

Direct Compression of Sustained-Release Hydrophilic Matrix Tablets Containing Hypromellose and MCC.



Part I: Initial Powder Flow and Tablet Physical Properties with Lactose Filler

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Purpose

Hydrophilic matrix tablets are a common and commercially successful means for prolonged oral drug delivery. Hydrophilic matrix tablets may be compressed directly after powder mixing, or in cases where powder flow is inadequate, from granules prepared by a number of granulation processes. The purpose of this work is to evaluate a new method of characterizing flow properties of dry blends of hypromellose^a, MCC and a water-soluble filler and to determine if the method can be used to predict the performance of such blends in direct compression tablet manufacturing.

Experimental

Materials:

Hypromellose USP substitution type 2208, 4000 cps nominal viscosity (METHOCEL[®] K4M Premium), lot KD23012N13 from The Dow Chemical Company, Midland, MI 48674 USA. Spray-dried lactose monohydrate (FFL) (Fast Flo), lot 8598022762 from Foremost Farms USA, Baraboo, WI 53913 USA. Microcrystalline cellulose (MCC) of five different grades: Emcocel 50M lot E5B8F40; Emcocel 90M lot E9B8F43; Emcocel HD90 lot H9B7C18; Emcocel LP200 lot 258009; and Emcocel SP15 lot SPDFC01, all from Penwest Pharmaceuticals Co., Patterson, NY 12563 USA. Magnesium stearate, lot 2256 KTMV from Mallinkrodt Baker, Paris, KY 40362 USA.

Methods:

Powder mixtures on a weight basis of MCC/FFL, Hypromellose/FFL, and MCC/Hypromellose/FFL were prepared by mixing for eight minutes in a laboratory scale Patterson-Kelly V blender (without intensifier bar). The bulk densities of all the raw materials (except Mg stearate) and mixtures were determined using USP 24 (616) Method I (graduated cylinder method), with the exception that a modified 100 mL cylinder was used. The tapped densities were determined using USP 24 (616) Method I (14 ± 2 mm drop height, 300 drops/minute, 500 taps). In addition, flow properties were recorded using an Aero-Flow powder flowability analyzer (TSI Inc., Amherst, MA). This instrument is based on chaos theory and fractal geometry concepts⁽¹⁾. Powder is placed in a transparent shallow cylindrical drum that rotates at a constant rate. In front of the drum is a light source, behind the drum a photocell array. When the drum has rotated sufficiently, the angle of incline of the powder becomes too great to be supported, resulting in an avalanche, which is sensed by the photocells as a change in voltage. A computer

records the transient voltage signal and calculates the time between avalanches, the mean time between avalanches, and the standard deviation of the time between avalanches. One way of representing the data is to plot ordered pairs of the time for the *n*th avalanche and the (*n* + 1)th avalanche, giving a so-called strange attractor plot. Following lubrication (0.25% w/w Mg stearate for 2 minutes in the V blender), the powder mixes were compressed using 13/32 inch (10.3 mm) F.F.B.E. tooling on an instrumented tablet press at constant final compression force, dwell time and forced feed rate; no precompression force was applied. Tablet physical properties (weight variation, thickness variation, hardness/crushing strength and friability) were determined by conventional methods.

Results and Discussion

Table 1 gives powder properties and the experimental quantities from the Aero-Flow analyzer for the individual excipients and powder mixtures. Selected strange attractor plots for the pure excipients and for a sequence of powder mixtures with a conventional MCC grade are given in Figures 1-11.

Hypromellose is a popular rate-controlling polymer for sustained-release tablets. This is a result of a hydrophilic nature and particle size distribution that enables rapid hydration and gel formation, leading to the establishment of a gel layer that both controls diffusion of water to the interior of the tablet (eliminating tablet disintegration) and regulates drug release. The hypromellose grade used in this study is of similar density to the MCC grades with the exception of the HD90 grade. Compressibility indices (CI) for traditional MCC grades (50M and 90M) are quite similar to those of METHOCEL K4M Premium. This is consistent with the similarity of the particle size distributions as determined by laser light scattering. Given the common cellulose backbones, it is also reasonable to expect similar cohesive energies of the powders. These two facts make it unlikely that hypromellose and MCC would segregate from each other during processing and handling subsequent to dry blending.

