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# Investigation of Hypromellose Particle Size Effects on Drug Release from Sustained Release Hydrophilic Matrix Tablets

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**Selected combinations of six model drugs and four hypromellose (USP 2208) viscosity grades were studied utilizing direct compression and in vitro dissolution testing. Experimental HPMC samples with differing particle size distributions (coarse, fine, narrow, bimodal) were generated by sieving. For some formulations, the impact of HPMC particle size changes was characterized by faster drug release and an apparent shift in drug release mechanism when less than 50% of the HPMC passed through a 230 mesh (63 μm) screen. Within the ranges studied, drug release from other formulations appeared to be unaffected by HPMC particle size changes.**

**Keywords** hypromellose; HPMC; controlled release; matrix system; particle size

## INTRODUCTION

The inability of very large HPMC particles to achieve sustained drug release in hydrophilic matrix tablets has been well-established. Alderman (1984) showed that sustained release tablets made from HPMC 2208 (K4M) particles retained on a 100 mesh (150 μm) screen resulted in practically immediate drug release, while smaller particles produced sustained drug release over many hours. Other researchers have also reported an increase in drug release rate when HPMC particles were larger than a critical threshold value. Mitchell et al. (1993b) found the release rate of propranolol hydrochloride with finer particle size fractions of HPMC (K15M) was similar to that for unsieved HPMC. However, coarser particle size fractions (210–255 μm and > 355 μm) gave faster drug release rates, depending on the amount of HPMC in the formulation. Studies with hypromellose USP 2910 (E4M) showed much faster propylthiouracil release for tablets containing HPMC retained on a 125 μm sieve vs. HPMC passing through the sieve (Kabanda et al., 1994). Data presented by Campos-Aldrete and Villafuerte-Robles (1997) suggest that metronidazole release at low HPMC levels (10%) increased noticeably at an HPMC particle size > 335 μm.

Heng et al. (2001) identified 113 μm as a critical particle size threshold for HPMC 2208 (K15M) in an aspirin formulation. They found that aspirin release rates increased markedly when the average HPMC particle size was above 113 μm, associated with an apparent shift in the drug release mechanism. The drug release rate was found to be much less sensitive to changes in HPMC particle size below 113 μm. Heng et al. concluded that their matrix formulation exhibited three different drug release characteristics as HPMC particle size was altered: tablet disintegration when HPMC particle size was large, diffusional time$^{0.5}$ release kinetics for medium HPMC particle sizes (> 113 μm), and first order release kinetics indicating a combination of both diffusion and erosion at finer HPMC particle sizes (< 113 μm).

The experimental HPMC samples in all of these studies were produced by sieving a typical batch of hypromellose into various particle size fractions. However, it appears that the investigators took different approaches to characterizing the particle size of the resulting HPMC samples that were utilized in the formulations. Alderman and Kabanda et al. appear to have defined the particle size of the fraction by the size of the mesh opening of the screen upon which the particles were retained (e.g., "> 150 μm" for the sample retained on a 100 mesh screen). Mitchell et al. appears to have utilized the same terminology, while also reporting the surface area of each sieve fraction determined by nitrogen adsorption testing. In contrast, Heng et al. characterized the particle size fractions using laser diffractometry, and reported the mean and span of the particle size distribution for each sieve fraction (e.g., the 70–80 μm mesh fraction had a mean particle size of 113 μm and a span of 1.24). Campos-Aldrete and Villafuerte-Robles also referred to each particle size fraction by an average particle size.

From these previous studies, it is clear that a possible outcome of such HPMC particle size manipulations is a "threshold effect" characterized by faster drug release when the particle size of the HPMC in the tablet surpasses some critical threshold value. However, this threshold effect has not been observed in all studies of this type (Velasco et al., 1999). Because of the

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various methodologies used, it was not clear what aspects of the observed behaviors were formulation-specific. The purpose of the present study was to better understand the effects of HPMC particle size on in vitro drug release behavior from hypromellose sustained release matrix tablets by studying a range of formulations under comparable experimental conditions and particle size characterization techniques. Combinations of six different model drugs and four different hypromellose (USP 2208) viscosity grades were studied utilizing direct compression and in vitro dissolution testing. Experimental HPMC samples with differing particle size distributions (coarse, fine, narrow, bimodal) were generated by sieving.

