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Production of salbutamol sulfate for inhalation by high-gravity controlled antisolvent precipitation

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Abstract

The purpose of this study was to produce salbutamol sulfate (SS) as a model anti-asthmatic drug using high-gravity controlled precipitation (HGCP) through antisolvent crystallisation. An aqueous solution of SS was passed through a HGCP reactor with isopropanol as antisolvent to induce precipitation. Spray drying was employed to obtain dry powders. Scanning electron microscopy, X-ray powder diffraction (XRD), density measurement, thermal gravimetric analysis, and dynamic vapour sorption were carried out to characterise the powder physical properties. The aerosol performance of the powders was measured using an Aeroliser connected to a multiple stage liquid impinger operating at 60 L/min. The HGCP SS particles were elongated with 0.1 μm in width but varying length of several μm, which formed spherical agglomerates when spray dried. The particles showed the same XRD pattern and true density (1.3 g/cm^3) as the raw material, indicating that they belonged to the same crystalline form. However, the spray dried agglomerates had a much lower tapped density (0.1 g/cm^3) than the raw material (0.6 g/cm^3). Compared with the powder obtained by spray drying directly from an aqueous solution, the SS powders obtained from HGCP were much less hygroscopic (0.6% versus 10% water uptake at 90% RH). The *in vitro* aerosol performance showed a fine particle fraction FPF_{loaded} and $FPF_{emitted}$ up to 54.5 ± 4.9% and 71.3 ± 10.0%, respectively. In conclusion, SS powder with suitable physical and aerosol properties can be obtained through antisolvent HGCP followed by spray drying.
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Keywords: Salbutamol sulfate; High gravity controlled precipitation; Antisolvent crystallisation; Inhalation drug delivery; Rotating packed bed

1. Introduction

Dry powder inhaler (DPI) formulations require drug particles with aerodynamic diameters under 5 μm for lung deposition and good flow properties to ensure accurate dosing of the drug and ease in the manufacturing processes (Louey et al., 2003; Gonda, 2004). Conventional crystallisation processes produce particles, which are too big (>10 μm) to inhale. Jet-milling micronisation has been one of the most frequently used techniques in the pharmaceutical industry to obtain particles with optimal respirable size. However, this micronisation process requires significant energy input, which can induce disorder, defects or even amorphous regions in the drug particles, consequently causing physico-chemical instability of the product. Amorphous materials and/or electrostatic charges generated during milling also present strong cohesive forces, which can cause agglomeration, leading to unsuitable aerosolisation properties (Brodka-Pfeiffer et al., 2003). Contamination from mechanical attrition during milling is potentially an additional concern. Therefore, alternative production processes are attractive to the pharmaceutical industry. Spray drying has been successfully used for production of pharmaceutical powders suitable for inhalation (Steckel and Brandes, 2004). However, depending on the compounds, spray drying may produce powders that are amorphous and hence physically unstable.

Previously, it has been shown that particles synthesized under a high-gravity environment have a narrow size distribution and that the reaction can be accelerated due to intensified micromixing and mass transfer (Chen et al., 2000). Further, the production of organic pharmaceutical nano-particles using the high-gravity precipitation (HGCP) technique has recently been demonstrated to be feasible using benzoic acid (Chen et al.,

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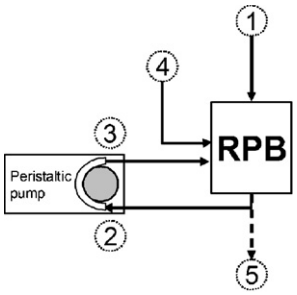

Fig. 1. Schematic of the modified HGCP configuration used; numbers refers to each step of the process.

2004). In the present study, we applied HGCP to produce salbutamol sulfate (SS), a β_2-adrenoceptor stimulant commonly used in the treatment of bronchial asthma. It has been found that spray drying aqueous solution of SS will lead to an amorphous powder. In contrast, if the precipitate in the suspension collected from the HGCP is crystalline, then the resulting powder produced from spray drying of the suspension would be crystalline.

In this paper a new approach combining HGCP and spray drying to prepare fine powders suitable for inhalation is reported, along with the solid state properties and aerosol performance of the powders.

2. Materials and methods

2.1. Materials

The active drug starting material, SS, was purchased from Inter-Chemical Ltd., China, and isopropyl alcohol (IPA) of AR grade from LabServ Pronalys, Australia.

