

EXCIPIENT UPDATE

Influence of Fillers, Compression Force, Film Coatings & Storage Conditions on Performance of Hypromellose Matrices

By: Marina Levina, PhD

INTRODUCTION

Tablets are by far the most popular dosage form when administering drugs to patients. The ever-increasing demand for sustained-release (SR) preparations has led to significant research in this field. Non-ionic cellulose ethers, and more frequently, hydroxypropyl methylcellulose (HPMC, hypromellose) have been widely studied for their applications in oral SR systems since the early 1960s.^{1,2} Formulation development is simple and reproducible release profiles are well documented. HPMC displays good compression properties, can accommodate high levels of drug loading, and is considered non-toxic.³ When in contact with water, HPMC hydrates rapidly and forms a gelatinous barrier layer around the tablet.^{4,5} The underlying mechanisms of drug release from these systems are complex, involving up to three moving boundaries, usually termed the swelling, diffusion, and erosion fronts.⁶ 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.⁷⁻¹²

This article describes the influence of commonly used fillers, lactose, microcrystalline cellulose (MCC), and partially pregelatinized maize starch (Starch 1500®) on drug release from HPMC SR matrices manufactured at different compression forces. The Majority of reported studies in the literature are based on uncoated matrices. However, a large proportion of the tablets produced around the world are film coated. Tablets are coated for a variety of reasons, such as aesthetics; taste or odor masking; enhanced mechanical strength; and protection from moisture, light, and/or air. Here, the influence of the four most commonly used aqueous immediate-release film coating systems on the performance of hypromellose tablets, stored under different conditions up to 12 months, is investigated.

EXPERIMENTAL

A model formulation containing; only 20% hypromellose (Methocel® K4M, Dow), 30% drug, 49.25% filler, 0.5% fumed silica (Aerosil® 200, Degussa) and 0.25% magnesium stearate (Peter Greven) was used. Lactose (Fast-Flo®, Foremost), microcrystalline cellulose (Avicel® PH102, FMC) and partially pregelatinized maize starch (Starch 1500®, Colorcon) were used as fillers. Chlorpheniramine maleate (CPM) and theophylline (TP) were used as model freely water-soluble and slightly water-soluble drugs, respectively.

Tablets (333 mg) containing 100 mg of 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. The ejection force and tablet crushing strength for the tablets were measured. Drug release from the matrices was determined using a Caleva ST7 dissolution tester, USP apparatus II (paddle), in water at 100 rpm.

Tablets containing MCC as a filler,

compressed at 10 kN, were coated with four different film-coating systems [Opadry® II (33G), Opadry® II (85F), Opadry® AMB and Opaglos® 2; Colorcon] at 4% weight gain (Figure 1) in a 38-cm side vented pan (Labcoat IIX, O'Hara) using a Schlick spray gun.

Uncoated and coated tablets were stored in Securitainer® polypropylene jars (Jaycare Ltd) at 25°C/60%RH, 30°C/60%RH, and 40°C/75%RH for up to 12 months. Tablet mechanical strengths and release profiles were

determined at the end of 1, 2, 3, 6, and 12 months, respectively, and compared with that of freshly prepared tablets.

RESULTS & DISCUSSION

Effect of Fillers & Compression Force on HPMC SR Tablets

Excipients play a unique functional role in formulation design of an SR tablet. Apart from HPMC, the release-rate controlling

