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Use of Pharmasep Unit for Processing Microspheres

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INTRODUCTION

Microsphere technology has been studied extensively for the sustained delivery of therapeutic agents [1-5]. One of the crucial steps in preparing drug-incorporated microparticulate products is recovery of the solid from slurry and having the final products in a dry form. This becomes increasingly difficult as the size of the microparticulate decreases. The standard methods such as centrifugation and filtration, followed by vacuum or freeze-drying, involves several transfer steps resulting in loss of product and risk of contamination, the latter being quite serious when an aseptic process is required [6].

As illustrated in Figure 1, the Sweco PharmASep technology, a Vibro-Filter Dryer™ system (Sweco, Inc, Florence, KY) [7-10], has been designed to facilitate aseptic transfer of all the solid-containing slurry from the reactor vessel and/or the quench tank, removal of the slurry liquid media, drying of the collected solid product by purge-air/vacuum application, and efficient recovery of the dried particles. The PharmASep unit also facilitates washing and rinsing of the particles before drying.

The purpose of this study was to assess the feasibility of the PharmASep technology for processing microspheres or microparticulate drug-delivery systems.

Key Words: PharmASep; Microspheres; Microparticulate; Purge-air drying

Figure 1. Illustration of the microsphere drying process of PharmASep unit.

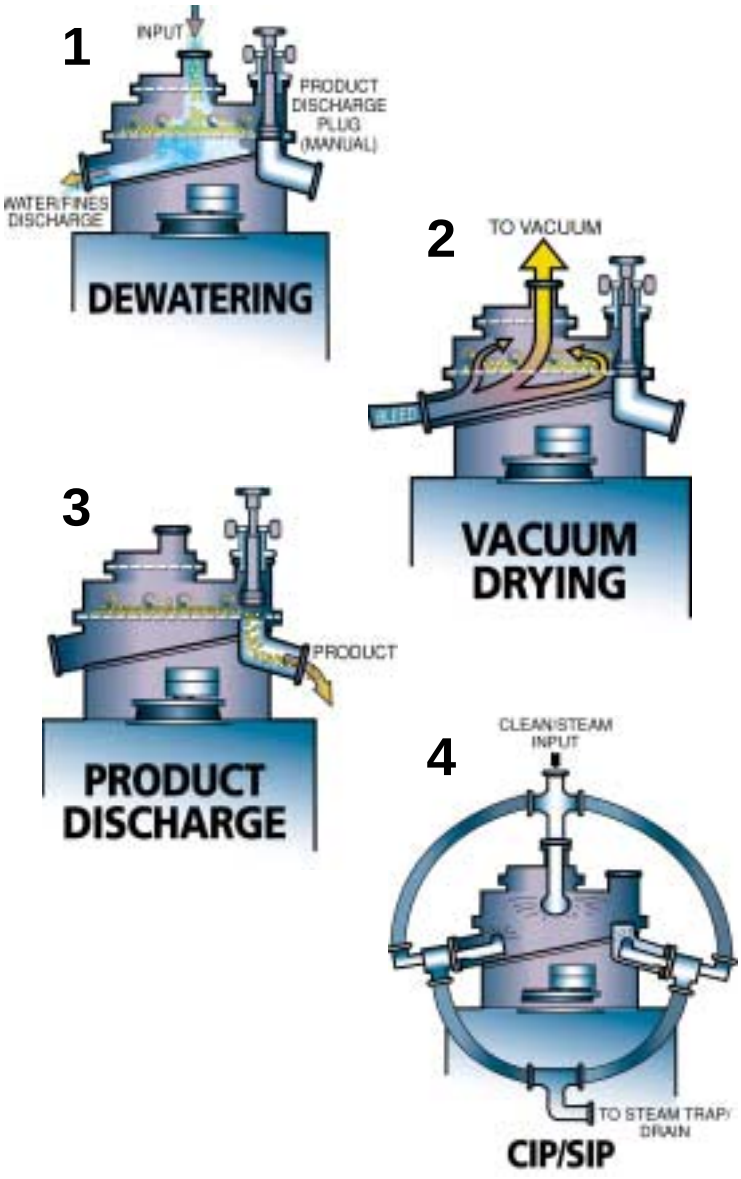

Figure 1. Illustration of the microsphere drying process of PharmASep unit.1) Slurry of microspheres was introduced to the PharmASep unit through the input port while the unit was vibrating; 2) at the completion of de-watering, the collected microspheres were dried by the simultaneous application of vacuum and introduction of dry air; 3) the dried microspheres were discharged through the discharging plug; and 4) the unit was cleaned using CIP (clean in place) or SIP (steam in place) nozzles.