## MATERIALS AND METHODS

### Materials

The model drugs utilized in this study were metoprolol tartrate (Mulji Meha & Sons Private LTD), theophylline (Knoll), caffeine (Spectrum), acetaminophen (Spectrum), ketoprofen (Spectrum), and hydrochlorothiazide (HCTZ, Abbott Labs). Before formulations were prepared, the drugs and lactose monohydrate (impalpable, Sheffield) were each hand sieved through a 20 mesh US Standard sieve (14 mesh sieve for ketoprofen because of static). Hypromellose was obtained from The Dow Chemical Company as METHOCEL™ K100M Premium CR, K15M Premium CR, K4M Premium CR, and K100 Premium LV CR. Experimental samples of hypromellose having various particle size characteristics were prepared by sieving and blending a single lot of one of the hypromellose products, as described below. Dicalcium phosphate (Astaris) and magnesium stearate (Mallinckrodt) were used as received from the supplier.

### Preparation of Experimental HPMC Samples

For each formulation, various experimental samples of HPMC having different particle size properties were prepared from a single product and lot of hypromellose. Sieving and blending techniques were utilized to manipulate the particle size properties of the hypromellose. Narrow particle size distributions were obtained by collecting the fraction between two sieves with similar opening size (e.g., a 200–230 mesh cut). Bimodal particle size distributions were obtained by blending together coarse and fine fractions (e.g., the > 100 mesh fraction blended with the < 325 mesh fraction).

To prepare the experimental HPMC samples, portions of each hypromellose lot as received were tapped on a W.S. Tyler RoTap Sieve Shaker, Model B. Samples were tapped for 15 min through U.S. Standard sieves into a pan, producing various particle size cuts of the original lot. After the particle size fractions had been collected, each fraction was separately blended for 10 min in a twin shell Patterson-Kelley V-blender to ensure homogeneity. The particle size distribution of each experimental HPMC sample was characterized using a Micron Powder Systems air-jet sieve (100 or 230 mesh U.S. Standard sieve, 6 minutes, vacuum level 300 mm water) and a Beckman Coulter RapidVUE particle shape and size analyzer (particles suspended in isopropanol). The properties of each experimental HPMC sample are summarized in Tables 3 and 4.

### Formulations

Controlled release formulations having the compositions shown in Tables 1 and 2 were prepared. Selection of the particular combinations studied (i.e., drug, HPMC pairings) was done arbitrarily, guided by practical considerations to achieve desired release profiles. The percent of HPMC in the formulations was fixed at 30%, representing typical minimum levels. A total of six different tablet batches were prepared for every formulation F1–F6, each incorporating a different experimental HPMC sample or an unsieved hypromellose material (as received). All components except magnesium stearate were blended together for 10 min. Magnesium stearate was then added and blended for an additional minute.

### Tablet Preparation

Tablets were prepared by direct compression on a Manesty Beta Press equipped with 10.3 mm flat face beveled edge B

TABLE 1
Drug, HPMC Combinations Studied

| Formulation | HPMC | Drug | Drug Solubility (mg/mL) |
|---|---|---|---|
| F1 | K4M | Metoprolol tartrate | >1,000 |
| F2 | K4M | Theophylline | 8 |
| F3 | K15M | Caffeine | 20 |
| F4 | K100M | Acetaminophen | 14 |
| F5 | K4M | Ketoprofen | 0.3 |
| F6 | K100 LV | HCTZ | 1 |

TABLE 2
Formulations Utilized in this Study

| Component (wt%) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| HPMC | 30 | 30 | 30 | 30 | 30 | 30 |
| Drug | 20 | 50 | 50 | 50 | 20 | 50 |
| Lactose | | 19 | 19 | 19 | 49 | 19 |
| Dicalcium phosphate | 49.5 | | | | | |
| Magnesium stearate | 0.5 | 1 | 1 | 1 | 1 | 1 |

