European Journal of Pharmaceutics and Biopharmaceutics 80 (2012) 149–155

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Thermal ink-jet spray freeze-drying for preparation of excipient-free salbutamol sulphate for inhalation

Wunlapa Mueannoom [a], Amon Srisongphan [a], Kevin M.G. Taylor [a], Stephan Hauschild [b,1], Simon Gaisford [a,c,*]

[a] School of Pharmacy, University of London, London, UK
[b] Institute of Physical Chemistry, University of Hamburg, Hamburg, Germany
[c] Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Australia

ARTICLE INFO

Article history:
Received 10 June 2011
Accepted in revised form 29 September 2011
Available online 7 October 2011

Keywords:
Thermal ink-jet
Spray freeze-drying
Salbutamol sulphate
Dry powder inhaler
Excipient-free
Porous particles

ABSTRACT

The use of thermal ink-jet spray freeze-drying (TIJ-SFD) to engineer inhalable, excipient-free salbutamol sulphate (SS) particles was assessed. A modified Hewlett-Packard printer was used to atomise aqueous SS solutions into liquid nitrogen. The frozen droplets were freeze-dried. It was found that TIJ-SFD could process SS solutions up to 15% w/v; the porous particles produced had a physical diameter of ca. 35 μm. Next generation impactor (NGI) analysis indicated that the particles had a smaller aerodynamic size (MMAD ranging from 6 to 8.7 μm). Particles prepared from the lowest concentration SS solution were too fragile to withstand aerosolisation, but the 5% w/v solution yielded particles having the best combination of strength and aerodynamic properties. Comparison with a commercial SS formulation (Cyclocap®) showed that the SFD preparation had an almost equivalent $FPF_{6.4\mu m}$ when analysed with a twin-stage impinger (TSI; 24.0 ± 1.2% and 26.4 ± 2.2%, respectively) and good performance when analysed with NGI ($FPF_{4.46\mu m}$:16.5 ± 2.0 and 27.7 ± 1.7, respectively). TIJ-SFD appears to be an excellent method to prepare inhalable particles. It is scalable yet allows assessment of the viability of the pulmonary route early in the development since it can be used with very small volumes (<0.5 mL) of solution.

1. Introduction

Dry powder inhaler (DPI) formulations are an established approach to inhalation therapy, but their formulation can be complex. For successful deposition in the lower respiratory tract, the drug must have an aerodynamic diameter below 6 μm [1]. Powders having such a small particle size may be difficult to aerosolise because of their intrinsic cohesiveness, caused by their large surface area to mass ratio, irregular morphology, disordered surface chemistry, electrostatic charge and the fact that gravitational forces acting on particles of this size are not as dominant as other physical forces [2].

In a typical DPI formulation, small drug particles are bound by a force of adhesion to the surface of a larger, crystalline carrier (often lactose) [3]. The larger physical size of the aggregates imparts better flowability, and they are easier to aerosolise. Upon inspiration by the patient, the turbulent air-flow generated within DPI devices overcomes the force of adhesion between the drug and carrier, the larger carrier particles impacting the back of the throat and the smaller drug particles entering the respiratory tract [4].

This mode of operation ensures aerosolisation is coordinated with inspiration (a common problem with pressurised metered dose inhalers). However, product performance is critically dependent upon the force of adhesion, which is in turn dependent upon the surface properties of the drug and carrier [5]. The size of the carrier has also been shown to affect aerosolisation performance [6]. The method of preparation of the components thus fundamentally affects final product performance [7].

Milling, the traditional method of producing particles of appropriate size for inhalation, is a high-energy process that imparts considerable forces to crystalline particles that may, as a result, become partially disordered (or amorphous), particularly at their surfaces (so-called mechanical activation [8]). Although milling is easier to scale up to industrial manufacture, the processes that lead to particle size reduction, and their effect on the physicochemical properties of the milled material, in particular at the surface, are not totally understood. On a commercial scale, this means it may well be the case that the milling process is optimised on particle size parameters alone, when surface factors may in fact be more important in ensuring consistency, and indeed efficacy, of product performance [9]. As a consequence, milled material may often be

* Corresponding author. School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK. Tel.: +44 (0) 207 753 5863; fax: +44 (0) 207 753 5942.
E-mail address: simon.gaisford@pharmacy.ac.uk (S. Gaisford).
[1] Present address: Department of Physical Chemistry I, University of Bayreuth, Universitaetsstrasse 30, 95447 Bayreuth, Germany.

0939-6411/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2011.09.016

'conditioned' prior to formulation (with humidity, time and/or temperature) as this is seen empirically to produce a more consistent product [10].

Many of these issues could be resolved if excipient-free DPI formulations could be developed, because there would be no requirement for a carrier and hence no dependence on surface properties and interactions. Ideally, the drug particles would be large enough to flow well and aerosolise effectively but be small enough to reach the lower airways. They would also need sufficient mechanical strength to withstand aerosolisation and be stable at ambient temperature and relative humidity (RH). The Turbuhaler™ device [11] can be used in some instances without additional excipients (for instance Pulmicort™ contains only budesonide). An alternative is to make porous particles, such as the PulmoSpheres™ pioneered in the past decade [12–14]. PulmoSpheres™ are prepared via spray drying (SD) and utilise a lipid framework in which the drug is encapsulated, so are not excipient-free. An alternative is spray freeze-drying (SFD). In SFD, a solution is atomised into a freezing liquid (usually liquid nitrogen); the frozen droplets are subsequently freeze-dried, removing the water by sublimation, leaving hollow spheres. SFD is frequently used to formulate thermally labile biological actives [15–21], but it has also been used for small molecular weight organic molecules [22–24]. Many of these formulations include a lipidic or sugar component as a co-former, but this may not be necessary if the drug has suitable physicochemical properties. There is a requirement, of course, that solutions are prepared in solvents that can be removed by freeze-drying. Practically, these are water and *t*-butanol, although small amounts of co-solvent may be added in cases where the active is insoluble in either.

