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Research paper

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

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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

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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.

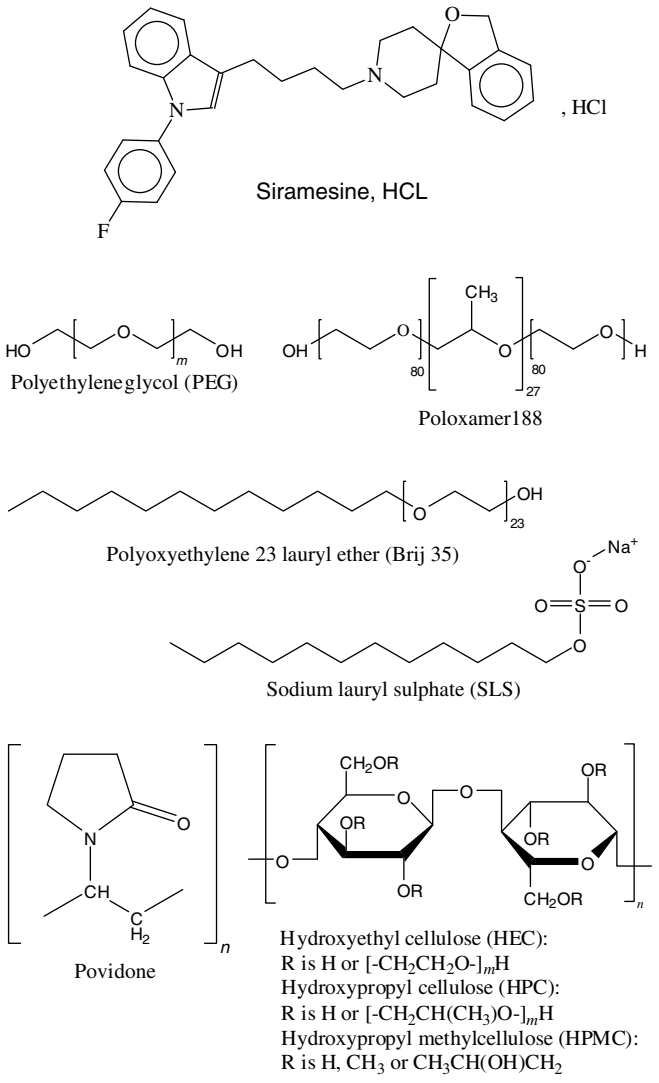


**Fig. 1.** Structure of siramesine hydrochloride and applied excipients.

## 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, p$K_a$ ~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;