Cellulase as an "active" excipient in prolonged-release HPMC matrices: a novel strategy towards zero-order release kinetics

Luca Palugan, Ilaria Filippin, Micol Cirilli, Saliha Moutaharrik, Lucia Zema, Matteo Cerea, Alessandra Maroni, Anastasia Foppoli*, 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

*Anastasia Foppoli

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 50324646
Email: anastasia.foppoli@unimi.it

ABSTRACT

Hydrophilic matrices are of utmost interest for oral prolonged release of drugs. However, they show decreasing release rate over time, mainly due to lengthening of the diffusional pathway across the gel formed upon glass-rubber transition of the polymer. Therefore, achievement of zero-order release kinetics, which would reflect in constant drug plasma levels, is still an open issue. With the aim of improving the release performance of hydroxypropyl methylcellulose (HPMC) systems, the use of cellulolytic enzymes was proposed to aid erosion of the swollen matrix, thereby counteracting the release rate decrease particularly toward the end of the process. The effectiveness of this strategy was evaluated by studying the mass loss and drug tracer release from tableted matrices consisting of high-viscosity HPMC (Methocel®K4M), Acetaminophen and increasing amounts (0.5-10% on HPMC) of a cellulolytic product (Sternzym®C13030). A faster erosion and progressive shift to linearity of the overall release profiles were observed as a function of the enzyme concentration. Release was markedly linear from matrices containing 5 and 10% Sternzym®C13030. In partially coated matrices with these cellulase concentrations, such results were in agreement with data of erosion and swelling front movement, which exhibited early and long-lasting synchronization.

KEYWORDS

Oral drug delivery systems, prolonged release, zero-order release kinetics, hydrophilic matrices, hydroxypropyl methylcellulose, cellulase, swelling and erosion fronts.

1. INTRODUCTION

Glycosidic hydrolases have many industrial applications thanks to their multiple uses and the ease with which they can be found, since they are produced by many microorganisms and also from animal and plant sources (Shrivastava, 2020).

Cellulases, in particular, are enzymatic complexes that hydrolyze β1-4 glycosidic bonds of cellulose through three different catalytic activities: endo-(1,4)-β-D-glucanase, exo-(1,4)-β-D-glucanase hydrolyzing cellooligosaccharides, and β-glucosidase having β-cellobiose as substrate, from which glucose is ultimately released (Lee and Fan, 1980). Cellulases are employed in a number of different fields where they have proved to be versatile and safe both for human health and environment. Their use is rather consolidated in food, feed, paper, textile, and biofuels. Each of these sectors has benefited from cellulase in terms of reduction of production time and costs, higher yield and better quality of the final product (Kuhad et al., 2011).

This type of enzymes has also found application in healthcare and medicine. There are food supplements available on the market that contain cellulases along with other enzymes, recommended to promote the digestion of macronutrients, especially for subjects with an unbalanced vegetable diet, such as vegetarians and vegans (Jayasekara and Ratnayake, 2019). Furthermore, their use in inhibiting biofilm formation on medical devices and in the treatment of phytobezoars is described (Loiselle and Anderson, 2003; Lee et al., 1977; Kramer and Pochapin, 2012;).

In the field of pharmaceutical formulation, the effect of cellulase on the release kinetics of a time-controlled oral delivery system (Chronotopic™) was recently investigated, following pioneering attempts to exploit glycosidases, namely pectinase, in the design of a capsular device (Krögel and Bodmeier, 1999; Bussemer et al., 2001; Foppoli et al., 2020b;). The Chronotopic™ system was based on a functional hydroxypropyl methylcellulose (HPMC) layer intended to defer the onset of release through progressive dissolution/erosion undergone in contact with aqueous fluids. (Maroni et al., 2016a, 2016b; Foppoli et al., 2019, 2020a; Melocchi et al., 2021). Cellulase, added to the HPMC coating, was shown able to

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prevent the undesired diffusional phase typically observed prior to the spike of delayed drug release especially with high viscosity polymer grades and/or press-coatings.