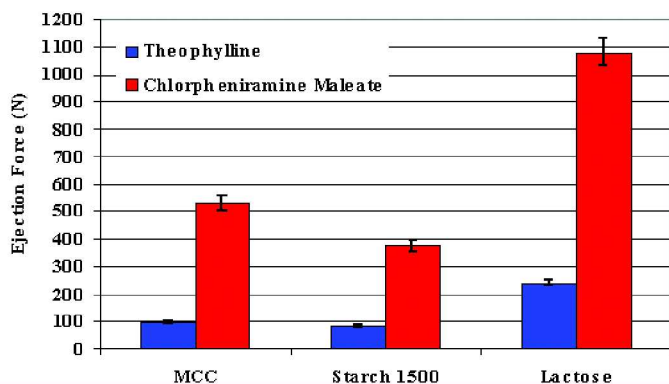
FIGURE 1

Coated HPMC Tablets



FIGURE 2

Effect of Fillers on Ejection Force



polymer, other excipients utilized in the fabrication of a hydrophilic matrix are fillers, binders, lubricants, glidants, etc. These materials are often necessary to enhance tablet formulation properties (to improve lubricity, powder flow, and compressibility) or to modify the drug-release profile. The effect of fillers on HPMC matrix performance will be dependent on the drug substance, the polymer level, and the level of the filler itself.

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

Figure 2 shows the ejection forces for the formulations containing theophylline or chlorpheniramine maleate. Formulations with lactose produced the highest ejection forces. In contrast, Starch 1500, due to its inherent lubricity, produced the lowest ejection forces.

Previously, it has been reported that the level of applied tablet compression force had no or very little influence on drug-release rate from HPMC SR tablets.^{10,13,14} In this study, it was found that applied pressure influenced drug-release rate, which was dependent on the type of filler used. Table 1 shows the time taken for 50% of drug to be released (T_{50%}) from tablets manufactured at different compression forces. The data suggests that an increase in compression force results in slower drug release. Gupta and Bansal suggested that compression force, by changing the dimensions of inter-particulate voids, modifies the drug-release kinetics.¹⁵ These voids govern both the rate of penetration of fluid into the tablet matrix and the release of the dissolved drug.

Melia suggested that there is considerable potential for interaction between the polymer network and added excipients, and this may influence the formation and properties of the gel layer and drug release.¹⁶ In this study, formulations containing lactose as a filler produced the fastest release profiles. Matrices containing partially pregelatinized starch (PPS) produced the slowest drug release at all compression forces for both drugs. In 2001, it was shown that increasing concentrations of partially pre-gelatinized maize starch (20%, 35%, and 49.25%w/w) in the HPMC

Table 1. The Influence of Compression Force & Fillers on Drug Release (T_{50%}) From HPMC SR Tablets

Drug	Filler	(T _{50%}) for tablets manufactured at different compression forces		
		4kN	10kN	14kN
Theophylline	Starch 1500	290	470	470
	MCC	230	340	360
	Lactose	190	200	230
Chlorpheniramine maleate	Starch 1500	215	380	420
	MCC	185	280	300
	Lactose	95	160	174

FIGURE 3

Chlorpheniramine Maleate Tablet Breaking Force

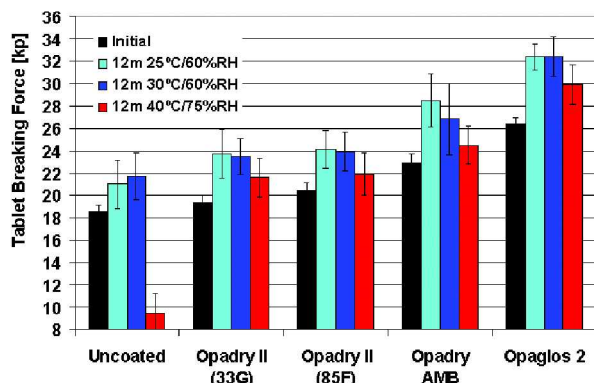


FIGURE 5 a

Effect of Coating on Chlorpheniramine Maleate Dissolution (a) Initial (b) After 12 Months Storage at 40°C/75%RH

