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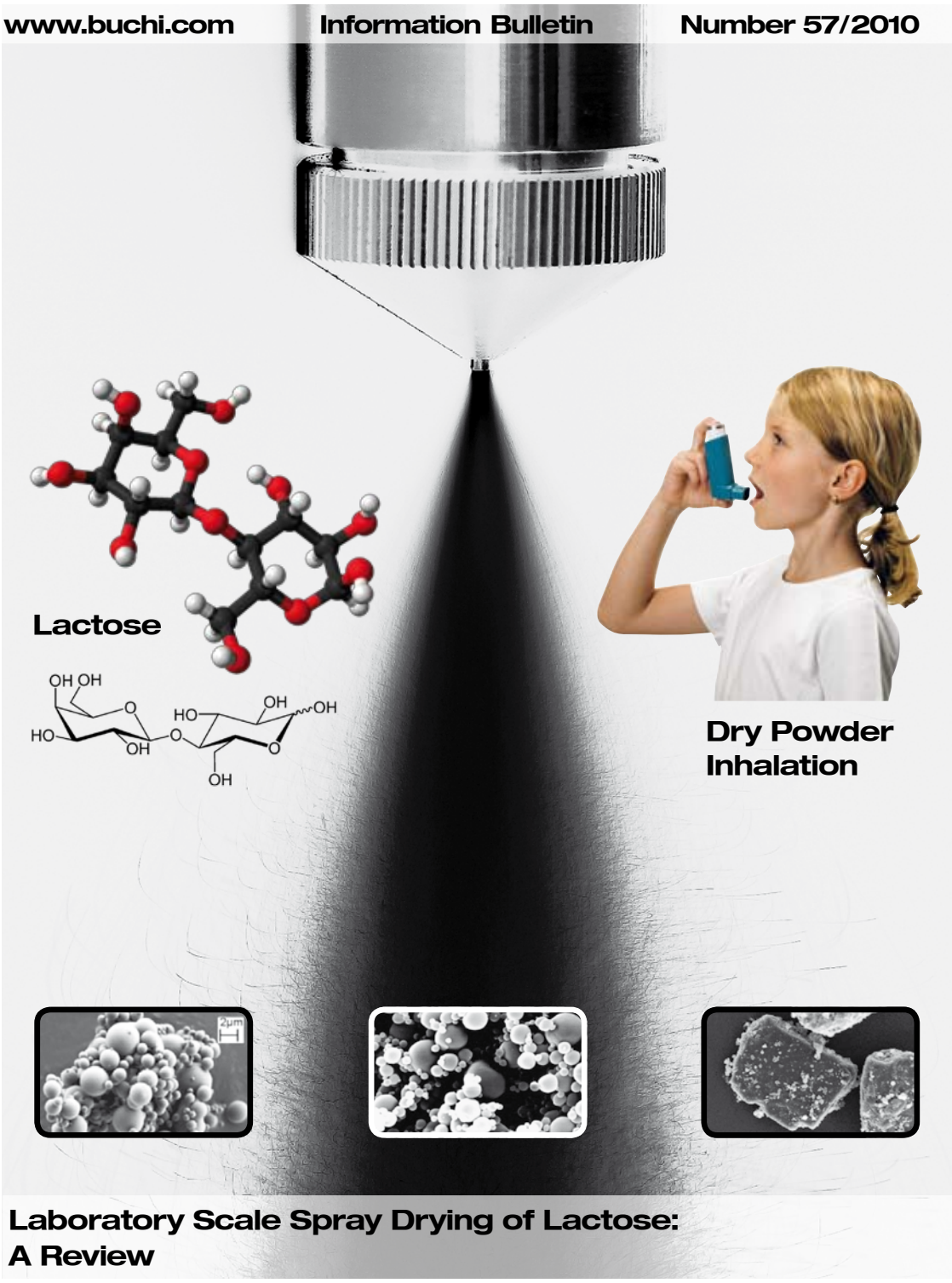

Laboratory Scale Spray Drying of Lactose: A Review

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Laboratory Scale Spray Drying of Lactose: A Review

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Introduction

Spray drying is a commonly practiced method to prepare inhalable powders and has been applied to a variety of substances, such as peptides, antibiotics, vaccines and biodegradable carrier particles [1, 2]. The described delivery technology can be used for lung-specific applications to treat cystic fibrosis, asthma, chronic pulmonary infections, lung cancer or tuberculosis [3, 4].

1997 - 1994
Mini Spray Dryer B-190

1994 - 2003
Mini Spray Dryer B-191

2003 - ongoing
Mini Spray Dryer B-290

2009 - ongoing
Nano Spray Dryer B-90

2009 - ongoing
Mini Spray Dryer B-290

Figure 1: Generations of BÜCHI laboratory scale spray dryers with the Mini Spray Dryer; B-190, B-191 and B-290 models and the new Nano Spray Dryer B-90

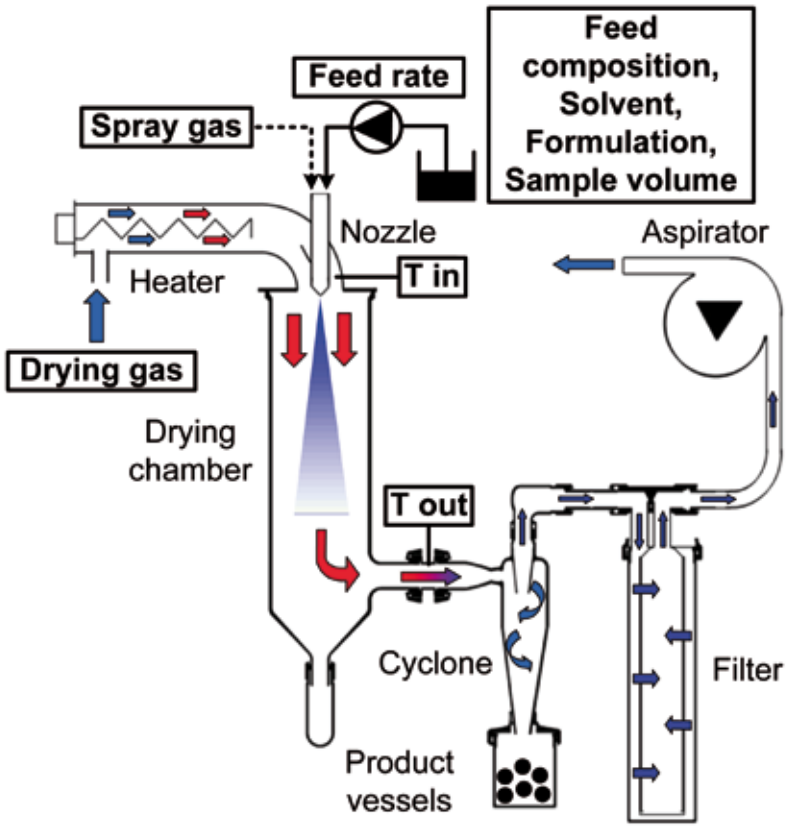


Figure 2: Process diagram of the Mini Spray Dryer B-190, B-191 and B-290 models with process parameters

