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Research Paper

Scaling Up the Spray Drying Process from Pilot to Production Scale Using an Atomized Droplet Size Criterion

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Purpose. The purpose of this study was to investigate the possibility of producing identical powders in pilot and production scale spray drying equipment by matching the droplet size distributions produced by two differently sized atomizers.
Methods. Particles were prepared by spray drying solutions of acetaminophen and polyvinylpyrrolidone K-30. The success of the up-scaling was evaluated by comparing the powders in terms of particle size distribution (laser diffraction), crystallinity (XPRD) and morphology (SEM). Furthermore, the influence of process parameters on other product characteristics such as stability and residual volatile content was also evaluated.
Results. The spray drying experiments resulted in spherical, amorphous particles with volumetric median diameters of typically 4–10 μm for pilot scale and 4–30 μm for production scale. The results showed that particles with similar morphology and crystallinity could be produced in the two applied spray dryers. However, scale-up based purely on matching droplet size distributions was not feasible.
Conclusions. The scale-up criterion did not account for the differences between the droplet-drying gas mixing and residence time distribution within the two spray dryers. Therefore, production scale experiments are required in order to obtain similar product characteristics as in pilot scale.

KEY WORDS: atomized droplet size criterion; microparticle characterization; pilot/production scale; scale-up; spray drying.

INTRODUCTION

Spray drying is a well-established technology for the production of solid particles (1–3). The process is very flexible with good possibilities to modify powder characteristics such as particle size, particle morphology, crystallinity and the amount of residual solvent. Many new drug candidates found by high throughput screening techniques are poorly soluble. The low solubility often results in a reduced dissolution rate and hence causes bioavailability problems. To achieve a better solubilization of a poorly soluble drug various approaches can be used, e.g. manipulation of the solid state properties of the drug and modification of the solvent by the addition of solubilization agents. The spray drying technique is often used for the production of amorphous powders (4). The amorphous form is often metastable and tends to revert to a more stable crystalline form. In order to improve the stability of the amorphous form of the drug, excipients are often included in the formulation. Excipients, which have been commonly recognized as stabilizing agents for amorphous materials, include the hydrophilic organic polymers: polyvinylpyrrolidone (5,6), various cellulose derivatives e.g. hydroxypropylcellulose (6), and hydroxypropylmethylcellulose (7). The proposed mechanism for the stabilizing effect of these polymers is an increase in glass transition temperature of the binary mixture and in some cases specific drug polymer interactions (8–10). Aqueous solutions or suspensions of drug and excipients are most commonly spray dried, but organic volatiles are also frequently used as solvents/dispersing agents. Spray drying using organic solvents is typically carried out using nitrogen as drying gas in a closed-cycle spray drying plant. The organic solvent is condensed out of the exhaust gas before being recycled to the drying chamber. Closed-cycle spray drying is done primarily for environmental reasons and can affect the drying process through the amount of solvent in the drying gas (4).

Optimization of the spray drying process involves evaluation of parameters related to the spray drying process as well as to the properties of the sprayed feed formulation. The influence of various process and formulation parameters on powder characteristics has previously been described in several articles, e.g. by Maa *et al*, Esposito *et al*. and Tewa-tagne *et al*. (11–13). Even though spray drying can be considered to be a well established technology, the scaling up from pilot to production plant is still a relatively unexplored research area. Most of the research published describes scale-up within the same equipment (14) or covers scale-up from

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laboratory to pilot plant (15). Only a few papers deal with spray drying in production scale (16,17), and none of these studies aimed at matching certain product characteristics such as particle size distribution. According to Zlokarnik (18), it is not surprising that scale-up of spray dryers has not been studied in detail. The simultaneous heat and mass transfer makes the process complex and non-linear. Therefore, intuition and practical experience are used for industrial design (18).

When scaling up a spray drying process, several areas have to be analyzed, as the overall drying process is composed of the following steps (4):

1. Atomization
2. Mixing of droplets and drying gas
3. Drying (drying kinetics and residence time)
4. Separation

Ideally, one would have to match all four criteria in order to maintain geometric, kinematic and dynamic similarity of the process when scaling up. Scale-up from a pilot to a production scale spray dryer will often require the use of an atomizer with a larger dimension. Therefore, atomization is considered as one of the most important issues in up-scaling. In a previous study, operating conditions resulting in matching droplet size distributions for a pilot and a production scale co-axial, externally mixing two-fluid nozzle was determined (19). In order to investigate the possibility of producing identical powders in pilot and production scale spray drying equipment by matching the droplet size distribution, these operating conditions are implemented in this study. Other operating conditions were fixed in order to minimize differences in the remaining areas.

It is prerequisite to have a detailed understanding of the spray drying process from laboratory or pilot scale experiments before scaling up. Furthermore, the spray dried powders obtained in small scale must be well characterized. In the current study, acetaminophen was chosen as model drug and polyvinylpyrrolidone K30 (PVP-K30) as the dispersion agent. Solid dispersions of acetaminophen and PVP have been prepared and characterized before. The applied methods include the spray drying method (20) as well as a variety of other methods (21,22). The system is regarded as well characterized and was therefore chosen as a good representative for studying the aspects of scale-up. The first part of this paper evaluates the effects of the spray drying process, i.e. the operating conditions. The effects are verified by way of specific product characteristics of the spray dried powder obtained in pilot scale. Effects related to the feed formulation are evaluated in addition. The second part of this paper covers the aspects of scaling up from pilot to production scale. As scale-up criterion, matching atomizer droplet size distributions are evaluated.

MATERIALS AND METHODS

Materials

Demineralized water from in-house supply was used. Ethanol 99.9% (CAS 64-17-5) was supplied by V&S Distillers (Aalborg, Denmark), acetaminophen (CAS 103-90-2) from Mallinckrodt Inc (NC, USA), and polyvinylpyrrolidone K30 (PVP-K30; CAS 9003-39-8) obtained from ISP Switzerland AG (Baar, Switzerland). Nitrogen (≥99.5%, pharmacopoeia grade) was used as atomization and drying gas.

Preparation and Properties of Feed Solutions

Acetaminophen and PVP-K30 in the different concentrations and ratios were dissolved in ethanol 99.9%. The compositions of the various feed solutions are found in Table I.

Methods

Fig. 1 provides a schematic illustration of the experimental spray drying set-up used in this study. This set-up was used both for the pilot and the production scale experiments. A more detailed description of the spray drying process is found in the following sections.

