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Research paper

Quality by design – Spray drying of insulin intended for inhalation

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ABSTRACT

Quality by design (QBD) refers to a holistic approach towards drug development. Important parts of QBD include definition of final product performance and understanding of formulation and process parameters. Inhalation of proteins for systemic distribution requires specific product characteristics and a manufacturing process which produces the desired product. The objective of this study was to understand the spray drying process of insulin intended for pulmonary administration. In particular, the effects of process and formulation parameters on particle characteristics and insulin integrity were investigated. Design of experiments (DOE) and multivariate data analysis were used to identify important process parameters and correlations between particle characteristics. The independent parameters included the process parameters nozzle, feed, and drying air flow rate and drying air temperature along with the insulin concentration as a formulation parameter. The dependent variables included droplet size, geometric particle size, aerodynamic particle size, yield, density, tap density, moisture content, outlet temperature, morphology, and physical and chemical integrity. Principal component analysis was performed to find correlations between dependent and independent variables. Prediction equations were obtained for all dependent variables including both interaction and quadratic terms. Overall, the insulin concentration was found to be the most important parameter, followed by inlet drying air temperature and the nozzle gas flow rate. The insulin concentration mainly affected the particle size, yield and tap density, while the inlet drying air temperature mainly affected the moisture content. No change was observed in physical and chemical integrity of the insulin molecule.

1. Introduction

Quality by design (QBD) encompasses designing and developing formulations and manufacturing processes which ensure predefined product specifications. An important part of QBD is to understand how process and formulation parameters affect product characteristics, and subsequent optimisation of these parameters with respect to the final specifications [1]. Therefore, critical parameters should be identified in order to monitor these parameters online in the production process. Thus, QBD is a holistic concept where final product specifications, manufacturing process and critical parameters are included in order to ease the final approval and the ongoing quality control of a new drug [2].

Pulmonary delivery has been stated as an attractive alternative to the subcutaneous and intravenous administration routes for proteins, which are presently the most frequent used administration routes for proteins. The large surface area and a thin lung epithelium in the deep lungs make the absorption of proteins easier compared with other noninvasive routes [3]. The deposition of particles in the deep lungs is controlled by a number of parameters including geometry of the airways, breathing behaviour of the individual and clearance mechanisms of the lungs. As a result, the inhaled particles must be designed to reach the deep lungs by overcoming the different natural defence mechanisms. The most important parameter for the deposition of particles in the deep lungs is the aerodynamic particle size, which should be in the range of 1–4 μm for optimal delivery [3]. Particles with the optimal aerodynamic particle size can be manufactured in several different ways, including milling and spray drying [4]. Spray drying has attracted great attention in the recent years and currently the only approved systemic protein drug administered through the lungs is manufactured by spray drying [5,6]. However, this product was recently removed from the market due to disappointing sales.

The advantages of spray drying are many and include the possibility to control particle size and particle size distribution, as well as other particle characteristics. In addition, the heat stress to which the proteins are exposed during the drying process is often negligible due to the short residence time in the drying chamber [4,7]. Furthermore, spray drying is a one step continuous drying process, which utilises less energy than freeze drying and thus makes it an attractive manufacturing process in the industry [8].

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Spray drying of insulin is popular in the industry, but little has been published regarding process knowledge and design. Exubera is produced by spray drying an insulin solution combining several excipients [6], while Stahl et al. examined the effect of different process parameters when spray drying an insulin solution without excipients [9]. However, the insulin concentration has so far not been incorporated in the experimental design, and the effect of insulin concentration has therefore not been addressed.

Design of experiments (DOE) is a well-established method for identifying important parameters in a process and optimising the parameters with respect to certain specifications [10]. Several studies have utilised DOE on the spray drying process [9,11,12], where the effect of process parameters on various particle characteristics have been studied. However, these studies have all focused on single prediction equations obtained from the statistical analysis and have not utilised multivariate data analysis.

The present study focuses on a deeper understanding of the spray drying process of insulin. The effect of the formulation parameter insulin concentration is investigated, in addition to the process parameters nozzle, feed and drying air flow rate and drying air temperature. The dependent variables include well-described variables such as geometric particle size, density, morphology, outlet temperature, moisture content, and physical and chemical degradation. However, less well-described variables such as aerodynamic particle size and droplet size are addressed as well. DOE and multivariate data analysis are utilised to generate maximum information and lead to a better understanding of the spray drying process of insulin.

