Mechanism of Lidocaine Release From Carbomer–Lidocaine Hydrogels

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ABSTRACT: Rheology, acid-base behavior, and kinetics of lidocaine release of carbomer–lidocaine (C–L) hydrogels are reported. A series of $(C-L)_x$ (x = mol% of L = 25, 50, 75, 100) that covers a pH range between 5.33 and 7.96 was used. Concentrations of ion pair ([R-COO$^-$LH$^+$]) and free species (L) and (LH$^+$) were determined by the selective extraction of (L) with cyclohexane (CH) together with pH measurements, i.e., CH in a ratio CH/hydrogel 2:1 extracted 48% of the whole concentration of lidocaine [L_T] of a $(C-L)_{100}$, {[L_T] = ([R-COO$^-$LH$^+$]) + (L) + (LH$^+$)}. The remaining species in the aqueous phase were distributed as: (L) 3.82%, (LH$^+$) 14.5%, and [R-COO$^-$LH$^+$] 81.7%. Rheology and pH as a function of (C–L) concentration are also reported. Delivery rates of free base L were measured in a Franz-type bicompartmental device using water and NaCl 0.9% solution as receptor media. (C–L) hydrogels behave as a reservoir that releases the drug at a slow rate. pH effects on rate suggest that, under the main conditions assayed, dissociation of [R-COO$^-$LH$^+$] is the slow step that controls releasing rates. Accordingly, release rate was increased upon addition of a second counterion (i.e., Na$^+$), or through the diffusion of neutral salts such as NaCl, into the matrix of the gel. © 2002 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 91:267–272, 2002

Keywords: carbomer; lidocaine; carbomer–lidocaine hydrogels; ion pairs; mechanism of kinetic release; release modulation

INTRODUCTION

In the realm of pharmaceutical formulation, several polyelectrolytes (PE) carrying acidic groups are currently used, mainly as suspending or viscosity-increasing agents in liquid and semisolid formulations[1] as well as in components of solid matrices.[2–4] Although less attention has been given to the use of acidic PE as carriers of basic drugs, there is increasing interest in their application in this field.[5–9] However, detailed reports about the mechanism of drug release from such products under different conditions are not currently available. This point is addressed in this report with the aim of characterizing equilibrium and kinetic behavior. A better knowledge of the factors that control drug release from C-basic drug systems would contribute to a more rational design of formulations containing them.

For that purpose, carbomer 934-P (C) and lidocaine (L) were selected as models of PE and basic drug, respectively. In this way, a series of hydrogels $(C-L)_x$ (x = mol % of L = 25, 50, 75, 100) that covers a pH range between 5.33 and 7.96 was prepared to determine rheology and drug speciation under equilibrium and releasing conditions.

Although the release of procaine, an anesthetic drug related to L has been reported,[7] as already mentioned, a discussion of results on the basis of equilibria involved in the system is not available.

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MATERIALS AND METHODS

Carbomer 934-P (Acritamer; RITA Corp., Woodstock, IL), lidocaine (Sigma, St. Louis, MO), NaCl (Titrisol®; Merck, Darmstad, Germany), and solutions 0.1 N of NaOH and HCl (Titrisol; Merck) were used.

Titration of C

The equivalents of carboxylic groups per gram of C were potentiometrically assayed by titration of a 0.5% dispersion with NaOH 0.1 N solution.

Preparation of (C−L)

A series of hydrogels was prepared by neutralizing a 0.5% dispersion of C with the appropriate amount of a concentrated ethanolic solution of L. The ethanol content in final products was lower than 2%. Freeze-dried C−L solid materials were again reconstituted to hydrogels upon addition of the appropriate amount of distilled water.

Rheology

Rheological assays were performed at 25°C in a Haake (Karlsrube, Germany) viscometer VT500 provided with software VT500/VT 3.01, and an MV1 sensor.

