1 Introduction

The traditional method for producing active drug particles within the respirable range involves solvent based crystallisation followed by filtering, drying and high energy micronisation. This processing sequence only provides limited opportunity for control over particle characteristics such as size, shape and morphology and introduces uncontrolled structural variations (decreased crystallinity, polymorphism) and surface modifications (increased surface free energy, adhesion, cohesiveness and charge). These uncontrolled variations have an adverse effect on dry-powder formulation and may even render the formulation ineffective. Salmeterol xinafoate (SX), selected as a model drug compound in this work, exhibits similar problems. SX is a long-acting $\beta_2$ adrenoreceptor agonist, widely used in the management of moderate and severe chronic asthma. This compound has been formulated for both metered-dose suspension (MDI) and dry powder inhalers (DPI). It is reported that SX materials are generated by a conventional crystallization process using dissolution in 2-propanol at elevated temperatures and natural cooling to induce supersaturation [1]. These products were highly cohesive and showed very poor powder flow properties making it unsuitable for fluid energy milling. A more advanced crystallization process therefore was developed in which a hot SX solution in 2-propanol is added to a chilled quench solvent inducing large (in the range between 100-250 $\mu$m) spherical aggregates. These granular SX powders have improved flow and handling properties and are used for micronisation [1].

Supercritical fluid (SCF) technology offers a more benign and commercially viable process capable of direct production of respirable drug particles. The advantages of this technology are related to the abil-
ity of supercritical solvents, the most important of which is supercritical carbon dioxide (scCO2), to be efficiently separated, by decompression, from both organic co-solvents and solid powders, facilitating one-step, clean and recyclable process engineering. Particle formation using SCF is a crystallisation process [2], with sufficient flexibility to produce single crystal, uniform particles with low surface energy. The benefits of SCF-processed particles in both DPI and MDI formulations have been demonstrated. For example, particles of several steroid drugs were produced by direct spraying of drug solutions into the medium of scCO2 [3] and an increase of fine particle fraction (FPF) for steroid formulations prepared with lecithin for an MDI was observed [3,4]. Protein powders were also prepared and tested using this method for DPI applications [5]. The SEDS™ method (Solution Enhanced Dispersion By Supercritical Fluids) [6] has an added advantage of very fast, homogeneous nozzle mixing between supercritical antisolvent and drug solution leading to consistent production of micron sized particulate products [7]. By changing the working conditions of pressure, temperature, solution concentration and flow rates, it is possible to control the size, shape, morphology and crystal form of the micron sized particles [2,7-9]. In studies with DPI formulations of salbutamol sulphate, increased FPF and targeted in vitro delivery have been demonstrated for SEDS-prepared powders when compared with micronised material [10,11]. For salmeterol xinafoate, aerosols of both polymorphs have been produced [12,13] and a detailed thermal analysis has shown a high degree of chemical and crystallographic purity of these compounds [13]. The present work represents a comparative study of the micronised and supercritically-processed powders with the aim to distinguish the solid-state properties important for successful formulation of dry-powder aerosols.

2. Materials and methods

2.1 Chemicals and reagents

Salmeterol xinafoate (SX) in the form of granulated material (G-SX) used for micronisation and micronised powder (M-SX) were generously supplied by GlaxoWellcome, Ware, UK. HPLC grade solvent for SEDS were purchased from BDH Chemicals, Leicester, UK. All analytical grade liquid probes used in IGC studies were purchased from Labscan, Dublin, Ireland. Industrial grade (>99.95% pure) CO2 was supplied by Air Products (Manchester, UK).

