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The effect of process variables on the degradation and physical properties of spray dried insulin intended for inhalation

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Abstract

The aim of this study was to investigate the effect of process variables on the degradation and physical properties of spray dried insulin intended for inhalation. A 2^4 full factorial experimentally designed study was performed to investigate the influence of the following independent spray drying variables: feed flow rate, nozzle gas flow rate, inlet air temperature and aspirator capacity (drying gas flow rate). Human insulin (biosynthetic and Ph.Eur. quality) was dissolved in distilled water to concentrations of 5 mg/ml. The solutions were spray dried in a Mini Spray Dryer Büchi and the dry powders produced were characterized by high performance liquid chromatography, size exclusion chromatography, laser diffraction, thermo gravimetric analysis, scanning electron microscopy and weighing. The degradation of insulin was found to be affected mainly by the process variables that determine the outlet air temperature, i.e.: inlet air temperature, aspirator capacity and feed flow rate. The outlet air temperature should be kept below 120 °C to avoid degradation. A statistical optimization of the spray drying variables was performed, and found to recommend an experiment with an outlet air temperature of 61 ± 4 °C. This experiment ought to generate a yield of $54 \pm 7\%$ by weight of particles with a mass median diameter 2.9 ± 0.4 μm, moisture content $3.9 \pm 0.5\%$ by weight, content of high molecular weight proteins $0.3 \pm 0.1\%$ by area, A-21 desamido insulin $0.3 \pm 0.05\%$ by area and other insulin related compounds $0.3 \pm 0.1\%$ by area.

Keywords: Spray drying; Insulin; Inhalation; Factorial design; Degradation; Particle size; Moisture content

1. Introduction

Particles delivered to the lung are preferentially within the size range 0.5–3.3 μm in order to deposit in the alveoli (Broadhead et al., 1992). Production of particles of this size can be

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achieved by various methods. Investigations on spray drying as a manufacturing method for powders intended for inhalation have attracted great attention during recent years (Vidgrén et al., 1987; Broadhead et al., 1994; Giunchedi and Conte, 1995; Venkatesh, 1996; Vanbever et al., 1999). The technique has been examined for various local and systemic drug delivery systems, containing both conventional organic molecules as well as biologic macromolecules. Different types of particles have been produced, such as conventional particles, encapsulated particles and porous particles.

The advantages of spray drying macromolecule particles of the inhalable size range are: (1) the possibility to spray dry macromolecules with negligible degradation and (2) the opportunity to spray dry particles in one step with control of other important particle characteristics (Masters, 1985a). In a one-step process a solution, suspension, emulsion or paste containing dry substance (plain or in a mixture) is sprayed into a hot drying medium. The liquid is evaporated immediately, whereby the droplets are cooled. This process step is naturally preferable when spray drying heat sensitive macromolecules. Thus, under optimal conditions no degradation takes place. By adjusting the feed concentration, nozzle feed rate, inlet air temperature of the drying gas etc., the particulate characteristics can be controlled.

Patent applications by Platz et al. (1996) and Platz et al. (1997) present methods where macromolecule drugs for systemic application, e.g. insulin, growth hormone and parathyroid hormone, are spray dried together with pharmaceutical carriers. In another patent application plain macromolecules, with insulin in a preferred embodiment, are spray dried (Robinson and Smith, 2000). Broadhead et al. (1994) have investigated the effect of the spray drying process on the properties of β-galactosidase whereas Mumenthaler et al. (1994) have performed a feasibility study on the spray drying of recombinant human growth hormone and tissue-type plasminogen activator.

Apart from the patent literature little has been published concerning the effects of spray drying on the product characteristics of insulin. The aim of the present study was, therefore, to investigate the effects of process variables on the degradation and physical properties when spray drying insulin particles intended for inhalation. Effects of the process variables were investigated using tools such as factorial experimental design and stepwise multiple linear regression (MLR).

2. Materials and methods

2.1. Materials

Human insulin of biosynthetic and Ph.Eur. quality was used. pH adjustments were made with HCl and NaOH; the concentrations used were 0.1 and 1.0 M, respectively, for the acid as well as the base.

2.2. Manufacturing method

Insulin solutions were prepared by adding distilled water to insulin, reducing the pH below the isoelectrical point (pH 5.4) to fully dissolve the insulin. Thereafter the pH was increased to physiological pH i.e. 7.4. The feed concentration was held constant at 5 mg/ml throughout all the experiments.

