a poorly water-soluble drug in the presence of excipients with affinity for the particle surface, leads to adsorption of these excipients to the drug surface during particle formation. The fact that the excipient interacts with the drug particle while it is formed offers the potential to greatly influence particle properties such as size, morphology, and wettability – properties which ultimately affect the dissolution rate [5].

Reducing the particle size offers a means of dissolution rate enhancement through an increase in the surface area available for dissolution [6,7]. The classical micronization technique is milling, but this technique may introduce undesired properties to the resulting powder. Breakage of crystals can give rise to disorder and defects on the crystal surface, which may influence the processing properties and the performance of a formulation. Depending on the energy input, amorphous regions may form, influencing the physical and chemical stability of the product [8,9].

Therefore, in recent years, a number of processes have been reported where micro – or nanonization has been achieved through precipitation of drugs in the presence of excipients. Utilizing this principle, particles are grown by association of molecules rather than breakage of crystals [10,11]. Particle size reduction is achieved because adsorption of excipients onto the particle surface

* Corresponding author. Faculty of Pharmaceutical Sciences, Department of Pharmaceutics and Analytical Chemistry, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen Ø, Denmark. Tel.: +45 35 33 63 66; fax: +45 35 33 60 30.
E-mail address: anz@farma.ku.dk (A. Zimmermann).
[1] Present address: Ferring Pharmaceuticals, Process Development and Maintenance, Saint-Prex, Switzerland.
[2] Present address: Novo Nordisk A/S, Preformulation and Delivery, Måløv, Denmark.

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inhibits particle growth [10,12]. Rasenack et al. prepared microcrystals by antisolvent precipitation, where a poorly water-soluble drug was dissolved in an organic solvent and precipitated by mixing with an aqueous antisolvent. They dissolved various excipients one at a time in the aqueous phase, and found that when excipients containing hydrophobic parts were present during precipitation, particle size could be reduced to around 1 μm [5,10]. Another precipitation process, evaporative precipitation into aqueous solution (EPAS), is capable of reducing the particle size to the nanometer size range. An organic drug solution is sprayed into an aqueous excipient solution to cause precipitation. However, particle size analysis by laser diffraction measured particle sizes in the micron range due to aggregation of primary particles. The crystallinity of particles produced by EPAS varies depending on the chosen conditions [13–15].

Crystal morphology may be altered by preferential adsorption of excipients onto specific faces of the growing crystal. Crystal morphology – or crystal habit – is determined by the slowest growing faces. Face specific adsorption alters the growth rates of the faces where adsorption takes place and thus changes the morphology of the crystal [12,16]. Modification of crystal habit can improve the dissolution rate by promoting growth of more hydrophilic faces, or inhibiting growth of more hydrophobic faces [17–19].

Powder wettability can be increased through adsorption of surface active excipients. The hydrophobic parts of the surface active molecules adsorb to the hydrophobic drug particle with the hydrophilic parts extending into the aqueous solution. In this way, the contact angle between the drug particles and the dissolution medium is reduced, and consequently the dissolution rate may be enhanced [5,15].

Thus it is clear that precipitation in the presence of excipients can have a positive effect on dissolution rate. There is, however, a need for further understanding of excipient adsorption, e.g., what is the level of adsorption needed to provide a pronounced effect on particle properties? In order to understand this, a quantitative determination of excipient adsorption should be carried out. This is not straight forward due to the lack of UV-absorbing chromophores of the most commonly employed excipients. Therefore many studies have concentrated on the effects of excipient adsorption, such as particle size, wettability, and dissolution rate, rather than on the amount of excipient adsorbed, or excipient coverage of the particle surface [5,11,13]. In studies where the degree of excipient adsorption has been estimated, it has been done indirectly by mass balance [14,15,20]. This requires that the adsorbed amount is larger than the limit of quantification of the analytical method employed to determine drug content, i.e., large enough to be excluded from experimental error. Studies, where amount of excipient adsorbed to drug particles prepared by antisolvent precipitation has been measured, have shown that the amount is very low; less than 2% w/w of the particle system [20,21]. This emphasizes the importance of determining the adsorbed amount directly to obtain accurate results.

The aim of this study was to investigate the effects of excipient adsorption on the physicochemical properties of microcrystals. The hydrochloride salt of the poorly water-soluble drug siramesine (Lu 28-179, HCl) was used as model compound (Fig. 1). Microcrystals were prepared by antisolvent precipitation by dissolving the drug in ethanol and precipitating by instantaneous mixing with an aqueous excipient solution. A series of polymeric excipients and surfactants of varying molecular size and hydrophobicity (Fig. 1) were applied and evaluated in terms of their effect on particle size, morphology, and dissolution rate of the formed particles. A further aim was to study the excipient adsorption in more detail. HPLC with evaporative light scattering detection was applied to quantify the degree of excipient adsorption directly. Furthermore, X-ray Photoelectron Spectroscopy (XPS) was used to investigate the chemical composition of the particle surface.