One potential drawback of excipient-free formulations is dose-metering (especially with high potency, low-dose drugs), in which case diluents must be added to the formulation. The advantage of engineering particles with SFD is that diluents may be incorporated directly into the particle, thus avoiding complicating issues such as dose uniformity and forces of adhesion as noted above. Inclusion of excipients into the particles is not the express focus of this work, but we will return to it in a future publication.

The method of atomisation into the freezing liquid will affect the droplet size and, consequently, the final particle size. Thermal ink-jetting (TIJ), a technology most commonly encountered in desktop printers, is a promising approach that affords extremely fine control of liquid droplets, and hence accuracy of drug dose. Briefly, a TIJ system comprises a reservoir of liquid to be jetted that is mounted above a printhead. The printhead, usually produced with photolithography, consists of a number of small chambers, filled with liquid from the reservoir, each in contact with a resistive element. Pulsing a current through the element results in a rapid rise in temperature, causing vaporisation of some of the liquid, nucleation and then expansion of a vapour bubble. As the bubble expands, some liquid is ejected from the chamber, forming a droplet. Eventually the vapour bubble collapses, causing a vacuum that is filled with fresh liquid from the reservoir. The process is repeated, controlled by the current pulses, producing droplets-on-demand (DOD). The resistive element can reach a temperature of up to 300 °C, albeit only momentarily, resulting in bubble expansion over 3–10 μs and a droplet ejected at up to 10 m s^{-1}, while droplet volumes of 2–180 pL can be achieved [25].

An additional benefit is that TIJ can atomise very small (<0.1 mL) volumes of solution, which means the technique may allow assessment of the viability of pulmonary delivery for an active component earlier in the development process. It is also scalable and can operate with a continuous feed. In this work, we evaluate the combination of TIJ and SFD to prepare excipient-free particles for inhalation, using salbutamol sulphate as a model drug.

2. Materials and methods

Salbutamol sulphate (SS) was supplied as a gift by Micron Technologies (UK). Silicone oil (density 1.05 g cm^{-3}) and 1-hexanesulphonic acid sodium salt hydrate (99% +) were purchased from Acros Organics (USA). Methanol and glacial acetic acid (both HPLC grade) were purchased from Fisher Scientific (UK). All materials were used as received. Aqueous solutions were prepared using deionised water. Salbutamol sulphate Cyclocaps® were purchased from AAH Pharmaceuticals (UK), and a Cyclohaler® device (Medicopharma BV, Netherlands) was used to aerosolise all formulations.

2.1. Modification of the ink-jet printer

A modified Hewlett-Packard Deskjet 340 printer was used throughout this study. Briefly, the modifications involved mounting the print cartridge on an external stand (by rerouting the ribbon cable through the body of the printer) and bypassing the paper feed sensor with an external switch. The top of the print cartridge (HP 51639Y) was carefully separated from the body, and the contents were removed. Any ink residues were removed by rinsing with copious volumes of deionised water, followed by absolute ethanol. The ink was replaced with the solution to be jetted, and the top of the cartridge was sealed with Parafilm. Sending image data to the printer resulted in whatever solution was in the print cartridge being jetted.

2.2. Spray freeze-drying

The print cartridge was mounted 3 cm above the surface of a small metal beaker containing liquid nitrogen. The beaker was contained in a polystyrene box to slow the evaporation rate. During jetting, the liquid nitrogen was replenished between each print cycle, maintaining its surface at a constant level. Each print cycle lasted for 1 min, and typically 40–50 cycles were required to produce sufficient material for freeze-drying. Aqueous SS solutions (2.5%, 5%, 10% and 15% w/v) were loaded into the printer cartridge. Templates (consisting of a black A4 square) to be printed were prepared in PowerPoint 2003 (Microsoft Inc.). The print settings were black cartridge, best print quality, and highest resolution. Printing one complete page constituted a single printing cycle. Typically, 45 cycles were printed before the excess liquid nitrogen was allowed to evaporate. As soon as evaporation was complete, the sample was stored in a freezer (−20 or −80 °C). Freeze-drying was accomplished with a Modulyo D-230 (Thermo Scientific, UK). The sample shelf was equilibrated at −50 °C before the sample was loaded and then placed under vacuum (0.5 mbar). The sample was held under these conditions for 22 h before commencement of a secondary drying stage at 10 °C for a further 6 h. Upon removal from the freeze drier, samples were stored in a vacuum desiccator over phosphorous pentoxide.

2.3. Spray drying

Aqueous SS (10% w/v) was spray-dried with a Buchi 191 spray-drier (Buchi, Switzerland) as described previously [26], operated with the following parameters; Aspirator level, 85%; pump, 7 mL min^{-1}; inlet temperature, 150 °C; and air flow rate, 800 L h^{-1}.

2.4. Particle sizing

Particle size distributions ($n = 10$) were measured with a HELOS/BR laser diffractometer (Sympatec GmbH, Germany). Two

sample dispersion techniques were used. For RODOS (dry powder) measurements, samples were placed in the powder feeder and pressurised air (4 bar) was used to disperse the powder into the measurement chamber. For INHALER (DPI device) measurements, samples were weighed (10 mg) into hard gelatin capsules (size 3) and loaded into a Cyclohaler®, and the device was used to disperse the powder into a low-pressure (4 mbar) air stream. An R4 lens (0.5–350 μm) was used to collect data. Data were analysed with the Windox 5 software.

