



Roll Compaction Granulation of a Controlled-Release Matrix Tablet Formulation Containing METHOCEL* K4M Premium

Effect of Process Scale-up on Robustness of Tablets

The use of hydrophilic cellulose ether polymers such as hypromellose[†] in controlled-release (CR) drug compounds has been well documented. Most investigations involved the use of cellulose ethers with direct-compression and wet-granulation technologies.¹⁻⁸ A few studies of cellulose ether polymers were based on roll-compaction techniques.⁹⁻¹⁴

Roll compaction is a dry compaction-granulation process in which uniformly mixed powders are compressed between two counterrotating roll pairs to form a compressed sheet or ribbon that is then milled (granulated). The advantages of roll compaction technology in the pharmaceutical industry include a dry granulation system, high-volume production of granules, and good control of final bulk density and flow properties.¹⁵

A granulation step is sometimes needed to obtain adequate flow properties in CR formulations in which the hypromellose polymer level is more than 20% of the final tablet weight. The formulation must flow evenly on high-speed tablet equipment to maintain uniform weight and drug content in each tablet. Because cellulose ether polymers are hydrophilic, water addition can make wet granulation challenging. Thus, a dry process that creates uniform powder flow and does not interfere with the final physical characteristics and drug release of the tablet could be useful.

Most previous studies of roll compaction and cellulose ethers included laboratory experiments and *in vitro* performance measurements.⁹⁻¹⁴ Scaling up a pharmaceutical roll-compaction process from laboratory equipment to larger equipment can involve several issues and technologies.¹⁶ This supplement summarizes a study involving the scale-up of a model drug formulation containing METHOCEL K4M Premium cellulose ether and the model drug theophylline from laboratory roll-compaction equipment to full-scale production equipment.^{17,18} The supplement discusses the effects of scale-up on granulation and tablet characteristics and performance.

The original study included stability testing and *in vitro/in vivo* correlation (IVIVC). The stability results will be described in a separate supplement. The IVIVC predictions will not be covered in this supplement in light of the fact that *in vivo* testing will be necessary to determine the true bioequivalence between the tablets produced by small- and large-scale equipment.

METHODS

Note: Complete details of materials and methods can be found in the published study.^{17,18}

Tablet Formulation

- CR polymer: METHOCEL K4M Premium, USP (wt % = 30)
- filler excipient: Fast Flo 316 lactose (wt % = 19.75)
- model drug compound: theophylline (wt % = 50)
- lubricant: magnesium stearate (wt % = 0.25)

Roll-Compaction Sequence

Table 1 lists the processing parameters used for the study. Initial testing was conducted in a laboratory-scale roll compactor (model TF-Mini, Vector Corporation) to determine the optimal parameters for the compaction granulation process. These parameters were then scaled directly to a pilot-scale roll compactor (model TF-156, Vector Corporation). The roll speed was scaled such that the linear velocity (74.2 in./min) used for the laboratory compactor was duplicated. This was done to maintain a comparable dwell time of material in the compaction zone. The compaction force was scaled to 5.6 tons; this reproduced the approximate force-per-linear-inch (3.1 tons/inch) of the roll width used with the laboratory compactor. The feed of the theophylline blend was optimized at a screw speed of 5.2 rpm. This established a baseline ratio of screw speed to roll speed of 1.3 (5.2 rpm/4.0 rpm). To determine the effect of compaction dwell time on the quality of the compacted ribbon, the roll speed was first increased by a factor of 2 (8 rpm) in Trials 7 and 8 and later by a factor of 4 (16 rpm) in Trials 9 and 10. This resulted in linear roll velocities of 148.4 and 296.8 in./min, respectively. A ratio of screw speed to roll speed of 1.3 was maintained for these trials.

*Trademark of The Dow Chemical Company

†Previously referred to as hydroxypropyl methylcellulose or HPMC.



Table 1. Processing parameters used for laboratory, pilot-plant, and production equipment.

