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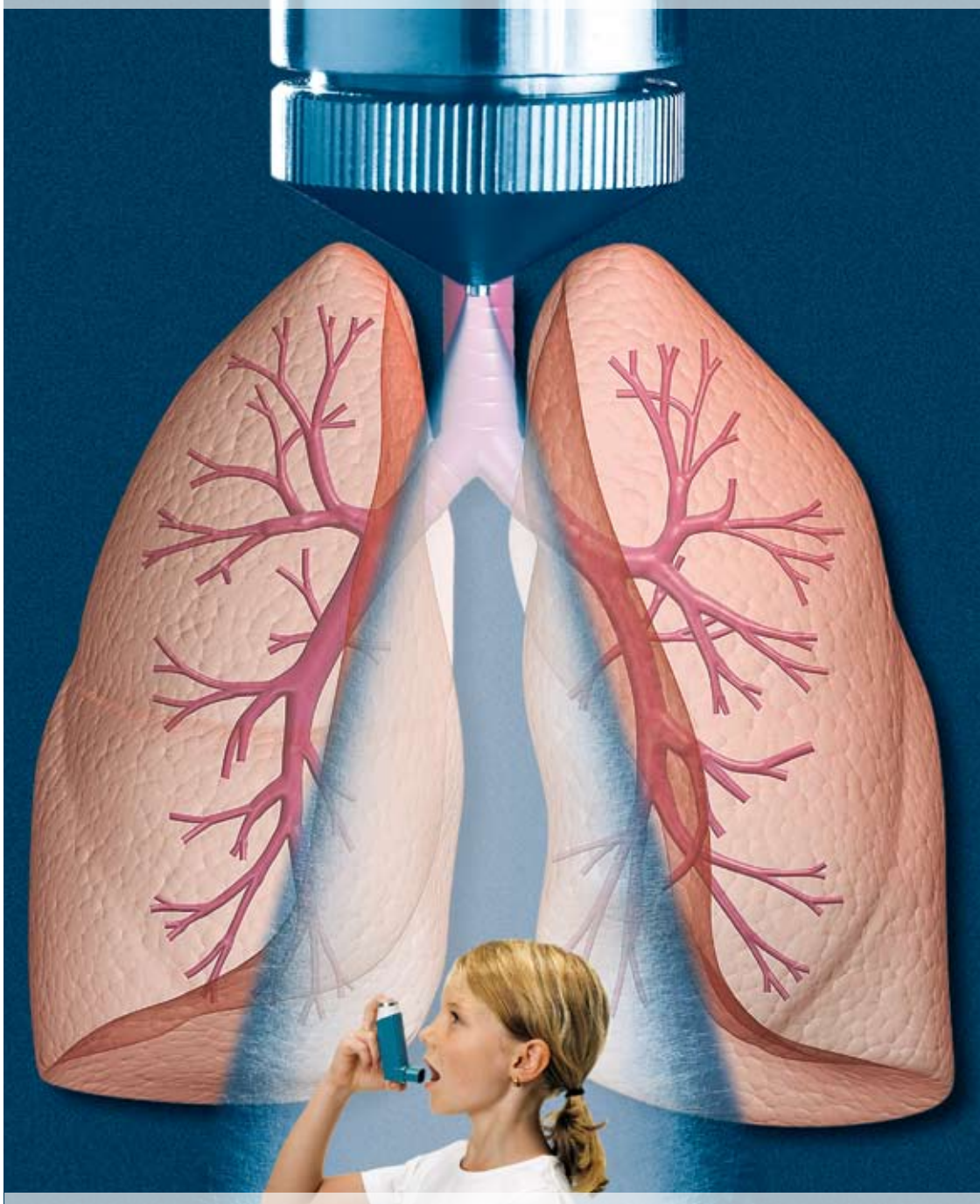

