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Studies on the spray dried lactose as carrier for dry powder inhalation

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ABSTRACT

The purpose of this study was to investigate the spray dried lactose as carrier for dry powder inhalation (DPI). The lactose particles were prepared by spray drying, then the particle size, shape and crystal form were characterized by laser diffraction, scanning electron microscopy (SEM), X-ray diffraction (XRD) and differential scanning calorimetry (DSC). The spray dried lactose particles were spherical and amorphous, but would transfer to crystal form when storage humidity was above 32%. Thus, the humidity of the storage environment should be controlled below 30% strictly in order to maintain the amorphous nature of spray dried lactose which is a great benefit to DPI development.

1. Introduction

Inhalation of drugs is a form of administration that is actuated by patient to deliver drugs to the therapeutic site and to achieve local or systemic effect [1–5]. The enormous surface area of the lung and the plentiful capillary vessels conduce to a rapid absorption rate for inhalation; meanwhile, the absorbed drug can directly go into the blood circulation to effectively avoid the elimination by the first-pass metabolism in the liver [1,5,6].

Dry powder inhalation (DPI) is a dosage form that delivers the micronized drug particles to the lung in the assistance of carrier particles by the inspiration of patient. Compared with the traditional pMDI, DPI requires no propellant, has superior chemical stability and has good patient compliance [1,5,7,8], thus now it has been a hotspot in the research of inhalation.

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To date, almost all marketed DPI products rely on jet-milled, micronized drugs [9]. However, this method showed many deficiencies including little control of particle size, shape and surface morphology, and highly cohesive powders produced with poor aerosolization properties [10]. Spray drying technique is one of the methods to prepare medicinal particles intended for lung delivery using dry powder inhalers [2,11,12]. The principle of spray drying is to disperse drug solution into very small droplets by the atomizer, then rapidly evaporate the solvent in a hot dry medium like hot air to obtain dry product of powder or granules. This process produces product with high degree of purity and narrow particle size distribution, and also is relatively easy to scale up for commercial production [2].

However, there are still some disadvantages for spray drying, such as, particles would be sucked by the airflow leading to low product yield and causing loss especially for expensive drugs; some drugs are not stable at elevated temperature and tend to degrade. To overcome these shortcomings, a widely used formulation approach is to blend drugs with carriers which can provide protection to drugs and then to process co-spray drying [13,14]. Fig. 1 showed the carrier-based and drug/excipient spray dried DPI dosage forms. Simply mix the drugs and carriers is the most favorite method for preparing DPI dosage forms due to the easy operation and avoiding the drug loss during the spray drying [3,6,8]. The ideal carriers for DPI should have low density, well size distribution, good spherical degree, flowability and reproducibility [6,9]. For DPI carrier, the size acts a subsidiary role for the drug separate itself form the carrier and only the active ingredient deposits in the pulmonary [6,11].

Lactose is the only authorized carrier to be used in dry powder inhalation by FDA mainly because of its well-investigated toxicity profile and broad availability [2,15]. Commonly crystal form α-lactose monohydrate is used in marketed DPI products. The amorphous lactose, which could be manufactured by the spray drying, could increase the stability of drugs and the effectiveness of drugs delivering to the lung and absorbing in the blood circulation when acting as DPI carrier [18]. The transformation of amorphous lactose to crystalline was a quick process especially in high humidity condition. The purpose of this article is to investigate characteristics of spray dried lactose in order to provide useful reference resources for future studies using this material as carrier for dry powder inhalation.

2. Materials and methods

2.1. Materials

α-lactose monohydrate was obtained from Meggle (Batch No: F20090032, Germany). Anhydrous α-lactose was obtained from DMV Ltd. (SuperTab 20AN, Batch No: CR190021, Holland). Anhydrous β-lactose was obtained from DMV Ltd. (SuperTab 21AN, Batch No: 10493390, Holland).

2.2. Spray drying

Microparticles of lactose were prepared by spray drying. Pre-calculated amount of lactose was solubilized in water to obtain lactose concentration of 5% (w/v). Then the solution was spray dried using a laboratory scale spray dryer (SD-1000 Spray Dryer, Eyela, Japan) with the following conditions: inlet temperature at 120 °C, atomizing pressure of 180 kPa, air flow of 0.7 m^3/min and solution feed rate at 3 rpm. Three batches of samples were prepared and stored in desiccator (under 25% relative humidity and room temperature) before use.

2.3. Particle size

Particle size was measured by laser diffraction (Malvern Mastersizer 2000, Malvern Instruments Ltd., UK) using the Scirocco dry dispersion unit at a feed pressure of 4 bars and feed rate of 50%. All samples were analyzed in triplicate with the obscuration values between 0.5% and 5%.

2.4. Particle morphology

Particle morphology of spray dried lactose and α-lactose monohydrate was visualized by scanning electron microscopy (SEM) (JSM-6330F, Japan) at 15 kV. Samples were mounted on carbon sticky tabs and gold-coated before imaging.

2.5. Crystal structure

The crystal structure of various forms of lactose was analyzed using X-ray diffraction (XRD) (D-MAX 2200 VPC, Rigaku Ltd., Japan) with Cu-Kα as X-ray source. Settings were as follows: scan rate of 5°/min, voltage of 40 kV, current of 30 mA and scan range of 5–55° 2θ.

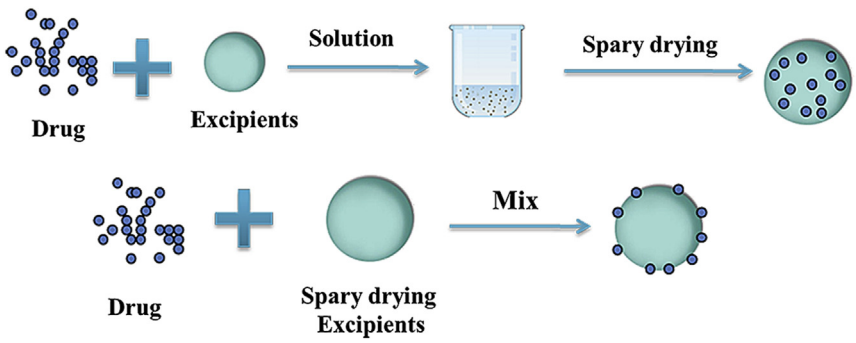

Fig. 1 – The carrier-based and drug/excipient spray dried for DPI dosage forms.