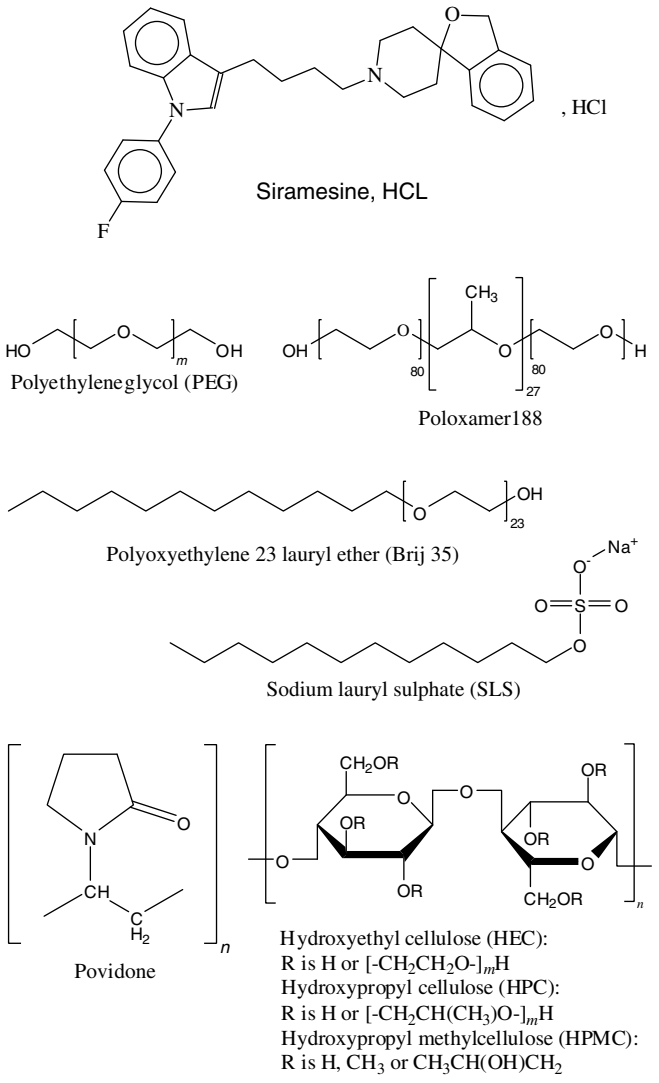

Fig. 1. Structure of siramesine hydrochloride and applied excipients.

2. Experimental

2.1. Materials

The active pharmaceutical ingredient was the hydrochloride salt of the compound 1′-[4-[1-(4-fluorophenyl)-1-H-indol-3-yl]-1-butyl]spiro[iso-benzofuran-1(3H), 4′ piperidine] (siramesine, molecular weight 491.06 g/mol, solubility of the hydrochloride salt in water 150 μg/ml, solubility of the hydrochloride salt in 96% ethanol 24 mg/ml, pK_a ~9, log$P$ ~8.5). The drug was supplied by H. Lundbeck A/S, Denmark. The excipients were hydroxypropyl methylcellulose (HPMC; Metolose® 90 SH 4000 SR and Metolose® 90 SH 100,000 SR, Shin Etsu, Japan), hydroxyethyl celloluse (HEC; Natrosol® Pharm G, Aqualon, France), hydroxypropyl cellulose (HPC; Klucel® LF Pharm and Klucel® MF Pharm, Aqualon, France), poloxamer 188 (Lutrol® F68, BASF, Germany), polyethyleneglycol (PEG; Macrogolum 6000, Unikem, Denmark), povidone K-30 (PVP; ISP Technologies, USA), sodium lauryl sulphate (SLS; Unikem, Denmark), polyoxyethylene 23 lauryl ether (Brij 35, Sigma Chemical Co. USA). Two types of the polymers HPMC and HPC were applied;

HPMC 4000 cP and 100,000 cP (viscosities of the polymers in 2% (w/w) aqueous solutions) and HPC molecular weight 95,000 and 850,000. HPLC grade acetonitrile and ammonium formate were obtained from Sigma–Aldrich (Germany), and deionized reagent water was prepared by a water purification system (Holm & Halby, Denmark). Potassium dihydrogen phosphate and di-sodium hydrogen phosphate were obtained from Merck KgaA (Germany), and Tween® 80 was obtained from Merck Schuchadt OHG (Germany).

2.2. Crystal formation by antisolvent precipitation

Microcrystals were prepared by antisolvent precipitation (Fig. 2). Siramesine hydrochloride was dissolved in ethanol (1% w/v, 50 ml) and mixed rapidly under stirring conditions with an aqueous solution containing an excipient (0.025% w/v, 200 ml). Experiments were carried out at room temperature. The mixing ratio between solvent and antisolvent of 1 + 4 was determined from the solubility of siramesine hydrochloride in ethanol:water mixtures to create maximum supersaturation. The particle size distribution of the resulting suspension was followed over 60 min, during which time the particles reached their equilibrium size. The particles were isolated by vacuum filtration followed by three consecutive washings with 10 ml of cold water to remove any non-adsorbed excipient. Following isolation, the particles were dried over anhydrous silica in a dessicator. Various excipients were tested and compared to a reference where purified water was used. Each experiment was performed in triplicate.

