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Original Research Paper

Effect of formulation ingredients on the physical characteristics of salmeterol xinafoate microparticles tailored by spray freeze drying

Mohammad Reza Rahmati, Alireza Vatanara *, Ahmad Reza Parsian, Kambiz Gilani, Khosrow Malek Khosravi, Majid Darabi, Abdolhossein Rouholamini Najafabadi

Department of Pharmaceutics, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Series of microparticles containing salmeterol xinafoate (SX) as active pharmaceutical ingredient (API) and lactose, mannitol or trehalose as a bulking agents were prepared using spray freeze drying (SFD) technique and the effects of sugar type and presence of hydroxy propyl beta cyclodextrin (HPβCD) on the physical properties of powders were evaluated. Precipitation of salmeterol in the presence of lactose and mannitol resulted in the formation of irregular shapes of microparticles with broad size distributions. However application of trehalose resulted in the formation of porous particles with spherical morphology. Addition of cyclodextrin in the formulations was generally helpful for formation of porous and spherical particles with narrow size distribution with a mean size of 10–30 μm. Dissolution of SX from processed particles was substantially higher (~90% drug release in 30 min) than that of unprocessed drug and physical mixture of drug and cyclodextrin (~22% drug release in 30 min). This study showed that, processing of SX by SFD technique could be a constructive approach to the production of various forms of drug and drastic changes in the physical characteristics of microparticles could be achieved by changing the composition of bulking agent and cyclodextrin.

Introduction

The efficacy of pharmaceuticals can be significantly influenced by their physicochemical properties such as particle size distribution, morphology, powder flow, compression characteristics, physical stability and bioavailability. Fine pharmaceutical powders are often produced by currently available micronization methods that allow particle engineering. Processes such as air jet milling, spray drying, freeze drying and supercritical fluids based techniques enable scientists to design solid dosage forms tailored to possess optimal physicochemical attributes [1,2].

SFD is a rather new method for particle engineering that is a combination of conventional spray-drying with freeze-drying. A typical SFD technique involves the atomization of the solution containing API and excipients via a nozzle into a chamber filled with a cryogenic liquid such as nitrogen, oxygen or argon. The spraying process can be performed beneath (spray-freezing into liquid) or above the surface of the cryogenic liquid, depending on the position of nozzle. The droplets are quickly frozen because of critical low temperature. Once the spraying process is completed, the frozen suspension in cryogenic liquid is transferred into lyophilizer to obtain the dried particulate powders [3,4]. SFD technique has several advantages compared to freeze drying and spray drying, including: (1) process with no heat is applicable to thermolabile APIs; (2) producing spherical and porous particles with controllable size; (3) minimizing the crystallization and phase separation of drug [5]. These advantages provide a resourceful process to improve the physicochemical characteristics of powders and producing tailored particles.

In this study, fine particles containing SX have been produced by SFD process and the effects of different carbohydrates on the physical characteristics of microparticles have been evaluated. SX was chosen as a model drug since it is a long-acting potent β-adrenoceptor agonist used via inhalation to improve lung function, reduce symptoms and provide a better quality of life for patients with asthma. Solubility of SX in water is limited (sparingly soluble) and it made it an appropriate candidate for this study [6].

In such a way, lactose, mannitol and trehalose were employed as bulking agents and HPβCD was applied as a solubilizing agent for dissolution enhancement of drug.

The sugars named above can fulfill many of the requirements to reduce damages to delicate molecules during SFD processing and also appear to be suitable as carriers for dry powder aerosols [3,7]. Cyclodextrins have been used extensively as pharmaceutical

* Corresponding author. Tel.: +98 21 66959057.
E-mail address: vatanara@tums.ac.ir (A. Vatanara).

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excipients to increase the solubility of poorly water soluble drugs by the formation of an inclusion complex between the host cyclodextrin molecule and the guest drug molecule [8,9].

Materials and methods

Materials

Salmetreol xinafoate BP was gifted by Jaber Ebne Hayyan Ltd., Iran. Lactose, mannitol, trehalose and HPβCD was purchased from Sigma–Aldrich, USA. Ethanol of analytical grade was purchased from Merck, Germany. Liquid nitrogen was purchased from Sabalan, Iran.