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tooling to produce 300 mg (F2–F6) or 500 mg (F1) tablets. The compression force for all tablets was 22.2 kN (5000 lbs) and the dwell time was 174–220 ms. Tablet thickness for 300 mg tablets (F2–F6) was about 3 mm, and about 4 mm for 500 mg tablets (F1). These formulations did not flow well enough to allow automated die filling, so the dies were hand fed with preweighed portions of the formulation.

### Release Studies

In vitro dissolution testing was performed on a Distek single bath dissolution system (Model 2100A) equipped with a Hewlett Packard flow controller (89092-69001), multi-cell transport automated sampling system, and Hewlett Packard diode array spectrophotometer (8452A). The dissolution media was 900 ml of degassed 0.05 M phosphate buffer (pH 5.8) at 37° C ± 0.5°C. Standard vessels were utilized with USP Apparatus II (paddles). The stirring rate for each formulation was selected to achieve desired drug release profiles, and was 75 RPM for F1, 50 RPM for F2-F5, and 100 RPM for F6. As described in the literature (Wingstrand et al., 1990; Abrahamsson et al., 1998), tablets ($n$ = 6) were placed into stationary hanging baskets to minimize variability in the measurement. The baskets were adapted from a USP Apparatus I basket and were suspended in the dissolution media approximately 25 mm from the center of the agitator shaft and 20 mm above the paddle tip. Samples were automatically drawn from each vessel through a 70 micron tip filter at specified time intervals and returned to the vessel after passing through a flow cell. Quantification of the amount of drug released was accomplished by UV detection. Good tablet-to-tablet reproducibility was achieved using this method (standard deviation of 1–4% drug release, $n$ = 6 tablets).

## RESULTS AND DISCUSSION

In vitro dissolution results at a selected time point for all six formulations are shown in Figures 1 and 2. The time point for each formulation was selected such that drug release was roughly 50–60% of the total dose contained in the tablet. Drug release from formulations F1, F2, and F3 appeared to be unaffected by the HPMC particle size changes studied (Figure 1), and formulations F4, F5, and F6 appeared to exhibit the threshold-type of behavior described in the literature (Figure 2). While Figures 1 and 2 depict the extent of drug release at a selected time point, Figures 3 and 4 present the entire drug release profile for each formulation and experimental HPMC sample studied.

The similarity factor $f_2$ (Moore & Flanner, 1996) for the drug release profiles in Figures 3 and 4 are summarized in Tables 3 and 4, respectively. For the calculation of $f_2$, the drug release profile for the unsieved (i.e., as received) HPMC sample for each formulation was used as the reference curve. The symbols shown in Tables 3 and 4 for each experimental HPMC sample correspond to the drug release profiles in Figures 3 and 4.

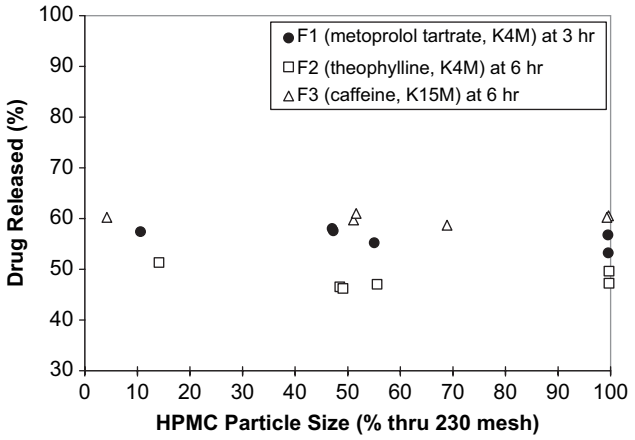


FIGURE 1. Extent of drug release for formulations F1, F2, and F3 at a selected time point.

