The formulation and evaluation of a dry powder for pulmonary delivery in cystinosis.

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OBJECTIVES

Cystinosis is a rare autosomal recessive disease characterised by raised intracellular levels of the amino acid, cystine. The disease affects most tissues and organs in the body. Without treatment, patients slowly decline towards end-stage renal failure by age 10. Treatment for cystinosis involves the 6-hourly oral administration of cysteamine (Cystagon™), an aminothiol which possesses an offensive taste and smell [1]. This treatment causes frequent nausea, vomiting and the odorous metabolites present in the breath and sweat. As part of our ongoing multidisciplinary approach to improving the treatment options for patients with cystinosis, a number of dry powder formulations were investigated with the aim of exploring the inhalation route of delivery. A dry powder inhaler for systemic delivery could eliminate the foul taste and disruptive dosage regime that is experienced with the current oral treatment.

METHODS

Cysteamine bitartrate was synthesised and spray-dried with poly (D,L-Lactide) in ethyl acetate. The bio-absorbable coating protects the drug from the environment, and also masks the foul taste. Immediately after harvesting from the collection vessel, the microspheres were placed into sealed density bottles, placed into a desiccator and stored at 4°C, due to their hygroscopic nature. The resulting powder was blended in various ratios with lactose (63-90 µm). SEM analysis was performed on the microspheres. Dissolution studies were undertaken using thiol specific DTNB reagent, in 50 mL of media (90% deionised water, 10% Tris buffer), stirred at 100 rpm and sampled every 5 mins. Testing was performed at 37°C.

Drug content was measured in parallel. Moisture content was analysed using TGA analysis. Aerodynamic particle size was analysed using a mastersizer, and an Anderson Cascade Impacter (ACI), with varying flow rates (Fig 1). Stability tests were performed at 4°, 21° and 30°C.

Fig 1. Powder collected on a stage of the Anderson Cascade Impactor.

RESULTS

SEM analysis revealed the microspheres were spherical and in the size range of 0.5-5 µm (Fig 2), the size required for optimal deep lung targeting.

The Mastersizer tests show a mean diameter of 25 µm however, and this is probably due to static forces causing particle agglomeration. Particles of this size are particularly affected by static, as gravity becomes less of an influence.
Cysteamine bitartrate was released instantly from the polymer, and 100% release was achieved within 8 minutes.
Microspheres were found to contain 50.33% cysteamine bitartrate.

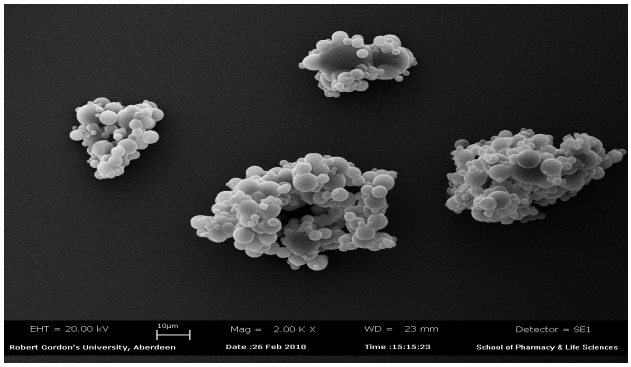

Fig. 2. Scanning electron microscopy (SEM) image of spray dried cysteamine bitartrate microspheres.

The ACI results show little impact from sample variation. Microspheres penetrated the lung further at 60 L/min flow rate compared to 28 L/min, and when stored at low temperatures and low humidity (Fig 3). Microspheres alone did not pass beyond stage 3 of the impacter; the inert carrier lactose was required to travel to deep lung regions. The fine particle fraction (FPF) was 6.1%.

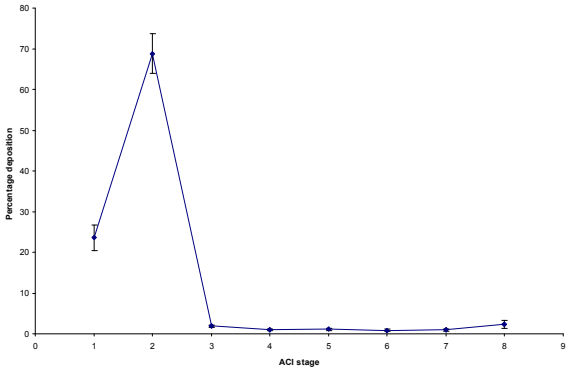

Fig 3. ACI plot, outlining stage distribution for a 50:50 blend with lactose.

Stability tests confirmed that the microspheres are very hygroscopic, and require storage at 4°C with low humidity.

CONCLUSIONS

Micro particles in the size range required for deep lung targeting were manufactured and characterised for drug content, surface characteristics, dissolution and lung penetration. In each of these areas the microspheres were found to possess ideal characteristics for optimum lung absorption. Further work will aim to improve the formulation, and also explore in vivo testing.

[1] E. Levtchenko, M. Besouw, H. Blom, A. Tangerman, de Graaf-Hess, "The origin of halitosis in cystinotic patients due to cysteamine treatment" *Mol. Gen. Met.*, **91** (2007) 228-233.

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