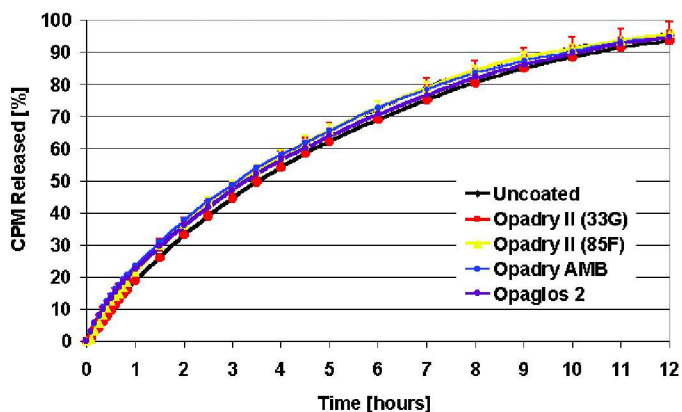
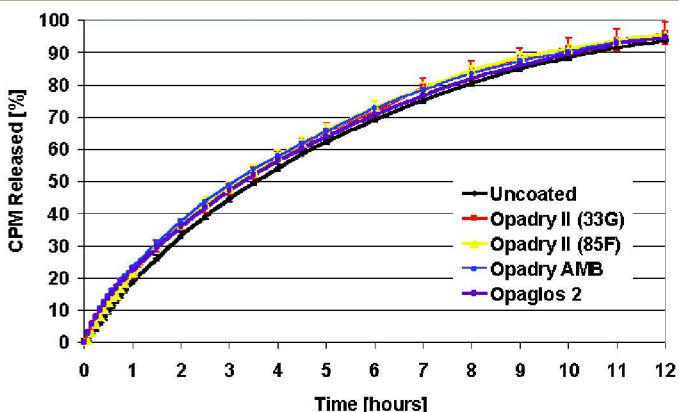


FIGURE 5 b



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FIGURE 4

Theophylline Tablet Breaking Force

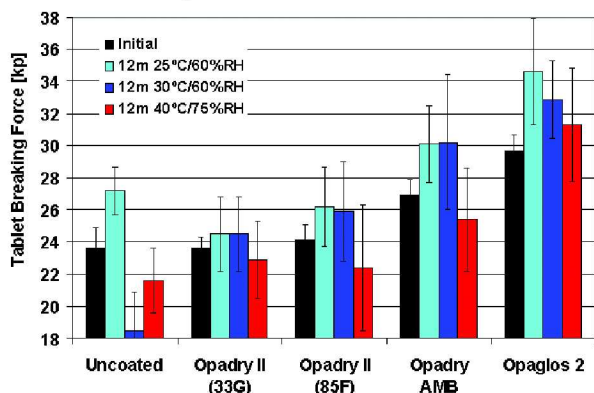


Table 2. Similarity Factor (f_2) for Comparison Between “0” Time Point Dissolution and After 12 Months 40°C/75%RH Storage

	CPM	TP
Uncoated	64	98
Opadry II (33G)	90	80
Opadry II (85F)	91	88
Opadry AMB	82	82
Opaglos 2	87	86

formulations caused a decrease in drug release rates.¹⁷ The effect seen with Starch 1500 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 PPS and hypromellose or the filler actively forming an integral structure within the HPMC gel layer.

Effect of Film Coating & Storage Conditions on HPMC SR Tablets

Alderman stated that cellulose ethers are generally very stable over a wide range of conditions.⁴ The polymer is non-ionic, so that it will not react with or bind drug substances. Normal storage conditions will not generally affect drug release. This claim was confirmed by the results of the present study. All coated and uncoated tablets had low weight variation and good mechanical strength initially and after 12 months storage. Application of film

coatings generally resulted in an increase in tablet breaking force initially and on storage (Figures 3 & 4).

Good stability results were produced at all storage conditions after 1, 2, 3, 6, and 12 months. No changes were observed in tablet appearance. No significant decrease in tablet mechanical strength was recorded. Dissolution profiles were compared using f_2 , a similarity factor.¹⁸ An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. The results in Table 2 indicate that no significant difference was observed in drug release rates after 12 months storage at all three storage conditions. For both chlorpheniramine maleate and theophylline, there were no differences between drug release from coated or uncoated matrices (Figures 5a through 6b).

