

Drug Formulation Studies Using a New Grade of Hypromellose Excipient Designed for Direct-Compression, Controlled-Release Applications

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Abstract

A new grade of hypromellose targeted at direct compression tableting was developed. The hypromellose excipient exhibits improved powder flow while retaining the controlled-release performance of hypromellose. The effect of active pharmaceutical ingredient particle size and solubility on tablet properties and controlled-release performance of formulations using the new excipient grade is examined.

Introduction

Hypromellose (HPMC) is a widely used rate-controlling polymer in oral controlled-release (CR) drug delivery applications. It offers flexibility in formulation and function for preparation of oral solid dosage forms. However, its application in direct compression (DC) tableting processes is limited in some cases and complicated in others because of its poor powder flow properties. Recent product development efforts have improved powder flow while maintaining suitable compressibility and CR performance and minimizing segregation. A study was conducted to investigate the performance of this DC grade hypromellose in formulations containing active pharmaceutical ingredients (APIs) with particle sizes ranging from 50 to 400 μm and solubilities ranging from 14 mg/mL to 1000 mg/mL. Control formulations using the CR grade HPMC were tested for comparison.

Experimental

Materials

Active pharmaceutical ingredients included granular acetaminophen (granular APAP), metoprolol tartrate, and naproxen sodium. The particle size and aqueous solubility of each API are listed in Table 1.

Table 1. Properties of active pharmaceutical ingredients.

API	Mean Particle Size (μm)	Solubility in water (mg/mL)
Granular APAP	400	~14
Metoprolol tartrate	160	~1000
Naproxen sodium	50	~200

Rate-controlling excipients included the new DC grade HPMC (METHOCEL™ K4M or K100M Premium DC) and the CR grade HPMC (METHOCEL™ K4M or K100M Premium CR), both from The Dow Chemical

Company. Table 2 lists the properties of the DC grade materials.

Table 2. Properties of DC grade METHOCEL™ products.

Property	K4M Premium DC	K100M Premium DC
Methoxyl ^a (%)	19.0–24.0	19.0–24.0
Hydroxypropyl ^a (%)	7.0–12.0	7.0–12.0
Substitution type	2208	2208
Viscosity (cP)	2663–4970 ^b	72,750–135,800 ^c
Bulk density ^a (g/mL)	0.12–0.15	0.12–0.15
Moisture ^a (%)	5 max	5 max

^aTypical values, not to be construed as sales specifications

^b“Pre-harmonized” range: 3000–5600

^c“Pre-harmonized” range: 75,000–140,000

Methods

The particle properties of each polymer excipient were characterized using a RapidVue 5X image analyzer (Beckman Coulter). Two formulations were prepared for each of three APIs evaluated, one formulation using a DC grade HPMC and one using a CR grade HPMC (Table 3). In each case, the drugs were combined with the HPMC and other excipients in the indicated proportions and V-blended for 10 minutes. Magnesium stearate was then added and blended for one additional minute. Five kilograms of each blend was prepared.

Each blend was evaluated for flow using a commercially available Aeroflow instrument (Amherst Process Instrument Inc., Figure 1). The Aeroflow tester measures the avalanching behavior of a powder blend, which is reported as the mean time to avalanche (MTA). A lower MTA indicates a better flowing powder.

Figure 1. Aeroflow tester.



Tablets (400 mg) were prepared from each blend via direct compression using a 16-station Manesty Beta press. The tablets were evaluated for tablet-to-tablet weight variability, hardness, content uniformity, and drug dissolution properties.

Table 3. Formulations of APIs and excipients (units = wt %).

Ingredient	Formulation		
	Granular APAP	Metoprolol Tartrate	Naproxen Sodium
HPMC K4M (DC or CR)	25	25	—
HPMC K100M (DC or CR)	—	—	30
API	30	10	25
Lactose	34.5	54.5	29.5
Starch	10	10	—
Microcrystalline cellulose	—	—	15
Magesium stearate	0.5	0.5	0.5

Tablet hardness measurements were made using an Ht-300 Hardness Tester (Key International, Inc.). For the granular APAP and metoprolol tartrate formulations, the hardness value is the average of 260 tablets. The naproxen sodium formulation average is based on 180 tablets. Tablet weights were measured using a Mettler Toledo balance.

Content uniformity was determined on the granular APAP and metoprolol formulations by collecting tablets at different time points during each respective tableting run and measuring the API content using an Agilent 1100 Series high-performance liquid chromatograph (HPLC) with UV/Vis detector.