2.2 Production of SX powders

The SEDS™ method was employed to prepare powders of SX, form I (S-SX). This technique (Fig. 1) is based on mixing between supercritical CO2 antisolvent and a drug solution using a twin-fluid nozzle. Methanol, acetone and tetrahydrofurane were tested in this work, after which methanol was selected for further studies because of high yield (>95%) and suitable particle size distribution (PSD) (X90=10 µm) of the SX products. The particle formation vessel (500 ml volume) with the nozzle was placed in an air-heated oven. The temperature in the vessel was monitored by a thermocouple with accuracy ±0.1°C and was kept constant at 40°C. Pressure in the vessel was controlled by an air-actuated back-pressure regulator (26-1761 with ER3000 electronic controller, Tescom, Elk River, MN, USA) and kept constant at 250±1 bar. The difference in the inlet and outlet pressure was typically within 1% of its absolute value. The CO2 flow rate, supplied by a water-cooled diaphragm pump Milton Roy B (Dosapro Milton Roy, Pont-Saint-Pierre, France) was typically between 25 and 50 NL/min as monitored after expansion using a gas flow meter (SHO-Meter 1355, Brooks Instruments B.V., Veenendaal, Holland) and also controlled before expansion using high-pressure liquid flow meter (DK34, Krohme Messtechnik GmbH, Duisburg, Germany). Solution concentration of SX varied between 1 and 10% w/v. Solution flow rate was provided by a metering pump PU-980 (Jasco Co, Tokyo, Japan) and varied from 0.5 to 10 ml/min.

Prior to crystallization experiments, an on-line dynamic solubility method [14] was used to determine the equilibrium solubility profile of SX in methanol/
CO₂ mixtures at different mole fractions of methanol. On this basis, the solution flow rate and the solution concentration were optimised to achieve maximum supersaturation and maximum yield according to a developed method [15]. Several batches were prepared with batch quantities between 1 and 10 g. The obtained cumulative PSD for all batches had d₅₀=10 µm and volume-moment mean particle diameter, d₄₃=5 µm, as determined using the laser diffraction (LD) method. Further improvement in nozzle geometry (the diameter, length and volume of the mixing zone) allowed the mean particle diameter to decrease down to d₄₃=3.5 µm with cumulative x₉₀=10 µm.

2.3 High resolution X-ray powder diffraction

This technique was used to determine the characteristic diffraction peaks of SX forms I and II and to distinguish crystallographic changes (peak shift and peak broadening) of G-SX, M-SX and S-SX compounds. The experiments were carried out at the Synchrotron Radiation Source (SRS) Daresbury Laboratory, station 2.3 (Warrington, UK). The X-ray wavelength was λ=1.4016 Å. The diffractometer had a flat-plate/parallel foils Hart-Parrish geometry and was calibrated using the diffraction peaks of crystalline silicon with accuracy 10⁻⁴ degrees. The instrumental broadening (shape of diffraction peaks related to the instrument geometry) was obtained using lanthanum hexaboride standard (NIST, Denver, USA). All samples were placed in rotating plate holders and scanned between 2θ=1–40° with resolution 0.01° (0.005° for the standard) and typical signal integration time 1 s.

The diffraction data of SX were corrected for the beam decay and indexed using program CHEKCELL [16] in order to find the crystal cell parameters. The exact position of a minimum of five characteristic diffraction peaks, 2θ, the Full Width at Half Maximum, FWHM, and the mixing parameter, η, of pseudo-Voigt function were determined using peak fitting option of program ORIGIN. The instrumental broadening was assessed using program shadow [16]. The obtained parameters were then input into program BREATH [16] to analyse the physical diffraction line broadening caused by distribution of domain size and strain in particles [17]. Alternatively, the diffraction data were examined using program POWDER CELL [16] applying the whole profile Le Bail fitting option of this software. In this case, the instrumental broadening FWHM was assumed to be 0.025° which is typical for an SRS diffractometer [18]. This procedure was less accurate then that using calibration line broadening and therefore only relative trends on the size/strain were interpreted from these results.

