Spray Drying
Inhalable Particles

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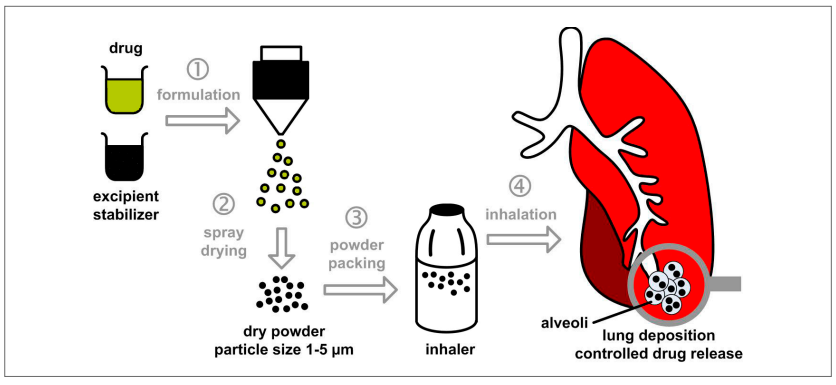
1. Introduction

A new trend in pulmonary drug delivery is to move from the liquid or pressurised formulations to dry powder inhalation formulations. This is due to the advantages of dry powder systems, including:

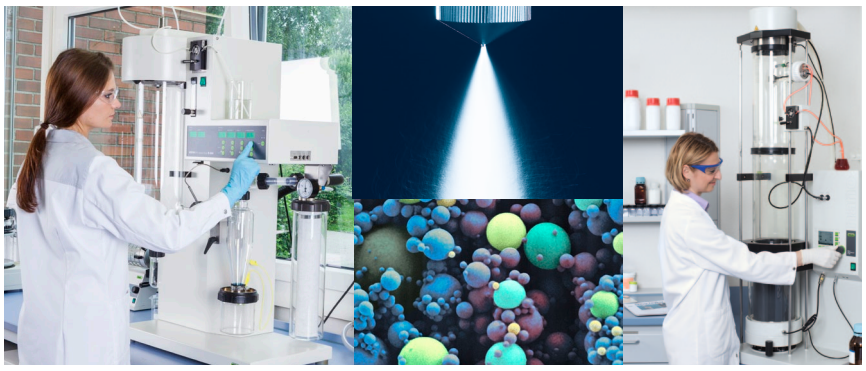
1. breath-actuated inhalation,
2. limited coordination requirements,
3. no propellant requirement and
4. short treatment time.

Spray drying is a simple, rapid, reproducible and easy to scale-up production process that has been intensively investigated for pulmonary drug delivery systems. It has the potential to generate highly dispersible powders for inhalation in the range from 1 to 5 µm size with a manipulable particle morphology.



2. BUCHI Laboratory Scale Spray Dryers

BUCHI Spray Dryers offers quick and gentle drying of aqueous and organic solutions, nanoemulsions or -suspensions to finest powder. They are the ideal aboratory spray dryers for new breakthroughs in R&D on innovative materials.

