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Research paper

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

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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

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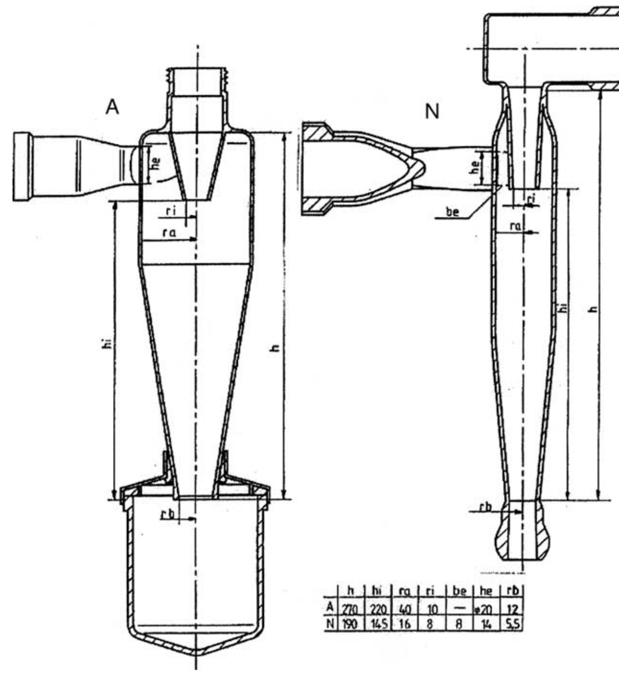
monoclonal antibody formulated with lactose or mannitol. Secondly, inadequate process conditions that cause particles to adhere to the inside wall of the spray-dryer. The interrelations between drying air inlet and outlet temperatures, liquid feed flow rate, and drying air flow rate were examined by 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.



	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. 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.

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.

2.4. Phase doppler analysis (PDA)

The droplet size distribution emerging from the cap-orifice of the Büchi's standard two-fluid nozzle was determined using a Beam Lok PDA, Model 2060-7S, Spectra Physics. The relevant measurement parameters were: $\lambda = 490$ nm; beam distance 40 mm; focal length 310 nm; receiving distance 500 nm; scattering angle 30 °C; distance between nozzle cap-orifice and measuring zone 140 mm.

3. Results and discussion

3.1. Performance of improved cyclone: influence of T_{inlet}/T_{outlet}

The improved cyclone shows substantially better powder yields than does the standard cyclone over the whole range of T_{outlet} examined, i.e. $T_{\text{outlet}} = 55$–145 °C corresponding to $T_{\text{inlet}} = 90$–210 °C (Fig. 2b). The improved cyclone gives absolute yield values that are 20–35% higher than those obtained with the standard cyclone. This difference becomes larger with increasing T_{outlet}. In contrast to the modified cyclones tested by Maa et al. [6] our improved cyclone has therefore a greatly superior performance to that of the standard cyclone. The reason for this is to be found in the smaller radii of the cyclone chamber, r_a, and exit duct, r_i, of the improved cyclone compared with the standard (Fig. 1). These smaller radii cause a greater resistance to air flow through the cyclone and hence a greater pressure drop across it. For the example of 90% aspirator rate the pressure drop across the improved cyclone was 65 mbar compared with 40 mbar across the standard cyclone. This must result in a lower volumetric air flow rate (Q, in m^3/h) at any particular % aspirator rate. Fig. 3a shows the measured values of Q through the spray dryer fitted with each of the cyclones on increasing % aspirator rate. The measured Qs are indeed approximately 35% lower through the improved cyclone than through the standard cyclone at all % aspirator rates measured. The major factor governing the separation of particles from the air in the vortex of a cyclone is the tangential velocity of the particles, $\vec{v}_t^p$, at the radius of the exit duct, r_i [9]. Appendix A gives the calculations of the particle/air separation efficiency of both cyclones based on Barth's classic model [10]. As shown in Table A1, despite the improved cyclone's lower Q, the smaller radius of the cyclone chamber, r_a, results in a higher velocity of the inlet air, v_{in}, of approximately 75 m/s compared with approximately 18 m/s for the standard cyclone. The smaller radius of the exit duct, r_i, now yields a $\vec{v}_t^p$ of 95 m/s for the improved cyclone and 32 m/s for the standard cyclone. Barth's approximation for a cyclone's cut-off point, $\bar{d}$, i.e. the smallest particle diameter that will move outwards in the cyclone's vortex and be deposited on the inside cyclone chamber wall, is [9]

$$\bar{d}^2 = \frac{9\eta Q}{(\vec{v}_t^p)^2 \rho_p \pi h_i} \qquad (1)$$

where η is air viscosity, ρ_p particle density, and h_i vortex height. Eq. (1) yields values of $\bar{d} = 1.43$ μm for the standard cyclone and 0.44 μm for the improved cyclone (see Table A1). It follows that the improved cyclone can also separate those particles between 1.43 and 0.44 μm which pass through the standard cyclone. Since both cyclones will be able to separate equally well the particles $> \bar{d}$, the result is the higher powder yield seen in Fig. 2b for the improved cyclone. The narrowest cyclone investigated by Maa et al. [6] had the dimensions $r_a = 3.4$ cm and $r_i = 1.0$ cm, compared with $r_a = 4.0$ cm and $r_i = 1.0$ cm for

