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Supercritical and Near-critical Carbon Dioxide Assisted Low-Temperature Bubble Drying

R. E. Sievers,* P. D. Milewski, S. P. Sellers, B. A. Miles, B. J. Korte, K. D. Kusek, G. S. Clark, B. Mioskowski, and J. A. Villa

Department of Chemistry and Biochemistry and CIRES, Campus Box 216, University of Colorado, Boulder, Colorado 80309

If supercritical or near-critical carbon dioxide is mixed with an aqueous solution and the mixture is subsequently decompressed through a flow restrictor, a dense aerosol plume is formed[1] that can be rapidly dried at 25−95 °C. This temperature range is lower than that typically needed in conventional spray-drying aqueous solutions. At 1100 psi and ambient temperature, up to ≈2 mol % of carbon dioxide can dissolve in aqueous solutions, and when the aqueous solution is ejected from a 5-cm-long flow restrictor, 50−130 μm in inner diameter, it is hypothesized that fine droplets and microbubbles are formed. This aerosol plume can be diluted with dry nitrogen (or air if there is no explosion hazard) at temperatures usually between 25 and 80 °C. In a drying chamber <1-m long, the bubbles and droplets become rapidly dried and the powder is collected on a filter. The particles are usually spherical or nearly spherical and residual moisture is typically 1% or less. For some substances, such as sodium chloride, mannitol, or tobramycin sulfate, hollow particles can be formed. For others, such as lactose and albuterol sulfate, the spherical particles are solid, with diameters mostly between 0.5 and 5 μm. Depending on the solute and conditions of drying, the particles are crystalline in some cases and amorphous in others.

Introduction

When supercritical or near-critical carbon dioxide is mixed with an aqueous solution and then decompressed through a flow restrictor (i.d., 50−130 μm), a dense fine-droplet, aerosol plume is formed that can be rapidly "bubble-dried" at temperatures between 25 and 95 °C. It is hypothesized that very fine droplets or microbubbles are formed that are rapidly bubble-dried in contact with warm nitrogen in a drying chamber only 30−80-cm long.

Albuterol sulfate (salbutamol sulfate) and cromolyn sodium (disodium cromoglycate) are two pharmacological agents used frequently in metered dose inhalers (MDIs) and dry powder inhalers for the treatment of asthma. α-Lactose is a diluent utilized in dry powder inhalers. Pharmacological agents that do not reach their target tissues will be limited in their desired effects. This limitation is especially problematic in systems of pulmonary drug delivery, with current systems delivering <30% of the metered dose to terminal lung alveoli.[1,2] Most of this inefficiency is due to average particle sizes that are too large to be transported and deposited into the distal alveoli through the smallest air passages in the lung. It has been shown that the optimum aerodynamic particle size for effective inhalation is 3 μm;[3] Johnson quotes the optimum aerodynamic diameter to be 1−5 μm.[4] Unfortunately, commercial techniques for producing these drugs, such as precipitation and jet-milling, have produced particles with average sizes ranging from 3 to 10 μm, leading to low inhalation efficiencies.

In this study the CO_2-assisted aerosolization and drying technique was used to produce spherical submicron particles of albuterol sulfate, cromolyn sodium, α-lactose, and combinations of drug and lactose. Closely related work was performed by Chawla and co-workers[5] and Vidgren and co-workers[6] using commercial spray dryers to produce spherical particles of albuterol sulfate and cromolyn sodium, respectively. Both studies reported products with particle sizes of 2−5 μm, in which some, if not most, of the particles were in the respirable size range. Both studies also used pneumatic nebulizers, which have lower throughput and generate less dense plumes than the technique reported here.