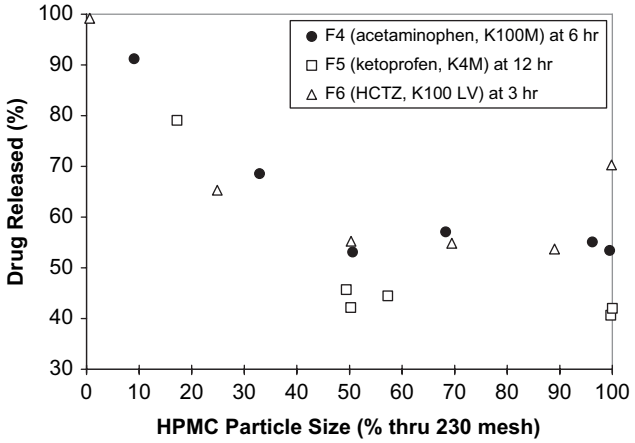


FIGURE 2. Extent of drug release for formulations F4, F5, and F6 at a selected time point.

The general drug release behavior from controlled release polymeric devices can be described by an exponential relation (Korsmeyer et al., 1983):

$$\frac{M_t}{M_\infty} = kt^n$$

The diffusional exponent of drug release ($n$) can give an indication of the release mechanism (Sinclair & Peppas, 1984; Ritger & Peppas, 1987a,b), and was determined for each drug release profile by a linear regression of ln(drug release) vs. ln(time) over the first 60% of drug release. These n values are summarized in Tables 3 and 4. A value of n near 0.5 indicates Fickian diffusion is the dominant drug release mechanism, while a value near 1 indicates Case II transport.

