



Stability of Physical Properties and Drug Release of Controlled-Release Matrix Tablet Formulations Containing METHOCEL Cellulose Ethers

Many years of commercial experience indicate that the physical properties and drug release of controlled-release (CR) tablets containing METHOCEL* cellulose ethers have excellent long-term stability. Several studies have confirmed this observation. Liu et al. examined the effect of storage time at elevated temperature on tablets containing mixtures of diclofenac sodium and hypromellose[†] USP 2910 combined with 1% silicon dioxide and 0.5% magnesium stearate.¹ The mixtures were

- 50/50 diclofenac sodium/4000 mPa·s hypromellose
- 50/37.5/12.5 diclofenac sodium/4000 mPa·s hypromellose/50 mPa·s hypromellose
- 50/25/25 diclofenac sodium/4000 mPa·s hypromellose/50 mPa·s hypromellose
- 50/12.5/37.5 diclofenac sodium/4000 mPa·s hypromellose/50 mPa·s hypromellose
- 50/50 diclofenac sodium/50 mPa·s hypromellose

Tablets were prepared using wet granulation; target tablet weight was 750 mg. Tablets were stored in amber bottles. No further details were given on containers used or number of tablets per container. Storage conditions were 1, 2, and 3 months at ambient temperature, 31, 37, and 43°C. Humidity was 75% for all temperature conditions

Table 1. Effect of storage time and conditions on drug degradation of hydrophilic matrix tablets containing alprolazam and METHOCEL K100P LV.

(45% METHOCEL K100P LV, 2.5% alprolazam, 20% microcrystalline cellulose, 31.5% lactose, 0.5% silicon dioxide, and 0.5% magnesium stearate)

Stability Sample (Time, Condition)	Composite Assay (mg)	Similarity Factor (f_2)
Initial	101.04	ref
<i>Ambient (25°C/60% RH)</i>		
3 months	100.15	83
6 months	102.75	94
12 months	100.21	85
<i>Accelerated (40°C/75% RH)</i>		
1 month	100.11	93
2 months	100.35	88
3 months	101.10	89
6 months	103.57	84

except ambient. The authors found that none of the five formulations showed a significant effect of storage time or temperature on drug degradation or dissolution.

A study conducted by Professor R.O. (Bill) Williams III, University of Texas at Austin, investigated the effect of storage time, temperature, and humidity on drug degradation and dissolution of matrix tablets containing alprolazam and either METHOCEL K100 LV or METHOCEL K4M. The formulation containing METHOCEL K100 LV included 45% METHOCEL K100 LV, 2.5% alprolazam, 20% microcrystalline cellulose, 31.5% lactose, 0.5% silicon dioxide, and 0.5% magnesium stearate. The formulation containing METHOCEL K4M included 37% METHOCEL K4M, 2.5% alprolazam, 20% microcrystalline cellulose, 39.5% lactose, 0.5% silicon dioxide, and 0.5% magnesium stearate. Tablets were prepared by direct compression; target tablet weight was 400 mg. The tablets were placed in 60-mL, white, high-density polypropylene (HDPE) bottles. Each bottle contained 80 tablets. Storage conditions were 25°C at 60% RH and 40°C at 75% RH.

Tables 1 and 2 show the effects of up to 12 months storage on drug assay and hardness. As shown by similarity factors

Table 2. Effect of storage time and conditions on drug degradation of hydrophilic matrix tablets containing alprolazam and METHOCEL K4MP.

(37% METHOCEL K4MP, 2.5% alprolazam, 20% microcrystalline cellulose, 39.5% lactose, 0.5% silicon dioxide, and 0.5% magnesium stearate)

Stability Sample (Time, Condition)	Composite Assay (mg)	Similarity Factor (f_2)
Initial	105.58	ref
<i>Ambient (25°C/60% RH)</i>		
3 months	102.01	84
6 months	103.15	96
12 months	105.09	81
<i>Accelerated (40°C/75% RH)</i>		
1 month	105.56	91
2 months	101.35	75
3 months	102.14	81
6 months	102.58	81

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



greater than 50, there was no significant effect of storage time or conditions on assay. Figures 1 and 2 give the results from drug dissolution testing for up to 12 months of storage. Storage time and conditions did not appear to affect drug dissolution in these formulations.

