Crystalline microparticles prepared by precipitation in the presence of stabilizing excipients

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Objectives

An increasing number of newly discovered drug substances suffer from poor aqueous solubility, which is associated to poor dissolution characteristics and thus poor oral bioavailability. One approach to overcome this problem is to alter the surface characteristics of these drugs e.g. by altering the size and morphology of API particles. In this study microparticles were prepared by precipitation in the presence of stabilizing excipients, and the effect of the added excipients on the particle size, morphology and dissolution rate was investigated.

Methods

Precipitation procedure

Microparticles were prepared by anti solvent precipitation. A poorly water soluble drug was dissolved in ethanol (1% w/v, 50 ml) and mixed rapidly under stirring conditions with an aqueous solution containing a stabilizing excipient (0.025% w/v, 200 ml). 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 then isolated by filtration and washed three times with cold water to remove any non-adsorbed excipient. Hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC), viscosity in 2% w/w aqueous solutions 10^3 and 10^{-3} P respectively, were tested and compared to a reference where purified water was used. Figure 1 shows a flow chart of the procedure.

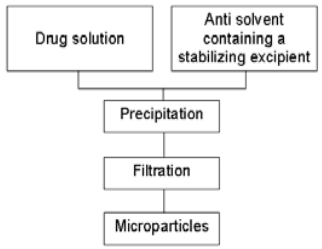

Figure 1. Flow chart of the precipitation procedure.

Particle characterization

Particle size:
The particle size distribution of the microparticles in suspension was measured by laser diffraction employing a Malvern Mastersizer S equipped with a small volume sample preparation unit. A 20% v/v aqueous ethanol solution was used as dispersion medium, and the suspension was added drop wise to the medium to an optical concentration between 10 and 30%.

Morphology:
The particle morphology was investigated by scanning electron microscopy (SEM). Samples were coated with a layer of gold/palladium before use.

Quantitative determination of surface adsorbed excipients:
The amount of excipient adsorbed to the surface of the drug particles was determined by HPLC-ELSD (evaporative light scattering detection). The excipient was separated from the drug using a mixed mode column (Shodex Asahipak GS-320HQ) and a mobile phase of acetonitrile:ammonium formate (20mM) (50:50 v/v). The detector was a PL-ELS 2100 from Polymer Laboratories.

Crystallinity:
The crystallinty of the microparticles was assessed by powder x-ray diffraction (X'Pert PRO, PANalytical).

Powder dissolution:
Dissolution characteristics were evaluated by the USP Apparatus II (paddle method), 100 rpm, 37ºC using spectrophotometric detection at 258 nm (VanKel Industries Inc., Edison, NJ USA). The microparticles were compared with physical mixtures of particles micronized by jet milling (2 µm, D(v, 0.5)) mixed with HPMC and HPC to achieve the same w/w concentrations as those determined for the precipitated microparticles.

Results

Particle size

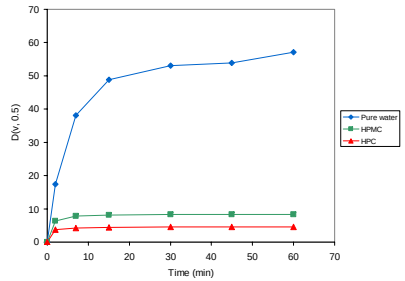

Figure 2. Particle median diameters (D(v, 0.5)) of the precipitated drug particles as a function of time.

When pure water was used as anti solvent the particles grew to a size (D(v, 0.5)) of 57 µm (figure 2). A lowering of D(v, 0.5) was achieved with both HPMC and HPC with D(v, 0.5)s of 8.3 and 4.5 µm respectively.

Excipient adsorption on drug particles

Table 1. Surface adsorption of stabilizing excipients on drug particles calculated as a weight percentage of the total product

Excipient	Adsorbed amount (% w/w)
HPMC	1.02
HPC	0.52

During precipitation and particle growth the amount of stabilizing excipient present was 10 % (w/w) of the total solids concentration. Following filtration and washing 10 % or less og this remained adsorbed on to the surface of the drug particles (table 1).