	Lab-scale trial		Pilot-scale trials							
Trial number	1	2	3	4	5	6	7	8	9	10
Throughput (kg/h)	2	12	12	11	11	11	19	23	45	40
Roll speed (rpm)	6	4	4	4	4	4	8	8	16	16
Linear roll velocity (in./min)	74.2	74.2	74.2	74.2	74.2	74.2	148.4	148.4	296.8	296.8
Screw speed (rpm)	17.9	5.2	5.2	5.2	5.2	5.2	10.4	10.4	20.8	20.8
Screw speed to roll speed ratio	3:01	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1
Roll force (tons)	3	5.6	5.6	5.6	6.6	4.6	5.6	6.6	5.6	6.6
Force per linear inch (tons/in.)	3.1	3.1	3.2	3.2	3.8	2.7	3.2	3.8	3.2	3.8
Milling method	Rotating impeller	Rotating impeller	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar
Granulator screen (mesh, US Standard)	12	12	16	14	14	14	14	14	14	14
Granulator speed (rpm)	500	500	117	117	117	117	117	117	117	117

	Production-scale trials									
Trial number	11	12	13	14	15	16	17	18	19A	19B
Throughput (kg/h)	75	75	75	130	130	135	242	228	228	228
Roll speed (rpm)	4	4	4	8	8	8	18.4	18.4	18.4	18.4
Linear roll velocity (in./min)	148.5	148.5	148.5	297	297	297	683	683	683	683
Screw speed (rpm)	5.2	5.2	5.2	10.4	10.4	10.4	23.4	23.4	23.4	23.4
Screw speed to roll speed ratio	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1
Roll force (tons)	10.8	9.8	11.9	10.8	9.8	11.9	10.8	9.8	11.9	11.9
Force per linear inch (tons/in.)	3.1	2.8	3.4	3.1	2.8	3.4	3.1	2.8	3.4	3.4
Milling method	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar
Granulator screen (mesh, US Standard)	14	14	14	14	14	14	14	14	14	14
Granulator speed (rpm)	87	87	87	87	87	87	87	87	87	87



Scale-up to a production-scale roll compactor (model TF-3012, Vector Corporation) was accomplished using the same methodology used for the pilot-plant compactor. Figure 1 shows the laboratory, pilot-plant, and production roll compactors used in this study. Like the laboratory compactor and the pilot-plant compactor, the production compactor was equipped with concavo-convex compaction rolls and a single-flight feed screw.

Figure 1. Comparison of laboratory, pilot-plant, and production roll-compaction equipment.



Parameters from Trial 7 (roll speed = 8 rpm, screw speed = 10.4 rpm, and roll force = 5.6 tons) were used for the scale-up to the production compactor. It was necessary to use these parameters to meet the minimum screw speed requirement (4 rpm) for the production unit. To achieve the same roll velocity of 148.4 in./min, a roll speed of 4 rpm was used with the production compactor. The roll force was scaled to 10.8 tons, which produced a force-per-linear-inch similar to that used with the pilot-plant compactor (i.e., 3.2 ton/in. roll width).

The screw speed was set at 5.2 rpm to maintain a ratio of screw speed to roll speed of 1.3 (5.2 rpm to 4.0 rpm), equal to that used with the pilot-plant compactor. This ratio provided an adequate delivery of the theophylline blend to the compaction zone. This was in contrast to the scale-up from the laboratory compactor to the pilot-plant compactor, which required an adjustment in the ratio of screw speed to roll speed.

To evaluate the effect of dwell time on the compaction process, the roll speed was increased by a factor of 2 (8 rpm) for Trials 14 through 16 and then by a factor of 4.6 (18.4 rpm) for Trials 17 through 19B. The screw speed was adjusted accordingly for all trials to maintain the ratio of screw speed to roll speed of 1.3. To determine the robustness of the process, low and high compaction pressures were used.