2.2. Powder preparation

2.2.1. High-gravity controlled precipitation of salbutamol sulfate

High-gravity controlled precipitation of SS was carried out in a modified HGCP (Fig. 1) where the key components of the rotating packed bed (RPB, Beijing University of Chemical Technology, China) (Chen et al., 2000) were retained. Briefly, the RPB is a reactor in which two liquid streams can be fed via distributors and mixed into the centre of a packed bed, which is subjected to high gravity due to centrifugal force, causing the mixture to flow through the packing before leaving the reactor. There is a port at the top of the RPB, which can be used to load the reactor with initial reagents or to clean the reactor. One hundred milliliters of IPA was initially loaded into the RPB (Fig. 1(1)) and was rapidly circulated continuously from the outlet (Fig. 1(2)) to the first liquid inlet (Fig. 1(3)) using a peristaltic pump (2 L/min, Model 5206, Heidolph, Germany). Four milliliters of SS solution at 250 mg/mL was introduced through the second liquid inlet (Fig. 1(4)). The RPB was set to run at the highest frequency (50 Hz) and four different running times, 30, 60, 90 and 120 min were used. Running started from when the SS solution was introduced and ended when the RPB was stopped. The resulting suspension containing the precipitated SS was collected from the outlet of the RPB (Fig. 1(5)) at the end of each run.

2.2.2. Spray drying

The collected suspensions of precipitated SS from the RPB were spray dried (191, Büchi, Switzerland) to obtain the dry powders using the following conditions: aspiration rate of 38 m^3/h, feed rate 5 mL/min, inlet and outlet temperatures of 150 and 85 °C, respectively, and atomising air rate of 800 L/h. The spray-dried powder collected was then transferred into a container and stored over silica gel until further use for characterisation and testing. Amorphous salbutamol sulfate was prepared by spray drying 10% (w/v) aqueous salbutamol sulfate using the same conditions as above. The powder was stored over phosphorous pentoxide immediately after preparation.

2.3. Solid-state characterisation

2.3.1. Particle size distribution

Particle size distribution of the precipitates from the RPB and the spray-dried powders were measured by laser diffraction (Mastersizer S, Malvern Instrument, UK). Both the RPB precipitate and the spray dried powder were resuspended in IPA as the dispersion medium with sonication (5 min, Ultrasonics, Australia) for the measurement. The measurements were carried out in triplicate. Particle size analysis was based on the refractive index (RI) of SS (1.553), $RI_{imaginary}$ of SS (0.100) and RI of IPA (1.378). The size distribution was expressed by the volume median diameter (VMD) and span. Span is a measure of the polydispersity of the PSD, defined as the difference in the particle diameters at 10 and 90% cumulative volume, divided by the volume median diameter.

2.3.2. Particle morphology

Particle morphology was examined by high-resolution scanning electron microscopy (SEM, JSM 6000F, Joel, Japan) operating at 15 keV. Samples were mounted on metal plates by carbon tape and sputter coated with platinum.

2.3.3. Particle crystallinity

Powder crystallinity was assessed by X-ray diffraction (XRD, D5000, Siemens, Germany) conducted at room temperature using Cu Kα radiation at 30 mA and 40 kV, with an angular increment of 0.05°/s and count time of 2 s.

2.3.4. Density determination

Both the tapped and true densities were measured. For tapped density, a known mass (approximately 50 mg) was loaded into a glass tube and the tube was tapped on a bench by hand (100 times), and the volume of the final packed powder was measured. True particle density was determined by a buoyancy method (Chew and Chan, 1999). Powder (approximately 1–2 mg) was loaded into different density gradient liquids (comprising different proportions of bromoform and 1-hexanol) and centrifuged (3500 rpm, 5 °C, 30 min, CT422, Jouan, France). The powder density is equal to the liquid density when the particles remain suspended after centrifugation.

2.3.5. Moisture content determination

Water content of the powders was determined by thermogravimetric analysis (TGA, 2050, TA instruments, USA). Samples (5 mg) were placed in the platinum sample pan and heated from room temperature to 200 °C at 5 °C/min under a nitrogen purge of 30 mL/min.

