Erodible Coatings Based on HPMC and Cellulase for Oral Time-Controlled Release of Drugs

Anastasia Foppoli, Alessandra Maroni*, Luca Palugan, Lucia Zema, Saliha Moutaharrik, Alice Melocchi, Matteo Cerea, Andrea Gazzaniga

Università degli Studi di Milano
Dipartimento di Scienze Farmaceutiche
Sezione di Tecnologia e Legislazione Farmaceutiche "Maria Edvige Sangalli"
via G. Colombo 71
20133 Milano, Italy

Corresponding author
*Alessandra Maroni
Università degli Studi di Milano
Dipartimento di Scienze Farmaceutiche
Sezione di Tecnologia e Legislazione Farmaceutiche "Maria Edvige Sangalli"
via G. Colombo 71
20133 Milano, Italy
Tel +39 02 50324654
email: alessandra.maroni@unimi.it

KEYWORDS

Swellable/erodible delivery systems, pulsatile release, hydroxypropyl methylcellulose, press-coating, cellulase, enzymatic degradation.

ABSTRACT

Oral drug delivery systems for time-controlled release, intended for chronotherapy or colon targeting, are often in the form of coated dosage forms provided with swellable/soluble hydrophilic polymer coatings. The latter are responsible for programmable lag phases prior to release, due to their progressive hydration in the biological fluids. When based on high-viscosity polymers and/or manufactured by press-coating, the performance of functional hydroxypropyl methylcellulose (HPMC) layers was not fully satisfactory. Particularly, it encompassed an initial phase of slow release because of outward diffusion of the drug through a persistent gel barrier surrounding the core. To promote erosion of such a barrier, the use of a cellulolytic product (Sternzym® C13030) was here explored. For this purpose, the dry mass loss behavior of tableted matrices based on various HPMC grades, containing increasing percentages of Sternzym® C13030, was preliminarily \studied, highlighting a clear and concentration-dependent effect of the enzyme especially with high-viscosity polymers. Subsequently, Sternzym® C13030-containing systems, wherein the cellulolytic product was either incorporated into a high-viscosity HPMC coating or formed a separate underlying layer, were manufactured. Evaluated for release, such systems gave rise to more reproducible profiles, with shortened lag phases and reduced diffusional release, as compared to the reference formulation devoid of enzyme.

1. INTRODUCTION

Several drug delivery systems for time-controlled release into the gastrointestinal tract, generally based on coated dosage forms or functional capsule shells, were proposed over the past three decades for chronopharmaceutical and colon targeting applications (Gazzaniga et al., 2011; Maroni et al., 2013, 2016; Melocchi et al., 2018). The relevant release-controlling layers were obtained using polymers having different physico-chemical properties, including swellable/soluble hydrophilic cellulose derivatives. By progressively interacting with the aqueous fluids, the latter polymers defer the onset of drug release until extensive dissolution/erosion of the gel barrier they form when undergoing glass-rubber transition.

The application of the erodible functional layer of delivery systems for time-controlled release posed a novel challenge in the manufacturing of solid pharmaceuticals. The available techniques, *i.e.* double-compression (press-coating) and spray-coating, were both attempted. Press-coating offered advantages related to its solvent-free nature and, therefore, to the circumvented need for time- and energy-consuming drying steps (Foppoli et al., 2017). For these reasons, it also represented a technique with limited impact on the overall stability of the products. On the other hand, it required considerable amounts of powdered material to be applied, thus restraining the flexibility of the delivery technology. Moreover, depending on the physico-chemical and physico-technological characteristics of the layer applied, it was demonstrated to yield excessively long-lasting lag phases prior to release, which would be inconsistent with both the chronotherapeutic and colon delivery goals pursued. Importantly, relatively thick coatings having porous structure, as resulting from compaction processes, were also shown to give rise to initially slowed release due to outward diffusion of the drug through the hydrated polymer layer before its complete dissolution/erosion (Foppoli et al., 2019). This phenomenon would clearly clash with the prompt and quantitative release mode that would be desired at the end of the lag phase, being associated with diverse sigmoidal patterns.

Spray-coating was subsequently employed making use of hydro-organic film-forming systems. The resulting coated units showed satisfactory physico-technological characteristics and release performance. However, the use of organic solvents would no longer be of choice. Aqueous spray-coating, undertaken mainly in view of greater regulatory acceptability, involved longer processing time along with feasibility issues given the rheological characteristics of the film-forming solutions. Despite all technical hurdles, aqueous-coated systems having the desired aspect and mechanical resistance were obtained following proper setup of the operating conditions. While the desired release patterns were attained with low-viscosity HPMC grades, the high-viscosity ones partly failed to meet expectations (Maroni et al., 2002). In this respect, Methocel® K4M was shown to bring about a phase of diffusional release that was poorly evident *in vitro* though of major impact *in vivo*, thus impairing the overall performance of the delivery system that turned out more alike to a reservoir formulation for prolonged release (Figure 1). Furthermore, due to the marked release-deferring ability of such polymers, possible difficulties were anticipated in fine modulation of the lag time through modification of the coating level.

Therefore, release issues associated with coatings based on high-viscosity swellable/soluble polymers and/or manufactured by double-compression technique are still to be addressed. In order to overcome the aforementioned limitations, thereby broadening the scope of application of such a technique and of such polymers, formulation changes, to be introduced into the original design of the erodible systems, were needed.

Based on these premises, the incorporation of cellulase, either in admixture with the functional coating polymer or separately loaded within a contiguous layer, was here explored with the aim of promoting erosion of the gel formed upon polymer hydration, thus preventing an enduring diffusional barrier from building up and affecting the rate of drug release over an extended time frame. Cellulases are enzymes or multienzymatic complexes produced by different microorganisms, which catalyze breakdown of cellulose and other structurally-related polysaccharides into glucose and cello-oligo saccharides (FAO, 1997). Such enzymes are widely

used in processing of food of plant origin, and in pulp and paper industry (Bhat, 2000; Bhat and Bhat, 1997; Jonas and Farah, 1998). They also have medical and biomedical applications, for the treatment of gastric phytobezoars and degradation of bacterial biofilms, and could be used as food supplements for fiber digestion and prebiotic purposes (Kramer and Pochapin, 2012) (Exercise.com. *Cellulase*, 2020). Exploitation of enzymes having cellulolytic activity has recently been proposed to turn pharmaceutical excipient microcrystalline cellulose into nanocellulose with improved tensile properties (Satyamurthy and Vigneshwaran, 2013).

In the present work, the potential impact of a cellulolytic product of common use in the food industry (Sternzym® C13030) on the dissolution/erosion behavior of various HPMC grades was preliminarily studied by incorporating it into tableted polymer matrices, used as a model compression-coating, and performing dry mass loss experiments. Moreover, Sternzym® C13030-containing erodible systems for time-controlled release having diverse configuration were manufactured, using different coating techniques, and subsequently evaluated for release behavior.