Laboratory Scale Spray Drying Of Inhalable Drugs: A Review

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Mini Spray Dryer B-290

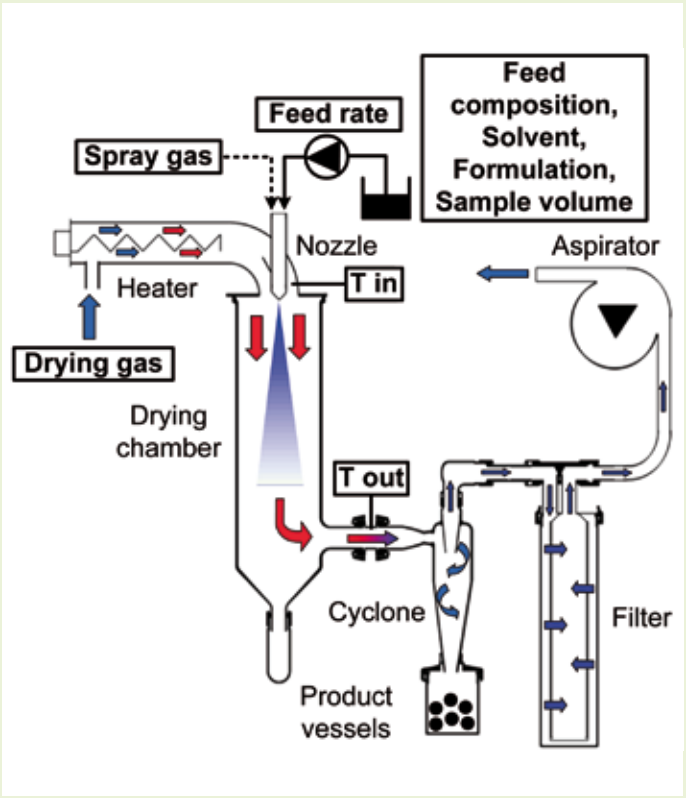

Figure 1: Mini Spray Dryer B-290

The Mini Spray Dryer B-290 from Büchi Labortechnik AG is a laboratory scale instrument to perform spray drying processes down to 30 mL batch volume and up to 1 litre of water or organic solvent per hour. Thanks to the glassware, the complete drying process from the two-fluid nozzle down to the powder collection vessel is visible.
Fine particles are produced because of the short residence time in such a compact spray dryer. The residence time of the drying air within the spray chamber is about 1.5 seconds. The powder collection is provided by a glass-made cyclone separator, which is internally coated with a thin nanosize antistatic film to reduce powder adhesion to the glass wall. The separation works by centrifugal forces by virtue of inertia of the solid particles.

The adjustable process parameters are:

- inlet and outlet temperature,
- sample feed rate,
- drying gas flow rate and
- spray gas flow

Features and benefits	Mini Spray Dryer B-290
Main benefit	for traditional spray drying, established process
Max. inlet temperature	220°C
Water evaporation	1.0 kg/h, higher for solvents
Nozzle types	two-fluid nozzle, three-fluid nozzle
Particle size	2 – 25 µm
Particle separation	cyclone
Typical yield	typically around 50% - 70%
Min. sample volume	30 mL
Max. sample viscosity	300 cps (viscous samples and juices possible)
Scale-up	possible to scale-up to kg- and tons-scale

