

# The Influence of Excipients on Drug Release from Hydroxypropyl Methylcellulose Matrices

MARINA LEVINA, ALI R. RAJABI-SIAHBOOMI

Colorcon Limited, Flagship House, Victory Way, Crossways, Dartford, Kent DA2 6QD, UK

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**ABSTRACT:** The influence of commonly used excipients, spray-dried lactose (SDL), microcrystalline cellulose (MCC), and partially pregelatinized maize starch (Starch 1500<sup>®</sup>) on drug release from hydroxypropyl methylcellulose (HPMC, hypromellose) matrix system has been investigated. A model formulation contained 30%w/w drug, 20%w/w HPMC, 0.5%w/w fumed silica, 0.25%w/w magnesium stearate, and 49.25%w/w filler. Chlorpheniramine maleate and theophylline were used as freely (1 in 4) and slightly (1 in 120) water-soluble drugs, respectively. It was found that for both drugs, addition of 20 to 49.25%w/w Starch 1500 resulted in a significant reduction in drug release rates compared to when MCC or SDL was used. The study showed that using lactose or microcrystalline cellulose in the formulations resulted in faster drug release profiles. Partially pregelatinized maize starch contributed to retardation of both soluble and slightly soluble drugs. This effect may be imparted through synergistic interactions between Starch 1500 and HPMC and the filler actively forming an integral part within the HPMC gel structure. © 2004 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 93:2746–2754, 2004

**Keywords:** hypromellose; HPMC; Starch 1500; sustained release; pregelatinized starch; matrix system

## INTRODUCTION

Nonionic cellulose ethers, and most frequently hydroxypropyl methylcellulose (HPMC, hypromellose) have been widely studied for their applications in oral sustained release (SR) systems.<sup>1</sup> When in contact with water, HPMC hydrates rapidly and forms a gelatinous barrier layer around the tablet. The rate of drug release from HPMC matrix is dependent on various factors such as type of polymer, drug, polymer/drug ratio, particle size of drug and polymer, and the type and amount of fillers used in the formulation.

Starch is one of the most widely used excipients in the manufacture of solid dosage forms. Most native starches consist of two polymers of glucose,

that is, branched amylopectin and essentially linear amylose. Physically or chemically modified starches have been used in sustained release tablets because of their cold water-swelling capacity and gel barrier formation. Rak et al.<sup>2</sup> and Van Aerde and Remon<sup>3</sup> studied the possibility of using thermally modified starches for controlled drug release. Herman and Remon<sup>4</sup> found that only fully pregelatinized starches containing a low amount of amylose (25% and lower) could produce a strong enough gel layer to ensure a sustained drug release. These findings are in agreement with Michailova et al.,<sup>5</sup> who claimed that the amylose molecules decrease the gel cohesion and accelerate the erosion of the gel layer. Mulhbachter et al.<sup>6</sup> studied crosslinked high amylose starch derivatives as matrices for controlled release of high drug loadings. They found that these polymeric excipients are able to control the release over 20 h from tablets loaded with 20 to 60% drug. Lenaerts et al.<sup>7</sup> used crosslinked high amylose starch for the

Correspondence to: Marina Levina (Telephone: +44 (0) 1322 293000; Fax: +44 (0) 1322 627200; E-mail: mlevina@colorcon.co.uk)

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preparation of sustained release matrix tablets. They claimed the possibility for high active ingredient core loading and achieving either zero-order or Fickian release for most drugs. Other advantages of crosslinked high amylose starches may be the absence of erosion, limited swelling and the fact that increasing degree of crosslinking results in increased water uptake rate, drug release rate, and equilibrium swelling.<sup>7</sup>

Partially pregelatinized maize starches are normally used as binder-disintegrants in immediate release tablet formulations.<sup>8</sup> Leach et al.<sup>9</sup> claimed that these materials have a very limited obstructive gel formation capability at the surface of the tablet, which makes them not particularly suitable for SR applications. However, the use of partially pregelatinized starches in combination with other polymers, such as hypromellose, in SR tablets have not been fully examined. Therefore, the influence of Starch 1500, in comparison to MCC and SDL, on drug release from HPMC 2208 has been investigated in this study.

