Tailoring Dry Microparticles for Pulmonary Drug Delivery: Ultrasonic Spray Freeze-Drying with Mannitol and Salbutamol Sulphate

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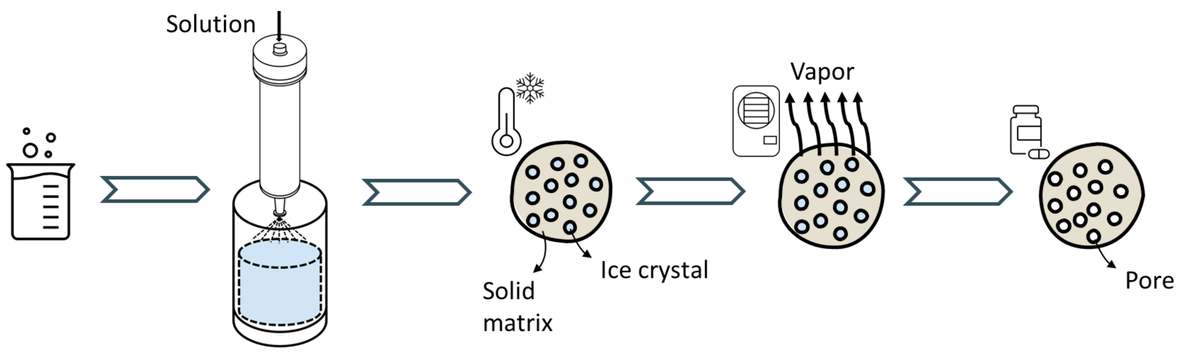
Introduction

Pulmonary delivery of drugs is attracting widespread interest in the pharmaceutical field for the treatment of both respiratory and systemic diseases. Inhalable fine powders can be produced by milling [1], spray-drying (SD) [2], spray freeze-drying [3], thin film freezing [4], and supercritical fluid technology [5]. Spray freeze-drying (SFD) is a promising approach consisting of three steps, i.e., atomisation, freezing, and drying [6]. During the first two stages a solution of drug and excipients is fed to a nozzle, atomised in small droplets and rapidly frozen using liquid nitrogen [7]. Freezing promotes the formation of ice crystals, which sublime during drying, giving the particles a porous structure [8]. The high porosity of spray freeze-dried particles allows for the reduction of particle density, improving the aerodynamic properties. This study aimed to comprehensively analyse SFD mannitol microparticles (MPs), investigating the impact of the solid concentration and the feed flow rate on MPs morphology, size, porosity, and crystallinity. The variation of such properties was also assessed upon the addition of salbutamol sulphate (SAS), a bronchodilator commonly used for the treatment of asthma. Furthermore, the aerodynamic behaviour of SAS-mannitol MPs was evaluated to assess their suitability for inhalation purposes.



Methods

Production

- **Formulation**: Mannitol and mannitol + 1% SAS
- **Solid concentration**: 5, 10, 15, 20%
- **Feed flow rate**: 1, 2.5, 5, 7.5, 10 ml min^{-1}
- **Primary drying**: 10 °C, 20 Pa
- **Secondary drying**: 20 °C, 20 Pa, 5 h

Characterisation

SEM
- Scanning Electron Microscopy;
- Evaluation of size;
- Evaluation of morphology;
- ImageJ analysis.

BET
- Brunauer Emmett Teller theory;
- N_2 adsorption;
- Evaluation of porosity;
- Evaluation of surface area.

XRD
- X-Ray Diffraction;
- Evaluation of crystallinity;
- Determination of polymorphism.

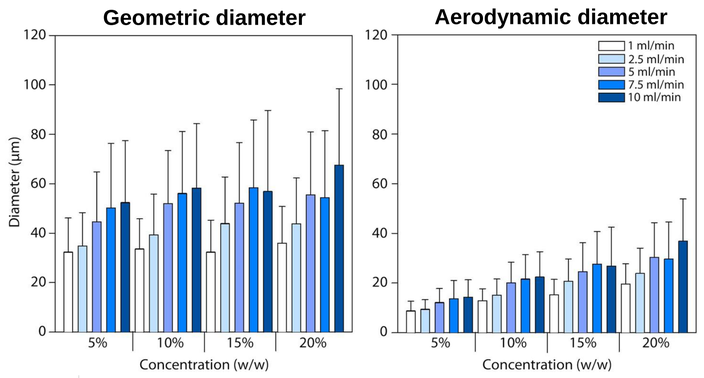
NGI
- Next Generation Impactor;
- In vitro drug deposition;
- Fine particle fraction (FPF) and mass median aerodynamic diameter (MMAD)

