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BINDER EFFECTIVENESS FOR BEADS WITH HIGH DRUG LEVELS

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ABSTRACT

Previous reports from these laboratories showed that microcrystalline cellulose (Avicel[R] MCC, PH-101) formulations with low and medium drug levels (10 and 50%) produced very uniform beads whereas formulations containing MCC with high drug

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levels (80%) were difficult to process without special treatment or required the incorporation of alternate excipients. In this study, several binders, at a 2% level, specifically: Carbomer (Carbopol^{R} 934-P), Sodium carboxymethylcellulose (CMC 7MF), Hydroxypropylcellulose (Klucel^{R} HXF), Methylcellulose (Methocel^{R} K-15). Povidone, USP (PVP K29-32) and Pregelatinized starch NF (Starch 1500^{R}), were evaluated to determine whether they might impart advantages in processing and whether any differences in dissolution behavior would result. Spheres containing 80% anhydrous theophylline, the binders and MCC were manufactured by the extrusion/ marumerization technique. In general, beads containing high drug levels produced with these binders are suitable for further processing (coating). Processing ease, bead shape, and bead hardness (friability) varied with the choice of binder. Beads with carbomer, hydroxypropylcellulose, and methylcellulose remained intact during dissolution testing; beads with starch, carboxymethylcellulose, PVP, and the control did not.

INTRODUCTION

Interest in spherical particles for pharmaceutical delivery systems has received significant attention since the introduction of equipment designed for spheronization. The technique involves the preparation of spheres via extrusion of a

moist powder bed followed by the spheronization process where the cylindrical segments originated on the extruder are rounded into beads on a rapidly rotating serrated plate on the marumerizer (1-4).

The most common application of spheres is as a drug vehicle in controlled release dosage forms (5-7). Nevertheless, the importance of beads is also due to the wide range of drug levels possible and the high drug loading which can be obtained with this physical form (6).

Microcrystalline cellulose has been reported in the literature (8) as an aid to the successful spheronization of single components. However, previous work has also shown that beads with high drug levels (e.g. 80%) are difficult to process with MCC (9) and, in fact, are only easily manufactured when special grades of MCC are used (7). These special grades of Avicel^{R} MCC are identified as those containing carboxymethyl-cellulose (RC-581, RC-591 and CL-611). Conversely, Avicel^{R} MCC (PH-101) appears to be an useful matrix material for obtaining acceptable beads with low and medium drug loading (10). The hypothesis for this study was that Avicel^{R} MCC (PH-101) combined with binders other than carboxymethylcellulose could produce acceptable beads with high drug loading.

Of special concern in this study was the well documented fact that binders can also affect the properties of the final product including the drug release (11-13).

The objectives of this work were to evaluate several binders (at a 2% level), to determine whether they might impart

advantages in processing beads with an 80% drug level, and to determine their effects on drug dissolution.

EXPERIMENTAL

Materials

The binders evaluated include: Carbomer (Carbopol^R 934-P, BFGoodrich, Cleveland, OH), Sodium carboxymethylcellulose (CMC 7MF, Aqualon Co., Wilmington, DE), Hydroxypropylcellulose (Klucel^R HXF, Aqualon Co., Wilmington, DE), Methylcellulose (Methocel^R K-15, Dow Chemical Co., Midland, MI), Povidone, USP (PVP K29-32, GAF Corporation, New York, NY) and a Pregelatinized starch, NF (Starch 1500^R, Colorcon, West Point, PA).

The matrix material used was microcrystalline cellulose (Avicel^R MCC, PH-101, FMC Corporation, Philadelphia, PA). The drug used was anhydrous Theophylline, USP (Knoll Fine Chemicals Inc., Whippany, NJ).

Bead Manufacturing

The general formulation for this work was 80% drug (anhydrous Theophylline), 2% binder and 18% Avicel^R MCC (PH-101). The control formulation contained the drug with 20% MCC and no binder. The batch size for these experiments was 0.5 Kg.