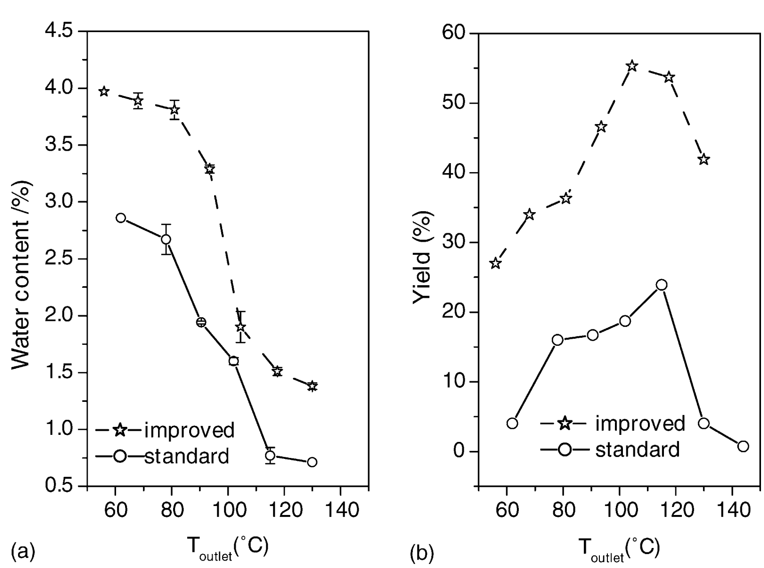


Fig. 2. Effects of variation in T_{outlet} on residual water content (a) and powder yield (b) of spray-dried trehalose from a 10% (w/w) liquid feed using standard and improved cyclones. $v_{da} = 35$ m^3/h or 45 m^3/h, $v_{aa} = 700$ L/h, $v_{lf} = 3.0$ ml/min, $n = 3$ spray-drying runs.

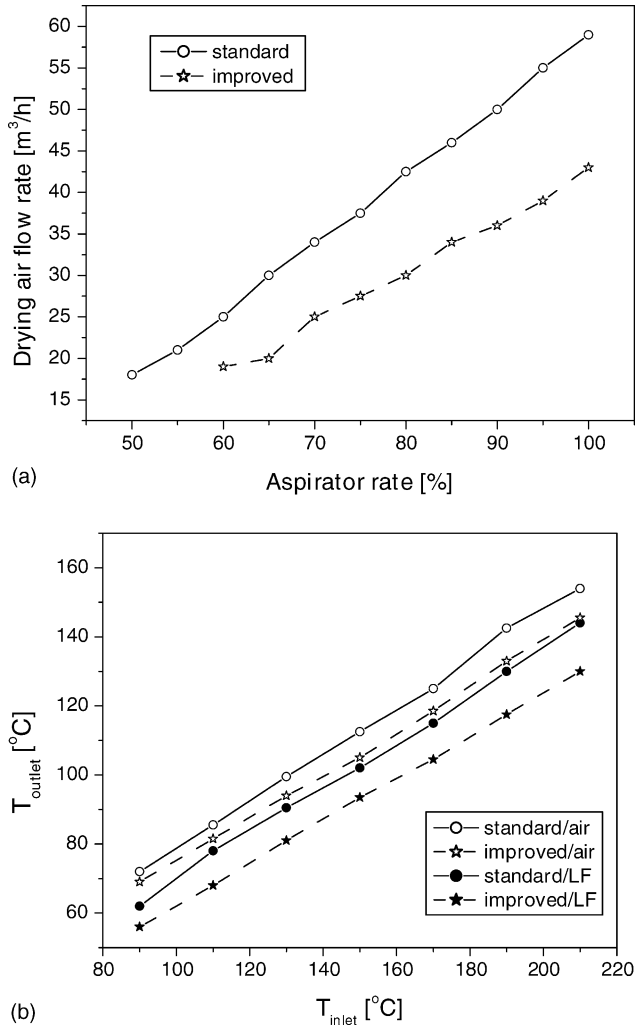


Fig. 3. Comparison of standard and improved cyclones. (a) Calibration of % aspirator rate to drying air flow rate in m^3/h. (b) Fixed T_{inlet} and corresponding measured T_{outlet} run on air or liquid feed (10%, w/w trehalose). $v_{da}=35$ m^3/h or 45 m^3/h, $v_{aa}=700$ L/h, and $v_{lf}=3$ ml/min.

the Büchi standard cyclone. Since no improved yield was obtained by Maa, this confirms the major importance of $\vec{v}_t^p$ being exerted at v_i for particle separation.

