Buffer Effects on Swelling Kinetics in Polybasic Gels

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Received February 13, 1991; accepted July 11, 1991

The swelling kinetics of polybasic gels consisting of copolymers of methyl methacrylate and dimethylaminoethyl methacrylate are studied in solutions at various acidic pH values, with monoacidic derivatives of acetic acid added as buffers. The effects of solution pH, as well as buffer pK_a and concentration, on swelling rate are assessed. Gel swelling rate shows a nearly linear dependence on the concentration of nonionized buffer in the solution, as determined by the Henderson–Hasselbach equation. This result is explained in terms of the increased availability of protons that are carried by the nonionized buffer to bare amines on the gel. In fact, the so-called pH sensitivity of these gels, under these conditions, can be attributed mainly to the effect of pH on the nonionized buffer concentration. A practical consequence is that these gels may not reliably mediate pH-sensitive swelling-controlled release in oral applications, since the levels of buffer acids in the stomach (where swelling and release are expected to occur) generally cannot be controlled. However, the gels may be useful as mediators of pH-triggered release when precise rate control is of secondary importance.

KEY WORDS: hydrogels; polyelectrolyte gels; swelling kinetics; pH sensitive; buffer effects; drug delivery.

INTRODUCTION

The pH-dependent aqueous swelling properties of polyelectrolyte networks, or gels, is of considerable interest since these materials may be applicable as mediators of environmentally controlled solute release (1–8). Inasmuch as the human body contains regions characterized by differing pH values, one can consider such gels for pH-sensitive drug release. In addition, local pH changes can be generated enzymatically in response to specific substrates, and this can be utilized as a method for modulating drug release (9–13).

Optimal utilization of pH-sensitive polymer gels requires an understanding of factors affecting their swelling rates. As in neutral polymers, one must consider the processes of solvent/polymer interdiffusion as well as polymer relaxation (14–19). However, due to the presence of fixed ionizable groups on the gel, ion exchange and diffusion processes may also be important (10,19–22). It has long been known that weak polyelectrolyte gels undergo changes in their equilibrium swelling state in response to changes in pH and ionic strength (23–25). In many studies, the aqueous solutions contain strong electrolytes (i.e., mineral acids, bases, salts), while in other studies a weak electrolyte buffer is added to stabilize solution pH. It is usually assumed that the important characteristics of the aqueous solution governing polymer response are the pH and ionic strength, with little consideration given to the explicit electrolyte composition of the solution.

In previous studies of weak cationic gels consisting of poly(methyl methacrylate-co-*N,N*-dimethylaminoethyl methacrylate), we observed that the nature of the buffer has a profound effect on both swelling equilibria (3,26) and swelling rates (27). Specifically, swelling in solutions buffered by weak organic acids may take place over periods of hours, whereas swelling in unbuffered media sometimes requires weeks or months to reach equilibrium. The latter can occur even though the equilibrium degree of swelling is higher for the unbuffered case than the buffered case. The possibility that the buffer might be acting as a plasticizing agent in the gel was ruled out, because swelling in unbuffered media in the presence of neutral organic analogues similar in structure to the organic buffers was no faster than the swelling in the absence of the analogues (27).

To explain the seemingly anomolous results regarding the effect of buffers on swelling, a "shuttle" mechanism was proposed, whereby hydrogen ions are transported as part of the acid form of the buffer from the outer solution to the unionized amine groups attached to the gel network (27). This mechanism predicts that an increase in the concentration of the acid form of the buffer should lead to an increased swelling rate. In the present paper we test this hypothesis using a series of monoacidic carboxylate buffers.

As a starting point, we rearrange the well-known Henderson–Hasselbach equation (28) to obtain an equation relating the nonionized (acid form) buffer concentration, C_{AH}, to the total buffer concentration, $C_{A,T}$, the log acidity constant (pK_a) of the buffer, and the solution pH:

$$C_{AH} = \frac{C_{A,T}}{1 + 10^{pH - pK_a}} \quad (1)$$

By varying $C_{A,T}$, pK_a, and pH systematically, we can ascertain the effect of C_{AH} on swelling rates, with ionic strength held constant.

