Chemically Treated Hard Gelatin Capsules for Colon-Targeted Drug Delivery: A Novel Approach

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ABSTRACT: Hard gelatin capsules, containing riboflavin-loaded poly (*N*-viny1–2-pyrrolidone)-polyacrylamide cylindrical hydrogels, were modified chemically by treating with an aqueous formaldehyde solution for the purpose of delayed release of drug along the gastrointestinal tract. The t_{dis} (disintegration time) of capsules was studied as a function of concentration of formaldehyde solution and the treatment time. The dynamic release of vitamin B_2 was studied as a function of crosslinking ratio of the hydrogels. The device studied seems to have potential to be used for colon-targeted drug delivery. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 89: 2277–2282, 2003

Key words: gelatin; zero-order release; riboflavin; colon; crosslinking

INTRODUCTION

Drug delivery to the colon has become attractive to researchers interested in the delivery of peptide drugs to the large intestine and the topical treatment of colonic disorders. Because of the unique physiological characteristics of the large intestine, drug delivery to the colon can be achieved in different ways. Of these, one strategy for colon-specific delivery is based on the fact that the luminal pH of the healthy distal colon is slightly higher than that of the proximal small intestine,[1] thus leading to the development of oral dosage forms that are intended to release the drug at the colonic pH (pH-controlled drug release).

In our laboratory, we have synthesized a number of pH-sensitive hydrogels and studied their drug-release behavior.[2–5] These devices are supposed to function on the generally accepted view that the pH of the human gastrointestinal tract increases progressively from the stomach (pH 2–3), to the small intestine (pH 6.5–7.0), to the colon (7.0–8.0).[6] Because these devices exhibit maximum swelling and release of the encapsulated drug in the pH range 7–8, they are supposed to bear the potential to be used for colon-targeted drug delivery.

However, these devices suffer from two major drawbacks. First is that, in spite of exhibiting minimum swelling in the acidic pH, some drug seep from the device through micropores of the device and therefore the device is not able to provide complete protection to the encapsulated drug, which may result in loss of the stability of the drug. Second, it has been reported[7,8] that in patients with inflammatory bowel disorder, the luminal colonic pH drops to values between 2.5 and 4.7. Moreover, recent studies with sensitive and reliable equipment contradict the traditional view and provide evidence of a decrease in pH at the gastrointestinal (GI) region between the ileum and the colon. Apparently, the colon has a lower pH value (6.5) than that of the small intestine (7.0–7.8).[9] Under these conditions the pH-sensitive devices, mentioned above, will be unable to deliver the maximum amount of drug in the colonic region as predicted because in the small intestine (where pH is 7.0–7.8), they will swell to maximum with subsequent release of drug, thus failing to deliver the maximum amount of drug at the colon.

To overcome these problems we have made a sincere attempt to formulate delayed-release delivery capsules, which utilize the fact that there is almost constant transit time in the small intestine of approximately 3–4 h. From the proposed device, almost no measurable drug release occurs during this time period and the release takes place only after 4 h, which is the arrival time of the dosage form at the colon. Moreover, because the device is composed of nonionic polymers, release of the drug occurs irrespective of pH of the release media (i.e., at the colon). The device, proposed by us, is better than the commercially available Pulsincap™ system, which is also capable of releasing its drug at a predetermined time.[10] The latter

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suffers from the drawback that the plug material Desmodur W [bis-(4-isocyanatocyclohexylmethane) crosslinked with hexane triol and polyethylene glycol of different molecular weight] is not FDA approved.[11]

EXPERIMENTAL

Materials

The monomer acrylamide (AAm; Sigma, St. Louis, MO) and the crosslinker *N,N'*-methylene bisacrylamide (MB; Sigma) were of analytical grade. The polymer poly(*N*-viny1–2-pyrrolidone) (PVP; Merck, Mumbai, India) with molecular weight 5×10^4 and the initiator potassium persulfate (KPS; Research Lab, Pune, India) were used as received. The model drug riboflavin (Sigma) was used as a crystalline powder (purity 99.7%; molecular mass 376.66). The formaldehyde was received from Research Lab and hard gelatin capsules were supplied by a local chemist (Veerumal and Sons, Jabalpur, India). The double-distilled water was used throughout the investigations.

