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Formulation, characteristics and aerosolization performance of azithromycin DPI prepared by spray-drying

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ABSTRACT

In this study, a number of dry powder formualtions of azithromycin for inhalation were designed to optimize the composition and further explore the relationship between the composition, the physical properties and the aerosolization performance, hence developing a dry powder inhalation (DPI) of azithromycin (AZI) as an alternative to its counterpart nebulizer. Dry powders of azithromycin with a variety of carrier types and carrier: drug ratios were prepared by spray-drying and characterized afterwards for different physical properties, including particle size and distribution, morphology, flowability, powder density and hygroscopic nature. *In-vitro* deposition was also evaluated after the aerosolization of powders at 60 L min^{-1} via the Aerolizer® into a twin-stage liquid impinger (TI). It was found that the type and amount of the carrier had significant effects on the aerosolization performance of DPI. The results also showed that the particle size and flowability were two critical physical properties responsible for the aerosolization performance. Specifically, moderate particle size around 5–6 μm produced relatively high respirable fractions (RF). In terms of the flowability, the angle of repose within the range of 43°–52° was in a good linear relationship (r=0.9523) with the RF value. In particular, the addition of L-leucine with the carrier:drug ratio of 1:5 showed the highest RF at 37.5%, which indicated that L-leucine is a promising carrier for the dry powder formulation of AZI for inhalation.

1. Introduction

The pulmonary delivery is a promising route for drug administration, both for effective local therapy and systemic administration. Aerosolized antibiotic agents have been used for the treatment of, and prophylaxis against, pulmonary infections since the 1950s mainly due to the fact that the targeted drug delivery can yield high concentrations at the site of infection in the lung while minimizing the systemic toxicity [1]. For the past few decades, the topical application of aerosolized antibiotics has been demonstrated for a number of compounds and indications, but more extensively for aminoglycosides in cystic fibrosis (CF), such as gentamicin [2,3] and the most frequently used tobramycin [4,5].

Azithromycin (AZI), which has been approved by the FDA for treatment of community acquired pneumonia and exacerbations of chronic obstructive pulmonary disease [6], was suggested by recent data [7] as the most promising anti-inflammatory therapy for patients with cystic fibrosis. Cystic fibrosis is a genetic disease that typically produces malnutrition and chronic respiratory infections, and ultimately leads to the death of most patients of this progressive respiratory disease [8]. In addition, several other respiratory disorders, like asthma, bronchiectasis, bronchiolitis obliterans syndrome after lung transplantation, diffuse panbronchiolitis, nontuberculous mycobacterial pulmonary diseases, pneumocystis jirovecii pneumonia and pulmonary nocardia infection, are attractive candidates for treatment with AZI [9]. AZI aerosols exhibit many advantages over the oral administration. Firstly, aerosolized AZI has a targeted effect without diffusing to other unnecessary sites in the body, consequently attaining higher concentrations in the lung (especially the epithelial lining fluid) [10], resulting in a dramatically reduced drug dose via pulmonary delivery. Secondly, oral AZI therapy is commonly associated with gastrointestinal symptoms and long-term use has been linked with hearing impairment, which can be avoided by the delivery of aerosolized AZI directly to the lung [6]. Finally, AZI, among all the macrolide antibiotics, has the strongest post-antibiotic effect (PAE) (up to 2.3–4.7 h) [11], resulting in a relatively short therapy period. Most recently, the first aerosolized AZI, the AZI nebulizer [10], has been developed for the topical treatment of infections. To our knowledge, no DPI study on this drug has been reported yet, therefore, the final objective of this research is to develop a DPI of AZI as an alternative to the reported nebulizer.

Powder engineering, especially the selection of appropriate carriers as well as the control of formulation properties, plays a significant role in DPI investigation and a recent study even suggested the more critical role for powder formulation than the device design [12]. In this study, four candidate carriers were chosen: glycine, lactose, mannitol, and L-leucine. Glycien was chosen as it is a component of commercial Exubera®. The remaining candidates were used as they are recognized as safe and widely used carriers in previous DPI studies [13–18]. Spray-drying, as a single-step processing technique with a great control over the particle characteristics [19–23] was applied for powder preparation. *In-vitro* deposition and main factors that have been reported to

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affect it [24], including morphology, powder density, hygroscopicity, flowability, and particle size were all investigated in this study.

2. Materials and methods

2.1. Materials

AZI raw material (Batch no. 0504076) (Shanghai Modern Pudong Pharmaceutical Co., Ltd), lactose, phosphoric acid and sodium hydroxide (Tianjin Chemical Reagent Company), mannitol (Tianjin Damao Chemical Reagent Factory), L-leucine and glycine (Shanghai Kangda Amino acids Factory), potassium dihydrogen phosphate (Guangdong Shantou Xilong Chemical Factory), and ammonium phosphate monobasic (Tianjin Bodi Chemical Co., Ltd) were obtained from the suppliers indicated.