A Mini Spray Dryer Büchi, model 191 (Büchi, Labortechnik AG, Flawil, Switzerland) equipment was used. The inlet air (drying gas) had initially, before heating, a relative humidity of about 20%. The nozzle was a two fluid (co-current) one with an orifice diameter of 0.5 mm. The atomizing gas was nitrogen. In order to avoid heat-generated degradation—hot air passing the nozzle increases temperature—cooling water was circulated around the nozzle while drying.

The spray dryer was equipped with the standard cyclone belonging to the apparatus. The cyclone is not optimal for separating particles that are as small as these in the inhalable size range, which means that a relatively low process yield is obtained. In industrial practice, effective separators such as for example filter systems, would have to be used to achieve a high yield.

In order to determine the outlet air temperature during drying the internal measuring equipment of the spray dryer was used. The temperature in

the product collection vessel was determined as exactly as possible by using an external surface thermometer. The thermometer was placed onto the outer surface of the vessel and it was this temperature that was detected. The vessel consists of glass and it is considered that the temperature within the vessel is approximately the same as the one measured on the outside.

2.3. Experimental design

The spray drying variables (factors) that were varied were: feed flow rate (F), nozzle gas flow rate (N), inlet air temperature (T_{in}), and aspirator capacity i.e. drying gas flow rate (A). Two levels were used, low and high. Between the levels a centerpoint was chosen (Table 1). A full factorial experiment was run and the number of experiments was 2^k i.e. 2^4 ($=16$). Three centerpoints were added and thus the total number of experiments was 19. The running order was randomized. For the evaluation of the product characteristics after spray drying, i.e. the responses, least squares model fitting by MLR was used. The regression coefficients were calculated for the individual variables, i.e. main factors (e.g. (F)) and for interaction terms of two variables, i.e. two factor interactions (e.g. ($T_{in} \times F$)). The statistical software program Model 4.0, Umetrics, Sweden was used.

2.4. Characterization

2.4.1. Process yield

The yield was calculated by dividing the powder quantity obtained in the product collection vessel after spray drying by the quantity introduced into the process. Thus giving the unit per cent by weight (%).

2.4.2. Particle size

Well-dispersed suspensions of the spray dried powder samples in oil were analyzed by laser diffraction (MS 20, Malvern Mastersizer). The particle size was given as D (v, 0.5), i.e. mass median diameter (MMD), in μm.

2.4.3. Particle morphology

The particle morphology was investigated by using a JEOL JSM-5200 scanning electron microscope (SEM). The powder sample was spread on a SEM stub and sputtered with gold.

2.4.4. Moisture content

The moisture content in the powder samples was analyzed by thermo gravimetric analysis (TGA) using a TGA 7, Perkin Elmer. A powder sample weighing approximately 10 mg was heated from 25 to 105 °C at a rate of 20 °C/min. The sample was kept at 105 °C for 15 min. The weight change caused by moisture loss was registered and expressed in per cent by weight (%).

2.4.5. Degradation product content

The amount of covalent aggregation i.e. high molecular weight proteins (HMWP) was analyzed by size exclusion chromatography (SEC), using a silica-based column. This method uses the fact that proteins can be separated depending on their hydrodynamic properties and molecular shape and size. The content of A-21 desamido insulin (desamido) and other insulin-related compounds (OIRC) was determined by

Table 1
Design matrix for the factorial experiment

Variable	Level −1	Center point	Level +1
Feed flow rate (F), ml/h	120	210	300
Nozzle gas flow rate (N), l/h	500	650	800
Inlet air temperature (T_{in}), °C	100	160	220
Aspirator capacity, i.e. drying gas flow rate (A), %[a]	60	80	100

[a] 100% corresponds to about 45–60 m^3/h.

