International Journal of Pharmaceutics 431 (2012) 45–52

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The development of a novel dry powder inhaler

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ARTICLE INFO

Article history:
Received 9 December 2011
Received in revised form 26 March 2012
Accepted 3 April 2012
Available online 20 April 2012

Keywords:
Dry powder inhaler
Active inhaler
In vitro evaluation
Animal test
Fluorescent image

ABSTRACT

A novel active and multi-dose dry powder inhaler (DPI) was developed and evaluated to deliver a small quantity (100–500 μg) of pure drug without any excipient. This dry powder inhaler utilized two compressed air flows to dispense and deliver drug powder: the primary flow aerosolizes the drug powder from its pocket and the secondary flow further disperses the aerosol.

In vitro tests by Anderson Cascade Impactor (ACI) indicated that the fine particle fraction (FPF) (<4.7 μm) of drug delivery could reach over a range of 50–70% (w/w). Emitted dose tests showed that delivery efficiency was above 85% and its relative standard deviation (RSD) was under 10%. Confocal microscopy was used to confirm the deposition of fluorescently labeled spray-dried powder in rabbit lungs. Also, a chromatographic method was used to quantify drug deposition. The results of animal tests showed that 57% of aerosol deposited in the rabbit lung and 24% deposited in its trachea. All the results implied that this novel active dry powder inhaler could efficiently deliver a small quantity of fine drug particles into the lung with quite high fine particle fraction.

1. Introduction

Pulmonary drug delivery is considered to be the most effective method of treating respiratory diseases, especially asthma and chronic obstructive pulmonary disease (COPD). As a relatively new method of drug delivery, dry powder inhalers (DPIs) have been increasingly accepted as treatment of asthma and COPD (Lavorini et al., 2011). When compared with pressure metered dose inhaler (pMDI), another primary pulmonary drug delivery method based on liquid propellant volatilization, most DPIs rely on patients' inhalation to disperse and drive the drug particles to avoid press-breath coordination. Better yet, the DPI does not require chlorofluorocarbons or hydrofluoroalkane as propellants so that DPI is more environmentally friendly (Newman, 2009). Hopefully, DPI may also be used for larger delivery doses, and is more chemically stable than pMDI, providing greater opportunities for pulmonary macromolecule delivery (Shoyele and Slowey, 2006).

According to package forms, DPI can be divided into 3 types: single-unit dose, multi-unit dose and multi dose reservoirs. The multi-unit dose and multi dose reservoir DPI are increasingly popular since it is convenient to administer multiple doses without charging and/or changing the inner packages. DPI can also be divided into two types in terms of its drive force, a passive DPI dependent on patients' inhalation and an active DPI dependent on external force (Daniher and Zhu, 2008; Islam and Gladki, 2008). In recent years, active DPI has become a preferred method to uniformly distribute drugs to a wide variety of people due to its independence on the inspiration flow. What is more, active DPI is particularly suitable to people who may have trouble producing enough air stream to disperse drug powder (i.e., children and elderly) (Son and McConville, 2008; Tobyn et al., 2004).

For dry powder pulmonary delivery, the drug particle size is critical. Optimally it should be smaller than 5 μm in aerodynamic diameter. As a result of high potency of respiratory delivery, the required dosage is usually very small. So, pharmaceutical companies often add excipients of much larger size, such as lactose, to facilitate flow and dispersion (Pilcer and Amighi, 2010). However, adhesion of fine drug particles to coarse carriers would decrease the delivery efficiency, and some patients may be intolerant to lactose (Saint-Lorant et al., 2007).

Consequently, a novel dry powder inhaler was developed to deliver very tiny dosage of pure active pharmaceutical ingredient (API) powder without any excipient (Zhu et al., 2011). It applies a two air flow design to produce complete dispersion of API powder with the break-up of most agglomerates of powder. The pure drug powder was metered and filled into multi-dose disks with great accuracy and reproducibility by our patented dispensing device (Zhu et al., 2004). Both ACI impaction and time-flight particle size measurement were carried out to confirm that fine drug powder could be effectively dispersed by this DPI with high fine particle fraction (FPF). In addition to in vitro tests, fluorescent imaging was

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http://dx.doi.org/10.1016/j.ijpharm.2012.04.019

utilized as a fast and effective method to confirm deposition of particles with fluorescence label in animal lung. Also, assaying in animal lung further demonstrated deposition of fine particles in lung and provided quantitative information on distribution.

2. Materials and method

2.1. Materials

Spray dried insulin, phenylalanine (PHE) was provided by GlaxoSmithKline (USA); sulfate salbutamol and nitrendipine were from Nanjing Pharmaceutical Factory, China; Fluorescein Isothiocynate (FITC) and other organic solvents were from Concord Technical Co. Ltd., Tianjin, China.

