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Buffer Effects on Drug Release Kinetics From Acidic Hydrophobic Gel Discs

Aracely Serrano-Medina and José Manuel Cornejo-Bravo*

Facultad de Ciencias Químicas e Ingeniería, Universidad Autónoma de Baja California, Calzada Universidad 14418, Parque Industrial Internacional, Mesa de Otay, Tijuana B.C. Mexico, 22300
e-mail: jmcornejo@uabc.edu. mx

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Abstract. Here we study the variability of drug release rates from hydrophobic polyacid gels, due to the presence of basic buffer species. Release kinetics of the model drug salicylic acid from crosslinked poly(methyl methacrylate-co-methacrylic acid) hydrogels were measured as a function of buffer concentration, buffer acidity (pKa), and solution pH, with total ionic strength (I) held constant. Results show that the release rate of salicylic acid is determined by the concentration of buffering species in the nonionized, conjugated basic form, and not by the pH itself. Since it is difficult to control the concentration and composition of weak electrolytes in the gastrointestinal tract, precise pH-modulated controlled release from hydrophobic polyacid gels may be difficult to achieve. These gels may be more suitable in cases where pH-triggered release is desired, but precise rate control is not warranted.
Keywords: hydrogel, polyelectrolyte gel, swelling-controlled release, buffer effect, methacrylates.

Resumen. En el presente trabajo se estudia la variabilidad en la velocidad de liberación de fármacos a partir de geles hidrofóbicos poliácidos debida a la presencia de amortiguadores básicos. Se evaluó la cinética de liberación del fármaco modelo ácido salicílico, a partir de hidrogeles entrecruzados de poli(metacrilato de metilo-co-ácido metacrílico), como función de la concentración de amortiguador, la constante de acidez (pKa) del amortiguador utilizado y el pH de la solución, manteniendo constante la fuerza iónica. Los resultados demuestran que la velocidad de liberación del ácido salicílico está determinada por la concentración de las especies amortiguadoras en la forma no ionizada (base conjugada) y no en el pH por si mismo. Los resultados implican que es difícil modular la liberación de fármacos modulada por el pH a partir de geles hidrofóbicos poliácidos, debido a la variabilidad en la concentración y composición de electrolitos débiles (amortiguadores) en el contenido intestinal. Estos geles tienen aplicación para liberación de fármacos iniciada por pH alcalinos, pero no se puede asegurar control de la liberación.
Palabras clave: hidrogel, gel polielectrolítico, liberación controlada, efecto de amortiguadores, metacrilatos.

Introduction

Due to their ability to change solute diffusion rate, as a response to the change in the environmental pH, polyelectrolyte hydrogels have been proposed for regional delivery of drugs and macromolecules into the gastrointestinal tract [1-10], and the vaginal cavity [11].

Particularly, glassy-hydrophobic polyelectrolyte hydrogels exhibit great potential as pH-sensitive drug delivery systems since, in their dry glassy state, these hydrogels prevent diffusional release of the drug; but, when exposed to an environment where the pH favors swelling, the drug is released. Hence, drug delivery is controlled by swelling and follows a quasi-linear kinetics [12-14].

The swelling studies using hydrophobic polybasic gel discs containing lightly crosslinked *N, N*-dimethylamino ethyl methacrylate (DMAEMA) and methyl methacrylate (MMA) 30/70 mol% demonstrated that swelling occurs by a moving front mechanism. At intermediate stages of swelling, the polymer disc consists of a glassy core and a swelling periphery. As the swelling progresses, at the front separating these phases, gel is converted from the dry-glassy state to a hydrated-swollen state [15]. It has been observed that the release of caffeine from these gels is determined by the rate of swelling. Moreover, when moving fronts meet in the middle of the disc most drug is released [12].

Further studies have shown that gel swelling rates are sensitive to concentration and acidity of the buffer (given by its pKa). Using a weak acid to buffer the solution, a positive correlation between its unionized form and the rate of swelling was found. So, it was concluded that the unionized molecules of the buffer act as proton carriers, from the outer solution to the amines within the gel, speeding the swelling process (shuttle mechanism) [16].