Table 2
Spray drying variable values for runs 1–19 and results from the characterization work

Run	F (ml/h)	N (l/h)	A[a] (%)	T_{in} (°C)	T_{out} (°C)	Yield (%)	MMD (μm)	Moisture (%)	HMWP (%)	Desamido (%)	OIRC (%)
1	120	500	60	100	63	51	3.4	4.5	0.41	0.32	0.6
2	120	500	60	220	132	44	3.9	2.4	0.82	0.46	1.08
3	120	800	60	100	62	9	2.0	4.6	0.53	0.30	1.04
4	120	800	60	220	120	8	2.1	3.3	0.77	0.42	1.38
5	120	500	100	100	74	44	3.1	3.1	0.44	0.37	0.35
6	120	500	100	220	150	61	4.2	1.9	3.32	0.94	3.59
7	120	800	100	100	72	27	1.6	3.3	0.37	0.32	0.62
8	120	800	100	220	141	22	1.6	2.9	2.36	0.74	2.59
9	300	500	60	100	50	49	3.2	5.1	0.36	0.32	0.37
10	300	500	60	220	117	45	3.6	3.2	0.47	0.36	0.45
11	300	800	60	100	51	13	2.2	4.9	0.33	0.32	0.99
12	300	800	60	220	114	11	2.4	3.8	0.45	0.35	0.72
13	300	500	100	100	61	61	3.3	4.1	0.35	0.33	0.30
14	300	500	100	220	141	61	4.4	2.2	1.7	0.64	2.04
15	300	800	100	100	59	35	1.6	4.3	0.36	0.33	0.42
16	300	800	100	220	137	33	1.8	2.8	1.29	0.53	1.54
17	210	650	80	160	100	35	2.2	3.1	0.49	0.36	0.46
18	210	650	80	160	98	38	2.3	2.8	0.45	0.35	0.79
19	210	650	80	160	99	39	2.4	2.9	0.42	0.34	0.75
Range	120–300	500–800	60–100	100–220	50–150	8–61	1.6–4.4	1.9–5.1	0.33–3.32	0.30–0.94	0.30–3.59

[a] 45–60 m^3/h.

Table 3
Fitted equations of the interaction models relating the physical properties to the process variables

Yield (weight%)	$Y_1 = 36.22 - 0.13T_{in}{}^{a} - 16.1N + 7.16A + 2.67F - 0.88(T_{in}N)^{a} + 1.41(T_{in}A)^{a} - 0.83(T_{in}F)^{a} + 2.41(NA)^{b}$	$R^2 = 0.961$; $Q^2 = 0.816$
Particle size (μm)	$Y_2 = 2.70 + 0.23T_{in} - 0.86N - 0.07A^{a} + 0.03F^{a} - 0.17(T_{in}N) + 0.07(T_{in}A)^{a} + 0.02(T_{in}F)^{a} - 0.19(NA)$	$R^2 = 0.941$; $Q^2 = 0.831$
Moisture content (weight%)	$Y_3 = 3.43 - 0.71T_{in} + 0.21N - 0.45A + 0.28F + 0.18(T_{in}N)^{b} + 0.09(T_{in}A)^{a} - 0.09(T_{in}F)^{a} + 0.04(NA)^{a}$	$R^2 = 0.914$; $Q^2 = 0.768$
Outlet air temperature (°C)	$Y_4 = 96.90 + 35.0T_{in} - 2.0N + 7.88A - 5.25F - 1.50(T_{in}N) + 2.88(T_{in}A) + 1.0(T_{in}F)^{a} - 0.13(NA)^{a}$	$R^2 = 0.997$; $Q^2 = 0.990$

T_{in}, inlet air temperature; N, nozzle gas flow rate; A, aspirator capacity; F, feed flow rate.
[a] Not significant.
[b] Significant at the 90% confidence level.

high performance liquid chromatography (HPLC). All amounts are given as per cent by area (%).

3. Results and discussion

3.1. Statistical evaluation of the experimental design

The obtained experimental data (Table 2) were used to set up the fitted equations (Tables 3 and 4). In the fitted equations the effects of the four spray drying variables on the product characteristics are shown. The factors and factor interactions included in each equation were significant for the model at the 95% confidence level unless otherwise marked. Adequate models were accepted at no lack of fit ($p > 0.05$), regression test ($p < 0.05$), high and similar goodness of fit (R^2) and prediction estimates (Q^2), which are ideally above 0.9 and 0.7, respectively.

Interaction models were used to compute the fitted equations in Table 3 and Table 4. Only two factor interactions were taken into account. The smallest interaction terms, $F \times N$ and $A \times F$, were excluded in all equations resulting in better models.

Experimental data of the responses concerning degradation (Table 4) were not normally distributed. Logarithmic transformations improved the statistical models for these responses i.e. increased the values of R^2 and Q^2, as can be seen in the right column in Table 4 (in italics). The functions in Table 4 are not linear and quadratic terms are needed in order to obtain better models. Only interaction models were used for identification of factors with substantial effect on the responses. Interaction models were found to be sufficiently descriptive for evaluation of all responses. Coefficients are also more easily interpreted in interaction models compared to logarithmic models.

