Colon-Specific Oral Delivery of Vitamin B_2 from Poly(acrylamide-*co*-maleic acid) Hydrogels: An *In Vitro* Study

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ABSTRACT: Hydrogels, composed of poly(acrylamide-*co*-maleic acid) were synthesized and the release of vitamin B_2 from these gels was studied as a function of the pH of the external media, the initial amount of the drug loaded, and the crosslinking ratio in the polymer matrix. The gels containing 3.8 mg of the drug per gram gel exhibit almost zero-order release behavior in the external media of pH 7.4 over the time interval of more than their half-life period ($t_{1/2}$). The amount of the drug loaded into the hydrogel also affected the dynamic release of the encapsulated drug. As expected, the gels showed a complete swelling-dependent mechanism, which was further supported by the similar morphology of the swelling and release profiles of the drug-loaded sample. The hydrophilic nature of the drug riboflavin does not contribute toward the zero-order release dynamics of the hydrogel system. On the other hand, the swelling osmotic pressure developed between the gels and the external phase, due to loading of the drug by equilibration of the gels in the alkaline drug solution, plays an effective role in governing the swelling and release profiles. Finally, the minimum release of the drug in the swelling media of pH 2.0 and the maximum release with zero-order kinetics in the medium of pH 7.4 suggest that the proposed drug-delivery devices have a significant potential to be used as an oral drug-delivery system for colon-specific delivery along the gastrointestinal (GI) tract. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 84: 1133–1145, 2002; DOI 10.1002/app.10402

Key words: vitamin B_2; gastrointestinal tract; drug-delivery systems; zero-order release; pH-sensitive hydrogels

INTRODUCTION

Hydrogel materials are unique with respect to their ability to release an encapsulated drug in an aqueous medium. Since these materials are capable of absorbing water with a simultaneous release of an encapsulated drug, the release rate of the drug is modified by the rate and extent of hydration of the drug/polymer device, which ultimately is affected by the nature and concentration of the drug in the polymer matrix. However, the chemical nature of the monomer units in the hydrogel system and nature of the drug also plays major roles in influencing the release behavior of the device.

In our previous work,[1–5] we synthesized and studied the swelling behavior of a number of pH-sensitive polymeric hydrogels and found that these gels showed excellent pH-dependent swelling behavior, thus exhibiting minimum swelling at pH 2.0 and maximum swelling in the range 7–8 of the external media. Such polymeric sys-

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tems, in fact, may have potential to be used as colon-specific oral drug-delivery devices along the gastrointestinal (GI) tract because they will keep the encapsulated drug almost protected from the highly acidic environment of the stomach by exhibiting minimum swelling while they release a maximum amount of the drug at the colon (where pH is 7.4) and, hence, may be employed for the treatment of colonic diseases like colon cancer and inflammatory bowel disorder (IBD).

The major goal of the present work was to achieve a delivery profile that would yield a high blood level of the drug over a desired period of time. With traditional tablets or injections, the drug level in the blood rises to the maximum value after each administration of the drug and then decreases to a minimum until the next administration. However, in controlled drug-delivery systems, the drug level in the blood remains constant, between the desired maximum and minimum, for an extended period of time, thus providing a constant therapeutic level at the receptor site.

In this study, we employed poly(acrylamide-*co*-maleic acid) hydrogels that can be easily synthesized at a moderate temperature without using any organic solvent, thus offering a minimum loss of drug activity in case the drug to be incorporated is mixed into the reaction system at the time of gel synthesis. However, in the present study, the drug riboflavin was incorporated by allowing the gels to swell in the aqueous solution of the drug, as this is the safest method for drug loading.[6]

The model drug riboflavin, a dimethyl iso-alloxazine attached to *d*-ribitol, is a part of riboflavin nucleotides which take part in enzymatic reactions.[7] Infants with hemolytic hyperbilirubinemia subjected to phototherapy are likely to be riboflavin-deficient.[8] The red blood cell is one of the active sites for the conversion of pyridoxal phosphate through the action of riboflavin. In riboflavin deficiency, this conversion is low.[9]

EXPERIMENTAL

Materials

The monomers acrylamide (AAm; Sigma, St. Louis, MO) and maleic acid (MA; BDH, Poole, UK), the crosslinker *N,N′*-methylene bisacrylamide (MB; Sigma), and the initiator potassium persulfate (KPS; Merck, Mumbai, India) were of analytical grade and used as received. However, the monomer AAm was recrystallized in methanol to remove the inhibitor. The drug riboflavin (Sigma) was used as a crystalline powder: purity 99.7% and molecular mass 376.36.

Synthesis of Cylindrical Gels

The method of synthesis of poly(acrylamide-*co*-maleic acid) hydrogels was described previously.[3] However, in brief, 4.50 g of the monomer AAm and 0.10 g of MA were dissolved in water to give a clear solution. To this, 0.15 g of the crosslinker MB and 0.10 g of the initiator KPS were added and the resulting solution, after being made up to 30 mL, was poured into PVC straws, each of 5.30-mm diameter, and kept in an electric oven (Tempstar, India) for a period of 4 h at 60°C. After the polymerization was over, the resulting transparent cylindrical gels were taken out of the straws, cut into small pieces, each 2.54 ± 0.02 cm in length, and then washed with distilled water to remove unreacted salts and, finally, dried in a vacuum chamber at 40°C for a period of 24 h. The length, diameter, and mass of the dry samples were found to be 16.0 ± 0.4 mm, 3.0 ± 0.02 mm, and 0.1220 ± 0.01 g, respectively . However, the variation of the mass of the samples did not affect the accuracy of the results because the calculations were made for 1 g of the hydrogel.

The blank and the drug-loaded samples will be denoted by HG (1.3) and HG $(1.3)_x$, where x is the amount of riboflavin present in 1 g of the polymer and the number in parentheses denotes the percent mol fraction of the monomer MA in the hydrogel.

Swelling Studies

To study the swelling behavior of hydrogels, three samples of known mass and dimension were completely dried, then each placed in a 250-mL solution of the swelling medium of the desired pH with the ionic strength 0.1*M* at a constant temperature 37°C. The swollen gels were taken out at regular time intervals, wiped superficially with filter paper, weighed accurately, and then placed in the same bath. The mass measurements were continued until the attainment of the constant mass for each sample. The percentage of mass swelling ($\% S_m$) was obtained using the following expression:

$$\%s_m = \frac{(m_t - m_0)}{m_0} \times 100$$

where m_0 and m_t are the initial mass and mass at different time intervals, respectively.

Loading of Drug into the Hydrogels

To load the riboflavin into the cylindrical dry samples, an aqueous alkaline solution was prepared by dissolving NaOH in distilled water to give a 3.5×10^{-4} molar solution with pH 9.78 ± 0.02 at 30°C. To this solution, varying amounts of riboflavin (100, 135, and 200 mg per 250-mL solution) were dissolved and 10 preweighed samples were placed in each solution for a period of 24 h to attain equilibrium. The solubility of the drug in the alkaline solution was found to be 0.889 g per liter at 30°C. After the attainment of equilibrium, the gels were taken out, washed with distilled water to remove the loosely bound drug on the surface, and then allowed to dry at 40°C in a vacuum chamber for a period of 96 h, which was found to be sufficient time for the complete drying of the drug-loaded gels. Here, it is worth mentioning that, during the whole loading process, surfaces of all the glassware used were coated with black paint so as to prevent the solution of riboflavin from being exposed to visible light.