Alone, the HD90 grade exhibited unexpectedly poorer flow properties (Fig. 4) as indicated by data from the Aero-Flow instrument, given the relatively favorable CI. However, when mixed with hypromellose and FFL, the HD90 grade was most effective in terms of improving overall flow properties of the mixes. In this case, the effects of density seemed to override the effects of particle size (see Table I, HD90 vs. LP200).

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¹Previously referred to as hydroxypropyl methylcellulose or HPMC.

As expected, apparent flow properties worsened as the percentage of MCC + Hypromellose increased due to particle size effects, density effects and probably MCC/Hypromellose cohesive force effects. For the two MCC grades with the finest particle size distributions, the 10/30/60 mixtures were essentially the same in avalanching behavior as the corresponding 10/20/70 mixtures. However, data from the Aero-Flow analyzer generally indicated better flow properties of mixes than would have been expected based on the CI or Hausner ratio of those mixes, especially at higher total cellulose polymer content.

Regressions of the parameters generated from avalanching behavior vs. CI were performed. A reasonable linear correlation was obtained with the standard deviation of the time between avalanches (see Fig. 12). A similar regression for the mean time between avalanches gave the equation $\text{mean time} = 0.241(\text{CI}) - 0.648$, $R^2 = 0.6315$. The bulk density values of the MCC lots determined in this work, although done carefully, were higher than those reported when a Scott volumeter was used (e.g., 0.25 vs. 0.17 g/cm³ for the SP15 grade). It is expected that improved correlations between compressibility indices and the quantities measured by the Aero-Flow apparatus may be obtained if bulk densities determined by USP 24 (616) Method II were used.

With some grades of MCC (e.g., HD90), linear combinations of the mean time or standard deviation of the individual components, scaled to a volume % basis in the mixture, were predictive of the respective experimental values.

Preliminary experiments with the Aero-Flow apparatus with lubricated powder mixes indicate that the effect of lubrication was small and variable for powder mixes that flowed relatively well, but was much larger and consistently positive (i.e., better flow) for powder mixes that exhibited relatively poor inherent flow.

The operating conditions of the tablet press were kept constant during compression of the 20 powder mixtures, but were not particularly demanding in terms of powder flow requirements. It was observed that there was adequate powder flow when the Emcocel 90M, HD90 and LP200 grades were used, with little change occurring with increase in hypromellose content. However, with Emcocel 50M and especially with SP15, the flow properties from the hopper to the feed frame and from the feed frame to the table and dies were observed to become less and less satisfactory as hypromellose content increased.

Tablet physical properties are given in Table 2. Overall, tablets compressed from the mixtures exhibited excellent hardness. With three of the MCC grades (90M, HD90 and SP15) hardness increased with the percentage of hypromellose, while with the other two grades hardness values were approximately constant across the composition range. At a given ratio of excipients, those with SP15 tended to produce the hardest tablets, whereas those with LP200 tended to produce the softest. Differences in the intrinsic compressibility of MCC grades commonly observed when compressed alone were not fully reflected when these powder mixtures were compressed. Friability values also were very good across the range of compositions, with only six of twenty mixes showing friabilities > 0.1%, and all were less than 0.52%.

Weight and thickness variation were very low, with coefficients of variation predominantly 0.5-0.75%. With Emcocel SP15, however, the variation was slightly higher; for example, the 10/30/60 mixture had weight variation of 1.07 %CV and a thickness variation of 1.04 %CV.

