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Equilibrium properties and mechanism of kinetic release of metoclopramide from carbomer hydrogels

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Abstract

Equilibrium properties and kinetics of metoclopramide release of carbomer-metoclopramide (C-M) hydrogels are reported. A set of $(C\text{-}M)_X$ (x = moles percent of $M = 50$, 75, 100) that covers a pH range between 6.49 and 8.40 was used. Hydrogels exhibited a high negative electrokinetic potential (ζ). Concentrations of ion pair [$R\text{-}COO^-MH^+$] and free species [M] and [MH^+] were determined by the selective extraction of M with 1,2-dichloroethane (DCE) together with pH measurements. The system (C-M) is characterized by a high proportion of drug present in the form of ion pairs and a negative ζ potential that attracts MH^+ and H^+ and repeals OH^-, providing a microenvironment of higher acidity than the bulk medium. Delivery rates of M were measured in a Franz type bi-compartimental device using water and NaCl 0.9% solution as receptor media. (C-M) hydrogels behave as a reservoir that releases the drug at a slow rate to water; the rate increases 14 times as water is replaced by NaCl solution. The pH effect on delivery rate suggests that, under the main conditions assayed, the rate of dissociation of $R\text{-}COO^-MH^+$ together with the low change of pH in the polyelectrolyte environment are the factors that control releasing rates.

Keywords: Carbomer hydrogels; Metoclopramide; Carbomer–Drug complexes; Ion pair interaction; Drug delivery; Mechanism of kinetics release

1. Introduction

Our interest is focused in the development of hydrophilic molecular matrices obtained from acid polyelectrolytes loaded by acid base reaction with protonable drugs. Previously we have reported a detailed study dealing with equilibria and mechanism of delivery of model hydrogels of carbomer (C) loaded with different proportions of lidocaine (L) (Jimenez-Kairuz et al., 2002). There, it has been shown that a high fraction of L is present in the form of ion pairs with carboxylate groups of C, and that such interaction largely determines the kinetics of drug delivery. Drug delivery from

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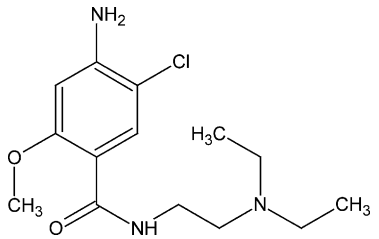
hydrogels of C loaded with fluoroquinolone antimicrobials were also studied (Vilches et al., 2002).

This paper reports results obtained from matrices of C loaded with metoclopramide (M).

This compound was selected upon consideration of its structure and acid–base properties, since it has a diethylamino moiety like L but of higher basicity (pK_a of diethilamino moiety of M (pK_{a_M}) is 9.71 (Pitrè and Stradi, 1987) and of L is 7.92 (Powell, 1986). The aromatic nitrogen of M is very weak (pK_{a_M} 0.42)). Therefore M would let to compare the ability of drugs of different basicity to form ion pairs with C and the role of such interaction on drug releasing behavior.



Besides, the physical characteristics of the system (C-M) are favorable to measure the electrokinetic potential of the dispersed particles.

On the other hand, there is an increasing interest in the development of new dosage forms of M, such as systemic nasal and oral formulations, that would be alternatives to the current per oral and parenteral routes (Clinical Pharmacology, 2000; The Pharmaceutical Codex, 1994).

2. Materials and methods

2.1. Materials

Carbomer 934-P (Carbopol® 934P-NF, BF-Goodrich, Cleveland, OH). M free-base was obtained by neutralizing a M hydrochloride (Parafarm, Bs. As., Arg.) solution with NaOH 1 N solution (Titrisol®, Merck, Darmstad, Germany) and further recrystallized with acetone p.a. (Sintogran®, Bs. As., Arg.). NaCl p.a. (Anedra, Bs. As., Arg.) was used.

2.2. Preparation of (C-M) hydrogels

Two series of $(C\text{-}M)_X$ hydrogels, 0.1% w/v and 0.25% w/v of C, were prepared by neutralizing an aqueous dispersion of C with the appropriate amount of M, (x refers to the mol% of M that neutralize the carboxylic groups of C: 50, 75 and 100%). Neutralization was carried out under constant stirring and at controlled temperature of 40 °C. The hydrogels were kept at room temperature for 20 h before used.