## EXPERIMENTAL

### Materials

Chlorpheniramine maleate (CPM) was obtained from Avocado Research Chemicals Ltd. (Lancas., UK), theophylline (TP) was obtained from Knoll AG (Ludwigshafen, Germany), and were used at 30%w/w in the formulation. Aqueous solubility for CPM is 1 in 4 (w/w), and for theophylline is 1 in 120 (w/w).

To study the effect of fillers on drug release, in all formulations only 20%w/w hydroxypropyl methylcellulose (HPMC, hypromellose) (Methocel K4M, International Flavors and Fragrances Inc., USA) was used. Higher HPMC levels may mask the differences impacted by the fillers on drug release. Higher HPMC levels may mask the differences impacted by the fillers on drug release.

Three commonly used fillers were studied: partially pregelatinized maize starch (PPS) (Starch 1500<sup>®</sup>, Colorcon, Dartford, UK), spray dried lactose (Fast Flo<sup>®</sup> #316, Foremost Farms, Wisconsin) and microcrystalline cellulose (MCC) (Avicel<sup>®</sup> PH102, FMC, Brussels, Belgium). Average particle size for Starch 1500 is 70, for MCC—90, and for spray dried lactose—100 microns. This relatively large particle size for all three materials can guarantee good powder flow in direct compression applications.

Fumed silica (Aerosil<sup>®</sup> A-200, Degussa AG, Dusseldorf, Germany) was used at 0.5%w/w level as a flow aid and magnesium stearate (Peter

Greven, Venlo, The Netherlands) was used at 0.25%w/w level as a lubricant.

Model formulations (Table 1) were blended in a Turbular mixer (Type T2A, Pleuger, Basel, Switzerland). All ingredients with the exception of magnesium stearate were blended for 10 min, then magnesium stearate was added and mixed for an additional 5 min.

### Bulk Properties of the Mixtures

The flow and packing properties of the powder mixtures were determined using an automatic tap volumeter (STAV 2003, J. Engelsmann AG, Ludwigshafen am Rhein, Germany). A 250-mL graduated glass cylinder was used. The tapping frequency was  $250 \pm 15$  taps/min and the lift height  $3.0 \pm 0.2$  mm. One hundred grams of powder were carefully filled into the measuring cylinder ensuring a flat top surface of the powder. The maximum bulk volume,  $V_o$ , was recorded. Then tapped volume,  $V_f$ , and compressibility index,  $100 \times (V_o - V_f) / V_o$ , were determined according to the USP.<sup>10</sup>

### Tableting

Tablets (333 mg, 100 mg drug load) were compressed on the instrumented rotary Piccola tablet press (Riva, Argentina) at 30 rpm using 9-mm concave tooling, at compression forces from 4 to 14 kN. Upper compression and ejection forces were recorded.

The tablet weight and tablet weight variation were obtained for 20 tablets taken during each tableting run for each formulation. The accuracy of the weight determination was  $\pm 1$  mg.

### Dissolution Testing

The drug release from the matrices was measured using a Caleva ST7 dissolution tester (G.B. Caleva Ltd., Dorset, UK), USP apparatus II

**Table 1.** Model HPMC Formulations Used in This Study

Ingredients	Concentration (%w/w)
Drug	30.00
HPMC	20.00
Filler	49.25
Fumed silica	0.50
Magnesium stearate	0.25

(paddle) at  $37 \pm 1^\circ\text{C}$  and 100 rpm. The drug concentration was measured using a UV spectrophotometer Model CE3021 (Cecil Instruments Ltd., Cambridge, UK), at 271 nm for theophylline and at 261 nm for chlorpheniramine maleate. The media used were purified water and phosphate buffer (pH 7.4). The buffer was prepared according to British Pharmacopoeia<sup>11</sup> by adding 250 mL of 0.2 M potassium dihydrogen orthophosphate to 393.4 mL of 0.1 M sodium hydroxide. For each formulation and condition, dissolution rates of at least three individual tablets were determined and means and standard deviation values were calculated.

