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RESEARCH PAPER

Gelatin–Poly(Ethylene Oxide) Semi-interpenetrating Polymer Network with pH-Sensitive Swelling and Enzyme-Degradable Properties for Oral Drug Delivery

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ABSTRACT

The study examined the effect of poly(ethylene oxide) (PEO) molecular weight and concentration in a gelatin–PEO semi-interpenetrating polymer network (semi-IPN) on the swelling behavior and enzyme-induced degradation in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2) at 37°C. Gelatin–PEO semi-IPN with PEO of molecular weight 1,000,000 daltons (1.0 M) at 20% (w/w) concentration had a higher swelling ratio in SGF as compared to SIF. In addition, the pH-sensitive swelling behavior was influenced by the concentration of incorporated PEO of 1.0 M molecular weight in the semi-IPN. The time required for complete hydrogel degradation in pepsin-containing SGF and pancreatin-containing SIF by surface erosion was also dependent on the molecular weight and concentration of PEO. Complete degradation of control gelatin hydrogels in SIF occurred in 2 hr. In contrast, complete degradation of gelatin–PEO semi-IPN in pancreatin-containing SIF occurred in less than 1 hr. Although no difference in riboflavin release kinetics was observed between gelatin and gelatin–PEO hydrogels, there was a marked effect in drug release in the presence of enzymes. In pancreatin-containing SIF, for instance, the total riboflavin load was released in 8 hr from gelatin–PEO semi-IPN. Surface degradation of the hydrogel decreases the diffusional path length of the drug for faster release as the gel degrades. By

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varying the PEO molecular weight and amount in gelatin–PEO semi-IPN, it is possible to design hydrogels for site-specific oral delivery in the stomach and upper intestine.

INTRODUCTION

Of the various routes of drug administration in the body, oral delivery through the gastrointestinal (GI) tract is considered to be the most convenient approach of administration to the systemic circulation (1). The advantages of GI tract for drug delivery include ease of drug administration for compliant therapy, large surface area for systemic absorption, and the flexibility of the GI tract in accommodating many different formulation designs. The role of spatial location of dosage forms in the GI tract for optimum therapy is an important factor that is recently receiving considerable attention in oral drug delivery. Site-specific delivery would be beneficial in the treatment of diseases of the GI tract, improve systemic absorption, and minimize premature degradation of drugs (2,3). In diseases that are localized in the GI tract, such as *Helicobacter pylori*-induced peptic ulcer disease, localized antibiotic delivery in the stomach or duodenum would be more beneficial than systemic therapy (4). In other instances, it is known that some drugs are preferentially absorbed from specific regions of the small intestine either by passive diffusion or by carrier-mediated transport. The bioavailability of riboflavin (5), methotrexate (6), angiotensin-converting enzyme inhibitors (7), and some cephalosporins (8) could be profoundly improved if these drugs were released from the dosage form prior to or at a specific absorption site in the upper intestine. Furthermore, colon targeting is considered as a strategy to increase the residence time of controlled-release oral dosage forms and to improve the bioavailability of protein drugs due to the lower proteolytic activity in this region of the GI tract (3).

Due to the variation of pH in the GI tract, pH-sensitive swelling hydrogels are considered as vehicles for site-specific oral drug delivery (9). Hydrogels made with pendant basic or acidic functional groups can ionize in the acidic or alkaline environment of the GI tract (10,11). Ionization of the functional groups leads to swelling of the polyelectrolyte network due to electrostatic repulsion between like charges and the osmotic effect of bound counterions (12). The equilibrium swelling of pH-sensitive hydrogel is governed by the charge density of the polyelectrolyte, pH and ionic strength of the medium, and the crosslinking density of the network (13). Previously, we have examined the pH-sensitive swelling and drug release properties of chitosan-poly(ethylene oxide) (PEO) semi-interpenetrating polymer network (semi-IPN) for localized drug delivery in the stomach (14,15). The primary amino group of D-glucosamine residues of chitosan can ionize in the acidic environment of the gastric fluid. Chitosan–PEO semi-IPN formulated with PEO of molecular weight 1,000,000 daltons had swollen almost 10 times more in the low pH environment of the gastric fluid (pH 1.2) as compared to the intestinal fluid (pH 7.2) (15).