Table 1: Features and benefits of the Mini Spray Dryer B-290

Nano Spray Dryer B-90

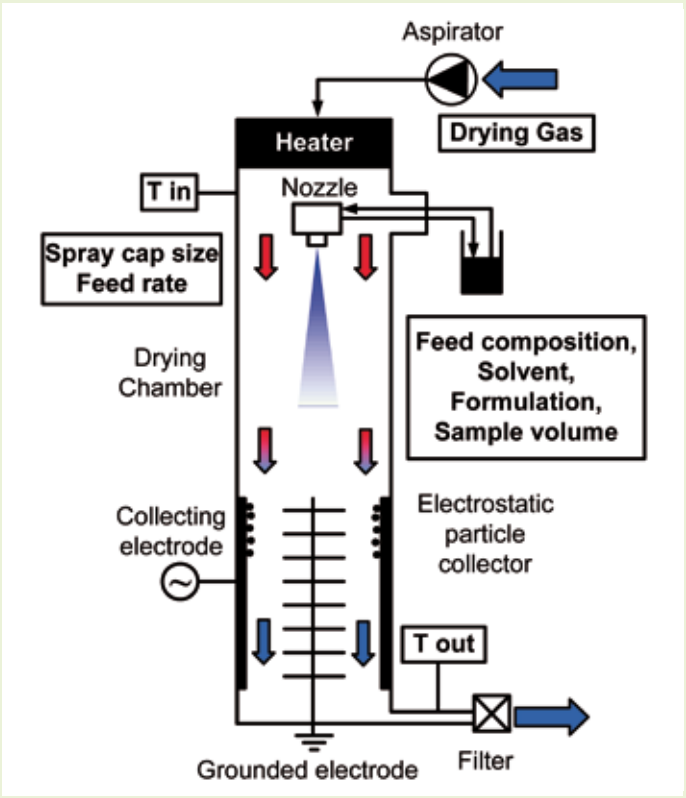

Figure 2: Nano Spray Dryer B-90

The new Nano Spray Dryer B-90 is based on a new spray drying concept. The drying gas enters the apparatus from the top where it is heated to the set inlet temperature, flows then through the drying chamber, and exits the spray dryer at the bottom outlet. The gas is additionally fine filtered before leaving the instrument. The inlet temperature and outlet temperature are measured just after the heater and before the fine filter.

The liquid sample is fed to the spray nozzle via a peristaltic pump in a re-circulation mode.

The generation of droplets is based on a piezoelectric driven actuator, vibrating a thin, perforated, stainless steel membrane in a small spray cap. The membrane (spray mesh) features an array of precise, micron-sized holes (4.0, 5.5 or 7.0 µm). The actuator is driven at around 60 kHz, causing the membrane to vibrate, ejecting millions of precisely sized droplets per second with a very narrow distribution. These extremely fine droplets are dried into solid particles and collected by electrostatic charging and subsequent deflection to the collecting electrode. Finally the resulting powder is collected using a rubber spatula.

Features and benefits	Nano Spray Dryer B-90
Main benefit	for small quantities, finest particles, highest yields
Max. inlet temperature	120°C
Water evaporation	max. 0.2 kg/h
Nozzle type	piezoelectric driven vibrating mesh
Particle size	300 nm – 5 µm
Particle separation	electrostatic particle collector
Typical yield	up to 90%
Min. sample volume	3 mL
Max. sample viscosity	10 cps (diluted samples)
Scale-up	limited by spray head and electrical particle collector

Table 2: Features and benefits of the Nano Spray Dryer B-90

Laboratory Scale Spray Drying Of Inhalable Drugs: A Review

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Introduction

The pharmaceutical industry addresses a number of demands on novel respirable particulates, which from a process technology perspective can be broadly categorized into the areas of: performance (e.g. total/local lung deposition, immediate versus controlled release), processing (e.g. achieve flow properties) and stability (e.g. physical/chemical stability and activity).

A new trend in pulmonary drug delivery is to move from the liquid or pressurised formulations to dry powder inhalation formulations. This, in part, is due to the advantages of dry powder systems, including breath-actuated inhalation, limited coordination requirements, no propellant requirement and short treatment time [1].

Spray drying is a simple, rapid, reproducible, economic and easy to scale-up production process [2] that has been intensively studied for pharmaceuticals and excipients for pulmonary drug delivery in dry powder inhalation systems [3, 4]. It has the potential to generate highly dispersible powders for inhalation in the range from 1 to 5 µm size with a particle morphology that can more easily be influenced compared to for example jet milling [5].

This study reports a review, regarding research work on particles for inhalation that have been published in the RDD proceedings database, using laboratory scale Büchi Mini Spray Dryer models B-190, B-191 and B-290

Literature Review

A search query in the RDD online database with the key word “spray drying” revealed 53 hits. Figure 3 visualizes the distribution of these published papers over the last several years. It seems that the full potential of the spray drying process for dry powder aerosols has not been fully exploited yet. Spray drying has become a well established technology in pulmonary drug delivery.

Table 3A and 3B reviews the spray drying research with regard to inhalable particles, based on the available RDD online proceedings database. The literature review showed breakthrough R&D innovations in the field of respiratory drug delivery with key information about available spray drying parameters and conditions.

Spray drying applications focused especially on anti-asthmatic drugs [2, 5-9], antibiotics [1, 9-12], proteins, such as insulin [13-15], bovine serum albumin [16] or human serum albumin [17], antibodies [18] and tuberculosis vaccine [19].

Various excipients were applied to stabilize drugs during formulation, predominately mannitol [13, 14, 17, 18, 20], poly(lactic-co-glycolic-acid) PLGA [8, 10, 19, 21], lactose [5, 8, 16] and chitosan [7]. SEM photographs of the spray dried powders exhibited mostly spherical shapes with corrugated surfaces, resin-like or even hollow structures, depending on the substance material and drying conditions (Table 3A and 3B).