2.3.6. Product stability

To compare the physical stability, both the spray dried amorphous and HGCP SS powders were examined by Dynamic Vapour Sorption (DVS, DVS-1000, Surface Measurement Systems, UK). Each sample was loaded into a glass sample pan and initially allowed to dry before being exposed to a series of regulated relative humidity (RH) where the samples were equilibrated at one RH until the change in mass over 5 min was less than 0.0002% before progressing to the next RH. Two cycles of 0% to 90% RH and back to 0% in steps of 10% RH were used, with mass and humidity recorded every 20 s. Isotherms were obtained through the software provided (DVS Analysis Suite Version 3.6) and the mass change was calculated relative to the dry mass.

2.4. Aerosol performance

The dispersion behaviour of the powders was assessed using an Aeroliser® (Novartis Pharmaceuticals, Australia) coupled through an USP stainless steel throat to a multi-stage liquid impinger (MSLI, Copley, UK), operating at 60 L/min. The powder (10.0 ± 0.5 mg) was filled into hydroxypropyl methylcellulose capsules (size 3, Capsugel®, USA) and three capsules were used in each experiment. Each experiment was performed in duplicate. SS deposited at different locations was assayed by UV spectrophotometry (U-2000, Hitachi, Japan) at 276 nm. A calibration curve of SS in water was constructed linear in the concentration range of 5–200 μg/mL [concentration (μg/mL)=188.38 × absorbance + 0.1386; $R^2 = 0.9999$, $n = 3$].

Fine particle fraction loaded (FPF_{loaded}) is defined as the mass fraction of drug particles smaller than 5 μm in the aerosol cloud relative to the total mass recovered, and $FPF_{emitted}$ the mass fraction of drug particles smaller than 5 μm in the aerosol cloud relative to the emitted dose. The *fine particle dose* is the mass of drug particles smaller than 5 μm in the aerosol cloud (interpolated from the mass of drug collected from stages 2, 3, 4 and filter) while *emitted dose* is the drug mass collected from the throat, stages 1–4 and filter. *Impaction loss* is the mass fraction of the powder collected from the throat and stage 1, relative to total mass recovered. *Capsule and device retention* is the mass of drug particles remaining in the capsules and the device. Total mass recovered is the sum of emitted dose and the capsule and device retention.

3. Results and discussion

The HGCP SS particles are elongated with 0.1–0.2 μm in width but varying length of 1–10 μm (Fig. 2a). As the RPB running time increased, the apparent volume median diameter (VMD) of the precipitated particles was decreased while the span increased (Table 1). Due to the non-isometric shape of the particles, the measured VMD is only an average value from the volume size distribution based on modelling the scattered light intensity data. This technique is thus only used qualitatively to compare the differences between samples and observe trends. Mixing will cease when the RPB is stopped; so if particle formation has not reached completion, particle size control is lost and larger particles will subsequently be formed post RPB. Longer running times thus ensure completion of particle formation.

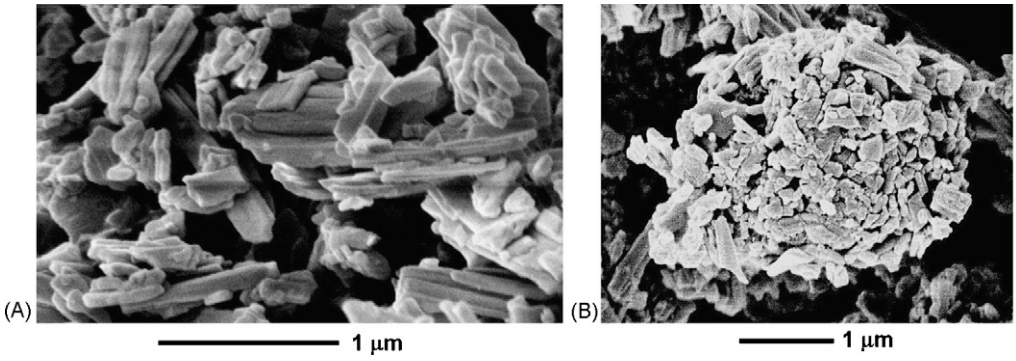

Fig. 2. SEM images of SS powder in: (a) primary form and (b) spray dried agglomerate.

