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Towards elucidation of the drug release mechanism from compressed hydrophilic matrices made of cellulose ethers. III. Critical use of thermodynamic parameters of activation for modeling the water penetration and drug release processes.

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ABSTRACT

The two main purposes of this work were: (i) to critically consider the use of thermodynamic parameters of activation for elucidating the drug release mechanism from hydroxypropyl methylcellulose (HPMC) matrices, and (ii) to examine the effect of neutral (pH 6) and acidic (pH 2) media on the release mechanism. For this, caffeine was chosen as model drug and various processes were investigated for the effect of temperature and pH: caffeine diffusion in solution and HPMC gels, drug release from and water penetration into the HPMC tablets. Generally, the kinetics of the processes was not significantly affected by pH. As for the temperature dependence, the activation energy (E_a) values calculated from caffeine diffusivities were in the range of Fickian transport (20-40 kJ mol^{-1}). Regarding caffeine release from HPMC matrices, fitting the profiles using the Korsmeyer-Peppas model would indicate anomalous transport. However, the low apparent E_a values obtained were not compatible with a swelling-controlled mechanism and can be assigned to the dimensional change of the system during drug release. Unexpectedly, negative apparent E_a values were calculated for the water uptake process, which can be ascribed to the exothermic dissolution of water into the initially dry HPMC, the expansion of the matrix and the polymer dissolution. Taking these contributions into account, the true E_a would fall into the range valid for Fickian diffusion. Consequently, a relaxation-controlled release mechanism can be dismissed. The apparent anomalous drug release from HPMC matrices results from a coupled Fickian diffusion-erosion mechanism, both at pH 6 and 2.

Keywords: Drug release mechanism; activation energy; swelling; diffusion; hydroxypropyl methylcellulose; caffeine.

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1. Introduction

Hydrophilic sustained release matrix tablets are frequently prepared from non-ionic cellulose ethers, among them usually hydroxypropyl methylcellulose (HPMC). When exposed to water, the surface polymer hydrates, and the gel layer formed on the glassy core is descriptively considered as the barrier controlling drug release by diffusion. However, the exact mechanism governing drug release from these swellable dosage forms has been the subject of intensive research and continues to be debated [1]. In particular, a swelling-controlled mechanism is often invoked without rationale, based only on simple data fitting to a mathematical model [2,3]. It was the purpose of the two previous papers of this series to gain a deeper insight into the drug release mechanism from compressed cellulose ether matrices using dimensionless analysis and parameters that were independently obtained, in either Part I [4] or Part II [5] of the work. Thus, a non-Fickian mechanism could be dismissed when calculating the Deborah and the Swelling interface numbers from relaxation, penetrant diffusion, swelling and drug diffusivity data.

The concept of swelling-controlled release systems, a term proposed by Hopfenberg [6], implies that drug release is governed by the solvent penetration rate, which is in turn limited by the rate of polymer relaxation (Case II transport). Such a limiting case for penetrant in glassy polymers (below the glass transition) is characterized by the following features [7-9]:

(a) A sharp advancing boundary separates the inner glassy core from the outer swollen rubbery shell, i.e., the swelling front; such boundary constitutes a necessary but insufficient condition for Case II transport because sharp advancing boundaries have also been observed for Fickian diffusion with a strongly concentration-dependent diffusivity.
(b) Behind the advancing front, the swollen polymer is essentially in an equilibrium state of swelling, i.e., there is no concentration gradient behind the front.
(c) The swelling front advances at constant velocity.
(d) Consequently, the initial weight gain is directly proportional to time (linear kinetics).

Departure from these features indicates either the other limiting case, Case I or Fickian diffusion, characterized by a linear weight gain of the sample undergoing sorption with the square root of time ($t^{0.5}$), or the intermediate case referred to as anomalous transport, for which both processes contribute.

Regarding water transport in HPMC tablets, Tritt-Goc and Pislewski [10] have shown using magnetic resonance imaging (MRI) that the distance diffused by pure water (pH 6) is proportional to $t^{0.5}$, which is in agreement with the results reported by Fyfe and Blazek [11,12]. The water concentration increases from the glassy core to the fully swollen region of the polymer. These data are indicative of Fickian diffusion and thus in line with the conclusion of our dimensionless analysis [5]. However, in a subsequent contribution [13], the same authors have concluded an anomalous diffusion for neutral water. An opposite behavior has been observed by Tritt-Goc et al. [10,13-15] for swelling kinetics at pH 2: a linear increase of the diffusion distance with time and constant water concentration throughout the swollen region of the polymer, two features allowing the determination of a Case II transport.

Our previous work based on a dimensionless analysis was performed using pure water as the release and swelling medium [5]. The present study was thus undertaken to examine whether a swelling-controlled (non-Fickian) mechanism could operate in an acidic medium. All diffusion, release and swelling experiments were thus performed at pH 2 and, for comparison, at pH 6. For experimental verification, the HPMC grade used was that of Tritt-Goc et al. [10,13] and caffeine was selected as a model drug because it is almost non-ionized in these media and because a comprehensive set of self-diffusivity data in normal water is available [16,17]. Then, two different approaches were exploited to look for a possible Case II transport mechanism for both water sorption in the tablets and drug release from the tablets:

1) The drug release, boundary advance and weight gain profiles of the tablets upon contact with the two aqueous media were monitored to examine the effect of pH and to verify whether the above-mentioned criterion of linear kinetics is fulfilled.
2) The temperature dependence of each phenomenon was evaluated by calculating the energy of activation (E_a). Much higher E_a values are generally observed for anomalous or Case II

transport (partially or fully relaxation-controlled) than for Fickian diffusion. The hypothesis of our work was thus to compare the E_a values obtained for drug diffusion in solutions or gels, a process known to be purely Fickian, to the E_a values for the transport mechanism under investigation, dealing with the determination of the water uptake and concomitant drug release characteristics of compressed HPMC matrix tablets.

Then, as a preliminary part of this study, we determined the caffeine self-diffusivities in solutions and gels at three different polymer weight fractions and four temperatures (25, 30, 37 and 45 °C). The caffeine release from compressed HPMC tablets was then studied along with the front movements and water uptake at both pH values, but only at 25, 30 and 37 °C. In fact, the 45 °C temperature condition was not kept after the preliminary investigations because clouding (opacification) and increased viscosity of the tablet gel layer (especially at pH 2) were observed, in accordance with the work of Hussain et al. [18], which reported clouding at 42 °C for a similar HPMC 2910 grade.

2. Materials and Methods

2.1. Materials

Anhydrous caffeine (Ph. Eur.) was supplied by Fluka AG (Buchs, Switzerland). The hydroxypropyl methylcellulose selected was the grade used by Tritt-Goc et al. [10,13], namely a HPMC (Ph. Eur./USP type 2910, 4000 mPa·s) with M_n of ca. 86000 from Sigma-Aldrich (Schnelldorf, Germany, ca. 29 wt % methoxy, 7 wt % propylene oxide). Deuterium oxide and deuterium chloride 0.1 M in deuterium oxide, both 99.8 atom % D, were purchased from Armar Chemicals (Döttingen, Switzerland). Deuterium chloride 0.01 M in deuterium oxide solution was prepared by diluting deuterium chloride 0.1 M with deuterium oxide.

2.2. Pulsed-field-gradient spin echo NMR (PFG-SE NMR)

As this technique necessitates the use of deuterated solvents, solutions and gels containing 1 % w/w anhydrous caffeine were prepared using pure deuterium oxide (pH ~ 6) and deuterium chloride 0.01 M in deuterium oxide solution (pH = 2). The solute was incorporated at a very low concentration to avoid disturbing the hydrogel structure and for comparison with the previous work [4]. Gels at the HPMC weight fractions w_p of 0.05, 0.10 and 0.15 were prepared by dispersing the powder in the solvent containing 1 % w/w caffeine, heating at 80 °C and storing the gels overnight at 4-8 °C. PFG-SE NMR diffusion experiments were carried out as previously [4], at 25, 30, 37 and 45 °C. Self-diffusion coefficients of caffeine were calculated for three different chemical shifts to give insight into the systematic deviation of the measurements.

2.3. Tablet preparation

Tablets for drug release, front movement and dynamic swelling studies were prepared as previously [5]. Briefly, caffeine (< 63 µm sieve fraction) and HPMC were geometrically mixed in a 1:99 weight ratio for 15 min (T2C Turbula blender, Bachofen, Basel, Switzerland). The powder mixture (500 mg) was then compressed at a compression force of 10 kN using a hydraulic press (Graesby Specac, Orpington, UK) and a 13-mm die with flat-faced punches.

2.4. Drug release

Caffeine release was studied in an automatic paddle Ph. Eur./USP apparatus (Erweka DT 600 HH, Heusenstamm, Germany) with a rotation speed of 75 rpm. The tablets (3 replicates) were locked between two transparent Plexiglas® discs to obtain a radial release [19]. The dissolution media (400 ml) were deaerated pure water (pH ~ 6) or 0.01 N HCl (pH = 2). The release of caffeine was monitored at 273 nm (Agilent Technologies 8453 UV-visible spectrophotometer, Madrid, Spain) at specified time intervals up to 8h. Release experiments were carried out at 25, 30 and 37 °C.

