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Reprocessing of Microcrystalline Cellulose Spheres With Low Drug Concentrations[1]

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Abstract

Spherical dosage forms have been reported to be an efficient and effective method for delivering drugs into the body and controlling their dissolution rate. Substantial work has been conducted in these laboratories illustrating the advantages of microcrystalline cellulose-based spheres for these purposes. Through various methodologies, but most routinely the extrusion and marumerization technique, it has been determined by Funck, *et al.* that not more than 50% drug can be incorporated into a sphere formulation without the addition of other binders.[1]

Because of the nature of the extrusion and marumerization manufacturing process, the type of drug being processed and the resultant particle size requirements of the spheres, the percent of spheres falling outside the desired particle size can range from between 3% and 20%. For this reason and the possibility of operator errors, our objective was to determine the parameters which needed monitoring when reprocessing was necessary.

Introduction

MCC has been reported in the literature as an aid to the successful spheronization of single excipient systems.[2] Although it is the most efficient aid in sphere processing, no process, regardless of the aids employed, can yield 100% within a

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specific/narrow mesh range. Nor can the use of MCC protect against operator error which might result in sub-potent or super-potent spheres.

The objective of this work was to determine the feasibility of reprocessing and to evaluate the reprocessing methods, milling *vs.* soaking, the effect of water level and the method of extrusion, single or double, would have on the reprocessed product.

Experimental

Materials

The sphere matrix consisted of microcrystalline cellulose (MCC) NF (Avicel® MCC PH 101, FMC Corporation, Philadelphia, PA) at a 90% level. Acetaminophen (APAP) USP (Penco Corp., Lindhurst, NJ) was used as the active ingredient.

Processing

Source spheres were initially prepared in 3 Kg batches containing 10% APAP *via* the extruder-marumerizer technique. The granulation was prepared in a 12-quart Hobart mixer using 2.9L of distilled water. The powders were blended for 5 minutes on speed setting 1. The water was added over a one-minute period, and wet massing took place for an additional 3 minutes. The resultant granulation was extruded through 1.0 mm screens at 50 rpm. 700 Ml charges of extrudate were placed in the marumerizer for 1 minute at 1000 rpm. The spheres were then dried in a conventional hot air oven at 45°C for 18 hours.

The source spheres were then split into two quantities, for reprocessing by either a milling or a soaking process. The milling method required the source spheres be passed first through a #1 mesh screen then a #60 mesh screen using a Fitz Mill model "J", at high speed and impact forward. The powder was then granulated with water to an appropriate extrudate endpoint in a Hobart Planetary mixer at a speed setting of 1. The extrusion and marumerization and drying parameters were identical to those used for the source spheres.

The soaking method required 0.5 kg of source sphere be placed in a mixing bowl with 0.25 kg of distilled water. Soaking took place for 18 hours. The amount of water lost due to evaporation was calculated and replaced. The soaked spheres were granulated for 5 minutes in a Hobart Planetary mixer at a speed setting of 2. Due to the distribution of the water, one portion of the batch was extruded twice, while the rest had only a single extrusion. Marumerization and drying parameters were identical to those used for the source spheres.

Testing

Physical properties investigated included particle size distribution and bulk and tapped densities. Particle size distribution was conducted using the Typer Sieve Shaker and an appropriate nest of sieves over 5 minutes. Densities were determined by standard procedures.

TABLE I
Sphere Size Distribution

Sieve No.	Percent Retained		
	Source	Milled	Soaked
12	1	0	1
20	37	38	30
30	60	42	60
40	1	10	7
60	1	8	2
80	0	2	0
PAN	0	0	0

TABLE II
Dissolution Profiles of
10% APAP Containing Spheres

Time (min)	% APAP Released		
	Source	Milled	Soaked
15	65	79	72
30	84	85	90
60	96	86	95
90	97	90	96
120	96	92	97
n=2			

Dissolution profiles for the various bead manufacturing processes were determined using USP/NF method I, at a basket rotational speed of 50; the media was distilled water at 37°C. A 20/30 mesh cut of the beads (unless otherwise indicated) was selected for dissolution studies. Samples were analyzed by UV spectroscopy at a wavelength of 249 nm.

Results & Discussion

Spheres were successfully prepared as initial source or reprocessed material using extruder-marumerizer technology. Processing ease relative to the reprocessed product varied according to the method used.