The fitted equations are to be interpreted as follows: a positive sign in front of the variable means that an increase in the variable value is followed by an increase in the response value. In the opposite case, i.e. when the sign in front of the variable is negative, an increase in the variable value results in a decrease of the response value.

3.2. Outlet air temperature

The outlet air temperature varied between 50 and 150 °C (Table 2). Increased inlet air temperature and aspirator capacity both increased the outlet air temperature because of the increased supply of heat energy. Increased feed flow rate lowered the outlet air temperature since the volume of liquid to be evaporated increased (Table 3).

3.3. Process yield

The yields varied between 8 and 61% (Table 2). The yield increased when the nozzle flow was

Table 4
Fitted equations of the interaction models relating the degradation to the process variables

HMWP (area%)	$Y_5 = 0.83 + 0.50T_{in} - 0.09N^a + 0.38A - 0.23F - 0.09(T_{in}N)^a + 0.40(T_{in}A) - 0.19(T_{in}F) - 0.09(NA)^a$	$R^2 = 0.900$; $Q^2 = 0.639$	$R^2 = 0.951$; $Q^2 = 0.892$
Desamido (area%)	$Y_6 = 0.43 + 0.11T_{in} - 0.03N^a + 0.08A - 0.04F - 0.02(T_{in}N)^a + 0.07(T_{in}A) - 0.04(T_{in}F) - 0.02(NA)^a$	$R^2 = 0.921$; $Q^2 = 0.734$	$R^2 = 0.949$; $Q^2 = 0.869$
OIRC (area%)	$Y_7 = 1.06 + 0.54T_{in} + 0.03N^a + 0.30A - 0.28F - 0.15(T_{in}N)^b + 0.47(T_{in}A) - 0.21(T_{in}F) - 0.17(NA)^b$	$R^2 = 0.924$; $Q^2 = 0.771$	$R^2 = 0.943$; $Q^2 = 0.866$

For the degradation the R^2 and Q^2 values for the interaction models are shown to the left and for the logarithmic transformed models at the right (in italics). The latter values are presented in order to show how the models improved when transformation into logarithmic models was performed. T_{in}, inlet air temperature; N, nozzle gas flow rate; A, aspirator capacity; F, feed flow rate.

[a] Not significant.

[b] Significant at the 90% confidence level.

decreased (Table 3). Decreased nozzle flow decreases the atomization energy and thus producing enlarged droplets. These droplets dry to larger particles, which are more easily captured through the centrifugal force in the cyclone. Fig. 1 serves as a confirmation of this theory; i.e. the plot shows that increased particle size gives increased yield. As expected, the yield increased with an increase in aspirator capacity (Table 3).

In 1994, Broadhead et al. showed that during spray drying of β-galactosidase the yield was increased with increased inlet air temperature and decreased feed rate. Broadhead et al. also showed that the highest yields were obtained for the batches with the lowest moisture content. In this study, interactions between inlet air temperature and feed rate were not significant (Table 3).

An approximate estimation of the distribution of the dried material throughout the spray dryer was made. On average 15% of the spray dried material was deposited on the walls of the spray dryer. Depending on process conditions, 24 to 77% of the spray dried material passed the cyclone with the outgoing air. The problem of separating inhalable particles from air is well known and alternatives to cyclones have to be used. In the patent application by Platz et al. (1997), filters of various kinds are suggested as product separators for particles intended for pulmonary delivery.

3.4. Particle size

The MMD of the particles was in the size range 1.6–4.4 μm (Table 2). The particle size distributions were mostly bimodal, with a minor maximum below 1 μm and a major above 1 μm.