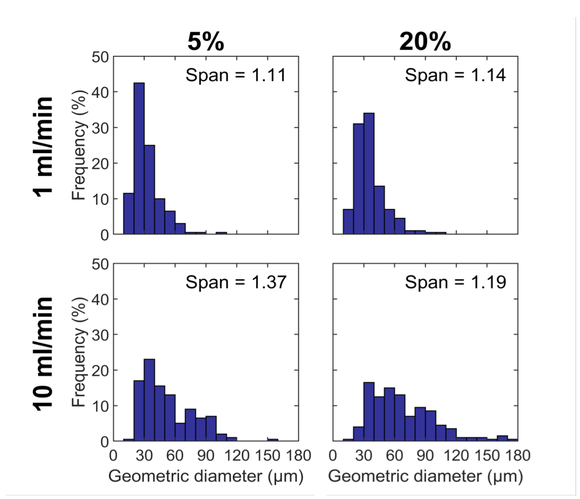
Results and Discussion

Size

The geometric and aerodynamic diameter increased at:
- ↑ solid concentration
- ↑ feed flow rate

The powders produced at low concentration and flow rates displayed:
- narrow particle size distribution
- low span values
- high uniformity of the powders' size





❖ ***What happened adding SAS?***

The particle size distributions associated with the geometric diameter of particles added with SAS showed the same shape observed without the drug. However, MPs embedding the drug displayed a significant increase in their mean sizes compared to bare mannitol.

Surface area and crystallinity

❖ BET surface area, a_{BET} ($m^2 g^{-1}$)

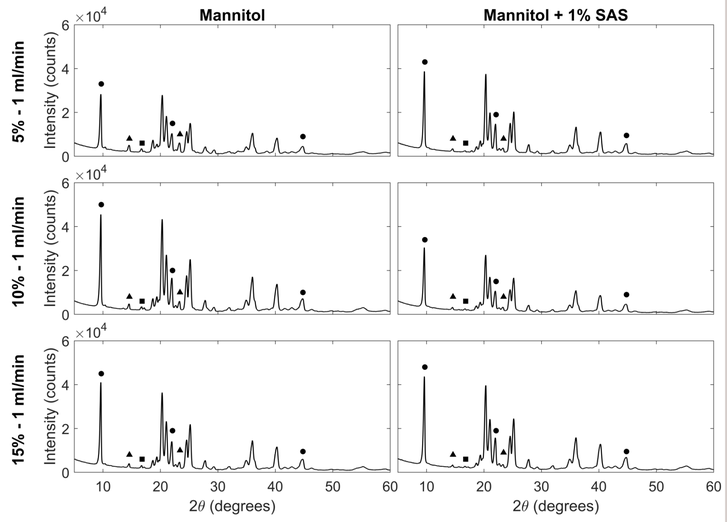
Mannitol	$a_{BET} = 5.52 - 10.10$
Mannitol and SAS	$a_{BET} = 21.62 - 23.86$

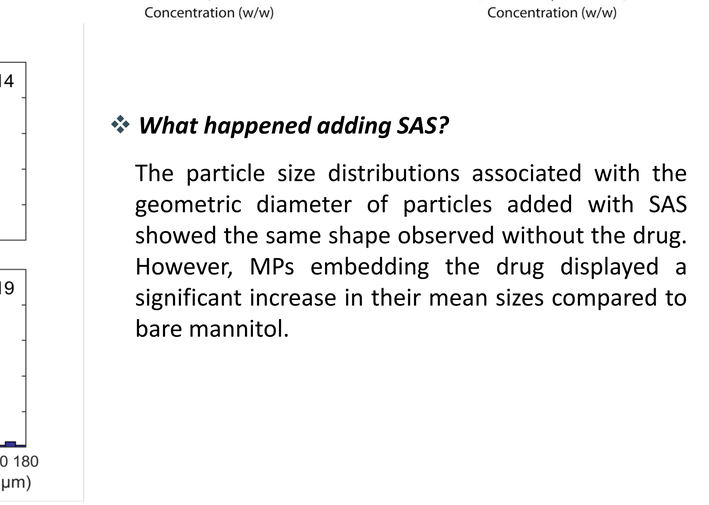
❖ ***Which is the cause?*** X-ray

The cause could be mannitol polymorphism:
(■) α-mannitol, a = 8.54 $m^2 g^{-1}$
(▲) β-mannitol, a = 0.37 $m^2 g^{-1}$
(●) δ-mannitol, a = 1.01 $m^2 g^{-1}$

