Processing of Spherical Crystalline Particles via a Novel Solution Atomization and Crystallization by Sonication (SAXS) Technique

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Purpose. The objective was to develop a single-step pharmaceutical particle engineering technique able to produce particles within a well-defined particle size range while controlling macroscopic spherical morphology and mesoscopic surface topography.

Methods. Paracetamol (acetaminophen) aerosol droplets were generated by spraying a solution via either an electrohydrodynamic atomizer (EHDA) or an air pressure atomizer. The highly supersaturated droplets were collected in a suitable nonsolvent of the drug and crystallized by ultrasonication. Suspended particles were filtered, and their physicochemical properties characterized.

Results. The SAXS processed particles showed a relatively homogeneous particle size distribution between 1 and 5 μm. Particles were nominally crystalline in structure. The chemical structure of the active ingredient did not apparently alter during processing. Controlling the solute concentration of the air pressure atomized solution provided a means of controlling the degree of sphericity and particle-size characteristics. In comparison to micronized paracetamol particles, SAXS-produced particulates were generally more uniform in shape with increased nanometer surface roughness.

Conclusions. The SAXS process provides a novel means of producing crystalline particles in a well-defined particle size range. Furthermore, the method offers a range of opportunities in controlling physical properties including surface topography and particle shape.

KEY WORDS: atomization; sonocrystallization; SAXS; electrospraying; particle engineering.

INTRODUCTION

The size and surface properties of solid-state particles have been shown to play a critical role in the behavior of active ingredients in a variety of pharmaceutical solid dosage forms (1). The aerosol delivery characteristics and therapeutic efficacy of suspension-based pressurized metered dose inhalation formulations and dry powder inhalation formulations, for example, depend critically on the physicochemical properties of the particles. Of these properties, particle size range and interfacial properties of the solid active ingredient are critical (2,3). Particle size can also improve the compression properties of crystalline powders for tableting and therapeutic efficacy of solid oral dosage forms, where the increase in surface area with decreasing particle size can dramatically alter the solubility profiles of low-solubility drug particulates (4). It is therefore desirable for a whole range of pharmaceutical solid dosage forms to produce active pharmaceutical ingredients within a narrow particle size distribution centered around the optimum particle size for reproducible and maximized therapeutic efficacy.

The limitations in conventional batch or continuous crystallization processes typically require an additional step to fine-tune particle size characteristics. These destructive-based techniques, such as micronization by air-jet milling, have been shown to adversely affect a range of highly important physicochemical properties (5,6). The high-energy input requirements of mechanical processing will inevitably introduce varying degrees of disorder within the crystal lattice, with the formation of crystal defects (point defects, edge and screw dislocations). If the degree of disorder is localized, domains of amorphous material may be generated. With the three-dimensional nature of crystal defects, these disordered regions will be ubiquitously present on the surfaces of processed particles. Recent atomic force microscopy (AFM) investigations by Begat *et al.* have identified the possible presence of these amorphous domains on the surfaces of cumulatively milled salbutamol sulfate crystals (7). The associated increase in surface free energy with the formation of amorphous states will directly influence interfacial interactions. Although disordered regions may occupy only an insignificant percentage of the total mass of the bulk powder, these uncontrollable alterations to the physicochemical properties of the surfaces of processed particles may consequently affect the overall stability, batch-to-batch performance, and therapeutic efficacy of active pharmaceutical ingredients (8).

Furthermore, conventional processing does not facilitate any significant control of the macroscopic shape and microscopic surface geometry of the fractured crystals. The flowability and dispersibility of sub-10-μm particles are controlled by interparticulate cohesive forces and adhesive interactions (9). These interfacial interactions are controlled, to a large degree, by the area of contact and average separation distances between contiguous particles (10). The unpredictable morphology and surface rugosity of micronized drugs may lead to large variations in the area of contact of adhesion. This property alone may significantly influence the handling and overall behavior of an active ingredient. There is, therefore, an increasing need to manufacture drug particles that are intrinsically more reproducible than those produced via high-energy comminution, especially in terms of particle architecture and degree of crystallinity.

Alternative processes for the production of solid drug particles, within an optimum particle size range, have included the use of supercritical fluids in the precipitation of active material, spraying of solutions into liquid nitrogen, complex spray-drying of emulsion-based formulations, and conventional antisolvent precipitation-based techniques (11–16). These constructive based techniques have provided a means of forming particulates with novel physicochemical properties, such as low-density porous spherical particles, particles with low surface free energy and well-defined morphologic structures.

However, there continues to remain a need to develop novel particle production technologies with an even greater control of the surface characteristics and surface geometry of active compounds while maintaining high throughput, low cost, and industrial scalability. In this article, we report for the first time the design of a single-stage processing technique

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that uses ultrasonic waves to produce increased sphericity in crystalline particles within a well-defined particle size range.

MATERIALS AND METHODS

Materials

Paracetamol (4-acetamidophenol) was supplied by Sigma-Aldrich, Steinheim, Germany. Ethanol and cyclohexane (HPLC grade) were supplied by Fisher Chemicals, Loughborough, UK.

Micronization Processing

Supplied paracetamol was micronized in a centrifuge mill (ZM100, Rentsch, Haan, Germany). The centrifugal speed was set at 18,000 rpm, employing an 80-μm sieve.

Particle Production by the Solution Atomization and Crystallization by Sonication (SAXS) Process

The solution atomization and crystallization by sonication (SAXS) process consists of three interdependent processes: (a) the production of aerosol droplets of the solute from a carrier solvent using a suitable aerosol generator; (b) the collection of the highly supersaturated droplets in a crystallization vessel containing a nonsolvent of the drug; (c) the application of ultrasonic waves to a crystallization vessel to controllably induce homogeneous nucleation and crystal growth. By combining these processes and controlling relevant parameters, high-purity micron-sized sphere-like crystalline particles could be readily produced in a single-step (solution to particle) operation.