The powder yields increase at higher T_{oulet} (Fig. 2b) reaching maximum values of 26% at $T_{outlet}/T_{inlet}=115/170$ °C and 61% at $T_{outlet}/T_{inlet}=105/170$ °C for the standard and improved cyclones, respectively. With further increase in drying air temperatures the yields fall to <5% at $T_{outlet}/T_{inlet}=130/210$ °C with the standard cyclone, and to 46% at $T_{outlet}/T_{inlet}=130/210$ °C with the improved cyclone. Maa et al. [6] obtained powder yields of 30–50% from the collecting vessel for a formulation of anti-IgE antibody plus mannitol or lactose spray-dried at $T_{outlet}/T_{inlet}=50–55/90$ °C, $v_{da}=600$ L/min (≡36 m^3/h), $v_{aa}=900$ L/h and $v_{lf}=5$ ml/min. These authors spray-dried, however, a volume of liquid feed of 100–200 ml of a 1% (w/w) protein liquid feed, equivalent to 1–2 g of protein per run. In our experiments only 3 ml of an 8.5% (w/v) liquid feed was spray-dried, equal to 255 mg of total solids per run at 100% yield. This substantially lower volume was chosen to represent a more realistic experiment with a protein available only in small amounts. To determine the influence of total liquid feed volume and solids' content on powder yield, we obtained a powder yield of 61% when spray-drying 60 ml of the 8.5% (w/v) trehalose at $T_{inlet}=170$ °C. This result illustrates two points. First, it confirms the superiority of the improved cyclone. Secondly, it indicates that yield is controlled not only by the separation efficiency of the cyclone, but also—as evident from Fig. 2b—by the process conditions. An explanation of the strong temperature-dependence of the powder yield observed in Fig. 2b is to be found in Fig. 2a which shows the residual moisture contents of the powder yields recovered from the collecting vessels in dependence of T_{outlet}. With both cyclones the residual moisture content decreases sigmoidally with increasing T_{outlet}. At low drying temperatures powder deposits were formed on the inside vertical wall of the drying chamber. Droplets emerging from the Büchi's two-fluid nozzle are inter alia projected in the direction of the drying chamber vertical wall. If droplet/particle drying has proceeded insufficiently before impact with the wall, the particles can adhere, resulting in formation of a wet deposit and hence a reduced powder yield. This is a well-known phenomenon with pilot and production scale spray-dryers [11]. The narrow drying chamber of the Büchi evidently makes it especially prone to this problem at low drying temperatures. On increasing T_{outlet} a progressively drier product is obtained (cf. Fig. 2a) and the extent of wall deposition was visibly reduced. Now sufficient droplet/particle drying occurs before impact with the wall of the drying chamber. The result is the progressive improvement in yield measured with increasing T_{outlet} in Fig. 2b. The maximum in each yield/T_{outlet} curve in Fig. 2b corresponds to the point of incipient renewed deposition of powder on the inside wall of the tower and cyclone as a glassy film. The powder yield now declines with further increase in T_{outlet}, although the residual moisture contents remain at a low level (cf. Fig. 2a). The formation of tower/cyclone deposits and hence a decreasing powder yield are a result of increasing temperature of the inside wall of the machine. This temperature, T_{wall}, is approximately that of T_{outlet} [7]. At $T_{outlet}\geq 105/115$ °C (improved and standard cyclones, respectively) T_{wall} has increased sufficiently close to the 'sticky point' of the trehalose particles moving outwards in the cyclone vortex ($\vec{v}_r^p$ is positive) that the particles adhere to the cyclone wall on contact. This behaviour is known with the spray-drying of lactose-containing milk products in production-scale machines [11], and necessitates the use of lower T_{outlet}. The sticky point of an amorphous powder is that (increasing) temperature, T_s, at which inter-particulate cohesion sharply increases [12]. Its relation to a powder's glass transition temperature, T_g, is still equivocal, although it is considered to lie 10–20 °C above T_g. It is—like T_g—a non-equilibrium kinetic value that also depends on moisture content. Recent studies on

Table 1
Measured glass transition temperatures, T_g (mid point), of spray-dried trehalose powders recovered from collecting vessels of standard and improved cyclones

T_{outlet}		T_g		$(T_g - T_{outlet})$	
Standard	Improved	Standard	Improved	Standard	Improved
62	56	80	73	18	17
78	68	83	68	5	0
90	81	90	69	−1	−12
102	93	94	77	−8	−17
115	105	106	93	−9	−12
130	118	110	97	−20	−21
144	130	112	99	−32	−31

the spray drying of milk stress that the sticky point in this case is an adhesive phenomenon, and that the nature of the drying chamber wall surface should also be considered [13]. The T_s of trehalose has not been reported in the literature. Table 1 shows the values of T_g and also $(T_g - T_{outlet})$ in dependence of T_{oulet}. As expected, the T_g's from the improved cyclone are lower than those from the standard cyclone because of the former's higher residual moisture content at the same T_{outlet} (cf. Fig. 2a). A trend in change of $(T_g - T_{outlet})$ with increasing T_{outlet} is evident. $(T_g - T_{outlet})$ is positive at low T_{outlet}, but decreases through zero to negative values with increasing T_{outlet}. Recall that the powder yield starts to decrease at $T_{outlet} = 115$ °C with the standard cyclone and = 103 °C with the improved cyclone. At these T_{outlet}'s the values of $(T_g - T_{outlet})$ reach the range −9 to −12 °C (Table 1). $(T_g - T_{outlet})$ has become negative because the residual moisture content approaches its minimal value in the lower section of the sigmoid curve in Fig. 2a, whereas T_{outlet} continues to increase with higher T_{inlet} (Table 1). This result agrees therefore with the previously accepted maxim that T_s is approximately 10 °C higher than T_g. The decreasing powder yield seen in Fig. 2b at high T_{outlet} is a result of dry particle adhesion to the tower and cyclone walls when T_{outlet} is more than approximately 10 °C above T_g. A maximum yield can therefore be obtained by finding that T_{outlet} which prevents wet deposits in the drying chamber because of insufficient drying, but is not so high as to cause molten deposits on the tower or cyclone walls above T_s.

