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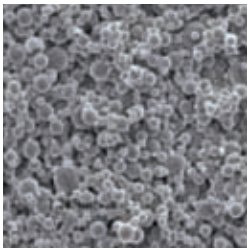

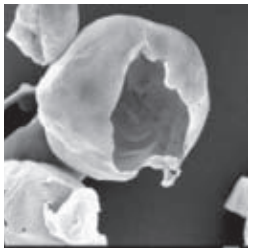

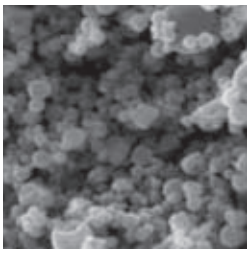

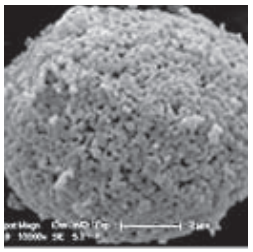

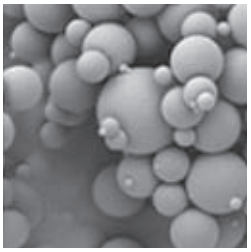

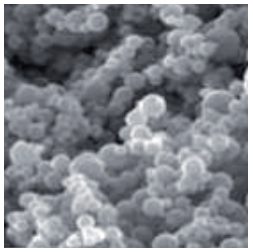

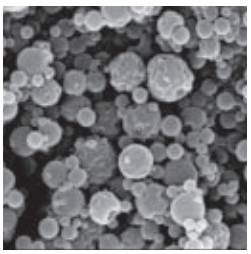

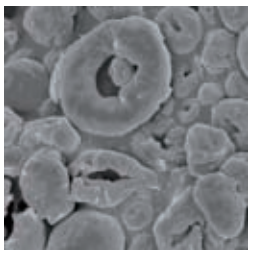

Nano Spray Dryer B-90
literature review and applications

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Nano Spray Dryer B-90: Literature review and applications

Author: Dr. Cordin Arpagaus, Product Group Manager Spray Drying
BÜCHI Labortechnik AG

Introduction

Spray drying is gaining more and more attention as a gentle, single-step, continous and scalable drying process which converts liquids into dry powders. In the field of particle engineering it opens the possibility to dry particles with controlled size and shape.

The recent rise of nanomedicine and nanotherapeutics has increased the pressure on existing spray dryer systems to produce nanoparticles with a good yield and a narrow size distribution [1, 2]. A search in the Web of Science online database with the key words "spray drying" AND "nano" revealed 202 hits in the last 18 years (Fig. 1). Seemingly, the potential of nanoparticle spray drying has not been fully exploited yet. Worldwide research activities can mainly be found in the fields of pharmaceutical, materials and food sciences.

Nanoparticles, with their reduced size and hence larger specific surface area, are a promising way to enhance the dissolution rates of poorly water-soluble drugs [1, 3, 4, 5]. Potential uses are the increasing of absorption rates, the improvement of bioavailability, and the enabling of target drug delivery systems for cancer therapy, diabetes, asthma and so forth [2, 5].

Due to their limited collection efficiency for particles < 2 µm with cyclone separators, conventional spray dryers are not suited to produce nanoparticles [1, 3, 6]. Overall yields are also limited in a laboratory-scale, at best reaching 50% to 70% [4, 5, 7]. Moreover, traditional spray dryers require a minimum of 30 mL of liquid sample in order to start a feasibility test [4]. But in the early stages of product development, most new drug candidates are only available in very small amounts (e.g. milligrams) for the formulation design [2, 4, 8].

The Nano Spray Dryer B-90 was developed in order to overcome these challenges (Fig. 2). It is BUCHI's fourth and newest generation of laboratory-scale spray dryers, following the Mini Spray Dryer B-290, B-191 and B-190 models [8, 9].

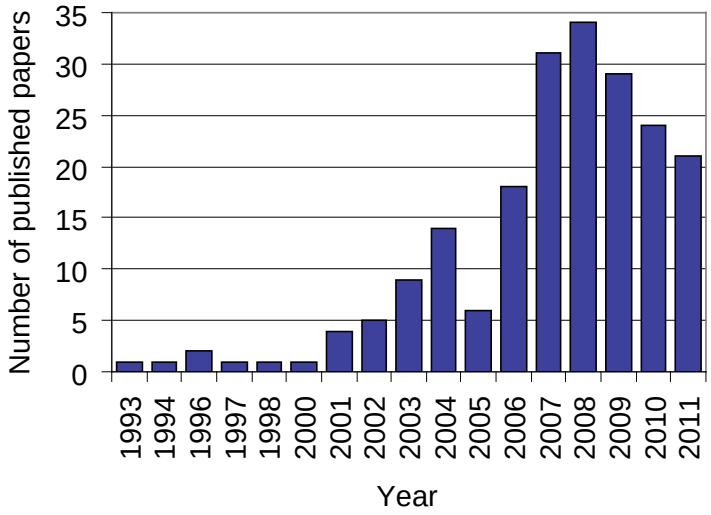


Fig. 1. Number of published papers found in the Web of Science online database (visited August 3, 2011) with the key words "spray drying" AND "nano" (total 202 hits)

This paper summarizes recent published scientific research dealing with the usage of the Nano Spray Dryer B-90. Readers will understand the principle function and fundamentally new concept of the spray drying technology and will also learn about the applicative potentials it promises within the scientific field.