The major advantage of this low-cost technique relates to the use of any suitable aerosol generator and that the whole process can be carried out under atmospheric pressure and ambient conditions. Furthermore, it has the potential for batch and continuous processing at an industrial scale. Additional information pertaining to each particular stage of the SAXS process has been described in detail below.

Aerosol Atomization

The main aim of an aerosol atomizer in the SAXS process is to produce highly supersaturated spherical constructs of the active pharmaceutical ingredient within a well-defined particle size for controlled crystallization. Although not limited to any particular atomization system, this study describes the use of an electrohydrodynamic (EHD) atomization system and a conventional air pressure atomizer, the latter of which is commonly used in conventional spray-drying systems.

Electrohydrodynamic Atomization (EHDA) System

Electrohydrodynamic atomization (EHDA), commonly known as electrospraying, has been widely used in producing monodispersed aerosol droplets (17–21). Briefly, the technique involves controllably flowing a solution of the drug through a flat-ended capillary (Hamilton Bonaduz AG, Bonaduz, Switzerland) with a suitable syringe driver (PHD2000, Harvard Apparatus, USA). The conducting capillary is charged via a high DC voltage with a variable power supply (2–20 kV) (Spellman CZE1000R, Plainview, USA). Together with the use of a grounded reference at a well-defined separation distance from the capillary, the electric force induced by the potential difference between the surrounding and the highly charged capillary, overcomes the surface tensional forces of the solution at the capillary producing a spray. A schematic representation of the experimental set-up of the EHD atomization system is shown in Fig. 1. By varying the flow rate, applied DC voltage, and separation distance between capillary and the grounded reference, various types of dripping and jet spray modes can be produced (20–22). A theoretical description of the various characteristics of jets formed at the capillaries was developed by Taylor in 1964, who focused on the deformation of the shape of the fluid immediately beneath the orifice of the capillary (23). By calculating the various stresses on a spheroid droplet by the applied electric field and the liquid surface tension, Taylor established that at a well-defined potential a stable cone would be produced at the capillary. This stable cone jet, or Taylor cone, allows the production of monodispersed aerosol droplets whose diameters can be controlled by varying the flow rate and voltage. A characteristic Taylor cone produced for a 10% (w/w) solution of paracetemol in ethanol is illustrated in Fig. 2.

Air Pressure Atomization

The low liquid throughput of capillary based atomizers, usually ranging from 0.5 ml/h to 25 ml/h, may preclude wider practical use of EHD atomization systems for particle production. Furthermore, utilizing a whole array of single-jet EHD atomizers in series has proven to be operationally and technically complex. To overcome these limitations, a conventional air pressure atomizer was used. A schematic diagram of the novel SAXS system is shown in Fig. 3. Solutions were sprayed via a 0.7-mm orifice with a supporting air flow rate of 600 L/h into a custom-built collection vessel. The side arm of a single-stage impinger-type vessel provided the escape route for the air, which was connected to an absolute filter. By controlling the separation distance between the atomizer and solution level in the crystallization vessel, aerosol droplets of varying particle sizes could be collected.

Crystallization Vessel

The atomized aerosol droplets are collected in a crystallization vessel containing a nonsolvent of the drug, which is

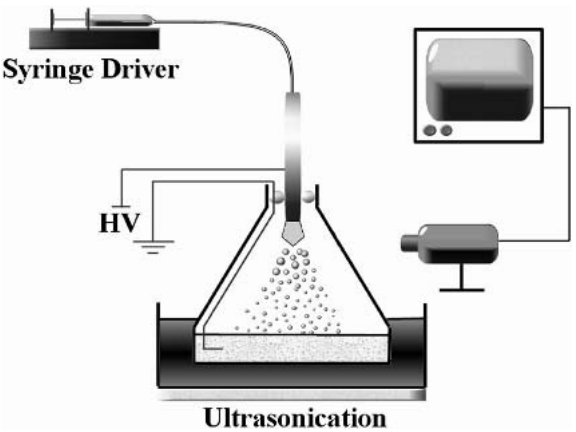

Fig. 1. Schematic representation of the electrohydrodynamic SAXS apparatus.

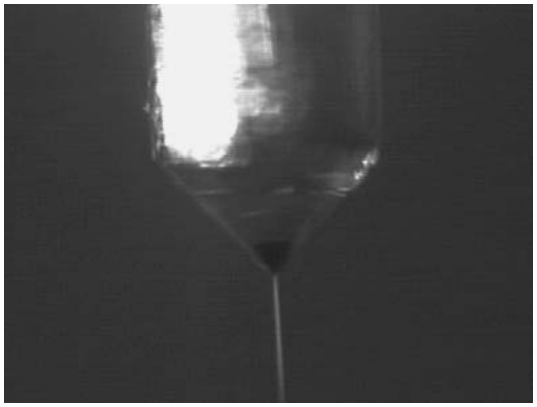

Fig. 2. Optical micrograph of a stable Taylor cone mode of a 10% (w/w) paracetamol solution in ethanol. The electrohydrodynamic conditions were established at a flow rate of 1.2 ml/h, an applied DC voltage of 3.8 kV, and a 5-cm separation distance between capillary and grounded reference.

preferably miscible with the solvent in which the drug is solubilized. The surface tension of the collecting solution in the crystallization vessel should be low or possibly minimized to prevent structural changes to the aerosol droplet shape on impingement. A common nonsolvent used was cyclohexane (surface tension 24.98 mN/m). The crystallization vessel is housed in a bath connected to an ultrasound supply (FS200b, Decon Laboratories, Hove, UK). The ultrasonic frequency is continually swept at a frequency of between 35 and 45 kHz.