MATERIALS AND METHODS

Methyl methacrylate (MMA) and *N,N* dimethylaminoethyl methacrylate (DMA), obtained from Polysciences, Inc., and divinyl benzene (DVB), obtained from Pfaltz and Bauer, Inc., were vacuum distilled. 2,2'-Azobisisobutyronitrile (AIBN), from Polysciences, was recrystallized from water/ethanol. Certified ACS-grade methanol and sodium chloride were obtained from Fisher Scientific. Glacial acetic acid (HAc) was obtained from Mallinckrodt, Inc. Methoxyacetic acid (MeOHAc) and chloroacetic acid (ClHAc) were obtained from Aldrich Chemical Co. Water used in all experiments was double distilled and deionized.

Preparation methods have been described elsewhere in detail (3–5,27). The comonomers MMA and DMA, at the ratio 70/30 mol%, were mixed with the cross-linker DVB (0.01%, w/w) and the initiator AIBN (0.5%, w/w). The mix-

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0724-8741/92/0100-0076$06.50/0

ture was degassed and injected between two silanized glass plates separated by a 0.38-mm-thick Teflon spacer. Polymerization was induced by incubation for 18 hr under argon at 60°C. After polymerization the resulting gel sheet was separated from the glass and punched into 11-mm-diameter disks. The disks were swollen for 2 days in methanol to extract the sol fraction and unreacted monomers, initiator, and cross-linker. Methanol was exchanged several times during this period. The disks were then placed in 50/50 (v/v) methanol/water overnight. Finally, the gels were air-dried at room temperature for 24 hr and then vacuum-dried at 50°C for another 24 hr. The resulting disk thicknesses varied between 0.33 and 0.37 mm as determined by a micrometer.

Swelling kinetics of the copolymer gels were measured in solutions of specified pH and buffer concentration in solutions buffered by HAc, MeOHAc, or ClHAc. Ionic strength (I) was set at 0.1 M by the addition of NaCl. The amount of NaCl to be added was determined by the difference between 0.1 M and the ionized buffer concentration, $C_{A,T} - C_{AH}$, with C_{AH} calculated using Eq. (1). At $I = 0.1$ M the pK_a's for HAc, MeOHAc, and ClHAc are 4.62, 3.42, and 2.74, respectively. These number were calculated by correcting the infinite dilution pK_a values for these buffers by a Debye–Huckel activity term (-0.12 at $I = 0.1$ M) (28).

Copolymer disks in duplicate were placed into baskets made from plastic centrifuge tubes with holes drilled in them, which were placed into 2-L Erlenmyer flasks containing 2000 ml buffer solution. Temperature was maintained constant at 25°C with a circulator. Vigorous stirring (>300 rpm) was provided by a magnetic stir bar. We have previously shown that this rate is sufficient to prevent significant boundary layer effects on swelling (4,27). Sorption was followed by periodically removing the disks, blotting excess surface water, and weighing. pH was then adjusted when necessary to the original value by the addition of appropriate amounts of HCl or NaOH.

RESULTS

According to Eq. (1), the nonionized buffer (acid form) concentration can be controlled by varying the buffer pK_a, the total buffer concentration C_{AT}, or the solution pH. Hence we have performed swelling experiments in which these parameters were varied individually. Table I lists the various solution conditions under which swelling experiments were performed. Buffer concentrations ranged between 0.01 and 0.063 M. The solution pH was varied between 2.5 and 4.0. Also listed in Table I are the buffer fractions in the conjugate acid form, $C_{AH}/C_{A,T}$, as well as the nonionized buffer concentration, C_{AH}.