2.5. Front movements and dynamic swelling

The number of replicates and the conditions for both sets of experiments were the same as for drug release. However, 0.004 % w/v methylene blue was added to the dissolution media to follow the movements of the water penetration, swelling and erosion fronts. At defined time intervals, each

Plexiglas® device was removed from the dissolution medium, photographed (Sony® DSC-F717 digital camera, Tokyo, Japan) and the photographs analyzed as described elsewhere [20]. The inward front movement was represented by a negative value, while the outward movement was indicated by a positive value (see Part II [5] for more details).
The media used to study the dynamic swelling of the tablets were the same as the media used for drug release. Water uptake was evaluated by removing each Plexiglas® device at defined time intervals, sweeping the excess water and weighing the device, and then returning it back to the water to continue swelling up to equilibrium.

2.6. Statistical analysis

Drug release and dynamic swelling profiles were compared for the effect of pH and temperature using a model-independent approach [21,22]: the similarity factor f_2 (a logarithmic transformation of the sum-squared error of differences between two profiles).
Moreover, a t-Student test was performed to evaluate the effect of pH on the E_a values as derived from diffusion, drug release and water uptake data. Differences were considered as significant if $p<0.05$.

3. Results and Discussion

3.1. Self-diffusivity of caffeine in solutions and hydrogels

An Arrhenius plot (ln D vs. $1/T$) is given for both sets of data (Figure 1a for pH 6 and Figure 1b for pH 2). Values at 45 °C for caffeine 1 % w/w solutions were excluded because the technical settings were not adapted to measure solute with high mobility. Activation energy theory seems applicable to diffusion in those media, as linear relations were observed. As expected from the Stokes-Einstein relation ($D \propto 1/\eta$), the self-diffusion coefficients obtained in heavy water were systematically lower than those reported [16,17] for caffeine solutions in normal water. For purposes of comparison, our data were corrected for the effect of viscosity. Thus, values of $6.92 \cdot 10^{-6}$ and $10.68 \cdot 10^{-6}$ $cm^2\ s^{-1}$ were obtained for a 1 % w/w caffeine solution in H_2O (pH ~ 6) at 25 °C and 37 °C, respectively. These results are in good agreement with the values reported by Price et al. [16,17] ($6.47 \cdot 10^{-6}$ and $9.27 \cdot 10^{-6}$ $cm^2\ s^{-1}$ at 25 and 37 °C, respectively), even though these values were obtained using a different method and are thus tracer diffusion (intradiffusion) coefficients.

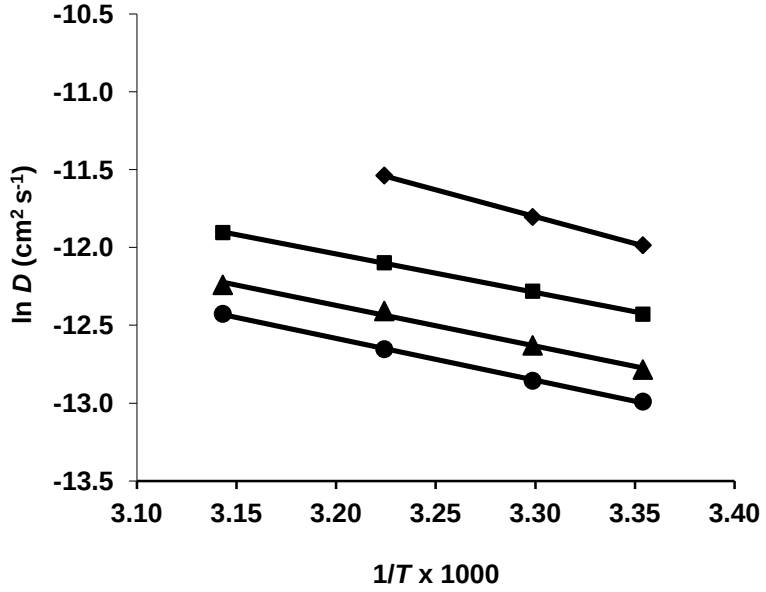

Fig. 1a. Arrhenius plot of caffeine 1 % w/w self-diffusion coefficient D in D_2O and HPMC gels (pH 6) of varying polymer fraction w_p. Key: (♦) $w_p = 0$, (■) $w_p = 0.05$, (▲) $w_p = 0.10$, (●) $w_p = 0.15$.

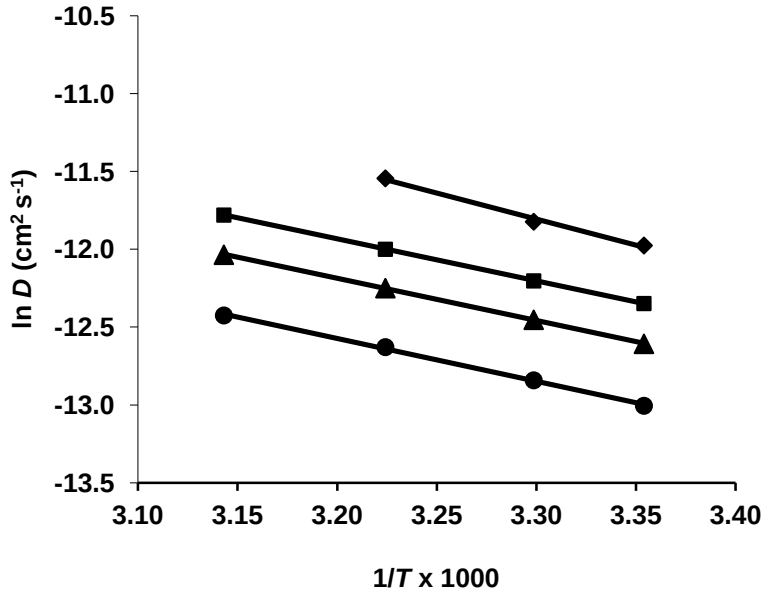

Fig. 1b. Arrhenius plot of caffeine 1 % w/w self-diffusion coefficient *D* in DCl and in DCl-based HPMC gels (pH 2) of varying polymer fraction w_p. Key: (♦) $w_p = 0$, (■) $w_p = 0.05$, (▲) $w_p = 0.10$ and (●) $w_p = 0.15$.

The effect of the presence of HPMC on caffeine diffusivity was analyzed according to the following equation, derived from the free-volume theory and describing an exponential polymer weight fraction w_p dependence of the self-diffusion coefficient *D* [23]:

$$\ln D = \ln D^0 - \beta \cdot w_p \qquad (1)$$

where D^0 is the coefficient of diffusion at infinite dilution (extrapolated coefficient at $w_p = 0$) and β is a constant indicative of the retardation effect of the polymer. Linear relationships between ln *D* and w_p were generally observed at the four temperatures and the two pH values, with β values not affected by temperature but slightly higher at pH 2 than at pH 6 (Supplementary Table 1). The extrapolated D^0 values increased with temperature and were slightly higher at pH 2. An exponential decay of drug self-diffusion with polymer concentration, as measured at 23 °C by PFG-NMR, was also shown [24] for HPMCs 2208 of various viscosity grades and adinazolam mesylate as model drug.

The energies of activation E_a for caffeine diffusion in the various media were calculated using the following equation:

$$E_a = R \cdot T^2 \cdot d \ln D / dT \qquad (2)$$

where *R* is the gas constant and *T* is the thermodynamic temperature. These self-diffusion coefficients obtained in deuterated solvents were not corrected for the effect of the viscosity for comparison with diffusivities in normal water because such a correction would not affect the slopes of the ln *D* vs. 1/*T* graphs.

Table 1 lists the E_a values obtained for the two pH media and three HPMC concentrations. Generally, diffusivity is not affected by pH or the HPMC fraction ($p>0.05$). In contrast, the values obtained for the gels significantly differ ($p<0.05$) from the caffeine solutions values.

The value of 28.8 kJ mol^{-1} calculated for the caffeine solution in pure D_2O must be compared with the value inferred for a caffeine H_2O solution of the same temperature and solute concentration ranges, i.e., 22.6 kJ mol^{-1} [16,17]. This discrepancy may be due to the different method used but most likely reflects a difference in the type of solute-solvent interactions. It can be added that E_a values of 20.9 to 22.2 kJ mol^{-1} were obtained by Gao and Fagerness [24] from PFG-NMR self-diffusivities measured at temperatures between 10 and 50 °C. Interestingly, the authors noticed a systematic deviation of the plot of ln *D* vs. 1/*T* near 50 °C.

Importantly, the calculated E_a values for caffeine diffusion are consistent with a Fickian process (typically 20-40 kJ mol^{-1} [25,26]). Moreover, because the self-diffusivity of the non-ionized solute was not affected by the pH and the E_a obtained for the self-diffusion of caffeine in D_2O was quite

similar to the value inferred from literature data in H_2O, we were able to use this drug to elucidate the release mechanism from HPMC-compressed matrices by determining the energy of activation.

Table 1. Calculated energies of activation (E_a±SD) for self-diffusion of caffeine at 1 % w/w as a function of polymer weight fraction w_p.

