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Research Article

Investigation of the Changes in Aerosolization Behavior Between the Jet-Milled and Spray-Dried Colistin Powders Through Surface Energy Characterization

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ABSTRACT

This study aimed to investigate the surface energy factors behind improved aerosolization performance of spray-dried colistin powder formulations compared with those produced by jet milling. Inhalable colistin powder formulations were produced by jet milling or spray drying (with or without L-leucine). Scanning electron micrographs showed the jet-milled particles had irregularly angular shapes, whereas the spray-dried particles were more spherical. Significantly higher fine particle fractions were measured for the spray-dried (43.8%-49.6%) versus the jet-milled formulation (28.4%) from a Rotahaler at 60 L/min; albeit the size distribution of the jet-milled powder was smaller. Surprisingly, addition of L-leucine in the spray drying feed solution gave no significant improvement in fine particle fraction. As measured by inverse gas chromatography, spray-dried formulations had significantly ($p < 0.001$) lower dispersive, specific, and total surface energy values and more uniform surface energy distributions than the jet-milled powder. Interestingly, no significant difference was measured in the specific and total surface energy values between the spray-dried formulation with or without L-leucine. Based on our previous findings in the self-assembling behavior of colistin in aqueous solution and the surface energy data obtained here, we propose the self-assembly of colistin molecules during spray drying contributed significantly to the reduction of surface free energy and the superior aerosolization performance.

Introduction

Oral and parenteral administrations of antibiotics are common clinical practices for the treatment of respiratory infections. However, for some antibiotics, only small proportions of drugs are present at the infection sites in airways, and hence, high doses are required to maintain the local drug concentration above the minimum inhibitory concentrations.[1] Such high doses via systemic routes can cause serious side effects.[2] For example, intravenous administration of colistin (the last-line antibiotic for many multidrug-resistant gram-negative bacteria) can cause nephrotoxicity in up to 45% of treated patients.[3,4]

In contrast, inhaled therapy can deliver antibiotics directly to the infection site in the respiratory tracts, such that optimal local drug concentration and prolonged action time can be achieved with a less dose and minimized systemic exposure.[1,5,6] For example, a pharmacokinetic study of nebulized colistimethate sodium solution (2 million IU) in cystic fibrosis patients demonstrated significantly higher drug concentrations in sputum (C_{max}, 6 mg/L) for a prolonged period (e.g., 12 h) and negligible systemic drug exposure (C_{max} in plasma <0.3 mg/L).[7] Inhaled therapy via nebulization of antibiotic solution has become popular in the clinic for the treatment of respiratory infections.[8] Compared to wet nebulization, dry powder inhalers (DPIs) are gaining increasing interest for inhaled antibiotic treatment because in general, powders are more stable than the wet formulations and provide access to higher dose in a single actuation,[9] and DPIs are more convenient to carry;[10,11] although local side effects may occur due to inhaling high-dose powders of some drugs.[5]

Jet milling is a common industrial approach to produce inhalable drug powders.[12] However, jet-milled powders are often highly

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cohesive because of the high surface energy generated during the milling process.[13] The jet-milled powder thus often possesses poor flowability, fluidization, and aerosolization properties.[14] As the dose of inhaled antibiotics is usually high (e.g., up to 100 mg), particle engineering approaches (e.g., spray drying) have been extensively used with the motivation to improve aerosol performance by altering the particle morphology, bulk density, and surface energy of the drug powder.[1,15] Particles formed from spray drying can be spherical,[16] porous,[17] wrinkled[18] and dimpled;[19,20] each of which is proposed to be optimized for improved aerosolization performance.[21] Excipients and spray drying parameters can be manipulated to control the particle size, morphology, and surface energy.[22] Aerosol performance of powders is strongly affected by the surface energy[23] as interparticulate forces are dependent on the surface energy of the particles.[24] Higher surface free energy results in larger cohesion or adhesion forces.[25] Incorporating excipients such as amino acids into the formulation before spray drying was shown to improve powder dispersion.[19,26,27] It was hypothesized that addition of L-leucine reduces the surface energy of the particle because of its surfactant-like properties, where the hydrophobic low-energy L-leucine migrates to the surface of the droplet during spray drying.[26]

In the recent years, inverse gas chromatography (IGC) has been increasingly exploited to measure surface energy and to investigate particulate interactions of the pharmaceutical powder formulations.[28-30] The principle of surface energy measurement by IGC has been extensively reviewed.[31,32] The surface energy characteristics can be determined under either the infinite or finite dilution conditions. At the infinite dilution, Henry's law is obeyed as the low probe concentration does not allow for probe–probe interaction,[33] thus only interacting with the highest energy sites of the sample. As infinite dilution only measures the highest energy sites of the particle surface (usually <0.1% of the total surface area), surface energy results from this method may not be a representation of the whole particle surface.[34] Finite dilution involves the gradual increase in probe concentration, hence determines the surface energy distribution over a proportion of the powder.[30]

