Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 269 (2004) 149–156
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

The improvement of aqueous chemical stability of a model basic drug by ion pairing with acid groups of polyelectrolytes

A.F. Jimenez-Kairuz, D.A. Allemandi, R.H. Manzo*

Departamento de Farmacia, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Edificio Ciencias 2, Ciudad Universitaria, 5000 Córdoba, Argentina

Received 29 August 2002; received in revised form 11 July 2003; accepted 5 September 2003

Abstract

Carbomer (C) and procaine (P) were selected respectively as models of polyelectrolyte (PE) and basic drug (B) of low stability in aqueous solution. The purpose of this investigation was to test if a (C–P) aqueous system provides a microenvironment in which P is less exposed to hydroxyl ion catalyzed degradation, its main degradation pathway over a wide pH range. It was determined that in (C–P) a high fraction of P was present in the form of ion pairs [$RCOO^-PH^+$] with the carboxylate groups of C. The [$RCOO^-PH^+$] fraction was above 97% for compositions containing higher than 50 mol% of P. The chemical stability of C–P was assayed at two selected pHs (7.5 and 8.5) in comparison with conventional reference solutions (RS) without C. Procaine in (C–P) was 4.2 and 6.2 times more stable than in its respective RS at the two conditions assayed. The stabilizing factor was calculated as the ratio of the rate constants $k_{obs}^{RS}/k_{obs}^{C-P}$.

Since C–B systems exhibit negative electrokinetic potential that attracts positive ions such as (H^+) and repels negative ones such as (OH^-), the stabilizing effect would be associated with the higher acidity of (C–P) environment, in which PH^+ molecules attached to the PE should also have lower kinetic energy than those in the bulk medium.

Keywords: Carbomer hydrogels; Polyelectrolyte–drug interaction; Chemical stability improvement; Polyelectrolyte stabilizing effect; Procaine stability improvement

1. Introduction

In the field of chemical stability of drugs, kinetics and mechanisms of specific acid and base catalyzed reactions are among the best described (Carstensen and Rhodes, 2000; Guillory and Poust, 1996; Connors et al., 1986; Kostenbauder and Bogardus, 1999). For many valuable drugs, these degradation pathways are the limiting factor that prevents the design of liquid pharmaceutical dosage forms. It is also well known that the pH of maximum stability of many drugs is <7 (Connors et al., 1986); in such cases the reactivity of the drug towards HO^--catalysis is higher than the reactivity towards H^+-catalysis. Consequently, the HO^--catalyzed pathway is of prime relevance in drug stability and will be addressed here.

In connection with this point, in previous works (Jimenez-Kairuz, 2002; Vilchez, 2002; Jimenez-Kairuz, 2003) we have reported equilibrium and releasing properties of aqueous systems consisting of an acid polyelectrolyte (PE), i.e. carbomer (C), loaded with a basic drug (B). In these transparent or quasi transparent hydrogels a high fraction of loaded B is

* Corresponding author. Tel.: +54-351-4334163; fax: +54-351-4334127.
E-mail addresses: alfejika@yahoo.com.ar (A.F. Jimenez-Kairuz), rubmanzo@dqo.fcq.unc.edu.ar (R.H. Manzo).

0378-5173/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2003.09.008

present in the form of ion pairs with the carboxylate groups of the PE [$RCOO^-BH^+$] forming a disperse system with a high negative electrokinetic potential (Z) (Jimenez-Kairuz et al., 2002; Vilchez et al., 2002).

Therefore, the important equilibria involved in C and P mixtures are depicted in Eqs. (1)–(3).

$$RCOOH \rightleftarrows RCOO^- + H^+ \quad (1)$$

where RCOOH = carboxylic groups of the PE.

$$B + H^+ \rightleftarrows BH^+ \quad (2)$$

$$RCOOH + B \rightleftarrows [RCOO^-BH^+] \quad (3)$$

Hence, an important fraction of the total drug [B], ([B] = (B) + (BH^+) + ([$RCOO^-BH^+$])), is placed in the PE environment (PEE) as [$RCOO^-BH^+$]. Such fraction reaches 82% in carbomer–lidocaine (Jimenez-Kairuz et al., 2002) and 87% in carbomer–metoclopramide (Jimenez-Kairuz et al., 2003) hydrogels.