Solvent	HPMC w_p	E_a (kJ mol^{-1})
D_2O (pH 6)	0	28.8±0.7
	0.05	20.5±0.3
	0.10	21.7±1.2
	0.15	22.3±0.5
DCl/D_2O 0.01 M (pH 2)	0	27.8±2.3
	0.05	22.5±0.1
	0.10	22.6±0.2
	0.15	22.9±0.6

3.2. Drug release from compressed matrices

Figures 2a (pH 6) and 2b (pH 2) show the caffeine release profiles from the compressed HPMC matrix tablets at 25, 30 and 37 °C. The low percentages of drug released at the end of the study are a consequence of the low drug loading (1 %) and the reduced tablet release surface area exposed to the dissolution medium. These conditions were intentionally chosen for comparison with previous studies [5], as it has been shown that, although these two factors had an effect on the amount and rate of drug released, they did not change the release mechanism [20,27].

Drug release appears to be affected by temperature only to a very limited extent. The influence is lower than that reported by Mitchell et al. [28] and Ford et al. [29] for the release of promethazine hydrochloride from HPMC 2208 15000 mPa·s tablets, the reason most likely lying in the higher percentage of drug in the matrices (14.3-33 %) and the higher solubility of the drug. The caffeine release is not affected by the pH of the medium, and none of the profiles, even at pH 2, are characterized by a non-Fickian mechanism. Dahlberg et al. [30] found also a diffusion-controlled mechanism when evaluating antipyrine release from HPMC 2210 tablets using NMR microimaging.

The release profiles were compared for the effect of pH and temperature using the similarity factor f_2. The calculated f_2 values were systematically greater than 50, which would suggest equivalence of the release profiles at the three temperatures, at both pH 6 and 2.

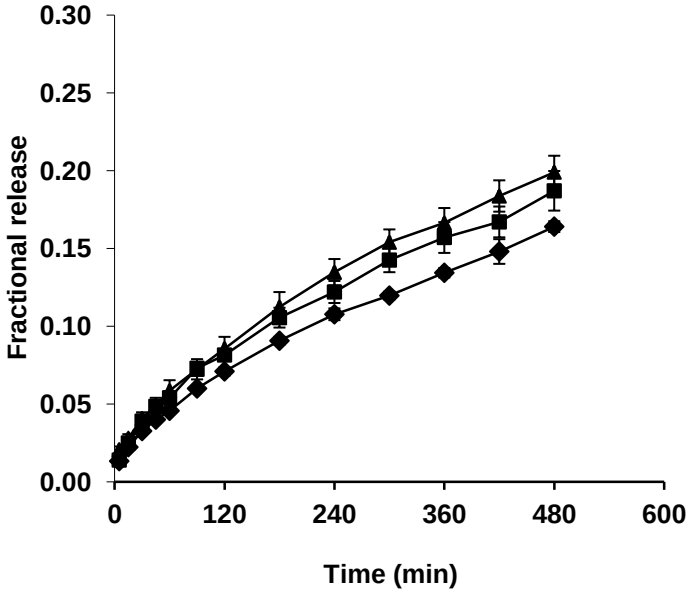

Fig. 2a. The effect of temperature on the release of caffeine in pure water (pH 6) from compressed HPMC 2910 matrices. Key: (♦) 25 °C, (■) 30 °C and (▲) 37 °C.

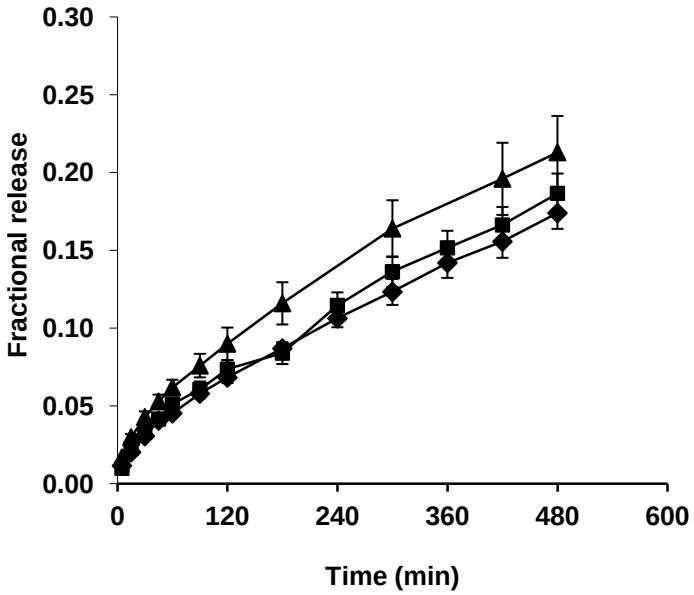

Fig. 2b. The effect of temperature on the release of caffeine in 0.01 N hydrochloric acid (pH 2) from compressed HPMC 2910 matrices. Key: (♦) 25 °C, (■) 30 °C and (▲) 37 °C.

The release profiles were also analyzed using two different models and non-linear least square fitting (SPSS® 18.0 software). To gain insight into the supposed drug release mechanism, the data were first fitted by the commonly used Korsmeyer-Peppas model [31]

$$\frac{M_t}{M_\infty} = k \cdot t^n \qquad (3)$$

where M_t/M_∞ is the fractional drug release at time t (M_∞ is considered equivalent to the drug loading); k is a kinetic constant that measures the release rate; and n is a diffusional exponent that depends on the release mechanism and the geometry of the system.

For radial diffusion from a cylindrical geometry, the value for purely Fickian diffusion would be 0.45, and the value for Case II transport (polymer relaxation- or swelling-controlled mechanism) would be 0.89 [32]. Examining the diffusional coefficient, n, which is higher than 0.45 (Table 2), would lead to the conclusion of anomalous (non-Fickian) transport. However, no clear trend for the diffusional exponent could be noted regarding the effect of temperature and the pH of the release medium.

Table 2. Model rate constants (±C.I.)[a] for caffeine release at 25, 30 and 37 °C and at pH 6 and 2 from HPMC-compressed matrices.

Model	Rate constant	pH 6 release medium			pH 2 release medium		
		25 °C	30 °C	37 °C	25 °C	30 °C	37 °C
Korsmeyer–Peppas Eq. (3)	n	0.59±0.02	0.57±0.02	0.58±0.02	0.64±0.03	0.65±0.05	0.59±0.02
	$k \cdot 10^3$ (min^{-n})	4.26	5.38	5.49	3.22	3.28	5.42
First-order Eq. (4)	$k_1 \cdot 10^4$ (min^{-1})	4.14±0.48	4.82±0.58	5.21±0.60	4.30±0.40	4.63±0.42	5.53±0.77

[a] For clarity, 95 % confidence intervals are provided only for n and k_1 values.

To calculate the activation energy for the release process, the release profiles were fitted according to the first-order kinetics model, which was considered to be more appropriate for comparison with previous published data in the field [28,29],

$$\ln\left(1 - \frac{M_t}{M_\infty}\right) = -k_1 \cdot t \qquad (4)$$

where k_1 is the first-order release rate constant.

Generally, k and k_1 values (Table 2) do not significantly differ ($p>0.05$) with pH or temperature, confirming the tendency described for the f_2 values.

The apparent activation energies for caffeine release were derived from the slope of ln k_1 vs. $1/T$ plot (Figure 3). Values of 14.4±4.0 and 16.3±2.5 kJ mol^{-1} were obtained for pH 6 and pH 2, respectively. These values are in line with those reported [28,29] for the release of promethazine hydrochloride from compressed tablets with varying drug/HPMC ratios, ranging from 18.2 to 27.5 kJ mol^{-1}. Note that the latter results were further interpreted by the use of compensation analysis to show that all tested formulations had a common release mechanism, except the formulation with low HPMC content [33].

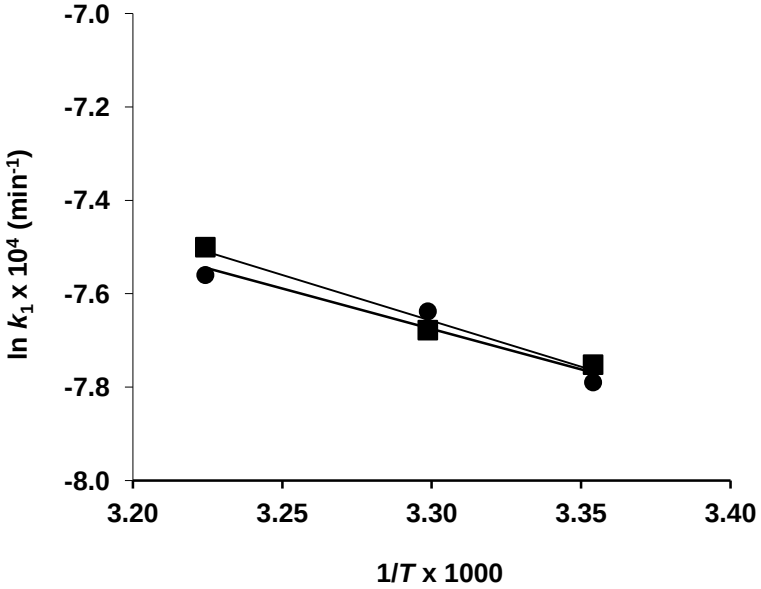

Fig. 3. Arrhenius plot of caffeine first-order release rate constant (k_1 x 10^4) from compressed HPMC 2910 matrices. Key: Release in (●) pure water (pH 6) and (■) 0.01 N hydrochloric acid (pH 2).