Differential Scanning Potentiometry (DSP)

The method was described previously.[10,11] Solutions 0.05 N of HCl and NaOH were used. The amount of L in the samples ranged from 0.012 to 0.05 mmol.

Partition Equilibrium With Cyclohexane (CH)

Samples of $(C-L)_x$ with 0.1% of C were shake flask partitioned at a CH/$(C-L)_x$ ratio of 2:1. Concentration of L in CH (L_{CH}) was spectrophotometrically assayed. pH were recorded before extraction and at equilibrium.

In the same way, the partition equilibrium of L free base was measured to obtain the true partition coefficient (PC_T).

Kinetic Release

In vitro release of L from a set of reconstituted hydrogels having 0.5% of C, was measured in a device containing as sample compartment a cylindrical tube of glass of 55-mm diameter, provided with a cellulose membrane (12000d; Sigma) attached to the bottom. After loading the cylinder with 15 mL of hydrogel, the sample cell was vertically placed into a longer diameter vas containing 250 mL of receptor medium and a magnetic stirring bar at the bottom. The sample cylinder was submerged to a depth of 4 mm from the surface of the receptor medium. The device was immersed in a 37°C constant temperature bath attached to a magnetic stirrer; samples 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 a measured volume of 0.1 N HCl solution and spectrophotometrically determined at 263 nm, to yield the concentration of L.

RESULTS AND DISCUSSION

Rheology

Hydrogels $(C-L)_x$, where x refers to the mol % of L incorporated, were either prepared by *in situ* neutralizing an aqueous dispersion of C with the appropriate proportion of L, or reconstituted by addition of water onto a previously lyophilized gel. As Figure 1 shows, such products exhibited a pseudoplastic flux with viscosities, which rose as

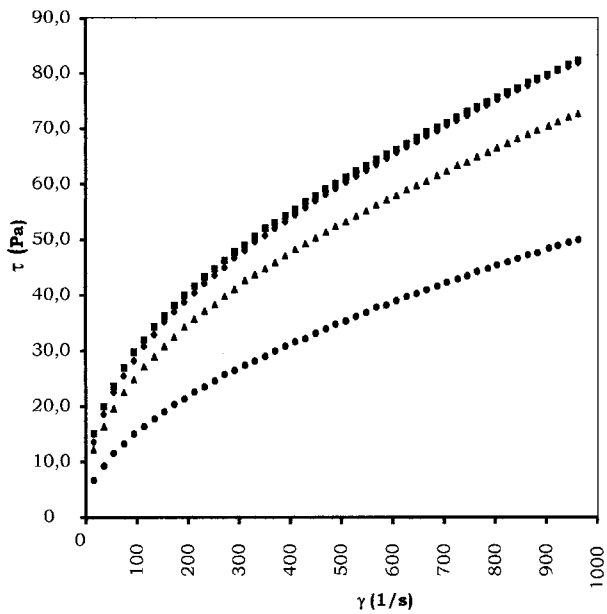


Figure 1. Rheology of $(C-L)_x$ hydrogels 0.2% of C prepared *in situ*. ◆, $(C-L)_{100}$; ■, $(C-L)_{75}$; ▲, $(C-L)_{50}$; ●, $(C-L)_{25}$.

Table 1. Acid-Base Properties of a Set of C–L Hydrogels

		pH						
$(C-L)_x$	L_T[a]	0.5% C[b]	0.1% C[b,c]		(L)[d]	(LH^+)[d]	$([R\text{-}COO^-LH^+])$[d]	$AUC_{(+)}$[e]
100	$6.00\ E^{-2}$	7.96	8.41	7.34	$2.40\ E^{-4}$	$9.12\ E^{-4}$	$5.14\ E^{-3}$	4.67
75	$4.50\ E^{-2}$	7.61	8.09	7.16	$1.59\ E^{-4}$	$9.15\ E^{-4}$	$4.16\ E^{-3}$	3.68
50	$3.00\ E^{-2}$	6.41	7.44	6.48	$6.25\ E^{-5}$	$1.72\ E^{-3}$	$2.75\ E^{-3}$	2.53
25	$1.50\ E^{-3}$	5.33	6.06	5.92	$1.01\ E^{-5}$	$7.31\ E^{-4}$	$2.07\ E^{-3}$	1.28