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MATERIALS AND METHODS

Materials

Poly(D,L-lactide-co-glycolide) (PLGA) polymers with hydrophilic end group (MW 28 000, copolymer ratio = 50:50, Resomer® RG503H) and hydrophobic end group (MW 30 000, copolymer ratio = 50:50, Resomer® RG503) were obtained from Boehringer Ingelheim (Ingelheim, Germany). Polyvinyl alcohol (PVA) (MW 30 000-70 000) was obtained from Sigma Chemical Co (St Louis, MO). All other chemicals were obtained commercially as analytical grade reagents.

A 6-inch Sweco Vibro-Filter Dryer, the PharmASep unit (model PharmASep PH-06Y), was provided by Sweco Inc (Florence, KY).

Methods

Microsphere preparation

Two methods were used to manufacture blank microspheres with high and low porosities. Highly porous microspheres were prepared by a water-in-oil-in-water double emulsion technique as described previously [11]. Briefly, a dispersed phase was prepared by adding 2.6 mL of 1.7 M NaCl in 0.2% PVA to 10 g hydrophobic PLGA (Resomer® RG503) dissolved in CH_2Cl_2 (10%, wt/wt) and emulsified by vortexing vigorously for 5 minutes. The vortex mixing was followed by sonication with a bath sonicator (Bransonic Ultrasonic Co, Danbury, CT) for 10 minutes. For production of the low-porosity blank microspheres, the conventional oil-in-water emulsion was used in a manner identical to that previously described [12]. A dispersed phase was prepared by dissolving 20 g hydrophilic PLGA (Resomer® RG503H) in CH_2Cl_2 (12.5%, wt/wt). The dispersed phase was introduced to 6 L continuous phase (77 mM NaCl in 0.2% PVA) by using a glass syringe with 18-gauge needle. The continuous phase was stirred at 700 rpm throughout the introduction of dispersed phase in an Applikon® reactor vessel (Applikon, Schiedam, Netherlands) at 4°C. After 10 minutes, the temperature of the mixing phases was adjusted to 40°C to drive off CH_2Cl_2. In addition to maintaining a 40>°C temperature, a mild vacuum was also applied to further accelerate CH_2Cl_2 removal.

Drying of Microspheres in the PharmASep Unit

To achieve the optimum motion on the product screen, the PharmASep unit was set to a top weight setting of 100%, a bottom weight setting of 90%, and a lead angle of 30°. At these settings the unit achieved horizontal amplitude of 0.052 inches, vertical amplitude of 0.103 inches, and a phase angle of 34.7° on the product screen. A 2-inch top screen with a 150-μm pore-opening screen cloth and a 6-inch product screen with a 25-μm pore-opening screen cloth were used. The motor speed was set at 1800 rpm. Vibration was maintained throughout the drying period.

The slurry of microspheres was introduced to the PharmASep unit through a feeding port at a predetermined optimum rate while the unit was vibrating. Aggregates and oversized microspheres were collected on the top screen, and microspheres in the size range of 25 μm to 150 μm were collected on the product screen. Extra-fine microspheres (those smaller than 25 μm) were discharged from the discharge spout along with the media. The microspheres collected on the product screen were rinsed 5 times with 300 mL of distilled water. At completion of de-watering following frequent rinsings, the collected microspheres were dried by application of a 22-inch Hg vacuum from the top and dry purged air (100-200 mL/min measured by a Gilmont® flow meter, Barnant Co, Barrington, IL) from underneath the screen. The drying period was 7 hours at room temperature. The dry purged air was introduced to facilitate removal of moisture and residual solvent. The extra-fine microspheres, which passed through the product screen during the slurry introduction and drying periods, were collected by membrane filtration (pore size: 0.45 μm), dried under vacuum, and characterized.