It must be emphasized that the E_a calculated for the release of solutes that are dispersed in the matrix system can be considered as "apparent activation energies" because they represent not only Fickian diffusion but also the temperature dependency of the equilibrium solute concentration in the release medium. Consequently, the apparent E_a calculated from release data overestimates or underestimates the true E_a in cases of exothermic or endothermic solution processes, respectively. However, it can be assumed, with the system tested, that the solute concentration in the release medium imbibing the HPMC matrix is far from saturation, even after the transition of the anhydrous caffeine into the hydrated form (20 % w/w at 25 °C [34,35]). No contribution of the so-called enthalpy of solution should thus be expected, and the calculated apparent E_a values could be considered as true activation energies for solute diffusion.

The E_a values calculated from the caffeine release data are lower than the values obtained for caffeine self-diffusion in pure solvents or gels (Table 1). Reasons that may account for these discrepancies include the presence of a high proportion of HPMC in the swelling tablet or the continuous dimensional increase of the system (see Section 3.3). Anyhow, the E_a values calculated for caffeine release at both pHs are not significantly different ($p>0.05$) and are not compatible with a swelling-controlled process mechanism, for which apparent activation energies in the range of 80 to 240 kJ mol^{-1} are observed [25,26].

3.3. Front movements and dynamic swelling

A second aspect to study when investigating the drug release mechanism from swellable systems is the kinetics of the penetrant (water). This behavior was studied in terms of front movements within the system and water uptake.

3.3.1 Front movement kinetics

Upon immersion of the tablet in the aqueous media, three moving fronts were clearly visible from the center to the periphery: the water penetration front (dry/hydrated glassy polymer interface), the swelling or transition front (hydrated glassy polymer/gel layer interface or glassy/rubbery interface),

and the erosion front (gel layer/dissolution medium interface) (see Figure 1 in Part II [5]). No diffusion front separating the gel layer with undissolved drug from the gel layer with dissolved drug could be observed because, as pointed out in section 3.2, the drug loading was intentionally low (1 % w/w). It should be stressed that the presence of a water penetration front has to be recognized, as it has been proven that the solvent does not decrease to zero beyond the glassy/rubbery interface, i.e., in the hydrated glassy zone. The swelling front takes place where the penetrant concentration is high enough to lower the polymer glass transition temperature to the experiment temperature, allowing macromolecule relaxation and extension. Regarding compressed tablets, both water penetration and swelling fronts have been observed visually in matrices based on sodium carboxymethylcellulose [36], although under different denominations, and in matrices made of various cellulose ethers [5]. They have also been recently identified in HPMC tablets [37-39] and xanthan tablets [40] using different MRI methods. In contrast, it is of interest to note that Tritt-Goc et al. monitored only the water penetration front using a simpler MRI technique [10,13,14]. Thus, to us, the conclusion of these authors that water transport into HPMC tablets was almost completely relaxation-controlled (Case II) at pH 2 and diffusion-controlled (Fickian) at pH 6 relied on the water penetration front movement kinetics and not on the kinetics of the true swelling front.

The fronts evolution over time at 37 °C at both pH 6 and 2 is presented in Figures 4a and 4b. An inward movement can be observed for the water penetration, whereas the swelling front moves slightly outward, a phenomenon observed previously [5,38,39] that can be ascribed to a significant increase in the volume of the swollen glassy polymer. The profiles are very close for both pHs and do not show linearity, except for the swelling front at pH 2, which seems to move rather constantly after an initial period of rapid advancement, most likely reflecting easy water diffusion within the tablet matrix, but not swelling. Notably, the front movement patterns are close to those reported for similar HPMC 2910 viscosity grades [5,41]. More importantly, the evolution of the water penetration front at pH 2 is not linear with time here, in contrast to the observation of Tritt-Goc et al. [10], which would mean Case II transport. In fact, profiles for these two fronts at both pH values can be better fitted with a $t^{0.5}$ relationship (Supplementary Figures 1a and 1b), which could indicate a Fickian diffusion process. The erosion front expands outward because of matrix swelling (solvent uptake dominates over polymer dissolution) and does not appear to be affected by the pH.

From these observations, it can be deduced that the position of the swelling front that recedes with time is simply the result of the opposite movements of this front. In these conditions, the evolution of the apparent front velocity cannot be used to draw a definitive conclusion regarding the water transport mechanism. For this reason, the front movements were not studied at the two other temperatures.

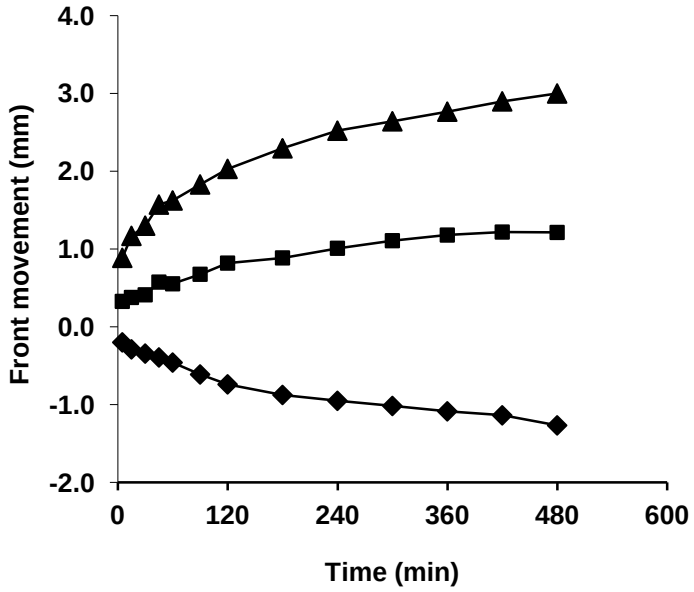

Fig. 4a. Water penetration (♦), swelling (■) and erosion (▲) front positions vs. time in compressed HPMC 2910 matrices, for pure water (pH 6) at 37 °C.

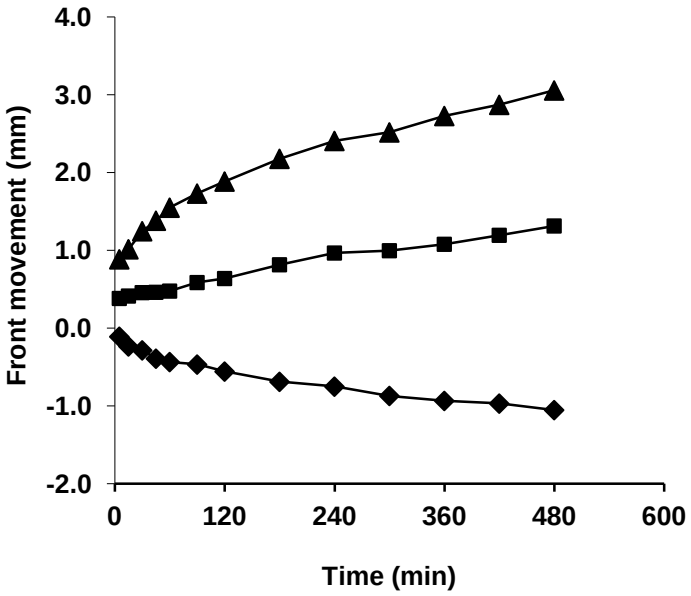

Fig. 4b. Water penetration (♦), swelling (■) and erosion (▲) front positions vs. time in compressed HPMC 2910 matrices, for 0.01 N hydrochloric acid (pH 2) at 37 °C.

3.3.2 Dynamic swelling

The dynamic swelling behavior is much more informative than the front movement kinetics. However, as the HPMC tablets undergo some erosion, especially at later times, it is rather speculative to estimate the equilibrium water absorbed and thus the fractional weight uptake at time *t*, and finally, to calculate the diffusion coefficient of water in the gelified matrix using an appropriate model. The water uptake data were thus analyzed in terms of the weight of water absorbed per original dry polymer weight, as proposed by Hopfenberg [7] to compute the E_a for solvent transport in polymers. This ratio is also referred to as the swelling degree *q* [42]:

$$q = \frac{m_t - m_0}{m_0} \qquad (5)$$

where m_t is the mass of the hydrated tablet at time *t* and m_0 is the mass of the dry tablet.

Figures 5a and 5b show plots of the swelling degree vs. time at 25, 30 and 37 °C and at pH 6 and pH 2, respectively. None of the profiles exhibit a linear weight gain with time, which could be one of the prerequisite for zero-order drug release. Comparing the various profiles using the similarity factor f_2, it becomes apparent that neither the temperature nor the pH influence water sorption, even at pH 2 and 37 °C (the calculated f_2 values were systematically greater than 50). It should be noted that the pH-independence of the hydration of HPMC matrices has been recently reported by other authors at 37 °C [43, 44].

As the rate of water transport appears to decrease continuously with time, the swelling degree was replotted as a function of $t^{0.5}$ according to the following equation:

$$q = k_2 \cdot t^{0.5} + a \qquad (6)$$

where k_2 is a kinetic constant and *a* is a constant.

The excellence of the fits observed (Supplementary Figures 2a and 2b) suggests an apparently diffusion-controlled transport mechanism for water sorption, in agreement with the results obtained by Kavanagh and Corrigan [43]. The k_2 values (Supplementary Table 2) confirm the absence of marked effects of the temperature and pH ($p>0.05$).