2.5. Electron microscopy

Samples were prepared by sputter-coating with gold to a thickness of 10 nm (Quorum model Q150). Images were collected using a scanning electron microscope (SEM, Quanta 200 FEG, FEI, Netherlands).

2.6. X-ray powder diffraction

X-ray powder diffraction (XRPD) data were recorded with a PW3830 (Philips) using a Cu Kα X-ray source operated at 40 mA, 40 kV with an angular increment of 0.05° s^{-1}. Measurements were taken from 0° to 30° on the 2θ scale.

2.7. Thermal analysis

Modulated temperature differential scanning calorimetry (MTDSC, Q2000, TA Instruments LLC) was used from room temperature to 200 °C with an underlying heating rate of 2 °C min^{-1}. The modulation parameters were amplitude 1 °C and period 60 s. Samples (4–6 mg) were loaded into aluminium T-zero pans fitted with non-hermetic aluminium lids. The cell constant and enthalpy calibrations were performed with indium (Certified Reference Material LGC2601, Batch E1, LGC, London, T_m = 156.61 °C, $\Delta_f H$ = 28.70 J/g) in accordance with the manufacturer's instructions. The measured values were always in excellent agreement with those of the reference material (T_m ± 0.03 °C, $\Delta_f H$ ± 0.1 J/g). Nitrogen (50 mL min^{-1}) was used as a purge gas, and data were analysed with Universal Analysis 2000.

Thermogravimetric analysis (TGA, Pyris 6, Perkin–Elmer Ltd.) was used from room temperature to 200 °C at 10 °C min^{-1}. Samples (4–6 mg) were weighed into a ceramic crucible. Nitrogen (20 mL min^{-1}) was used as a purge gas. The mass loss between 40 and 100 °C was used to determine water content of samples.

Dynamic vapour sorption (DVS-1, SMS Ltd., UK) was operated at 25 °C. Samples (2–3 mg) were loaded onto the pan and allowed to equilibrate under a dry atmosphere for 10 h. The RH was then increased in discrete steps (5% h^{-1}) to 90%.

2.8. HPLC analysis of salbutamol sulphate

A calibration curve for SS was prepared using High-Pressure Liquid Chromatography (HPLC) fitted with a UV-detector (Hewett Packard, Germany) using a mixture of 5 mM sodium-1-hexanesulphonate in water and methanol (75:25% v/v) containing glacial acetic acid (1% v/v) as the mobile phase, delivered at a rate of 1.0 mL min^{-1}. The stationary phase was a Discovery® C-8 column (150 mm × 4.6 mm × 5 μm; Supelco analytical, USA) kept at 40 °C. The injected sample volume was 100 μL. Peaks were evaluated at 276 nm and the method was linear (r^2 = 0.9993) between salbutamol sulphate concentrations of 0.5 and 200 μg/mL.

2.9. Aerosol performance

Deposition profiles were determined with apparatus A (twin-stage impinger, TSI, Copley Instruments Ltd., UK) and apparatus E (next generation impactor, NGI, Copley Instruments Ltd., UK) operated under standard conditions (Appendix XII part C, British Pharmacopoeia 2010).

The Cyclohaler device was attached to the throat of the TSI with a rubber mouthpiece adaptor. Measurements were taken at 60 L min^{-1} (with a rotary vane pump connected via a solenoid valve and timer) for 5 s. Ten capsules (size 3), manually filled (10 mg SFD powder in each), were discharged into the TSI before the apparatus was disassembled. The contents of the device, capsules, mouthpiece and throat and each impinger stage were washed with deionised water into volumetric flasks and made up to volume. Drug concentrations were determined with HPLC, and the data analysed to give the recovered dose (RD, the total amount of drug collected in the device, capsule, mouthpiece and throat, upper and lower stages), emitted dose (ED, the total amount of drug collected in the mouthpiece and throat and upper and lower stages) and fine particle fraction (FPF, the ratio of drug in the lower stage to the RD). The lower stage had a cut-off diameter of 6.4 μm.

The Cyclohaler was attached to the NGI via a rubber mouthpiece adaptor and tested at 60 L min^{-1} for 4 s. Prior to use, the impaction cups in each of the seven stages were coated with 1% w/v silicone oil in hexane and allowed to dry for 30 min. The surface coating prevented 'bounce' and re-entrainment of particles between stages. Ten capsules were discharged into the NGI. After actuation, the contents of the device, capsule, throat, pre-separator and each stage were washed with deionised water into volumetric flasks and made up to volume. Drug concentrations were determined with HPLC and the data analysed to give the RD (drug collected in the device, capsule, mouthpiece and throat, pre-separator, stages 1–7 and the micro-orifice collector, MOC), ED (drug collected in the mouthpiece and throat, pre-separator, stages 1-MOC) and FPF (ratio of drug collected in stages 3-MOC to the RD). Stage 2 had a cut-off diameter of 4.46 μm. Drawing a log probability graph (log diameter versus log cumulative fraction) enabled determination of the mass median aerodynamic diameter (MMAD, diameter value at 50% of the cumulative weight undersize) and geometric standard deviation (GSD, calculated as the slope of the log probability graph against the cut-off diameter for the NGI stages).