2.4 Time-resolved small-angle X-ray powder diffraction

Dynamic analysis of polymorphic transition of SX was carried out at the SRS Daresbury Laboratory using temperature-controlled small-angle X-ray scattering (SAXS) arrangement at station 8.2. The experimental method [19] involved time-resolved detection of the SX polymorphic transition with characteristic peaks at diffraction angles 2θ<5°. Measurements were carried out at wavelength λ=1.54 Å. The quadrant SAXS detector was placed at a distance 1 m from the sample. Samples were placed in a modified aluminium DSC pan. The pan top and bottom were removed with a punch and replaced with thin mica discs. Sealed pans were placed in a spring-loaded holder in a modified Linkam TM H600 (Linkam Scientific Instruments, Tadworth, UK) hot stage mounted on the optical bench in the center of X-ray beam. Heating rates between 5°C/min and 40°C/min were used. Prior to X-ray measurements, the Linkam temperature range was calibrated using potassium nitrate (melting onset 128°C), indium (154°C) and tin (230°C). The diffraction pattern of silver behenate was used to calibrate the SAXS detector. Incident and transmitted beam intensity monitored by ionization detectors were used to correct for X-ray beam decay, detector sensitivity and background scattering. The signal integration time was 6 s.

2.5 Inverse gas chromatography (IGC)

IGC was performed on a Hewlett Packard Series II 5890 Gas Chromatograph (Hewlett Packard, Wilmington, DE, USA) equipped with an integrator and flame ionization detector. Injector and detector temperatures were maintained at 100 and 150°C respectively. Glass columns (60 cm long and 3.5 mm i.d.) were deactivated with 5% solution of dimethyl dichlorosilane in toluene before being packed with SX powder. The columns were plugged with silanised glass wool at both ends and maintained at 40°C. Data were obtained for a known weight and surface area of the sample using a nitrogen gas (purity>99.995%) flow at 20.0 ml/min. The column was weighed before and after the experiment to ensure no loss of materials during the run. A trace amount of vapour from non-polar and polar probes was injected. The retention times and volumes of the injected probes were measured at infinite dilution and thus were independent of the quantity of probes injected. The non-polar
Probes employed were pentane, hexane, heptane, octane and nonane; the polar probes were dichloromethane, chloroform, acetone, ethyl acetate, tetrahydrofuran and diethyl ether. Triboelectric measurements in separate columns were made for G-SX, M-SX and S-SX powders. Differences in surface energetics were reflected in the calculated dispersive component of the surface free energy, $\gamma_D$; specific component of surface free energies of adsorption, $-\Delta G_a$; and the acid-base parameters, $K_A$ and $K_D$. A more detailed theory of these measurements is discussed elsewhere [13,20-22].

Data on specific surface areas required for IGC studies were determined by BET nitrogen adsorption using a Surface Area Analyzer Coulter SA 3100 (Coulter Corp., Miami, FL, USA). Samples were placed in glass sample holders and out-gassed with helium (purity >99.999%) at 40°C for 16 hours before analysis. Nitrogen (purity >99.999%) was used as adsorbate and BET surface area was recorded as specific surface area of the samples. All measurements were performed in triplicate using the same batch of each material.

### 2.6 Electric charge and adhesion measurements

Triboelectrification was undertaken against a stainless steel contact surface using either a turbula mixer or a cyclone separator. Triboelectrification in a turbula mixer (Glen Creston, UK) was carried out by agitating a powder sample for 5 minutes at 30 rpm in a 100 ml stainless steel vessel at ambient temperature and relative humidity. A sample was poured in a reproducible manner into a Faraday well connected to an electrometer (Keithley 610, Keithley Instruments, Reading, UK). Charge and mass of sample was then recorded to give specific charge before and after triboelectrofication. % w/w adhesion to the inner surface of the mixing vessel was calculated from the original mass of sample and the mass of sample poured into the Faraday well. During triboelectrification in a cyclone separator, a powder was fed from a steel vibratory table into a venturi funnel. Compressed air (velocity 8 m/s, relative humidity below 10% ambient temperature) was used to convey the powder from the venturi along a horizontal pipe into the cyclone separator. The Faraday well and force compensation load cell was fitted at the base of the cyclone and used to collect charged particles. Final specific charge was recorded for non-adhered powder residing in the Faraday well and, where possible, powder adhering to the cyclone wall was dislodged by a stream of air and its charge and mass recorded. In both cases, the results were obtained from triplicate measurements.

