Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 275 (2004) 259–269
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Modeling of swelling and drug release behavior of spontaneously forming hydrogels composed of phospholipid polymers

Kwangwoo Nam, Junji Watanabe, Kazuhiko Ishihara*

Department of Materials Engineering, School of Engineering, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

Received 14 September 2003; received in revised form 24 January 2004; accepted 11 February 2004

Abstract

Physically cross-linked hydrogel had been investigated in order to make use of oral polypeptide drug delivery carrier. By using 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymer, we had prepared a spontaneously forming hydrogel showing controllable dissociation via pH changes. In this study, the dissociation and release of polypeptide drugs from the MPC polymer hydrogel loaded with polypeptide drugs, which had been prepared from aqueous solutions containing water-soluble poly[MPC-co-methacrylic acid (MA)] (PMA) and poly[MPC-co-*n*-butyl methacrylate (BMA)] (PMB) had been executed. The polymer concentration was 10 wt.% and PMA/PMB feed ratio (A/B feed ratio) was 5/5. Insulin labeled with fluorescein-4-isothiocyanate (FITC) and cytochrome *c* had been loaded for the examination of the release behavior. The hydrogel in pH 1.8 aqueous solution would be swelling, for the hydrogel would absorb outside water. However, during this process, the polymer is dissoluting out from the hydrogel due to the widening of the polymer network. The cytochrome *c* followed anomalous transport while insulin depended on the swelling and dissolution of the polymer chains. The hydrogel showed surface erosion in neutral condition, although the hydrogel is composed of two different polymer possessing divergent physical properties. The release followed anomalous transport, but the erosion rate slightly changed with as the hydrophobicity of the loaded drugs. The total amount of the drugs released in neutral condition was larger compared to the acidic condition. When the eroded percentage and the release percentage were compared with each other, it showed that release was slightly slower than erosion, indicating that the erosion was controlling the release phenomenon.

Keywords: Swelling; Dissociation; 2-Methacryloyloxyethyl phosphorylcholine polymer; Physically cross-linked hydrogel; Polypeptide delivery; Controlled release; Erosion mechanism

1. Introduction

1.1. Background of this study

The hydrogels is the polymeric material that exhibits the ability to swell in water and retain a significant fraction of water in its structure, but which will not dissolve in water. There exists two kinds of hydrogels; chemically and physically cross-linked hydrogel. Big difference between these two kinds is the formation of cross-link point or junctions, which is consisted of chemical bonds or physical interactions. In the case of physically cross-linked hydrogel, the cross-link junctions are consisted of ionic interactions, hydrophobic association, or coiled–coil interactions (Watanabe et al., 1996; Qu et al., 1999; Wang et al., 1999). Recently, the stereocomplex formation between polymers of opposite chirality was utilized for the for-

* Corresponding author. Tel.: +81-3-5841-7124; fax: +81-3-5841-8647.
E-mail address: ishihara@bmw.t.u-tokyo.ac.jp (K. Ishihara).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.02.009

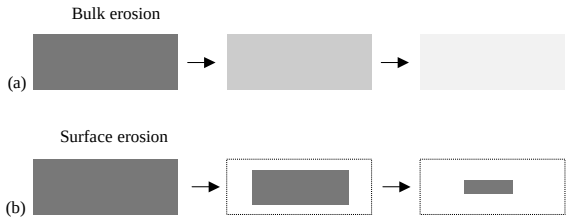


Fig. 1. Schematic pictures of bulk erosion (a) and surface erosion (b).

mation of physically cross-linked hydrogel (de Jong et al., 2000, 2001). The major advantage of the physically cross-linked hydrogel is that no cross-linking agents are required, which may avoid the toxicity and the damage of the incorporated polypeptide drugs. In order to make use of the hydrogel as a good drug carrier, the hydrogel should possess biocompatibility and exhibit good response to the outer stimuli, which induces controlled release of the drugs. In general, controlled release can be expressed by Fickian diffusion equation, which is based on the diffusion of the loaded drugs.

Degradation is the chain scission of the polymer chains which would eventually cleaved into the monomers. Erosion is the loss of the material from the bulk. The term degradation and erosion are often used conjunctionally. This is true when the degradation of the polymer induces the erosion of the system, but not all erosion process is stimulated by degradation. From the chemical standpoint, Heller has pointed out erodible system in terms of three dissolution mechanisms: (1) water-soluble polymers insolubilized by degradable cross-links; (2) water-insoluble polymer solubilized by hydrolysis, ionization, or protonation of pendant side groups; and (3) water-insoluble polymers solubilized by polymer backbone cleavage to small water-soluble molecules (Heller, 1980).