[a]Total molar concentration of L in 0.5% C hydrogels.
[b]Concentration % w/v of C.
[c]Left and right columns correspond respectively to pH before and after extraction with CH.
[d]Species molar concentrations after extraction with CH of 0.1% C hydrogels.
[e]Obtained by DSP.

the proportion of L increased to reach a plateau between 75 and 100%. Reconstituted hydrogels as compared with those *in situ* showed no further difference than a slight, nonsignificant, decrease in viscosity.

Acid-Base Properties

Table 1 reports the pH of the set of hydrogels. Loading a 0.5% dispersion of C with L from 25 to 100% promotes a rise in pH from 5.33 to 7.96 (2.63 pH units).

It is well known that acid PE exhibit a rather different acid base and salt-forming behavior than monomeric acids.[12–15] In fact, pKa of PE becomes progressively higher as the fraction of dissociated groups increases. However, the ion pairing between dissociated groups and bulky organic cations would also play a significant role in determining the properties of such systems.

DSP

To obtain information about the reversibility of the acid-base reactions, as well as of all other additional processes potentially involved in the interaction between C and L, the set of hydrogels was subjected to titrations according to the technique of DSP. Profiles shown in Figure 2 were consistent with the proportion of L in each sample. In fact, the area under the curve of the positive section of each profile was proportional to the amount x of L in the gel $[(AUC)_+ = 4.53 \cdot 10^{-2} x + 0.21;\ r^2 = 0.997]$ which means that L was fully titrated during scans.

However DSP of a reconstituted hydrogel did not show any difference with that of a similar one prepared *in situ*.

Species Distribution

Because drug speciation produces free forms (L) and (LH^+) together with ion pairs with carboxylic groups of C, $([R\text{-}COO^-LH^+])$, the total drug molar concentration in the hydrogel (L_T) is distributed as:

$$[L_T] = (L) + (LH^+) + ([R - COO^-LH^+]) \quad (1)$$

CH selectively extracts the free base L from the hydrogel. Then, the measure of the experimental apparent partition coefficient (PC_{ap}) CH/hydrogel yielded:

$$PC_{ap} = \frac{(L_{CH})}{(L) + (LH^+) + ([R - COO^-LH^+])} \quad (2)$$

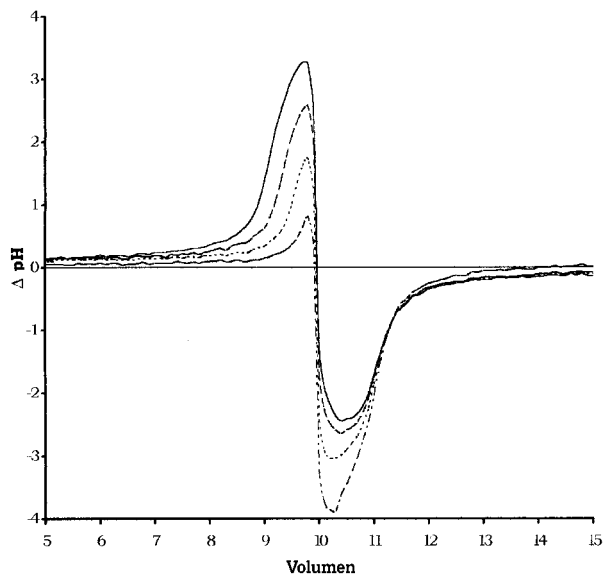


Figure 2. DSP of $(C-L)_x$ hydrogels. ——, $(C-L)_{100}$; — –, $(C-L)_{75}$; -----, $(C-L)_{50}$; ———, $(C-L)_{25}$.

