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Swellable drug-polyelectrolyte matrices (SDPM) Characterization and delivery properties

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Abstract

The objective of the study is to develop and characterize the delivery properties of swellable drug-polyelectrolyte matrices (SDPM). Solid complexes $(C–D)_X$ of carbomer (C) neutralized with different proportions of model basic drugs (D), in which D is atenolol, lidocaine, and metoclopramide, and $X = 25$, 50, 75 and 100 mol of D per 100 equivalents of carboxylic groups of C, were prepared and characterized by DSC-TG, IR, and X-ray diffraction studies. Mechanistic studies with hydrophilic and hydrophobic basic drugs were conducted to explore the drug release patterns of SDPM. Besides, release and up-take studies were carried out in water and NaCl solution to examine the influence of ionic effects. The authors concluded that drugs can be loaded in a high proportion on to the polymer and therefore the resulting (C–D) material could be diluted with other polymers to modulate delivery properties of SDPM. Matrices of atenolol and lidocaine exhibited robust delivery properties with regard to change in proportion of loading D.

Keywords: Swellable matrices; Polyelectrolyte–drug complexes; Drug delivery; Controlled release; Carbomer-drug ion pairs

1. Introduction

Development and evaluation of drug delivery systems, consisting of swellable hydrophilic matrices (SHM), have attracted the attention of many authors in recent years (Roy and Rohera, 2002; Colombo et al., 1995, 1999; Brazel and Peppas, 1999). These matrices are monolithic systems having one or more powdered drugs homogeneously dispersed in a hydrophilic polymeric matrix (Colombo et al., 1995). Drug delivery from SHM may be either diffusion controlled or dissolution-rate limited (Jantzen and Robinson, 1996). A strong dependency of the rate

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of delivery with the degree of swelling of SHM is currently observed (Colombo, 1993; Colombo et al., 1996).

Swellable drug-polyelectrolyte matrices (SDPM) could be seen as a particular class of SHM, which are obtained by compaction of powdered complexes of a polyelectrolyte (PE) fully or partially neutralized with an ionizable drug (D). Unlike other SHM, SDPM's contain a molecular dispersion of D in the mass of the matrix since D is ionically bonded to the functional groups of PE.

Although some polyelectrolyte–drug complexes (PE–D) have been previously used in pharmaceutical systems, e.g. carrageenan-D (Bonferoni et al., 1993, 1994) and carbomer-erythromycin (Lu and Borodkin, 1989), a systematic knowledge about their properties is not available.

In the same way as it has been described for SHM (Colombo et al., 1995), the external surface of a SDPM in contact with an aqueous medium is quickly wetted and swollen, developing a hydrogel coat that acts as a barrier between the external medium and the unwetted portion of the matrix. The process of wetting and swelling develops three clearly defined zones in the system. These are, the remaining unwetted amorphous glassy matrix, the swollen hydrogel-like layer surrounding it, and the external aqueous medium. The properties of each of these domains contribute to determining the kinetics and mechanism of delivery of the matrix constituents.

In this context, the aim of this work was the characterization of the delivery properties of SDPM's obtained by compacting carbomer–drug complexes (C–D). With such purpose three basic drugs (atenolol (Atn), lidocaine (L) and metoclopramide (Me)) were selected on the basis of their different aqueous solubility and lipophilicity (Table 2).

In order to get information about the main mechanisms of drug delivery from SDPM under different conditions, water, neutral saline (NaCl) and acidic (HCl) solutions were selected as delivery media. The release kinetics of the model drugs under such conditions were determined, and measurements of up-take and dynamics of radial fronts of swelling, erosion and diffusion were performed.

2. Materials and methods

2.1. Materials

Carbomer 934-P (Carbopol 934-P NF, BF-Goodrich Co, Cleveland, OH, USA), atenolol (USP-grade, Parafarm, Bs. As., Arg.), lidocaine (Sigma-Aldrich Chem., USA) were used. Metoclopramide was prepared from its hydrochloride (USP-grade, Parafarm®, Bs. As., Arg.) which was dissolved in water, neutralized with NaOH solution (p.a., Merck®, Darmstad, Ger.) and recrystallized from acetone (p.a., Sintogran®, Bs.As., Arg.).

2.2. Preparation of carbomer–drug complexes (C–D)

Two methods were used to prepare (C–D) materials: (a) freeze-dried of a frozen hydrogel $(C–D)_X$ at 0.5% (w/v) of C and (b) solvent evaporation after mixing C and D during 30 min with an appropriate volume of ethanol. Products obtained were dried at 45–50 °C, to constant weight, before using.

Three series of $(C–D)_X$ were obtained (D = Atn, L, Me), where X refers to the mol% of basic drug that neutralizes the carboxylic acid groups of C (X = 25, 50, 75 and 100 mol%).

2.3. Characterization of solid (C–D) materials

All studies were performed on samples of (C–D) materials along with their respective physical mixtures.

The solid products were characterized using powder X-ray diffraction with a Rigaku Miniflex diffractometer equipped with specific software, Standard monitoring 3.2. Scan range was 3–60° $2\theta/\theta$ with a scan speed 0.066° 2θ/s.

Infrared spectroscopy on 1.5% of (C–D) dispersed in a KBr disks were performed with a Nicolet 5SXC FT-IR Spectrometer.

Thermal behavior was evaluated by differential scanning calorimetry (DSC) (TA-Instruments Modulated-DSC 2920, Universal Analysis-NT software).

Besides, enthalpy of fusion (ΔH_{melt}) of pure drugs Atn, L and Me were also determined by DSC. Such data allowed calculation of the excess free energies in water (ΔF_{excess}) according to reference (Manzo and Ahumada, 1990).

Table 1
Composition of C–D materials used to prepare 200 mg SDPM

D in the SDPM	$(C–Atn)_X$				$(C–L)_X$			$(C–Me)_X$		
mol%[a]	100	75	50	25	75	50	25	100	75	50
%, w/w	68.5	60.0	54.5	43.5	68.0	58.5	41.5	78.3	73.3	64.3

[a] Moles of D neutralizing 100 eq. of carboxylic groups of C.

2.4. SDPM preparation

The SDPM were obtained by compacting 200 mg of the powdered (C–D) material at 1.5 t for 10 s, in a hydraulic press equipped with flat punches 12.8 mm in diameter. Table 1 reports SDPM's compositions.

