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Investigation of Processing Parameters of Spray Freezing Into Liquid to Prepare Polyethylene Glycol Polymeric Particles for Drug Delivery

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ABSTRACT

The objective of this study was to investigate the influence of processing parameters on the morphology, porosity, and crystallinity of polymeric polyethylene glycol (PEG) microparticles by spray freezing into liquid (SFL), a new particle engineering technology. Processing parameters investigated were the viscosity and flow rate of the polymer solution, nozzle diameter, spray time, pressure, temperature, and flow rate of the cryogenic liquid. By varying the processing parameters and feed composition, atomization and heat transfer mechanisms were modified resulting in particles of different size distribution, shape, morphology, density, porosity, and crystallinity. Median particle diameter (M50) varied from 25 μm to 600 μm. Particle shape was spherical or elongated with highly irregular surfaces. Granule density was between 0.5 and 1.5 g/mL. In addition to producing particles of pure polymer, drug particles were encapsulated in polymeric microparticles. The encapsulation efficiency of albuterol sulfate was 96.0% with a drug loading of 2.4%, indicating that SFL is useful for producing polymeric microparticles for drug delivery applications. It was determined that the physicochemical characteristics of model polymeric microparticles composed of PEG could be modified for use as a drug delivery carrier.

KEYWORDS: particle engineering, spray-freezing into liquid, polymeric carrier

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INTRODUCTION

Particle engineering techniques to make pharmaceutical powders have been reviewed recently.[1] Relatively new solution-based particle formation techniques were discussed that involved the use of conventional liquids, compressed gases, near-critical liquids, or supercritical fluids functioning either as solvents, antisolvents, or cryogenic media for freezing. These techniques were shown to involve phase separation of solvent and active pharmaceutical ingredient (API), either by evaporation, rapid expansion, change in solvent composition, or solidification by freezing. The spray configuration in many of these processes produces atomized droplets with high surface areas. Thus, phase separation and rapid nucleation result in small primary particles or highly porous microparticles.

A freezing method reported in the literature is spray freezing into vapor over liquid (SFV/L). Gombotz et al[2] and Gusman and Johnson[3] reported on spray-freezing into nitrogen vapor over liquid for producing API-loaded particles. In the SFV/L experiments reported by Webb et al,[4] the authors reported that when the distance from the nozzle to the surface of the liquid nitrogen was about 8 cm, the individual droplets fell through the vapor phase for about 1 second before reaching the liquid nitrogen surface. This occurrence impacted the stability of the protein in this study because during this 1 second, the protein was able to diffuse and concentrate at the air/liquid interface, where significant aggregation occurred. Heller et al[5] reported that rapidly cooling samples during the SFV/L process minimized the time that the formulation was exposed to temperatures in which phase separation was induced by freezing, and therefore decreased the degree of phase separation. Costantino et al[6] reported that the atomization conditions influenced the physicochemical characteristics of the particles

produced by SFV/L, specifically reporting that the percent protein monomer content decreased as the particle size was decreased. Sonner et al[7] reported on the use of SFV/L to make particles containing protein for epidermal delivery, in which the stability of trypsinogen during SFV/L was influenced by the composition of the formulation. Maa et al[8] compared spray drying and SFV/L for producing protein powders for inhalation and found that SFV/L produced protein particles with light and porous characteristics.

The SFL process is a novel method for the production of microparticles and the encapsulation of drugs into water-soluble polymeric matrix microparticles.[9-12] The microparticles are produced by spraying an aqueous solution or suspension of drugs and/or polymeric materials through a nozzle directly into a cryogenic liquid to produce a frozen powder. Organic solvents and hydro-organic mixtures that have suitable freezing points may also be used to prepare drug and excipient solutions and suspensions. Liquid CO_2 and liquid N_2 are the preferred cryogenic liquids because of their relative inertness and physical properties such as density and viscosity, which vary significantly with pressure and temperature. The size as well as the porosity of the microparticles produced by the process is dependent upon the processing parameters such as the velocity of the spray, the diameter of the nozzle orifice, and the temperature and flow rate of the cryogenic liquid. Other physicochemical properties such as crystallinity and encapsulation efficiency are also influenced by the processing conditions. SFL has been used to make porous microparticles containing insulin[9] and to enhance the dissolution rates of poorly water-soluble drugs, such as danazol[10-12] and carbamazepine.[11,12]

The objective of this study was to demonstrate the influence of SFL processing parameters on the physicochemical properties of polymeric microparticles comprising polyethylene glycol (PEG), and their use as carriers for the model drug albuterol sulfate. The viscosity and flow rate of the polymer solution, nozzle diameter, spray time, pressure, temperature, and flow rate of the cryogenic liquid were varied to manipulate the physical properties (eg, size, shape, porosity) of the polymeric microparticles. The ability to control these properties enables their use for many pharmaceutical applications, including oral controlled release and pulmonary delivery.

MATERIALS AND METHODS

Materials

Albuterol sulfate (Sigma Chemical Co, St Louis, MO) was used as the model drug. Purified water was obtained from a Milli-Q^{UV} Plus Filtration System (Millipore SA, Molsheim, France). Polyethylene glycol (MW 8000 and MW 18 500; Polysciences Inc, Warrington, PA) was used as the model water-soluble polymer in the preparation of polymeric microparticles. Dry ice and 100% anhydrous ethanol (EM Science Inc, Gibbstown, NJ) were used to prepare a cooling bath. High purity, anhydrous CO_2 (Matheson Co, Kyle, TX) was the cryogenic liquid in these studies and was used as received.