3. Results and discussion

3.1. Preparation of SS particles

SFD successfully produced spherical particles, although the temperature at which the samples were stored prior to freeze-drying affected surface morphology. Storage at −80 °C resulted in particles with a surface crust, while storage at −20 °C resulted in what appeared to be a completely porous matrix (Fig. 1). Leuenberger et al. [19] imaged the cross section of a particle of dextran prepared by SFD and noted that while the material at the core was denser than the material at the surface (a result of the freezing rate), the entire matrix was porous. XRPD of the SFD particles (Fig. 2) confirmed that the matrix was amorphous, which also suggests that the rate of freezing was reasonably rapid. Maa and Prestrelski [27] estimate the freezing time of the droplets in liquid nitrogen to be on the order of milliseconds. Implicitly, these observations suggest that one droplet produces one particle, so controlling droplet size should allow control of final particle size and so aerodynamic performance. In a previous study [28], no evidence was found that surface tension of the jetted solution affected droplet size.

If it is assumed that at the point, the samples are placed in the freezer and the particles still contain liquid nitrogen in their pores, then the difference in surface structure may arise as a result of different evaporation rates: At −80 °C, evaporation is relatively

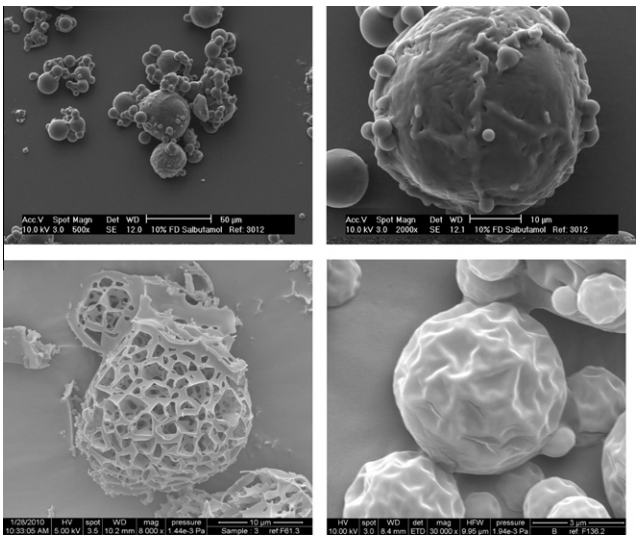

Fig. 1. SS particles prepared with spray freeze-drying held at −80 °C prior to freeze-drying (top left and right) and −20 °C prior to freeze-drying (bottom left). Shown for comparison are SS particles made with spray drying (bottom right).

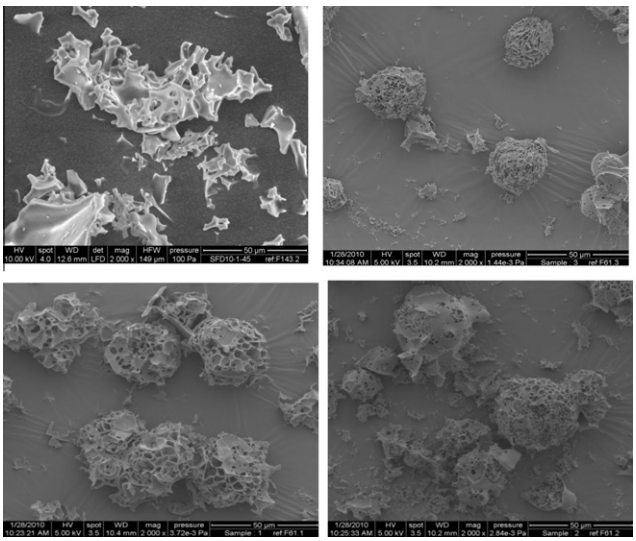

Fig. 3. SEM images of SFD salbutamol sulphate particles as a function of feed concentration. Top left, 2.5% w/v; top right, 5% w/v; bottom left, 10% w/v; bottom right, 15% w/v.

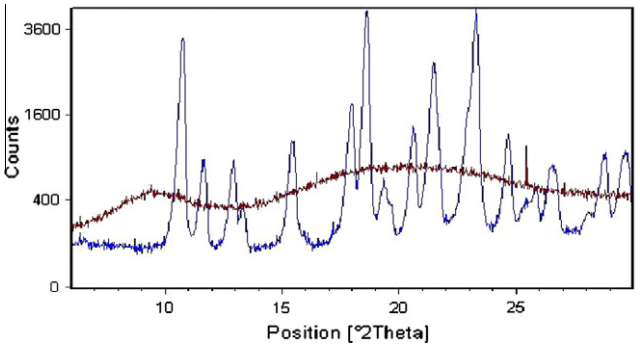

Fig. 2. XRPD data for SS starting material (crystalline, lower trace) and SFD material (amorphous, upper trace). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

slow and a surface crust has time to form (a similar phenomenon is seen in spray-dried samples [29]), while at −20 °C, evaporation is more rapid and crust formation is prevented. Since the geometric size of the particles is greater than the 6 μm maximum needed for effective lung deposition, successful delivery of the SFD particles would require that they have a lower MMAD, something likely to be achievable only with the porous particles. Hence, production of all subsequent batches of SFD material proceeded with storage at −20 °C prior to freeze-drying. For comparison, particles produced with spray drying had a smooth, dimpled surface (Fig. 1), an observation consistent with previous findings [15,26]).

SEM images of the SFD particles as a function of concentration are shown in Fig. 3. At concentrations of 5% w/v and greater, the technique produced spherical particles, while the lowest concentration of 2.5% w/v produced non-spherical fragments. The rapid freezing time noted above means there should be little time for particles to shrink, or solute to reorganise, once the droplets are in contact with the liquid nitrogen. This should result in particles with the same physical diameter, irrespective of concentration of the solution being jetted. The particle size data are given in Table 1, where this phenomenon is seen. Droplet volumes for a range of current Hewlett-Packard printers are available online and typically range between 10 and 14 pL. Although the droplet size is not available for the printer cartridge used in this work, droplets in the range 10–14 pL would have diameters between 26.7 and 29.9 μm, in good agreement with the particle sizes reported in Table 1. This supports the hypothesis above that one droplet produces one particle.