To solve eq. 2, on one hand, true partition coefficient (PC_T) CH/water of L was measured.

$$PC_T = \frac{(L_{CH})}{(L)} = 11.89 \quad (3)$$

On the other hand, pH of the hydrogel at the equilibrium with CH was recorded and (H^+) introduced into eq. 4, in which Ka was taken from the literature.[16]

$$K_a = \frac{(L)\,(H^+)}{(LH^+)} = 1.202 \cdot 10^{-8} \quad (4)$$

(L), (LH^+), and ([R-COO^-LH^+]) for each hydrogel were calculated by using eqs. 2–4 and are quoted in Table 1.

Such results reveal that a high proportion of drug is under the form of ion pair. For example, a $(C-L)_{100}$ 0.1% after equilibration with CH in a ratio 2:1, 48% of drug is placed in the organic phase. The remaining drug in the aqueous phase is distributed as follows: (L) 3.82%, (LH^+) 14.5%, and ([R-COO^-LH^+]) 81.7%.

Loading C with L from $(C-L)_{25}$ to $(C-L)_{100}$ yields an increase of 2.5 times of ([R-COO^-LH^+]) paralleled by a rise of 24 times in (L). The correlation of both magnitudes gives the linear isotherm shown in Figure 3 that may be expressed by:

$$([R-COO^-LH^+]) = 13.5\,(L) + 1.9 \cdot 10^{-4} \quad (5)$$

which may be rearranged to:

$$([R-COO^-LH^+]) = 13.5\,K_a\frac{(LH^+)}{(H^+)} + 1.9 \cdot 10^{-4} \quad (6)$$

Slope and intercept of eqs. 5 and 6 are measure of the affinity between L and C to form the ion pair.

Kinetics of Lidocaine Release

Rates of L release from the set of 0.5% hydrogels were measured under non-sink conditions in a two-compartment device, using distilled water as the receptor medium.

Figure 4 shows that release rates parallel the proportion of L_T in the hydrogels. Such release occurs essentially through the Fickian diffusion of the neutral species L, because diffusion of LH^+ is prevented by the electrostatic gradient provided by the polyanion.

It has been reported that neutral or charged molecules of similar MW to that of L, dissolved in viscous hydrogels, exhibited diffusion coefficients and Fickian transport which were not different from those observed in water.[15]

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

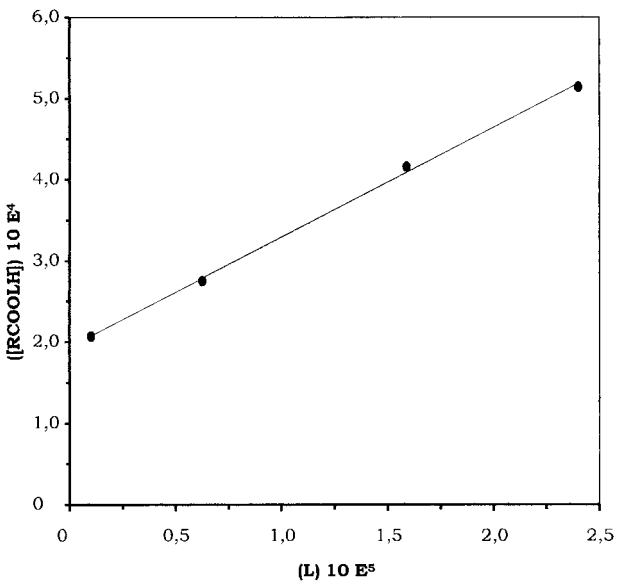


Figure 3. Correlation between ion pair (R-COO^-LH^+]) and free base (L).