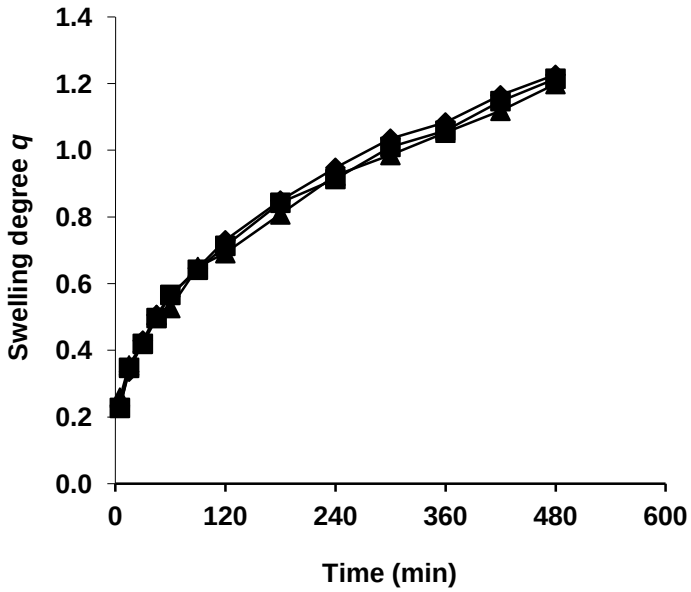

Fig. 5a. The effect of temperature on the swelling degree of compressed HPMC 2910 matrices immersed in pure water (pH 6). Key: (♦) 25 °C, (■) 30 °C and (▲) 37 °C.

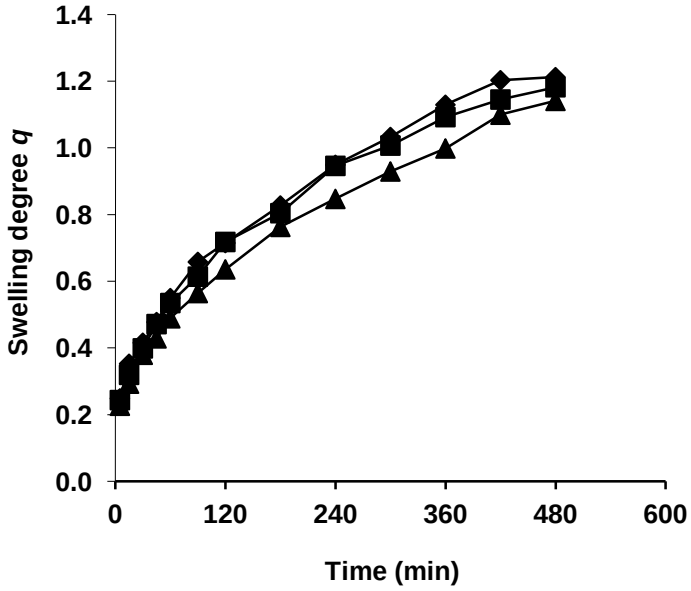

Fig. 5b. The effect of temperature on the swelling degree of compressed HPMC 2910 matrices immersed in 0.01 N hydrochloric acid (pH 2). Key: (♦) 25 °C, (■) 30 °C and (▲) 37 °C.

The apparent activation energies of water diffusion in the initially glassy HPMC matrix were derived from Arrhenius plots of ln k_2 vs. $1/T$ (Figure 6).

Unusually, the activation energies calculated for pH 6 and pH 2, which did not significantly differ ($p>0.05$), were negative (-3.9±0.1 and -4.8±0.5 kJ mol^{-1}, respectively), and they are certainly much lower than the typically reported E_a values for true diffusion (20-40 kJ mol^{-1} [25,26]). However, careful examination of the swelling process shows that this result is not so surprising because, as before, the observed apparent activation energies reflect several exo- and endothermic processes: (i) water sorption, i.e., the energy necessary for the penetrant to dissolve in the dry polymer before diffusing; (ii) dimensional change of the system, i.e., the volume work performed due to the expansion of the polymer network (chain extension); and (iii) erosion of the matrix, i.e., the heat produced upon progressive polymer dissolution. In fact, the true E_a for diffusion is undoubtedly positive, as diffusivity always increases with increasing temperature.

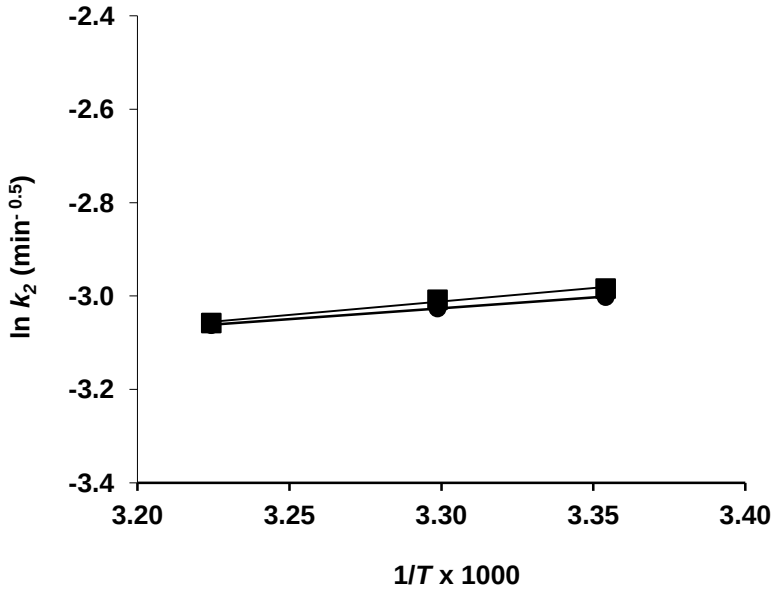

Fig. 6. Arrhenius plot of water uptake rate constant k_2 (min$^{-0.5}$) by compressed HPMC 2910 matrices. Key: Immersed in (●) pure water (pH 6) and (■) 0.01 N hydrochloric acid (pH 2).

The enthalpy of solution $\Delta_{sol}H$, or the enthalpy of mixing of the dry polymer and an infinite amount of water, can be calculated using the Gibbs-Helmholtz equation [42]:

$$\Delta_{sol}H = R \cdot T^2 \cdot d \ln q_\infty / dT \qquad (7)$$

where R is the gas constant, q_∞ is the swelling degree of the system at equilibrium and T is the thermodynamic temperature. The profiles in Figures 5a and 5b would indicate an absence or a very weak temperature dependence of the equilibrium water content and thus an approximately zero or slightly negative $\Delta_{sol}H$ value. In our case, this approach is not applicable, as the HPMC matrix undergoes progressive dissolution in water, which undoubtedly affects q_∞. However, $\Delta_{sol}H$ can reasonably be anticipated to be an exothermic process because the affinity of HPMC for water becomes lower as the temperature approaches the desolvation temperature [45]. A decreasing polarity of this type of HPMC with temperature can be inferred from the negative value of the so-called "specific" (acid-base interactions) component of the enthalpy of adsorption [46]. Another report [47] provides some indirect insight into the impact of the dimensional change of the system upon water penetration and of polymer dissolution on the E_a values. This study deals with the same type of HPMC used in the present work crosslinked with divinylsulfone, a polymer that undergoes extensive volume increase but does not dissolve upon contact with water. Apparent activation energies of -7.3 and -14.7 kJ mol^{-1} were calculated from the swelling data for HPMC gels with nominal divinylsulfone doses of 4.0 and $0.5 \cdot 10^{-4}$ mol g^{-1}, respectively. Hence, it could be concluded that as swelling increases, the apparent E_a diminishes because of the negatively increasing expansion work.

As a consequence, it may be inferred that deducing the negative contributions of the water sorption by HPMC, the dimensional change of the system and the partial HPMC dissolution pushes the true E_a for water diffusion in the system to an endothermic process, as expected. Thus, the experimentally determined apparent E_a from the water uptake clearly underestimates the true E_a, even though the latter is difficult to estimate accurately. Anyway, as water transport is considered to be a low activated process necessitating only local cooperation of few polymer repeating units, a rather low true E_a can most likely be anticipated.

Finally, it is of interest to compare our findings with the apparent E_a values reported in the literature [48-53] for water sorption in glassy polymers (Supplementary Table 3). No trend can be observed for a direct relationship between the apparent E_a and the transport mechanism or the extent of swelling at equilibrium. Examination of the literature reports confirms the combined contributions of the enthalpy of solution and of the volume expansion of the system to the E_a values.

4. Conclusions

Based on simple fitting of drug release profiles to some power law, usually the Korsmeyer-Peppas model, a swelling-controlled mechanism is frequently proposed for compressed cellulose ether matrices. However, three criteria, not all sufficient, must be fulfilled for constant drug release (Case II transport): (i) the existence of a sharp advancing swelling front; (ii) a constant concentration profile behind this front; and (iii) a constant velocity of the swelling front.

The main originality of the present work is the reconsideration of thermodynamic parameters of activation for discriminating diffusion and relaxation control for the solvent penetration and drug release processes in HPMC matrices. The effect of pH on the transport mechanisms was also investigated as we were intrigued by the different water transport behavior reported by other authors [10, 13-15]: Fickian diffusion for pure water (pH 6) and Case II transport at pH 2.