The CO_2-assisted aerosolization and drying technique has been shown to be effective in the formation of rhDNase particles.[1] Approximately 75% of the aqueous buffered rhDNase was recovered in a wet-walled impinger in particle sizes 3 μm and smaller. We have also demonstrated that aqueous solutions of proteins such as lysozyme and lactate dehydrogenase, when stabilized with buffers, disaccharides, and surfactants, can be bubble-dried and collected without significant loss of activity.[7] For some substances, for example, sodium chloride, tobramycin sulfate, and mannitol, hollow particles can be formed, as indicated by transmission electron microscopy. The CO_2-assisted aerosolization and drying technique has also been shown to be effective in the synthesis of oxides and various other materials in spherical, ≈1 μm in diameter, particle form.[8,9]

Two methods of aerosolization have been demonstrated: (1) the dynamic method, which utilizes a low-dead-volume tee, and (2) the static method, in which the carbon dioxide and water are in contact ≈30 min up to a few hours before the aqueous solution is decompressed through the flow restrictor.

The new patented process[2] is inherently a sustainable technology because only water and carbon dioxide are used as solvents, and drying temperatures are lower

* To whom correspondence should be addressed. Tel.: (303) 492-7943. Fax: (303) 492-1414.

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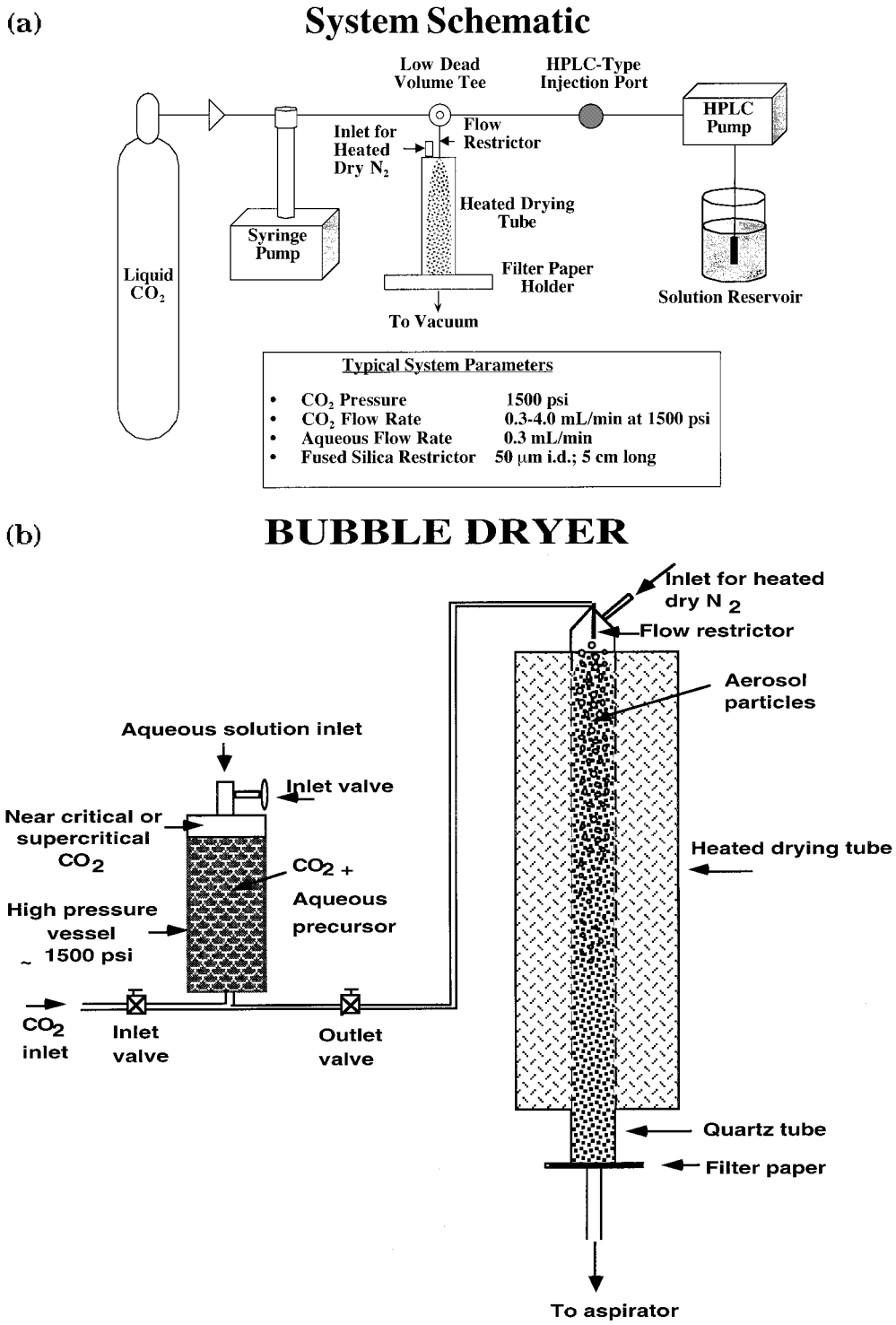