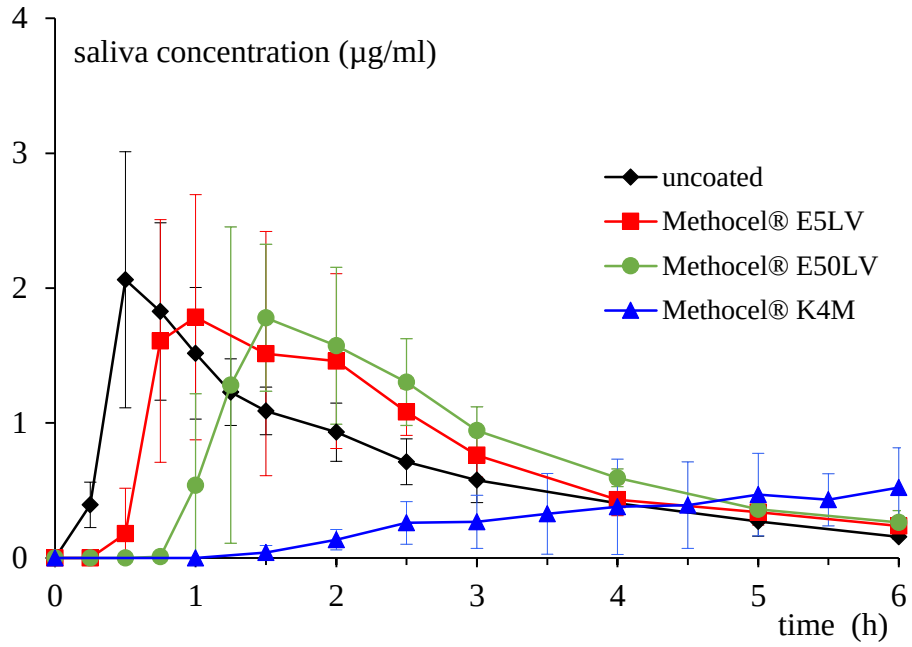

Figure 1: saliva concentration profiles of acetaminophen after intake of uncoated cores and units coated with Methocel® E5LV, E50LV and K4M up to 20% weight gain [adapted from Maroni et al., 2002].

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2. MATERIALS AND METHODS

2.1 Materials

Acetaminophen for direct compression (AMP, C.F.M., Italy), cellulose acetate propionate (CAP 482-20, Eastman-Kodak, Tennessee), colloidal silica (Aerosil® 200, Evonik, Germany), ethylcellulose (Ethocel®, Dow Italia, Italy), hydroxypropyl methylcellulose 2910 USP (Methocel® E50LV, M_n=20000, Dow Italia) and 2208 USP (Methocel® K100LV, M_n=26000; Methocel® K4M, M_n=86000; Methocel® K15M, M_n=120000; Methocel® K100M, M_n=220000), magnesium stearate (Carlo Erba Reagenti, Italy), maltodextrin (Glucidex® IT19W, Roquette, France), microcrystalline cellulose (Vivapur®101, JRS Pharma, Germany), sodium starch glycolate (Explotab®, JRS Pharma, Germany), Sternzym® C13030 (SternEnzym, Germany, a kind gift from IMCD Italia, Italy; 2500 u/g enzymatic activity, expressed as hemicellulase according to DNS method at pH 6.0 as reported in the product technical data sheet).

2.2 Methods

Manufacturing of matrices

Flat-faced cylindrical matrices (diameter 25 mm, nominal weight 1.0 g) were prepared by a rotary press (AM 8S, Officine Ronchi, Italy) from HPMC (Methocel® E50LV, Methocel® K100LV, Methocel® K4M, Methocel® K15M and Methocel® K100M), either as such or in admixture with Sternzym® C13030 (1, 5 and 10%) or maltodextrin (10%), under approximately 2000 kg compaction force so that the resulting tablet had crushing strength in the range 70-100 N (crush tester TBH30 Erweka, Germany; n=10). The matrices were provided with an impermeable film, covering their whole surface except for one base, that was obtained by dipping into a 15% w/v CAP solution in acetone.

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149 Mass loss experiments

150 Partially coated units exposing a surface of constant area (n=3) were placed in the vessels of a
151 paddle dissolution apparatus (Dissolution System 2000, Distek, New Jersey) containing 150 mL of
152 deionized water thermostated at 37±1°C, so that the distance from the stirrer bottom and the matrix
153 surface exposed to the fluid was 1.5 cm. The paddle rotation speed was set at 100 rpm. At fixed
154 time points, 15 ml of fluid was withdrawn, replaced with fresh medium, and dried at 80°C to
155 constant weight. Mass loss was assessed as the amount of solids recovered after drying of each fluid
156 sample, and the relevant data were plotted against time to build cumulative curves. The rate of mass
157 loss was calculated as the slope of the regression lines in the 1.5-6 h time frame.

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159 Manufacturing of tablet cores

160 Acetominophen (80.0%), microcrystalline cellulose (14.5%), sodium starch glycolate (4.5%),
161 magnesium stearate (0.5%) and colloidal silica (0.5%) were mixed in a V-blender (Erweka,
162 Germany). The mixture was tableted by a rotary press equipped with concave punches (diameter 4
163 mm, curvature radius 4 mm). The tablets were checked for weight (analytical balance BP211D
164 Sartorius Mechatronics, Germany; n=20), height and diameter (digital micrometer Mitutoyo, Japan;
165 n=20), crushing strength, friability (friabilometer TA3R Erweka, Germany) and disintegration time
166 (three-position disintegration apparatus DT3 Sotax, Switzerland, n=6). The weight, height,
167 diameter, crushing strength, friability and disintegration time were 39.0±0.5 mg, 3.092±0.028 mm,
168 4.034±0.003 mm, 70±4N, < 1% and <5 min, respectively.

169

170 Coating of tablet cores

171 One-layer systems: Methocel® K4M, either as such or manually mixed with Sternzym® C13030 at 1
172 and 5%, was applied onto tablet cores by manual press-coating using 80 mg of coating powder. Half
173 of the powder was first introduced into the die (Ø 6 mm) of the tableting machine. The tablet core

was positioned centrally onto the pre-compressed powder bed. Then, the remainder of the coating powder was fed into the die and compaction forces of approximately 500 kg were applied, using concave punches with 6 mm curvature radius.

