Direct Compression of Sustained-Release Hydrophilic Matrix Tablets Containing Hypromellose and MCC: Effects of a Lubricant

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Purpose

Preparation of a sustained-release tablet utilizing a matrix of a hydrophilic polymer is a well-established method of achieving prolonged oral drug delivery. The most straightforward and economic manufacturing process is to simply mix dry components and compress into tablets. Because many of the resulting powder mixtures exhibit poor flow properties, an intermediate granulation process may be required. The purpose of this study (the third in a series) is to continue the evaluation of a new method of characterizing flow properties of dry blends of excipients commonly used in hydrophilic matrix tablets with a focus on the effects of a lubricant, and to compare this method with established techniques. The long-term goals of this work are to develop practical ways of characterizing the flow properties of small volumes of powders and to optimize formulations with respect to their ability to be directly compressed.

Methods

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 (SDL) (Fast-Flo lot 8598022762) from Foremost Farms USA, Baraboo, WI 53913 USA. Microcrystalline cellulose (MCC) (Emcocel 50M lot E5B8F40, Emcocel 90M lot E9B8F43, Emcocel HD 90 lot H9B7C18, Emcocel LP 200 lot 2S8009, Emcocel SP15 lot SPD7C01) from Penwest Pharmaceuticals Co., Patterson, NY 12563 USA. Magnesium stearate (Hyqual lot 2256 HTMV) from Mallinckrodt Baker, Paris, KY 40362 USA.

Powder mixtures (w/w) without lubricant were prepared by mixing for eight minutes in a laboratory scale Patterson-Kelly V blender. For lubricated mixtures, magnesium stearate (0.25%) was added to the V blender and mixed for two minutes following the mixing sequence above. The bulk densities of the raw materials and mixtures were determined using USP 24 <616> Method II (Scott volumeter); the reported values are the average of at least three determinations. Tapped densities were determined using USP 24 <616> Method I (500 taps). Flow properties were recorded using an Aero-Flow® powder flowability analyzer. 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 greater than the angle of repose, resulting in an avalanche that is sensed by the photocells as a change in voltage. A computer records the voltage signal and calculates the time between avalanches, the mean time between avalanches (MTBA) and the standard deviation of the time between avalanches (SDTBA). A convenient way of visualizing such data is the "strange attractor diagram." Approximately 100 avalanches occurred during each determination; the reported values for each excipient or mixture are the average of at least three determinations.

Results

Previous studies have examined the physical and apparent flow properties of hypromellose, spray dried lactose, various grades of MCC and silicified MCC (differing in particle size distribution and/or density), and mixtures of these excipients in the presence and absence of a glidant (2,3). In addition, preliminary observations on weight and thickness variation of tablets prepared from some of these mixtures have been made (1). However, the earlier studies did not examine the effects that the magnesium stearate lubricant may have had on the apparent flow properties. In addition, the first study used a simple graduated cylinder to determine the bulk density of the excipients and their mixtures, which was later suspected to overestimate the actual value.

Tables 1 and 2 give the values of bulk and tapped density, compressibility index, and the parameters generated by the Aero-Flow instrument for unlubricated and lubricated mixtures, respectively. Comparison of the bulk densities given in Table 1 with those given in Table 1 of reference 1 reveals that use of a simple graduated cylinder produced values that were typically 10-14% higher than those obtained with the Scott volumeter used in this work. In the case of Emcocel SP15 (a micronized powder), the difference was 35%. This difference in bulk density is reflected in correspondingly higher values of the compressibility index (CI), normally indicative of poorer flow properties. This relatively simple correction is noteworthy because the CI frequently gives an overly optimistic estimation of flow properties. Furthermore, comparisons of corresponding bulk and tapped densities in Tables 1 and 2 show that both of these are affected when 0.25% magnesium stearate is added. Bulk densities increased by 3.4-9.6% and tapped densities increased by 1.0-7.7% with lubrication. In 18 of 20 cases, the CI for the lubricated mixture was less than that of the unlubricated mixture, although not by large margins in most cases. Given the improved precision and accuracy in the determination of the compressibility index, it is expected that lubricated mixes would flow better than the corresponding unlubricated powder mixtures. A reduction in the particle-particle friction caused by the presence of the lubricant apparently leads to improved packing, even in the very low shear environment experienced by the powder mixtures during the determination of the densities. In this sense, the lubricant is acting in a manner similar to that of a glidant (4). These results are in contrast to an earlier study that did not show a change in the CI or flow with the addition of magnesium stearate to a maltodextrin (5).

The results of the avalanching behavior of the powder blends are consistent with that predicted by the compressibility indices. Briefly, powders that flow poorly characteristically have a longer (given by the MTBA) and a more widely variable (given by the SDTBA) time between avalanches than do powders that flow well. For example, see the SDL and Emcocel SP15 entries in Table 1. There is a generally observed trend within a series as the percentage of MCC + hypromellose increases. In 15 of the 20 pairs of powder blends examined, the MTBA for the lubricated blend was less than the unlubricated blend. The SDTBA of lubricated blends also were less than the corresponding unlubricated blends in 15 of 20 cases. In only 3 of 20 blends were both the MTBA and the SDTBA higher in the absence of lubricant; interestingly, all were blends of just MCC and SDL. Figures 1 and 2 are strange attractor diagrams for a corresponding pair of powder mixtures.