An earlier study reported that spray drying colistin without any excipient can successfully produce an inhalable powder with FPF total of >80% via an aerolizer at 100 L/min.[35] However, the aerosolization performance of spray-dried colistin (SDC) has not been compared with the traditional jet-milled formulation. Furthermore, the mechanisms of high aerosol performance of SDC powders have yet been investigated. In the present study, we compared the aerosol performance of inhaled colistin powders produced by jet milling or spray drying via a low-resistance device (Rotahaler) at a moderate flow rate of 60 L/min. We also investigated the potential use of L-leucine to improve aerosolization of colistin and notably examined the surface energy characteristics of engineered particles. Our study provides a better understanding in the relationship between surface energy and powder aerosolization of colistin DPI formulations.

Materials and Methods

Materials

Colistin sulfate was purchased from Zhejiang Shenghua Biok Biology Co., Ltd. (Hangzhou, China). Analytical grade L-leucine, trifluoroacetic acid (TEA), and HPLC grade dichloromethane were purchased from Sigma-Aldrich (Castle Hill, Australia). HPLC grade acetonitrile (Fisher Scientific, Fair Lawn, NJ), absolute ethanol (AR grade; Merck, Australia), and Milli-Q grade water (Millipore Corporation, Billerica, MA) were also used in the study. GC grade undecane, decane, nonane, octane, heptanes, and ethyl acetate were purchased from Fluka Aldrich (Castle Hill, Australia). Methane 5.0, helium 5.0 (both from Linde, North Ryde, Australia), compressed instrument air, and hydrogen (Coregas, Yennora, Australia) gas were used. The Rotahaler was provided by GSK (Middlesex, UK). Gelatin capsules were donated by Capsugel (Peapack, NJ).

Spray Drying

The feed solutions were prepared with 2% wt/vol of colistin sulfate in MilliQ water. Various amounts of L-leucine (5%, 10%, and 20% wt/wt) were added into the feed solution before spray drying for those L-leucine–containing formulations. The spray drying (Büchi 190 Mini Spray Dryer; Postfach, Switzerland) conditions were set as follows: 2 mL/min pump speed; 100 ± 5°C inlet temperature; spray flow rate, 600 L/h; and aspirator setting, 100%. The outlet temperature remained steady at 60 ± 5°C.

Jet Milling

A spiral jet mill (model 50AS; Hosokawa Alpine, Augsburg, Germany) was used to micronize the colistin powder. Colistin powder was fed manually into the feed chute, where it came into contact with 4 nozzles (0.8-mm diameter). An inlet air pressure of 5 bar and a grinding pressure of 6 bar were used.

Particle Size Distribution

A Mastersizer S (Malvern Instruments, Malvern, UK) coupled with a 300-mm Fourier lens was used to measure the particle size distribution of colistin powder formulations. A 150-mL liquid dispersing unit was filled with ethanol and used to disperse colistin particles. The spray-dried formulations were added until an obscuration between 10% and 25% was achieved.

Scanning Electron Microscopy

Each powder formulation was placed onto a scanning electron microscope (SEM) mount and was coated for 3 min by an Emitech, K550X Sputter coater (Quorum Technologies Ltd., East Sussex, UK) to form a thin layer of gold with 20-nm thickness. SEM images were taken under a Phenom SEM (FEI Company, Hillsboro, OR).

In Vitro *Aerosol Deposition*

In vitro aerosol deposition of the DPI formulations was assessed using a twin stage impinger (TSI; Apparatus A, British Pharmacopeia 2005; Copley Scientific, Nottingham, UK). Although the TSI provides only a single cut with limited aerosol quality information, it was selected as considered suitable for this study to prevent particle bounce for high-dose powder aerosols that may be experienced with current impactors. Stage 1 (S1) and stage 2 (S2) were filled with 7 mL and 30 mL of water, respectively. An airflow of 60 L/min was drawn through the TSI by a Dynavac pump (Model OD5/2; Dynavac Engineering, Australia) for 4 s to pass 2.4 L air through the Rotahaler device. Hard gelatin capsules (Size 3) were filled manually with 15 mg of powder and loaded into the Rotahaler. All TSI measurements were performed in 5 replicates. Recovered dose was defined as the total amount of drug collected in the inhaler, S1 and S2. The recovery was calculated using Equation 1. Fine particle fraction (FPF) was calculated using Equation 2.