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RESEARCH PAPERS

POWDER CHARACTERISTICS OF PROTEINS SPRAY-DRIED FROM DIFFERENT SPRAY-DRYERS

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ABSTRACT

The powder characteristics of bovine somatotropin and casein spray-dried from laboratory, pilot and production spray-dryers were investigated. The powder characteristics examined included particle size distribution and morphology; bulk density; and flowability as measured by angle of repose, compressibility index and shear cell indices. Morphology classification showed internal voidage, blowholes, expanded, smooth and folding for somatotropin and casein spray-dried from the various spray-dryers. Particle size distributions of the bovine somatotropin and casein were unimodal and skewed. As the drying-chamber size of the spray-dryer increased, the particle sizes of both somatotropin and casein increased from mean volume diameters of 6-8 μ using the laboratory and pilot spray-dryers to 13-24 μ when using the production size spray-dryers. Spray-dried bovine somatotropin and casein had bulk densities of 0.090 to 0.195 g/cm^3. Three flowability tests showed casein and somatotropin spray-dried from the different spray-dryers exhibited poor flow which could result in pharmaceutical manufacture challenges. The morphology and flowability of the two spray-dried proteins remained the same when comparing material produced from all four spray-dryers. However, the mean volume diameter, particle size distribution and bulk density did vary which might change critical product characteristics during scale-up. In general, similar morphology, particle size distributions, flowability and bulk densities were observed when comparing spray-dried casein and bovine somatotropin produced from the same model spray-dryer. Casein is recommended as a model protein for powder characterization during spray-drying and early formulation manufacture process development when adequate quantities of the recombinant protein are not available.

INTRODUCTION

Bovine somatotropin is an 191 amino acid polypeptide hormone produced in the bovine anterior pituitary gland. Asimov and Krouze in 1937 first demonstrated injections of pituitary extract increased milk production in dairy cows(1). Investigators since then have shown bovine somatotropin regulates metabolic processes resulting in more efficient milk synthesis, greater milk production and increases lean tissue synthesis(2-4). With the advancement in recombinant DNA technology, production and isolation of bovine somatotropin became commercially feasible. A formulation capable of delivering exogenous bovine somatotropin to dairy cows to increase lactation was required.

The process of designing a drug product involves first formulating small batches of product before increasing to production size lots. Pharmaceutical scientists and the FDA are concerned with how well early research and clinical batches compare to the final marketed product with respect to physicochemical properties and bioequivalency. One important comparison is between the methods of formulation manufacture for different size batches. Knowing the effect of manufacturing method on the characteristics of a formulation allows a pharmaceutical scientist and the FDA to decide whether formulations produced at production scale need clinical testing to bridge the clinical data obtained from smaller batches. Gathering this information is especially important for the biotechnology products(5).

The isolation and formulation of proteins derived from recombinant DNA technology has focused on lyophilization. Lyophilization is advantageous because water concentrations below 2 to 4% w/w are achievable, often resulting in an adequate shelf-life due to minimized water associated with the protein. An alternative method of isolating a protein powder is by spray-drying a protein solution or suspension. Advantages of spray-drying include cost effective isolation of a protein powder, capability for aseptic production, possibility for a continuous operation and opportunity for co-spraying with excipients. Disadvantages associated with spray-drying are possible destruction of heat sensitive drugs, low yield, undesirably high water levels, residual solvents and variation obtained when changing process conditions and equipment.

Realizing the possibility for powder physical changes when utilizing different spray-dryers, this study was conducted to determine the powder characteristics of bovine somatotropin and casein spray-dried from four different spray-dryers. The various spray-dryers were utilized to produce laboratory, pilot and production spray-dried batches. The powder characteristics examined included particle size distribution and morphology; bulk density; and flowability as measured by angle of repose, compressibility

index and shear cell indices. A second goal was to assess the use of spray-dried casein as a model for predicting powder characteristics of spray-dried bovine somatotropin.

MATERIALS AND METHODS

Spray-drying. The laboratory spray-dryer utilized was a Pulvis Mini-spray (Model GA-31) made by Yamato Scientific Co. (Tokyo, Japan). The chamber had a cylinder height of 53 cm and a diameter of 15 cm fitted with a top-spraying, two-fluid nozzle with an orifice diameter of 0.4 mm. The pilot spray-dryer (Model BLSA) was produced by Bowen Engineering, Inc. (Somerville, NJ). The chamber had a cylinder height of 74 cm, a diameter of 76 cm and a 46 cm cone height fitted with a top-spraying two-fluid nozzle. Two production spray-dryers were examined including one (Model NA S-28) produced by Niro Atomizer (Columbia, MD). The Niro spray-dryer had a cylinder height of 198 cm with a diameter of 274 cm and an 122 cm cone height. A top-spraying high pressure spray system (Type 69/421) was utilized. The second production spray-dryer was an Unison made by Bepex Corporation (Minneapolis, MN). This spray-dryer had an approximate cylinder height of 610 cm with a diameter of 122 cm. The top-spraying nozzle was a Pulse Combustor (Model UN-1).