Two-layer systems: an inner layer of Sternzym® C13030 and an outer layer of Methocel® K4M were applied by aqueous spray-coating in rotating pan (Ø 12 cm, GS, I) equipped with a two-way nozzle (mod 970/7-1 S75, Ø 1.2 mm, Düsen-Schlick, Untersiemau, Germany) and press-coating, respectively. Sternzym® C13030 amounted to 1% or 5% w/w of the applied amount of Methocel® K4M. In the two cases, coating solutions differing in composition were used for application of Sternzym® C13030 (Table I). Particularly, the addition of maltodextrin was aimed at having the same amount of solid material applied onto the cores by spray-coating, also enabling easier in-process monitoring of the substrate growth. The cores were coated up to nominal weight gain of 11%, under the following operating conditions: batch size 100 g; inlet air temperature 60 °C; product temperature 38 °C; pan rotation speed 30 rpm; nebulization air pressure 0.2 bar; solution spray rate 2.9 g/min . Methocel® K4M was then applied by press-coating, as described above.

Table I. Percentage composition of the coating solutions used for application of Sternzym® C13030 at 1% (A) or 5% (B) w/w of Methocel® K4M

	A	B
Sternzym® C13030	2	10
Maltodextrin	8	-
PVP	1	1
Distilled water	89	89

Characterization of coated systems

Coated systems were characterized for weight, height, diameter (n=20), crushing strength (n=10) and friability. Coating thickness was calculated as half of the mean difference between the height and diameter of coated units and tablet cores, respectively. Photomicrographs of cross-sectioned systems were acquired by scanning electron microscope (SEM). Samples were gold-sputtered using a plasma evaporator under vacuum, and the photomicrographs were acquired at an accelerated voltage of 10 kV at 20 and 80x magnifications (Leo 1430, Carl Zeiss, Switzerland).

For release studies, an adapted disintegration test method was used in order to avoid previously observed sticking of the swollen units to the vessels of the dissolution apparatus (Zema et al., 2007). Tests (n=3) were performed by Ph. Eur. 9.8 disintegration apparatus. Each unit was inserted into a basket-rack assembly so that only one of the 6 available tubes was occupied. The basket-rack assemblies moved in separate vessels at a constant 29 to 32 cycles/min frequency through a 55±2 mm distance, immersed in 800 ml of distilled water at 37±1 °C. Fluid samples were withdrawn automatically at predetermined time points, and acetaminophen was quantified by

spectrophotometer at 248 nm (Lambda 25, Perkin Elmer, Italy). In the cumulative release profiles obtained, the duration of the lag phase prior to release (lag time) was assessed as the last time point before steep increase of the curve.

3. RESULTS AND DISCUSSION

3.1 Evaluation of mass loss from HPMC matrices containing cellulase

The impact of cellulolytic enzymes on the performance of drug delivery systems based on hydrophilic cellulose derivatives has never been in-depth investigated, at least to the best of our knowledge. In order to preliminarily verify whether the enzyme may play any role in formulations for time-controlled release, the mass loss behavior of HPMC matrices was studied in the presence of cellulase. A commercially available enzymatic product (Sternzym® C13030), used in fruit and vegetable processing, was employed for this purpose. Sternzym® C13030 contains, in admixture with maltodextrin as a bulking agent, enzyme proteins with cellulolytic and various other hydrolytic activities, such as xylanase, glucanase and pectinase. Sternzym® C13030 appeared as a light brown powder formed from particles having d_{10} =45.52 μm, d_{50}=99.88 μm and d_{90}=203.01 μm size, as measured according to (Foglio et al., 2016).

Different HPMC grades, covering a broad spectrum of applications in pharmaceutical formulation, were selected for the study: Methocel® E50LV, Methocel® K100LV, Methocel® K4M, Methocel® K15M and Methocel® K100M, having viscosity of 2% w/v aqueous solutions in the 50-100000 cps range at 20°C. Cylindrical matrices based on each of these polymers, containing concentrations of Sternzym® C13030 of 1, 5 and 10%, were obtained by compaction and afterwards provided with an impermeable partial coating, so that a single surface of constant area could be

exposed to the medium. Partially coated matrices containing no cellulase, either composed of HPMC as such or in admixture with 10% of maltodextrin in the place of Sternzym® C13030, were also manufactured for comparison purposes. All matrices were tested in stirred thermostated water, and aliquots of fluid, withdrawn at programmed time points, were dried to constant weight in order to assess the amount of solids lost throughout the experiment. Particularly, the dry mass retrieved would result from *i*) dissolution of undegraded polymer, *ii*) enzymatic degradation of the polymeric chains and/or *iii*) mechanical erosion of swollen portions of the sample.

The profiles of mass loss from matrices based on HPMC grades of increasing viscosity, with or without Sternzym® C13030, are reported in Figures 2-6. During the test, the free surface of the matrices showed smooth and homogeneous aspect, devoid of rough areas or evident dips, upon interaction with water. Moreover, no eroded fragments of the swollen polymer matrix were noticed in the medium.

The process of mass loss in the time frame from 1.5 to 6 h was almost linear in all cases, although a tendency to initially slow mass loss could be observed, which was less pronounced with increasing enzyme percentages. Mass loss was found clearly affected by the enzyme, turning out to be enhanced in a concentration-dependent mode. Such an effect was generally highlighted even when the cellulolytic product was added at 1%, *i.e.* at the lowest percentage in the investigated range. Sternzym® C13030 was shown to impact on the mass loss behavior of matrices to a different extent depending on the HPMC grade. In particular, when the enzymatic product was added at 10% w/w, the rate of the process was almost doubled in the case of Methocel® E50LV and Methocel® K100LV, while an approximately ten-fold higher rate of mass loss was observed with Methocel® K4M, Methocel® K15M and Methocel® K100M. The greater differences observed in the case of the high-viscosity grades of HPMC could be ascribed to the inherently thicker and thus more persistent gel they form upon hydration, which would make enzymatic degradation of the polymer be reflected in a more evident tendency to dissolution and susceptibility to mechanical erosion.

For comparison, the rates of mass loss obtained in the time frame from 1.5 to 6 h are comprehensively reported in Figure 7. From the histograms, the more marked stepwise increase in mass loss rate as a function of the concentration of Sternzym® C13030 shown by Methocel® K4M, Methocel® K15M and Methocel® K100M matrices is highlighted. In spite of the diverse molecular mass and viscosity, no major differences were observed among these polymers, which would be in line with comparable mass loss behavior of the relevant matrices devoid of enzyme under the investigated hydrodynamic conditions.

Moreover, the low-viscosity polymers, namely Methocel® E50LV and Methocel® K100LV, considerably differed from each other in terms of extent to which the relevant mass loss behavior was influenced by the enzyme. Indeed, although the mass loss rate in the absence of Sternzym® C13030 was comparable, a much greater value was reached in the case of Methocel® K100LV when the enzymatic product was present at 10%. This gap might be due to the higher hydrophilicity of Methocel® K100LV *vs* Methocel® E50LV, in view of the lower degree of methoxyl substitution of series K polymers, and/or to its greater viscosity.