Conclusions

The Aero-Flow apparatus provides reproducible data for ternary mixtures of excipients and may be used as an additional tool in evaluating powder flow of formulas intended for direct compression. Results suggest that the grade of MCC may be an important consideration in the development of robust sustained-release formulations containing hypromellose. When using the conventional grades of MCC and METHOCEL K grade products, the relative amounts may be varied with little or no effect on the overall powder flow. This may be useful in making adjustments to optimize release profiles, for example. The availability of an array of grades of excipients makes it possible that certain combinations will produce powder mixes having flow behavior suitable for direct compression of tablets.

References

1. B.H. Kaye. Characterizing the flowability of a powder using the concepts of fractal geometry and chaos theory. *Part. Part. Syst. Character.* 14:53-66 (1997).

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Figure 1 – METHOCEL K4M Premium

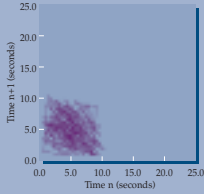


Figure 2 – Fast Flo Lactose 316

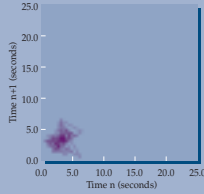


Figure 3 – Emcocel 90M

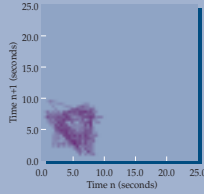


Figure 4 – Emcocel HD90

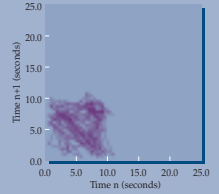


Figure 5 – Emcocel LP200

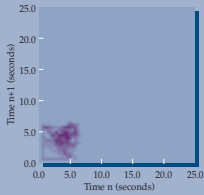


Figure 6 – Emcocel 50M

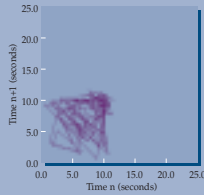


Figure 7 – Emcocel SP15

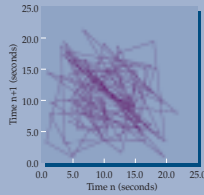


Figure 8

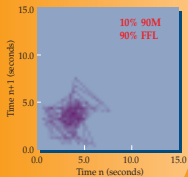


Figure 9

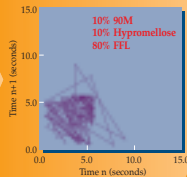


Figure 10

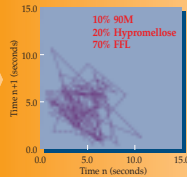


Figure 11

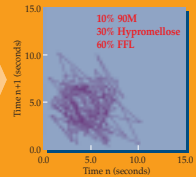


Figure 12 – Correlation of Standard Deviation of Time Between Avalanches and Compressibility Index

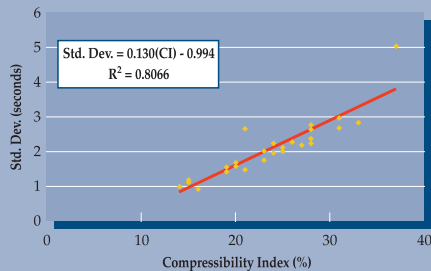


Table 1 – Powder Properties (Unlubricated)