### Contact Angle Analysis

The process of water penetration into the hydrophilic matrix tablets was examined using FTÅ200 dynamic contact angle analyser (Camtel Ltd., UK) with a flexible video system allowing fast image acquisition (up to 60 images per second). Twenty-microliter droplets of purified water were deposited on the face surface of dry tablet samples by positioning the dispenser tip just above the surface and growing the pendant drop until its bottom touched the sample and the droplet detached. The contact angle was measured over the first 15 seconds as the water spread/absorbed and recorded as a function of time. Nonlinear capture timing was used with fast timing at the beginning of the test (15 measurements/s) and the slow capture (2 measurements/s) during the final absorption stage.

## RESULTS AND DISCUSSION

### Tableting Properties of Matrices

All formulations, regardless of type of excipient, had good flow (Table 2) with compressibility index

of no more than 20. Tablet weight variations for all batches prepared in this study were found to be less than 1%, also an indication of good flow.

Table 2 also shows that both CPM and TP formulations with lactose produced the highest ejection forces, whereas Starch 1500 due to its inherent lubricity produced the lowest ejection forces.

All tablets had high mechanical strength. The rank order for tablet breaking force was: formulations containing MCC > spray dried lactose > PPS.

### Influence of Different Fillers and Compression Force on Drug Release

Several authors<sup>12–17</sup> have stated that compression force had very little (not statistically significant) effect on drug release from HPMC matrices. However, in this study it was found that the applied compression force influenced drug release rate (Table 3), the extent of which was dependent on the type of filler used. The time taken for 50% drug release from formulations manufactured at different compression forces indicates that drug release become slower with increasing applied force. This effect is particularly profound when comparing tablets manufactured at a very low compression force of 4 kN with the tablets manufactured at higher compression forces of 10 and 14 kN. Depending on the compressibility behavior of the fillers, the porosity of the matrices may be reduced with increasing compression force, leading to slower water uptake and water front movement into the matrix, which in turn, may lead to slower drug release.

Figures 1 and 2 show drug release profiles from matrices compressed at 4 and 14 kN, for chlorpheniramine maleate and theophylline, respectively. Drug release from tablets made with lactose as a tiller was the fastest. Matrices containing partially pregelatinized starch produced the slowest drug release at all compression forces for both drugs.

**Table 2.** Powder and Tablet Characterization of HPMC Matrix Formulations Studied Here

Drug	Filler	Bulk Volume (g/cm <sup>3</sup> ) <i>n</i> = 3	Tapped Volume (g/cm <sup>3</sup> ) <i>n</i> = 3	Compress. Index	Tablet Ejection Force (N)	Tablet Weight Variation (%) <i>n</i> = 20
CPM	PPS	141 ± 1	115 ± 1	18	374 ± 22	0.2–0.4
	MCC	200 ± 1	166 ± 0	17	530 ± 27	0.4–0.7
	lactose	194 ± 2	165 ± 0	15	1079 ± 48	0.1–0.6
TP	PPS	84 ± 1	71 ± 1	15	82 ± 3	0.2–0.4
	MCC	230 ± 2	185 ± 1	20	96 ± 4	0.1–0.8
	lactose	197 ± 0	172 ± 0	13	238 ± 9	0.1–0.9