2.3. Particle characterization

2.3.1. Particle size

During precipitation and crystal growth, the particle size of the resulting suspension was followed by laser diffraction (Malvern Mastersizer S, Malvern, UK). 80 ml of dispersion medium (20% ethanol) was placed in the small volume sample preparation unit, and suspension was added to an obscuration between 10% and 30%. Measurements were performed at times 2, 7, 15, 30, 45, and 60 min following initial mixing of solvent and antisolvent.

2.3.2. Scanning electron microscopy (SEM)

Micrographs were taken using a Philips XL30 scanning electron microscope (FEI Europe, Eindhoven, Netherlands). Samples were mounted on aluminium stubs with double adhesive carbon tape and coated with gold/palladium at 15 mA for 120 s in a nitrogen atmosphere (Polaron SC7640 sputter coater, Newhaven, UK).

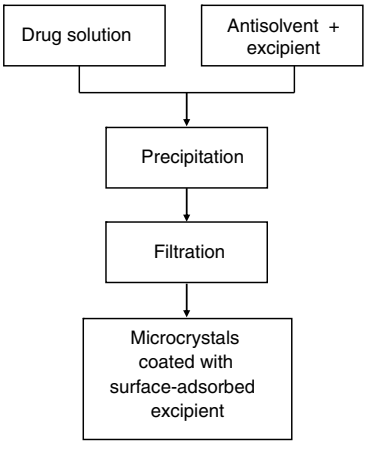

Fig. 2. Flow chart of the antisolvent precipitation procedure.

2.3.3. X-ray powder diffraction (XRPD)

X-ray powder diffractograms were measured on a PANalytical X'Pert PRO X-Ray Diffractometer (Netherlands) using $CuK_{\alpha 1}$ radiation with a wavelength of 1.5406 Å. The voltage and current were 45 kV and 40 mA respectively. Samples were measured in reflection mode in the 2θ-range 5°–40° using an X'celerator detector; the resolution was 0.0334 °2θ. Data were collected using X'Pert Data Collector and viewed using X'Pert Data Viewer (PANalytical B.V., The Netherlands).

2.3.4. Quantification of surface adsorption

The amount of excipient adsorbed to the surface of the microcrystals was determined by size exclusion chromatography with evaporative light scattering detection (ELSD) as described by Zimmermann et al. [22].

2.3.5. Analysis of surface composition

X-ray Photoelectron Spectroscopy (XPS), also known as Electron Spectroscopy for Chemical Analysis (ESCA), was used to probe the elemental composition of the powder surfaces with an analysis depth of less than 100 Å. The XPS measurements were performed with an AXIS HS photoelectron spectrometer (Kratos Analytical, UK). The instrument uses a monochromatic Al Kα X-ray source. The pressure in the vacuum chamber during analysis was less than 10^{-7} Torr. In the present investigation, a take-off angle of the photoelectrons perpendicular to the sample holder was used throughout. The area analysed consisted of a region <1 mm^2, and three measurements were made for each sample. The patch model was used for data evaluation, which assumes that all components are present in patches that are thicker than the depth of analysis (≈5 nm for these powders). The surface composition in terms of molecular species is calculated, assuming that the surface composition is a linear combination of the different molecular species, as described in detail by Fäldt et al. [23]. In addition, samples containing SLS were analysed using a layer model.

2.3.6. Powder dissolution

Dissolution studies were performed according to the USP paddle method in phosphate buffer (0.05 M; pH 6.4) containing 0.25% (v/v) Tween 80 using a VanKel 7000 apparatus (VanKel Industries Inc, Edison, NJ, USA). All samples were analysed in triplicate. The sample size was 20 mg, dissolution volume 900 ml, and stirring speed 100 rpm. The temperature was maintained at 37 °C. The amount of drug dissolved was determined spectrophotometrically at 258 nm (Varian Cary 50 BioUV-Visible). Data acquisition was performed using Cary WinUV software. Statistic evaluation of results was performed in Statistica; one way ANOVA and Duncan's test were applied to test for significant differences in percent dissolved after 15 min.

3. Results and discussion

3.1. Particle size

Following mixing of the drug solution with the antisolvent solution, the particle size of the formed suspension was followed using laser diffraction. All particle systems reached equilibrium size within 30 min. Table 1 shows particle median diameters of the prepared crystal measured at 60 min immediately before the crystals were isolated. Fig. 3 shows SEM micrographs of siramesine hydrochloride starting material and prepared microparticles. Even when pure water was used as antisolvent (Fig. 3b), particles of reduced size compared to the starting material were formed. This can be explained in terms of the high degree of supersaturation created upon mixing of solvent and antisolvent, which results in the formation of a large number of small primary particles.