For Trials 12, 15, and 18, the roll force was decreased to 9.8 tons (2.8 tons/in.). For Trials 13, 16, 19A, and 19B, the roll force was increased to 11.9 tons (3.4 tons/in.). After granulation, tablets were prepared according to conventional methods.^{17,18} A target tablet weight of 400 mg \pm 3% was used.

Evaluation of Roll-Compacted Ribbons, Granules, and Tablets

Roll-compacted ribbons were evaluated visually and with scanning electronic microscopy (SEM). The milled granules were analyzed for density, percent compressibility (Carr's or compressibility index, CI), flow, and particle-size distribution.¹⁹

Tablets were tested for friability, thickness, hardness, and drug release according to conventional methods.^{17,18} Drug-release testing of six tablet samples from each variable run was performed using a dissolution system with simulated gastric fluid as the medium for the first hour and pH 6.0 phosphate buffer thereafter.

Drug-Release Profile Testing

Drug-release profiles from each pilot-plant formulation and each production formulation were compared to the laboratory formulation using the equation for the f_2 metric.^{20,21} The value for the f_2 metric is calculated from:

$$f_2 = 50 \log \left\{ 1 + \frac{1}{n} \sum_{t=1}^n w_t (R_t - T_t)^2 \right\}^{-0.5} \times 100$$

where f_2 metric is the similarity factor, and R_t and T_t are the percent drug dissolved at each time point for the test and reference products, respectively. The value for f_2 metric is used to evaluate drug-release profile similarity. Generally, profiles of controlled-release products are deemed similar if $f_2 \geq 50$.²² Product from the laboratory compactor was considered the reference product.

Dissolution samples were taken at very frequent intervals (including every 5 min for first 60 min) until 24 h, for a total of 40 samples. Because an objective of this work was to compare the similarity of drug-release profiles across manufacturing scales, and because f_2 values are dependent on the selection of sample times, three more progressively smaller subsets of all the drug-release data were considered (labeled sets A, B, C, and D). All four data sets were subjected to profile similarity.



RESULTS AND DISCUSSION

Roll-Compacted Ribbon/Granule Testing

Figure 2 shows SEM photographs (500X) of the external surfaces of roll-compacted ribbons manufactured under laboratory, pilot-plant, and production conditions. The five samples were prepared using similar range of force-per-linear-inch of roll width (3.1 to 3.8 tons/inch) but different roll speeds (dwell time). The Trial 1 sample (laboratory) (Figure 2a) showed the smoothest surface of the samples tested. There were a few small cracks and voids. This sample displayed a relatively clean fractured surface. The Trial 4 sample (pilot plant, 4 rpm roll speed) (Figure 2b) displayed a slightly rougher surface than that shown in Trial 1. There were more small cracks and voids present on the sample surface. The Trial 8 sample (pilot plant, 8 rpm) (Figure 2c) showed a considerably rougher surface than the previous two samples. Cracks and voids of increasing number and size were observed. Numerous voids contained what appeared to be fibers and fiber debris. Some loose material was also observed on the surface of the cross-section. The Trial 10 sample (pilot plant, 16 rpm) (Figure 2d) showed large, clearly visible cracks and voids. Loose material was observed in the cracks and voids. The Trial 19B sample (production, 18.4 rpm) (Figure 2e) showed cracks and voids similar to the Trial 10 sample.

The Trial 10 sample (pilot plant) and the Trial 19B sample (production) were manufactured using similar roll speeds (16 rpm and 18.4 rpm) and similar roll force-per-linear-inch of roll width (3.8 tons/in. and 3.4 tons/in.), respectively. The range of thickness values of the roll-compacted ribbons were as follows: laboratory compactor 0.048 to 0.50 in., pilot-plant compactor 0.065 to 0.072 in., and production compactor 0.78 to 0.118 in. The physical characteristics of the ribbon surfaces appeared to be related to the relative pressure applied to the powders during the compaction process.

