

## Superior performance of engineered mannitol as a carrier in dry powder inhalations containing salbutamol sulphate

Item Type	Working paper
Authors	Nokhodchi, A.;Kaialy, Waseem
Publisher	PBP 9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology
Download date	2026-06-16 12:48:01
Link to Item	<a href="http://hdl.handle.net/2436/620753">http://hdl.handle.net/2436/620753</a>

# Superior performance of engineered mannitol as a carrier in dry powder inhalations containing salbutamol sulphate

Ali Nokhodchi, Medway School of Pharmacy, University of Kent, Chatham Maritime, ME4 4TB, Kent, UK, [a.nokhodchi@kent.ac.uk](mailto:a.nokhodchi@kent.ac.uk); **Waseem Kaialy**, Medway School of Pharmacy, University of Kent, Chatham Maritime, ME4 4TB, Kent, UK, [waseemkaialy@hotmail.co.uk](mailto:waseemkaialy@hotmail.co.uk)

## INTRODUCTION

The increasing incidence of respiratory diseases such as cystic fibrosis, asthma, chronic obstructive pulmonary disease, infectious diseases, lung cancer and tuberculosis, makes pulmonary drug delivery a main point of focus in current drug delivery research. Dry powder inhalers (DPIs) have been the subject of widespread research interest over the past few years. However, obtaining high drug aerosolization efficiency is a major challenge for DPI formulations because most DPIs still have relatively poor drug aerosolization performance (1). Despite the extensive research on lactose as a carrier in DPI formulations (2–4), lactose still suffers from some serious pitfalls including unsuitability for diabetic patients, interaction with certain drugs containing amino groups, for example, formotrol and budesonide, and interaction with peptides and protein drugs due to its reducing function (5). Therefore the objective of this study was to introduce freeze-dried mannitol as an alternative promising carrier in DPI formulations containing salbutamol sulphate (SS) as a model drug. This study was performed with a view to propose optimal mannitol product (freeze-dried mannitol *versus* spray-dried mannitol and commercial mannitol) for SS based drug-carrier dry powder inhaler formulations.

## MATERIALS AND METHODOLOGY

Commercial mannitol (CM) and spray dried mannitol (SDP) and micronized salbutamol sulphate (LB Bohle, Germany) were purchased. Mannitol was freeze dried using a SCANVAC CoolSafe™ freeze-dryer. Different mannitol powders were sieved to collect 63-90 µm particles and then characterized in terms of size (laser diffraction), shape (scanning electron microscopy, SEM), surface morphology (Atomic force microscopy (AFM)), solid state (differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FT-IR) and powder X-ray diffraction (PXRD)), density (ultrapycnometer 1000) and flowability. SS-mannitol aerosol formulations were evaluated in terms of drug homogeneity, SS-mannitol adhesion and *in vitro* aerosolization performance of SS using a multistage liquid impinge and Aerolizer® inhaler device at 92 L/min flow rate.

## RESULTS AND DISCUSSION

SEM images of all mannitol used and their aerosolization pattern through MSLI were shown in Figure 1. Figure 1 shows that Freeze dried mannitol demonstrated had

superior DPI performance with a fine particle fraction believed to be the highest so far reported in literature for salbutamol sulphate (SS) under similar protocols (FPF=46.9 %) (Figure 1). To a lesser extent, spray dried mannitol produced better aerosolization performance than commercial mannitol. Freeze dried mannitol demonstrated elongated morphology and poor flowability, whereas spray dried mannitol demonstrated spherical morphology and excellent flowability. Commercial mannitol demonstrated angular morphology and good flowability (Figure 1).