The ingredients were blended in a planetary mixer (Kitchen Aid Model K 5SS, Hobart Co., USA). Distilled water was added to form granulations of suitable consistency. In each case, granulations were carried out to a subjective end-point. The granulations were processed through an Extruder (Model EXDS-60, LUWA Corporation, Charlotte, NC), equiped with a 1.5 mm screen and operated at 50 rpm. The extrudate was spheronized via a marumerizer (Model Q-230, LUWA Corporation) equipped with a 2 mm serrated plate and operated at 1000 rpm. The residence time varied from 45 seconds to 2 minutes, depending upon the material. The spheres were dried for 12 hours in a conventional hot air oven (Model 38C, F.J. Stokes Coorporation, Philadelphia, PA) at a temperature of 45 ^{o}C.

Testing

The physical properties investigated included size distribution, friability and bulk and tapped densities. The friability of the beads was assessed by testing the resistance to abrasion of a 10 g sample, mesh cut 12/30, together with 200 glass beads (average diameter of 4 mm) on a Friabilator (Erweka Apparatebau - GMBH, West Germany) equipped with an abrasion wheel.

Sieve analysis as well as bulk and tapped densities were determined by standard procedures.

Dissolution profiles for the various bead formulations were determined using the USP/NF method I, at a basket rotation speed

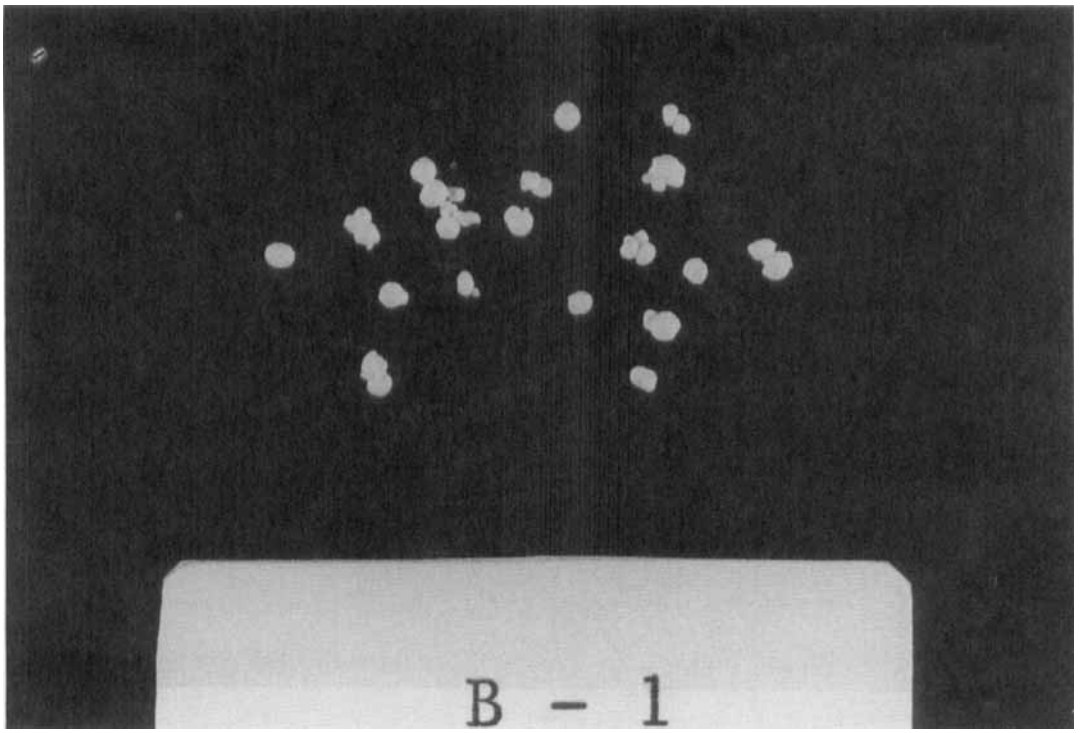

Figure 1- Control Beads [Theophylline 80% / Avicel^{R} MCC (PH-101)]

of 50 rpm, with purified water at 37 ^{o}C as the test medium. For beads containing carbomer, both water and pH 7.4 phosphate buffer were used as a test medium. Beads of a 12/30 mesh cut were selected for dissolution studies. Samples were analyzed by UV spectrophotometry at 272 nm.