The results of correlations between MTBA or SDTBA and the compressibility index were mixed. A quite good linear correlation between SDTBA and CI for the unlubricated powder blends was obtained (Figure 3). A similar correlation between MTBA and CI for the unlubricated blends was fair ($R^2 = 0.7772$). However, correlations between either MTBA or SDTBA and CI for the lubricated blends were poor ($R^2 \cong 0.4$). The reason for the lack of correlation in the case of lubricated blends is unknown at this time.

Conclusion

In dry mixtures of excipients commonly used to prepare sustained-release hydrophilic matrix tablets, a common lubricant was shown to predict improved flow using both conventional methods and a newer method based on chaos theory. While improvements in the flow properties of individual excipients are worthwhile, lubricants and glidants still remain important by influencing the overall flow of multicomponent mixtures. Optimization of flow by controlling particle size distributions, bulk densities, surface properties, etc., of the individual components and by the rational selection of formulation composition to minimize particle-particle cohesion has the potential to minimize the necessity for intermediate granulation processes.

References

1. B.H. Kaye, Part. *Part. Syst. Character.*, **14** (1997) 53-66.
2. T.D. Cabelka and P.J. Sheskey, *AAPS PharmSci*, **1(4)** (1999) #3075.
3. T.D. Cabelka, *Proceed. Int'l. Symp. Control. Rel. Bioact. Matl.*, **27** (2000) # 8432.
4. A. Castellanos, *et al.*, *Phys. Rev. Lett.*, **82** (1999) 1156-1159.
5. M.V. Valasco, *et al.*, *Drug Dev. Ind. Pharm.*, **21** (1995) 2385-2391.

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[†] Previously referred to as hydroxypropyl methylcellulose or HPMC.

***Table 1.** Unlubricated Powder Mixtures*

	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index-CI (%)	Mean Time Between Avalanches-MTBA (s)	Std. Dev. of Time Between Avalanches-SDTBA (s)
HPMC	0.2963	0.496	40.3	4.95	2.68
Spray-dried lactose (SDL)	0.5131	0.661	22.4	3.25	0.99
Emcocel 90M	0.2671	0.387	31.0	5.62	2.28
10% MCC/90% SDL	0.4658	0.617	24.5	3.79	1.11
10% MCC/10% Hypromellose/80% SDL	0.4452	0.604	26.3	4.00	1.67
10% MCC/20% Hypromellose/70% SDL	0.4167	0.590	29.4	4.57	2.01
10% MCC/30% Hypromellose/60% SDL	0.3878	0.568	31.7	4.65	2.23
Emcocel HD90	0.3690	0.520	29.0	6.14	2.67
10% MCC/90% SDL	0.4884	0.637	23.3	3.35	0.92
10% MCC/10% Hypromellose/80% SDL	0.4543	0.629	27.8	3.93	1.48
10% MCC/20% Hypromellose/70% SDL	0.4264	0.617	30.9	4.15	1.96
10% MCC/30% Hypromellose/60% SDL	0.3946	0.597	33.9	4.45	2.19
Emcocel LP200	0.3051	0.424	28.0	3.98	1.41
10% MCC/90% SDL	0.4852	0.621	21.9	3.79	1.18
10% MCC/10% Hypromellose/80% SDL	0.4474	0.613	27.0	3.96	1.58
10% MCC/20% Hypromellose/70% SDL	0.4109	0.599	31.4	4.62	2.01
10% MCC/30% Hypromellose/60% SDL	0.3981	0.584	31.8	4.65	2.24
Emcocel 50M	0.2499	0.396	36.9	7.77	2.78
10% MCC/90% SDL	0.4624	0.626	26.1	4.32	1.56
10% MCC/10% Hypromellose/80% SDL	0.4351	0.617	29.5	4.61	1.75
10% MCC/20% Hypromellose/70% SDL	0.4057	0.598	32.2	4.91	2.11
10% MCC/30% Hypromellose/60% SDL	0.3796	0.580	34.6	4.83	2.37
Emcocel SP15	0.1853	0.394	53.0	10.50	5.05
10% MCC/90% SDL	0.4616	0.717	35.6	6.96	2.64
10% MCC/10% Hypromellose/80% SDL	0.4351	0.705	38.3	7.13	2.98
10% MCC/20% Hypromellose/70% SDL	0.4057	0.670	39.4	7.55	2.75
10% MCC/30% Hypromellose/60% SDL	0.3796	0.643	41.0	7.31	2.84