The trehalose powders obtained with the improved cyclone have higher residual moisture contents than those from the standard cyclone at equal T_{outlet} (Fig. 2a). Recall from Fig. 3a that the air flow rate Q (Nm^3/h) through the improved cyclone is approximately 35% lower than that through the standard cyclone. A lower Q should cause a lower T_{outlet} at fixed T_{inlet} when run on air [7]. Fig. 3b shows the T_{inlet} versus T_{outlet} curves for the Büchi fitted with either the standard or improved cyclone. When run on air, the value of $\Delta_{Toutlet}(=T_{outlet}^{standard} - T_{outlet}^{improved})$ increases from approx. 3 °C at $T_{inlet} = 90$–10 °C at $T_{inlet} = 210$ °C because of decreasing air density. When run on water over the same range of T_{inlet}, the ΔT_{outlet} increases from 6 to 14 °C, and T_{outlet} is lower than on air because of consumption of enthalpy to evaporate the water. The lower T_{outlet} of the improved cyclone at equal T_{inlet} explains the higher residual moisture contents of the powders obtained from the improved cyclone in Fig. 2a. The tendency to a smaller difference in water content between the trehalose powders from the improved and standard cyclones with increasing T_{outlet} (cf. Fig. 2a) is a result of the increasing ΔT_{outlet} in Fig. 3b.

The two non-superimposed curves in Fig. 2a show that T_{outlet} cannot be the single factor controlling residual moisture content of the trehalose powders. A simple calculation shows that the difference between the two curves cannot be a result of differing droplet/particle residence times in the drying tower. Both curves were obtained using an aspirator rate of 90% which from Fig. 3a yields $Q = 49$ N m^3/h with the standard cyclone and 35 Nm^3/h with the improved cyclone. The residence time of the drying air within the drying chamber (= chamber volume/$Q = 4.37 \times 10^{-3}$ m^3/Q m^3/h) is 0.5 s for the improved cyclone and 0.35 s for the standard cyclone. The improved cyclone has therefore a longer residence time, but produces a higher residual moisture content than the standard cyclone, even after T_{outlet} has been accounted for in the representation of Fig. 2a. Appendix B gives the calculation of enthalpy balance for the 10% trehalose solutions spray-dried on the Büchi at $T_{inlet}/T_{outlet} = 170$ °C/115 °C. It is seen that the total enthalpy consumption of 123 kcal/h required to dry the trehalose completely is provided by a v_{da} of just 9.3 m^3/h under the process conditions used. The rates of 45 and 35 m^3/h for v_{da} used in the experiments with the standard and improved cyclones, respectively, are clearly much higher than this minimum requirement (albeit idealized). This means that the throughput of drying air with either cyclone cannot be a limiting factor for drying, and also cannot explain the non-superimposition of the curves in Fig. 2a. The widely believed reliance on T_{outlet} as the controlling factor for production moisture must therefore be viewed with circumspection, at least with the laboratory-scale machine.

A T_{outlet} of 105 or 115 °C thus demarcates the highest process temperatures that can be used to give the largest powder yield of trehalose with the improved and standard cyclones, respectively. T_{outlet} is, however, a dependent variable that is affected not only by T_{inlet} but also by v_{lf}, v_{da} and v_{aa} [7]. Maximizing powder yield necessitates therefore

Table 2
Effects of increasing water flow rate (v_{lf}) on T_{outlet} (determined at T_{inlet} = 170 °C, v_{da} = 45 m^3/h, and v_{aa} = 700 L/h′) and PDA analysis of spray cloud

v_{lf} (ml/min)	$m_{aa/lf}$	T_{outlet} (°C)	Phase doppler analysis			
			Droplet velocity (m/s)	Mean droplet diameter (μm)	Data rate (kHz)	Spherical shape (%)
3.2 (2.7)	4.41	104	12.0±3.5	17.3±5.6	0.80	100
4.2 (4.4)	3.36	99	12.1±3.4	17.8±5.9	1.23	100
5.2 (5.5)	2.71	94	12.2±3.5	18.8±6.3	1.55	100
6.3 (6.5)	2.24	90	11.5±3.6	18.8±6.9	1.60	100
7.2 (7.6)	1.96	84	12.0±3.6	19.0±7.2	2.00	100
8.2 (8.6)	1.72	80	12.6±3.6	19.4±6.7	2.54	100
9.2	1.53	75	–	–	–	–

$m_{aa/lf} = (700(\mathrm{L/h}) \times 10^{-3} \times (\mathrm{m^3}/L) \times 1.21(\mathrm{kg/m^3}))/v_{lf}(\mathrm{ml/min}) \times 60\left[\frac{\mathrm{min}}{\mathrm{h}}\right] \times 10^{-3}(\mathrm{L/ml}) \times 10^{-3}(\mathrm{m^3/L}) \times 1000(\mathrm{kg/m^3})$. Droplet velocity and diameter are given as mean±SD. Data rate is the number of droplets passing the measuring volume per unit time. Spherical shape describes sphericity on a % scale. The values of v_{lf} given in brackets are those used for the PDA analysis.

adjustment of T_{outlet} to the stated values under particular atomizing and drying air flow conditions.

