Available online at www.sciencedirect.com

SCIENCE DIRECT®

European Journal of Pharmaceutics and Biopharmaceutics 59 (2005) 565–573

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejpb

Research paper

Effects of process variables on the powder yield of spray-dried trehalose on a laboratory spray-dryer

Michael Maury[a], Keith Murphy[b], Sandeep Kumar[b], Lei Shi[b], Geoffrey Lee[a,*]

[a]*Department of Pharmaceutics, Friedrich-Alexander University, Erlangen, Germany*
[b]*Amgen Inc., Thousand Oaks, CA, USA*

Received 12 July 2004; accepted in revised form 14 October 2004
Available online 9 December 2004

Abstract

A systematic examination is presented of the effects of process variables on the powder yield of amorphous trehalose obtained from the Büchi Model 191 laboratory-scale mini spray dryer. By using a specially made, narrow cyclone the powder yield could be greatly improved at all process temperatures examined. Calculations of the separation efficiencies of the improved cyclone and the manufacturer's standard cyclone are given, which show that the former's higher tangential particle velocity at the radius of the exit duct is responsible for the improved performance. The powder yield increases with higher process temperatures, owing to improved droplet drying and reduced droplet/particle deposition on the walls of the drying chamber. A maximum in the powder yield is reached, however, after which it decreases sharply. This is caused by heating of the cyclone wall to >10 °C above the so-called 'sticky point' of the trehalose, causing increased particle deposits on the walls of the tower and cyclone. Increasing liquid feed flow rate or decreasing atomizing air flow rate too extensively were both detrimental to powder yield. The drying air flow rate should be as high as possible to ensure sufficient enthalpy throughput to dry the trehalose adequately to give a high powder yield. The enthalpy balance calculation for drying trehalose with the new cyclone was used successfully to interpret the results obtained. Some recommendations for optimizing powder yield of an amorphous material are given.

Keywords: Spray-drying; Protein; Trehalose; Yield; Cyclone; Enthalpy balance

1. Introduction

When developing a formulation and identifying the best process conditions for the production of a spray-dried protein-loaded powder it is usual that only small quantities of the protein are available. For this reason the development experiments are routinely performed on a laboratory-scale mini spray dryer [1]. The Büchi Model 190 and its successors the Models 191 and 290 are the most frequently used machines, as evidenced by a number of publications and patents citing work with this spray-dryer. Despite its undoubted suitability the Büchi has a number of limitations. Its low drying capacity of 1 kg/h of water at its highest inlet air temperature of 220 °C [2] and its short droplet/particle residence time in the drying chamber limit achievable particle size to ≤ 20 μm, independent of nozzle selection and total solids' content of the liquid feed. A further limitation is the low powder yield typically obtained with amorphous formulations of interest for stabilizing proteins. In publications where the yield is mentioned, values of 20–50% [3] are cited. A powder yield substantially below 50% is, however, disadvantageous, since this limits the amount of material available for essential, powder-consuming tests such as Karl–Fischer titration or wide-angle X-ray scattering [4].

There are two main reasons for a low powder yield obtained on the Büchi with amorphous formulations. First, the design of the cyclone separator, which cannot trap particles of diameter <2 μm, but lets them pass through into the outlet air [5]. Maa et al. [6] investigated various alternative cyclone geometries, none of which, however, produced an improvement in yield of an anti-IgE

---

* Corresponding author. Address: Lehrstuhl fur Pharm. Technologie, Friedrich-Alexander Universitat, Erlangen-Nurnberg, Erlangen, Cauerstr. 4, Erlangen 91058, Germany. Tel.: +49 9131 8529552; fax: +49 9131 8529545.

E-mail address: lee@pharmtech.uni-erlangen.de (G. Lee).

0939-6411/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2004.10.002

monoclonal antibody formulated with lactose or mannitol. Secondly, inadequate process conditions that cause particles to adhere to the inside wall of the spray-dryer. The interrelations between drying air inlet and outlet temperatures, liquid feed flow rate, and drying air flow rate were examined by Maa et al. [7] in a second paper. The effects of these process conditions on powder yield or moisture content were not, however, considered systematically. No recommendations for optimization of the powder yield could therefore be made. Detailed information about the relation between powder yield and process conditions is not available in the published literature.