In accord with the current knowledge of colloidal chemistry, the loaded PE, having a negative Z potential, will attract positive ions such as (H^+) and (BH^+) and repel negative ions e.g. (HO^-). Therefore, the loaded PE would be seen as a microenvironment of higher acidity than the bulk solution medium. Besides, the protonated basic drug molecules attached to the PE should also have lower kinetic energy than those in the bulk owing to the higher microviscosity of PEE.

In order to test if such factors are able to produce a significant effect on the chemical stability of OH^--catalyzed reactions, carbomer (C) and procaine (P) were selected as the PE and B models, respectively.

It is well known that P is easily hydrolyzed to *p*-aminobenzoic acid (PABA) and diethylaminoethanol (Eq. (4)).

$$p\text{H}_2\text{N–C}_6\text{H}_4\text{–COO–CH}_2\text{–CH}_2\text{–N(CH}_2\text{–CH}_3)_2 + \text{H}_2\text{O} \rightarrow p\text{H}_2\text{N–C}_6\text{H}_4\text{–COOH} + \text{HOCH}_2\text{–CH}_2\text{–N(CH}_2\text{–CH}_3)_2 \quad (4)$$

Since this is a classical model of drug, which undergoes specific acid and base catalyzed hydrolysis, its kinetics and mechanism has been studied extensively (Connors et al., 1986; Schmid, 1961; Higuchi et al., 1950).

The pH-rate profile (Connors et al., 1986) of P, $\log k_{obs.}$ versus pH, indicates that the pH of maximum stability is about 3.5. Although the referenced authors used a variety of buffer systems to keep a constant pH during kinetic runs of P, neither evidence of general acid nor basic catalysis were noticed in any case.

The basic sites of P, having a pK_{a1} of 2.45 (Connors et al., 1986) and a pK_{a2}, early reported as 8.05 (Connors et al., 1986), and later as a more reliable value of 8.95 (Strobel and Bianchi, 1970), determine the speciation as a function of pH ($^+$[$p\text{H}_3\text{N–C}_6\text{H}_4\text{–COO–CH}_2\text{–CH}_2\text{–NH(CH}_2\text{–CH}_3)_2$]$^+$, [$p\text{H}_2\text{N–C}_6\text{H}_4\text{–COO–CH}_2\text{–CH}_2\text{–NH(CH}_2\text{–CH}_3)_2$]$^+$ and $p\text{H}_2\text{N–C}_6\text{H}_4\text{–COO–CH}_2\text{–CH}_2\text{–N(CH}_2\text{–CH}_3)_2$), which will be regarded as (PH_2^{2+}), (PH^+) and (P), respectively).

Intrinsic reactivities of each species towards H^+ and HO^- catalyzed reactions (Connors et al., 1986) have been well established. The highest second order rate constant ($k_{OH}^- = 2.47\,M^{-1}\,s^{-1}$ at 37 °C) corresponds to the pathway depicted by Eq. (5), which produces the greatest contribution to the overall degradation rate in the range of pH 5–9 (Connors et al., 1986).

$$\text{Rate contribution} = k_{OH}{}^-(PH^+)(OH^-) \quad (5)$$

If the contribution of this pathway to the overall degradation rate would be decreased by lowering (HO^-) and/or the reactivity of PH^+ by ion pairing, then a significant increase of stability would be observed. With regard to this point, it was early observed (Testa and Etter, 1975) that at pH 6 the rate of P degradation was lowered almost to a half by addition of carbomer to the solution. Such observation was ascribed to the rise of the macroviscosity.

The stabilizing effect of micellar solutions on the hydrolysis of P has also been reported (Tomida et al., 1978).

In the following sections some relevant aspects of equilibrium properties of C–P systems together with kinetic results on P degradation are reported.