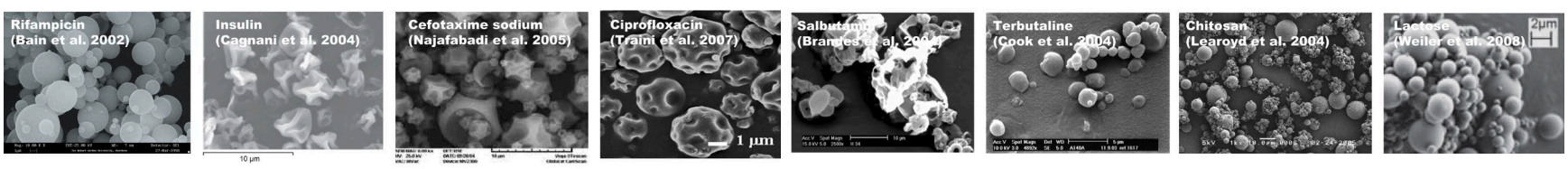


Technical data	Mini Spray Dryer B-290	Nano Spray Dryer B-90
Particle size	2 – 25 µm	300 nm – 5 µm
Droplet size	20 – 80 µm	8 – 21 µm
Typical yield	40 – 70 %	up to 90 %
Evaporation capacity	max. 1.0 L/h H_2O	max. 0.2 L/h H_2O
Sample volume	30 mL – 1L	1 mL – 200 mL
Heating power	max. 2300 W	max. 1400 W
Inlet temperature	max. 220 °C	max. 120 °C
Spray principle	two fluid nozzle	piezoelectric driven vibrating mesh
Particle collection	cyclone separator	electrostatic particle collector

3. SEM pictures, particle morphology and size

Advantages of spray dried inhalable particles:

- particles were in the respirable size range with roughly 1 – 5 µm aerodynamic diameters
- high fine particle fractions were achieved, ranging from 30 – 60% to over 85 %
- Inhaler emitted powder doses of over 90% were reported
- amorphous powders were typically generated due to the short drying time in the lab scale spray dryers
- compared to jet milled samples, higher fractions of potentially inhalable aerosol particles of antibiotic cefotaxime sodium were measured for spray dried formulations
- deagglomeration of spray dried protein formulations was possible
- higher powder dispersibility compared to jet milled particles was explained by spherical particle shape and therefore smaller surface contact