2.5. Up-take measurements

The sorption (up-take) kinetics of water or 0.9% NaCl solution of SDPM's were determined using an apparatus described by Nogami et al. (1969), which was adapted in our lab as described in (Llabot et al., 2002).

2.6. Drug delivery

Delivery kinetics were measured in a USPXXIV apparatus 2 (Hanson Res., USA) at 75 rpm, 37 °C using 900 ml of liquid for (C–Atn) and (C–Me) matrices, and 500 ml for (C–L) matrices. Liquid media were water, pH 1.2 USP-simulated gastric fluid without pepsine and 0.9% NaCl solution.

The SDPM's were attached on the surface of a circular device to keep them at the bottom of the vessels. Samples of 5 ml were taken at defined time intervals and the drug released was determined spectrophotometrically at their maximum UV absorbance (Atn: 273 nm, Me: 272.8 nm and L: 263 nm) in a Shimatzu 1240-mini spectrophotometer (Tokyo, Japan).

Drug release data were analyzed as a function of time according to Korsmeyer's model (Eq. (1)) (Korsmeyer et al., 1983):

$$\frac{D_t}{D_\infty} = kt^n \quad (1)$$

where D_t and D_∞ represent drug delivered at time = t and time = ∞, respectively.

The apparent release rate constant (k) and diffusion exponent (n) were obtained from experimental points covering up to 60% drug release.

2.7. Radial front movement

Special devices were used in order to obtain a rigorous radial movement of swelling fronts (Ferrero et al., 2000). The SDPM were locked between two transparent glass plates. The assembled devices were introduced in the vessels containing either water or 0.9% NaCl solution at 37° C. Photographs were taken at defined time intervals, an afterwards analyzed with appropriate software. Assays were performed in duplicate.

The initial diameter of the SDPM was 12.8 mm. The positions of the different fronts were obtained by measuring their radii (Ferrero et al., 2000). The interface between matrix and delivery medium at the beginning of experiment (initial time) was indicated by position 0.

3. Results

3.1. (C–D) materials

Table 1 reports molar and weight composition of (C–D) materials used to prepare SDPM's showing the high proportion in which active constituents can be incorporated in the matrices.

A preliminary characterization of the solid state of these materials was obtained through FT-infrared spectroscopy, powder X-ray diffraction, and DSC. Figs. 1–3 show examples of typical results obtained.

The X-ray diffraction patterns of Fig. 1(a–c) reveal the amorphous state of the (C–Atn) products since they exhibit an absence of significant signals that are present in crystalline Atn powder and also in the physical C–Atn mixtures.

FT-Infrared spectra in Fig. 2 show a decrease of the absorption band ascribed to the carbonyl of undis-

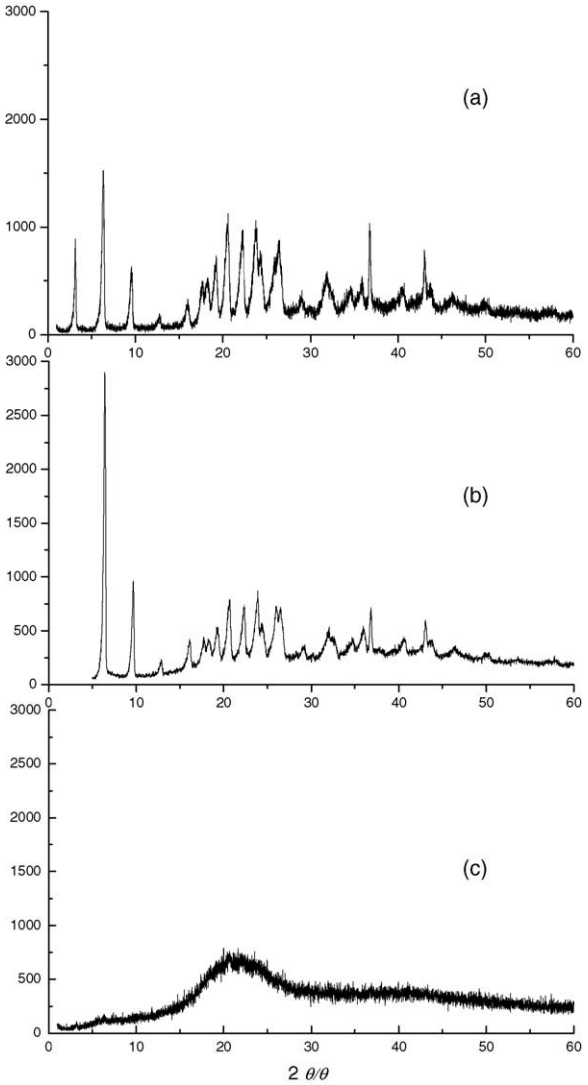


Fig. 1. Powder X-ray diffraction patterns of (a) crystalline atenolol; (b) mechanical mixture and (c) $(C–Atn)_{50}$ material.

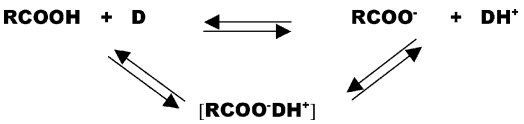
sociated carboxylic groups of C (1720 cm^{-1}) as the proportion of Atn in the material is increased. Such changes are paralleled by the increase of the band at 1562 cm^{-1} ascribed to the dissociated carboxylic groups. The band at 1400 cm^{-1} also ascribed to dissociated carboxylic groups overlaps with that of –NH-amide of Atn. Also, the specific bands of Atn at 1640, 1511 and 1244 cm^{-1} are observed. These results are consistent with an ionic bonding between $AtnH^+$ and dissociated carboxylic groups of C. In addition, DSC profiles in Fig. 3 show that the fusion endotherm of Atn, which is clearly present in the physical mixtures, is absent in the respective (C–Atn) materials.

3.2. Properties of SDPM

As a SDPM is put in contact with an aqueous medium, a number of physical and chemical processes take place. Such processes that contribute to the final delivery of free D are schematically depicted in Scheme 1 and will be discussed in the following sections.

The development of the hydrogel layer, as a consequence of wetting and swelling, is a relevant step in the process of delivery. Therefore, the information available on equilibrium and delivery properties of C–D hydrogels would contribute to understanding the delivery process of SDPM.