The spray-drying operating conditions utilized to produce material from the different spray-dryers were selected by experienced operators familiar with each spray-dryer. If different inlet and outlet temperatures or flow rates were used, it was because they were necessary for the particular spray-dryer operation. Optimization of spray-drying parameters occurred at a later time when both physical and chemical critical properties were identified. Powder characteristics we monitored are often affected by residual water. Identical water contents were difficult to achieve, but were kept in the 4.6 to 6.8% range for the seven different batches. All powder was produced by spray-drying solutions which contained no additives. Since the isoelectric point of pituitary bovine somatotropin is 8.5, the bovine somatotropin solutions were adjusted to pH 9.7 to 10.5 to maintain solutions(6). The casein solutions were also adjusted to pH 10 to 10.5.

Casein Spray-dried Utilizing the Yamato Spray-dryer. Twenty-five g casein (Sodium salt from bovine milk, C-8654, Sigma, St. Louis, MO) was dissolved in 500 ml of water with the final pH adjusted to 10.0 with sodium hydroxide. This 5.0% casein solution was spray-dried using the Yamato spray-dryer with an inlet air temperature of 90°C and an outlet air temperature of 65°C. The feed rate was 0.13 l/hr.

Casein Spray-dried Utilizing the Bowen Spray-dryer. One and two-tenths kg of casein was dissolved in 26.8 l of water with the final pH adjusted to 10.5. This 4.5% casein solution was spray-dried using the Bowen spray-dryer with

the inlet air temperature adjusted to obtain an outlet air temperature of 75°C.
Casein Spray-dried Utilizing the Niro Spray-dryer. A 4.8% casein solution with pH adjusted to 10.0 was spray-dried using the Niro spray-dryer with an inlet temperature of 180°C and an outlet air temperature of 75°C. The air flow rate was 19.7 kg/hr and the solution feed rate was 73 l/hr.
Casein Spray-dried Utilizing the Unison Spray-dryer. A 5% casein solution was spray-dried using the Unison spray-dryer with an inlet air temperature of 165°C.
Bovine Somatotropin Spray-dried Utilizing the Yamato Spray-dryer. Bovine somatotropin (The Upjohn Co., Kalamazoo, MI) at a concentration of 4.0% was pH adjusted to 9.7 with sodium hydroxide. This solution was spray-dried using the Yamato spray-dryer with an inlet air temperature of 100°C and an outlet air temperature of 50°C. The feed rate was 0.3 l/hr.
Bovine Somatotropin Spray-Dried Utilizing the Bowen Spray-dryer. A 4.6% bovine somatotropin solution with a pH adjusted between 10.1 and 10.4 by adding sodium hydroxide was spray-dried using the Bowen spray-dryer with an inlet air temperature of 121°C and an outlet air temperature of 75°C. The feed rate was 6 l/hr.
Bovine Somatotropin Spray-dried Utilizing the Niro Spray-dryer. Previously spray-dried bovine somatotropin was redissolved in water with a final pH adjusted between 10.1 and 10.4 by adding sodium hydroxide. This 4.4% bovine somatotropin solution was spray-dried using the Niro spray-dryer with an inlet air temperature of 191°C and an outlet air temperature of 85°C. The feed rate was 69.5 l/hr and the air flow rate was 19 kg/hr.

Particle Size Determination. Three microscopic slides were prepared for each batch by placing approximately 3 mgs of powder on a microscopic slide. A Nikon (Garden City, NY) Optiphot-Pol microscope with Numonics (Lansdale, PA) Model 2210 Digitizing Tablet/Imager linked to an IBM (Armonk, NY) PC-XT and a data handling package by SigmaScan Program (Jandel, San Rafael, CA) were used to determine the diameter of 150 particles on each slide. Size-frequency distributions and particle diameters were calculated for each lot of material.

Scanning Electron Microscopy. A scanning electron microscope (JSM-T300, Jeol LTD, Tokyo, Japan) was utilized to visually examine the spray-dried material. Samples were mounted on an aluminum stub and coated with a gold and palladium alloy using a sputter coater (Model ES5400, Bio-Rad, Cambridge, MA) with the vacuum set at 0.1 Torr and a current of 20 μA. Samples were coated twice for 1.5 minutes to achieve continuous coverage. Photomicrographs were taken with the emission current at 20 μA and an accelerating electron voltage of 10 or 15 KeV.

Densities. Each sample of powder was sifted into a stainless steel funnel which was mounted on a tared 100 ml glass graduated cylinder. Sifted powder

was allowed to fill the graduate to the 100 ml mark. The gross weight of the graduate and powder was obtained and the net weight of the powder calculated. The filled graduate was secured to the mounting plate of a QuantaChrome Dual Autotap (Syosset, NY) and the apparatus was run for 3000 taps. The volume and number of taps were recorded after 100, 300, 500, 1000, 2000 and 3000 taps. The final tap volume was defined as that recorded after the 3000 taps. The bulk density was calculated as the ratio of net weight to initial volume of powder. The tap density was calculated as the ratio of net weight to final volume of powder. The compressibility index was calculated as the percent of difference in volume compared to the initial volume. Each powder sample was run in triplicate.