2.3. Partition equililibrium with 1,2-dichloroethane

1,2-Dichloroethane (DCE) p.a. (Dorwil®, Bs. As., Arg.) was used. Samples of $(C\text{-}M)_X$ at 0.1% of C placed in stoppered test tubes were shake flask partitioned with DCE at 1:1 ratio during 6 h with appropriate agitation at room temperature. After that samples were centrifuged. Drug concentration in DCE [M_{DCE}] was spectrophotometrically assayed at 267.5 nm (Shimadzu UV-160A, spectrophotometer, Tokyo, Japan). The pH of each hydrogel was recorded before the partition and at equilibrium.

In the same way, the partition equilibrium of M in DCE/Water was measured in order to get the true partition coefficient (PC_T).

2.4. Electrokinetic potencial (ζ)

It was determined with a particle microelectrophoresis apparatus (Marck II, Rank Brothers LTD, UK), with 10 cm length between the electrodes and 52 V of potential at controlled temperature 25 °C. The hydrogels were diluted at 0.01%.

2.5. Kinetic release

In vitro release of M of a set of $(C\text{-}M)_X$ hydrogels 0.25% of C, was measured in a bicompartimetal device that was previously described (Jimenez-Kairuz et al., 2002). Experiments were carried out at 37° loading the sample compartment with 15 g of hydrogel. Samples of 5.0 ml were withdrawn from the receptor medium at selected time intervals. The volume was kept constant upon

addition of equivalent amounts of fresh medium. Samples were acidulated with 0.1 ml of 0.1N HCl and the concentration of M was spectrophotometrically determined at 272.8 nm.

3. Results and discussion

Hydrogels $(C\text{-}M)_X$, were prepared by in situ neutralizing an aqueous dispersion of C with the appropriate proportion of M. Thus, a 0.25% dispersion of C loaded with 50–100% mole equivalents of M yields a set of hydrogels, with pH ranging from 6.49 to 8.40 (Table 1), which exhibit low transparency and pseudoplastic flux. The addition of 25 mol% of NaOH increases both viscosity and transparency. The negative ζ exhibited by the dispersed particles (−64.4 mV for a $(C\text{-}M)_{50}$) was slightly lowered as the proportion of M was increased (Table 1). In contrast, the addition of NaOH produced a rise of ζ which was paralleled by an increase of transparency and viscosity.

3.1. Species distribution

Since drug speciation produces free forms (M) and (MH^+) together with ion pairs between MH^+ and carboxylate groups of C, [R-COO^-MH^+], the total drug molar concentration in the hydrogel [M_T] is distributed as:

$$[M_T] = [M] + [MH^+] + [\text{R-COO}^-\text{MH}^+] \quad (1)$$

It was found that DCE selectively extracts the free base M from the hydrogel. Then, the measure of the experimental apparent partition coefficient (PC_{ap}) DCE/hydrogel yielded:

$$PC_{ap} = \frac{[M_{DCE}]}{([M] + [MH^+] + [\text{R-COO}^-\text{MH}^+])} \quad (2)$$

To solve Eq. (2), true partition coefficient (PC_T) DCE/water of M was measured.

$$PC_T = \frac{[M_{DCE}]}{[M]} = 169.4 \quad (3)$$

Then, the pH of the hydrogel after equilibration with DCE was recorded and [H^+] introduced into Eq. (4) together with Ka_M.

$$Ka_M = \frac{[M][H^+]}{[MH^+]} = 1.95 \times 10^{-10} \quad (4)$$

By using Eqs. (2)–(4) [M], [MH^+], and [R-COO^-MH^+] were calculated for each hydrogel and are quoted in Table 2.

The expression ion pair is used here in a broad sense, to refer to the fraction of drug that is not present in the bulk medium. Then, it is believed that such fraction exists essentially as cationic species MH^+ electrostatically interacting with anionic groups of C (Jimenez-Kairuz et al., 2002).

Results of Table 2 reveal that a high proportion of drug is present in the form of R-COO^-MH^+. For example, it was found that a $(C\text{-}M)_{100}$ 0.1%, after equilibration with DCE in a ratio 2:1, transfers 29% of drug to the organic phase. The remaining drug in the aqueous phase is distributed as follows: [M] 0.24%, [MH^+] 32.3% and [R-COO^- MH^+] 67.4%.