The produced particles were in the respirable size range with roughly 1 - 5 µm aerodynamic diameters. High fine parti-

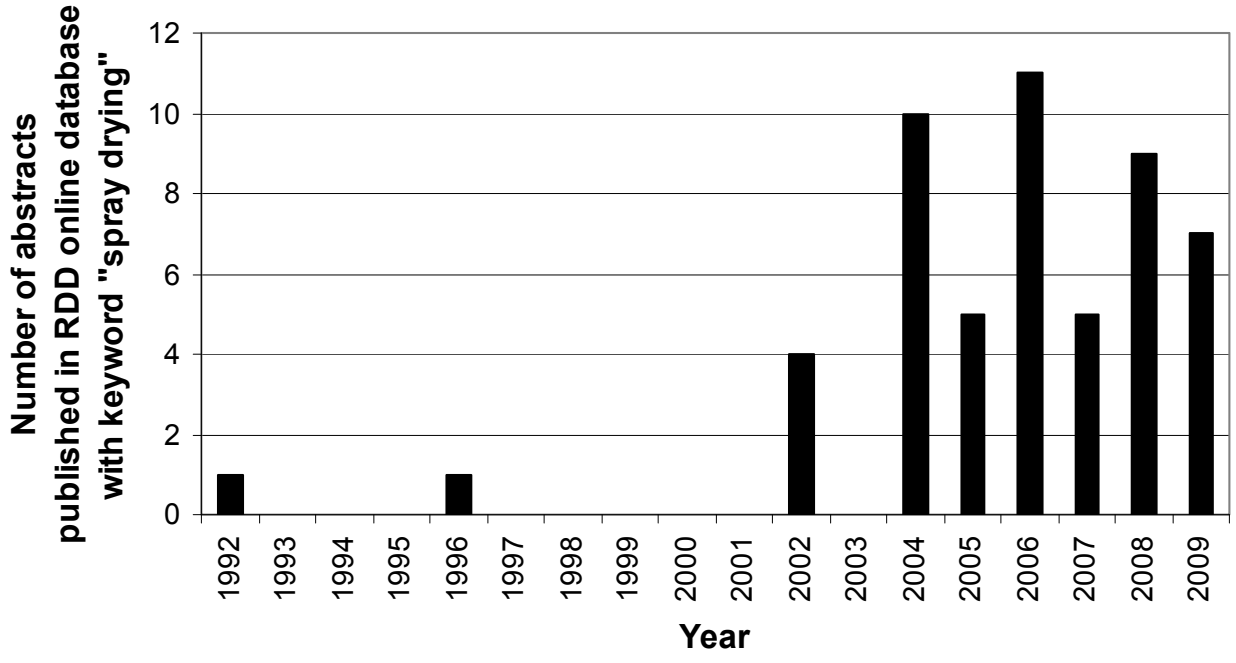


Figure 3: Number of abstracts published in the RDD online database (www.rddonline.com, visited January 8, 2010) with key word “spray drying” (total 53 abstracts)