Among non-conventional oral dosage forms, hydrophilic matrices have always been the subject of great interest and study being one of the most common drug delivery systems (DDSs) for prolonged release. These systems generally consist of a compressed tablet obtained from a mixture of drug and swellable polymers (Gazzaniga et al., 1993; Ghori and Conway, 2015). The release control mechanism is based on the combination of various, often concomitant, processes such as diffusion, swelling and erosion (Siepmann et al., 1999; Siepmann and Peppas, 2001; Maderuelo et al., 2011). The typical release profile of an active ingredient from a hydrophilic matrix shows an initial "burst", caused by dissolution of drug particles from the surface of the system. The burst phase is followed by a period of almost constant release rate, and a final one with decreasing rate due to lengthening of the diffusional pathway and progressive reduction of the area at the interface between glassy and rubbery portions of the matrix. Thus, the resulting release profile fails to follow the desired zero-order kinetics, the achievement of which would enable constant plasma levels of drugs and therefore has always been pursued as a major goal in pharmaceutical

[redacted]

Several approaches were proposed over the years to avoid the slowdown of drug release in hydrophilic matrices. Such strategies may involve mechanical restriction of swelling, application of partial coatings, non-uniform drug distribution and/or design of modified geometries (Colombo et al., 1987, 1990; Gazzaniga et al., 1993; Grassi et al., 2004; Kim, 1995; Cerea et al., 2018, 2020a, 2020b; Lee, 1984; Sangalli et al., 1994, 2003).

In the present work, the effect of the addition of cellulase to hydrophilic matrices was studied in view of the demonstrated ability of the enzyme to catalyze hydrolysis of HPMC and promote erosion of gel barriers based on this polymer (Caceres et al., 2020; Foppoli et al., 2020b). Indeed, the use of cellulase as an “active” excipient appeared a strategy of potential interest to counteract the increase in the diffusional path length, thereby preventing reduction of release rate over time. Cylindrical matrices consisting of HPMC and a soluble drug tracer, with or without a commercial cellulolytic product (Sternzym® C13030), have been prepared. The systems have undergone mass loss experiments and

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release testing to assess whether and how the enzyme could impact on the release kinetics.

2. EXPERIMENTAL PART

2.1. MATERIALS

Acetaminophen (AMP, C.F.M., Italy; water solubility 14 g/L at 25°C), hydroxypropyl methylcellulose 2208 USP (HPMC, Methocel® K4M, M_n=86000, Dow Italia, Italy), Sternzym® C13030 (SternEnzym GmbH and Co. KG, 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), cellulose acetate propionate (CAP 482-20, Eastman-Kodak, Tennessee, US)

2.2 METHODS

2.2.1. *Manufacturing of matrices*

Matrices of different size were prepared from AMP and HPMC in 1:1 weight ratio, either as such or in admixture with Sternzym® C13030, according to the composition reported in the Results and Discussion Section (Table I). The powders were blended in mortar for 5 min and tableted by a rotary press (AM 8S, Officine Ronchi, Italy). Cylindrical flat-faced (diameter 25 mm, height 3.15 mm, nominal weight 1.5 g) and convex-faced units (diameter 11 mm, height 2.2 mm, nominal weight 0.24 g) were obtained using 91 MPa and 207 MPa compression pressure, respectively. In both cases, the resulting compacts had crushing strength in the 70-100 N range (crush tester TBH30 Erweka, Germany; n=10).

2.2.2 *Testing of matrices*

While matrices of 11 mm in diameter were subjected to release studies only, those of 25 mm underwent release, mass loss and swelling and erosion front studies. Before testing, the latter matrices were provided with an impermeable film covering their whole surface except for one base, which was manually applied by dipping into

a 15% w/v CAP solution in acetone. The resulting systems were ballasted by gluing the coated base to a stainless-steel disk (diameter of 25 mm and weight of 6.2 g).

2.2.2.1. *Release studies*

Release testing was carried out in triplicate by a Eur. Ph. 10th Ed. dissolution apparatus 2 (AT 7, Sotax, Switzerland), using distilled water thermostated at 37 ± 1 °C as the medium.

The rotation speed was set at 100 or 50 rpm, and the fluid volume was 500 or 900 ml for matrices of 25 and 11 mm, respectively. With the former systems, the paddle height was adjusted so that the distance between the stirrer and the matrix surface exposed to the fluid was 2.5 cm.

AMP was quantified spectrophotometrically at λ = 243 (Lambda 25, Perkin Elmer, Italy).

Release data were processed according to exponential equations (1) or (2) (Ritger and Peppas, 1987).

$$M_t = at^n \quad (1)$$

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

where M_t is the amount of drug released at time t

M_∞ is the amount of drug released at infinite time

a and *k* and are constants related to the matrix characteristics

n is a release exponent

In both cases, *n* values were used in a merely descriptive way to evaluate the tendency of the profiles to linearity.