Assessing the PharmASep Unit

For comparing the effect of the drying process on PLGA microspheres with high and low porosities, approximately 6 L of slurry from each type was divided into 4 identical fractions (4 sub-batches). From both high- and low-porosity types, 3 sub-batches were rinsed and dried in the PharmASep unit while the fourth sub-batch was membrane filtered (pore size: 0.45 μm), rinsed on filter, and dried under vacuum for 3 and 5 days, respectively, for high- and low-porosity microspheres.

Analysis of Microspheres

To assess the utility of the PharmASep unit, each microsphere sub-batch was characterized for yield, moisture content, particle size, surface morphology, bulk density, and specific surface area. The moisture content was determined with a Moisture Analyzer (Mettler-Toledo, AG, Schwerzenbach, Switzerland). The mean particle size distribution of the microspheres was determined using a Malvern 2600 laser sizer (Malvern Instruments, Malvern, UK). The surface morphology was examined by scanning electron microscopy (SEM) (Hitachi Model S800, Tokyo, Japan) after palladium-gold coating of the microsphere samples on an aluminum stub. Specific surface area was determined using a BET analyzer (ASAP 2000, Micromeritics Instrument Corporation, Norcross, GA).

RESULTS AND DISCUSSION

Table 1 shows that the sub-batches of the highly porous PLGA microspheres have similar physical properties in bulk density, specific surface area, and moisture contents in the range of 1.7% to 2.3%, with small deviations in particle size. The 3 sub-batches of microspheres processed in the PharmASep unit show the same morphology (Figure 2a-c) by SEM. Table 1 and Figure 3a-c show the characteristics and morphologies of the 3 sub-batches of the low-porosity microspheres. The microspheres have similar properties and a narrow range in moisture content (3.5% to 3.9%), albeit higher than the highly porous microspheres. This suggests that the higher porosity and greater specific surface area contribute to more efficient drying.

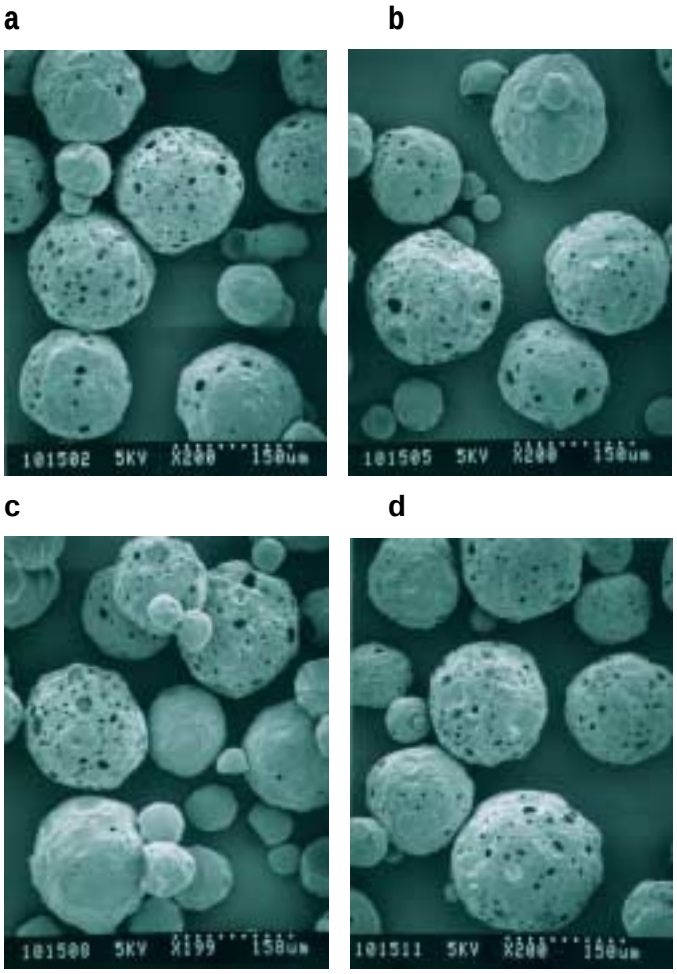

Figure 2. Scanning electron micrograph of highly porous microspheres processed with PharmASep unit (a-c) and membrane filtered and vacuum dried (d).