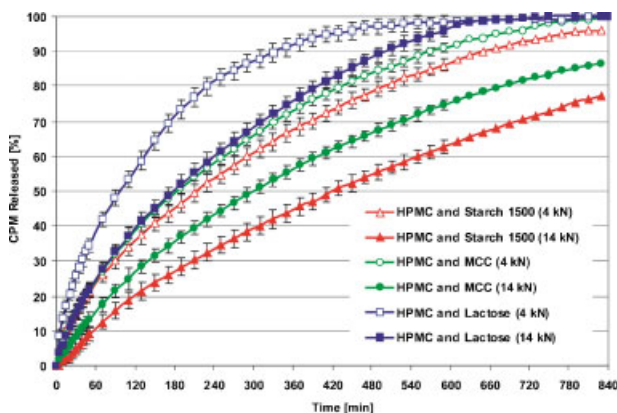
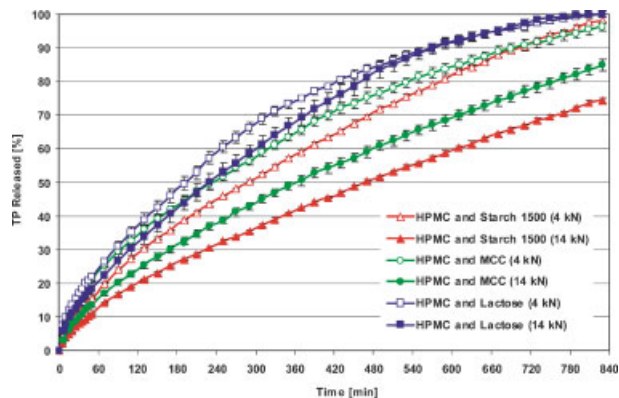
**Table 3.** The Influence of Compression Force on Drug Release ( $T_{50\%}$ ) from HPMC Matrices Containing Different Fillers

Drug	Filler	$T_{50\%}$ (min) for Tablets Manufactured at Various Compression Forces		
		4 kN	10 kN	14 kN
CPM	PPS	215 ± 2	380 ± 2	420 ± 2
	MCC	185 ± 2	280 ± 2	300 ± 2
	lactose	95 ± 2	160 ± 2	175 ± 2
TP	PPS	290 ± 1	470 ± 1	470 ± 1
	MCC	230 ± 1	340 ± 1	360 ± 1
	lactose	190 ± 2	200 ± 2	230 ± 2

The drug release differences between tablets containing excipients such as lactose and MCC can be attributed mainly to the excipients solubility. However, the effect of Starch 1500 on drug release cannot be explained only by its solubility in water. It is more soluble compared to MCC, and produces slower drug release. Use of partially pregelatinized starch in HPMC matrices may bring about different effects resulting from interactions between HPMC and Starch 1500 that can affect the properties of the gel layer around the tablet.

To investigate the mechanism of drug release and to compare the performance of various matrix formulations, the percent drug released versus time profiles were used. Data corresponding to 5–60% release show a good fit to the Power Law Model<sup>18</sup> expressed in eq. 1:

$$M_t/M_{inf} = kt^n \quad (1)$$

**Figure 1.** The influence of compression force (4 and 14 kN) on chlorpheniramine maleate release in water from HPMC matrices containing different fillers. [Color figure can be seen in the online version of this article, available on the website, www.interscience.wiley.com.]**Figure 2.** The influence of compression force (4 and 14 kN) on theophylline release in water from HPMC matrices containing different fillers. [Color figure can be seen in the online version of this article, available on the website, www.interscience.wiley.com.]

where  $M_t$  is the amount of drug released at time  $t$ ,  $M_{inf}$  is the amount of drug released after infinite time,  $k$  is a kinetic constant incorporating structural and geometric characteristics of the tablet, and  $n$  is the diffusional exponent indicative of the drug release mechanism. The values of the kinetic constant ( $k$ ), the release exponent ( $n$ ), and correlation coefficient ( $R^2$ ) determined from the drug release data are presented in Table 4. The correlation coefficients for the data were  $>0.99$ . For matrix tablets, an  $n$  value of near 0.5 indicates diffusion control, and an  $n$  value of near 1.0 indicates erosion or relaxation control.<sup>19,20</sup> Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism. The values of  $n$  and  $k$  are inversely related. A very high  $k$  value may suggest a burst drug release from the matrix.<sup>21</sup>

Values of  $n$  for all matrices studied here were between 0.54 and 0.81, indicating an anomalous behavior corresponding to diffusion, erosion, and swelling mechanisms. In all these matrices availability of the water within the gel structure is also limited, and therefore a dissolution-controlled release is also involved. Comparing tablets manufactured at the same compression force, separately for chlorpheniramine maleate and theophylline, a linear trend of decreasing  $n$  values can be observed from PPS to MCC and to lactose. Matrices containing lactose exhibited a drug release closer to a diffusion-controlled process compared to MCC and Starch 1500.