In Vitro Drug-release Study

To obtain information about the possible mode of action of the proposed drug-delivery system in the human body, it is often more convenient to perform the same studies in an environment almost similar to that in the body.[10] Hence, for the purpose of carrying out the drug-release study in an *in vitro* manner, a series of buffer solutions of pH 2.0, 4.0, and 7.4 were prepared; the buffer concentration was fixed at 0.01*M* and the total ionic strength was adjusted to 0.1*M* by adding a precalculated quantity of NaCl. For the solutions of pH 2.0 and 4.0, a citrate buffer was used; for pH 7.4, a phosphate buffer was used. To study the drug-release kinetics, three preweighed samples of the drug-loaded device were each placed in 25 mL of the buffer solution of the desired pH at the physiological temperature of 37°C. The amount of the drug released at different time intervals was determined spectrophotometrically (Systronics, India) at 437 nm.[11] After each time interval, the gels were placed in fresh buffer solutions. The concentrations of the drug released was computed by comparing the absorbancy with the standard curve prepared for the pure drug in the buffer in the appropriate concentration region. Here, a significant point to be mentioned is that all the release experiments were carried out using glassware with completely blackened surfaces so that the exposure of the drug-loaded devices and the release media to visible light was minimized.

To determine the total amount of the drug loaded into the sample, the sample was ground into a fine powder and a known quantity of it was placed in a definite volume of water at 37°C for a period of 24 h. Then, the solution was filtered and its absorbance was measured, which finally gave the initial amount of drug loaded into the hydrogels.

Stability Test for Riboflavin

To test the stability of riboflavin, solutions of known concentrations were prepared in the buffer solutions of pH 2.0, 4.0, and 7.4 at 30°C. The absorbance of these solutions was measured at the time interval of 24 h for a period of 7 days. Here, it is to be regretted that, because of unavailability of the instruments, stability could not be tested by reverse-phase HPLC, which is comparatively a more accurate and sensitive method to test the stability of drugs.[12]

RESULTS AND DISCUSSION

In our previous communication,[3] we described a detailed study of the swelling behavior of poly(acrylamide-*co*-maleic acid) hydrogels. However, in a preliminary study for the present work, a number of hydrogels with different amounts of the monomers AAm and MA and the crosslinker MB were synthesized and their equilibrium swelling was determined in the swelling media of pH 2.0 and 7.4 so as to obtain the maximum difference between the percent mass equilibrium swelling at pH 2.0 and 7.4. The purpose of carrying out the preliminary study was to obtain a hydrogel system which would swell minimally at pH 2.0 of the external media, thus releasing a minimum amount of the encapsulated drug and releasing the maximum drug in the swelling media of pH 7.4 by exhibiting maximum swelling. Finally, the percent mass equilibrium swelling for the hydrogels synthesized was found to be 1116.3 ± 18.6 and 618.5 ± 12.4 in the swelling media of pH 7.4 and 2.0, respectively.

In this study, we examined the release dynamics of only dried drug-loaded samples, because starting off with the drug dispersed in a dehydrated hydrogel offers several advantages over the hydrated system. When dried, the drug substance is essentially immobile, trapped in the matrix, and contact with the penetrating water is necessary to unlock the immobilized solute and trigger the release process.[13]

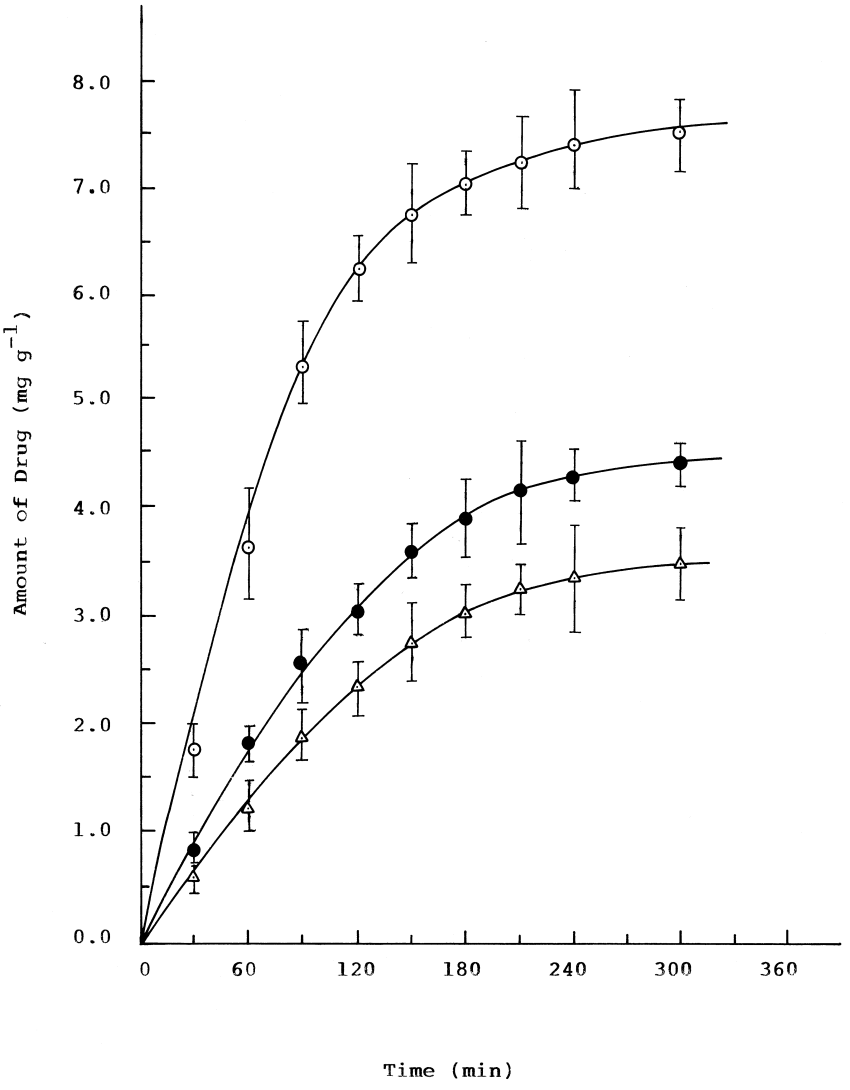

Figure 1 Riboflavin released from HG (1.3) hydrogels as a function of time for different loaded amounts of riboflavin: (○) 7.8 mg, (●) 4.6 mg, and (△) 3.8 mg per gram of gels in pH 7.4 at 37°C. Error bars represent standard deviations for three experiments.