In order to verify whether highly water-soluble maltodextrin contained in Sternzym® C13030 may have played any role in bringing about the observed increase in mass loss rate, high-viscosity HPMC-based matrices containing this excipient at 10% in the place of the enzymatic product were also evaluated (Figures 4-6). The influence of the sole maltodextrin turned out negligible. Indeed, the profiles of the maltodextrin-loaded matrices were almost superimposed on those relevant to the matrices based on HPMC as such. Therefore, it could be ruled out that simple osmotic and/or channeling effects, due to the soluble diluent contained in the enzymatic product, may be responsible for the enhanced rate of mass loss. Moreover, these results indicate that the cellulolytic activity of Sternzym® C13030 would not be impaired by compaction, at least at the forces employed for manufacturing of the matrices.

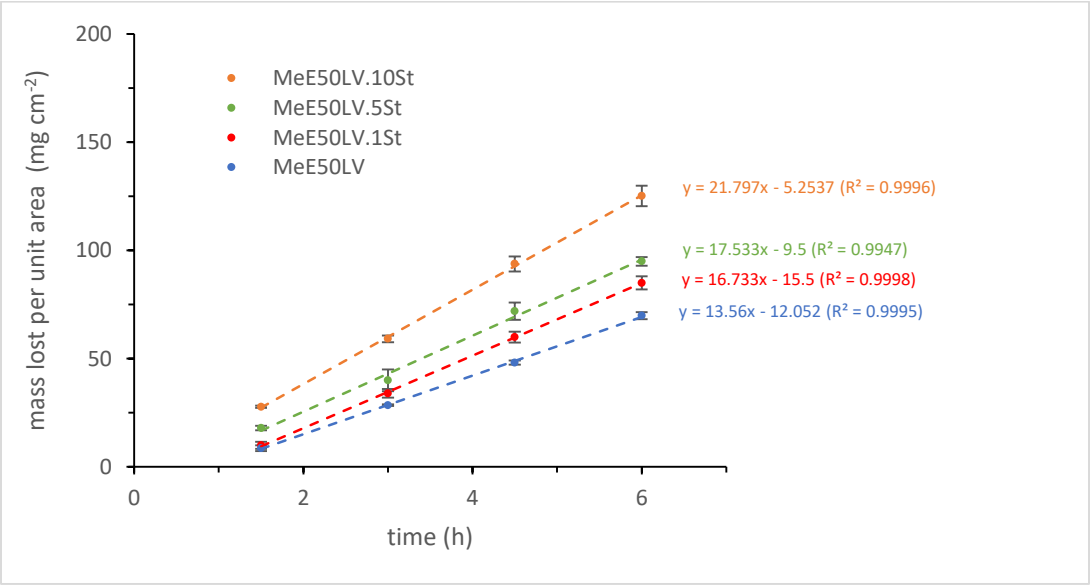


Figure 2: profiles of mass loss vs time from Methocel® E50LV matrices containing differing amounts of cellulase (bars indicate SD).

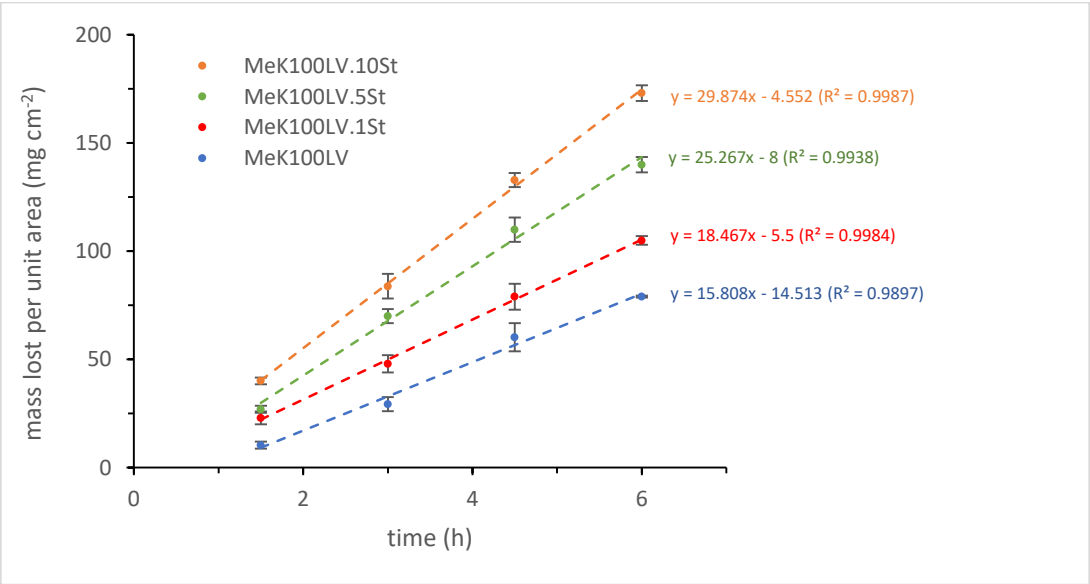


Figure 3: profiles of mass loss vs time from Methocel® K100LV matrices containing differing amounts of cellulase (bars indicate SD).

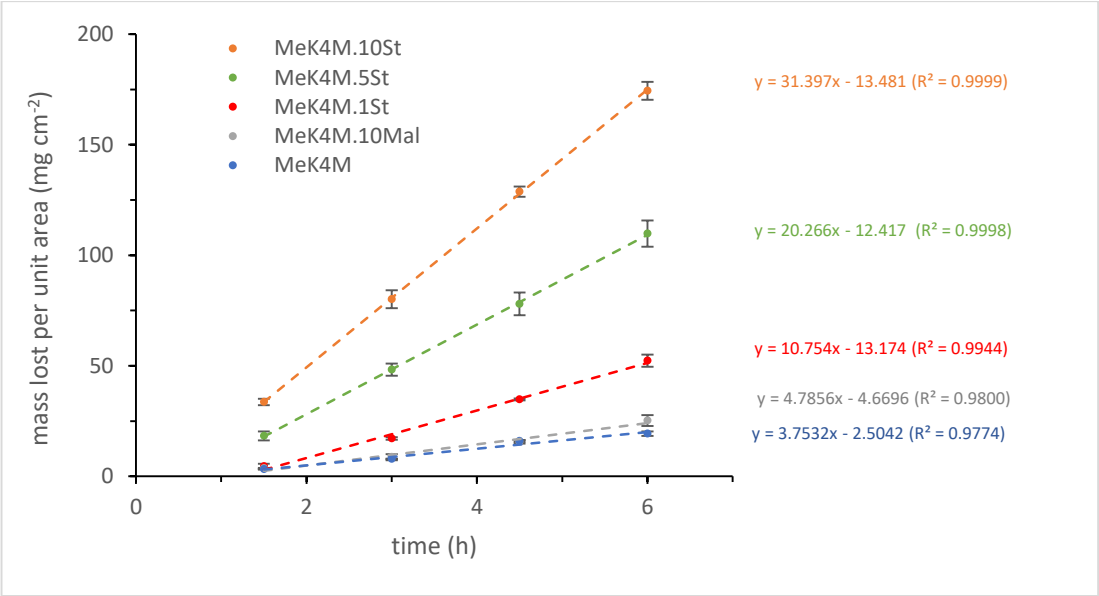


Figure 4: profiles of mass loss vs time from Methocel® K4M matrices containing differing amounts of cellulase (bars indicate SD).