Lactose is one the most common excipients used for dry powder lung delivery. The main properties of lactose are listed in Table 1.
Beside lactose, leucine, mannitol, glucose, trehalose and sucrose are other carriers which have been studied over the past few years as new inhaled drug delivery formulations [5, 6]. These excipients are approved by the Food and Drug Administration (FDA) for pulmonary delivery, and so, widely applied in aerosolization. This is due to their non-toxic, readily degradable properties after administration.
Lactose has the advantageous material property of a low stickiness behaviour compared to other sugars (see Table 2). Moreover, the higher glass transition temperature (Tg 101 °C) enables an easy flowing powders.

This study reviews recently published scientific work in the field of lactose spray drying for inhalable applications using BÜCHI laboratory scale spray dryers. The generations of the Mini Spray Dryer; B-190, B-191 and B-290 models and the new Nano Spray Dryer B-90 are illustrated in Figure 1.

The adjustable spray drying process parameters are (see Figure 2):

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

Chemical structure	Lactose (or milk sugar) is a disaccharide that consists of galactose and glucose fragments
Molecular formula	$C_{12}H_{22}O_{11}$
Molar mass	342.3 g/mol
Appearance	White solid
Solubility in water	21.6 g/100 mL at 25 °C
Density	1.53 g/cm
Melting point	223 °C
Glass transition point	101 °C

Table 1: Lactose properties

In the presented research studies (see Table 5), the inlet air temperatures in the Mini Spray Dryer models ranged from 90 °C to 210 °C depending on the application, the feed rate was set between 2 mL/min to 15 mL/min, the drying gas flow rate was set typically to 40 m³/h and the spray gas was 300-700 L/h.
Mainly aqueous solutions were prepared by dissolving an active ingredient (drug, nanoparticles) and excipient (lactose and others) in water at different solid concentrations. In some studies ethanol was added to the solution to enhance evaporation [3, 5, 7, 8]. The sample volume varied between 50 and 450 mL. The resultant spray dried powder was separated by a cyclone and collected in a vessel. The exhaust gas was extracted from the cyclone and filtered.

In contrast, the new Nano Spray Dryer B-90 is based on a new spray drying concept, as illustrated in Figure 3. A comparison with the traditional Mini Spray Dryer B-290 is given in Table 3.

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 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. Typical operating conditions for experiments are: inlet air temperature 120 °C, outlet temperature around 45-56 °C, feed rates range from 3 to 25 mL/h (depending on the solution viscosity, composition, spray rate), the drying gas flow rate 130 L/min and 4.0 µm spray mesh. Commonly applied analytical methods to characterize the powders after spray drying are:

SEM	Particle morphology and size
Laser Diffraction	Particle size
Anderson Impactor	Fine particle fraction
X-Ray Diffraction	Amorphous/crystalline state
DSC	Glass transition temperature
Gas adsorption	Mass specific surface area
Karl Fisher	Moisture content

Sugars	Hygro-scopicity (relative)	Melting point (°C)	Water solubility at 60 °C (w%)	Tg (°C)	Stickiness (relative)
Lactose	+	223	35	101	+
Maltose	++	165	52	87	++
Sucrose	+++	186	71	62	+++
Glucose	+++++	146	72	31	+++++
Fructose	++++++	105	89	5	++++++

Table 2: Physical properties of sugars and stickiness behaviour (Tg: glass transition temperature)

Literature review

Figure 4 illustrates the research trends and activities of lactose spray drying by the number of journal articles listed in the Web of Science. 261 journal papers were found in the last 30 years with the search key words “lactose” AND “spray drying”. A steady increase is seen with about 50% of subject areas in pharmacology & pharmacy, 30% in food science & technology, then followed by chemistry (18%), chemical engineering (11%), agriculture, dairy & animal science (4%), biotechnology & applied microbiology (4%) and others.
Table 5 shows a review of scientific works in the field of lactose spray drying made on the BÜCHI Mini Spray

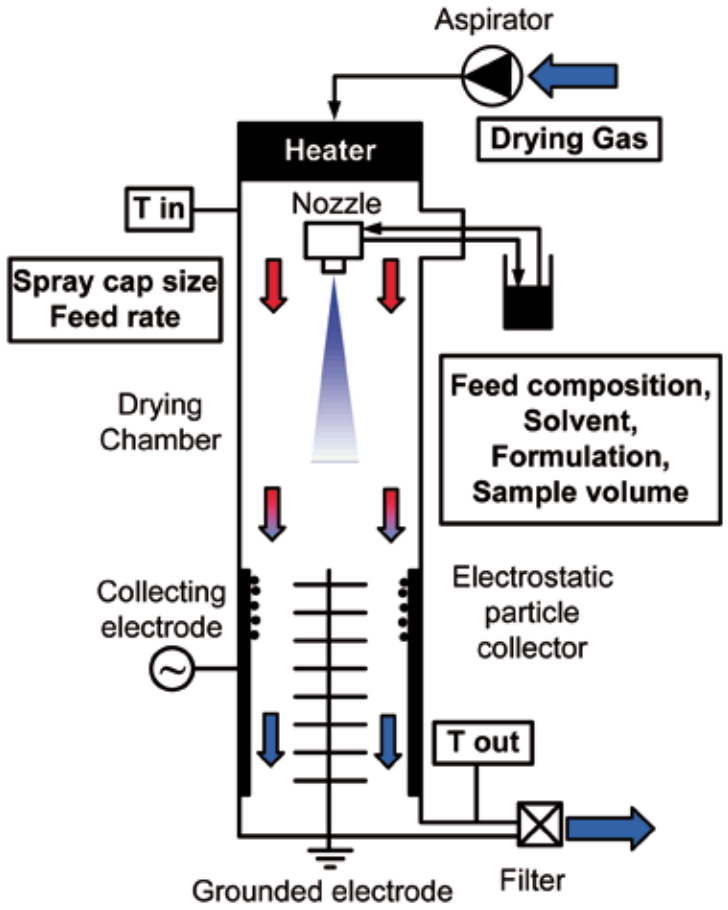


Figure 3: Process diagram of the new Nano Spray Dryer B-90 with process parameters

Dryer B-190, B-191 and B-290 models. Experiments with the new Nano Spray Dryer B-90 are results of BÜCHI internal trials.