3.2. Effect of atomizing conditions (improved cyclone)

The droplet size distribution emerging from the cap-orifice of a two-fluid nozzle depends on solution viscosity, surface tension, and the mass ratio of atomizing air to liquid feed ($m_{aa/lf}$) [14]. Increase in liquid feed flow rate (v_{lf}) at constant atomizing air flow rate (v_{aa}) should result in larger spray-droplets and hence larger particles with a better likelihood of being retained in the cyclone. To determine the scope for improving powder yield in this way, v_{lf} was varied in the range of 3–9 ml/min at v_{da} = 45 m^3/h. If T_{inlet} is fixed to 170 °C, then increasing v_{lf} with water leads to a decrease in T_{outlet} (Table 2) because of the higher enthalpy consumption required to dry larger amounts of water [7]. T_{outlet} was therefore held constant at 100 °C (98–102) when varying v_{lf} by adjusting T_{inlet} accordingly. This allows observation of the isolated effects of v_{lf} on powder dryness and yield independent of T_{outlet}. Fig. 4a illustrates the effect of increasing v_{lf} on the powder yield and residual moisture content of spray-dried trehalose from a 10% (w/v) liquid feed at a constant T_{outlet} = 100 °C. Despite the scatter observed (n = 3 spray drying runs) the powder yield decreases only marginally with increasing v_{lf}, whilst the moisture content of the powder recovered from the collecting vessel remains approximately constant at around 2%. Although the constant T_{outlet} is evidently responsible for those results, the question of any change in droplet size on altering v_{lf} needs also to be addressed. The increase in v_{lf} from 3 to 9 ml/min produces a substantial reduction in calculated $m_{aa/lf}$ from >4 to approximately 1.5 (Table 2). A change in $m_{aa/lf}$ of this magnitude and in this range is known to increase mean droplet diameter of atomized water from a two-fluid nozzle by 50–100% [14]. The PDA results obtained show, however, that the mean droplet size emerging from the nozzle has only a small increase from 17.3 to 19.4 μm as v_{lf} changes from 2.7 to 8.6 mL/min (Table 2). Droplet speed remains unchanged, as this will be controlled by the atomizing air flow rate. The number of droplets passing through the PDA field per unit time (‘data rate’ in Table 2) increases in direct proportion to v_{lf}, confirming that droplet means size changes little. Although unexpected, the weak influence of v_{lf} on mean droplet

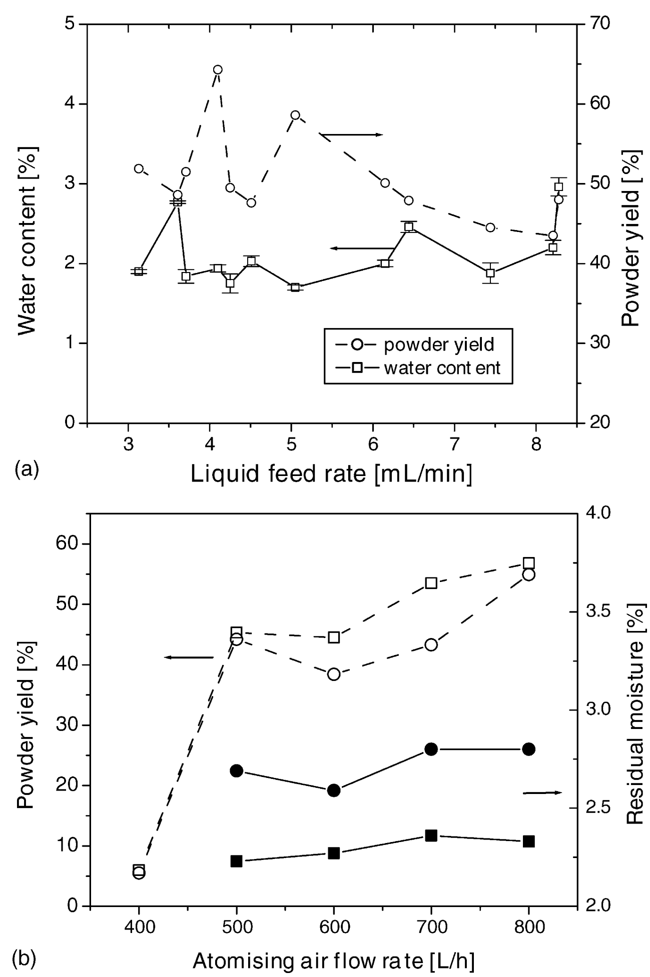


Fig. 4. Effect of nozzle parameters on residual moisture and powder yield of spray-dried trehalose with improved cyclone. (a) Effect of liquid feed flow rate (v_{lf}) with T_{outlet} = 100 °C, v_{da} = 45 m^3/h and v_{aa} = 700 L/h. (b) Effect of atomizing air flow rate (v_{aa}) with v_{lf} = 3 ml/min. T_{outlet} was either kept constant at 99 °C (□, ■) by adjusting T_{inlet} accordingly, or allowed to vary (○, ●) by keeping T_{inlet} constant at 130 °C v_{da} = 45 m^3/h.

Table 3
Effects of decreasing atomizing air flow rate (v_{aa}) on T_{outlet} (determined at $T_{inlet}=170$ °C, $v_{da}=45$ m^3/h and $v_{lf}=3$ ml/min) and PDA analysis of spray cloud

v_{aa} (L/h)	$m_{aa/lf}$	T_{outlet} (°C)		Phase doppler analysis			
		Air	Water	Droplet velocity (m/s)	Mean droplet diameter (μm)	Data rate (kHz)	Spherical shape (%)
800	5.20	–	–	15.9±4.3	17.4±5.3	0.89	100
700	4.71	101.5	117.5	12.6±3.4	18.0±5.6	0.85	100
600	4.03	104.5	120	8.8±2.5	16.2±6.1	1.12	100
500	3.36	107.0	122	5.4±1.9	17.9±7.8	0.51	100
400	2.69	110.5	123.5	3.5±1.5	21.2±1.0	0.20	100
300	2.02	113.0	124	–	–	–	–
200	1.34	115.5	124	–	–	–	–