2. Materials and methods

2.1. Materials

Carbomer 934P (C) was kind gift from BF-Goodrich (Carbopol® 934P, Brecksville, OH). Procaine free base (P) was obtained as a precipitate by neutralizing a P HCl (USP-grade Montreal®, Córdoba, Arg.) solution with 1N NaOH solution (Titrisol®, Merck,

Darmstad, Germany), washed with cold water and dried under vacuum to constant weight. Lidocaine (L) (Sigma, St. Louis, MO), *p*-aminobenzoic acid (PABA) (USP-grade, Parafarm®, Bs. As., Arg.), Methylcellulose NF (Montreal®, Córdoba, Arg.), NaCl p.a. (Sintogran®, Bs. As., Arg.), KH_2PO_4 p.a. (Anedra®, Bs. As., Arg.) and distilled water were used.

2.2. Preparation of carbomer–basic drugs hydrogels

Two series of C–procaine $(C–P)_x$ hydrogels were prepared by neutralizing 0.1 or 0.25% aqueous dispersions of C with the appropriate amount of P in solid form (x refers to the mol% of P that neutralize the carboxylic group of C: 25, 50, 75 and 100%). Dispersions were then stirred for ≅1 h, using magnetic stirring bar, at room temperature. The series of C–lidocaine $(C–L)_x$ hydrogels were prepared in a similar way.

2.3. Species distribution determination

Samples of $(C–P)_x$ at 0.1% of C were shake flask partitioned with a 1:1 cyclohexane (CH)/hydrogel ratio. Concentration of P in CH (P_{CH}) was spectrophotometrically assayed at 271 nm (Shimatsu UV-160A, spectrophotometer, Tokyo, Japan). The pH was recorded before extraction and at equilibrium. In order to calculate species distribution as was previously described (Jimenez-Kairuz et al., 2002), the true partition coefficient of P between water and CH was calculated by measuring partition concentrations and pH at equilibrium.

2.4. Degradation measurements

Reference solutions (RS) of P to be used in degradation measurements were made by dissolving P in the appropriate phosphate buffer (pH: 7.50 or 8.50).

Stability experiments were carried out at 20 and 40 °C. The pH of (C–P) hydrogels at 0.25% of C was measured and when needed, adjusted by addition of NaOH to pH 7.50 or 8.50. Samples of (C–P) hydrogels and RS were withdrawn at predetermined intervals, appropriately diluted with buffer solution of pH: 6.40 and spectrophotometrically assayed at two analytical wavelengths (289 and 266 nm) as per reference (Higuchi et al., 1950), in order to get P and PABA concentrations.

3. Results and discussion

3.1. Equilibrium properties

Fig. 1 reports the species distribution of a set of $(C–P)_x$ hydrogels as a function of mol% of P (x = mol% of P = 25, 50, 75 and 100). The figure also shows observed pH values of the aqueous phase after partition with CH, which selectively extracted the free base. The methodology to calculate compositions was previously reported (Jimenez-Kairuz et al., 2002). As can be seen in the figure, in the range of pH 7.4–8.7, the percent of $[RCOO^-PH^+]$ is above 97%, and drops to 91.9% at the more acidic pH of 6.15, indicating that equilibrium 3 is remarkably shifted to the left, as mol% of B is decreased.

The figure also shows that the species of the highest chemical reactivity PH^+ remains below 1.7% in the three higher loaded compositions, but rises to 8.13% at the lowest one.

Equilibrium 3 may be perturbed in several ways. For instance, the addition of a neutral salt such as NaCl produced a lowering of pH paralleled with a rise of conductivity as shown in Fig. 2. Such protogenic effect would be due to the migration of PH^+ and H^+ from the PEE to the bulk medium as a consequence of ionic exchange with Na^+ together with the presence in the bulk solution of the counter ion Cl^-. To get complementary information regarding this point, a set of measurements was made using the system carbomer–lidocaine (C–L). Lidocaine, having higher chemical stability than P, allowed more detailed experiments. Such measurements included the determination of the changes in the proportion of ionic pairs after addition of increasing amounts of NaCl. As can be seen in Fig. 3, the decreasing of pH is effectively accompanied by a concomitant lowering of ($[RCOO^-LH^+]$). Such changes are also paralleled by a strong decrease in viscosity (η) as it is shown in Fig. 4.

