Leucine Coated Cyclodextrin/Corticosteroid Drug Powders for Pulmonary Delivery

INTRODUCTION
Poor solubility of corticosteroids may impact the bioavailability of drugs in the pulmonary tract. Cyclodextrins are cyclic oligosaccharides that have been shown, via complexation, to increase solubility of poorly soluble drugs, including corticosteroids. Here we report leucine coated particles composed of hydroxypropyl-β-cyclodextrin (CD) complexed with beclomethasone dipropionate (BDP), prednisolone (PRE), and fludrocortisone acetate (FLU) prepared by an AEROSOL FLOW REACTOR. We examined the aerosolization properties using two inhalers, Twister™ and Easyhaler® at two pressure drops and also performed drug dissolution experiments.

RESULTS AND DISCUSSION
The lowest drug inclusion was in CD-BDP-L and the highest in CD-PREL. We see in the inset tables in the Figure 1 (determined by HPLC in DQ). The inclusion variability is most likely related to the water solubility; BDP 2.28 x 10^7 g/L and PRE 0.272 g/L. The solubility of FLU is not known but the solubility of fludrocortisone is 0.140 g/L. The particles had wrinkled surface coated with small leucine crystals (see Figure 1). The evaporation of water from a surface active matrix leads to hollow particles which are likely to collapse and form wrinkled particle morphology.

Figure 1. SEM images of the fine powders, BDPM/L is micronized beclomethasone dipropionate powder.

Drug dissolution experiments
CD-PREL and CD-FLU-L showed a significant increase in dissolution compared to their physical mixtures and bulk drugs (see Figure 2). On the other hand, the dissolution of BDP showed no difference between the powder formulation and physical mixture. While the CD appeared to significantly increase the solubility of BDP, it does not seem to translate to increased dissolution compared to the physical mixture. This may be explained by the fast complexation process for BDP in the physical mixture when exposed in the buffer solution, which results in the similar dissolution as in the CD-BFPL.

Aerosolization results of carrier-free powders using two inhalers and pressure drops
Easyhaler: 2 kPa = 40 L/min; 4 kPa = 55 L/min. Twister: 2 kPa = 43 L/min; 4 kPa = 55 L/min