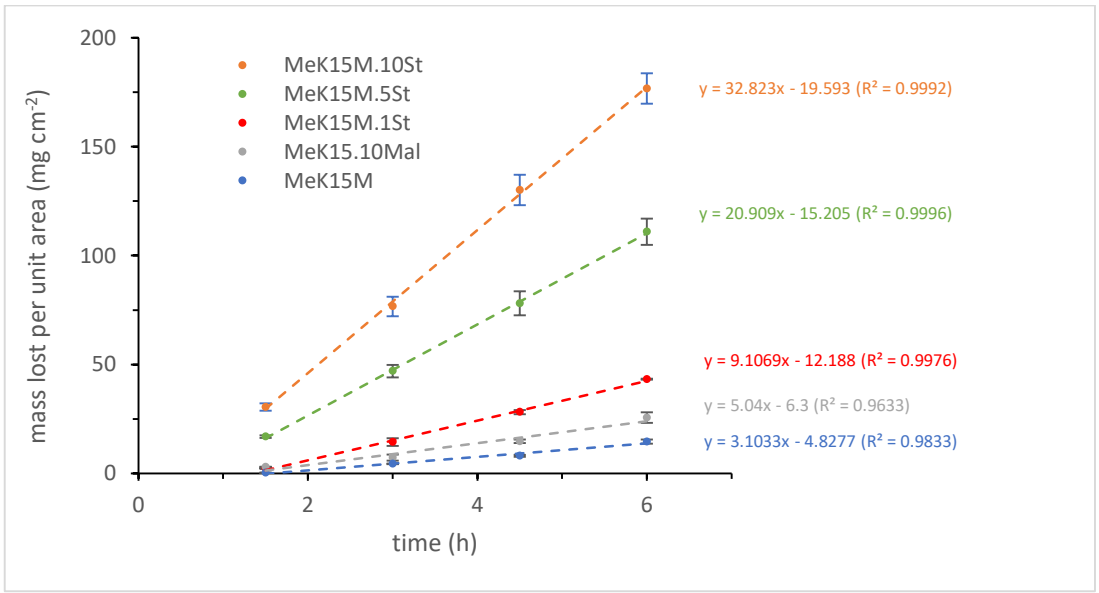
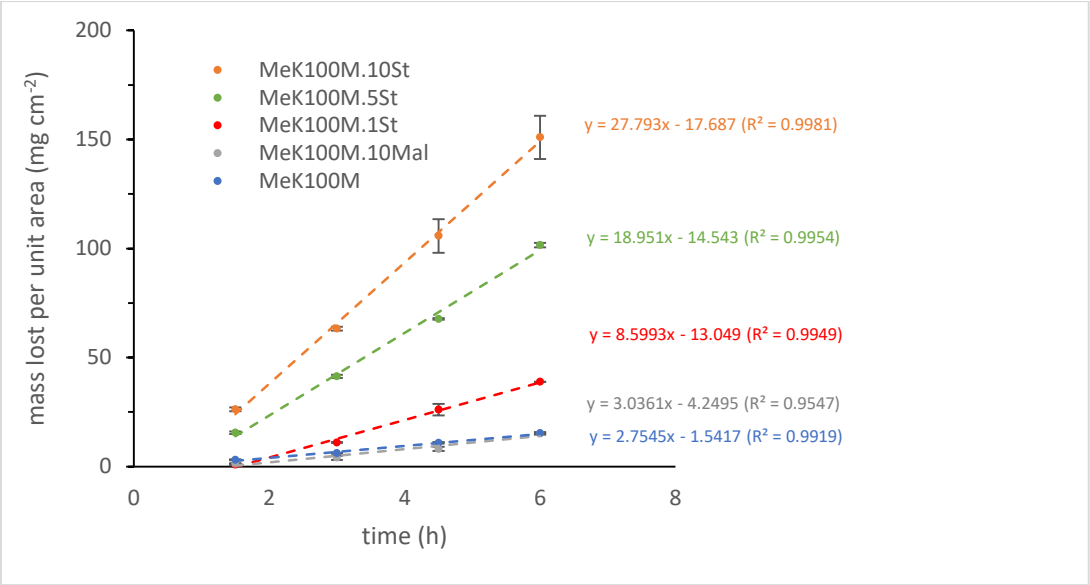


Figure 5: profiles of mass loss vs time from Methocel® K15M matrices containing differing amounts of cellulase (bars indicate SD).



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318 Figure 6: profiles of mass loss vs time from Methocel® K100M matrices containing differing
319 amounts of cellulase (bars indicate SD).

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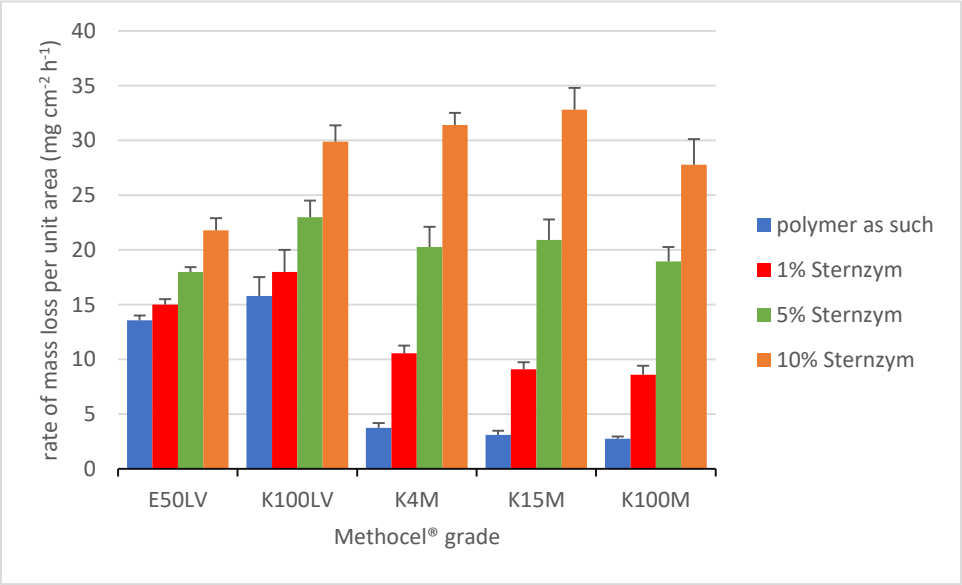

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325 Figure 7: mass loss rate per unit area of matrices based on different HPMC grades as a function of
326 Sternzym® C13030 concentration in the 1.5-6 h time frame (bars indicate 95% confidence
327 interval).

