

Leucine Coated Cyclodextrin/Corticosteroid Drug Powders for Pulmonary Delivery



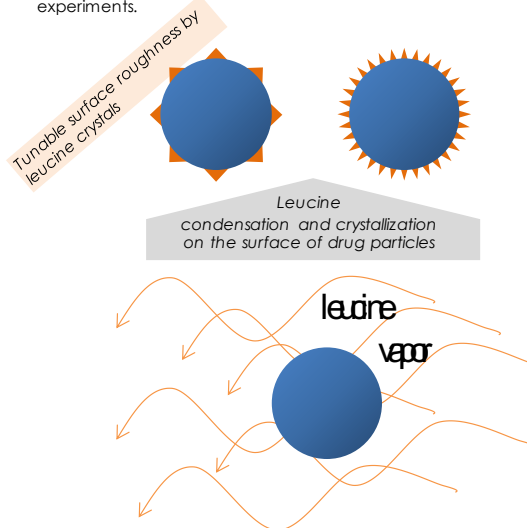
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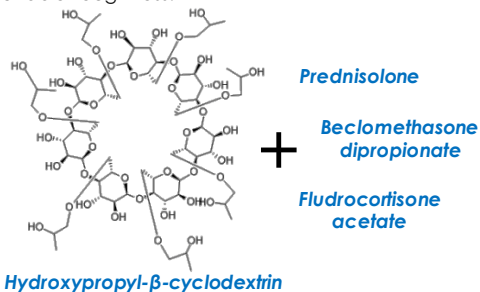
INTRODUCTION

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.



STEP 2: Continuous aerosol flow reactor method to produce fine particles with the leucine coating of tunable roughness.



STEP 1: Inclusion complexation between HP- β -CD and corticosteroids

RESULTS AND DISCUSSION

The lowest drug inclusion was in CD-BDP-L and the highest in CD-PRE-L see the inset tables in the Figure 1 (determined by $^1\text{H-NMR}$ in D_2O). The inclusion variability is most likely related to the water-solubility: BDP 2.38 $\times 10^3$ 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.

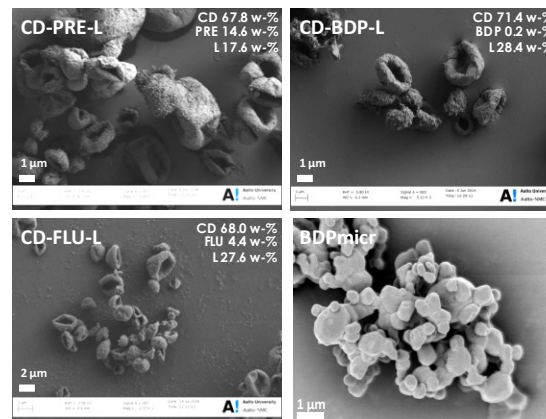


Figure 1. SEM images of the fine powders. BDPmicr is micronized beclomethasone dipropionate powder.

Drug dissolution experiments

CD-PRE-L 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 shows 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 complexation as in the CD-BDP-L.

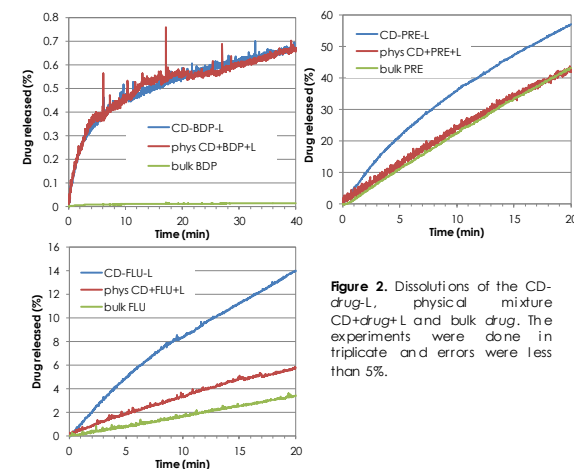


Figure 2. Dissolutions of the CD-drug-L, physical mixture CD+drug+L and bulk drug. The experiments were done in triplicate and errors were less than 5%.

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

Easyhaler®



MULTI-DOSE, RESERVOIR INHALER

Twister™



SINGLE-DOSE, CAPSULE INHALER

Sample	ED (mg/dose)		CV _{ED}		FPF (% <5.5 μm)		FPD ($\mu\text{g}/\text{dose}$)		MMAD (μm)		GSD	
	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa
CD-BDP-L	1.2	1.2	0.11	0.14	55	56	1.3	1.3	2.6	2.3	2.1	1.9
CD-PRE-L	2.0	2.0	0.10	0.13	60	54	175.2	157.7	3.2	2.4	1.8	1.8
CD-FLU-L	1.7	1.6	0.15	0.17	61	67	45.6	47.2	2.1	2.3	1.7	1.7
BDP _{micr}	1.0	0.8	0.30	0.33	5.2	5.7	5.2	4.6	3.9	3.8	2.5	2.1

Sample	ED (mg/dose)		ED _{off} (%)		CV _{ED}		FPF (% <5.5 μm)		FPD ($\mu\text{g}/\text{dose}$)		MMAD (μm)		GSD	
	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa	2 kPa	4 kPa
CD-BDP-L	4.0	4.4	79.2	87.4	0.05	0.09	56	52	4.5	4.6	1.3	1.3	1.6	1.6
CD-PRE-L	3.6	3.7	72.6	73.2	0.07	0.08	67	70	352.1	378.1	1.7	1.7	1.8	1.7
CD-FLU-L	4.1	4.2	81.0	84.6	0.09	0.08	66	62	119.1	114.6	1.4	1.3	1.6	1.6
BDP _{micr}	3.1	3.4	61.8	67.8	0.18	0.15	27	51	837.0	1734.0	3.6	3.0	2.2	1.6