Visual observation of the compacted ribbons showed that the edges or borders of the ribbons were broken and not perfectly uniform in appearance. This is typical of ribbons generated on a roll compactor even though there is a rather even force applied across the roll face. Powders with poor flow properties are fed to the nip region of the roll pair by an auger system which may not be as consistent as, for instance, a powder feed system used on a tablet press. Another factor that can result in rough-edged ribbons is powder adhesion to the roll surfaces. This is why powder lubricants and anti-adherents such as magnesium stearate and talc are typically incorporated in powder mixes used in roll compaction. The idea, similar to tablet tooling, is to provide lubrication between moving equipment parts and powders and to minimize powder sticking (adhering) to the roll pair.

Figure 2. SEM photographs (500X) of the external surfaces of roll-compacted ribbons of a model drug formulation manufactured under laboratory, pilot-plant, and production conditions. Results are from (a) Trial 1, (b) Trial 4, (c) Trial 8, (d) Trial 10, and (e) Trial 19B.

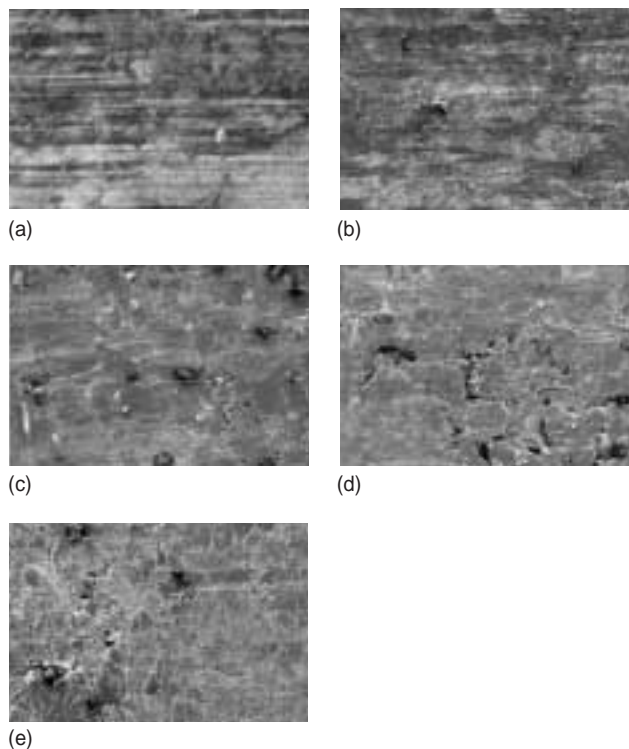




Table 2 lists the properties for the original formulation (uncompressed) and the granules from the milled, roll-compacted formulations. Figure 3 shows representative particle-size distributions (PSD) from the same milled roll compaction formulations. In general, granulations produced using the production compactor exhibited a reduction in the bulk density and an increase in the compressibility index (CI) as compared to those produced using the laboratory compactor or pilot-plant compactor. The average bulk density for the pilot-plant trials was 0.550 g/cm³ compared to 0.528 g/cm³ for the production trials. This decrease in bulk density may be due to an increase in the percentage of fines present in the granulations. The increased level of fines may have also contributed to the increase in the CI value due to a

slight reduction in the flowability of the granulations. The production trials produced an average of 32.7% particles finer than 100 mesh compared to only 23.0% for the pilot-plant trials and 19.0% for the laboratory trials. These fines were generated during the milling process and may have been due to a longer retention time inside the mill. An increased retention time may be explained by the increased volume of compacted ribbons within the mill due to the higher production rate.

Tablet Property Testing

Table 3 shows the physical properties of the tablets produced from the ANDA product, direct compression, and the milled, roll-compacted samples. Tablet friability values usually relate

Table 2. Summary of physical testing of original mix and granulations.