Table 1
Median particle diameters of microcrystals prepared in the presence of excipients

Excipient	Median particle diameter (μm)
HPC LF	5 ± 1.0
HPMC 4000	7 ± 0.5
HPMC 100.000	8 ± 0.9
HPC MF	8 ± 1.2
PVP	10 ± 1.5
HEC G	10 ± 0.6
Brij 35	16 ± 8.0
Poloxamer	17 ± 7.2
No excipient	**57 ± 4.7**
PEG	70 ± 8.7
SLS	147 ± 28.5

The presence of excipients in the antisolvent was able to markedly reduce the particle size of the formed crystals due to inhibition of crystal growth. Like all crystallization processes, precipitation consists of three basic steps – supersaturation, nucleation and growth. Nucleation involves the diffusion of molecules through the bulk of the solution, collision with each other, and formation of nuclei of a critical size [24]. Once the critical size is reached, crystal growth can take place either by condensation, where molecules diffuse to the crystal surface and become incorporated into the solid phase, or by aggregation of crystals [11]. Adsorption of polymeric excipients and surfactants to the surface of the newly formed crystals can hinder aggregation of crystals through steric or electrostatic stabilization of the formed suspension [5,25,26]. This effect is predominant when the crystals are less than one micrometer in size [27]. Excipient adsorption also affects growth by condensation by blocking the sites for incorporation of new growth units. Thus, crystal growth is inhibited and consequently crystals of reduced size are formed [24,28].

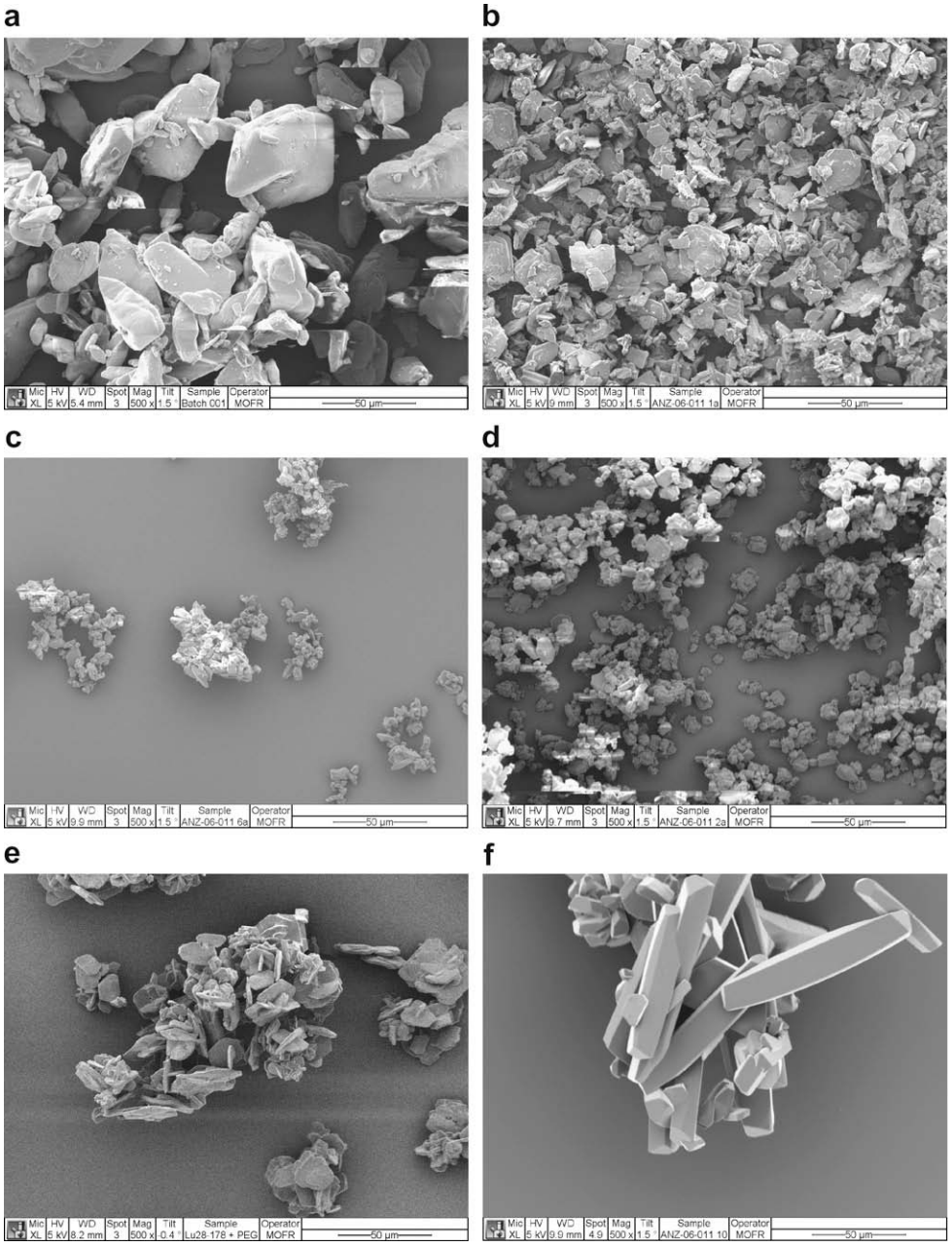

Fig. 3. SEM micropgraphs of siramesine hydrochloride starting material (a) and particles prepared by antisolvent precipitation in the presence of (b) pure water, (c) HPC MW 95,000, (d) HPMC 4000 cP, (e) PEG, and (f) SLS.

