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REPROCESSING OF MICROCRYSTALLINE CELLULOSE SPHERES WITH HIGH DRUG CONCENTRATIONS

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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 to delineate the role of microcrystalline cellulose in the extrusion-spheronization method of manufacturing.[1] O'Connor determined and reported the advantages of using microcrystalline cellulose as the matrix ingredient in the extrusion-spheronization process; however, he reported that with simple formulations, using only water as the granulating agent, drug loading above 50% was at best difficult.[2] Later work conducted by Funck *et al* examined the incorporation of adjuvant binders such as hydroxypropyl cellulose, carbomer and starch, to enhance binding capacity and increase drug concentrations to 80%.[3]

Because of Funck's work, it was decided to examine the only commercially available MCC product coprocessed with a binder. Although three grades of Avicel® MCC:CMC are marketed, it was decided that only the RC-591 grade would be examined for its reprocessing characteristics. As more companies turn toward sustained release technology to extend patent protection or afford a novelty to marketing, high drug loaded (80%+) spheres will become the norm rather than the exception. Since no process yields 100% or guarantees outcomes, there will always be some quantity of spheres that are either too large or too small or where an entire batch must be reprocessed. On the basis of earlier work performed in these laboratories,[4] it was decided to examine the milling and

soaking methods of reprocessing spheres. With the presence of a binder, it was uncertain if the previously reported outcomes for reprocessing would be the same.

EXPERIMENTAL

Materials

The active ingredient used in this study was acetaminophen (APAP) USP (Penco Corporation; Lindhurst, NJ). The matrix materials were microcrystalline cellulose and carboxymethylcellulose sodium NF (Avicel® MCC RC-591, FMC Corporation, Philadelphia, PA). Avicel® RC-591 is a spray dried, co-processed material containing between 8.3 and 13.8% of a moderate viscosity CMC.[5]

The formulation used for these experiments consisted of 2400g APAP (80%), 600g of Avicel® MCC RC-591 and 1100 mL distilled water. Because of the presence of the CMC, a significantly larger quantity of water was required to achieve an acceptable granulation for spheronization.

Processing

Source spheres were prepared from the above formulation via the extrusion-spheronization method. This method involved a 5-minute dry blending step in a Hobart 20-quart planetary mixer at a speed setting of 1, followed by water addition over a 1-minute period of time. Wet massing took place at speed setting 1 for an additional 5 minutes.

The resultant granulation was extruded through a Luwa model N-50 twin screw extruder at 50 rpm, equipped with 1.5mm screens. The extrudate was spheronized in 700cc quantities in a Luwa marumerizer using a 2mm serrated plate operated at 1000 rpm for a residence time of 2 minutes. The resultant spheres were then dried in a conventional hot air oven at 45°C for 18 hours.

The source spheres were split into two quantities for reprocessing by either a milling or soaking operation. The milling operation required 1300g of dried source spheres be passed through a Model J Fitzpatrick Mill, impact forward using a number 1 mesh screen. The resultant granulation was then passed through the mill again using a number 60 mesh screen. The powder was then granulated using water to an appropriate endpoint in the Hobart Planetary mixer at a speed setting of 1.

Extrusion and drying parameters were identical to those used for the source spheres. Residence time in the marumerizer was increased by 30 seconds from the source spheres to 2.5 minutes.

The soaking operation required that 500g of source spheres be placed in 185 mL of distilled water. An immediate paste was formed and granulation proceeded for 20 minutes in the Hobart mixer at a speed setting of 2. Extrusion, spheronization and drying parameters were identical to those used for the milled spheres.

Testing

The following physical properties of the source and reprocessed sphere were measured using standard methods of analysis: size distribution, friability, bulk and tapped densities.

Dissolution for the formulations was determined on a 16/30 mesh cut of spheres using USP Method I (Basket) at 50 rpm with 900 mL of either 0.1N HCl, 7.2 pH phosphate buffer or distilled water as the media.

RESULTS AND DISCUSSIONS

Milling Process

Relative to observation made in prior studies,[4] the spheres were easily reduced to a fine powder suitable for regranulation. The length of times required to reduce the spheres to a powder that would pass through a 60 mesh screen was no greater than that required for a normal granulation.

Table 1 lists the physical properties of the source spheres and spheres reprocessed via the milling procedure.

