

Low-temperature manufacturing of fine pharmaceutical powders with supercritical fluid aerosolization in a Bubble Dryer^{®*}

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Abstract: Aerosols play an important role in thin film deposition, fine powder generation, and drug delivery. Green processes to form aerosols are needed to eliminate the use of toxic organic solvents and minimize the production of liquid wastes and the emission of halogenated and oxidant-forming organic compounds. We have developed a new patented process, Carbon Dioxide-Assisted Nebulization with a Bubble Dryer[®] (CAN-BD), that can generate a dense aerosol with small droplet and microbubble sizes that are dried to form particles less than 3 μm in diameter [1–9]. The process uses carbon dioxide as an aerosolization aid, and this permits drying at lower temperature than usually needed in conventional spray-drying. Intimate mixing of supercritical carbon dioxide with aqueous protein solutions causes the formation of microbubbles, which are rapidly dried in less than 5 s. The process is more environmentally benign than traditionally used methods, and is superior when thermally unstable materials are being processed. Fine-particle pharmaceutical powders can be rapidly and easily made by this new CAN-BD process, requiring less energy and eliminating residues of toxicologically or environmentally objectionable solvents. Manufacturing dry powders of pharmaceuticals for pulmonary drug delivery and increasing bioavailability are the purposes of developing and marketing the new Temco Bubble Dryer.

The Bubble Dryer uses the CAN-BD process for low-temperature drying of several drugs, as well as proteins stabilized in sugar matrices. Using a Bubble Dryer is superior for drying enzymes and other proteins and pharmaceuticals compared to lyophilization in a freeze-dryer. The latter is less desirable, primarily because the time required for drying is much longer (hours rather than seconds) and there is no need for additional milling or micronization.

Water and carbon dioxide are the only fluids needed for this micronization process, and these do not pose the environmental waste disposal and consumer and/or worker safety issues that chlorinated or halogenated solvents or dispersants have, such as methylene chloride. Organic solvents used previously have contaminated water and air resources, as well as leaving objectionable residues in the final products. Some organic solvents also denature sensitive proteins, which then become useless. By contrast, water and carbon dioxide are ubiquitous and are usually innocuous.

Some of the compounds that have been nebulized and dried into 1–3 μm particles are models, while others are physiologically active materials. The scanning and electron micrographs of hollow

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clusters of sodium chloride particles (Fig. 1) indicate that a 10% salt solution can be dried to form hollow clusters of tiny crystals in less than 5 s. Finely divided dry powder particles of the protein ovalbumin were generated by the addition of the stabilizing sugar trehalose in an equal mass amount with the aqueous solution containing 10% solids by weight (Fig. 2). Examples of drugs that we have made respirable particles of include Pulmozyme[®] (or recombinant human DNase), albuterol sulfate, cromolyn sodium, Cipro[®], and tobramycin sulfate.

Fine particles have been historically made by pulverization, but there are limits on particle stabilities and on how small the particles can be made with acceptable yields. More recently, spray-drying has been adapted to pharmaceuticals with mixed success. In conventional spray-drying, temperatures well above 100 °C are normally used, and thermally sensitive drugs such as many proteins are often degraded. By contrast, because the nebulizer in the Bubble Dryer produces smaller droplets and microbubbles, much lower temperatures (25 to 65 °C) can be used, resulting in less degradation and lower energy consumption.

Another obstacle in the development of drugs for pulmonary delivery is the need to maintain drug stability during shipping, storage, and administration. This stability issue is particularly critical for protein therapeutics because proteins are very unstable and rarely can be formulated to have sufficient stor-

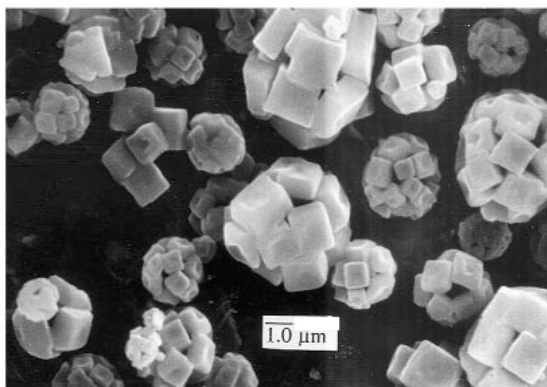


Fig. 1 SEM of NaCl particles generated from a 10% aqueous solution.

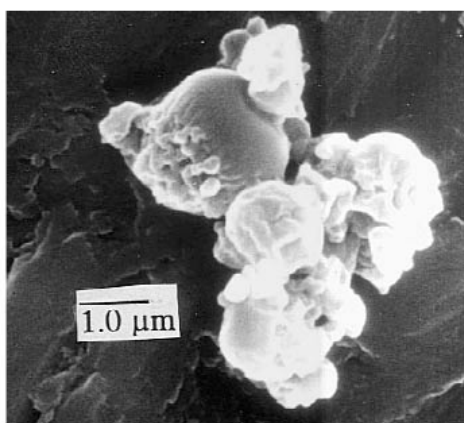


Fig. 2 SEM of ovalbumin:trehalose particles generated from an aqueous solution containing 5 wt % of each.

age stability (i.e., 18–24 months) as aqueous solutions. Thus, dried powder formulations, in which the protein can be stabilized by additives, are required for protein therapeutics. For drugs that are to be delivered by direct inhalation, the powders produced by conventional technology (e.g., spray-drying or freeze-drying followed by milling) are often too large for effective pulmonary delivery and must be jet-milled or mechanically ground after dehydration. The additional physical stress may impart further loss of protein activity. In addition, there can be economically unacceptable low yields of product during these added processing steps. Furthermore, the processing methods themselves subject proteins to denaturing stresses such as high temperature during conventional spray-drying, freezing during lyophilization, and dehydration during both processes. This damage can be inhibited to varying degrees through the rational selection of excipients (such as stabilizing sugars, buffers, or surfactants) for inclusion in the formulation. The CAN-BD process also provides a method for producing dry powders of stable formulations of proteins and other therapeutics.

