Impact of Drug Particle Shape on Permeability and Cellular Uptake in the Lung

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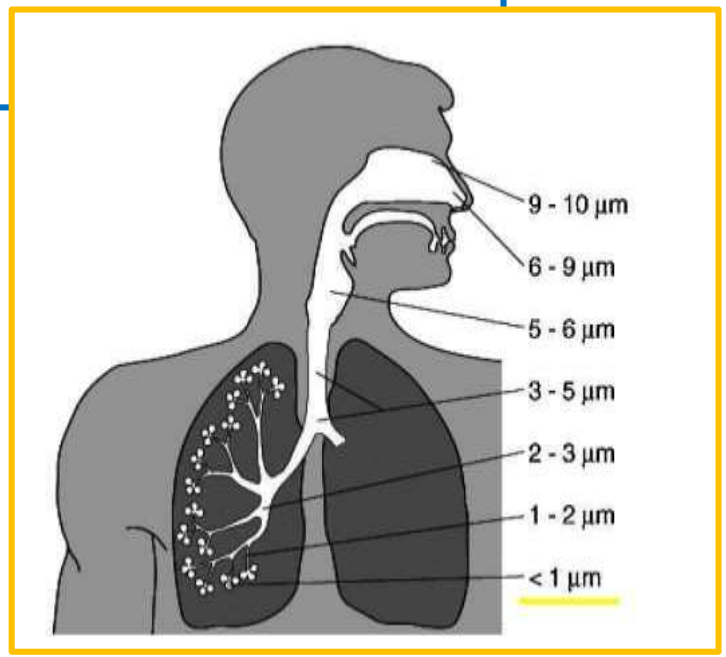
Abstract

The aim of the present study was to investigate whether particle properties, especially shape, change the biological action of the inhaled particles as well.

Introduction

The target particle size for administering active pharmaceutical ingredients (APIs) to the lung is 1–5 µm. Different technologies are available to manufacture small inhalable particles. Different size reduction technologies can lead to APIs with distinct properties, such as particle shape, particle size distribution, particle density, surface energy and solid-state.



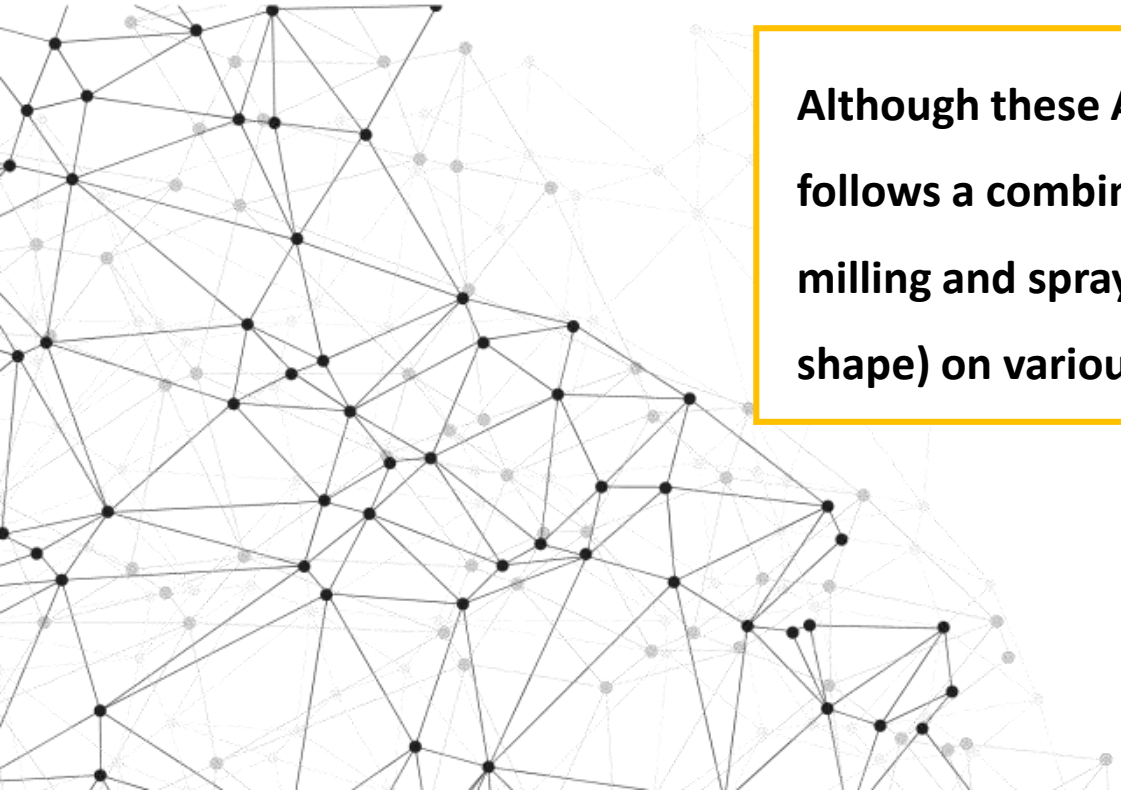
The most common method is jet milling which keeps the irregular shape of the drug crystals, as an alternative, spray drying has been shown to be a suitable technique to generate spherically shaped particles for inhalation.