The densities of the particles should, therefore, increase with increasing concentration of print solution, although these values were not experimentally measured. It seems likely that under the vacuum applied to prepare samples for SEM imaging, the least dense 2.5% w/v particles fractured, while the remaining samples had sufficient mechanical strength to remain intact. No further experiments were thus undertaken with the 2.5% w/v sample.

The particle size data in Table 1 show that the diameters of the SFD samples decrease slightly (but not significantly, $P > 0.05$) with increasing print concentration (d_{50} from 36.59 to 32.44 μm) when dispersed from the Cyclohaler® but are significantly different ($P < 0.05$) when dispersed using RODOS. It seems that since the RODOS employs high-pressure air to achieve dispersion, the SFD particles fracture using this method; the extent to which fracturing occurs is dependent upon the density, and hence mechanical strength, of the particle, which in turn is dependent upon the initial concentration of the solution printed. The spray-dried sample had the smallest diameter (d_{50} ca. 5 μm) and was not affected by the method of dispersion, implying that it was mechanically strong. The Cyclocaps® data show a larger than expected diameter (d_{50} 18.62 ± 14.53 μm) which suggests that the dispersion technique did not achieve full separation of the drug from the carrier and/or the sizing technique was unable to resolve the size distribution containing a population of small drug particles and larger carrier lactose particles.

3.2. Stability of the SFD particles

One concern with amorphous matrices, especially when they have a large surface area, is reversion to the crystalline state, an event that usually proceeds with collapse of a matrix structure and is heavily influenced by moisture content [30]. Although crystallisation is inevitable from a thermodynamic perspective, the rate will be affected by many factors, including the glass transition temperature (T_g), water content, temperature and relative humidity (RH). In general, the T_g needs to be high and the other factors as low as possible. MTDSC data showed that the T_g values for the SFD samples, and the spray-dried sample, were around 118 °C

Table 1
Particle size data (μm) for various salbutamol sulphate samples.

Formulation	RODOS powder dispersion			INHALER dispersion		
	d_{10} ± SD	d_{50} ± SD	d_{90} ± SD	d_{10} ± SD	d_{50} ± SD	d_{90} ± SD
2.5% SFD SS	0.79 ± 0.02	3.76 ± 0.12	12.19 ± 0.23	3.77 ± 0.97	36.59 ± 12.06	122.82 ± 6.02
5% SFD SS	1.29 ± 0.04	5.80 ± 0.13	16.26 ± 1.47	12.93 ± 2.31	35.45 ± 7.40	110.36 ± 12.98
10% SFD SS	1.34 ± 0.03	9.64 ± 0.30	52.71 ± 2.76	5.72 ± 2.74	34.52 ± 14.12	98.45 ± 12.26
15% SFD SS	2.45 ± 0.05	16.25 ± 1.43	271.64 ± 10.29	5.04 ± 0.59	32.44 ± 5.05	132.27 ± 9.28
Spray-dried SS	1.73 ± 0.02	4.97 ± 0.94	9.54 ± 0.76	1.86 ± 0.23	5.03 ± 0.39	9.70 ± 0.66
Cyclocaps®	N/A	N/A	N/A	1.95 ± 0.75	18.62 ± 14.53	84.21 ± 58.32

(Fig. 4), much higher than the value of 64 °C reported by Ward and Schultz [31].

In their work, Ward and Schultz [31] studied micronised SS; as such, their sample contained a low level of amorphous content (below 10% as it was not distinguishable by XRPD). Corrigan et al. [32] report T_g values lower than 64 °C for SS co-spray dried with polyethylene glycols, but their DSC data also show an unspecified step-change around 115–120 °C, as well as crystallisation of amorphous SS around 145–150 °C in some cases.

The position of the T_g is known to vary with method of manufacture, water content and the experimental method and parameters used to measure it [33]. No water contents were specified in the work of Ward and Schultz [31], but the SFD samples prepared here all had very low water contents (Table 2). Further, the heating rate employed (1 °C min^{-1}) is slow and might allow the sample to dry further during heating. Both effects would act to maximise the T_g. In a study of amorphous SS by dynamic vapour sorption, Columbano et al. [34] noted that water movement occurred in the sample over extended time periods. DVS data for 5% w/v SFD SS are shown in Fig. 5 and show that the sample required 10 h to equilibrate under a dry atmosphere. Similar effects of water were seen in a study of SS using isothermal microcalorimetry [2], and in their original study, Ward and Schultz [31] suggest that even the crystal structure of SS permits room for water. It may therefore be the case that the physical properties of the drug are fundamentally affected by water content.

The DVS data in Fig. 5 show that recrystallisation of the SFD sample occurs between 70% and 75% RH, again in excellent agreement with the results of Columbano et al. [34] and a later study by Burnett et al. [35]. The data suggest that SFD samples should be reasonably stable when stored at room temperature, so long as the RH does not approach 70% or greater.

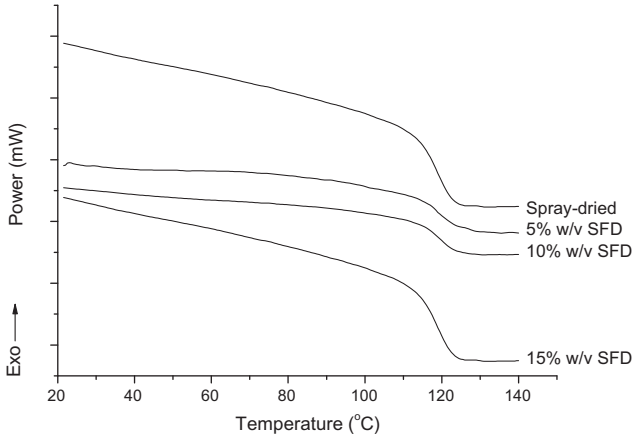

Fig. 4. TMDSC reversing heat-flow data for SFD and spray-dried salbutamol sulphate.