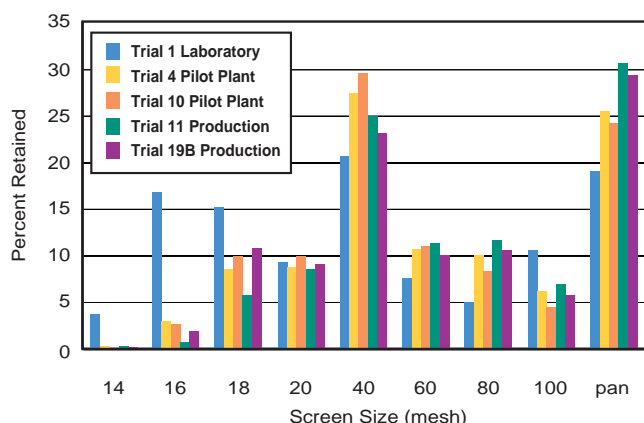
Trial Description	Bulk Density (g/cm ³)	Tap Density (g/cm ³)	Compressibility Index (%)
<i>ANDA Rx product</i>	na	na	na
<i>Original Mix</i>	0.420	0.645	36
<i>Laboratory trial</i>			
Trial 1	0.610	0.802	24
<i>Pilot-plant trials</i>			
Trial 2	0.617	0.730	15
Trial 3	0.516	0.697	26
Trial 4	0.536	0.705	24
Trial 5	0.546	0.683	20
Trial 6	0.528	0.695	24
Trial 7	0.539	0.690	22
Trial 8	0.558	0.735	24
Trial 9	0.558	0.715	22
Trial 10	0.556	0.713	22
<i>Production trials</i>			
Trial 11	0.539	0.745	28
Trial 12	0.535	0.746	28
Trial 13	0.531	0.757	30
Trial 14	0.525	0.748	30
Trial 15	0.517	0.727	29
Trial 16	0.533	0.741	28
Trial 17	0.525	0.735	29
Trial 18	0.531	0.743	28
Trial 19A	0.526	0.741	29
Trial 19B	0.534	0.751	28

Table 3. Summary of tablet physical testing results.

Trial Description	Ave. Tablet Crushing Strength (scu, sd)	Ave. Tablet Thickness (inches)	Ave. Tablet Weight (mg, sd)
<i>ANDA Rx product</i>	16.7, 1.6	0.232	390.0, 3.0
<i>Original Mix</i>	36.1, 2.5	0.229	401.1, 5.3
<i>Laboratory trial</i>			
Trial 1	24.3, 2.6	0.227	401.5, 8.3
<i>Pilot-plant trials</i>			
Trial 2	25.1, 2.2	0.229	402.1, 6.6
Trial 3	26.1, 2.2	0.229	403.1, 3.3
Trial 4	28.9, 2.0	0.229	404.8, 9.3
Trial 5	28.5, 2.1	0.228	404.1, 3.8
Trial 6	29.7, 1.9	0.229	402.9, 4.1
Trial 7	28.9, 1.9	0.227	397.5, 7.8
Trial 8	27.7, 1.7	0.229	402.9, 4.1
Trial 9	28.9, 1.6	0.227	398.8, 3.6
Trial 10	26.7, 1.6	0.228	400.8, 4.4
<i>Production trials</i>			
Trial 11	29.7, 1.6	0.225	400.1, 3.6
Trial 12	30.6, 1.4	0.223	401.1, 2.4
Trial 13	29.5, 1.9	0.225	402.5, 3.8
Trial 14	31.1, 1.4	0.227	400.9, 2.4
Trial 15	30.4, 1.1	0.227	399.9, 3.1
Trial 16	28.4, 1.8	0.225	400.3, 4.0
Trial 17	31.2, 1.4	0.224	401.5, 3.6
Trial 18	30.7, 1.2	0.224	401.5, 2.6
Trial 19A	31.4, 1.3	0.223	400.3, 3.1
Trial 19B	30.3, 1.8	0.228	400.0, 3.6



Figure 3. Particle-size distribution of granulations prepared at laboratory, pilot-plant, and production conditions.



to tablet hardness (crushing strength) values in that the lower the hardness value, the higher the friability value. The friability of all samples was less than 1% (data not shown). This means that all tablets exhibited acceptable tablet physical characteristics. All tablets exhibited strong physical properties with very little chipping and no breaking. The tablets showed no physical defects such as capping or lamination.