Morphology

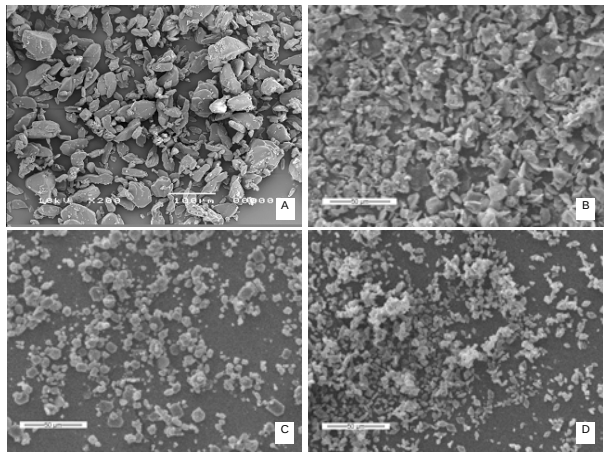

Figure 3. SEM micrographs of original material (A) and particles precipitated in the presence of different excipients. Antisolvent compositions: B. Pure water, C. HPMC, D. HPC.

As illustrated in figure 3, the composition of the anti solvent solution greatly influenced the morphology of the particles. As evidenced by table 1 adsorption of the excipients to the particle surfaces take place. The excipients may adsorb to different faces of the crystals to inhibit or facilitate growth in different directions. Adding HPMC to the antisolvent (C) resulted in more well defined platelet shaped particles compared to particles precipitated from pure water (B), whereas the presence of HPC resulted in diamond shaped particles (D). Examination by powder x-ray diffraction proved that the original crystal structure of the drug was retained in the products.

Dissolution

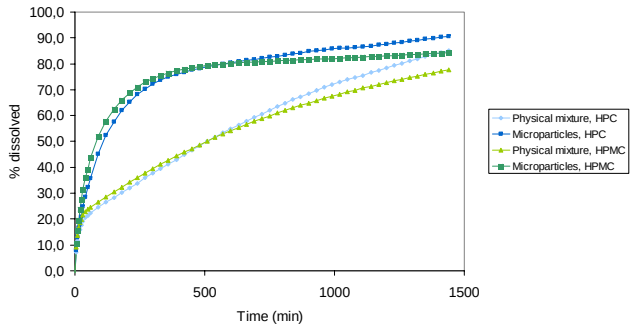

Figure 4. Dissolution profiles of microparticles prepared by precipitation compared to particles micronized by jet milling.

Microparticles prepared by precipitation exhibited superior dissolution characteristics compared to particles micronized by jet milling. Both techniques increase the surface area of the drug and thus the area available for dissolution. In addition precipitation in the presence of surface active excipients provides a hydrophillic coating, which increases the dissolution rate through an increase in wettability. Hence, the dissolution properties of particles prepared by precipitation were improved compared to jet milled particles, even though the jet milled particles were the smallest in size.
Since the excipients are only present at the surface of the particles, a marked effect is observed even at a very low excipient:drug ratio, the drug loads being 99.0 and 99.5 for particles produced in the presence of HPMC and HPC respectively.

Conclusion

Precipitation in the presence of stabilizing excipients greatly altered the particle size distribution and morphology of the drug. Platelet shaped particles of 8.3 µm (D(v, 0.5)) were the result of precipitation in the presence of HPMC, whereas the presence of HPC resulted in diamond shaped particles with a D(v, 0.5) of 4.5 µm. Control particles precipitated from pure water were 57 µm in size. The dissolution profiles of microparticles prepared by precipitation were improved compared to particles micronized by jet milling due to a hydrophilic surface coating. Thus dissolution rate enhancement can be achieved through precipitation in the presence of excipients.