The extent of linearity of release profiles was evaluated through the Durbin-Watson statistics (Durbin and Watson, 1950; Van der Voet et al., 1983). The release data were analyzed at time intervals of 30 min (90% c.i.).The extent of linearity of release profiles was evaluated through the Durbin-Watson statistics (Durbin and Watson, 1950; Van der Voet et al., 1983)(Durbin and Watson, 1950) (Van der Voet et al., 1983). The release data were analyzed at time intervals of 30 min (90% c.i.).

2.2.2.2. *Mass loss studies*

At scheduled time points during the test, 50 ml of fluid was withdrawn, replaced with fresh medium, and dried at 80 °C to constant weight (Foppoli et al., 2020b). Mass loss was assessed as the amount of solids recovered after drying of each fluid sample, and the relevant data were plotted against time to build cumulative curves. The rate of mass loss was calculated as the slope of the regression lines. Mass loss was also expressed net of tracer released (mass loss$^{\#}$), calculated by subtracting the amount of AMP released at each time point from the overall dry mass.

2.2.2.3. *Swelling and erosion front studies*

At scheduled time intervals during the test, matrices were recovered from the fluid and placed under a 0.01 mm-calibrated penetrometer (Dial Thickness Gage 7305, Mitutoyo, Japan) provided with a 0.9 mm diameter pin. The pin was carefully lowered until contact with the outer surface of the gel layer (erosion front) and inner glassy core of the matrix (swelling front), respectively.

3. RESULTS AND DISCUSSION

The present study was performed with tableted hydrophilic matrices based on high viscosity HPMC2208 (Methocel® K4M, the 2% w/v aqueous solution of which has 4000 cps viscosity at room temperature). The choice of the polymer was derived from previous findings highlighting the role of cellulase in pulsatile-release systems, where the enzyme promoted the dissolution/erosion of different grades of HPMC used as the main component of functional barriers (Foppoli et al., 2020b). Moreover, this polymer is the most widely employed for the production of oral hydrophilic matrices intended for prolonged release of drugs.

As previously described, the release profiles from hydrophilic matrices show an initial burst effect and a final decrease in the release rate, due to the increasing gel layer thickness and decreasing area at the boundary between swollen and non-swollen matrix, *i.e.* the area of drug particles exposed to the penetrating medium. From these matrices, it is thus not possible to achieve zero-order kinetics, and consequently constant drug concentrations *in vivo*, unless substantial changes are introduced into the formulation and/or geometry of the unit.

In this study, the role of cellulase was evaluated on cylindrical tableted matrices consisting of drug tracer and HPMC in a ratio of 1:1 w/w and Sternzym® C13030 at different concentrations, *i.e.* 0.5, 1, 5 and 10% w/w calculated on the polymer (Table I). Sternzym® C13030 is a powder product containing different enzymes having cellulolytic and other hydrolytic activities in admixture with maltodextrin. Its nominal activity is 2500 U/g, expressed as hemicellulolytic activity. For comparative purposes, binary matrices without the enzymatic product were also studied. The matrices were prepared in two different sizes, namely with 25 mm and 11 mm diameter. The systems having diameter of 25 mm were coated with an impermeable film on all the surface except for one base (code CM) and then subjected to mass loss and release tests. Mass loss determination, concomitant with spectrophotometric assay of drug tracer released, was carried out via gravimetric analysis by means of a simple and efficient method previously set up, which required that the employed matrices expose a relatively large area (4.91 cm^2) (Ghori et al., 2014)~~)(Ghori et~~

al., 2014; Foppoli et al., 2020b). On the other hand, the matrices having 11 mm diameter were evaluated as such (code UM) by release testing. In this study, the role of cellulase was evaluated on cylindrical tableted matrices consisting of drug tracer and HPMC in a ratio of 1:1 w/w and Sternzym® C13030 at different concentrations, *i.e.* 0.5, 1, 5 and 10% w/w calculated on the polymer (Table I). Sternzym® C13030 is a powder product containing different enzymes having cellulolytic and other hydrolytic activities in admixture with maltodextrin. Its nominal activity is 2500 U/g, expressed as hemicellulolytic activity. For comparative purposes, binary matrices without the enzymatic product were also studied. The matrices were prepared in two different sizes, namely with 25 mm and 11 mm diameter. The systems having diameter of 25 mm were coated with an impermeable film on all the surface except for one base (code CM) and then subjected to mass loss and release tests. Mass loss determination, concomitant with spectrophotometric assay of drug tracer released, was carried out via gravimetric analysis by means of a simple and efficient method previously set up, which required that the employed matrices expose a relatively large area (4.91 cm^2) (Merging Citations). On the other hand, the matrices having 11 mm diameter were evaluated as such (code UM) by release testing.