RESULTS AND DISCUSSION

Spheres containing high drug levels (80% theophylline) were successfully prepared via extruder/marumerizer technology with a

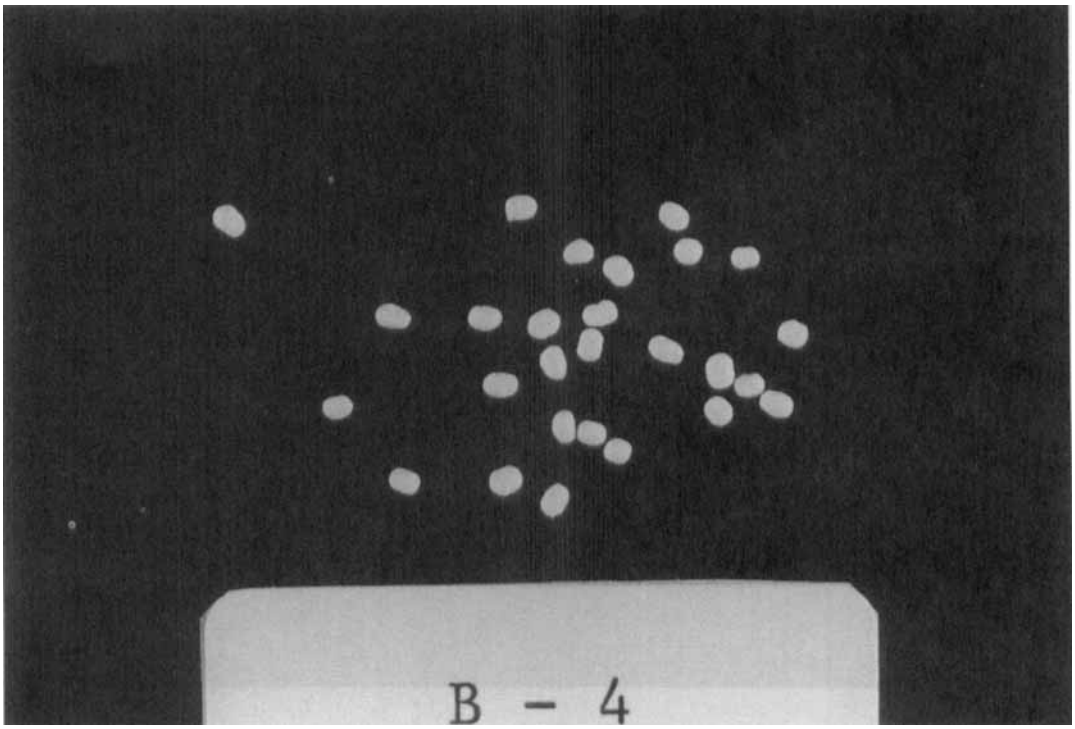

Figure 2- Theophylline 80% / Carbomer 2% / Avicel^{R} MCC (PH-101)

variety of binders as demonstrated by Figures 1, 2, and 3 as examples.

Processing ease as well as the bead shape varied according to the binder used, e.g. the extrudate of the material containing methylcellulose was long and unnotched and therefore not easily breakable. As a result when it was spheronized for two minutes in the marumerizer it yielded rods rather than spheres.