For therapy the most important regions of the respiratory tract are small airways and alveoli. While epithelial cells represent the lining of the respiratory tract, macrophages are the main clearance mechanism for particles in the alveolar region of the lung.

Particles that only slowly dissolve will be removed by alveolar macrophages to a greater extent than fast dissolving particles. Fast removal by macrophages decreases the amount of API that permeates the alveolar barrier and may reduce efficacy.

Particle uptake by epithelial cells and macrophages differs regarding the size. Only macrophages can efficiently ingest particles > 500 nm by a process termed phagocytosis. Among other parameters, drug particle shape and orientation influences cellular uptake.

For the present study, two different model APIs, frequently used in the treatment of bronchial asthma and (COPD) were selected. Salbutamol sulphate, a short acting beta agonist representing an API with good aqueous solubility and budesonide, a synthetic glucocorticoid with low water solubility.



Although these APIs are well studied for pulmonary application, the present study follows a combined approach and investigates two different engineering routes (jet milling and spray drying) and the effect of the resulting particle properties (mainly shape) on various parameters relevant for inhalation.

List Materials & Methods Used in Study

Materials

Preparation of Adhesive Mixtures

Material Characterization

1. *Scanning electron microscopy (SEM)*
2. *Particle size characterization*
3. *Differential scanning calorimetry (DSC)*
4. *Specific surface area*
5. *Particle true density*