	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Hausner ratio	Compressibility Index (%)	Mean Time Between Avalanches (s)	Std. Dev. of Time Between Avalanches (s)
Hypromellose (METHOCEL K4M Prem.)	0.34	0.49	1.44	31	4.95	2.68
FFL	0.57	0.66	1.16	14	3.25	0.99
Emcocel 90M	0.29	0.39	1.34	26	5.62	2.28
10% MCC/90% FFL (% w/w)	0.53	0.62	1.17	15	3.79	1.11
10% MCC/10% Hypromellose/80% FFL	0.48	0.60	1.25	20	4.00	1.67
10% MCC/20% Hypromellose/70% FFL	0.44	0.59	1.34	25	4.57	2.01
10% MCC/30% Hypromellose/60% FFL	0.41	0.57	1.39	28	4.65	2.23
Emcocel HD90	0.41	0.52	1.27	21	6.14	2.67
10% MCC/90% FFL (% w/w)	0.54	0.64	1.19	16	3.35	0.92
10% MCC/10% Hypromellose/80% FFL	0.50	0.63	1.26	21	3.93	1.48
10% MCC/20% Hypromellose/70% FFL	0.47	0.62	1.32	24	4.15	1.96
10% MCC/30% Hypromellose/60% FFL	0.44	0.60	1.36	27	4.45	2.19
Emcocel LP200	0.34	0.42	1.23	19	3.98	1.41
10% MCC/90% FFL (% w/w)	0.53	0.62	1.17	15	3.79	1.18
10% MCC/10% Hypromellose/80% FFL	0.49	0.61	1.24	20	3.96	1.58
10% MCC/20% Hypromellose/70% FFL	0.46	0.60	1.30	23	4.62	2.01
10% MCC/30% Hypromellose/60% FFL	0.44	0.58	1.32	24	4.65	2.24
Emcocel 50M	0.28	0.39	1.39	28	7.77	2.78
10% MCC/90% FFL (% w/w)	0.51	0.63	1.24	19	4.32	1.56
10% MCC/10% Hypromellose/80% FFL	0.48	0.62	1.29	23	4.61	1.75
10% MCC/20% Hypromellose/70% FFL	0.45	0.60	1.33	25	4.91	2.11
10% MCC/30% Hypromellose/60% FFL	0.42	0.58	1.38	28	4.83	2.37
Emcocel SP15	0.25	0.40	1.59	37	10.50	5.05
10% MCC/90% FFL (% w/w)	0.52	0.72	1.38	28	6.96	2.64
10% MCC/10% Hypromellose/80% FFL	0.49	0.71	1.45	31	7.13	2.98
10% MCC/20% Hypromellose/70% FFL	0.48	0.67	1.40	28	7.55	2.75
10% MCC/30% Hypromellose/60% FFL	0.43	0.64	1.49	33	7.31	2.84

The data provided for these properties are typical values, intended only as guides, and should not be construed as sales specifications.

Table 2 – Tablet Physical Properties

	Ave. Hardness (std. dev.) in SCU	% Friability (6 min.)
Emcocel 90M		
10% MCC/90% FFL (% w/w)	41.8 (2.1)	0.40
10% MCC/10% Hypromellose/80% FFL	45.2 (1.3)	0.52
10% MCC/20% Hypromellose/70% FFL	47.6 (0.9)	0.03
10% MCC/30% Hypromellose/60% FFL	49.1 (1.4)	0.03
Emcocel HD90		
10% MCC/90% FFL (% w/w)	44.0 (1.3)	0.24
10% MCC/10% Hypromellose/80% FFL	45.3 (1.1)	0.36
10% MCC/20% Hypromellose/70% FFL	46.3 (0.9)	0.07
10% MCC/30% Hypromellose/60% FFL	47.6 (1.0)	0.20
Emcocel LP200		
10% MCC/90% FFL (% w/w)	44.9 (1.0)	0.12
10% MCC/10% Hypromellose/80% FFL	42.0 (0.8)	0.06
10% MCC/20% Hypromellose/70% FFL	43.2 (0.8)	0.04
10% MCC/30% Hypromellose/60% FFL	43.5 (0.9)	0.05
Emcocel 50M		
10% MCC/90% FFL (% w/w)	49.2 (2.2)	0.02
10% MCC/10% Hypromellose/80% FFL	47.5 (0.9)	0.01
10% MCC/20% Hypromellose/70% FFL	47.0 (0.8)	0.01
10% MCC/30% Hypromellose/60% FFL	48.1 (0.9)	0.02
Emcocel SP15		
10% MCC/90% FFL (% w/w)	48.4 (1.6)	0.04
10% MCC/10% Hypromellose/80% FFL	49.7 (1.0)	0.03
10% MCC/20% Hypromellose/70% FFL	51.3 (1.0)	0.06
10% MCC/30% Hypromellose/60% FFL	52.7 (1.5)	0.06

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