Hydrogels constituted by dispersed hydrophilic polymers are well described as biphasic systems in which each phase is interpenetrated by the other (Martin, 1993). The polymer phase, having a high microviscosity produces the main contribution the macroscopically observed η.

Consequently, in the present situation, the observed drop of η may be associated with the migration of ba-

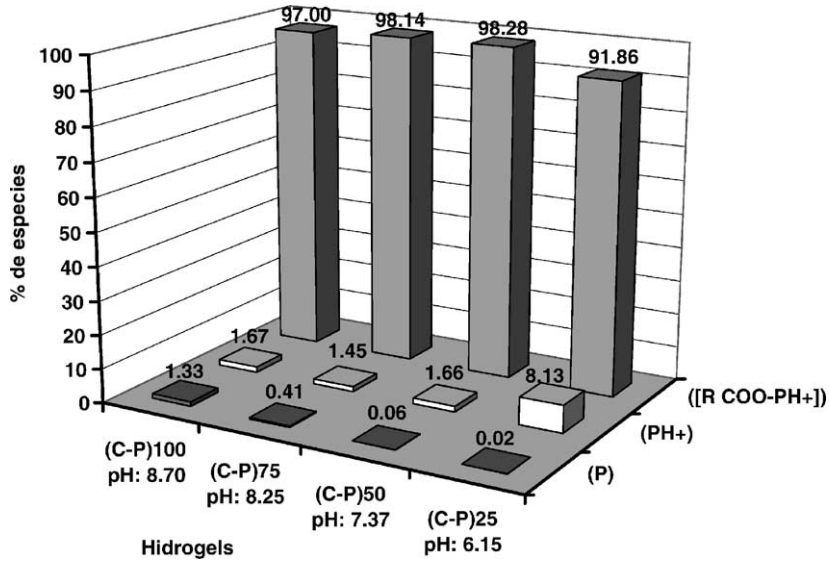

Fig. 1. Species distribution at equilibrium of a set of hydrogels $(C–P)_x$ after the partition with CH.

sic drug molecules placed in the PEE to the aqueous fluid phase.

This is consistent with the observation that when a non electrolyte such as glycine is added instead of NaCl, it does not produce any significant change in pH (Fig. 3) or viscosity (Fig. 4) as would be expected based on equilibria 1–3.

To further illustrate this point the conductivity of both electrolytes, NaCl and L HCl, were measured in a set of hydrogels of increasing concentration of

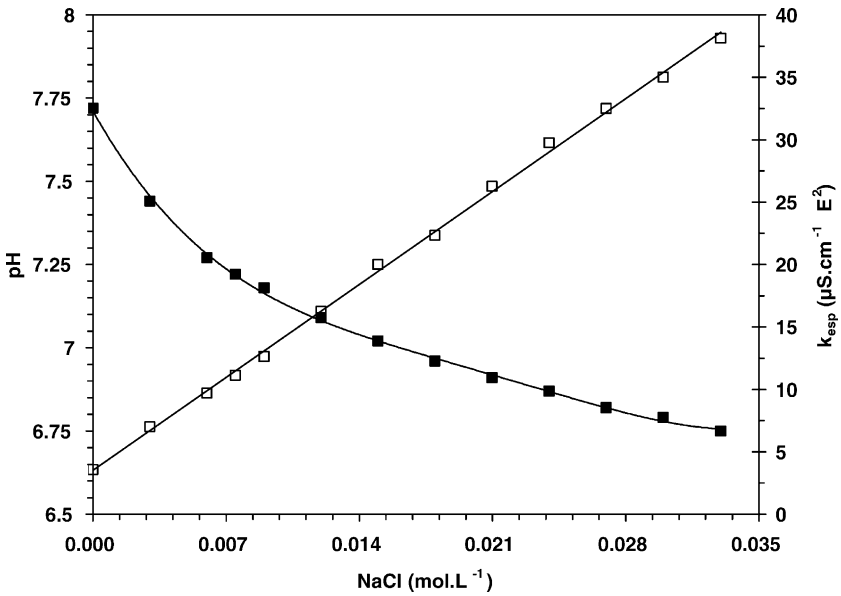

Fig. 2. Variation of pH (■) and conductivity (k_{esp}) (□) of a $(C–P)_{75}$ hydrogel with the addition of NaCl.

