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Physicochemical characterization and aerosol dispersion performance of organic solution advanced spray-dried microparticulate/nanoparticulate antibiotic dry powders of tobramycin and azithromycin for pulmonary inhalation aerosol delivery

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ABSTRACT

The purpose of this study was to systematically design pure antibiotic drug dry powder inhalers (DPIs) for targeted antibiotic pulmonary delivery in the treatment of pulmonary infections and comprehensively correlate the physicochemical properties in the solid-state and spray-drying conditions effects on aerosol dispersion performance as dry powder inhalers (DPIs). The two rationally chosen model antibiotic drugs, tobramycin (TOB) and azithromycin (AZI), represent two different antibiotic drug classes of aminoglycosides and macrolides, respectively. The particle size distributions were narrow, unimodal, and in the microparticulate/nanoparticulate size range. The SD particles possessed relatively spherical particle morphology, smooth surface morphology, low residual water content, and the absence of long-range molecular order. The emitted dose (ED%), fine particle fraction (FPF%) and respirable fraction (RF%) were all excellent. The MMAD values were in the inhalable range (<10 μm) with smaller MMAD values for SD AZI powders in contrast to SD TOB powders. Positive linear correlations were observed between the aerosol dispersion performance parameter of FPF with increasing spray-drying pump rates and also with the difference between thermal parameters expressed as $T_g - T_o$ (i.e. the difference between the glass transition temperature and outlet temperature) for SD AZI powders. The aerosol dispersion performance for SD TOB appeared to be influenced by its high water vapor sorption behavior (hygroscopicity) and pump rates or T_o. Aerosol dispersion performance of SD powders were distinct for both antibiotic drug aerosol systems and also between different pump rates for each system.

1. Introduction

Pulmonary delivery of therapeutics locally to the lung has many advantages over other administration routes (Hickey and Mansour, 2009). Pulmonary drug delivery systems comprise four main categories: nebulizers, pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft-mist inhalers (SMIs). Within each class further differentiation is determined by metering, means of dispersion, or design. DPIs have some advantages over other devices, including relatively high dose delivery and greater chemical stability of the solid-state compare to the liquid state.

There are several methods available to make respirable particles, including micronization, precipitation, freeze drying, and spray drying (Hickey and Mansour, 2008, 2009; Mansour et al., 2009). Spray drying is a one-step high through-put process with the ability to engineer and produce particles in a more controlled manner (such as directing particle size and size distribution, particle and surface morphology) which are important particle features (Wu et al., 2010) for pulmonary dry powder drug delivery by inhalation. The chronic lung infections occurring in cystic fibrosis (CF) reside predominantly in the lower respiratory tract and small peripheral airways (Taylor et al., 1992) where disease progression starts (Tiddens, 2002; Worlitzsch et al., 2002). Microparticulate and nanoparticulate aerosols in the aerodynamic diameter range of ~0.5–2 μm in diameter (Murray and Nadel, 1988; Stahlhofen et al., 1980; Usmani et al., 2005) which can target and deposit in those lung regions exhibit sedimentation and diffusion (Raabe, 1982) particle deposition mechanisms, respectively.

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As two model first-line CF antibiotic drugs in this comprehensive and systematic study, tobramycin (TOB) and azithromycin (AZI) are aminoglycoside and macrolide antibiotics, respectively. TOB and AZI represent different antibiotic drug classes with different physicochemical properties such as hydrophobicity. At present, nebulized liquid inhalation antibiotic aerosols of TOB and aztreonam are approved by the United States Food and Drug Administration (U.S. FDA) for administration by nebulized liquid aerosol inhalation (Park et al., 2011; Paterson, 2006). TOBI® Podhaler® (TOB DPI) has recently gained approval in Europe and in the United States. AZI, a new generation macrolide antibiotic, has been approved by the FDA for treatment of community acquired pneumonia and exacerbations of chronic obstructive pulmonary disease (Prescott and Johnson, 2005) and possesses favorable anti-inflammatory pulmonary effects that have been reported in a long-term study with oral aizthromycin in lung transplant recipients with bronchiolitis obliterans syndrome (BOS) (Shitrit et al., 2005). The clinical success in the treatment of pulmonary infections in a targeted manner providing high therapeutic concentrations locally in the lung, minimizing systemic exposure, and hence decreasing the factors that give rise to the major medical problem of bacterial antibiotic resistance has been reported recently (Garcia-Contreras and Hickey, 2002; Hayes et al., 2009; Park et al., 2011; Song, 2008).