In addition to pH-sensitive swelling, hydrogels for drug delivery application should degrade in the GI tract, preferably by the digestive enzymes. Park (16) synthesized and characterized enzyme-degradable hydrogels with functionalized albumin as a cross-linker for oral delivery. The ability of albumin-cross-linked poly(vinyl pyrollidone) hydrogels to degrade by surface or bulk erosion in pepsin-containing gastric fluid was related to the cross-linking density of the matrix (17). Hydrogels that degrade by surface erosion, characterized by a localized dissolution process occurring at the surface, will release the entrapped drug as the gel surface is gradually dissolved. In the present study, we examined the possibility of using gelatin-PEO semi-IPN for localized drug delivery in the specific region of the GI tract. Gelatin is a natural proteinaceous macromolecule obtained from acidic or alkaline hydrolysis of collagen (18). The safety and biocompatibility of gelatin has been established and the material is approved in the United States for use in food and pharmaceutical products (19,20). Gelatin–PEO semi-IPN was formulated by varying the PEO molecular weight and concentration in the network to optimize the swelling and proteolytic degradation in the stomach and the small intestine. Due to the ionization of the basic amino acid residues of gelatin and the osmotic effect of PEO, the hydrogel is expected to swell in the acidic pH of the gastric fluid. The pH-sensitive swelling of the hydrogels, enzyme-induced degradation, and drug release properties were

examined in vitro in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2) at 37°C.

MATERIALS AND METHODS

Materials

Gelatin (type A, 275 bloom) was purchased from Fisher Scientific (Pittsburgh, PA). PEO with an average molecular weight ranging from 10,000 to 1,000,000 daltons was either purchased from Sigma Chemical Company (St. Louis, MO) or obtained from Union Carbide (Danbury, CT). The cross-linking agent, glyoxal, was obtained from Aldrich Chemicals (Milwaukee, WI). Porcine pepsin (480 units/mg), porcine pancreatin, and riboflavin were all purchased from Sigma. Deionized distilled water (DDW, NANOpure II, Barnsted/Thermolyne, Dubuque, IO) was used exclusively to prepare all aqueous solutions. All other chemicals and reagents were of analytical grade or better.

Hydrogel Synthesis

Gelatin solution at a concentration of 2.0% (w/v) was prepared by the addition of gelatin to DDW and warming the solution up to 40°C for complete dissolution. PEO of different molecular weights was dissolved in DDW to prepare a 2.0% (w/v) solution. Filtered gelatin and PEO solutions were mixed thoroughly to form a blend with the concentration of PEO in the semi-IPN ranging from 10% (w/w) to 30% (w/w). The gelatin–PEO blend was cross-linked with glyoxal at a final concentration of 8.0 mg/ml to form the semi-IPN. Control gelatin hydrogels were prepared similarly without the addition of PEO. The hydrogels were cut into circular disks (~20 mm diameter) and washed extensively in DDW to remove residual cross-linking agent. Gelatin and gelatin–PEO hydrogels were dried to a constant weight at room temperature for approximately 48 hr.

pH-Sensitive Swelling Studies

Dried gelatin and gelatin–PEO hydrogels were allowed to swell in 50 ml of enzyme-free SGF (pH 1.2) or SIF (pH 7.2) at 37°C. SGF and SIF, without pepsin and pancreatin, respectively, were prepared according to the protocols described in the United States Pharmacopeia (21). At a specific time period, the hydrogel was removed from the swelling medium and was blotted with a piece of Kimwipe® tissue (Kimberly–Clark, Roswell, GA) to absorb excess fluid from the surface. The swelling ratio (Q) of gelatin and gelatin–PEO hydrogels was calculated according to the following expression:

$$Q = W_s/W_d$$

where W_s is the weight of the swollen hydrogel and W_d is the weight of the dry hydrogel. The results indicate mean ± *SD* from four independent experiments.