Angle of Repose. Each sample of powder was sifted through a stainless steel funnel. A tared weighing paper of known width and length was placed directly below the funnel. A constant distance was maintained between the funnel and the paper for all samples. The powder was allowed to flow through the funnel onto the weighing paper forming a cone-shaped powder heap. A cathetometer was used to measure the distance between the weighing paper and the funnel, the height of the counter top and the height of the powder cone. The circumference of the cone was drawn around the powder cone. The powder was removed from the weighing paper and the resulting circle was cut-out and weighed. The ratio of the weight of the cut-out paper circle to the total weight of the weighing paper prior to use was assumed equal to the ratio of the cut-out circle area to the area of the uncut weighing paper. From this assumption the area of the circle and its radius were calculated. The base angle of the cone or angle of repose was determined using the height and radius of the cone to calculate the tangent of the angle. The angle of repose was determined for each powder in triplicate.

Simplified Shear Cell Method. The sample powder was sifted onto the lower stationary surface to form a thin layer of powder between a lower stationary rough surface (knurled aluminum) and an upper moveable rough surface (also knurled aluminum) of a Shear Cell Testing Apparatus(7). The layer of powder was then brought to a uniform state of consolidation by: 1) applying a consolidating load of 3170 g to the powder bed via weights on the upper moveable surface of the apparatus, 2) applying a shear force to the powder bed by pulling the upper moveable surface using a tow line attached to a load cell, 3) monitoring the force applied to the powder bed through a load cell until shear was initiated and then 4) rapidly returning the shear force to zero. This process was repeated until a series of nearly identical shear-force measurements were obtained. Once the uniform state of consolidation was obtained, some weight was removed and a single determination of the shear strength at the reduced load was made. The consolidation process was repeated for each reduced load. The shear strength as a function of reduced load was then fitted to the Warren Sprain equation using NONLIN 84 (Statistical Consultants, Inc.

Lexington, KY). From the curve the shear index (n), which refers to the curvature of the yield locus and ultimately the flowability of the powder, was estimated(7).

RESULTS AND DISCUSSION

The administration of spray-dried bovine somatotropin to lactating dairy cows increases milk production. Zinn *et al.* administered once weekly 50, 100 or 150 mg spray-dried bovine somatotropin to Holstein cows and observed 0, 12 and 25% increase milk production, respectively(8). Similarly, Brouk *et al.* delivered the same three doses to Holstein cows and reports increases of 7, 14 and 10%, respectively(9). The development of a formulation requires detailed study of the pharmacological, chemical and physical properties of the drug substance and the final formulation. With it known that spray-dried bovine somatotropin produced biological responses, this study was conducted to examine the powder characteristics of spray-dried bovine somatotropin. The understanding of these powder characteristics was important to determine critical powder characteristics to monitor during manufacture scale-up.

Particle Sizes and Distributions. An unimodal, skewed particle distribution was observed for the casein and bovine somatotropin spray-dried using the four spray-dryers. The asymmetrical distributions were made symmetrical by plotting the percent number frequency versus the logarithms of the particle diameters. These log-normal distributions are shown in Figs. 1 and 2 for the casein and bovine somatotropin, respectively. It is typical to observe log-normal distributions for spray-dried material. Observations of dried particles having a log-normal function means the wet spray droplets followed a square-root normal function(10).

Casein spray-dried using the Yamato and Bowen spray-dryers had particle distributions with the majority of the particle sizes ranging between 4 and 20 μ. Less than 5% of the total particles were greater than 20 μ when using either the Yamato or Bowen spray-dryers. The use of production spray-dryers resulted in larger particle distributions than the laboratory or pilot models, with a majority of the particles ranging from 10 to 52 μ. Sixteen percent of the total particles were larger than 52 μ when using the Niro spray-dryer and 7.6% were larger than 52 μ when using the Unison spray-dryer. Similar to the casein, examination of Fig. 2 shows the spray-dried bovine somatotropin had particle distributions with the majority of the particle diameters between 4 and 20 μ when spray-drying using the Yamato and Bowen spray-dryers. The use of the production size spray-dryer resulted in particles with diameters ranging from 4 to 38 μ.

