Spray Dried Formulations for Nasal Applications – Challenges and Opportunities in Filling and Drug Delivery

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INTRODUCTION

Dry powder formulations are more commonly used in oral inhalation than in nasal drug delivery. Commonly used for dry powder lung delivery are blends of up to 2% micronized active pharmaceutical ingredient (API) attached to larger carrier particles. This strategy may also be used in nasal delivery [1], although the low API concentration limits its applicability. Spray dried powders are gaining more attention as they can be engineered to carry a larger amount of API compared to powder blends, and their aerodynamic properties can be tailored for specific purposes [2]. However, spray dried formulations have different bulk properties compared to interactive blends, such as a high specific surface area and low bulk density. These properties oftentimes result in adhesive powders exhibiting poor flowability, which can hamper bulk powder handling during the filling process and may also affect device emptying. In this study spray dried formulations for nasal application are evaluated to point out challenges and opportunities encountered in the filling process and during aerosol generation.

MATERIAL AND METHODS

Model Formulations

One batch of nasal particles (N/MS/2%; nasal and mostly spherical particles containing 2% Brilliant Blue (BB) in the powder) were obtained by spray drying an aqueous solution of 10% mannitol (Pearlitol C, Roquette) and 0.2% erioglaucine disodium (commonly known as Brilliant Blue, Sigma-Aldrich), with a spray dryer (Niro Atomizer, Copenhagen). The atomizer was operated with a centrifugal disc at 18,100 rpm. The inlet temperature was set to 150˚C and outlet temperature adjusted to 90˚C. BB was used as a water soluble model drug that is easily quantified by spectrometry at 630 nm. Another batch of powder (N/S/0.5%; nasal spherical particles) was prepared from an aqueous solution of 10% mannitol and 0.05% BB using a Büchi Mini Spray Dryer (B-290) and a high performance cyclone (Büchi Labortechnik, Switzerland). The operating conditions were 130˚C inlet temperature, 61˚C outlet temperature, an aspirator rate of 35 m^3/h, and an ultrasonic nozzle (60 kHz) set to 1.6 W. Use of two spray driers operated with different settings and two concentrations of BB allowed formation of powders with a range of properties.

Particle Size Distribution

The particle size distribution (PSD) was measured by laser diffraction using a HELOS laser diffractometer connected to the RODOS dispenser system with dispersion at 0.2 bar (n = 3). Windox 5.8.0.0 software (Sympatec GmbH, Germany) based on Fraunhofer theory was used for data analysis.

Bulk Density and Specific Surface Area

Bulk density was assessed by measuring the volume of 3 g of powder in a measuring cylinder. Specific Surface Area (SSA) was determined with the Gemini 2360 (Micromeritics, USA) using nitrogen (n = 3) according to the Brunauer-Emmett-Teller-equation. Each sample's true density was measured with the Pycnomatic ATM (Porotec GmbH, Hofheim, Germany).

Flowability

The flow function coefficient (ffc) was measured using the FT4 powder rheometer (Freeman Technology, UK). The measurement was performed three times with the 1 mL shear cell. An ffc between 4 and 10 indicates a good flowing powder, and above 10, a free flowing powder.

Nasal Delivery

Nasal deposition was assessed with a male nasal cast (Figure 1A) generated from a CT scan [3] utilizing the unit dose system (UDS) powder device (Aptar Pharma, Figure 1B). The nasal cast enables the quantification of the powder in different nasal zones. The nostrils are flexible, so the device can be placed in human nostrils. We believe this measurement method is reliable and accurate, and *in vitro* results have been correlated to *in vivo* results [3, 4]. Before each powder administration test, an ultrasonic aerosol generator (MHZ Atomisor AMGH, La Diffusion Technique Française, France) was used to condense water droplets on the internal surfaces of the cast and increase the humidity of the airspaces. Delivery angles of 45˚ and 60˚ to horizontal plane and insertion depths of 10 mm and 15 mm were tested. Inspiration conditions ranging from no flow to 15 and 70 L/min of ambient air were simulated. A vacuum pump and flow meter were

connected to the "lung" exit of the cast (Figure 1A). The flow was set to 15 or 70 L/min without the UDS powder device in the nostrils. The device was then placed in one nostril (leaving the other nostril open) and a dose delivered. A second dose was delivered into the opposite nostril using the same process. After deposition of the powder formulations, each cast segment was rinsed with water and the powder content assessed spectroscopically.

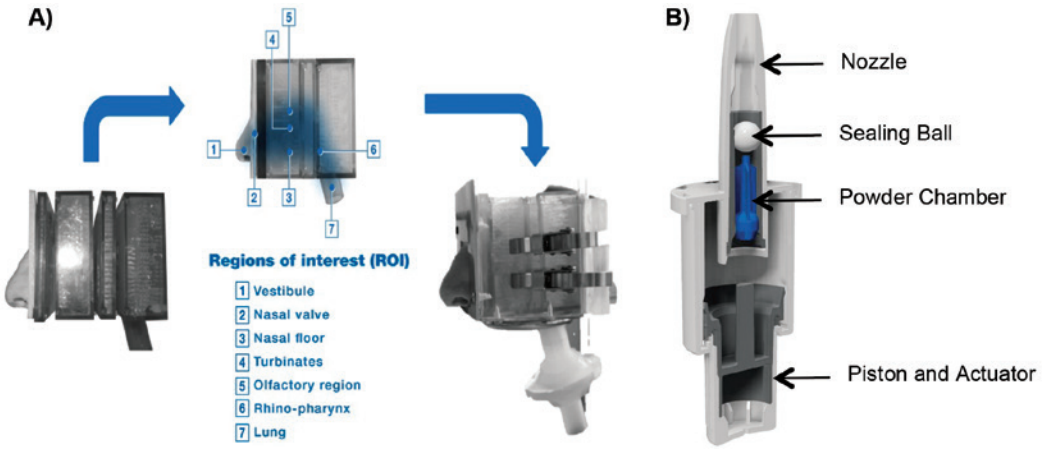

Figure 1. A) Nasal cast from Aptar Pharma. B) UDS powder device.