Figures 1–3 display typical swelling curves at $I = 0.1$ M obtained for various solution conditions. Data are displayed as the swelling ratio $Q(t)$, defined as the mass of water in the gel at time t, divided by the initial mass of the dry polymer. Figure 1 shows a typical set of swelling curves, measured at pH 3.0 and total buffer concentration $C_{A,T} = 0.02$ M, but with different buffers. Swelling is fastest for HAc, followed by MeOHAc and ClHAc. Thus swelling rate increases with increases pK_a. Figure 2 shows swelling curves, measured at pH 3.5 in HAc buffer at different concentrations $C_{A,T}$. Here swelling rate increases with $C_{A,T}$. Finally, in Fig. 3 release is plotted for 0.02 M HAc with varying pH. For this set swelling rate increases with decreasing pH. All of these results are consistent with the hypothesis that any change in the solution which increases the unionized buffer concentration will increase the swelling rate. A more quantitative appraisal follows.

Table I. Buffer Conditions for Swelling Experiments[a]

Buffer acid	pH	$C_{A,T}$	$C_{AH}/C_{A,T}$	C_{AH}	t_{accel}	$R = 10^5/t_{accel}$
HAc						
(pK_a = 4.62)	2.5	0.02	0.992	0.0199	150	667
	3.0	0.02	0.977	0.0195	185	541
	3.5	0.01	0.930	0.0093	400	250
	3.5	0.02	0.930	0.0186	200	500
	3.5	0.05	0.930	0.0465	90	1111
	4.0	0.02	0.806	0.0161	250	400
MeOHAc						
(pK_a = 3.42)	2.5	0.02	0.893	0.0179	220	455
	3.0	0.02	0.724	0.0145	315	317
	3.0	0.034	0.724	0.0246	207	483
	3.0	0.048	0.724	0.0348	160	625
	3.5	0.02	0.454	0.0091	480	208
ClHAc						
(pK_a = 2.74)	2.5	0.02	0.635	0.0127	220	455
	2.5	0.047	0.635	0.0298	120	833
	2.5	0.063	0.635	0.0400	80	1250
	3.0	0.02	0.355	0.0071	420	238
	3.5	0.02	0.148	0.0030	1210	83

[a] HAc, acetic acid; MeOHAc, methoxyacetic acid; ClHAc, chloroacetic acid; $C_{A,T}$, total (ionized + nonionized) buffer concentration; C_{AH}, nonionized buffer concentration; t_{accel}, time at which acceleration occurs; R, derived swelling rate parameter. For all conditions, $T = 25$°C, $I = 0.1$ M, where the ionic strength I is set by addition of NaCl.

DISCUSSION

Swelling Equilibria

In previous work we observed that the equilibrium degree of swelling of polybasic gels is sensitive to the nature of the buffer system bathing the gel, as well as the degree of ionization of the gel network (3,26). At fixed pH and ionic strength, buffers containing multivalent anions (e.g., citrate,

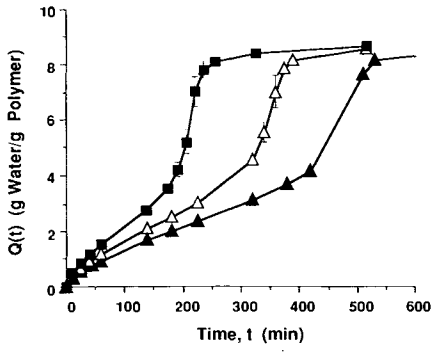

Fig. 1. Swelling kinetics for MMA/DMA gels at pH 3.0, ionic strength 0.10 M, in solutions with total buffer concentrations $C_{A,T} = 0.02$ M. (■) HAc buffer; (△) MeOHAc buffer; (▲) ClHAc buffer.