There are two different modes for the erosion process: surface and bulk erosion (Fig. 1). For surface eroding device, lose of the materials occurs at the surface only, leading to the decrement of the size. For bulk eroding device, the erosion would not be concentrated on the surface of the device, which would bring proper size of the device for considerable portion of time during application. The majority of the polymer that had been applied to investigate the erosion studies are hydroxypropyl methylcellulose (HPMC), poly(anhydride), poly(hydroxybutyrate), and so forth (Hopfenberg, 1976; D'Emanuele et al., 1992; Yasin and Tighe, 1993; Siepmann et al., 1999; Bettini et al., 2001; von Burkersroda et al., 2002). These materials were used to investigate the erosion mechanism and the drug release behavior of the device. The erosion process had been explained by mathematical model theoretically and empirically. The theoretical model is based on the dissolution of the polymer chains which is brought up by chain disentaglement or diffusion (Ju et al., 1995a,b; Siepmann and Göpfrerich, 2001). On the other hand, empirical model only describes the results, which makes it much easier to handle (Göpferich, 1996).

The aim of this study is to define the swelling and dissociation mechanism of the physically cross-linked hydrogel composed of two distinguished components and how it is affecting the release of the loaded model polypeptide drugs in gastrointestinal tract (GI tract). The polymers we had adopted were the phospholipid polymers containing 2-methacryloyloxyethyl phosphorylcholine (MPC) unit. The MPC polymers are well-known for its excellent biocompatibility and it is widely used in biomedical fields (Ishihara et al., 1990, 1992; Yoneyama et al., 1998; Konno et al., 2001; Watanabe et al., 2002). Poly[MPC-co-methacrylic acid] (PMA) which possesses carboxyl groups and poly[MPC-co-*n*-butyl methacrylate] (PMB) which possesses *n*-butyl methacrylate unit can form a hydrogel in aqueous condition spontaneously when mixed together (Nam et al., 2002a,b). This hydrogel shows pH response, in which makes the hydrogel to dissociate in the neutral condition while swells in acidic condition. The pH sensitivity and good biocompatibility can be adopted to make use for this hydrogel as an oral polypeptide delivery carrier. In this paper, the term erosion is used to imply the decrement of the hydrogel body, dissolution to indicate the polymer moving out from the hydrogel (or diffuse out), and dissociation polymer cross-links gradually being soluble to the aqueous solution.

1.2. Theoretical section

We had mentioned in our paper that the hydrogel would be stabilized in acidic condition, while dissociate in neutral condition. The cross-link junction is composed of hydrogen bond brought up by carboxyl

groups of PMA side chains. The hydrogen bonds were formed in hydrophobic domains, which were provided by the association of PMB.

1.2.1. In acidic pH condition

The hydrogel composed of PMA and PMB chains would be in stabilized condition. The chains would be strong enough to hold each other to maintain their structures, which disable the erosion process.

The absorption of water brings the swelling process of the hydrogel. The kinetic of water absorption into the hydrogel can be calculated using the semi-empirical equation (Sinclair and Peppas, 1984; Peppas, 1985; Khare and Peppas, 1995):

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t is the amount of absorbed water at any time t, M_∞ is the amount of water at equilibrium state, and M_t/M_∞ is the fractional water absorption. k is the kinetic constant and n is the diffusion exponent. $n = 0.5$, $0.5 < n < 1$, $n = 1$, or $n > 1$ indicates Fickian diffusion, anomalous transport (non-Fickain), Case II transport, or Super Case II transport. In the case of cylinder, $n = 0.45$, $0.45 < n < 0.89$, or $n = 0.89$ indicates Fickian release, anomalous transport, or Case II transport (Ritger and Peppas, 1987; Park et al., 1993).

Simply, the swelling triggers the release of the loaded drugs. The widened space between the chains brings the release of the loaded drugs. Eq. (1) was made to explain the release profile of the loaded drugs and is being widely used for explaining release phenomena from the swellable hydrogels, for its simplicity. M_t would be the amount of released drug at any time t, M_∞ is the amount of released drug at equilibrium state, and M_t/M_∞ is the fractional released drug. Sometimes, M_0 which stands for amount of drug at $t = 0$ are being used instead of M_∞. However, this equation is limited to monolithic reservoir system. Furthermore, the physical properties should not change during the release process (Khare and Peppas, 1995). To make this equation sufficiently accurate, the release profile had been calculated limiting its M_t/M_0 until 0.6. To obtain the diffusion coefficient of the hydrogels with diverse drugs by adopting the geometrical parameter into the fractional release, it is possible to calculate the diffusion coefficient in terms of time. This had been proposed by Baker and Lansdale (Baker and Lansdale, 1974; Shaheen and Yamaura, 2002):

$$\frac{M_t}{M_0} = kt^n = 4\left(\frac{Dt}{\pi l^2}\right)^{1/2} \tag{2}$$

where D is the diffusion coefficient, l is the thickness or length of the hydrogel matrix.

1.2.2. In neutral pH condition

The hydrogel would be dissociated when it encounter with neutral pH. The absorption of water in neutral condition would turn the carboxyl groups into carboxylate anions, and they starts to push each other. That is, the polymer chains inside the hydrogel would have enough space free to move and there is no interaction that would hold them together.