Table 1
Summary of characteristics of the salbutamol sulfate suspensions and powders

	Sample RPB running time			
	1 (30 min)	2 (60 min)	3 (90 min)	4 (120 min)
VMD (μm) [suspension]	6.8 (±0.3)	4.7 (±0.1)	2.6 (±0.3)	3.5 (±0.2)
Span (suspension)	1.9 (±0.1)	1.9 (±0.1)	3.4 (±0.5)	2.5 (±0.4)
VMD (powder) (μm)	4.8 (±0.3)	4.1 (±0.1)	1.5 (±0.1)	2.2 (±0.1)
Span (powder)	2.0 (±0.2)	1.8 (±0.1)	4.4 (±0.4)	3.5 (±0.2)

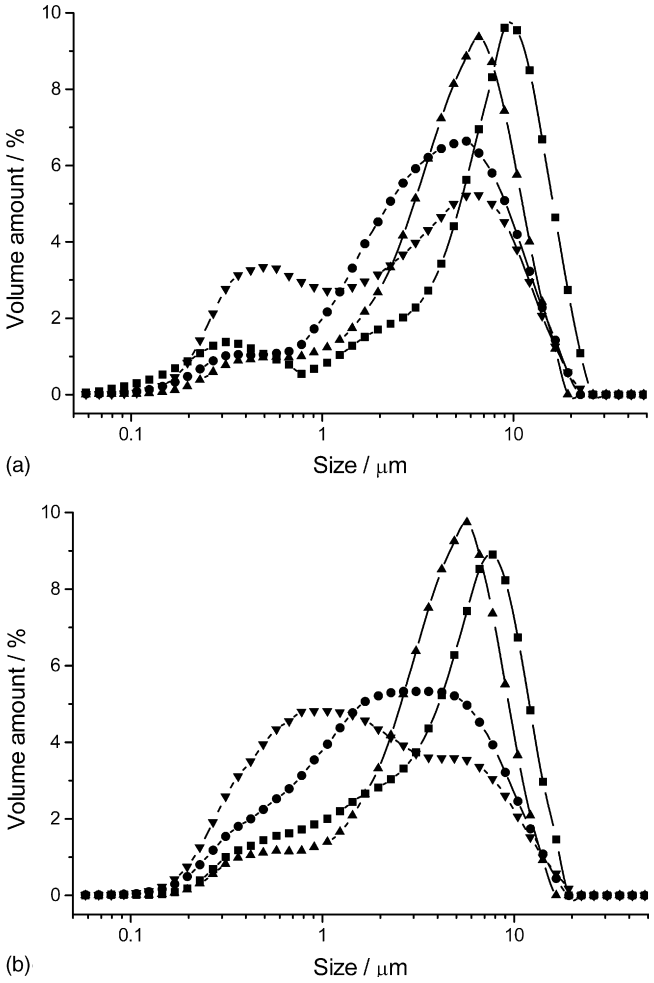

Fig. 3. Particle size distributions of salbutamol sulfate: (a) suspension collected from the RPB and (b) spray dried powder: (■) sample 1; (▲) sample 2; (▼) sample 3; (●) sample 4.

Spray drying was necessary to remove the liquid after high gravity precipitation in order to obtain the dry powders. After spray drying, the VMD of the primary particles was slightly reduced (Table 1) with a shift of the particle size distribution towards the smaller size range (Fig. 3a and b). It is expected that smaller particles tend to escape collection in the cyclone of the spray drier. However, smaller particles will also be accommodated better than larger particles in small droplets and subsequently recovered during the particle size measurement. In addition, the high shear at the nozzle during spray drying could break the elongated particles into small fragments. This was confirmed by the SEM images of the particles in the suspension before (Fig. 4a) and after spraying (Fig. 4b) through the nozzle.

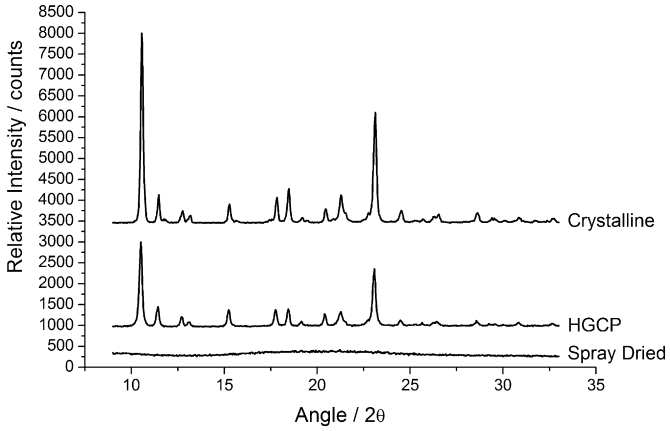

Fig. 5. XRD patterns of the spray dried HGCP SS sample, comparing with the crystalline starting material and amorphous spray dried SS.