***Table 2.** Lubricated Powder Mixtures*

	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index-CI (%)	Mean Time Between Avalanches-MTBA (s)	Std. Dev. of Time Between Avalanches-SDTBA (s)
HPMC					
Spray-dried lactose (SDL)					
Emcocel 90M					
10% MCC/89.75% SDL	0.4895	0.656	25.4	3.83	1.58
10% MCC/10% Hypromellose/79.75% SDL	0.4602	0.626	26.5	3.64	1.70
10% MCC/20% Hypromellose/69.75% SDL	0.4327	0.606	28.6	3.44	1.79
10% MCC/30% Hypromellose/59.75% SDL	0.4054	0.586	30.8	3.65	1.69
Emcocel HD90					
10% MCC/89.75% SDL	0.5264	0.675	22.0	3.85	1.70
10% MCC/10% Hypromellose/79.75% SDL	0.4930	0.657	25.0	4.01	1.43
10% MCC/20% Hypromellose/69.75% SDL	0.4568	0.641	28.7	3.38	1.60
10% MCC/30% Hypromellose/59.75% SDL	0.4222	0.609	30.7	3.82	1.70
Emcocel LP200					
10% MCC/89.75% SDL	0.5120	0.643	20.4	3.36	1.65
10% MCC/10% Hypromellose/79.75% SDL	0.4844	0.630	23.1	4.28	1.24
10% MCC/20% Hypromellose/69.75% SDL	0.4443	0.620	28.3	3.96	1.64
10% MCC/30% Hypromellose/59.75% SDL	0.4156	0.601	30.8	3.68	1.78
Emcocel 50M					
10% MCC/89.75% SDL	0.4980	0.666	25.2	4.34	1.85
10% MCC/10% Hypromellose/79.75% SDL	0.4683	0.633	26.0	3.55	1.55
10% MCC/20% Hypromellose/69.75% SDL	0.4355	0.611	28.7	3.53	1.51
10% MCC/30% Hypromellose/59.75% SDL	0.4061	0.586	30.7	3.69	1.69
Emcocel SP15					
10% MCC/89.75% SDL	0.5057	0.765	33.9	6.15	2.31
10% MCC/10% Hypromellose/79.75% SDL	0.4751	0.759	37.4	5.13	1.75
10% MCC/20% Hypromellose/69.75% SDL	0.4399	0.689	36.2	5.43	1.90
10% MCC/30% Hypromellose/59.75% SDL	0.4106	0.662	38.0	5.87	2.26

Figure 1 *- Strange Attractor Diagram – Unlubricated*

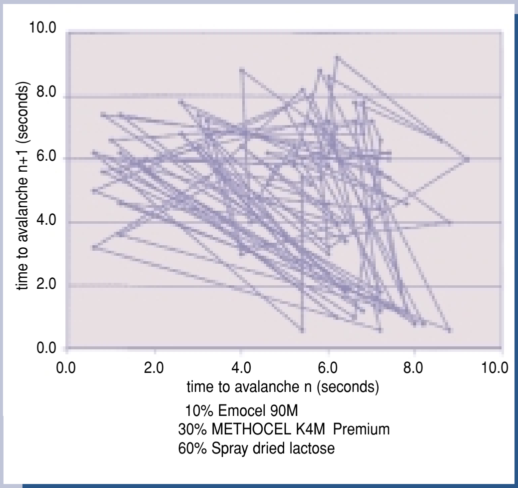


Figure 2 *- Strange Attractor Diagram – Lubricated*

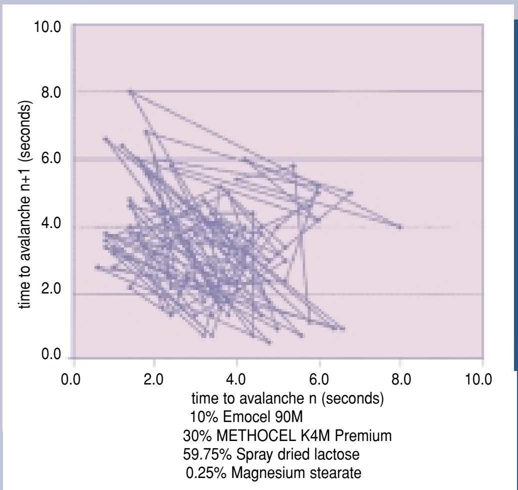
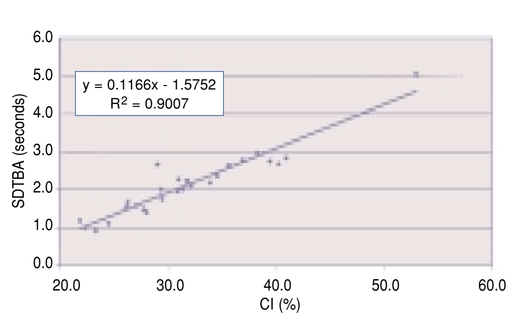


Figure 3 *- Correlation of SDTBA and CI, Unlubricated Powder Mixtures*



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