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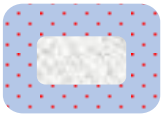
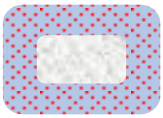
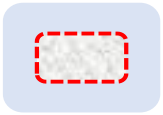
3.2 Evaluation of systems coated with high-viscosity HPMC and cellulase

Once a clear effect of cellulase on mass loss from the polymeric matrices was demonstrated, especially evident with the higher viscosity HPMC grades, the outcome of incorporating Sternzym® C13030 into coated formulations for time-controlled release was evaluated. Among the high-viscosity polymers investigated, which all showed comparable mass loss behavior, Methocel® K4M was selected for the study based on *in vivo* results previously obtained when it was applied as a functional coating layer. Indeed, such a polymer was demonstrated to impair the release performance of the coated dosage forms by generating an extended phase of slow release possibly due to diffusion of the drug through a persistent gel layer.

In order to broadly explore the potential role of the enzyme, the cellulolytic product was incorporated, in nominal amounts of 1% and 5% with respect to the HPMC mass, into either the HPMC coating (one-layer configuration: 1LC-1St and 1LC-5St) or an underlying layer (two-layer configuration, 2LC-1St and 2LC-5St) of the delivery system (Table II). Press-coating was employed for application of Methocel® K4M, both as such and in admixture with Sternzym® C13030, onto immediate-release tablet cores. This technique was used in view of its well-known benefits as a simple dry-coating process coupled, however, with the critical impact of the rather elevated amount of coating powder needed, which would worsen the issues related to the use of a high-viscosity polymer. When the system was manufactured in its two-layer configuration, the application of Sternzym® C13030 as an aqueous solution was carried out by spray-coating.

Coated units having uniform aspect and satisfactory physico-technological characteristics were obtained, irrespective of the configuration of the system (Figure 8). The compression-coatings exhibited even surface. While the inner Sternzym® C13030 film appeared continuous and uniform in thickness, the tableted layer, as expected, showed a more porous structure and higher variability in thickness.

Table II: outline of the systems under investigation and main physico-technological characteristics

		Code	Nominal Sternzym concentration (% w/w on HPMC)	Weight (mg)	Coating (1 or 2 layers) thickness (µm)	Sternzym layer thickness* (µm)
uncoated core		UC		39.0±0.5		
one-layer HPMC coated system		1L.Me	-	120.2±1.5	813±14	
one-layer HPMC/Sternzym® coated systems		1L.Me1St	1	120.1±0.9	813±17	
		1L.Me5St	5	118.8±1.2	811±10	
two-layer HPMC/Sternzym® coated systems		2L.Me1St	1	120.0±1.6	801±12	70±9
		2L.Me5St	5	122.4±1.2	805±14	75±11

*thickness measured before application of the HPMC layer by press-coating

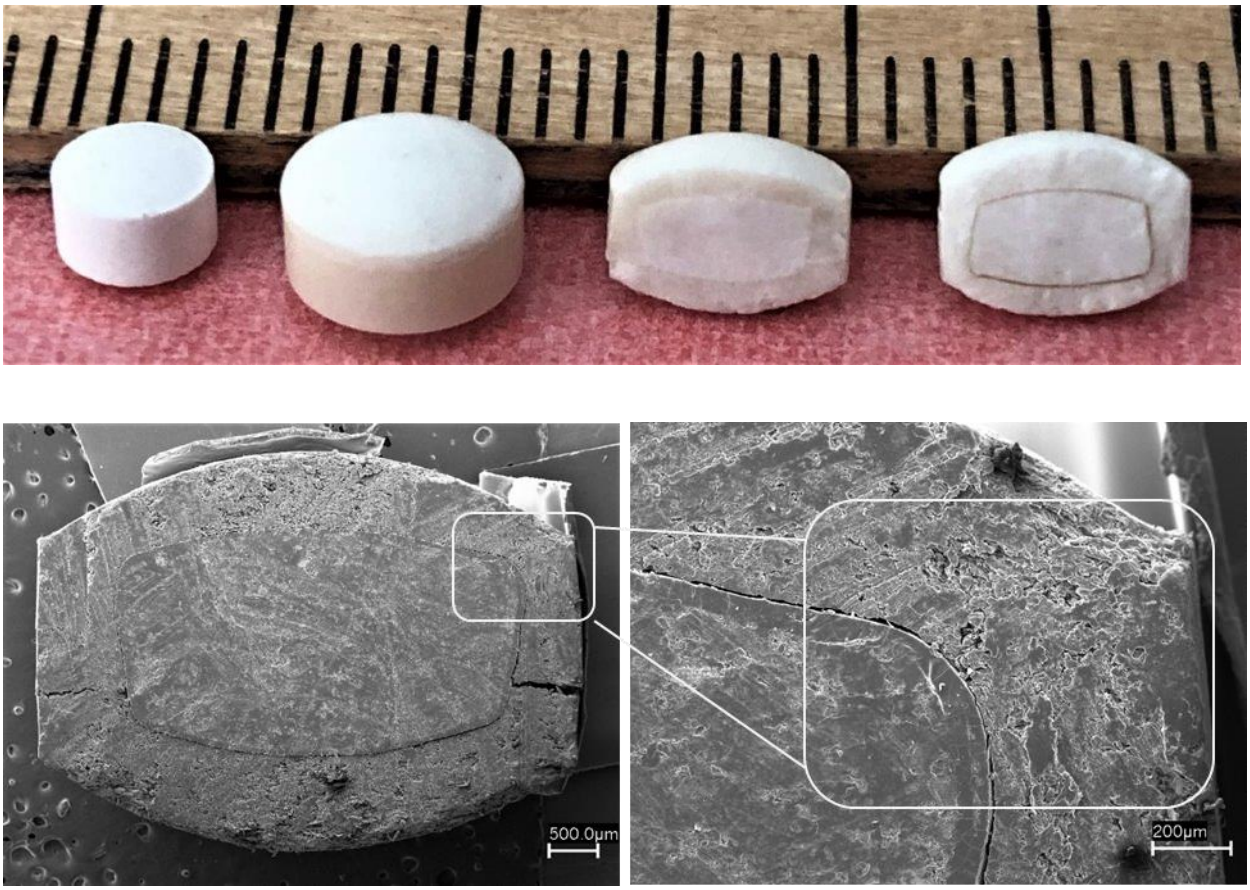


Figure 8: picture of a core tablet, a coated system and one- and two-layer cross-sectioned systems (top image, left to right; graded notches in mm); SEM photomicrographs of a two-layer cross-sectioned system at 20x and 80x magnification (bottom images, left to right).