### 2.7 Particle size analysis

The instrument consisted of a laser diffraction sensor HELOS and dry-powder air-dispersion system RODOS (Sympatec GmbH, Germany) with WINDOS OS computer interface. The dispersion process was controlled by means of adjusting pressure of the compressed air flow between 0.5 and 5 bar. The pressure of 2 bar was found to be sufficient to disperse most of the agglomerates avoiding, at the same time, attrition of the primary particles. All measurements were performed in triplicate. The particle shape factor, $f$, was calculated as $f=\sqrt{S/S_0}$ where $S$ is the experimental specific surface area and $S_0$ is the specific surface area determined using the LD instrument assuming the particle sphericity.

### 3. Results and discussion

#### 3.1 Crystallinity

Analysis of diffraction patterns (Fig. 2) showed that peak-fitting, background determination and indexing were performed more consistently and with higher accuracy using the S-SX sample than with the M-SX and G-SX samples. This fact is related to the smaller diffraction line-broadening and higher signal-to-noise ratio for the S-SX sample (see Fig. 2). The strongest characteristic peaks of SX were identified as (001), (113) and (134). The crystal cell calculated from this diffraction pattern is of triclinic P-1 (or P1) form with parameters: $a=9.487$, $b=16.242$, $c=21.372$ Å; $\alpha=93.16$, $\beta=97.73$, $\gamma=90.94^\circ$, calculated cell volume $V=3257.3$ Å$^3$ and theoretical crystal density $\rho=1.256$ g/cm$^3$.

Physical broadening of diffraction peaks is a cumulative measure of crystal lattice imperfections. This is grouped into size effects (grains, small-angle boundaries, stacking faults) or as strain defects (point defects and dislocations). The basis for discrimination between these effects lies in the fundamental principle that the size term does not depend on the diffraction angle whereas the strain does [17]. Comparison of the diffraction peaks (Fig. 2) indicates that the peak broadening is much smaller for S-SX sample than for both G-SX and M-SX samples. Quantitatively, these differences can be expressed through the shift in the peak position, $2\theta$, the peak width, FWHM, and the integral breadth, $\beta$ (all expressed in the degree units). The latter parameter is defined as the width of rectangle having the same area, $A$, and height, $I$, as...
the observed line profile:

$$\beta = \frac{A}{I}$$  \hspace{1cm} (1)

Table I shows these parameters for two characteristic diffraction peaks. S-SX sample shows higher crystallinity (smaller FWHM and $\beta$) than the other two compounds. In addition, there is a small but significant shift of the diffraction peaks produced by M-SX and G-SX compounds towards smaller $2\theta$, relative to the same peaks of S-SX compound. Such shift is between 0.001-0.003° for different lines which corresponds to a relative increase of $d$-spacing, $\Delta d/d$ between $\pm 1$ and 2% and to correspondent increase of crystal volume, $\Delta V/V$ between $\pm 1$ to 2% for both M-SX and G-SX samples.

