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Inhalable budesonide porous microparticles tailored by spray freeze drying technique

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ABSTRACT

Budesonide is a poorly water soluble corticosteroid used in the treatment of asthma and chronic obstructive pulmonary disease (COPD). The aim of the present study was to develop micronized porous particles containing budesonide in a mannitol-based dry powder formulation using spray freeze drying (SFD) technique. Hydroxy propyl beta cyclodextrine (HPbCD) and/or L-leucine were employed as complementary excipients and their effects on the particle shape and morphology of processed powders were evaluated. As well, the produced particles were characterized in terms of thermal behavior, porosity, dissolution rate and suitability for pulmonary delivery. The results demonstrated that aerosolisation performance of the microparticles containing both L-leucine and HPbCD were considerably improved in comparison to other formulations and the fine particle fraction (FPF) increased substantially. Different ratios of excipients resulted in the formation of particles with different aerodynamic behaviors.

1. Introduction

The respiratory tract has been widely used as a route of drug delivery for treatment of diseases such as asthma, COPD and pulmonary infections [1]. The effectiveness of an inhalation therapy, particularly for a dry powder formulation, depends on factors that are related to the patient, the device and characteristics of the formulation [2]. Respiratory deposition is governed by characteristics of the powder, such as particle size, crystallinity, density, porosity, hygroscopicity, and inter-particulate forces. The aerodynamic diameter (AD) is the indicator of aerosol performance and relates to particle dynamic behavior and describes the main mechanisms of aerosol deposition. To reach the peripheral airways, where the drug is most efficiently absorbed, particles need to be in the range of 1–5 μm of AD [3].

When preparing respirable powders, it is generally intended to reduce particle sizes to less than 5 μm. Numerous conventional techniques such as milling, spray drying, freeze-drying and supercritical fluids based techniques have been used for particle size reduction. But there are a number of obstacles including residual solvents, thermal and chemical degradation of products, high-energy requirements and broad particle size distributions [4–6]. In this size range, powders exhibit strong inter-particulate cohesion leading to poor flow properties. Therefore, interest in the production of porous particles for inhalation has increased in the last decade. Porous particles with low density and high porosity have shown low aerodynamic diameters in the greater volume diameters [7,8]. SFD is a relatively new method for particle engineering in which, a solution containing dissolved material is sprayed into a super-cool phase to form frozen and solid particles. After that these particles will be dried using lyophilization and these processes generally produce powders with a larger median particle size, larger specific surface area and higher fine particle fraction (FPF) [9].

In this study, budesonide, a widely used corticosteroid in the management of asthma [10,11], was selected as a model drug with low aqueous solubility. Budesonide is a potent drug and only small quantity of the drug is required for therapeutic purposes. Subsequently, finite variations in the dose of the drug have been reported to result in serious consequences and side effects such as acute adrenal insufficiency [12].

The co-processing of active pharmaceutical ingredients and excipients has been proposed to produce powders with desired content uniformity in order to overcome some problems regarding low dose drugs [13,14]. In this manner, sugar based excipients like lactose, mannitol and trehalose could play the role of bulking agents and other excipients can serve as ternary components to increase the fine-particle fraction (FPF) of drug particles [15].

In general, leucine derivatives, have been shown to improve powder dispersion by reduction in surface forces between adjacent particles [16,17]. Also, cyclodextrins are useful additives which enhance the dissolution of drugs in aqueous mediums and thus improve the delivery of many useful pharmaceutical agents to a biological system [18–20].

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Table 1
Composition of spray freeze dried formulations and the resulting fine particle fraction.

Formulation code	Powder composition (%w/w)					
	Budesonide	Mannitol	Cyclodextrin	Leucine	FPF (%)	ED (%)
Run 1	1	99	0	0	19.3	45.1
Run 2	1	94	0	5	44.6	44.3
Run 3	1	89	0	10	37.3	67.5
Run 4	1	79	20	0	45.5	70.7
Run 5	1	59	40	0	49.9	68.3
Run 6	1	74	20	5	57.0	72.8
Run 7	1	69	20	10	51.7	72
Run 8	1	54	40	5	58.0	73.7
Run 9	1	49	40	10	53.2	77.7

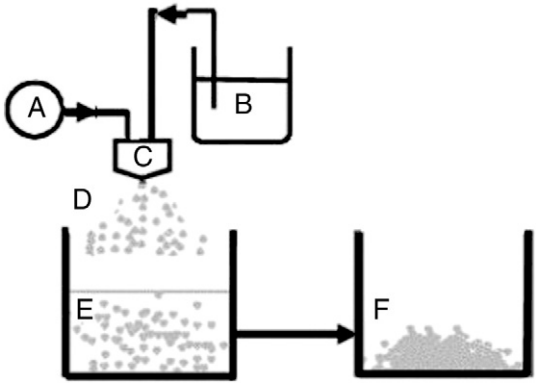

Fig. 1. Schematic diagram of spray freezing stage: (A) compressed air inlet, (B) solution feed, (C) two fluid nozzle, (D) liquid spray containing drug, (E) liquid nitrogen as cryogen, and (E) drug powder collected after freeze drying.