Solubility Studies

Particle Engineering

In vitro Aerodynamic Performance and Dissolution Testing

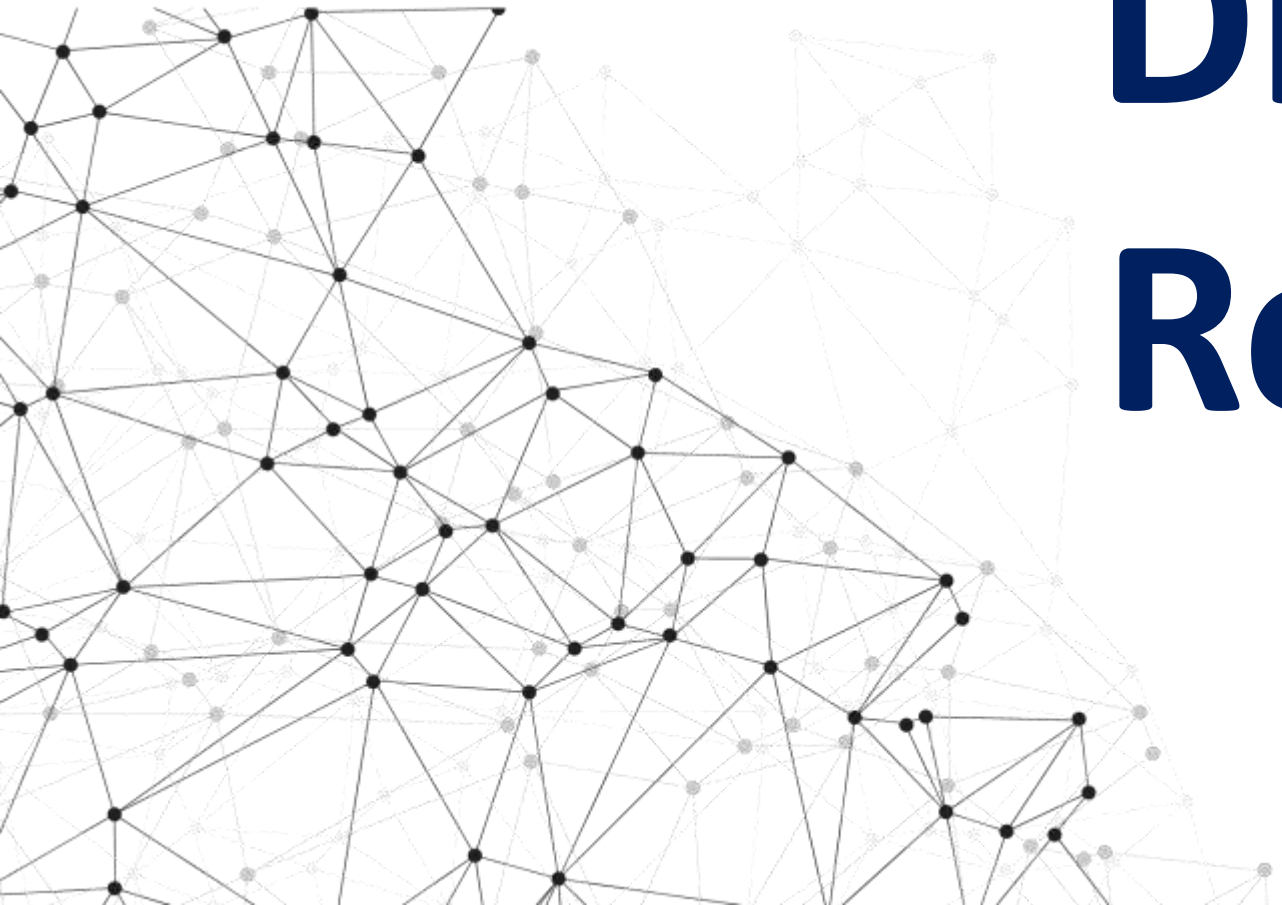
Biological Testing

Statistics

1. Cell lines
2. Generation of monocyte derived macrophages (MDM)
3. Uptake studies
4. Permeability
5. High performance liquid chromatography (HPLC)