$m_{aa/lf}=(v_{aa}(\mathrm{L/h})\times10^{-3}\times(\mathrm{m^3/L})\times1.21(\mathrm{kg/m^3}))3(\mathrm{mL/min})\times60\left[\frac{\mathrm{min}}{\mathrm{h}}\right]\times10^{-3}(\mathrm{L/ml})\times10^{-3}(\mathrm{m^3/L})\times1000(\mathrm{kg/m^3})$. Explanations of PDA data are given in Table 2.

diameter explains the consistency of both powder yield and residual moisture content observed in Fig. 4a. As illustrated in Appendix B, the enthalpy throughput (kcal/h) of the Büchi is determined by ($T_{inlet}-T_{outlet}$) and v_{da}, and is sufficient to dry the 10% trehalose solution at $v_{lf}=9$ ml/min equally well as it can at $v_{lf}=3$ ml/min, 3 ml/min a v_{da} of 9.3 m^3/h is necessary to dry the liquid feed, and at 9 ml/min a v_{da} of 27.3 m^3/h. In the experiments a v_{da} of 45 m^3/h was used which is more than enough to dry the liquid feed at approximately the same droplet size.

The second nozzle parameter of relevance is the atomizing air flow rate, v_{aa}. This was varied in the range 800–200 L/h for ambient air at a constant v_{lf} of 3 ml/min and $v_{da}=45$ m^3/h. If T_{inlet} is fixed at 170 °C, Table 3 shows that a decrease in v_{aa} causes an increase in T_{outlet} when run either on air or on water. This is clearly a result of the lower volumes of ambient air passing through the nozzle into the drying chamber. Fig. 4b shows that at fixed $T_{inlet}=170$ °C the powder yield decreases slightly when v_{aa} is reduced from 800 to 500 L/h. Further decrease to 400 L/h sharply reduces powder yield to <10%. Large deposits of powder were now visible in the drying tower, and liquid water was also observed to form on the drying tower's inside wall. If spray-drying continued for 5 min then threads of water streamed down the inside wall of the drying tower. The same behaviour is seen when T_{outlet} is held constant at 99 °C by varying T_{inlet} accordingly (Fig. 4b). It is therefore evident that effective spray-drying does not take place when v_{aa} is ≤400 L/h at $v_{lf}=3$ ml/min. Table 3 shows that $m_{aa/lf}$ is approximately 2.7 at this v_{aa}. The same value of $m_{aa/lf}$ is reached in Table 2 by increasing v_{lf} (with $v_{aa}=700$ L/h) to 5 ml/min, where however, powder yield is still >50% (cf. Fig. 4a). The PDA results show no change in mean droplet diameter when v_{aa} is decreased from 800 to 500 L/h (Table 3) despite the reduction in $m_{aa/lf}$. Both the droplet speed and data rate decrease because of reduced kinetic energy imparted to the liquid by the air. Only at $v_{aa}=400$ L/h does mean droplet diameter tend to increase (Table 3), and at even lower v_{aa}'s both PDA measurement and spray-drying of the trehalose liquid feed were not possible. The residual moisture content of the powder yield decreases only slightly with lower v_{aa} (Fig. 4b) at both constant and varying T_{outlet}. At $v_{aa}=400$ L/h insufficient powder to perform a Karl–Fischer titration was obtained. The goodness of these spray-drying runs cannot therefore be judged alone by the properties (i.e. residual moisture) of the powder in the collecting vessel. Knowledge of the powder yield and the extent of powder deposition within the drying tower and cyclone are vital to interpreting the effectiveness of the spray-drying procedure with the laboratory spray-dryer. It is evident that altering either nozzle parameter (v_{lf} or v_{aa}) cannot be used as an effective method to improve powder yield of the trehalose.

3.3. Effect of drying air flow rate (improved cyclone)

The drying air flow rate, v_{da}, determines both of the rate of enthalpy throughput (kcal/h) of the spray-dryer and the droplet/particle residence time within the spray-dryer. Table 4 shows that reducing v_{da} produces a linear decrease in the powder yield. There was a corresponding visual increase in deposit on the inside wall of the drying chamber. The lowest v_{da} of 15 m^3/h examined (≡50% aspirator) produced a highly fused product in the collecting vessel having a high residual moisture content (Table 4). Recall from the enthalpy balance in Appendix B that a v_{da} of 9.3 m^3/h is required to dry the liquid feed completely at $T_{inlet}/T_{outlet}=$ 170 °C/115 °C. It follows that 50% aspirator is insufficient enthalpy throughput to dry the product, despite the increased residence time at the lower v_{da}. The reduced rate of enthalpy throughput is directly reflected in the lower T_{outlet} (Table 4),

Table 4
Effects of drying air flow rate (v_{da}) on powder yield and moisture content of spray-dried trehalose

v_{da} (m^3/h)	T_{outlet} (°C)	Yield (%)	Moisture (% w/w)
45	84.5	58	2.8±0.2 ($n=3$)
35	75.5	44	3.3±0.3 ($n=3$)
15	63.0	27	9.4 ($n=1$)

$T_{inlet}=130$ °C, $v_{aa}=700$ L/h, $v_{lf}=3$ ml/min, 10% (w/v) trehalose in water. A single experiment was performed at each v_{da}. The Karl–Fischer analysis was performed on n samples from the powder yield recovered from the collecting vessel.

resulting in higher residual moisture content. The highest powder yield requires the highest degree of drying of the amorphous trehalose, without causing stickiness. This is achieved by using the highest v_{da} on the Büchi.