The following equilibria, involving the carboxylic groups (RCOOH) of C and the basic group of D, operate in (C–D) hydrogel systems:



(2)

where $[RCOO^-DH^+]$ represents an ionic pair between the protonated drug and a carboxylate of C. It is known that $[RCOO^-DH^+]$ represents a high fraction of the total D loaded in the hydrogel, e.g. in a carbomer–lidocaine hydrogel (C–L) the species depicted in Eq. (2) are distributed as: (L) = 3.82%; (LH^+) = 14.5% and $[RCOO^-LH^+]$ = 81.7% (Jimenez-Kairuz et al., 2002).

With regard to the delivery properties of $(C–D)_X$ hydrogels, the effect of pH on the delivery rate of D, measured in Franz cells, revealed that the dissociation of the ionic pair is the slowest step that controls the rate (Jimenez-Kairuz et al., 2002, 2003; Vilches et al., 2002). Under such conditions, delivery takes place by diffusion of species D and DH^+, since the semipermeable membrane, that limits the compartments of the cell, prevents the passage of (C–D) (convection process).

In the presence of salts in the receptor medium, diffusion of their ions to the hydrogel compartment originates an ionic exchange with the $(C–D)_X$ complex that contributes to an increase in the drug delivery rate.

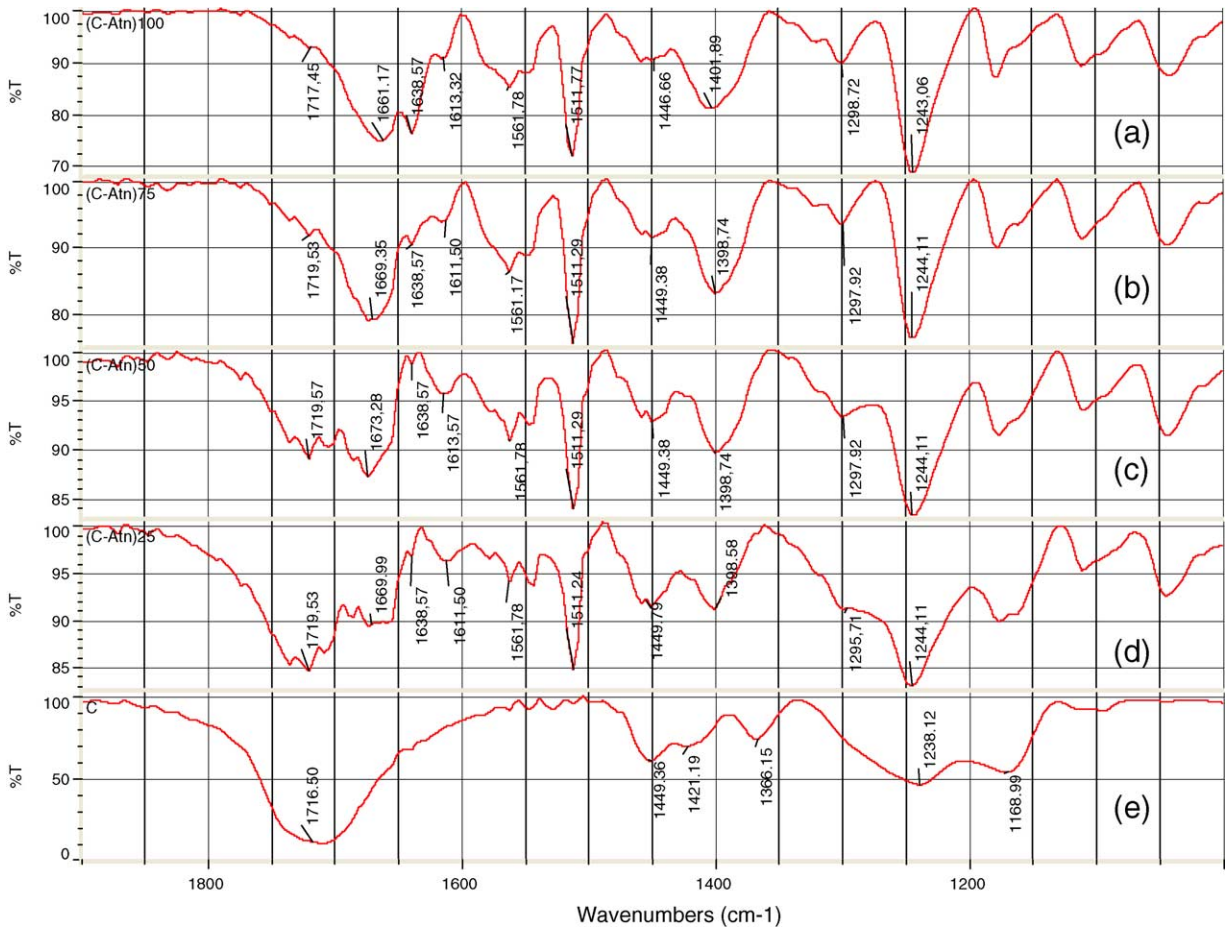


Fig. 2. FT-IR spectra of (C–Atn) complexes with different proportions of drug. (a) $(C–Atn)_{100}$; (b) $(C–Atn)_{75}$; (c) $(C–Atn)_{50}$ and (d) $(C–Atn)_{25}$ and (e) Carbomer 934P.

3.2.1. *Up-take measurements*

The first steps of wetting and swelling were evaluated by determining up-take rates and the dynamics of radial front movements.

Rates of fluid sorption (water and 0.9% NaCl solution) were measured on SDPM's prepared with $(C–D)_{50}$. As can be seen in Fig. 4 up-take rates approached zero order kinetics. Table 2 reports the up-take rate coefficients along with some physical and chemical parameters of the drugs that would be useful to characterize the process.

Thus, it may be recognized that up-take rates in both media follow a reverse order with both octanol–water partition coefficients (log PC) and excess free energies in water (ΔF_{excess}) of each drug. The former is currently regarded as a measure of lipophilicity (Hansch et al., 1995) and the second measures water–solute interactions (Manzo and Ahumada, 1990).

Additionally, it should be mentioned that the basic group of Atn is a secondary amine while those of L and Me are tertiary amines. The former has a greater ability to interact with water, which would also contribute to a rise in the up-take rate.

On the other hand, in saline solution, up-take rates of (C–Atn) and (C–L) were significantly reduced, but that of (C–Me) was increased. The differentiated behavior exhibited by C–Me will be further discussed.