Stability of Riboflavin

The stability of the riboflavin solution of at a definite concentration (2 mg per liter) was tested at pH 2.0, 4.0, and 7.4. The absorbance of these solutions at the λ_{max} (i.e., 437 nm) was monitored at 24-h time intervals for a total period of 7 days. The results thus obtained suggest that riboflavin is more stable in the acidic pH as compared to the alkaline one. The percentage of the drug decomposed in pH 2.0, 4.0, and 7.0 was found to be 0.48, 0.49, and 1.20, respectively. Since the gels were loaded by equilibrating in the solution of riboflavin for a period of 24 h, and the total transit time for a formulation to pass through whole GI tract[14] is only 48 h, the stability of riboflavin is not much affected during this duration and, hence, it is quite safe to load the drug into the gels.

Effect of Drug Loading

Figure 1 describes the amount of riboflavin released from HG $(1.3)_x$ gels as a function of time for different amounts of the loaded riboflavin (3.8, 4.6, and 7.8 mg g^{-1} gel. The results, thus obtained, show good agreement with the literature[11]: The amount released depends upon the initial amount of the drug present in the polymer matrix. Thus, the amount of riboflavin released is in the following order:

$$HG(1.3)_{7.8} > HG(1.3)_{4.6} > HG(1.3)_{3.8}$$

where each subscript denotes the initial amount of the drug present in 1 g of the hydrogel. The total percentage of the drug released for the initial load of 3.8, 4.6, and 7.8 mg of the drug per gram of the gel was found to be 92.1 ± 2.4, 95.2 ± 3.1, and 97.1 ± 1.6, respectively. Here, a significant point to be noted is that when the sample with 10.2 mg of drug g^{-1} gel was put in the phosphate buffer for the release study the sample was found to break into a number of pieces within 1 h of the start of swelling. This suggests that the amount of the drug loaded should be less than 10.2 mg g^{-1} gel for the proposed polymer matrix. The breaking up of the drug-loaded sample into small pieces may be attributed to that the greater hydrophilicity of riboflavin tends to promote solvent entrance into the gel matrix with simultaneous swelling of the gel, while the crosslinked structure of the gel inside the bulk opposes this extensive swelling. This finally results in breaking up of the polymer matrix into small pieces. The initial release rates for the samples HG $(1.3)_{3.8}$, HG $(1.3)_{4.6}$, and HG $(1.3)_{7.8}$ were determined for the release of the drug for the first hour. For this, the incremental concentration difference at 10-min intervals was used over a total duration of 60 min. This method is supposed to be more sensitive and accurate and less subjective in detecting subtle changes in the release profile.[12] Finally, the initial rates, as determined for the first hour of release, were found to be $(1.34 \pm 0.03) \times 10^{-2}$, $(3.07 \pm 0.06) \times 10^{-2}$, and $(6.62 \pm 0.04) \times 10^{-2}$ mg g^{-1} polymer min^{-1} for the initial load of 3.8, 4.6, and 7.8 mg per gram gel, respectively.

pH Effect

As mentioned earlier, prediction for the possible use of the proposed hydrogel system for colon-specific oral drug delivery is based on that the sample must release the maximum amount of the drug in the swelling medium of pH 7.4. For this, the release behavior of the hydrogel HG $(1.3)_{3.8}$ was studied in buffer solutions of pH 2.0, 4.0, and 7.4, at the physiological temperature of 37°C. The results are depicted in Figure 2, which clearly indicates that the drug-loaded sample releases a maximum amount of riboflavin in the medium of pH 7.4, whereas a minimum amount of the drug is found to release at pH 2.0. The percentage of the total drug released from the device HG $(1.3)_{3.8}$ in the release media of pH 2.0, 4.0, and 7.4 was found to be 48.6 ± 3.6, 61.2 ± 4.5, and 97.1 ± 1.6, respectively. The $t_{½}$ values (time required for the release of 50% of the total drug loaded) for the sample in the external solutions of pH 4.0 and 7.4 were found to be 243 and 96 min, respectively. For pH 2.0, the total release was less than 50%. Moreover, the release rate was also evaluated at different time intervals from the above profiles, and gradients of the curves were plotted between the release rate and corresponding time intervals for the release of riboflavin in the three solutions of different pH (see Fig. 3).

It is very clear from Figure 3 that the drug-loaded sample HG $(1.3)_{3.8}$ shows almost zero-order release in the medium of pH 7.4 over a time period of 105 min, which is more than its $t_{½}$ value. However, the release rate was not found to be uniform in the media of pH 2.0 and 4.0. Finally, the values of the diffusional exponent n, as calculated from the double logarithmic plot of equation $M_t/M^\infty = Kt^n$ for 60% release data were found to be 0.52, 0.58, and 1.0 in the swelling media of pH 2.0, 4.0, and 7.4, respectively. These values clearly suggest that the hydrogel, when put in the swelling media of pH 2.0, follows Fickian or diffusion–controlled release behavior, while in the medium of pH 4.0, the sample follows a diffusional mechanism with a small chain-relaxation contribution. However, the value of n (i.e., 1.0) in the swelling media of pH 7.4 provides the right relaxational characteristics for zero-order release behavior.

Qualitative evidence to support the above values of the diffusional exponent n is shown in Figure 4, the plot of the fractional release M_t/M^∞ of the drug from the sample HG $(1.3)_{3.8}$ versus the square root of time in the release medium of pH 2.0, 4.0, and 7.4. Figure 4 clearly indicates that the device exhibits almost Fickian or diffusion-controlled release behavior at pH 2.0, whereas an anomalous release with a full chain-relaxation contribution is observed in the phosphate buffer at pH 7.4.

The observed transition of the release behavior from Fickian to a zero-order release, with the change in pH of the swelling media from 2.0 to 7.4, may be explained on the basis of that, at pH 2.0 of the swelling media, the carboxylic groups present in the matrix due to MA are almost in an unionized state, thus imparting nonionic and hydrophobic character to the device, which finally results in Fickian release behavior of the polymer matrix. However, when the pH of the external solution becomes 7.4, these groups undergo almost complete ionization inside the polymer ma-