Pilot Scale Spray Drying

The pilot scale experiments were carried out using a Mobile Minor spray dryer (GEA Niro A/S, Soeborg Denmark) with the dimensions: Chamber diameter 0.8 m, cylindrical height 0.84 m and a 60° cone. The atomizer was a Niro Mobile Minor Two-fluid Nozzle (GEA Niro A/S, Soeborg Denmark) mounted with a 1.0 mm liquid orifice diameter and 2.0 mm atomization gas annular. A peristaltic pump (Watson Marlow, Cornwall, England) was used to pump the feed to the atomizer. The spray drying was carried out in a co-current mode using nitrogen as drying gas at a rate of approximately 70 kg/h. An atomization gas flow rate of 9.0 kg/h was used for all experiments. When the plant was operated in closed-cycle, ethanol was condensed in a surface condenser cooling the gas to approximately −16°C. Hereby, the solvent content was reduced to approximately 2 g EtOH/kg N_2 before being recycled. The resulting process parameters were dependent on the experiment. The spray dried products were collected under the cyclone and kept in a dessicator until the characterization. All process parameters were recorded

Table I. Compositions and Properties of Feed Solutions

Feed solution	Total solid conc. (% *w*/*w*)	Drug/polymer ratio	Acetaminophen conc. (% *w*/*w*)	PVP-K30 conc. (% *w*/*w*)	Viscosity at 20°C (10^{-3} Pa·s)	Surface tension (10^{-3} N/m)
Solution A10	10	1:2	3.3	6.7	4	23
Solution B10	10	1:9	1.0	9.0	5	23
Solution A20	20	1:2	6.7	13.3	14	23
Solution B20	20	1:9	2.0	18.0	20	23

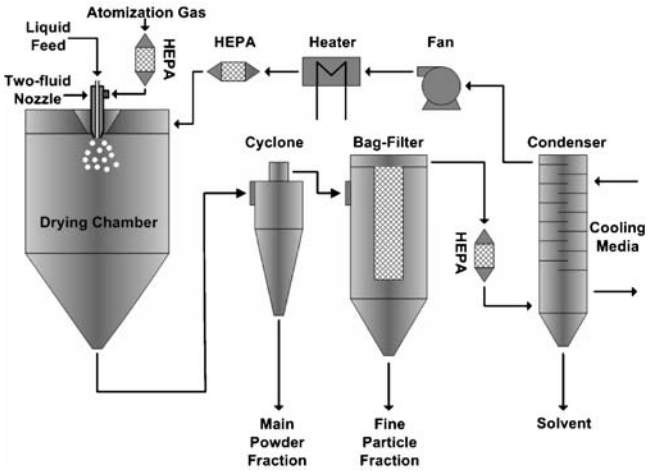

Fig. 1. Schematic illustration of the experimental spray drying set-up.

continuously during each experiment. From the pilot scale closed-cycle experiments, a number of experimental conditions were selected for scale-up to production scale.

Experimental Design for Pilot Scale Spray Drying

The influence of five parameters on product characteristics obtained in pilot scale was determined. The parameters were: Outlet temperature, liquid feed flow rate, solids concentration of the feed solution, drug/polymer ratio, spray dryer operation (open-/closed-cycle). The outlet temperature is reported during the process, but cannot be directly controlled, i.e. it is controlled indirectly by way of the other spray drying parameters. However, as the particles are exposed to a temperature equal to the outlet temperature for the longest time during the spray drying process, i.e. in the collection device, it was selected as parameter. The outlet temperature does not refer to the particle temperature but to the measured temperature of the outlet gas. In this study, two levels of each parameter was studied. The levels of spray drying operating conditions and feed properties were chosen on behalf of preliminary experiments. The levels used in this study were varied in accordance with Table II. The inlet temperature was varied in order to adjust the outlet temperature in the individual experiments.

The experimental setup suggested in Table II gives a total of $2^5=32$ experiments, 16 performed in open-cycle and 16 in closed-cycle. All the experiments performed in closed-cycle were carried in duplicate in order to evaluate the repeatability of the spray drying process.

Production Scale Spray Drying

The production scale experiments were performed in a SD-12.5 closed cycle plant (GEA Niro A/S, Soeborg Denmark) with the dimensions: chamber diameter 2.5 m, cylindrical height 2.5 m and a 60° cone. The atomizer was a Schlick-05 two-fluid nozzle (Düsen-Schlick, Untersiemau, Germany) with a liquid orifice diameter of 4.0 mm and an atomization gas cap with a diameter of 10.0 mm. The feed was supplied to the atomizer by a Mono-pump (Netzsch Mohnopumpen GMBH, Waldkraiburg, Germany). The spray drying was carried out in co-current mode using nitrogen as drying gas. The flow rate of the drying gas was approximately 1,250 kg/h, and the atomization gas flow rate varied from 70 kg/h to 210 kg/h. All experiments were carried out as closed-cycle with the gas in the condenser cooled to approximately −16°C. The spray dried products were collected under the cyclone.

Characterization of Spray Dried Powder

Particle Morphology

Shape and surface of the particles were determined by SEM (scanning electron microscopy) (JSM 5200, JEOL, Tokyo, Japan). The samples were mounted on stubs using double faced adhesive tape and sputter coated for 120 s. with a thin gold–palladium layer in an auto sputter coater (E5200, BIO RAD, Watford, England). An acceleration voltage of 10 kV, and a working distance of 20 mm were used for the experiments.

Particle Size Distribution

The particle size distribution of the spray dried powders were analysed by means of laser diffraction. The measurements were carried out using a Malvern Mastersizer S (Malvern Instruments, Worcestershire, UK) with a MS7 magnetically stirred dry sampling system and a lens with a focal length of 300 mm. A pressure of 2 bar was used to disperse the particles. The particle size was given by D_{50} (Volume Median Diameter). It was necessary to modify all particle size distribution measurements by removing all measured particles with a size above 88.91 μm (channel 15). Micrographs of the produced powders showed that all primary particles were smaller than 88.91 μm and tended to form aggregates. Therefore, the information from the micrographs supported the performed data modification.

Total Content of Volatiles

The total content of volatile substances was determined on a HR73 halogen moisture analyzer (Mettler Toledo, Greifensee, Switzerland). The samples were kept at 105°C until constant weight. The total content of volatiles in the samples corresponds to the weight difference between the sample at room temperature and the sample dried at 105°C.

