Polymer-surfactant mixtures for production of griseofulvin nanoparticles by wet-bead milling

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Abstract The advent of wet-bead milling, in which drug is milled in presence of stabilisers such as polymers and surfactant, has enabled the successful formulation of poorly water-soluble drugs as nanoparticles. Despite the success of wet-bead milling, an understanding of the mechanism behind the polymer/surfactant stabilisation of nanoparticles is lacking. Using griseofulvin (BCS class II), the effect of surfactants and/or polymers on nanoparticle production/stabilisation has been investigated. Griseofulvin nanoparticles could only be produced in presence of anionic stabilisers, which are sub-optimal for formulation purposes. Consequently, the potential of anionic surfactant/polymer co-stabilisation using the non-ionic polymer hydroxypropylmethylcellulose (HPMC) was investigated. The presence of HPMC reduced the amount of anionic surfactant required to stabilise the griseofulvin nanoparticles.

INTRODUCTION

Wet-bead milling achieves particle size reduction of drug to within the nanometer size range using a high impact bead mill to fracture drug particles dispersed in a crude concentration suspension. The presence of polymer and/or surfactant is required during the milling process to ensure the stabilisation of the resulting nanoparticles against agglomeration. The polymer and/or surfactant adsorbs to the freshly formed drug crystal surfaces during milling, to provide either a steric and/or ionic barrier around the drug nanoparticles. Unfortunately, however, the use of an ionic surfactant to stabilise drug nanoparticles can lead to a range of challenges with the formulation, for example the risk of incompatibility with charged molecules, membrane irritation and toxicity.

MATERIALS AND METHODS

Griseofulvin, a poorly water-soluble antifungal, was selected as the model drug. A range of ionic and non ionic polymers and surfactants were screened for their ability to produce griseofulvin nanoparticles. Wet-bead milling was carried out using a Retsch MM 200 mill as reported in [1]. Dynamic light scattering was used to determine particle size. Surfactant adsorption isotherms were obtained using the colorimetric stains all assay [2].

Table 1. Size and surfactant adsorption of griseofulvin nanoparticles stabilised by anionic surfactant and non ionic polymer

Surfactant/polymer combinations (wt)	Weight ratio of drug: stabiliser	Particle size (nm) after 6 h milling	Total amount of surfactant adsorbed (mg/m^2)
SDS			
0.5 SDS	50:1	269.2 4.3	0.986 0.08
0.25 SDS	100:1	304.3 4.2	0.627 0.02
0.1 SDS	125:1	1000	N/D
AOT			
0.5 AOT	50:1	254.4 3.3	0.874 0.06
0.25 AOT	100:1	290.5 2.6	0.692 0.04
0.1 AOT	125:1	1000	N/D
SDS/HPMC			
1.88 HPMC 0.5 SDS	11:1	250.4 2.3	0.687 0.02
1.88 HPMC 0.25 SDS	12:1	306.1 4.7	0.656 0.03
1.88 HPMC 0.1 SDS	13:1	321.4 4.3	0.379 0.02
1.88 HPMC 0.05 SDS	13:1	330.5 3.6	0.197 0.01
1.88 HPMC 0.025 SDS	13:1	1000	N/D
AOT/HPMC			
1.88 HPMC 0.5 AOT	11:1	274.1 4.8	0.694 0.13
1.88 HPMC 0.25 AOT	12:1	301.9 3.3	0.643 0.03
1.88 HPMC 0.1 AOT	13:1	335.8 3.2	0.396 0.03
1.88 HPMC 0.05 AOT	13:1	1000	N/D

RESULTS AND DISCUSSION

Griseofulvin nanoparticles could only be stabilised by anionic surfactants and polymers: HPMCAS (hydroxypropylmethylcellulose acetate succinate), SDS (sodium dodecyl sulphate) and AOT (sodium dioctyl sulfosuccinate). Nanoparticles were achieved even outside the optimal drug to stabiliser weight ratio of 20:1 and 2:1 reported by Merisko-Liversidge [3]. The non-ionic polymer, HPMC 8000 (xed concentration of 1.88 wt) was selected for use in combination with anionic surfactant for nanoparticle stabilisation. Note that

HPMC 8000 was not able to stabilise griseofulvin nanoparticles when used alone. Inclusion of HPMC 8000 in the stabilising mixture allowed a reduction in the amount of surfactant required for nanoparticle stabilisation fi a ten and ve fold reduction in the amount of SDS and AOT respectively. Anionic surfactant adsorption isotherms con rmed a reduction in the amount of anionic surfactant absorbed in the presence of HPMC 8000 (Table 1), suggesting that HPMC 8000 was absorbed onto the griseofulvin nanoparticles in the presence of anionic surfactant

CONCLUSIONS

Anionic surfactant or a combination of anionic surfactant with non ionic polymer can be successfully employed to produce griseofulvin nanoparticles.

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Predicting Compaction Parameters for Producing Inhalation Powder Compacts for Use in the Wright's Dust Feeders

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INTRODUCTION

Inhalation compounds are delivered as dry clouds by dust feeder in early safety studies. The dust feeder requires micronised powder to be compressed into a cake, which is then scraped to release compound for aerosolisation. Having the correct cake characteristics is essential for the generation of a good particle cloud to give the desired inhalation exposure required.

Historically, powder compacts were produced in a manual press using a stainless steel canister and plunger by trial and error. If the compact is over-compressed, it would render the compact unsuitable for use. If the compact is under-compressed, it will collapse when incised. In this early stage development, drug substance is in short supply and timings are tight. A more predictable process was desired.

A method has been developed whereby the compression properties of the material can be modelled and used to predict the optimum punch pressure required to give good delivery.

EXPERIMENTAL

The Compaction Simulator uses less than 400 mg of material to measure the compaction properties of a powder. The two parameters chosen to assess compaction properties from the compaction simulator data were the yield pressure and the ejection force.

Yield pressure, which relates the relative density to compaction pressure, was determined using the Heckel equation [1].

Three model materials, compounds R, E and L, covering a range of hardness and stickiness were used to gather information about how the compaction pressure affects the performance of the cake. From this a suitable working range of compaction was determined for each model material.

RESULTS AND DISCUSSION

A chart of yield pressure versus compaction pressure used to produce the cake was plotted for the model materials fi see Figure 1. This shaded area on the chart shows the range of compaction pressures over which a good cake can be produced for a new compound whose yield pressure has been measured on the compaction simulator. For softer materials the range is narrower making suitable selection more critical, e.g. compound R.

A high ejection force shows compounds are sticky and when compressed close to the predicted optimum pressure they tend to stick to the punch and perform poorly in the dust feeder. These sticky compounds therefore require a slightly lower pressure to allow for this effect and are compressed close to the bottom of the range on the chart.