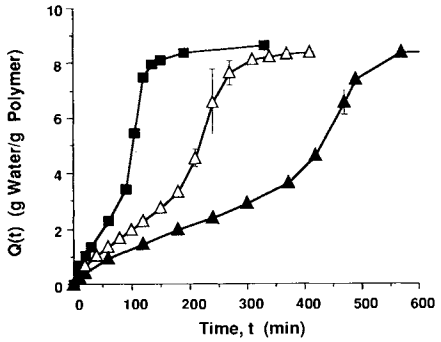

Fig. 2. Swelling kinetics for MMA/DMA gels at pH 3.5, ionic strength 0.10 M, in HAc buffered solutions. (■) $C_{A,T} = 0.05\ M$; (△) $C_{A,T} = 0.02\ M$; (▲) $C_{A,T} = 0.01\ M$.

phosphate) lead to lesser degrees of swelling than solutions containing only monovalent species (3,4,26). This is in accord with the Donnan equilibrium theory of swelling (3,25,26,29). Although the present experiments were not carried out to final equilibrium, it is noteworthy that all of the swelling curves enter a final plateau at a swelling ratio of approximately 8.0–8.5. We expect that the equilibrium swelling values for all conditions studied here will be similar, because (i) at the pH values studied, we can assume that virtually all the DMA units will be ionized, (ii) ionic strength is the same in all cases, and (iii) all anionic species in the solutions are monovalent. Thus there should be no buffer or pH sensitivity in the swelling equilibria under these conditions. Evidently, buffer effects on swelling kinetics need not be related to buffer effects on swelling equilibria.

Swelling Kinetics

The curves in Figs. 1–3 all have sigmoidal morphologies, characterized by an initial "slow" phase, followed by an accelerated phase, and then a second slow phase. This morphology has been attributed previously to a moving front swelling mechanism (4,5,27). The gels are glassy in their initial dry state, and during the early stages of swelling the gel consists of a central dry glassy core surrounded by a hydrated, rubbery periphery. The core imposes a swelling constraint on the gel, such that expansion can occur only in the direction normal to the swelling front. For a gel with slab geometry, with both faces exposed to the swelling medium, there will be two moving fronts, one corresponding to each face. When these fronts meet, the core disappears and the swelling constraint vanishes. Swelling can now occur in all three dimensions. This explains the accelerated phase of the swelling curves. The terminal slow phase is probably due to final mechanical and chemical (ion exchange) relaxations.

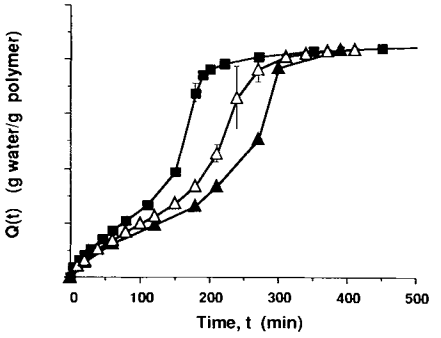

Fig. 3. Swelling kinetics for MMA/DMA gels in HAc buffered solutions with $C_{A,T} = 0.02\ M$ and ionic strength 0.10 M. (■) pH 2.5; (△) pH 3.5; (▲) pH 4.0.

The shape of the swelling curves enables a simple semiquantitative test of the hypothesis that the swelling rate is determined by C_{AH}. As noted above, the accelerated phase occurs after the two moving fronts meet at the midplane of the slab. The time t_{accel} at which acceleration occurs, therefore, marks the meeting of the fronts. We define, therefore, a rate parameter

$$R = 10^5/t_{accel}$$

with the expectation that R should correlate positively with C_{AH}.

In order to evaluate t_{accel} and hence R, we adopt the following procedure. For each swelling kinetics curve, lines are drawn to fit the later part of the initial slow phase and the early part of the accelerated phase. The time corresponding to the point where the two lines meet is taken to be t_{accel}, and R is computed as above. Values of t_{accel} and R obtained in this manner are listed for each condition in Table I.

Figure 4 plots values of R versus C_{AH} for all the conditions listed in Table I. A clear trend is indicated, with increasing C_{AH} leading to increasing R. For these data, Spearman's rank order correlation coefficient is 0.952 ($P < 0.001$). Thus we can state with great certainty that the nonionized buffer concentration is a major determinant of swelling rate. It should be noted that the values of R listed in Table I and plotted in Fig. 4 are derived from a procedure that involves subjective judgments as to the precise location of the lines which are drawn to determine the acceleration point. Hence the R values are open to a degree of uncertainty. Nevertheless, the strong rank-order correlation is unlikely to be altered by the specific R values that would be determined by different judges.