Functional principle of the Nano Spray Dryer B-90

Fig. 2 and 3 illustrate the Nano Spray Dryer B-90 and its functional principle. This novel laboratory spray dryer is based on a fundamentally new concept within the spray drying technology which allows producing and collecting submicron particles from a solution [1, 5]. The technological novelty of this patented spray dryer lies in the gentle laminar drying flow, the vibrating mesh spray technology and the highly-efficient electrostatic particle collector [8, 10].

A brief explanation: the liquid stream is atomized into fine droplets by a piezoelectric driven vibrating mesh atomizer, then subjected to drying in a drying chamber in order to yield solid particles, and finally, separated and collected by a suitable electrostatic dry powder collector.

The vibration mesh spray technology incorporates a small spray cap with a thin membrane which is perforated with an array of tiny micron-sized holes (4.0, 5.5 or 7.0 µm). An actuator moving at ultrasonic frequency causes the membrane to vibrate, thereby creating millions of precisely sized droplets in a size range of 3-15 µm (median diameter 5-7 µm, depending on the mesh size) with narrow droplet size distribution and span values of approx. 1.2 [6]. It is possible to spray liquids with viscosities of up to 10 cPa s [11].

The drying gas passes through a compact porous metal heater that provides optimal energy transfer and short heating-up rates of up to 120°C inlet temperature. The heater enables a laminar gas flow in the drying section and very short droplet drying times in the order of 11.3 ms (calculated with an initial droplet of 7.0 µm, 75°C drying temperature and 100 L/min drying air flow rate) [12]. Due to this, the instrument is suited for spray drying, heat-sensitive biopharmaceutical products [2, 6, 8].

The electrostatic particle collector is capable of capturing nanoparticles at excellent particle recovery rates (e.g. yields) for small batch sizes in a range of 30 to 500 mg [2, 4, 5, 13].
The collection mechanism is based on electrostatic charging of the particles, which is independent of particle mass in contrast to cyclones. The electrostatic precipitator collects even thin walled particles without breaking those [12, 14].

The powder is gently collected from the internal wall of the electrode cylinder with a particle scraper. Due to the modular glass assembly of the spray cylinder the set-up is simple, the cleaning easy, and process time in the daily lab work can be saved.

Drug delivery applications

Up to date, the new Nano Spray Dryer B-90 technology has been successfully used for a variety of drug delivery applications (see Table 1), such as

Trehalose as a stabilizer for biological, active pharmaceutical ingredients and to help increase their shelf life [4, 6, 12, 13]
Mannitol as pharmaceutical excipient [4]
Chitosan as an excipient and bioresorbable biopolymer [15]
Arabic gum, whey protein, polyvinyl alcohol, modified starch and maltodextrin as different polymeric wall materials for encapsulation [5]
Sodium alginate as emulsifier and immobilization agent [16]
Sodium chloride as salt example [5]
Griseofulvin as antifungal drug [4]
Furosemide as diuretic to treat hypertension and edema [5]
Salbutamol encapsulated in lactose to treat asthma [7]
L-leucine amino acid as dispersing agent and food additive [12]
Bovine serum albumin as model protein [2]
ß-galactosidase as model enzyme with trehalose as stabilizer [13]

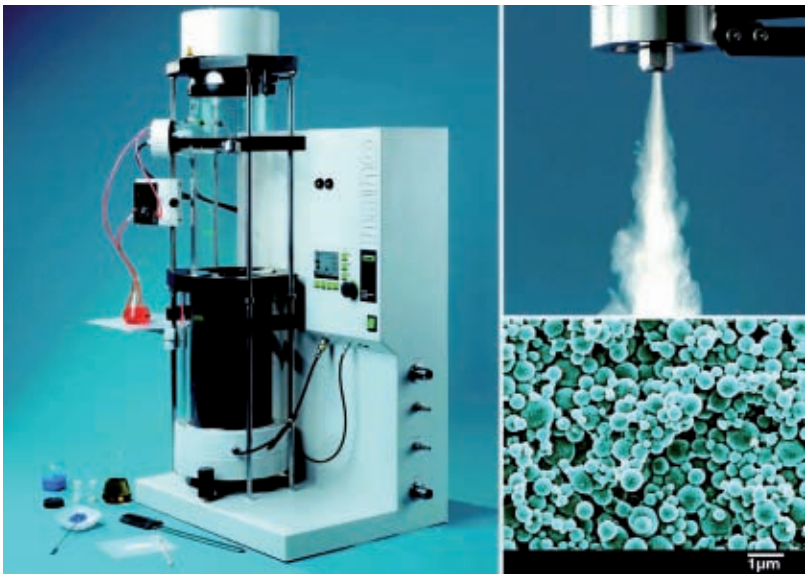


Fig. 2. Nano Spray Dryer B-90 [8, 9]