Slower drug release from matrices with pregelatinized starch may be due to a slower penetration

**Table 4.** Values of the Kinetic Constant ( $k$ ), Diffusional Exponent ( $n$ ) Derived from Equation 1 and Correlation Coefficients ( $R^2$ ), for HPMC Matrices Containing Different Fillers

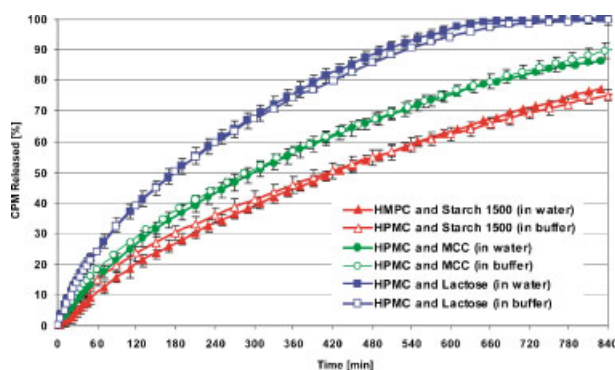
Filler	Compression Force	CPM			TP		
		$k$	$n$	$R^2$	$k$	$n$	$R^2$
PPS	4 kN	1.1332	0.6878	0.9999	1.2495	0.6517	0.9982
	10 kN	0.5638	0.8048	0.9948	0.8673	0.6591	0.9997
	14 kN	0.3861	0.8081	0.9976	0.7816	0.6755	0.9997
MCC	4 kN	1.4910	0.6759	0.9976	2.4406	0.5540	0.9994
	10 kN	0.7197	0.7426	0.9971	1.1485	0.6371	0.9996
	14 kN	0.6304	0.7708	0.9967	1.1077	0.6451	0.9998
Lactose	4 kN	3.5188	0.5822	0.9993	2.6826	0.5497	0.9952
	10 kN	1.2356	0.7268	0.9961	2.6563	0.5508	0.9915
	14 kN	1.2152	0.7367	0.9966	2.6339	0.5614	0.9956

of the water front towards the central core of the matrix. Matrices with swelling restrictions, like those with Starch 1500, exhibit a shift towards drug release by erosion mechanism.<sup>22</sup> Tablets with partially pregelatinized starch would result in a more concentrated gel and increased gel tortuosity. Thus, the diffusional path would become more convoluted and the diffusion rate would therefore decrease. The effect of increased tortuosity and a delayed water penetration is expressed as low kinetic constant  $k$  values for tablets made with Starch 1500.

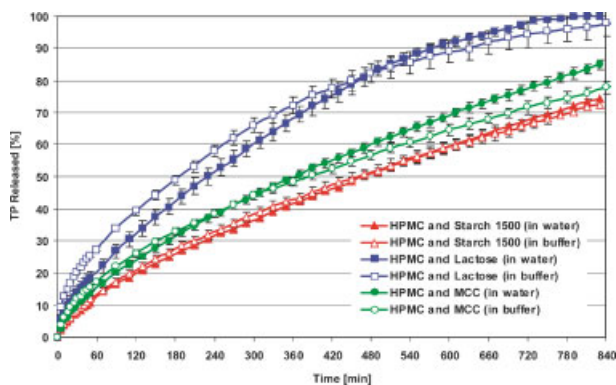
Although HPMC hydration and gel formation is not affected by changes in pH<sup>23</sup> (at pH ranges of gastrointestinal tract), the pH of the dissolution fluid is known to affect release rates of drugs from HPMC matrices.<sup>24</sup> Attempts have been made to quantify the influences of the solutions containing phosphate and chloride ions at different ionic strengths on dissolution rates from HPMC SR tablets.<sup>25</sup> In this study the effect of phosphate buffer (pH 7.4) on the matrix integrity and drug release from HPMC compacts containing different fillers was investigated. No significant changes in drug dissolution in buffer compared to water medium were observed for chlorpheniramine maleate (Fig. 3). Theophylline release in phosphate buffer compared to water was slightly different for lactose and MCC containing matrices (Fig. 4). Theophylline dissolution profiles for tablets made with pregelatinized starch were similar in water and in buffer. Drug release from matrices containing Starch 1500 in both water and phosphate buffer was slower than when lactose or MCC was used.

