International Journal of Pharmaceutics 403 (2011) 192–200

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Nano spray drying: A novel method for preparing protein nanoparticles for protein therapy

Sie Huey Lee [a], Desmond Heng [a,*], Wai Kiong Ng [a], Hak-Kim Chan [b], Reginald B.H. Tan [a,c,**]

[a] Institute of Chemical and Engineering Sciences, A*STAR (Agency for Science, Technology and Research), 1, Pesek Road, Jurong Island, Singapore 627833, Singapore
[b] Advanced Drug Delivery Group, Faculty of Pharmacy, A15, The University of Sydney, Sydney, NSW 2006, Australia
[c] Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117576, Singapore

ARTICLE INFO

Article history:
Received 30 July 2010
Received in revised form 3 October 2010
Accepted 7 October 2010
Available online 15 October 2010

Keywords:
Nano spray dryer
Protein therapy
Nanoparticles
Bovine serum albumin
Spray drying

ABSTRACT

There has been an increasing interest in the development of protein nanotherapeutics for diseases such as cancer, diabetes and asthma. Spray drying with prior micro mixing is commonly used to obtain these powders. However, the separation and collection of protein nanoparticles with conventional spray dryer setups has been known to be extremely challenging due to its typical low collection efficiency for fine particles less than 2 μm. To date, there has been no feasible approach to produce these protein nanoparticles in a single step and with high yield (>70%). In this study, we explored the feasibility of the novel Nano Spray Dryer B-90 (equipped with a vibrating mesh spray technology and an electrostatic particle collector) for the production of bovine serum albumin (BSA) nanoparticles. A statistical experimental design method (Taguchi method based on three levels, five variables L_{18} orthogonal array robust design) was implemented to study the effect of and optimize the experimental conditions of: (1) spray mesh size, (2) BSA solution concentration, (3) surfactant concentration, (4) drying air flow rate and (5) inlet temperature on: (1) size and (2) morphology (axial ratio). Particle size and morphology were predominantly influenced by the spray mesh size and surfactant concentration, respectively. The drying air flow rate and inlet temperature had minimal impact. Optimized production of smooth spherical nanoparticles (median size: 460 ± 10 nm, axial ratio: 1.03 ± 0.00, span 1.03 ± 0.03, yield: 72 ± 4%) was achieved using the 4 μm spray mesh at BSA concentration of 0.1% (w/v), surfactant concentration of 0.05% (w/v), drying flow rate of 150 L/min and inlet temperature of 120 °C. The Nano Spray Dryer B-90 thus offers a new, simple and alternative approach for the production of protein nanoparticles suited for a variety of drug delivery applications.

1. Introduction

Although protein therapy has been around for a number of years, it is still an important and evolving area of research in view of the current clinical delivery limitations and the increasing emphasis placed on vaccines, hormones, growth factors, monoclonal antibodies and enzymes to treat the wide array of diseases afflicting the human population (Larry, 2005).

Therapeutic proteins are hardly administered orally due to their low oral bioavailability as a result of enzymatic degradation, poor membrane permeability and short physiological half-lives in the gastric and intestinal fluids (Lee et al., 2007; Shaji and Patole, 2008). These drugs are rapidly cleared before successful tissue penetration. Therefore, the parenteral route is still the standard delivery option for current and emerging biopharmaceuticals.

However, the quest to improve patient compliance has fuelled development into alternative non-invasive delivery options such as controlled peroral delivery, pulmonary delivery, nasal delivery and transdermal delivery (Cleland et al., 2001). As some of these alternative delivery methods involve formulation in the dry powdered form, formulation strategies (e.g. size, morphology) thus have to be re-developed and optimized for the specific delivery system.