Method of Preparing Powder Formulations

Preparation of Polyethylene Glycol Microparticles by the SFL Process - Apparatus

The apparatus used to produce polymeric matrix microparticles by the SFL process is depicted in **Figure 1**. The polymeric feed solution is held in a feed reservoir [A] made from 11/16-inch inner diameter (i.d.) x 1-inch outer diameter (o.d.) stainless steel tubing with appropriate end fittings (Part No. 10-LM16-12; Pressure Equipment Co, Erie, PA). Also, the feed reservoir is equipped with a stainless steel piston, sealed with o-rings (Buna 90, size 112; American Packing and Gasket Co, Houston, TX). The piston is driven by CO_2 pressure controlled by a digital syringe pump [B] (Model 260D; ISCO Inc, Lincoln, NE). The feed reservoir is connected to a nozzle [C], which is attached to the precipitation cell [D]. The precipitation cell is a stainless steel cylinder having the dimensions 4-inch id × 6-inch length (Part No. 4561, 300-mL reactor vessel; Parr Instrument Co, Moline, IL). High pressure valves (Part No. 15-11AF1; 1/16 inch, High Pressure Equipment Co, Erie PA) are placed between ports to open and close the flow of solution from the feed reservoir through the nozzle and into the precipitation cell. The atomizing nozzle is made of polyetheretherketone (PEEK) tubing of either 172-µm (0.005-inch) or 63.5-µm (0.0025-inch) id and 1/16-inch od (Upchurch Scientific, Oak Harbor, WA). Several other ports also lead to the precipitation cell. One such port is the inlet for the cryogenic liquid, liquid CO_2 [E] for these experiments. Liquid CO_2 is pumped from a compressed gas tank by passing through stainless steel tubing, 1/8-inch od x 0.060-inch id [F] (Part No. 15-9A2; HIP Co), which is immersed in a chilled ethanol and dry ice bath, into the precipitation

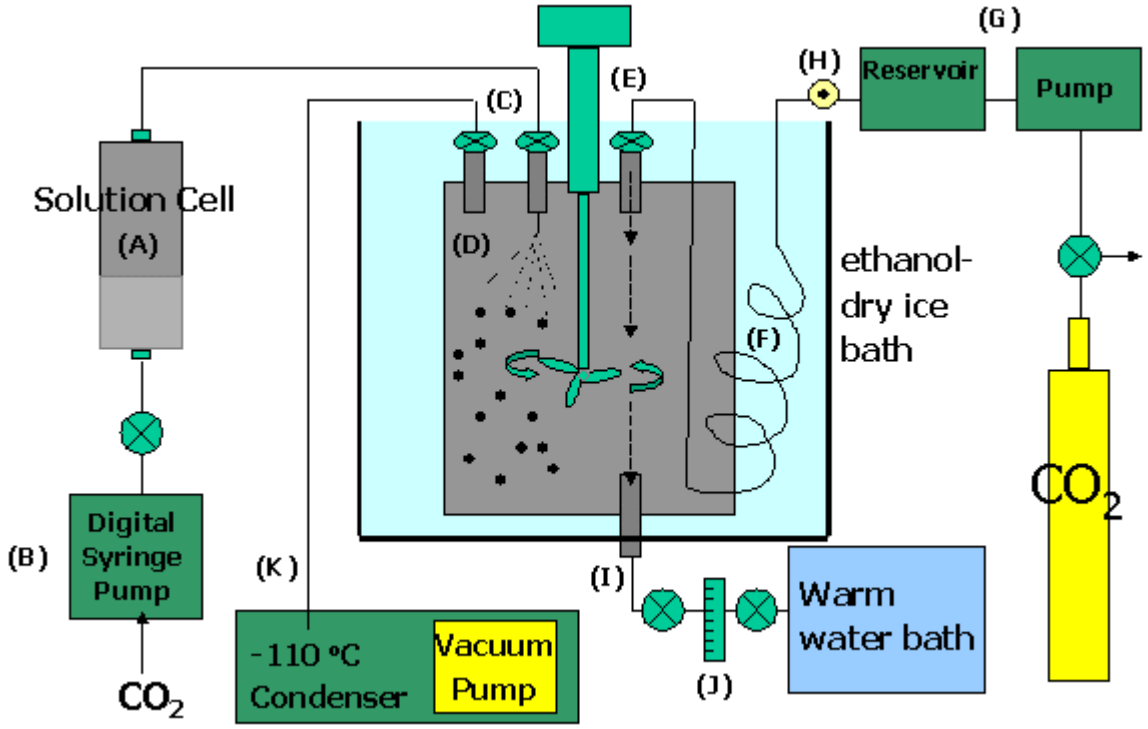

Figure 1. Schematic diagram of the spray freezing into liquid (SFL) process apparatus and its components.

cell. Pressure is monitored with a pressure gauge [G]. The flow rate of liquid CO_2 from the gas tank into the precipitation cell was adjusted with a high-pressure regulator [H]. Other ports to the precipitation cell include a release valve, a digital pressure transducer and display (Sensotec Inc, Columbus, OH), a temperature probe and digital display (Omega Inc, Stamford, CT), and an outlet port [I]. The outlet port is 1/4-inch-od × 1/8-inch-id stainless steel tubing immersed in a warm water bath connected to a flow meter [J]. The corresponding flow rate of liquid CO_2 through the precipitation cell is determined by the flow of CO_2 gas registered by the flow meter. The precipitation cell is also equipped with a paddle stirrer on a shaft with a cylindrical magnet at the top coupled to an outer drive motor. During the SFL process the precipitation cell is immersed in an ethanol and dry ice bath. The frozen solvent is removed by lyophilization [K].

Production of Polymeric Polyethylene Glycol Microparticles

Aqueous solutions of polyethylene glycol molecular weight (MW) 8000 or 18 500 were prepared in volumetric flasks and placed in the feed reservoir. Microparticles were produced by atomizing the PEG solution through the nozzle to freeze the solution droplets in the cryogenic liquid. By using the digital ISCO pump to record the flow parameters, the pressure required to achieve a specific flow rate of polymer solution through a nozzle was evaluated with respect to the polymer solution viscosity and nozzle diameter. The pump was set to maintain a constant pressure of 5000 psi to move the solution through the nozzle into an empty beaker at atmospheric pressure. The resulting flow rate, Q, was recorded from the digital display of the pump. The Reynold's number, $Re = Dv\rho/\mu$, was calculated: where D is the diameter of the nozzle; $v = Q/A = Q/\pi r^2$; ρ is the density of the polymer solution; μ is the viscosity of the polymer solution; Q is the mass flow; r is the radius of the inner diameter of the tube; and μ is the viscosity of the liquid.[13] After atomization, the PEG particles were collected and transferred to a tray lyophilizer consisting of a stainless steel cell fitted with a vial holder and having several ports. The ports were as follows: a temperature probe and digital display (Omega Inc, Stamford, CT), a pressure transducer and display, and a vacuum port that was connected to a low temperature condenser (-110°C; ATR Inc, Laurel, MD) using 1-inch id x 1½-inch od vacuum tubing. The low tem-

perature condenser was connected to a vacuum pump (ATR Inc). The stainless steel chamber was submerged in 100% anhydrous ethanol (EM Science Inc), which was chilled to -50°C with dry ice. After chilling the sample chamber, the frozen samples were placed in the vial holder, and the chamber was sealed. The vacuum pump was started, and the samples were allowed to vacuum dry until a vacuum pressure of 15 mtorr was attained. During drying, the temperature and pressure inside the sample chamber were maintained below 1000 mtorr and below -20°C by cooling the sample chamber with a dry ice/ethanol bath. The lyophilization program was manually controlled as follows:

1. Precool sample chamber and tray to -50°C.
2. Place frozen samples on tray (without caps).
3. Vacuum to a pressure of 500 mtorr (has to be ≤1000 mtorr).
4. Hold @ -50°C until vacuum pressure is 100 mtorr.
5. Ramp T °C to -20°C @ 0.5°C/min (keep vacuum pressure ≤500 mtorr).
6. Hold @ -20°C until vacuum pressure is 15 mtorr.
7. Stop and slowly release vacuum.