Figure 1. (a) Schematic diagram of the dynamic system with a low dead volume tee. (b) Schematic diagram of the CO_2-assisted nebulizer and spray drier (static method).

than those in traditional spray-drying, presumably because the microbubbles present larger surface areas per volume of aqueous solution than droplets to the drying gas. The process forms dry powders that can be administered by dry powder inhalers for pulmonary delivery, which avoid the use of chlorofluorocarbons or fluorocarbons.

Experimental Equipment

In the CO_2-assisted aerosolization and drying technique, aqueous precursors are prepared by dissolving the drugs in distilled water. The aqueous precursors are combined with supercritical CO_2 in one of two ways. In the "dynamic" approach, the precursor is pumped into one arm of a low-dead-volume tee, while supercritical CO_2 is pumped through the other. These come into intimate contact with each other and form an emulsion. When this emulsion is released from the tip of a capillary restrictor into dry air, it forms a dense aerosol of drug particles. A schematic diagram of the "dynamic approach" apparatus is shown in Figure 1a. In the "static" approach, supercritical CO_2 is bubbled into the

bottom of a high-pressure vessel filled with the aqueous precursor and mixed. The mixture is then allowed to reach equilibrium, at which time CO_2 is dissolved in the solution up to a maximum of ≈2 mol %.[10] The mixture is then released through a capillary restricting orifice to produce a fine, dense aerosol of aqueous drug in gaseous CO_2. A schematic diagram of this apparatus is shown in Figure 1b. Wet drug particles using either approach are dried by mixing the sprayed droplets with warm dry nitrogen and collecting the dried particles on a cellulose acetate filter. Alternatively, in small-scale experiments, the plume can be dried by passing the aerosol over concentrated sulfuric acid, which serves as a desiccant to dry the aerosol plume diluted with dry air or nitrogen before collection on a filter. Nitrogen is used in preference to air when the materials being dried are combustible and pose an explosion hazard.

Materials and Methods

Cromolyn sodium (Eagle-Pitcher), albuterol sulfate (Sigma-Aldrich), and α-lactose (Sigma-Aldrich) were each dissolved in distilled water to concentrations of 0.1 M. Much larger concentrations can also be used, up to saturated solutions of several weight percent. In the "dynamic" method, a Bio-Rad model 1330 high-pressure liquid chromatography pump was used to deliver the precursor (at 0.3 mL/min) to the tee. Food-grade (or welding-grade in some experiments) CO_2 was pressurized in an ISCO model 260D high-pressure syringe pump to a pressure of 1500 psi and used to deliver the CO_2 (at ≈4 mL/min) to the other side of the tee. The CO_2 and precursor solution were mixed in a low-dead-volume Valco tee (<1 μL) and the emulsion was released into air through a 50-μm fused silica capillary restrictor (Poly micro Tech.) to form a fine dense aerosol. In the "static" approach, typically a 10-mL stainless steel high-pressure vessel was filled with 8 mL of the precursor solution. Vessels with capacities as large as 100 cm^3 have been used. The vessel was pressurized to 2500 psi with CO_2 and allowed to equilibrate. The best aerosols, in terms of small particle size, were obtained when equilibrium times of 8 h or more were used, but times as short as 30 min have been employed. The solution was then released through a 50-μm-diameter, 5-cm-long fused silica capillary restrictor (Poly micro Tech.) to form a fine dense aerosol. Stainless steel capillaries have also been used. The aerosol was sprayed into an expansion chamber containing dry air and then through a cellulose acetate filter to collect dry powders. In some experiments aerosols were passed over a pool of reagent-grade concentrated sulfuric acid to dry the aerosol but this was later shown to be unnecessary. The water vapor diluted with warm nitrogen passed through the filter under positive pressure in the later, improved method.