The research was carried out at various universities globally in countries such as Australia, Canada, Denmark, Finland, Germany, Iran, Ireland Singapore, Sweden, UK and USA.

The investigated applications with lactose are all concerned with pulmonary (aerosol, respiratory) drug delivery with specific therapy to anti-allergies [7], asthma [9], non-viral gene delivery [6, 10, 11] or antibiotics [3].

Overall, spray drying is described as a suitable alternative method for producing inhalable dry powders for pulmonary applications. The main advantages compared to freeze dried and jet milled products are summarized in Table 4.

Today, the market of DPI products relies on freeze dried and jet milled micronized drugs [6]. However, comparable geometric size distributions are achieved of the same substances with spray dried or jet milled spray dried powders, but particle morphology can more easily be

	Nano Spray Dryer B-90	**Mini Spray Dryer B-290**
Main benefit	for small quantities, finest particles, highest yields	for traditional spray drying, established process
Max. inlet temperature	120 °C	220 °C
Water evaporation	max. 0.2 kg/h	1.0 kg/h, higher for solvents
Nozzle type	piezoelectric driven vibrating mesh	two-fluid nozzle
Particle size	300 nm – 5 µm	2 – 25 µm
Particle separation	electrostatic particle collector	cyclone
Typical yield	up to 90%	typically around 60%
Min. sample volume	1 mL	30 mL
Max. sample viscosity	10 cps (diluted samples)	300 cps (viscous samples and juices possible)
Scale-up	limited by spray head and electrical particle collector	possible to scale-up to kg- and tons-scale

Table 3: Comparison of main features and benefits between Nano Spray Dryer B-90 and Mini Spray Dryer B-290

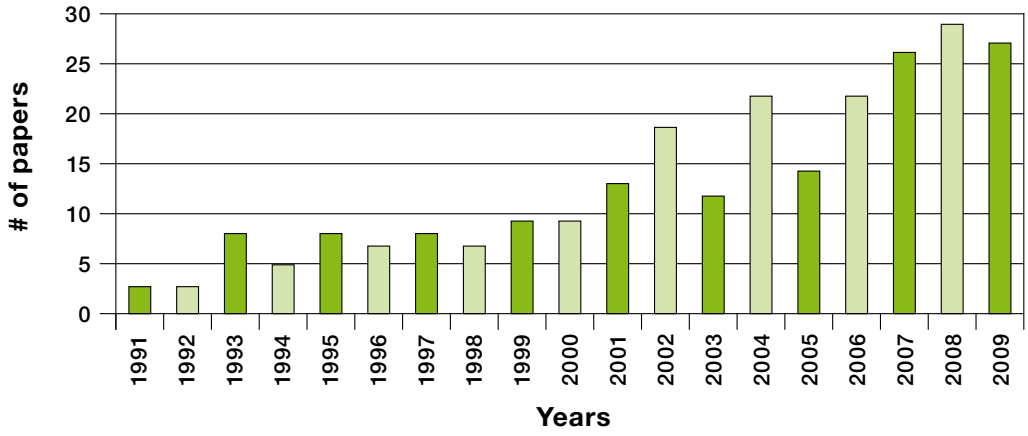


Figure 4: Journal articles over the last years listed in the Web of Science with the search key words "lactose" AND "spray drying"

Advantages of spray drying

1. Highly dispersible and spherical particles in a range of 1 to 5 µm with narrow particle size distribution
2. Control of particle shape, morphology and density depending on spray drying conditions
3. One-step process directly from liquid to dry formulations
4. Process simplicity, cost effectiveness and scale-up capability

Table 4: Advantages of spray drying compared to freeze dried and jet milled products to produce inhalable dry powder for pulmonary applications

influenced by spray drying than by jet milling [9].
Compared to freeze drying, spray drying generates highly dispersible powders for inhalation without the use of carrier particles. The jet milling process leads to small and also flat particles and stronger cohesive forces with poor flow properties.
Compared to the crystalline nature of jet milled lactose, the structure of spray dried lactose is amorphous [12].

The mean particle sizes reported in almost all of the literature studies were in a range of 1 to 5 µm, which is generally considered to be effective for pulmonary delivery. Blank lactose carrier particles for blending were in the 50-80 µm size range. Moreover, spray drying is a one-step process with narrow particle size distribution of respirable dimensions directly from liquid formulations [10].

Spray drying allows control of particle shape, morphology and density depending on the spray-drying conditions [9].

Spherical particles can be prepared which provide a low contact area and homogeneous particle size distribution resulting in a higher respirable fraction than mechanically micronized drugs.

Particle morphology

The SEM analysis showed that most of the spray dried lactose micro-particles were spherical in shape. The fine microparticle agglomerates appeared round and compact with a smooth surface. By further dilution of the spray dried fluticasone and salbutamol from 10% to 1% solution, the Nano Spray Dryer B-90 (Figure 6, Images M and N) appeared able to produce spherical submicron particles with smooth surface at high yields.