Characterization of Powder Formulations

Scanning Electron Microscopy

Microparticles produced by the SFL process were evaluated using a JSM 35C scanning electron microscope (SEM) (Joel Co, Peabody, MA). Samples were sputter-coated with gold-palladium prior to examination. Digital images of the microparticles were obtained by interfacing an image scanner with the electron microscope display tube and using Adobe Photoshop 5.0 software (Adobe Systems Inc, San Jose, CA) to enhance the contrast and darkness of the images.

X-ray Diffraction of Polymeric Polyethylene Glycol Microparticles

A 1710 x-ray diffractometer with a copper target and nickel filter (Philips Electronic Instruments Inc, Mahwah, NJ) and Jade 5 XRD pattern processing software (Materials Data Inc, Irvine, CA) were used to obtain the x-ray diffraction patterns of polymeric microparticles prepared by the SFL process. Approximately 500 mg of polymeric microparticles were placed in a glass tray sample holder and leveled with a glass microscope slide. The scan parameters were set at a step size of 0.05 2-θ degrees, a dwell time of 1.5 seconds over the range of 2-θ from 5°C to 50°C. The composition of the samples was determined qualitatively by identification of peak location and pattern of the 3 strongest lines. Crystallinity was approximated by peak height ratios (I/I_c) of the strongest peak of a test sample (I) to the strongest peak of a control sample (I_c), which was material used "as is" from the manufacturer and not subjected to SFL processing. By multiplying the peak intensity ratio by 100, the results are expressed as a percentage change in crystallinity.

Thermal Analysis of PEG Microparticles and PEG Solutions

A differential scanning calorimeter (DSC 2920) and Thermal Analyst 2000 software (TA Instruments, New Castle, DE) were used to evaluate the melting point (T_m) and heat capacity (C_p) of polymeric microparticles prepared by the SFL process. Samples of approximately 5 mg were hermetically sealed in aluminum containers and heated at 5°C/min from 25°C to 250°C. The measurements were conducted in triplicate.

The freezing and melting points of the polymer solutions prepared for SFL processing were evaluated by DSC. An aliquot of the solution was placed in aluminum pans and the weight recorded. The samples were heated at 10°C/min from 25°C to -45°C, held at -45°C for 5 minutes then further heated at 5°C/min back to 25°C. The respective freezing and melting points, as well as the onset of freezing and melting, were determined using Thermal Analyst 2000 software.

Particle Size Distribution of PEG Microparticles

Laser light diffraction (SALD-1100 Particle Size Analyzer; Shimadzu Inc, Columbia, MD) was used to determine the particle size distribution of a suspension of PEG microparticles in anhydrous ethanol. The size distribution is reported as the cumulative percentage of particles undersized by number. The median diameter by volume (M50) was determined, as was the polydispersity, described by the span index, which is calculated by (M90 – M10)/M50.[1] The particle size distribution was determined prior to and after sonication for 5 minutes at 25°C.

Density and Intragranule Porosity of PEG Microparticles

An AccuPyc Model 1330 helium pycnometer was used to determine the density of the powders (Micromeritics Inc, Norcross, GA). Either a 1-mL or a 0.1-mL sample cup was used, depending on the amount of material available. The pressure of the helium gas was set a 19.5 psig. At least 5 measurements were repeated for each sample. Nonprocessed polymeric materials were ground into fine powders using a porcelain mortar and pestle prior to density determination. Microparticles prepared by the SFL process were evaluated without grinding in a mortar. The intragranule porosity (IP) of the microparticles was calculated from the true density (ρ_t) and granule density (ρ_g) by the equation $IP = 1 - \rho_g/\rho_t$. The solid fraction was derived from the ratio of the density of the PEG microparticles (granule density) to the density of the finely ground PEG starting material (true density).

Encapsulation Efficiency of the SFL Process

Determination of the amount of albuterol sulfate per mg of PEG microsphere was performed using a Diode Array 8425A spectrophotometer at 240 nm (Hewlett Packard, Germany). A 500-mg aliquot of drug-loaded PEG microparticles was dissolved in 5.0 mL of purified water. The absorbance detection of each sample was conducted in triplicate.

Viscosity of Polymer Solutions

The viscosity of polymer solutions prepared for SFL processing was evaluated by a falling ball viscometer (Size No. 1, 2, and 3; Gilmont Instruments, Barrington, IL).

Statistical Analysis

The data were compared using 1-way ANOVA to evaluate each treatment effect. A level of $P < .05$ was considered statistically significant.

RESULTS AND DISCUSSION

The Influence of Polymer Solution Flow Rate

Flow conditions, atomizer dimensions, and properties of the feed solution and cryogenic liquid into which the liquid jet is atomized, have been shown to influence the mean drop size in a spray.[14] A plain orifice atomizing nozzle was employed in this study for the development of the SFL process for encapsulation and production of microparticles. The tip of the nozzle was immersed directly into the cryogenic liquid to produce the aerosol cloud upon freezing of the sprayed solution. Mass flow rate of the polymer feed solutions was varied from 1 to 20 mL/min. As the aqueous solution exited the nozzle at the orifice, atomization occurred as a result of shear forces at the point of impact with the cryogenic liquid.