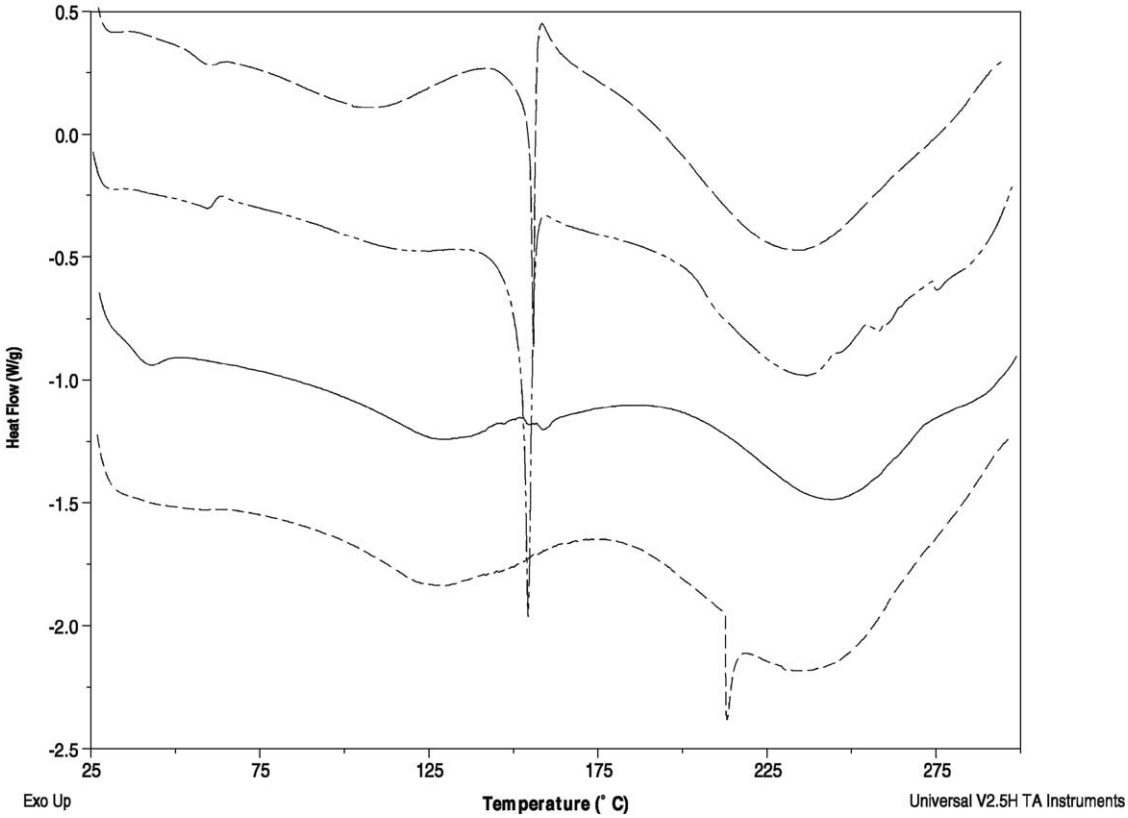


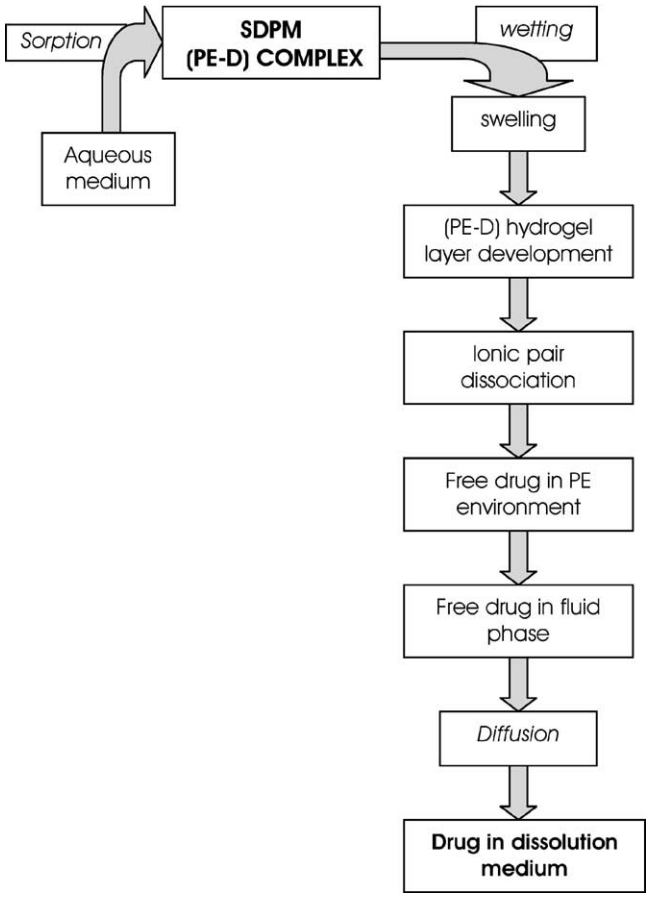
Fig. 3. DSC profiles of the (C–Atn) complexes, and their respectives mechanical mixtures (mm). —— $(C–Atn)_{50}$ (mm), —– – $(C–Atn)_{100}$ (mm), — $(C–Atn)_{100}$ complex, – – – $(C–Atn)_{50}$ complex.

3.2.2. Radial front movement

Erosion and swelling fronts were measured by a technique reported by several authors (Colombo et al., 1995, 1996, 1999; Ferrero et al., 2000). In addition, a diffusion front was determined by adding to the delivery medium a small amount of an acid-base indicator (bromotymol blue (BTB), $1.6.10^{-5}$ M, blue at pH > 6 and yellow at pH < 6)). As water and NaCl solutions were used as delivery media, the indicator placed in the bulk media is yellow; however, during the run, a blue halo surrounding the erosion front quickly develops as a consequence of the basic drug that is being released to the media. The indicator remains in its anionic blue form in the outer portions of the hydrogel layer, changing sharply to yellow in the inner ones. Visual inspection of photographs taken along time allows determination of the dynamics of this front.

Comparison of front movements of the three SDPM's was performed on matrices of $(C–D)_{75}$ using water and NaCl solution as delivery media (Figs. 5 and 6).