Ethanol Content

The residual content of ethanol was determined by gas chromatography. A 100 mg sample was dissolved or dispersed in 2 ml of demineralised water in 22 ml headspace vials and

Table II. Parameters and Levels Studied in the Pilot Scale Experiments

Parameters	Levels	
Outlet temperature	40°C	65°C
Liquid feed flow rate	1.5 kg/h	2.5 kg/h
Total solids concentration	10% *w/w*	20% *w/w*
Drug/polymer ratio	1:2	1:9
Spray dryer operation	Open-cycle	Closed-cycle

sealed with gas-tight caps. The system consisted of a Perkin Elmer AutoSystem GC configured with flame ionization detector (Perkin Elmer, Norwalk, CT, USA). Samples were injected via a HS 40 Headspace sampler (Perkin Elmer, Norwalk, CT, USA). The samples were kept in the headspace sampler at 90°C for 30 min. before injected into the GC. A DBwax column (30 m length×0.32 mm i.d.×0.5 μm film thickness, J&W Scientific, Folsom, CA, USA) was used. Helium was used as carrier gas at 15 psi. Oven, injector and detector temperature was 40°C, 200°C and 250°C, respectively. The ethanol content in the samples was calculated from the GC area from the samples and a GC area from a standard solution with known ethanol content.

X-Ray Powder Diffraction (XRPD)

The data were collected on a Philips X'Pert Pro MPD diffractometer (PANalytical, Almelo, The Netherlands) using monochromated Cu $K\alpha$ radiation (40 kV/50 mA) and 0.04 Rad Soller slits. In both the incidence and diffracted beam, path 1° slits were used. All diffractographs were measured over the 2θ range 5–30° with a step size of 0,04° and a measuring time of 3 s per step.

Isothermal Microcalorimetry

The heat flow of the samples was monitored for up to 7 days under constant temperature (25°C) and different relative humidity (60% and 75%). A 2277 Thermal Activity Monitor (Thermometric, Sweden) was used for the determination, and the miniature humidity technique (23) was employed for the purpose. Approximately 10 mg of sample was placed into a small glass ampoule together with a small container filled with salt solution and then sealed hermetically. A reference ampoule without any sample was prepared accordingly. The salt solutions were prepared as described by Angberg *et al.* (24). The ampoules were immediately transferred to the calorimeter, equilibrated at 25°C and placed in the equilibrium position. After 20 min, the samples were put in the measuring position. This time point was settled to be the zero point on the timescale.

RESULTS

Pilot Scale Spray Drying

All product characteristics were found to be unaffected of the operating mode (open-/closed-cycle). Therefore, the issue will not be discussed further in this paper, and only the results obtained in closed-cycle will be presented here. Table III provides an overview of the spray drying conditions together with the measured particle size and the residual content of ethanol for the two replicates of experiments performed in closed-cycle.

Repeatability and Product Yield

It is evident from Table III that the repeatability of the process was acceptable. In general, the difference between the two replicates was below 10% regarding both the ethanol content and the particle diameter.

In all experiments, except experiments with solution B20, the product yield from the cyclone was above 70%. For solution B20, the yield ranged from 17% to 85%. The low yield could be ascribed to atomization difficulties.

Particle Size Distribution and Porosity

Assuming that one droplet dries into one particle, the final size of the particle is directly related to the concentration of the feed solution (25). The relationship between the diameter of the particle, D_P, and the droplet diameter, D_D, can be approximated by Eq. 1:

$$D_P \approx D_D \cdot \left[\frac{\rho_D}{\rho_P} \cdot x_s\right]^{1/3} \quad (1)$$

Table III. Spray Drying Conditions and Product Characteristics for the Two Replicates of Experiments performed in Closed-Cycle in Pilot Scale

Test	Solid conc. (% *w/w*)	Drug/polymer ratio	Feed flow rate (kg/h)	T_{out} (°C)	Residual ethanol content(% *w/w*)		D_{50} (μm)	
					Rep.1	Rep.2	Rep.1	Rep.2
1	10	1:2	1.5	40	4.7	4.8	4.1	4.0
2	10	1:2	2.5	40	5.5	5.1	4.9	4.9
3	10	1:9	1.5	40	6.2	6.3	5.2	5.2
4	10	1:9	2.5	40	7.0	7.3	5.9	7.5
5	10	1:2	1.5	65	3.1	2.9	3.9	4.0
6	10	1:2	2.5	65	3.6	3.7	5.1	4.9
7	10	1:9	1.5	65	3.3	4.2	5.0	4.6
8	10	1:9	2.5	65	5.2	5.1	5.2	5.6
9	20	1:2	1.5	40	5.2	5.3	6.4	5.8
10	20	1:2	2.5	40	6.1	6.9	7.2	8.5
11	20	1:9	1.5	40	6.4	6.6	7.2	6.9
12	20	1:9	2.5	40	7.5	8.0	10.0	10.3
13	20	1:2	1.5	65	3.9	3.5	6.2	5.8
14	20	1:2	2.5	65	4.4	4.6	7.4	7.4
15	20	1:9	1.5	65	4.9	4.7	7.3	7.9
16	20	1:9	2.5	65	5.2	5.7	9.5	9.8

where ρ_D is the droplet density, ρ_P the particle density, and x_S the total concentration of solids in the droplet. The formula assumes spherical droplets and particles, negligible volatile content in the particles, and that all droplets contain the same concentration of solids. For calculation of the minimum particle size, the true density should be used as particle density (calculated assuming additive volumes).

The measured mean particle size varied between 3.9 and 10.3 μm. The particle size distributions were broader for the concentrated solutions. The span, calculated as D_{90}–D_{10}/D_{50}, was >2.0 for the 20% *w*/*w* and <2.0 for the 10% *w*/*w* feed solutions. The mean particle size was related to the concentration of solids in the feed solution. In general, the particles obtained after spray drying the 20% *w*/*w* feed solutions were 32–105% (average of 63%) larger than for the 10% *w*/*w* solutions. Thus, smaller particles were obtained with the lower concentrated feeds. Another parameter affecting the particle size was the atomization gas to liquid flow rate mass ratio (ALR). According to Masters (1), the ALR is the most important variable involved in the control of droplet size for a two-fluid nozzle. In a previous study it was shown that the droplet size decreased as the ALR increased (19). Therefore, it was also expected that smaller particles could be obtained, if the atomization was done at higher values of ALR. As evident from Table III, the obtained data met our expectations. The particles obtained after spray drying with a feed rate of 2.5 kg/h (low ALR) were 9–73% (average of 33%) larger than the particles obtained with a feed rate of 1.5 kg/h (high ALR). Furthermore, the measured particle sizes were larger for the solutions containing a higher content of polymer when comparing experiments with same total solid concentration. Again, this could be a result of larger droplets due to increased viscosity (19) or differences in morphology as presented later.