The influence of polymer solution flow rate on the M50 of the PEG particles is shown in **Figure 2**. Significant differences in the M50 were found with the 10% PEG 18 500 polymer solution formulation in the flow rate range of 1 to 5 mL/min ($P < .05$). These particles were much larger than the others in the figure. The low flow rate was not enough to atomize this highly viscous (11.16 cP) solution to produce particles smaller than 100 micrometers. For the other conditions, the viscosities were much lower (1.65 to 3.85 cP), and atomization led to particles smaller than 100 μm in diameter. For these conditions, an increase in flow rate produced a slight decrease in particle size, reflecting more intense atomization. Higher flow rates decreased the M50 of samples produced by the 10% PEG 8000 polymer solution formulation ranging from 60 μm at 2 mL/min to 45 μm at 20 mL/min produced at -40°C and 1000 psi. At -50°C and 300 psi, the M50 ranged from 70 μm at 5 mL/min to 60 μm at 20 mL/min. Although not statistically significant, a decreasing trend in the M50 of microparticles produced by the 10% PEG 18 500 polymer solution formulation was also observed within the flow rate range investigated. The span index, which is a measure of polydispersity, was influenced by the polymer solution flow rate.

The influence of polymer solution flow rate on the spherical shape and morphology of the PEG microparticles is shown in **Figure 3A-D**. Within the range of 2 to 5 mL/min, the PEG microparticles (**Figures 3A** and **Figure 3B**) were spherical and porous. At 10 to 20 mL/min, the spherical particles (**Figure 3C**) appeared fragmented and were highly nonspherical. The particles were porous and brittle and readily collapsed under their own weight.

The x-ray diffraction pattern of the original nonprocessed PEG 8000 is shown in **Figure 4**. Peaks 1 and 2 of the PEG 8000 diffractogram correspond to 19.25 and 23.40 2-θ degrees and have intensities of 1544 and 1946, respectively (**Figure 4**). Peak 1 and peak 2 of the PEG 18 500 diffractogram are located at 19.40 and 23.50 2-θ degrees and have intensities of 1270

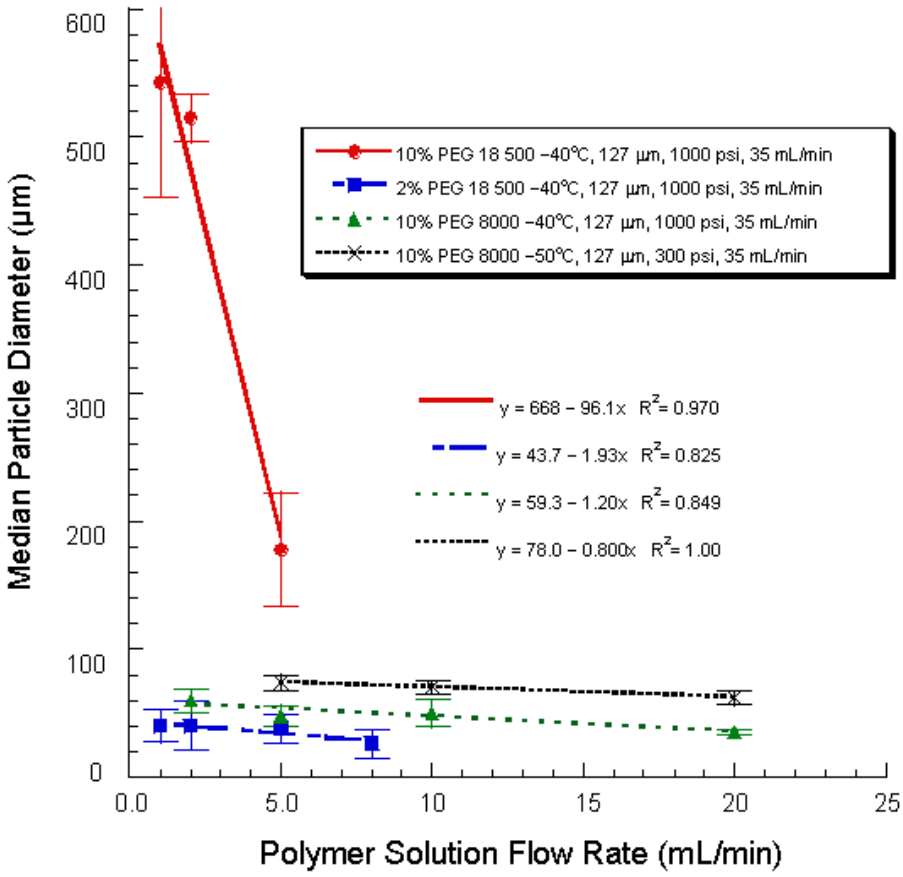

Figure 2. The influence of polymer solution flow rate and polymer molecular weight on the median particle diameter of polymeric polyethylene glycol (PEG) microparticles.

and 1709, respectively (diffraction pattern similar to **Figure 4**). The peak intensities of the non-SFL-processed PEG were used as the control peak intensities (I_c). In order to discern the relative effect of the processing parameters on crystallinity, the SFL-processed sample peak intensities were normalized by the corresponding control (non-SFL processed) peak intensity. SFL processing of a 10% solution decreased the normalized crystallinity of PEG 18 500 to 52.6% at 19.40 2-θ degrees and to 73.8% at 23.50 2-θ degrees. SFL processing of a 2% solution resulted in a decrease in the crystallinity of PEG 18 500 to 23.1% at 19.40 2-θ degrees and to 37.7% at 23.50 2-θ degrees. The SFL processing conditions for these measurements were as follows: cryogen pressure was 1000 psi; polymer solution feed rate was 2 mL/min; cryogen flow rate was 35 mL/min; and temperature was -40°C.

The Influence of Polymer Solution Viscosity

The flow and spray characteristics of most atomizers are strongly influenced by the liquid properties of density, viscosity, and surface tension, and by the liquid into which the droplets are discharged. In many respects, viscosity is the key liquid property that governs atomization. At very high viscosities the normal conical spray may collapse into a straight stream of relatively large ligaments and droplets.[6] Viscosity inhibits instability in the emerging jet and generally delays the onset of jet disintegration, causing atomization to occur further downstream in regions of lower relative velocity. Consequently, droplet size may increase proportionally with liquid viscosity. Solution viscosity exerts a stabilizing effect on atomization by opposing the onset of turbulence in the emerging jet.