In early experiments with a vacuum pump, the aerosol plume was drawn through the apparatus, as it was diluted with dry air, and the particles were collected on a 0.2-μm pore size cellulose acetate membrane filter (Advantec MFS) or an Anderson 8 stage nonviable 20-800 series cascade impactor. Filtration was facilitated by use of a vacuum pump initially. Subsequent experiments have shown that vacuum pumps are unnecessary and that particles can be collected using a small positive pressure of warmed (30−95 °C) dry nitrogen. The mass of the particles was measured and samples were stored in a desiccator over Drierite or P_4O_{10}.

Analyses of Particles

Scanning electron microscope (SEM) images were prepared by placing a small quantity of the particles onto a piece of double-sided carbon tape followed by gold coating. Transmission electron microscopy (TEM) samples were prepared by suspending the particles in ethanol and adding a few drops of the solution to a carbon holey grid (Ted Pella) and allowing the ethanol to evaporate. Fourier transform infrared (FTIR) spectroscopy samples were prepared by mixing the particles with Nujol for the albuterol sulfate and methylene chloride for the cromolyn sodium, and spectra were obtained using a Nicolet Impact 410. X-ray diffraction analysis (XRD) was performed on a Philips diffractometer using Cu $K\alpha_1$ radiation coupled with a monochromator. Samples for XRD analysis were prepared by applying a thin layer of particles mixed with silicone vacuum grease over a piece of microscope slide.

Solvent annealing experiments were performed to crystallize the amorphous spheres initially isolated by placing the aerosol-synthesized particles into absolute ethanol for various periods of time. Various conditions were employed to determine the effects on the morphology and crystallinity of the drugs. In the first set of experiments, three 0.025-g samples of sprayed and dried amorphous spherical albuterol sulfate particles were each added to 10 mL of 100% ethanol and treated for 1 week. In the first sample, the sample was heated to ≈50 °C and stirred rapidly with a magnetic stir bar. The second sample was also heated to 50 °C, but not stirred. The third was stirred rapidly at room temperature (about 22 °C). After crystallization, all samples were isolated and dried by drawing off the ethanol under vacuum.

In a second set of experiments, CO_2-sprayed, then dried, and collected drug particles were solvent-treated under identical conditions as the as-received powder from the manufacturer. Six 0.02-g samples of albuterol sulfate (three of the bubble dried and three of the as-received) were each added to 10 mL of absolute ethanol. Once again three sets of experiments were performed. The first two samples were stirred at room temperature (≈22 °C) for 3 h and 15 min. The second two were stirred at room temperature for 2 days. The final two were stirred in an ice bath (0 °C) for 2 days. Samples were then centrifuged at 6000 rpm for 10 min. The supernatant was decanted and the remaining solvent absorbed in the pellet was removed under vacuum.

Results

Spherical particles of albuterol sulfate and cromolyn sodium can be produced near room temperature using both experimental configurations, as shown in Figure 2a,b. In some experiments at higher drying temperatures (75−95 °C) using the "dynamic" method, lifeboat-shaped particles of cromolyn sodium were observed (Figure 2c). In Figure 2c, several lifeboat-shaped particles of cromolyn sodium are present. The conditions for this bubble-drying experiment were aqueous solution flow rate (0.25 g of cromolyn sodium in 10 mL), 0.3 mL/min, supercritical CO_2 (1500 psi) flow rate, 0.6 mL/min through low dead volume (≈1 μL) tee, into drying chamber 95 °C at inlet, 75 °C at outlet, where the aerosol plume was mixed with heated nitrogen, flow rate 14 L/min.