4. Literature review

Drug and application	Carrier and sample concentration	Solvent	Spray drying process parameters	Particle size and shape, yield, fine particle fraction (FPF) and emitted dose (ED)
L-leucine and trehalose (dispersing agent for inhalable drugs)	20 to 35 mg/mL total feed, concentration L-leucine to trehalose ratio varied from 0 – 100 %	Water	Spray cap 4.0 µm, T_{in} 75 °C, T_{out} 45 °C, drying air flow 100 L/min	2.1 – 5.4 µm aerodynamic diameter, well dispersing
Chitosan (bioresorbable biopolymer)	0.1 % w/v chitosan (non-animal origin, 30 kDa) in 1 % v/v acetic acid	Water	Spray cap 5.5 µm, T_{in} 120 °C, T_{out} 55 °C, feed rate approx. 50 mL/h, drying air flow 130 L/h	1.1 ± 0.5 µm, very high yields up to 90 %
Drug-loaded lipid-polymer hybrid nanoparticles	PLGA, lecithin, w-in-oil-in-w double emulsion, total solid concentration 1 %, excipients: PVA, leucine, ratio nanoparticles to excipients 50 – 80 %	Water / DCM, ethanol/water (10 % v/v)	T_{in} 80 °C, T_{out} 40 – 45 °C, feed rate 3 mL/min, spray flow rate 333 L/h	2.6 – 8.7 µm median size, yield 16 – 69 %, ED up to 68 %, FPF up to 23 %, spherical and hollow morphology
Coumarin (model drug)	Poly(D,L-lactic-co-glycolic acid)(PLGA), Poly(vinyl alcohol), Mowiol 4 – 88, 0.2 – 2 % total concentration, spray drying of nano suspensions	Water / DCM	Spray cap 4.0, 5.5, 7.0 µm, drying air flow 100 L/min, T_{in} 30 – 50 °C Tout 20 – 30 °C, spray rate 50 – 100%	Mean size 2.8 – 4.4 µm, spherical particles with smooth surface, nano particle characteristics not affected by spray drying
Bacterial plasmid (pEGFP-N1)	Chitosan (2 g/100 mL in 0.005 M acetic acid), plasmid 50 µg/mL, further excipients: leucine and lactose, total solid concentration 4 – 10 %	Water	T_{in} 120 – 160 °C, spray gas flow 500 – 700 lL/h, feed rate 3 – 9 mL/min	Yield 26 – 62 %, DNA stability 63 – 100 %, mean size 3 – 12 µm, spherical particles with either smooth or wrinkled surface
Beclomethasone dipropionate (asthma steroid)	Cyclodextrine, 2.5 % sample concentration	Water / ethanol (25 % v/v)	T_{in} 55 – 70 °C, T_{out} 48 °C, feed rate 5 – 11 mL/min	Spherical particles, 1 – 5 µm
Budesonide (asthma steroid) and bendroflumethiazide (hypertension)	Trehalose / ammonium carbonate	Water / Ethanol (80 % v/v)	T_{in} 78 – 95 °C	Spherical particles with wrinkled surface
Rifampicin (antibiotic)	900 mg rifampicin in 30 mL anhydrous ethanol (recrystallization before spray drying)	Ethanol	T_{in} 70 °C, T_{out} 40 – 43 °C, spray flow rate 500 L/h, feed rate 5 mL/min, aspirator 100 %	Crystalline thin flaky structure, median aerodynamic diameter of 2.2 µm, FPF 68 %
Sildenafil (erectile dysfunction)	Poly(D,L-lactic-co-glycolic acid)(PLGA), Poly(vinyl alcohol), Mowiol 4 – 88, 0.2 – 2 % total concentration, spray drying of nano suspensions	Water / DCM	Spray cap 4.0, 5.5, 7.0 µm, drying air flow 100 L/min, T_{in} 30 – 50 °C Tout 20 – 30 °C, spray rate 50 – 100 %	Mean size 2.8 – 4.4 µm, spherical particles with smooth surface, nano particle characteristics not affected by spray drying
Trehalose (protein stabilizer)	0.1 % and 1 % concentration of α-trehalose dihydrate	Water	Spray cap 7 µm or 3 µm µm, drying air flow 115 L/min, T_{in} 60, 80, 100 °C, Tout 30 – 45 °C	600 nm (span 1.6) at 0.1 % and 1.2 µm (span 0.8) at 1 %
Zinc-alginate microparticles (protein delivery)	1 % alginate, 0.5 % ZnSO4, 2.5 % ammonia, various BSA content (5 – 30 %)	Water	T_{in} 140 – 145 °C, T_{out} 70 – 80 °C, spray gas 600 – 650 L/h, feed rate 5 – 7 g/min, aspirator 100 %	Mean size 2.8 – 5 µm, FPF 17 – 40 %, ED 87 – 97 %
Bovine serum albumin (model protein)	0.1 % solution with 0.05 % surfactant Tween 80	Water	Spray cap 4.0 µm, drying air flow 150 L/min, T_{in} 120 °C T_{out} 51 – 55°C, T_{in} 100 °C T_{out} 42 – 45 °C, T_{in} 80 °C T_{out} 36 – 40 °C	460 ± 10 nm (span 1.03) to 2.6 µm in all 18 runs, median particle size <5 µm, smooth spherical particles, yield 72 ± 4 %.
B-galactosidase (model enzyme)	5 % concentration with 1:2 w/w enzyme to trehalose ratio	Water	Spray cap 4.0 µm, T_{in} 80 °C, Tout 36 – 53 °C, drying air flow 100 – 110 L/min, spray rate 100 %	1 – 5 µm (respirable) spherical and smooth particles, residual enzyme activity 75 – 100 % (after 3 weeks), yields 60 – 94 %, 500 mg sample amounts

The table reviews the spray drying research with regard to inhalable particles, based on the available RDD online proceedings database. Spray drying applications focused especially on: anti-asthmatic drugs, antibiotics, proteins (insulin, bovine serum albumin or human serum albumin), antibodies and tuberculosis vaccine.

5. Conclusion

Spray drying is well suited to produce inhalable dry powders with predetermined specifications for lung delivery (light particles in the size of 0.5 – 3.3 µm for lung alveoli deposition). Treating several diseases like asthma, tuberculosis, diabetes and bacterial infection of the lung seems possible by spray dried particles. The key benefits of this technology are the possibilities to control the size and morphology of the particles. The fact that it is a very gentle method enables to spray dry even heat-sensitive materials like protein based drugs. Recent developments offer new possibilities in the field of laboratory scale spray drying and eliminate some weak points of traditional spray dryers, such as limited recovery and possibility to spray dry milligram sample amounts.

Visit our detailed on-line Spray Drying Application Database www.buchi.com

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