Figure 1. Effect of storage time, temperature, and humidity on drug dissolution of hydrophilic matrix tablets containing alprolazam and METHOCEL K100P LV. (45% METHOCEL K100P LV, 2.5% alprolazam, 20% microcrystalline cellulose, 31.5% lactose, 0.5% silicon dioxide, 0.5% magnesium stearate)

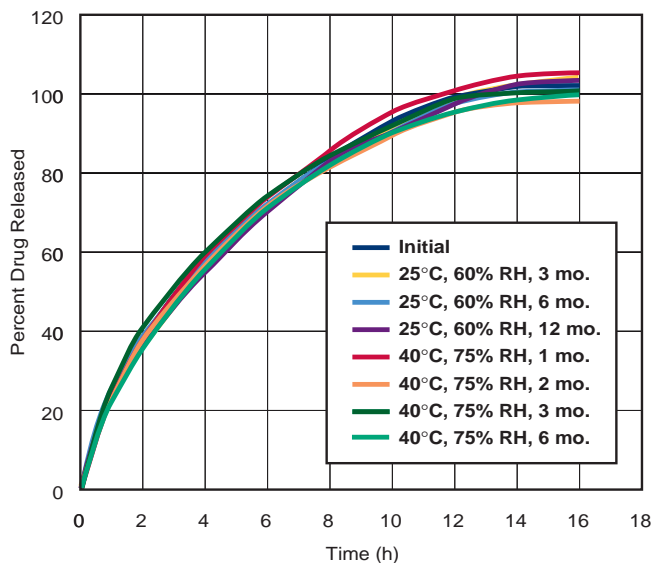


Figure 2. Effect of storage time, temperature, and humidity on drug dissolution of hydrophilic matrix tablets containing alprolazam and METHOCEL K4MP. (37% METHOCEL K4MP, 2.5% alprolazam, 20% microcrystalline cellulose, 31.5% lactose, 0.5 silicon dioxide, 0.5% magnesium stearate)

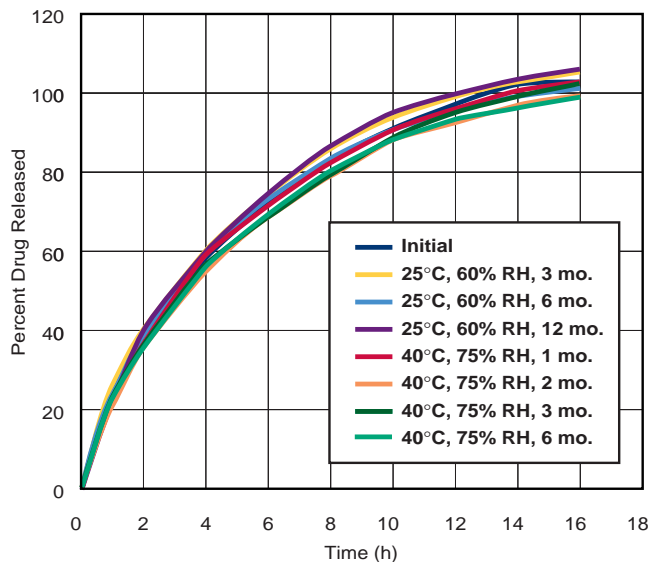
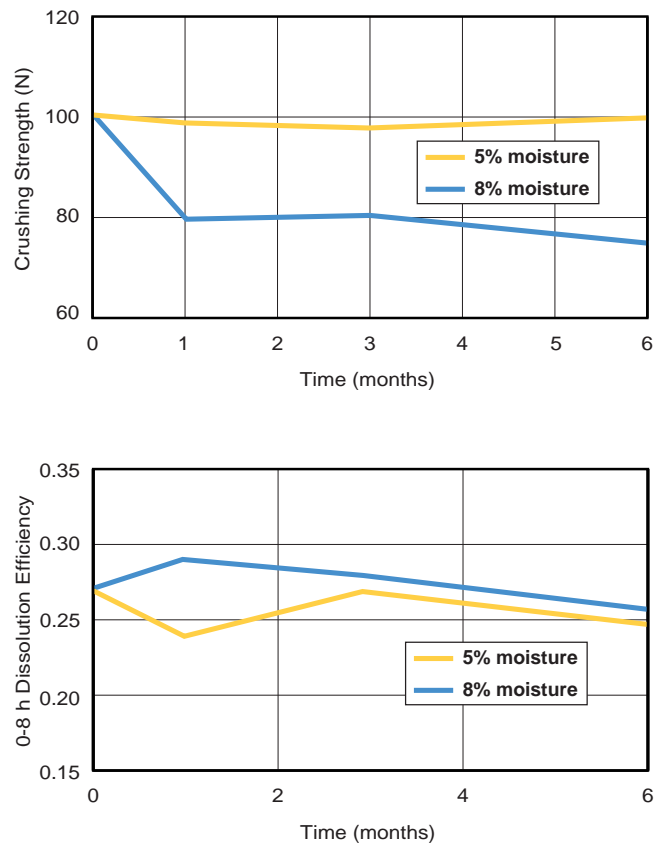