Calculations of the theoretical particle diameter from the volumetric droplet diameter of the solutions suggested a porous interior of the particles. The measured particle diameters (D_{50}) were considerably higher than the ones calculated from droplet diameters. The porosity, ε_P, of the particles can be estimated by Eq. 2:

$$\varepsilon_P = 1 - \left(D_{P,\,calculated}/D_{P,\,measured}\right)^3 \qquad (2)$$

For the produced powders, particle porosities up to 60% were calculated. Due to the number and nature of the assumptions in calculating the porosity, the exact value can be discussed. However, it can be used as an indication of porosity. The results show no general relation between the estimated porosity and the five investigated parameters, although there seems to be a tendency towards higher particle porosity with higher polymer content and lower feed flow rates.

Residual Content of Volatiles

The amount of residual ethanol in the spray dried product may affect the long term stability. The content of ethanol after drying ranged between 2.6% and 8.0% depending on the operating conditions. Table III shows that higher outlet temperature, lower feed flow rate, lower concentration of solid, and a lower drug/polymer ratio minimize the content of ethanol.

Particle Morphology

Shape, size and surface morphology of the spray dried powders were evaluated by means of scanning electron microscopy. Representative micrographs are presented in Fig. 2. Depending on the composition of the solution being dried and the drying temperature, the surface of the spray dried particles appeared different. When drying at the higher outlet temperature, the 1:2 drug/polymer ratio solutions resulted in spherical particles with a smooth surface, whereas a rougher surface was observed when drying at the lower outlet temperature. Independent of the outlet temperature, the solutions with the 1:9 drug/polymer ratios tended to form a rough surface. No incidence of drug crystals was observed on the surface of any of the spray dried particles.

Atomization difficulties are evident from the micrographs of the powders resulting from solution B20 (Fig. 2B,D). As seen, threads of polymer make the particles stick together. This occurrence was not a consequence of the drug/polymer ratio, as powders resulting from solution B10 showed no polymer threads.

Crystallinity

Fig. 3 shows the comparison of PXRD of acetaminophen starting material, PVP-K30 as received from supplier, two physical mixtures (drug/polymer ratio 1:2 and 1:9), and two examples representative of the spray-dried material. The X-ray diffraction pattern of the drug showed intensive peaks at 2θ values of 12.18, 15.54, 18.18, 20.46, 23.50, 24.38 and 26.58, indicating its crystalline nature. The positions of all peaks were characteristic to the monoclinic polymorph I of acetaminophen (26). PVP-K30 being amorphous showed a halo diffraction pattern. For the physical mixtures, the intensity of the diffraction peaks decreased with increased ratio of added polymer, but the crystallinity was still confirmed. This observation was in agreement with previously recorded results after mechanical mixing in Turbula Mixer (21).

The absence of crystallinity for the spray dried powders could be explained by the formation of a solid dispersion, where acetaminophen was either dissolved in PVP-K30 or was precipitated in the amorphous state. Thus mixing must occur at a molecular level in order to alter the crystallinity of the drug compound. The same tendency has previously been reported for a number of other drug compounds (27).

Stability

From previous studies (22,28), the crystallization potential of amorphous acetaminophen is known, and also the stabilizing effect of PVP has been verified (22). Therefore, only a short term stability study was conducted in order to confirm that the stability was not affected by the preparation method used in this study.

The measurements were performed on two formulations prepared under similar operating conditions but with different drug/polymer ratio. In Fig. 4, only the heat flow curves for measurement at 75% RH are shown. Instantaneously after applying gas containing vapour to the samples, a decrease in the heat flow was observed. The decline in heat flow was due to the absorption of water. The uptake of water continued