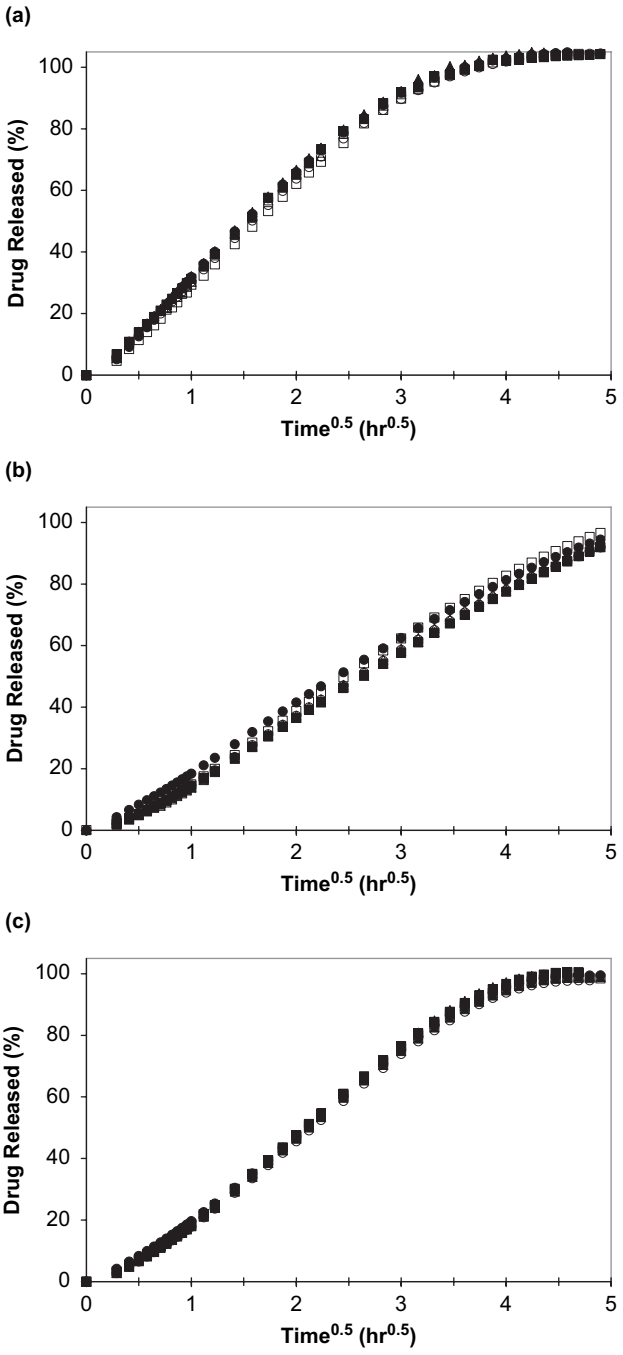


FIGURE 3. Drug release profiles for formulations F1, F2, and F3: (a) F1 – metoprolol tartrate/K4M; (b) F2 – theophylline/K4M; (c) F3 – caffeine/K15M. HPMC properties and metrics for each drug release profile are summarized in Table 3.

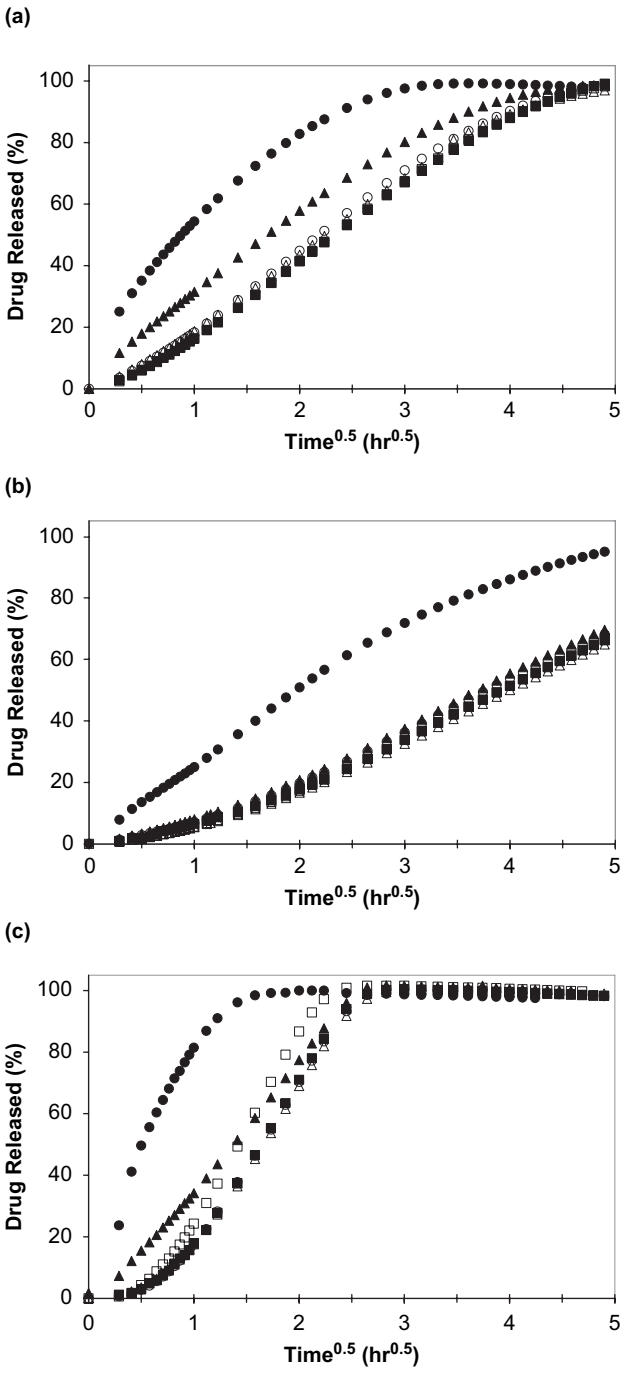


FIGURE 4. Drug release profiles for formulations F4, F5, and F6: (a) F4 – acetaminophen/K100M; (b) F5 – ketoprofen/K4M; (c) F6 – HCTZ/K100 LV. HPMC properties and metrics for each drug release profile are summarized in Table 4.