Table 1. Characteristics of Microspheres

Characteristics	High-porosity Microspheres				Low-porosity Microspheres			
	PharmASep Dry			Vacuum Dry	PharmASep Dry			Vacuum Dry
Sub-batch No.	1	2	3	4	1	2	3	4
Yield (%)	99.8	97.9	97.7	98.0	89.8	88.9	91.2	90.0
Particle Size (μm)	113.6	113.0	108.9	62.2	62.3	59.7	61.8	30.7
Bulk Density (g/mL)	0.100	0.101	0.106	0.101	0.885	0.908	0.855	0.891
Specific Surface Area (m^2/g)	2.49	2.45	2.42	2.50	0.08	0.08	0.08	0.11
Moisture Content (%)	2.3	1.7	2.1	1.7 (9.5)[a]	3.5	3.7	3.9	2.7(12.5) [a]

[a] The values in the parentheses represent the moisture content of microspheres dried for 7 hours under 22-inch Hg vacuum.

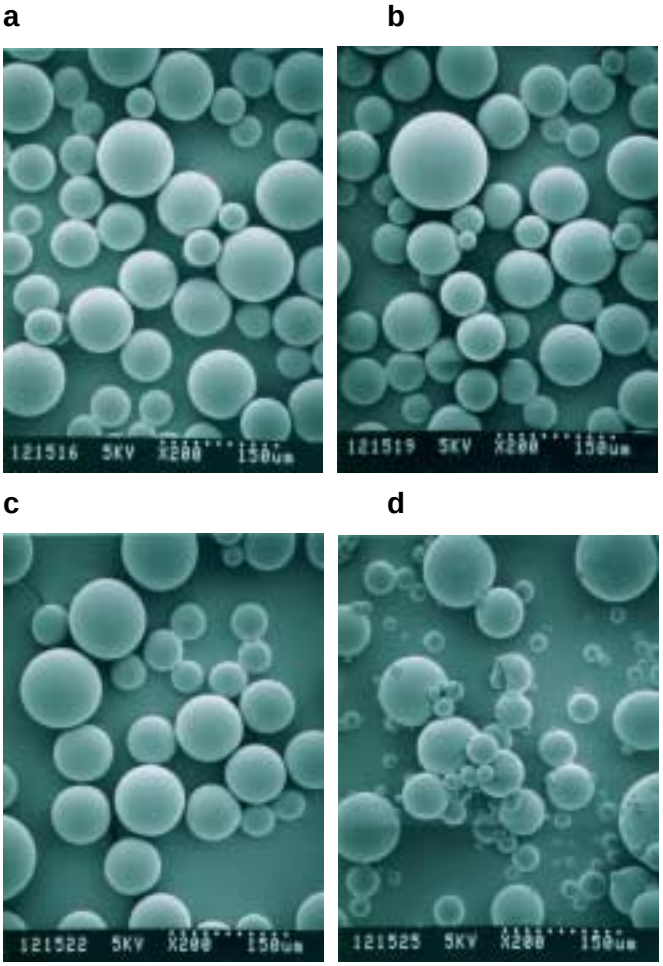

Figure 3. Scanning electron micrograph of low-porosity microspheres processed with PharmASep unit (a-c) and membrane filtered and vacuum dried (d).

The characteristics and morphologies of PLGA microspheres were very similar between the sub-batches processed in the PharmASep unit and by a conventional filtration method (Table 1 and Figures 2d and 3d) with the exceptions of particle size, moisture content, and specific surface area. The differences in particle size distribution and specific surface area of microspheres are due to the smaller particles (less than 25 μm) passing through the product screen when rinsed and dried in the PharmASep unit with the 25-μm product screen. These smaller particles would be retained using the filtration/vacuum drying method - hence the smaller mean particle size and larger specific surface area. The moisture content of the microspheres dried in the PharmASep unit for 7 hours was similar to the moisture content of the microspheres dried by the conventional vacuum dry method for 3 and 5 days. However, when compared with drying in the conventional manner for 7 hours, the PharmASep unit was much more efficient. This suggests that the PharmASep unit could significantly reduce the required microsphere processing time by using the purge-air drying method rather than the conventional vacuum drying method.

The PharmASep unit is capable of separating microspheres from slurry media, washing them on the screen, and drying the recovered microspheres. The original characteristics of microspheres are maintained reproducibly for all batches. Therefore, the PharmASep unit, a unique Vibro-Filter Dryer™ system, is the best choice for processing microspheres and microparticulates.

ACKNOWLEDGEMENTS

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