Viscosities of PEG 8000 and 18 500 solutions were determined and used to evaluate the influence of molecular weight on the characteristics of the microparticles produced by the SFL process. The viscosity of

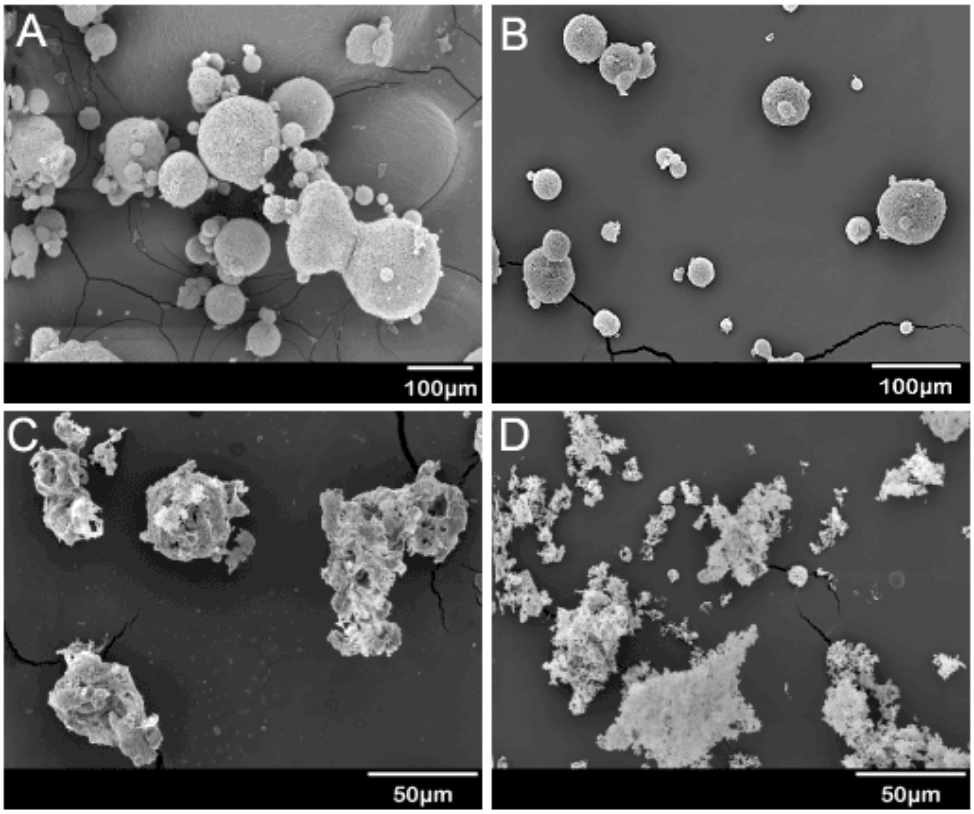

Figure 3. Scanning electron microscope (SEM) photographs of 10% polymeric polyethylene glycol 18 500 microparticles produced by different polymer solution flow rates: (A) 2 mL/min; (B) 5 mL/min; (C) 10 mL/min; and (D) 20 mL/min. The SFL processing conditions were cryogen pressure, 1000 psi; temperature, -40°C; and cryogen flow rate, 35 mL/min.

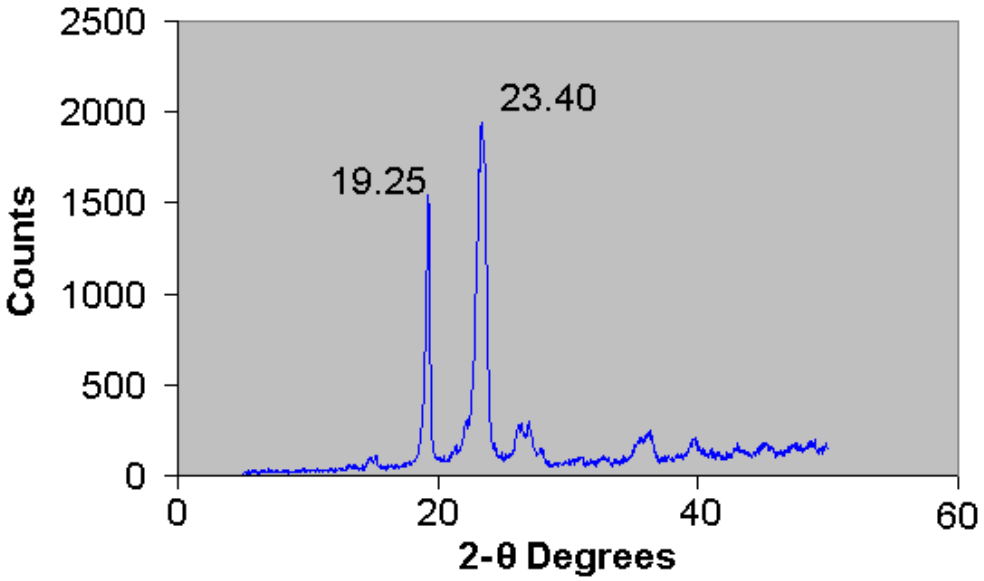

Figure 4. The x-ray diffraction patterns of polymeric polyethylene glycol (PEG) 8000 not subjected to spray freezing into liquid (SFL) processing.

