



## The Influence of Fillers on Tableting and Drug Release From HPMC Matrices

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### Purpose

To investigate the influence of compression force on tableting and drug release from HPMC matrices formulated with three commonly used fillers.

### Introduction

Non-ionic cellulose ethers and most frequently HPMC, have been widely studied for their applications in oral slow drug release systems (1). Here, the influence of commonly used fillers, lactose, microcrystalline cellulose (MCC) and partially pregelatinized starch (PPS) on compressibility, ejection force and drug release from HPMC matrices, is investigated.

### Materials and Methods

A model formulation containing; 20% HPMC [Methocel K4M Premium (Dow)], 30% drug [chlorpheniramine maleate (CPM) or theophylline (TP)], 49.25% filler [Starch 1500<sup>®</sup> (Colorcon) or Avicel<sup>®</sup> PH102 (FMC) or Fast-Flo<sup>®</sup> lactose (Foremost)], 0.5% Aerosil<sup>®</sup> 200 (Degussa AG) and 0.25% magnesium stearate (Peter Greven) was used.

Tablets (333 mg) containing 100 mg drug were directly compressed using an instrumented Piccola rotary 10-station tablet press, with 9 mm concave tooling, at compression forces from 4 to 14 kN. Ejection forces and tablet mechanical strengths were measured. Drug release from the matrices was determined using a Caleva ST7 dissolution tester, USP apparatus II (paddle), in water at 100 rpm.

### Results

All formulations, regardless of type of filler, had good flow, low weight variation and good mechanical strength. Tablet weight variations for all tested batches were less than 1%.

Table 1 shows the ejection forces for the formulations containing theophylline or chlorpheniramine maleate. Formulations with lactose produced the highest ejection forces. Starch 1500 due to its inherent lubricity produced the lowest ejection forces.

**Table 1. Ejection Forces**

Drug	Filler	Ejection Force (N)
TP	Starch 1500	82 ± 3
TP	lactose	238 ± 9
TP	MCC	96 ± 4
CPM	Starch 1500	374 ± 22
CPM	lactose	1079 ± 48
CPM	MCC	530 ± 27

It has been reported that for a formulation containing HPMC and diclofenac sodium, the compression force had no or very little influence on drug release rate (2).

In this study it was found that applied pressure influenced drug release rate, which was dependent on the type of filler used.

Formulations containing lactose as a filler produced faster release profiles but they were least affected by compression force. However, when MCC or PPS was used, drug release became slower with increasing applied force.

Table 2 shows the time taken for 50% of drug to be released (T50%) from formulations manufactured at different compression forces. These data suggest that when an insoluble (MCC) or partially soluble (PPS) filler is used in HPMC matrices, drug release rate may be influenced by applied force.

**Table 2. T50% (min)**

Drug	Filler	Compression Force (kN)		
		4	10	14
TP	Starch 1500	290	470	470
TP	MCC	230	340	360
TP	lactose	190	200	230
CPM	Starch 1500	215	380	420
CPM	MCC	185	280	300
CPM	lactose	95	160	175

Matrices containing PPS produced slowest drug release at all compression forces for both drugs. It was previously shown that increasing concentrations of Starch 1500 (20, 35 and 49.25%w/w) in the formulations caused a decrease in their release profiles (3).

Figures 1 & 2 show CPM release profiles from matrices compressed at 4 and 14 kN, respectively. Similar patterns were observed for formulations with theophylline (Fig. 3-4). Therefore, the effect seen with PPS is not just a spatial effect due to the presence of any insoluble or partially soluble filler, but it actively contributes to drug release kinetics. This contribution is imparted through possible interaction between Starch 1500 and HPMC or the filler actively forming an integral structure within the HPMC gel layer.

Figure 1. CPM Release in Water from Matrices Manufactured at 4 kN.