## Formulations F1, F2, and F3

No substantial change in the extent of drug release (Figure 1) or in the drug release profiles (Figure 3) was observed for formulations F1-F3 over the range of HPMC particle sizes and distributions studied. Drug release was stable even with the coarsest HPMC particles size studied (< 20% through 230 mesh). The drug release profiles for each formulation were very similar over the entire HPMC particle size range studied, with f2 values greater than 70 for each profile (Table 3), indicating less than 5% average difference between each profile

TABLE 3
Experimental HPMC Samples Utilized in Formulations F1, F2, and F3. Values for the Similarity Factor ($f_2$) and Diffusional Exponent of Drug Release (n) for Resulting Drug Release Profiles are also Presented. Symbols Correspond to Drug Release Profiles in Figure 3

| | | HPMC Description | % Through 100 mesh | % Through 230 mesh | D1,0 (μm) | D4,3 (μm) | Viscosity 2% Solution (cps) | $f_2$ | *n* |
|---|---|---|---|---|---|---|---|---|---|
| F1 | ● | 100–200 mesh | 99.7 | 10.6 | 112.0 | 161.3 | 3,943 | 87 | 0.7 |
| F1 | ▲ | >100 mesh (50%) + 270–325 mesh (50%) | 54.9 | 47.0 | 46.7 | 165.0 | 3,221 | 81 | 0.6 |
| F1 | ■ | >100 mesh (50%) + <325 mesh (50%) | 57.1 | 47.3 | 35.2 | 153.4 | 2,750 | 89 | 0.6 |
| F1 | ❍ | unsieved | 92.3 | 55.1 | 46.7 | 115.9 | 3,180 | ref | 0.6 |
| F1 | △ | 270–325 mesh | 99.5 | 99.5 | 44.0 | 60.6 | 2,812 | 89 | 0.6 |
| F1 | □ | <325 mesh | 99.4 | 99.6 | 33.0 | 43.9 | 1,807 | 88 | 0.7 |
| F2 | ● | 100–200 mesh | 99.8 | 14.1 | 98.7 | 147.0 | 3,784 | 71 | 0.6 |
| F2 | ▲ | >100 mesh (50%) + 270–325 mesh (50%) | 58.6 | 48.5 | 43.8 | 162.7 | 3,084 | 97 | 0.7 |
| F2 | ■ | >100 mesh (50%) + <325 mesh (50%) | 57.8 | 49.1 | 34.3 | 165.3 | 2,816 | 97 | 0.7 |
| F2 | ❍ | unsieved | 92.1 | 55.6 | 43.7 | 109.7 | 3,144 | ref | 0.7 |
| F2 | △ | 270–325 mesh | 99.6 | 99.7 | 42.0 | 59.4 | 2,846 | 94 | 0.7 |
| F2 | □ | <325 mesh | 99.5 | 99.7 | 33.6 | 44.8 | 1,881 | 75 | 0.7 |
| F3 | ● | >100 mesh | 28.3 | 4.2 | 57.3 | 243.1 | 21,249 | 86 | 0.6 |
| F3 | ▲ | >100 mesh (50%) + 200–230 mesh (50%) | 64.5 | 51.1 | 55.3 | 173.1 | 19,849 | 96 | 0.7 |
| F3 | ■ | >100 mesh (50%) + <325 mesh (50%) | 65.0 | 51.6 | 34.1 | 110.8 | 14,046 | 83 | 0.7 |
| F3 | ❍ | unsieved | 96.2 | 68.9 | 43.7 | 104.7 | 17,751 | ref | 0.7 |
| F3 | △ | <325 mesh | 99.8 | 99.3 | 34.5 | 47.4 | 9,869 | 83 | 0.7 |
| F3 | □ | 230–270 mesh | 99.7 | 99.6 | 56.6 | 78.2 | 20,447 | 89 | 0.7 |

and the reference profile containing unsieved HPMC (Moore & Flanner, 1996). Calculated values for the diffusional exponent of drug release (*n*) were about 0.6 for F1 and 0.7 for F2 and F3, and were relatively constant over the range of HPMC particle sizes studied indicating no discernable shifts in the drug release mechanism as the particle size of HPMC changed.