It is possible to spray dry an aqueous solution of salbutamol sulfate to form small (~4.4 μm) particles which, however, is amorphous in nature (Chawla et al., 1994). In contrast, the HGCP powder was found to be crystalline with the same true density (1.3 g/cm^3) and XRD diffraction pattern (Fig. 5) as the raw material. After spray drying, the HGCP particles formed spherical agglomerates (Fig. 2b), showing a much lower tapped density (0.1 g/cm^3) compared with the raw material (0.6 g/cm^3). The residual water content of the HGCP powder was less than 0.3% (w/w) by TGA. As expected, the crystalline HGCP particles were much less hygroscopic (0.6% water uptake at 90% RH) than the amorphous SS powders (10.1% water uptake) (Fig. 6). The low moisture uptake, along with the fact that the repeat cycle of the DVS run showed a similar isotherm as the first cycle, indicate only a low level of amorphous content (if any) present in the high gravity material. For any product to be useful, it has to have sufficient shelf-life at the storage conditions. Amorphous

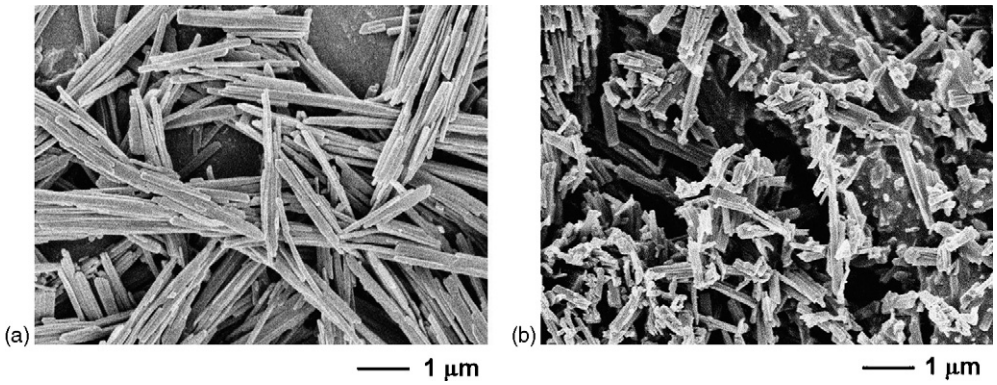

Fig. 4. SEM images of SS needles: (a) before and (b) after spraying a suspension of SS (collected from a 120 min RPB run) through the spray drier nozzle at the same atomising pressure as spray drying (800 L/h) without any heating.

Table 2
Aerodynamic properties of SS powders dispersed at 60 L/min with Aeroliser®

Sample	FPF	Dispersibility	Capsule and device retention	Impaction loss
1	37.2 (±1.1)	52.3 (±2.2)	23.5 (±1.5)	14.9 (±0.9)
2	43.5 (±2.1)	60.2 (±3.2)	22.7 (±1.5)	13.4 (±0.7)
3	48.5 (±4.3)	67.1 (±7.8)	24.6 (±3.9)	9.1 (±1.2)
4	54.5 (±4.9)	71.3 (±10.0)	20.2 (±1.0)	7.3 (±0.5)

SS powder is known to recrystallise at a relative humidity (RH) of around 75% (Columbano et al., 2002). The DVS isotherm of amorphous spray dried SS shows a continuous uptake of moisture until 70% RH at which the powder started to expel the absorbed water as it recrystallised. Recrystallisation is expected to make the powder poorly dispersible (Chan, 2003).

Although the use of spray drying did alter the form as the particles were agglomerated, the aerosol performance of the spray-dried powder was high as confirmed by the results (Fig. 7). The rough surface of the agglomerates prevents close packing (between agglomerates), which effectively increases the inter-agglomerate distance and lowers the van der Waals attractive force. The surface asperities may also reduce the effective area

