Design, Characterization, and Aerosol Dispersion Performance Modeling of Advanced Co-Spray Dried Antibiotics with Mannitol as Respirable Microparticles/Nanoparticles for Targeted Pulmonary Delivery as Dry Powder Inhalers

XIAOJIAN LI,[1] FREDERICK G. VOGT,[2] DON HAYES JR.,[3,4] HEIDI M. MANSOUR[5]

[1]University of Kentucky College of Pharmacy, Department of Pharmaceutical Sciences-Drug Development Division, Lexington, Kentucky 40536-0596
[2]GlaxoSmithKline, Analytical Sciences, Product Development, King of Prussia, Pennsylvania 19406
[3]The Ohio State University College of Medicine, Departments of Pediatrics and Internal Medicine, Lung and Heart-Lung Transplant Programs, Columbus, Ohio 43205
[4]The Ohio State University College of Medicine, The Davis Heart and Lung Research Institute, Columbus, Ohio 43205
[5]The University of Arizona-Tucson, College of Pharmacy, Skaggs Pharmaceutical Sciences Center, Tucson, Arizona 85721-0202

Received 12 February 2014; accepted 4 March 2014

Published online 16 April 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23955

ABSTRACT: Dry powder inhalation aerosols of antibiotic drugs (a first-line aminoglycoside, tobramycin, and a first-line macrolide, azithromycin) and a sugar alcohol mucolytic agent (mannitol) as co-spray dried (co-SD) particles at various molar ratios of drug:mannitol were successfully produced by organic solution advanced co-spray drying from dilute solute concentration. These microparticulate/nanoparticulate aerosols consisting of various antibiotic drug:mannitol molar ratios were rationally designed with a narrow and unimodal primary particle size distribution, spherical particle shape, relatively smooth particle surface, and very low residual water content to minimize the interparticulate interactions and enhance *in vitro* aerosolization. These microparticulate/nanoparticulate inhalation powders were high-performing aerosols as reflected in the aerosol dispersion performance parameters of emitted dose, fine particle fraction (FPF), respirable fraction (RF), and mass median aerodynamic diameter (MMAD). The glass transition temperature (T_g) values were significantly above room temperature, which indicated that the co-SD powders were all in the amorphous glassy state. The T_g values for co-SD tobramycin:mannitol powders were significantly lower than those for co-SD azithromycin:mannitol powders. The interplay between aerosol dispersion performance parameters and T_g was modeled where higher T_g values (i.e., more ordered glass) were correlated with higher values in FPF and RF and lower values in MMAD. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2937–2949, 2014

Keywords: anti-infectives; glass transition; spray drying; pulmonary drug delivery; aerosols; particle size respiratory delivery; lung; confocal Raman microscopy; solid state particle engineering design

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease with a high mortality rate in the pediatric and young adult populations due to chronic pulmonary infections[1–3] that are not adequately targeted nor treated. Hence, there are unmet medical needs in the treatment of pulmonary infections in CF patients in terms of directly targeting specific lung regions where the infection resides. However, CF is a multifactorial disease that affects the lungs through inhibition of the mucociliary escalator function, viscous mucus accumulation, and consequently, bacteria colonization.[4] Our recent studies[5,6] reported on the design, characterization, and aerosolization of high-performing one-component dry powder inhalers (DPIs) for the first-line CF aminoglycoside antibiotic tobramycin ("TOB"), the first-line macrolide antibiotic azithromycin ("AZI"), and the mucolytic nonreducing sugar alcohol mannitol ("MAN") designed and produced from organic solution advanced spray drying in closed mode. These microparticulate/nanoparticulate dry powder inhalation aerosols possessed the essential particle properties necessary for targeting the smaller airways and deep lung bronchioalveolar region with high local deposition.

Co-spray drying a solution containing two active pharmaceutical particles is a potential alternative to produce particles with uniform drug composition.[7] In particular, it can deliver all the therapeutic agents to the same target regions in the lungs of CF patients by pulmonary delivery without variation in dose for different therapeutic agents. In addition, two-component aerosol particles may have synergistic effects because of the simultaneous deposition and colocalization in the same lung region (compared to delivering two separate individual aerosols in CF patients), as has been demonstrated clinically to be superior in the treatment and management of asthma and chronic obstructive pulmonary disease (COPD). Since chronic lung infections occurring in CF reside in the lower respiratory tract and

Correspondence to: Heidi M. Mansour (Telephone: +520-626-2768; Fax: +520-626-7355; E-mail: mansour@pharmacy.arizona.edu)

Journal of Pharmaceutical Sciences, Vol. 103, 2937–2949 (2014)

small peripheral airways[8] where disease progression starts,[9,10] typically microparticulate and nanoparticulate aerosols (~0.5–2 μm in diameter)[11–13] are required to have effective particle deposition in high enough local concentrations in those regions by particle deposition mechanisms of sedimentation and diffusion[14], respectively.