Enzymatic Degradation Studies

Enzyme-induced degradation of gelatin and gelatin–PEO hydrogels was evaluated with pepsin and pancreatin in SGF and SIF, respectively, at 37°C. The concentration of pepsin in SGF was 0.1 mg/ml and that of pancreatin in SIF was 10 mg/ml (15). Dried gelatin and gelatin–PEO hydrogels were placed in 50 ml of enzyme-containing SGF and SIF. At predetermined time intervals, the hydrogel sample was removed from the medium and the swelling ratio was calculated as described above. The results indicate mean ± *SD* from four independent experiments.

Riboflavin Loading and Release Studies

Riboflavin was mixed with gelatin and gelatin–PEO solutions in DDW to give a final concentration of 1.0 mg/ml. Drug-loaded hydrogel was prepared by cross-linking with glyoxal as described above. Riboflavin-containing gelatin and gelatin–PEO hydrogels were placed in 50 ml of SGF or SIF, with and without the enzymes, at 37°C. At a given time point, 1.0 ml of the medium was removed and assayed for the released drug at 445 nm with a Shimadzu UV-160U spectrophotometer (Columbia, MD). Cumulative amount of drug released from the hydrogel was calculated from the appropriate calibration curves. The results indicate mean ± *SD* from four independent experiments.

RESULTS AND DISCUSSION

pH-Sensitive Swelling of Gelatin–PEO Semi-IPN

To determine the effect of pH of the medium on the swelling behavior of gelatin–PEO semi-IPN, the hydrogels were swollen in enzyme-free SGF and SIF for

10 hr at 37°C. Figure 1 shows the relationship between the equilibrium swelling ratio and the molecular weight of PEO incorporated into the semi-IPN. The concentration of PEO in the semi-IPN was maintained constant at 20% (w/w). Control gelatin hydrogels had an equilibrium swelling ratio of 3.81 in SGF and 2.80 in SIF. The swelling ratio of gelatin–PEO semi-IPN was dependent on the molecular weight of PEO. The swelling ratio in SGF of gelatin–PEO semi-IPN made with PEO of molecular weight 10,000 daltons (10K) and 100,000 daltons (100K) was 5.90 and 6.30, respectively. Increasing the molecular weight of PEO to 1,000,000 daltons (1.0M) increased the swelling ratio to 6.83. In SIF, although the swelling ratio was significantly lower than in SGF, there was a marked effect of PEO molecular weight on the swelling behavior of the hydrogels. The swelling ratio of gelatin–PEO semi-IPN containing PEO of molecular weight 10K and 100K in SIF was 3.64 and 4.29, respectively. Increasing the molecular weight of PEO to 1.0M increased the swelling ratio to 4.51.

The relationship between PEO concentration in the network and the swelling behavior of gelatin–PEO semi-IPN in SGF and SIF is shown in Fig. 2. The equilibrium swelling ratio was highly dependent on the concentration of PEO-1.0M. The swelling ratio in SGF of gelatin–PEO semi-IPN made with PEO at concentrations of 10% (w/w) and 20% (w/w) were 5.31 and 6.63, respectively. Increasing the PEO concentration to 30% (w/w) increased the swelling ratio to 7.04. In SIF as well, the swelling ratio was dependent on the concentration of incorporated PEO. The swelling ratios of gelatin–PEO semi-IPN containing PEO-1.0M at a concentration of 10% (w/w) and 20% (w/w) were 3.66 and 4.51, respectively. Increasing the PEO concentration to 30% (w/w) increased the swelling ratio to 4.82. The mechanical integrity of swollen hydrogels made with PEO at 30% (w/w), however, was quite poor.