Nanoemulsion encapsulation of Vitamin E acetate (smaller than 100 nm) in arabic gum, modified starch; maltodextrin; and whey protein [5]

Materials science applications

Applications for the Nano Spray Dryer B-90 are not only limited to biological samples. Indeed, **battery-grade lithium carbonate (Li_2CO_3) crystals** can be prepared from purified lithium bicarbonate ($LiHCO_3$) precursor, as shown by Sun et al. (2011).

The spray drying process was successful applied to perform decomposition, crystallization, drying and crystal shape control in just one process step. SEM images show self-assembled hollow spheres of lithium carbonate in the size

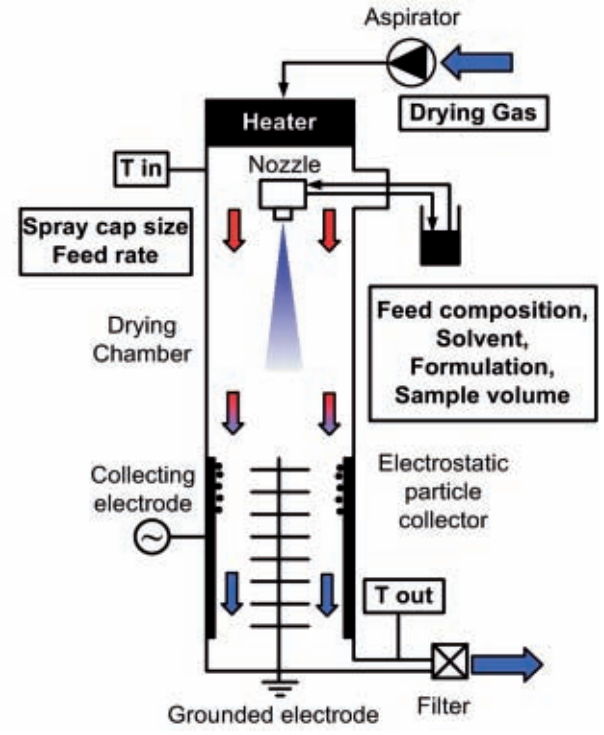


Fig. 3. Principle of the Nano Spray Dryer B-90 [8]

range of 4 to 9 µm scale composed of about 200 nm crystalline primary particles. The surface area of the product according to BET reached 7.24 m^2/g, which is much higher than the best value reported in current literature.

The product has great potential application prospects in the lithium-battery industry [14].

Discussion of the spray drying parameters

A) Droplet size

A good correlation between the applied spray mesh size and the resulting droplet size was found by Schmid et al. (2011). Fig. 4 illustrates these findings. Mean droplet sizes of 4.8, 6.0 and 7.2 µm were obtained (± 0.5 µm, using water) from the 4.0, 5.5 and 7.0 µm spray meshes, respectively. The obtained droplets are smaller than those produced with a conventional Mini Spray Dryer B-290 (0.7 mm two-fluid nozzle), which generates droplets as small as 14 µm mean value [4]. Moreover, the aerosols from the Nano Spray Dryer B-90 showed a narrower size distribution (span values approx. 1.2) than the Mini Spray Dryer B-290 aerosols (span values approx. 1.8).

B) Spray dried particle size

The smallest spray dried particles created with the Nano Spray Dryer B-90 go down to

- 500, 600 and 800 nm from disodium phosphate, trehalose and mannitol solutions (0.1 w% solid concentrations) [4]
- below the 1 µm scale (typically 460-730 nm), attaining sizes as small as 350 nm with a standard deviation of 100 nm for arabic gum (0.1 w%) [5]
- 460 nm (median size) with the 4.0 µm spray cap, 0.1% w/v bovine serum albumin concentration and addition of 0.05% (w/v) of surfactant to the solution [2]

C) Spray cap size

The particle size is mainly influenced by the spray cap size [2, 4, 5, 6]. The correlation between the spray cap size and the solid particle size after drying is displayed in Fig. 4. The submicron particle size area is typically reached when using the 4.0 µm spray cap and highly diluted solutions with about 0.1 w% solid concentrations.