Table 1
pH, electrokinetic potential and releasing rate of $(C\text{-}M)_X$ hydrogels 0.25% of C

Hydrogel	M_T[a] (mol.L^{-1})	pH	ζ[b] (mV)	k_L[c] (mg h^{-1})	k_L[d] (mg h^{-1})
$(C\text{-}M)_{50}$	1.50×10^{-2}	6.49	−64.8	0.45	6.27
$(C\text{-}M)_{75}$	2.25×10^{-2}	7.53	−63.3	0.77	9.64
$(C\text{-}M)_{100}$	3.00×10^{-2}	8.40	−60.9	1.40	–
$((C\text{-}M)_{75}$ $Na_{25})$	2.25×10^{-2}	8.46	−68.7	0.55	–

[a] M stoichometric concentration.
[b] Electrokinetic potential of hydrogels diluted to 0.01%.
[c] Release rate in water as receptor medium.
[d] Release rate in 0.9% NaCl soln. as receptor medium.

Table 2
Species distribution of $(C\text{-}M)_X$ hydrogels, 0.10% of C, after equilibration (eq) witch DCE

Hydrogel	pH		% M^a_{eq}	$[M]^b_{eq}$	$[MH^+]^b_{eq}$	$[R\text{-}COO^-MH^+]^b_{eq}$
	Before eq	After eq				
$(C\text{-}M)_{50}$	6.96	6.91	43.9	4.30×10^{-6} (0.08%)	2.70×10^{-3} (51.17%)	2.57×10^{-3} (48.75%)
$(C\text{-}M)_{75}$	7.88	7.39	57.6	1.23×10^{-5} (0.18%)	2.58×10^{-3} (37.29%)	4.32×10^{-3} (62.53%)
$(C\text{-}M)_{100}$	8.72	7.58	71.1	2.05×10^{-5} (0.24%)	2.76×10^{-3} (32.32%)	5.76×10^{-3} (67.44%)
$((C\text{-}M)_{75}\ Na_{25})$	8.81	8.03	52.1	1.59×10^{-5} (0.26%)	7.89×10^{-4} (12.88%)	5.34×10^{-3} (86.86%)

[a] Mol% of M that remains in hydrogels after extraction with DCE.
[b] Molar concentrations and percent distribution of species.

Fig. 1 also shows that, as the proportion of loaded drug is raised, log $[RCOO^-MH^+]$ and log[M] both increases linearly with the pH of the resulting hydrogels, with slopes of 0.51 and 1.00, respectively. Then, at pHs in which $[MH^+] \gg [M]$, log[M] is the sensitive variable that accompanies pH changes, since $\log[MH^+]$ remains nearly constant as can also be seen in Fig. 1. The intensity of the effect of pH on log[M] is not different from that expected for the base M in a homogeneous system according to the Henderson–Hassellbach equation.

It was also observed that the increase of [M] ($\Delta[M] = 1.62 \times 10^{-5}$ M) is linearly paralleled by a rise of $[R\text{-}COO^-MH^+]$ ($\Delta[R\text{-}COO^-MH^+] = 3.19 \times 10^{-3}$ M). The correlation of both magnitudes gives the isotherm shown in Fig. 2 that may be expressed by:

$$[R\text{-}COO^-MH^+] = 197.3[M] + 1.8 \times 10^{-4} \quad (5)$$

This behavior suggests that the following non-protogenic equilibrium is operating:

$$R\text{-}COO^-MH^+ \rightleftarrows R\text{-}COOH + M \quad (6)$$

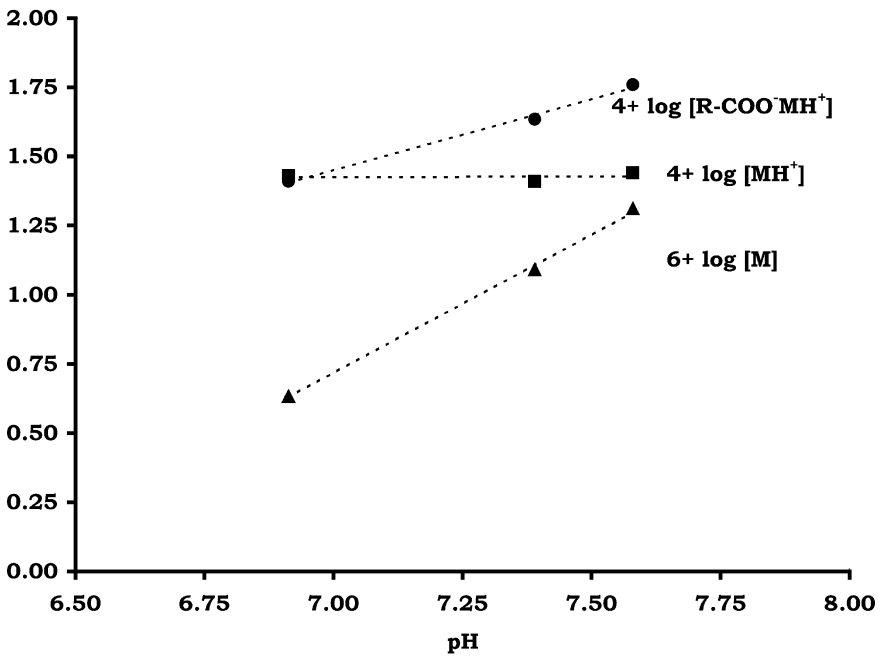


Fig. 1. Relationship between pH and species concentrations in $(C\text{-}M)_X$ hydrogels after equilibration with DCE.

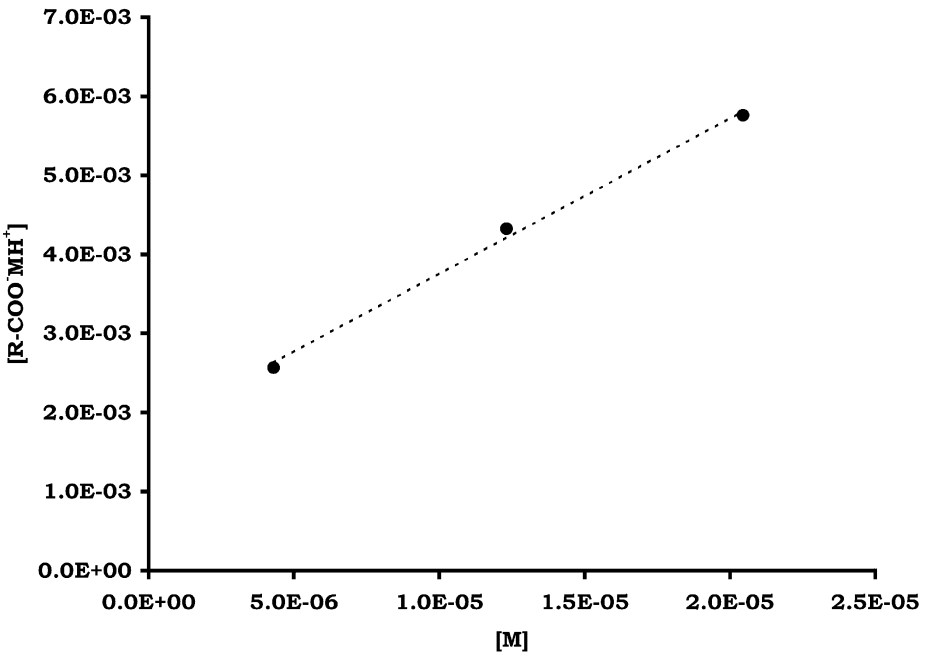


Fig. 2. Correlation between ion pair [R-COO$^-$MH$^+$] and free base M molar concentrations.

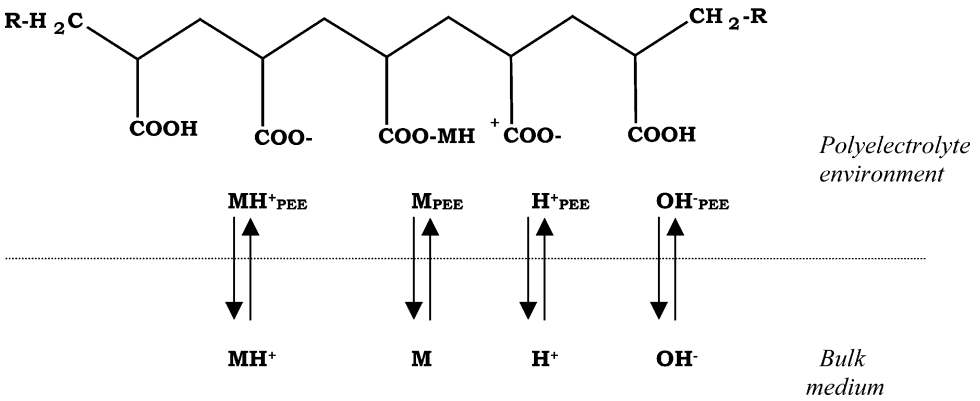
The understanding of the properties of these hydrogels under equilibrium and delivery conditions requires a treatment of the results in terms of the current ideas about the electrostatic interactions in colloidal systems (Martin, 1993).