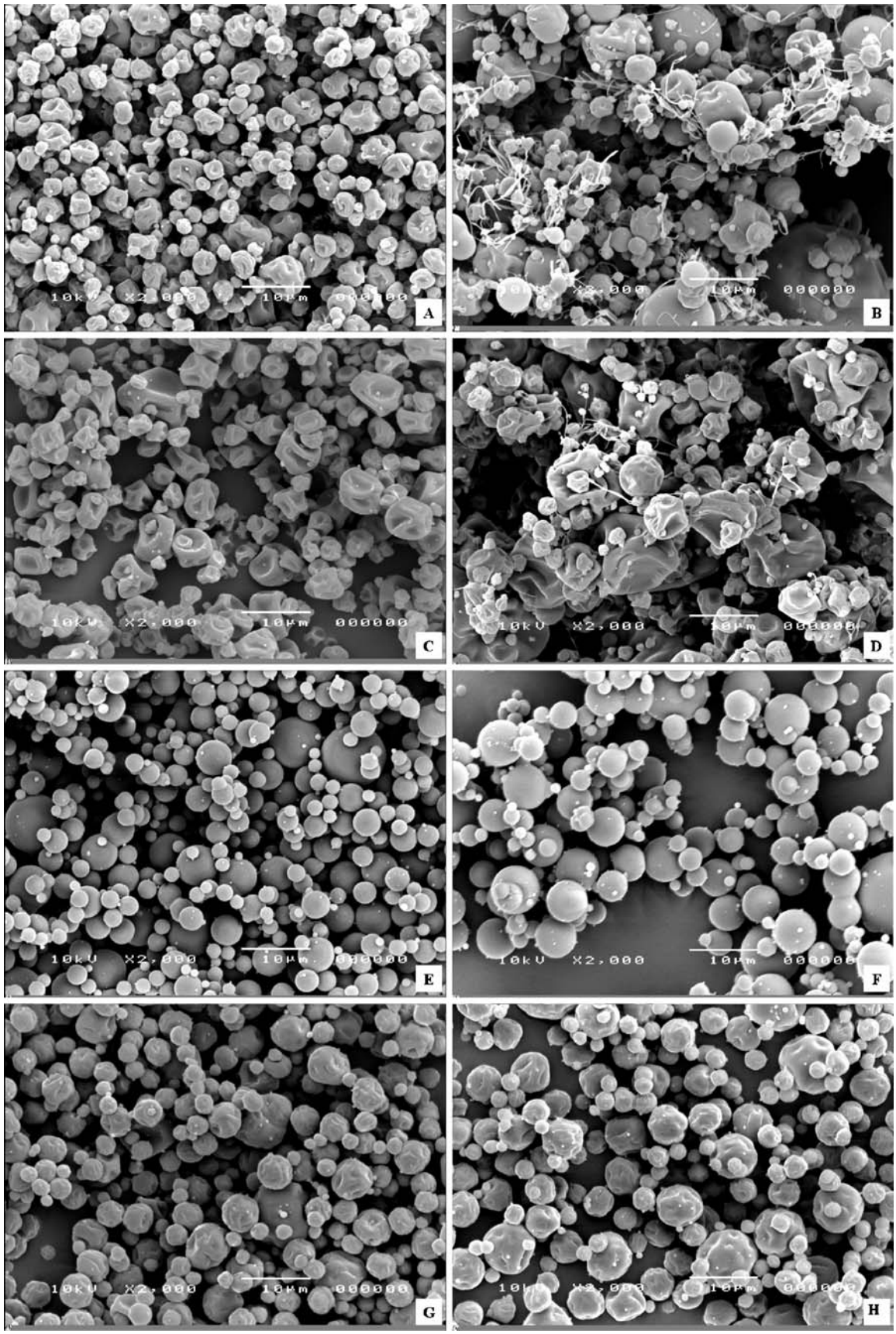

Fig. 2. Scanning electron micrographs of powders obtained from closed-cycle pilot scale spray drying. Feed flow rate of 1.5 kg/h. **A** Solution B10 T_{out}=65°C, **B** Solution B20 T_{out}=65°C, **C** Solution B10 T_{out}=40°C, **D** Solution B20 T_{out}=40°C, **E** Solution A10 T_{out}=65°C, **F** Solution A20 T_{out}=65°C, **G** Solution A10 T_{out}=40°C, **H** Solution A20 T_{out}=40°C. The *horizontal bar* marks 10 μm.

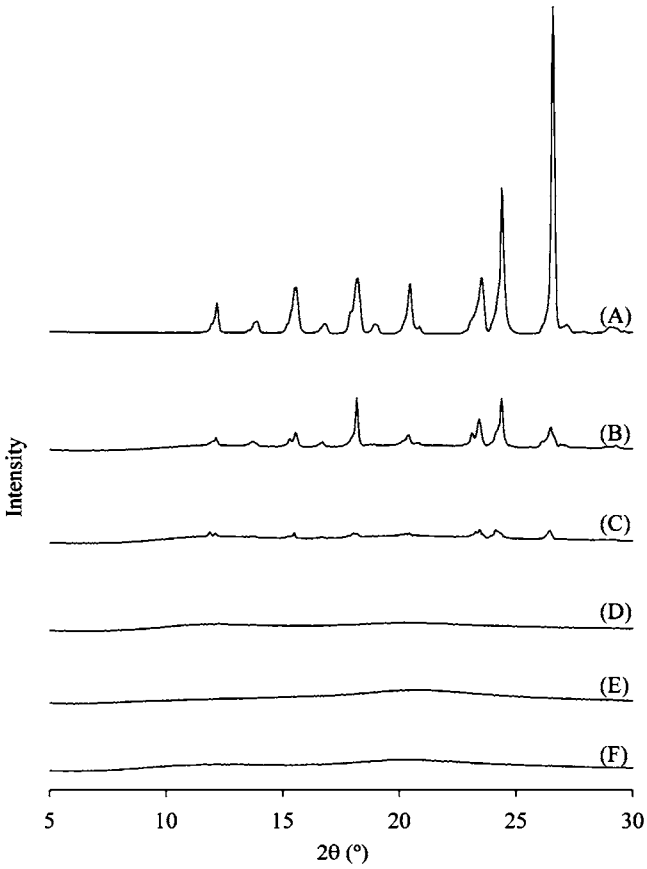

Fig. 3. X-ray diffraction patterns of starting materials and mixtures. **A** Acetaminophen, **B** 1:2 *w/w* physical mixture, **C** 1:9 *w/w* physical mixture, **D** PVP-K30, **E** 1:2 *w/w* ratio spray dried material and **F** 1:9 *w/w* ratio spray dried material.

longer for the formulation with a high amount of polymer, even though the uptake reduced to about zero within 20 h for both formulations. When storing the samples at lower humidity, the water uptake occurred slower for both formulations (data not shown). At both 60% and 75% relative humidity, no exothermic crystallization reactions were observed for any of the samples. This was confirmed by a humidity chamber X-ray measurement performed immediately after the microcalorimtric stability study, where no peaks were observed in 24 h.

Decreased molecular mobility in combination with interactions between acetaminophen and PVP are suggested to contribute to an increased stability (22) not present for the pure amorphous form of acetaminophen (28).

Production Scale Spray Drying: Scale-Up

Considering the results from the pilot scale experiments, feed solutions with a drug/polymer ratio of 1:2 (Solution A10 and Solution A20) were chosen to be spray dried in the production scale spray dryer. The nozzle operating conditions were based on previous findings (19). Even though the droplet size measurements were carried out with water, they were used to evaluate matching droplet size distribution as scale-up criteria in this study. The operating conditions used for the up-scaling experiments based on matching droplet size distributions are shown in Table IV. Thus, both the feed and the drying gas flow rates will be scaled up 18 times, whereas the atomization gas flow rate is only increased 8 times. The rationale behind increasing the atomization gas flow rate less than the other parameters was to obtain similar droplet size distributions, i.e. the ALR where the two nozzles produced similar droplet sizes was lower for production scale nozzle than for the pilot scale nozzle.