Synthesis of cylindrical gels

The method of synthesis of drug-loaded poly(*N*-viny1–2-pyrrolidone)-*crosslinked*-poly acrylamide gels was previously described.[12] In brief, 2.0 g of AAm and 0.04 g of crosslinker MB and 1.0 g of PVP were dissolved in water to give 10 mL clear solution. To this, a definite amount of drug riboflavin was dispersed, followed by the addition of 0.02 g of initiator KPS. The reaction mixture was stirred vigorously, poured into PVC straws, and kept in an electric oven (Tempstar, India) at 60°C for a period of 2 h. After the polymerization was over, gels were removed, cut into small pieces (length 2.0 ± 0.1 cm), washed with distilled water to remove the unreacted salts, and allowed to dry in a vacuum chamber at 40°C for 48 h.

The above polymer matrix was designated as HG $(X)_y$, where subscript y denotes the amount of drug present in 1 g of polymer and the number in parentheses represents the percentage crosslinking ratio (i.e., mole MB/mol AAm × 100).

Preparation of delayed-release drug delivery capsules

The completely dried drug-loaded cylindrical gel (as described above) was poured into the hard gelatin capsule and the joint of the capsule was sealed with 4% (w/v) ethanol solution of ethy1 cellulose. Then, the capsule was placed in an aqueous solution of formaldehyde for a definite time along with thorough stirring, then removed and placed on a Teflon-coated tray, and finally allowed to dry at room temperature for 24 h. These were designated as DRDDC (delayed-release drug delivery capsules). The device is well described in Figure 1.

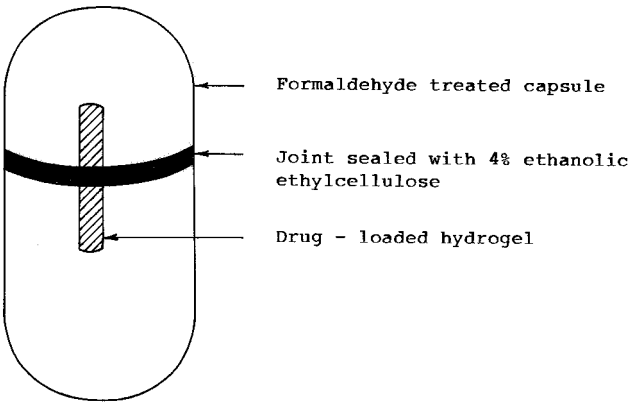

Figure 1 Schematic diagram of delayed-release drug delivery capsule (DRDDC).

Disintegration test for blank DRDDC

The formaldehyde-treated capsule, containing 300 mg of a finally ground homogeneous mixture of hydroxypropy1 methy1 cellulose (200 mg), microcrystalline cellulose (180 mg), and the indicator methylene blue (20 mg) was placed in 500 mL of aqueous buffer solution of pH 2.0 (for 120 min), then in pH 4.0 (for the next 120 min), and finally in pH 7.4 until it started to disintegrate. The disintegration was followed by measuring the absorbance of the solution, which increased very sharply as soon as the capsule disintegrated. Throughout the disintegration study, the solution was stirred at 50 rpm with a magnetic stirrer. For each study, experiments were repeated with five samples.

The *in vitro* drug release study

The method[13] based on simulated gastrointestinal pH variation was employed in this study. A total of 900 mL of dissolution medium (pH 2.0) was poured into the standard USP XXIII dissolution apparatus. The DRDDC was placed in the basket and agitated at the rate of 50 rpm at the physiological temperature of 37°C. After every 30 min, 10-mL aliquots were withdrawn and fresh release media was replaced in the vessel to maintain a constant volume of 900 mL. The absorbance of the aliquot was measured spectrophotometrically at 437 nm.[14] After 2 h, the basket was filled with release media (pH 4.0) and the absorbance was monitored at predetermined time intervals. After 2 h, again, the basket was filled with the media (pH 7.4) and kinetics was followed for the next 6 h by measuring the absorbance of aliquots taken out at regular time intervals.