In fact, under equilibrium conditions the concentration of cationic species H^+ and MH^+ in the PE environment (PEE) should be higher than those in the bulk medium due to the electrostatic attraction of the negative charge of carboxylate groups. Accordingly, a high negative ζ was found. In the same way, the concentration of OH^- should be higher in the bulk medium than in the PEE. Also, electroneutrality requires that:

$$[MH^+] + [H^+] = [OH^-] \quad (7)$$

Scheme 1 depicts the main interactions that would occur in the PEE and in the bulk medium.

According with the scheme, the PEE is characterized by a lower pH than that of the bulk



Scheme 1.

solution and a high amount of MH^+ present in the form of ion pairs; the model also assumes that [M] is equal in both PEE and bulk medium.

3.2. Release kinetics of metoclopramide

Rates of M release were measured on a set of 0.25% C hydrogels under non-sink conditions in a two-compartment device, using distilled water or 0.9% NaCl solution as receptor media. Solution of NaCl was selected to simulate saline properties of biological fluids.

Release to water receptor medium occurs essentially through the Fickian diffusion of the neutral species M, since diffusion of MH^+ is prevented by the electrostatic gradient provided by the polyanion. It has been reported that neutral or charged molecules of similar MW than that of M, dissolved in viscous hydrogels, exhibited diffusion coefficients and Fickian transport which were not different from those observed in water (Nakanishi et al., 1998a,b; Realdon et al., 1998; Upadrashta et al., 1993).

Fig. 3 shows that M is slowly released from the matrix to the water receptor medium. Then, such conditions were considered to be appropriated to get information on the effect of pH on releasing rates.

Values of the experimental delivery rate coefficient (k_M), quoted in Table 1 were calculated as the ratio $\Delta[M]/\Delta t$ for the time interval between 2 and 4 h. Such an approach to the true value of k_M was deemed accurate enough to discuss results.

In Fig. 4, log k_M was plotted against the pH of each hydrogel. There it can be seen that the rise of log k_M is linearly related to the pH of the hydrogel, however, the slope of 0.26 is revealing a low intensity of the effect of pH on releasing rates of M.

Therefore, the main question to answer refers to the fact that pH effects on log k_M is about four times lower than that on log[M]. According with Scheme 1, kinetic results suggest that under delivery conditions to the water receptor medium, the kinetic control would be a consequence of the steady state of free base (M_{st}) in the PEE, which is the reservoir of the main amount of drug. The