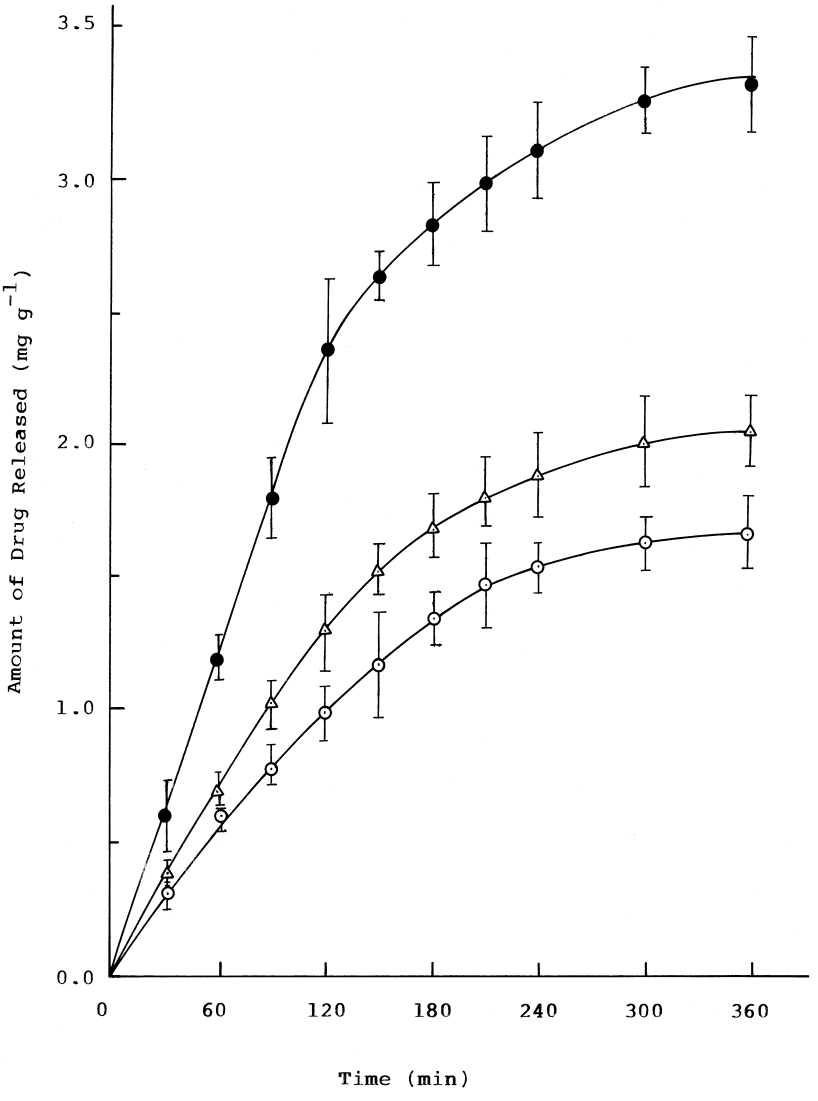

Figure 2 Riboflavin released from HG $(1.3)_{3.8}$ gels as a function of time with varying pH: (●) pH 7.4; (△) pH 4.0; (○) pH 2.0 at 37°C. Error bars represent standard deviations for three experiments.

trix and, hence, the gel exhibits polyelectrolyte-type behavior. Now, the swelling of the gel (and, hence, the drug release) is attributed not only to the swelling osmotic pressure between the interior and exterior of the gel, but also to the enhanced chain relaxation due to repulsion among the carboxylate groups along the macromolecular chains inside the gel matrix. Moreover, the hydrophilicity of riboflavin also contributes toward the zero-order release behavior of the hydrogel in the swelling media of pH 7.4.

One more significant factor which may also contribute toward the pH-dependent release behavior is the ionic nature of the riboflavin.[15] But, since the pK_a value of riboflavin is 10.2 and the release studies were carried out at pH 7.4, the possibilities of any type of electrostatic interaction between the molecules and the carboxylate groups along the macromolecular chains are almost nil. This argument is further supported by the work done by Lee and coworkers[11] who studied the release of riboflavin from amphiphilic urethane hydrogels and explained the observed increase in the amount released with the pH of the medium only on the basis of ionization of the carboxylic groups present along the macromolecular chains. However, since riboflavin is present inside the device as its sodium salt, due to loading being done by the equilibration of blank gels in its alkaline solution, there exist repulsive forces be-

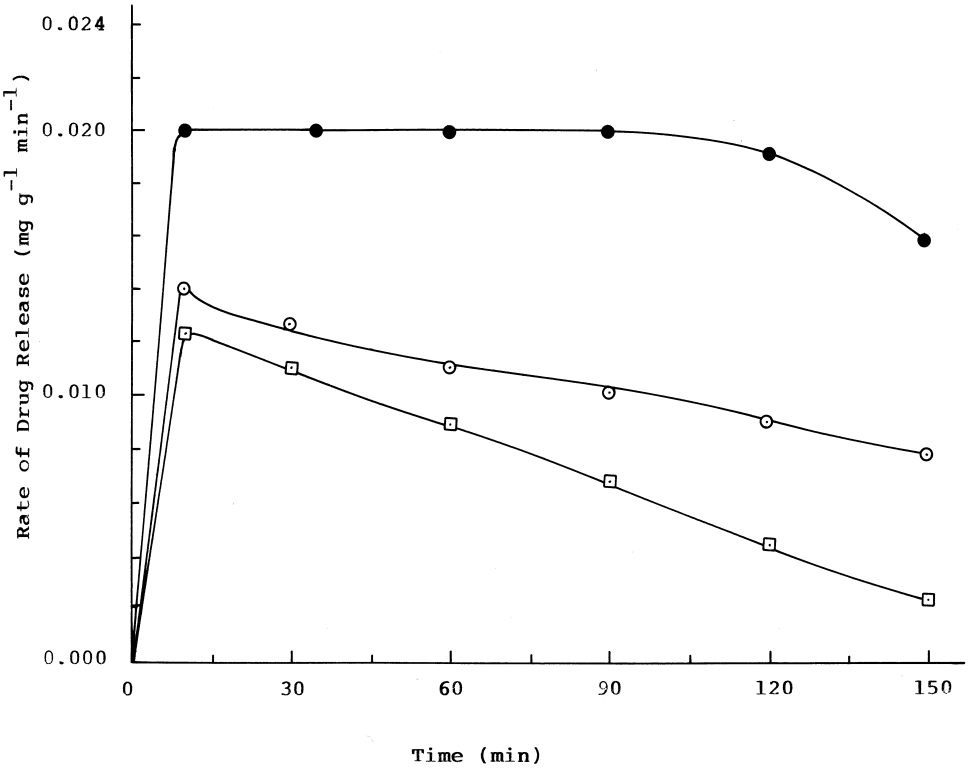

Figure 3 Release rates versus time profiles for the release of riboflavin from the sample HG $(1.3)_{3.8}$ in the media of varying pH: (●) pH 7.4, (○) pH 4.0, and pH 2.0 (□) at 37°C.

tween negatively charged molecules and carboxylate groups present along the macromolecular chains, thus encouraging the release of riboflavin from the gel phase at pH 7.4. Similar arguments were also given by Lee et al.[15] in the study of pH-dependent release of the ionic solute cefazolin from an IPN composed of poly(vinyl alcohol) and poly(acrylic acid). This may also be the reason for a high release level of riboflavin at pH 7.4.

Finally, the pH-dependent release behavior was also studied by placing the sample HG $(1.3)_{3.8}$ in the buffer solution of pH 2.0 for a period of 2 h and then transferring the same sample to the pH 7.4 medium to follow the rest of the release dynamics. This type of study gives a more realistic picture of the possible mode of action of a colon-targeted drug-delivery device. The results, as shown in Figure 5, clearly show that the curve obtained for the release of the drug at pH 7.4 is much steeper than that for pH 2.0, indicating that the release rate is much faster in the pH 7.4 medium. Moreover, the device releases only 26.3 ± 3.9% of the total drug at pH 2.0, while 68.4 ± 4.1% of the drug is released in the phosphate buffer at pH 7.4.