As expected, later experiments showed that caffeine release from these gels is controlled jointly by pH, buffer concentration and acidity, since these three variables are determinants for concentration of the unionized form of the buffer [17].

A systematic study on swelling of polyelectrolyte gels showed that these variables also affect the swelling kinetics of acidic gels, such as the poly(methyl methacrylate-co-methacrylic acid) (PMMA/MAA) 78/22 mol%. Using weak bases to buffer the media, an increment of the rate of swelling was observed as the concentration of unionized base increased [18].

Studies on swelling and drug release from PMMA/MAA 56/46 mol% gel beads were also performed [13]. At pH 7.4, the results showed that the gel swelling and the rate of release of oxyprenolol · HCl increased as a response to increased phosphate buffer concentration. According to this observation, it was concluded that the increase in buffer concentration will decrease Donnan potential, allowing the influx of basic phosphate and hydroxide ions into the gel more readily, and ionizing the pendant carboxyl groups. Moreover, it was proposed that another factor was a higher concentration of the HPO_4^{-2} ion (as a result of the increased buffer concentration); arguing that this

ion will act as a proton extractor for the carboxyl group in the polymer chains and increase the rate of ionization [16].

Further studies with the PMMA/MAA gel beads showed that the increase of pH between 6.9 and 9, at a total phosphate concentration of 0.2 M, leads to an increment in the swelling and drug release rates from the polyacid gels [14]. The faster swelling at high pH was attributed to an increase of the hydroxide ion concentration; along with the argument that the shift from $H_2PO_4^{-1}$ to HPO_4^{-2}, which is a stronger base, results in a more efficient ionizing agent of the carboxyl groups from the gel beads. This has been proposed regarding the higher concentration of the dibasic phosphate ion, compared to the hydroxide ion, at the pH and buffer concentration used.

Buffer composition media has been observed to affect drug release from extended release products [19, 20]. This has been attributed to differences in pH, buffer capacity and ionic strength, among the dissolution media. Other effects, such as the "shuttle mechanism" observed in polyelectrolyte gels, can also affect drug dissolution, making it difficult to find an appropriate dissolution medium to obtain accurate *in vivo-in vitro* relationships.

Our aim is to evaluate the extent to which the buffer composition has an effect on the rate of drug release from hydrophobic polyacid gels by the "shuttle mechanism", which is depicted in Figure 1. The Figure shows that swelling of an acidic gel in phosphate buffer is halted by the exclusion of anionic bases from the ionized (swollen) layer of the gel. On the other hand, buffering with unionized weak bases causes complete ionization of the gel. Here we report the salicylic acid (SA) release kinetics from gels constituted of PMMA/MAA 78/22 mol% slightly crosslinked by ethylenglycol dimethacrylate (EGDM);

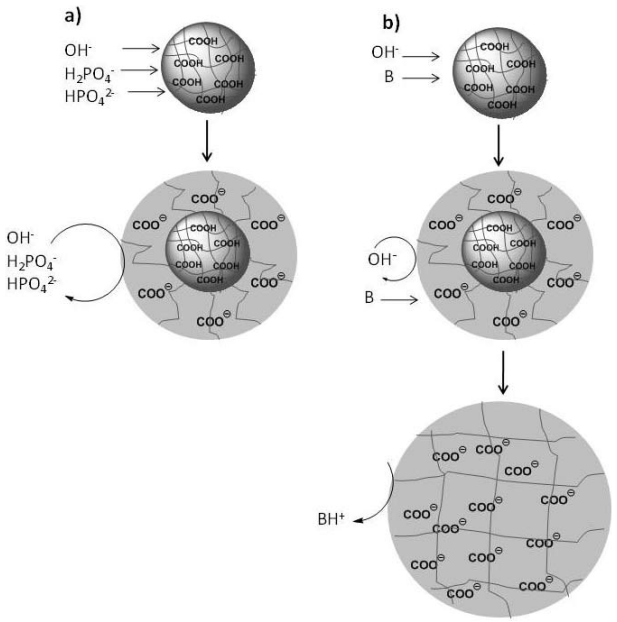

Fig. 1. Proposed mechanism of ionization (shuttle mechanism) and subsequent swelling and drug release, from an acidic gel, when the media is buffered by a) phosphates, or b) a weak base (B).

as well as the comparative analysis of the effect of the release rate using different alkaline buffers.