Table 1: composition (%) of the partially coated and uncoated matrices under investigation. Percentage of Sternzym® C13030 is also reported as calculated on HPMC.

Code		AMP	HPMC	Sternzym® C13030	Sternzym® C13030 *with respect to HPMC*
Ø 25 mm partially coated	Ø 11 mm uncoated				
CM_0	UM_0	50.00	50.00	-	-
$CM_{0.5}$	$UM_{0.5}$	49.88	49.88	0.25	*0.5*
CM_1	UM_1	49.75	49.75	0.50	*1*
CM_5	UM_5	48.78	48.78	2.44	*5*
CM_{10}	UM_{10}	47.62	47.62	4.76	*10*

Enzymatic cleavage of the polymer was expected to be crucial for the release mechanism and kinetics, possibly leading to the formation of polymer chains having lower molecular mass and, therefore, higher dissolution rate.

The time course of mass loss from CM_0 to CM_{10} tested is reported in Figure 1.

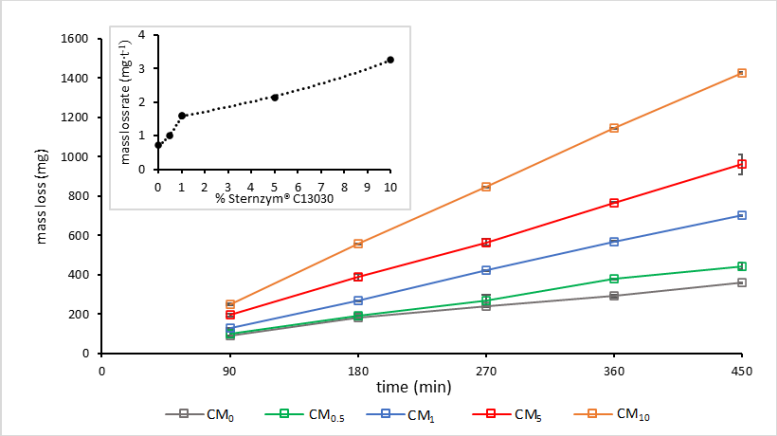

Figure 1: profiles of mass loss from partially coated matrices of 25 mm in diameter containing different amounts of Sternzym® C13030. Vertical bars indicate s.d. (*n=3*). The relationship between mass loss rate and enzyme product percentage is shown in the figure inset, where the dotted line represents fitting according to two exponential equations, in the 0–1% (R^2>0.99) and 1–10% (R^2>0.99) ranges, respectively.

The effect of the enzyme was clearly evident. The mass loss *vs* time profiles turned out to be well fitted by linear regression (R^2> 0.99), thus enabling evaluation of data by simple comparison of the slopes. The use of the enzymatic product at 1% (w/w on HPMC) led to more than doubled rate of mass loss, which would indicate a marked impact of cellulase even when present at relatively low concentrations. The relationship between mass loss rate and Sternzym® C13030 concentration could be described by two different exponential equations in the 0–1% and 1–10% concentration ranges, respectively (inset of Figure 1). Figure 2 shows the release profiles from the matrices, which exhibited a similar trend as mass loss, both being characterized by a clear increase in rate as a function of the percentage of Sternzym® C13030 present in the formulation. In this respect, the gel layer

the tracer had to pass through would have been of lower thickness and higher permeability as compared with that formed from matrices without enzyme. These changes in the barrier properties of the swollen polymer layer may account for the observed increase in the release rate.

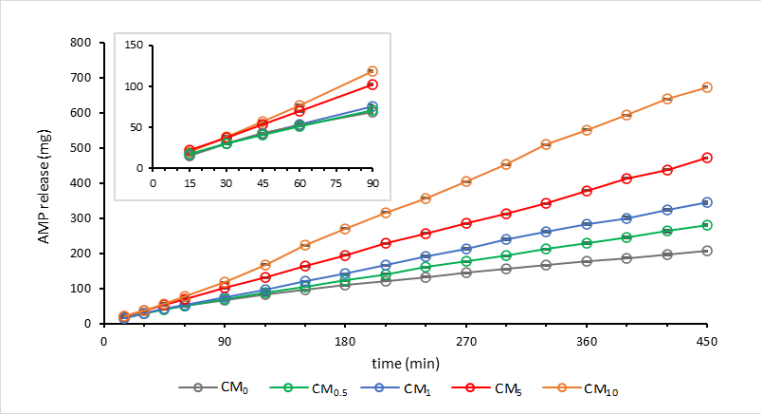

Figure 2: release profiles of tracer from partially coated matrices of 25 mm in diameter containing different amounts of Sternzym® C13030. Vertical bars indicate s.d. (*n=3*). The 0-90 min time interval is highlighted in the figure inset.