According to the model, increased atomization nozzle flow reduced the particle size. This means that for production of small particles the atomization flow is to be kept high (Table 3). The higher atomization flow, the more energy is supplied for breaking up the liquid into droplets during the atomization step, resulting in smaller droplets (Masters, 1985b). Increased inlet air temperature increased the particle size (Table 3), which has also been observed before. Hsu et al. (1996), present a theory based on the fact that at high inlet air temperatures a skin is formed on the outer surface of the spray droplets. When the inner water phase is evaporated the skin is destroyed and the outer

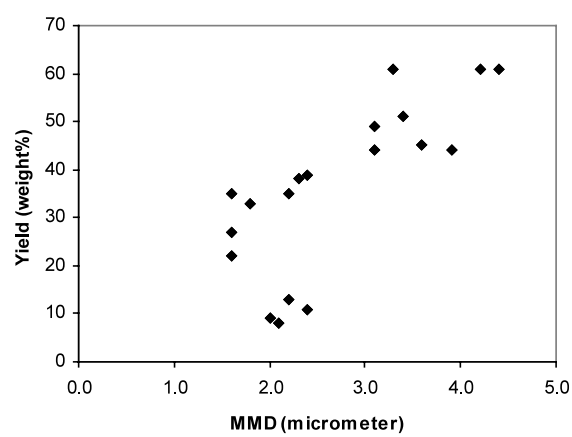
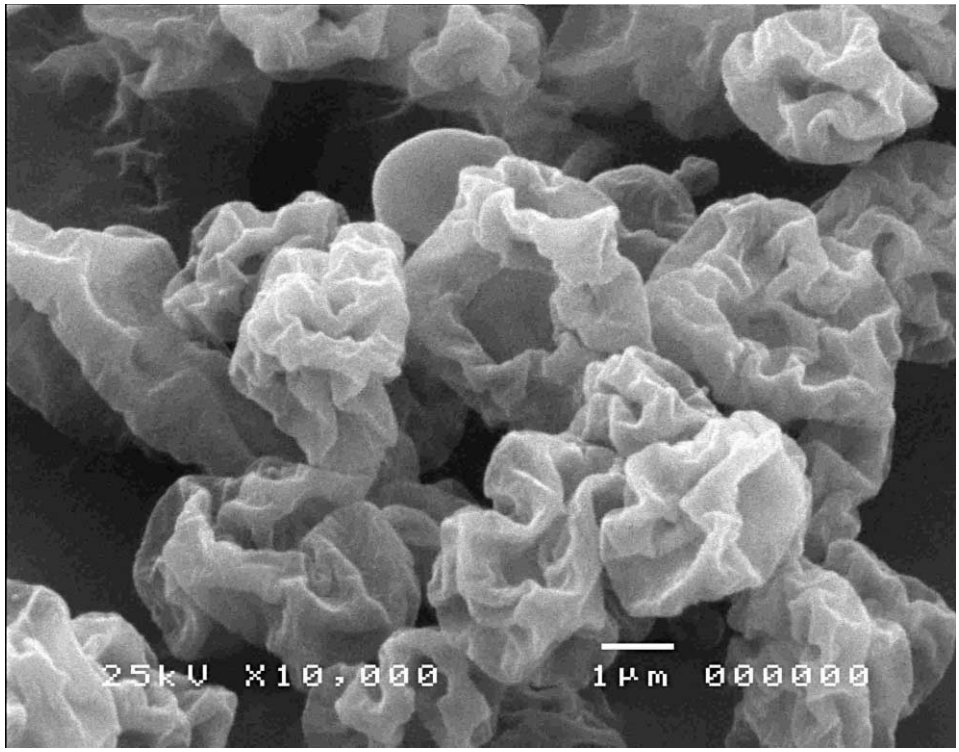
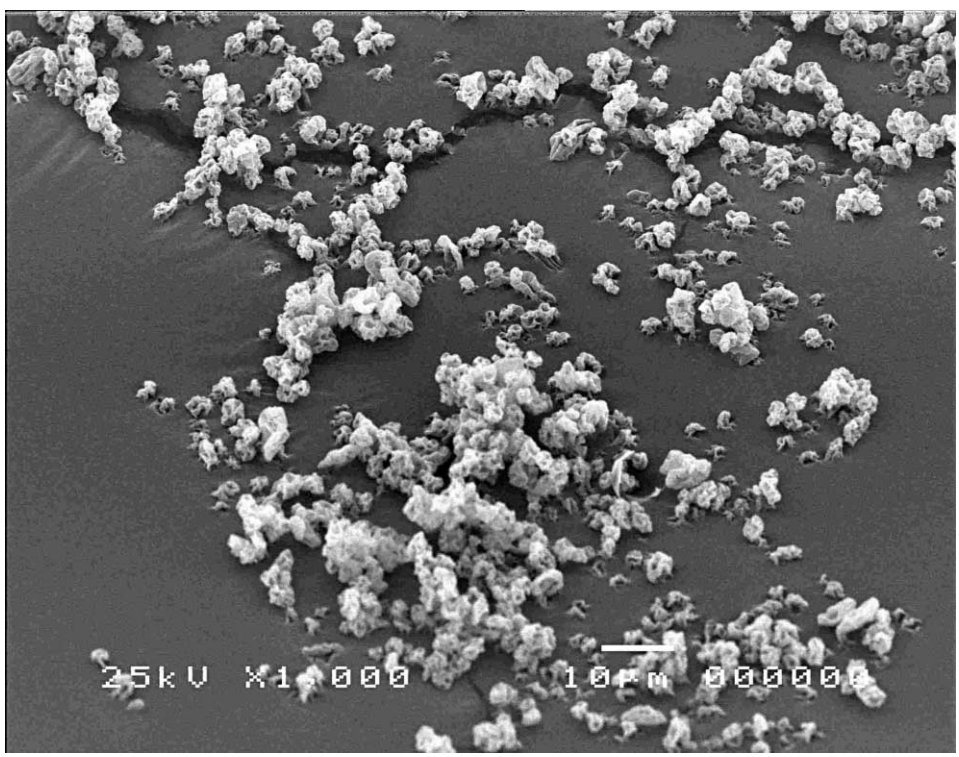