Results and Discussion

Three kinds of buffers and different physico-chemical conditions were used to study the release of SA from discs of polyacid gel. The conditions of each set of experiments are listed in Table 1. Each condition represents the variation of one of the experimental conditions, such as buffer, pH, total buffer concentration (C_{BT}), and drug loading. Conditions selected were similar to those used in most studies. For instance pH 7.4 was selected since it is the physiological pH and the pH expected in the intestines, while pH 9.0 was selected since higher swelling is expected for acidic gels. Release experiments were performed using an AT7 Sotax Dissolutor at 100 RPM and 25 °C.

The concentration of unionized base form, C_B is calculated using the formula

$$C_B = \frac{C_{BT}}{(1 + 10^{pKa-pH})} \quad (1)$$

The buffer pKa values are corrected for ionic strength according to the Debye-Hückel theory [21].

To study the effect of the buffer and the concentration of the ionized form, we performed a drug release kinetics experiment at constant pH, ionic strength, and drug loading. Figure 2 shows the SA release kinetics from gels at pH 7.4 in media buffered by 0.05 M imidazole (■), ethanolamine (▲), and phosphates (○), at 9 %w/w loading. Drug release rate is considerably higher in imidazole solution, achieving the complete release in 7 h compared with the other buffer solutions, in which fractions released in 24 h were 0.05 and 0.25 for ethanolamine and phosphates, respectively. In fact, the release rate in phosphate solutions is 2-3 fold higher than those in ethanolamine. The effect of unionized base form in the kinetics of drug release is evident. At pH 7.4, 72% of the imidazole remains in the basic unionized-form while only 0.7% of the ethanolamine is unionized and phosphate exists as the anionic bases $H_2PO_4^{-1}$ (16%) and HPO_4^{-2} (84%). Besides the considerable higher rate release in imidazole solutions, the rate of release in ethanolamine buffer appears slower than the rate in phosphate buffer. This can be explained considering that the carboxylic groups inside the gel have a pKa around 4-5 [18] and the HPO_4^{-2} (pKa = 6.78) ion is able to extract protons from the carboxylic acid groups. The concentration of this ion (4.2×10^{-2} M) is six orders of magnitude higher than the hydroxide ion concentration (3.16×10^{-8} M). For instance, the total base concentration in the phosphate buffer is considerably higher than in the ethanolamine buffer, where the unionized base concentration is 3.5×10^{-4} M. Moreover, at pH 7.4, far from its pKa, ethanolamine has a very low buffer capacity. Ionization of the gel and the drug, as well as CO_2 uptake from the air, decreases the pH up to one unit after a 24 hour release process in the solutions buffered

Table 1. Conditions for release experiments and regression analysis according to Eq. (2).[a]

Buffer	pH	C_{BT} (M)	C_B (M)	% C_B	Loading %	n	R^2
Imidazole (pKa = 7.09)	7.4	0.01	0.0072	72%	29	0.672	0.972
	7.4	0.03	0.0215	72%	29	0.699	0.987
	7.4	0.05	0.0359	72%	29	0.841	0.99
	7.4	0.05	0.0359	72%	9	0.375	0.982
	9.0	0.05	0.0494	99%	29	0.817	0.978
Ethanolamine (pKa = 9.64)	7.4	0.05	0.0003	0.7%	9	0.755	0.850
	7.4	0.05	0.0003	0.7%	29	0.665	0.993
	9.0	0.05	0.0093	18.6%	29	0.638	0.999
Phosphates (pKa´s = 1.98, 6.78, and 11.96)	7.4	0.05	*	*	9	1.242	0.987
	7.4	0.05	*	*	29	0.672	0.975
	9.0	0.05	**	**	29	0.645	0.999

[a] C_{BT}: Total buffer concentration; C_B: Free buffer base; $\%C_B$: Percentage of free buffer base; n: Exponent from Eq. (2); R^2: correlation coefficient.
* [$H_2PO_4^{-1}$] = 0.008M (16%) and [HPO_4^{-2}] = 0.042M (84%).
** Most phosphates are in the HPO_4^{-2} form.

by ethanolamine. This pH decrease halts the gel swelling and consequent drug release.