In water $(C–Atn)_{75}$ exhibited a quick rise of the erosion front at the beginning of the run, which afterwards progressively increased with time. The expansion of the hydrogel layer is accompanied by a progressive decrease of the diameter of the unwetted portion of the matrix, which is regarded as the swelling front. The figure also shows the diffusion front, which parallels the rise of the erosion one. A similar behavior was observed with $(C–L)_{75}$ although with a greater expansion of the hydrogel layer with time. On the other hand $(C–Me)_{75}$ exhibited a differentiated pattern. In fact, although the progress of swelling was analogous to the former matrices, the increase of both erosion and diffusion fronts were considerable lower,



Scheme 1.

which is in line with the results observed in water uptake.

In NaCl solution the progress of the swelling fronts were similar to those observed in water. However, the change of water by saline solution produced a lower expansion of the hydrogel layer in $(C–Atn)_{75}$ and $(C–L)_{75}$ but a higher expansion in $(C–Me)_{75}$. As a consequence, the rise of erosion fronts was quite similar in the three cases.

It should be observed that, regardless of the drug or medium used, the progress of swelling was quite similar in the six runs. This behavior suggests that wetting and initial swelling would be controlled mainly by the porosity of the material rather than by other variables such as greater or lower availability of water or specific properties of D.

3.2.3. Drug delivery

To gain some knowledge on the release properties of SDPM's, dissolution profiles of SDPM's with different molar compositions were measured in three media: water, 0.9% NaCl solution, and 0.1N HCl solution.

They were selected on the basis that the presence of NaCl in the medium would contribute to the release of D through ionic exchange and that the presence of HCl would also contribute by repressing the dissociation of R–COOH during delivery.

Fig. 7 shows release profiles of SDPM's having the same molar composition $(C–D)_{50}$ of each drug. It can be seen there that drugs were slowly released from the matrix, following in the three media the same pattern of a reverse order between delivery rate and lipophilicity of D observed in water up-take.

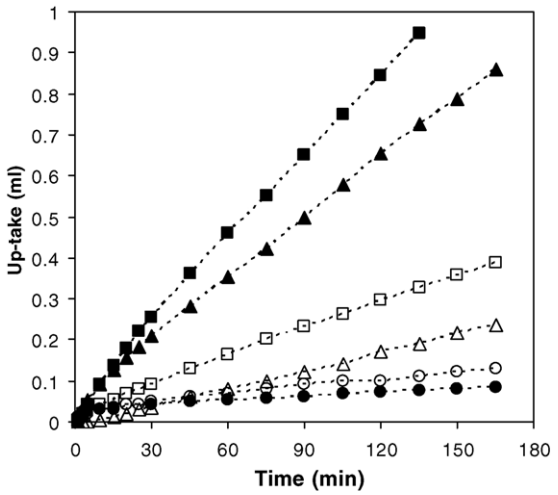


Fig. 4. Uptake of 200 mg SDPM. (a) In water: black symbols and (b) In 0.9% NaCl solution: empty symbols. (■) $(C–Atn)_{50}$; (▲) $(C–L)_{50}$; (●) $(C–Me)_{50}$.

In water, release rates remained almost constant over time approaching zero order kinetics. Table 3 reports the analysis of kinetic data of ten different SDPM's through the classical Korsmeyer's model (Eq. (1)). Which afforded an average exponent n of 1.04 ± 0.12.

As water was replaced by NaCl solution, delivery rates were not appreciably modified but the kinetics

Table 2
Physical and chemical properties of D and SDPM

Properties	D		
	Atenolol	Lidocaine	Metoclopramide
MW	266.34	234.34	299.82
Amine type	Secondary	Tertiary	Tertiary
pK_a[a]	9.55	7.92	9.71
$\log P_{oct/w}$[b]	0.16	2.26	2.62
T_{melt} (K)	427.7	342.5	421.0
ΔF_{excess} (kcal/mol K)	3.15	4.33	4.46
Solubility (mg/ml) 25 °C	12.80[c]	1.98[d]	0.20[d]
Up-take rate in water[e]	41.61	29.98	2.39
Idem in NaCl solution[e]	13.64	8.76	4.03

[a] Taken from references (Caplar et al., 1984; Powell, 1986; Pitré and Stradi, 1987).
[b] Taken from reference (Hansch et al., 1995).
[c] Determined in our lab.
[d] Taken from references (Powell, 1986; Pitré and Stradi, 1987).
[e] Up-take rates (ml/h × 10^2) measured on 200 mg disks of $(C–D)_{50}$.

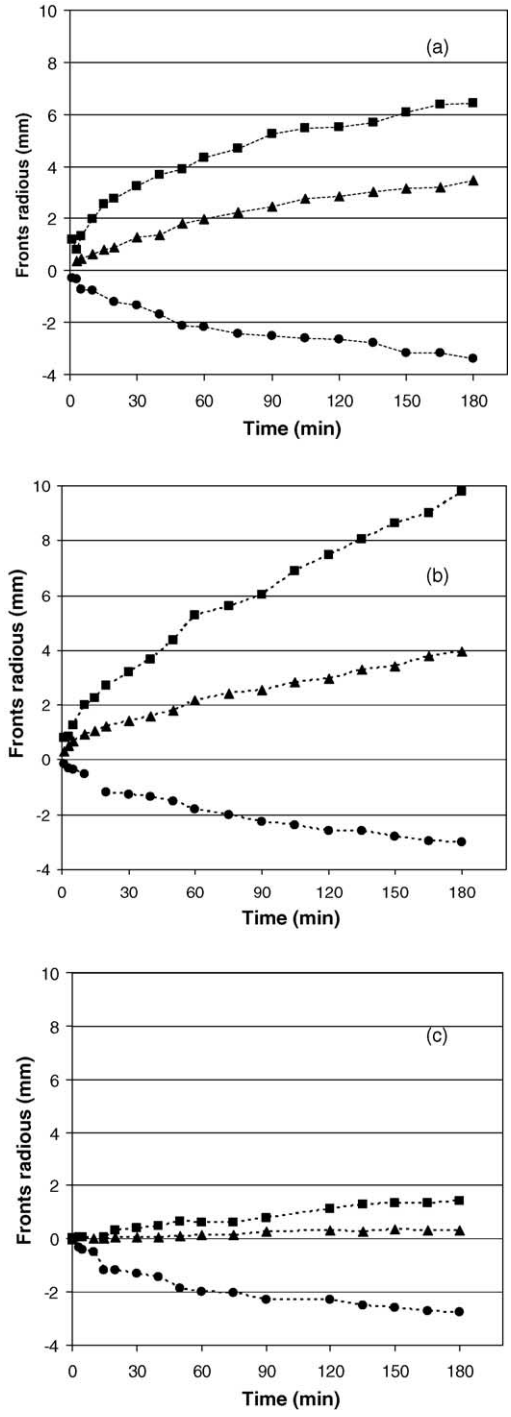


Fig. 5. Front movements of the SDPM in water. (■) Erosion front; (▲) diffusion front; (●) swelling front. (a) $(C–Atn)_{75}$; (b) $(C–L)_{75}$ and (c) $(C–Me)_{75}$.