Spiral Jet Mill
50 AS

Buchi Nano spray
dryer B-90

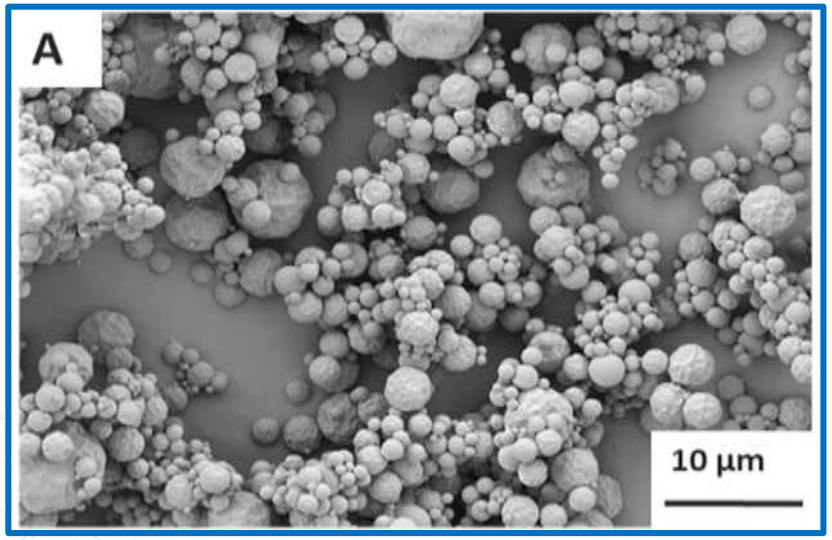


Discuss Results

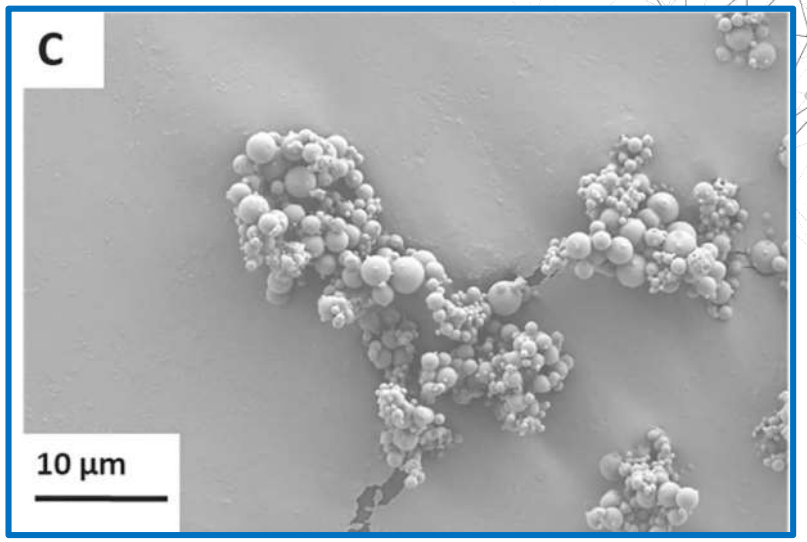
Characterization of API Particles

1 Particle Shape

Spray Drying

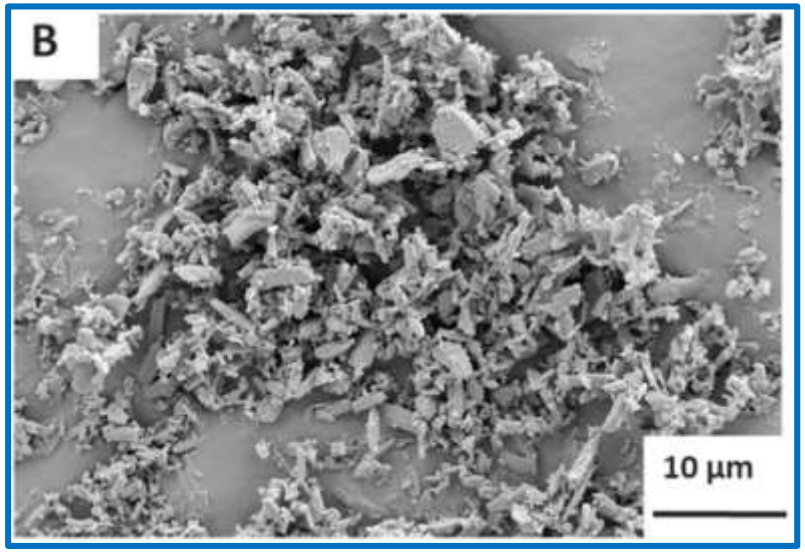


Spherically shaped Salbutamol Sulphate particles

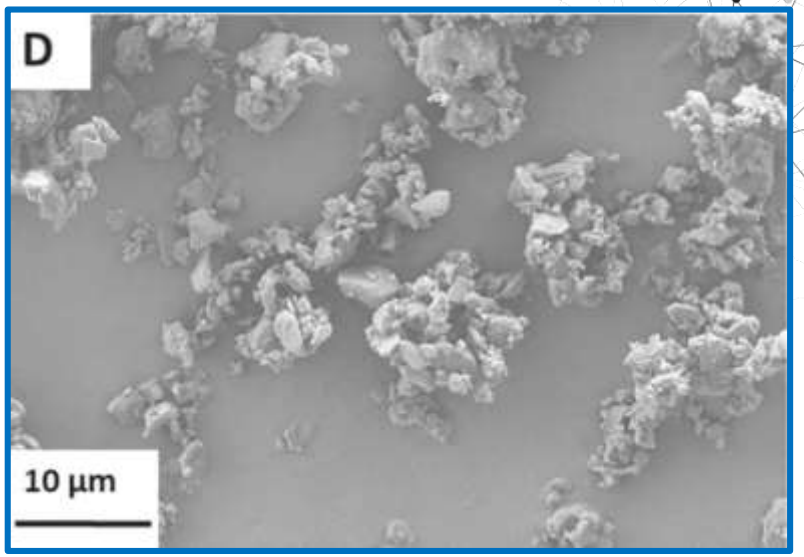


Spherically shaped Budesonide particles.

Jet Milling



Needle rod shaped Salbutamol Sulphate particles.



Compact cubic Budesonide particles.

2 Particle Size

Particle size analysis proved that both engineering techniques resulted in inhalable sized particles with a median particle size below 5 μm

	X10/μm	X50/μm	X90/μm	SPAN	SMD/μm
SBS raw material	1.13	7.2	20.65	2.71	2.21
SBS JM	0.65 ± 0.03	2.65 ± 0.08	6.35 ± 0.19	2.15	1.74
SBS SD	0.63 ± 0.02	3.47 ± 0.52	7.40 ± 0.71	1.95	1.70
BUD raw material	0.57 ± 0.06	3.82 ± 0.02	12.07 ± 0.04	11.92	1.67
BUD JM	0.59 ± 0.07	1.75 ± 0.19	4.25 ± 0.32	2.09	1.07
BUD SD	0.69 ± 0.06	1.63 ± 0.10	3.04 ± 0.15	1.44	1.28