Clearly, the swelling ratio of gelatin–PEO semi-IPN in SGF was significantly higher than in SIF regardless of the molecular weight or the concentration of incorporated PEO. In the low pH environment of SGF, basic amino acid residues of gelatin will be ionized and contribue to the higher swelling of the hydrogels by electrostatic repulsion and counterion binding. Incorporation of high molecular weight PEO in the hydrogel does also have a profound influence on the hydrogel swelling. As part of the network, PEO is expected either to function as an osmotic agent in facilitating the

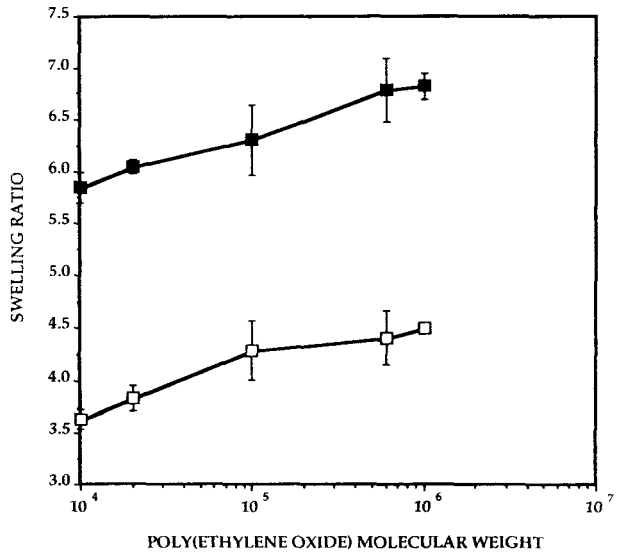

Figure 1. pH-sensitive swelling in enzyme-free simulated gastric fluid (pH 1.2: ■) and simulated intestinal fluid (pH 7.2: □) at 37°C of gelatin-poly(ethylene oxide) semi-interpenetrating network as a function of the molecular weight of incorporated PEO. The concentration of PEO in the semi-IPN was 20% (w/w) and the hydrogels were swollen for 10 hr. The average swelling ratio of control gelatin hydrogels was 3.81 in SGF and 2.80 in SIF.

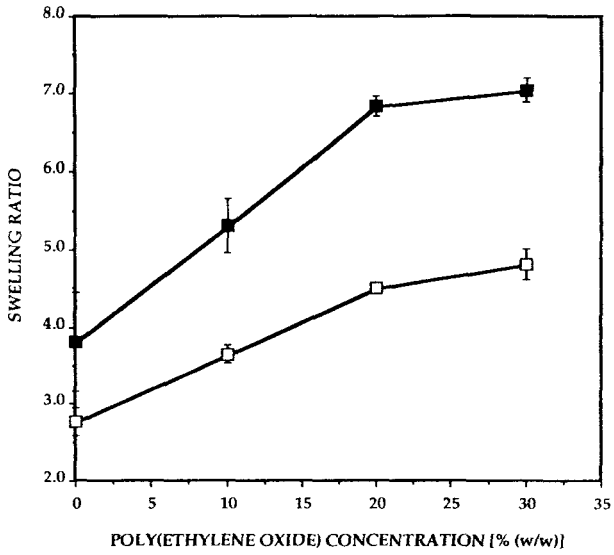

Figure 2. pH-sensitive swelling of gelatin–poly(ethylene oxide) semi-interpenetrating network as a function of the concentration of incorporated PEO (MW 1,000,000 daltons) in the semi-IPN. The hydrogels were swollen for 10 hr in enzyme-free simulated gastric fluid (pH 1.2: ■) and simulated intestinal fluid (pH 7.2: □) at 37°C.

initial uptake of the medium into the hydrogel or to decrease the crystallinity of the gelatin matrix by interpenetration to facilitate the transition from a glassy to a rubbery state in the aqueous medium.