Particle Size Distribution

Fig. 5 presents the particle size (D_{50}) as a function of ALR for the feed solutions spray dried in production scale. When using the operating conditions presented in Table IV (marked with an arrow in Fig. 5), the particles produced in production scale were larger than the particles produced in pilot scale (shaded area). Therefore, up-scaling based on matching atomizer droplet size distributions was not successful. This criterion did not account for all the differences between the two spray dryers during the drying of the particles. In order to account for these differences during scale-up, other operating conditions were investigated. Equal

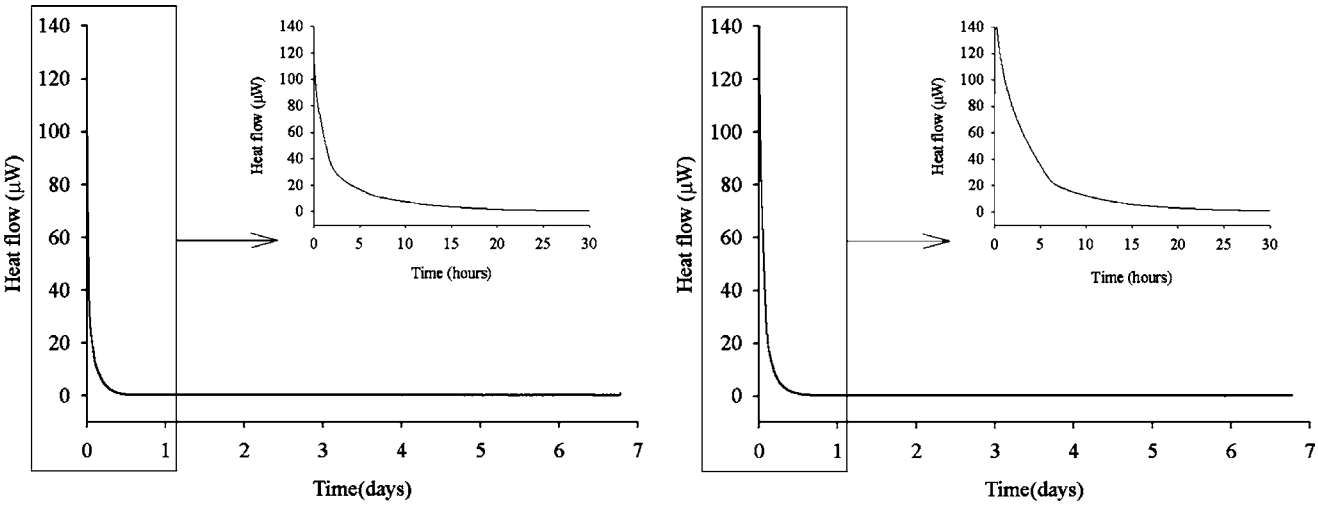

Fig. 4. Heat flow curves for spray dried mixtures of acetaminophen and PVP-K30 with ratio1:2 (*left*) and 1:9 (*right*) monitored at 75% relative humidity.

Table IV. Operating Conditions for Experiments done in Pilot and Production Scale

	Closed-cycle pilot scale	Closed-cycle production scale
Drug/polymer ratio	1:2	1:2
Feed flow rate (kg/h)	2.5	45
Atomization gas flow rate (kg/h)	9.0	73.0
Drying gas flow rates (kg/h)	70	1,250
Total concentration of solids (% *w*/*w*)	10 or 20	10 or 20
T_{out} (°C)	40 or 65	40 or 65

to the experiments performed in pilot scale, the particle size decreased as the ALR was increased. Fig. 5 shows that for solution A10 it was possible to produce particles in the same size range as obtained in pilot scale only by adjusting the ALR. This was found not to be the case for solution A20. Even with the largest values of ALR it was not possible to produce particles as small as obtained in pilot scale if a feed flow rate of 45 kg/h was used. Therefore, lower feed flow rates were tested. The results for solution A20 spray dried in production scale are presented in Table V. Particle sizes from the pilot scale experiments are also included in this table. When comparing the size of the particles produced in pilot scale with the ones produced in production scale, it is evident that it is possible to obtain particles of equal sizes by using lower feed flow rates.

Similar to the pilot scale experiments, the particle size was influenced by the total concentration of solid in the feed. Thus, the largest particles were obtained from solution A20. In contrast to the pilot scale experiments, the size of the particles resulting from solution A20 was different for the two outlet temperatures. As evident from Fig. 5, the particles produced with the higher outlet temperature were remarkably larger compared to the ones dried at the lower temperature. Therefore, differences in temperature profile and residence time are expected to exist between the two dryers. As these differences will influence on the product, the scale-up cannot be based on a single criterion such as matching droplet size distribution.

Particle Morphology

As for the pilot scale spray drying, the particles spray dried in production scale were spherical in shape. The smoothness of the surface is related to the reported outlet temperature, i.e. the lower outlet temperature, the rougher surface. Fig. 6 shows representative micrographs of powder obtained after spray drying in production scale with an outlet temperature of 65°C. It is evident from Fig. 6A that some of the particles are hollow. Interestingly, this effect was only visible for solution A20 when operating at low ALRs (Fig. 6A), whereas for the higher ALRs no blow holes could be observed (Fig. 6B). For solution A10, no hollow interiors of the particles were evident on the micrographs. In addition, it appears from the micrographs that droplet/particle collisions have occurred during the drying process.

DISCUSSION

The spray drying process is a method primarily used for the isolation of dry materials from solutions or suspensions. However, the spray drying method has also been used to modify the solid state properties of drugs. In this study, formulations of acetaminophen and PVP-K30 were produced both in pilot and production scale spray dryers and subsequently characterized. The scale-up criterion for maintaining a constant droplet size distribution was not sufficient to ensure equivalent performance during scale-up of the spray drying process. When scaling up, an increase in the mean volumetric diameter of the particles was seen for both solution A10 and solution A20. The increase was more pronounced for the feed with the higher concentration. The shift towards larger particle size could be attributed to differences in drying conditions in the two spray dryers. This section is devoted to discuss possible reasons for the missing success in using matching droplet distribution as scale-up criterion.