A comparison of particle size distributions of casein and bovine somatotropin spray-dried from the pilot and production spray-dryers is shown

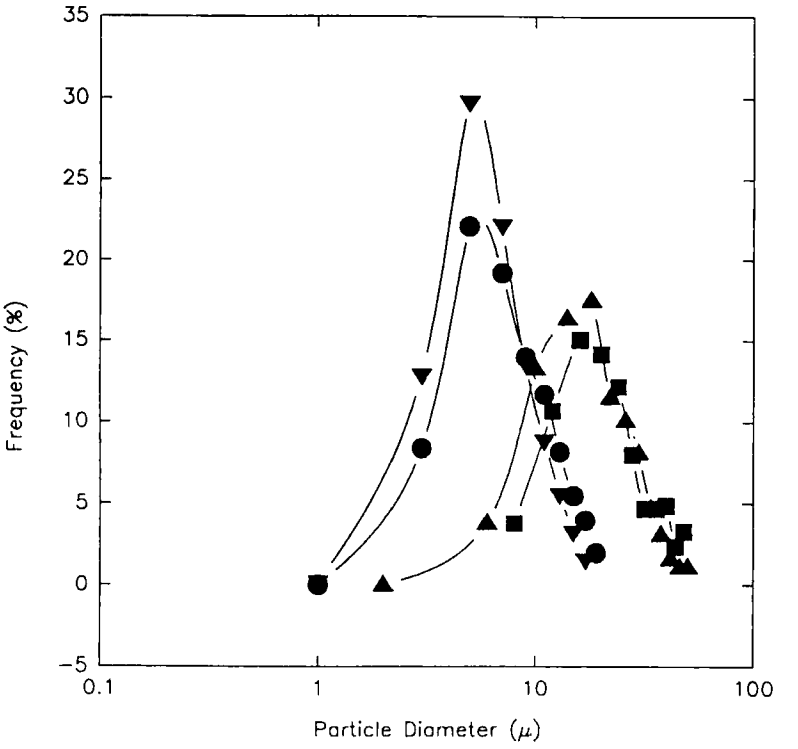

FIGURE 1

Size-frequency plot for casein spray-dried using different types of spray-dryers: ● Yamato, ▼ Bowen, ■ Niro and ▲ Unison spray-dryers.

in Fig. 3. The particle size distributions were superimposed for the casein and bovine somatotropin spray-dried using the Bowen spray-dryer. This suggested casein was a good protein model for assessing particle size distributions when spray-drying. Examining the particle distributions of casein and somatotropin spray-dried using the Niro spray-dryer showed similar, but not identical distributions. Spray-dried particle distributions may vary depending on nozzle dimensions, feed parameters and operating conditions. Although these variables were maintained as similar as possible, they were not identical. For example, the concentration changed from 4.8 g/l for the casein solution to 4.35 g/l for the bovine somatotropin solution. The inherent differences between the molecules and their concentration differences may have collectively changed the viscosity. Increased viscosity of the feed solution can increase the dried particle size by increasing the size of the wet droplet formed during spraying. Additionally, the slightly faster feed rate of 73 l/hr for the casein solution

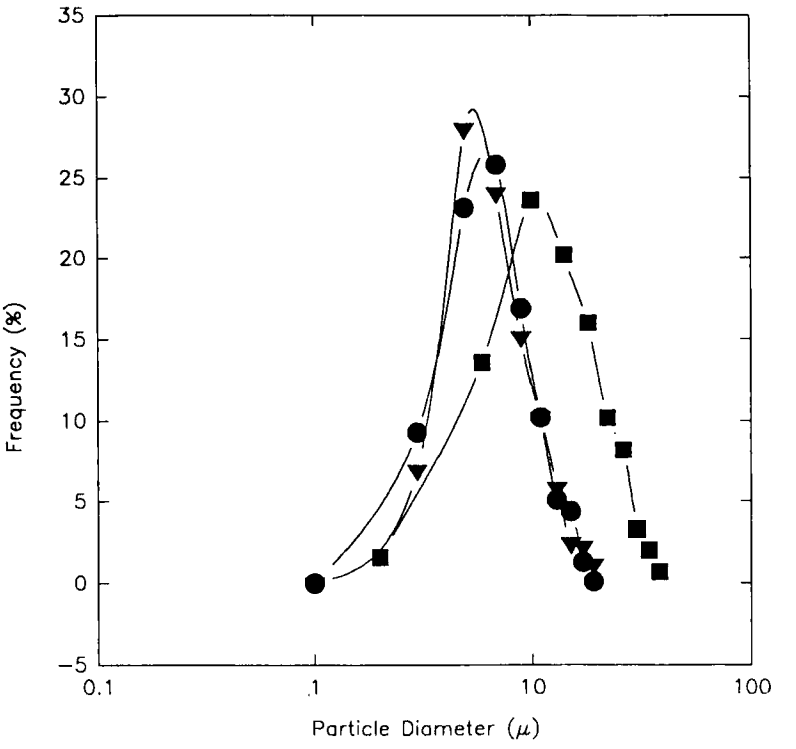

FIGURE 2
Size-frequency plot for bovine somatotropin spray-dried using different types of spray-dryers: ● Yamato, ▼ Bowen, and ■ Niro spray-dryers.

compared to 69.5 l/hr for the somatotropin solution may have contributed to the larger casein particles. These seeming small differences highlight the need for understanding totally the spray-drying process when using a model protein.