Nitrendipine and PHE labeled FITC (PHE–FITC) powders were prepared by Mini Spray Dryer (Bucchi, B-290, Switzerland). 0.5% nitrendipine in ethanol solution was sprayed out with 5 ml/min feed rate. Meanwhile, fluid rate was set as 675 ml/h in Nitrogen, and inlet and outlet temperature was 130 °C and 75 °C, respectively. 10–20% FITC (based on PHE) was added to 0.5% PHE water solution which contain 10% (w/w) $NaHCO_3/Na_2CO_3$ buffer, and the whole solution was stirred for 12 h in 0–4 °C. Then, the liquid was sprayed out with 5 ml/min feed rate, and air fluid rate was 675 ml/h, inlet and outlet temperatures were 140 °C and 80 °C. Salbutamol was spray dried from a 10% (w/v), aqueous solution, with 150 °C inlet air and 75 °C outlet air, and the flow rate was 675 ml/h (Corrigan et al., 2004).

The size of the particles produced by spray drier was measured by Particle Size Distribution Analyzer (PSD) (TSI corporation model 3603, USA). The volumetric median diameter (VMD) result of aerosol for nitrendipine, PHE–FITC, insulin, salbutamol was 7.01 μm, 4.14 μm, 3.78 μm and 2.94 μm, respectively.

The shape and size of particles were also observed with scanning electron microscope (SEM) (Hitachi S-2600, Japan). SEM photos (Fig. 4a–d) confirmed that the particles were in the range of 1–7 μm. The SEM photos also clearly showed the shape of those particles: the nitrendipine particles was irregular plate, the PHE–FITC particles was irregular sphere with multi concaves, the insulin was nearly sphere with concave in the center, and salbutamol was of regular sphere.

The angle of repose and bulk density of powders were evaluated by Powder Tester (HOSOKAWA MICRON corporation, Japan). The angle of repose of insulin and PHE–FITC was 48° and 54°, respectively; and tapped bulk density was listed as following: nitrendipine 0.485 g/cm^3, PHE–FITC 0.440 g/cm^3, insulin 0.314 g/cm^3 and salbutamol 0.281 g/cm^3.

Fig. 1. The appearance of the novel dry powder inhaler.

2.2. The novel dry powder inhaler

The appearance of the novel active and multi-dose inhaler is shown in Fig. 1 and its detailed structure in Fig. 2. The inhaler provides a rotating multi-dose disk with pure drug pre-metered in small pocket holes drilled through the disk (Fig. 2b). The disk is inserted between the air tubule and compress chamber, leaving only one drug pocket in the air passage for a given time (Fig. 2a). The blister pack is arranged to have a sufficient number of doses for patient's use, 12–64 doses (Fig. 2b).

As shown in Fig. 2a, the DPI works by positive pressure from the patient pushing at the bottom button of the inhaler to produce compressed air in the sealed chamber. Then the compressed air directly goes through the drug pocket as primary air flow (solid arrow), carrying drug powder along the air tubule (diameter is 2 mm, length 35 mm) until ejecting the powder out mouthpiece. A secondary air flow is perpendicular to primary air flow above the drug pocket, produced by parallel but much smaller tubule (secondary air tubule in Fig. 2a). The secondary air flow (hollow arrow) provides an additional shear flow, and assists in entraining the fluidized powder into the primary air flow. As a conclusion, this device

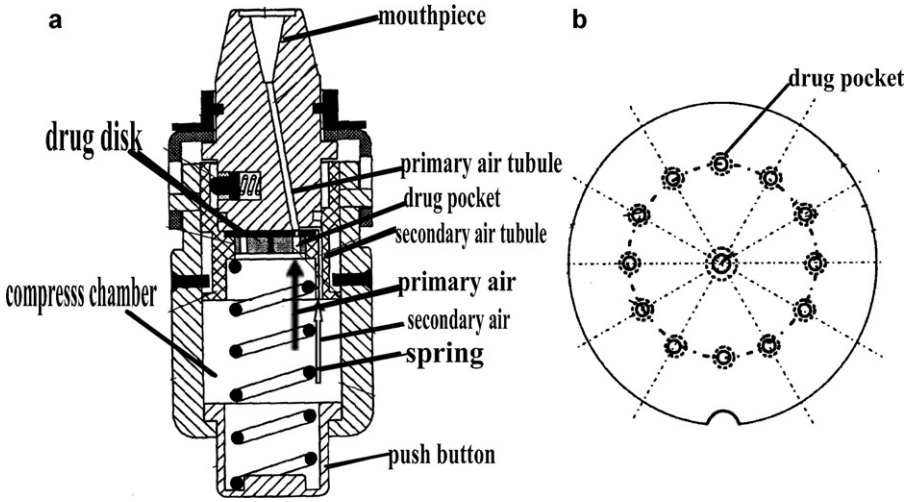

Fig. 2. Schematic diagram of the new designed dry powder inhaler (a) and multi-dose disk (b). Primary air flow (the solid arrow) goes through the drug pocket and carries drug powder along the air tubule; secondary air (the hollow arrow) goes upward directly and then becomes perpendicular to primary air flow above the drug pocket.