The excipients which most effectively reduced particle size were the cellulose polymers HPC (Fig. 3c) and HPMC (Fig. 3d). The smallest particles with a median diameter (D(v, 0.5)) of 5 μm were formed when HPC MW 95,000 was present during precipitation. The polymers HEC, poloxamer, PVP, and Brij reduced the size, but not as effectively as HPC and HPMC. When PEG (Fig. 3e) was present, particle size was not reduced compared to precipitation with pure water. In a study on the effect of excipient adsorption on the size of ibuprofen crystals, Rasenack et al. found that HPMC, methylhydroxyethyl cellulose (MHEC) and polyvinyl alcohol (PVA) most effectively inhibited crystal growth. They concluded that the affinity of the excipient to the newly formed crystal surface was decisive, and that particle size decreased with increasing hydrophobicity of the excipient [5]. These findings are in agreement with the results presented here. HPC and HPMC contain hydrophobic substituents, which have affinity for the hydrophobic drug particles, whereas PEG is more hydrophilic, and thus should not adsorb to the hydrophobic particle surface. HEC, poloxamer, PVP, and Brij take an intermediate position.

With SLS present in the antisolvent (Fig. 3f), crystal growth seemed to be enhanced rather than inhibited. SLS is a small molecule compared to the polymeric excipients applied in this study. Therefore, a possible explanation is that SLS adsorbs to the surface and acts as an impurity, which enhances surface nucleation and hence increases the growth rate of the crystals [29]. For SLS the particle size determined by laser diffraction is greater than the size observed from SEM. This might be due to aggregation of crystals during the laser diffraction measurement.

3.2. Morphology

As evident from Fig. 3 the morphology of the crystals varied greatly. XRPD analysis revealed that the prepared crystals were not isomorphous with the starting material, as the drug transformed into a monohydrate during the precipitation process. The water molecule was incorporated into the crystal structure through hydrogen bonding with chloride. All of the prepared crystals were, however, isomorphous with each other, enabling a comparison of the effect of excipient adsorption on particle morphology. When pure water was used as antisolvent, crystals of irregular shapes were formed. This was also the case when PEG was present in the antisolvent. All other excipients formed more regularly shaped crystals. As was also the case with particle size, the excipients which exhibited the greatest effect on morphology were HPC, HPMC, and SLS. Adsorption of HPC resulted in prism-shaped crystals, whereas adsorption of HPMC gave rise to plate-shaped crystals (Fig. 4). The difference between the prisms and the plates seems to be only two-dimensional, indicating that the adsorption patterns for HPC and HPMC are similar. Large, needle-shaped crystals were formed when SLS was present in the antisolvent. These observations indicate that HPC, HPMC, and SLS interact differently with the growing crystal surface. The drug molecule is very hydrophobic, and therefore interactions between the crystal surface and the excipients are most likely explained by hydrophobic interactions. HPC, HPMC, and SLS all contain hydrophobic moieties, which can adsorb to the crystal surface. As suggested in Fig. 5, it is likely that they adsorb to the same faces of the crystals, but influence growth rate through different mechanisms. HPC and HPMC inhibit growth, and consequently the morphology is dominated by the faces which the polymers adsorb to. SLS enhances growth as described above, and therefore the face of SLS adsorption disappears, giving rise to the needle-shaped morphology. The cross section of the needles is hexagonal, although not as symmetric as the large planar surfaces of the plates formed in the presence of HPMC. Evidence that surface adsorption of excipients is face specific was provided earlier by studies of poloxamer adsorption onto polystyrene spheres. XPS and time-of-flight secondary ion mass spectrometry (ToF SIMS) indicated that multiple layers were formed in localized areas, while in other areas bare patches of particle surface were exposed [30,31].

3.3. Excipient adsorption

Table 2 shows the degree of adsorption of excipients onto the formed microcrystals. In the crystallization medium the drug-to-

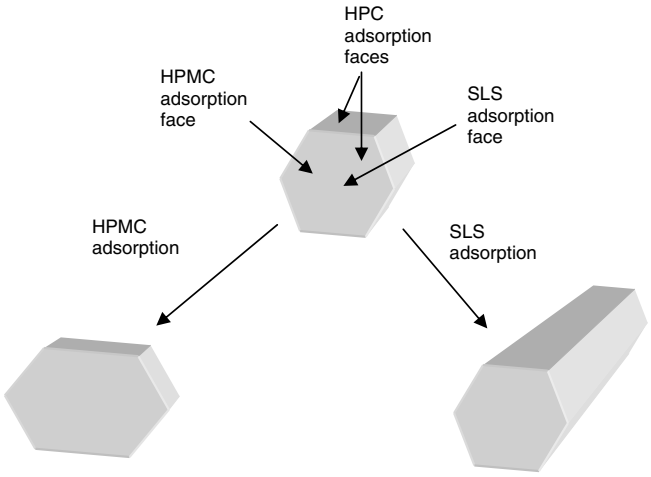

Fig. 5. Face specific adsorption of excipients onto drug particles.