A critical criterion for the stabilization of protein during processing and during subsequent storage in the dried solid is inhibition of processing-induced unfolding [10,11]. Dehydration-induced structural transitions have been shown to be inhibited by the addition of certain stabilizers, such as sucrose, to the protein solution before processing [12]. In order to determine the degree to which proteins are damaged with our nebulization and drying system, a model protein, lysozyme, was processed with our technique [7]. Results indicate that lysozyme was not irreversibly damaged by our nebulization and drying process. The conformational transitions observed in the drying process can be inhibited by the addition of stabilizers such as sucrose or other disaccharides.

In order to further probe the feasibility of our nebulization process, studies using a significantly more labile enzyme, lactate dehydrogenase (LDH), were undertaken [13]. LDH is known to be damaged by conventional drying processes [14]. The results of these experiments indicate that the damage experienced by LDH during the CAN-BD process can be inhibited by the addition of a sugar stabilizer and even further with the combination of 10% sucrose and 0.01% surfactant, Tween 20. Enzyme activities were measured before and after CAN-BD, and the results showed no change in the activities when appropriately stabilized.

In conclusion, these preliminary results indicate that the damage experienced by model proteins, lysozyme and LDH, can be inhibited through proper formulation with excipients such as sucrose. As a result, the formulated protein appears to be successfully protected throughout the dehydration process experienced during the CAN-BD process.

In related stability studies of a small-molecule drug, stable dry powder particles of albuterol sulfate generated by the CAN-BD process (Fig. 3) were stored over desiccant for three years without showing any physical signs of degradation (Fig. 4). The particles remained in the amorphous state through-

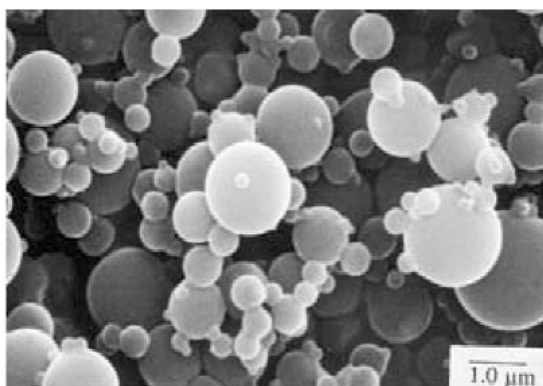


Fig. 3 SEM of albuterol sulfate particles.

out the duration of the storage period. But, after the amorphous particles were suspended in ethanol and stirred for only 2 h at room temperature, the particles became transformed into crystalline needles (Fig. 5).

There are now several hundred protein drug formulations in various stages of clinical trials, and many others in the pipeline. The Bubble Dryer will be a valuable aid in rapidly making test samples of a wide variety of formulations. In new drug development, changing the ratios of active ingredients, stabilizers, buffers, and excipients, and forming samples of fine powders is presently arduous and time-consuming for chemists and formulation scientists. The introduction of the Bubble Dryer in biotech and pharmaceutical laboratories and pilot plants should greatly accelerate development of new and more efficacious formulations.

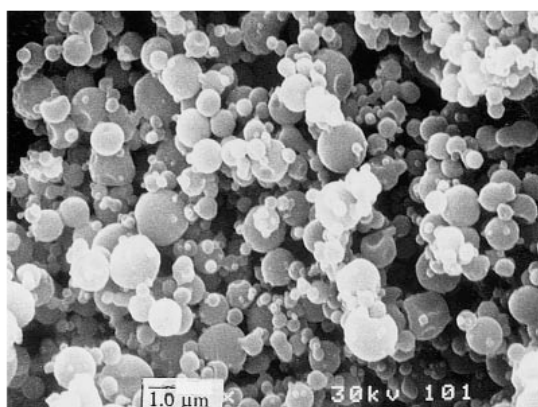


Fig. 4 SEM of albuterol sulfate particles in Fig. 3 after 3 years storage over desiccant.

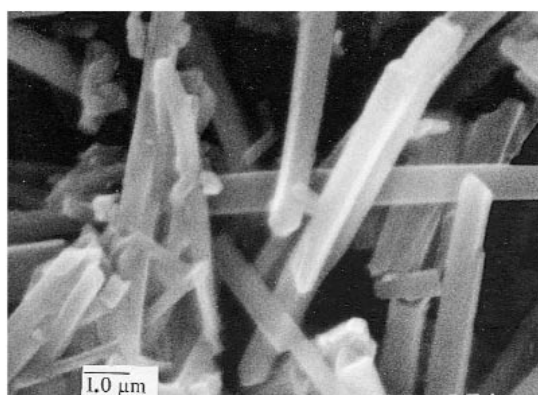


Fig. 5 SEM of albuterol sulfate needles generated by stirring above particles in absolute ethanol for 2 h at room temperature.

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