All of the samples had a weight variation of 1.2% or less of the 400 mg ideal tablet weight. This is well within USP guidelines. All tablets made with roll compaction showed higher hardness values compared to the ANDA product and lower hardness than tablets made by direct compression. Tablets manufactured using the laboratory compactor (Trial 1) had an average crushing strength value of 24.3 scu. Tablets manufactured using the pilot-plant compactor (Trials 2-10) had an average crushing strength range of 25.1 scu (Trial 2) to 29.7 scu (Trial 6). Tablets manufactured from granulations from the production compactor (Trials 11-19B) had an average crushing strength range of 29.7 scu (Trial 11) to 31.4 scu (Trial 19A).

Drug-Release Profile Testing

Drug-release profiles from laboratory and pilot-plant formulations are illustrated in Figure 4. Drug-release profiles from production formulations are illustrated in Figure 5. The production formulations were more rapidly releasing, compared to the laboratory formulation.

Table 4 lists the f_2 values in the comparison of drug-release profiles from pilot-plant and production trials to drug-release profiles from the laboratory trials. In the comparison of pilot-plant trials to laboratory trials, f_2 was always large (> 80), regardless whether data set A, B, C, or D was used. Set A was composed of all 40 of the original dissolution time points, with sets B, C, and D having progressively fewer points included. Interestingly, f_2 values for the comparison of each production trial to the laboratory trial were approximately 50. A value of 50 is generally deemed the lower limit for similarity.

These results emphasize that, in the context of f_2 , pilot-plant formulations were similar to the laboratory formulation. Meanwhile, production compactor formulations yielded f_2 values of about 50. The exact value was either higher or lower than 50, depending upon the selection of profile time points. Elimination of early time points reduced f_2 values, since early time points were most similar, while elimination of late time points increased f_2 values. These circumstances are opposite to those often found with immediate release (IR), where f_2 is often increased when early points are deleted and late points retained due to larger differences early and smaller differences late in IR profiles, e.g., at complete release.

CONCLUSIONS

All tablets, regardless of equipment scale, exhibited acceptable physical characteristics. No physical defects such as capping or lamination were observed. Tablet crushing strength increased from laboratory through pilot-plant to production trials.

Table 4. f_2 Values in comparing each formulation to the laboratory formulation.

Dissolution Data Set	Pilot-plant trials			Production trials	
	Trial 4	Trial 10	Trial 12	Trial 14	Trial 19B
A	86.5	84.8	54.9	54.0	52.8
B	84.2	82.2	50.5	50.5	49.4
C	87.6	82.6	55.2	54.3	53.1
D	83.3	81.2	49.8	49.1	48.0



Figure 4. Drug-release profile from laboratory and pilot-plant formulations.

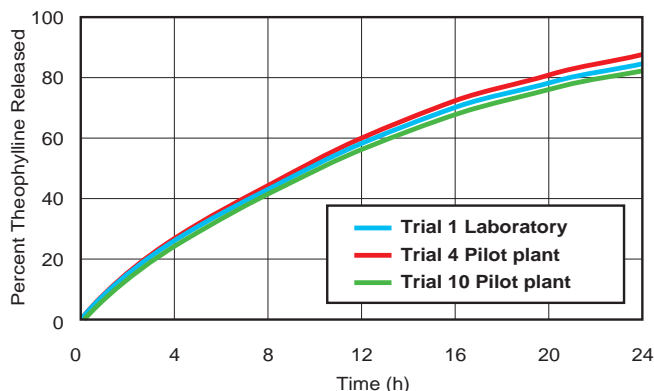
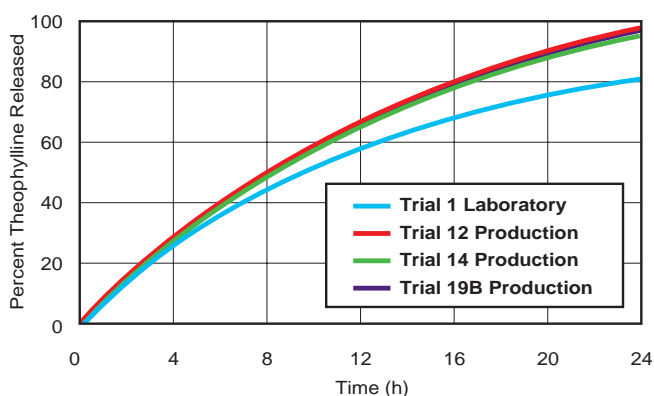