In this study, HPbCD and L-leucine were employed in the processing of budesonide and mannitol by an SFD technique and the effects of the excipients on the physical characteristics of microparticles were evaluated.

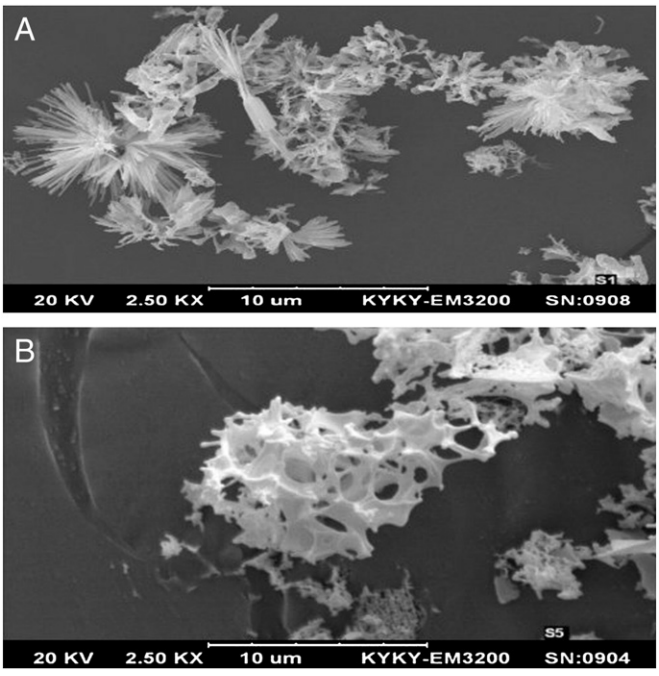

Fig. 2. SEM micrographs of SFD processed particles containing budesonide and mannitol: (A) Run1; (B) Run5.

2. Materials

Budesonide was kindly gifted by Cipla Co Ltd., India. L-leucine (hereafter referred to as "leucine"), HPbCD and mannitol were purchased from Sigma-Aldrich, USA. Methanol and ethanol were of analytical grade, purchased from Merck, Germany. Deionized-distilled water was used throughout the study. Liquid nitrogen was supplied by Sabalan, Iran.

3. Methods

3.1. Spray freeze drying of formulations

A series of solutions containing budesonide and excipients were prepared in hydro-ethanolic solvent (4:1) according to Table 1. Briefly, budesonide was dissolved into ethanol and excipients were dissolved in water and then mixed together under stirring.

To produce spray freeze dried powders, the feed solution was sprayed through a two fluid nozzle at the pressure of 5 bar and flow rate of 6 mL/min into the vapor above a cryogenic liquid (e.g. liquid nitrogen). The atomization occurs outside the nozzle by acceleration of the liquid through an expanding gas. In each experiment, 0.4 L of liquid nitrogen was filled in a glass container in volume of 2 L in order to provide cryogenic vapor. Fig. 1 provides a schematic diagram of the spraying set up used in this study.

The resulting suspension (frozen droplets of the solution in liquid nitrogen) was transferred into the lyophilizer (Christ, Germany). Vacuum was applied as soon as all nitrogen was evaporated.

During the first 24 h, the pressure was set at 0.005 mbar and the shelf temperature at −50 °C. During the second 24 h, the shelf temperature was gradually raised to −20 °C. After removing the samples from

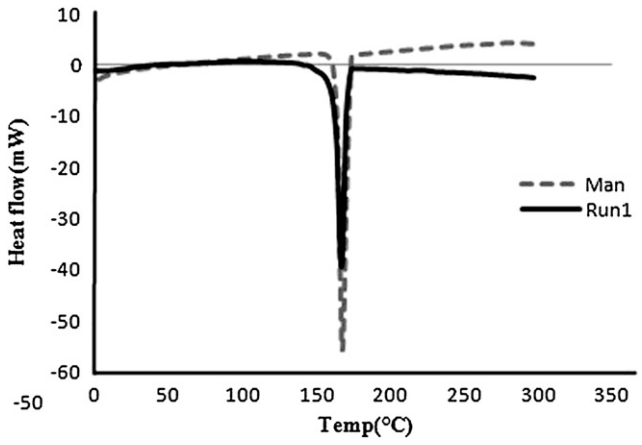

Fig. 3. DSC thermograms of commercial mannitol (Man) and SFD processed particles containing budesonide and mannitol (Run1).