Fig. 1. Correlation between the yield and MMD.



(a)



(b)

Fig. 2. Scanning electron microphotographs of one of the spray dried batches. (a) The folded surfaces of the particles are seen at the higher magnification of 10 000 × . (b) An overview of the particles, at the lower magnification of 1000 × .

surface collapse. Broadhead et al., (1994), suggested that the increase in particle size might be an effect of increased agglomeration at the higher inlet air temperatures.

3.5. Morphology of the spray dried particles

All the surfaces of the spray-dried particles were folded. Scanning electron microphotographs from one of the batches are shown in Fig. 2a–b. All the different experiments generated particles with similar morphology and the effect of the process variables on this response could therefore not be evaluated by the factorial experimental design. Most particles seemed to be free primary particles. The conclusion of Broadhead et al., (1994), that agglomeration increases with increasing inlet air temperature, was thus not shown by this investigation. Maa et al. (1997), investigated the influence on morphology during spray drying of a model protein and concluded that decreased outlet air temperature gives rise to more regular, spherical particles, which was not shown in our study. The same researchers showed that the composition of the protein formulation also was of major importance. Addition of a surfactant to the formulation resulted in smoother outer particle surfaces.

3.6. Moisture content

The moisture content was 1.9–5.1% (Table 2). The content of moisture in the mainly amorphous starting material was 7.4%. Increased aspirator capacity and increased inlet air temperature both resulted in decreased moisture content (Table 3). This shows that increased supplies of heat energy allows a more efficient drying. Increased feed flow reduced the outlet air temperature, resulting in lower drying capacity and thus higher moisture content in the powder product. The correlation between moisture content and outlet air temperature shown in Fig. 3 is in agreement with previous reports (Broadhead et al., 1994 and Masters, 1985b). Labrude et al., (1989) showed that when spray drying oxyhemoglobin increased inlet air temperature decreased the moisture content.

The influence of the moisture content upon long time storage was outside the scope of this work. However, it should be mentioned that, in general, small particles within the inhalable size range may quickly adsorb moisture from air if they are hygroscopic and stick together in ways so that they are not dispersed prior to inhalation.

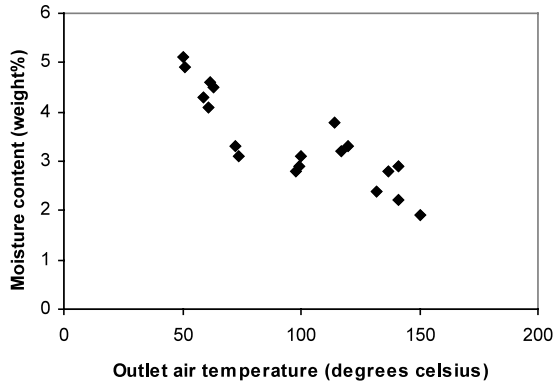


Fig. 3. Correlation between the moisture content and outlet air temperature.

3.7. Degradation of insulin

3.7.1. High molecular weight proteins

The fraction of HMWP was 0.3–3.3% (Table 2). The amount in the starting material was 0.3%. In some of the batches the HMWP consisted of dimers and in some of both dimers and oligomers.