3.4. Effect of liquid feed solid's content (improved cyclone)

The concentration of dissolved trehalose was varied between 5 and 25% (w/v) in the liquid feed, and spray-dried at a $T_{inlet}=170$ °C, $T_{outlet}=98$–101 °C, $v_{da}=45$ m^3/h, $v_{aa}=700$ L/h, and $v_{lf}=3$ ml/min. Fig. 5 shows that trehalose concentrations between 5 and 14% give the expected powder yield of 55 and 60% under these process conditions. This, however, decreases at higher trehalose concentrations. A higher solid's content of the liquid feed will produce larger particles [4], although this was not measured here. After the critical point, the larger particles will dry more slowly than do the smaller ones obtained at lower solid's content. This will increase deposition in the drying chamber and hence reduce yield. Counteracting this effect, however, is that less water needs to be removed from each droplet with increasing solid's content. At constant ($T_{inlet}-T_{outlet}$) v_{da} and hence constant enthalpy throughput this effect should produce dryer particles. Fig. 5 shows that increasing trehalose concentration causes a slight increase in residual moisture content of the powder recovered from the collecting vessel, which, however, falls marginally at the highest concentration examined. Increased deposit formation on the inside wall of the drying chamber was observed at trehalose concentrations $>14\%$. The properties of the powder yield are not necessary representative of the drying process when substantial deposits are formed. The decrease in powder yield at high solid's content is therefore a result of higher residual moisture content of the larger particles. Under any particular set of process conditions (T_{inlet}, T_{outlet}, nozzle parameters, v_{da}) a high liquid feed total solid's content can therefore be detrimental to drying rate and hence powder yield.

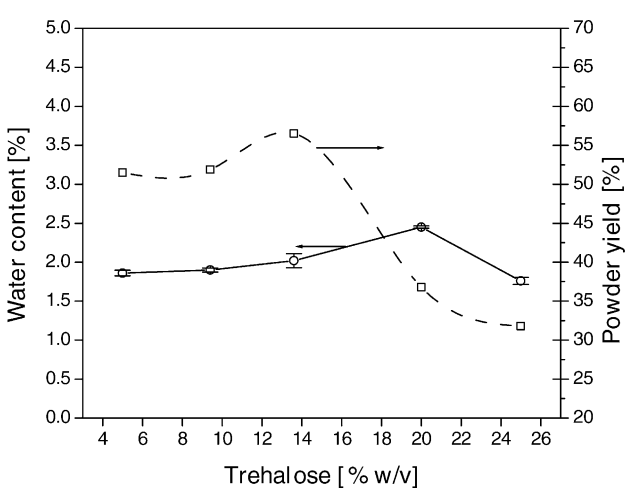


Fig. 5. Effect of liquid feed solid's content (trehalose) on residual moisture content and powder yield with improved cyclone. $v_{da}=35$ m^3/h, $v_{aa}=700$ L/h, $v_{lf}=3$ ml/min, $T_{inlet}=170$ °C, $T_{outlet}=100$ °C.

4. Conclusions

The most effective way to improve the powder yield of an amorphous material such as trehalose on the Büchi 191 is to use a cyclone having a narrow outlet duct. The narrower cyclone geometry reduces, however, the volumetric air flow rate through the cyclone and causes a larger pressure drop across the cyclone. The most important process condition to optimize the powder yield of trehalose is T_{inlet}/T_{outlet}. If T_{inlet}/T_{outlet} is too high, however, this causes the inside walls of the spray-dryer to exceed the sticky point of the powder by > approximately 10 °C. This should be avoided to maximize the powder yield. The nozzle parameters have little influence on powder yield, provided that excessively large droplets are not generated at very low v_{aa}. Similarly, the drying air flow rate has little influence on powder properties and yield, and should be run on its maximum value. The enthalpy balance calculation corresponded well to the experimental drying air flow rate necessary to obtain good powder yield and dryness. In summary, careful selection of process parameters is necessary to optimize amorphous powder yield on the Büchi 191.

Appendix A

The downward spiraling vortex of air in a cyclone of the design examined in this work exerts two opposite forces on a suspended particle. The centrifugal force acting outwards towards to cyclone wall at $x=r_a$, and the drag force acting inwards towards the inner edge of the vortex approximated by the radius of the exit duct, $x=r_i$. According to Barth [10], a particle rotating at $x=r_i$ with zero radial velocity, $\partial r(x,t)/\partial t|_{x=r1}=0$, represents the low limit of particle size that can be separated from the air vortex. Barth equated the centrifugal and drag forces acting on this particle of limiting diameter $\bar{d}$, to obtain

$$\bar{d}^2 = \frac{18\eta \bar{v}_{r_i}^{air} r_i}{(\bar{v}_t^p)^2 \rho_p} \tag{A1}$$

where η is air viscosity (Pa s), $\bar{v}_{r_i}^{air}$ is radial air velocity (m/s) at the radius of the exit duct, $\bar{v}_t^p$ is the tangential particle velocity (m/s) at r_i for the non-slip boundary condition, and ρ_p is particle density (kg/m^3). Table A1 shows the results obtained from Eq. (A1) for the standard and improved cyclones. The radial air velocity was calculated from [9]

$$\bar{v}_{r_i}^{air} = \frac{Q}{2\pi r_i h} \tag{A2}$$

Table A1
Details of calculation of separation efficiency of the standard and improved cyclones. For definition of symbols see Fig. 1 and Appendix A