Controlled Induction of Nucleation and Crystal Growth

The generation of micrometer-sized aerosols of a drug solution typically leads to rapid vaporization of the solvent and the production of highly supersaturated droplets of the solute molecules. However, rapid crystallization within these droplets does not readily occur because of the dramatic increase in the viscosity, which limits the mass transport properties of the solute molecules to form a critical nucleus for nucleation and subsequent crystal growth (24). Indeed, at a well-defined intersection—the glass transition temperature (T_g)—the increasing viscosity leads to the vitrifcation of the droplets into an amorphous structure. To induce homogeneous nucleation within these highly supersaturated aerosol droplets requires the collection of the droplets at a specific interval, allowing a sufficient degree of molecular motion (directly related to viscosity) within the droplets (25,26). The relative viscosity of these droplets will be drug specific and highly dependent on the rate of vaporizaton of the drug solvent. Monitoring such dynamic changes in droplet size and its effect on viscosity would be extremely onerous. The vaporization process is dependent on a number of parameters including vapor pressure of the solvent, dimensions of the initial atomized droplet, solute-to-solvent composition, temperature, flow rate, and time of flight.

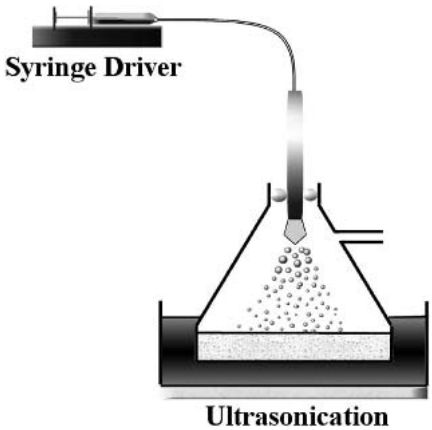

Fig. 3. Schematic representation of the air pressure SAXS apparatus.

In the SAXS process, the degree of vaporization of the solvent was crudely controlled by altering the separation distance between the atomizer and the nonsolvent solution. To avoid fluctuations in evaporation, the temperature of the spray nozzle and crystallization vessel was held at 20°C (Haake K20, Thermo Haake, Karlsruhe, Germany). The separation distance was empirically chosen by determining the separation at which droplets did not change their size or shape on collection on a microscope glass slide at various preset distances. It was assumed that this distance corresponded to a high degree of evaporation of the solvent while the viscosity of the collected droplets remained below the viscosity of the drug at its glass transition temperature (T_g). Clearly, if the viscosity of a supersaturated droplet was greater than the viscosity at the rubbery transition (around 10^{13} Pa·s), crystallization within a droplet would be significantly hindered without plasticizing the material (27). Paradoxically, for the formation of crystalline particles with a greater degree of sphericity, there is a requirement for a critical degree of viscosity within the droplets to minimize their propensity for deformation on impingement with the nonsolvent of the crystallization vessel (28). Thus, the overall shape and size of the drug constructs for crystallization will be dependent on the size and degree of deformation of the aerosol drug particulates on collection at the solution interface of the crystallization vessel.

However, the collection of highly supersaturated droplets at a viscosity below its glass transition properties does not provide sufficient kinetic energy for the formation of a stable cluster of molecules for crystal growth. To enhance the kinetically limiting diffusion within the droplets, ultrasonic waves were continually applied to the crystallization vessel. Ultrasonication has previously been shown to reduce the metastable zone width for nucleation, to minimize the degree of agglomeration of suspended material, and to improve powder-handling properties of crystallized particles (29–31). Applying ultrasonic radiation to the system creates areas of high and low pressure, producing cavitations. On implosion of the cavitations, areas of extremely high pressure and temperature are created over a short time interval. This process may induce an increase in the diffusion of the drug molecules within the viscous droplets and a concomitant decrease in the activation energy barrier for the formation of a stable nucleus or nuclei for crystal growth (32). Variations in the amplitude and frequency of the ultrasonic energy may further control the rate of nucleation and crystal growth. As a batch process, the crystallized particles are subsequently filtered from the resulting suspension (0.2 μm GTBP, Isopore™ membrane filters, Millipore, Ireland) and dried over silica-gel at room temperature.

Experimental Setup

SAXS Process with EHDA

Solutions of 7.5% and 10% (w/w) paracetamol were prepared in ethanol. The electrohydrodynamic experimental parameters were optimized in establishing a stable Taylor cone. For a 7.5% (w/w) solution, stable conditions were established with a 1.6-mm inner diameter capillary, a 4.2 ml/h flow rate, and a 10.5-kV applied DC voltage. The electrohydrodynamic conditions for a 10% (w/w) solution were obtained with a 0.31-mm inner diameter capillary, a 1.2 ml/h flow rate, and a 3.8-kV applied DC voltage. The separation distance between the capillary and grounded reference was kept constant for all experimental studies at 5 cm.

SAXS Process with Air Pressure Atomization

Solutions of 1%, 2.5%, 5%, 7.5%, and 10% (w/w) paracetamol in ethanol were sprayed at a constant flow rate of 16 ml/h. Solutions were sprayed via a 0.7-mm orifice with a supporting air flow rate of 600 L/h .The separation distance between atomizing nozzle and collecting nonsolvent was held constant at 15 cm.

Physical Characterization

Particle Size Measurement by Laser Diffraction

A small amount of the active material was dispersed in cyclohexane with 0.1% lecithin as a surfactant. The suspension was sonicated for 5 min (FS200b, Decon Laboratories, Hove, UK). Particle size distributions were measured by laser diffraction (Mastersizer X, Malvern, UK), using a 100-mm lens. The measurement took place in a small stirring cell (volume 10 ml) at an obscurity level of 0.12–0.18.

Scanning Electron Microscopy (SEM)

General morphology of the processed particles was investigated by scanning electron microscopy (SEM) (Jeol 6310, Jeol, Japan) at 10 kV. Samples were mounted on carbon sticky tabs and gold-coated before analysis (Edwards Sputter Coater, UK).