### Influence of Starch 1500 Concentration on Drug Release from HPMC Matrices

Figures 5 and 6 show drug release profiles from HPMC matrices containing partially pregelatinized starch and lactose at different ratios, for CPM and TP, respectively. For both drugs, as the level of PPS increased the dissolution of drugs became significantly slower. Data in the range of 5–60% drug release were fitted into eq. 1, and the results are shown in Table 5. The correlation coefficients for most of the data were  $>0.99$ . For chlorpheniramine maleate matrices studied here, the values of  $n$  ranged from 0.7367 to 0.8081, and the  $k$  values ranged from 0.3861 to 1.2152. For theophylline tablets, the values of  $n$  ranged

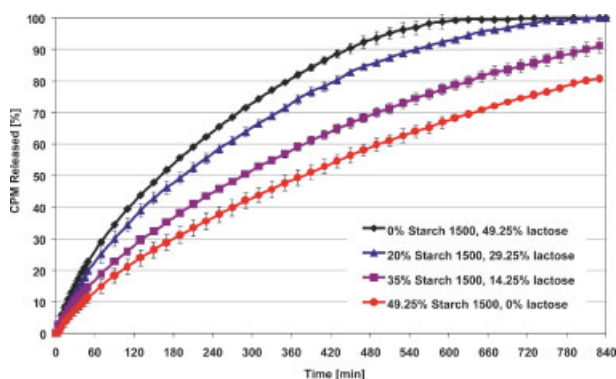


**Figure 3.** Chlorpheniramine maleate release from HPMC matrices containing different fillers manufactured at 14 kN in water and in phosphate buffer (pH 7.4). [Color figure can be seen in the online version of this article, available on the website, [www.interscience.wiley.com](http://www.interscience.wiley.com).]

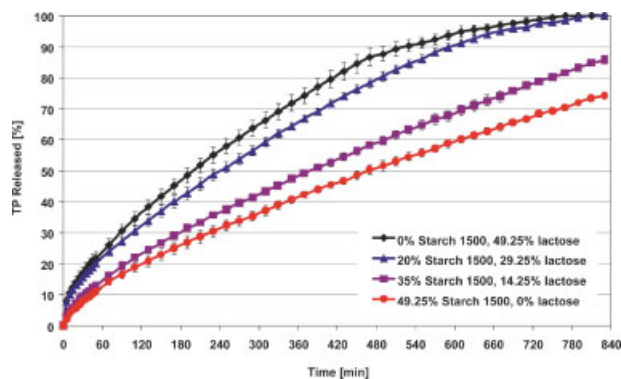


**Figure 4.** Theophylline release from HPMC matrices containing different fillers manufactured at 14 kN in water and phosphate buffer (pH 7.4). [Color figure can be seen in the online version of this article, available on the website, [www.interscience.wiley.com](http://www.interscience.wiley.com).]

from 0.5614 to 0.6755, and the  $k$  values ranged from 0.7816 to 2.6339. Values of  $n$  for all matrices studied here were between 0.56 and 0.81, indicating an anomalous behavior corresponding to diffusion, erosion, and swelling mechanisms. Comparing tablets with the same drug, separately for chlorpheniramine maleate and theophylline, a linear trend of increasing  $n$  values can be observed with an increase in PPS concentration. Matrices containing more lactose exhibited a drug release closer to a diffusion-controlled process compared to tablets containing higher levels of Starch 1500. Thus, the effect seen with Starch 1500 is not just a spatial effect due to the presence of any filler, but PPS actively contributes to the dissolution kinetics. This contribution is imparted



**Figure 5.** Effect of Starch 1500 levels on chlorpheniramine release from HPMC matrices manufactured at 14 kN. [Color figure can be seen in the online version of this article, available on the website, [www.interscience.wiley.com](http://www.interscience.wiley.com).]