Crosslinking Effect

The degree of crosslinking in the polymer matrix not only influences its drug-releasing capacity but it also may cause a transition in its release mechanism, that is, from Fickian to non-Fickian and even sometimes zero order.[16] Figure 6 describes the release of riboflavin from the hydrogels as a function of the crosslinking ratio at 37°C in the phosphate buffer of pH 7.4. The crosslinking ratio may be given as mol MB/mol AAm in the polymer matrix. The release behavior was studied for the drug-loaded sample HG $(1.3)_{4.6}$ having different crosslinking ratios, that is, 0.009, 0.015, and 0.023, respectively.

It is very clear from Figure 6 that as the crosslinking ratio in the polymer matrix increases the amount of drug released from the device decreases. The observed result may be explained on the basis of that as the crosslinking ratio inside the gel matrix increases the relaxation of the polymer segments becomes restricted, thus discouraging solvent entrance and subsequent drug release from the device. Similar results were also reported elsewhere.[17] Finally, the percentage of

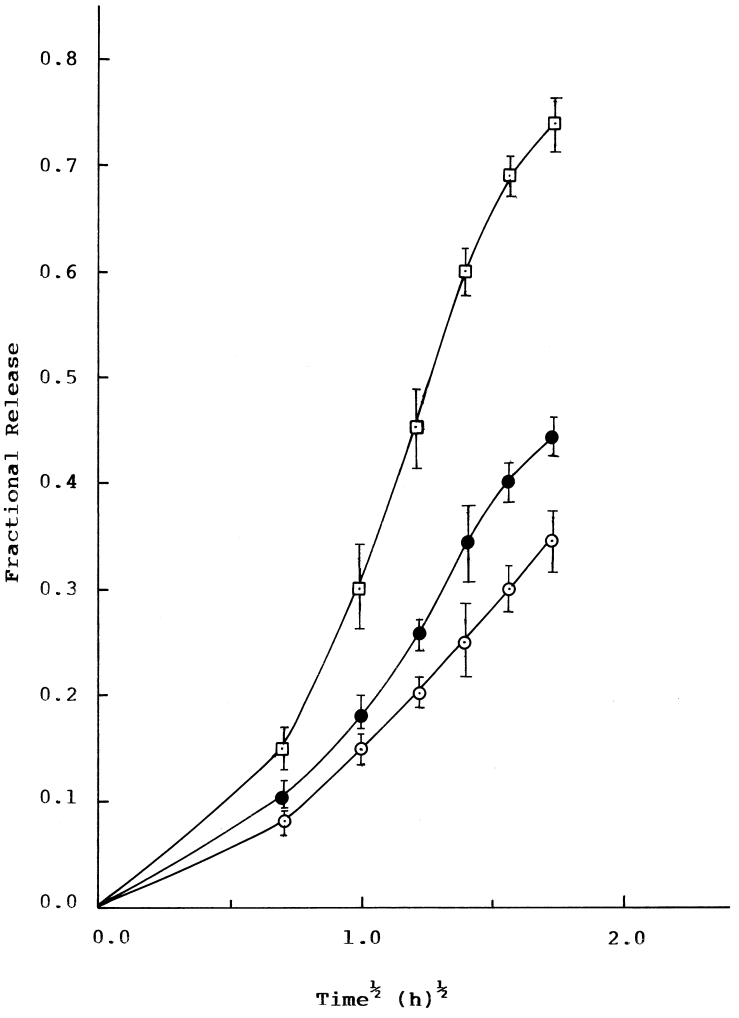

Figure 4 Fractional release of riboflavin from HG $(1.3)_{3.8}$ gels as a function of $(\text{time})^{1/2}$ with varying pH: (□) pH 7.4, (●) pH 4.0, and (○) pH 2.0 at 37°C. Error bars represent standard deviations for three experiments.

the total drug released from the device with crosslinking ratios of $2.3 \times 10^{-2,}$ 1.5×10^{-2}, and 0.9×10^{-2} was found to be 38.1 ± 5.6, 82.6 ± 6.8 and 93.4 ± 4.2, respectively. The values give the mean $\pm$ the SD for the three samples.

Comparison of Kinetics of Swelling and Drug Release

The rate of swelling of a hydrogel is usually affected by the presence of the active additive.[18] To confirm this in the present case, the swelling profile of the drug-loaded hydrogel HG $(1.3)_{3.8}$ was compared with that of the blank sample in the swelling media of pH 7.4 (see Fig. 7). It is very clear from the figure that the presence of riboflavin in the polymer matrix causes an appreciable increase in the water uptake of the hydrogel as compared to the unloaded gel sample. This may be attributed to the greater hydrophilicity of the riboflavin present, as well as the increased swelling osmotic pressure between the gel and the solution phase. To estimate the extent of the contribution of the hydrophilicity of the drug toward extensive water uptake, we also synthesized drug-loaded gels (amount of drug 3.8 mg per gram gel) by dispersing the calculated amount of the drug into the reaction mixture (we will call them HG_{disp}) and compared their swelling dynamics with those of experimental gels, which were prepared by equilibrating the blank samples in the alkaline drug solution (designated as HG_{equil}). It was found that the gels HG_{disp} showed almost the same swelling capacity as that shown by the blank gels. This contradicts our presumption that the extensive water uptake of experimental drug-