Atomic Force Microscopy (AFM)

Atomic force microscopy topographic measurements were performed using a NanoScope IIIa controller and a Multimode AFM head (Digital Instruments, Santa Barbara, CA) with a J-type scanner. Surface imaging was recorded in TappingMode™ operation (TM-AFM). Tetrahedral-tipped silicon etched cantilevers (OTSP, Digital Instruments) with a nominal tip radius of curvature <10 nm, force constant ~42 N/m, and a resonant frequency 200–400 kHz were used for imaging. Variations in the surface topography of processed particles were computed by root-mean-square roughness measurements (R_q). The relative invariance of particle surface roughness with changes of scale was measured by fractal dimension (F_d) analysis. The geometric complexity of the surface roughness of the AFM imaged particles were computed with algorithms supplied with the AFM software.

Differential Scanning Calorimetry (DSC)

Thermal analyses were performed using a DSC-2920 (TA instruments, Surrey, UK). Powder samples (ca. 5–7 mg) were accurately weighed into hermetically sealed aluminum pans. Samples were cooled to –70°C before heating at 10°C min^{-1} to 300°C.

X-Ray Powder Diffraction (XRPD)

X-ray diffraction spectra of paracetamol samples were obtained using a Phillips x-ray powder diffraction system (Phillips X-Ray Analytical, Cambridge, UK) fitted with a 4-kW x-ray generator (PW 1730/00). Scanning was performed in steps of 0.02° over the range of $2\theta = 5–60°$ to produce each spectrum.

RESULTS

The morphology and microscopic surface properties of micronized paracetemol as supplied and SAXS-produced paracetemol particles were investigated using a combination of scanning electron microscopy (SEM) micrographs and atomic force microscopy (AFM) topographic studies. The physicochemical characteristics of the paracetemol samples were analyzed via conventional particle sizing, x-ray powder diffraction (XRPD), and differential scanning calorimetery (DSC) measurements.

Scanning Electron Microscopy (SEM)

As-Supplied and Micronized Paracetamol Particles

Scanning electron micrographs of as-supplied and post-micronized paracetamol powders are shown in Fig. 4A,B, respectively. Particles in the sub-10-μm size range were routinely obtained on micronization. Although material specific, high-energy comminution of paracetamol crystals led to the formation of particles with irregular morphologies and relatively smooth surface profiles.

EHD Atomized SAXS Process

Figure 5 shows a scanning electron micrograph of paracetamol particles obtained from EHD atomization of a 7.5% (w/w) solution of the solute in ethanol under stable Taylor cone conditions. The photomicrographs of the SAXS-processed particles indicate similarities in particle shape and surface texture to the micronized paracetamol particles.

Air Pressure Atomized SAXS Process

Low- and high-magnification scanning electron micrographs of particles obtained from air pressure atomization solutions of 1, 5, and 10% (w/w) paracetamol in ethanol, at a constant atomizer-to-solution separation distance, are shown in Fig. 5. Varying the solute concentration yielded considerable modification to the morphology, topography, and overall particle size of the SAXS-processed paracetamol particles. The atomization of very low concentrations of the active ingredient [1% (w/w)] led to the processing of two different morphologic forms (Fig. 6A,B), with the formation of thin flake-like particles and particulates with a greater degree of sphericity. These two forms of particles also showed consid-

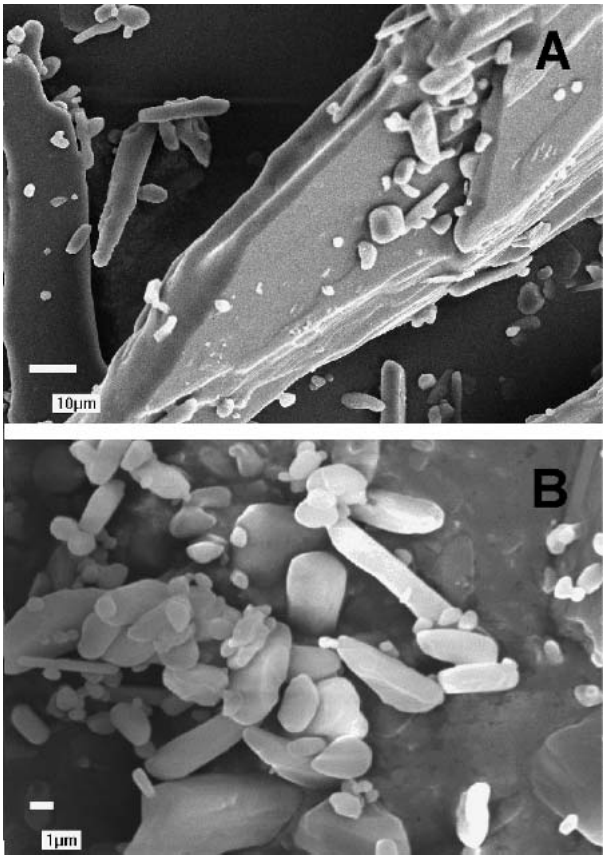

Fig. 4. Scanning electron micrographs of (A) untreated and (B) micronized paracetamol samples.

erable variations in surface topography, with the spherical particles exhibiting a marked increase in the degree of surface roughness. It was apparent that spraying such low concentrations of drug might lead to a bimodal particle size distribution. Increasing the solute concentration from 1% (w/w) to 5% (w/w) led to the increased formation of the spherically shaped particles, as shown in Fig. 6C,D. A further increase in paracetamol concentration [10% (w/w)] led to the formation of highly spherical particles (Fig. 6E). High-resolution imaging of the particulate surfaces (Fig. 6F) indicated a degree of surface roughness on the nanometer scale.