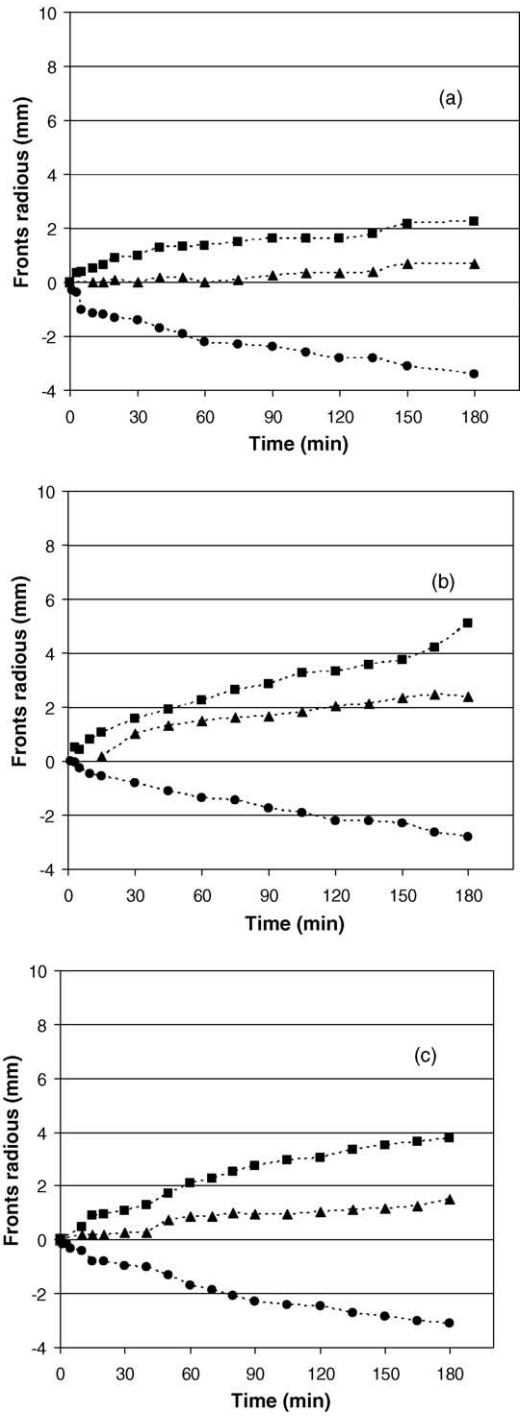


Fig. 6. Front movements of the SDPM in 0.9% NaCl solution (■) Erosion front; (▲) diffusion front; (●) swelling front. (a) $(C–Atn)_{75}$; (b) $(C–L)_{75}$ and (c) $(C–Me)_{75}$.

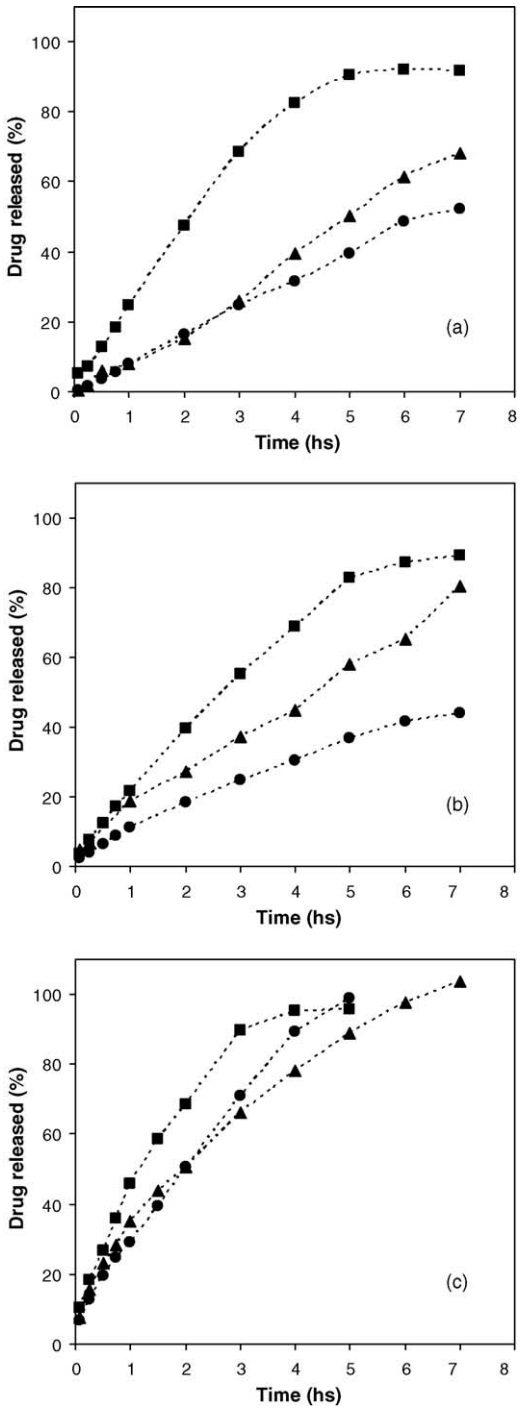


Fig. 7. Drug release profiles of SDPM in different media: (a) destilled water, (b) 0.9% NaCl solution and (c) USP–gastric solution without pepsine. (■) $(C–Atn)_{50}$; (▲) $(C–L)_{50}$; (●) $(C–Me)_{50}$.

exhibited a departure from zero order since the average n dropped to 0.69 ± 0.05 (Table 3).

On the other hand, acidic media produced increased rates along with a moderate burst effect, with different kinetics, from that observed in water.