Because the initial extrusion of the soaked spheres exhibited an uneven distribution of water, a second extrusion pass was employed. Although the use of a

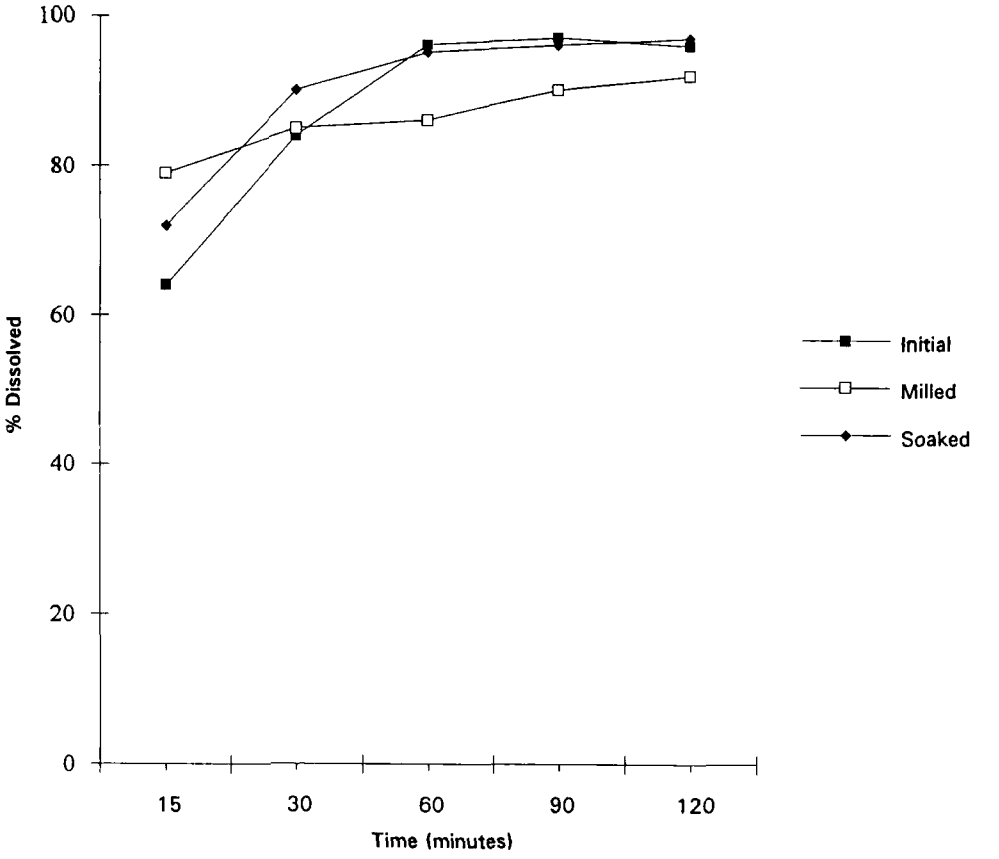

FIGURE 1

Dissolution Profiles of MCC Spheres Containing 10% APAP

second extrusion pass provided a more uniform distribution of water throughout the extrudate, satisfactory spheres were obtained from material exposed only to a single extrusion step. Since the fewer number of processing steps is most desirable, spheres prepared from the single extrusion method were used for analysis.

Physical properties of the spheres are listed in Table I. In general, all the formulations exhibited narrow size distribution. The mean sphere sizes were determined using a computer program developed at PCPS based upon the analysis for log-normal distribution.[3] Loose and tapped densities listed in Table I indicate that some rearrangement occurred during tapping, but also reflect the mean sphere size.

Dissolution values for the spheres tested are listed in Table II. With only limited variation, all the profiles are identical. By 60 minutes, all samples, regardless of processing method or sieve fraction, released 85+% of the labeled

amount. By 90 minutes, all samples released 90+%. The sample reprocessed *via* milling yielded a slightly lower total percent dissolved. This might be attributed to the loss of material to the milling process, but further analysis is required to confirm this.

For all samples at the conclusion of dissolution testing, the spheres were intact and the solutions were clear.

Conclusions

Spheres containing 90% Avicel® MCC PH 101 can be reprocessed *via* a double milling procedure or an overnight soaking procedure without requiring additional excipients or negatively impacting the dissolution profiles. The resultant reprocessed products have a narrow particle size distribution, suitable for further processing, such as column coating or compression.

Because of work previously reported in the literature concerning the use of binders and sphere processing[4] additional studies are required to elucidate the reprocessing characteristics of high drug concentrations spheres and spheres initially manufactured with microcrystalline cellulose and binders or special grades of MCC.

References

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