To evaluate and compare the rate of drug release at different drug loadings, we performed experiments, at the same experimental conditions using gel discs loaded with 3-fold concentration of SA. Figure 3 shows the kinetics of drug release preserving conditions as in Figure 2 except that drug load was 9% w/w for the experiments shown in Figure 2 and 29% w/w for the experiments shown in Figure 3. The same pattern is observed, however the release rates are higher than those observed from lower loadings (Figure 2). The extra osmotic force induced by the drug could explain the faster kinetics observed [14]. An alternate explanation could be the increase of solubility of SA upon ionization by the buffering base. However, the later factor must be minimal since the rate of release is also increased for the ethanolamine solution when base concentration is very low. In these experiments, a small but noticeable

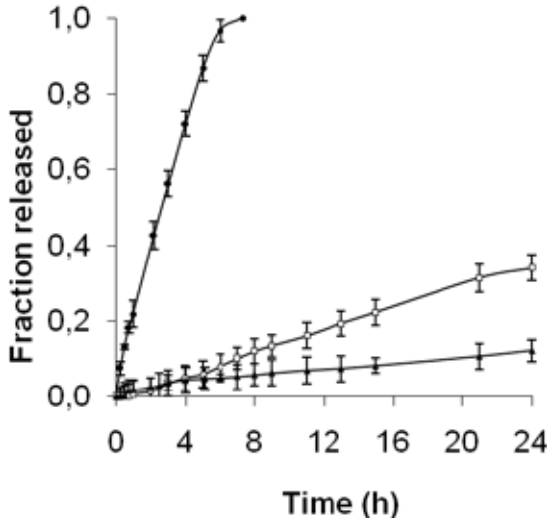

Fig. 2. Release kinetics of SA from MMA/MAA copolymer gels (9% w/w/ drug loading) in release media containing different weak base buffers. Total buffer concentration 0.05M, pH 7.4, I = 0.015M. Drug loading 9 %w/w. Imidazole (•), phosphates (□), ethanolamine (▲). Faster kinetics are observed for the imidazole buffer due to a higher concentration of unionized base. Rate of release from ethanolamine buffer is lower than phosphate buffer since most ethanolamine exists as the ionized form.

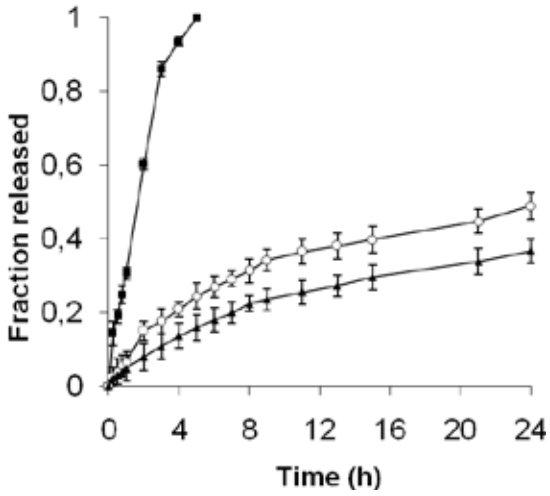

Fig. 3. SA release kinetics from MMA/MAA copolymer gels (29% w/w drug loadings) in release media containing different weak bases buffers. Total buffer concentration 0.05M, pH 7.4, I = 0.015M. Imidazole (■), phosphates (○), ethanolamine (▲). Release rates are higher than those observed for lower loading (Figure 2).