D) Solid concentration in the sample

Decreasing the solid concentration in the sample solution favored a reduction of the particle size. Representative cases were found for arabic gum and whey protein solutions at 0.1, 1 and 10 w% concentrations [5]. At 0.1 w%, outstandingly tiny particle sizes were achieved with peaks at 353 ± 107 and 421 ± 144 nm for arabic gum and whey protein respectively. An increased sample concentration of 1 w% also increased the size and polydispersity to 581 ± 363 nm and 593 ± 374 nm, respectively. Further increase to 10 w% resulted in an enlargement of the peak width while the peak location remained roughly unchanged at 549 ± 545 and 537 ± 618 nm, respectively.

E) Powder recovery and sample amount

Under optimized conditions and compared to traditional laboratory-scale spray dryers, uniquely high yields for tiny sample amounts are achieved with the Nano Spray Dryer B-90:

- 43% to 94.5% yields for 30 mg to 300 mg of powder amounts of different polymeric wall materials [5]
- 60% to 94% for 500 mg of sample amounts for ß-galactosidase with trehalose [13]
- 50% to 78% for 50 mg of powder amounts of trehalose, mannitol or disodium phosphate [4, 6]
- 72 ± 4% at optimized conditions for bovine serum albumin [2]

Depositions around the spray cap [4] and the manual collection of the powder with a spatula may lead to variations in the yield results and are potential loss factors [2, 13].

F) Particle morphology

Scanning electron microscope photographs (Table 2) of the spray dried particles display different types of morphologies, ranging from smooth spherical particles [2, 4, 6, 13], to shriveled/wrinkled [2, 13], mixed/wrinkled, donut-shaped and granules [2].
Research proved that the addition of surfactant increased the smoothness and sphericity of the spray dried particles [2, 4, 6, 13]. The surfactant balances the surface-to-viscous forces in the drying droplet and promotes the formation of a smooth spherical surface of the dry particle.

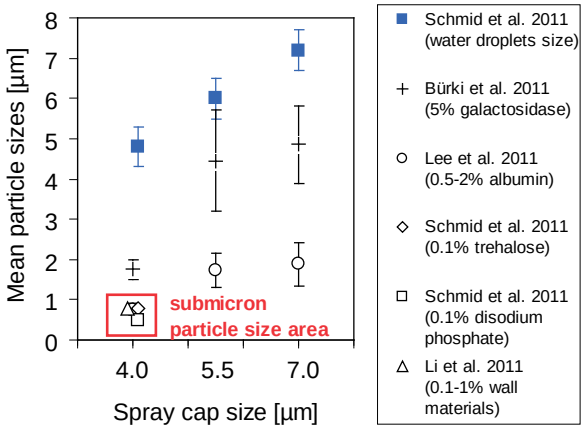


Fig. 4. Correlation between droplet and particle size (data from literature). The submicron particle size area is typically reached when using the 4.0 µm spray cap and diluted solid concentrations of about 0.1 w%.

Feng et al. (2011) spray dried leucine trehalose particles and recognized a correlation between crystallinity and change in morphology, reduction in powder density, and improvement in dispersibility. As an example, leucine crystallinity was necessary to obtain low-density, well dispersing particles.

A distinct transition in leucine crystallinity with increasing leucine mass fraction in the formulation was observed. A minimum leucine mass fraction of about 30% was necessary to disperse with a particle size in the commonly accepted range for respirable particles (1-5 µm). The trehalose component remained amorphous across all formulations.

G) Drying temperature

The driving force for spray drying is controlled by the liquid content and the temperature difference in the inlet and outlet drying gas. A potential concern of spray drying is the chemical degradation of the drug caused by the heat involved. Although the drying gas temperature can be relatively high (e.g. up to 120 °C), the actual temperature of the evaporating droplets is significantly lower due to the cooling effect caused by the latent heat of vaporization. Thus, in reality thermal degradation of the active ingredients is not so much a problem as it may first appear [3].

The range of possible outlet temperatures for the Nano Spray Dryer B-90 lies between 28 °C and 59 °C for aqueous solutions (Fig. 5). These low outlet temperatures are highly favorable for spray drying heat-sensitive biologicals [1]. The drying gas flow rate and the inlet temperature have only a minimal impact on the particle size, as shown by Lee et al. (2011) using a statistical experimental design.

H) Feed rate

The feed rate varies from 10 mL/h [11] to 16 mL/h [14] and 3 to 25 mL/h [5] when using a 4.0 µm spray cap, and approx. 50 mL/h when using a 5.5 µm spray cap [15]. The feed rate depends mainly on the spray cap membrane's hole-size, on the formulation of the substance, on the inlet temperature and on the setting of the relative spray rate.