Lactose as well as lactose plus drug combinations also were isolated as spherical particles when exposure to

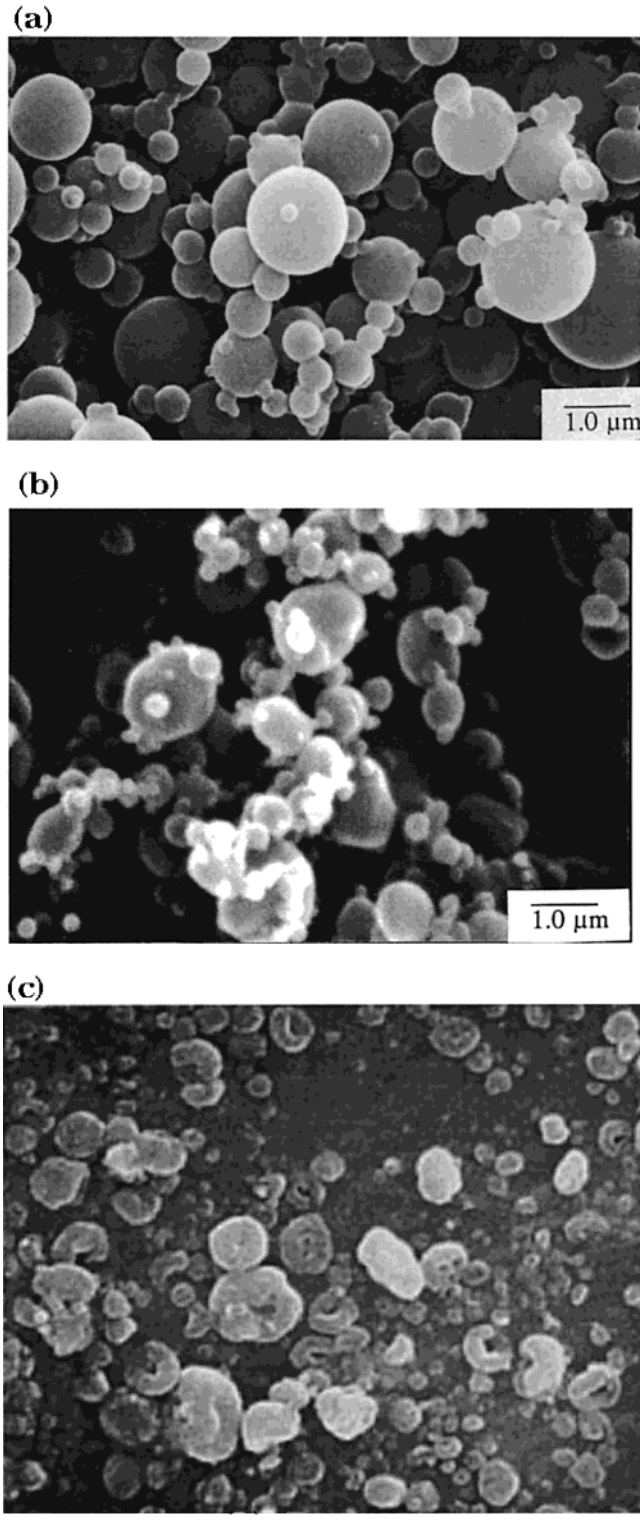

Figure 2. (a) SEM of albuterol sulfate produced by the static method at 35 °C; the aqueous solution of albuterol sulfate was pre-equilibrated for 2 h by pumping into the canister near-critical CO_2 at 25 °C and 2500 psi, after which the valve leading to the flow restrictor was opened; the drying chamber was maintained at 75−95 °C. (b) SEM of cromolyn sodium produced by the dynamic method with a drying chamber at 35 °C (under similar conditions as in Figure 2c). (c) SEM of cromolyn sodium produced by the dynamic method with a drying chamber at 75−95 °C; flow restrictor capillary diameter, 75 μm; 5-cm length; initial concentration of cromolyn sodium, 0.5 g/10 cm^3 of H_2O; flow rate of N_2 drying gas added to spray plume, 14 L/min; aqueous solution pumped at 0.3 cm^3/min, mixed with supercritical CO_2 at 0.6 cm^3/min at 1500 psi.