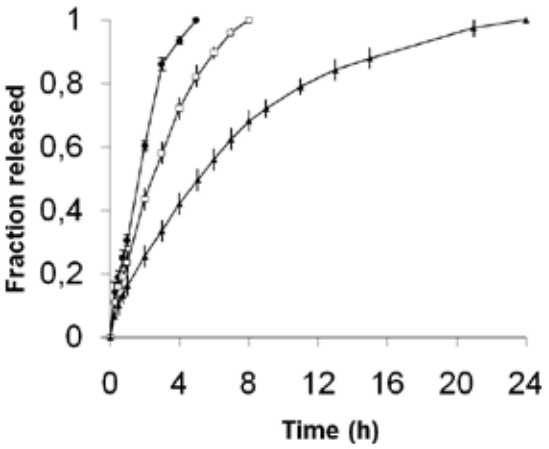

Fig. 4. Kinetics of SA release from polyacid gels under varied concentrations of imidazole buffer. 0.05M (●), 0.03 M (□), 0.01 M (▲). pH, I, and drug loading were as in Figure 2. It shows that rate of release increases as the concentration of imidazole increases.

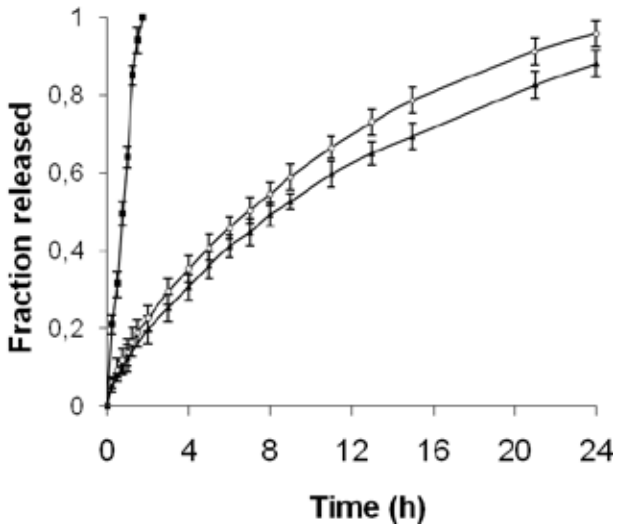

Fig. 5. SA release kinetics from MMA/MAA copolymer gels in release media containing different weak base buffers. Total buffer concentration 0.05M, pH 9.0, I = 0.015M. Drug loading 29 %w/w. Imidazole (■), phosphates (▲), ethanolamine (○). Rate of release is higher than at pH 7.4 (Figure 2). In this case release rate from ethanolamine buffer is higher than phosphate buffer since 18.6% of ethanolamine exists as the unionized base form.

burst of drug occurs. This may be due to the presence of drug precipitated forming pores in the gel, as has been observed previously [10, 22].

To estimate the effect of buffer concentration, we carried out experiments using different concentrations of imidazole, preserving the pH, ionic strength and drug loading constant. The effect of buffer concentration is shown in Figure 4. As the concentration of imidazole increases, so does the rate of release, in accordance with previous studies [13, 17]. Kim and Lee's solutions are buffered with phosphate. They claim that the increase in buffer concentration decreases the Donnan potential, allowing negatively charged ions (hydroxide and phosphate) to enter the gel. In our experiments ionic strength is kept constant so that changes in the Donnan potential are minimal. In other words, the results can be explained in terms of the shuttle mechanism, where the unionized base, which concentration changes considerably, enters into the gel and extracts the protons from the carboxylic acid groups.

Finally, we study the effect of a highly basic pH over the drug release in different buffers. Figure 5 presents the rate of SA release from the gels (29% w/w loading) at pH 9.0 buffered by imidazole, ethanolamine and phosphates 0.5 M. The release rates at pH 9.0 are higher than as at pH 7.4 as seen in Fig. 3 where all other experimental conditions are the same, as expected for the increase in hydroxide ion concentration. Furthermore the concentration of unionized base from for imidazole and ethanolamine increases. The rate of drug release in solutions buffered by ethanolamine is higher than that for phosphates. At pH 9.0, almost all the phosphates are in the HPO_4^{-2} form, which represents just a 16% increase from the concentration of this ion at pH 7.4. On the other hand, the unionized form of ethanolamine increases 26-fold, producing a shuttle mechanism for the gel ionization and faster drug release.