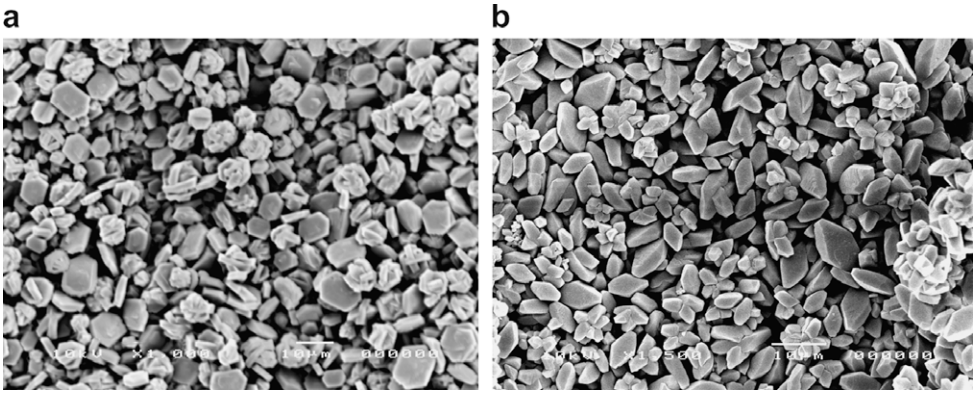

Fig. 4. Morphology of microcrystals precipitated in the presence of (a) HPMC 4000 cP and (b) HPC MW 850,000.

Table 2
Molecular weight of excipients and degree of excipient adsorption onto microcrystals

Excipient	Molecular weight	Excipient content of microcrystals (% w/w)
Poloxamer 188	8000	0.07
PEG	6000	None detectable
Brij 35	1200	0.09
HEC	300,000	0.11
HPMC 4000 cP	[a]	1.02
HPMC 100,000 cP	[a]	1.03
HPC MW 95,000	95,000	0.52
HPC MW 850,000	850,000	0.68
SLS	288	1.39
PVP K30	40,000	NA

[a] The molecular weights of the HPMCs were not given by the supplier. The viscosities of the polymers in 2% (w/w) aqueous solutions were 4000 cP and 100,000 cP.

excipient ratio was 10:1, and thus the excipients constituted 9% of the total solids' concentration. Following isolation, the excipients constituted 1.39% or less of the resulting particle systems, which means that only about 1–10% of the excipient present during precipitation adsorbed to the particles. The particles were isolated after 60 min, and therefore the measured values are not equilibrium adsorption values.

SLS exhibited the largest degree of surface adsorption, constituting 1.39% (w/w) of drug particles formed in its presence. Adsorption of SLS may be explained either by hydrophobic interactions between the alkyl chain and the particle surface or in terms of electrostatic interactions. HPMC and HPC also exhibited a high degree of adsorption compared to the other excipients with 1.02 and 1.03% (w/w) for HPMC 4000 cP and HPMC 100,000 cP and 0.52 and 0.68% (w/w) for HPC MW 95,000 and HPC MW 850,000 respectively. Precipitation in the presence of HPMC, HPC, and SLS had the greatest impact on particle size and morphology, and thus it can be concluded that the greater the excipient adsorption, the greater the influence on physicochemical properties of the formed crystals. These findings are in agreement with previous work by Lechuga–Ballesteros et al. who concluded that the effect of additives on growth kinetics of L-alanine crystals could be explained by assuming that the growth rate inhibition was proportional to the degree of coverage of the additive molecules onto the crystal surface [16].

Daniels and Barta studied adsorption of polymers on hydrophobic silicon dioxide. They found that equilibrium adsorption values increased with increasing hydrophobicity of the polymers [32]. In the study presented here, excipients containing hydrophobic parts adsorbed to the greatest degree, whereas none of the hydrophilic polymer PEG could be detected. For the cellulose polymers, the more hydrophilic HEC did not adsorb to the same extent as HPC and HPMC. The presence of an extra hydrophobic group in HPMC compared to HPC seemed to increase adsorption. Tian et al. studied the influence of various excipients on growth of carbamazepine dihydrate crystals from anhydrous carbamazepine. The solubility parameter was used to describe the hydrophobicity of the excipients. HEC, which had the highest solubility parameter, did not inhibit crystal growth to the same extent as HPMC and HPC, which had lower solubility parameters. Of all tested polymers, HPMC most effectively inhibited growth of dihydrate crystals [33].

Adsorption of poloxamer and Brij were 0.07% and 0.09% (w/w) respectively, which is in a range similar to adsorption of HEC. Poloxamer is a nonionic block copolymer of polyoxyethylene–polyoxypropylene–polyoxyethylene (PEO–PPO–PEO). The suggested mechanism of adsorption is adsorption of the hydrophobic PPO part onto the particle surface with the PEO chains extending into the solution [31]. The reason for the relatively low adsorption observed in this study compared to cellulose polymers and SLS, could be that the methyl groups of the PPO chain do not render the chain sufficiently hydrophobic to adsorb to the very hydrophobic particle surface. Similarly, Brij contains a PEO chain which may prevent its adsorption, despite the fact that Brij has an alkyl chain comparable to that of SLS. The adsorption of PVP was not measured. However, the effect on size and morphology was similar to the effects observed for HEC, poloxamer, and Brij, and therefore it can be assumed that it adsorbed to a similar extent.