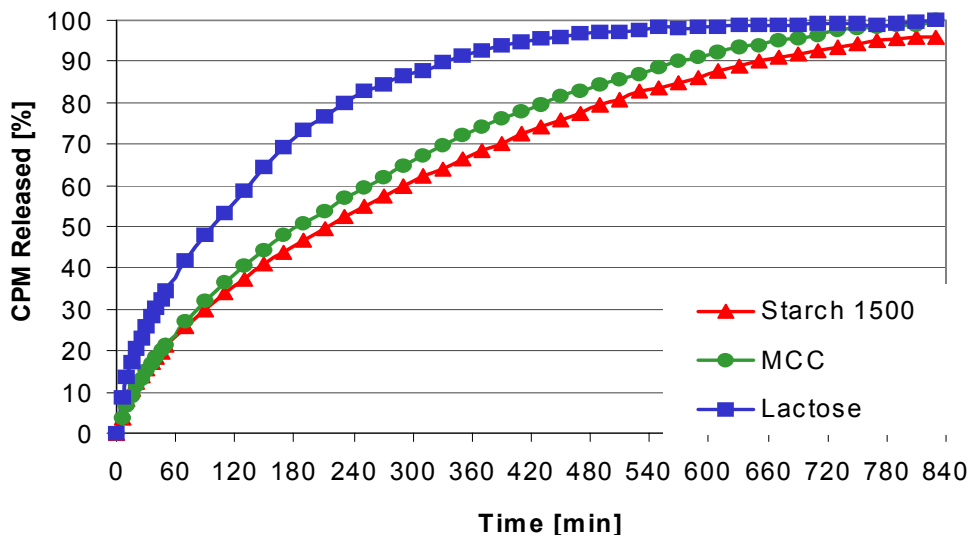


Figure 2. CPM Release in Water from Matrices Manufactured at 14 kN

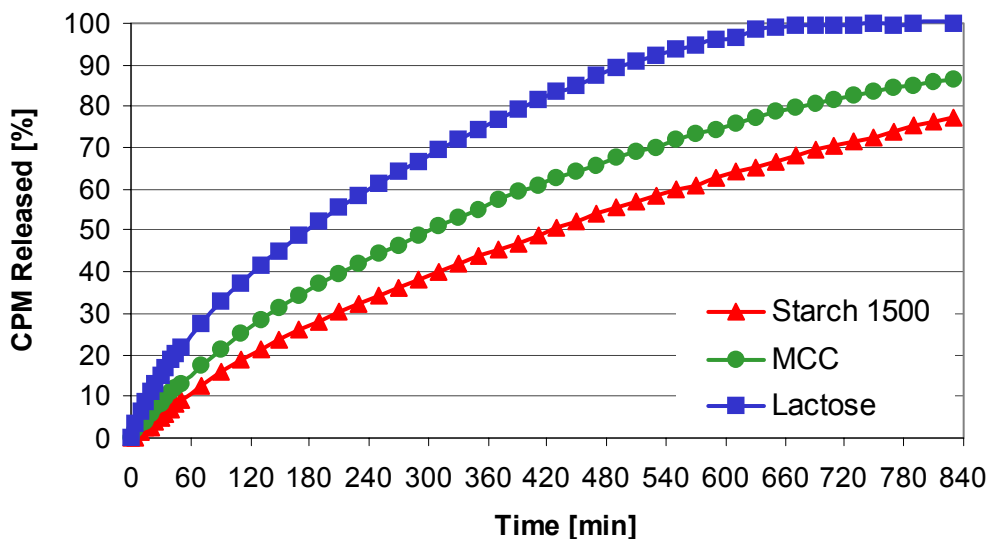
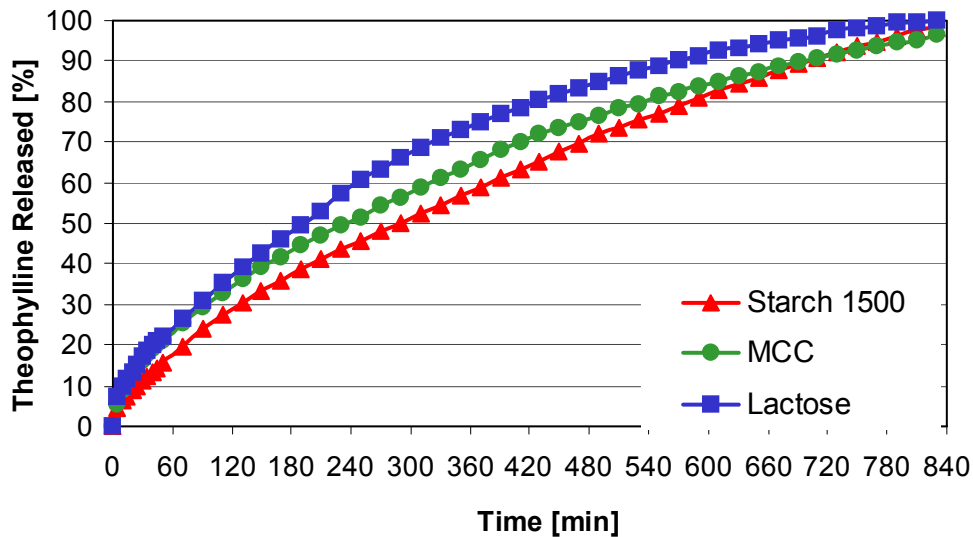
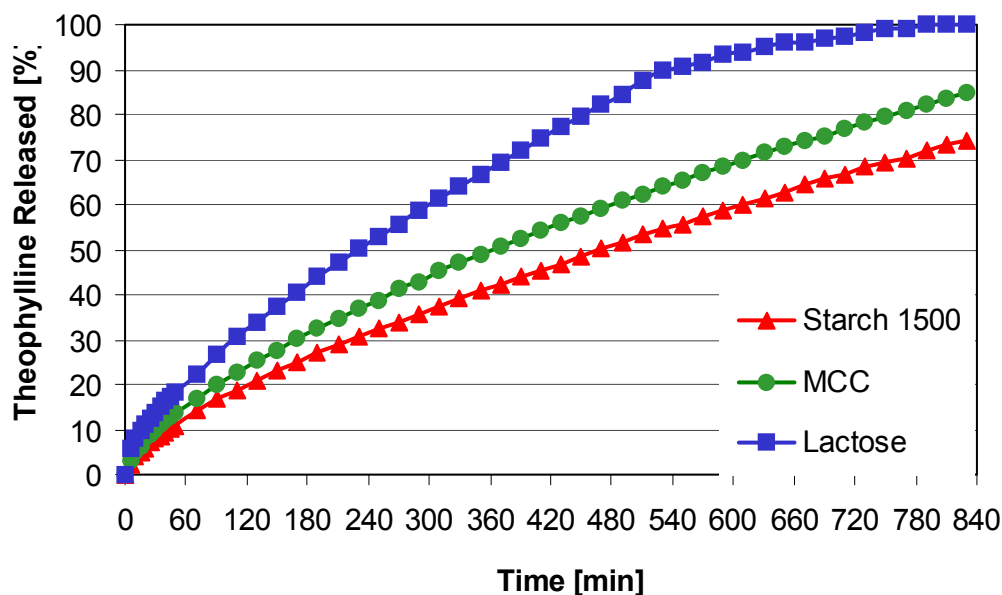


Figure 3. TP Release in Water from Matrices Manufactured at 4 kN.



**Figure 4. TP Release in Water from Matrices Manufactured at 14 kN.**



### Conclusions

All formulations had good powder flow, tablet weight uniformity and mechanical strength.

Drug release was found to be most affected by applied compression force, when Starch 1500 or MCC was used as a filler.

At all compression forces and with both drugs studied here, when Starch 1500 was used, drug release was slower compared to formulations containing MCC or lactose.

### References

1. Rajabi-Siahboomi, A.R. & Jordan M.P. European Pharm. Rev., 5, 4, 21-23 (2000).
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3. Levina, M. et.al., AAPS (2001).

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