Application	Carrier and sample concentration	Solvent	Spray drying process parameters	Spray dryer model	Particle size, shape, yield, fine particle fraction (FPF) and emitted dose (ED)	Reference and institution
Disodium cromoglycate (antiallergic drug)	6% solution αlactose monohydrate as inhalation carrier particles	80% Water 20% Ethanol	T in 180 °C, T out 80 °C Spray gas 800 NL/h Drying air 2.4 m³/min Feed rate 60 mL/min Sample volume 450 mL	Mini Spray Dryer B-190	1-5 µm, spherical amorphous crystal structure high dissolvation rate	Vidgrén et al. 1987 [7] Department of Pharmaceutical Technology, University of Kuopio, Finland
rhDNase (Aerosol Delivery)	15-90 mg/mL Recombinant Human Deoxyribonuclease Mannitol (43 µm), NaCl (87 µm) and lactose (42 µm, 115 µm) as carrier particles	Water	T in 90 °C T out 55 °C Feed rate 5 mL/min	Mini Spray Dryer B-190	2.6-5.5 µm (pure rhDNase) FPF 50% lactose carrier particles with irregular shape and monolayer adhesion of rhDNase particles	Chan et al. 1997 [13] Deparment of Pharmacy, University Sydney, Genentech Inc., Inhale Therapeutics, Aradigm Corporation Hyward, California, Roche Basel
a-Lactose monohydrate (Pharmaceutical excipient)	αLactose monohydrate 10g, 20g, 30g and 40g in 100 mL	Water	T in 185 °C, T out 85 °C Heating rate setting 11.5 Spray gas 400 NL/h Drying air setting 12 Feed rate varied	Mini Spray Dryer B-190	7.2-13.9 µm 82%-100% amorphous lactose	Chidavaenzi et al. 1997 [14] School of Pharmacy, University of London, SmithKline Beecham Pharmaceuticals, UK
Lactose/PEG particles	5% and 10% lactose monohydrate solution and lactose/PEG 4000 (containing 5, 10, 20 30% polyethylene glycol)	Water	T in 118-123 °C T out 76-80 °C Spray gas 600 NL/h Feed rate setting 5	Mini Spray Dryer B-190	lactose particles: 1-4 µm smooth spherical lactose/PEG 10% particles: 2-5 µm spherical	Corrigan et al. 2002 [21] Department of Pharmaceutics and Pharamceutical Technology, School of Pharmacy, Trinity College, Dublin, Ireland
pDNA (non-viral gene delivery)	pDNA (lipid:polycation:pDNA) in 3% w/v lactose solution leucine and amino acids as dispersibility enhancers	Water	T in 150 °C T out 80 - 85 °C Spray gas 600 L/h Drying gas 35 m³/h Feed rate 7.5 mL/min Sample volume 50 mL	Mini Spray Dryer B-191	2.7-3.9 µm uniform spherical particles (compared to 18 µm after freeze drying and grinding) ED up to 96% FPF up to 52%	Seville et al. 2002 [6] Li et al. 2003 [10] Li et al. 2005 [11] Welsh School of Pharmacy, Cardiff University School of Pharmacy, University of London, UK Aston Pharmacy School, Aston University, Newport Chest Clinic, Newport, UK
Fluticasone propionate (respiratory drug delivery	Fluticasone propionate as model drug 5-10% feed concentration Blends with lactose monohydrate (45-75 µm) containing 2% fluticasone propionate	Acetone	T in 100 °C Spray gas (1-3 bar) N2 as drying gas Feed rate 5 mL/min	Mini Spray Dryer B-191	1-10 µm size range spherical and respirable particles	Louey et al. 2004 [24] School of Pharmacy, University of North Carolina, USA GlaxoSmithKline, North Carolina, USA
Gelatine nanoparticles in lactose (Aerosol delivery)	5 g of lactose dissolved in 75 mL (heated up to 40 °C to increase solubility) mixed with 25 mL of either gelatin (242 nm) or polybutylcyanoacrylate nanoparticles (173 nm)	Water	T in 170-180 °C T out not mentioned Spray gas 700 L/h (80 psi) Drying gas 40 m³/h Feed rate 2 mL/min	Mini Spray Dryer B-191	3.0 ± 0.2 µm spherical FPF 38-42% even distribution of gelatin nanoparticles throughout the lactose carrier particles	Sham et al. 2004 [4] University of Alberta, Edmonton, Canada
Large hollow carrier particles of nanoparticle drugs (inhaled drug delivery	Silica nanoparticles suspension (5-150 nm) with lactose (3:1 w/w) in 60 mL buffer solution, mixed with 140 mL of ethanol	30% Water 70% Ethanol	T in 130 °C T out 60-80 °C Spray gas 250 L/h N2 drying gas 40 m³/h Feed rate 1.5 mL/min Sample volume 200 mL	Mini Spray Dryer B-290 and Inert Loop B-295	4.9-7.7 µm large and hollow carrier particles high flowability and therapeutic efficacy	Hadinoto et al. 2006 [8] Department of Chemical and Biomolecular Engineering, National University of Singapore
Lactose and polyethylene glycol (PEG)	10 g lactose in 100 mL with various PEG concentrations	Water	T in 100 °C T out 64-67 °C T product vessel 45-47 °C T Feed 25-29 °C Spray gas 550 NL/h Drying gas 100% Feed rate 250-300 mL/h	Mini Spray Dryer B-191	amorphous lactose Tg of spray dried lactose 118 °C PEG promoted crystallization of lactose when co-spray dried	Mosén et al. 2006 [17] The Danish University of Pharmaceutical Sciences, Copenhagen Department of Chemical Engineering, Lund University, Sweden AstraZeneca R&D, Lund, Sweden
Morphine (opiate drug)	90 w% morphine, 6 w% lactose, 4 w% leucine (protectors and particle shapers) 2% solid concentration	Water	T in 90 °C T out 39-40 °C Spray gas 600 L/h Feed rate 3.25 mL/min	Mini Spray Dryer B-191	4.0 µm, spherical, amorphous morphine Yield 53% Water content 8.5%	Russo et al. 2006 [15] Department of Pharmacy, University of Parma, Department of Pharmaceutical Sciences, University of Salerno, Italy

Table 5: Review of scientific works in the field of lactose spray drying made on BÜCHI spray dryers