Drug and application	Carrier and sample concentration	Solvent	Spray drying process parameters	Particle size, shape, yield, fine particle fraction (FPF) and emitted dose (ED)	Spray dryer model applied	Reference and institution
Terbutaline sulphate (asthma drug)	Matrix forming exipients	Water	-	Spherical particles 3.7 µm size throat impaction 23.9 % ED 93%, FPF 46%	Mini Spray Dryer B-191	Cook et al. 2004 University of London School of Pharmacy, UK AstraZeneca, UK
Terbutaline sulphate (asthma drug)	4% w/w terbutaline sulfate 6-36% w/w leucine and 25-50% w/w chitosan 2 % total solid concentration	Water / ethanol (30 % v/v)	T_{in} 180 °C gas spray 600 L/min feed rate 10 % aspirator 85%	1 - 15 µm particle size range yield 78% FPF around 40% ED > 90%	Mini Spray Dryer B-290	Learoyd et al. 2006a Aston University, Birmingham, UK Pfizer, UK
Salbutamol sulphate (asthma drug)	Hydrated egg phosphatidylcholine, poloxamer 188, calcium chloride dihydrate, Solkane 227	Water / DCM	T_{in} 120 °C T_{out} 59 °C aspirator 100%	Hollow to porous particles, reduced agglomeration tendency compared to jet-milled powders, 40% drug load, FPF 30 - 60 %	Mini Spray Dryer B-191	Brandes et al. 2004 Christian Albrecht University, Germany
Salbutamol sulphate (asthma drug)	PLGA, beclomethasone dipropionate, PVA, leucine, lactose	Chloro-phorm / water	T_{in} 180 °C spray gas 600 L/min feed rate 3.2 mL/min aspirator 85%	Spherical particles 0.25 - 3.0 µm yield 74 % FPF < 40 % ED > 90 %	Mini Spray Dryer B-290	Learoyd et al. 2006b Aston University, Birmingham, UK Pfizer, UK
Salbutamol sulphate (asthma drug)	Lactose monohydrate	Water	-	Spherical particles 3.2 µm , FPF around 70 %, dispersion factor around 40 % for 40 L / min	Mini Spray Dryer B-191	Weiler et al. 2008 Johannes Gutenberg-University Mainz, Boehringer Ingelheim, Germany
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	Mini Spray Dryer B-191	Cabral Marques and Coimbra 2009 University of Lisbon, Portugal
Insulin (diabetes)	Hydrochloric acid, sodium hydroxide, polyalcohols, mannitol	Water	T_{in} < 140 °C T_{out} 40 - 60 °C	Raisin-like particles 3.8 µm size respirable particles FPF > 85 %	Mini Spray Dryer B-191	Cagnani et al. 2004 University of Parma, Parma, Italy
Insulin (diabetes)	Aqueous solution of insulin and additives (mannitol, polymer)	Water	T_{in} 100°C T_{out} 62 - 65°C spray gas 550 NL/h feed rate 3 mL/min	Particle diameter < 5.8 µm sponge-like morphology suitable for respiratory delivery FPF 36 - 47% ED 59 - 81% dispersability 57 - 60 %	Mini Spray Dryer B-191	Najafabadi et al. 2007 University of Medical Sciences, Tehran, Iran Pasteur Institute of Iran, Tehran, Iran
Insulin (diabetes)	Aqueous solution 30 experiments performed	Water	Drying air humidity <20% T_{in} 75 - 220°C spray gas 7 - 17 L/min feed rate 2 - 5 mL/min aspirator 80 - 100%	Resin-like morphology particle size of 4 µm suitable for inhalation	Mini Spray Dryer B-290	Maltensen and van de Weert 2008 University of Copenhagen, Denmark
Gentamicin (antibiotic)	Gentamicin with small amounts of trileucine	Water	-	Spherical to corrugated shape particles of inhalable size ED up to 75% FPF up to 48%	Mini Spray Dryer B-190	Lechuga-Ballesteros et al. 2004 Nektar Therapeutics, USA

Table 3A: Literature review of spray dried inhalable products using the laboratory scale Büchi Mini Spray Dryer models B-190, B-191 and B-290. "Part 1"