The performance of DPI formulations is influenced by particle properties (such as size and size distribution) and particle surface properties (such as surface morphology and interparticulate forces including van der Waals, electrostatic, and capillary forces), as described in detail by the authors (Hickey and Mansour, 2008, 2009; Hickey et al., 2007a,b; Suarez and Hickey, 2000; Wu et al., 2010; Xu et al., 2010, 2011). The advantages of particle engineering by spray drying for the design of DPI formulations are related to the optimization of important particle properties such as surface morphology, particle morphology, particle size, and size distribution by controlling and tailoring spray drying parameters such as feeding solution conditions (i.e. solvent type, concentration, and feeding rate) and drying gas condition (i.e. gas type, inlet and outlet temperatures, and flow rate) (Hickey and Mansour, 2008; Mansour et al., 2009; Mizoe et al., 2007). In this study, organic solution closed-mode spray drying technique is employed utilizing organic solvent (i.e. an alcohol) for minimization of residual water content and smaller particle size due to its non-aqueous nature and lower surface tension. No water is present in the solvent feed systems, as they are pure alcohol solutions. Compared to the high surface tension of water at ~72 mN/m, alcohols such as methanol (which are also regarded as "green chemicals") have a much lower surface tension in the range of 22–25 mN/m.

One of the novel aspects of this reported study is that we demonstrate for the first time that inhalable microparticulate/nanoparticulate dry powders of these two antibacterial drugs (representing two different major antibiotic drug classes) can be produced and optimized using organic solution advanced spray-drying conditions in closed-mode (no water but only alcohol) which we have previously reported for the first time for pulmonary delivery applications as DPIs (Li and Mansour, 2011; Meenach et al., 2013; Wu et al., 2013a,b). In addition, this comprehensive and systematic study aims to design, optimize, and develop novel microparticulate/nanoparticulate antibiotic (TOB and AZI) dry powder aerosols using advanced organic solution spray drying, comprehensively examine the effect of spray-drying conditions on the solid-state physicochemical properties and aerosol dispersion performance of particles for each antibiotic drug, and systematically compare the influence of different physicochemical properties on aerosol dispersion performance as novel DPIs. Moreover, this study probes and correlates the fundamental interplay between various spray-drying conditions, particle physicochemical properties, and aerosol dispersion performance as DPIs.

2. Experimental materials and methods

2.1. Materials

Tobramycin (TOB) (U.S.P. grade) ($C_{18}H_{37}N_5O_9$; M.W.: 467.515 g/mol) was obtained from Spectrum (New Brunswick, New Jersey). Azithromycin (AZI) (U.S.P. grade) ($C_{38}H_{72}N_2O_{12}$; M.W.: 748.984 g/mol) was purchased from APAC pharmaceutical LLC (Columbia, MD) with a purity of 98%. Methanol (HPLC grade, ACS-certified grade, purity 99.9%) and chloroform (HPLC grade, ACS-certified grade, purity 99.9%) were obtained by Fisher Scientific (Pittsburgh, PA, USA). HYDRANAL®-Coulomat AD was from Sigma–Aldrich (St. Louis, Missouri). AQUA STAR anhydrous methanol was from EMD chemical Inc. (Gibbstown, New Jersey). Raw TOB and AZI were stored in sealed glass desiccators over Indicating Drierite/Drierite™ desiccant at 4 °C under ambient pressure. Water was obtained by Milli-Q P-QOD set-up from Millipore (Fair Lawn, NJ, USA) with a resistivity of 18.1 MΩ cm. All nitrogen gas used for experiments was an ultra-high purity (UHP) nitrogen gas manufactured by Scotts Gross, Lexington, KY. All powders were used as stored in desiccators in the freezer at −20 °C. All materials were used as received.

2.2. Methods

2.2.1. Preparation of spray dried particles by organic solution advanced spray-drying (no water) in closed-mode

Organic solution advanced spray-drying process in the absence of water using dilute drug solutions was performed in closed-mode using a Büchi B-290 Mini Spray Dryer with a high performance cyclone in closed-mode using UHP dry nitrogen gas as the atomizing drying gas and connected to the B-295 Inert Loop (Büchi Labortechnik AG, Flawil, Switzerland) under UHP nitrogen gas (Scott-Gross, Lexington, Kentucky). The feeding solution was prepared by dissolving each drug in methanol to make a dilute drug solution with a concentration of 0.1% w/v. The following conditions were used during the spray-drying process: Atomization rate, 600 L/h; Aspirate rate, 35 m^3/h; Pump rate, 3 mL/min (10%) (low pump rate), 15 mL/min (50%) (medium pump rate), and 30 mL/min (100%) (high pump rate). The inlet temperature was set at 150 °C. The corresponding outlet temperatures for different formulations are summarized in Table 1. The stainless steel nozzle diameter was 0.7 mm. The spray-dried (SD) particles were separated from the nitrogen drying air in the high-performance cyclone and collected in a sample collector. All SD powders were carefully stored in sealed glass vials that were stored in sealed glass desiccators containing Indicating Drierite/Drierite™ desiccant at −20 °C under ambient pressure.

2.2.2. Scanning Electron Microscopy (SEM)

Visual imaging and analysis of particle size, morphology, and surface morphology was achieved by SEM using a Hitachi S-800 microscope (Tokyo, Japan), using conditions previously reported

Table 1
Summary of organic solution advanced spray drying conditions in closed-mode from methanol solution.

Antibiotic drugs	Pump rate (%)	Inlet temperature (°C)	Outlet temperature (°C)
Tobramycin	10	150	88
	50	150	69
	100	150	35
Azithromycin	10	150	89
	50	150	75
	100	150	50