3 Particle Density

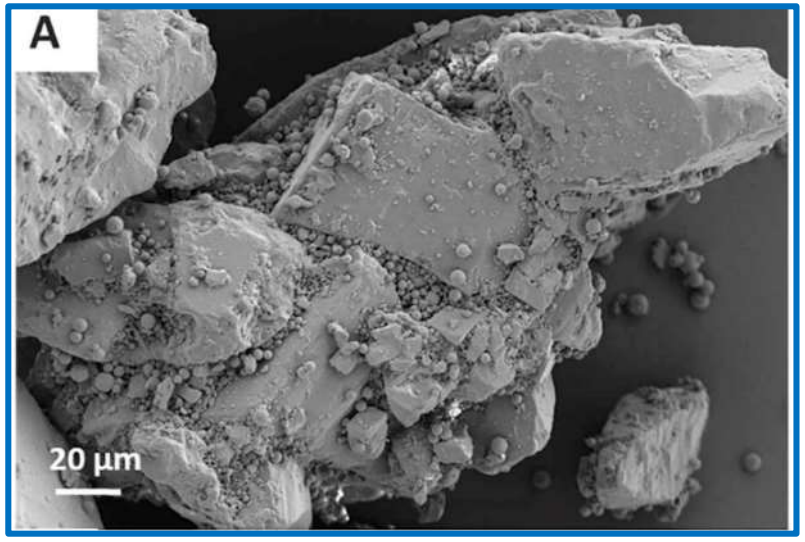
Spherical spray dried particles have a lower true density compared to jet milled crystalline particles.

4 Surface Area

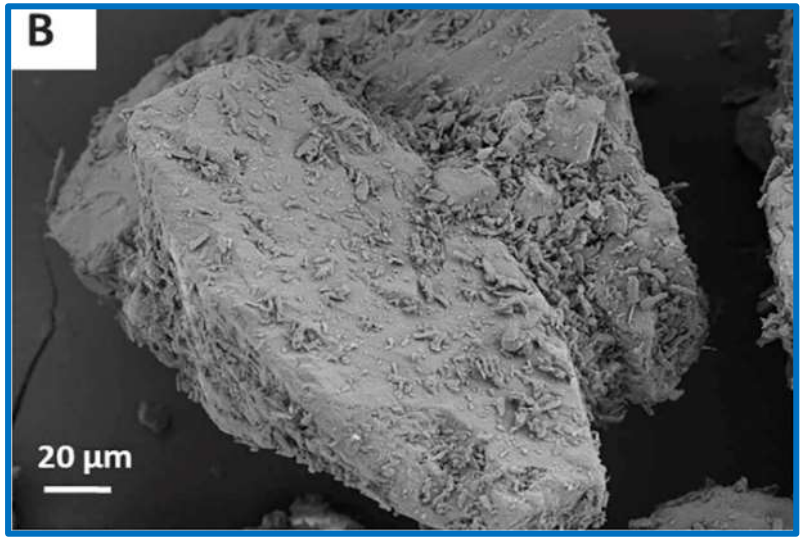
Jet milled salbutamol sulphate particles exhibit an eight times larger specific surface area compared to spray dried salbutamol sulphate particles of comparable size. The same trend could also be observed for spray dried and jet milled budesonide Particles

In Vitro Aerodynamic Performance

After blending, both mixtures showed a deviation from the mean API content of below 5%, indicating a homogenous distribution of API over the carrier surface. The images allow a clear discrimination between spherical spray dried and more irregular shaped jet milled particles distributed over the carrier surface.