Enzymatic Degradation of Gelatin–PEO Semi-IPN

Examination of the rate and the extent of enzymatic degradation is necessary in the optimization of hydrogels for site-specific oral drug delivery system. We have examined the degradation properties of gelatin and gelatin–PEO hydrogels with pepsin and pancreatin in SGF and SIF, respectively, by measuring the swelling ratio of the hydrogel as a function of time at 37°C. Based on the swelling studies in enzyme-free media, gelatin–PEO semi-IPN made with PEO of molecular weight 1.0M at 20% (w/w) concentration were used in the degradation studies. Figure 3 shows the change in the swelling ratio of gelatin and gelatin–PEO hydrogels as a function of time in pepsin-containing SGF. Since enzyme-induced degradation occurs only in the rubbery state, the initial hydrogel swelling time is necessary to correlate with in vivo parameters such as the transit time of the dosage form in different regions of the GI tract. The maximum swelling of gelatin hydrogen required up to 6 hr of hydration in SGF. In contrast, the maximum swelling of gelatin–PEO semi-IPN required only 2 hr in SGF. The maximum swelling ratio of gelatin hydrogel was 3.91 as compared to the swelling ratio of 5.20 for the gelatin-PEO semi-IPN. Increasing the duration of incubation in pepsin-containing SGF led to the degradation of the hydrogels. During degradation, it was observed that the actual size of the hydrogel was reduced over time, while the gel integrity remained intact. This observation is consistent with surface degradation of the hydrogel in the presence of pepsin.

In pancreatin-containing SIF, as shown in Fig. 4, the enzymatic degradation of gelatin and gelatin–PEO semi-IPN was significantly faster than in pepsin-containing SGF. This is due to the presence of multiple proteolytic enzymes in commercially available pancreatin extract. The maximum swelling of gelatin and gelatin–PEO hydrogels in SIF occurred in 15 to 20 min of incubation. Following hydration, the hydrogels were rapidly degraded by pancreatin in SIF. Unlike gelatin hydrogels, which took almost 2 hr to completely degrade in SIF, gelatin–PEO semi-IPN degraded completely in less than 1 hr. In pancreatin-containing SIF, we observed that the degradation of the hydrogels occurred by surface erosion as well. Incorporation of high molecular weight PEO does profoundly influence the degradation of gelatin–PEO semi-IPN by pepsin and pancreatin. The results

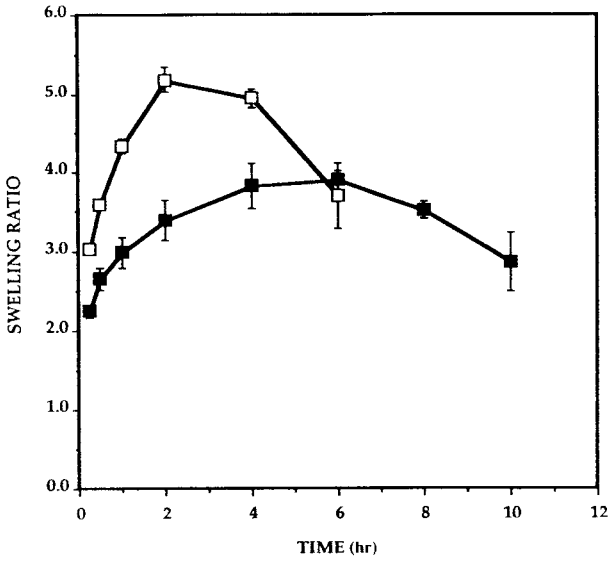

Figure 3. Enzymatic degradation kinetics of gelatin (■) and gelatin–poly(ethylene oxide) semi-interpenetrating network (□) in pepsin-containing simulated gastric fluid at 37°C. Gelatin–PEO semi-IPN was made with PEO of molecular weight 1,000,000 daltons at a concentration of 20% (w/w).