**Figure 6.** Effect of Starch 1500 levels on theophylline release from HPMC matrices manufactured at 14 kN. [Color figure can be seen in the online version of this article, available on the website, [www.interscience.wiley.com](http://www.interscience.wiley.com).]

through possible contribution of Starch 1500 in gel formation of HPMC, that is, the filler actively forming an integral structure within the HPMC gel layer at lower concentrations of HPMC in the formulation.

Michailova et al.<sup>26</sup> characterized HPMC/pregelatinized starch hydrogels as “filled” composite systems where starch filler functions as a supporting frame, while the linear hypromellose forms the continuous disperse medium. In comparison with the cellulose derivative, the pregelatinized starch hydrates to a considerably lower degree due to the formation of intramolecular hydrogen bonds in the highly branched amylopectin.<sup>27</sup> These bonds suppress the polymer segments’ mobility and diminish the degree of HPMC/pregelatinized starch hydration<sup>28</sup> resulting in a reduced gel layer diffusivity and decreased drug velocity from matrices containing higher pregelatinized starch quantity. For this reason, at 20% of HPMC and low concentration of the pregelatinized starch gel structure is quite porous with increased diffusion capability. With the increase in PPS concentration (35–49%), the swelled starch particles form strong supporting structure with comparatively strong rigidity. This HPMC/PPS gel structure may explain the slower drug release with increasing pregelatinized starch concentration in the formulation.

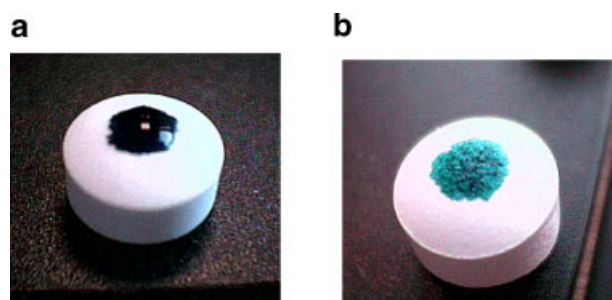
### Testing of Water Absorption Rate

Drug release from HPMC matrix tablets is based on the glassy transition of the polymer into a rubbery gel that occurs as a result of water absorption/hydration of the polymer in the

**Table 5.** Values of the Kinetic Constant ( $k$ ), Diffusional Exponent ( $n$ ) Derived from Equation 1 and Correlation Coefficients ( $R^2$ ), for HPMC Matrices Containing Various Levels of Starch 1500 and Manufactured at 14 kN

PPS Concentration (%w/w)	Lactose Concentration (%w/w)	CPM			TP		
		$k$	$n$	$R^2$	$k$	$n$	$R^2$
0.00	49.25	1.2152	0.7367	0.9966	2.6339	0.5614	0.9956
20.00	29.25	0.9771	0.7462	0.9957	2.4985	0.6116	0.9893
35.00	14.25	0.8780	0.7516	0.9992	0.9678	0.6639	0.9999
49.25	0.00	0.3861	0.8081	0.9976	0.7816	0.6755	0.9997

matrix. The drug release mechanism is determined by the structural characteristics of the gel layer (swelling, uniformity of polymer hydration, diffusion capability, and gel strength), and by gel layer erosion. Therefore, rapid gel formation (rubbery phase) to prevent rapid ingress of water into the matrix as well as high gel strength are critical factors in drug release from HPMC matrices. It was found that water penetration into tablets containing Starch 1500 was much slower compared to matrices containing MCC or lactose (Fig. 7). This observation was confirmed by contact angle measurements (Fig. 8). Table 6 shows that the initial contact angle for all the samples was similar ( $57\text{--}72^\circ$ ) and less than  $90^\circ$ , indicating good surface wettability behavior of these matrices, when the water drop flattens out and spreads on the tablet surface. However, for MCC and lactose containing matrices, the water droplet was rapidly absorbed into the matrix (within 2–7 s), which was much faster (6–13 times) than for the matrices containing Starch 1500 ( $>30$  s). It was also found that the rate of contact angle change was significantly faster for chlorpheniramine maleate as a freely water soluble drug compared to theophylline.