Drug and application	Carrier and sample concentration	Solvent	Spray drying process parameters	Particle size, shape, yield, fine particle fraction (FPF) and emitted dose (ED)	Spray dryer model applied	Reference and institution
Doxycycline (antibiotic), Ciprofloxacin (antibacterial)	-	Water	-	Corrugated particles 3.7 µm size FPF < 34 %	Mini Spray Dryer B-191	Traini et al. 2007 University of Sydney, Monash University, Victoria, Australia
Rifampicin (antibiotic)	Poly(D,L-lactide) (PDLLA) Resomer	Water, haltothane	-	Spherical particles 80 % in range 0.3 - 3.0 µm	Mini Spray Dryer B-191	Bain et al. 2002 Quintiles (UK) Ltd, University of Strathclyde, Glasgow, Scotland John Moores University, Liverpool, England
Cefotaxime sodium (antibiotic)	10% sample concentration	Water	T_{in} 100 °C T_{out} 87 - 89 °C	Spherical particles 5.0 µm size better aerolisation compared to jet milling	Mini Spray Dryer B-191	Najafabadi et al. 2005 University of Medical Sciences, Tehran, Iran
Tobramycin (antibiotic)	Sodium stearate 0.25 - 2.0 % sample concentration	Water / ethanol	-	Spherical particles with corrugated surfaces < 3.0 µm size yield 60 % in vitro drug deposition 25 %	Mini Spray Dryer B-191	Parlati et al. 2008 University of Sydney, Australia
Bovine Serum Albumin	Lactose / Brij 76 2.25% sample concentration	Water	T_{in} 180 °C / 95 °C T_{out} 70 °C / 45 °C aspirator 85% spray gas 600 L/h	Corrugated particles 5.4 / 12.8 µm size FPF 43.4 % recovery of drug after inhalation >95 %	Mini Spray Dryer B-290	Li and Seville 2008 Aston University, Birmingham, UK
Human immunoglobulin (antibody)	Mannitol 10% sample concentration	Water	T_{in} 95 °C T_{out} 50 °C spray gas 670 L/h feed rate 3 mL/min	No change in secondary proteins structure	Mini Spray Dryer B-290	Schüle et al. 2004 University of Munich, Boehringer Ingelheim, Germany
Immunoglobulin (antibody) and Human Serum Albumin	Protein/mannitol ratio 70:30 (w/w) 10% sample concentration	Water	T_{in} 90 °C T_{out} 40 °C spray gas 700 L/h feed rate 9 mL/min	Spherical particles 2.5 µm (HSA) 4.4 µm (IgG1)	Mini Spray Dryer B-191	Zimontkowski et al. 2005 University of Bonn, Boehringer Ingelheim, Germany
Proteins secreted by mycobacteria	Poly (lactic-co-glycolic acid) (PLGA)	Water	T_{in} 105 °C feed rate 7 ml/min	1.95 µm particle size yield 53.9 % activity > 93 %	Mini Spray Dryer B-191	Garcia-Contreras et al. 2004 University of North Carolina, USA
Lysozyme (enzyme for immune protection)"	200 mL solutions of lysozyme (5 mg/ml) in phosphate buffer (pH 6.24)	Water	T_{in} 99 ± 2°C T_{out} 50 ± 2°C spray gas 500 L/h feed rate 5 mL/min	Spherical particles 5 µm particle size yield 42% FPF 41% after 12 weeks storage 66% retained enzymatic activity	Mini Spray Dryer B-190	Shoyele et al. 2008 University of Bradford, UK 3M Drug Delivery Systems, Loughborough, UK
Morphine (opiate drug)	2% w/v sample concentration of morphine HCl, mannitol and lecithin (90:6:4)	Water	T_{in} 90°C spray gas 600 L/h feed rate 3.2 mL/min	Mean size 4 - 10 µm satisfactory morphine stability in agglomerated amorphous form	Mini Spray Dryer B-191	Colombo et al. 2008 University of Parma University of Salerno University of Ferrara, Italy
Mannitol (excipient)	Mannitol with 1 - 10% w/w different additives	Water	T_{out} 60 °C feed rate 0.1 mL/s	Particle volume concentrations up to 35 ppm in air mean particle size around 5 µm	Mini Spray Dryer B-190	Morton et al. 2008 Monash University, Victoria, Australia

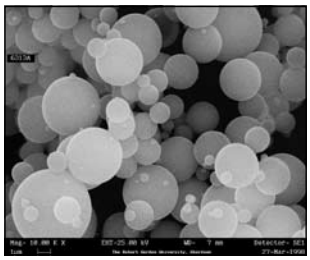
Table 3B: Literature review of spray dried inhalable products using the laboratory scale Büchi Mini Spray Dryer models B-190, B-191 and B-290. "Part 2"

cle fractions were achieved, ranging from 30 - 60% [6-8, 16] to over 85% [13]. Inhaler emitted powder doses of over 90% were reported [2, 7, 8]. Amorphous powders were typically generated due to the short drying time in the laboratory scale spray dryers [3, 22]. Aerosolized powder clouds with maximal volume concentrations of up to 35 ppm particles in air were achieved [20].