More fundamental analysis of line broadening consists of the “double-Voigt” method [17] which approximates the physically broadened line profile as a convolution of Cauchy (C) and Gauss (G) integral breaths, containing size (S) and strain (distortion, D) contributions according to the equations:

$$\beta_C = \beta_{CS} + \beta_{CD} s_0^2$$ \hspace{1cm} (2)

$$\beta_G = \beta_{GS} + \beta_{GD} s_0^2$$ \hspace{1cm} (3)

The integral breaths, $\beta$, are given in the units (Å⁻¹) of the wave-vector, $s$:

$$s = 2 \sin \theta / \lambda$$ \hspace{1cm} (4)

$$\beta = \beta \cos \theta / \lambda$$ \hspace{1cm} (5)

Here, $\beta_{CD}/s_0^2$ and $\beta_{GD}/s_0^2$ are constant for the whole pattern (taken at zero-value of the wave-vector, $s_0$ of the first peak). The integral breaths found from the

![Fig. 2](image)

**Fig. 2** X-ray diffraction patterns of salmeterol xinafoate samples: granulated (G-SX), micronised (M-SX) and SEDS-produced (S-SX) obtained at the wavelength 1.4 Å. The inserted diagram allows a comparison between characteristic (113) diffraction peaks for these samples.

**Table I** The position ($2\theta$), width (FWHM) and integral breadth ($\beta$) of characteristic diffraction peaks of the salmeterol xinafoate samples.

|          | S-SX       | M-SX       | G-SX       |
|----------|------------|------------|------------|
| (113)    |            |            |            |
| $2\theta$| 15.7420±0.0003 | 15.7396±0.0003 | 15.7395±0.0003 |
| FWHM     | 0.084±0.001  | 0.122±0.001  | 0.171±0.001  |
| $\beta$  | 0.093±0.001  | 0.132±0.001  | 0.178±0.001  |
| (134)    |            |            |            |
| $2\theta$| 22.3613±0.0005 | 22.3595±0.0005 | 22.3605±0.0005 |
| FWHM     | 0.080±0.002  | 0.110±0.002  | 0.141±0.002  |
| $\beta$  | 0.088±0.002  | 0.119±0.002  | 0.150±0.002  |
experimental diffraction profiles allow calculation of the surface-weighted, $D_s$, and volume-weighted, $D_v$, domain size and a mean-square (Gaussian) strain, $\varepsilon$, which is the total strain averaged over infinite distance:

$$D_s = \frac{1}{2\beta \lambda}$$
$$D_v = (\frac{\varepsilon}{\varepsilon_G}) \exp(\frac{\beta^2}{\varepsilon_G^2})$$
$$\varepsilon = \frac{\varepsilon_G}{(\frac{\beta}{\pi})^{1/2}}$$

Here $\varepsilon$ denotes a complementary error function related to the background determination [17].

The results of computation using eqs. [2-8] are given in **Table II**. Clearly, S-SX compound consists of larger crystalline domains (by about 20%) and smaller strain (by about 60%) than both M-SX and G-SX compounds. The granulated batch under investigation, G-SX, was shown to be the least crystalline material. **Table II** also presents the data obtained using the alternative computation method with Le Bail diffraction profile fitting. Both methods gave consistent results in terms of domain size and strain.

It should be emphasized that S-SX shows higher crystallinity compared to both M-SX and G-SX compounds. In the first instance, this fact seems to be contradictory. It is widely believed that micronisation procedure is the major factor responsible for the crystallinity decrease, and in general, for transition into a higher free energy solid state. The analytical results obtained in this work indicate that “aggressive” crystallisation procedures [1] may also lead to crystal disordering which is comparable to or greater than those defects induced by micronisation. It is unlikely that micronisation can improve the crystallinity. The fact that G-SX sample has a higher crystal strain and specific surface free energy is likely to indicate that M-SX compound was obtained from a different batch of granular SX than that available for the present study. Low consistency of batch solution crystallisation has been acknowledged in the pharmaceutical industry.

### 3.2 Polymorphic purity

SX has two polymorphs which are related enantiotropically [1,12,13]. The estimated transition temperature is between 90 and 110°C [13]. Although the X-ray analysis shows that there is no significant presence of form II in form I substances produced using both SEDS and micronisation, the polymorphic purity of these compounds was under question because they showed different melting-recrystallization behaviour according to differential scanning calorimetry (DSC). This problem was addressed in the present work using time-resolved X-ray diffraction combined with a thermal analysis.