Application	Carrier and sample concentration	Solvent	Spray drying process parameters	Spray dryer model	Particle size, shape, yield, fine particle fraction (FPF) and emitted dose (ED)	Reference and institution
Cefotaxime sodium (inhalation therapy)	10% cefotaxime sodium 40% lactose	Water	T in 100°C T out 87-89 °C Spray gas 600 Nl/h Drying gas setting 70% Sample volume 100 mL	Mini Spray Dryer B-191	4.6 µm sphere-like with smooth surface amorphous 0.9% final water content true density 1.55 g/cm³	Najafabadi et al. 2006 [12] Tehran University of Medical Sciences, Pasteur Institute of Iran
Milk powder	8.8% and 41.2% skimmed milk 11% whole milk 8.8% lactose-free skimmed milk	Water	T in 120 °C and 200 °C (skimmed milk and whole milk) T in 200 °C (lactose-free skimmed milk and skimmed milk) Spray gas 538 L/h Drying gas 38 m³/h Feed rate 11 mL/min Sample volume 500 mL	Mini Spray Dryer B-290	14-24 µm (8.8% skimmed milk) 35 µm (41.2% skimmed milk) Yield 65.8 to 82.7% (skimmed milk) Yield 10.4 to 18.6% (whole milk) Moisture content 2-11%	Langrish et al. 2006 [19] School of Chemical and Biomolecular Engineering, The University of Sydney, Australia
PBCA nano-particles and ciprofloxacin (antibiotic inhalation therapy)	7% lactose solution, or solution containing PEG 6000 and L-leucine, or effervescent formulation with 7 mL of polybutylcyanoacrylate nanoparticle suspension, or 100 mg ciprofloxacin hydrochloride hydrate	Water Ethanol	T in 150 °C, T out 130 °C (lactose solution) T in 130 °C, T out 110 °C (effervescent formulation) Heating rate 10-15 Spray gas 800 Nl/h Drying gas setting 15 Feed rate 2 mL/min	Mini Spray Dryer B-191	spherical lactose powder: 10 µm, FPF 14% effervescent particles (carrier particles containing nanoparticles): 2.2 µm, FPF 46%	Ely et al. 2007 [3] Faculty of Pharmacy, Department of Oncology and Department of Mechanical Engineering, University of Alberta, Edmonton, Canada
Salbutamol sulphate (asthma drug)	Lactose monohydrate and salbutamol sulfate	Water	not given	Mini Spray Dryer B-191	3.2 µm, solid interior spherical particles, amorphous lactose, FPF about 20%, dispersion factor 80-100%	Weiler et al. 2008 [9] Johannes Gutenberg-University Mainz, Boehringer Ingelheim, Germany
Brij 76-coated lactose-BSA (pulmonary delivery)	3% w/v lactose solution 1 % w/v Bovine Serum Albumin 2.25% total sample concentration 1g spray dried lactose-BSA powder in 40 mL acetone with 0.25% w/v Brij 76 (surfactant)	Water	T in 180 °C, T out 70 °C (lactose-BSA) T in 95 °C, T out 45 °C (lactose-BSA-Brij 76) Spray gas 600 L/h N2 drying gas 85%	Mini Spray Dryer B-290	5.4, 12.8 µm corrugated particles FPF 43.4% recovery of drug after inhalation >95%	Li and Seville 2008 [23] Aston University, Birmingham, UK
Lactose	15% w/v solid concentration	Water	T in 134 °C (amorphous) T in 210 °C (crystalline) T out not mentioned Spray gas 1200 L/h Drying gas 100% Feed rate 6.4 g/min	Mini Spray Dryer B-290	Degree of crystallinity increased from 55% to 76% with higher inlet temperature (134 °C to 210 °C)	Chiou et al. 2008 [22] School of Chemical and Biomolecular Engineering, The University of Sydney, Australia
Lactose and salts (NaCl and KCl)	Lactose-salt solutions (5:2 and 5:1 w/w ratio) NaCl and KCl	Water	T in 170 °C Spray gas 473 L/h Drying gas 38 m³/h Feed rate 11 mL/min	Mini Spray Dryer B-290	Yield 26-51% Moisture content 3-7%	Islam and Langrish 2008 [20] School of Chemical and Biomolecular Engineering, The University of Sydney, Australia
Lactose	10% (w/v) lactose solution	Water	T in 170 °C, T out 90 °C T in 200 °C, T out 157 °C (insulated drying chamber) Drying gas 38 m³/h Spray gas 600 L/h Feed rate 1.5 mL/min, 11 mL/min	Mini Spray Dryer B-290	Yield 47% more beta-lactose	Islam and Langrish 2010 [18] School of Chemical and Biomolecular Engineering, The University of Sydney, Australia
Biocompatible silica nanoparticles	0.8% concentration of colloidal silica nanoparticles (25 nm), 0.2 w% leucine, 1.2% lactose	90% Water 10% Ethanol	T in 105 °C Spray gas 320 L/h Feed rate 0.17 L/h	Mini Spray Dryer B-290	2-4 µm hollow spherical nano-aggregates	Kho and Hadinoto 2010 [5] School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore
Fluticasone propionate (respiratory drug delivery)	10% homogeneous dispersion 0.1g Fluticasone propionate (particle size D90 = 3 µm), 0.1g Tween 80 and 9.8 g lactose dissolved in 100 mL	Water	T in 120 °C, T out 45-56 °C Spray rate 100% Drying gas 130 L/min Feed rate 10 g/h 4.0 µm spray mesh	Nano Spray Dryer B-90	0.5-3.0 µm Sprayed amount 27 g dispersion Powder recovery 2.0 g Yield 77%	Büchi Spray Dryer Application Lab (internal study 2010)
Salbutamol sulphate (inhalation)	10% clear solution 0.125 g salbutamol sulphate and 9.875 g lactose dissolved in 100 mL	Water	T in 120 °C T out 52-56 °C Spray rate 100% Drying gas 130 L/min Feed rate 10 g/h 4.0 µm spray mesh	Nano Spray Dryer B-90	0.5-3.0 µm Sprayed amount 20 g solution Powder recovery 1.4 g Yield 70%	Büchi Spray Dryer Application Lab (internal study 2010)