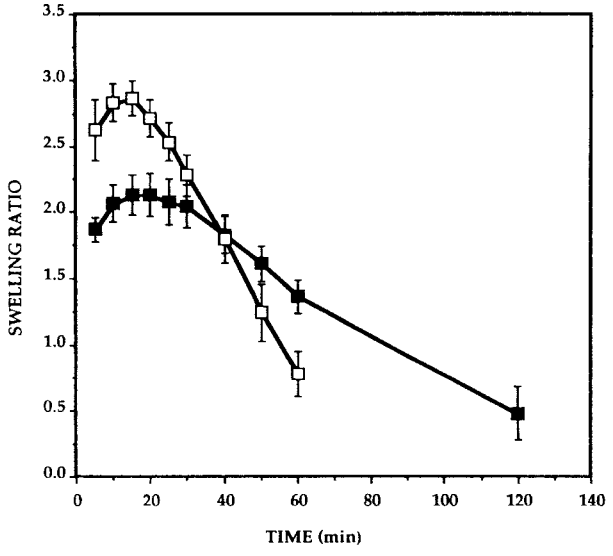

Figure 4. Enzymatic degradation kinetics of gelatin (■) and gelatin–poly(ethylene oxide) semi-interpenetrating network (□) in pancreatin-containing simulated intestinal fluid at 37°C. Gelatin–PEO semi-IPN was made with PEO of molecular weight 1,000,000 daltons at a concentration of 20% (w/w).

suggest that it is possible to design an oral drug delivery system that can be degraded by the digestive enzymes and release the entrapped drug at or before a specific region of the GI tract.

Riboflavin Release from Gelatin–PEO Semi-IPN

For the riboflavin release studies, gelatin–PEO semi-IPN was made with PEO-1.0M at a concentration of 20% (w/w). The drug release in enzyme-free SGF and SIF at 37°C, as shown in Fig. 5, was used to evaluate the effect of pH of the medium on riboflavin release from gelatin and gelatin–PEO hydrogels. Unlike the swelling studies in enzyme-free SGF, which showed a significant difference in the swelling ratios of gelatin and gelatin–PEO hydrogels (Fig. 1), the drug release profiles from these two hydrogels were almost identical. After 6 hr in SGF, for instance, 41% of riboflavin was released from gelatin hydrogel and 39% of riboflavin was released from gelatin–PEO semi-IPN made with PEO-1.0M. In SIF, although the cumulative amount of riboflavin released was lower at a given time point than in SGF due to the pH effects, the drug release profiles were again almost identical in gelatin and gelatin–PEO hydrogels. After 6 hr in SIF, 31% of entrapped riboflavin was released from both gelatin and gelatin–PEO hydrogels. In the absence of enzymes, drug release from loaded gelatin–PEO semi-IPN does not correlate with the swelling behavior of the unloaded hydrogel. Interactions between riboflavin and PEO could have decreased the swelling of riboflavin-loaded gelatin–PEO semi-IPN.

Figure 6 shows the riboflavin release kinetics from gelatin and gelatin–PEO hydrogels in pepsin-containing SGF and pancreatin-containing SIF at 37°C. Similar to the drug release profile seen in enzyme-free SGF (Fig. 5), the riboflavin release profiles in pepsin-containing SGF from gelatin hydrogels and gelatin–PEO semi-IPN made with PEO-1.0M were almost identical. After 6 hr, 36% entrapped riboflavin was released from gelatin hydrogel and 35% of the drug was released from gelatin–PEO semi-IPN. The addition of pepsin in SGF decreased the drug release by about 10% in each case. The proteolytic enzyme can complex with the positively charged gelatin and gelatin–PEO matrices at low pH. The pepsin–gelatin complexation in SGF would alter the rate of drug release by forming additional diffusional barrier and/or by clogging the pores in the hydrogel matrix. The riboflavin release profiles from gelatin and