Release data were processed according to exponential equation (1), here intended for merely descriptive purposes (Table II).

Table II: fitting parameters of release data according to equation (1).

Matrix code	k (mg·min^{-1})	*n* (± 95% confidence limit)	R^2
CM_0	2.440	0.731±0.010	0.992
$CM_{0.5}$	1.876	0.813±0.015	0.998
CM_1	1.379	0.901±0.067	0.999
CM_5	1.676	0.918±0.016	0.999

CM_{10}	1.041	1.064±0.018	0.999

The values of *n* exponent rose from 0.73 in the case of the enzyme-free matrix to around 1 in CM_{10}. This trend pointed out a remarkable and progressive shift to linearity of the release profiles –*i.e.* to release rates practically independent of time- as a function of the percentage of Sternzym® C13030 added.

In CM_5 and CM_{10}, the achievement of a nearly constant overall release rate, starting from the very beginning, was supported by the finding that release rate values after about 1 h were very similar to those relevant to the burst phase where, because of the time taken for glass-rubber transition of the polymer, release was not yet effectively controlled by the swollen matrix (inset in Figure 2). In other words, the effect of the enzyme speeding up release would lead to early alignment of portions of the release curves originally characterized by different rates.

The release profiles of $CM_{0.5}$ and CM_1 took longer to differentiate from that of CM_0, as compared with those containing higher amount of enzyme (CM_5 and CM_{10}). This may be due to the need for more time before the effect of the enzyme, present at lower percentages in these formulations, could take place and also be highlighted. The improved linearity of these release curves with respect to CM_0, however, could only be attributed to the enzymatic degradation of the polymer.

In order to better highlight the role the enzyme may play in promoting the matrix erosion, the mass loss profiles of CM_0-CM_{10}, net of the amount of tracer released (mass loss[#], *i.e.* amount of polymer and Sternzym® C13030), are presented in comparison with the corresponding release curves (Figure 3). The position of the erosion and swelling fronts in the matrix was also measured (Lee and Peppas, 1987). Profiles describing movements of these fronts over time are reported in Figure 4. In such profiles, point 0 on the y axis corresponds to the matrix surface before interaction with the fluid, which is depicted by the schematic aside.