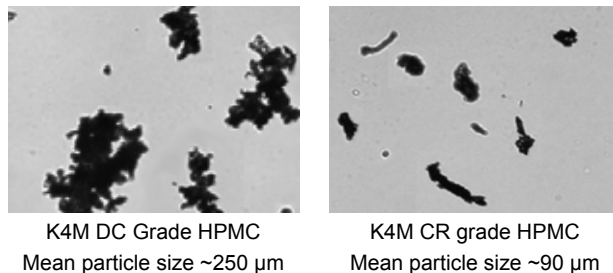
The rate of drug release was measured using six tablets from each formulation. The tablets were dissolved in deionized water using a Varian Total Solution w/Dual VK 7025 dissolution system.

Results and Discussion

HPMC Particle Characterization

Figure 2 shows photomicrographs of the DC and CR grade polymers obtained from the RapidVue image analyzer (photos shown at 2589 x 1940 μm scale). As measured by the RapidVue, the mean particle size of the DC grade HPMC is over two times that of the CR grade HPMC.

Figure 2. Comparison of particle size of DC and CR grades of HPMC.



Flow Characteristics and Tablet-to-Tablet Weight Variability

Table 4 indicates that formulations prepared with DC hypromellose showed improved flow properties vs. those formulations made with CR grade polymer. The MTA results for granular acetaminophen are the same for both formulations. It is likely that the granular APAP (a very free flowing API) dictated the overall flow of the formulation, resulting in similar avalanching behavior regardless of the type of HPMC used in the formulation.

Table 4. Flow characteristics for formulations containing granular acetaminophen, metoprolol tartrate, or naproxen sodium.

API	HPMC Grade	Mean Time to Avalanche (s)	SD
Granular APAP	DC	5.5	0.3
Granular APAP	CR	5.3	0.1
Metoprolol tartrate	DC	5.5	0.3
Metoprolol tartrate	CR	9.1	0.6
Naproxen sodium	DC	5.4	0.1
Naproxen sodium	CR	6.9	0.1

An additional indication of improved flowability of a blend is the free flow of the material through a hopper (3 ft³, with 2.25-inch diameter outlet) and into the press during tableting. For example, the metoprolol tartrate formulation made with DC grade HPMC flowed freely through the hopper. In comparison, the metoprolol tartrate formulation using CR grade HPMC did not flow freely and required external vibration to move material through the hopper outlet and into the press. Consequently, this formulation produced tablets

with higher tablet-to-tablet weight variability since the die cavities were not consistently filled (1). A comparison of the tablet-to-tablet weight variability for the metoprolol tartrate and naproxen sodium formulations is shown in Table 5.

Table 5. Tablet-to-tablet weight variability for formulations containing metoprolol tartrate or naproxen sodium.

Formulation	HPMC Grade	Avg Tablet Weight (mg)	SD
Metoprolol tartrate	DC	401.0	4.1
Metoprolol tartrate	CR	377.8	31.4
Naproxen sodium	DC	401.4	4.2
Naproxen sodium	CR	404.1	6.2

Tablet Hardness

The average hardness values are shown in Table 6. The tablet hardness results are comparable between formulations made with the DC polymer and those made with the CR polymer for a given API. It should be noted that in all cases, the standard deviations are lower for tablets made using the DC grade, further supporting the better flow arguments made in favor of DC hypromellose.

Table 6. Tablet hardness for formulations containing granular acetaminophen, metoprolol tartrate, or naproxen sodium.

API	Avg. Tablet Hardness (kp) [SD]	
	DC HPMC	CR HPMC
Granular APAP	14.7 [0.8]	16.9 [1.4]
Metoprolol tartrate	23.5 [2.4]	25.5 [8.7]
Naproxen sodium	30.1 [1.4]	29.1 [2.1]

Drug Content Uniformity

Drug content uniformity of tablets containing granular acetaminophen (Figure 3) or metoprolol tartrate (Figure 4) was also evaluated. HPLC measurements of tablet drug content through the course of the tableting runs indicate that no significant change in levels of either API was seen using the DC or CR hypromellose. This work indicates that the potential for drug segregation using the larger mean particle size DC polymer is similar to the low potential for segregation that is seen using the CR grade polymer. Both formulations for each API produced tablets within the acceptable limits for content uniformity as described in the USP monographs.

Drug Dissolution

The tablets were also evaluated for CR performance. As shown in Figures 5 through 7, the overlapping dissolution profiles (average of six tablets) indicate that the DC and CR grades of HPMC provide similar levels of CR performance for formulations containing

granular acetaminophen ($f_2 = 85$), metoprolol tartrate ($f_2 = 95$), or naproxen sodium ($f_2 = 80$).

Figure 3. Drug content uniformity for granular acetaminophen formulations.