Narasimhan pointed out that dissolution system would occur as the polymer chains slowly disentangle, leading to complete dissolution of the matrix (Narasimhan, 2000). He also mentioned that this system would occur only in uncross-linked polymer carriers. Based on this, the MPC polymer hydrogel would lose its cross-link junction as they starts to absorb outside water, calculation of the polymer dissolution rate constant k_{diss} was executed:

$$M_t = M_0 - k_{\text{diss}} A_t t \tag{3}$$

where M_t is the mass of the dry matrix at any time t, M_0 is the mass of the dry matrix at $t = 0$, A_t is the surface area at any time t. Polymer dissolution k_{diss} is an adjustable parameter. So the equation can be referred to as a mass balance for the polymer chains adjacent to the polymer–water interface. Truly, the term dissolution is referred to as the dissolution phenomenon of the matrix in the surrounding media. Many references use the term erosion and dissolution together, since they are mainly applied to the study of the erosion of the dry matrix such as tablets. However, in this study, the term dissolution was strictly restricted to the polymer, since the dissolution of the polymer that is induced by the reptational movement of the polymer chain is caused by the erosion.

The release mechanism in the erosion system is difficult to apply the Fickian relationship, for the system does not satisfy the hypothesis for the system. To obtain the information on the erosion mechanism of the

hydrogel in neutral condition, the release model was calculated by using the Hopfenberg model that had been modified (Katzhendler et al., 1997). The Hopfenberg model is based on the surface-eroding release device (Hopfenberg, 1976):

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_a t}{C_0 a_0}\right)^n \quad (4)$$

where M_t is the amount of released drug from the device in time t, M_∞ is the total amount of released drug when the device is exhausted. a_0 is the initial radius for a sphere or cylinder or the half-thickness for a slab and C_0 is the uniform initial concentration of the drug in the matrix. $n = 1$ is for a slab, $n = 2$ is for a cylinder, and $n = 3$ for a sphere. Since the equation rules out the parameter on the surface area, the release kinetics is independent of time-dependent diffusional resistances internal or external to the eroding matrix.

The model covers not only spherical geometry but also slabs, cylinder displaying heterogeneous erosion:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_a t}{C_0 a_0}\right)^2 \left(1 - \frac{2k_b t}{C_0 b_0}\right) \quad (5)$$

where M_t is the amount of released drug from the device in time t, M_∞ is the total amount of released drug when the device is exhausted, and a_0 is the initial radius for a sphere or cylinder or the half-thickness for a slab and b_0 is the thickness. k_a and k_b are the erosion rate constants for coordinates a and b. C_0 is the uniform initial concentration of the drug in the matrix. When k_a is roughly equal to k_b, Eq. (5) would be transformed into following expression:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{C_0 a_0}\right)^2 \left(1 - \frac{2k_0 t}{C_0 b_0}\right) \quad (6)$$

where $k_a \approx k_b = k_0$.

As can be seen in the equation, the fractional release depends on the a_0 and b_0, or k_a and k_b. By analyzing the change of a_0, b_0, k_a, and k_b, the equation can be shortened or be returned to original Hopfenberg model. This is because the equation recognizes the change of the secondary surface area and time dependence of the eroding matrix by the release process.

2. Experimental

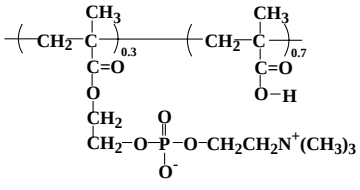
2.1. Preparation of hydrogels

The MPC polymers were prepared by the conventional radical polymerization in aqueous media (Ishihara et al., 1990; Ueda et al., 1992).

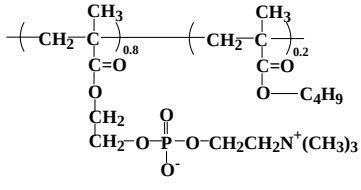
Two kinds of water-soluble polymer PMA [MPC mole fraction: 0.3, number-average molecular weight (M_n) = 6.0×10^4, weight-average molecular weight (M_w) = 2.9×10^5] and PMB (MPC mole fraction: 0.8, $M_n = 1.2 \times 10^5$, $M_w = 1.0 \times 10^6$) were chosen for preparation of the hydrogel. The chemical structures of these MPC copolymers are shown in Fig. 2. In order to prepare a polypeptide-loaded hydrogel, the fluorescein-4-isothiocyanate (FITC)-labeled insulin (1.3 mol/mol FITC content; extracted from bovine pancreas, Sigma, USA) (INS), and cytochrome *c* (Sigma, USA) (Cy*c*) were added to PMB aqueous solution, respectively. Then the PMA aqueous solution was added to the PMB-polypeptide solution (PMA:PMB = 1:1 (v/v)). The concentration of PMA and PMB aqueous solution was all controlled to 10 wt.% and then vigorously mixed for 10 s with vortex stirrer to prepare a hydrogel loaded with polypeptide.