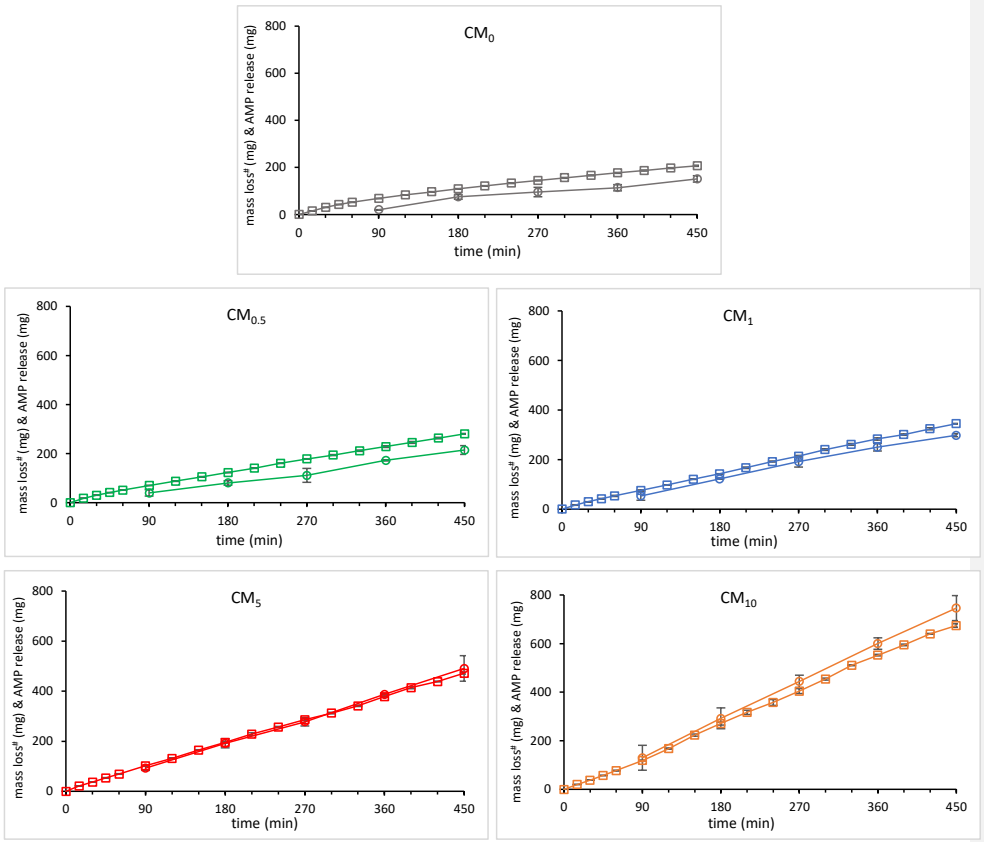

Figure 3: profiles of mass loss[#] (o) and tracer release (□) from partially coated matrices of 25 mm in diameter, containing different amounts of Sternzym® C13030. Vertical bars indicate s.d. (*n=3*). [#]*mass loss data are calculated net of the amount of tracer released*

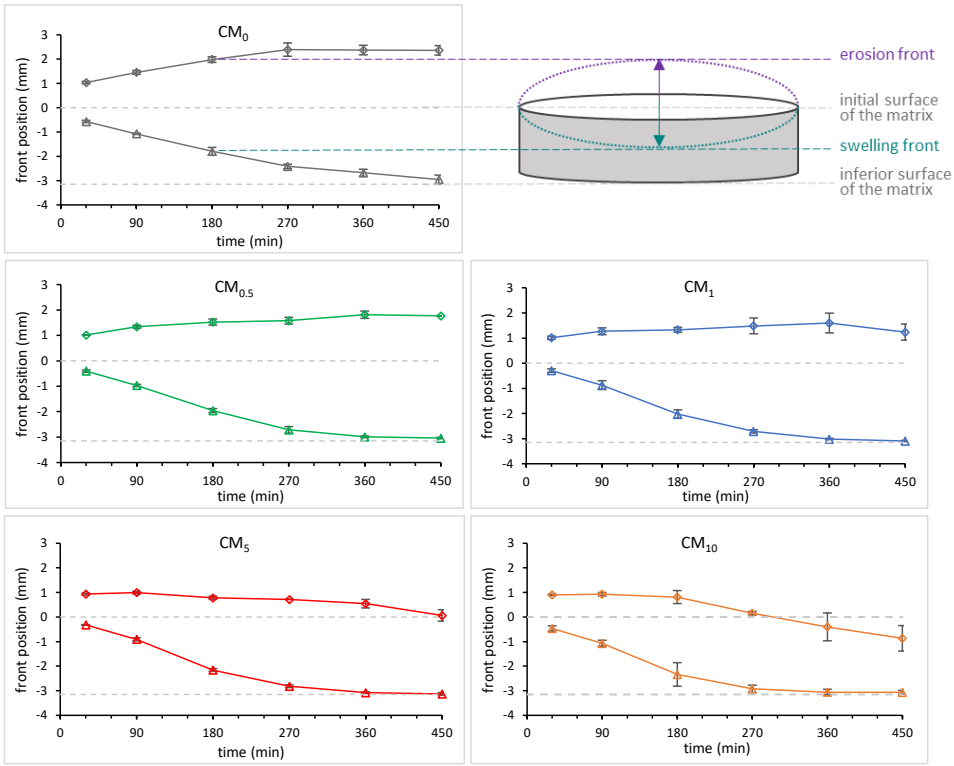

Figure 4: swelling (◊) and erosion (Δ) front position vs time profiles of partially coated matrices of 25 mm in diameter containing different amounts of Sternzym® C13030. Front position=0 on the y axis corresponds to the initial surface of the matrix. The schematic aside indicates the position of the swelling and erosion fronts at t=180 min in M_0. Vertical bars indicate s.d. (*n=3*).

In the case of CM_0, the mass of tracer released was greater than that of polymer and Sternzym® C13030 lost at all time points. Such a gap would suggest persistence of a gel layer, formed upon interaction of the polymer with the aqueous fluid, which would act as a diffusional barrier opposing release of the tracer. This would also be confirmed by the relative swelling and erosion front movement observed. Inward progression of the swelling front took approximately 450 min to reach the bottom face of the matrix, *i.e.* for its quantitative hydration following glass-rubber transition of HPMC. In the same time interval, because of swelling, the matrix increased in volume as pointed out by the outward movement of the erosion front. After 270 min, such a front reached a *plateau*, thus implying that expansion of the matrix was counterbalanced by the extent of dissolution/erosion. As a result, a maximum gel layer thickness of approximately 5.5 mm was observed at 450 min.

