Novel Temperature Controlled Surface Etching of Excipient Particles for Carrier Based DPI Formulations

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Aim

To investigate the influence of nanometre scale roughness of dry powder inhaler excipients on the aerolisation properties of respirable drug particles. The surface texture of a commercial grade carrier particles (lactose monohydrate) is typically rough on a micrometer scale, with an array of asperities and clefts on its surface. The site of such clefts can be classified as areas of high energy interactions as they become preferential areas to which active drug particles can be readily attracted and strongly adhered. It would be, therefore, highly advantageous to decrease and/or control the surface morphology to reduce the potential of high energy adhesion sites

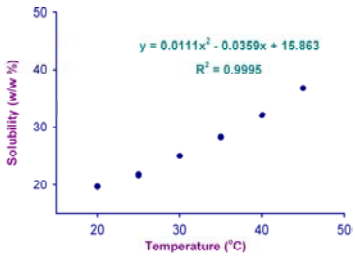

Figure 1. Solubility profile of α-lactose monohydrate in water.

Background

In a dry powder inhaler formulation, micronized drug particles have high adhesion/cohesion properties (due to a high surface area to mass ratio). Therefore coarse carrier particles are utilized to ensure accurate dose metering and to aid in the delivery of the drug to peripheral regions of the lung. Physical characterization of α-lactose monohydrate carrier particles, in terms of surface roughness, appears to be of significant importance with regards to determining the adhesive properties of the powder formulation to be delivered. Various attempts have been carried out to modify the surface characteristics of lactose carrier particles. Such attempts include increasing surface smoothness by means of complete recrystallization of carrier particles (Kassem and Ganderton 1990), high speed wet granulation (Colombo *et al*, 2000), crystal engineering which, involved modifying both the shape and surface rugosity of lactose particles also through crystallization (Larhrib *et al*, 2003) and surface treatment achieved by wetting with aqueous-alcohol solution (Iida *et al*, 2002). The resulting particles, however, exhibit relatively unpredictable alterations of surface morphologies due to relative difficulties in controlling treatment conditions.

Controlled surface etching of α-lactose monohydrate particles

A saturated solution of α-lactose monohydrate, in water, was prepared and continually stirred at a constant temperature of 25ºC. Temperature within the vessel was controlled to within 0.1ºC via a refrigerated controlled water bath. A known volume of the saturated solution (100ml) was subsequently filtered into a dissolution vessel, which was maintained at the saturation temperature, and a pre-determined amount of 63-90µm sieved α-lactose monohydrate was added to the saturated solution in the dissolution vessel. Surface controlled etching of the lactose particles surfaces was achieved by ramping the temperature within the dissolution vessel either at controlled rate (0.1 - 0.5 ºC/min) or directly to the etching temperature.

With prior knowledge of the temperature dependence of the solubility of α-lactose monohydrate (Figure 1), the undersupersaturation conditions and degree of etching of the sieve fractioned crystals can be quantified. This is achieved by utilising the following expression for undersupersaturation (σ):

$$\%\sigma_{under} = -\frac{C_T - C_S}{C_S} \times 100$$

C_T : Solubility at etching temperature

C_s : Solubility at saturation temperature

Temperature difference $\Delta T = T_{etch} - T_{sat}$ (ºC)	% Undersupersaturation $\%\sigma = -(\{C_T - C_s\} / C_s) \times 100$	% of initial mass etched $\%M = (\{C_T - C_s\} / M_{added}) \times 100$
5	-12.15	5.27
10	-28.47	12.35
15	-48.96	21.24
20	-73.63	31.94
25	-102.461	44.45

Table 1. % mass etched of α-lactose monohydrate particles in relation to degree of temperature difference.

Surface Morphology

Surface smoothed lactose carrier particles have shown to significantly improve the deposition efficiency of drug particles compared to commercially available lactose. Representative SEM images (Figure 2) indicate a dramatic decrease in surface roughness and removal of fine lactose particles. In addition, atomic force microscopy studies (Figure 3) suggested the surface morphology of the treated lactose to be dependent on the degree of etching and the resulting morphology.

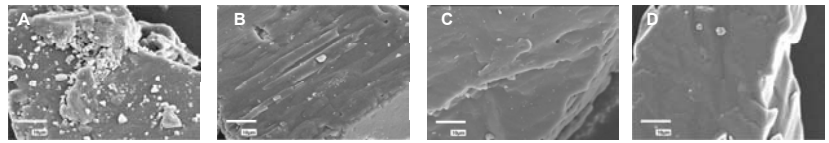

Figure 2. Scanning electron micrographs of A. untreated B. 5% etch C. 12% etch D. 44% etch α-lactose monohydrate particles.

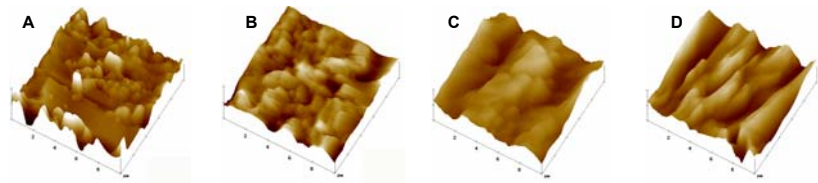

Figure 3. AFM images of A. untreated B. 5% etch C. 12% etch D. 44% etch α-lactose monohydrate particles.

In-vitro Performance

The liberation of micronised drug particles from lactose-drug blends was investigated using the twin stage impinger. Data was processed and is represented (Figure 4) as fine particle dose (FPD) (therapeutic dose reaching the lung from a 400µg dose capsule).

Clear statistical differences between the processed and un-processed lactose were observed. In addition, the performance of drug delivered from the modified lactose was dependent on the degree of etching. Blends resulting in the highest deposition of salbutamol sulphate was achieved through the 21% mass etched particles (I.e 15ºC), suggesting the importance of optimizing the degree of surface etching of carrier particles. This is most likely related to the observed variation in morphology (Figures 2 & 3) as the degree of etching was increased (Figure 5).

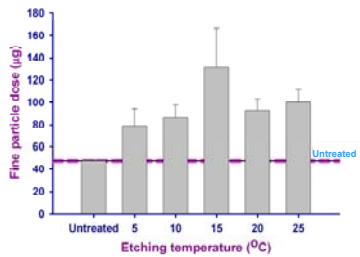

Figure 4. Salbutamol sulphate deposition profile (FPD(µg)).

Figure 5. Schematic diagram of proposed interactions as a degree of etching.

Conclusions

- Nanometer scale roughness of excipient particles in a carrier based dry powder inhalation formulation have shown to significantly influence the behavior of respirable drug particles.
- Surface smoothing of commercial grade α-lactose monohydrate particles to a certain extent was found to be highly advantageous with regards to increasing the amount of drug particles delivered to the peripheral regions of the lung, as a result of manipulating the adhesive properties of interacting particulates.

References

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