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Original Research Paper

The influence of amino acids on aztreonam spray-dried powders for inhalation

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ABSTRACT

The dry powder inhalation of antibiotics for the treatment of lung infections has attracted drastically increasing attention as it offers rapid local therapy at lower doses and minimal side effects. In this study, aztreonam (AZT) was used as the model antibiotic and spray-dried to prepare powders for inhalation. Amino acids of glycine (GLY), histidine (HIS) and leucine (LEU) were used as excipients to modify the spray-dried particles. It was demonstrated that the GLY-AZT spray-dried powders formed huge agglomerates with the size of 144.51 μm, which made it very difficult to be delivered to the lungs (FPF: 0.29% w/w only). In comparison with the AZT spray-dried powders, HIS-modified spray-dried powders showed increased compressibility, indicating larger distance and less cohesion between particles; while the LEU-modified spray-dried particles showed a hollow structure with significantly decreased densities. The fine particle fraction for HIS- and LEU-modified powders was 51.4% w/w and 61.7% w/w, respectively, and both were significantly increased (one-way ANOVA, Duncan's test, $P < 0.05$) compared to that of AZT spray-dried powders (45.4% w/w), showing a great potential to be applied in clinic.

1. Introduction

Inhaled antibiotics attract increasing attention for the treatment of lung infections, as they are directly delivered to the local sites of infection, which therefore generate quick treatment at low dose and avoid systemic side effects [1]. The delivery of antibiotics through inhalation has developed into a typical approach for the management of lung infections such as chronic *Pseudomonas aeruginosa* associated with cystic fibrosis and mycobacterial pulmonary infections [2]. As a well recognized antibiotic for the remedy of respiratory infections, aztreonam (AZT) has been formulated as inhalation solution (Cayston®, 75 mg/dose, approved by US FDA) and is nebulized to the lungs for the effective treatment of local infections that are associated with cystic fibrosis in most cases

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[3]. However, the use of nebulization has several drawbacks associated with its usage including inconvenience of bulk device, low delivery efficiency and the possibility of damage to the drug molecules by the high shear force [4,5]. In contrast, dry powder inhalers (DPIs) are portable, easy to use and relatively cost-effective. Additionally, rather than the use of propellent to produce aerosols as does the pressurized metered dose inhalers (pMDIs), DPIs utilize patients' inhalation to aerosolize drug particles and therefore avoid the coordination between the inhalation and actuation, which may be a problem associated with pMDIs [6]. Furthermore, the biotherapeutics of proteins, peptides and genes may be more stable in dry state than in aqueous solutions. DPIs therefore have become an attractive approach for drug delivery to the lungs and have gained rapid development in the past decades.

Spray-drying has been confirmed to be an effectual approach to prepare dry powders with sizes within the inhalable range [7]. More importantly, spray-drying technology favors manipulation of particles' physiochemical properties including particle size and size distribution, density, particle shape and morphology [8], which may therefore enhance the powder flowability, dispersibility and deposition in the lower respiratory tract during inhalation. A few studies reported that excipient-free antibiotic (e.g. colistin) spray-dried powders have miraculous aerosolization performance [9], and the combination of different antibiotics (e.g. colistin and rifampicin) can create spray-dried powders with multifunctional characteristics of high delivery efficiency and moisture protection [10]. However, the excipients are usually used in spray-drying formulations to facilitate adjustment of the physiochemical properties of spray-dried powders in order to enhance their dispersibility and delivery efficiency, where some of amino acids including arginine (ARG), phenylalanine (PHE) and leucine (LEU) have been investigated and verified as effective dispersibility enhancers. Based on their chemical structures, the mechanism for dispersibility enhancement is induced by the electrostatic repulsion (ARG, positively charged) and surface modification by hydrophobic molecules (PHE and LEU, low solubility) [11]. However, the histidine (HIS), containing the imidazol functional group, and the hydrophilic glycine have not been investigated in terms of influencing the physiochemical properties and subsequent aerosolization performance of spray-dried powders. Although LEU has been proven to be every effective in enhancing the dispersibility of spray-dried powders, there are no data to fully disclose the function of LEU on the AZT spray-dried powders for inhalation.

Therefore, in this study, AZT was used as a model drug and spray-drying was employed to prepare the dry powders for inhalation. GLY, HIS and LEU were used as the excipients and were dissolved in the spray-drying solution to modify the spray-dried AZT particles. The physiochemical properties, including shape and morphology, particle size distribution, density, moisture content, aerosolization performance and lung deposition, were fully investigated and compared, with the aim to generate dry powder formulations that have enhanced lung delivery efficiency. This will help further construct the links between the structure of amino acids and the aerosolization performance of spray-dried powders.

2. Materials and methods

2.1. Materials

AZT was bought from Shanghai Hongrui Chemical Co. Ltd (Shanghai, China). The amino acids glycine (GLY), histidine (HIS) and leucine (LEU) were purchased from National Medicine Group Chemical Reagent Co. Ltd. (Shanghai, China). Potassium dihydrogen phosphate and ammonia solution were purchased from Sinopharm Chemical Reagent Co. Ltd (Shanghai, China). Methanol at HPLC grade was bought from Spectrum Chemicals & Laboratory Products (Cali, USA). The capsules (3 # Gelatine) were acquired from Suzhou Capsule Company (Suzhou, China). All other chemicals were of analytical grade and used as received.

2.2. Preparation of spray-dried powders

AZT spray-dried powders: two grams of AZT were dissolved in 40 mL of deionized distilled water (dd H_2O) that was subsequently adjusted to pH 4.5 using 1% of ammonia solution to ensure complete drug dissolution. A laboratory scale spray dryer (Büchi Mini Spray Dryer B-290, Büchi Labortechnik AG, Switzerland) was used to prepare the spray-dried AZT powders in an open-cycle system with a pressure nozzle (co-current flow). The standard operation parameters were as follows: inlet temperature 125 °C, aspiration rate 100%, spray flow rate 550 L/h and pump setting 8% (2.4 mL/min). These conditions resulted in an outlet temperature of 76–78 °C.

2.2.1. Amino acid modified spray-dried powders

The amino acids of GLY, HIS and LEU were used respectively as the excipients to prepare spray-dried powders. For the preparation, a total mass of 2 g containing AZT and amino acid of GLY, HIS or LEU at the mass ratio of 40:60 was dissolved in dd H_2O to prepare the spray-drying solutions that were subsequently spray-dried under the standard operation parameters to prepare dry powders. After spray drying, all dry powders were collected from the collection vessel, weighted, and stored in vacuum desiccators for further use. Each formulation was spray-dried in triplicate, and the spray-dried yields were reported.

2.3. Powder characterization

The morphology of spray-dried powders was visualized using scanning electron microscope (SEM, S-5700, Hitachi Co., Tokyo, Japan), operated at 15 kV under high vacuum. Samples of spray-dried powders were sputter-coated with a thin layer (~50 nm) of gold under partial vacuum (HITACHI E-1010, Tokyo, Japan). Representative images of the spray-dried powders were taken under a magnification of 3000–5000×.

Laser diffraction with a dry dispersion system (Mastersizer 2000E, Malvern Instrument, Malvern, UK) was utilized to determine the size distribution of dry powders. Approximately 200 mg of spray-dried powders was used to achieve the obligatory obscuration of 0.5–5%, and the size distribution was subsequently measured in triplicate for each sample. The average particle size was expressed as the volume-weighted mean. The particle size distribution is expressed in terms of