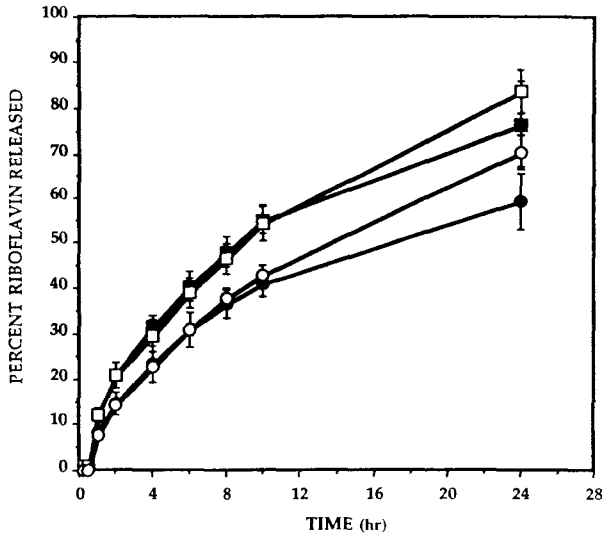

Figure 5. Release kinetics of riboflavin in enzyme-free simulated gastric fluid and simulated intestinal fluid at 37°C from gelatin and gelatin–poly(ethylene oxide) semi-interpenetrating network made with PEO of molecular weight 1,000,000 daltons at a concentration of 20% (w/w). The symbols represent gelatin (■) and gelatin–PEO (□) hydrogels in SGF and gelatin (●) and gelatin–PEO (○) hydrogels in SIF.

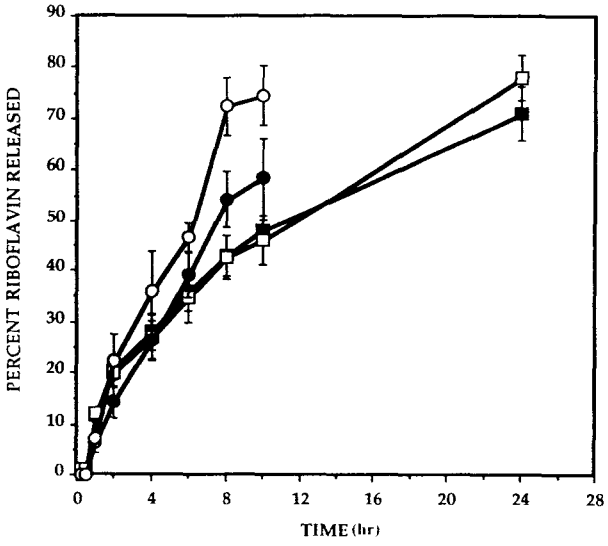

Figure 6. Release kinetics of riboflavin in pepsin-containing simulated gastric fluid and pancreatin-containing simulated intestinal fluid at 37°C from gelatin and gelatin–poly(ethylene oxide) semi-interpenetrating network made with PEO of molecular weight 1,000,000 daltons at a concentration of 20% (w/w). The symbols represent gelatin (■) and gelatin–PEO (□) hydrogels in SGF and gelatin (●) and gelatin–PEO (○) hydrogels in SIF.

gelatin–PEO hydrogels in pancreatin-containing SIF, on the other hand, were significantly affected by the enzymatic degradation of the hydrogels. Relatively faster riboflavin release profiles were observed in SIF as compared to SGF. This was due to the relatively high efficiency of pancreatin in hydrogel degradation. After 6 hr, almost 39% of riboflavin was released from gelatin hydrogel and 47% of the drug was released from gelatin–PEO semi-IPN. The addition of PEO did significantly influence riboflavin release in pancreatin-containing SIF. Increasing the duration to 8 hr resulted in the release of total drug load and complete degradation of gelatin–PEO semi-IPN. The rapid release is characteristic of surface erosion of the hydrogel that decreases the path length of riboflavin diffusion as the gel size decreases. The results of riboflavin release studies indicate that gelatin–PEO semi-IPN with PEO-1.0M at a concentration of 20% (w/w) can effectively release the entire amount of entrapped drug within 8 hr in pancreatin-containing SIF at 37°C.

CONCLUSIONS

Gelatin–PEO semi-IPN containing different molecular weights of PEO and composition ratios of gelatin to PEO were synthesized for site-specific oral drug delivery. The swelling behavior of gelatin and gelatin–PEO hydrogels was dependent on the pH of the medium and the presence of high molecular weight PEO. The equilibrium swelling ratio of gelatin–PEO semi-IPN containing PEO-1.0M at a concentration of 20% (w/w) was significantly higher in SGF than in SIF. In the presence of pepsin in SGF and pancreatin in SIF, the hydrogels degraded by surface degradation as the size decreased, without any changes in the integrity of the hydrogels. Addition of high molecular weight PEO influenced the degradation of the hydrogels in enzyme-containing SGF and SIF. Complete degradation of gelatin hydrogels in pancreatin-containing SIF occurred in 2 hr. Gelatin–PEO semi-IPN containing PEO-1.0M, on the other hand, degraded completely in 1 hr or less. Enzyme-induced surface degradation is expected to significantly influence drug release by decreasing the diffusional path length of the drug with time. Riboflavin release from gelatin and gelatin–PEO hydrogels, in the absence of enzymes, depended on the pH of the medium. There was, however, no effect of high molecular weight PEO on drug release. This could be due to less swelling of the gelatin–PEO semi-IPN after the addition of riboflavin. In pancreatin-containing SIF, riboflavin release occurred rapidly with the degradation of gelatin–PEO semi-IPN. The full load of the drug was released in about 8 hr from gelatin–PEO semi-IPN in pancreatin-containing SIF.