The diffusional exponent *n* of the Korsmeyer-Peppas model could indeed suggest anomalous drug release (coupling of diffusion and relaxation), but this mechanism can be dismissed when considering the water uptake results. In fact, it was demonstrated that *n* values between 0.45-0.89 originate from a combined diffusion-erosion mechanism [5]. This is further supported by the fact that polymer chain release rate from HPMC tablets has been shown to be constant [54].

The apparent E_a values for both pHs did not differ and were rather low, in line with the values reported in the literature for similar systems. These low values could be attributed to the dimensional change of the system during the drug release process and were not compatible with a swelling-controlled mechanism.

The true swelling front and the water uptake front kinetics could not be associated with Case II or non-Fickian swelling and were also not affected by the medium pH. Thus, these results do not verify the conclusion of a Case II or anomalous transport of the acidic medium into HPMC [10,13].

As for the parameters of activation, the true E_a calculated from the caffeine release and water uptake data can be anticipated to be positive and rather low, but this result is insufficient to conclude Fickian transport mechanisms. A general conclusion from the present work and from the literature survey is that the use of narrow ranges of activation energies for ascertaining the mechanism of drug release or of penetrant uptake is rather hazardous and cannot be recommended, particularly when the polymeric system undergoes extensive volume change. Consideration of the drug release in parallel with water uptake kinetics is essential.

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Table(s)

Table 1. Calculated energies of activation (E_a±SD) for self-diffusion of caffeine at 1 % w/w as a function of polymer weight fraction w_p.

Solvent	HPMC w_p	E_a (kJ mol^{-1})
D_2O (pH 6)	0	28.8±0.7
	0.05	20.5±0.3
	0.10	21.7±1.2
	0.15	22.3±0.5
DCl/D_2O 0.01 M (pH 2)	0	27.8±2.3
	0.05	22.5±0.1
	0.10	22.6±0.2
	0.15	22.9±0.6

Table 2. Model rate constants (±C.I.)[a] for caffeine release at 25, 30 and 37 °C and at pH 6.0 and 2.0 from HPMC-compressed matrices.

Model	Rate constant	pH 6 release medium			pH 2 release medium		
		25 °C	30 °C	37 °C	25 °C	30 °C	37 °C
Korsmeyer–Peppas Eq. (3)	n	0.59±0.02	0.57±0.02	0.58±0.02	0.64±0.03	0.65±0.05	0.59±0.02
	$k \cdot 10^3$ (min^{-n})	4.26	5.38	5.49	3.22	3.28	5.42
First-order Eq. (4)	$k_1 \cdot 10^4$ (min^{-1})	4.14±0.48	4.82±0.58	5.21±0.60	4.30±0.40	4.63±0.42	5.53±0.77

[a] For clarity, 95 % confidence intervals are provided only for n and k_1 values.

Figure legends

Figure 1a. Arrhenius plot of caffeine 1 % w/w self-diffusion coefficient D in D_2O and HPMC gels (pH 6) of varying polymer fraction w_p. Key: (♦) $w_p = 0$, (■) $w_p = 0.05$, (▲) $w_p = 0.10$, (●) $w_p = 0.15$.

Figure 1b. Arrhenius plot of caffeine 1 % w/w self-diffusion coefficient D in DCl and in DCl-based HPMC gels (pH 2) of varying polymer fraction w_p. Key: (♦) $w_p = 0$, (■) $w_p = 0.05$, (▲) $w_p = 0.10$ and (●) $w_p = 0.15$.

Figure 2a. The effect of temperature on the release of caffeine in pure water (pH 6) from compressed HPMC 2910 matrices. Key: (♦) 25 °C, (■) 30 °C and (▲) 37 °C.

Figure 2b. The effect of temperature on the release of caffeine in 0.01 N hydrochloric acid (pH 2) from compressed HPMC 2910 matrices. Key: (♦) 25 °C, (■) 30 °C and (▲) 37 °C.

Figure 3. Arrhenius plot of caffeine first-order release rate constant (k_1 x 10^4) from compressed HPMC 2910 matrices. Key: Release in (●) pure water (pH 6) and (■) 0.01 N hydrochloric acid (pH 2).

Figure 4a. Water penetration (♦), swelling (■) and erosion (▲) front positions vs. time in compressed HPMC 2910 matrices, for pure water (pH 6) at 37 °C.

Figure 4b. Water penetration (♦), swelling (■) and erosion (▲) front positions vs. time in compressed HPMC 2910 matrices, for 0.01 N hydrochloric acid (pH 2) at 37 °C.

Figure 5a. The effect of temperature on the swelling degree of compressed HPMC 2910 matrices immersed in pure water (pH 6). Key: (♦) 25 °C, (■) 30 °C and (▲) 37 °C.

Figure 5b. The effect of temperature on the swelling degree of compressed HPMC 2910 matrices immersed in 0.01 N hydrochloric acid (pH 2). Key: (♦) 25 °C, (■) 30 °C and (▲) 37 °C.

Figure 6. Arrhenius plot of water uptake rate constant k_2 ($min^{-0.5}$) by compressed HPMC 2910 matrices. Key: Immersed in (●) pure water (pH 6) and (■) 0.01 N hydrochloric acid (pH 2).

Fig. 1a

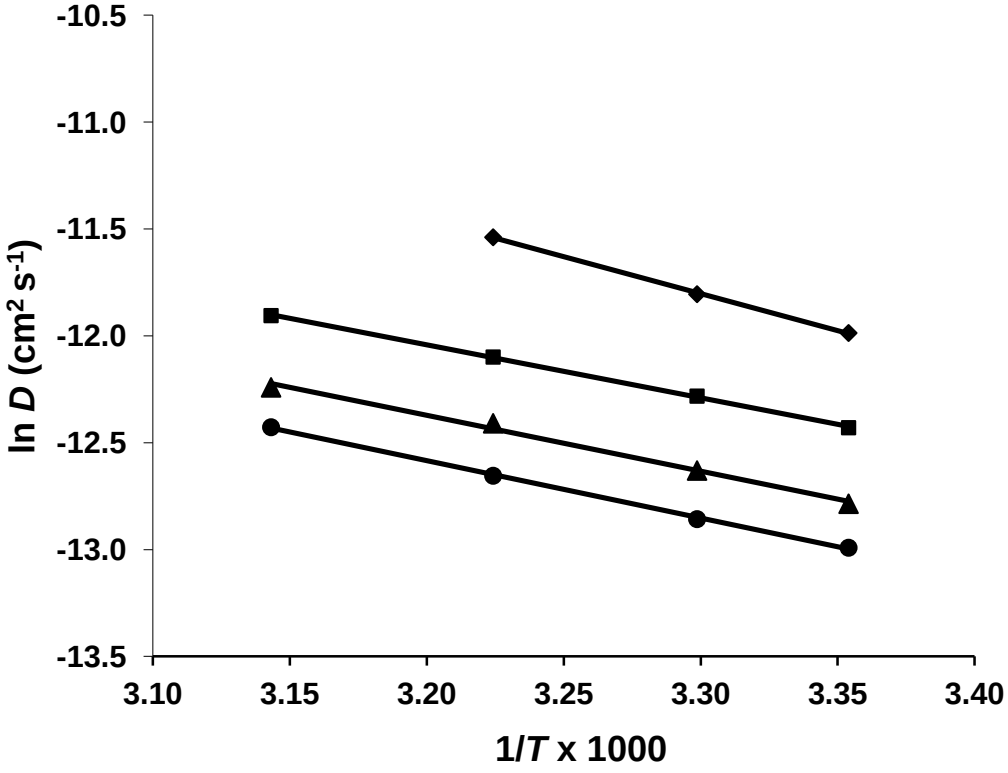
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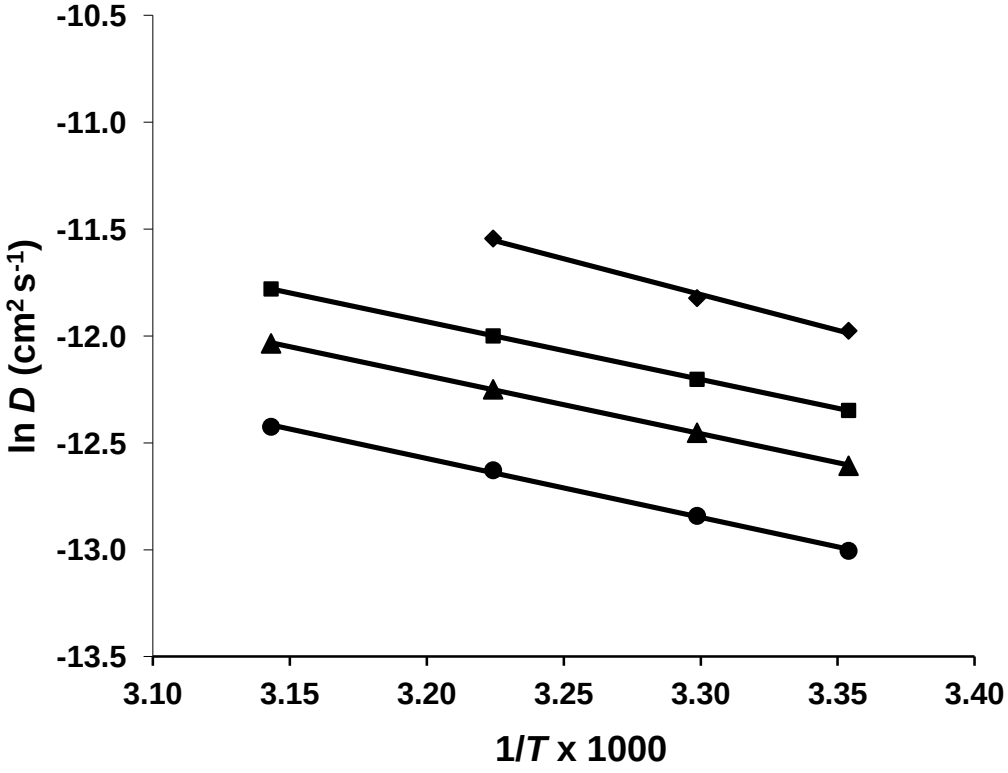
Fig. 1b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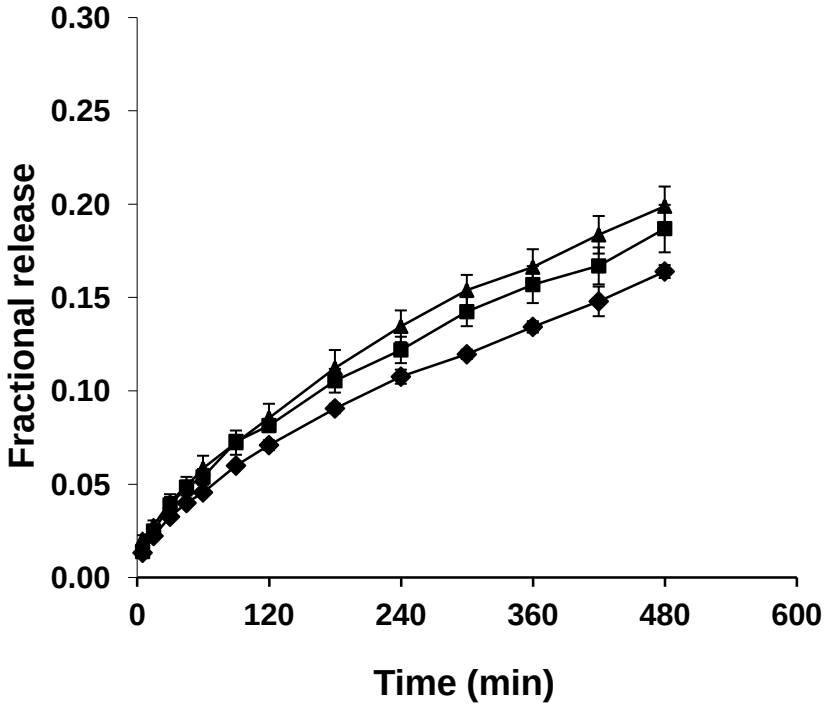
1/T x 1000