The three filled symbols in Fig. 4 correspond to the three buffers at total concentration $C_{AT} = 0.02\ M$, with pH allowed to vary in each case. The open symbols correspond to data taken at higher concentrations. It is apparent that the effect of pH on swelling rate is determined primarily by the

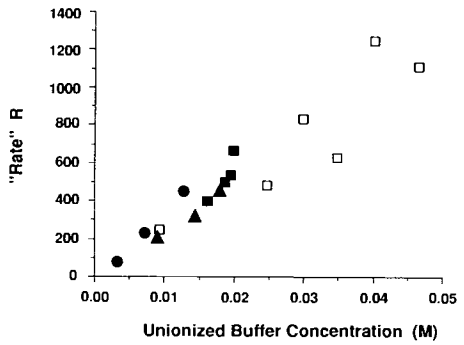

Fig. 4. "Rate" parameter $R = 10^5/t_{accel}$ versus nonionized buffer concentration C_{AH} for all conditions studied (see Table I). (■) HAc, $C_{A,T} = 0.02\ M$ at various pH's; (▲) MeOHAc, $C_{A,T} = 0.02\ M$ at various pH's; (●) ClHAc, $C_{A,T} = 0.02\ M$ at various pH's; (□) results for the three buffers at higher values of $C_{A,T}$.

pH effect on C_{AH}, and less so by a direct pH effect on the gel. Clearly in buffered systems, one should not speak of pH-dependent gel swelling without also specifying the buffer species and concentration. This point is obvious from Figs. 1 and 2.

A rather simple explanation can be provided for the observed buffer-dependent enhancement of swelling rates. Only two conditions are required: (i) the pK_a of the buffer should be below the pK_a of the gel amine groups, and (ii) delivery of protons to the fixed ionizable amines should be a rate-limiting step in gel swelling. If the first assumption holds, then protons will "prefer" gel amine groups to the buffer's conjugate base, and acid–base proton transfer from protonated buffer molecules to free amine groups will occur when the former come into the vicinity of the latter. Thus the buffer provides an alternative source of protons for binding to the amines, in addition to the hydronium ions in the aqueous solution. As hydronium ions are generally at a low concentration (e.g., 10^{-3} M at pH 3), the addition of millimolar quantities of buffer in its acidic form should increase the rate by which gel ionization and (by the second condition) gel expansion occurs.

The two conditions of the previous paragraph are present in the gel/buffer system studied here. The pK_a of the DMA amine is approximately 7.7 (30), while the pK_a's of all buffers studied are well below 5. Ionization of the amine groups is likely to be a slow step in the absence of buffer, in that the ionizable amine concentrations are of the order 0.2 M,[4] compared to the typical free H_3O^+ concentrations (10^{-4}–$10^{-2.5}$ M) (27).

Besides simply augmenting the number of available protons, buffers can also facilitate swelling by circumventing Donnan exclusion. When ionized, the MMA/DMA gel acquires a net positive charge. Since the fixed charge density in the gel (>0.2 M) can be considerably higher than the ionic strength of the medium (0.1 M), a significant Donnan potential may inhibit the entry of hydronium ions into the gel (21,27,31), thus retarding further ionization of the gel by the protons carried by the H_3O^+. Neutral buffer acids will not be inhibited by such a Donnan potential, however, and they will be free to enter the gel and transport protons to the free amines.

In a previous study it was shown that acetate and citrate buffers can enhance swelling rates in MMA/DMA gels by orders of magnitude, compared with unbuffered mineral acids (27). A hypothesis that the organic buffers plasticize the polymer was rejected since the addition of organic analogues of acetic acid (methyl acetate and acetamide) to mineral acid solutions did not accelerate swelling. In view of the present experiments, in which acetate is one of the buffers under study, the results for acetate are well understood in terms of the simple mechanism just described. The mechanism can also explain the results for citrate buffered solutions. At the pH's where measurements were made, citrate is primarily in its mono- and divalent state in the external solution. In either case, this triprotic buffer is still capable of being a proton donor to the gel amines. Also, in the case of citrate, the Donnan effect may further accelerate the process, because partitioning of the negatively charged citrate ions into the positively charged gel is favored.