With the aim of discerning the possible mechanisms and types of release, data was fit, up to 80% release, to the phenomenological equation (2) [23]

$$\frac{M_t}{M_\infty} = kt^n \quad \text{or} \quad \ln\left(\frac{M_t}{M_\infty}\right) = n\ln(t) + \ln(k) \qquad (2)$$

The terms in this equation are as follows: Mt, the amount of drug released at time t; M∞, the total drug released over a long time period; k the kinetics constant; and n, the mechanism of drug release. The value of n ranges from 0.5 ($t^{1/2}$ dependence, generally referred to as Fickian release) to 1 (representing the case-II transport which is purely relaxation controlled). The values in between indicate an anomalous behavior corresponding to coupled diffusion/relaxation. Results are also presented in Table 1 showing that release in most of the conditions has an anomalous behavior with a combination of gel swelling (relaxation) and drug diffusion (Fickian) mechanisms.

As a concluding remark, there are some implications of our results on the utility of polyacid hydrogels in GI drug delivery. These systems will release their contents in the basic environment of the small and large intestines. Considering that the content of the intestine can vary considerably, particularly after meals, amino acids and other weak bases will act on the rate of swelling in a manner similar to the buffers used in our experiments. Since the concentrations and identities of these weak bases are generally unpredictable, swelling and drug release rates are also expected to be quite variable, even at constant pH. Hence, a highly controlled release rate based on pH is a difficult goal with polyacid gels. For many drugs, however, absorption and elimination rates are relatively slow, and precise release rate control provides no advantage. In such cases the hydrophobic, glassy polyacid gels may have advantages in the areas of taste masking, drug stability enhancement and site specific release.

Materials and methods

MMA, MAA, EGDM and 2,2'-azobisisobutyronitrile (AIBN) were purchased from Polysciences, Inc. MMA was distilled in the presence of hydroxyquinone (Aldrich Co.). MAA and EGDM were vacuum distilled in the presence of the polymerization inhibitor, 1,3,5-trimethyl-2,4,6-tris[3,5-di-*tert*-butyl-4-hydroxybenzyl] benzene (Ethanox 330) from the Ethyl Corp. The free-radical initiator for polymerization, AIBN, was recrystallized from water-ethanol prior to use. SA, crystalline imidazole , 99% ethanolamine, dibasic sodium phosphate, and crystalline sodium chloride (Aldrich Chemical Co.) were used as provided.

The hydrogel P(MMA/MAA) 78/22mol% crosslinked by 0.1% w/w EGDM was synthesized following a previously reported method [24]. Briefly, MMA, MAA and EGDM were mixed in the appropriate proportions with the free radical initiator AIBN (0.5% w/w). The mixture was vacuum degassed and placed in silanized glass molds of 0.4 mm thickness. The polymerization was performed at 70 °C under argon atmosphere. The gel formed was cut as 1 cm dia. discs. The gel discs obtained were extracted for several days with methanol to eliminate unreacted monomers and initiator. Afterwards the gels were collapsed with a water/methanol 50/50 v/v%, air dried for 24 h then dried under vacuum at 60 °C for 12 h.

The gels were loaded with SA by re-swelling the disks in tetrahydrofuran/water 50/50% v/v containing SA. The disks were then air dried for several hours and vacuum dried at 60 °C for 24 h. SA in the surface of the disks was removed by washing the disk for 2 min in phosphate buffer solution (pH 7.0), and repeating the drying steps.

Release experiments were performed using an AT7 Sotax Dissolutor. All experiments were on 300 mL of buffer, at 100 RPM (with blades) and 25 °C. The total ionic strength of the buffers was fixed at 0.15 M by adding the appropriate amounts of NaCl. At predetermined time intervals, 3-mL samples of the dissolution medium were withdrawn and assayed for SA by UV spectrophotometry at 295 nm. All release experiments were carried out by triplicate sampling.

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