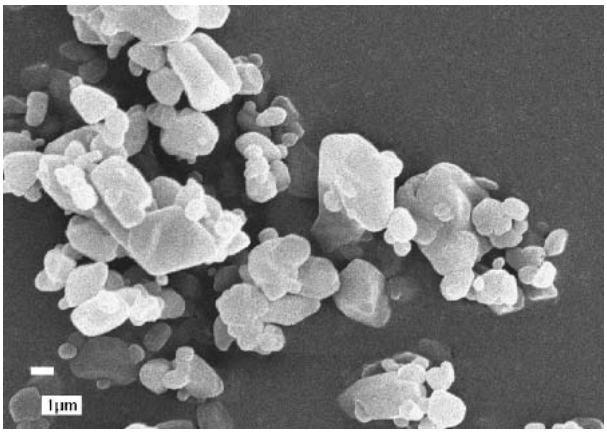

Fig. 5. Scanning electron micrograph of paracetamol particles obtained from an electrohydrodynamic SAXS process.

Atomic Force Microscopy (AFM)

The relatively smooth surface texture of micronized paracetamol particles in the SEM photomicrographs correlates well with the corresponding high-resolution AFM image of a small sectional area (1 μm × 1 μm) of a micronized particle surface (Fig. 7A). The root-mean-square surface roughness and fractal geometry of these surface areas were found to be between 5.86 nm < R_q < 12.78 nm and 2.038 < F_d < 2.042, respectively. Figure 7B shows a representative surface topographic AFM image of a 1-μm^2 area of a SAXS-processed particle obtained from air-pressure atomization of a 10% (w/w) paracetamol solution. The particles exhibited an array of nanometer-high surface asperities. These surface protrusions concomitantly increased the root-mean-square surface roughness 45.32 < R_q < 79.75 nm and the fractal geometry 2.179< F_d <2.183 of the SAXS-processed particles.

Particle Characterization

Particle Size Distribution

Figure 8A shows the cumulative particle size distribution analysis of micronized, EHD-sprayed and air pressure atomized SAXS-processed paracetamol particles. A 10% (w/w) paracetamol in ethanol solution was used for both EHD and air pressure-based SAXS systems. The efficiency of all three methods is displayed by the controlled production of sub-10-μm particles. As expected, the monodispersed aerosol droplets formed through electrohydrodynamic (EHD) spraying under stable Taylor cone conditions produced the narrowest particle size distribution. The variations in the aerosol formation of an air pressure atomization system may be the major reasons for the broad dispersion in the particle size measurements of the SAXS processed particles.

The use of the air pressure atomization SAXS process in the formation of spherical particulates should ideally allow controlled modification of the particle size distribution through variations in the concentration of the mother liquor. This is enabled via the conservation of mass of the active ingredient in the atomized droplets to the resultant crystalline particles. The concentration of the solute in the aerosol droplet is directly proportional to the mass and volume of the resultant particle. However, because the diameter of a sphere varies with its volume as a function of $d \propto V^{1/3}$, variations in particle diameter will be proportional to the cube root of the concentration of the active solute.

For spherical particles, with a particle shape factor of $\chi = 1$, the size distribution measurements of air pressure atomization SAXS particles can be directly discussed in terms of their diameter. Figure 8B shows the relationship between the particle diameter and the cube root of the solute concentration. The particle diameter was measured at the mode of each particle size distribution. The dotted line in Fig. 8B shows a theoretical fit of the diameter of perfectly spherical particles as a function of concentration. Variations in solute concentration generally showed good correlation with the observed changes in particle diameter. Deviations from the theoretical plot are most likely to be associated with variations in spraying conditions and particle shape characteristics, particularly at low concentrations.