The effects of the proportion of D on delivery properties of (C–D) materials are illustrated in Fig. 8a–c through plots of milligram of D delivered against time using water as the dissolution medium.

SDPM's having 50, 75 and 100 mol% of Atn exhibited quite similar release rates although that of the latter is a bit slower. The rate of the lowest composition $(C–Atn)_{25}$ is slower and clearly differentiated from the rest of the set. In the same way, SDPM's having 25, 50 and 75 mol% of L exhibited remarkable similar delivery rates. The fact that a wide range of compositions of (C–Atn) or (C–L) delivered almost the same mg/h of D is consistent with the zero order kinetics observed.

On the other hand, the less hydrophilic SDPM's of Me exhibited clearly differentiated delivery rates following the order $75 > 50 > 100$.

The change of water by NaCl solution does not significantly modify the observed patterns.

4. Discussion

4.1. The meaning of the diffusion front

Hydrogels are currently described as biphasic systems in which the aqueous and macromolecular phases are mutually interpenetrated (Martin, 1993). The indicator (BTB) is a weak acid that in solution contains undissociated (neutral) species along with anionic ones. Therefore, an acid–base interaction of BTB with the acid groups of C is unexpected. Thus, the shift from yellow to blue in going from inner to outer zones of the hydrogel layer can be associated with the rise of concentration of free drug [D] in the aqueous phase. In turn, the rise of [D] would be a consequence of the degree of hydration and subsequent relaxation of the (C–D) complex to produce some degree of dissociation of ionic pairs according to Eq. (2).

The average concentration of C at the maximum expansion of the hydrogel layer is about 8% (w/v). This concentration was estimated from the amount of C in the layer as well as its volume. Both magnitudes were

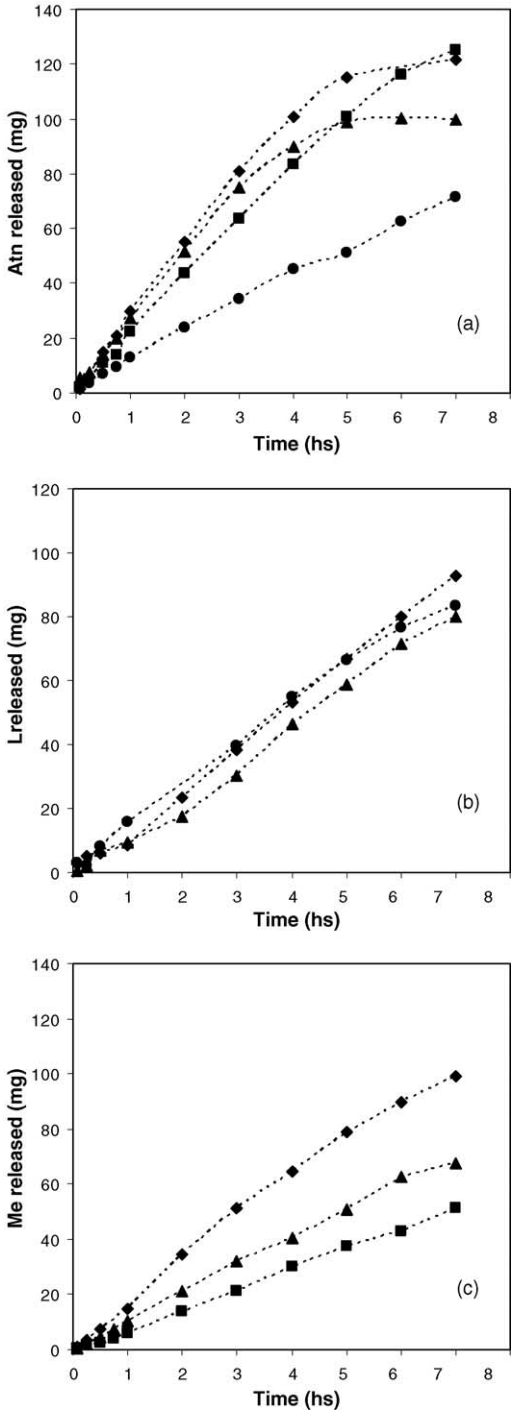


Fig. 8. Drug release profiles of $(C–D)_X$ in water; X: (■) 100; (□) 75; (▲) 50; (●) 25. (a) $(C–Atn)_X$; (b) $(C–L)_X$; (c) $(C–Me)_X$.

Table 3
Kinetics data of drug release from 200 mg SDPM processed through Korsmeyer's equation

SDPM	Release in water			Release in 0.9% NaCl solution		
	n	k (h^{-n})	r^2 (e)	n	k (h^{-n})	r^2 (e)
$(C–Atn)_{100}$	0.97	0.162	0.994 (7)	0.61	0.234	0.997 (7)
$(C–Atn)_{75}$	1.14	0.234	0.991 (7)	0.70	0.244	0.996 (7)
$(C–Atn)_{50}$	0.92	0.246	0.999 (6)	0.76	0.230	0.996 (7)
$(C–Atn)_{25}$	0.89	0.150	0.999 (11)	0.68	0.213	0.992 (7)
$(C–L)_{75}$	1.17	0.077	0.993 (6)	0.66	0.175	0.992 (7)
$(C–L)_{50}$	1.24	0.067	0.995 (6)	0.78	0.170	0.993 (5)
$(C–L)_{25}$	0.89	0.175	0.984 (5)	0.71	0.244	0.991 (4)
$(C–Me)_{100}$	1.09	0.041	0.997 (11)	0.65	0.134	0.999 (11)
$(C–Me)_{75}$	1.03	0.112	0.998 (10)	0.66	0.137	0.998 (10)
$(C–Me)_{50}$	1.08	0.073	0.998 (11)	0.70	0.115	0.997 (11)
n means	1.04 (± 0.12)			0.69 (± 0.05)		

e, number of experimental points.

calculated from diameters of wetted and unwetted disk portions at time zero and time t.

With this information a lineal gradient of hydrogel layer with increasing degree of hydration was simulated in the following way: series of test tubes each one containing the same amount of a given $(C–Atn)_X$ ($X = 50$, 75 and 100), but increasing volumes of a diluted aqueous solution of BTB, were allowed to equilibrate. As Table 4 shows, the development of blue color is a function of both, degree of hydration and proportion of Atn in the complex.