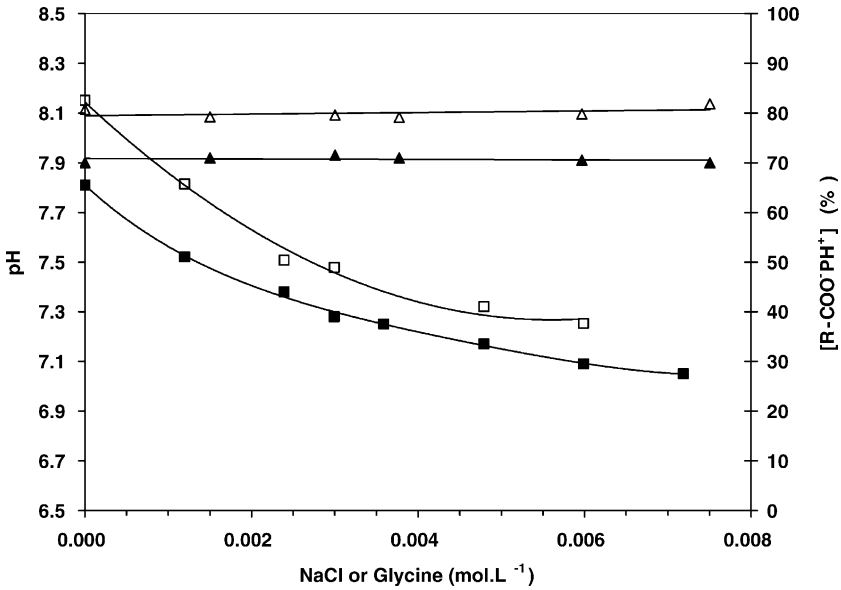

Fig. 3. Variation of pH (black symbols) and mol% of ion pair (empty symbols) with the addition of NaCl (■ or □) or glycine (▲ or △) in a (C–L) hydrogel.

the neutral hydrophilic polymer methylcellulose. As Fig. 5 shows, the system does not follow Warren's rule that relates conductivity with η in homogeneous systems (Brockris and Reddy, 1998) since in both cases the conductivity remained almost constant regardless of the increase of η. This behavior indicates that the electrolytes were essentially placed in the aqueous fluid phase in presence of NaCl keeping their

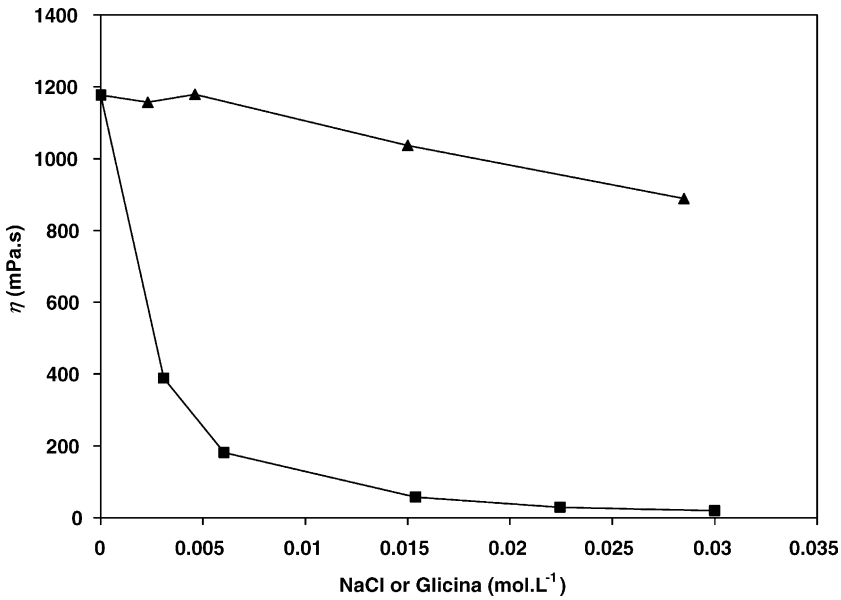

Fig. 4. Variation of dynamic viscosity (η) of a (C–L) hydrogel with addition of NaCl (■) or glycine (▲).