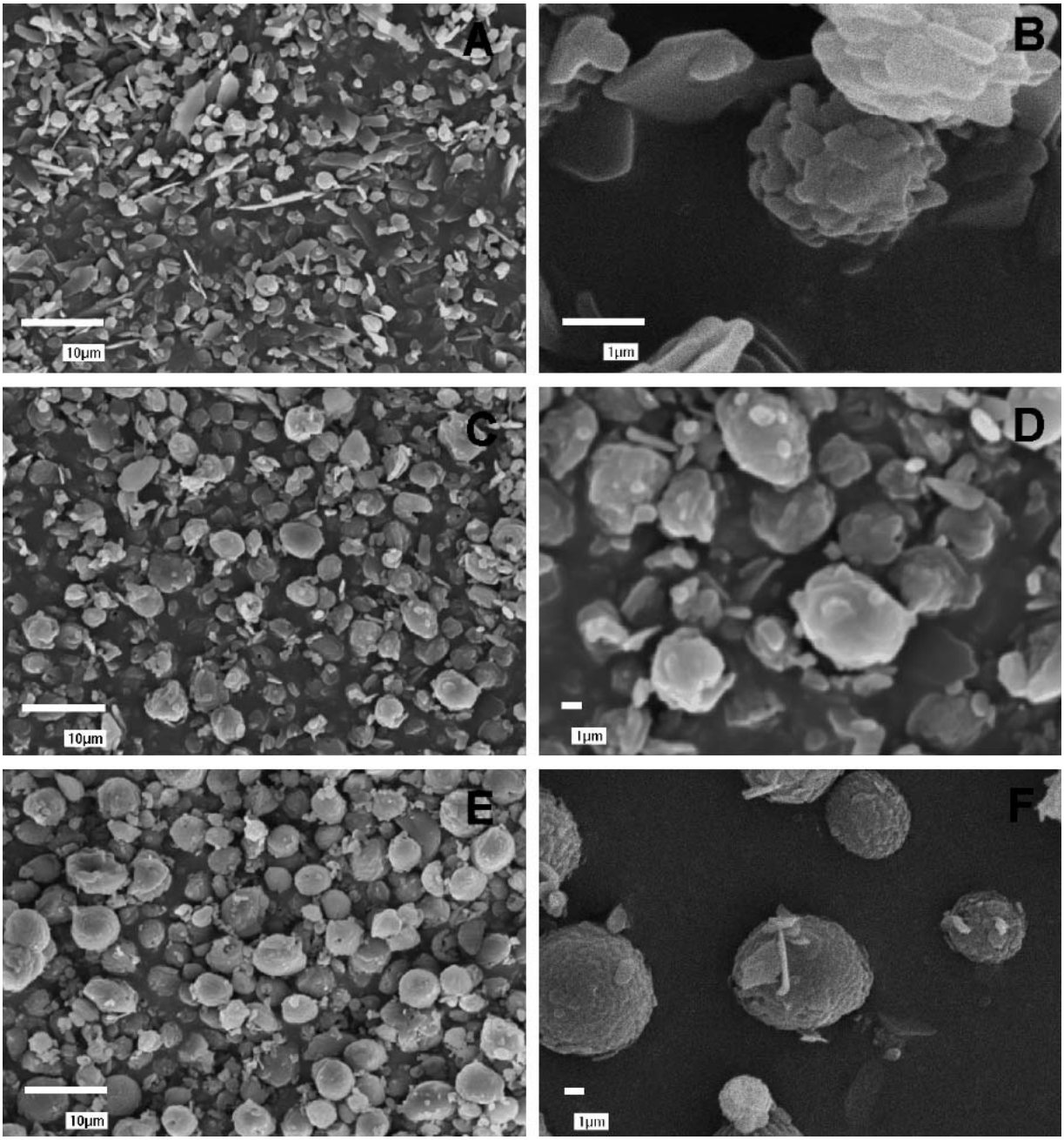

Fig. 6. Scanning electron micrographs of paracetamol particles obtained from an air pressure SAXS process of (A, B) a 1% (w/w) solute concentration, (C, D) a 5% (w/w) solute concentration, and (E, F) a 10% (w/w) solute concentration.

Differential Scanning Calorimetry (DSC)

Figure 9A shows representative DSC thermograms of untreated, micronized, and air pressure atomized processed paracetamol particles. The low production rates of the EHD atomization SAXS system precluded measurement of its thermal and structural properties. For all samples, there was neither an observed change in molar heat capacity associated with a glass transition nor a related exothermic recrystallization peak. The data suggest, within the limits of detection of the DSC system, that the particles were nominally crystalline. The endothermic peak centered at 169°C for all three samples corresponded well with literature values for the melting endotherm of the polymorph I of paracetamol. The heat uptake at this peak was similar for all three materials (~198 ± 5 J/g).

X-Ray Powder Diffraction (XRPD)

X-ray powder diffractograms for untreated, micronized, and air pressure atomized processed paracetamol particles are shown in Fig. 9B. All three samples showed characteristic sharp diffraction peaks associated with highly crystalline material. The XRPD traces are indicative of the formation of the stable monoclinic crystal structure of paracetamol (Form I). The orthorhombic structure (Form II), which can be formed from highly supersaturated solution under fast cooling rates, was not observed for any of the SAXS-processed particles.

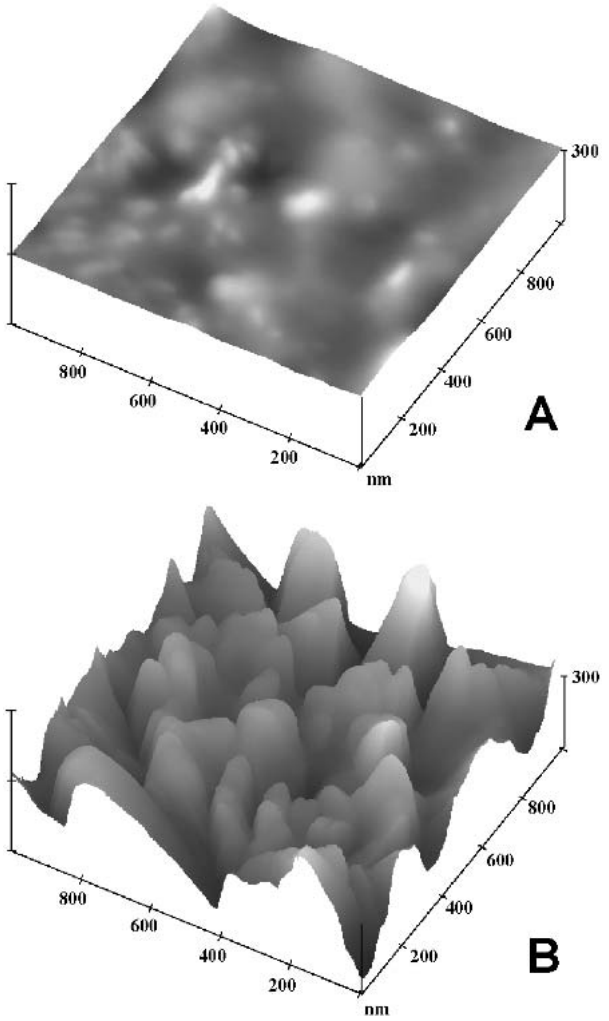

Fig. 7. Atomic force microscopy (AFM) images of (A) micronized paracetamol particle and (B) air pressure atomized SAXS paracetamol particle [10% (w/w) solute concentration]. AFM scan size of 1 μm × 1 μm.