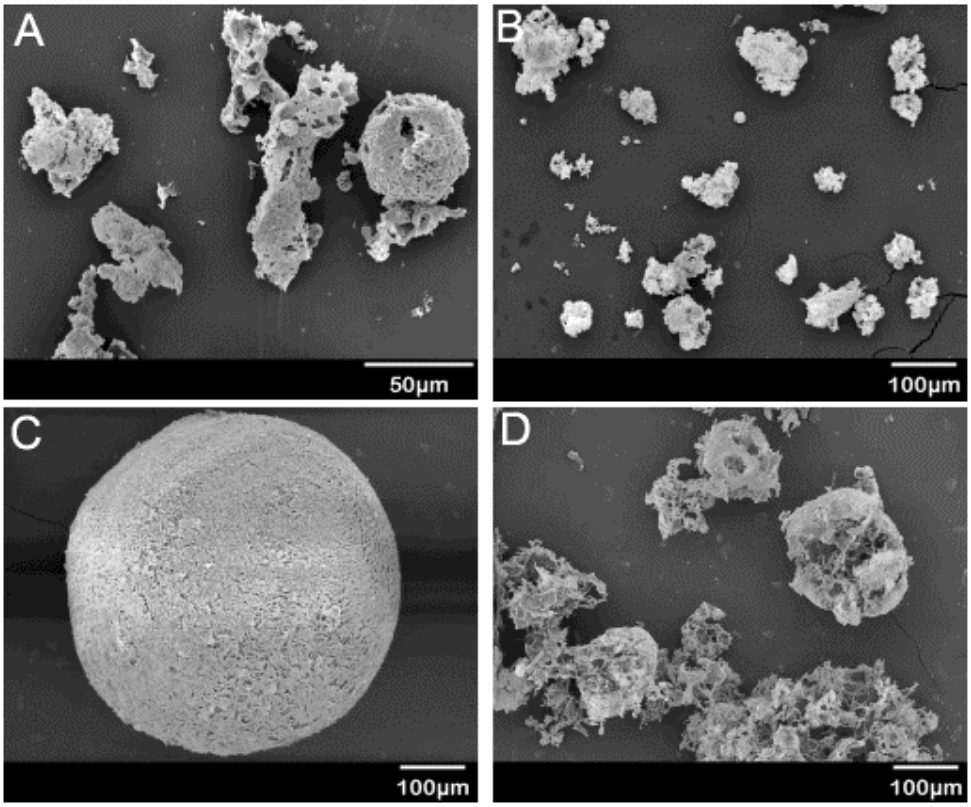

Figure 5. Scanning electron microscope (SEM) photographs of polymeric polyethylene glycol (PEG) microparticles produced by spray freezing into liquid (SFL) from polymer solutions, where the viscosity of the solution was controlled by polymer concentration: (A) 10% PEG 8000; (B) 8% PEG 8000; (C) 4% PEG 8000; (D) 10% PEG 18 500. The SFL processing conditions were cryogen pressure 1000 psi; temperature, -40°C; nozzle diameter, 127 micrometers; feed solution flow rate, 10 mL/min; and cryogen flow rate, 35 mL/min.

the polymeric solutions was shown to have a significant influence on the physicochemical properties of the microparticles prepared by the SFL process. By raising the concentration and hence the viscosity of the polymer solutions, the M50 of the microparticles increased for either PEG 8000 or PEG 18 500, as shown in **Figure 2**. Also, the influence of polymer solution viscosity on the M50 was evaluated by increasing the MW of the PEG polymer. As shown in **Figure 2**, the M50 of the microparticles produced by the SFL process increased as the viscosity of the PEG polymer solution was increased due to the MW of the PEG polymer for a concentration of 10% PEG. By combining data from both PEG 18 500 and PEG 8000 solutions for various concentrations, it is evident that the particle size distribution of the microparticles produced by the SFL process may be correlated to the viscosity of the polymer solution.

Figure 5A-D shows the influence of polymer solution viscosity varied by polymer concentration on particle shape and morphology of the resulting microparticles. PEG 8000 solution produced spherical particles, but irregularly shaped particles were also present (**Figure 5A,B**). PEG 18 500 produced spherical, porous particles at a concentration of 10% (**Figure 5C**). At 2% PEG 18 500 concentration, the particles were slightly spherical but appeared brittle because of loose interlacing polymeric strands (**Figure 5D**).

By lowering the polymer concentration, the polymer solution viscosity decreased and the porosity in-

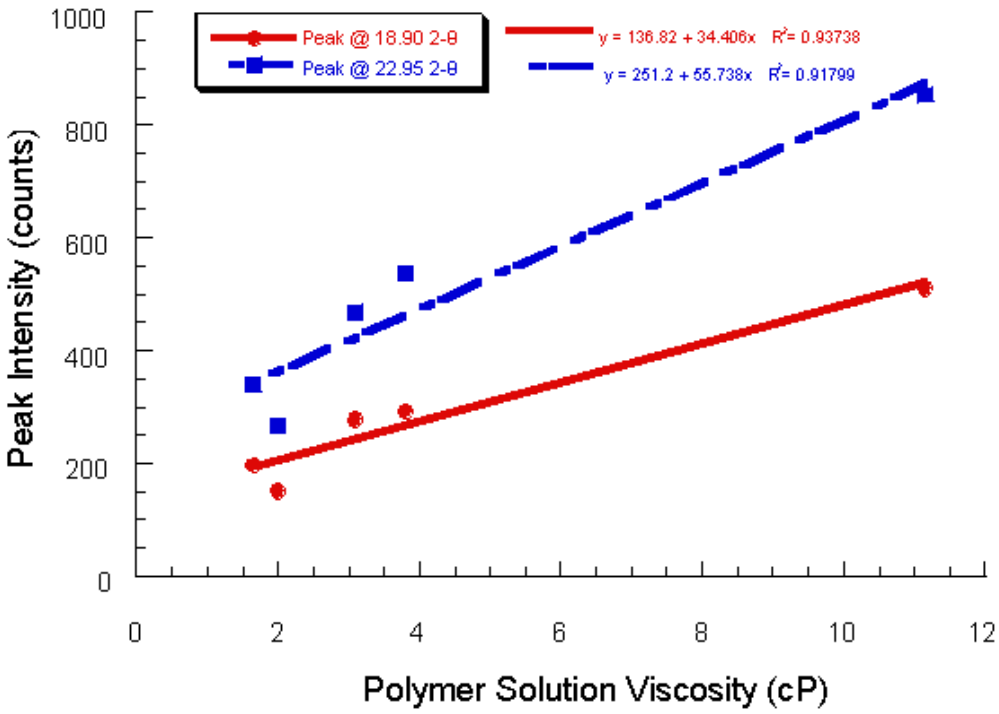

Figure 6. The influence of polymer solution viscosity on the crystallinity of polymeric polyethylene glycol (PEG) 18 500 microparticles.

creased ($P < .05$). This decrease in concentration lowers the amount of dispersed phase produced relative to the amount of ice crystals, resulting in increased porosity. However, the change in viscosity will also vary the atomization and heat transfer, which may influence porosity. To understand the effect of viscosity independently of that of polymer concentration, experiments were performed at constant concentration for the 2 molecular weights. In this case, no significant difference in porosity was found, indicating the porosity was influenced more by the fraction of dispersed phase formed than by the atomization ($P > .05$).

A significant increase in normalized crystallinity of the PEG microparticles produced by PEG 18 500 and PEG 8000 polymer solutions occurred as the polymer solution viscosity was increased ($P < .05$) as shown in **Figure 6**. Furthermore, the peak intensity increased, independently of whether the increase in viscosity arose from PEG concentration or molecular weight. The increase in viscosity may be expected to decrease atomization and the rate of heat transfer. With larger droplet domains and slower freezing, the time for crystallization increased. The ability to control the degree of crystallization is highly advantageous in SFL processing.

The Influence of SFL Processing Parameters on Drug-Loaded Microparticles

The shape and morphology of PEG 8000 microparticles loaded with albuterol sulfate are shown in **Figure 7A** and **B**, and the drug loading parameters are shown in **Table 1**. The yield for the SFL process was greater than 95%, demonstrating the efficiency of the process. The SEM photographs show that the 17.9% albuterol sulfate-loaded PEG 8000 microparticles (**Figure 7B**) appear similar to the PEG 8000 control microparticles (**Figure 7A**) produced at the same SFL processing parameters.