Adhesive mixtures containing LH100 and spray dried salbutamol sulphate particles



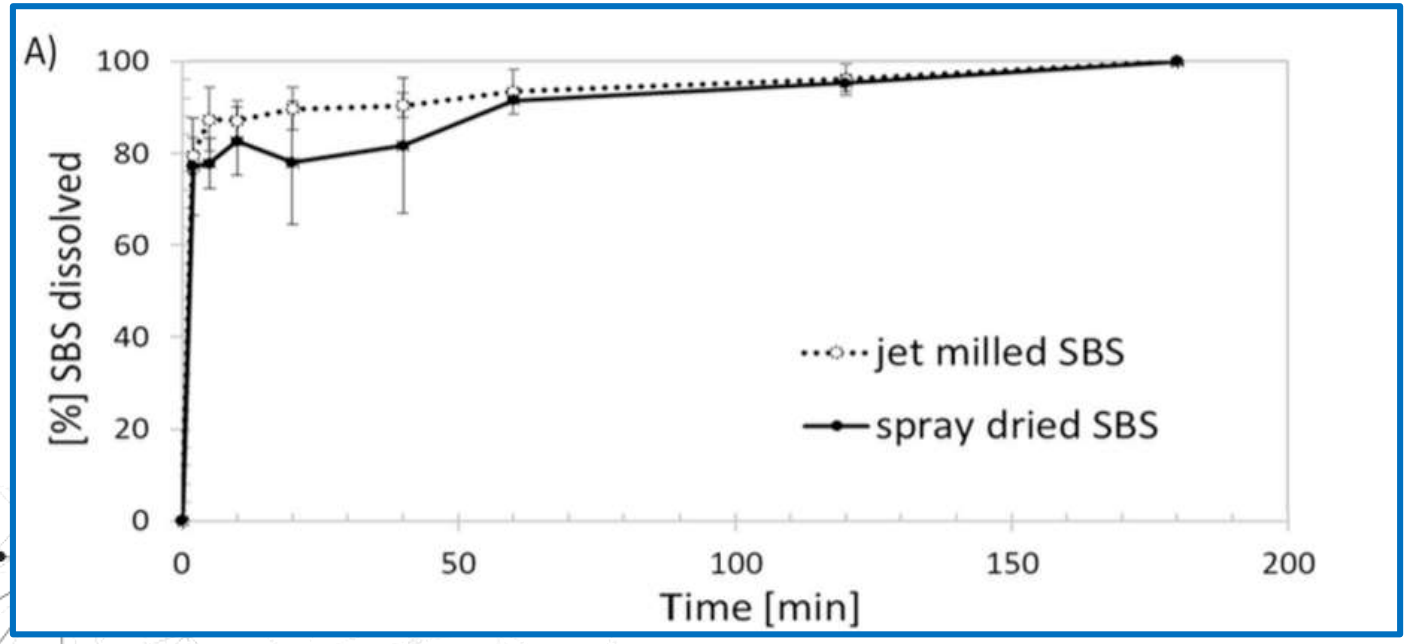
Adhesive mixtures containing LH100 and jet milled salbutamol sulphate particles

Solubility, Permeability & Dissolution

- Solubility of salbutamol sulphate and budesonide was higher in SLF compared to MEM at 37 °C.

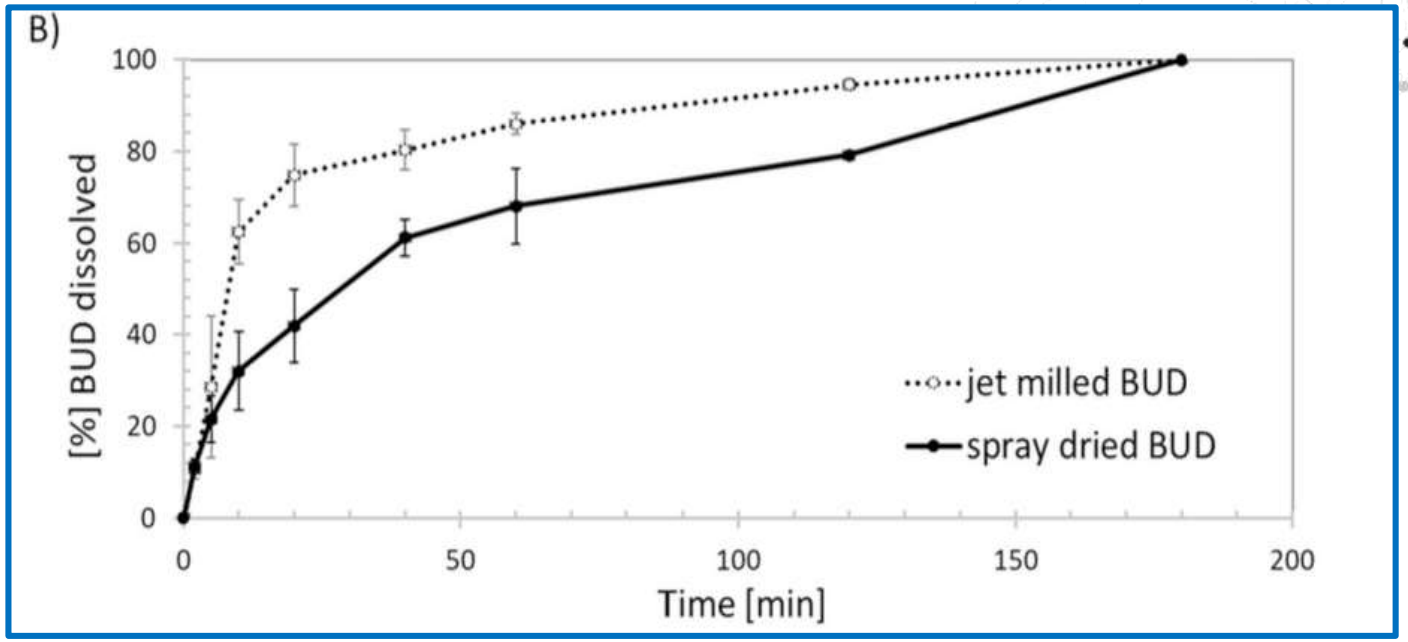
- Solubility of salbutamol sulphate in water is very high with 250 mg/ml and much lower in budesonide with 10 µg/ml in water at room temperature.