Also in the previous study (27), it was shown that a decrease in pH does cause the swelling rate to increase in unbuffered systems, although the rate is much slower than in suitably buffered systems at the same pH value. Since this holds even when the solution pH is well below the gel amine pK_a, the swelling rate increase with decreasing pH must be attributed to increased proton concentration, which permits faster proton transfer from the outer solution to the gel amine groups.

Finally, it should be noticed that the ability to control the swelling rate by altering the strong and weak electrolyte content of the outer solution indicates that models for the swelling of nonionic polymers, which typically consider solvent diffusion and polymer relaxation as the rate-determining factor, are insufficient to explain swelling of polyelectrolyte gels. A proper model must include the effects of mass transfer of protons and other solution species on the ionization rate of the gel.

Relation to Other Buffer-Enhanced Kinetic Processes

Buffers are known to play a rate-enhancing role in a number of processes. Perhaps the best-known example is general acid–base catalysis, which can occur in free solution (28,32). Buffers can also be used to speed up the titration of protein crystals (33) and can enhance the effectiveness of immobilized enzymes (34,35). Recently, analyses have appeared of the effect of basic buffers on the dissolution rates of acidic drugs (36–38) and of polyacids used as bioerodible matrices for controlled drug release (39). Dissolution systems are somewhat simpler to consider than the gels studied here, since all the interesting processes occur in a thin boundary layer near the surface whose thickness does not change at steady state. The explanation for buffer enhancement of dissolution can be summarized as follows. In solution, the drug will exist in both the nonionized and the ionized forms, each of which contributes to the dissolution flux. At the solid/liquid interface where dissolution occurs, the nonionized drug concentration is very close to solubility. The concentration of ionized (anionic) drug at the interface (and hence the total dissolution flux) will increase with increasing local pH, as described by the Henderson–Hasselbach equation. On the other hand, the dissociation of the acidic drug will tend to lower the pH near the surface. The latter effect can be mitigated by introducing a proton-

[4] To estimate the amine concentration in the swollen gel, we note that in the dry state, the polymer mass is given by two equal quantities: $X_{MMA}MW_{MMA} + X_{DMA}MW_{DMA} = 1000\rho_p V$, where X_i and MW_i are, respectively, the number of monomoles and the molecular weight of the ith monomer (i = MMA, DMA) in the dry gel, and ρ_p and V are the density and volume of the dry gel, respectively. For the 70/30 MMA/DMA gel, $X_{MMA} = (7/3)X_{DMA}$. Therefore, in the dry state the amine concentration is given by $(X_{DMA}/V)_{dry} = 1000\rho_p/[MW_{MMA} + (7/3)MW_{DMA}]$. The polymer volume fraction in the wet gel is given by $1/(1 + \rho_p Q)$, where Q is the degree of swelling. Hence the amine concentration in the swollen state is $(X_{MMA}/V)_{wet} = 1000\rho_p/\{(1 + \rho_p Q)[MW_{MMA} + (7/3)MW_{DMA}]\}$. For the present system, ρ_p = 1.1 g/ml, MW_{MMA} = 100.1, and MW_{DMA} = 185.28. Thus when Q = 8 (nearly maximum swelling), the computed amine concentration is 0.24 M. Before the accelerated phase of swelling, amine concentrations are even higher.

accepting (basic) buffer species. The basic buffer must be provided continuously to the surface, and the newly protonated buffer removed. At steady state the latter processes occur at equal rates. Based on this mechanism, it follows that dissolution should be accelerated with increasing pK_a and/or concentration of the buffer, as well as increased efficiency of mass transfer in the boundary layer adjacent to the interface. This is indeed predicted theoretically and has been demonstrated experimentally (36–39). The buffer enhancement of dissolution flux will be most efficient when the buffer pK_a is well above the pK_a of the acidic drug, since protons will effectively transfer from the drug to the buffer.

