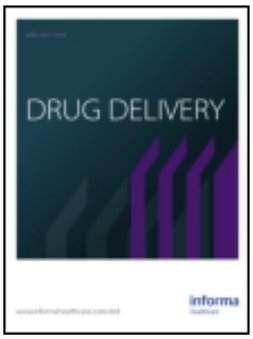

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RESEARCH ARTICLE

Swellable drug-polyelectrolyte matrices of drug-carboxymethylcellulose complexes. Characterization and delivery properties

María V. Ramírez Rigo, Daniel A. Allemandi, and Ruben H. Manzo

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Abstract

This article reports the development and delivery properties of swellable drug-polyelectrolyte matrices prepared with complexes of the acid form of carboxymethylcellulose (HCMC). Drug-polyelelectrolyte complexes (HCMC-D) were obtained by neutralization of HCMC with two model basic drugs (atenolol and metoclopramide). Characterization through FT-infrared spectroscopy, power X-ray diffraction, and DSC indicates the ionic nature of the interaction between the carboxylic groups of HCMC and the basic group of D. Matrices prepared by compacting (HCMC-D) alone or in a mixture with sodium carboxymethylcellulose were subjected to measurements of solvent up-take, dynamics of swelling, and release kinetics. Delivery rate of mixed matrices is a function of its composition and may be widely modulated. They exhibited anomalous delivery kinetics with Korsmeyer exponent *n* in the range 0.67–0.87. Experimental results indicate that the erosion of the hydrogel layer is the main delivery process.

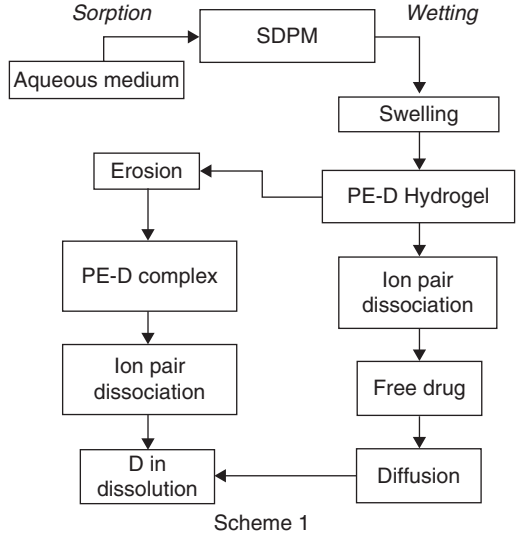
Keywords: *Polyelectrolyte-drug interaction; drug delivery; drug release mechanism; swellable drug-polyelectrolyte matrices; carboxymethylcellulose*

Introduction

The properties of swellable drug polyelectrolyte matrices (SDPM) obtained by compacting drug-polyelectrolyte (D-PE) complexes were previously reported (Jimenez-Kairuz et al., 2005; Ramírez Rigo et al., 2006). Such SDPM were developed using complexes of carbomer or alginic acid–sodium alginate as acid PE and a set of model drugs having basic groups. Development of extended release tablets based on SDPM was also reported (Bermudez et al., 2008).

Both carbomer or alginic acid-based SDPM in contact with an aqueous medium develop a hydrogel layer that modulates the release of the drug loaded in the matrix, as depicted in Scheme 1.

In carbomer-based SDPM, the diffusion process has been proposed as the main mechanism of drug release. On the contrary, in alginic acid–sodium alginate-based SDPM the erosion of the hydrogel layer appears to be the main process of delivery.



Scheme 1

This article reports the properties of matrices of complexes of the acid form of carboxymethylcellulose and model basic drugs (HCMC-D).

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Among acid PE, carboxymethylcellulose is widely used in pharmacy. In particular, carboxymethylcellulose sodium (NaCMC) is currently used in oral and topical pharmaceutical formulations, primarily for its viscosity increasing properties on aqueous solutions and as a tablet binder and disintegrant (Wade and Weller et al., 1994; Dabbagh et al., 1999; Takka et al., 2001; Lotfipour et al., 2004; Conti et al., 2007a,b). Carboxymethylcellulose calcium is also used in tablet formulations.

Carboxymethylcellulose in its acid form (HCMC) is water insoluble, behaving as an ionic exchange resin that may be easily loaded with drug molecules having protonable basic groups to yield also insoluble products according to:

$$RCOOH^{\circ} + DH^{+} + Cl^{-} \rightleftharpoons (RCOO^{-}DH^{+})^{O} + HCl \qquad (1)$$

in which $RCOOH^{\circ}$ represent a carboxylic group of HCMC and $(RCOO^{-}DH^{+})^{\circ}$ the product loaded with DH^{+}.

As previously reported, affinity constants according to equation (1) of a set of basic drugs lay in the range 10^{5}–10^{8} M^{-1}, revealing a high affinity between HCMC and D (Ramírez Rigo et al., 2004). Therefore, HCMC-D complexes in solid state are easily prepared. In this study, Atenolol (At) and Metoclopramide (Me) were selected to prepare complexes to be further processed as compacted matrices.