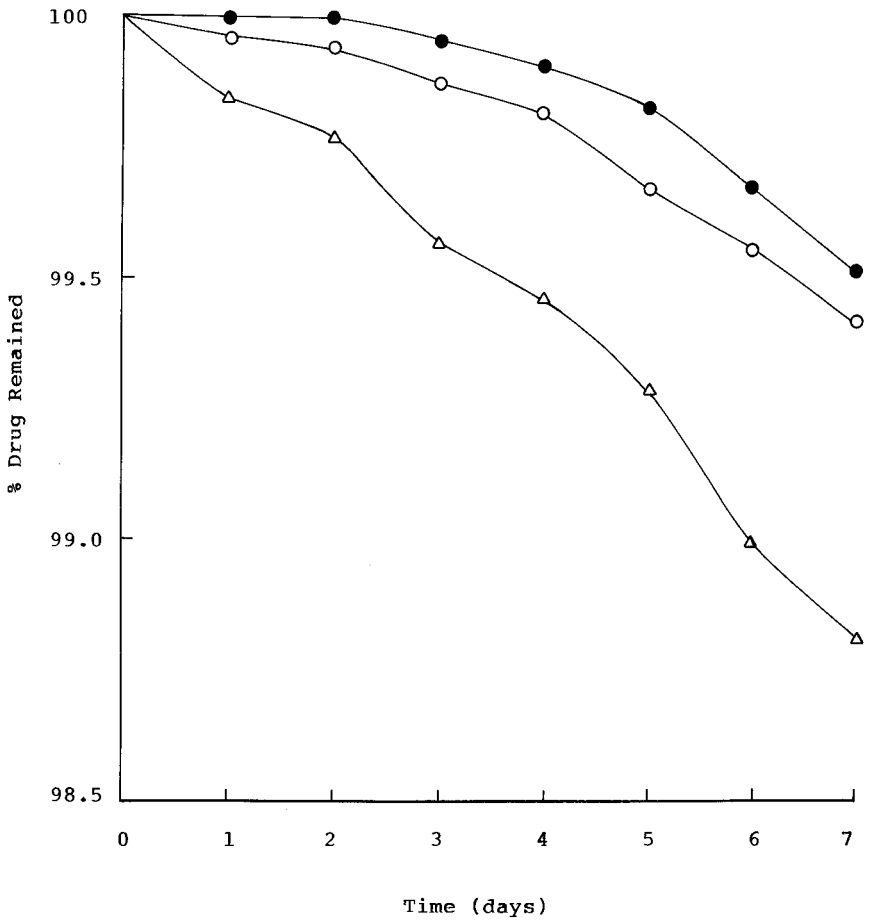

Figure 2 Stability curve for riboflavin in the buffer solution of different pH values: pH 2.0 (●); pH 4.0 (○); and pH 7.4 (△).

RESULTS AND DISCUSSION

Stability of riboflavin

The stability of the riboflavin solution of a definite concentration (10 mg/L) was tested at pH 2.0, 4.0, and 7.4 (Fig. 2). 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 compared to that at alkaline pH. Percentages of the drug decomposed at pH 2.0, 4.0, and 7.4 were 0.48, 0.49, and 1.20, respectively. Because the total transit time for a formulation to pass through the whole GI tract[15] is not more than 48 h, the stability of riboflavin is only slightly affected during this duration and thus it is quite safe to load the drug into the gels. Here, we emphasize that riboflavin was selected only as a model drug and may be replaced by other drugs that are actually used for the treatment of colonic diseases.

Effect of formaldehyde concentration on disintegration time

Gelatin is readily soluble in biological fluids at body temperature and is a good film-forming material. Crosslinking between gelatin proteins attributed to the presence of aldehyde groups in formaldehyde reduces the solubility of the capsule shell.[16]

The disintegration test was carried out with capsules, treated for 45 s is aqueous formaldehyde solutions of varying concentrations from 0.0 to 0.6% in the buffer media of varying pH (as mentioned previously) at the physiological temperature of 37°C. The results, as depicted in the Figure 3, clearly indicate that the disintegration time (t_{dis}) of the capsules increases with the concentration of formaldehyde solutions. This may simply be attributable to the fact that with the increase in percentage of formaldehyde in the solution, the degree of crosslinking also increases, further resulting in a decrease in the solubility and hence increase in the disintegration time of the capsules.

A close look at the Figure 3 also reveals that the capsules, treated with 0.53% solution, disintegrate in almost 245 ± 12 min, which matches the time during which a formulation passes from mouth to colon. Therefore, treatment of capsules with 0.53% formaldehyde solution may allow the drug to be retained within the device for nearly 4 h.