Fig. 2a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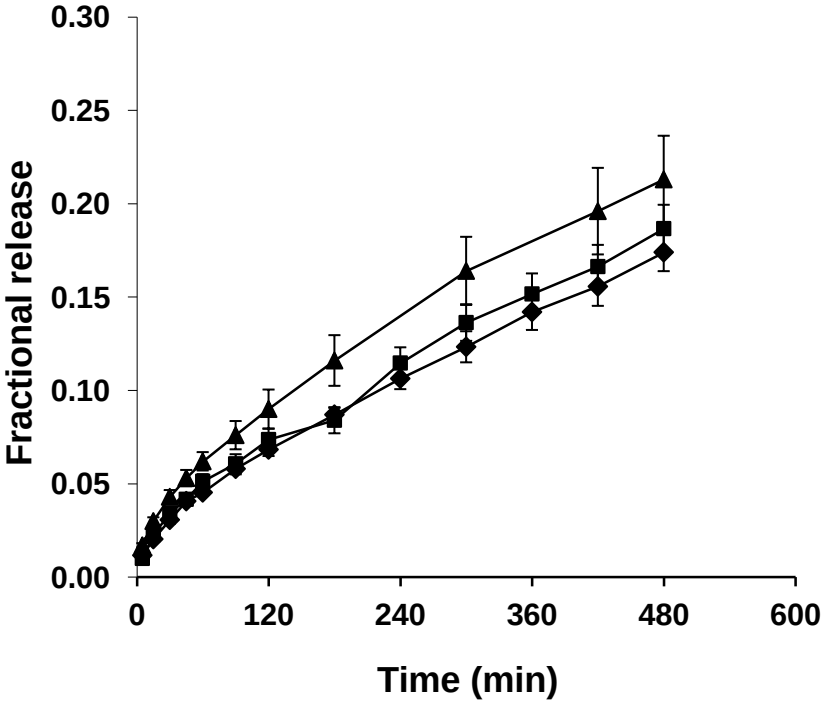
Time (min)

Fig. 2b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Fractional release
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Time (min)

Fig. 3

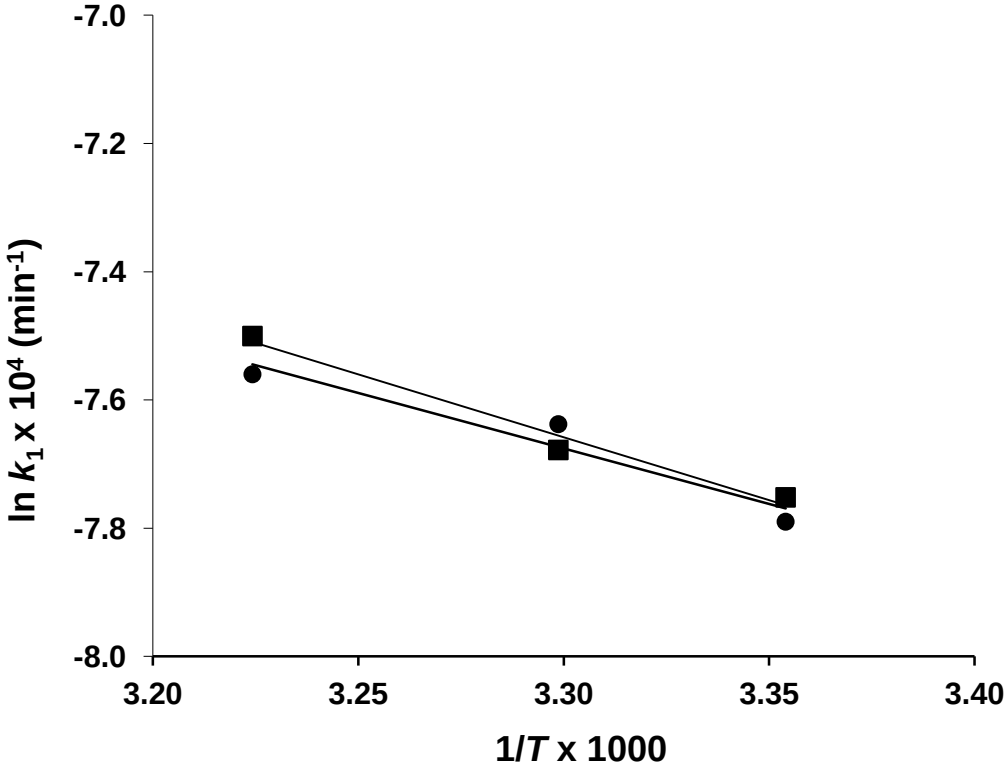
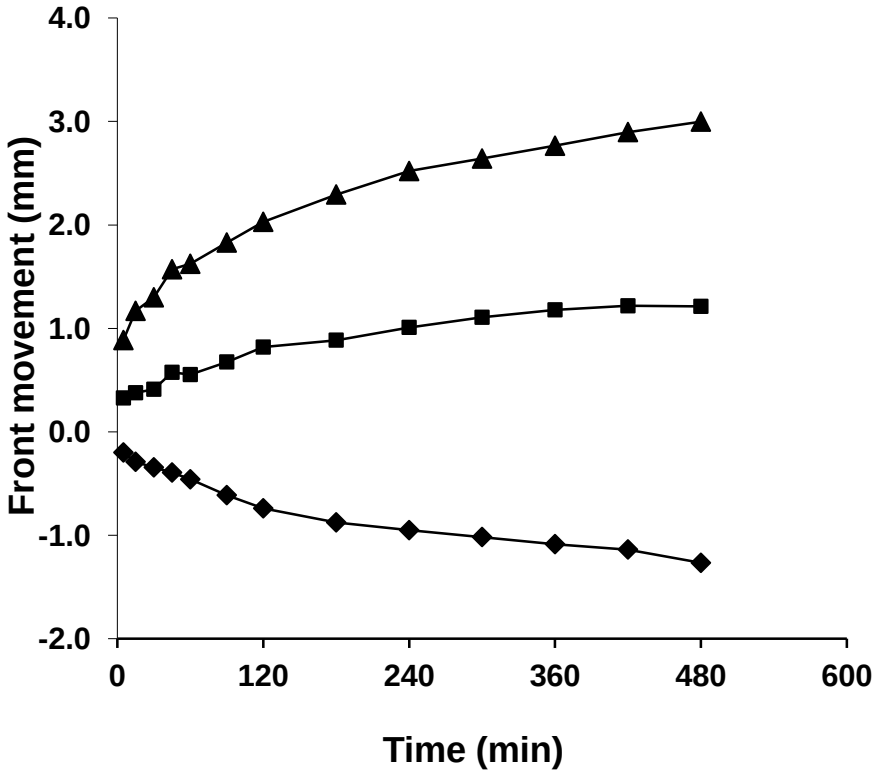