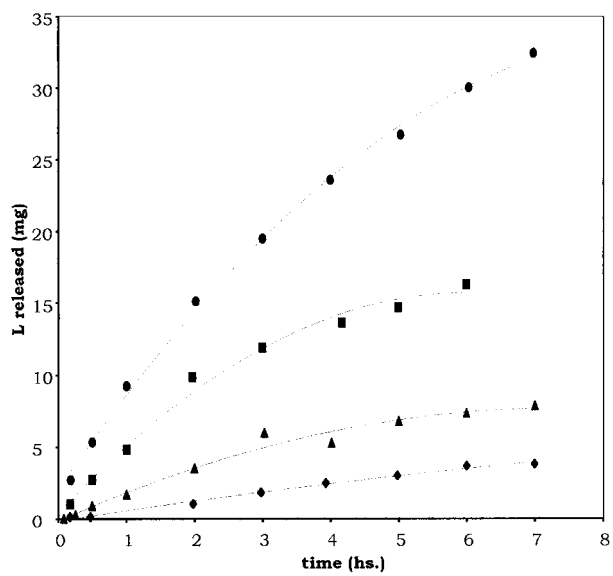


Figure 4. Release rate of $(C-L)_x$ hydrogels at 37°C. ●, $(C-L)_{100}$; ■, $(C-L)_{75}$; ▲, $(C-L)_{50}$; ◆, $(C-L)_{25}$.

Table 2. Release Rate of L Under Different Conditions

Hydrogels	pH	Receptor Medium	k_L (mg/h)
$(C-L)_{25}$	5.33	H_2O	0.77
$(C-L)_{50}$	6.41	H_2O	1.05
$(C-L)_{75}$	7.61	H_2O	1.70
$(C-L)_{100}$	7.96	H_2O	4.30
$[(C-L)_{75}\ Na^+_{25}]$	8.12	H_2O	3.30
$(C-L)_{75}$	7.48	NaCl[a]	11.47

[a]Aqueous solution 0.9% NaCl.

In Figure 5, the logarithms of k_L, ([R-COO^-LH^+]) and (L), taken from Tables 1 and 2, were plotted against pH. The figure allows comparison of the effect of pH on such magnitudes. It can be seen that, in the range of 5.92 to 7.16, as pH increases, the rise of log k_L is nearly paralleled with the rise of log ([R-COO^-LH^+]) but not with the rise of log (L). This result suggests that kinetic control is caused by the relative slow dissociation of ion pairs rather than by the equilibrium concentration of free base (L) (see Scheme 1).

In line with this view, during delivery, (L) in the hydrogel compartment would remain lower than that of equilibrium as a consequence of the rate of diffusion of the free base L, which would be higher than the rate of dissociation of ([R-COO^-LH^+]). Likewise, the higher increase of log k_L observed between $(C-L)_{100}$ and $(C-L)_{75}$ suggests that as pH approaches pKa of L, (L) becomes high enough to be the main factor that controls the rate of delivery. Then, under such conditions, pH effects on (L) and on log k_L should be parallel.

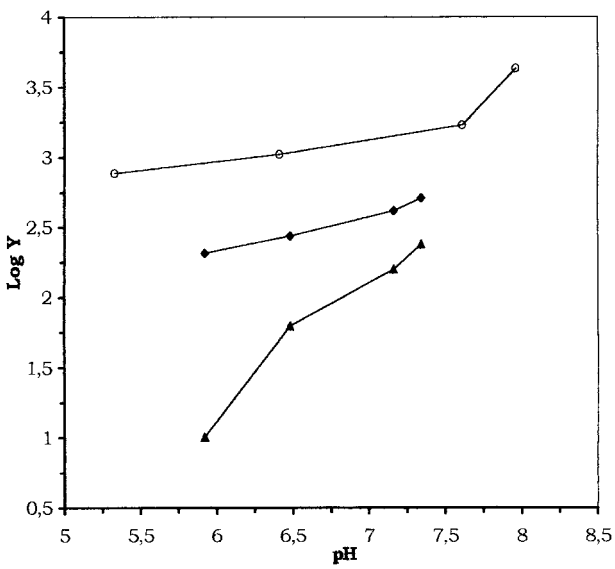
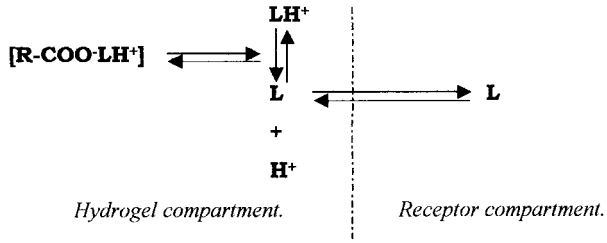