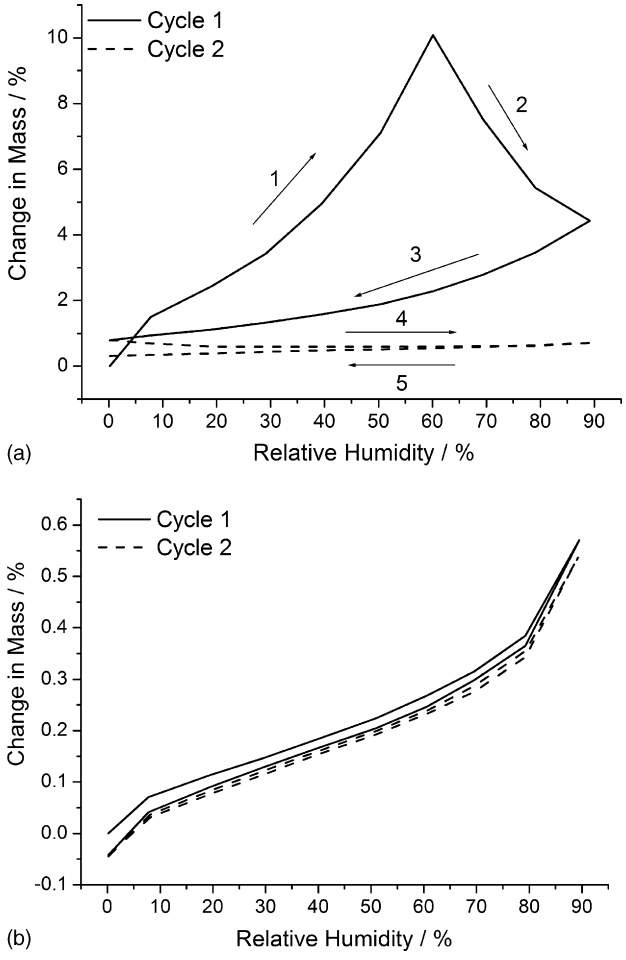

Fig. 6. Dynamic vapour sorption isotherms of SS (a) spray dried from solution and (b) spray dried HGCP powder. The numbers show the direction of the isotherm. Recrystallisation of spray dried SS from solution was complete in the first cycle as the second cycle showed only minimal moisture uptake.

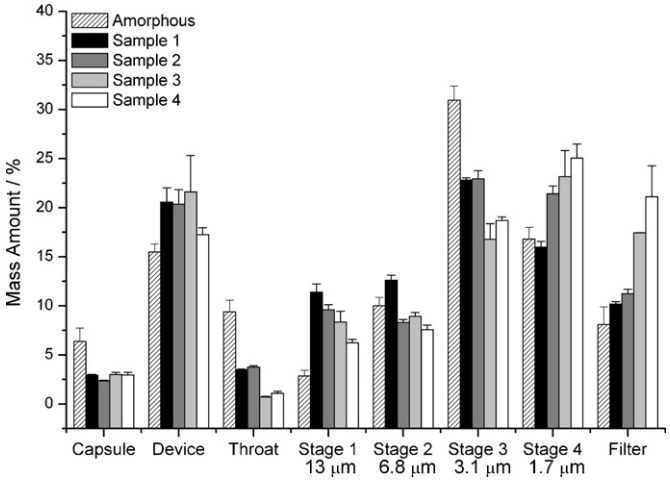

Fig. 7. Comparison between the powder dispersion behaviour of amorphous SS spray dried from solution and the spray dried HGCP samples.

of contact between agglomerates. Further, a higher drag force on the irregular surface will lead to a smaller aerodynamic size (Chew et al., 2005). Less cohesive powders generally flow better so the agglomerates can be readily emptied from the capsule (retention <5%, Fig. 7). It is possible that during dispersion, the agglomerates may further break into individual particles by the shear forces from the air and/or collision between the agglomerates or between the agglomerate and the inhaler device (Coates et al., 2005).

The aerosol performance of the pure HGCP SS powders indicates lower impaction loss and higher FPF for samples with longer running times (Table 2), corresponding to a decrease in the throat and stages 1–3 along with a subsequent increase in stage 4 and filter in the MSLI (Fig. 7). The 120-min sample showed the highest fine particle fraction FPF_{loaded} and $FPF_{emitted}$ of $54.5 \pm 4.9\%$ and $71.3 \pm 10.0\%$, respectively. It is worth to note that the amorphous spray dried SS is also dispersible with a FPF_{loaded} of 41.8 ± 0.3 and $FPF_{emitted}$ 55.7 ± 3.9, using the Aeroliser® at 60 L/min. However, as discussed above, the amorphous SS is highly hygroscopic and will undergo recrystallisation leading to physical instability and poor dispersibility.

In conclusion, salbutamol sulfate powder suitable for pulmonary drug delivery was obtained by HGCP followed by spray drying. The process is simple and no additives are required to achieve the particles in the size range produced.

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