The strongest characteristic diffraction peaks (001) of both SX polymorphs are located at low angles $2\theta=4.13°$ (form I) and $2\theta=2.87°$ (form II) at $\lambda_c=1.54$ Å. These high intensity peaks enable presence of form II to be detected above 0.5% w/w in samples prepared by mixing the two polymorphs. **Fig. 2** shows that, within this sensitivity, the S-SX, M-SX and G-SX are the form I compounds. However, the dynamic X-ray studies of melting behaviour (**Fig. 3**) indicated that at relatively fast heating rates equal or above 10° min, a single diffraction profile of form I, without recrystallization into form II was obtained for S-SX samples. At the same heating rate, M-SX samples showed melting of form I and immediate recrystallization into form II. The characteristic (001) peak of form II appeared

| Table II | The integral breaths of Voigt-approximated diffraction profile, $\beta$, and calculated values of the surface-weighted, $D_s$, and volume-weighted, $D_v$, domain size and the Gaussian strain, $\varepsilon$. The corresponding size and strain parameters, $D_v$ and $\varepsilon$ were calculated on the basis of the diffraction profile Le Bail fitting and the instrument broadening FWHM = 0.025°. |
|----------|---------------------------------|-----------------|-----------------|
|          | S-SX                           | M-SX            | G-SX            |
| $\beta_{CS}$, Å⁻¹ | 0.11×10⁻²                      | 0.13×10⁻²       | 0.15×10⁻²       |
| $\beta_{CO}$, Å⁻¹   | 0.30×10⁻⁵                      | 0.13×10⁻⁴       | 0.21×10⁻⁴       |
| $\beta_{GS}$, Å⁻¹   | 0.39×10⁻³                      | 0.40×10⁻³       | 0.38×10⁻³       |
| $\beta_{GD}$, Å⁻¹   | 0.63×10⁻⁴                      | 0.97×10⁻⁴       | 0.12×10⁻³       |
| $D_s$, Å          | 453±44                         | 382±60          | 326±50          |
| $D_v$, Å          | 785±60                         | 662±86          | 606±74          |
| $\varepsilon$     | $(0.53±0.02)×10⁻³$             | $(0.83±0.03)×10⁻³$ | $(0.101±0.006)×10⁻²$ |
| $D_v\ GÅ$         | 1320                           | 670             | 640             |
| $\varepsilon\ \square$ | $0.70×10⁻³$                  | $0.17×10⁻²$     | $0.22×10⁻²$     |
simultaneously with the corresponding (001) peak of form I and coincided with the exothermic DSC peak at this temperature. When the heating rates were decreased below 10°/min, both S-SX and M-SX materials showed recrystallization into form II at about 130°C. These data indicate that S-SX compound has a higher activation energy barrier to recrystallization into form II than M-SX compound. Assuming that S-SX compound, as evidenced by time-resolved diffraction analysis. It is likely that the micronization and solution crystallisation processes employed for production of these particles created nuclei of form II which accelerate the polymorphic transition at high temperature. It is also possible that supercritical fluid processing removes some impurities (soluble in the supercritical phase) from the starting salmeterol compound also lowering the activation energy of nuclei formation.

3.3 Surface free energy and specific surface area

The fundamental quantity of inverse gas chromatography is the net retention volume, V_n, determined from the retention time of a given solvent [20]. Adsorption of the probe molecules on solid surfaces can be considered in terms of both dispersive and specific components of surface free energy, corresponding to non-polar and polar properties of the surface. By virtue of their chemical nature, non-polar probes of the alkane series only have dispersive component of surface free energy, which can be determined from the slope of the plot based on the following equation:

\[ RT \ln V_n = 2aN_A(\gamma_S^D)^{1/2}(\gamma_L^D)^{1/2} + \text{const} \]  

where R is the gas constant, T is the absolute temperature of the column, a is the probe’s surface area, N_A is the Avogadro’s number, \( \gamma_S^D \) is the dispersive component of surface free energy of a SX powder and \( \gamma_L^D \) is the dispersive component of surface free energy of the solvent probes.