When the swelling front was still progressing and glass-rubber transition of the polymer had extensively occurred, at around 450 min, only a relatively small amount of the loaded tracer was released (approximately 150 *vs* 750 mg, corresponding to 20%). It is therefore evident that front synchronization did not occur in CM_0, thus hindering attainment of a constant gel layer thickness that is required for zero-order release kinetics to be achieved (Harland et al., 1988). The release rate, which had been characterized so far by a progressive decrease, would be expected to maintain the same trend until complete tracer release, due to reduction over time of the concentration gradient along the diffusional pathway.

The matrices containing 0.5% and 1% of Sternzym® C13030 ($CM_{0.5}$ and CM_1) exhibited higher mean rates both for tracer release and mass loss[#], as compared with CM_0 (Figure 3).

Upon exposure to the aqueous fluid, an initial expansion of $CM_{0.5}$ and CM_1 was observed, which reached a maximum at 180 and 90 min, respectively. Hydration of these matrices, as indicated by progression of the swelling front, was completed slightly earlier than with CM_0, and the gel thickness kept well below 5 mm for the whole test duration (Figure 4).

The release from both formulations tended to linearity, as confirmed by data processing through the Durbin-Watson statistics indicating practically constant rate from 120 to 450 min. As a clear and enduring phase of front synchronization was not observed, the achievement of a constant release rate at least in the considered time interval, could mainly

be ascribed to less effective barrier properties of the gel layer as a result of enzymatic cleavage of the polymer into lower molecular weight chains.

Formulations CM_5 and CM_{10} showed a progressive further increase in release and mass loss[#] rates. Apart from the difference in rate, an analogous trend was observed for release and mass loss[#], as also seen in the case of the corresponding swelling and erosion front movement. Linearity of the release curves was evident in both cases. The increase in volume of these matrices was relatively limited with respect to all other formulations, and also the thickness of the relevant gel layers was lower.

It can be noted, however, that front synchronization, and subsequent progressive reduction of the gel layer, occurred earlier with CM_{10} than CM_5. In either case, the swelling front reached the bottom face of the unit within approximately 270 min. While movement of such a front was reasonably comparable in all the matrix systems, including the enzyme-free one, the same would not apply to the erosion front progression, which differed considerably between CM_5 and CM_{10} on the one hand, and CM_0, $CM_{0.5}$ and CM_1 on the other.

It ensues that to play a decisive role in governing the release kinetics, rather than the rate of glass-rubber transition, would be that of enzymatic degradation of the polymer. Thus, the desired zero-order release kinetics would appear to be brought about by the enzyme that could ultimately modulate both the tendency to erosion and the permeability of the swollen matrix.

It is noteworthy that, unlike all other matrices, in the case of CM_{10}, wherein release was mainly governed by erosion phenomena, the mass loss[#] data exceeded those of drug tracer released. This is due to the fact that in the original formulation the cumulative amount of polymer and Sternzym® C13030 (785 mg-47.62%) was greater than the amount of drug tracer (714.3 mg-52.38%).

The results reported so far were obtained from partially coated matrices, where the area was kept constant and only unidirectional movement was allowed both for the fluid penetrating into the matrix and the drug tracer diffusing outwards. Therefore, the study was subsequently broadened to include bare compacts wherein diffusion of the medium and of the tracer could take place without any physical constraints. In particular, the impact of cellulase was explored by release testing of uncoated matrices (UM) having cylindrical shape

with convex bases and diameter of 11 mm, which contained different amounts of Sternzym® C13030 (Table I). A binary matrix without enzyme (UM_0) was also tested as a reference. Overall, the release data obtained were consistent with those from the partially coated systems previously evaluated. As the enzyme concentration increased, the rate of release progressively increased in the same rank order of CM_0-CM_{10} (Figure 5 and Table III).

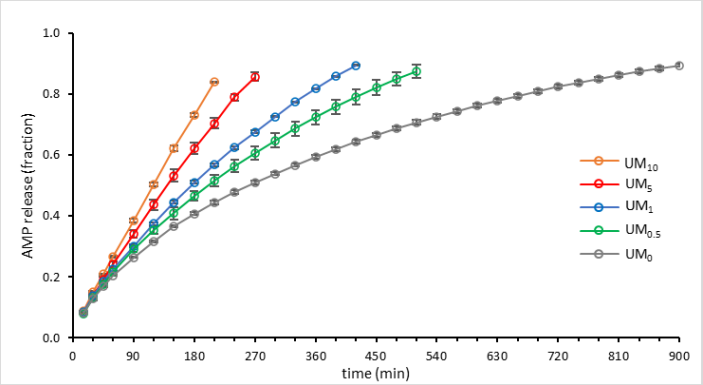

Figure 5: profiles of tracer release from uncoated matrices of 11 mm in diameter, containing different amounts of Sternzym® C13030.