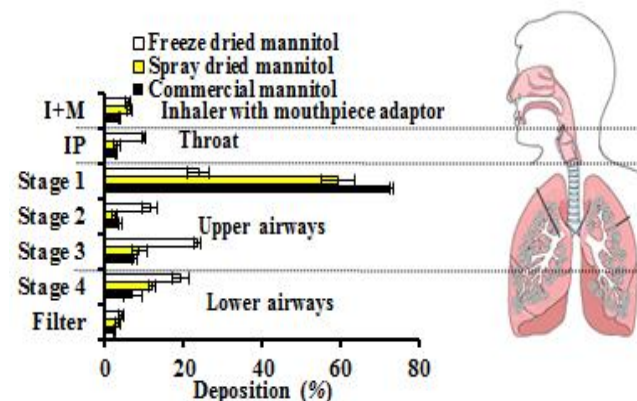
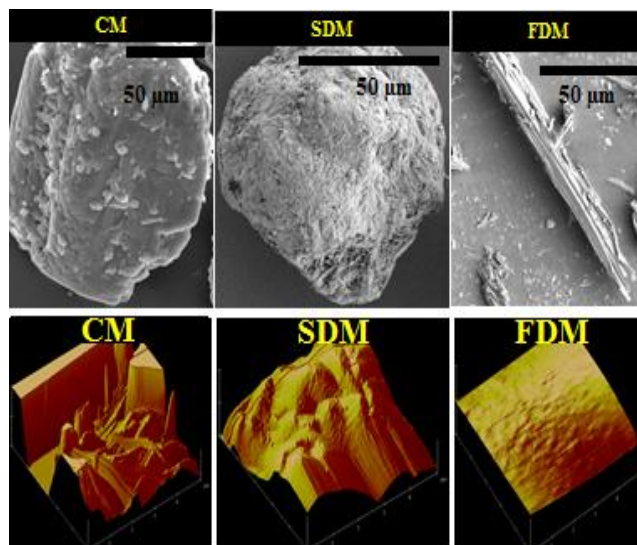


Figure 1. SEM images various mannitol samples (top figure) and the amounts of SS deposited on inhaler plus mouthpiece adaptor (I&M), induction port (IP) and different multi stage liquid impinger stages.

Solid state analyses (Figures not shown) demonstrated that CM was  $\beta$ -mannitol whereas SDM was mixtures of  $\alpha$ - and  $\beta$ -mannitol and FDM sample crystallized as a mixture of  $\alpha$ -,  $\beta$ -, and  $\delta$ -mannitol forms. Such results indicate the suitability of the applied freeze drying method to prepare crystalline mannitol product.  $\alpha$ -,  $\beta$ -, and  $\delta$ -mannitol polymorphic forms are stable for minimum 5 years in dry atmosphere at 25 °C.

Roughness analysis ( $5 \times 5 \mu\text{m}$ ) confirmed that CM particles ( $R_q = 300.1 \pm 37.9 \text{ nm}$ ,  $R_a = 220.0 \pm 17.4 \text{ nm}$ ) have relatively rougher surfaces than SDM particles ( $R_q = 189.5 \pm 17.6 \text{ nm}$ ,  $R_a = 157.2 \pm 13.9 \text{ nm}$ ) which in turn demonstrated quantitatively rougher surface than FDM particles ( $R_q = 14.2 \pm 10.3 \text{ nm}$ ,  $R_a = 8.7 \pm 1.9 \text{ nm}$ ) (Figure 1). Freeze dried mannitol did not show smaller geometric size than spray dried mannitol, however, demonstrated the highest powder porosity.

CM showed similar true density (particle density) to the value reported in literature for  $\beta$ -D-mannitol ( $1.52 \text{ g/cm}^3$ ). However, SDM and FDM particles showed different true densities compared to CM (1.45 and  $1.47 \text{ g/cm}^3$  respectively) which could be ascribed to their different molecular configuration induced by their different polymorphic form and different size.