- Permeability of both APIs was higher for spray dried than for jet milled formulations.

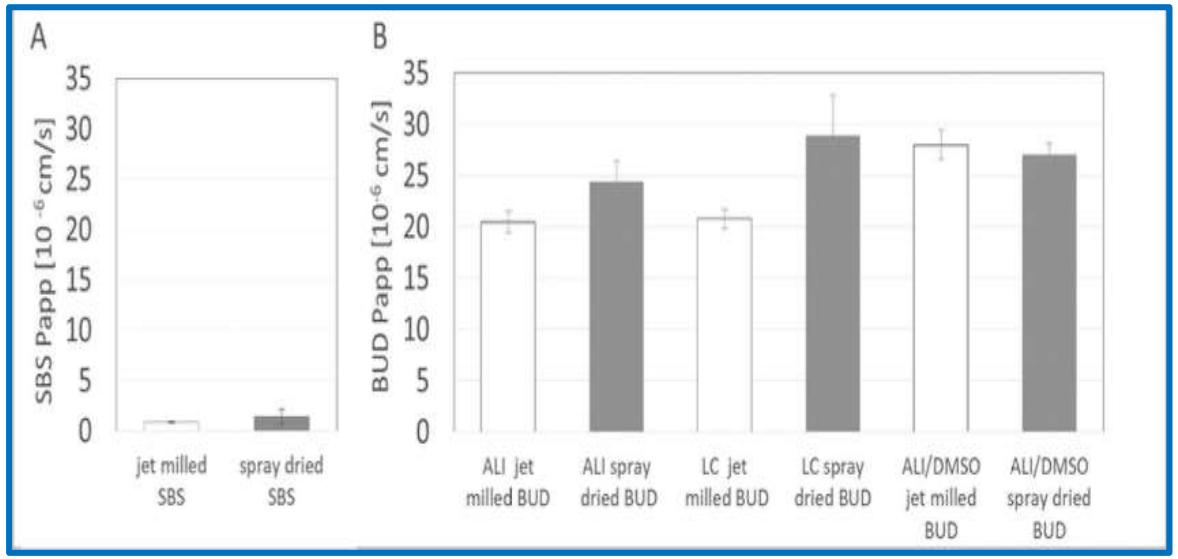


A) Jet milled and spray dried salbutamol sulphate rapidly dissolve in SLF, almost after 2 min nearly everything was dissolved

B) Compared to salbutamol sulphate, budesonide dissolved slower over time

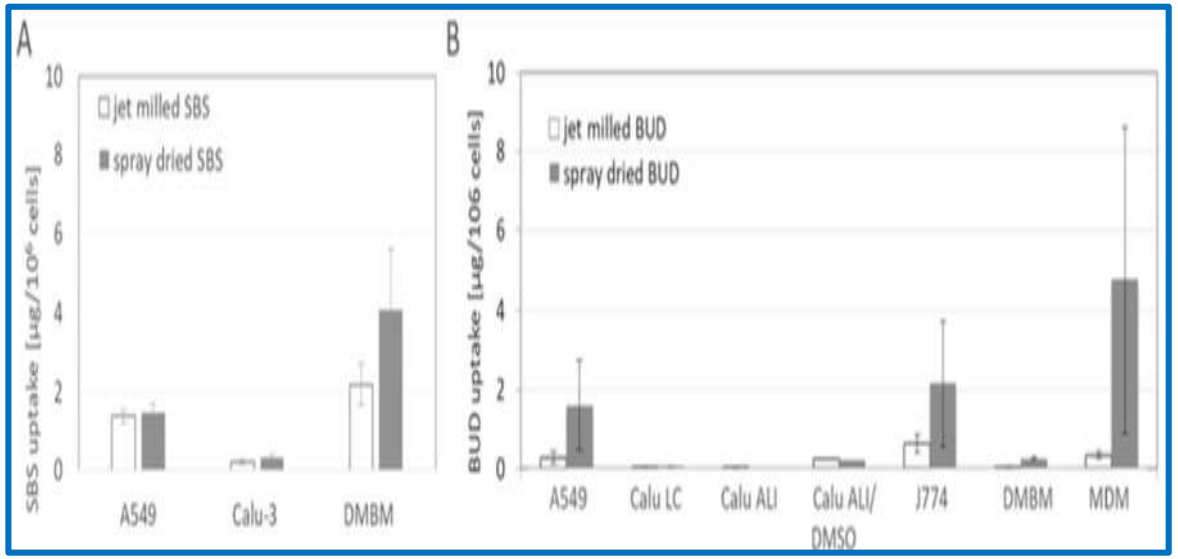


Cellular Uptake



Due to the slower dissolution budesonide particles should be more prone to clearance by macrophages.