Fig. 4a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Front movement (mm)
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600
Time (min)

Fig. 4b

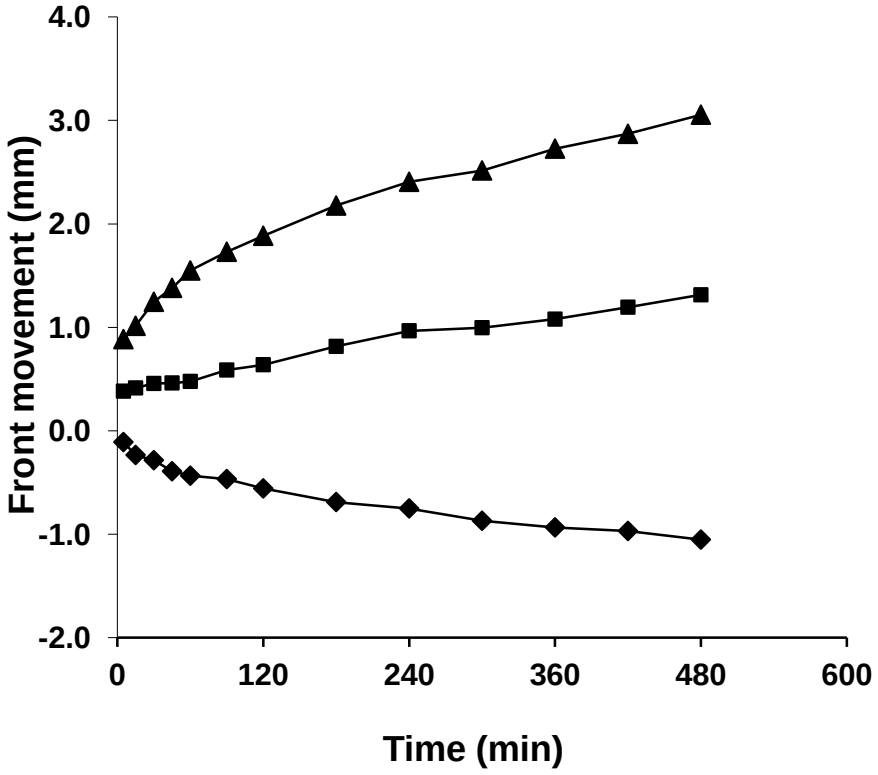

4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
Front movement (mm)
0
120
240
360
480
600
Time (min)

Fig. 5a

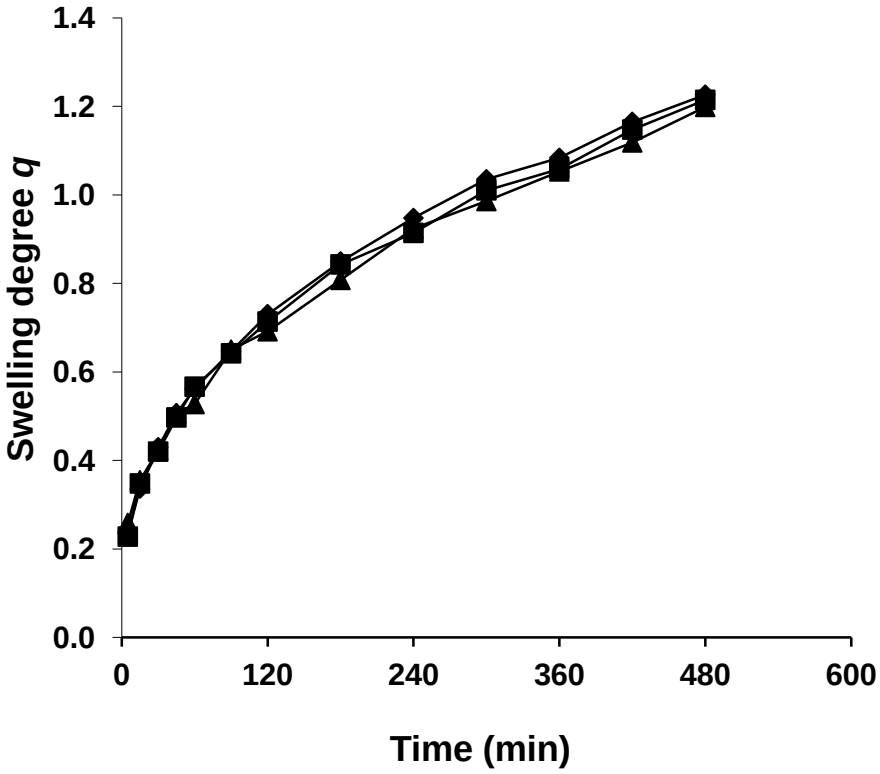

Swelling degree q
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
120
240
360
480
600
Time (min)

Fig. 5b

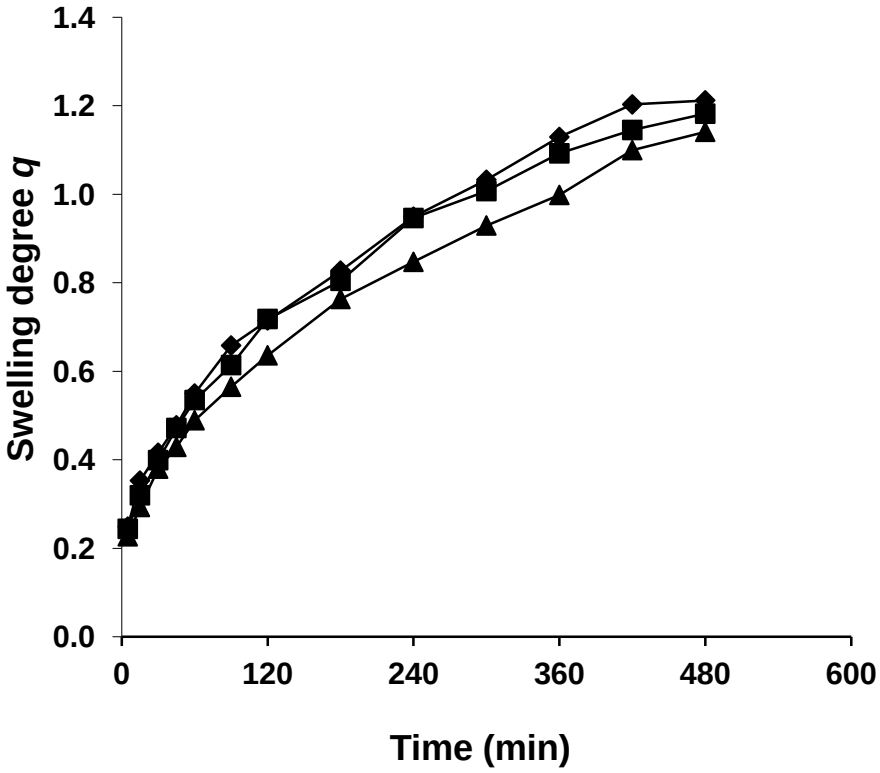
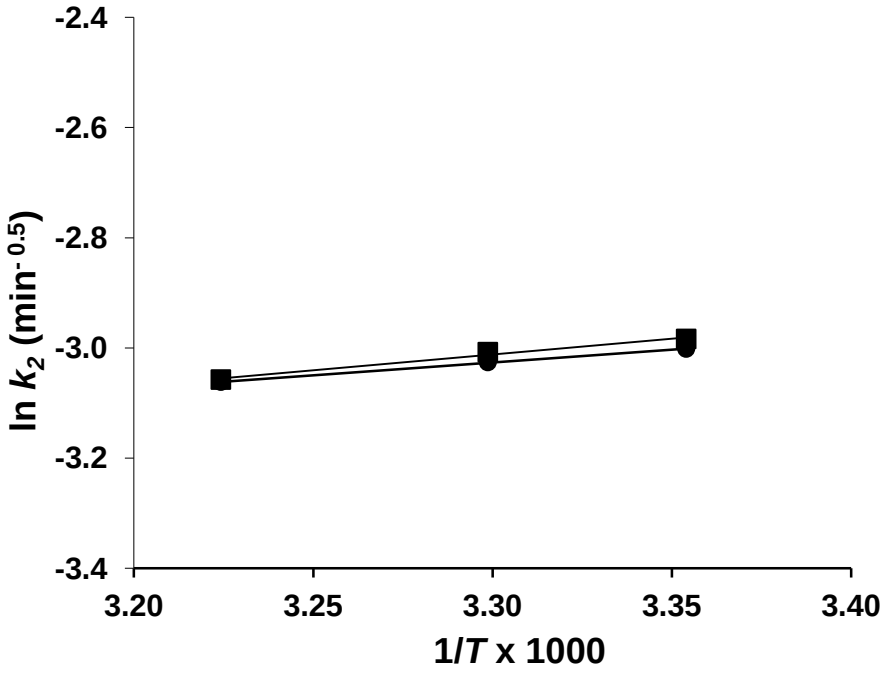

Swelling degree q
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
120
240
360
480
600
Time (min)

Fig. 6



Supplementary Material

Click here to download Supplementary Material: Supplementary Material (new submission II).docx