Preparation of spray freeze dried powders

Series of solutions containing SX and lactose, mannitol or trehalose were prepared using hydroethanolic solvent (3:1) according to Table 1. SX dissolves into ethanol and the carrier dissolves in water. The concentration of salmeterol was 0.05% in all of the solutions. In the case of solutions containing HPβCD, aqueous solutions of drug and cyclodextrin were prepared and mixed for 24 h. The amount of HPβCD had to be 1% (20 times more than salmeterol concentration).

To produce spray freeze dried powder, the feed solution was loaded into the solution cell and then sprayed 10 cm above the surface of 300 ml cryogenic liquid (e.g. liquid nitrogen) through a polyetheretherketone (PEEK) capillary nozzle at the pressure of 400 PSI which was provided by a high pressure pump (Jasco, Japan) with a flow rate of 10 ml/min. 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 freeze dryer (Christ, The Netherlands). 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 −70 °C. During the second 6 h, the shelf temperature was gradually raised to −20 °C. After removing the samples from the freeze drier, they were stored over silica gel in a desiccator at room temperature.

Scanning electron microscopy

A Philips Model XL30 scanning electron microscope (Philips, The Netherlands) was used to obtain the SEM photographs. The sample powders were glued onto aluminum stages using double adhesive carbon conducting tape. Particles of representative samples were coated with gold–palladium at room temperature before the examination. The accelerator voltage for scanning was 25.0 kV.

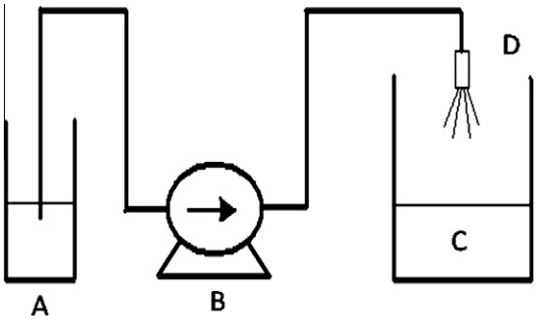

Fig. 1. Schematic diagram of spray freezing stage: (A) formulation solution, (B) high pressure pump, (C) liquid nitrogen, and (D) polymeric nozzle.

Particle size analysis of microparticles

The size distribution of dried powders was measured by laser light scattering using a Malvern Mastersizer X (Malvern Instruments, UK). For particle size analysis, a mass of 10 mg of powder was suspended in 10 ml of pure ethanol and the suspension was then sonicated for 2 min using a water bath sonicator (Starsonic, Italy).

Differential scanning calorimetry

Thermal behavior of SFD processed particles were studied quantitatively and qualitatively by differential scanning calorimetry using a PL-DSC apparatus (Polymer Laboratories, UK). The samples (5–10 mg) were accurately weighed into standard aluminum pans and sealed. Thermograms were then recorded during heating and cooling runs at a scan rate of 10 °C per minute between 25 and 300 °C.

In vitro dissolution testing

Dissolution profiles of samples from Run_4, Run_8 and Run_{12} formulations were evaluated in comparison with unprocessed SX and physical mixture of drug and HPβCD. In each case, amounts of samples equivalent to 5 mg of drug was prepared for test and the amount of HPβCD was held 20 times more than SX concentration. Drug dissolution was carried out by placing sample in 50 ml freshly prepared deionized water previously heated to 37 °C in a horizontal shaker (Dorsa, Iran) at 100 rpm [10]. Samples of 2 ml were drawn at time interval of 5, 10, 20 and 30 min. Change in volume of solution due to sample withdrawal was considered during concentration determinations. Samples were filtered using 200 nm inline syringe filter (PTFE, 17 mm, Alltech) to remove any suspended particles.

Table 1
Composition of spray freeze dried formulations and the resulted particle sizes.

Run no.	Bulking agent	Amount of bulking agent (%)	Cyclodextrin	$d_{50\%}$ (μm)
1	Lactose	5	–	23.8
2	Lactose	5	+	ND
3	Lactose	10	–	22.1
4	Lactose	10	+	ND
5	Mannitol	5	–	11.1
6	Mannitol	5	+	10.9
7	Mannitol	10	–	17.8
8	Mannitol	10	+	18.9
9	Trehalose	5	–	34.9
10	Trehalose	5	+	23.4
11	Trehalose	10	–	30.8
12	Trehalose	10	+	19.8

ND: not determined because of rapid dissolution of powder in ethanol.