The modes, geometric mean diameters and geometric standard deviations of casein and bovine somatotropin spray-dried using the different spray-dryers are shown in Table 1. The geometric mean diameters of 8 and 6 μ for casein spray-dried utilizing the Yamato and Bowen spray-dryers were smaller than the 20 and 24 μ observed with the Unison and Niro spray-dryers, respectively. A larger geometric mean diameter of 13 μ was observed with the Niro spray-dried bovine somatotropin compared to the geometric diameter of 7 μ observed with either the Bowen or Yamato spray-dryers. The size of the particles obtained during spray-drying depended on the type of nozzle, the atomizing conditions including air flow, and the characteristics of the fluidized

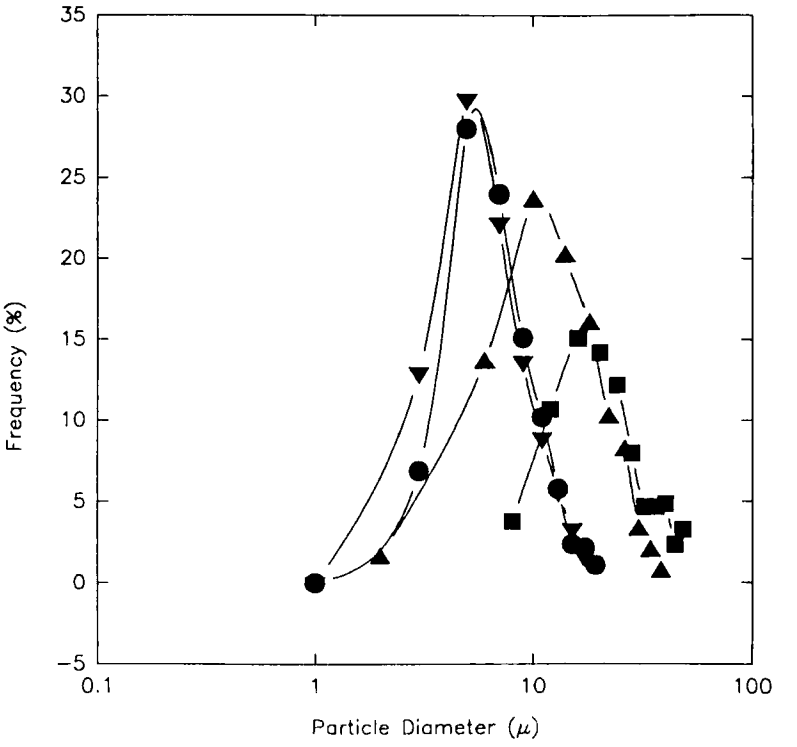

FIGURE 3
Size-frequency plot comparison of casein and bovine somatotropin spray-dried on Bowen and Niro spray-dryers: ▼ casein from Bowen spray-dryer, ■ casein from Niro spray-dryer, ● bovine somatotropin from Bowen spray-dryer and ▲ bovine somatotropin from Niro spray-dryer.

solution/suspension. The larger particles observed using the production spray-dryers were caused by the original drops of liquid excreted from the spray-drying nozzle as larger droplets. Because of the longer and wider chambers in these production spray-dryers, the increased amount of time for solvent evaporation from larger liquid drops was accommodated before movement of the particles into the cyclone collecting chamber.

The approximate two-fold increase in bovine somatotropin particle diameters observed when using a production size spray-dryer could result in different biological activity of the formulation. For example, if the dissolution of bovine somatotropin particles after administration was the rate controlling step, larger particles could decrease the rate of somatotropin available for

TABLE 1
Particle Diameters of Bovine Somatotropin and Casein Spray-dried Utilizing Different Spray-dryers

Type of Spray-dryer	Material Spray-dried	Mode (μ)	Geometric Mean Diameter (μ)	Geometric Standard Deviation (μ)
Yamato	Casein	5	8	1.9
Bowen	Casein	5	6	1.9
Niro	Casein	16	24	1.8
Unison	Casein	18	20	1.8
Yamato	Somatotropin	7	7	1.8
Bowen	Somatotropin	5	7	1.8
Niro	Somatotropin	10	13	1.8

absorption. Hageman *et al.* has suggested that the Noyes-Whitney relationship, often used with conventional organic molecules, is not adequate to model the dissolution rate of bovine somatotropin(11). Thus, the hypothesis of decreased dissolution rate due to increased particle size may not be applicable. Further research examining the effect of protein particle diameters on biological activity is warranted.

Morphology. Figure 4a-b shows the SEM photomicrographs of casein spray-dried using the Bowen and Niro spray-dryers. Figure 4c-d shows SEM photomicrographs of bovine somatotropin spray-dried using the Bowen and Niro spray-dryers. The morphology of the particles will directly influence the bulk density, affect drying rates, and can influence the rehydration characteristics and volatile losses(12). Furthermore, upon parenteral administration the migration of the spray-dried particles from a formulation and the subsequent release may depend on particle morphology.