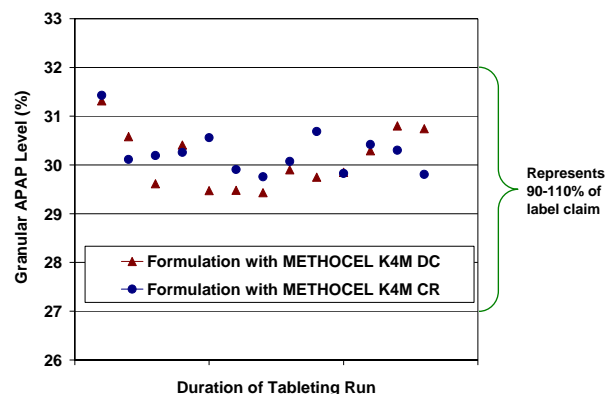


Figure 4. Drug content uniformity for formulations containing metoprolol tartrate.

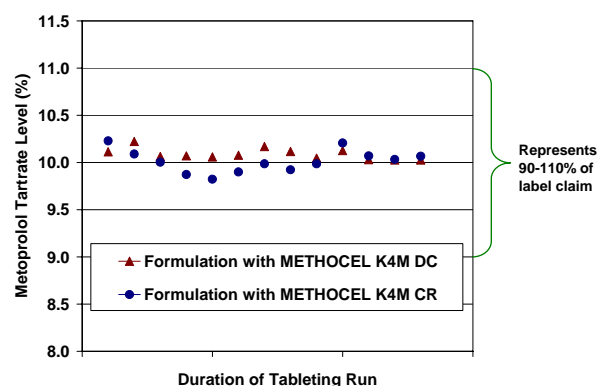


Figure 5. Drug release for formulations containing granular acetaminophen.

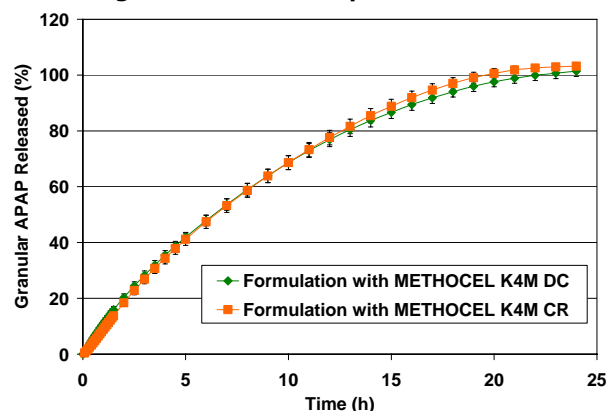


Figure 6. Drug release for formulations containing metoprolol tartrate.

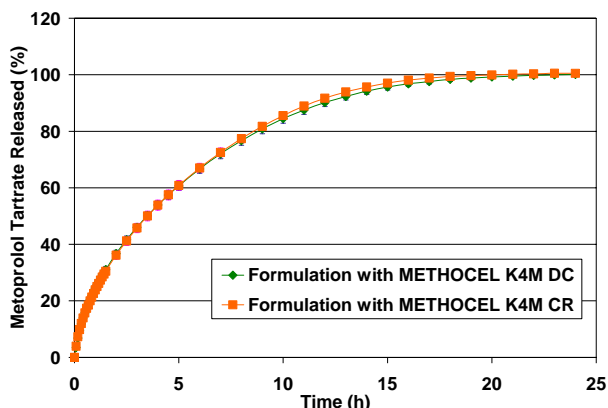
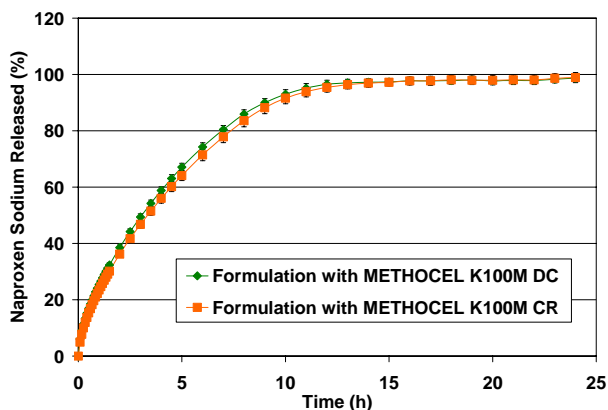


Figure 7. Drug release for formulations containing naproxen sodium.



Conclusions

Based on the results of these experiments, the new DC grade HPMC improved the flow of API formulations while maintaining the controlled-release performance, good tablet hardness, and minimal segregation properties seen in formulations using CR grade HPMC. The improvement in flow was demonstrated by Aeroflow measurements and was observed during the actual tabletting runs as reduction in variability for both tablet weight and tablet hardness. Formulations using a range of API particle sizes and solubilities were evaluated.

References

1. Fan, A., Pallerla, S., Carlson, G., Ladipo, D., Dukich, J., Capella, R., Leung, S. *Am. Pharm. Rev.*, 8(2): 73–78 (2005).

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