Consequently, development of a blue zone at the outer zones of the hydrogel layer during the process of delivery indicates that [Atn] is high enough to diffuse to the external medium.

4.2. The mechanism of drug delivery

As previously mentioned, results with (C–D) systems under more diluted conditions, concentration of C below 0.6% (Jimenez-Kairuz et al., 2002, 2003), showed that (a) delivery kinetics in water is controlled by the slow dissociation of ionic pairs [$RCOO^-DH^+$] and (b) addition of neutral salts (NaCl) to the water of the receptor compartment produces a strong increase of drug delivery rate due to the contribution of an ionic exchange mechanism.

Table 4
Water content simulated gradient of three compositions of (C–Atn)

% C	BTB indicator color[a]		
	$(C–Atn)_{100}$	$(C–Atn)_{75}$	$(C–Atn)_{50}$
8.0	Y	Y	Y
5.0	G	Y	Y
3.0	B	Y	Y
2.0	B	Y	Y
1.0	B	G	Y
0.5	B	B	Y
0.25	B	B	G
0.1	B	B	B

[a] BTB: bromotimol bleu; B: blue, G: green, Y: yellow.

However, delivery kinetics from SDPM's in water was characterized by an average exponent n of 1.04 which suggests that the availability of free drug molecules able to diffuse remains constant over time producing the zero order observed. Besides, different compositions of (C–Atn) or (C–L) delivered almost the same mg/h of drug (Fig. 8). This behavior suggests that the sequence of processes of wetting, expansion of the macromolecular complex, ionic pair dissociation and diffusion of free drug are controlled by the availability of water in the matrix rather than by the number of ionic pairs.

According to Scheme 1, at the wetting front, in the early steps of development of the hydrogel layer, water is mainly consumed by the hydration of the macromolecular complex. The fraction of water molecules that remains self-aggregated generates a fluid phase in contact with the macromolecular environment. Then, free drug molecules, originated by dissociation of the complex, according with Eq. (2), diffuse from the macromolecular environment to the incipient fluid phase. At the same time, diffusion of water from the dissolution medium produces the expansion of the fluid phase originating a decreasing gradient of [D] that contributes to its diffusion towards the erosion front.

Therefore, the zero order observed would be a consequence of a steady state of [D] in the incipient fluid phase.

The fact that hydrophilicity (ΔF_{excess}) and water solubility of the three D follow the same sequence (Table 2) as indicated by their respective delivery rates (Fig. 7) suggests that one or both of such properties would participate in the relevant steps of kinetic control of delivery. However, present results do not allow to get definitive conclusions on this point.

In favor of this view, it should be mentioned that we have recently reported that in the interaction between the acid PE carboxymethylcellulose and basic drugs, the extent of the ion pair formation depends on both basic strength and lipophilicity of the drugs tested (Ramirez Rigó et al., 2004).

On the other hand, the addition of NaCl to the dissolution medium produced the following effects on delivery: (a) delivery rates were not significantly raised, (b) a lowering of the average *n* from 1.04 to 0.69 and (c) a lowering of the expansion of the hydrogel layer of (C–Atn) and (C–L) together with a shift of the diffusion front towards the erosion front.

Such effects would be seen as a consequence of two opposite factors. On one hand water activity in NaCl solution is lower than in pure water; besides, the presence of ions in the dissolution medium should depress the electrokinetic potential ζ and chain repulsion of the macromolecular complex. As a consequence, hydration, relaxation and ionic pair dissociation according to Eq. (2) would also decrease.

On the other hand, the ionic exchange between NaCl and the macromolecular complex contributes to produce free DH^+. Such contribution to delivery should be proportional to the number of ionic pairs of the matrix as depicted in Eq. (3):

$$[RCOO^-DH^+] + Na^+ + Cl^- \rightleftarrows [RCOO^-Na^+] + Cl^- + DH^+ \quad (3)$$

Therefore, the overall delivery rate results form the contribution of two mechanisms, the one described previously and the other, the ionic exchange process that would be proportional to the number of ionic pairs. In agreement with this view, the shift of the diffusion front towards the erosion front would indicate that D is accompanied by significant amounts of DH^+, generated by the ionic exchange process. Nevertheless, the ratio $[D]/[DH^+]$ remains high enough to keep a basic pH in which the indicator is blue.

The case of (C–Me) presents some particularities. On one hand release rates in water and NaCl solution followed almost the same pattern exhibited by (C–Atn) and (C–L). Besides, in saline solution the dynamics of fronts is analogous to those of Atn and L. Also, up-take rates in that medium follow an interesting relationship with structural parameters of each D. Nevertheless, although in water the progress of the wetting front does not differ from those of (C–Atn) or (C–L) the hydrogel layer expansion was remarkably low. Therefore, the lower up-take rate of (C–Me) observed in water should be ascribed to the expansion process of the macromolecular complex rather than to the wetting process.

In HCl solution the increase of rate observed in all SDPM's would be ascribed to a high contribution of the ionic exchange mechanism. In addition the high concentration of H^+ would repress the dissociation of free carboxylic groups R-COOH, turning the exchange H^+/DH^+ depicted in Eq. (4) essentially irreversible, which result in an increase of $[DH^+]$.

$$[RCOO^-DH^+] + H^+ + Cl^- \rightleftarrows [RCOOH] + Cl^- + DH^+ \quad (4)$$

Last, although the transference of (C–D) chains into the delivery media (convection mechanism) does not appear to occur to a significant extent, at least in water and saline solutions, it has not been explicitly evaluated.

On the other hand, the mechanisms that operate in SDPM drug delivery would also operate to the same extent in physical mixtures of C and D as long as D has a high aqueous solubility and an appropriate basic group.

5. Conclusions

Solid (C–D) materials exhibit interesting delivery properties and can find a place in the design of monolithic as well as multiparticulate delivery systems, which is an advantage over conventional SHM.

Carbomer can be loaded with a high proportion of D, and therefore the resulting (C–D) material could be used in the design of high dose formulations or be diluted with other polymers to modulate delivery properties of the SDPM.

Matrices of Atn and L exhibited robust delivery properties with regard to changes in the proportion of loading D.

Delivery rates observed in water were not substantially modified in NaCl solution but were raised in 0.1N HCl. Therefore, the ion-exchange delivery mechanism, promoted by ions contained in the dissolution medium, appears to be relevant only under extreme conditions of acidity.

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