Figure 5. Drug-release profile from laboratory and production formulations.



For the pilot-scale trials, f_2 was always large (>80), indicating similarity to results from the laboratory trials. Samples from the production trials showed faster drug release than those from the laboratory trials. The values for f_2 were usually about 50 for the production-scale trials, which is generally deemed the lower limit for similarity. *In vivo* testing will be necessary to determine the true bioequivalence between the tablets produced by small- and large-scale equipment. Nevertheless, roll compaction using METHOCCEL K4MP was easily scaled from the laboratory to full scale.

REFERENCES

Note: Although the official monograph name of “hydroxypropyl methylcellulose” (“HPMC”) has been changed to “hypromellose”, reference listings here continue to use the prior nomenclature to facilitate reference to existing publications in libraries and other information retrieval systems.

¹ D.A. Alderman, “A Review of Cellulose Ethers in Hydrophilic Matrices for Oral Controlled-Release Dosage Forms,” *Int. J. Pharm. Tech. & Prod. Mfg.* **5** (3), 1-9 (1984).

- J.L. Ford et al., “Importance of Drug Type, Tablet Shape, and Added Diluents on Drug Release Kinetics from Hydroxypropyl Methylcellulose Matrix Tablets,” *Int. J. Pharm.* **40**, 223-234 (1987).
- C.D. Melia, “Hydrophilic Sustained Release Systems Based on Polysaccharide Carriers,” *Crit. Rev. in Therap. Drug Carrier Systems* **8** (4), 395-421 (1991).
- P. Timmins et al., “Evaluation of the Granulation of a Hydrophilic Matrix Sustained-Release Tablet,” *Drug Dev. Ind. Pharm.* **17** (4), 531-550 (1991).
- T.C. Dahl and A.P. Bormeth, “Naproxen Controlled-Release Matrix Tablets: Fluid-Bed Granulation Feasibility,” *Drug Dev. Ind. Pharm.* **16** (4), 581-590 (1990).
- T.D. Reynolds et al., “Polymer Erosion and Drug-Release Characterization of Hydroxypropyl Methylcellulose Matrices,” *J. Pharm. Sci.* **87** (9), 1115-1123 (1998).
- P.J. Sheskey and D.M. Williams, “Comparison of Low-Shear and High-Shear Wet-Granulation Techniques and the Influence of Percent Water Addition in the Preparation of a Controlled-Release Matrix Tablet Containing HPMC and a High-Dose, Highly Water-Soluble Drug,” *Pharm. Technol.* **20** (3), 80-92 (1996).
- L.W.S. Cheong, P.W.S. Heng, and L.F. Wong, “Relationship between Polymer Viscosity and Drug Release from a Matrix System,” *Pharm. Res.* **9** (11), 1510-1514 (1992).
- P.J. Sheskey et al., “Use of Roller Compaction in the Preparation of Controlled-Release Hydrophilic Matrix Tablets Containing Methylcellulose and Hydroxypropyl Methylcellulose Polymers,” *Pharm. Technol.* **18** (9), 132-150 (1994).
- M.A. Murray, “Effect of Formulation and Roller Compactor Processing Variables on Granule and Tablet Characteristics,” PhD Dissertation, Univ. of Cincinnati (1997).
- J.P. Remon, “Attempts to Model the Roller Compaction Process and Development of a New Method to Improve Product Quality,” *1998 AAPS Annual Meeting Abstracts* **1** (1), S-127 (1998).
- P.J. Sheskey and T.P. Dasbach, “Evaluation of Various Polymers as Dry Binders in the Preparation of an Immediate-Release Tablet Formulation by Roller Compaction,” *Pharm. Technol.* **19** (10), 98-112 (1995).