2.2. Swelling and dissociation behavior of hydrogels

The hydrogel were fabricated to disk shape (diameter: 15 mm, height: 6 mm). To observe how the



(a)



(b)

Fig. 2. The chemical structures of PMA (a) and PMB (b).

hydrogel would behave in GI tract, each hydrogel were characterized in pH 1.8 aqueous solution (stomach condition) and pH 6.8 phosphate buffer solution (PBS) (small intestine condition) (Hörter and Dressman, 2001). In order to maintain the buffer condition, the ratio of hydrogel and the buffer solution was controlled in the ratio of 1:99 (v/v). The sample bottles with PBS were changed every 30 min in order to retain clean environment. Between changing the sample bottle, the weight of the hydrogel was weighed until full dissociation. The swelling degree for the hydrogel in acidic condition was calculated by using the following equation:

$$\text{Swelling ratio, } S\,(\%) = \frac{W_{a,s} - W_{a,r}}{W_{a,r}} \times 100 \qquad (7)$$

$$\text{Water absorption ratio, } W_{ch}\,(\%) = \frac{(W_{a,s} - W_{p,s}) - (W_{a,r} - W_{p,r})}{W_{a,r} - W_{p,r}} \times 100 \qquad (8)$$

$$W_{w,s} + W_{p,s} = W_{a,s}$$

$$W_{w,r} + W_{p,r} = W_{a,r}$$

S indicates the swelling ratio, $W_{a,s}$ indicates the total weight of the hydrogel after swelling and $W_{a,r}$ indicates the total weight of the hydrogel before swelling. W_{ch} implies the pure water absorption ratio. $W_{p,r}$ and $W_{p,s}$ indicate the polymer weight before and after swelling, respectively. $W_{w,r}$ and $W_{w,s}$ is the pure amount of water in the hydrogel before and after swelling. The swelling ratio S indicates the total weight change of the hydrogel, water absorption ratio W_{ch} implies the change in the water content during swelling, and polymer loss indicates the loss of the polymer portion during swelling.

To measure the weight of the hydrogel at desired time, the hydrogels were taken out from the solution and put into the nylon mesh bag to measure their weights. Then the hydrogel was completely lyophilized for overnight and the weight was measured to gain the weight of the remaining polymer. From this, the weight of the polymer and water was calculated with the polymer content of the hydrogel at respective time. All the experiments were repeated seven times.

By using Eq. (7), we calculated the swelling of the hydrogel in acidic condition. And by using Eqs. (3) and (7), we analyzed the dissolution behavior of the polymer and the eroding process of the hydrogel in neutral condition.

2.3. Release behavior of polypeptide from hydrogels

Drug-loaded hydrogels were prepared by the same methods as written above. The release of the INS was measured with the fluorescence spectrometer (FP-750, Jasco, Tokyo, Japan) ($\lambda_{EX} = 490$, $\lambda_{EM} = 518$ nm) and the release of Cy*c* was measured with UV spectrometer (V-650, Jasco, Tokyo, Japan) ($\lambda = 409$ nm) every 30 min for first 6 h and every 1 h afterward. In order to maintain the buffer condition, the ratio of hydrogel and the buffer was controlled in the ratio of 1:99 (v/v). Small amount of aliquot was taken out and put into the quartz cell to measure the fluorescent and UV intensity. The aliquot was then put back into the sample solution. The time between the measurements was 30 min for acidic condition, and 10 min for neutral condition.

The measurement was continued for 24 h in the case of acidic condition, while the measurement was continued until full dissociation of the hydrogel in the case of neutral condition. The FITC-insulin could remain stable in PMB solution without any precipitation for 1 week in acidic pH condition (pH 1.8) and 2 days in neutral pH condition (pH 6.8). With the acquired data, we calculated the diffusion exponent for the drug loaded hydrogels in acidic and neutral condition. Eq. (6) was used to analyze the surface eroding release phenomenon of the hydrogel in neutral condition.

3. Results and discussion

3.1. Swelling and release behavior of hydrogels in acidic pH condition

We have mentioned in our previous reports that the hydrogel would swell in acidic condition (pH 1.8) and dissociate in neutral condition (pH 6.8) (Nam et al., 2002a,b). The swelling/dissociation behavior is due to the existence of the carboxyl groups in the hydrogel, which makes the polymer network to response to the pH condition of the hydrogel at certain time.