Results from the enzyme-free matrix showed that switching from two-dimensional (planar) systems (CM_0) to three-dimensional ones (UM_0) was associated with an expected decrease in the *n* exponent, which shifted from 0.73 to 0.57 (Ritger and Peppas, 1987). The lower value obtained with the uncoated system is due to the already mentioned progressive reduction of the area at the interface between the rubbery and the glassy portions of the matrix.

The matrix without Sternzym® 13030 gave rise to an evident burst effect, which was still present in the case of $UM_{0.5}$ and UM_1. In the phase immediately after the burst, their release profiles differed from that of UM_0, exhibiting an incremental deviation over time.

In the case of systems containing 5 and 10% of Sternzym® C13030, the value of *n* exponent rose up to 0.82 and 0.86, respectively, thus highlighting a clear tendency to zero-order release kinetics. This was supported by data analysis through the Durbin-Watson statistics, which pointed out linearity of the curves in the range from 0.34 to 0.79 for UM_5 and 0.15 to 0.84 for UM_{10}. The apparent linearity of the release profiles of these systems would result

404 from an accelerated release in the phase following the burst, the latter being masked
405 because of comparable release rates in the two portions of the curve. This would be an
406 artifact that, however, would strictly be dependent on the characteristics of formulation
407 components.
408
409 Table III: fitting parameters of the UM_0 – UM_{10} release data according to equation (2).

Matrix code	a (min^{-1})	n (± 95% confidence limit)	R^2
UM_0	0.020	0.573±0.002	0.992
$UM_{0.5}$	0.014	0.677±0.060	0.998
UM_1	0.012	0.715±0.033	0.999
UM_5	0.008	0.827±0.064	0.999
UM_{10}	0.008	0.862±0.002	0.999

410
411
412 **4. CONCLUSIONS**
413
414 Constant drug levels *in vivo* may be advantageous to reduce the frequency of administration
415 and incidence of side effects, thus enhancing the therapeutic outcome and patient
416 compliance. To this end, DDSs able to provide zero-order release kinetics are pursued.
417 In the present work, the issue of release rate decreasing over time in hydrophilic matrices
418 for oral prolonged release, hindering achievement of zero-order kinetics, was addressed
419 through a novel formulation strategy. Particularly, a marketed product (Sternzym® C13030)
420 containing cellulolytic enzymes was incorporated into matrix systems based on a high-
421 viscosity grade of HPMC to aid erosion of the swollen polymer, through the relevant
422 cleavage into lower molecular weight chains. This was indeed expected to counteract the
423 increase in thickness of the gel layer formed upon matrix hydration and ultimately limit the
424 progressive lengthening of the diffusional path.

To verify whether such an approach could be effective in improving the release kinetics of hydrophilic matrices, the mass loss, drug tracer release and front movement were studied in HPMC compacts with or without Sternzym® C13030.

The results obtained from systems containing increasing weight percentages of cellulase pointed out a clear increase in the rate of mass loss and tracer release, which supported the starting hypothesis. Accordingly, the release profiles largely shifted to linearity.

While progression of the swelling front was found to be only poorly affected by the presence of the enzyme, that of the erosion front was accelerated as a function of its amount.

Because in the case of matrices containing 0.5 % and 1 % of Sternzym® C13030 an evident front synchronization was not achieved, the observed tendency to zero-order kinetics was deemed to mainly be associated with a change in the gel permeability characteristics.

On the other hand, the swelling and erosion fronts turned out to move in a synchronized mode for a relatively long time lapse with systems at 5 % and 10 % of enzymatic product.

The release curves of matrices containing these percentages of Sternzym® C13030, in both partially coated and uncoated configurations, appeared linear from the beginning due to masking of the initial burst effect. This was ascribed to acceleration of the release phase where control was exerted by incipient gelation of the polymer, thus resulting in unforeseen alignment of the two portions of the curves. It should be noted, however, that the extent of burst masking would depend on the quali-quantitative composition of the system, being affected by the solubility of the active pharmaceutical ingredient, type and amount of functional polymer and enzymatic product used.

It should not be disregarded that the use of cellulase may have a negative impact on the duration of release, considering the enzyme-free matrix as a reference. Nonetheless, proper changes of relatively simple implementation may be introduced into the formulation in order to restore the original time frame of release while preserving the attained linearity.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of interest

The authors report no conflict of interest.

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