CONCLUSIONS

Drug release from HPMC matrices was found to be affected by applied compression force. At all compression forces and with both drugs studied here, when Starch 1500 was used, drug release was significantly slower compared to formulations containing microcrystalline cellulose or lactose. Partially pre-gelatinised 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. The effect of PPS on drug release from HPMC matrix tablet will be dependent on the drug substance and its level, the type and quantity of HPMC, and the amount of Starch 1500 used.

The model chlorpheniramine maleate and theophylline formulations, with Methocel K4M as the rate controlling polymer, show extended-release characteristics with excellent reproducibility after 12 months storage at 25°C/60%RH, 30°C/60%RH, and 40°C/75%RH. The four film coating systems used in this study [Opadry® II (33G), Opadry® II (85F), Opadry® AMB, and Opaglos® 2] improved tablet mechanical strength and did not influence drug-release profiles initially and during 12 months storage under different conditions.

FIGURE 6 a

Effect of Coating on Theophylline Dissolution (a) Initial (b) After 12 Months Storage at 40°C/75%RH

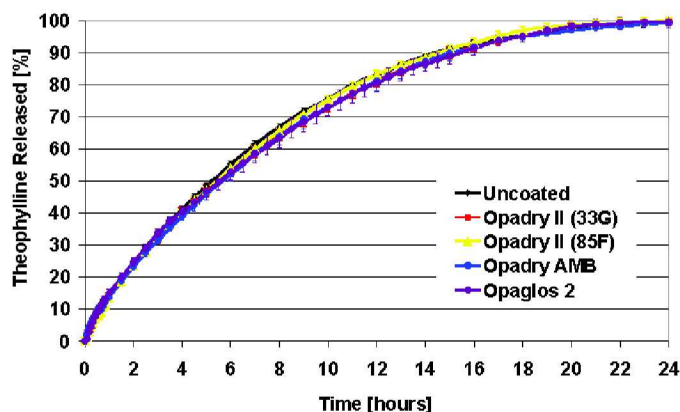
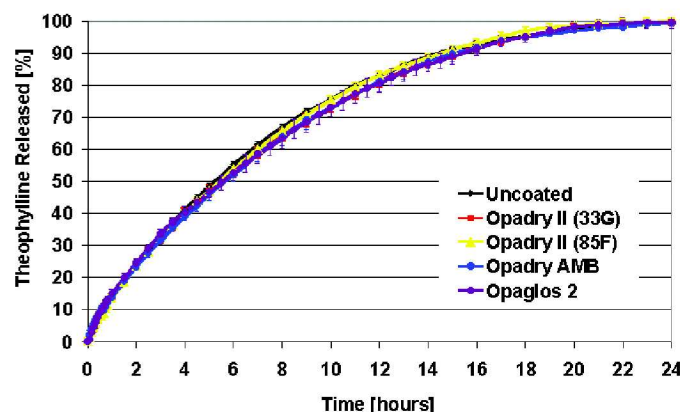


FIGURE 6 b



BIOGRAPHY



Dr. Marina Levina is the Global Technical Manager for Excipients at Colorcon. She earned her MSc in Chemistry (1992) from Mendeleev University of Chemical Technology of Russia (Moscow), her MSc in Environmental Sciences (1993) from Moscow International University, and her PhD in Pharmaceutical Technology (1999) from Liverpool John Moores University (UK). Throughout her academic career, Dr. Levina has conducted several research projects relating to the compaction characteristics of pharmaceutical powders. She has several publications on the principles and effects of ultrasonic vibration on drug compaction. Dr. Levina's technical expertise focuses on the development of solid oral dose formulations for both immediate-release and sustained-release applications.

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