Spray drying is a well-established method commonly used in the pharmaceutical industry for producing a dry powder from a liquid phase (Broadhead et al., 1992). In recent years, it has been identified as a suitable method for the preparation of proteins intended for pulmonary (Chan et al., 1997; Salama et al., 2009), nasal (Kaye et al., 2009) and controlled oral delivery (Coppi et al., 2002). It offers the advantage of drying and particle formation in a single-step continuous and scalable process with particle engineering possibilities

* Corresponding author. Tel.: +65 67963861; fax: +65 63166183.
** Corresponding author at: Institute of Chemical and Engineering Sciences, A*STAR (Agency for Science, Technology and Research), 1, Pesek Road, Jurong Island, Singapore 627833, Singapore. Tel.: +65 67963855; fax: +65 63166183.
E-mail addresses: desmond_heng@ices.a-star.edu.sg (D. Heng), reginald_tan@ices.a-star.edu.sg (R.B.H. Tan).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.10.012

(Masters, 1976). Furthermore, various particle properties such as particle size, bulk density and flow properties can easily be tuned via simple manipulation of the process parameters or spray dryer configuration. Therefore, spray drying is potentially a versatile and commercially viable technique for formulating protein and peptide drugs.

The typical spray drying process encompasses four fundamental steps: (a) atomization of feed into a spray, (b) spray–air contact, (c) drying of spray, and (d) separation of dried product from the drying air (Masters, 1976). A liquid feedstock is atomized into a spray of fine droplets and then brought into contact with the hot drying gas at sufficient temperature for the moisture evaporation to take place. As the moisture evaporates from the droplets, the solid product is formed, and the powder is readily recovered from the drying gas. The field of spray drying is constantly evolving. Since the first development of spray drying technology in the early 1870s (Cal and Sollohub, 2010), there have been numerous efforts undertaken to refine the equipment and technology to ensure relevance and attractiveness to the food and pharmaceutical industry.

As nanotechnology is increasingly finding niche applications in drug delivery, many pharmaceutical companies are hence enthusiastically embracing nanoparticles into their formulations. The definition of a nanoparticle depends on the discipline and in the pharmaceutical industry, it is commonly described as having a size between a few nanometers to 1 μm (Heng et al., 2008; Muller and Junghanns, 2006).

In drug delivery, nanoparticles are favored over microparticles due to their small size and higher specific surface area which favorably results in much improved dissolution rates and bioavailabilities (Heng et al., 2008; Noyes and Whitney, 1897). Its other benefits include dose minimization/toxicity reduction, and improved drug penetration (Koster et al., 1996; Souto and Muller, 2008).

During the early stage development of a drug candidate, where the samples are available only in small amounts and are usually expensive, it would be highly beneficial if a formulation could be prepared and studied on a much smaller scale. Therefore, a spray dryer capable of generating nanoparticles directly from solution in a single step and on a much reduced scale would be highly novel and valuable at the research and development stage. The applications of peptide nanostructures have previously been demonstrated in tissue engineering (Ellis-Behnke et al., 2006) and in the development of antibacterial agents (Ghadiri et al., 1994). Furthermore, insulin nanoparticles had also been identified to be a suitable formulation approach for poorly water soluble Zn-insulin (Merisko-Liversidge et al., 2004).

More recently, Buchi® has introduced a new generation (i.e. 4th generation) of laboratory scale spray dryer that is able to generate particles in the size range of 300 nm to 5 μm for milligram sample quantities at high yields (BÜCHI Labortechnik AG, 2009; Schmid et al., 2010). As the desired particle size of most drug delivery applications in the oral, intravenous, transdermal and pulmonary fields fall within this size range, the appeal of this spray dryer to the drug delivery community would indeed be significant (Chiou et al., 2008; Heng et al., 2009; Koster et al., 1996; Souto and Muller, 2008).