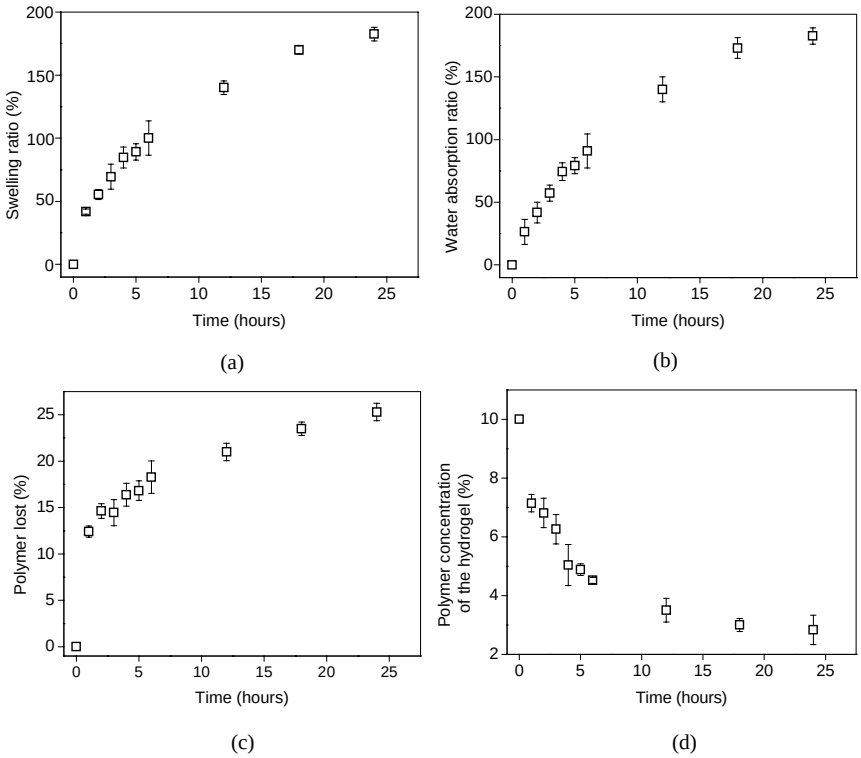


Fig. 3. The swelling ratio of the hydrogel (a), water absorption ratio (b), the polymer lost percentage (c), and polymer concentration of the hydrogel (d).

The elastic modulus for the hydrogel was 4900 ± 400 N/m^2. The elastic modulus would drop to 1800 ± 160 N/m^2 when the polymer concentration of the hydrogel is 5 wt.%. The further study on the elastic modulus and the viscosity of the hydrogel is being prepared and be reported in our next article.

Fig. 3 shows the basic change in the swelling ratio, water absorption, polymer lost, and the polymer concentration of the hydrogel according to the time. Swelling ratio is increasing up to 200% in 24 h. Fig. 3b and c show that the hydrogel absorbed aqueous solution of the outside, while releasing the polymer portion. Since the carboxyl groups that constitute the hydrogel network would remain stable (methacrylic acid $pK_a = 2.4$) (Nam et al., 2002a), it is thought that the uncross-linked portion of the polymer had been leaked out from the hydrogel. The widened space inside the hydrogel would give more free space to the polymer chains, which makes it easier for them to mobile. We have mentioned in our previous paper that the leaking of the polymer was mainly PMA, which is thought to have higher mobility and lower viscosity than that of PMB (PMA: $D = 1.46 \times 10^{-8}$ cm^2/s, $[\eta] = 0.32$ dl/g. PMB: $D = 2.29 \times 10^{-9}$ cm^2/s, $[\eta] = 1.20$ dl/g) (Van Krevelen, 1990; Nam et al., 2002b). The polymer leaking continues, since the hydrogel have enough ability to absorb aqueous solution, which makes the hydrogel to swell. If the leaking polymer is uncross-linked polymer having no interaction, this polymer can be referred to as dissoluting out from the hydrogel. Fig. 3d shows that the change in the polymer concentration of the hydrogel. Ten wt.% hydrogel at the start point would turn into 3 wt.% hydrogel in 24 h. The mechanical strength of the hydrogel would be weakened as time goes by. This would bring the decrement of the water absorption ability which would directly affect the swelling. Since the hydrogel would remain in the stomach for 2 h (Hörter and Dressman, 2001), it is thought that the hydrogel would maintain between 4900 ± 400 N/m^2 and 1800 ± 160 N/m^2.

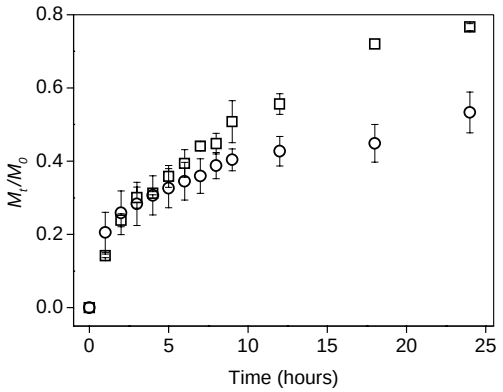


Fig. 4. The release behavior of the insulin and cytochrome *c* in acidic aqueous solution. (□) Cyc and (○) INS. Notice that the release would be almost the same for first 4 h and slowly be faster for Cyc than INS.