According to Table 4, increased inlet air temperature was the main spray drying variable, which increased the aggregation of monomeric

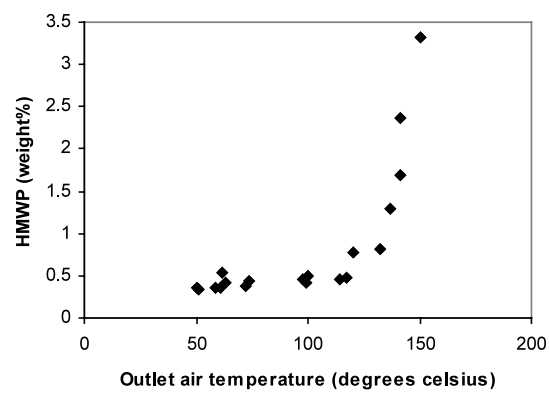


Fig. 4. Degradation to HMWP as function of the outlet air temperature.

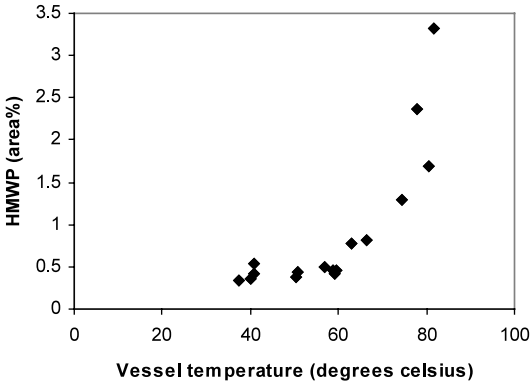


Fig. 5. Degradation of insulin to HMWP as a function of surface temperature of the product collection vessel. (Surface temperature values were missing for three runs so the number of runs used for the table is only 16).

insulin to HMWP. The outlet air temperature was also found to be important (Fig. 4). The correlation between inlet and/or outlet air temperature and degradation/activity upon spray drying has been found for other heat sensitive macromolecules (Daemen and van der Stege, 1982; Labrude et al., 1989; Broadhead et al., 1994). Fig. 4 shows that the degradation increased remarkably at an outlet air temperature of about 120 °C. Consequently, this is the highest outlet air temperature that can be accepted for insulin in order to avoid degradation to HMWP. When spray drying β-galactosidase Broadhead et al. (1994) observed that the residual activity was lost even at the lowest outlet air temperatures used. At an outlet air temperature of about 50–60 °C degradation occurred and at higher temperatures the loss of activity increased markedly. Increased aspirator capacity and interaction between the inlet air temperature and aspirator capacity ($T_{in} \times A$) was also found to increase the extent of aggregation (Table 4).

Pneumatic two fluid nozzles, like the one used in this report, are known to create high frictional forces over liquid surfaces during the disintegration of the liquid into the spray droplets (Masters, 1985b). However, no correlation between the atomization (nozzle) gas flow rate and the degradation to HMWP was to be found (Table 4). This indicates that insulin is not sensitive for the friction forces formed in the nozzle during atomization, at least not at the nozzle rates used.

The surface temperature of the product collection vessel ranged from 40–82 °C. A correlation was found between the surface temperature and the degradation to HMWP (Fig. 5). According to the figure, the surface temperature is not to exceed 60 °C in order to avoid degradation. However, it is difficult to predict whether this surface temperature in reality affected the product, since the highest outlet air temperatures also resulted in the highest surface temperatures of the vessel. In addition, there may be a time dependent effect due to the residence time in the product collection vessel. The first product powder particles were in the fastest run kept in the collector for 2 h 40 min and in the slowest run kept for 6 h 40 min. Future experiments could be made by using solutions of the same feed concentration, drying them for the same period of time at various outlet air temperatures during cooling of the collection vessel (e.g. with surrounding circulating cool water). Due to this the real effect on HMWP, depending on the outlet air temperature and surface temperature of the collection vessel, might be determined.

Increased quantities of HMWP were also correlated to decreased moisture content (Fig. 6). This is probably due to the fact that low moisture content is correlated to high outlet air temperature, which increases the degradation. A similar relationship was found for the other degradation products. Accordingly, the outlet temperature should be controlled to avoid degradation.