2. Materials and methods

2.1. Materials

2Zn human insulin was kindly supplied by Novo Nordisk A/S. Deionized water was filtered using a Millipore system (Millipore, Billerica, MA, USA). Insulin solutions were prepared by lowering the pH to 2.5 with 0.2 M icecold HCl, which is below the isoelectric point of the insulin monomer (5.3) and hexamer (6.4) [13]. After dissolution of the insulin, the pH was adjusted to 8.0 with 0.2 M icecold NaOH and the concentration was adjusted to 60 mg/mL. For 30 and 5 mg/mL the stock solution was diluted with water.

2.2. Spray drying

Spray drying was performed with a Büchi B-290 spray dryer (Büchi Labortechnik AG, Postfach, Switzerland). The spray drying process was performed according to standard procedures and the design was similar to the process illustrated by Mosen et al. [14]. The humidity of the inlet drying air was controlled and kept below 20%. The nozzle, a two fluid design with nitrogen as atomising gas used in a co-current mode, was standard equipment provided with the Büchi B-290 spray dryer. The orifice diameter was 0.7 mm. Spray dried particles were separated from the drying air by a high-performance cyclone provided by Büchi. The process parameters investigated were nozzle gas flow rate (7.3–17.5 L/min), feed flow rate (1.8–5.25 mL/min), drying air temperature (75–220 °C) and aspirator capacity (80–100%) (see Table 1 for details). The temperature of the outlet drying gas (T_{out}) was measured between the drying chamber and the cyclone. The spray dried powders were stored in vials at 5 °C and at a relative humidity of 20%.

Table 1
Process and formulation parameters included in the CCF design

Parameter		Low level	Centre level	High level
Nozzle gas flow rate (L/min)	N	7.3	11.1	17.5
Feed flow rate (mL/min)	F	1.8	3.6	5.25
Inlet air temperature (°C)	T_{in}	75	150	220
Aspirator capacity (%)	A	80	90	100
Insulin concentration (mg/mL)	I	5	30	60

2.3. Droplet size

The droplet size and droplet size distribution were analysed by laser diffraction using a Malvern Spraytec (Malvern Instruments Ltd., Malvern, UK). The nozzle was placed in horizontal position and the laser was focused in the centre of the spray. Gravitational settling of the droplets was neglected due to the high velocity of the spray compared to the short distance between nozzle tip and laser beam. The distance between nozzle and Fourier lens was 50 mm and the distance between nozzle tip and the laser beam was 30 mm. The setup was calibrated with water before each experiment. The running time for each experiment was 30–60 s with a sampling frequency of 2 Hz. The mass median diameter is used as the droplet diameter (D).

2.4. Aerodynamic particle size

The aerodynamic particle size was analysed by a time of flight principle with an Aerodynamic Particle Sizer 3321 (TSI Incorporated, Shoreview, MN, USA). The aerodynamic particle size is given as mass median aerodynamic diameter (MMAD).

2.5. Geometric particle size

The median particle size was analysed by laser diffraction with a Helos system (Sympatec GmbH, Clausthal-Zellerfeld, Germany). The powder was dispersed in isopropanol with Tween 20 and the optical density of the dispersion was adjusted to approx-

Table 2
CCF experimental design

Run No.	Parameters				
	N (L/min)	F (mL/min)	T_{in} (°C)	A (%)	I (mg/mL)
1	11.1	5.25	150	90	30
2	17.5	5.25	75	80	5
3	17.5	5.25	75	100	60
4	7.3	5.25	75	100	5
5	11.1	3.6	150	90	30
6	17.5	3.6	150	90	30
7	11.1	3.6	75	90	30
8	11.1	3.6	150	90	30
9	17.5	5.25	220	80	60
10	7.3	3.6	150	90	30
11	11.1	1.8	150	90	30
12	7.3	5.25	220	80	5
13	11.1	3.6	220	90	30
14	17.5	1.8	220	100	60
15	7.3	1.8	220	100	5
16	17.5	1.8	75	80	60
17	7.3	5.25	75	80	60
18	11.1	3.6	150	90	30
19	11.1	3.6	150	90	30
20	7.3	1.8	220	80	60
21	17.5	5.25	220	100	5
22	11.1	3.6	150	90	5
23	11.1	5.25	150	90	30
24	17.5	1.8	75	100	5
25	11.1	3.6	150	90	60
26	11.1	3.6	150	100	30
27	7.3	1.8	75	100	60
28	11.1	3.6	150	80	30
29	7.3	1.8	75	80	5
30	17.5	1.8	220	80	5
31	7.3	5.25	220	100	60