The data indicate that there is no change in density after reprocessing with a milling method. This is extremely important since density plays an important role in capsule filling of sustained release particles. Although a slight difference in particle size distribution is reported with the milled spheres, it is believed that this could easily be eliminated by optimizing the water level and mixing times.

Soaking Process

Unlike that reported for low drug loaded spheres prepared from 100% MCC, high drug loaded spheres containing the co-processed MCC:CMC product acted as miniature sponges absorbing the water immediately and although remaining discrete particles, the spheres were pliable with the ability to be "molded". This effect is attributed to the water absorptive activity of the CMC and its uniform distribution throughout the matrix.

Table 2 lists the physical properties of the source spheres and spheres reprocessed via the soaking procedure.

A slightly greater than 10% difference in density exists between the source and soaked spheres. It is the opinion of the authors that, when this difference is more closely examined, it will be reduced through tighter processing controls such as % LOD of the reprocessed dried spheres. Particle size distribution appears to be very reproducible, thus allowing for ease of manufacturing.

Dissolution

Dissolution on all three sets of spheres was conducted using 0.1 N HCl and 7.2 pH phosphate buffer and distilled water for the purpose of eliminating errant

TABLE 1
Physical Properties of Source Spheres and Spheres Reprocessed *Via* Milling

Density (g/cc)	Source	Reprocessed
Loose	0.6579	0.6944
Tapped	0.7352	0.7353

Size Distribution	% Retained	
Sieve Number		
10	0	0
12	4	0
16	32	12
20	48	48
30	16	32
50	0	8
Pan	0	0
Friability (% Loss)	0	1

TABLE 2
Physical Properties of Source Spheres and Sphere Reprocessed *Via* Soaking

Density (g/cc)	Source	Reprocessed
Loose	0.6579	0.7353
Tapped	0.7352	0.8333

Size Distribution	% Retained	
Sieve Number		
10	0	0
12	4	4
16	32	32
20	48	52
30	16	12
50	0	0
Pan	0	0
Friability (% Loss)	0	1

TABLE 3
Mean Percent APAP Dissolved from Source Spheres vs. Spheres Reprocessed *Via* Soaking

Time (min)	Media					
	Water		7.2 pH Phosphate		0.1N HCl	
	Source	Soaked	Source	Soaked	Source	Soaked
15	16	15	52	46	57	44
30	27	27	67	67	69	69
60	35	36	76	77	88	88
90	42	47	79	85	92	96
120	48	53	80	85	97	99
180	57	62	75	86	100	97
240	63	79	84	87	99	100

TABLE 4
Mean Percent APAP Dissolved from Sources Spheres vs. Spheres Reprocessed *Via* Milling

Time (min)	Media					
	Water		7.2 pH Buffer		0.1N HCl	
	Source	Milled	Source	Milled	Source	Milled
15	16	37	52	55	57	51
30	27	42	67	70	69	73
60	35	59	76	80	88	93
90	42	67	79	82	92	96
120	48	75	80	80	97	96
180	57	76	75	84	100	97
240	63	90	84	83	99	100