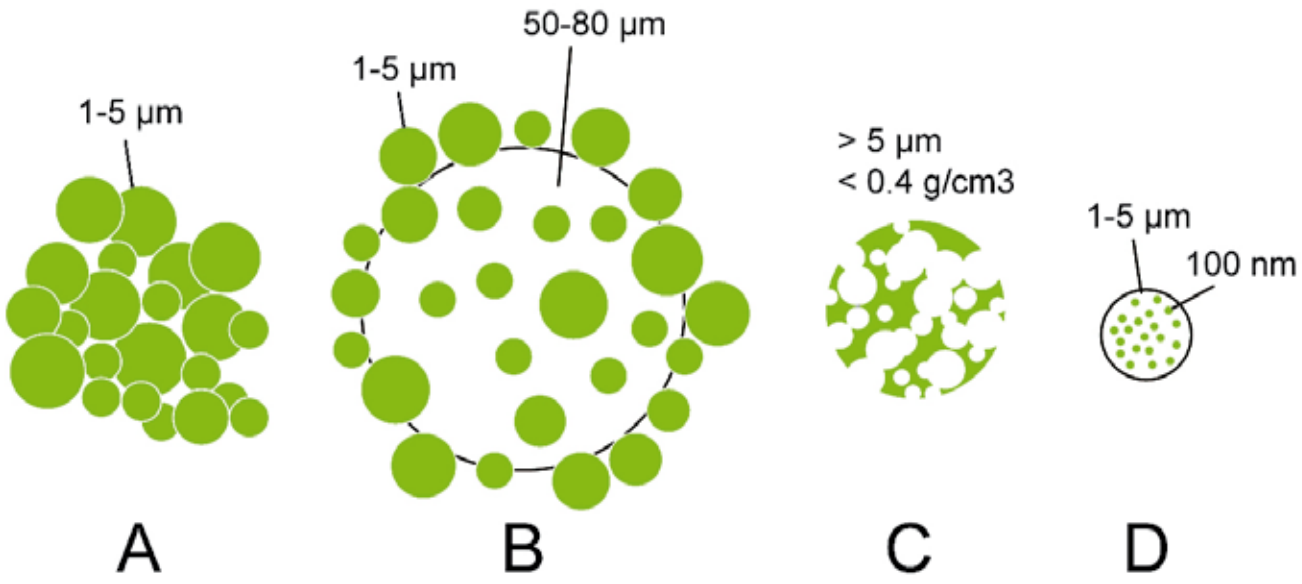


Figure 5: Strategies of dry powder formulations for inhalable applications:
Group A: Small carrier-free drug particles
Group B: Small drug and larger carrier particles
Group C: Large porous drug particles
Group D: Encapsulated nanoparticle drugs in carrier particles

Dry powder formulations

Four main strategies are predominantly followed to formulate dry powders for inhalation applications based on lactose, as illustrated in Figure 5.

Group A: Small carrier-free drug particles

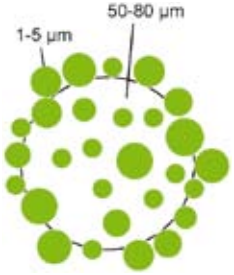
Aerosol powders ranging from 1 to 5 µm are considered the optimum size for deposition beyond the increasingly narrow airways into the alveoli. However, such small particles often stick together, are very cohesive with poor flow properties, which makes physical handling of the particles difficult and lowers the fine particle fraction.

Studies by Li et al. 2003 [10] and Li et al. 2005 [11] demonstrated that the dose emission and dispersibility of spray dried lactose particles were considerably enhanced in the presence of amino acids, specifically leucine, phenylalanine and arginine. Incorporation of NaCl and its relative proportion was also efficient to control the aerosol properties of spray dried rhDNase powders [13]. The presence of NaCl changed the morphology and crystallinity of the co-spray dried powders, and this was paralleled by improvement in the fine particle fraction of rhDNase. In particular, in blends with about 50 µm lactose carrier particles the rhDNase particles adhered apparently in the form of a monolayer to the carrier (see Figure 6, Image K).

Ely et al. 2007 [3] produced inhalable effervescent powders and used a mixture of acids such as citric acid and carbonates. Different ingredients such as ethanol, polysorbate 80, L-leucine and PEG 6000 were added to the basic formulation to improve the particle size and to achieve an appropriate mass medium particle diameter.

The experiments with the Nano Spray Dryer B-90 illustrate the promising potentials with high fabrication yields and very narrow size distributions. The asthma drugs salbutamol and fluticasone propionate were spray dried in 10% lactose solution and the resulting size distributions were shown to be in the 1-3 µm range (see Figure 6, Images M and N). At further diluted concentrations, the Nano Spray Dryer B-90 appeared to provide very satisfactory results for the formulation of submicron particles from small sample amounts. This novel spray drying technology offers promising perspectives for new pharmaceutical applications using spray drying.

Group B: Small drug and larger carrier particles

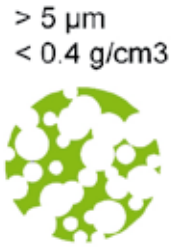


The most common approach to overcome the cohesiveness of small particles is the use of carrier particles markedly larger than the drug parti-

cles [7, 13, 14]. The aggregation problem is solved by particle size enlargement, which involves an additional blending step of the small drug particles (active ingredients, such as budesonide and formoterol fumarate dehydrate) with large lactose carrier particles to improve their flow through the inhaler [2]. Lactose is the most commonly used carrier for Dry Powder Inhaler (DPI) formulations, where it is usually designed to have a size of about 50 µm to 80 µm for this purpose [12]. During inhalation, the smaller drug particles separate from the carrier particles and are deposited in the alveoli.
Trehalose and mannitol are also known to improve protein stability, although the use of mannitol in this regard is limited due to its susceptibility towards crystallization. While the spray dried trehalose was amorphous, spray dried mannitol recrystallised [5].

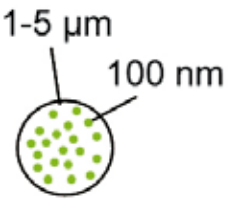
For nasal administration, an agglomeration step is successfully applied to transform primary spray dried microparticles into spherical and flowable agglomerates, as shown by Russo et al. 2006 [15] for morphine particles.

Group C: Large porous drug particles



A breakthrough in inhaled dry powder aerosols research was made with the development of large porous prticles (>5 µm) with low mass density (<0.4 g/cm^3) by Edwards et al. 1997 [16]. It has been shown that larger particles aggregate less and disaggregate more easily. These large porous particles are specifically designed to serve as an alternative to the conventional small non-porous drug particles (Group A). They can be manufactured via spray drying because of its process simplicity, cost effectiveness, and scale-up capability. By virtue of their larger size, the porous particles have better flowability and are capable of evading the phagocytic clearance mechanism in the lungs, which leads to an improved therapeutic efficacy of the inhaled drug.

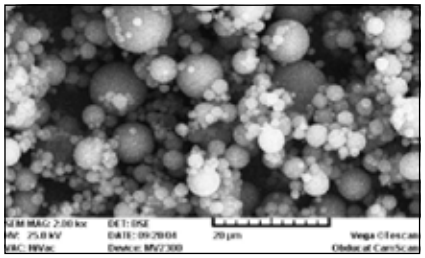
Group D: Encapsulated nanoparticle drugs in carrier particles