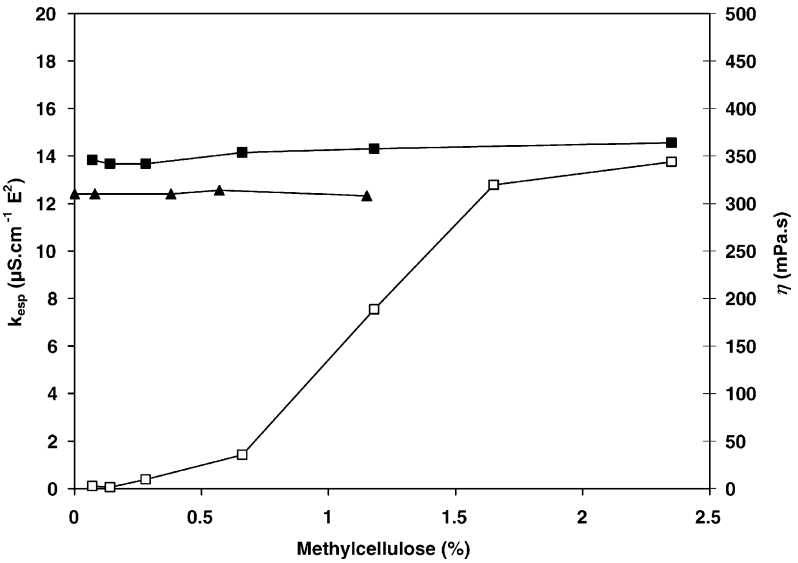

Fig. 5. Conductivity (k_{esp}) of NaCl (■) or L HCl (▲) in methylcellulose hydrogels of increasing viscosities (η) (empty symbol).

activities constant. Therefore, changes in chemical reactivity as a consequence of the increase of η would be unexpected in this case.

3.2. Procaine degradation

Comparative kinetic runs of (C–P) hydrogels and RS were performed at two selected pHs (7.5 and 8.5); at such pHs $\log k_{obs}$ is linearly related to pH with a positive slope (Connors et al., 1986).

Reference solutions were prepared with the same pH and concentration of P as the corresponding (C–P). The pH of RS were regulated by phosphate buffers (ionic strength $\mu = 0.1$) while those of (C–P) were adjusted by either the addition of NaOH or the appropriate amount of P.

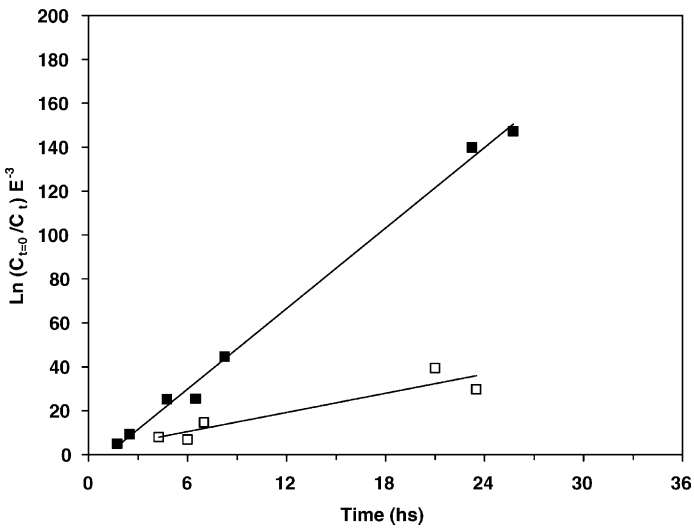

Fig. 6. Degradation kinetics of P in a (C–P) hydrogel (□) and RS (■), at pH 7.5 and 40 °C.