Figure 8A-D shows the x-ray diffraction patterns of albuterol sulfate-loaded PEG 8000 microparticles (**Figure 8A**), nonprocessed albuterol sulfate (**Figure 8B**), PEG 8000 microparticles (**Figure 8C**), and a physical mixture of PEG 8000 and albuterol sulfate (**Figure 8D**). The crystallinity of nonprocessed albuterol sulfate (**Figure 8B**) was decreased due to mixing with PEG 8000 (**Figure 8D**) and the rapid freez-

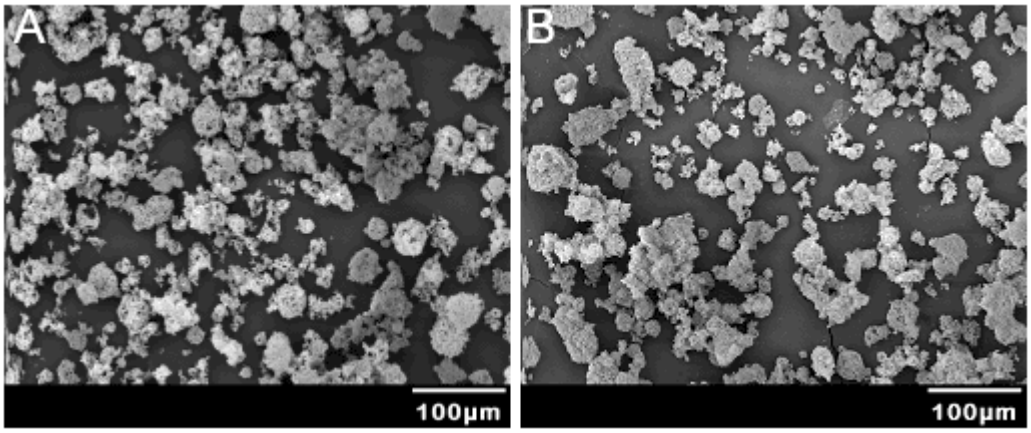

Figure 7. Scanning electron microscope (SEM) photographs of drug-loaded polymeric polyethylene glycol (PEG) microparticles and control formulations: (A) 17.9% albuterol sulfate in PEG 8000 and (B) only PEG 8000.

Table 1. The Encapsulation Efficiency of PEG Microparticles Loaded With Albuterol Sulfate Produced by the SFL Process*

Polymer Solution Formulation	Before Processing	After Processing	Encapsulation	
	mg drug/0.5 g polymer		Drug Load (%)	Efficiency (%)
10% PEG 8000 and 0.25% albuterol sulfate	12.5	12.0	2.40	96.0
10% PEG 8000 and 0.50% albuterol sulfate	25.0	22.5	4.50	90.0
10% PEG 8000 and 2.0% albuterol sulfate	100	89.4	17.9	89.4

*PEG indicates polymeric polyethylene glycol; SFL, spray freezing into liquid. SFL process conditions are 127 µm nozzle, –50°C, 300 psi, 5 mL/min polymer solution flow rate, and 35 mL/min cryogen flow rate.

ing from the SFL processing and was highly amorphous after processing with PEG 8000 (**Figure 8A**). It has been demonstrated that lyophilization of albuterol sulfate and other active pharmaceutical agents with PEG 3350 influences PEG crystallinity.[15] **Table 2** describes the influence of encapsulated materials on the crystallinity of PEG 8000 after SFL processing. Processing 10% PEG 8000 alone resulted in a decrease in crystallinity to 29.2% at 18.95 2-θ degrees and to 35.7% at 23.05 2-θ degrees (**Figure 8C**). Addition of albuterol sulfate to the polymer feed solution resulted in a further decrease in PEG 8000 crystalline content (**Figure 8A**); whereas the crystallinity of the physical mixture was 100% (**Figure 8D**). The decrease in PEG 8000 crystallinity was dependent on the concentration of albuterol sulfate ranging from 13.3% to 8.80% at 18.80 2-θ degrees and 17.4% to 13.5% at 22.95 2-θ degrees for 0.25% and 2.0% albuterol sulfate, respectively.

Figure 9A-D shows the DSC thermograms of PEG 8000 microparticles and a 5:1 (wt/wt) physical mixture of PEG 8000 and albuterol sulfate. Also, thermograms of PEG 8000 and albuterol sulfate non-SFL processed controls are shown. Before processing, the melting point and enthalpy of PEG 8000 were 62.81°C and 209.1 J/g, respectively (**Figure 9A**). Nonprocessed albuterol sulfate was found to have a melting point of 193.1°C and enthalpy of 240.3 J/g (**Figure 9B**). The melting point and enthalpy of PEG 8000 in the 5:1 (wt/wt) physical mixture was not significantly different from the nonprocessed PEG 8000 control (**Figure 9C**). However SFL processing resulted in significant differences in the thermal properties of both PEG 8000 and albuterol sulfate. The melting point and enthalpy of PEG 8000 were lowered to 60.53°C and 149.1 J/g, respectively (**Figure 9D**).

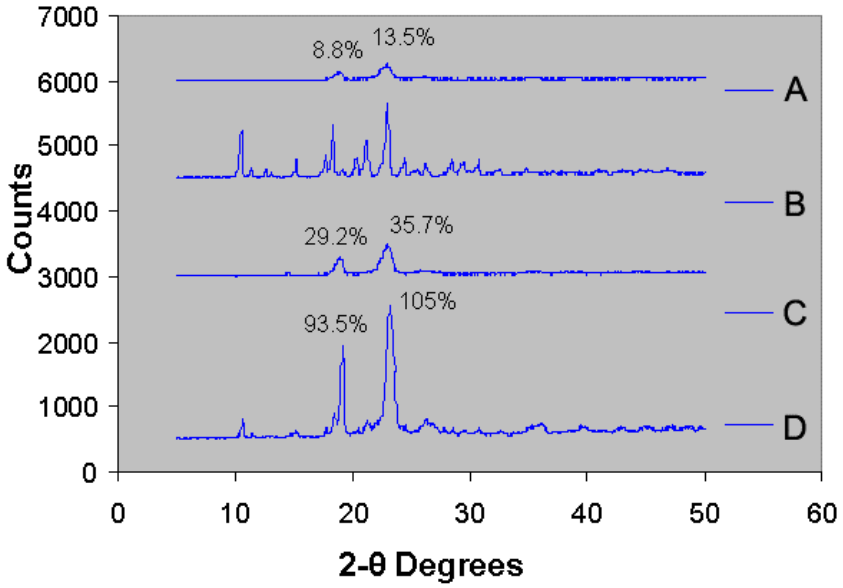

Figure 8. Scanning electron microscope (SEM) photographs of 10% polymeric polyethylene glycol 18 500 microparticles produced by different polymer solution flow rates: (A) 2 mL/min; (B) 5 mL/min; (C) 10 mL/min; and (D) 20 mL/min. The SFL processing conditions were cryogen pressure, 1000 psi; temperature, -40°C; and cryogen flow rate, 35 mL/min.