The release performance of the systems manufactured in the one- and two-layer configurations was comparatively evaluated *vs.* the Methocel® 4KM-coated reference formulation (1LC.Me). In the absence of Sternzym® C13030, an average lag time of 540 min, *i.e.* the time to breakup of the system as indicated by steep increase in the release rate, was obtained (Figure 9). The profiles were characterized by marked variability and diffusional release covering most of the overall lag phase, up to approximately 20% of the drug content. This particular release pattern would be in agreement with the aforementioned pharmacokinetic results (Maroni et al., 2002).

The release curves from one-layer systems having Sternzym® C13030 within the HPMC coating (1LC.Me1St and 1LC.Me5St) were reproducible, and lag times turned out considerably reduced as a function of the amount of enzyme incorporated (Figure 10). The phase of slow outward diffusion of the drug through the swollen polymer layer appeared largely restrained both in terms of extent and duration. However, an earlier onset of this diffusion phenomenon was noticed with respect to the Methocel® K4M-coated units devoid of enzyme. Because the time to first detection of the drug in the test medium would result from the time the solvent takes to reach the core (swelling front movement) on the one hand, and the time the drug in solution takes to diffuse through the hydrated HPMC layer on the other, the presence of cellulase could have brought about faster water penetration due to polymer degradation and consequently decreased viscosity of the gel barrier. These concomitant phenomena would have also promoted erosion of the hydrated layer, thus leading to shorter diffusional path to be covered by the drug tracer. Such findings would be consistent with previously presented data of mass loss from matrices.

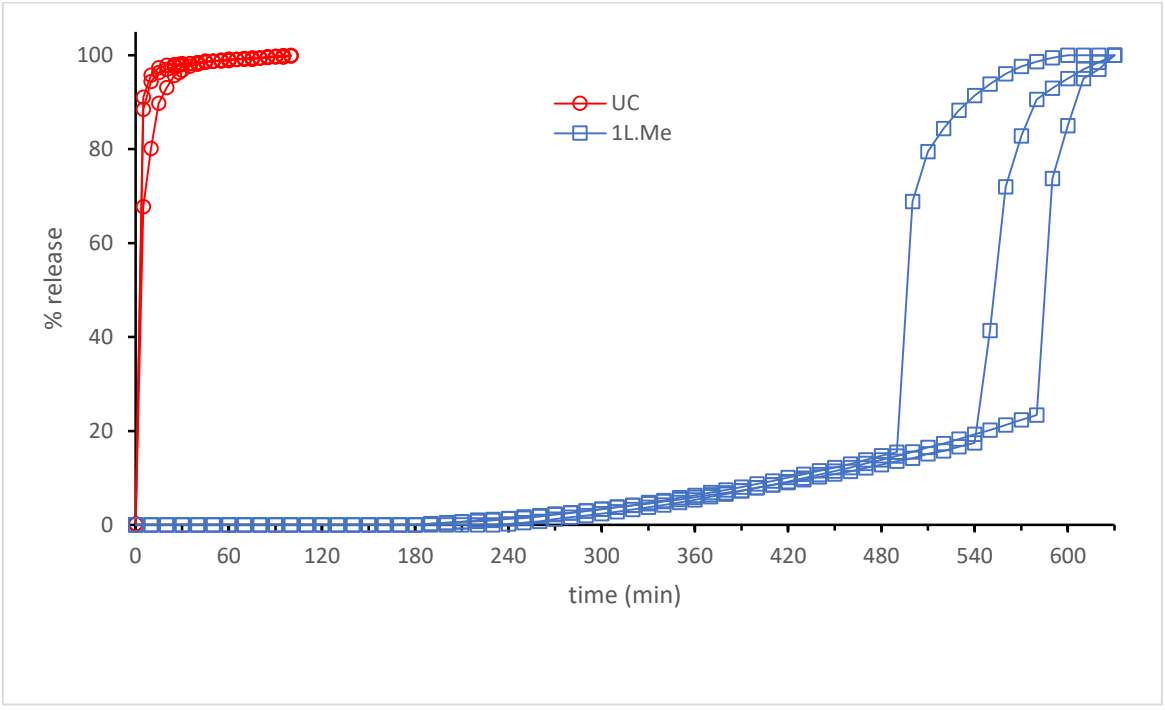


Figure 9: acetaminophen release profiles from uncoated cores and one-layer Methocel® K4M-coated systems.