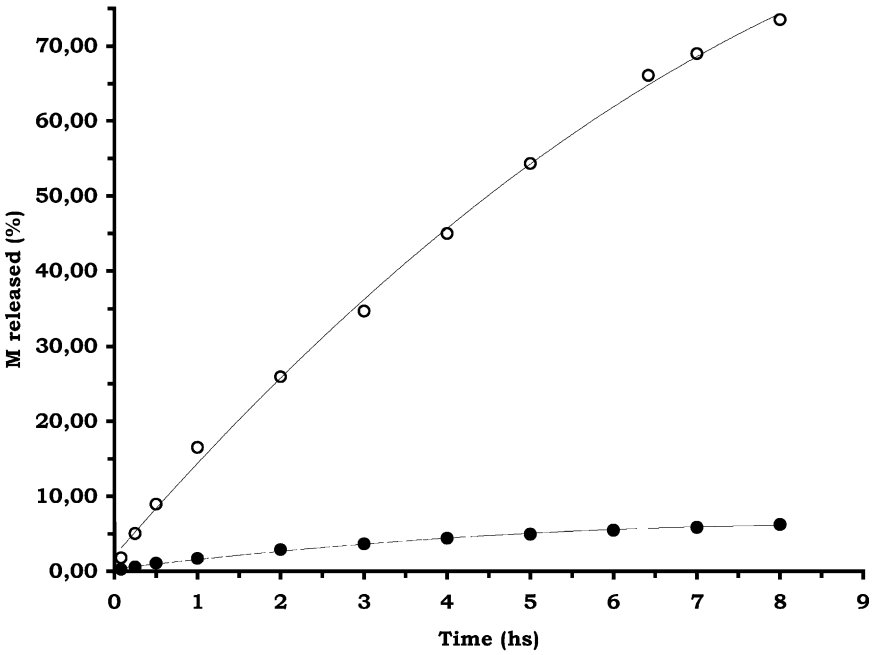


Fig. 3. Metoclopramide release from $(C\text{-}M)_{75}$ hydrogels in water (●) and 0.9% NaCl solution (○) as receptor media.

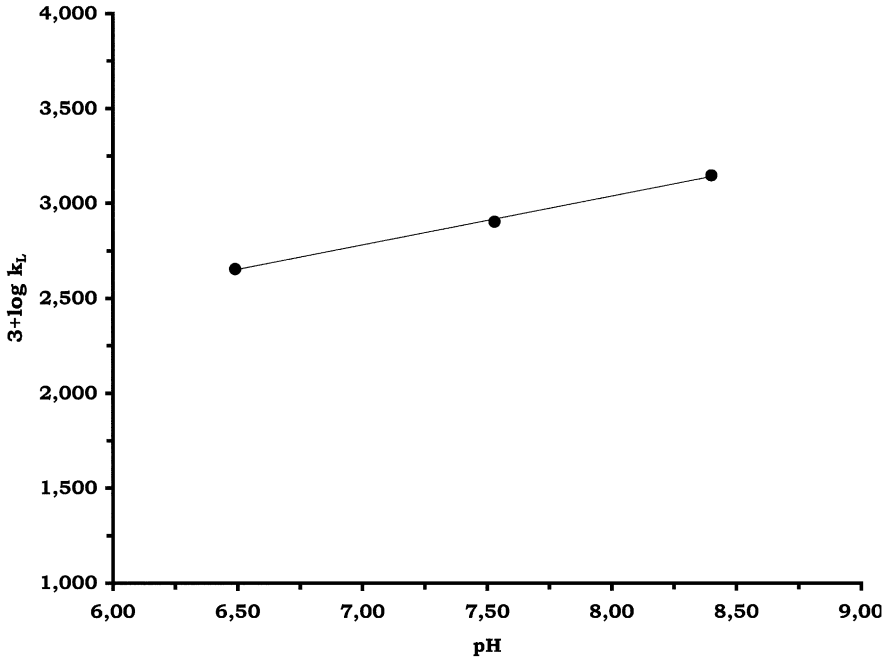


Fig. 4. Release rate variation with pH of $(C\text{-}M)_X$ hydrogels series.

steady state would be governed by both the rate of dissociation of $R\text{-}COO^-MH^+$ and pH_{PEE}. It should be noted that, the low intensity observed in the effect of bulk pH on log K_M, would be a consequence of a concomitant low change of pH_{PEE}.

As NaCl 0.9% was placed as receptor medium instead of water, a 14 times rise in the release rate of a $(C\text{-}M)_{75}$ was found. This result may be associated to the diffusion of Cl^- and Na^+ from the receptor compartment to the hydrogel. On one hand Cl^- would promote the diffusion of MH^+ by acting as a counterion; on the other hand, the ionic exchange between Na^+ and MH^+_{PEE} would also promote drug release from the polyanion. This condition provides some illustration regarding the expected interactions between hydrogels and biological fluids.

4. Conclusions

The C-M system behaves as a reservoir of M in which a high proportion of drug is present in the form of $R\text{-}COO^-MH^+$. The concentration of free-base M in the bulk medium is determined by both its ion pairing ability and its pK_a.

Both, slope and intercept of Eq. (5) are a measure of the ability of M to form ion pairs with C.

The effect of pH on delivery rates suggest that, under the conditions assayed, the rate of dissociation of ion pairs together with the low change of pH in the PEE are the factors that control drug delivery.

Release rate is increased by the diffusion of neutral salts such as NaCl, into the gel matrix.

Deeper understanding of the ion pairing affinity between drugs and polyelectrolytes along with information regarding the effects of other species on such equilibrium would help to predict their delivery properties under different conditions.

Acknowledgements

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