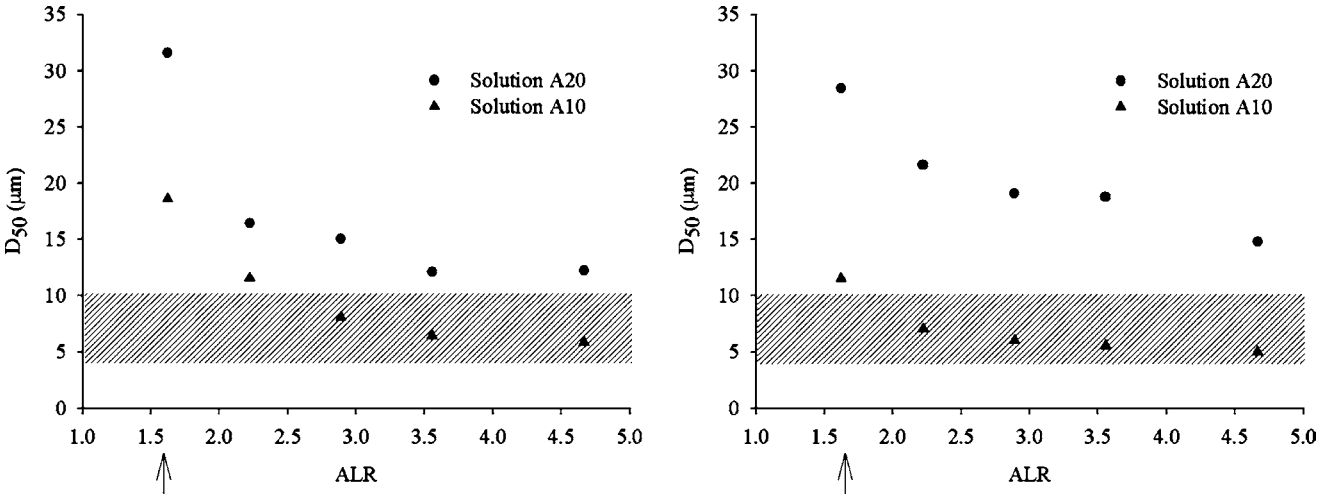

Fig. 5. Particle size (D_{50}) as function of ALR for the two feed solutions spray dried in production scale. Feed flow rate=45 kg/h. Atomization gas flow rates varied between 70 and 210 kg/h. T_{out}=40°C (*left*) and T_{out}=65°C (*right*). The *arrows* represent the ALR value used to produce similar droplet size distribution as in pilot scale. The *shaded areas* illustrate the particle size range obtained in pilot scale.

Table V. Production Scale Operating Conditions used to Produce Particles with Similar Particle Sizes as Obtained in Pilot Scale for Solution A20

	Gas flow rate (kg/h)	Feed flow rate (kg/h)	D_{50} (μm)
Pilot scale, T_{out} 40°C	9.0	2.5	7.9
Production scale, T_{out} 40°C	210	45	12.3
	210	35	9.7
	210	25	7.9
Pilot scale, T_{out} 65°C	9.0	2.5	7.4
Production scale, T_{out} 65°C	210	45	14.8
	210	35	11.1
	210	25	6.7

Drying kinetics is a subject of paramount importance with regard to particle characteristics. In a previous study, single droplets of the same feed solutions, as used for these experiments, were dried in a drying kinetics analyzer while studied (Brask *et al.*, Proceedings of the 6th international conference on multiphase flow, 2007). Here it was observed that the precipitation of solids occurred by skin formation. The skin was formed within seconds, enclosing the solvent still present internally. Although the droplets injected to the levitator were much larger than the droplets formed after atomization by a two-fluid nozzle, the morphology of the final particles was found to be quite similar. Furthermore, the study supported the idea of the particles having a more or less hollow interior. The information from these experiments is very valuable, and many of the topics discussed here originate from the knowledge of the drying behaviour.

Droplet/particle residence time is of great importance in spray drying, as it is one of the factors influencing on particle characteristics. In addition, both the chemical and physical stability could be affected by this parameter. Furthermore, the residence time profile becomes very important in this study, as the boiling point of ethanol is found between the inlet and outlet temperature. If the particles are exposed to temperatures above the boiling point, inflation will be more likely (1). This statement is supported by the data in Fig. 5 that shows increased particle size for the high outlet temperature compared to the low for solution A20. Furthermore, this is supported by the SEM-micrograph in Fig. 6A, which shows the particles to be thin-walled shells. Blowholes are also visible on almost all individual particles. There is geometric similarity between the pilot scale and production