We have used spray-drying to produce stable powders of an immunoglobulin G [8]. Since this IgG was only available in extremely small quantities it was necessary to identify spray-drying conditions that give the highest possible powder yield on the Büchi. To help us achieve this aim we conducted a systematic investigation of the effects of the spray-drying process conditions on the yield and moisture content of a model powder. The relevant process conditions are drying air inlet and outlet temperatures, liquid feed flow rate, atomizing air flow rate, drying air flow rate, and solid's content of the liquid feed. We selected trehalose as a model powder because it is known to form amorphous particles on spray drying [4]. A specially constructed, improved cyclone separator was used in an effort to obtain a major improvement in powder yield over the 'standard' Büchi cyclone. The results obtained illustrate some relevant aspects of cyclone design suitable for a laboratory-scale mini spray dryer. Additionally they demonstrate how a judicious selection of spray-drying conditions can produce an improved yield on the Büchi whilst maintaining adequate powder properties.

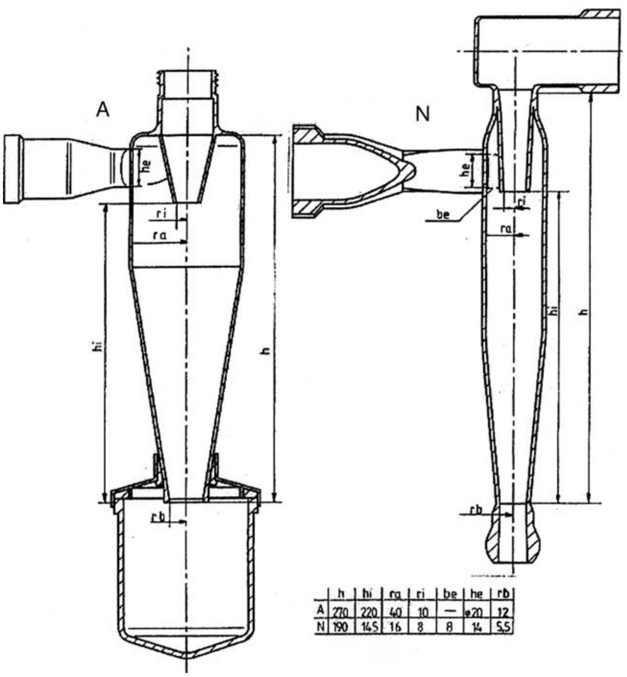
2. Materials and methods

2.1. Materials

Trehalose dihydrate was used as received from Sigma Chemicals (Munich). Water was double-distilled from an all-glass apparatus.

2.2. Spray-drying

Liquid feed was prepared by dissolving the appropriate amount of trehalose dihydrate in water at room temperature. Three millilitres of liquid feed were spray-dried using a Büchi Model 191 laboratory spray-dryer fitted either with the standard cyclone provided by Büchi or with a specially constructed glass cyclone intended to improve powder separation from the outlet air. Fig. 1 shows the construction and relevant dimensions of both the 'standard' (A) and 'improved' (N) cyclones. A two-fluid nozzle with cap-orifice diameter of 0.7 mm was used. The following process conditions were varied: drying air inlet temperature (T_{inlet}), drying air outlet temperature (T_{outlet}), liquid feed volumetric flow rate (v_{lf}), atomizing air volumetric flow rate (v_{aa}), drying air volumetric flow rate (v_{da}), and the trehalose concentration in the liquid feed. v_{aa} can be directly read-off the spray dryer in L/h. v_{da} is, however, given only as a % of total aspirator rate. The value of v_{da} in m^3/h on ambient inlet air was therefore measured using an FA 20 R Flow Meter (Krohne, Germany) attached to the outlet of the cyclone via a 30 cm length of bicycle tubing to dampen pressure fluctuations.



	h	hi	ra	ri	be	he	rb
A	270	220	40	10	—	⌀20	12
N	190	145	16	8	8	14	5,5

Fig. 1. Design and relevant dimensions (mm) of the standard Büchi cyclone (A) and the improved cyclone (N).

2.3. Powder yield, residual moisture content and glass transition

We define powder yield [%] as that % weight fraction of the amount of trehalose originally contained in the atomized liquid feed volume that could be recovered from the collecting vessel attached to the bottom of the cyclone (and also from the underside of its metal lid, in the case of the standard cyclone). Powder present on the inside wall of the cyclone was not considered as being part of the yield. The residual moisture content of each powder yield was determined using Karl–Fischer-titration on a Mitsubishi CA-06 Titrator fitted with a VA Water Vaporizer. About 80–100 mg samples were examined using pre-heating at 150 °C. The glass transition temperature (T_g) of each powder yield by determined using a Mettler Toledo Model DSC 822. A 5–10 mg sample was examined in the temperature range 55–110 °C at a heating rate of 10 °C/min. T_g was calculated at the mid-point of the endothermic shift.