Figure 3. Effect of storage time and humidity on selected physical properties and drug dissolution of hydrophilic matrix tablets containing hydrochlorothiazide and METHOCEL K4MP. (87% METHOCEL K4MP, 12.5% hydrochlorothiazide, 0.5% magnesium stearate)



Mosquera et al. examined the effects of storage time and humidity on the physical properties and drug release of hydrophilic matrix tablets containing the model drug hydrochlorothiazide and either METHOCEL K4MP or METHOCEL K100MP.² The formulation included 87% METHOCEL K4MP or K100MP, 12.5% hydrochlorothiazide, and 0.5% magnesium stearate. Tablets were prepared using direct compression; tablet weight was adjusted to 200 mg. Tablets were stored for 1, 3, and 6 months at 20°C in air-tight boxes. According to the authors, the boxes contained reservoirs of sulfuric acid at the dilution required to establish relative humidity such that the equilibrium moisture content of the METHOCEL product was 5% or 8%. The lower humidity corresponded to the prestorage equilibrium moisture content of the cellulose ethers. We would interpret the actual relative humidity to be roughly 35-40% and 50-55%, respectively.



Figure 3 shows representative data. The results for K4MP and K100MP were similar. Drug release was not significantly affected by storage time. In addition, storage at the lower relative humidity had no significant effect on tablet properties. However, storage at the higher humidity resulted in reductions in crushing strength and increases in total porosity and mean pore diameter. Most changes occurred within 1 month of storage. The authors concluded that storage of hypromellose-based tablets for 6 months at 20°C has no significant effect on physical properties unless storage humidity is such that the tablets absorb a significant amount of water. Drug release, as measured by the fraction of the area under the dissolution curve between 0 and 8 h relative to the total area under the curve, was not significantly affected by storage time or humidity.

A study involving CR tablets containing theophylline as the model drug and METHOCEL K4MP CR cellulose ether examined the effects of process scale-up, storage time, temperature, and humidity on the stability of physical properties and drug release.³ The formulation included 30%

METHOCEL K4MP CR, 50% theophylline, 19.75% lactose, and 0.25% magnesium stearate. Tablets were prepared from laboratory, pilot-plant, and full-scale granulations using roll compaction. Target tablet weight was 400 mg. Tablets were stored in 60-mL, opaque, polypropylene (PP) bottles, 60 tablets per bottle. Stability was evaluated under ambient conditions (21°C/50% relative humidity) and accelerated conditions (40°C/75% relative humidity). The testing intervals were 1, 2, 3, 6, 9, and 12 months.

Table 3 shows the results of 12-month stability testing on the physical properties of production-scale samples. Tablets stored under ambient conditions showed little change in tablet crushing strength, tablet thickness, and tablet weight over the 12-month period. Tablets stored under accelerated conditions showed a slight lowering of tablet crushing strength values during the same 12-month period. However, tablet thickness and tablet weight values showed only minor differences. No correlation was observed between slight reductions in tablet crushing strength values under accelerated conditions and tablet thickness and tablet weight. Similar results were seen

Table 3. Effect of storage time and conditions on physical properties of hydrophilic matrix tablets containing theophylline and METHOCEL K4MP CR (production scale).

(30% METHOCEL K4MP CR, 50% theophylline, 19.75% lactose, 0.25% magnesium stearate)

Stability Sample (Time, Condition)	Ave. Tablet Crushing Strength (scu, sd)	Ave. Tablet Thickness (mm)	Ave. Tablet Weight (mg, sd)
Initial	30.6, 1.4	5.7	401, 2
<i>Ambient (21°C/50% RH)</i>			
1 month	29.1, 3.0	5.7	402, 9
2 months	27.1, 2.5	5.8	400, 5
3 months	25.9, 1.4	5.9	403, 4
6 months	23.8, 1.4	5.8	403, 4
9 months	27.1, 1.8	5.9	401, 5
12 months	26.5, 1.5	5.7	403, 5
<i>Accelerated (40°C/75% RH)</i>			
1 month	26.2, 2.1	5.7	405, 7
2 months	24.4, 1.5	5.9	404, 4
3 months	24.4, 1.2	5.9	400, 4
6 months	23.1, 1.2	5.8	402, 4
9 months	15.9, 1.1	6.0	404, 6
12 months	18.8, 1.2	6.0	413, 6



Table 4. Effect of storage time and conditions on physical properties of hydrophilic matrix tablets containing dihydroergotamine mesylate and METHOCEL E4MP CR.