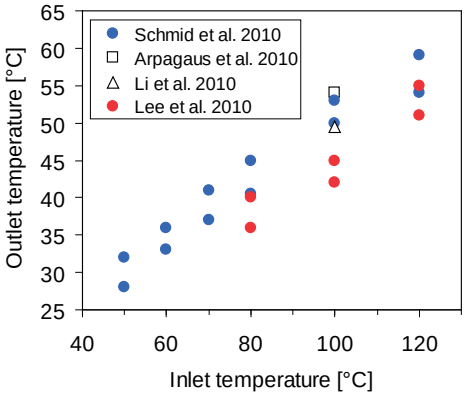


Fig. 5. Correlation between inlet and outlet drying gas temperature in the Nano Spray Dryer B-90 while spray drying aqueous substances (data summarized from literature).

As this spray dryer initially has been designed for the early stages of product development, the technology is not yet expected to be widely adopted for large scale industrial applications [9]. It is currently limited by a low throughput and as a consequence, by processing times which take a few hours. A possible scale-up solution could be the usage of multiple nozzles or of a larger nozzle unit [1].

Enzyme activity

In an experimental factorial design Bürki et al. (2011) studied the effects of inlet temperature, spray mesh size and ethanol concentration in the spray solution on the activity, size, span, yield and shelf life of the model enzyme ß-galactosidase with trehalose as stabilizer.

Full activity was retained at optimized process parameters. Enzyme activity loss was minimized when using larger spray mesh sizes (e.g. 7.0 µm) and pure aqueous solutions (no ethanol). Full activity and high yields (about 90%) were achieved with a low inlet temperature of 80 °C. Furthermore, the protein exhibited higher storage stability when a larger spray cap size was used during the spray drying process.

Conclusions

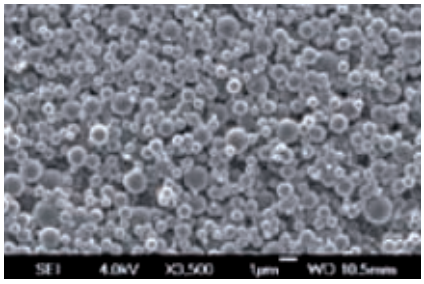
The Nano Spray Dryer B-90 is a spray dryer with the ability to effectively formulate temperature-sensitive compounds (e.g. proteins [2], enzymes [13], and amino acids [12]) in the submicron scale. Therefore it is an "indispensable partner" for formulation scientists in the new decade and beyond, as stated in an expert opinion by Heng et al. (2011).

Tiny spray dried particles down to 350 nm [5], 460 nm [2] and 500 nm [4] of size can be created. The unique electrostatic particle collector enables the gentle collection of very small powder amounts down to 30 mg, which can not be achieved with traditional cyclone separators [6]. Uniquely high yields can be obtained; 72% [2], 78% [4, 6], 94% [13] up to 94.5% [5].

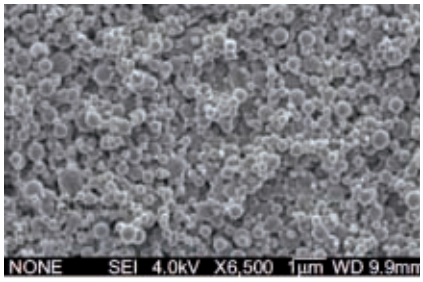
This allows for the economical use of expensive pharmaceutical ingredients [12] and makes it possible to spray dry minimal sample quantities from 5 to 20 ml [4]. This makes the Nano Spray Drier B-90 highly desirable for drug delivery applications for research and early development studies in the oral, transdermal and inhalation fields.
Potential applications lie in the inhalation drug delivery [2, 13], the nanotherapeutics [2], the encapsulation of nanoemulsions and formulation of nanocrystals [5], the novel nanoparticulate pharmaceuti-