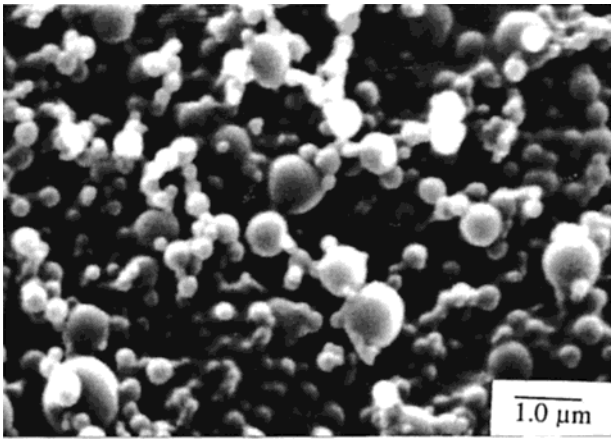

Figure 3. SEM image of α-lactose formed by CO_2-assisted aerosolization and bubble-drying. Conditions same as in Figure 2c.

the humid ambient was minimized, as shown in Figure 3. Particle size was measured directly from SEM images, and the ranges were subsequently independently confirmed by laser light scattering measurements. A typical particle size histogram for albuterol sulfate prepared by the "static" aerosolization method is shown in Figure 4a. While the number-average particle diameter size is fairly small (0.7 μm), the volume-average particle size (0.95 μm) indicates that most of the drug is of the ideal size for inhalation. Eighty-five particles in a typical segment of the SEM were counted for this distribution shown. Figure 4b shows a very similar distribution for cromolyn sodium prepared by the "dynamic" method. Again, the number-average particle size was 0.58 μm while the volume-average particle size was 0.70 μm. Seventy-eight particles were counted to obtain this distribution, and laser light scattering measurements (Figure 4c) have confirmed that particle size distributions of bubble-dried powders of albuterol sulfate typically are in the range of 0.1−5 μm, with the bulk of the mass lying in particles from 1 to 3 μm. Moisture contents of dried powders are usually about 1% or less.

FTIR showed that the bubble dried spherical submicron drug particles were identical chemically to the as-received drug. X-ray diffraction studies indicated that both the as-received albuterol sulfate and the commercial cromolyn sodium originally contained at least some quantity of crystalline material, resulting in a weak but detectable X-ray diffraction pattern. Bubble-dried albuterol sulfate showed no detectable crystallinity; only a very broad, low-angle amorphous feature was observed from the X-ray diffraction analysis of the spherical submicron particles.

Solvent treating of the submicron spherical bubble-dried amorphous albuterol sulfate particles resulted in the formation of fine crystalline needles, as shown in Figure 5. In general, the needle diameter was a simple function of solvent-annealing treatment temperature, while the needle length was a complex function of treatment time. The needle diameter was about 3−10 μm for the samples heated to 50 °C, about 0.5−1 μm for room temperature, and 0.2−0.6 μm for the ice-water-cooled (0 °C) sample. Needle lengths were >100 μm for the sample treated for 1 week. Submicron-sprayed amorphous particle samples treated for 2 days were 2−5 μm in length and those treated for the 3.25 h 5−20 μm in length. Solvent-treated particles all showed crystal-