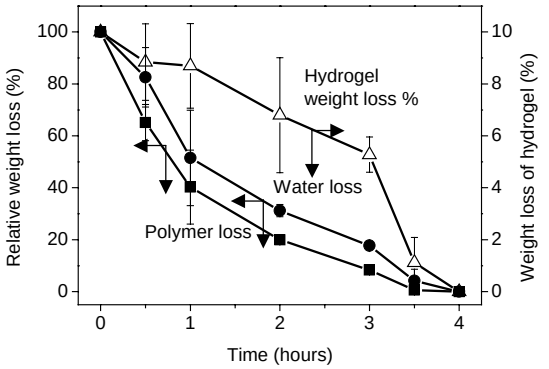


Fig. 5. The change in the polymer weight loss, water weight loss, and the weight loss of the hydrogel according to time.

The release of the loaded drugs in acidic condition had been compared between INS and Cyc. The release behavior of the INS and Cyc are shown in Fig. 4. For Cyc, the release was almost similar to that of insulin for 4 h. Then after 24 h, the release of Cyc was much higher, although the Cyc ($M_w = 12{,}000$) has higher molecular weight than INS ($M_w = 5500$). The higher release for Cyc after 4 h indicates that the affect of the hydrophilicity would appear, for the dissolution of the polymer would be suppressed. The diffusion exponent n was 0.49 for Cyc, while 0.28 for INS. The diffusion coefficient D for Cyc was $3.17 \times 10^{-5}\,\mathrm{cm}^2/\mathrm{s}$, while for INS was $2.01 \times 10^{-5}\,\mathrm{cm}^2/\mathrm{s}$ ($0.4 \leq M_t/M_\infty \leq 0.6$). The low diffusion exponent that is shown to be off-limit ($n < 0.45$) indicates that the release of the INS would not follow either diffusion of the drugs or relaxation of the polymer chains. When Figs. 3c and 4 are compared, we can see that the time for stabilization of the INS release was almost in match with the leaking out of the polymer. Low diffusion coefficient and high hydrophobicity of INS had sustained the release due to the stabilization of the hydrogel. From these results, we can see that the Cyc would follow diffusion process, independent from dissolution of the polymer chains. However, in the case of INS would not diffuse out. The polymer portion dissoluted out from the hydrogel would control the release of INS. And as the hydrogel becomes stabilized, the release of the INS would also be stabilized.

3.2. Dissociation and release behavior of hydrogels in neutral pH condition

The hydrogel would erode as soon as the hydrogel is immersed into the pH 6.8 PBS. The dissociation of the polymer chain is caused by the anionization of the carboxyl groups, in which they lose their role as cross-linking junctions and push each other away. During this process, the loss of water and the polymer was continued as shown in Fig. 5. The polymer was going out from the hydrogel faster than water, which brought the change in the polymer weight loss. The reason for faster polymer loosing is due to the absorption of outside PBS which surrounds the hydrogel, which is a significant factor for the erosion. For the carboxyl groups to be anionized, the hydrogel would absorb the PBS on the first hand, which implies that there is phase exchange between inside water and out PBS. However, loss of water indicates that the water within the hydrogel had left the system together with the polymer, and its speed would be faster than absorption of PBS. The polymer weight percentage of the hydrogel suddenly drops rapidly, indicating that the dissolution of the polymer would be speeded up. The reason for relatively slower loss of water comparing to polymer loss can be also thought due to the decrement of the network density. Since the total weight percentage of the hydrogel is going down as time goes by, it can be thought that the network density is also decreasing. This brings the relatively higher water uptake which makes the release of water inside the hydrogel slower.

Decrease of size of the hydrogel when the drugs are loaded into the hydrogel is shown in Fig. 6. The

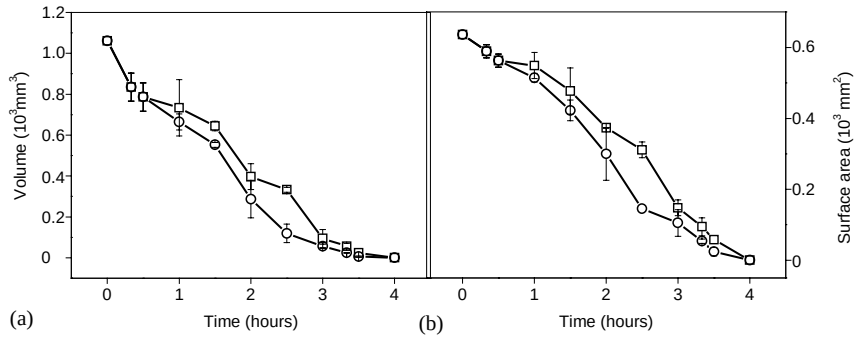


Fig. 6. The change in the volume (a) and the surface area (b) of the hydrogel with loaded drugs. It can be seen clearly that the erosion of INS loaded hydrogel (□) would be decreasing slower than that of Cyc loaded hydrogel (○).

volume and the surface area are decreasing almost constantly, with slightly faster dissociation for Cyc loaded hydrogel. According to Göpferich, the erosion of the hydrogel can be directly affected by the loaded drugs (Göpferich, 1996). From this, it can be thought that the hydrophobicity of the insulin have caused the slight time lag.