Table 2
Water content for SFD and spray-dried salbutamol sulphate.

Formulation	Moisture content (%) ± SD (n = 3)
5% SFD SS	1.1026 ± 0.15
10%SFD SS	1.8743 ± 0.12
15% SFD SS	1.1046 ± 0.26
Spray-dried SS	1.7407 ± 0.05

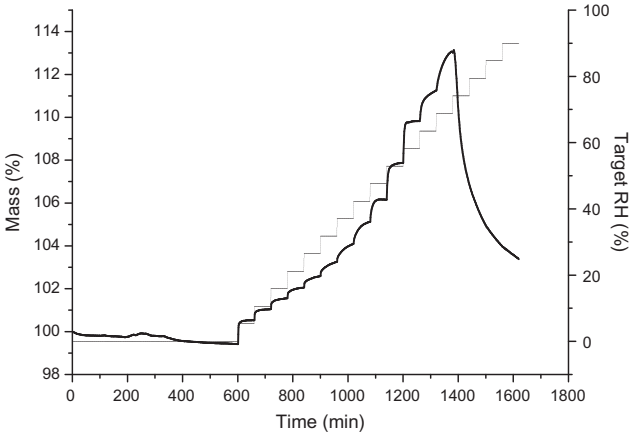

Fig. 5. Water sorption isotherm for 5% w/v SFD salbutamol sulphate.

3.3. Aerosol deposition studies

The aerosol performance of particles delivered from the Cyclohaler was assessed with TSI (Table 3) and NGI (Table 4 and Fig. 6). The SFD samples were compared with spray-dried SS and a commercial SS formulation (Cyclocaps®). The lower stage of the TSI has a higher aerodynamic particle size cut-off (6.4 μm) than the NGI (4.46 μm); as such, TSI is a less rigorous challenge for each formulation and this manifests in higher FPF figures. Dealing with the TSI data first, the commercial formulation gave the greatest FPF (26.4 ± 2.2%) followed by the spray-dried sample (24.2 ± 1.6%). The commercial formulation contains micronised drug and a lactose carrier, while the spray-dried formulation contains solid, dimpled spherical particles without a carrier. Comparability between micronised and spray-dried salbutamol sulphate DPI formulations has been demonstrated previously [26].

Table 3
Emitted dose and fine particle fractions determined using TSI (n = 3).

Formulation	Emitted dose (ED)% ± SD	Fine particle fraction (FPF)% ± SD
5% SFD SS	98.9 ± 1.3	24.0 ± 1.2
10% SFD SS	98.1 ± 3.0	13.2 ± 0.9
15% SFD SS	98.7 ± 1.6	8.7 ± 1.5
Spray-dried SS	94.1 ± 2.1	24.2 ± 1.6
Cyclocaps®	93.3 ± 1.9	26.4 ± 2.2

Table 4
Aerosol parameters determined using NGI ($n = 3$).

Formulation	Fine particle fraction (FPF)% ± SD	MMAD ± SD (μm)	GSD ± SD
5% SFD SS	16.5 ± 2.0	6.06 ± 0.1	2.78 ± 0.1
10% SFD SS	12.84 ± 2.9	6.13 ± 0.3	3.35 ± 0.7
15% SFD SS	5.43 ± 0.1	8.68 ± 0.4	3.34 ± 0.1
Spray-dried SS	14.84 ± 0.3	5.39 ± 0.2	3.30 ± 0.1
Cyclocaps®	27.7 ± 1.7	2.90 ± 0.1	2.20 ± 0.1

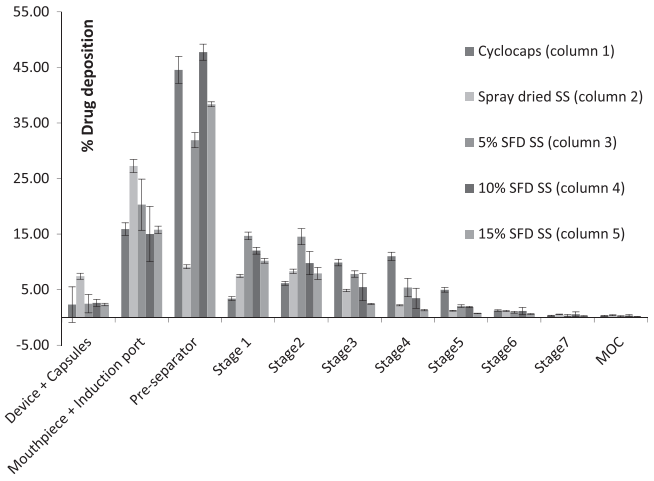

Fig. 6. Drug deposition profile determined with NGI.

The performance of the SFD samples is seen to be dependent upon the concentration of the print solution, and so presumably particle density and porosity. The less dense (most porous) 5% w/v sample gave the highest FPF (24.0 ± 1.1%), encouragingly close to that of the commercial product. As the density of the SFD samples increases, the FPF decreases (10% w/v, 13.2 ± 1%; 15% w/v, 8.7 ± 1.5%). Taking into account the fragility of the 2.5% w/v SFD sample noted earlier, 5% w/v seems to be the concentration that produces particles with the best combination of mechanical strength and in vitro aerosol performance. In all cases, the ED for the SFD samples is greater than those of the commercial and spray-dried formulations, which is probably a reflection of the (presumably lower) force of cohesion in the SFD powder.