Application	Carrier, concentration, solvent	Spray drying process parameters	Particle size, morphology, yield, powder amount	Reference and affiliation
Salbutamol sulphate (for asthma relief)	10% aqueous solution salbutamol sulphate to lactose ratio 1:10 (w/w)	spray cap 4.0 µm T in 120 °C, T out 52-56 °C spray rate 100% drying air flow 130 L/min feed rate 10 mL/h	0.5-3.0 µm sprayed amount 20 g solution powder recovery 1.4 g yield 70%	Arpagaus et al. (2010) [11] BÜCHI Labortechnik AG, Flawil, Switzerland
ß-galactosidase (model enzyme) with trehalose	5% aqueous concentration with 1:2 (w/w) enzyme to trehalose ratio	spray cap 4.0 µm T in 80 °C, T out 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% to 100% (after 3 weeks) yields 60% to 94% sample amounts 500 mg	Bürki et al. (2011) [13] University of Basel, Switzerland; BÜCHI Labortechnik AG, Flawil, Switzerland
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%	spray cap 4.0 µm T in 75 °C, T out 45 °C drying air flow 100 L/min droplet drying time 11.3 ms	2.1-5.4 µm aerodynamic diameter solid and spherical and hollow pure trehalose amorphous with >25% leucine content crystalline low-density, well dispersing sample amounts <80 mg	Feng et al. (2011) [12] University of Alberta, Edmonton, Canada; Lovelace Respiratory Research Institute, Albuquerque, USA
Bovine serum albumin (model protein)	0.1% aqueous solution with 0.05% surfactant polyoxyethylene sorbitan monoleate (Tween 80)	spray cap 4.0 µm 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 drying air flow 150 L/min	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%	Lee et al. (2011) [2] A*STAR, Singapore; National University of Singapore; University of Sidney, Australia
Polymeric wall materials **Furosemide** (diuretic drug) **Vitamin E acetate** nano-emulsion	0.1, 1 and 10 w% polymeric wall materials (arabic gum, whey protein, polyvinyl alcohol, modified starch, maltodextrin) 1.25 w% furosemide in acetone Vitamin E acetate nano-emulsion in wall materials at 1:4 weight ratio	spray cap 4.0 µm T in 100 °C, T out 38-60 °C drying air flow 100 L/min feed rate 3-25 mL/h closed loop for organic solvents (N_2 drying gas, O_2 < 4%)	460-730 nm distributions mainly < 1 µm yields 43-94.5% for 30-300 mg powder amounts encapsulated oil-in-water nanoemulsions with oil droplets below 100 nm	Li et al. (2010) [5] University of Strasbourg, Illkirch Cedex, France; BÜCHI Labortechnik AG, Flawil, Switzerland
Trehalose (protein stabilizer)	α,α-trehalose-dihydrate as 1% and 0.1% aqueous solutions, either with or without 0.05% polysorbate 20	spray cap 7 µm or 3 µm T in 60, 80 and 100 °C T out 30-45 °C sample volumes 5-20 mL drying air flow 115 L/min	600 nm and span 1.6 at 0.1% 1.2 µm and span 0.8 at 1% smallest powder amounts down to 10 mg	Schmid et al. (2009) [6] Ludwig-Maximilian-University Munich, Germany; BÜCHI Labortechnik AG, Flawil, Switzerland
Griseofulvin (antifungal drug) **Mannitol** and polysorbate 20	0.44% griseofulvin in methanol/acetone 1% salicylic acid in ethyl acetate 5% salicylic acid in acetone 1% benzocaine in ethanol 0.1% disodium phosphate 1% mannitol or trehalose with 0.05% polysorbate 20	spray cap 4.0 µm T in 50-120 °C, T out 28-59 °C sample amounts 10 mL drying air flow 120 L/min in open mode for aqueous solutions closed loop for organic solvents (N_2 drying gas, O_2 < 4%)	500 nm disodium phosphate 800 nm trehalose down to 4.8 µm mean droplet sizes (span approx. 1.2) disodium phosphate yield 75% mannitol yield 65-78% trehalose yield 50-75% sample amounts 50 mg	Schmid et al. (2011) [4] Ludwig-Maximilian-University Munich, Germany; BÜCHI Labortechnik AG, Flawil, Switzerland
Sodium alginate (emulsifier and immobilization agent)	0.13% (w/v) low-viscosity sodium alginate (< 5 cPa s)	spray cap 4.0 µm and 7.0 µm T in 110 °C drying air flow 100 L/min pressure 50 mbar spray rate 100%	761 ± 433 nm (4.0 µm mesh) 5.5 ± 2.1 µm (7.0 µm mesh) spherical with smooth surface yield higher than 90%	Blasi et al. (2010) [16] Università degli Studi di Perugia, Italy
Chitosan (bioresorbable polymer)	0.1% (w/v) chitosan of non-animal origin (KiOmedine-CsU, molecular weight 30'000) in 1% (v/v) acetic acid	spray cap 5.5 µm T in 120 °C, T out 55 °C drying air flow 130 L/min feed rate approx. 50 mL/h	1.1 ± 0.5 µm high yields up to 90% for 100 mg quantities	Gautier et al. (2010) [15] KitoZyme S.A., Herstal, Belgium; BÜCHI Labortechnik AG, Flawil, Switzerland
Lithium carbonate (material for rechargeable lithium batteries)	Lithium carbonate ($LiHCO_3$) solution with 130 mol/L concentration in deionized water	spray cap 4.0 µm T in 90 °C drying air flow 8 m3/h feed rate 16 mL/h	4-9 µm porous hollow spheres consisting of pure Li_2CO_3 crystalline 200 nm primary particles BET surface area 7.24 m^2/g	Sun et al. (2011) [14] East China University of Science and Technology, Shanghai, China

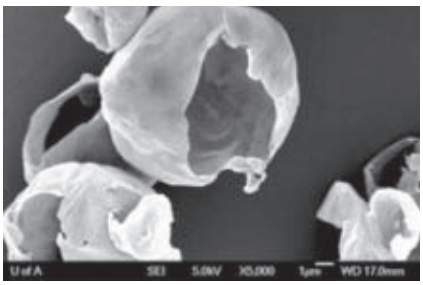
Table 1: Applications list of spray dried products using the laboratory scale Nano Spray Dryer B-90 from BÜCHI Labortechnik AG (derived from literature).