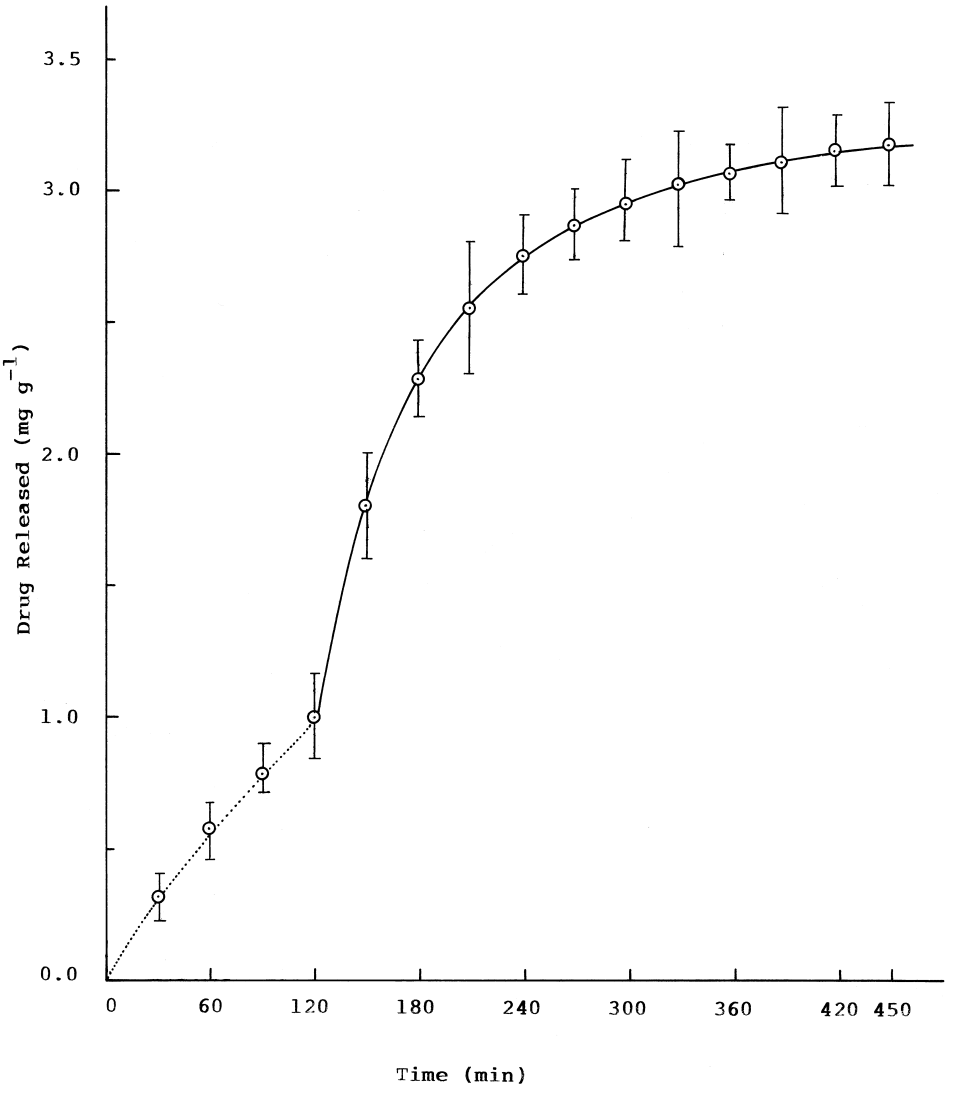

Figure 5 Release of riboflavin from the sample HG $(1.3)_{3.8}$ as a function of time; release (· · ·) for first 2 h in pH 2.0 and (—) for next 22 h in pH 7.4 at 37°C. Error bars represent standard deviations for three experiments.

loaded gels is due to the presence of a hydrophilic drug. Therefore, higher water uptake of these (HG_{equil}) gels may be attributed to that loading of the drug, by equilibrating the blank gels in an alkaline drug solution, causes an appreciable increase in the number of counterions inside the gel phase.

The reason for the existence of a higher concentration of mobile ions inside the gel phase is due to that, because the equilibration of the blank gels was done in an alkaline solution, the riboflavin is incorporated into the gels in the form of sodium salt. This produces a higher concentration of Na^+ ions and negatively charged drug molecules inside the swelling drug-loaded device. Hence, when these gels, after drying, are placed in the release media of pH 7.4, the great swelling osmotic pressure between the gel phase and the external solution causes extensive swelling of the drug-loaded device. To confirm this reasoning, we equilibrated these (i.e., HG_{equil}) drug-loaded gels in different molar solutions of NaCl having ionic strengths of 0.1, 0.2, 0.3, and 0.4*M*. It was found that the percent equilibrium swelling of the drug-loaded device decreased with increase in the ionic strength. This confirms our argument that this device contains a higher concentration of counterions which ultimately play a significant role in deciding the extent of swelling. However, it should clearly be understood that this does not

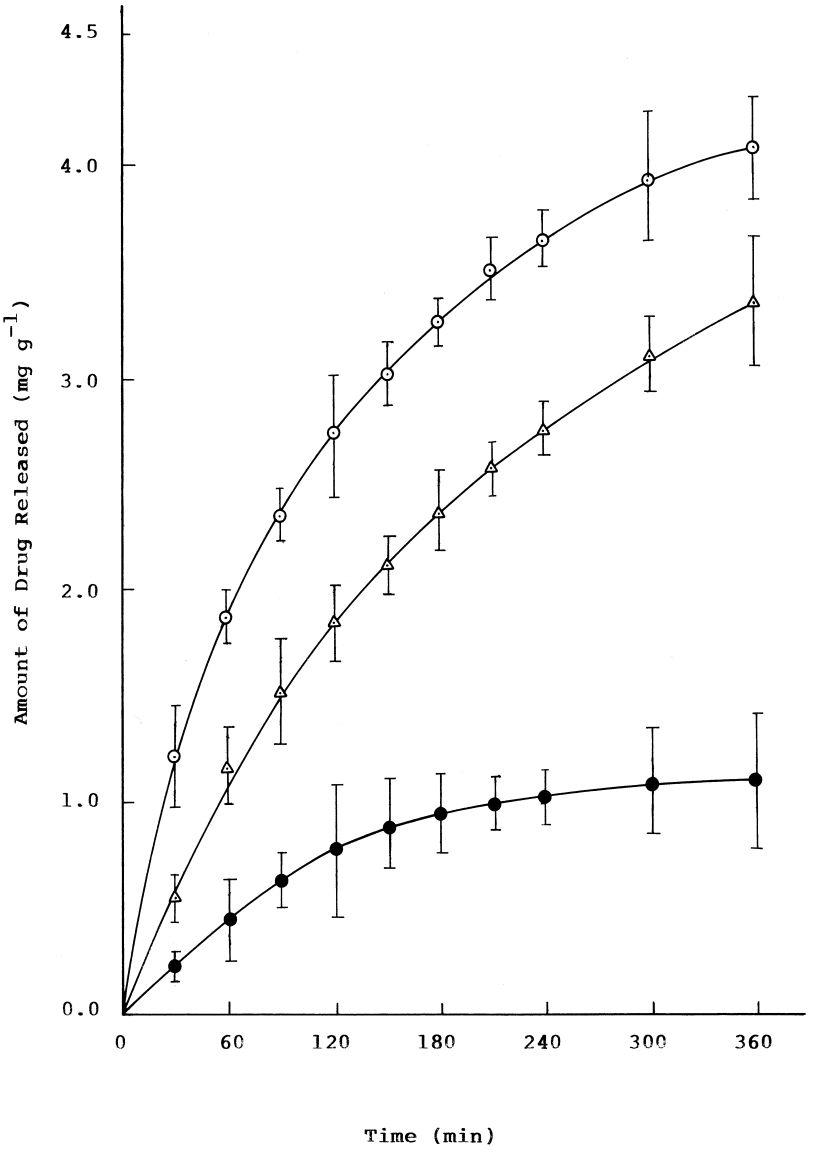

Figure 6 Riboflavin released from HG $(1.3)_{4.6}$ gels as a function of time with varying crosslinking ratios: (△) 0.009, (●) 0.015, and (●) 0.023 in pH 7.4 at 37°C. Error bars represent standard deviations for three experiments.

indicate that the nature of the polymer (i.e., its polyelectrolyte-type nature due to the presence of the carboxylic groups of MA) does not play a key role in governing the release behavior: If this were true, then even at pH 2.0, the drug-loaded sample should have demonstrated an appreciable swelling capacity. However, this was not found to be so. The gel showed minimum swelling (and also drug-releasing capacity) in the solution of pH 2.0, thus confirming that the hydrophobicity provided by the presence of unionized carboxylic groups played a key role in suppressing the swelling and drug-releasing capacity of the device. Figure 7 also describes the release dynamics of the drug-loaded sample (see the curve superimposed), so that the water uptake of the drug-loaded and blank hydrogel samples can be simultaneously compared to show the drug-release dynamics.