Consider now the dissolution of a basic drug or polybasic polymer. Here one would use *acidic* buffers to enhance the delivery of protons to the solid/liquid interface. The number of protons that can be delivered in this manner will increase with increased buffer pK_a and with increased buffer concentration. Efficient proton transfer from the buffer acid to the basic drug (or polymer) will require, however, that the pK_a of the latter exceed that of the former.

The acidic buffer-induced acceleration of swelling rates seen in polybasic gels in the present study is analogous to the dissolution rate enhancement of basic drugs by acidic buffers predicted in the previous paragraph. While the precise mechanistic details may differ (e.g., the diffusional path length increases with time for the gel, but not the dissolving system), the same basic principle is shared. In both cases, the acidic buffer acts as an added proton source to a basic moiety.

A second important effect, absent in dissolution systems but possibly present in polyelectrolyte gels, needs to be considered in light of recent theories of proton diffusion in charged physiological systems, such as muscle. It has been argued that, in the absence of buffers, proton transport in such physiological systems would be unacceptably slow, due to the high concentration of immobile ionizable groups compared to physiologic proton concentrations. The ionizable groups would function as traps for the protons, thus reducing the protons' mobility (20,22). To explain the transport rates that are consistent with physiologic function, some authors have proposed a mechanism by which a large fraction of the protons are carried by mobile buffers in the physiologic media (40,41). The effectiveness of a buffer in facilitating proton transport increases if the buffer pK_a is greater than the pK_a of a fixed ionizable groups, and if the ratio of buffer ion to fixed ionizable group concentration increases, since this leads to a higher fraction of protons carried by the buffer. It is noteworthy that in this circumstance, one is using the higher pK_a of the buffer in order to transport the proton *past* the ionizable group. In the present study, we depend on a buffer pK_a that is *lower* than the amine pK_a in order to ensure that the proton is transferred from the buffer to the amine.

Implications for Controlled Release

The finding that buffer concentration and pK_a strongly affect swelling rates has broad implications for controlled release. If release of an incorporated solute from a polybasic gel is controlled by the rate of swelling, as can occur with MMA/DMA gels (5), then the release rate will be influenced by the buffer composition of the physiological environment, as well as the pH. Thus, *in vitro* tests of release properties should be carried out in buffer systems that resemble the intended *in vivo* environment. Moreover, in some cases the latter cannot be controlled. For example, if a polybasic gel is given orally, it will swell in the acid environment of the stomach. The stomach fluid will also contain weak acids whose composition will vary according to food intake, as well as other physiologic factors. Therefore, one probably cannot expect precise pH-sensitive rate control of drug release into the stomach from polybasic gels, and this may limit their utility as rate-controlling carriers. It should be noted, however, that precision of release rate is not always required and if, for example, one is concerned only with *pH-triggered* release, then polybasic gels might still be useful drug carriers for oral delivery.

CONCLUSION

In previous work it was shown that weak acid buffers can play a rate enhancing role in the swelling of polybasic gels. It was conjectured that such buffers act as proton carriers from the outer solution to the amines within the gel. The present work confirms this hypothesis and, also, shows that pH-sensitive swelling can be mediated primarily by the effect of pH on the concentration of the conjugate acid form of the buffer, rather than a direct effect of pH on the gel. The importance of this result with respect to "pH-sensitive" controlled release is evident.

ACKNOWLEDGMENTS

This work was supported in part by NIH Grants DK38035 (R.A.S.) and HL38475 (C.A.H.), by a grant from the Whitaker Foundation, and by a training grant from the California Biotechnology Research and Education Program. Some of the results were initially presented at the 16th International Symposium on Controlled Release of Bioactive Materials, in Chicago, 1989.

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