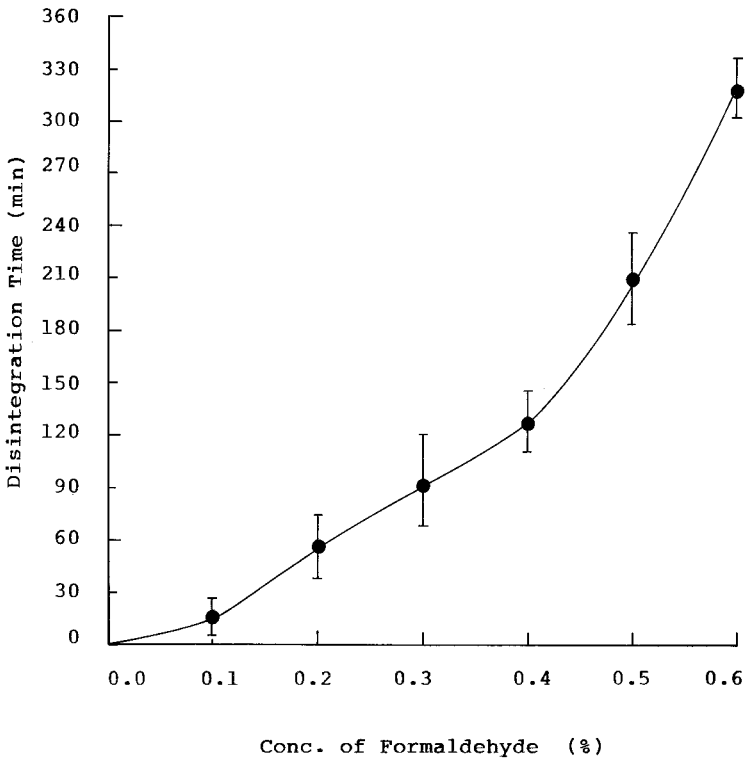

Figure 3 Disintegration time versus formaldehyde concentration plot for gelatin capsules, at constant treatment time. The values shown are means ± SD for five samples.

Effect of treatment time on t_{dis}

The effect of treatment time of capsules on disintegration was studied by treating the plain capsules with 0.53% formaldehyde solution for various times (see Fig. 4). It is very clear from Figure 4 that as the treatment time increases, the disintegration time of the capsules also increases. This is simply attributed to the fact that with the increase in the treatment time, the degree of crosslinking of capsules also increases, which finally increases the disintegration time. A close look at Figure 4 reveals that the capsules, treated for 45 s, take almost 240 ± 11 min and hence are most suitable for causing the desired delayed release of the drug from the device.

The overall conclusion, drawn from the above studies, is that the plain gelatin capsules, treated with 0.53% aqueous formaldehyde solution for a period of 45 s, may allow the desired delay in the release of drug from the polymer matrix.

Kinetics of drug release

Coupe et al.[18] reported that after a light breakfast, emptying occurs essentially in a randomized manner. Most subjects demonstrated a lag phase in gastric emptying. A mean gastric emptying time of 105 ± 45 min was reported. Relying on these data, we therefore opted to expose the device for a maximum period of 2 h at pH 2.0 and then 4.0, which realistically represent the gastric pH environment, followed by an additional 6 h in the medium of pH 7.4.

Figure 5 depicts the dynamic release of the model drug riboflavin from the three drug-loaded devices HG $(0.3)_{3.5}$, HG $(0.7)_{3.5}$, and HG $(1.2)_{3.5}$ in the media of varying pH, as mentioned above, at the physiological temperature of 37°C. A close look at Figure 5 reveals many interesting facts. First of all, the sample HG $(0.3)_{3.5}$ does not release any amount of drug up to 2 h and then very little quantity of drug is released in the next 2 h, which is almost 10.8 ± 2.6% of the total drug released from the device. In spite of the fact that the capsule has not started to disintegrate, release of only a slight amount of drug may be attributed to the fact that initially the highly crosslinked structure of capsules does not permit the release media to enter into the capsule body. After 2 h, because of plasticization of macromolecular chains, a slight amount of solvent might have entered into the capsule body, thus causing an extremely small quantity of drug to seep out, which is almost 10.8 ± 2.6% of the total release. However, after nearly 4 h, the capsule starts to dissolve with subsequent disintegration into small pieces. As a result, the drug-loaded hydrogel, present inside the capsule body, seeps out and begins to release the drug along with swelling. Further, because the device is loosely crosslinked, a nearly zero-order release is ob-