(75% METHOCEL E4MP CR, 12% dihydroergotamine mesylate, 86% lactose, 0.5% sodium lauryl sulfate, 9.8% microcrystalline cellulose, 5% polyvinylpyrrolidone)

Time (days)	2-8°C	25°C/NMT60% RH	30°C	37°C	45°C	25°C/80% RH
<i>Assay (%)</i>						
0	-	104.4	-	-	-	-
32	103.3	104.1	103.3	103.1	102.7	102.7
91	104.1	104.1	103.3	103.1	102.0	103.8
186	102.7	104.1	102.3	104.4	103.2	107.7
375	101.8	101.6	102.4	101.4	100.3	102.6
<i>Degradation products (%)</i>						
0	-	0.40	-	-	-	-
91	0.41	0.41	0.53	0.90	1.20	0.40
186	0.55	0.55	0.55	0.95	1.60	0.70
375	0.55	0.55	0.60	0.85	1.45	0.70
<i>Tablet hardness (N)</i>						
0	-	32.6-54.0	-	-	-	-
32	25.6-38.7	35.6-41.2	35.6-36.5	33.1-45.2	41.7-44.8	34.6-37.8
91	37.7-45.8	38.7-50.9	47.9-58.1	30.1-44.4	37.6-56.2	32.6-48.8
186	32.6-35.6	32.6-44.8	22.4-39.7	33.6-43.8	35.6-44.4	43.8-56.0
375	33.6-42.8	24.4-40.7	28.5-35.6	30.5-34.6	44.8-64.2	32.6-38.7

Table 5. Effect of storage time and conditions on crushing strength of hydrophilic matrix tablets containing a Class I drug and 60% hypromellose.

Time (months)	Crushing Strength (N)			
	Nonstressed (25°C/60% RH)		Stressed (40°C/75% RH)	
	Range	Mean	Range	Mean
0	249-283	269	249-283	269
1	N/E	N/E	208-241	226
2	N/E	N/E	166-199	186
3	260-288	276	159-186	173
4	N/E	N/E	163-180	173
6	256-277	268	158-183	172

N/E - Not examined

Table 6. Effect of storage conditions at 5 months storage on the release of theophylline from hydrophilic matrix tablets containing theophylline and METHOCEL K4MP.

(25% METHOCEL K4MP, balance not described)

Time (h)	Amount Dissolved (mg)			
	Time 0	Ambient	Warm Dry Air	Warm Moist Air
1	13	12	14	11
4	34	31	34	33
8	58	56	58	57



for both laboratory and pilot-plant samples. Drug-release profiles from ambient and accelerated stability for all conditions were essentially unchanged (Figures 4 and 5). Values for f_2 metric on drug release for the ambient samples were greater than 88, indicating similarity between profiles. Values for f_2 metric on drug release for the accelerated samples were greater than 75, also indicating similarity between profiles.

A study involving dihydroergotamine mesylate investigated the effect of storage time, temperature, and humidity on drug release, assay, degradation products, and tablet hardness.⁴ One formulation included 39.8% METHOCEL E4MP CR, 6.4% dihydroergotamine mesylate, 45.7% lactose, 0.3% sodium lauryl sulfate, 5.2% microcrystalline cellulose, and 2.7% polyvinylpyrrolidone. Tablets were prepared using fluid bed granulation; target tablet weight was not specified. Tablets were placed in glass containers for stability testing. No further details on containers or number of tablets per container were given. Storage times were 32, 91, 186, and 375 days; storage conditions were 2-8°C, 25°C/NMT60% RH, 30°C, 37°C, 45°C, and 25°C/80% RH.

The authors found the formulation to be stable at elevated humidity conditions (Table 4). At elevated temperature conditions, degradation products of the drug increased. However, the tablet hardness and dissolution profile (data not shown) were not affected by either storage time or storage conditions.

Similar dissolution results were found in a study involving pseudoephedrine HCl.⁵ The formulation contained 61% METHOCEL K4MP, 13% pseudoephedrine HCl, and 26% sodium carboxymethylcellulose (NaCMC). Tablets were prepared by direct compression; target tablet weight was not specified. Tablets were placed in amber glass bottles.