Materials

The following materials were used: NaCMC (PA grade, Fluka AG, Buchs SG, Switzerland), atenolol, metoclopramide hydrochloride (Pharmaceutical grade, Parafarm, Bs. As, Argentina), sodium chloride, potassium monobasic phosphate, acetone (PA grade, Cicarelli, Santa Fe, Argentina), ethanol 96° (USP-Pharmacopoeia grade, Porta, Cordoba, Argentina), 1 M sodium hydroxide solution and 1 M hydrochloride acid solution (Merck, Darmstadt, Germany).

Free base of metoclopramide was obtained by neutralization of its hydrochloride solution with NaOH. Solid product obtained was filtered, washed with distilled water, and dried in an oven at 50°C to constant weight.

Methods

Preparation of HCMC

HCMC was obtained by adding 1 M HCl solution to an aqueous hydrogel of 3.6% NaCMC until pH = 2, and further precipitation of HCMC with ethanol. The solid was separated by filtration, washed with water, filtered, and dried in an oven at 50°C to constant weight. The product was milled and sieved through 40 and 70 mesh sieves. The equivalents of carboxylic groups per gram of HCMC (1.84×10^{-3}) were assayed by acid base titration.

Preparation of (HCMC-D)$_{50}$

Complexes were prepared by mixing an aqueous suspension of HCMC with an appropriate amount of D, to neutralize 50% of the HCMC acid groups. Then, subscript 50 refers to the mole % of basic drug that neutralizes the carboxylic acid groups of HCMC. The product was separated and dried in an oven at 50°C to constant weight.

Characterization of (HCMC–D)$_{50}$

A preliminary characterization of the complexes was performed by FT-infrared spectroscopy (FT-IR) (Avatar 360, ESP Nicolet, with KBr 1.5% disks), powder X-ray diffraction (Rigaku Miniflex diffractometer, scan range was 5–70°), differential scanning calorimetry (DSC) (TA-Instruments Modulated-DSC 2920, Universal Analysis-NT software, 1–2 mg samples were run at 10°C/min ramp in aluminium hermetic pans under nitrogen atmosphere, flowing at 60 ml/min), and thermogravimetry (TG) (samples were run in open aluminium pans). Physical mixtures of HCMC and D and HCMC or D alone were also assayed.

Interaction of the complexes with water vapor was determined by measuring sorption and desorption of water as a function of relative humidity (RH) at constant temperature and in equilibrium conditions (USP 31, 2007). Samples of 100 mg were stored at 20°C in closed recipients containing appropriated saline-saturated solutions to control RH. The samples were reweighed periodically to calculate the percent of water uptake at each RH. The saturated salt solutions used were: potassium hydroxide, calcium chloride, sodium bromide, and potassium bromide to get, respectively, 9, 31, 58, and 84% RH (Wade, 1980).

Finally bulk and tap densities were determined as described by Wade and Weller (1994).

Preparation of SDPM

Matrices of (HCMC-D)$_{50}$ alone or mixed with different proportions of NaCMC ((HCMC-D)$_{50}$:NaCMC) were obtained by compacting 200–400 mg of powder at 2 tonnes for 30 s in a hydraulic press equipped with flat punches 12.8 mm in diameter.

Solvent up-take

Sorption of water or aqueous solutions (buffer of pH 6.8 and 0.1 M HCl) by the matrices was determined using a device described by Nogami et al. (1969) and Llabot et al. (2002).

Radial front movement

Erosion and swelling fronts were measured in water by a technique previously reported by several authors (Bettini et al., 1994; Colombo et al., 1995, 1996, 1999; Ferrero et al., 2000).

Drug delivery from SDPM

Release of D was measured in a USP 31 dissolution apparatus 1 (Hanson Res., USA) at 50 or 100 rpm using 500 ml of degassed dissolution medium for $(HCMC\text{-}At)_{50}$ matrices and 900 ml for $(HCMC\text{-}Me)_{50}$ matrices at 37°C. Dissolution media were distilled water, 0.9% NaCl solution, buffer pH 6.8, and 0.1 M HCl solution. The basket apparatus was selected to avoid sticking of the matrices on the wall of the dissolution vessel. Standard baskets of 40-mesh size were used.

Samples of 3 ml were taken at defined time intervals, filtered through a teflon membrane (10 μm pore size), and replaced with equivalent amounts of fresh medium preheated to 37°C. The release of D was spectrophotometrically determined at 273 nm (At) and 309 nm (Me).