- P.J. Sheskey and J. Hendren, “The Effects of Roll Compaction Equipment Variables, Granulation Technique, and HPMC Polymer Level on a Controlled-Release Matrix Model Drug Formulation,” *Pharm. Technol.* **23** (3), 90-106 (1999).
- T.L.D. Rogers, “Content Considerations for Low Dose Drug Formulations Processed by Roller Compaction,” PhD Dissertation, Purdue University (1997).
- G.E. Peck, “Principles of Tablet Granulation,” in *Proceedings of Tablet Manufacturing '93* (Medical Manufacturing TechSource, Inc., Ann Arbor, MI, 1993), pp. 240-265.
- R.W. Miller, “Roller Compaction Technology,” in *Handbook of Pharmaceutical Granulation Technology*, D.M. Parikh, Ed. (Marcel Dekker, Inc., New York, 1997), pp. 99-150.
- Sheskey, P., Sackett, G., Maher, L., Lentz, K., Tolle, S., Polli, J., “Roll Compaction Granulation of a Controlled-Release Matrix Tablet Formulation Containing HPMC: Effect of Process Scale-up on Robustness of Tablets and Predicted In Vivo Performance,” *Pharm. Technol. Tableting & Granulation Yearbook* 6-21 (1999).
- Sheskey, P., Pacholke, K., Sackett, K., Maher, L., Polli, J., “Roll Compaction Granulation of a Controlled-Release Matrix Tablet Formulation Containing HPMC: Effect of Process Scale-Up on Robustness of Tablets, Tablet Stability, and Predicted In Vivo Performance,” *Pharm. Technol.* **24** (11), 30-52 (2000).
- R.L. Carr, “Evaluating Flow Properties of Powders,” *Chem. Eng.* **72**, 163 (1965).
- J.W. Moore and H.H. Flanner, “Mathematical Comparison of Dissolution Profiles,” *Pharm. Technol.* **20** (6), 64-74 (1996).
- J.E. Polli et al., “Methods to Compare Dissolution Profiles and a Rationale for Wide Dissolution Specifications for Metoprolol Tartrate Tablets,” *J. Pharm. Sci.* **86** (6), 690-700 (1997).
- FDA, “SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation,” Center for Drug Evaluation and Research (October 1997).

**For more information, complete literature, and product samples,
you can reach a Dow representative at the following numbers:**

From the United States and Canada:call 1-800-447-4369
.....fax 1-989-832-1465

In Europe:toll-free +800 3 694 6367†
.....call +32 3 450 2240
.....fax +32 3 450 2815

From Latin America and Other Global Areas:call 1-989-832-1560
.....fax 1-989-832-1465

†Toll free from Austria (00), Belgium (00), Denmark (00), Finland (990), France (00), Germany (00), Hungary (00), Ireland (00), Italy (00), The Netherlands (00), Norway (00), Portugal (00), Spain (00), Sweden (00), Switzerland (00), and the United Kingdom (00).

Or you can contact us on the Internet at
www.methocel.com

NOTICE: No freedom from any patent owned by Seller or others is to be inferred. Because use conditions and applicable laws may differ from one location to another and may change with time, Customer is responsible for determining whether products and the information in this document are appropriate for Customer's use and for ensuring that Customer's workplace and disposal practices are in compliance with applicable laws and other governmental enactments. Seller assumes no obligation or liability for the information in this document. NO WARRANTIES ARE GIVEN; ALL IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE ARE EXPRESSLY EXCLUDED.