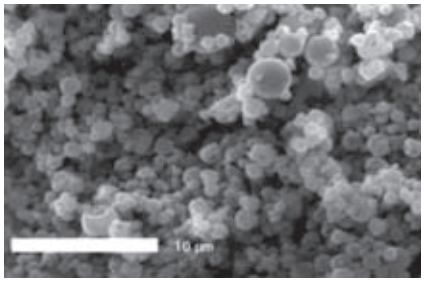
Trehalose
Schmid et al. (2009) [6]



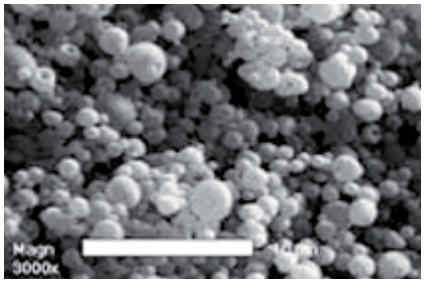
Disodium phosphate
Schmid et al. (2011) [4]



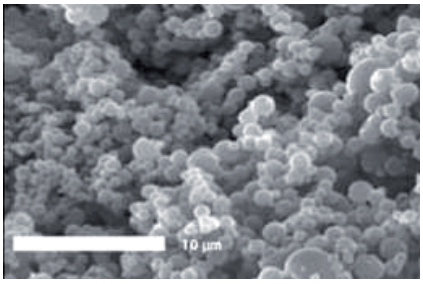
Leucine
Feng et al. (2011) [12]



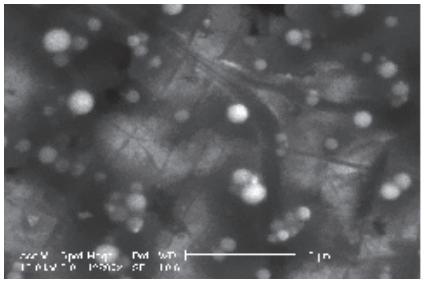
Modified starch
Li et al. (2010) [5]



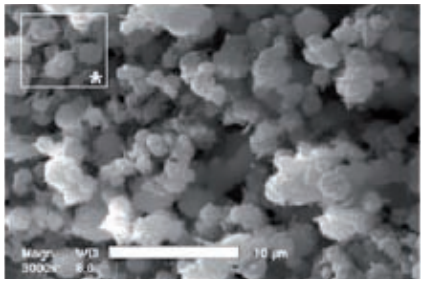
Vitamin E oil-in-water nanoemulsion in whey protein
Li et al. (2010) [5]



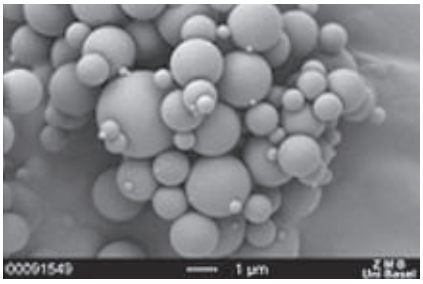
Arabic gum
Li et al. (2010) [5]



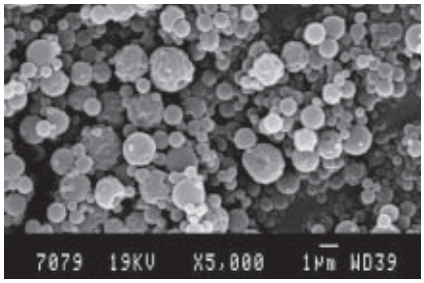
Sodium alginate
Blasi et al. (2010) [16]



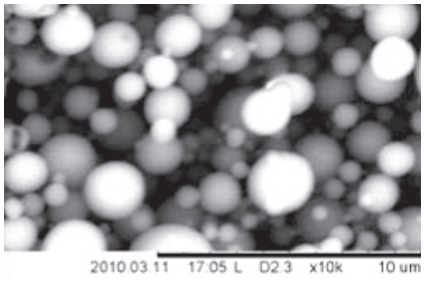
Furosemide
Li et al. (2010) [5]



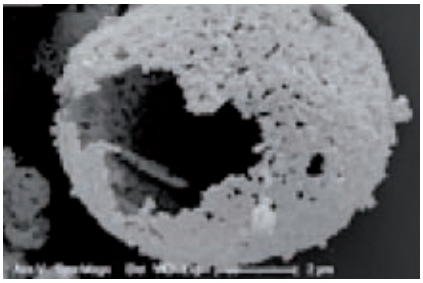
ß-galactosidase/trehalose
Bürki et al. (2011) [13]