Experimental results were fitted according to the following equation (Korsmeyer et al., 1983; Ritger and Peppas, 1987):

$$M_t / M_\infty = kt^n \tag{2}$$

where M_t/M_∞ is the fraction (0.1–0.7) of D released at time t and ∞, respectively, k is the apparent release rate constant, and n is the diffusion exponent whose value is related to the release mechanism (Takka et al., 2001; Lotfipour et al., 2004; Ranga Rao et al., 1988; Talukdar and Kinget, 1995; Colombo et al., 2000).

Besides, mean dissolution time (MDT) was also calculated (Möckel and Lippold, 1993).

$$\mathrm{MDT} = \frac{n}{n+1} k^{-(1/n)} \tag{3}$$

The same experimental device and conditions were used to measure matrix erosion, according to Sinha Roy and Rohera (2002). With such purpose, SDPM were removed from the medium at determined time intervals and lightly patted using tissue paper. Then, they were dried at 60°C until constant weight to determine percent mass loss.

All experiments were performed in triplicate.

Results and discussion

Complexes of HCMC in which 50% of its carboxylic groups were neutralized with At or Me ($(HCMC\text{-}At)_{50}$ and $(HCMC\text{-}Me)_{50}$) were prepared as described in the experimental section.

Characterization of $(HCMC\text{-}D)_{50}$ complexes

The body of information provided by FT-infrared spectroscopy, power X-ray diffraction, DSC, and TG supports the conclusion about the ionic nature of the interaction between the carboxylic groups of HCMC and the basic group of D (Jimenez-Kairuz et al., 2005; Ramírez Rigo et al., 2006; Bermudez et al., 2008; Takka, 2003; Esteban, 2007; Quinteros, 2008).

Figures 1–3 show representative results. The FT-IR spectrum of $(HCMC\text{-}At)_{50}$ shows a decrease in the intensity of the characteristic band of C=O vibrations of the carboxylic acid groups of carboxymethylcellulose at 1700 cm^{-1}. In addition, it shows new absorption bands at 1613 and 1398 cm^{-1}, which were assigned to the symmetric and asymmetric vibrations of COO^- group of the PE. The absorption band associated with the protonated nitrogen of D is observed at 2525 cm^{-1} (Figure 1).

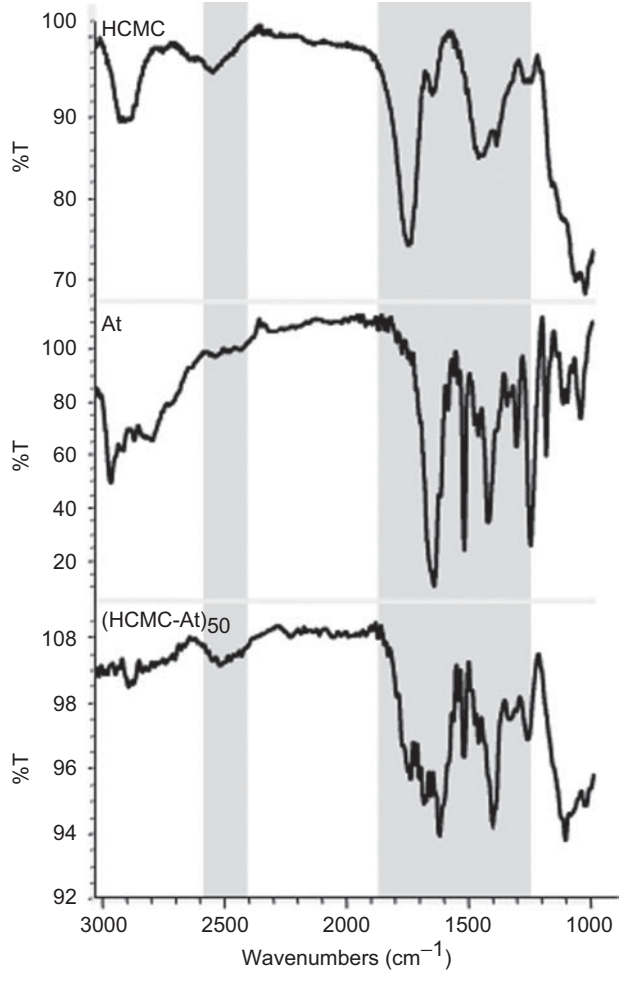

Figure 1. FT-IR spectra of HCMC, At. and $(HCMC\text{-}At)_{50}$.

The X-ray power diffraction of At, HCMC, physical mixtures, and the product $(HCMC\text{-}At)_{50}$ were studied comparatively. Both HCMC and $(HCMC\text{-}D)_x$ are amorphous. In $(HCMC\text{-}D)_x$ products, the amorphous state is evidence of absence of free D (Figure 2) because in the physical mixtures the reflections of the crystalline D are present (Bonferoni et al., 2000).

Finally, DSC profiles of HCMC and its products were analyzed. The melting endotherm corresponding to crystalline At (153°) was absent in $(HCMC\text{-}At)_{50}$ (Figure 3). In addition, the carbonization process of HCMC and $(HCMC\text{-}D)_{50}$ can be observed at high temperatures (from 227°C), that is also described for NaCMC (Wade and Weller, 1994).