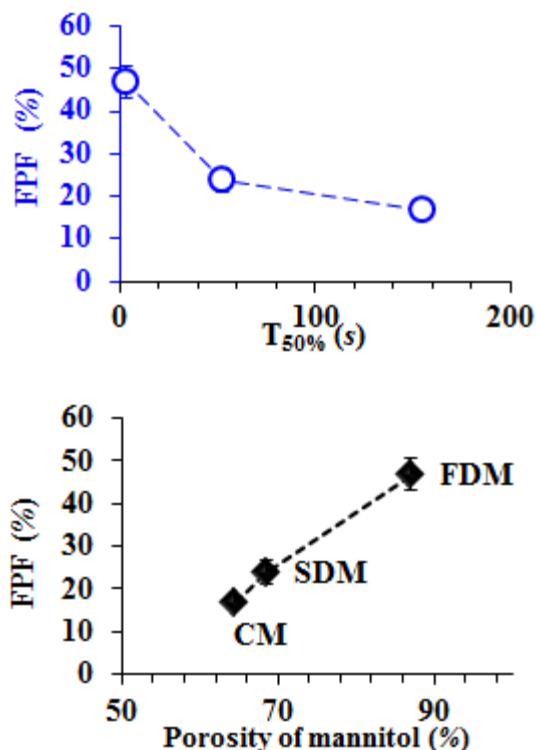
Freeze dried mannitol generated the weakest SS–mannitol adhesive forces whereas commercial mannitol generated the highest SS–mannitol adhesive forces. It was clear that the smoother the mannitol surface the weaker the SS–mannitol adhesive forces.

Among mannitol powders, SDM showed the best flow properties (excellent flow character,  $CI = 14.0 \pm 0.8 \%$ ) whereas FDM showed the poorest flow properties (poor flow character,  $CI = 27.2 \pm 1.2 \%$ ). It is believed that spherical shape of SDM powder particles renders the SDM powder better flowability. Poorer flowability for FDM powder could be ascribed to its more irregular particle shape (Figures 1) which induces pronounced internal friction (geometric interlocking) within FDM powder.

No apparent relationship was obtained between fine particle fraction and mannitol size, shape, or flowability descriptors. However, mannitol products with higher powder porosity and weaker SS–mannitol adhesive forces produced higher a fine particle fraction of SS (Figure 2).

It was suggested that the porosity of carrier powder is an important physical property that can be considered as a key optimization parameter, which might be predictive of in vitro aerosolization performance of dry powder inhaler formulations.

Among angular, spherical and elongated shaped mannitol particles, formulators can anticipate better drug delivery to the lung in case of elongated shape mannitol (Figure 1).



**Figure 2. FPF of SS in relation to  $T_{50\%}$  (the time at which 50% of particles detach from carrier particles due to sieving) and porosity of mannitol powder.**

## CONCLUSIONS

The use of freeze drying technique can constitute an important step used in the pharmaceutical industry towards preparing freeze dried carrier particles which could help to solve some problems connected to drug-carrier dry powder aerosol formulations.

## REFERENCES

1. Steckel, H. and Muller B.W. In vitro evaluation of dry powder inhalers II: influence of carrier particle size and concentration on in vitro deposition. *Int. J. Pharm.* 154, 31-37 (1997).
2. Larhrib, H.; Zeng, X.M.; Martin, G.P.; Marriott, C.; and Pritchard J. The use of different grades of lactose as a carrier for aerosolised salbutamol sulphate. *Int. J. Pharm.* 191, 1–14 (1999).
3. Kaijaly, W.; Ticehurst, M. and Nokhodchi A. Dry-powder inhalers: mechanistic evaluation of lactose formulations containing salbutamol sulphate. *Int. J. Pharm.* 423, 184–194 (2012).
4. Kaijaly, W.; Alhalaweh, A.; Velaga, S.P. and Nokhodchi A. Influence of lactose carrier particle size on the aerosol performance of budesonide from a dry-powder inhaler. *Powder Technol.* 227, 74–85 (2012).
5. Patton, J.S. and Platz, R.M. Pulmonary delivery of peptides and proteins for systemic action. *Adv. Drug Deliv. Rev.* 8, 179–228 (1992).