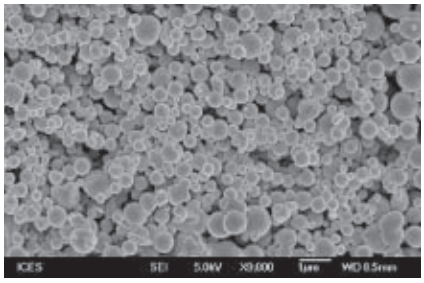
Chitosan
Gautier et al. (2010) [15]



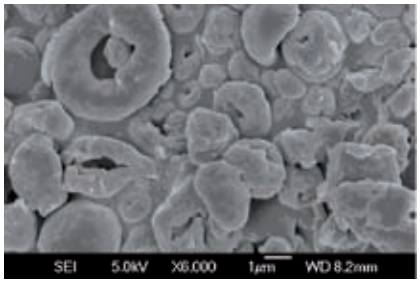
Salbutamol sulphate in lactose
Arpagaus et al. (2010) [11]



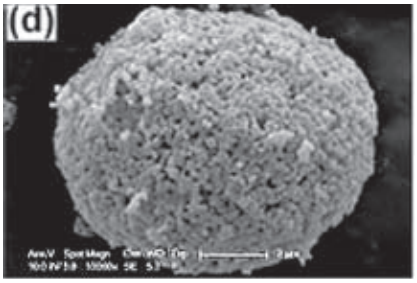
Lithium carbonate hollow sphere
Sun et al. (2011) [14]



Bovine serum albumin (4.0 µm spray cap, 0.1 w%)
Lee et al. (2011) [2]



Bovine serum albumin (without surfactant)
Lee et al. (2011) [2]



Lithium carbonate
Sun et al. (2011) [14]

Table 2: Scanning electron microscope pictures of spray dried particles derived on the Nano Spray Dryer B-90.

cal excipients [4, 6] and the polymeric nanoparticles [5]. Increased customer demand for the laboratory model coupled with promising new applications are expected to eventually encourage and stimulate the development of more industrial-relevant models [1].
The introduction of the Nano Spray Dryer B-90 has made spray drying of protein nanotherapeutics reality [2].

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BÜCHI Labortechnik AG
CH – 9230 Flawil 1
T +41 71 394 63 63
F +41 71 394 65 65
buchi@buchi.com
www.buchi.com

BÜCHI Labortechnik GmbH
DE – 45127 Essen
Freecall 0800 414 0 414
T +49 201 747 490
F +49 201 237 082
deutschland@buchi.com
www.buechigmbh.de

BUCHI Sarl
FR – 94656 Rungis Cedex
T +33 1 56 70 62 50
F +33 1 46 86 00 31
france@buchi.com
www.buchi.fr

BUCHI UK Ltd.
GB – Oldham OL9 9QL
T +44 161 633 1000
F +44 161 633 1007
uk@buchi.com
www.buchi.co.uk

BÜCHI Labortechnik GmbH
NL – 3342 GT
Hendrik-Ido-Ambacht
T +31 78 684 94 29
F +31 78 684 94 30
netherlands@buchi.com
www.buchi.nl

BUCHI Italia s.r.l.
IT – 20090 Assago (MI)
T +39 02 824 50 11
F +39 02 57 51 28 55
italia@buchi.com
www.buchi.it

BUCHI Hong Kong Ltd.
HK – Central
T +852 2389 2772
F +852 2389 2774
china@buchi.com
www.buchi.com.cn

BUCHI Shanghai
CN – 200052 Shanghai
T +86 21 6280 3366
F +86 21 5230 8821
china@buchi.com
www.buchi.com.cn

BUCHI (Thailand) Ltd.
TH – Bangkok 10600
T +66 2 862 08 51
F +66 2 862 08 54
bacc@buchi.com
www.buchi.com

Nihon BUCHI K.K.
JP – Tokyo 110-0008
T +81 3 3821 4777
F +81 3 3821 4555
nihon@buchi.com
www.nihon-buchi.jp

BUCHI India Private Ltd.
IN – Mumbai 400 055
T +91 22 667 18983 / 84 / 85
F +91 22 667 18986
india@buchi.com
www.buchi.in

PT. BUCHI Indonesia
ID – Tangerang 15321
T +62 21 537 62 16
F +62 21 537 62 17
indonesia@buchi.com
www.buchi.com

BUCHI Korea Inc
KR – Seoul 153-782
T +82 2 6718 7500
F +82 2 6718 7599
KR-Sales@buchi.com
www.buchi.com

BUCHI Canada Ltd.
CA – Thornhill, Ontario L4J 6Z2
T +1 416 277 7407
F +1 905 764 5139
canada@buchi.com
www.mybuchi.com

BUCHI Corporation
US – New Castle,
Delaware 19720
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