The novel technologies at the spray head, heating system and particle collector of the Nano Spray Dryer B-90 have made 'nano' spray drying a possibility. Unlike conventional spray dryers that use rotary atomizers (atomization by centrifugal energy) and pressure nozzles (atomization by pressure energy) or two-fluid nozzle (atomization by kinetic energy) for forming the spray droplets, the new Nano Spray Dryer B-90 utilizes a vibrating mesh technology for fine droplets generation. Basically, the piezoelectric crystal driven spray head is incorporated with a small spray cap that contains a thin perforated membrane (spray mesh) having an array of precise micron-sized holes (i.e. spray meshes of 4 μm, 5.5 μm or 7 μm hole size). When the piezoelectric actuator is driven at an ultrasonic frequency (i.e. 60 kHz), the mesh will vibrate upwards and downwards, injecting millions of precisely sized droplets from the holes and generating the aerosols. Fig. 1 illustrates the functional principle of mesh vibration occurring at the piezoelectric driven spray head of the Nano Spray Dryer B-90.

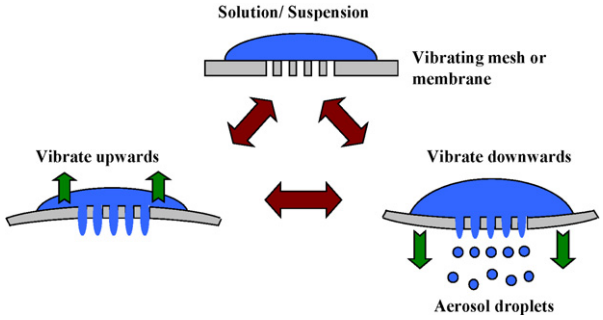

Fig. 1. The functional principle of mesh vibration occurring at the piezoelectric driven spray head of the Nano Spray Dryer B-90, adapted by permission from BÜCHI Labortechnik AG (2009), Flawil, Switzerland.

Although turbulent flow in a spray dryer promotes more efficient drying as a result of higher heat transfer efficiency, exposure of the particles to elevated temperatures can sometimes result in a loss of activity for heat-sensitive materials. Favorably, the heating system of the Nano Spray Dryer B-90 operates on a laminar flow principle, whereby the laminar flow is generated by air passing through a compact porous metal foam that is conducive for optimal energy input and has short heating-up rates. With laminar flow, gentle heating is achievable, thus making the system extremely ideal for heat-sensitive biopharmaceutical products. Furthermore, the vertical configuration of the spray dryer facilitates direct and straight-down collection of the particles into the collector, which helps to minimize particle adherence to the side walls of the glass chamber, and hence allowing for much higher collection yields.

In contrast to the common cyclone technology where particles smaller than 2 μm are typically not captured (Mosen et al., 2004), particle separation in the Nano Spray Dryer B-90 involves the use of the electrostatic precipitator whereby the collection mechanism is independent of particle mass. Collection of fine particles with high efficiency is achieved with the novel electrostatic particle collector consisting of a grounded star electrode (cathode) and cylindrical particle collecting electrode (anode). The presence of a high voltage around the particle collector creates an electrostatic field that accelerates the deposition of negatively charged particle onto the inner wall of particle collecting electrode. This is followed by a discharging process. Fig. 2 illustrates the functional principle of an electrostatic particle collector in the Nano Spray Dryer B-90.

As the fields of biotechnology and nanotechnology increasingly overlap and mature, more emphasis will be placed on protein nanotherapeutics and their associated development. Suitable production methods have to be established to meet the demands of this novel hybrid field. In this work, the novel Nano Spray Dryer B-90 was used to investigate the effects of various spray drying process (spray mesh size, nitrogen flow rate and inlet temperature) and formulation parameters (solute solution concentration and surfactant concentration) on the particle characteristics (i.e. particle size and particle morphology) of a protein. Bovine serum albumin (BSA) was used as the model protein. To the best of the authors' knowledge, the use of this novel spray dryer for the production of protein nanoparticles have not been thoroughly examined. Therefore, the aims of this work are to study and optimize the production of protein nanotherapeutics via the novel Nano Spray Dryer B-90.