Figure 4. Effect of storage time at 21°C/50% RH on drug dissolution of hydrophilic matrix tablets containing theophylline and METHOCEL K4MP CR (production scale). (30% METHOCEL K4MP CR, 50% theophylline, 19.75% lactose, 0.25% magnesium stearate)

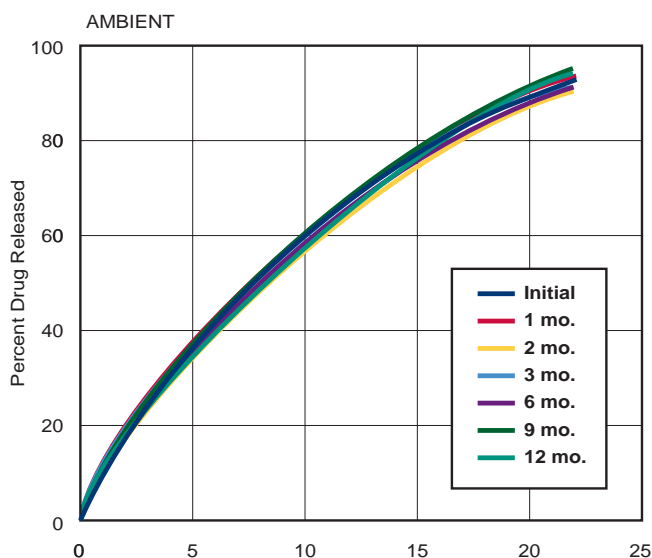


Figure 5. Effect of storage time at 40°C/75% RH on drug dissolution of hydrophilic matrix tablets containing theophylline and METHOCEL K4MP CR (production scale). (30% METHOCEL K4MP CR, 50% theophylline, 19.75% lactose, 0.25% magnesium stearate)

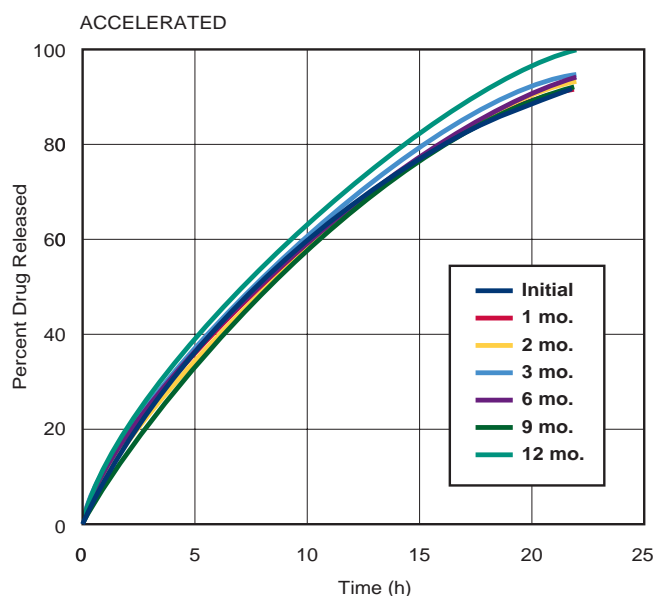




Figure 6. Effect of storage conditions at 5 months storage on weight of hydrophilic matrix tablets containing theophylline and METHOCEL K4MP.
(25% METHOCEL K4MP, balance not described)