The trends in the FPF values from the NGI data broadly mirror those of the TSI study, in that, the commercial formulation performs best (27.7 ± 1.7%) and the performance of the SFD samples correlates with density. In all cases, FPF values for SFD samples were lower by NGI than TSI, an effect most probably due to the lower aerodynamic cut-off for the NGI as noted earlier. Interestingly, the spray-dried formulation performed worse than both the commercial and the 5% w/v SFD samples. The data in Table 1 give a d_{50} value around 5 μm for this sample, below the cut-off for FPF using the TSI and above the cut-off for FPF using the NGI.

Processing the NGI data also allows determination of the MMAD values for the powders. The MMAD for spray-dried SS (5.39 ± 0.2 μm) was consistent with the d_{50} values recorded in Table 1. This is consistent with the fact that the SD samples had solid surfaces when imaged with SEM. The MMAD for the Cyclohaler® formulation was considerably lower than that recorded in Table 1, which suggests that the low air pressure dispersion combined with a laser diffraction sizing methodology is not suitable for prediction of how such a carrier-based formulation will perform as an aerosol. The MMAD values for the 5% and 10% w/v SFD samples (6.06 ± 0.1 μm and 6.13 ± 0.3 μm, respectively) are slightly larger than ideal for inhaled particles, which manifests in the lower FPF values for these systems. However, they are certainly not hugely outside the respirable range, and a proportion of the population is delivered in the fine particle fraction. It is anticipated that using a different ink-jet head that produces slightly smaller droplets would result in an optimised product. The 15% w/v SFD sample had a larger MMAD (8.68 ± 0.4 μm), significantly above the cut-off for stage 2 of the NGI and thus have a poor FPF.

4. Summary

The TIJ system used in this work was capable of jetting aqueous SS solutions of concentration up to 15% w/v. SFD processing of the jetted droplets resulted in porous particles with a physical diameter between 30 and 35 μm, the final size varying slightly with print solution concentration. NGI analysis showed that the particles had a much smaller aerodynamic size (MMAD ranging from 6 to 8.7 μm). The lowest concentration particles were too fragile to withstand aerosolisation, but the 5% w/v particles showed the best combination of strength and dispersibility as an aerosol. Comparison with a commercial salbutamol sulphate formulation (Cyclocap®) showed that the SFD preparation had an almost equivalent FPF when analysed with TSI (24.0 ± 1.2 and 26.4 ± 2.2, respectively) and good performance when analysed with NGI (16.5 ± 2.0 and 27.7 ± 1.7, respectively). The difference in FPF values between the techniques arises from their different particle size cut-offs for the stages of the two apparatus used to calculate FPF.

TIJ appears to be an excellent technique with which to prepare porous particles. It is easily scaled up in volume (either by using a larger printhead or by using additional printer systems) yet allows assessment of the viability of the pulmonary route early in development since it can be used with very small volumes (<0.1 mL) of solution. Reducing the diameter of the ink-jet chamber should act to reduce the size of the porous particles produced—if the size of the final particles could be reduced below 5 μm, the technique would be optimised to engineer inhalable particles.

Acknowledgements

The authors thank Mr David McCarthy for the SEM images and Dr Hardyal Gill for his advice regarding HPLC.

References

[1] J.N. Pritchard, The influence of lung deposition on clinical response, J. Aerosol Med. 14 (2001) S19–S 26.
[2] S. Gaisford, M. Dennison, M. Tawfik, M.D. Jones, Following mechanical activation of salbutamol sulphate during ball-milling with isothermal calorimetry, Int. J. Pharm. 393 (2010) 74–78.
[3] D. Prime, P.J. Atkins, A. Slater, B. Sumby, Review of dry powder inhalers, Adv. Drug Del. Rev. 26 (1997) 51–58.
[4] M. Telko, A.J. Hickey, Dry powder inhaler formulations, Respir. Care 50 (2005) 1209–1227.
[5] Z. Xu, H.M. Mansour, A.J. Hickey, Particle interactions in dry powder inhaler unit processes: a review, J. Adhes. Sci. Technol. 25 (2011) 451–482.
[6] J. Ooi, D. Traini, S. Hoe, W. Wong, P.M. Young, Does size matter? A fundamental study of drug aerosolisation from carrier based dry powder inhalation systems, Int. J. Pharm. 413 (2011) 1–9.
[7] A.H.L. Chow, H.H.Y. Tong, P. Chattopadhyay, B.Y. Shekunov, Particle engineering for pulmonary delivery, Pharm. Res. 24 (2007) 411–437.
[8] K. Brodka-Pfeiffer, P. Langguth, P. Graβ, H. Hausler, Influence of mechanical activation on the physical stability of salbutamol sulphate, Eur. J. Pharm. Biopharm. 56 (2003) 393–400.
[9] M.D. Jones, H. Harris, J.C. Hooton, J. Shur, G.S. King, C.A. Mathoulin, K. Nichol, T.L. Smith, M.L. Dawson, A.R. Ferrie, R. Price, An investigation into the relationship between carrier-based dry powder inhalation performance and formulation cohesive–adhesive force balances, Eur. J. Pharm. Biopharm. 69 (2008) 496–507.
[10] K. Brodka-Pfeiffer, H. Häusler, P. Graβ, P. Langguth, Conditioning following powder micronization: Influence on particle growth of salbutamol sulphate, Drug Dev. Ind. Pharm. 29 (2003) 1077–1084.