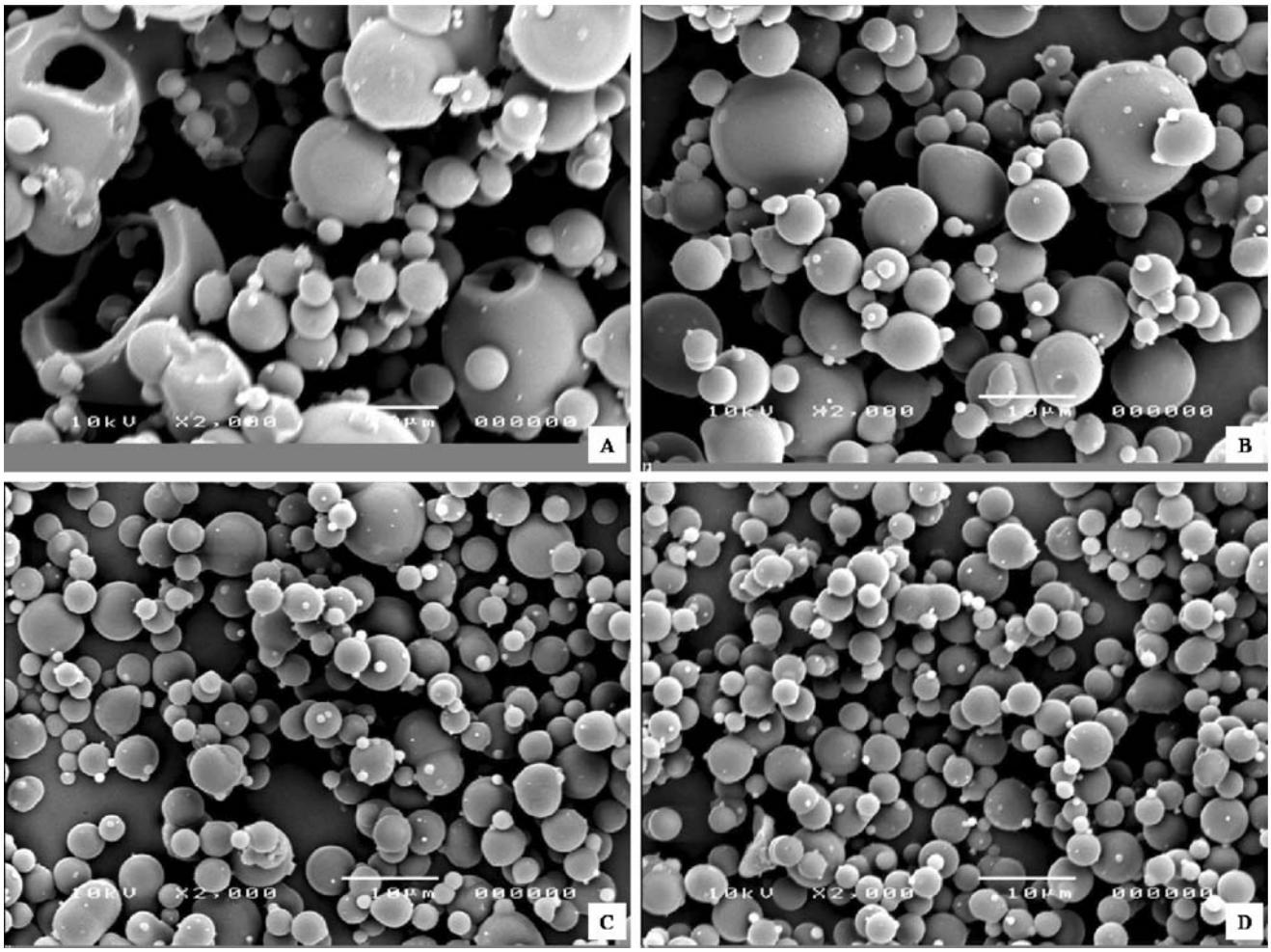

Fig. 6. Scanning electron micrographs of powder obtained after production scale spray drying. Atomization gas flow rate=210 kg/h. T_{out}=65°C. **A** Solution A20 feed flow rate of 45 kg/h **B** Solution A20 feed flow rate of 25 kg/h **C** Solution A10 feed flow rate of 45 kg/h **D** Solution A10 feed flow rate of 25 kg/h.

scale spray dryer as the ratio of the drying chamber diameter to cylinder height is 1 for both the pilot (diameter and cylinder height 0.8 m, cone angle is 60°) and the production plant (diameter and cylinder height 2.5 m, cone angle is 60°). However, if the residence time is based on the spray dryer chamber volumes and the combined process gas flow rate (atomization gas + drying gas), it is found that the average residence time is almost twice as long in the production scale spray dryer as in the pilot (~40 s and ~20 s), i.e. the two spray dryers are not kinematically similar. The "true" particle residence time is very difficult to determine, and the values provided here can only be used as guidelines. Even though the subject is a highly complex area and still in its infancy, it is being heavily investigated through the use of computational fluid dynamics. For example, it has been shown that droplets/particles have different residence times in a spray dryer depending on their size (Ullum, Proceedings of the 15th international drying symposium, 2006).

The mixing of the droplets and drying gas is another factor that might be different within the two spray dryers. Ideally, the gas dispersers in the two spray dryers should result in the same degree of mixing between droplets and drying gas, and ensuring similar flow patterns. However, it should be noted that while the ratio of atomization gas to drying gas is 1:8 for the pilot scale, it is 1:18 for the production scale. This will significantly influence both temperature and residence time distribution in the particle formation zone. The above hypothesis is partly supported by the additional experiments with increasing atomization gas flow rate, which results in a decrease in particle diameter and the disappearance of blowholes (however, the particles are probably porous). However, there is naturally also a direct effect on droplet size by the increase in atomization gas flow rate, and the two effects can not be separated.

If matching droplet size distributions should work as scale-up criterion, the particle separation must be comparable for the two spray dryers. Thus, in this study the differently sized cyclones must show identical cut diameters i.e. identical collection efficiency for the same particle size. It was found that the cyclones used in this study provided similar cut-size diameters.

Another factor that could account for the altered particle size is feed preparation. A small magnetic stirrer was used to mix up the feed for the pilot scale experiments, whereas a high speed vertical agitator was used in the production scale feed preparation. The higher speed is expected to raise the entrapment of air in the feed solution. In accordance to Masters, the presence of air bobbles in the feed solution could result in ballooning of the particles during drying (1). By visual inspection, the presence of air in the feed solutions could be detected while stirring, but after a few minuets no air bubbles were seen. Non-visible bubbles could still be present in the solution. The maximum amount of air, which could be entrapped in the ethanolic solutions, was calculated to approximately 0.2 g air/kg ethanol. This amount is considered to be of minor importance in relation to particle characteristics. However, in order to remove or minimize the amount of entrapped air, the high speed vertical agitator was stopped after complete mixing of the components, and the solution was left unstirred for at least 1 h before drying. Therefore, the dissimilarity in feed preparation is not expected to be the main contributing factor for the increase in particle size.

In order to account for the differences in drying behaviour, other selections of operating conditions for the production spray dryer were evaluated with the purpose of obtaining the same particle size as achieved on the pilot plant. By operating at a higher atomization gas flow rate (~210 kg/h instead of ~70 kg/h) and at a lower feed flow rate (~25–35 kg/h instead of ~45 kg/h), we were able to match the particle size produced in the pilot plant (gas flow 9 kg/h, feed flow 2.5 kg/h) for both feed concentrations. So for the studied formulations, the simple scale-up criterion failed. Therefore, in order to determine the operating conditions resulting in similar product characteristics as obtained in pilot scale, experiments done in production scale are required. Better knowledge and control of the mixing of the drying gas and droplets (dimensionless numbers) i.e. gas distributor, in addition to temperature profile in the droplet evaporation zone (relation between feed flow rate, temperature of feed and inlet temperature) must be obtained.

CONCLUSION

In order to scale up from pilot to production scale spray dryers, the influence of five parameters were evaluated in pilot scale. The studied parameters were: Outlet temperature, feed flow rate, solid concentration in feed solution drug/polymer ratio and open/closed cycle were. The effects were determined in terms of particle size, morphology, residual solvent, crystallinity, yield and stability.

The study showed no differences in product characteristics when operating open/closed cycle, and no incidence of crystallinity was evident in any of the spray dried powders. The particle size was influenced by the concentration of solids in the feed solution, feed flow rate and drug polymer ratio. The outlet temperature mainly showed effect on the particle morphology and on the amount of residual solvent for the particles produced in pilot scale. For the powders produced in production scale, the outlet temperature mainly influenced on the size of the particles.

The results demonstrated that up-scaling based on matching atomizer droplet size distributions was not successful for the applied formulations, as the criterion did not account for the differences in droplet temperature and residence time histories between the spray dryers. However, it was possible to scale-up the process by varying the operating conditions. Further research is needed in the areas on determining dimensionless numbers for the mixing of the drying gas and droplets in order to attain similar droplet temperature and residence time histories.

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