### Formulations F4, F5, and F6

Drug release from formulations F4, F5, and F6 was impacted by the HPMC particle size changes in this study, as shown in Figure 2 for a selected time point. These formulations appeared to exhibit the threshold-type of behavior described in the literature where drug release increased markedly if HPMC particle size exceeded some threshold value. In this study, the threshold HPMC particle size for all three formulations appeared to be exceeded when less than 50% of the material passed through a 230 mesh screen. Drug release appeared to be relatively stable when HPMC particle size was smaller than this threshold value. Below this value, f2 values were 50 or less (Table 4), indicating > 10% average difference between each profile and the reference profile containing unsieved HPMC (Moore & Flanner, 1996).

As previously reported by Heng et al. (2001) for an aspirin formulation, the drug release mechanism for formulations F4–F6 appeared to transition from a combination of diffusion and erosion ($0.5 < n < 1$), to diffusion-dominated ($n \sim 0.5$), and then finally to a disintegration mechanism ($n < 0.5$, faster than diffusion) as HPMC particle size increased. Similar transitions can be seen in Figure 4 as well as the $f_2$ and n values summarized in Table 4. The HPMC particle size where the transitions occurred was similar for all three formulations when expressed as the percent passing through a 230 mesh screen (Figure 2). The number-weighted mean particle size ($D1,0 = \Sigma d/n$) of the HPMC sample also correlated well with these transitions, but the volume-weighted mean HPMC particle size ($D4,3 = \Sigma d^4/\Sigma d^3$) did not. Therefore, the D1,0 mean HPMC particle size may be more relevant than D4,3 to sustained drug release performance in matrix tablets. Since the D1,0 value of an HPMC sample is dominated by the number of small particles in the population, this observation is consistent with previous

TABLE 4
Experimental HPMC Samples Utilized in Formulations F4, F5, and F6. Values for the Similarity Factor ($f_2$) and Diffusional Exponent of Drug Release ($n$) for Resulting Drug Release Profiles are also Presented. Symbols Correspond to Drug Release Profiles in Figure 4

| | | HPMC Description | %Through 100 mesh | %Through 230 mesh | D1,0 (μm) | D4,3 (μm) | Viscosity 2% Solution (cps) | $f_2$ | $n$ |
|---|---|---|---|---|---|---|---|---|---|
| F4 | ● | >170 mesh | 84.5 | 9.0 | 82.0 | 177.4 | 142,260 | 27 | 0.3 |
| F4 | ▲ | 100–200 mesh | 99.6 | 32.9 | 66.4 | 131.5 | 122,675 | 50 | 0.4 |
| F4 | ■ | >100 mesh (50%) + < 325 mesh (50%) | 69.5 | 50.6 | 36.2 | 153.2 | 69,895 | 78 | 0.7 |
| F4 | ❍ | unsieved | 96.2 | 68.3 | 44.1 | 100.3 | 81,792 | ref | 0.6 |
| F4 | △ | 200–230 mesh | 100 | 96.2 | 51.2 | 85.6 | 90,417 | 89 | 0.6 |
| F4 | □ | <325 mesh | 99.9 | 99.5 | 34.9 | 50.5 | 43,855 | 79 | 0.7 |
| F5 | ● | 100–200 mesh | 99.6 | 17.2 | 102.3 | 154.9 | 3,848 | 28 | 0.5 |
| F5 | ▲ | >100 mesh (50%) + 270–325 mesh (50%) | 60.5 | 49.4 | 44.1 | 173.8 | 3,090 | 91 | 0.7 |
| F5 | ■ | >100 mesh (50%) + <325 mesh (50%) | 59.6 | 50.3 | 34.1 | 164.1 | 2,655 | 85 | 0.8 |
| F5 | ❍ | unsieved | 93.6 | 57.3 | 45.7 | 117.7 | 3,215 | ref | 0.7 |
| F5 | △ | 270–325 mesh | 99.8 | 99.7 | 42.3 | 59.8 | 2,587 | 76 | 0.8 |
| F5 | □ | <325 mesh | 99.9 | 100 | 42.4 | 59.8 | 2,622 | 82 | 0.8 |
| F6 | ● | >140 mesh | 72.8 | 0.6 | 139.7 | 242.3 | 177 | 16 | |
| F6 | ▲ | 100–200 mesh | 100 | 24.9 | 92.1 | 142.6 | 151 | 45 | 0.6 |
| F6 | ■ | >100 mesh (50%) + <325 mesh (50%) | 62.4 | 50.3 | 32.0 | 161.2 | 105 | 98 | 1 |
| F6 | ❍ | unsieved | 97.5 | 69.5 | 41.2 | 105.0 | 107 | ref | 1 |
| F6 | △ | 200–230 mesh | 100 | 89.0 | 61.0 | 88.0 | 118 | 93 | 1 |
| F6 | □ | <325 mesh | 99.9 | 99.9 | 32.0 | 43.9 | 55 | 52 | 1 |