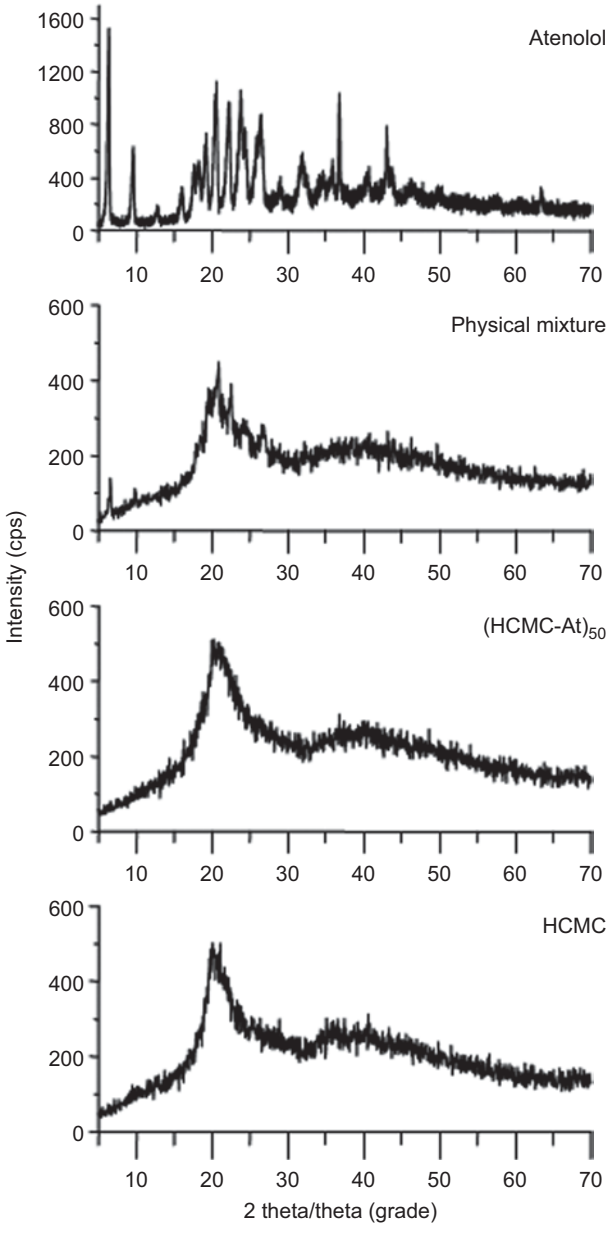

Figure 2. Powder X-ray diffraction patterns.

Similar results were obtained with $(HCMC\text{-}Me)_{50}$ complexes.

Water vapor sorption and flow properties

The sorption isotherm was determined with the $(HCMC\text{-}At)_{50}$ complex. The increase of weight as a function of the relative humidity (RH) is shown in Figure 4. The desorption isotherm can be superposed to the former, indicating the reversibility of the process. It should be mentioned that the proportion of water in $(HCMC\text{-}At)_{50}$ at different RH is lower than that informed for NaCMC (Wade and Weller, 1994).

Complementarily, the lost of weight of complexes stored under ambient conditions was determined by TG runs. Both $(HCMC\text{-}At)_{50}$ and HCMC lost 6.6–8.9%

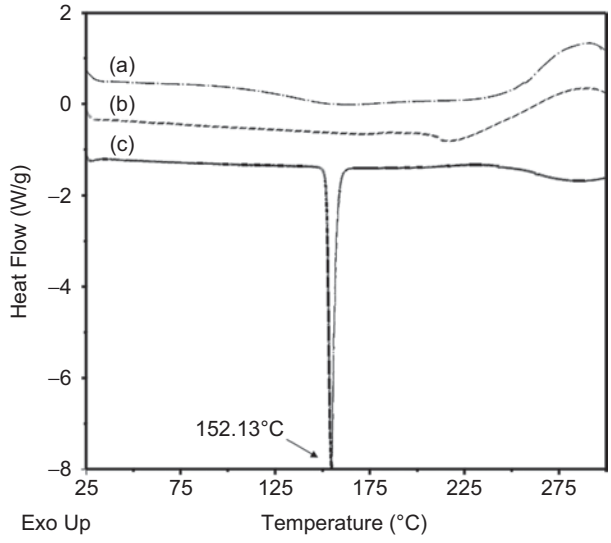

Figure 3. DSC heating curves of (A) HCMC, (B) $(HCMC\text{-}At)_{50}$, and (C) Atenolol.

