AAPS PharmSciTech

AAPS PharmSciTech 2001; 2 (2) Technical Note 3
(http://www.pharmscitech.com)

Freeze-Drying of Microparticulates in a Vibro-Separator

Submitted: June 15, 2001; Accepted: June 28, 2001

Kyu-Heum Na,[1] Byung Ho Woo,[1] Yeong Woo Jo,[1] Azar M. Hazrati,[2,3] and Patrick P. DeLuca[1]*

[1]Faculty of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536

[2]Sweco, Inc, Pharmaceutical Research & Development, 7120 Buffington Road, Florence, KY 41042

[3]Current address: 2955 Kimberly Drive, Maineville, OH 45039

KEYWORDS: PharmASep; Vibro-Separator; Microspheres; Microparticulate; Freeze-drying

INTRODUCTION

There has been considerable interest in developing biodegradable, injectable microspheres for the controlled release of proteins and peptides [1-4]. Several transfer-required processes such as filtration, centrifugation, and vacuum- or freeze-drying are necessary for preparation of microspheres, and these processes might be obstacles when scaling-up the manufacturing process to produce sufficient quantities of sterile material for clinical trials and, ultimately, commercialization [5].

A vibro-filter dryer system using Sweco PharmASep (Sweco Inc, Florence, KY) technology [6-10] has been designed to facilitate aseptic transfer of all of the solid-containing slurry from a reactor vessel and/or a quench tank, to remove the slurry liquid media, to dry the collected solid product by purge-air/vacuum application, and to efficiently recover the dried particles. The PharmASep unit would also facilitate washing and rinsing of the particles before drying.

In a previous study [10] the feasibility of using the PharmASep unit to separate microspheres from an aqueous slurry, rinse them on a screen, and vacuum-dry them before recovery was assessed. The purpose of this study was to assess reproducibility of results using the Sweco PharmASep unit and to determine its utility for freeze-drying, often the final step in the preparation of microspheres.

***Corresponding author:** Patrick P. DeLuca, Ph.D., Faculty of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Rose Street, Lexington, Kentucky 40536, USA; Telephone: 859-257-5292; Facsimile: 859-323-0242; E-mail: ppdelu1@pop.uky.edu

MATERIALS AND METHODS

Materials

This study used Avicel microcrystalline cellulose, Type PH-103 (~50 µm, cylindrical crystals, FMC Co, Newark, NJ), as a model particle for microspheres. All other chemicals were obtained commercially as analytical grade reagents.

A 6-inch Sweco PharmASep vibro-filter dryer (model PH-06Y) was provided by Sweco Inc. A schematic diagram of the Sweco 6-inch PharmASep unit was published previously [10]. A Trivac CE vacuum pump (Leybold Vakuum, Köln, Germany) and a Flexi Dry condenser (FTS Kinetics, Stone Ridge, NY) were used for freeze-drying.

Methods

Assessing reproducibility for freeze-drying

To determine whether an aqueous slurry could be frozen and freeze-dried in the PharmASep unit, 3 batches were processed as follows. Twenty grams of microcrystalline cellulose was suspended in 80 mL of deionized water. The suspension was poured into the unit and frozen below -30°C by simply wrapping the unit with dry ice for 1 hour. The temperature of the suspension was monitored using a digital thermometer (Cole-Parmer Instrument Co, Vernon Hills, IL) with a temperature probe that touched the surface of the suspension. The unit was connected to the freeze-dryer system via the top of the scalping screen. A vacuum (~50 µm Hg) was applied, and the sample was left to sublime under a noncontrolled temperature profile. The vacuum was monitored with a vacuum gauge in the condenser unit. A vacuum probe was positioned at the vacuum line about 5 inches away from the vacuum outlet port of the PharmASep unit. During freezing and drying, the unit was not subjected to vibration.

Assessing effect of water volume and batch size

For preparing wet slurries with 75%, 80%, and 90% (wt/wt) water content, 20 g of microcrystalline cellulose was mixed with 60, 80, and 180 mL of deionized water. A suitable slurry required 75% and higher water percentage. For assessing the effect of batch size, small (10 g), medium (20 g), and large (40 g) loads with 80% water content were also prepared. Each suspension was poured onto the unit and freeze-dried for 15 to 28 hours as described above.

Analysis of freeze-dried material

To assess the utility of the PharmASep unit for freeze-drying, each batch was characterized for freeze-dried form, moisture content, ability to resuspend, and recovery yield. The moisture content was determined with a Metrohm 701 KF Tritino and 703 Ti Stand (Metrohm Ltd, Herisau, Switzerland).

Table 1. Freezing and freeze-drying process and reproducibility among different processing batches.