findings based on HPMC surface area and water uptake studies where it was hypothesized that a sufficient quantity of small HPMC particles was needed in the matrix so that there would be fewer pores and a gel layer could form without water penetrating too far into the matrix (Mitchell et al., 1993b).

### HPMC Particle Size and Molecular Weight

Drug release from the finest particle size fraction (< 325 mesh) in formulation F6 was faster than expected (~70% in Figure 2) and did not have the expected drug release profile (see □, Figure 4c). This variance is believed to be attributable to a lower molecular weight for this HPMC sample since the apparent viscosity of its 2% aqueous solution was only 55 cps. As shown in Tables 3 and 4, when a sample of HPMC powder was separated into particle size fractions by sieving, the solution viscosity of each fraction was not necessarily the same as the original sample. Viscosity shifts of more than ± 50% were observed for extremely fine or extremely coarse particle size fractions. Associated HPMC molecular weight differences may influence drug release and polymer release rates from matrix tablets (Ju et al., 1995a,b). Therefore, it is possible that HPMC particle size and molecular weight effects may be convoluted when altering HPMC particle size by sieving a sample. The influence of HPMC molecular weight is stronger for erosional drug release mechanisms ($n \approx 1$) where drug release scales with the inverse of HPMC molecular weight (Reynolds et al., 1998), which may explain why this variance was observed for formulation F6. Additional studies are needed in this area.

### Formulation Dependence

It is not known why certain formulations exhibited threshold particle size behavior while others appeared to be unaffected by similar changes in HPMC particle size. It is possible that formulations F1, F2, and F3 would have also exhibited threshold behavior if the particle size of HPMC had been increased even further than the ranges used in this study. Mitchell et al. (1993a) reported that matrix swelling and gel layer formation can be affected by the drug contained in the matrix. It seems reasonable that the presence of different drugs and different formulation components, by altering the rate of swelling and gel properties, could influence how well a formulation can tolerate larger HPMC particles, since slower rates of swelling would

allow more time for larger HPMC particles having less surface area to hydrate and effectively participate in gel layer formation. Development of a screening test to measure the relevant drug/polymer/water interactions and predict the relative sensitivity of a formulation to HPMC particle size fluctuations could potentially aid in the development of robust formulations.

## CONCLUSION

For some formulations, the impact of HPMC particle size changes was characterized by faster in vitro drug release and an apparent shift in drug release mechanism when HPMC particle size exceeded a critical threshold value. The threshold for these formulations was exceeded when less than 50% of the HPMC passed through a 230 mesh (63 μm) screen. In vitro drug release from other formulations appeared to be unaffected by HPMC particle size changes; however, the threshold particle size may have been beyond the range studied. When a sample of HPMC powder was separated into particle size fractions by sieving, the solution viscosity of each fraction was not necessarily the same as the original sample. Therefore, particle size and molecular weight effects may be convoluted when altering HPMC particle size by sieving a sample.

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