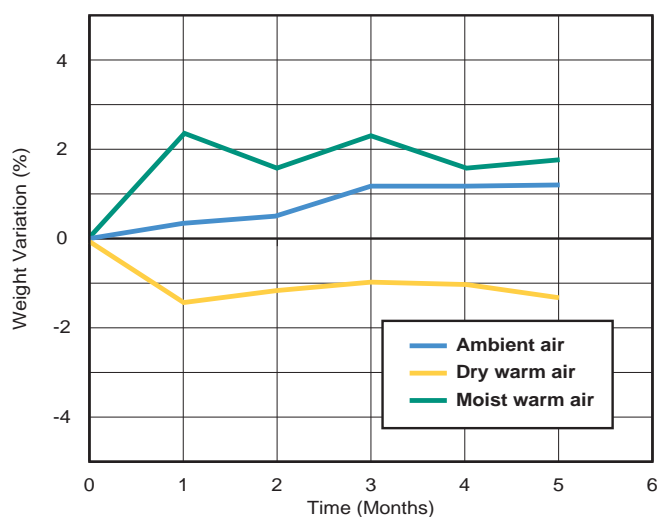
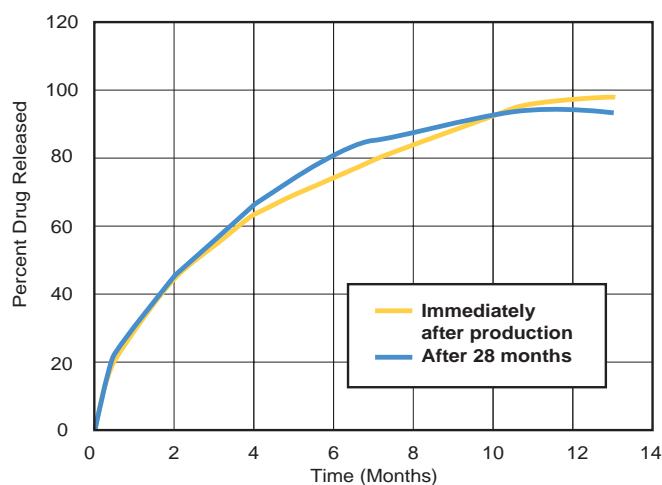


Figure 7. Effect of storage time at room temperature on release of pseudoephedrine HCl from hydrophilic matrix tablets containing METHOCEL K4MP.
(26.6% METHOCEL K4MP, 16.0% pseudoephedrine HCl, 56.7% lactose, 0.7% magnesium stearate)



No further details on containers or number of tablets per container were given. Storage conditions included 37°C, 45°C, and 37°C/80% RH for 3 months. Drug dissolution was very similar under all three conditions. The authors concluded that the release integrity of the tablets under these accelerated conditions indicated good stability.

Stark et al. studied the effect of accelerated stability conditions on tablet crushing strength, *in vitro* dissolution, and *in vivo* performance of tablets containing a Class I drug and 60% hypromellose.⁶ No information was given on tablet preparation. Tablets were stored in 100-mL, white, HPDE bottles, 100 tablets per bottle. Two conditions were used: 25°C/60% RH (nonstressed) and 40°C/75% RH (stressed). Crushing strength and *in vitro* drug dissolution were determined over 6 months. *In vivo* evaluations involving C_{max} and AUC parameters were performed on stressed and nonstressed tablets stored for 3 months. This study is unusual in that it included *in vivo* as well as *in vitro* evaluation.

Table 5 shows the effect of storage time and conditions on tablet crushing strength. At 3 months, the crushing strength of the stressed tablets was 37% lower than that of the nonstressed tablets, dropping from 269 N to 173 N. Most of the decrease occurred in the first two months. Storage at accelerated stability conditions did not affect either *in vitro* dissolution profiles or *in vivo* results, indicating that stressed and nonstressed tablets were bioequivalent.

Joly and Brossard studied the effect of storage time, temperature, and humidity on the physical properties and release characteristics of tablets containing theophylline and METHOCEL K4M.⁷ The formulation described in the article contained 20% METHOCEL K4M, 50% theophylline, 25% lactose, 4% polyvinylpyrrolidone, and 1% magnesium stearate. However, stability testing was described as conducted on tablets containing 25% METHOCEL K4M, with no additional information on the remainder of the formulation. Tablets were prepared by wet granulation. Target tablet weight was 400 mg. Stability conditioning was done on loose tablets with no packaging or wrapping. Stability was studied over 5 months under three conditions: ambient air, warm dry air (40°C), and warm moist air (40°C/80% RH).

Figure 6 shows the effect of storage conditions on weight of tablets containing 25% METHOCEL K4M. The tablet weight did not vary significantly from the first to the fifth month, although there was a slight increase in weight variation in



warm air. Table 6 shows the effect of storage conditions on drug dissolution from tablets containing 25% METHOCEL K4M. The authors concluded that the release of theophylline was independent of the storage conditions tested.

Figure 7 shows the stability of METHOCEL K4M Premium in hydrophilic matrix tablets containing pseudoephedrine HCl. The formulation included 26.6% METHOCEL K4M Premium, 16% pseudoephedrine HCl, 56.7% lactose, and 0.7% magnesium stearate. Tablets were prepared by direct compression. No description of containers or number of tablets per container was given. Tablet dissolution was measured immediately after manufacture and again after 28 months storage at room temperature and humidity. Minimal change in *in vitro* dissolution resulted over this storage interval.

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.

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