[11] G. Braunstein, The Turbuhaler, Rev. Malad. Resp. 9 (1992) R83–R86.
[12] A.I. Bot, T.E. Tarara, D.J. Smith, S.R. Bot, C.M. Woods, J.G. Weers, Novel lipid-based hollow-porous microparticles as a platform for immunoglobulin delivery to the respiratory tract, Pharm. Res. 17 (2000) 275–283.
[13] L.A. Dellamary, T.E. Tarara, D.J. Smith, C.H. Woelk, A. Adractas, M.L. Costello, H. Gill, J.G. Weers, Hollow porous particles in metered dose inhalers, Pharm. Res. 17 (2000) 168–174.
[14] D.E. Geller, J. Weers, S. Heuerding, Development of an inhaled dry-powder formulation of tobramycin using PulmoSphere (TM) technology, J. Aerosol Med. Pul. Drug Del. 24 (2011) 175–182.
[15] Y.F. Maa, P.A. Nguyen, T. Sweeney, S.J. Shire, C.C. Hsu, Protein inhalation powders: spray drying vs spray freeze drying, Pharm. Res. 16 (1999) 249–254.
[16] H.R. Constantino, L. Firouzabadian, K. Hogeland, C. Wu, C. Beganski, K.G. Carrasquillo, M. Córdova, K. Griebenow, S.E. Zale, M.A. Tracy, Protein spray-freeze drying. Effect of atomization conditions on particle size and stability, Pharm. Res. 17 (2000) 1374–1383.
[17] H.R. Constantino, L. Firouzabadian, C. Wu, K.G. Carrasquillo, K. Griebenow, S.E. Zale, M.A. Tracy, Protein spray freeze drying. 2. Effect of formulation variables on particle size and stability, J. Pharm. Sci. 91 (2002) 388–395.
[18] D.-J. van Drooge, W.L.J. Hinrichs, B.H.J. Dickhoff, M.N.A. Elli, M.R. Visser, G.S. Zijlstra, H.W. Frijlink, Spray freeze drying to produce a stable Δ^9-tetrahydrocannabinol containing inulin-based solid dispersion powder suitable for inhalation, Eur. J. Pharm. Sci. 26 (2005) 231–240.
[19] H. Leuenberger, M. Plitzko, M. Puchkov, Spray freeze drying in a fluidized bed at normal and low pressure, Dry Technol. 24 (2006) 711–719.
[20] Z.L. Wang, W.H. Finlay, M.S. Peppler, L.G. Sweeney, Powder formation by atmospheric spray-freeze-drying, Powder Technol. 170 (2006) 45–52.
[21] V. Saluja, J.-P. Amorij, J.C. Kapteyn, A.H. de Boer, H.W. Frijlink, W.L.J. Hinrichs, A comparison between spray drying and spray freeze drying to produce an influenza subunit vaccine powder for inhalation, J. Control. Rel. 144 (2010) 127–133.
[22] G.S. Zijlstra, W.L.J. Hinrichs, A.H. de Boer, H.W. Frijlink, The role of particle engineering in relation to formulation and de-agglomeration principle in the development of a dry powder formulation for inhalation of cetrorelix, Eur. J. Pharm. Sci. 23 (2004) 139–149.
[23] L.G. Sweeney, Z. Wang, R. Loebenberg, J.P. Wong, C.F. Lange, W.H. Finlay, Spray-freeze-dried liposomal ciprofloxacin powder for inhaled aerosol drug delivery, Int. J. Pharm. 305 (2005) 180–185.
[24] J.-Y. Her, C.-S. Song, S.J. Lee, K.-G. Lee, Preparation of kanamycin powder by an optimised spray freeze-drying method, Powder Technol. 199 (2010) 159–164.
[25] P.A. Meléndez, K.M. Kane, C.S. Ashvar, M. Albrecht, P.A. Smith, Thermal inkjet application in the preparation of oral dosage forms: dispensing of prednisolone solutions and polymorphic characterization by solid-state spectroscopic techniques, J. Pharm. Sci. 97 (2008) 2619–2636.
[26] A. Chawla, K.M.G. Taylor, J.M. Newton, M.C.R. Johnson, Production of spray dried salbutamol sulphate for use in dry powder aerosol formulation, Int. J. Pharm. 108 (1994) 233–240.
[27] Y.F. Maa, S.J. Prestrelski, Biopharmaceutical powders: particle formation and formulation considerations, Curr. Pharm. Biotechnol. 1 (2000) 283–302.
[28] A.B.M. Buanz, M.H. Saunders, A.W. Basit, S. Gaisford, Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing, Pharm. Res. 28 (2011) 2386–2392.
[29] R. Vehring, Pharmaceutical particle engineering via spray drying, Pharm. Res. 25 (2007) 999–1022.
[30] P. Bonelli, C. Schebor, A.L. Cukierman, M.P. Buera, J. Chirife, Residual moisture content as related to collapse of freeze-dried sugar matrices, J. Food Sci. 62 (1997) 693–695.
[31] G.H. Ward, R.K. Schultz, Process-induced crystallinity changes in albuterol sulfate and its effect on powder physical stability, Pharm. Res. 12 (1995) 773–779.
[32] D.O. Corrigan, O.I. Corrigan, A.M. Healy, Predicting the physical state of spray dried composites: salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems, Int. J. Pharm. 273 (2004) 171–182.
[33] R.J. Seyler (Ed.), Assignment of the Glass Transition, ASTM Special Technical Publication 1249, Amer. Soc. Test. Mater., Philadelphia, 1994.
[34] A. Columbano, G. Buckton, P. Wikeley, A study of the crystallisation of amorphous salbutamol sulphate using water vapour sorption and near infra-red spectroscopy, Int. J. Pharm. 237 (2002) 171–178.
[35] D.J. Burnett, F. Thielmann, J. Booth, Determining the critical relative humidity for moisture-induced phase transitions, Int. J. Pharm. 287 (2004) 123–133.