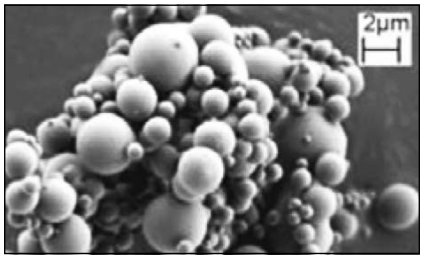
Nanoparticulate drugs as therapeutic carriers has become the subject of very active research [8]. Nanomedicine is an emerging field in the biomedical sciences [3]. Nanoparticles have also been proposed for pulmonary administration to utilize their advantages in drug delivery to the lungs [4]. However, one issue is that their small size limits their lung deposition. Aerosolized nanoparticles have only very limited sedimentation, inertial impaction or diffusion, which causes them to be predominantly exhaled from the lungs after inhalation. Research focus is therefore on the incorporation of nanoparticles into carrier particles to produce the appropriate size for pulmonary drug delivery [8]. Sham et al. 2004 [4] incorporated for example gelatine nanoparticles into lactose powders by spray drying. The gelatine nanoparticles were evenly distributed throughout the lactose carrier particles. After spray drying the nanoparticles remained in the nano-range size. This promising technique was also used to incorporate biodegradable polymer and protein-based nanoparticles into lactose carrier particles.
Spray dried silica nanoparticles in lactose was studied by Hadinoto et al. 2006 [8] and Kho and Hadinoto 2010 [5]. Here, the degree of hollowness decreased as the concentration of nanoparticles increased. Spray drying of lactose in the absence of nanoparticles yielded large solid spherical particles, whereas the presence of nanoparticles leads to an apparent decrease in the molecular diffusivity of the lactose solutes and produced hollow particles (see Figure 6, Image O). Such large, hollow nanoparticulate aggregates may serve as new micron-sized carriers of nanoparticulate drugs for delivery by dry powder inhalers.
Moreover, Kho and Hadinoto 2010 [5] found that a multiple-excipient formulation of leucine and lactose at a 1:6 concentration ratio was capable of producing optimal results in terms of both the nanoaggregate morphology and aqueous re-dispersibility. The high aqueous solubility of lactose facilitated the effective re-dispersion of the nano-aggregates, whereas the presence of hydrophobic leucine stabilized the nano-aggregates by reducing their cohesiveness.

Lactose structure after spray drying

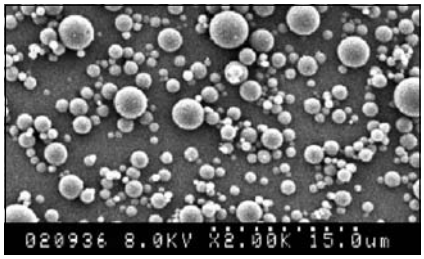
Control of the structural state of spray dried pharmaceuticals is of major importance. Spray drying is often used to produce amorphous composites which are generally attributed to the rapid drying process leaving very short time for evaporation and formation of the solid phase [17]. Lactose is typically 100% amorphous after spray drying because of the short residence time in the spray dryer [14] and its high glass transition temperature [18] (see Table 2).
A drawback of the amorphous state is that this metastable form will, if not stabilized, spontaneously crystallize over time, which may result in agglomeration and caking of the primary particles so that the product becomes non-inhalable.
Major factors affecting the physical instability of amorphous lactose are the physico-chemical properties of the materials; in particular the glass transition temperature of the applied materials and the crystallization temperature, as well as the spray drying processing variables such as the drying temperature and the relative humidity of the drying air.
The absorbed water has a plasticizing effect on the lactose. The critical relative humidity at which the glass transition temperature falls below room temperature (25 °C) is quoted in most publications as around 48% relative humidity [14].



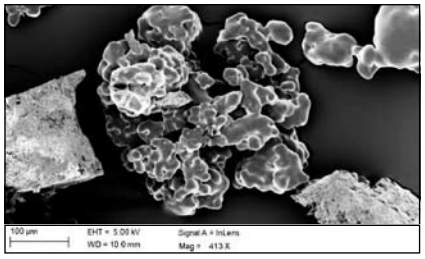
A: Lactose
(Najafabadi et al. 2006 [12])



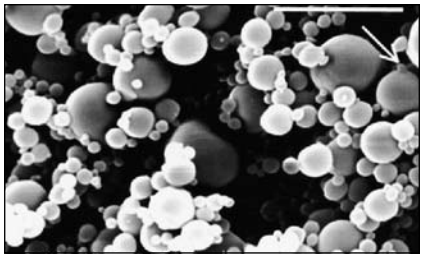
B: Lactose
(Weiler et al. 2008 [9])



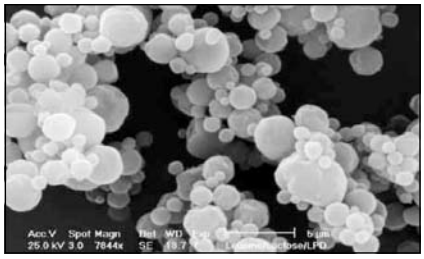
C: Lactose from 7% solution
(Ely et al. 2007 [3])



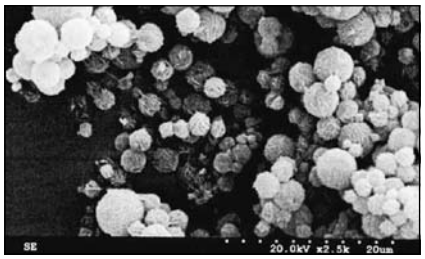
D: Amorphous and crystalline lactose produced at 220 °C inlet temperature
(Islam and Langrish 2010 [18])



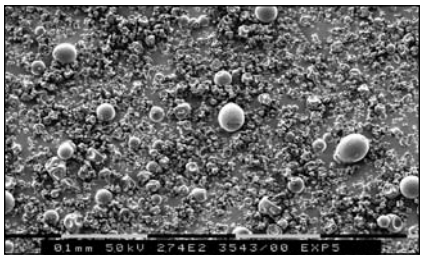
E: Lipid:polycation:pDNA (LPD) vectors in 3% lactose
(Seville 2002 [6])



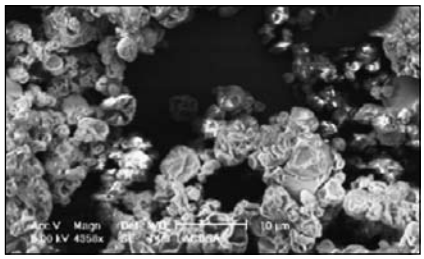
F : Leucine-lactose-(lipid : polycation: pDNA)
(Li et al. 2003 [10])



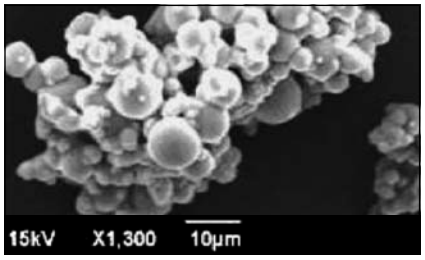
G: Lactose/PEG 10%
(Corrigan et al. 2002 [21])