Table 1
Degradation rate constants of procaine in (C–P) and RS

pH	Temperature (°C)	Time interval (h)	k_{obs} (10^7 s^{-1})		Stabilizing effect
			RS	(C–P)	
7.5	40	0–24	17.0	4.04	4.21
		0–120	–	3.79	–
		0–24	–	5.92[a]	–
8.5	20	0–120	13.3	2.17	6.12

[a] Rate obtained in hydrogel with 12% of NaCl.

Fig. 6 shows comparative kinetic results at pH 7.5 and 40 °C that were obtained by sampling at the early stages of degradation (low conversion fractions).

As can be seen in the figure, a significant stabilizing effect is observed in (C–P) with respect to RS. The kinetics of degradation of P in (C–P) also adheres to the first order law. The stabilizing effect, calculated as the ratio of the rate constants $k_{obs}^{RS}/k_{obs}^{(C-P)}$, which is equivalent to the ratio of their respective half lives $t_{1/2}^{C-P}/t_{1/2}^{RS}$, was 4.21 (Table 1).

Samples were taken at low conversion fractions in order to minimize some shortcomings of the comparison between (C–P) and RS. In fact, generation of PABA results in a lowering of the pH as the reaction progress. The rate of pH lowering, that was linear with time, expressed in pH units per hour (ΔpH/h) was 7.4×10^{-3} for (C–P) and 5.1×10^{-3} for RS. Therefore, although P in RS is hydrolyzed at a higher rate than in (C–P), it exhibited a lower shift in pH with time due to the higher buffer capacity of RS. Sampling at low conversion fractions minimized pH changes and provided more reliable results.

However, a run of (C–P) extended during 120 h. (Fig. 7, Table 1) yielded a k_{obs}^{C-P} similar to that obtained within the first 24 h. This result would be a consequence of two opposite effects since on one hand, the lowering of pH lowers (HO^-), but at the same time the presence of PABA in the bulk medium contributes to shift equilibrium 3 to the left and equilibrium 2 to the right with a concomitant rise of the high reactive free PH^+.

It should also be noted that the rate of hydrolysis of P in buffered systems increases as the ionic strength decreases (Connors et al., 1986). Thus, if k_{obs}^{RS} would be corrected to the same μ as (C–P) a higher value would arise affording a higher value of the stabilizing effect reported.

Therefore, it is clear that the observed stabilizing effect of 4.21 times the half life of P would be ascribed mainly to the lowering of the proportion of drug that is degraded through the pathway depicted in Eq. (5).

These results confirm the initial hypothesis that the interaction of B–PE produces a microenvironment of

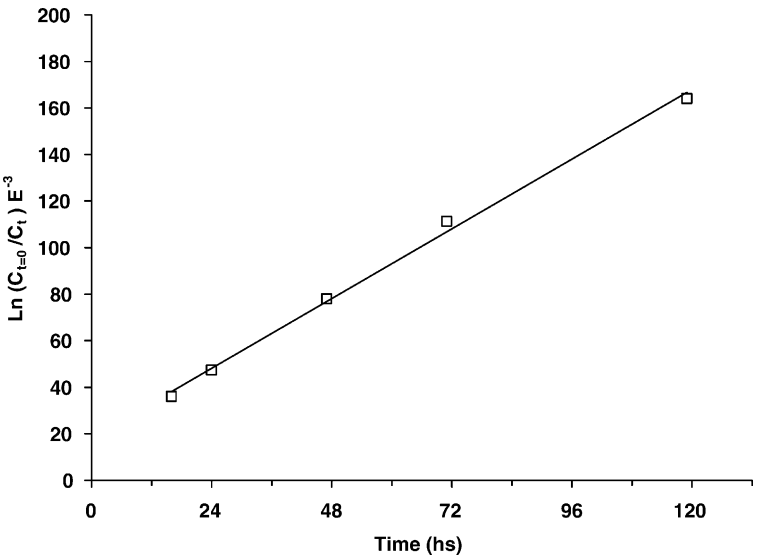

Fig. 7. Degradation kinetic of P in a (C–P) hydrogel at pH 7.5 and 40 °C between 0 and 120 h.

high viscosity, in which the drug degradation rate is considerably lowered due to higher acidity and/or lower reactivity of the reactant group of the drug. However, present results do not reveal how much of the observed effect is due to each possible stabilizing mechanism. With regard to this point, it should be noted that in the early report of Testa and Etter, they did not find significant differences in the second order rate constant of P degradation in a set of C_{940} hydrogels covering η from 656 to 983 Pa. Consequently, It appears that under such conditions the increase of η is not a critical variable.