Pulmonary drug delivery systems as inhalation aerosols offer many important advantages for the local treatment of pulmonary diseases.[15] The four principal categories are nebulizers, pressurized metered-dose inhalers, soft-mist inhalers, and DPIs. This classification is based on the physical states of the dispersed phase and continuous medium. Within each class, further differentiation is determined by metering, means of dispersion, and device design. DPIs offer unique and important advantages[15–18] including high dose delivery locally at the site of action and higher physicochemical stability relative to liquid-based therapeutic aerosols. The performance of DPI formulations is influenced by particle size distribution, surface morphology, and interparticulate forces including van der Waals, electrostatic, and capillary forces, as described in detail by the authors and others.[16–21] Minimization of residual water content and smaller primary particle size in the solid state is achieved through the use of an organic solvent (i.e., an alcohol) because of its nonaqueous nature and lower surface tension relative to water (72 mN/m). We have reported on the design, characterization, and modeling of high-performing microparticulate/nanoparticulate DPIs[22–25] for delivery of a wide variety of drugs from different therapeutic classes to treat different pulmonary diseases. Building on our recent studies on high-performing one-component microparticulate/nanoparticulate DPIs of TOB,[6] AZI,[6] and MAN,[5] organic solution co-spray drying in closed mode has been employed in this study for the preparation of high-performing two-component DPIs consisting of microparticles and nanoparticles. To the authors' knowledge, this systematic study is the first to report on inhalable microparticulate/nanoparticulate dry powders of these two antibacterial drugs (representing two different first-line antibiotic drug classes) co-spray dried (co-SD) with MAN using organic solution advanced co-spray drying in closed mode, comprehensive physicochemical characterization, and *in vitro* aerosolization performance as high-performing DPIs. In addition, this comprehensive and systematic study examines and correlates the interplay between solid-state physicochemical properties, glass transition temperatures, and DPI aerosol dispersion performance parameters.

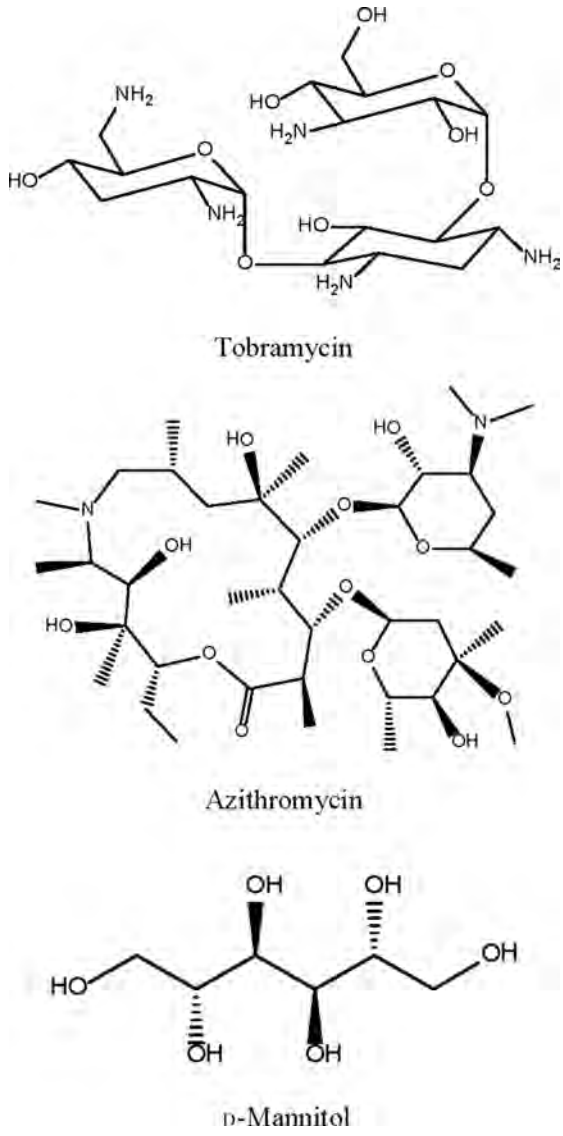

Figure 1. The chemical structures of antibiotic drugs (tobramycin and azithromycin) and D-mannitol.

MATERIALS AND METHODS

Materials

TOB [United States Pharmacopeia (USP) grade] [$C_{18}H_{37}N_5O_9$; molecular weight (MW): 467.515 g/mol], shown in Figure 1 (ChemDraw Ultra® Ver. 10.0.; CambridgeSoft, Cambridge, Massachusetts), was obtained from Spectrum (New Brunswick, New Jersey). AZI (USP grade) ($C_{38}H_{72}N_2O_{12}$; MW: 748.984 g/mol), shown in Figure 1 (ChemDraw Ultra® Ver. 10.0.; CambridgeSoft), was purchased from APAC pharmaceutical LLC (Columbia, Maryland). Raw D-MAN ($C_6H_{14}O_6$; MW: 182.17 g/mol) (Fig. 1) was from Sigma–Aldrich (St. Louis, Missouri). Methanol (HPLC grade, ACS-certified grade, purity 99.9%) and chloroform (HPLC grade, ACS-certified grade, purity 99.9%) were obtained from Fisher Scientific (Fair Lawn, New Jersey). HYDRANAL® -Coulomat AD was from Sigma–Aldrich. AQUA STAR anhydrous methanol was obtained 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. Raw D-MAN was used as received and stored under room conditions. Other chemicals were stored under room conditions. The nitrogen gas used was ultra-high purity (UHP) nitrogen gas (Scotts Gross, Lexington, Kentucky).

Methods

Preparation of Co-SD Particles by Organic Solution Advanced Co-Spray Drying (No Water) in Closed Mode

Organic solution advanced co-spray drying processing in the absence of water 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