Table 2. The Influence of Degree of Loading of Albuterol Sulfate Into PEG Microparticles Produced by the SFL Process on Crystallinity*

Polymer Solution Formulation	Peak 1		I_1/I_c (%)	Peak 2		I_2/I_c (%)
	($2\theta^o$)	(I_1)		($2\theta^o$)	(I_2)	
PEG 8000 not processed	19.25	1544	100.0	23.40	1946	100.0
10% PEG 8000	18.95	451	29.2	23.05	694	35.7
10% PEG 8000 and 0.25% albuterol sulfate	18.85	205	13.3	23.00	339	17.4
10% PEG 8000 and 0.50% albuterol sulfate	18.80	141	9.1	22.85	263	13.5
10% PEG 8000 and 2.0% albuterol sulfate	18.80	136	8.8	22.95	263	13.5

*PEG indicates polymeric polyethylene glycol; SFL, spray freezing into liquid. SFL process conditions are 127 μm nozzle, –50°C, 300 psi, 5 mL/min polymer solution flow rate, and 35 mL/min cryogen flow rate.

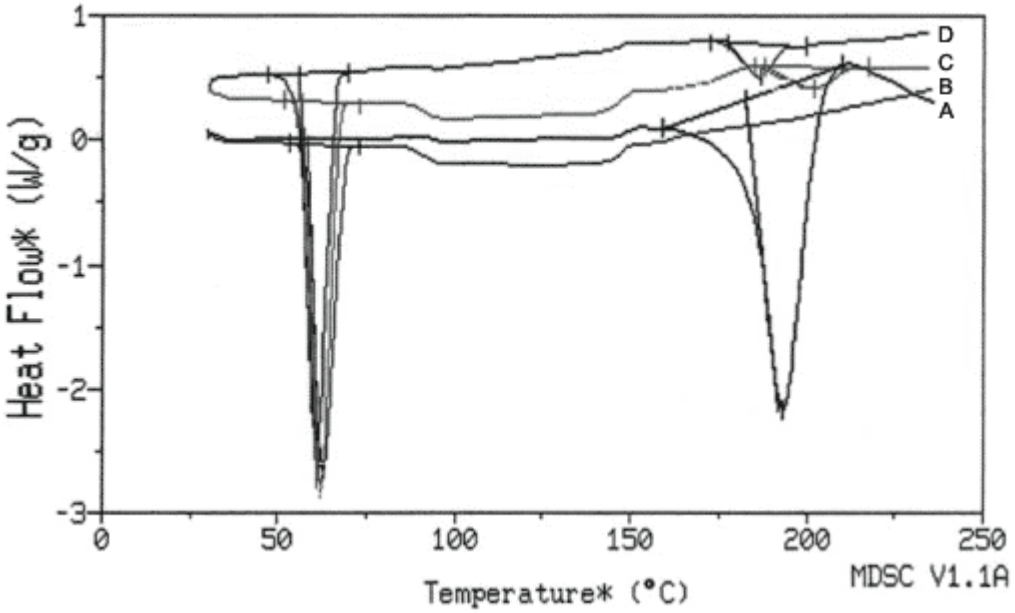

Figure 9. Differential scanning calorimeter (DSC) thermal graphs of drug-loaded polymeric polyethylene glycol (PEG) microparticles and controls: (A) PEG 8000 "as received," (B) albuterol sulfate "as received," (C) physical mixture of PEG 8000 and albuterol sulfate in a 5:1 ratio, and (D) PEG 8000 by spray freezing into liquid (SFL) processing.

In this study, it was shown that by varying the process parameters, the physicochemical characteristics of model polymeric microparticles of PEG were modified to investigate their use in drug delivery. Increased atomization of the jet produced by increasing the polymer solution flow rate resulted in smaller droplets and, therefore, a smaller particle size distribution of the PEG microparticles. Particle size distribution, particle shape and morphology, intragranule porosity, granule density, and crystallinity were influenced by the rate of freezing.

Ideally any liquid that may be chilled to temperatures below the freezing point of the emitted aerosol solution and is an antisolvent for the emitted aerosol solution may be utilized as a cryogenic liquid. Liquid CO_2 is a preferred nonsolvent since it is not miscible with water and does not solubilize most polymers, active pharmaceutical ingredients, or pharmaceutical excipients. However, its utility as a cryogenic medium in this process is limited because of its triple point,[12] 180 psig, and -56.6°C. Temperatures lower than -56.6°C may be necessary to rapidly freeze the aerosol droplets produced by atomizing at very rapid solution flow rates. In this case, liquid nitrogen or other cryogenic liquids may be substituted in place of liquid CO_2. Polymer solution viscosity influenced the atomization process. The M50 and density of the PEG microparticles increased as the viscosity of the polymer solution was increased. Also, the crystallinity of the PEG microparticles increased as the polymer solution viscosity was increased. The higher viscosity reduced the droplet breakup in atomization. Both the larger droplets and slower heat transfer in the viscous droplets increase the time for crystallization prior to complete freezing. The higher viscosity was achieved by raising polymer concentration or molecular weight. The ability to manipulate the particle size, porosity, and crystallinity by manipulating polymer concentration or polymer molecular weight is highly advantageous for producing drug delivery devices. Reduction of the melting point and heat capacity of PEG 8000 with encapsulated albuterol sulfate demonstrated that SFL processing may be utilized to reduce crystallinity.

CONCLUSION

SFL was demonstrated to be a useful and efficient particle engineering technology for preparation of polymeric microparticles. It was demonstrated that the polymeric microparticles could be formulated with the model drug, albuterol sulfate. SFL will be quite useful for other types of polymers for preparing drug

delivery systems for oral controlled release, pulmonary, and depot injectable administration.

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