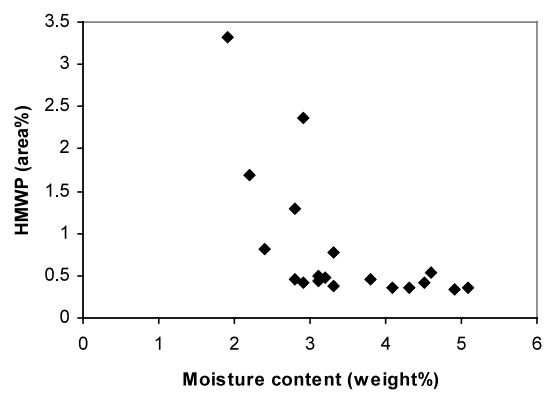


Fig. 6. Correlation between degradation to HMWP and moisture content.

3.7.2. A-21 desamido insulin

The content of A-21 desamido insulin (desamido) ranged from 0.3 to 0.9% (Table 2). The starting material had a content of 0.3%. The degradation seemed to be affected by the same process conditions discussed for HMWP. Increasing the inlet air temperature, aspirator capacity and the interaction between inlet air temperature and aspirator capacity ($T_{in} \times A$) increased the deamidation (Table 4). As for the aggregation to HMWP, the outlet air temperature is advantageously kept below 120 °C to avoid deamidation.

3.7.3. Other insulin related compounds

The content of OIRC ranged from 0.3 to 3.6% (Table 2). The original value in the starting material of insulin was 0.4%. As for the other degradation products (HMWP and desamido) high inlet air temperature, high aspirator capacity and the interaction of these (high $T_{in} \times A$) led to high amounts of OIRC (Table 4). The degradation profile theories used for HMWP are also shown to be valid for OIRC.

3.7.4. HMWP, desamido and OIRC—general

The contents of these degradation products were shown to be influenced by the thermal conditions of the spray drying process. Minor degradation occurred at outlet air temperatures below 120 °C. Thus, it is concluded that insulin is stable i.e. resistant against degradation, under mild spray drying conditions.

For other macromolecules, stabilization has been shown necessary during spray drying. Broadhead et al. (1994) found that β-galactosidase had to be stabilized by an excipient during the spray drying process. By using a formulation of β-galactosidase and trehalose it was shown that degradation did not occur at outlet air temperatures lower than about 100 °C. Spray drying of the pure β-galactosidase resulted in increased degradation at about 50 °C. Labrude et al., (1989) found that the oxidation of oxyhemoglobin during spray drying could be hindered by addition of sucrose.

3.8. Statistical optimization of process variables

A theoretical optimization was performed using statistical models to find the optimal settings of the spray drying variables to receive a product with the desired properties. Only optima within the experimental region were examined. All the product characteristics were considered equally important to the final product. The yield was ideally maximized and the particle size, moisture content, outlet air temperature, HMWP, desamido and OIRC were preferably minimized.

According to the statistical prediction the optimal values of the spray drying variables were: feed flow rate 300 ml/h, nozzle gas flow rate 550 l/h, inlet air temperature 100 °C and aspirator capacity 100%. By using these suggested process variables the resulting outlet air temperature is to be 61 ± 4 °C. A product with the following properties was predicted to be obtained: yield 54 ± 7%, MMD 2.9 ± 0.4 μm, moisture content 3.9 ± 0.5%, HMWP content 0.3 ± 0.1%, desamido insulin 0.3 ± 0.05% and OIRC 0.3 ± 0.1% (95% confidence level).

4. Conclusions

The effects of four variables (feed flow rate, nozzle gas flow rate, inlet air temperature and aspirator capacity) on the degradation and physical properties of spray dried insulin intended for inhalation have been evaluated by factorial experimental design. The degradation of insulin was found to be affected mainly by the process variables that determine the outlet air temperature i.e. inlet air temperature, aspirator capacity and feed flow rate. The outlet air temperature should be kept below 120 °C to avoid degradation. According to the theoretical optimization of the process the resulting outlet air temperature is to be 61 ± 4 °C.

The nozzle gas flow rate was shown not to influence the degradation of insulin.

The results show that spray drying of insulin can be performed to produce particles in the inhalable size range with negligible degradation. The process yields obtained in the investigation were relatively low, due to ineffective separation of the spray dried particles and air in the cyclone. For industrial purposes, more effective separators such as filter systems, have to be applied.

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