Batch	A	B	C
Batch size (grams of MC*)	20	20	20
Water % (wt/wt) in slurry	80	80	80
Freezing process			
Inner temperature (°C)	-38	-36	-42
Processing time (hr)	1	1	1
Freeze-drying process			
Temperature of condenser (°C)	-55	-55	-55
Average vacuum (µm Hg)	55	55	50
Processing time (hr)	15	15	15
Characteristics			
Recovery yield (%)	89.7	90.3	90.6
Freeze-dried form	cake	cake	cake
Ability to resuspend	VG**	VG**	VG**
Moisture content (%)	3.24	3.35	3.65

*** MC = microcrystalline cellulose Type PH-103**
**** VG = very good (almost same level as crude MC)**

Table 2. Effect of water volume on freeze-drying

Batch	D	B	E
Batch size (grams of MC*)	20	20	20
Water % (wt/wt) in slurry	75	80	90
Recovery yield (%)	89.8	90.3	90.6
Freeze-dried form	cake	cake	cake
Ability to resuspend	VG**	VG**	VG**
Moisture content (%)	3.18	3.35	3.60

*** MC = microcrystalline cellulose Type PH-103**
**** VG = very good (almost same level as crude MC)**

RESULTS AND DISCUSSION

During freezing of the suspension of 20 g microcrystalline cellulose in 80 mL of deionized water in the PharmASep unit, the temperature inside the unit fell below -30°C in 30 minutes and the suspension was fully solidified in 1 hour. A full vacuum was then applied and maintained below 60 mm Hg during the drying. The temperature of the condenser was between -50°C and -60°C. Table 1 shows that the freeze-dried materials of three batches had similar properties in freeze-dried form as well as the ability to resuspend and moisture content in the range of 3.24% to 3.65%, with a high recovery yield in the range of 89.7% to 90.6%.

Table 2 shows the effect of water volume on freeze-drying. Wet slurries with 75%, 80%, and 90% (wt/wt) water content were successfully freeze-dried as a cake. Freeze-dried materials have a good ability to resuspend and have yields in the range of 89.8% to 90.6%, with no significant difference in moisture content (3.18%-3.6%). No slurry could be prepared with less than 75% water content. The slurry with less than 80% water content could be freeze-dried in 15 hours, whereas at above 80%, more processing time was required.

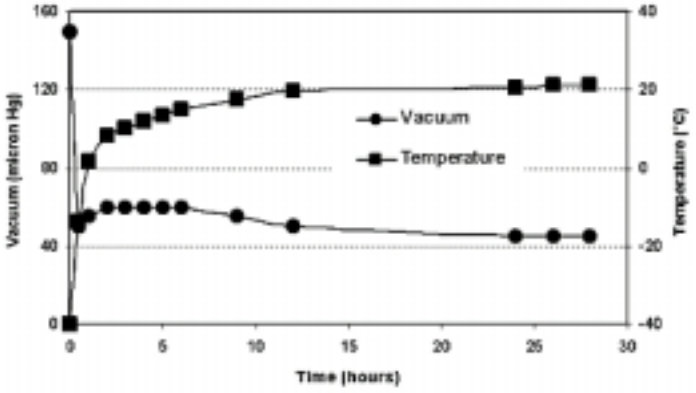

Figure 1. Vacuum and temperature profiles inside the PharmASep unit during the freeze-drying process of the large batch (batch G).

Table 3. Effect of batch size on freeze-drying

Batch	F	B	G
Batch size (grams of MC*)	10	20	40
Water % (wt/wt) in slurry	85	80	80
Recovery yield (%)	85.6	90.3	95.0
Freeze-dried form	cake	cake	cake
Ability to resuspend	VG**	VG**	VG**
Moisture content (%)	3.43	3.35	3.94

*** MC = microcrystalline cellulose Type PH-103**
**** VG = very good (almost same level as crude MC)**

To assess the effect of batch size on freeze-drying, small (10 g), medium (20 g), and large (40 g) batches of slurries were processed. As summarized in Table 3, the cake-formed dried materials of each batch resuspended well with distilled water. Recovery yield increased from 85.6% to 95.0% as batch size increased from small to large. The large batch showed moisture content of 3.94%, somewhat higher than the water content of small and medium batches (3.43% and 3.35%, respectively). Figure 1 shows the change of vacuum and temperature inside the unit during the freeze-drying process of the large batch (batch G). The temperature inside the unit rapidly increased from -40°C to 8.2°C rapidly during the initial 2 hours, followed by a slower increase to 20°C at 12 hours (1.2°C/hr). The vacuum was lowered quickly to 50 μm Hg in 30 minutes and kept below 60 μm Hg during the full period of processing. There was no significant difference in the vacuum and temperature profiles between small and large batch sizes.

The PharmASep unit is capable of freeze-drying microcrystalline cellulose with more than 75% water content and a load of 40 g, producing good recovery and reproducibility. Therefore, the PharmASep unit can be adapted for use in freeze-drying microparticulates and microspheres.

ACKNOWLEDGEMENTS

This study was supported in part by Sweco Inc, Division of Emerson Electric Co.

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