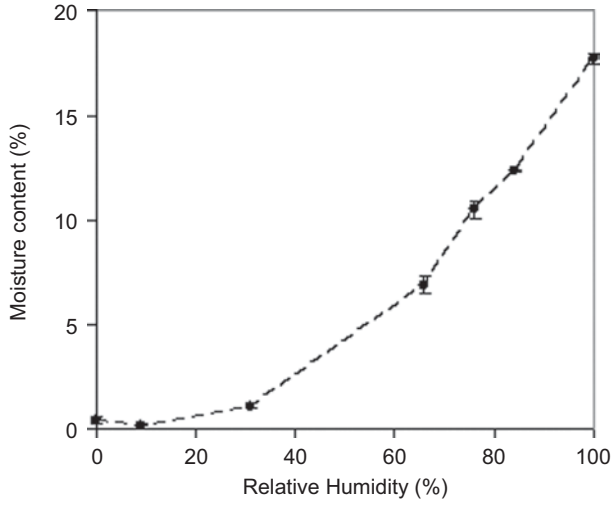

Figure 4. Equilibrium moisture content of $(HCMC\text{-}At)_{50}$ at 20°C.

Table 1. Flow properties of particulated materials.

Material	Angle	Carr index	Hausner ratio
HCMC	35°	6.94	1.07
NaCMC	87°	44.39	1.80
$(HCMC\text{-}At)_{50}$	23°	4.03	1.04
$(HCMC\text{-}Me)_{50}$	34°	4.10	1.04

Table 2. Matrices composition.

Matrices	Matrix weight (mg)	Amount of D in the matrix (mg)
$(HCMC\text{-}At)_{50}$	200	48.0
$(HCMC\text{-}Me)_{50}$	200	42.9
$(HCMC\text{-}At)_{50}$:NaCMC		
(a) (1:1)	200	24.0
(b) (1:2)	300	24.0
(c) (1:3)	400	24.0
$(HCMC\text{-}Me)_{50}$:NaCMC (1:3)	400	21.4

of its weight near 100°C, which was ascribed to the dehydration of the materials.

On the other hand, Table 1 reports compressibility index and flow indicators of HCMC and $(HCMC\text{-}D)_{50}$ complexes. Both particulated materials exhibited good flow properties and appear to be adequate to prepare matrices.

Preparation and characterization of matrices

Matrices were obtained by compacting $(HCMC\text{-}D)_{50}$ complexes alone or as a mixture with NaCMC, as reported in Table 2.

Matrices of $(HCMC\text{-}D)_{50}$ complexes

Fluid uptake (water and aqueous solutions) from matrices of 200 mg of $(HCMC\text{-}D)_{50}$ was fast, reaching quickly a *plateau* after having incorporated approximately 4-times its weight (Figure 5). Matrices swell without developing a continuous hydrogel layer on their surfaces; therefore water diffuses quickly through the matrix pores to completely wet them in a few minutes.

As the matrices $(HCMC\text{-}Me)_{50}$ and $(HCMC\text{-}At)_{50}$ were immersed in the dissolution media to determine release rates, they take solution quickly, swell, and finally disintegrate in a very short period of time.

$$\text{In water}: [\text{R-COO}^{-}\text{DH}^{+}] \rightleftarrows \text{R-COOH} + \text{D} \tag{4}$$

$$\text{In NaCl solution}: [\text{R-COO}^{-}\text{DH}^{+}] + \text{Na}^{+} + \text{Cl}^{-} \rightleftarrows \text{R-COONa} + \text{DH}^{+} + \text{Cl}^{-} \tag{5}$$

$$\text{In acid solution}: [\text{R-COOH}^{-}\text{DH}^{+}] + \text{H}^{+} + \text{Cl}^{-} \rightleftarrows \text{R-COO} + \text{DH}^{+} + \text{Cl}^{-} \tag{6}$$

In water, release of D from $(HCMC\text{-}At)_{50}$ and $(HCMC\text{-}Me)_{50}$ matrices is fast. However, in both cases the release stops after having released approximately 10% of D (Figure 6). This behavior is a consequence of the high affinity constant of the complexes (equations 1 and 4); i.e., the concentration of At in water at the end of the experiment was 1.84×10^{-2} mg/ml, significantly lower than its water solubility (12.80 mg/ml).

As water was replaced by either HCl or NaCl solutions, D release approached 100%. This is a consequence of the fast exchange between the cations of the dissolution media and DH^{+} (Ramírez Rigo et al., 2004; Moreno-Villoslada et al., 2005) as it is depicted in equations (5) and (6).