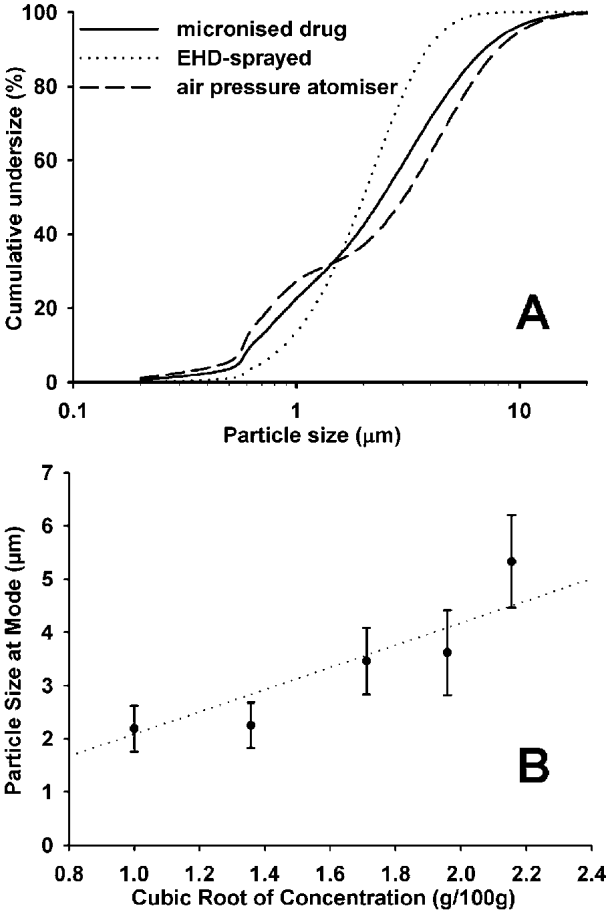

Fig. 8. (A) Cumulative particle size distributions of micronized electrohydrodynamic SAXS and air pressure SAXS processed paracetamol particles. (B) The influence of initial solute concentration on the modal particle diameter of air pressure SAXS-produced paracetamol particles.

DISCUSSION

The macroscopic shape and mesoscopic surface topography of sub-10-μm particles play a critical role in the interfacial properties and characteristic behavior of a powder formulation. The potential for manipulating these physical properties while maintaining the low surface free energy characteristics of a crystalline structure may provide a novel means of enhancing flowability, deaggregation, and dispersion of fine particulates. This paper highlights the development of a solution atomization and crytallization by sonication (SAXS) process for the production of uniform, spherical crystalline particles within a narrow particle size distribution and characteristic nanometer surface roughness.

The major advance in controlling the morphology and surface topography of mesoscopic crystalline particles is via modification of the contact area for adhesional interaction. The transformation of a planar surface into a curved surface would dramatically reduce the radius of contact. Meanwhile, nanometer surface asperities not only aid in the minimization of the contact area but also maintain large separation distances (r) between the main bodies of contiguous surfaces. The increased separation between two surfaces may directly affect particle adhesion by reducing the short-range attractive van der Waals force as it decays as a function of r^{-2}. Furthermore, the decrease in contact area may influence the capillary force by limiting the surface tensional force and, under high relative humidity conditions, the formation of stable capillary bridges between asperities.

Topographic atomic force microscopy (AFM) imaging and surface geometric analysis of micronized and SAXS-processed paracetamol particles indicated that the array of nanometer-high asperities on the surfaces of the SAXS paracetamol particles may lead to a marked reduction in the available contact area with a relatively smooth contiguous surface. Furthermore, fractal dimension analysis of the SAXS particles implied relative invariance in the spatial features under changes of scale, therefore suggesting surface structure similarity between processed particles. These modifications to the surface geometry of micrometer-sized particles and their resultant effect on interparticulate forces may significantly alter interfacial interactions, leading to increased flowability and powder handling.

Scanning electron microscopy (SEM) photomicrographs of the processed particles suggested that the particles obtained from an air pressure SAXS process were more repro-

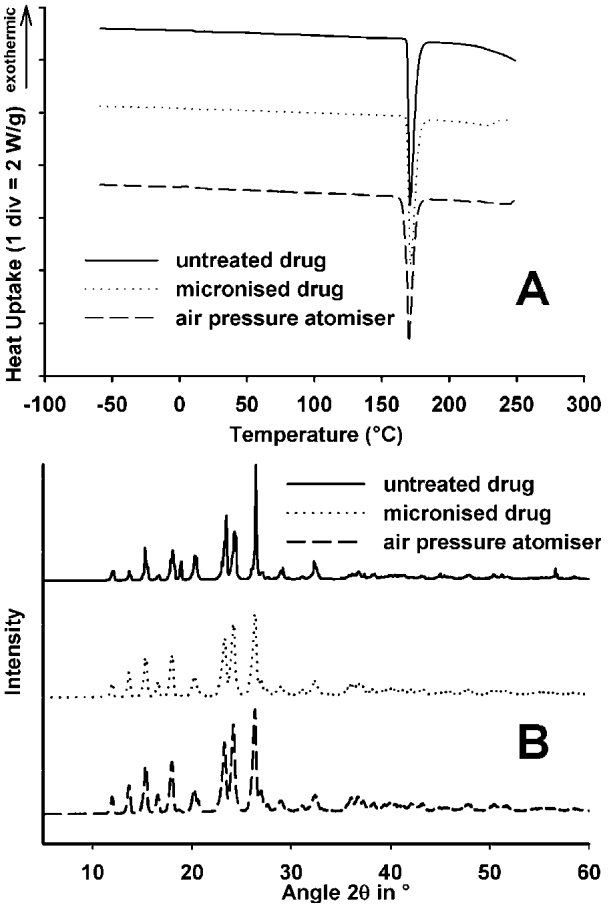

Fig. 9. (A) Differential scanning calorimetry scans at 10°C min^{-1} of untreated, micronized and air pressure SAXS-processed paracetamol particles. (B) X-ray powder diffractograms of untreated, micronized and air pressure SAXS-processed paracetamol particles.

ducible in terms of particle morphology than particles obtained via micronization and the electrohydrodynamic SAXS process. Micrographs of air pressure SAXS particles at various spraying conditions showed an apparent increase in sphericity of paracetamol particles with increasing concentration. The greater degree of sphericity suggested that the modifications to particle shape may be directly associated with the viscosity of the supersaturated droplets on collection. Although surface tension effects may play a role, its variation in a drug–solvent mixture at various concentrations would be negligible compared with the change in viscosity on vaporization of the carrier solvent or during a phase change from solute to a solid either via crystallization or vitrification.