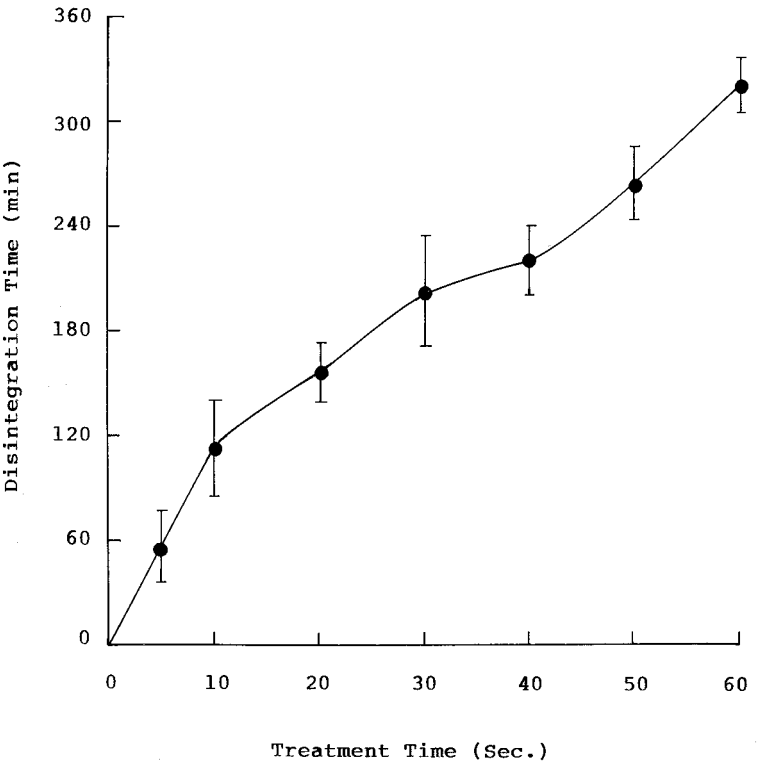

Figure 4 Disintegration time versus treatment time plot for the gelatin capsules at a fixed concentration of formaldehyde solution. The values shown are means ± SD for five samples.

served for the next 4.5 h, which is also confirmed from the value of diffusion exponent ($n = 0.98$). However, the values of n for devices HG $(0.7)_{3.5}$ and HG $(1.2)_{3.5}$ were 0.61 and 0.52, respectively, as calculated from the 60% data. These values suggest that the drug-release process can be governed by the crosslinking ratio of the polymer matrix. Now, the sample HG $(0.3)_{3.5}$, which is the most loosely crosslinked drug-loaded device, provides the right relaxational characteristics for the zero-order release, which may be attributed to the large-scale segmental motion of polymeric segments that also enhance the formation of water-filled macropores through which the drug molecules may diffuse. The rate of drug release from the device HG $(0.3)_{3.5}$ was found to be 9.33×10^{-3} mg g^{-1} gel min^{-1}. Moreover, the total amount of drug released from the three devices HG $(0.3)_{3.5}$, HG $(0.7)_{3.5}$, and HG $(1.2)_{3.5}$ was found to be 89.4 ± 4.8, 45.7 ± 5.2, and 31.4 ± 3.9%, respectively. We also previously reported such zero-order release from a loosely crosslinked matrix.[4,12] To sum up, it can be concluded that the chemically treated hard gelatin capsules (0.53% formaldehyde solution; treatment time 45 s) containing riboflavin-loaded poly(*N*-viny1–2-pyrrolidone)-polyacrylamide cylindrical gel with crosslinking ratio 0.3 (in mol %) may prove to be an effective device for causing the desired delay in release of drug for colon-targeted delivery of protein and peptide drugs.

CONCLUSIONS

It can be concluded from the above study that the chemical treatment of plain gelatin capsules, containing pH-independent drug-loaded polymer matrix, by aqueous solution of formaldehyde, results in a delayed-release delivery system that is capable of causing the delay in release of drug in a predetermined manner so that it is possible to target the drug at the colon or any desired site along the gastrointestinal tract.