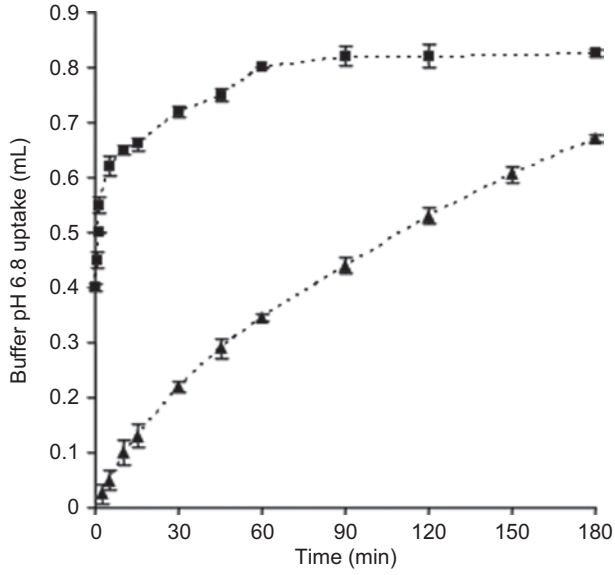

Figure 5. Up-take of buffer pH 6.8 in matrices of 200 mg: (■) $(HCMC\text{-}At)_{50}$ and (▲) $(HCMC\text{-}At)_{50}$:CMCNa (1:3).

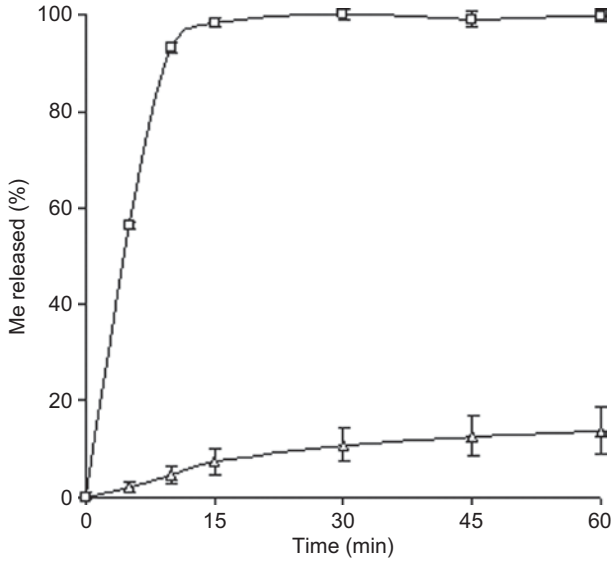

Figure 6. Release profile of Me from $(HCMC\text{-}Me)_{50}$ matrices in (Δ) water and (□) 0.9% NaCl solution.

In summary, D release from these matrices is governed by a fast sorption of the aqueous solution, which facilitates the exchange DH^+-inorganic cation generating a quick diffusion of $DH^+ Cl^-$. Therefore, such matrices behave as immediate release dosage forms.

Mixed matrices of $(HCMC\text{-}D)_{50}$ and NaCMC

Incorporation of NaCMC into the matrix composition decreases the sorption rate due to the generation of a hydrogel layer surround ing its surface, which modulates the fluid uptake. Figure 5 shows the results obtained with $(HCMC\text{-}At)_{50}$:NaCMC ratio 1:3 mixed matrix, while Figure 7 shows the development of the erosion and diffusion fronts of the matrix immersed in water.

Therefore, as the matrices $(HCMC\text{-}Me)_{50}$:NaCMC and $(HCMC\text{-}At)_{50}$:NaCMC were immersed in the dissolution media to determine release rates, a gel layer surrounding the matrix core was generated. Then, such matrices exhibit a similar behavior to those SDPM of carbomer or alginic acid complexes in which drug delivery is modulated by the properties of the hydrogel layer (Jimenez Kairuz et al., 2005; Ramírez Rigo et al., 2006).

The complex $(HCMC\text{-}At)_{50}$ was selected to determine the effect of increasing proportions of NaCMC on the release rates of the matrices. With such purpose, a set of mixed matrices having a fixed amount (200 mg) of $(HCMC\text{-}At)_{50}$ and $(HCMC\text{-}At)_{50}$:NaCMC) ratios of 1:1, 1:2, and 1:3 was prepared. Figure 8 shows that the release rate decreases with increasing proportions of NaCMC in the matrix.

The ratio (1:3) was selected to study the release profiles of the mixed matrices in different media (water, buffer solution of pH 6.8, and 0.1 M HCl solution) (Figure 9).

Kinetic data were processed by applying the classical Korsmeyer treatment using equations (2) and (3), and the results are reported in Table 3.

The values of n obtained from the kinetic analysis were in the range of 0.67–0.87, which suggests an anomalous release kinetic in both media.