For all particle systems the excipient adsorption was less than 1.4% (w/w). Thus, powders of a very high drug load were obtained, which is desirable for safety reasons and also from a formulation point of view.

3.4. Surface composition

XPS was carried out for samples containing excipients which greatly altered size and morphology of crystals, as well as the dissolution properties. The XPS analysis provides the elemental surface composition in a surface layer of 2–10 nm, depending on the material properties. For organic materials, the depth of analysis is typically 5 nm, and the signal decays exponentially with increasing depth. The elemental surface composition of raw materials and prepared crystals is presented in Table 3. These data show that polymer was adsorbed to the surface of the particles, identified as an increase in oxygen coverage and decrease in N, F, and Cl. Three points were analysed for each sample, and the deviation between points varied substantially for samples containing HEC and HPC (up to 5%), which indicates inhomogeneity in these samples. All other samples had a low standard deviation, 0.1–0.4%, which is in the normal range for powder analyses. The patch model [23] was applied to analyse the data in terms of molecular surface compositions, and these data are presented in Table 4. The patch model was chosen, since it is unlikely that the polymers would adsorb in very thin layers (<5 nm in thickness), and a 'loop and tail' organi-

Table 3
Atomic surface composition of powders as determined by XPS

Sample	Surface coverage (atom%)						
	C	O	N	F	Cl	S	Na
HEC	63.9	35.1					
HPMC 4000 cP	61.9	38.1					
HPC MW 95,000	64	36					
SLS (theoretical)	66.7	22.2				5.6	5.5
Drug substance	87.6	3.2	5.3	3.0	0.9		
Drug + HPMC 4000 cP	77.3	17.1	3.3	1.4	0.9		
Drug + HPMC 100,000 cP	77.9	16.3	3.3	1.7	0.8		
Drug + HEC	84.9	5.0	6.1	3.1	0.8		
Drug + HPC, 95,000	79.3	13.0	4.1	2.3	1.3		
Drug + HPC, 850,000	78.9	15.2	3.3	1.8	0.8		
Drug + SLS	85.2	6.6	4.4	2.4	0.7	0.7	n.d.

Table 4
Molecular surface composition of microcrystals, calculated from atomic surface compositions presented in Table 3

Sample	Surface coverage (%)	
	Drug	Additive
Drug + HPMC 4,000 cP	60	40
Drug + HPMC 100,000 cP	62	38
Drug + HEC	95	5
Drug + HPC, 95,000	70	30
Drug + HPC, 850,000	64	36
Drug + SLS	84	16

zation of the adsorbed layer is more likely to occur. However, the situation is different for SLS, which may adsorb as a well organised monolayer or multilayer structure.

The surface composition data (Table 4) were correlated with data for the excipient content in the prepared crystals (Table 2), and it was found that the polymers clearly adsorb to the surfaces, since the surface coverage is considerably higher than the overall polymer content. Further, the polymers do not cover the entire particle surfaces, indicating that adsorption may be face specific as discussed previously. When comparing adsorbed amounts with XPS data, we also find that SLS provides the highest adsorbed amount, but the lowest surface coverage. This apparent contradiction may be explained by SLS being adsorbed on a large surface in thin layers (about 2 nm thick), leading to an XPS signal that is composed of the outermost SLS layer and the underlying drug crystal. When the SLS coverage is calculated according to the layer model [34], i.e., assuming a pure SLS layer covering pure drug substance, a theoretical layer thickness of 0.6 nm is obtained. Since this value is smaller than the length of the SLS molecule, a complete monolayer is obviously not present. A patchy monolayer structure may be assumed, and then the monolayer coverage is about 30%. Considering the shape of the SLS-drug particles (Fig. 3f), this indicates that the long crystal faces are not completely covered by SLS. XPS has been used to study the surface composition of other crystals prepared with poloxamer 188 [31], and it was found that poloxamer adsorbed inhomogeneously, in thin layers as well as in multilayers. The present XPS data are not conclusive on the localisation of the polymers and surfactant, but a patch wise distribution of varying thickness appears likely. To study the adsorption in further detail, adsorption of excipients onto each face of single crystals of the drug could be performed by XPS. This is however, beyond the scope of this study.

3.5. Powder dissolution

Dissolution of particles prepared by antisolvent precipitation compared to the starting material is shown in Fig. 6. Simultaneously with the dissolution of drug particles in the dissolution vessels, some of the dissolved drug precipitated as the free base. The aqueous solubility of the free base is extremely low, and thus the dissolved amount did not reach 100% in all vessels. In terms of bioavailability, initial dissolution rate is of great importance. Therefore, the following discussion will be based on percent dissolved after 15 min (Fig. 7). One way ANOVA showed a significant difference in percent dissolved after 15 min between the samples, and Duncan's test proved that percent dissolved from the starting material was significantly different from percent dissolved from particles prepared by precipitation. The increased dissolution rate observed for particles precipitated from pure water could be attributed to an increase in surface area as a result of particle size reduction and irregular shape. In spite of the fact that particles prepared in the presence of SLS were larger compared to the other particle systems, they exhibited the highest dissolution rate. SLS adsorbed to the drug particles to the greatest extent, and since SLS is an anionic surfactant, the wettability of the particles may be markedly increased. Previous studies have shown that surface adsorption of surface active molecules decrease the contact angle between particles and the dissolution medium [5,11,13]. Particles prepared in the presence of HPMC and HPC also showed increased dissolution rate compared to the starting material, but not to the same extent as particles prepared in the presence of SLS, even though the particle sizes were smaller. This may be due to the fact that the surfactant properties of HPMC and HPC are not as pronounced as in the case of SLS.