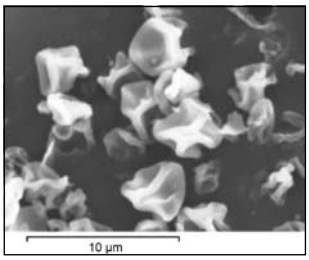
sulphate nanoparticles (an anti-asthmatic drug) into microparticles [2]. Physically and chemically stable non-cohesive spray dried particles, with small aerodynamic diameters were designed to be efficiently delivered as a dry powder aerosol [11]. Spray drying produced powders with superior biochemical stability upon formulation compared to spray freeze drying; acting inhaled drug particles (about 0.5 - 3.3 µm which represents deposition in the lung alveoli).

The key benefits of this technology are the possibilities to control the size and morphology of the particles under a relatively gentle processing method. Indeed, this method has been proven for the preparation of heat-sensitive materials such as protein based drugs.

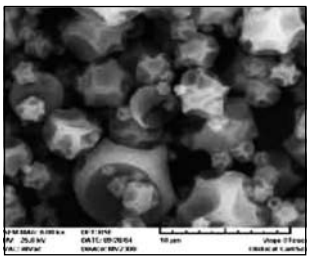
Rifampicin
(Bain et al. 2002)



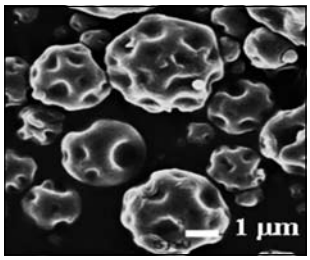
Insulin
(Cagnani et al. 2004)



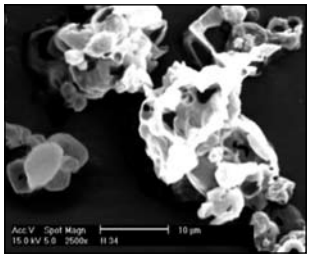
Cefotaxime sodium
(Najafabadi et al. 2005)



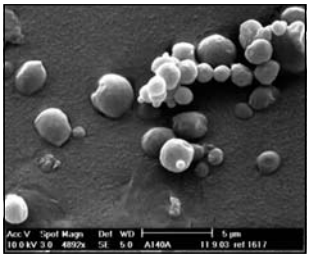
Ciprofloxacin
(Traini et al. 2007)



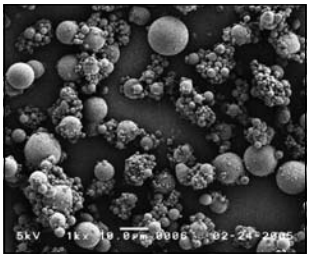
Salbutamol
(Brandes et al. 2004)



Terbutaline
(Cook et al. 2004)



Chitosan
(Learoyd et al. 2004)



Lactose
(Weiler et al. 2008)

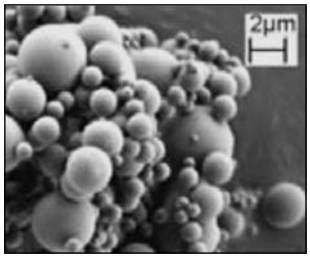


Figure 3: SEM photographs of inhalable spray dried powder from literature.

Compared to jet milled samples, higher fractions of potentially inhalable aerosol particles of antibiotic cefotaxime sodium were measured for spray dried formulations [23]. Deagglomeration of spray dried protein formulations was possible [17]. Higher powder dispersibility of spray dried powders compared to jet milled particles was explained by their spherical shape and therefore smaller surface contact area [5].

Particularly, high values of respirable fractions were found for insulin because of the spray dried particle size [13]. The capability for inhalation with relatively high drug loading was shown, for example by incorporation of terbutaline although with less efficient aerosol properties [24]. Sustained release of highly dispersible amino acid leucine incorporated PLGA powders was exhibited over several days [8].

Conclusions

Spray drying is a very useful technique to produce inhalable dry powders with predetermined specifications. There is significant research activity in dry powder aerosol formulation to treat several diseases including asthma, tuberculosis, diabetes and bacterial infection in the lung. Spray drying offers great potential to these applications because of the easy achievement of the accepted optimum size range for locally

While the traditional bench-top spray dryers have been shown capable tools for the laboratory aim generation of respiratory sized particles, the area of process technology is ever-evolving. The Nano Spray Dryer B-90 offers new possibilities in the field of laboratory scale spray drying and eliminates some weak points of traditional spray dryers; including increased recovery (up to 90%), small quantity production (100 mg amounts) and highly definable particle size ranges (300 nm - 5 µm) [25].

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