The physical properties for the bead formulations are listed in Table I. The beads in general exhibited narrow particle size

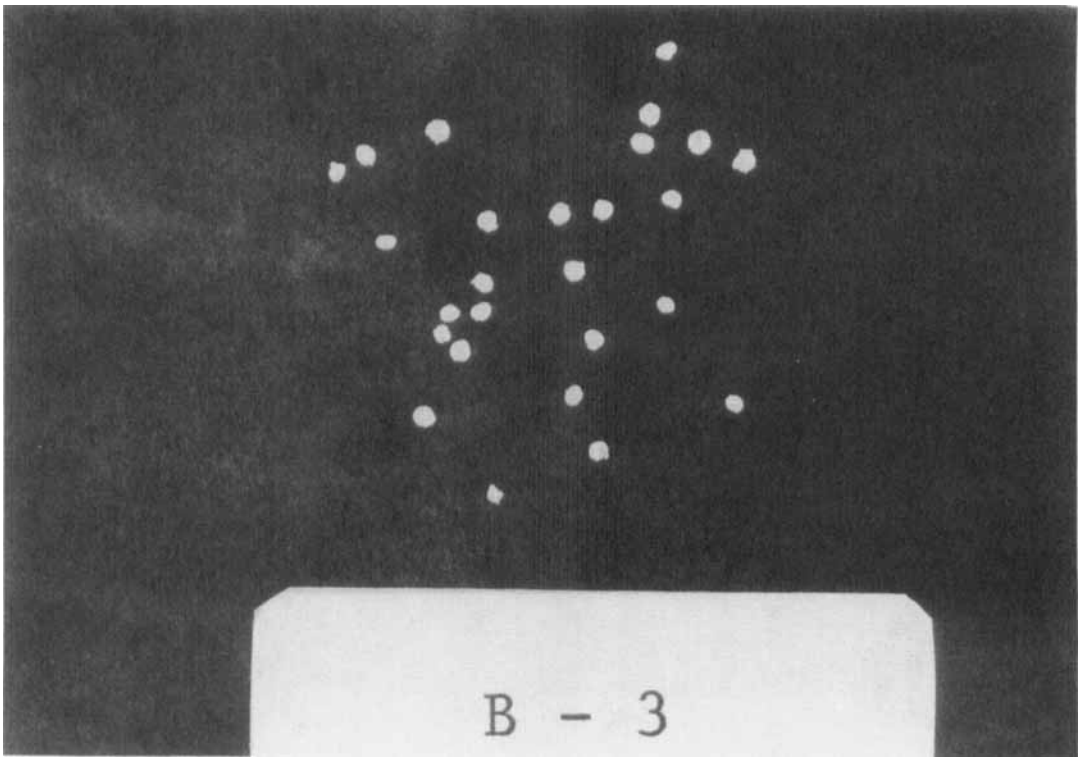

Figure 3- Theophylline 80% / PVP 2% / Avicel^{R} MCC (PH-101).

distributions and similar mean sizes (approximately 1 mm) as listed in Table II. The mean bead sizes were determined using a computer program developed at the Philadelphia College of Pharmacy & Science, based on analyses for log-normal distributions (14).

Loose and tapped densities listed in Table I indicate that the beads were probably arranged in the closest packing, since the differences between the two densities are not significant. It is interesting, however, to note that some of the tapped

Table I

Physical Properties of the Beads

80% Theophylline/ 18% Avicel^{R} MCC (PH-101)/ 2% Binder

	Binder						
	Starch	Carbomer	PVP	HPC	CMC	MC	Control
Density (g/cm^3)							
Bulk	0.510	0.500	0.588	0.675	0.735	0.676	0.568
Tapped	0.641	0.521	0.610	0.675	0.714	0.714	0.641
Sieve analysis (% retained on)							
8	10.0	0.0	0.0	1.0	1.9	0.0	8.2
12	19.4	0.0	0.0	3.8	11.5	0.0	16.3
16	36.9	74.0	0.0	83.7	57.7	72.0	34.7
20	27.2	18.0	27.1	10.6	23.1	20.0	30.6
30	5.4	4.0	47.9	1.0	5.8	4.0	8.2
40	0.8	2.0	18.8	0.0	0.0	2.0	2.0
pan	0.3	2.0	6.3	0.0	0.0	2.0	0.0
Friability							
%	1.7	0.26	*	0.0	0.0	0.0	2.15

* Not determined due to electrostatic charges (see text).