- δ-mannitol was the prevalent polymorph and its content increased adding SAS

↑ SAS → ↑ δ-mannitol content → ↑ a_{BET}

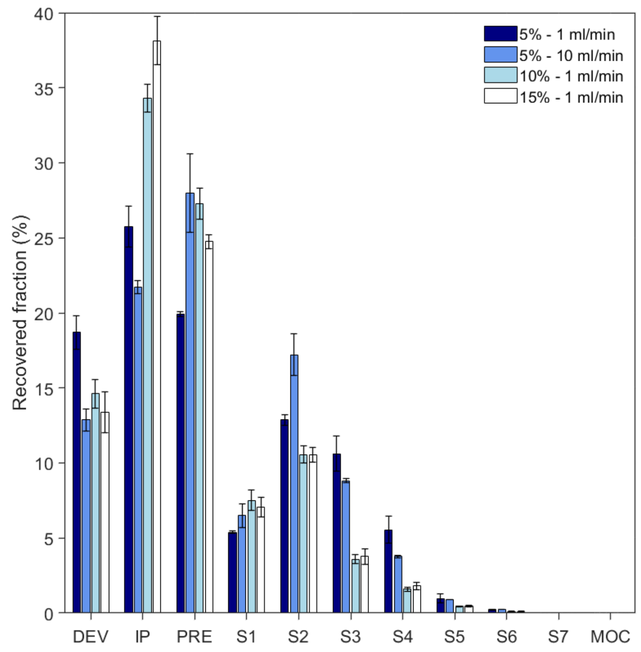




Morphology

Mannitol MPs showed:
- spherical shape
- porous structure
- ↑ robustness at ↑ solid concentrations

❖ ***Adding SAS:***
- Better defined structure



In vitro drug deposition

In all samples, the major fraction of MPs was retained in device (DEV), induction port (IP), and preseparator (PRE) suggesting the large presence of non-inhalable MPs in the powder.

	Deposition fraction (%)
5% - 1 ml/min	35.6
15% - 1 ml/min	23.7

	FPF (%)	MMAD (μm)
5% - 1 ml/min	26 ± 3	4.4 ± 0.2
15% - 1 ml/min	9.9 ± 1.3	6.0 ± 0.3

↑ solid concentration → ↑ density → ↑ MMAD

Conclusions

1) Mannitol
2) Mannitol + 1% SAS

→ SFD →

Production of spherical porous MPs
- High surface area
- Good aerosolization properties

❖ ***Mannitol MPs***:
- ↑ solid concentration → ↑ geometric diameter
- ↑ feed flow rate → ↑ geometric diameter
- ↑ solid concentration → ↑ aerodynamic diameter
- ↑ feed flow rate → ↑ aerodynamic diameter
- Prevalence of δ-mannitol

❖ ***Mannitol + 1% SAS MPs:***
- ↑ particle size
- ↑ BET surface area
- ↑ δ-mannitol content
- ↑ solid concentration → ↑ FPF and ↑ MMAD
- Optimal condition: 5% (w/w) – 1 ml/min

References

1. Ye, T.; Yu, J.; Luo, Q.; Wang, S.; Chan, H.-K. Inhalable clarithromycin liposomal dry powders using ultrasonic spray freeze drying. *Powder Technol*. **2017**, *305*, 63–70.
2. Jara, M.O.; Warnken, Z.N.; Sahakijpijarn, S.; Moon, C.; Maier, E.Y.; Christensen, D.J.; Koleng, J.J.; Peters, J.I.; Hackman Maier, S.D.; Williams Iii, R.O. Niclosamide inhalation powder made by thin-film freezing: Multi-dose tolerability and exposure in rats and pharmacokinetics in hamsters. *Int. J. Pharm*. **2021**, *603*, 120701.
3. Kim, Y.H.; Shing, K.S. Supercritical fluid-micronized ipratropium bromide for pulmonary drug delivery. *Powder Technol*. **2008**, *182*, 25–32.
4. Adali, M.B.; Barresi, A.A.; Boccardo, G.; Pisano, R. Spray freeze-drying as a solution to continuous manufacturing of pharmaceutical products in bulk. *Processes* **2020**, *8*, 709.
5. Duong, T.; López-Iglesias, C.; Szewczyk, P.K.; Stachewicz, U.; Barros, J.; Alvarez-Lorenzo, C.; Alnaief, M.; García-González, C.A. A Pathway From Porous Particle Technology Toward Tailoring Aerogels for Pulmonary Drug Administration. *Front. Bioeng. Biotechnol*. **2021**, *9*, 671381.
6. Vishali, D.A.; Monisha, J.; Sivakamasundari, S.K.; Moses, J.A.; Anandharamakrishnan, C. Spray freeze drying: Emerging applications in drug delivery. J. *Control. Release* **2019**, *300*, 93–101.
7. Yu, H.; Tran, T.-T.; Teo, J.; Hadinoto, K. Dry powder aerosols of curcumin-chitosan nanoparticle complex prepared by spray freeze drying and their antimicrobial efficacy against common respiratory bacterial pathogens. Colloids Surf. A Physicochem. *Eng. Asp*. **2016**, *504*, 34–42.
8. Yu, H.; Teo, J.; Chew, J.W.; Hadinoto, K. Dry powder inhaler formulation of high-payload antibiotic nanoparticle complex intended for bronchiectasis therapy: Spray drying versus spray freeze drying preparation. *Int. J. Pharm*. **2016**, *499*, 38–46.

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