Cyclone	r_a (m)	r_i (m)	h_i (m)	Q (m^3/s)	v_{in} (m/s)	$(r_a/r_i)^{0.5}$	$\bar{v}_t^p$ (m/s)	η (Pa s)	ρ_p (kg/m^3)	$\bar{d}^2$ (m^2)	$\bar{d}$ (m)
Standard	0.040	0.01	0.22	1.389×10^{-2}	18.227	1.761	32.10	1.82×10^{-5}	1470	2.036×10^{-12}	1.427×10^{-6}
Improved	0.016	0.008	0.145	1.00×10^{-2}	74.617	1.275	95.14	1.82×10^{-5}	1470	1.919×10^{-13}	0.438×10^{-6}

where Q is the measured air flow rate (m^3/h) for the example of 90% aspirator rate (cf. Fig. 3a), and h_i is the vortex height (m) (see Fig. 1). Substitution of Eq. (A2) into Eq. (A1) yields the Eq. (1) given in Section 3. The tangential particle velocity was estimated by using [9]

$$\bar{v}_t^p = v_{in}\left(\frac{r_a}{r_i}\right)^{1/2} \tag{A3}$$

with $v_{in} = Q/(\pi/4)r_a^2$. Note that although both Q and $(r_s/r_i)^{1/2}$ are smaller for the improved cyclone, v_{in} and hence $\bar{v}_t^p$ is much higher (cf. Table A1) as a result of the substantially narrower cyclone radius, r_a. The larger $\bar{v}_t^p$ of the improved cyclone is the major cause of the lower $\bar{d}$ obtained at r_i.

Appendix B

The enthalpy balance was calculated for the Büchi 191 fitted with the improved cyclone and run at $T_{inlet} = 170$ °C and a liquid feed flow rate of 3 ml/min. The humidity of the inlet air was neglected. The additional values given in brackets are for the highest liquid feed flow rate of 9 ml/min examined. Following the method given in detail by Masters [15] yield the following vaues. The enthalpy required for evaporation, $E_1 = 101.7$ kcal/h (339.0 kcal/h). The enthalpy required for heating the dried trehalose powder, $E_2 =$ 0.79 kcal/h (2.37 kcal/h). The heat loss through the drying chamber, $E_3 = 4.0$ kcal/h. The enthalpy to heat the atomizing air, $E_4 = 16.4$ kcal/h. The total enthalpy requirement is therefore:

$$E_{tot} = \sum_{n=1}^{n=4} E_n = 123 \text{ kcal/h } (362 \text{ kcal/h})$$

The required drying air rate, v_{da}, to provide this enthalpy throughput is:

$$v_{da} = E_{tot}/(T_{inlet} - T_{outlet})C_p^{air} = 9.3 \text{ m}^3\text{/h } (27.3 \text{ m}^3\text{/h})$$

References

[1] G. Lee, Spray drying of proteins, in: J. Carpenter, M. Manning (Eds.),, Rational Protein Formulation: Theory and Practice, Plenum Press, New York, 2002, pp. 135–158.

[2] Technical Data B-290, available at: www.buchi.com, Drying, Mini Spray Dryer B-290. Available Sept. 23, 2004.

[3] P. Labrude, M. Rasolomanana, C. Vigneron, C. Thiron, B. Chailott, Protective effect of sucrose on spray drying of oxyhemoglobin, J. Pharm. Sci. 78 (1989) 223–229.

[4] M. Adler, G. Lee, Stability and surface activity of lactate dehydrogenase in spray dried trehalose, J. Pharm. Sci. 88 (1999) 199–208.

[5] K. Prinn, H. Costantino, M. Tracy, Statistical modeling of protein spray drying at the lab scale, AAPS Pharm. Sci. Tech. 3 (1) (2002).

[6] Y.-F. Maa, P.-A. Nguyen, K. Sit, C. Hsu, Spray drying performance of a bench-top spray dryer for protein aerosol powder preparation, Biotech. Bioeng. 60 (1998) 301–309.

[7] Y.-F. Maa, H. Costantino, P.-A. Nguyen, C. Hsu, The effect of operating and formulation variables on the morphology of spray dried protein particles, Pharm. Dev. Technol. 2 (1997) 213–223.

[8] M. Maury, K. Murphy, S. Kumar, A. Mauerer, G. Lee, Spray-drying of proteins: effects of sorbitol and trehalose on aggregation and FT-IR amide I spectrum of an immunoglobulin G, Eur. J. Pharm. Biopharm. 2004; in press.

[9] L. Wang, C. Parnell, B. Shaw, R. Lacey, Analysis of cyclone collection efficiency, Proceedings of 2003 ASAE Annual International Meeting, Las Vegas, Paper # 034114, 2003, available at: http://caaqes.tamu.edu/publications.html#VII.

[10] W. Barth, Design and layout of the cyclone separator on the basis of new investigations, Brenn. Warme Kraft 8 (1956) 1–9.

[11] J. Pisecky, Handbook of Milk Powder Manufacture, Niro A/S, 1997, pp. 19–35.

[12] M. Lazar, A. Brown, G. Smith, F. Wong, F. Linquist, Experimental production of tomato powder by spray drying, Food Technol. 11 (3) (1956) 129–134.

[13] L. Ozmen, T. Langrish, An experimental investigation of the wall deposition of milk powders in a pilot scale spray dryer, Drying Technol. 18 (2003) 1253–1272.

[14] K. Masters, Spray Drying in Practice, Spray Dry Consult, Denmark, 2002, pp. 157.

[15] K. Masters, Spray Drying Handbook, Longman Scientific, New York, 1991, p. 30.5.