2.2. Formulation design

Dry powders for inhalation customarily consist of coarse carrier particles and micronized drugs and the dose of the active drug is often in a microgram amount. Inhalant powders in this study, however, were not produced into such an 'ordered mixture' but obtained by spray-drying a solution of drug and carrier. The reasoning behind this was based mainly on the relative large oral therapeutic dose of AZI (a single dose of 250 or 500 mg). A study on the effect of carrier type was carried out with four formulations, i.e., Lac-1, Man-1, Leu-1 and Gly-1 as listed in Table 1. The carrier:drug ratio was 1:5 for these formulations. To investigate the effect of carrier amount (drug load), three different carrier:drug ratios were applied with respect to each carrier. In particular, the carrier:drug ratios of sugar/polyol carriers were higher than those of amino acid carriers as the former is supposed to meet the need of extra bulking agents after the determination of exact drug dose via the pharmacodynamic effect study. In addition, a carrier-free formulation was also prepared as a control.

2.3. Preparation of AZI powders for inhalation

A quantity of AZI raw material was weighed and added to a suitable volume of distilled water, and phosphoric acid was then added dropwise with continuous stirring until a clear solution was obtained. The carrier, accurately weighed according to the carrier:drug ratios in Table 1, was dissolved in distilled water and then mixed with the drug solution. The pH of the obtained solution was adjusted with saturated sodium hydroxide solution to 7.0±0.1 which is reported to be suitable for the lung fluid environment [25], then diluted to volume and passed through a 0.22 μm cellulose acetate filter.

The final solution was spray-dried using an SD-1000 spray dryer (EYELA, Japan) under the following conditions: temperature of the aqueous solution, ambient temperature; inlet temperature, 125±5 °C; airflow rate, 0.60±0.05 m^3 min^{-1}; atomizing pressure, 15–17×10 kpa; pump rate level, 1.8–2.0 (approx. 6–7.5 ml min^{-1}). These conditions resulted in an outlet temperature of 75±5 °C. Once the aqueous solution was consumed, the outlet temperature was maintained at ~80 °C for approx. 15 min by regulating the inlet temperature so as to provide a secondary drying. The resulting dry powders were stored in a vacuum desiccator over silica gel until required for use. All the formulations were prepared from solutions with a same solid concentration (10%) following the same procedure and spray-drying conditions.

Table 1
Formulation design for the investigation into DPI containing AZI

Formulation ID	Type of carrier	Ratio (carrier:drug) (w/w)
Carrier-free	None	/
Lac-1[a]	Lactose	1:5
Lac-2		1:3
Lac-3		1:1
Man-1[a]	Mannitol	1:5
Man-2		1:3
Man-3		1:1
Leu-1[a]	L-leucine	1:5
Leu-2		1:10
Leu-3		1:20
Gly-1[a]	Glycine	1:5
Gly-2		1:10
Gly-3		1:20

[a] Formulations designed for investigating into the effect of carrier types.

2.4. Characterization of spray-dried powders

2.4.1. Particle morphology observations

A small amount of sample was scattered on mutually conductive double-sided adhesive tape placed on an aluminum stub and gold-coated using a JFC-1200 Fine Coater (JEOL, Japan) with a current of 20 mA for 200 s. Scanning electron micrographs were imaged with a scanning electron microscope (SEM) (SSX-550, Shimadzu, Japan) with an accelerating voltage of 15 kV and an emission current of 170 μA by scanning fields randomly at several suitable magnifications.

2.4.2. Powder density and flowability

The packed bulk density (ρ_p) and the angle of repose as the most frequently used index for evaluating powder flowability were measured by a Powder Characteristics Tester PT-R (Hosokawa Micron Corp., Japan). The effective particle density (ρ_e), which is necessary for the calculation of aerodynamic volume mean diameter (D_a), could be obtained from Eq. (1) [26].

$$\rho_e \approx 1.26\rho_p. \quad (1)$$

2.4.3. Hygroscopicity test

Moisture is well known to affect powder cohesion through capillary force at high RH, therefore, a hygroscopicity test is critical for the optimization of powders for inhalation. Triplicate powders were precisely weighed for each formulation (m_1) and added to glass weighing bottles (50 mm×15 mm). All bottles were then placed in the simulated climate cabinet (CLIMACELL 222t, MMM Medcenter Einrichtungen GmbH, Germany) which was working fluently at the set temperature of 25±1 °C and at relative humidities (RH) of 30%, 45%, 60%, 75%, and 80%, respectively. After 24 h running of the unit, the bottles were taken out and weighed again (m_2). The %weight gained of each formulation after storing at each RH was then calculated from Eq. (2), and accordingly, the moisture sorption isotherms were made by plotting the %weight gained against the RH.

$$\text{Weight gained} = (m_2 - m_1)/m_1 \times 100\%. \quad (2)$$

The 60% RH was used to examine the moisture absorption rate because this RH value proved to be the identical inflection point in all the moisture sorption isotherms (see Fig. 1) and rather, at 60% RH, powders containing sugars/polyols dissolved in the sorbed moisture after 24 h. The %weight gained was measured after 2, 4, 8, 12, 16, 20 and 24 h storing. A linear equation was made by plotting %weight gained against the corresponding time and the slope was considered as the moisture absorption rate (MAR).

2.4.4. Particle size analysis

The particle size was determined by both laser diffraction and Time-of-flight (TOF) techniques in order to obtain more reliable results.

A Beckman Coulter LS 230 particle size analyzer was applied for particle sizing by laser diffraction. In this method, powders were poured carefully into the sample cup until the obscuration reported on the title bar of the run window reached about 4%. The measurement was then performed for a sample run time of 90 s. Each sample was