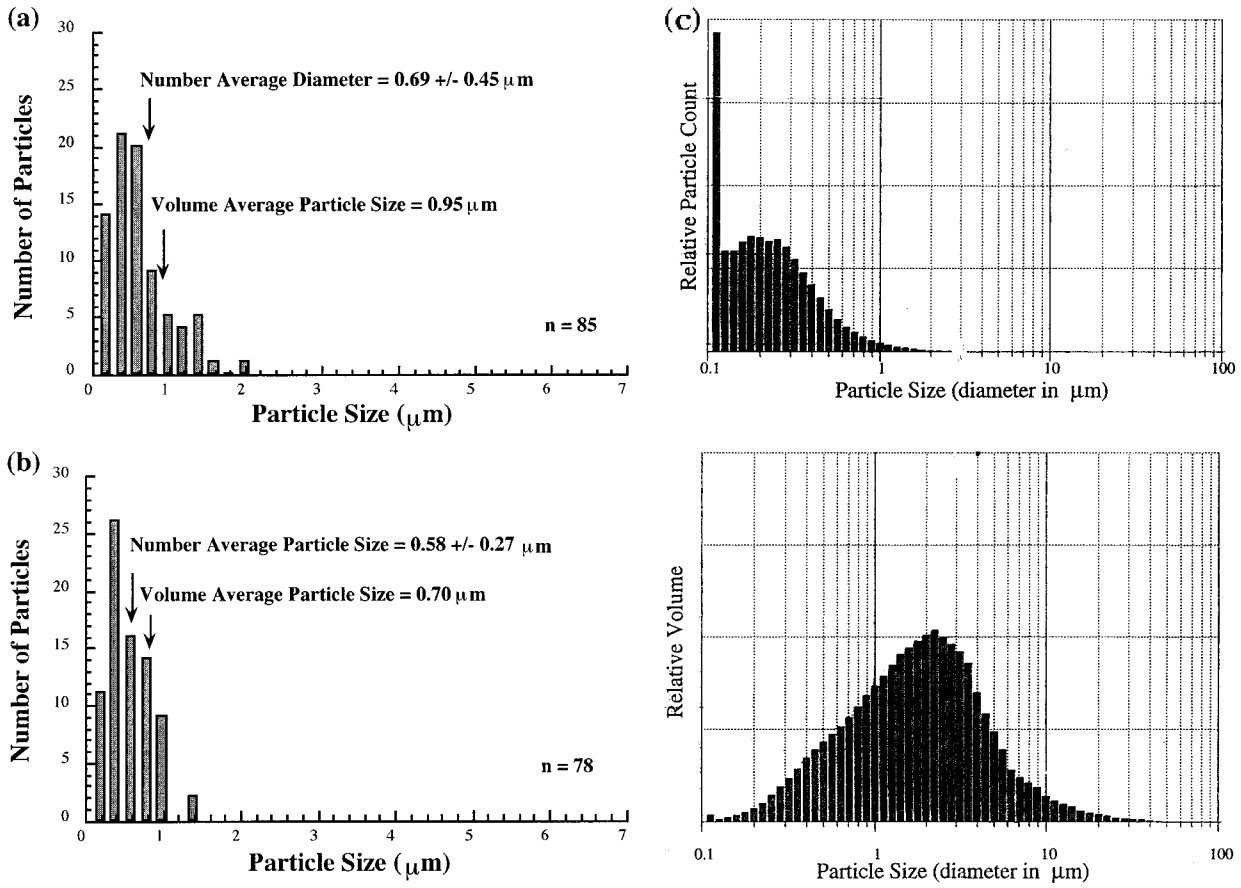

Figure 4. Particle size histograms for (a) albuterol sulfate by the static method (Figure 2a) and (b) cromolyn sodium prepared by the dynamic method (Figure 2c). (c) Particle size distribution of bubble-dried albuterol sulfate estimated by laser light scattering: (above) measured number-weighted distribution; (below) calculated volume-weighted distribution, assuming spherical particles.

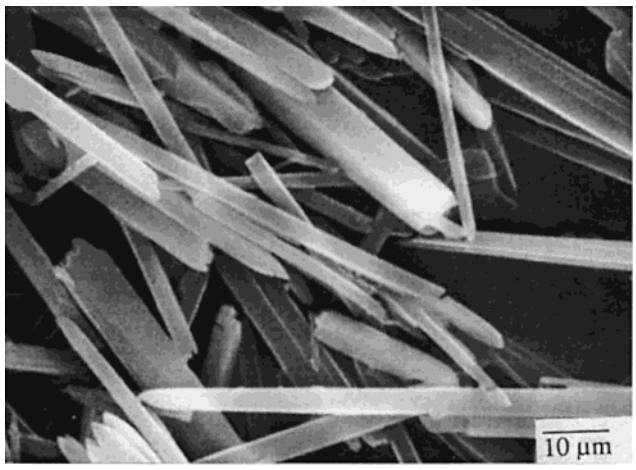

Figure 5. SEM image of ethanolic-solvent-annealed albuterol sulfate particles, exhibiting the 100-μm-long needles formed upon stirring a suspension of 1−3-μm-diameter spherical particles of amorphous albuterol sulfate for 1 week at room temperature the particles previously bubble-dried at 75−95 °C.

linity. In general, the crystallinity was strongest for the heated samples and least for the samples treated at 0 °C. As-received drug powder samples showed almost no change in morphology when solvent-annealed, regardless of the treatment conditions examined for the smaller bubble-dried amorphous particles. As-received drug powder seemed only to become more agglomerated after solvent treatment.