Fine particle fraction (FPF) was assessed with the next generation impactor and a 2 L expansion chamber (Copley Scientific, UK), coated with a mixture of propylene glycol and Brij dissolved in ethanol. For each assessment, two unit dose powder devices were filled with 25 mg of spray dried powder, and tested at a flow rate of 15 L/min. BB was quantified as described previously. The UDS powder devices were either manually or semi-automatic filled. The latter was performed with an Omnidose machine (Harro Höfliger, Germany) utilizing the drum system.

RESULTS AND DISCUSSION

Spray drying resulted in spherical (N/S/0.5%) or mostly spherical particles (N/MS/2%) with a mean geometric diameter of 22.2 ± 0.1 µm for N/S/0.5% (span = 1.01) and 24.6 ± 0.3 for N/MS/2% (span = 2.09), which is within the target size for nasal delivery of 20-30 µm. The bulk density was 0.485 ± 0.005 g/mL (N/S/0.5%) and 0.438 ± 0.002 g/mL (N/MS/2%), suggesting the N/MS/2% particles with a more uneven appearance had a slightly lower bulk density due to their shape. The ffc was 7.36 ± 0.12 (N/S/0.5%) and 7.28 ± 1.33 (N/MS/2%), which classifies both powders as good flowing. Smaller spray dried materials engineered for pulmonary delivery (mean diameter ~ 2.5 µm) showed an ffc of only 3.30 ± 0.6 [5], suggesting that the larger particle size is the main reason for improved flowability. We anticipate our nasal powders will perform well during automatic filling due to this improved flowability. The SSA was determined to be 0.381 ± 0.032 m^2/g (N/S/0.5%) and 0.239 ± 0.049 m^2/g (N/MS/2%). The N/S/0.5% formulation could be easily filled with an RSD of 2 % (n = 70, mean fill weight 43.04 mg). Device actuation resulted in an emitted fraction of 99.02 ± 0.85% by weight. Deposition in the nasal cast showed high levels of BB in the olfactory region (upper turbinates). This region is a target for nose-to-brain delivery, but is often considered difficult to access [6]. The highest overall nasal deposition of 59% was achieved at an angle of 45° independently of insertion depth (10 or 15 mm, respectively; Figure 2).

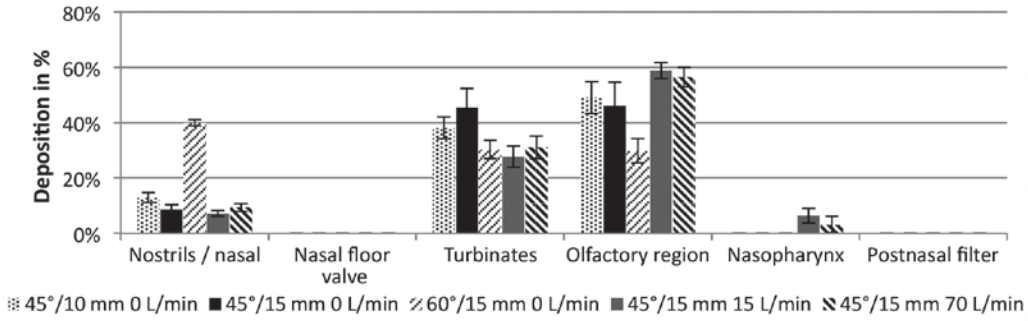

Figure 2. Deposition of BB in N/MS/2% in the male nasal cast at different insertion depths (10 and 15 mm), different angles (45° and 60°) and different inspiration rates of 0 L/min, 15 L/min, and 70 L/min (n = 3, error bars are standard deviation).

The tests with constant air flow rates showed more powder deposited in the olfactory region than those conducted under no-flow conditions (Figure 2). The N/S/0.5% formulation showed even higher deposition in the olfactory region during these preliminary experiments (data not shown). A female cast model resulted in comparable deposition profiles (data not shown). Downstream of the nasal model we observed a FPF of only 0.250 ± 0.005% (N/S/0.5%) and 0.440 ± 0.036% (N/MS/2%), which indicates that most particles are retained in the targeted nasal regions.

CONCLUSIONS

This study showed that dry powder formulations for nasal delivery can be produced by spray drying. Such powders are fillable using standard powder filling equipment. Our *in vitro* tests suggest a very small fraction of nasally administered powder will pass the nose and enter the lungs. We observed high deposition in the olfactory region of the model when powder was administered utilizing the UDS powder device. This may be interesting for nose-to-brain-delivery. The influence of particle morphology will be considered in future studies.

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