The different spray-dried classifications of morphology include internal voidage, surface shrivelling, blowholes, expanded, smooth and folding(12-19). Internal voidage was observed in casein and bovine somatotropin spray-dried from the various spray-dryers as noted in Fig. 4. The internal voidage resulted in low bulk densities as shown in Table 2. Verhey attributed the formation of internal voidage to air incorporation into the liquid during droplet formation and expansion of air bubbles due to case hardening during drying(16). He also described how this can be prevented by using steam flushed over the air nozzle to prevent development of vacuoles(17).

The formation of blowholes, expanded particles and smooth surfaces can be attributed to the internal voidage. Air nucleation in the droplets occurred by desorption as the temperature of the droplets increased. The increased internal pressure resulted in expanded particles which ruptured at structural weak points to create blowholes. The expansion may also create smooth surfaced particles if the entrapped air does not escape. Examples of blowholes, expanded particles and smooth surfaces were seen in all photomicrographs.

Surface shrivelling, the appearance of small ridges on the particle surface, was not observed. Folding, an extreme case of surface shrivelling, was seen with the spray-dried bovine somatotropin and casein. Shrivelling and folding were formed by uneven shrinkage forces during the drying process of the liquid droplets. According to King, the viscosity of the droplet (or solution being spray-dried) is the important parameter that determines whether shrivelling or folding occurs(20). The tendency to shrivel or fold decreases as the viscosity of the feed solution decreases. The Yamato spray-dried bovine somatotropin (photograph not shown) had no folding or shrivelling. The feed solution used to spray-dry these particles had a concentration of 4%, somewhat lower than the 4.35 to 5% used for other feedstock. The critical viscosity to prevent shrivelling and folding can be determined if this was deemed a necessary critical parameter.

Fractured spray-dried particles are often seen in the photomicrographs. The fractured particles were extreme examples of blowholes where the outer crust of the sphere could not withstand the internal pressure. These fractures can also occur during the movement of the particles in the chamber and cyclone if weak and thin walls of the spray-dried particles existed.

The observed differences in spray-dried morphology when utilizing the Bowen and Niro spray-dryers were small and changes in activity between the two materials due to morphology were not expected. In fact, reversed phase-HPLC potency of the material spray-dried from the same fermentation batch using the Bowen and Niro spray-dryers showed no difference in potency (735 mcg/mg and 736 mcg/mg for the Bowen and Niro spray-dried material, respectively).