The dissolution behavior of the polymer was investigated by using Eq. (3). The result, as shown in Table 1, shows that the k_{diss} would occur at constant rate and suddenly increases approximately 1.7 times measurement after 2 h. The sudden increase is thought to due to small size of the hydrogel. Although the k_{diss} had increased from 3 h, the eroded portion of the hydrogel had decreased, indicating that the release of water had speeded down. From this, we can predict that the polymer concentration of the hydrogel would be decreased rapidly. We had mentioned that the water uptake by the hydrogel would increase due to lower cross-link density in Figs. 5 and 6. The result from Figs. 5 and 6, and Table 1 implies the same results. Comparing INS loaded hydrogel and Cyc loaded hydrogel, we found that in the case of Cyc loaded hydrogel, the dissolution rate would be almost the same for first 1 h, but be two times faster afterward. We can only assume that the hydrophobic drug had affected the dissolution rate, but why the dissolution rate have so large difference is not yet clear. Further investigation is on its way for clear explanation.

Table 1
Surface area and dissolution rate constant according to the time

Time (h)	Surface area (mm^2)		Dissolution rate constant ($mg/min\,mm^2$)	
	INS	Cyc	INS	Cyc
0.5	0.59	0.59	2.3×10^{-3}	2.3×10^{-3}
1	0.57	0.51	2.0×10^{-3}	2.3×10^{-3}
2	0.37	0.23	2.0×10^{-3}	3.3×10^{-3}
3	0.16	0.08	3.4×10^{-3}	7.2×10^{-3}
3.5	0.09	0.05	5.6×10^{-3}	1.1×10^{-2}

Fig. 7 shows the release behavior of the INS and Cyc in neutral condition according to the time. Simple release phenomenon in neutral PBS was observed by using Eq. (1). The INS and Cyc showed almost similar release behavior for 4 h, indicating that the release mechanism would be almost the same in neutral condition. The diffusion exponent n was 0.69 for INS and 0.87 for Cyc. Diffusion exponent shows that the release of the drugs would basically follow the anomalous transport, which implies that the release would not fully depend on the diffusion of the drugs.

Whether polypeptide drugs release phenomena would be caused by the surface erosion was explained by using Eq. (6). The erosion rate constant is almost the same for the INS loaded hydrogels and Cyc loaded hydrogels. The erosion rate constant k_0 was 1.94×10^{-2} mg/min mm^2 for INS and 1.99×10^{-2} mg/min mm^2 for Cyc. When the theoretical release profile using the average k_0 and experimental release profile was compared, it could be seen that the release was in match with each other until 3 h (Fig. 7). However, the experimental release profile showed that the release would be slowed down. The rise of lag time is thought to be due to the property of the loaded drugs (Konar and Kim, 1997). This is in match with the dissolution phenomenon as stated before.

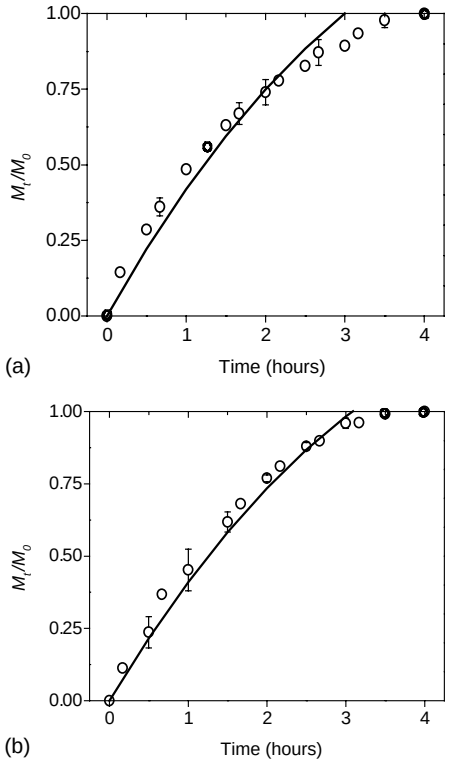


Fig. 7. The release behavior of the INS (a) and Cyc (b) in neutral PBS. The line indicates the theoretical release using Eq. (6) when the k_0 is 1.94×10^{-2} mg/min mm^2 ($R^2 > 0.97$) for INS and k_0 is 1.99×10^{-2} mg/min mm^2 ($R^2 > 0.98$) for Cyc, respectively.

However, the fact that although there was big difference in dissolution rate between INS loaded hydrogel and Cyc loaded hydrogel, but similar erosion rate constant implies that the release in neutral condition does not fully rely on the dissolution of the polymer chains. The dissolution of the polymer chain might be affected by the loaded drugs, but the surface erosion would not. The dissolution rate showed to be increased two-folds every 1 h, but the erosion rate constant is monotonous. This is because the water movement had been considered in the surface erosion, but dissolution did not. We had shown that the water is also going out from the hydrogel, but relatively slower speed, for the absorption of water. Erosion generally considers water going out from the hydrogel. So, in the case of hydrogel, the dissolution rate and erosion rate shows the different aspect.