Uptake was higher for spray dried than for jet milled formulations with greater differences for budesonide than for salbutamol sulphate formulations.



Conclusion

1. The distinct particle properties did not affect the dissolution behavior of the highly soluble salbutamol sulphate.
2. Budesonide with lower solubility spray dried particles dissolved slower compared to jet milled particles.
3. This shows that a greater surface area (jet milled particles) causes more prominent effects than amorphous solid state(spray dried particles).
4. Increased uptake of spray dried compared to jet milled salbutamol sulphate was seen in epithelial cells and macrophages to similar extent.

For spray dried budesonide the increase in macrophage uptake in general was higher than that for epithelial cells.

5

This may suggest that for targeting of low solubility drug like budesonide to macrophages spray drying might be advantageous

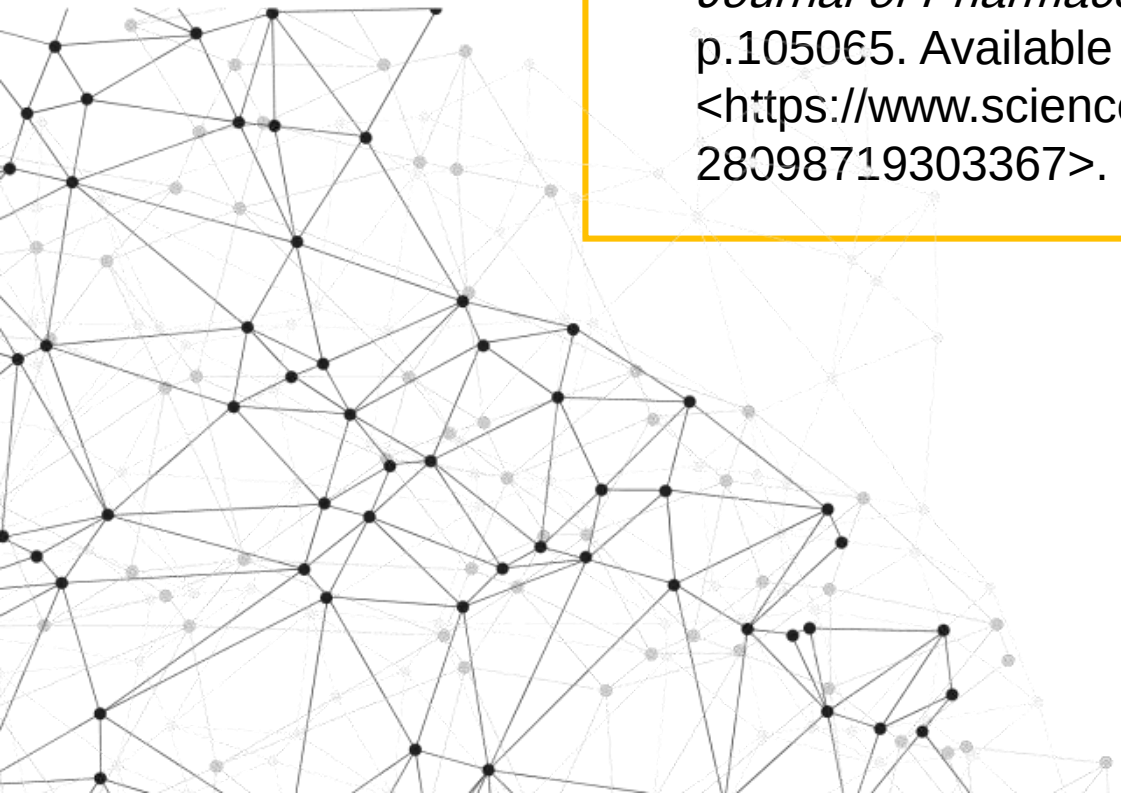
6

Other low solubility drug shave to be tested in order to confirm this hypothesis.

7

Reference:

Zellnitz, S., Zellnitz, L., Müller, M., Meindl, C., Schröttner, H. and Fröhlich, E., 2019. Impact of drug particle shape on permeability and cellular uptake in the lung. *European Journal of Pharmaceutical Sciences*, [online] 139, p.105065. Available at: <https://www.sciencedirect.com/science/article/abs/pii/S0928098719303367>.

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