TABLE II

Geometric Mean Particle Size of the Beads.

Binder	Mean diameter (micrometers)
Control	1102
Starch	1168
Carbomer	1042
PVP	616
Hydroxypropylcellulose	1190
CMC	1101
Methylcellulose	1492

densities are greater than the loose densities. This fact was previously observed and reported in the literature (7) as a result of a disturbance of the closest packing arrangement by shaking.

The bead friability also varied with the binder used. However, as observed in Table I, a very low degree of loss on abrasion was verified with all the formulations. The control showed the highest friability which was expected since no binder was present. A considerable electrostatic charge developed when the beads containing PVP were tested; this prevented the test from being completed.

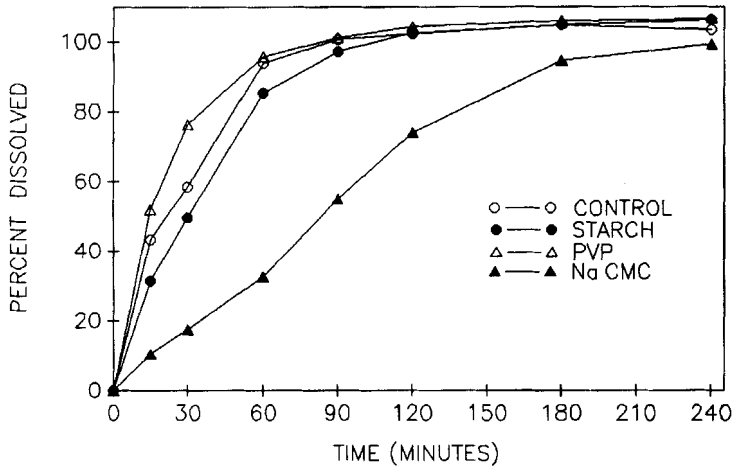

Figure 4- Dissolution profiles for beads in water [80% Theophylline / Avicel^{R} MCC (PH-101) / 2% binder]

Of concern in these formulations would be the fact that binders could affect, among other properties, drug release. The dissolution profiles, as observed in Figures 4 and 5, were not dramatically affected by the low binder levels (i.e., 2%). Methylcellulose and Carboxymethylcellulose appeared to alter the drug release only slightly. No differences in dissolution profiles were observed with beads containing carbomer tested in both, water and pH 7.4 buffer media.

Bead behavior during dissolution testing varied with the binder selected. Beads with Hydroxypropylcellulose, Methylcellullose and Carbomer remained intact, although a small reduction in size was observed (Figure 6). Beads with Starch, PVP and CMC disintegrated as did the control.

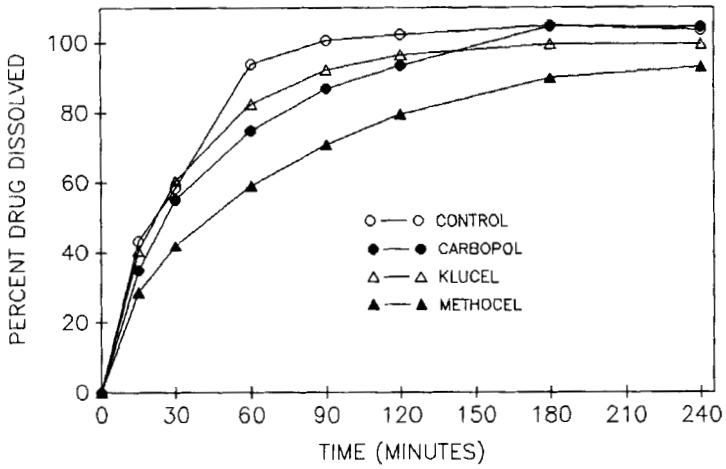

Figure 5- Dissolution profiles for beads in water [80% Theophylline / Avicel^{R} MCC (PH-101) / 2% binder]