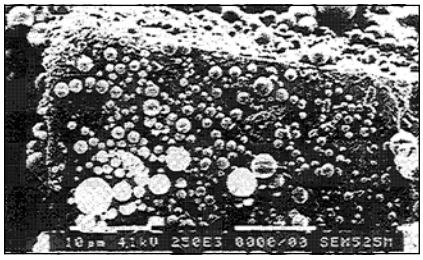
H: 8.8% Skim milk powder
(Langrish et al. 2006 [19])



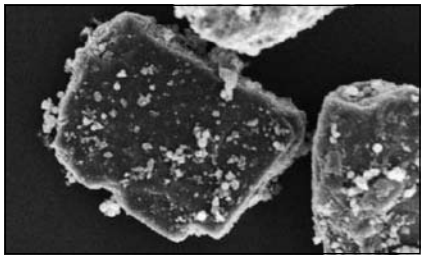
I: Lactose-Bovine Serum Albumin
(Li and Seville 2008 [23])



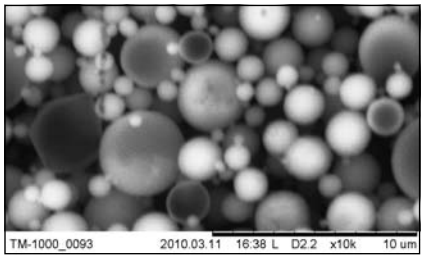
J: Silica-leucine-lactose nanoaggregates
(Kho and Hadinoto 2010 [5])



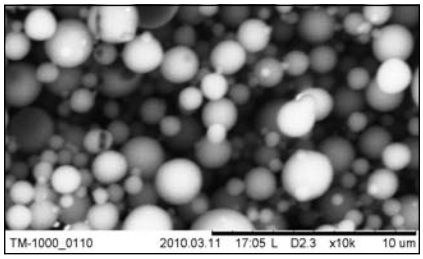
K: Adhesion of spray dried rhDNase particles to lactose
(Chan et al. 1997 [13])



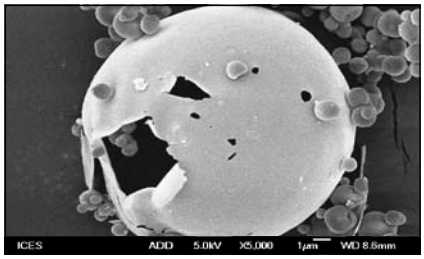
L: Lactose blend with spray dried Fluticasone propionate particles
(Louey et al. 2004 [24])



M: Fluticasone propionate in lactose
(BÜCHI internal study 2010)



N: Salbutamol sulphate in lactose
(BÜCHI internal study 2010)



O: Silica nanoparticles at 0.18% concentration (hollow particles) *(Hadinoto et al. 2006 [8])*

Figure 6: Particle morphologies of lactose based inhalable particles from literature study

Residual moisture contents of about 2% to 11% are typically measured for spray dried powders containing lactose [19, 20].
Co-spray drying of lactose and polyethylene glycol (PEG) was shown to promote crystallization of lactose [14, 17, 21]. Crystallization was favoured by a low molecular weight and a high concentration of PEG [17]. The presence of PEG 6000 changed the surface texture of the carrier particles from a smooth surface to a more aspirated surface [21]. An increase in lactose content in the feed solution resulted in a decrease in amorphous lactose percentage in the spray dried products [14].
Islam and Langrish 2008 [20] studied the effect of NaCl and KCl salts on lactose crystallization and obtained the most crystalline product at a lactose to NaCl ratio of 5 to 2 (w/w). The effect of varying the inlet air temperature on the degree of crystallinity for spray dried lactose powders was studied by Chiou et al. 2008 [22] and Islam et al. 2010 [18]. A higher degree of crystallinity (from about 55% to 76%) was observed in spray dried lactose when an inlet gas temperature of 210 °C was used, compared with an inlet gas temperature of 134 °C [22]. Moreover, an insulated spray chamber was beneficial to reduce heat losses due to radiation [18].
Langrish et al. 2006 [19] investigated spray drying of skimmed and whole milk in the Mini Spray Dryer B-290. Yield values of up to 82.7% (skimmed milk) and 18.6% (whole milk) were found. The lower yields were associated to wall deposition due to the sticky nature of milk types with higher levels of fats and sugars, such as whole milk and lactose free skimmed milk.

Conclusions

Inhalable applications

- Spray drying is able to produce stable, efficient and inhalable dry lactose powder systems for respiratory delivery with adequate particle size and shape for deep lung deposition [3, 4, 6, 7].

Spray drying versus jet milling

- Spray drying and jet milling showed insignificant differences in fine lactose particle size of the same formulations [12].
- Spray dried particles showed higher dispersibility compared to jet milled particles due to spherical shape and smaller surface contact area [9].
- The dissolution and inhalation behaviour of spray dried powder is even more advantageous than that of mechanically micronized powder. Spray dried particles free themselves from the large lactose carrier particles as easily as mechanically micronized particles [7].

Aerosol properties and dispersibility

- The aerosol properties and dispersibilty of spray dried powders can be enhanced by incorporation of suitable excipients, such as NaCl salt [13, 20] or amino acids [5, 10, 11] before spray drying, allowing the development of stable and viable formulations for pulmonary inhalation.

Amorphous/crystalline structure

- The rapid solidification in spray drying causes lactose in suspension to become amorphous [14]. Various polymorphic proportions can be manufactured by selection of the appropriate feed concentrations.
- Spray drying process conditions may be utilized to alter the final spray dried lactose product, where the inlet gas temperature has a significant impact on the crystallinity [18, 22].
- The presence of polyethylene glycol promotes crystallization of lactose when the two components are co-spray dried [14, 17, 21].
- Crystallization is favoured by a low molecular weight and a high concentration of PEG [17].

Nanoparticles

- Incorporation of nanoparticles into respirable carrier particles can be a straightforward process when formulating via spray drying [4]. Spray dried nanoparticle aggregates are capable of serving as micrometer-sized carriers of nanoparticulate drugs. This facilitates the nanoparticle delivery to the lung for potential inhaled drug delivery applications in Dry Power Inhalers [5, 8].
- The Nano Spray Dryer B-90 provides a novel spray drying technique in laboratory scale to prepare submicron particles for pulmonary delivery dry powder formulations.

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