Figure 5. pH effects on release rate of $(C-L)_x$ hydrogels on species distribution. Log Y = 5 + log k_L, ○; 5 + log ([R-COO^-LH^+]), ◆; and 6 + log (L), ▲.



Scheme 1.

Effects of the Addition of Some Reactives on Release Rate

The addition of 25% mol of Na^+ to a $(C-L)_{75}$ produces a hydrogel in which the pH is shifted from 7.61 to 8.12. Consequently, the ratio (L)/(LH^+) is raised and also an ionic exchange between Na^+ and LH^+ should operate on [R-COO^-LH^+]. Both effects should contribute to raise L. The effect shown in Figure 6 was a two-fold increase in release rate.

On the other side, as NaCl 0.9% was placed as receptor medium instead of water, a 6.75 times rise in the release rate of a $(C-L)_{75}$ was found. This result may be associated to the diffusion of

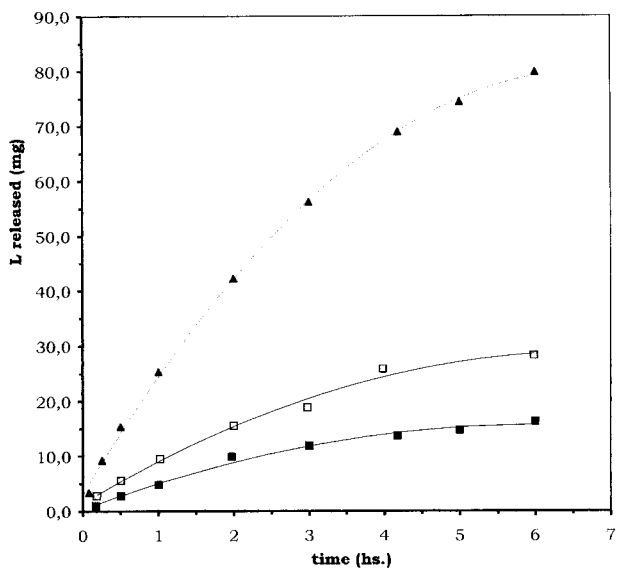


Figure 6. Release rates of a $(C-L)_{75}$ hydrogel against water (■) and against 0.9% NaCl solution (▲); and release rate of a $[C-L)_{75}Na_{25}]$ hydrogel against water (□).

Cl^- and Na^+ from the receptor compartment to the hydrogel. On one hand, Cl^- would promote the diffusion of LH^+ by acting as a counterion; on the other hand, the ionic exchange between Na^+ and LH^+ also promotes drug release from the polyanion. This condition provides some illustration regarding the expected interactions between hydrogels and biological fluids.

CONCLUSIONS

The C–L system behaves as a reservoir of L in which a high proportion of drug is under the form [R-COO^-LH^+]. The proportion of drug under the form of free base L is determined by both its ions' pairing ability and its pKa.

Both slope and intercept of eq. 5 are a measure of the ability of L to form ion pairs with C.

Kinetic results suggest that, under the main conditions assayed, dissociation of ion pairs is the step that controls delivery rates of L.

Release rate can be increased upon addition of a second counterion (i.e., Na^+), or through the diffusion of neutral salts such as NaCl, into the gel matrix.

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

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