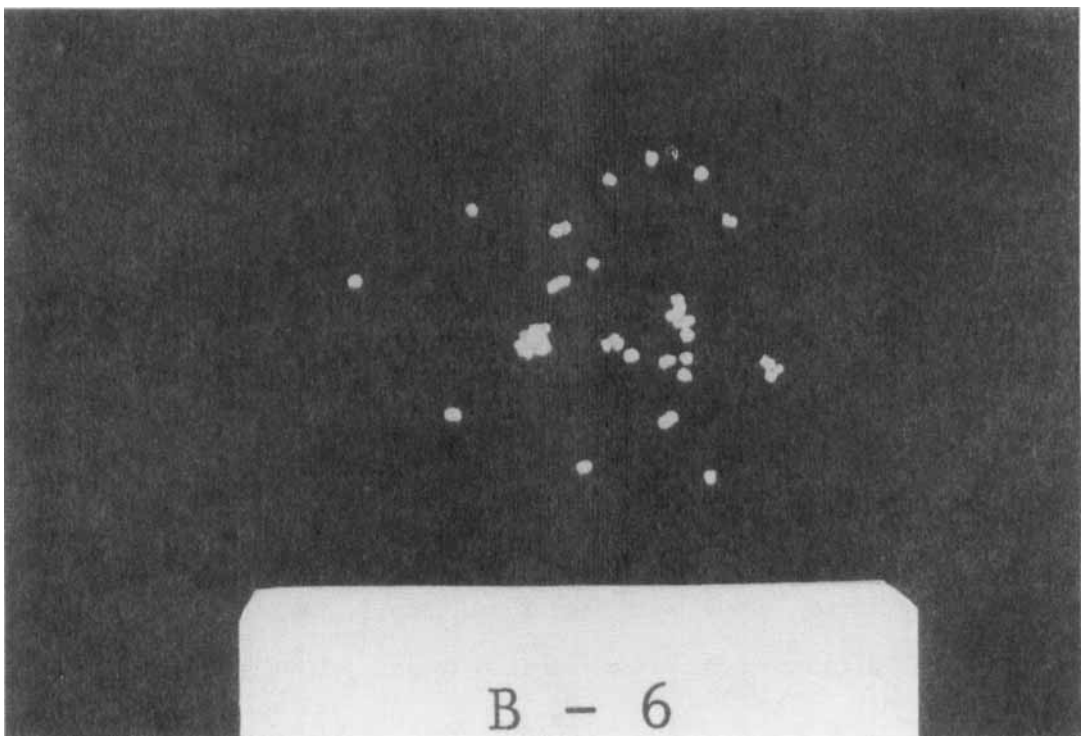

Figure 6- Intact beads after dissolution test [Theophylline 80% / Carbomer 2% / Avicel^{R} MCC (PH-101)

CONCLUSIONS

Beads at high drug levels (80%) acceptable for coating can be manufactured when Avicel^{R} MCC (PH-101) is combined with binders.

Processing ease, bead shape and bead hardness (friability) varied with the choice of binder.

Beads with carbomer, hydroxypropycellulose and methycellulose remained intact during dissolution testing; beads with starch, carboxymethylcellulose, PVP and the control did not.

No significant differences have been observed in drug release from beads manufactured with binders as compared to the control, which demonstrated that the low concentration of binders used did not affect the drug release.

The use of small quantities of binders can provide the formulator with the capability of simple bead formulations with high drug levels.

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