From equilibrium data presented in this report it is clear that, as only a small fraction of drug remains as free species P and PH^+ in the aqueous environment, their contribution to the overall degradation rate is considerably lowered. Therefore, a mechanistic explanation to the early observation of Testa and Etter is now available.

In addition to the above results, a (C–P) was added with 12 mol% of NaCl to depress the amount of $[RCOO^-PH^+]$, and the pH adjusted to 7.5. As expected, when it was subjected to hydrolysis exhibited a k_{obs}^{C-P} 1.47 times higher than that of the reference (C–P) without NaCl (Table 1).

Table 1 also shows results obtained at pH 8.5 and 20 °C in which a stabilizing effect of 6.12 was observed.

Recognition of the stabilizing effect described here would be of interest not only for applied purposes but also for its theoretical description. In the first field, since a number of valuable drugs are subjected to analogous stability problems as that of P, the use of the strategy described here would contribute to improve their chemical stability in solution.

References

Brockris, J. O'M., Reddy, A. K., 1998. Ion transport in solution. In: Modern Electrochemistry, 2nd ed. Plenum Press, New York, pp. 461–463 (Chapter 4).

Carstensen, J.T., Rhodes, C.T., 2000. Drug Stability. Marcel Dekker Inc., New York.

Connors, K.A., Amidon, G.L., Stella, V., 1986. Chemical Stability of Pharmaceuticals, 2nd ed. Willey Intersciences, New York, pp. 33–61, 693–703.

Guillory, J.K., Poust, R.I., 1996. Chemical kinetics and drug stability. In: Banker, G. S., Rhodes, C.T. (Eds.), Modern Pharmaceutics. Marcel Dekker Inc., New York, pp. 179–211.

Higuchi, T., Havinga, A., Busse, I.W., 1950. The kinetics of the hydrolysis of procaine. J. Am. Pharm. Assoc. Sci. Ed. 39, 405–410.

Jimenez-Kairuz, A., Allemandi, D., Manzo, R.H., 2002. Mechanism of lidocaine release from carbomer–lidocaine hydrogels. J. Pharm. Sci. 91, 267–272.

Jimenez-Kairuz, A., Allemandi, D., Manzo, R.H., 2003. Equilibrium properties and mechanism of kinetic release of metoclopramide from Carbomer hydrogels. Int. J. Pharm. 250, 129–136.

Kostenbauder, H.B., Bogardus, J.B., 1999. Cinética de las Reacciones. In: Remington. Farmacia, 190th ed. Panamericana Ed., Bs. As., Arg. (Spanish version).

Martin, A., 1993. Polymer science. In: Physical Pharmacy, 4th ed. Williams & Wilkins, Baltimore, pp. 556–593 (Chapter 20).

Schmid, H.W., 1961. Reakionskinetische untersuchungen der esterhydrolyse von novocain, farmocain, intracain, stadacain und pantocain. Pharm. Acta Helv. 36, 423–444.

Strobel, G.B., Bianchi, C.P., 1970. The effects of pH gradients on the action of procaine and lidocaine in intact and desheathed sciatic nerves. J. Pharmacol. Exp. Ther. 172, 1–17.

Testa, B., Etter, J.C., 1975. Hydrolysis of procaine in carbopol hydrogels. Can. J. Pharm. Sci. 10, 20–23.

Tomida, H.Y., Yotsuyanagi, T., Ikeda, K., 1978. Effect of micellar interactions on base-catalyzed hydrolysis of procaine. Chem. Pharm. Bull. 26, 148–154.

Vilchez, A.P., Jimenez-Kairuz, A., Alovero, F., Olivera, M.E., Alemandi, D., Manzo, R.H., 2002. Release kinetics and up-take studies of model fluoroquinolones from carbomer hydrogels. Int. J. Pharm. 246, 17–24.