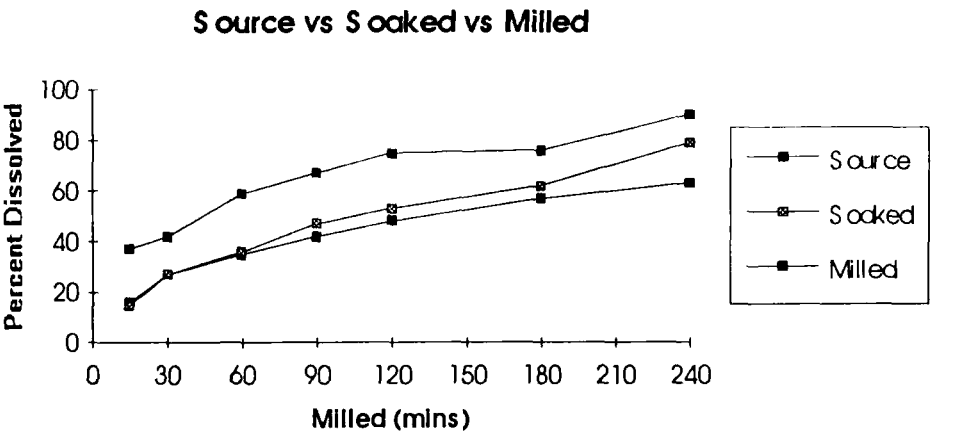

FIGURE 1
Mean Percent Dissolved from 60-Mesh Spheres in Water

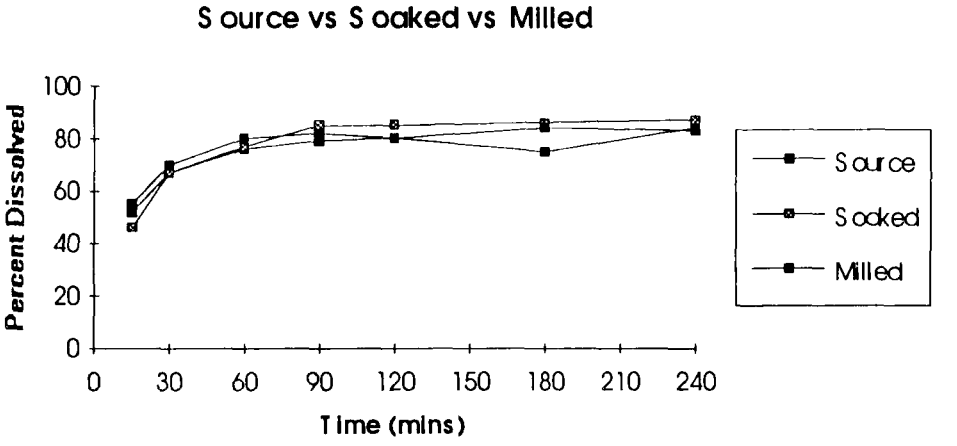

FIGURE 2
Mean Percent Dissolved from 60-Mesh Spheres in 7.2 pH Buffer

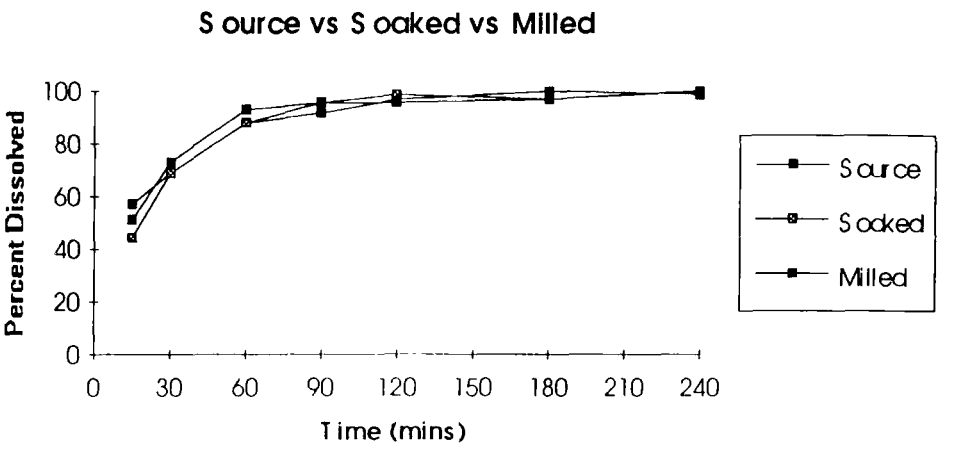

FIGURE 3
Mean Percent Dissolved from 60-Mesh Spheres in 0.1N HCl

profile due to the CMC gelling capability in distilled water but not in fluids more representative of gastro-intestinal tract conditions.

Tables 3 and 4 list the mean percent dissolved of source spheres vs. milled or soaked spheres, respectively, in the various media. As anticipated, spheres examined in distilled water were noted to have congealed into a gelled mass in the dissolution basket. With the exception of those reprocessed by milling, those tested in water had the slowest dissolution profiles. Figures 1, 2 and 3 illustrate the release profiles of the source and reprocessed spheres in water, 7.2 pH phosphate buffer and 0.1N HCl, respectively.

Although much additional work would be required to optimize and validate either of these reprocessing methods, it would appear that either a simple milling process or quick soaking process is sufficient to prepare the spheres with high drug concentrations using MCC:CMC material for reprocessing. Additionally, the time requirements for reprocessing are significantly more favorable as compared to those for MCC spheres with low drug concentration employing the same methods.

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