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REFERENCES

1. S. S. Davis, J. G. Hardy, and C. G. Wilson (eds.), *Drug Delivery to the Gastro-Intestinal Tract*, Ellis Horwood, Chichester, U.K., 1989.
2. P. K. Gupta and J. R. Robinson, in *Treatise on Controlled Drug Delivery* (A. Kydonieus, ed.), Marcel Dekker, New York, 1992, Chap. 6, p. 255.
3. A. Rubinstein and D. R. Friend, in *Polymeric Site-Specific Pharmacotherapy* (A. J. Domb, ed.), John Wiley & Sons, Chichester, U.K., 1994, p. 267.
4. A. Ateshkadi, N. P. Lam, and C. A. Johnson, Clin. Pharm., 12, 34 (1993).
5. G. Levy, M. Gibaldi, and J. A. Procknal, J. Pharm. Sci., 61, 798 (1972).
6. V. S. Chungi, D. W. A. Bourne, and L. W. Dittert, J. Pharm. Sci., 68, 1552 (1979).
7. M. Hu and G. L. Amidon, J. Pharm. Sci., 77, 1007 (1988).
8. P. J. Sinko and G. L. Amidon, Pharm. Res., 5, 645 (1988).
9. R. A. Siegel, M. Falamarzian, B. A. Firestone, and B. C. Moxley, J. Controlled Rel., 8, 179 (1988).
10. P-Y. Yeh, P. Kopeckova, and J. Kopecek, J. Polym. Sci., Part A: Polym. Chem., 32, 1627 (1994).
11. K-D. Yao, T. Peng, H-B. Feng, and Y-Y. He J. Polym. Sci., Part A: Polym. Chem., 32, 1213 (1994).
12. J. H. Kuo, G. L. Amidon, and P. I. Lee, Pharm. Res., 5, 592 (1988).
13. R. A. Siegel and B. A. Firestone, Macromolecules, 21, 3254 (1988).
14. M. Amiji and V. Patel, Polym. Prepr., 35, 403 (1994).
15. V. Patel and M. Amiji, in *Hydrogels and Biodegradable Polymers for Bioapplications* (R. Ottenbrite, S. Huang, and K. Park, eds.), ACS Symposium Series Publication, American Chemical Society, Washington, DC, in press.
16. K. Park, Biomaterials, 9, 435 (1988).
17. W. S. W. Shalaby, W. E. Blevins, and K. Park, in

Water-Soluble Polymers: Synthesis, Solution Properties, and Applications (S. W. Shalaby, C. L. McCormick, and G. B. Butler, eds.), ACS Symposium Series Publication, Vol. 467, American Chemical Society, Washington, DC, 1991, p. 484.

18. A. Veis, *The Macromolecular Chemistry of Gelatin*, Academic Press, London, 1964.
19. C. M. Klech, in *Encyclopedia of Pharmaceutical Technology* (J. Swarbrick and J. C. Boylan, eds.), Marcel Dekker, New York, 1988, p. 415.
20. S. Bogdansky, in *Biodegradable Polymers as Drug Delivery Systems* (M. Chasin and R. Langer, eds.), Marcel Dekker, New York, 1990, p. 231.
21. The United States Pharmacopeia/National Formulary, Vol. XXII, The United States Pharmacopeial Convention, Rockville, MD, 1990, p. 1786.