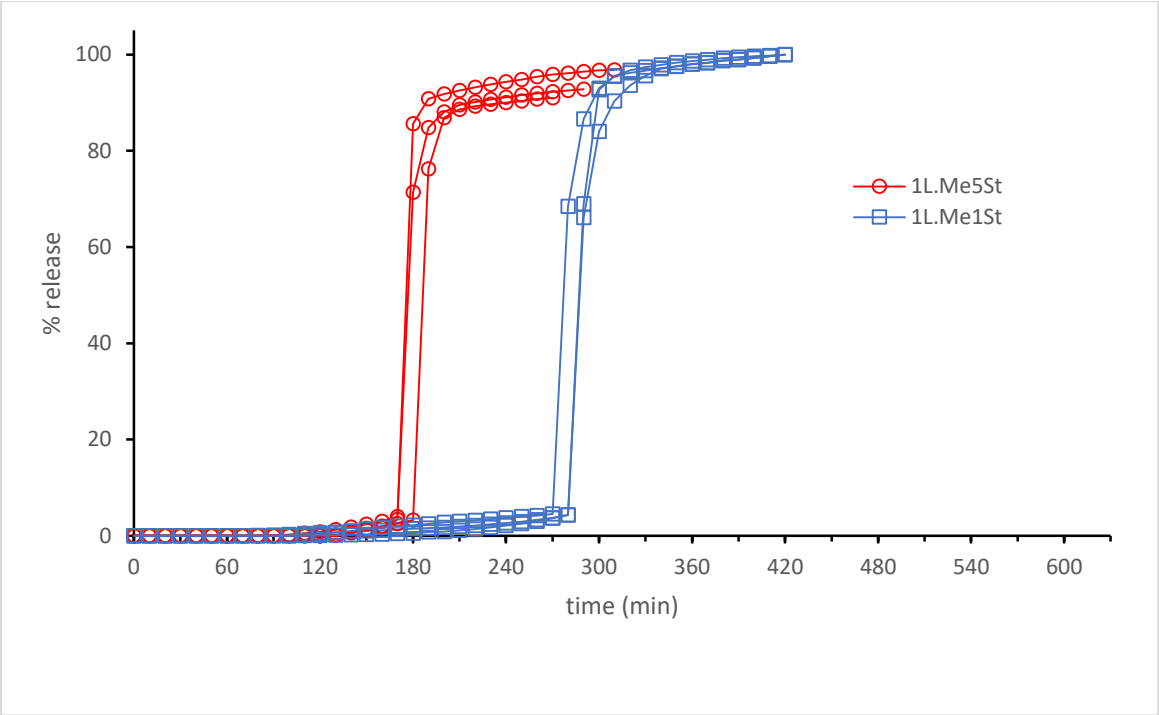


Figure 10: acetaminophen release profiles from one-layer Methocel® K4M/Sternzym® C13030-coated systems with increasing percentages of the enzymatic product.

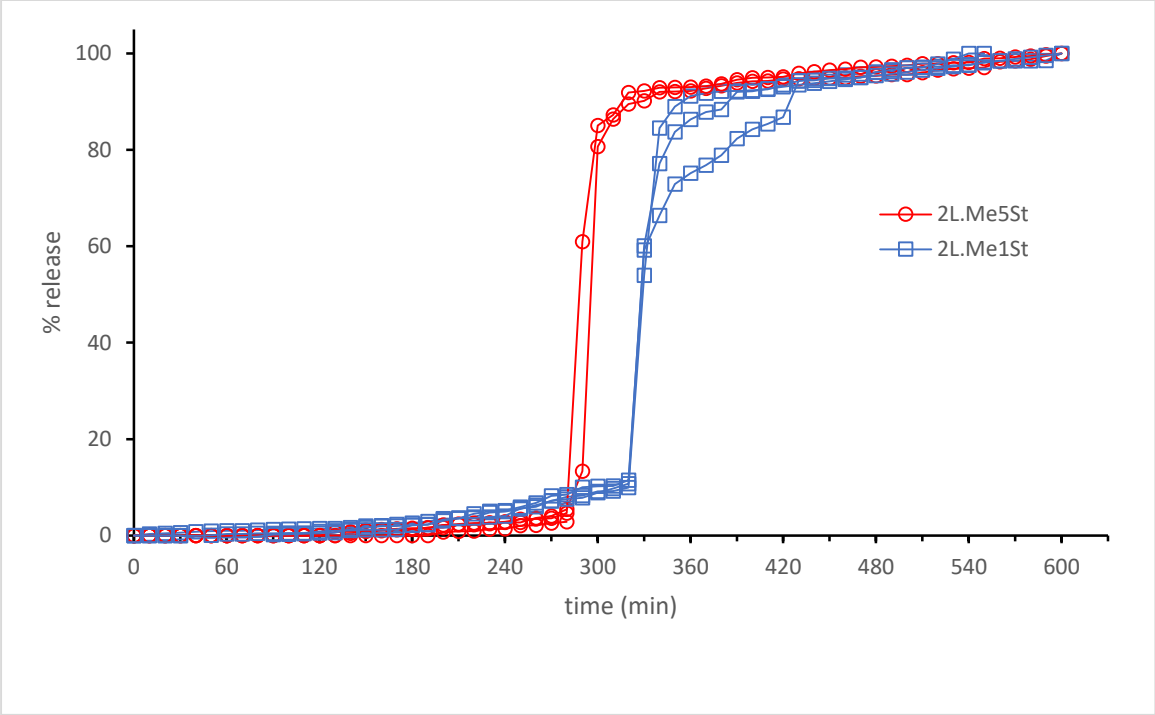


Figure 11: acetaminophen release profiles from two-layer Methocel® K4M/Sternzym® C13030-coated systems with increasing percentages of the enzymatic product.

In the profiles relevant to two-layer systems, having overlaid Sternzym® C13030 and Methocel® K4M layers (2LC.Me1St and 2LC.Me5St), the presence of the enzyme resulted in shortened lag phases, less evident diffusional release and reduced variability as compared with the system coated with HPMC only (1LC.Me) (Figure 11). Thus, the aqueous spray-coating process used to apply Sternzym® C13030 did not apparently hinder the effects of cellulase, at least to a major extent.

The difference in lag time observed between the one-layer reference formulation (1LC.Me) and the Sternzym® C13030-containing two-layer systems (2LC.MeSt1 and 2LC.MeSt5) could only be ascribed to the phase of acetaminophen release, occurring by diffusion and unit breakup, rather than to that of aqueous medium penetration. Indeed, because of composition, thickness and manufacturing techniques of the HPMC coatings being equal, the time the solvent takes to reach the inner enzyme layer in the two-layer systems would be expected to approximately correspond to that it takes to reach the core in the one-layer reference formulation without enzyme.

The impact of cellulase as incorporated in a separate layer (2L.MeSt1 and 2L.MeSt5), however, was lower with respect to when it was mixed with the swellable polymer (1L.MeSt1 and 1L.MeSt5), and the influence of the enzyme concentration was also less pronounced.

4. CONCLUSIONS

Unsolved issues inherent in the performance of swellable/erodible coatings for time-controlled release, particularly manufactured by press-coating and/or from high-viscosity HPMC needed to be addressed. With the aim of promoting faster and more consistent erosion of the diffusional barrier established upon polymer swelling, the incorporation of cellulolytic enzymes into either the coating or an underlying layer was here proposed. The viability of this approach was first assessed by studying the mass loss behavior of tableted matrices including increasing percentages of a commercially-available cellulolytic product in admixture with HPMC of viscosity grades spanning a wide range. Supported by the positive outcome of the preliminary

investigation, novel cellulase-containing systems were manufactured in the two differently devised configurations and evaluated. The release performance they provided was greatly improved as compared to the original formulation without enzymes. Indeed, previously observed issues of variable, excessively deferred in time and initially diffusional release were effectively prevented. Based on these overall results, the use of cellulase was shown to be a potentially advantageous strategy to obtain the desired pulsatile release behavior from time-controlled delivery systems having high-viscosity HPMC coatings, particularly when applied by press-coating. This would open up new perspectives in the application of such a technique, allowing functional cellulosic coatings to be manufactured with no need for using organic or aqueous solvents. Interestingly, the work performed not only would point out a potential role of cellulase as a release modulator but also suggest coupling diverse release-controlling polysaccharide agents with related hydrolytic enzymes might represent a novel approach in oral delivery and formulation, worthy of future investigation.

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Disclosure of interest

The authors report no conflict of interest.