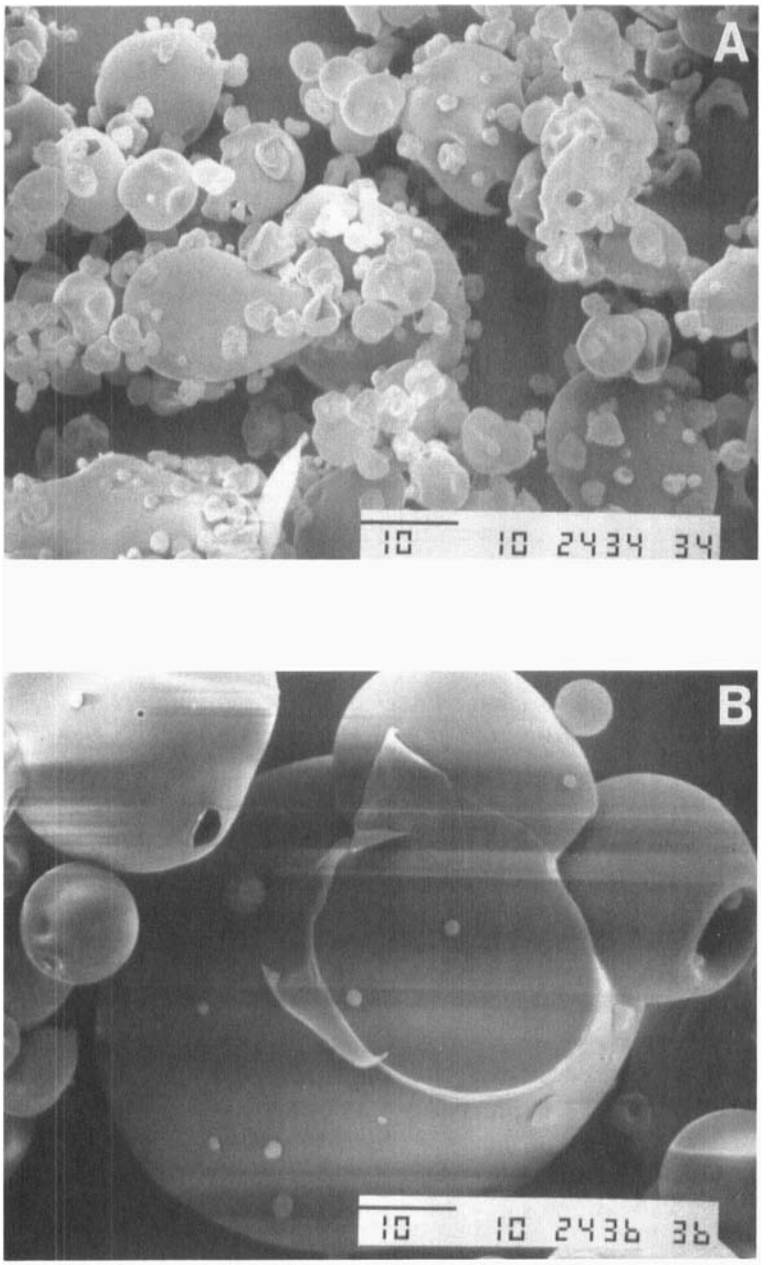

FIGURE 4
Scanning electron microscope photomicrographs of a) casein spray-dried using a Bowen spray-dryer, b) casein spray-dried using a Niro spray-dryer, c) bovine somatotropin spray-dried using a Bowen spray-dryer and d) bovine somatotropin spray-dried using a Niro spray-dryer.

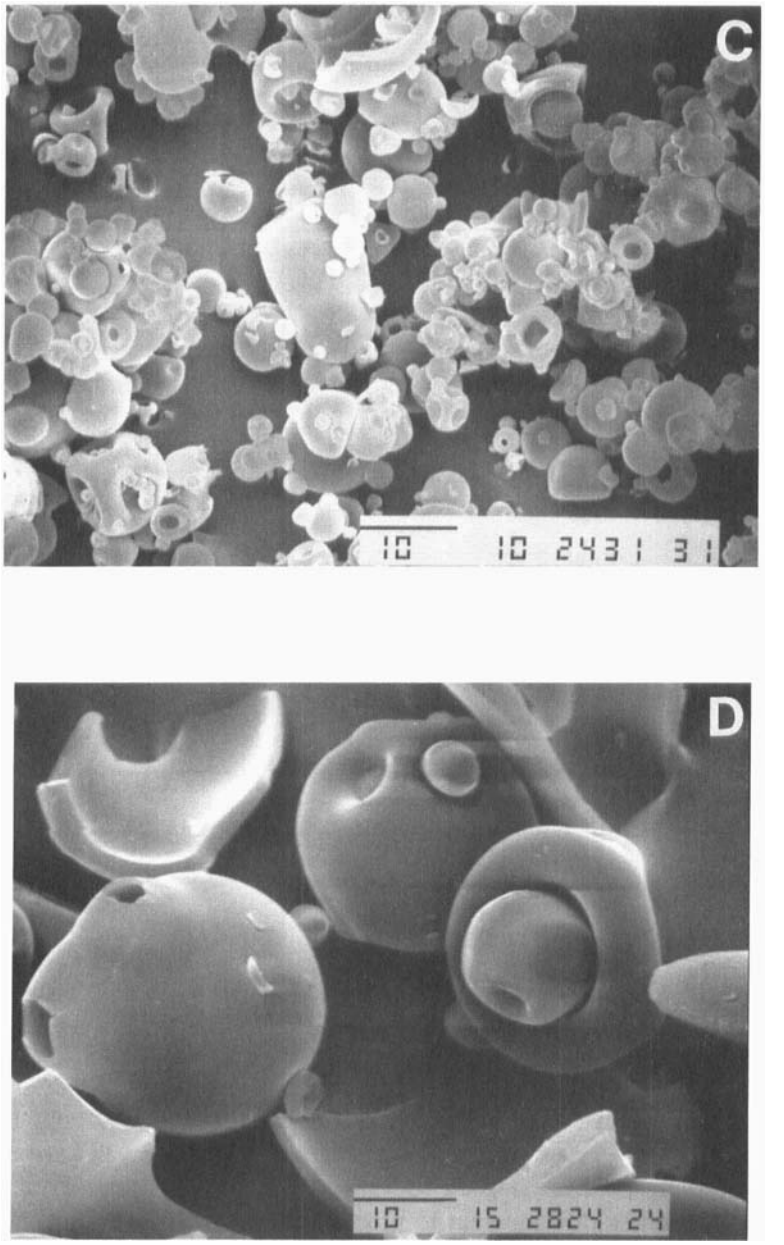

FIGURE 4. Continued

TABLE 2
Bulk and Tap Densities for Spray-dried Casein and Bovine Somatotropin Produced from Various Spray-dryers

Type of Spray-Dryer	Material Spray-dried	Bulk Density (g/cm^3)[1]	Tap Density (g/cm^3)[1]
Yamato	Casein	0.195(0.007)	0.380(0.034)
Bowen	Casein	0.096(0.005)	0.204(0.011)
Niro	Casein	0.138(0.015)	0.235(0.012)
Unison	Casein	0.174(0.012)	0.331(0.023)
Yamato	Somatotropin	0.096(0.013)	0.185(0.036)
Bowen	Somatotropin	0.090(0.006)	0.211(0.028)
Niro	Somatotropin	0.159(0.004)	0.310(0.003)

[1] Average (standard deviation) of triplicate determinations.