Polar probes have both dispersive and specific components of surface free energy of adsorption. The specific component of surface free energy of adsorption (\( \Delta G_{s}^{sp} \)) can be estimated from the vertical distance between the alkane reference line and the polar probes of interest. This free energy term can be related to the donor number (DN) and acceptor number (AN) of the polar solvent by the following equation:

\[ \Delta G_{s}^{sp} = K_A DN + K_D AN \]  

DN describes the basicity or electron donor ability of a probe whilst AN defines the acidity or electron acceptor ability. Here AN denotes a correction for the contribution of the dispersive component and the entropy contribution into the surface energy is assumed negligible [22]. Thus plotting \( -\Delta G_{s}^{sp}/AN \) versus DN/AN yields a straight line where \( K_A \) and \( K_D \) correspond to the slope and intercept respectively. The IGC data for the various SX samples analysed by the above approach are summarized in Tables III and IV. Comparison between different materials shows that the magnitude of \( \gamma_S^D \) is 15% smaller for S-SX compounds than for both M-SX and G-SX com-
pounds. In addition, \( \Delta G_{\text{ASP}} \) for all polar probes used reduced by at least half for S-SX compound compared to the other two materials. Comparison between M-SX and G-SX materials indicates that, although the \( \gamma_D \) are almost equal within the experimental error, \( \Delta G_{\text{ASP}} \) for all the polar probes is larger for the granulated material.

The reduced magnitude of \( \gamma_D \) for S-SX compound implies that the surfaces of these particles are less energetic for non-polar, dispersive surface interactions than the other two compounds. The overall strength of the polar interactions (\( \Delta G_{\text{ASP}} \)) is also the smallest for S-SX compound. Comparison between the \( K_A \) and \( K_D \) values of the three samples indicate that the acidity constant has the following trend: \( K_A(\text{S-SX}) < K_A(\text{M-SX}) < K_A(\text{G-SX}) \). The basicity constants follow the reverse order with \( K_B(\text{S-SX}) \) being the largest. Thus S-SX sample which has the weakest acidic property exhibits the strongest basic interactions with respect to its exposed polar groups at the interface. This suggests that S-SX crystal surfaces have, in relative terms, more exposed basic groups but fewer exposed acidic groups than both G-SX and M-SX compounds. Particles of all three samples have a similar platelet shape with the dominant \{001\} crystal faces. However, S-SX particles have the largest shape factor, \( f \) (see Table III), which means that platelets of G-SX and M-SX are thicker. The other materials have more energetic lateral crystal surfaces as a result of the solution crystallisation procedure (G-SX) and particle breakage on micronisation (M-SX). Therefore the observed differences in \( K_A \) and \( K_D \), combined with the smallest value of \( \Delta G_{\text{ASP}} \) and \( \gamma_D \) for S-SX compound, suggest a combination of three different factors affecting the specific surface energy: (a) difference in the crystal habit, i.e. the \{001\} crystal faces have stronger basic and weaker acidic interactions than the lateral crystal faces, (b) smaller overall specific surface energy of the \{001\} crystal planes as compared to any other crystallographic planes and (c) disturbances of the crystal structure which also contribute to the higher surface energy of G-SX and M-SX compounds.

It is clear that solvent adsorption progresses more rapidly with the M-SX and G-SX samples than with S-SX material. This fact indicates that supercritical fluid process is capable of producing particles with lower surface activity (and greater surface stability) than powders produced by solution crystallisation and micronisation.