How the crystallization of amorphous particles of albuterol sulfate (most of which are 1−3 μm in diameter) forms needlelike crystals of various sizes is not known with certainty. One can postulate at least two different processes. The first is slow dissolution of the amorphous spheres in ethanol and subsequent crystallization. This could occur either at room temperature or at elevated temperatures. The high surface area of the small spheres may facilitate dissolution. The second process, perhaps less likely except at elevated temperatures, is a glass-to-crystal transition. We have not seen any evidence of morphology changes in the spherical amorphous albuterol sulfate powders upon standing for several (24) months at room temperature.

Discussion

The spherical morphology and amorphous nature of the aerosolized particles were consistent with the results of previous studies in which the syntheses of albuterol sulfate and cromolyn sodium were demonstrated using conventional spray dryers.[5,6] Estimates of number-average and volume-average particle sizes using the CO_2-assisted aerosolization technique were significantly smaller than those in these previous studies. Spherical morphology might be expected for particles formed by drying microbubbles or droplets; liquid droplets synthesized by aerosol methods maintain a spherical shape to minimize surface energy. The lack of crystallinity in some substances was also not surprising because a room temperature synthesis process is used in which drug crystallization rates are relatively slow. Although the crystalline phase of these drugs has been assumed to be the thermodynamically stable form, the crystallization rate kinetics are still unknown. What is known,

however, is that amorphous samples can be strongly hygroscopic, particularly evident during periods of high humidity.[11] Differences in drying conditions can lead to different morphologies of particles of the same drug. In Figure 2c, cromolyn sodium, when the aerosol plume was bubble-dried by the dynamic method by mixing with dry nitrogen at temperatures between 75 and 95 °C, lifeboat-shaped particles are obtained. By contrast, when cromolyn sodium was dried at or near room temperature by passing the aerosol plume over the desiccant, concentrated sulfuric acid, more nearly spherical particles were observed (Figure 2b).

The results of solvent treatment in ethanol to induce crystallization of amorphous dried small particles have been quite interesting and potentially useful. The presumably crystalline form is reported to be slightly soluble in ethanol. The bubble-dried amorphous particles appear to dissolve fully and form crystals upon solvent annealing. Starting with bubble-dried ultrafine amorphous particles evenly dispersed in the solution is probably essential, therefore, to achieve the formation of crystalline needles. Similar needle morphology has been reported for cromolyn sodium, which was solvent-treated in absolute ethanol.[12] It is interesting and significant that the very small spray-dried amorphous particles can be converted to beautifully defined larger crystalline needles shown in Figure 5, by suspension in ethanol, while if as-received commercial powders are substituted, crystalline needles are not formed under the same conditions.

Conclusions

Bubble-drying of aqueous solutions yields fine particles, most of which are 0.1−3 μm in diameter. Drying can be rapidly accomplished at temperatures from 25 to 95 °C. Use of a higher concentration of initial aqueous solutions leads to somewhat larger particles, but even 50% solutions of sugars such as trehalose yielded particles, most of which were smaller than 5 μm.

Drying the aqueous microbubbles at temperatures near the boiling point of water sometimes yields hollow particles, while those dried at 35 °C tend to be solid. Morphologies are usually spherical or nearly spherical, although shapes resembling doughnuts, lifeboats, and crumpled ping-pong balls have been observed. Whether the particles are crystalline or amorphous tends to be dictated by the substance and to a lesser extent by the specific drying conditions in the apparatuses used so far. For example, powders from bubble drying sodium chloride and mannitol are crystalline, while those of albuterol sulfate, lactose, and sucrose have been isolated as amorphous spheres.

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