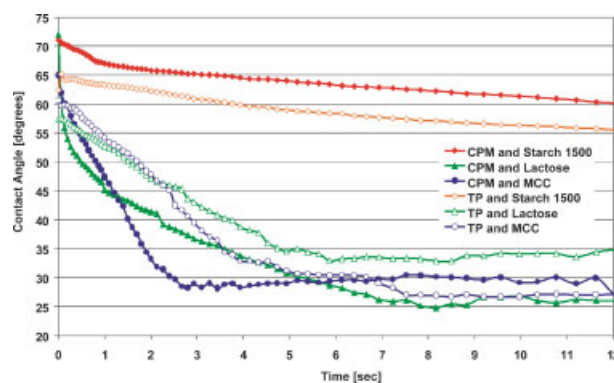
**Figure 7.** Water droplet and its absorption into (a) PPS and (b) microcrystalline cellulose or lactose containing HPMC matrices. [Color figure can be seen in the online version of this article, available on the website, [www.interscience.wiley.com](http://www.interscience.wiley.com).]

The presence of free water within the gel layer plays an important part in drug movement across this barrier. Decreased availability of free water may lead to decreased drug diffusion across the gel layer. Partially pregelatinized starch and hypromellose combinations may be producing a gelled interlocked frame consisting of HPMC fibers and amylose reinforced by the swollen starch granules.<sup>29,30</sup> This network restrains water penetration into SR matrices and prevents fast drug release.<sup>31</sup>

## CONCLUSIONS

All HPMC SR formulations had good powder flow, tablet weight uniformity, and mechanical strength. Formulations with lactose produced the highest ejection forces. On the other hand, partially pregelatinized starch due to its inherent lubricity produced the lowest ejection forces.

All formulations regardless of type of filler resulted in a slow drug release for both candidate drugs. Drug release was found to be affected by

**Figure 8.** Contact angle measurements for water droplets on the surface of HPMC matrices containing different fillers. [Color figure can be seen in the online version of this article, available on the website, [www.interscience.wiley.com](http://www.interscience.wiley.com).]

**Table 6.** Contact Angle Analysis of Purified Water on the Surface of HPMC Matrices Containing Different Fillers

Drug	Filler	Initial Contact Angle (Degrees)	Absorption Time (Seconds)	Rate of Contact Angle Change (Degree/s)
CPM	PPS	71	>30.0	1.1
	MCC	65	2.4	14.5
	lactose	72	7.0	6.6
TP	PPS	62	>30.0	0.5
	MCC	60	6.7	4.6
	lactose	57	5.4	4.2

applied compression force. At all compression forces and with both drugs, when Starch 1500 was used, drug release was slower compared to formulations containing MCC or lactose. Similar results were produced in phosphate buffer. These results may suggest that partially pregelatinized starch is not an inert filler in HPMC matrices (with low HPMC contents), but it actively contributes to the mechanism of drug release.

It was shown that for both drugs, increasing concentrations of Starch 1500 (20, 35 and 49.25%w/w) in the formulations caused a decrease in drug release rates. Therefore, use of blends of Starch 1500 with other fillers (e.g. lactose) can be used for tailoring the desired release profile of HPMC matrix systems.

It was found that water absorption into tablet containing partially pregelatinized starch was much slower compared to matrices containing MCC or lactose. This observation was confirmed by contact angle analysis. These results may explain the slower drug release from HPMC matrices containing Starch 1500 compared to those containing MCC or lactose.

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