### 3.4 Electrostatic charge and adhesion

Table V presents results on the charge, \( Q \), and fraction of adhered material, \( AD \). S-SX particles exhibited significantly less (between one and two orders of magnitude) accumulated charge than the micronised powder before and after turbula mixing and also for the non-adhered drug in cyclone separator. Correspondingly, the fraction of adhered material is several times smaller for S-SX powder than for M-SX powder in both the turbula mixing and cyclone separator tests.

These results are consistent with the superior powder flow properties of S-SX material. Although the bulk powder density of S-SX material is very low (about 0.1 g/cm\(^3\) vs. 0.5 g/cm\(^3\) for M-SX) it flows well and does not adhere to the container walls.

### Table IV

| Compound | Dichloromethane | Chloroform | Acetone | Ethyl acetate | Diethyl ether | Tetrahydrofuran |
|----------|-----------------|------------|---------|---------------|---------------|----------------|
| S-SX     | 2.808 (0.147)   | 0.153 (0.080) | 3.797 (1.173) | 2.705 (0.613) | 1.488 (0.390) | 2.446 (0.279) |
| M-SX     | 0.810 (0.053)   | 4.560 (0.096) | 3.995 (0.013) | 2.774 (0.041) | 3.609 (0.027) |
| G-SX     | 1.885 (0.047)   | 5.454 (0.154) | 4.739 (0.015) | 2.958 (0.038) | 4.854 (0.069) |
3.5 Particle size and powder dispersability

The difference in particle size distribution (PSD) of S-SX and M-SX powders is reflected in the magnitude of the mean particle sizes $d_{4,3} = 3.5 \mu m$ (S-SX) and $1.8 \mu m$ (M-SX) as measured using the LD technique. For both materials the cumulative PSD $> 98\%$ is within respirable particle size range $0.5< x<10 \mu m$. However, a significant difference was observed between the dispersion behaviour of micronised and supercritically-processed powders. At high dispersing pressures above $\approx 2$ bar, $d_{4,3}$ is smaller for M-SX powder, as indicated by the primary PSD for this compound. This situation changes dramatically at dispersing pressures below 2 bar. At low pressures, S-SX powders consistently produce a large fraction of primary particles in the respiratory size range, whereas M-SX powders form stable agglomerates outside the $5 \mu m$ range which are not be dispersed at such pressures.

The enhanced dispersability of S-SX powders means a decrease of the inter-particulate contact area and/or reduction of the cohesive forces leading to better performance of S-SX compound in the inhalation devices as shown in our work [23]. Despite a larger geometric (and volume) diameter for S-SX particles, the Andersen cascade impactor measurements indicated a greater than two-fold increase (from 25.15 to 57.80%) of FPF for S-SX powder compared with FPF of M-SX powder.

### Table V

| Turbula Mixer | Cyclone Separator |
|---------------|-------------------|
| Q, nCg$^{-1}$ (before mixing) | Q, nCg$^{-1}$ (after mixing) | AD$_1$, %w/w (for non-adhered drug) | Q, nCg$^{-1}$ (for adhered drug) | AD$_1$, %w/w |
| S-SX | $-0.52$ (51) | $-0.17$ (431) | 1.5 (14) | $+4.9$ (6.8) | $-34.6$ (42) | 5.5 (1.6) |
| M-SX | $-12.1$ (7.3) | $-42.6$ (53) | 27 (58) | $-48.4$ (17.5) | $-49.7$ (14.8) | 16.7 (9.7) |

4. Conclusion

The physical properties of micronised and supercritically-processed powders for respiratory drug delivery have been quantitatively defined in terms of specific surface energy, polymorphic purity, acquired charge and crystallinity. The enhanced physical properties for S-SX powders correlate well with the enhanced dispersion and flow behaviour of this powder. However, new analytical approaches are required to discriminate between the specific contributions such as aerodynamic forces and powder cohesive-ness, nature and statistics of inter-particulate forces, contact area and average distance between non-spherical particles. These problems will be addressed in our following study.

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