To obtain more information about the possible mechanism of drug release from the device, a comparison of the swelling and release rates of both loaded and blank samples is depicted in Figure 8, which clearly shows that the swelling rate and release rate profiles of the drug-loaded sample exhibit similar morphology, that is, a clear swelling-dependent release behavior is demonstrated by the drug-loaded hydrogel. However, for the unloaded sample, the swelling rate is not uni-

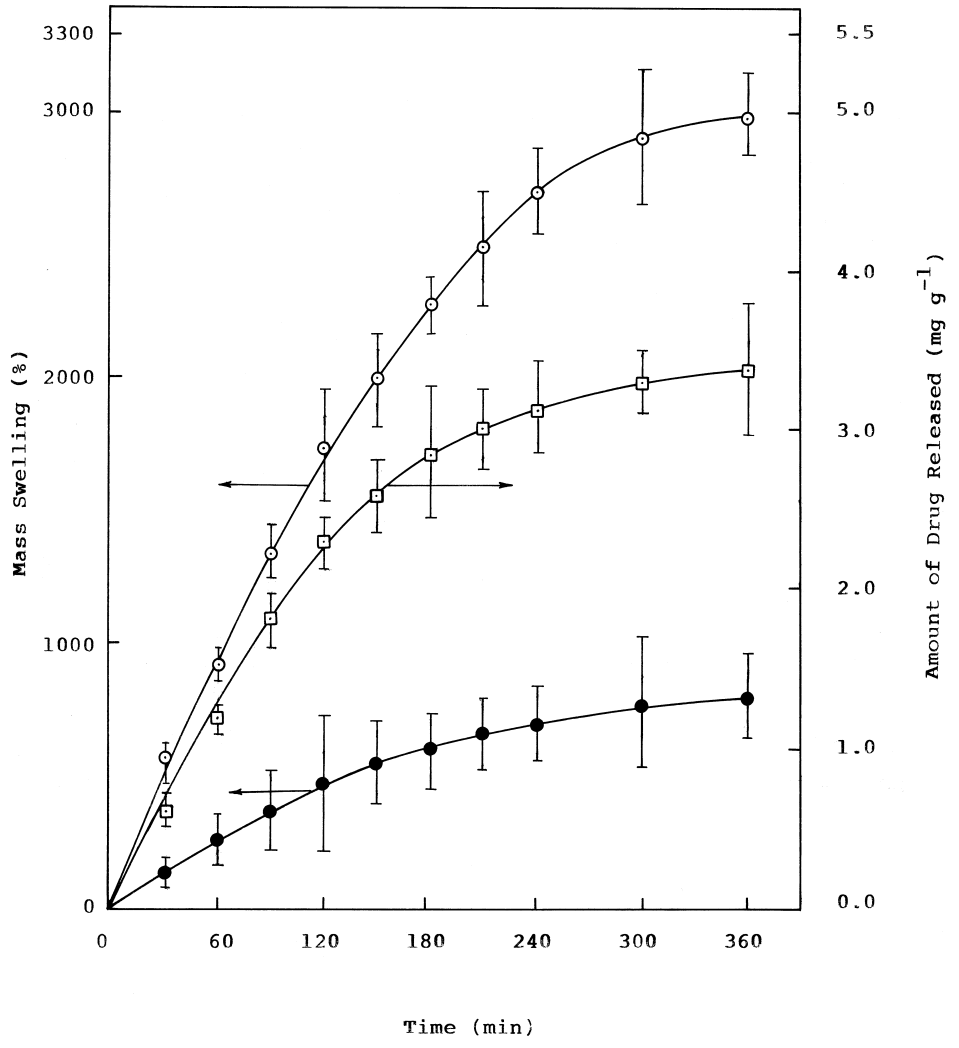

Figure 7 (□) Release profile for the drug-loaded sample HG $(1.3)_{3.8}$; (○) swelling profile for an identical sample; (●) swelling profile for blank sample. All at 37°C in pH 7.4. Error bars represent standard deviations for three experiments.

form, but it decreases slightly with time as shown in Figure 8. This suggests that, although the unloaded sample does not provide a uniform swelling rate, the sample when loaded with riboflavin gives zero-order swelling behavior. This is quantitatively supported by the swelling exponent values which are calculated to be 0.76 and 1.0 for the plain and drug-loaded samples, respectively. Hence, Lee and Kim's observation that the nature of the additive affects the swelling behavior of the hydrogels[19] is not found to be true in the present study.

Mechanism of Drug Release

There are three primary mechanisms by which an encapsulated drug can be released from a delivery system: diffusion, degradation, and swelling followed by the diffusion. Any or all of these mechanisms may occur in a given release system. In diffusion-controlled release devices, the diffusion of the drug may occur on a macroscopic level, as through pores in the polymer matrix, or on a molecular level, by passing between polymer chains. For the diffusion-controlled system, the drug-delivery device is fundamentally stable in the biological environment and does not change its size through swelling. As the present device undergoes an appreciable change in the pH-dependent swelling behavior and also in the drug-releasing capacity, we expect that the release of riboflavin must occur through a swelling-controlled mechanism. A general mechanism for such a type of a swelling-dependent release device may be given as below.