The study may be extended to obtain programmed drug delivery from hard gelatin capsules containing a hydrophilic plug (like hydroxypropyl methyl cellulose or guar gum). It is also possible to fabricate floating drug-delivery systems by introducing a layer of air in the middle. Also, if in the case of combined products of two drugs in a delivery device, the degradation of one drug is accelerated because of the presence of the other drug,[19] thus resulting in the reduced bioavailability of the drug, then such problems can be solved by placing one drug under the tablet plug and the other one above the tablet plug.

There are a number of factors, however, that still require thorough investigation: the mechanical strength of chemically treated capsules; the thickness of the capsules; the composition of polymer matrix inside the capsule; and, above all, the feasibility of the

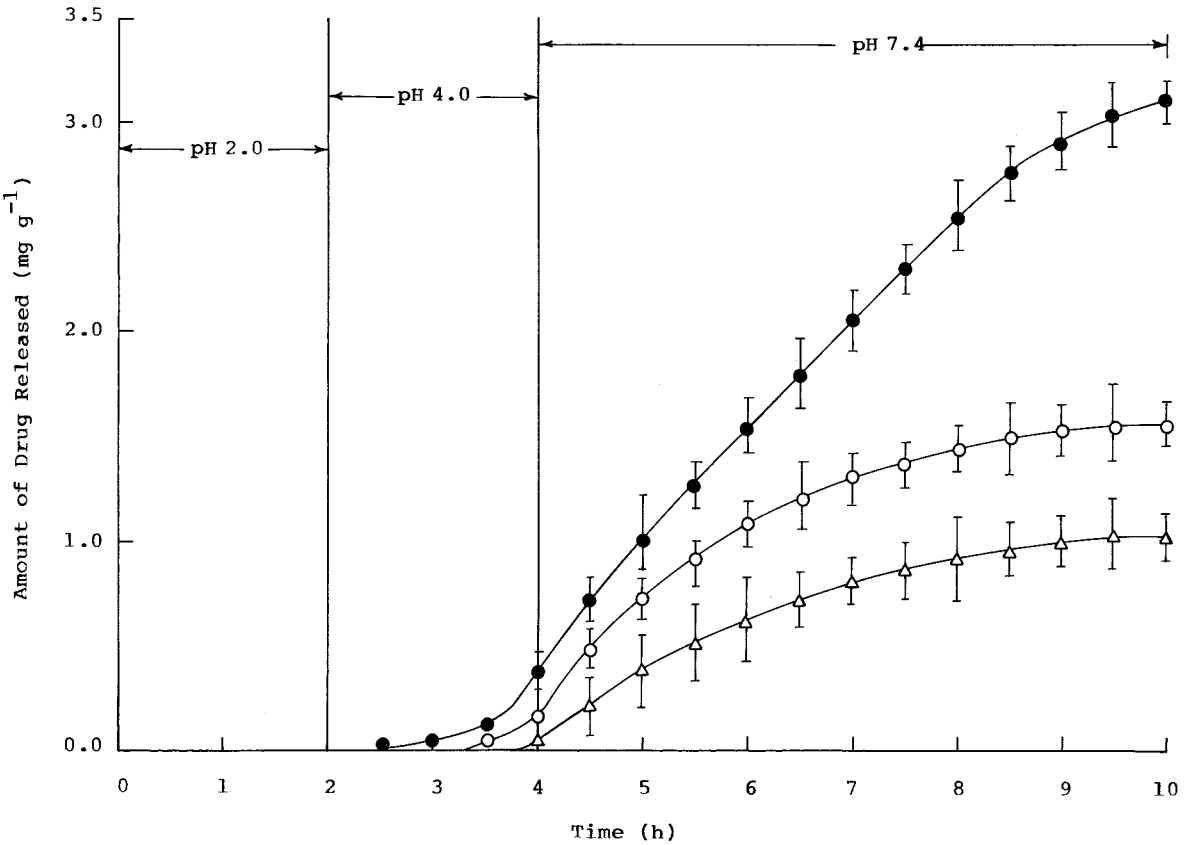

Figure 5 Dynamic release of riboflavin from the DRDDC containing samples of different crosslinking ratio at the physiological temperature of 37°C: HG $(0.3)_{3.5}$ (●); HG $(0.7)_{3.5}$ (○); and HG $(1.2)_{3.5}$ (△). The values shown are means ± SD for five samples.

action of the proposed device under *in vivo* conditions. However, at first sight it seems that the proposed device may achieve the target of obtaining programmed drug delivery by a systemic formulation approach.

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