It is conceivable that for a set distance between atomizer and collection vessel the atomization of solutions with low solute concentration may lead to incomplete evaporation of the carrier solvent. This may result in a marked reduction in the viscosity of the aerosol droplets on impingement with the nonsolvent in the crystallization vessel. The minimal resistance to flow within the droplets may subsequently lead to deformation of the aerosol droplets, leading to the crystallization of more irregular, flake-like paracetamol crystals. On the other hand, if the time of flight of the volatile aerosols is too long, or the vapor pressure of the carrier solvent is excessively high, the molecular mobility within the collected droplets may be insufficient to allow nucleation of stable nuclei for crystal growth. Consequently, if the material passes through its glass transition temperature, droplets would become amorphous and remain in a frozen state of a disordered liquid. As a result, the major controlling parameters in the SAXS process are solute concentration, solvent vapor pressure, and the separation distance between atomizer and crystallization vessel.

The effects of solvent evaporation and temperature on the critical viscosity of an active ingredient solution can be modeled using the empirical Williams-Landel-Ferry (WLF) relationship (33). The WLF equation allows evaluation of the viscosity of a rubbery solution at different temperatures when they are known at some reference temperature. Theoretical estimates of the variations in glass transition temperature (T_g) for a two-component mixture can be estimated by combining the Simha-Boyer rule and Gordon-Taylor equation [Eq. (1)]:

$$T_{g-mix} = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} \tag{1}$$

where,

$$k = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \tag{2}$$

and w1, w2, ρ1, and ρ2 are the weight fractions and densities of the two components, respectively (34,35). Consequently, T_g can be theoretically calculated for every ratio of solute and solvent concentration during solvent evaporation. With knowledge of the dynamic variation in T_g, the Williams-Landel-Ferry equation can be used to derive the viscosity of the drug solution via:

$$\eta = \eta_g \exp\left(\frac{c_1(T - T_g)}{c_2 + (T - T_g)}\right) \tag{3}$$

where η is viscosity, η_g is the viscosity of the active ingredient at its T_g, T is the ambient temperature, and c_1 and c_2 are constants relating to the properties of the solvent (33). The viscosity of the active ingredient at its T_g can be approximated as 10^{13} Pa·s (25). Further, Maltini and Anese postulated that the solution-related constants ($c_1$and c_2) are independent of the solute concentration (36). Thus, by using previously published measurements of the viscosity of an ethanol solution as a function of temperatures (37) together with the WLF equation, the solution constants for an ethanolic solution were calculated as $c_1 = -40.0195$ and $c_2 = 16.85$.

Figure 10 shows a simulation of the apparent increase in viscosity of a paracetamol–ethanol solution as a function of increasing solute concentration at 293°K (29°C) using the WLF approach. The simulation is not strictly accurate because the model does not account for any variations in temperature of the solution on continuous evaporation of the solvent. Although not shown in Fig. 10, below 80% drug concentration the viscosity of the solution increased only about 10-fold from the viscosity of pure ethanol (0.0011 Pa·s). It should be noted that the viscosity at 80% solute concentration remains approximately three orders of magnitude less than that of a highly viscous syrup solution (~10 Pa·s) (38). Above

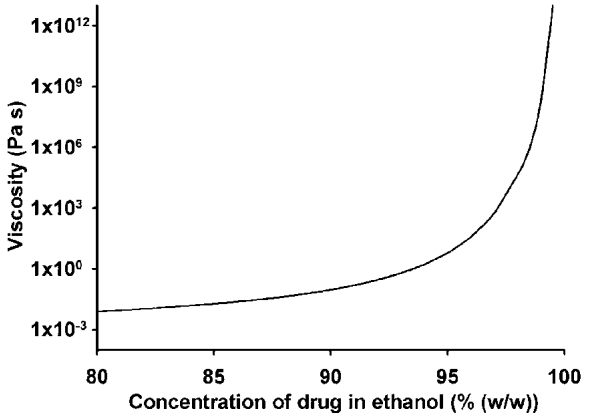

Fig. 10. Theoretical simulation of the change in viscosity of a paracetamol solution at 293°K (20°C), as a function of increasing solute concentration.

80% solute concentration, the viscosity of the solution seems to increase much more dramatically.

The critical viscosity and related solute concentration required to withstand deformation or allow elastic and/or viscoelastic relaxation on impingement cannot be readily approximated. This would require complex modeling of the potential and kinetic energy of the aerosol droplets and the interfacial properties of the aerosol droplets at the air–solution interface. However, it is conceivable that the range of viscosities of the aerosol droplets may be small. This is further limited by the upper viscosity requirements in allowing sufficient mass transport diffusion of the solute molecules in the formation of stable nuclei for crystal growth.

CONCLUSIONS

The highly important issues in the therapeutic delivery of sub-10-μm drug particles such as physicochemical stability and interactive mixing are directly related to the degree of control in the formation and processing of active pharmaceutical ingredients. Of these, particle shape and surface topography play a critical role in the overall performance and handling characteristics. The development of the novel particle engineering SAXS process may provide a key advance in controlling such characteristics through modifying the degree of sphericity and surface topography of the crystalline particles. Together with the potential for tailoring the particle size distribution of the active by varying solute concentration, the SAXS technique may show considerable potential as a constructive, single-step process for the production of active pharmaceutical ingredients.

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