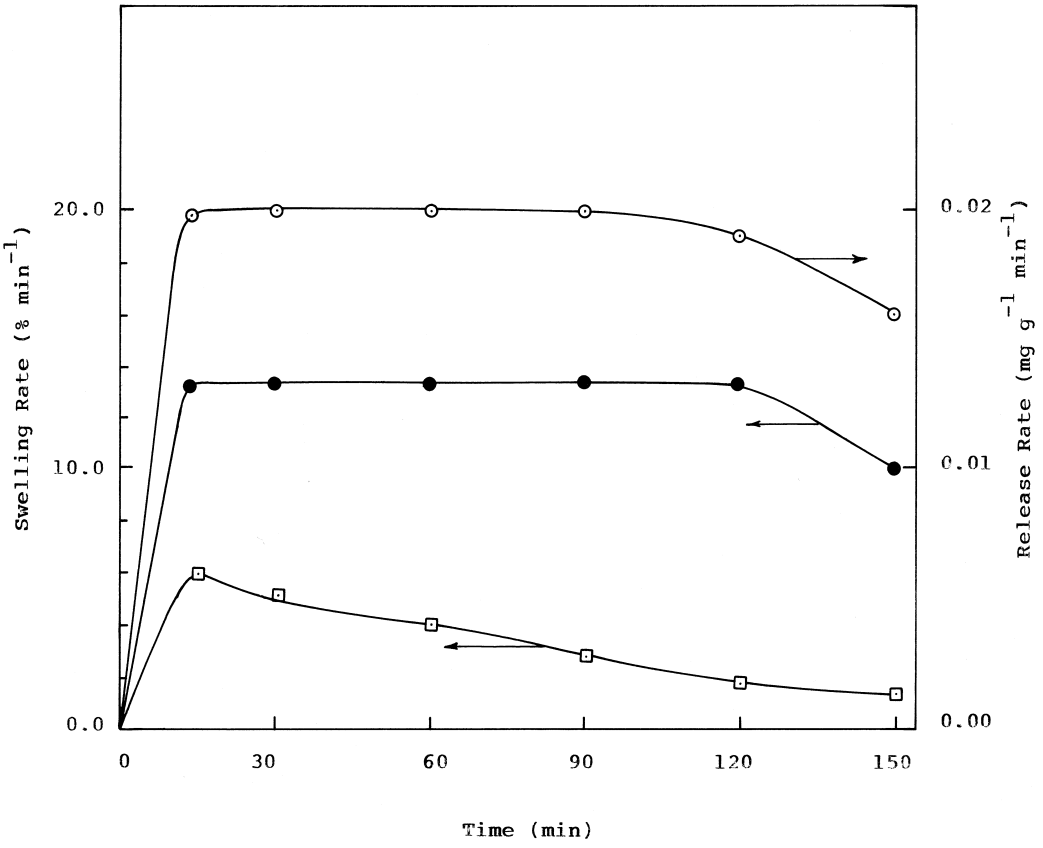

Figure 8 (○) Release rate versus time profiles for the drug-loaded sample HG $(1.3)_{3.8}$; (●) swelling rate versus time profile for an identical sample; (□) swelling profile for blank sample. All at 37°C in pH 7.4.

When the initially dry drug-loaded sample is placed is the swelling media [Fig. 9(A)], the solvent diffuses into the outermost surface of the device with which it is in immediate contact, thus causing the polymeric chains to undergo swelling with a subsequent release of the drug into the external media. Hence, a clear demarcation can seen between the unswollen interior dry core and the exterior swollen core. [see Fig. 9(B)]. As the solvent fronts move toward the bulk of the gel, the thickness of the unswollen core continues to decrease and finally disappears when the two solvent ports from the opposite sides meet each other in the middle [Fig. 9(C)]. After this, the polymer chains are separated further due to the electrostatic repulsion among the carboxylate groups along the macromolecular chains, thus causing the gel to swell more with a simultaneous release of the drug [Fig. 9(D)]. However, in the later stage of this swelling process, the release rate becomes very slow as the swelling approaches the limiting value.

CONCLUSIONS

The release of riboflavin from the poly(acrylamide-*co*-maleic acid) hydrogels, as studied at the physiological temperature of 37°C, exhibits a strong pH-dependent release behavior, thus offering minimum release at pH 2.0 and maximum release at pH 7.4. The pH-dependent release behavior is totally governed by the presence of —COOH groups along the macromolecular chains, which ionize at higher pH while providing hydrophobicity to the gels at lower pH. Although the hydrophilic nature of the drug riboflavin does not contribute much toward the swelling (and, hence, release) behavior of the device, due to the loading of the drug by equilibration of the gel in the alkaline solution of riboflavin, swelling of the drug-loaded device, is appreciably enhanced. The most significant part of the study is that a zero-order release, extended over a half-lifetime ($t_{½}$) of the drug-loaded device was obtained, thus indicating that the device is able to maintain a constant drug level for a definite period, which is the

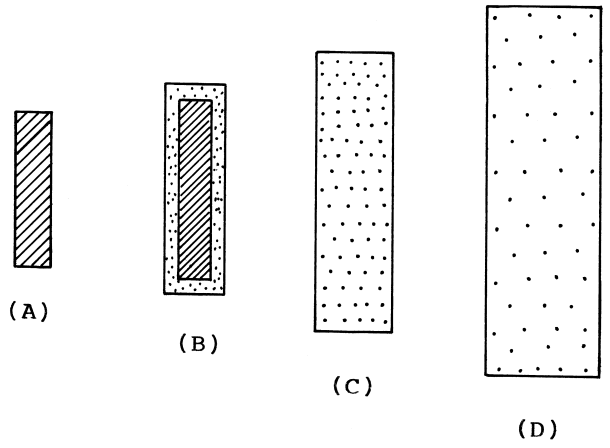

Figure 9 (A) Drug-loaded cylindrical device placed in the swelling medium. (B) Outermost surface swelling with the subsequent release of the drug, thus showing a clear demarcation between the swollen core and dry drug-loaded regions in the bulk. (C) When the solvent fronts from opposite sides meet in the middle of the device, the dry region disappears completely. (D) Repulsion among negatively charged carboxylate groups produced due to ionization of carboxylic groups causes further relaxation and swelling, thus letting more drug to come out of the device.

basic criteria for an optimal delivery system. However, by varying the crosslinking ratio and the amount of drug loaded, it may be possible to achieve a therapeutic drug level for a particular drug. Here, we would like to make it clear that the proposed device maintains a constant drug level only in our *in vitro* study. It is not possible to predict its behavior in *in vivo* experiments until a thorough investigation is carried out.

The proposed device has significant potential to be used as an oral drug-delivery system for the treatment of IBDs or even colon cancers as the encapsulated drug will remain protected at pH 2.0 (which is the pH of the fluid in the stomach). Another advantage with the system is that the method of synthesis does not involve use of an organic solvent or high temperature, and, hence, it may be possible to load the drug into the gel at the time of synthesis so that the probability of the loss of drug activity will be minimal. However, this is just our prediction and we have not verified it experimentally.

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REFERENCES

1. Bajpai, S. K. Asian J Chem 1998, 10, 964.
2. Bajpai, S. K. Iran Polym J 1999, 8, 231.
3. Bajpai, S. K. J Appl Polym Sci 2001, 80, 2782.
4. Bajpai, S. K.; Sonkusley, J. J Macromol Sci Pure Appl Chem A 2001, 38, 365.
5. Bajpai, S. K.; Sonkusley; J. J Appl Polym Sci 2002, 83, 1717.
6. Kim, S. W.; Bae, Y. H.; Okano, T. Pharmaceut Res 1992, 9, 283.
7. Antia, F. P.; Abraham, P. In Clinical Dietetics and Nutrition, 4th ed.; Oxford University: New Delhi, India, 1998.
8. Rivlin, R. S. Nutr Rev 1979, 37, 241.
9. Lakshmi, A. V.; Bamji, M. S. Nutr Metab 1976, 20, 228.
10. Dutta, P. K.; Vishwanathan, P.; Mimrot, L.; Ravi Kumar, M. N. V. J Polym Mater 1997, 14, 351.
11. Lee, D. H.; Kim, J. W.; Suh, K. D. J Appl Polym Sci 1999, 72, 1305
12. Torres-Lugo, M.; Peppas, N. A. Macromolecules 1999, 32, 6646.
13. McNeill, M. E.; Graham, N. B. J Biomed Sci Polym Ed 1993, 5, 111.
14. Reddy, S. M.; Sinha, V. R.; Reddy, D. S. Drugs Today 1999, 35, 537.
15. Shin, H. S.; Kim, S. Y.; Lee Y. M.; Lee, K. H.; Kim, S. J.; Rogers, C. E. J Appl Polym Sci 1998, 69, 479.
16. Peppas, N. A.; Am Ende, D. J. J Appl Polym Sci 1997, 66, 509.
17. Dengre, R.; Bajpai, M.; Bajpai, S. K. J Appl Polym Sci 2000, 76, 1706.
18. Lee, P. I. J Control Rel 1985, 16, 277.
19. Lee, P. K.; Kim, C. J. J Control Rel 1991, 16, 229.