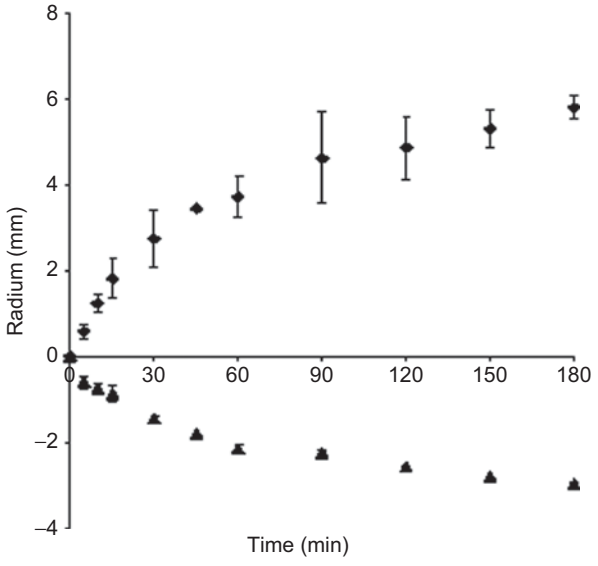

Figure 7. Hydrogel layer expansion of $(HCMC\text{-}At)_{50}$:NaCMC (1:3) of 200 mg as a function of time in water: (♦) Erosion front and (▲) Swelling front.

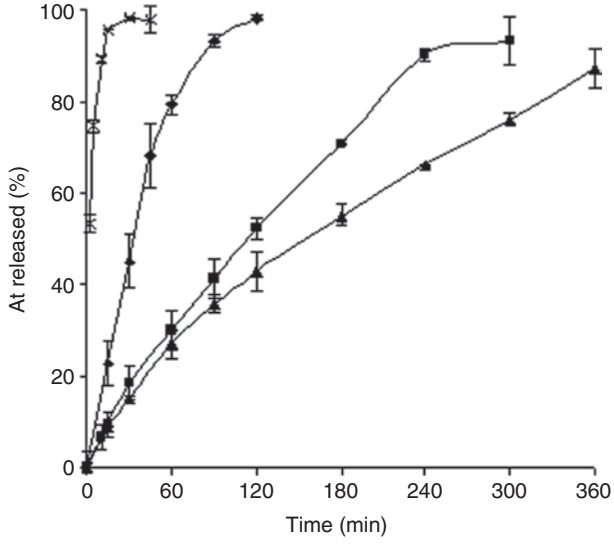

Figure 8. Release profiles of At in buffer 6.8 from matrices: (X) $(HCMC\text{-}At)_{50}$, $(HCMC\text{-}At)_{50}$:CMCNa: (♦) (1:1), (■) (1:2), and (▲) (1:3).

Table 3. Kinetics data of drug release from mixed matrices processed through Korsmeyer's equation.

	Kinetics data of drug release from matrices					
Matrices	Medium	Speed (rpm)	n	k (min^{-n})	r^2 (N)*	MDT(min)
$(HCMC\text{-}At)_{50}$:NaCMC						
(a) (1:1)	Buffer of pH 6.8	50	0.87	2.37×10^{-2}	0.991 (5)	34
(b) (1:2)		50	0.75	1.47×10^{-2}	0.996 (7)	119
(c) (1:3)		50	0.72	1.36×10^{-2}	0.993 (8)	164
		100	0.67	6.08×10^{-2}	0.982 (8)	26
	HCl solution	50	0.73	2.32×10^{-2}	0.981 (6)	73
$(HCMC\text{-}Me)_{50}$:NaCMC						
(1:3)	Buffer of pH 6.8	50	0.76	1.31×10^{-2}	0.994 (6)	130
		100	0.70	3.13×10^{-2}	0.990 (5)	60
	HCl solution	50	0.83	1.53×10^{-2}	0.985 (6)	70

* (N) = number of points. They cover a range of 0–70% of delivery.

Rate constants *k* of At and Me in HCl acid were, respectively, 1.7- and 1.2-times higher than in buffer pH 6.8. This behavior would be associated to the neutralization of the CMC carboxylate groups by the H^+ of the acid medium. Nevertheless, *n* exponents remain unchanged.

As depicted in Scheme 1, the ways of drug release in SDPM would be the diffusion of free drug molecules arising from the complex across the gel layer or the erosion of the layer to deliver macromolecules of the complex.

To obtain more information on this point, the effect of the agitation speed on release rate was determined. It was observed that release rate increases with the increase of agitation speed (Table 3). Since such behavior is currently associated to erosion of the gel layer (Ramírez Rigo et al., 2006; Dabbagh et al., 1999; Zuleger and Lippold, 2001; Kavanagh and Corrigan, 2004), the loss of weight of the matrices as a function of time in buffer pH 6.8 was determined. Figure 10A shows that the decrease of the matrix mass along time is almost paralleled by a concomitant drug release; therefore, the erosion contribution to the release mechanism seems to be relevant. Figure 10B also shows that similar erosion is produced when water is used as delivery medium. However, in such a situation the drug remains attached to HCMC as an insoluble complex.

The results presented show that HCMC-D complexes may be easily prepared as particulate materials. They exhibit appropriate physical properties to be compacted in matrices. Incorporation of NaCMC into the matrix composition yields SDPM in which drug release may be widely modulated. Such mixed matrices exhibit a behavior similar to those SDPM based on carbomer or alginic acid-sodium alginate previously reported.