The crystalline state of the drug was changed from anhydrate to monohydrate during precipitation. The influence of the solid state

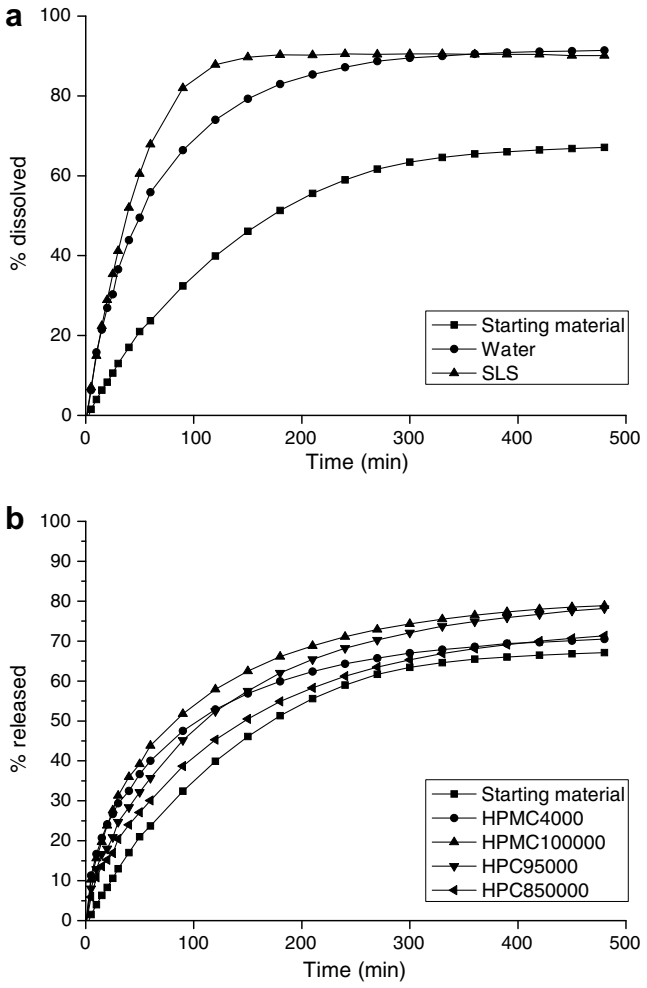

Fig. 6. Powder dissolution. Error bars are removed for clarity.

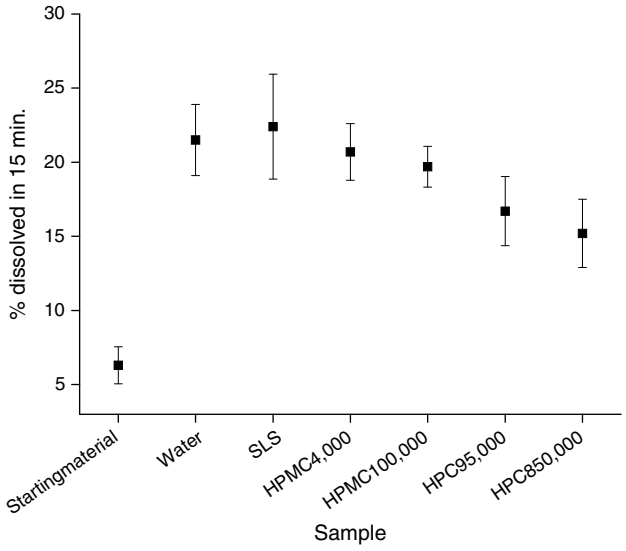

Fig. 7. Powder dissolution. % dissolved after 15 min.

on physicochemical properties e.g., solubility and dissolution rate of siramesine hydrochloride is under investigation and will be reported in a later paper.

4. Conclusion

Adsorption of pharmaceutical excipients onto the surface of drug particles markedly altered the size and morphology of the resulting particle systems. The effects of reduced particle size and increased wettability provided particles with significantly enhanced dissolution rate compared to the starting material. The excipients, which most effectively altered the physicochemical properties, were the ones which exhibited the greatest affinity for the surface of the drug particles e.g., HPC, HPMC, and SLS.

Applying a quantitative determination of the amount of excipient adsorbed onto the particles in combination with XPS provided a deeper understanding of the adsorption phenomenon. It was found that only a very small amount of excipient – less than 1.4% w/w – was sufficient to exert a pronounced effect on the physicochemical properties of the particles. Thus, the use of excipients to optimize particle properties does not compromise the drug load of the resulting powder. The studies on particle size and morphology suggested that the excipients adsorb to specific faces of the crystals. This was supported by surface analysis by XPS, which showed that the excipient coverage of the particle surfaces was incomplete.

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