The casein and bovine somatotropin spray-dried utilizing the Bowen and Niro spray-dryers resulted in particles of similar morphology. Overall, gross differences were not noted between spray-drying casein or bovine somatotropin using one particular spray-dryer. The limitations of gross appearance and the variability which occurred due to the different spray-drying conditions used for the various spray-dryers and test runs was realized. However, the use of casein as a model protein for assessing the morphology of protein spray-dried particles is suggested. Process development to produce certain shaped particles could be conducted using the less expensive casein.

Bulk Density. The bulk and tap densities for casein and bovine somatotropin spray-dried using various spray-dryers are shown in Table 2. Bulk densities varied between 0.090(0.006) and 0.195(0.007) g/cm^3 while tap densities ranged

between 0.185(0.036) and 0.380(0.034) g/cm^3. The bulk density is an important parameter because it determines the space required for storage of bulk drug, can influence powder flowability and may influence characteristics of the formulation. The space requirement is particularly critical during aseptic pharmaceutical manufacture. It may be advantageous to increase bulk density to enhance flow and decrease the space required for drug storage. Methods to increase spray-dried protein bulk density include deaeration of the feed, increase residual moisture, decrease inlet drying air temperature and addition of binding agents to feed to prevent particle ballooning during evaporation(20).

A comparison of casein and bovine somatotropin spray-dried on the Bowen and Niro spray-dryer showed casein mimicked the bulk densities of bovine somatotropin. Casein spray-dried had bulk densities of 0.096(0.005) and 0.138(0.015) g/cm^3 when utilizing the Bowen and Niro spray-dryers, respectively. While spray-dried bovine somatotropin had bulk densities of 0.090(0.006) and 0.159(0.004) g/cm^3 using the Bowen and Niro spray-dryers, respectively. A t-test ($P<0.05$) compared the bulk density means of Bowen spray-dried casein and somatotropin showed no statistical difference. Similarly, no statistical difference was observed between the bulk density means of Niro spray-dried casein and bovine somatotropin. Casein again proved useful as a model compound.

Flowability. Three measures of flowability were utilized to analyze the flow of the spray-dried bovine somatotropin and casein. The spray-dried powder must adequately flow from holding containers during pharmaceutical manufacture. A minimal amount of residual in the containers is wanted of expensive recombinant DNA-derived drugs. Furthermore, minimal manipulation of the holding containers will achieve enhanced sterility assurance during pharmaceutical manufacture.

Angles of repose are able to provide gross measurements of the flowability of powders. Most free flowing material have angles less than 40°. Powders with angles greater than 50° have flow problems if they flow at all(21). The spray-dried casein and bovine somatotropin had angles of repose equal to or greater than 39° as noted in Table 3. The spray-dried casein and bovine somatotropin were classified as non-free-flowing powders.

The compressibility index is a simple and fast method for estimating flow of powders. Carr showed the relationship between the compressibility index and flowability(22). Carr's comparison stated that powder with compressibility above 40% had flow which was very, very poor. Table 3 shows that all spray-dried casein and bovine somatotropin had flow which was very, very poor according to Carr's comparison.

TABLE 3
Compressibility Index, Angle of Repose and Shear Cell Indices for Spray-dried Casein and Bovine Somatotropin Produced from Different Spray-dryers

Type of Spray-Dryer	Material Spray-dried	Compressibility Index (%)[1]	Angle of Repose (Degrees)[1]	Shear Cell Estimator (n)[1]
Yamato	Casein	48(4)	54(1)	1.49(0.02)
Bowen	Casein	53(5)	52(1)	1.60(0.04)
Niro	Casein	41(4)	61(1)	1.49(0.02)
Unison	Casein	47(2)	39(3)	1.73(0.03)
Yamato	Somatotropin	47(3)	49(1)	1.48(0.07)
Bowen	Somatotropin	57(3)	56(2)	1.56(0.04)
Niro	Somatotropin	49(1)	57(1)	1.29(0.01)

[1] Average (standard deviation) of triplicate determinations.

Shear cell measurements confirmed what had been observed with angles of repose and compressibility indices. The shear cell index, n, is a simple measure of the flowability. Ranges for n reported by Amidon and Houghton vary from excellent flow at n=0.99 to extremely poor flow at n=1.62 (7). The shear cell indices ranged from 1.49 to 1.73 for the spray-dried casein and bovine somatotropin indicated poor flow of the powders.

The reasons for the poor flow included the presence of electrostatic charge, some nonspherical particles due to shattering or collapsing of the spray-dried particles, and the low bulk density due to internal voidage. Poor flow will result in problems removing the spray-dried bovine somatotropin from bulk drug transfer containers and could result in special manipulation of the containers to remove all powder.

CONCLUSIONS

The operating conditions and size of the spray-dryer changed the protein particle sizes and distributions when using laboratory, pilot and production spray-dryers. The bulk and tap densities also varied. It is critical to assess these parameters to assist in pharmaceutical manufacture scale-up and insure homogeneous batches of the formulated product. In general, the flowability and morphology of the two spray-dried proteins remained similar. Casein worked well as a model protein and is recommended for spray-drying and early formulation manufacture process development when adequate quantities of the recombinant protein are not available.

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