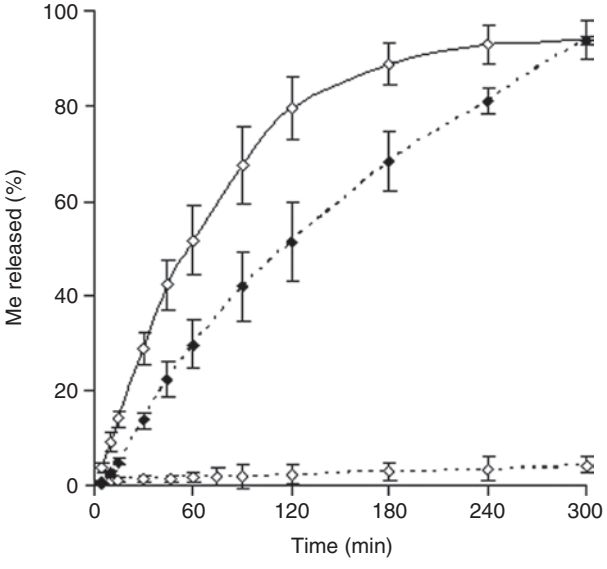

Figure 9. Release profile of Me from $(HCMC\text{-}Me)_{50}$:NaCMC (1:3) in different media: (—◊—) acid solution, (--◆--) buffer pH 6.8 solution, and (--◊--) water.

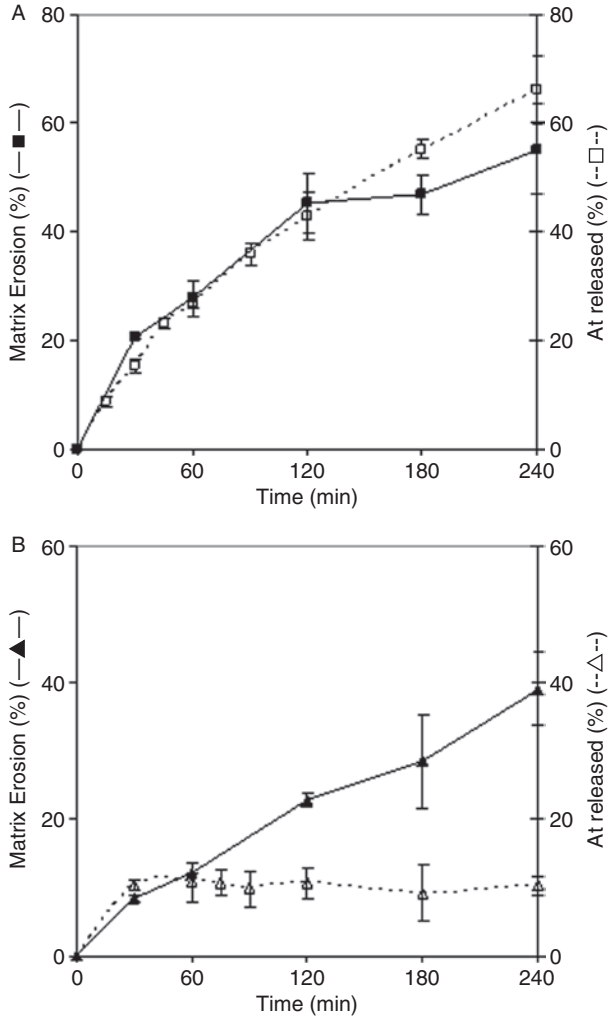

Figure 10. Matrix erosion of $(HCMC\text{-}At)_{50}$:NaCMC (1:3) as a function of time in (A) buffer pH 6.8 and (B) water.

Table 4. Mechanisms involved in D release from SDPM

		Release rate/extent		
PE-D material	Hydrogel layer thickness	Water	Saline and acid solutions	Release mechanism
(Carbomer-D)	extended	Slow*/ complete	Slow*/ complete	Ionic-exchange/ diffusion
(Alginic-D)	narrow	Moderate/ complete	Moderate/complete	Ionic-exchange/ erosion
(Alginic-D): sodium alginate	intermediate	Slow*/ complete	Slow*/ complete	Ionic-exchange/ erosion
(HCMC-D)	no present	Fast/ not extended	Fast/ complete	Ionic-exchange/ diffusion
(HCMC-D): NaCMC	intermediate	Slow*/ not extended	Slow*/ complete	Ionic-exchange/ erosion

* Able to be modulated.

Hence, a summary of the main properties of SDPM based on the three PE is presented in Table 4. It can be seen there that carbomer, being a ramified PE, generates an erosion-resistant hydrogel layer in which diffusion of free D molecules across the layer is the main way of delivery. However, linear PE as alginic acid and HCMC generate erodible hydrogel layers in which the transfer of the macromolecular complexes to the delivery medium takes place as the main route of delivery.

In conclusion, acid polyelectrolyte-protonable drug complexes exhibit interesting delivery properties and can find a place in the design of monolithic as well as multiparticulate delivery systems.

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