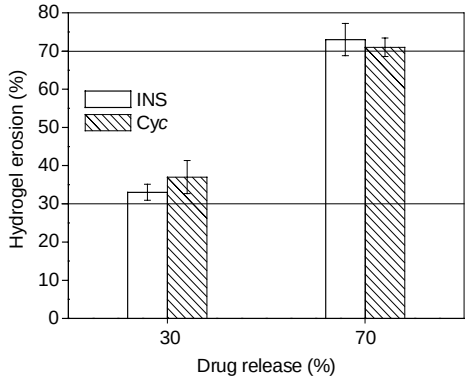


Fig. 8. The relationship of the release of the loaded drugs vs. the erosion of the hydrogel where 30 and 70% of release had taken place.

3.3. Relationship between erosion and release

To compare the erosion process and the release phenomenon of the INS and Cyc, hydrogel erosion when 30 and 70% release of loaded drugs had occurred were picked. Then the erosion percentage of the hydrogel at this time was chosen (Fig. 8). When 30 and 70% of release had occurred, the erosion of the hydrogel was more than 30 and 70%, respectively. The erosion and release is competitive, which implies that the release would occur constantly as the hydrogel starts to erode away and continues until it ends dissociation. Similar phenomenon could be seen in the work of Zuleger et al., using proxyphylline-tablets and acetonenetidin-tablets (Zuleger and Lippold, 2001).

Comparing INS and Cyc, there is no significant difference between these two kinds. We had found that the change in polymer concentration and PMA/PMB feed ratio may alter the release behavior of polypeptide drugs (Nam et al., submitted for publication). However, at this polymer concentration and PMA/PMB feed ratio, we could not detect big changes between INS and Cyc.

4. Conclusion

We tried to explain how this two polymer component system would behave in GI tract. Unlike the existing single polymer component systems, this hydrogel would be ruled by the two important factors:

(1) the characteristics of the respective polymers; and (2) the formation of the cross-link junctions. The intrusion of outside water starts from the surface and gradually penetrates into the core. In the case of acidic aqueous solution, the cross-link junction of the hydrogel remains stable, control release of the loaded drugs was regulated by diffusion process. However, the effect of the diffusivity would be eliminated for the hydrophobic drugs. The hydrophobic drugs were released together with the dissoluting polymers. When the hydrogels immersed into neutral PBS, the hydrogel would dissociate as the carboxyl groups turns into the carboxylate anions. The dissociation of the hydrogel followed surface erosion and could well adopt the equation developed for the tablets.

The release of the drugs would not depend on one point of aspect. Basically, the release would depend on the erosion of the hydrogels, but diffusion caused by the phase exchange between inside and outside aqueous solution also affected the release profile contemporarily. In the case of acidic condition, the release was almost the same for hydrophilic and hydrophobic for 4 h and be separated, indicating that the release would depend on the dissolution of the polymer, but would follow diffusion of the loaded drugs afterward. In neutral condition, the release mainly depended on the surface erosion of the hydrogel. The release in neutral condition did not show big difference between hydrophilic and hydrophobic drugs.

We have defined how the hydrogel would swell, erode, and release the loaded polypeptide drugs in gastrointestinal tract condition. We are going to investigate how to control release the loaded polypeptide drugs in our next research paper.

Acknowledgements

A part of this study was financially supported by Grant-in-Aid for the Development of Innovative Technology (13202) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan.

The research is carried out under supported to one of the authors (K. Nam) by a Grant for 21st Century COE Program “Human-Friendly Materials based on Chemistry” from the MEXT of Japan.

References

Baker, R.W., Lansdale, H.K., 1974. Controlled Release: Mechanism and Rates. Alza Corporation, Palo Alto, CA 93404 and Bend, OR 97701.

Bettini, R., Catellani, P.L., Santi, P., Massimo, G., Peppas, N.A., Colombo, P., 2001. Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. J. Control. Release 70, 383–391.

de Jong, S.J., De Smedt, S.C., Wahls, M.W.C., Demeester, J., Kettenes-van den Bosch, J.J., Hennink, W.E., 2000. Novel self-assembled hydrogels by stereocomplex formation in aqueous solution of enantiomeric lactic acid oligomers grafted to dextran. Macromolecules 33, 3680–3686.

de Jong, S.J., De Smedt, S.C., Demeester, J., van Nostrum, C.F., Kettenes-van den Bosch, J.J., Hennink, W.E., 2001. Biodegradable hydrogels based on stereocomplex formation between lactic acid oligomers grafted to dextran. J. Control. Release 72, 47–56.

D’Emanuele, A., Hill, J., Tamada, J.A., Domb, A., Langer, R., 1992. Molecular weight changes in polymer erosion. Pharmacol. Res. 9, 1279–1283.

Göpferich, A., 1996. Mechanisms of polymer degradation and erosion. Biomaterials 17, 103–114.

Heller, J., 1980. Controlled release of biologically active compounds from bioerodible polymers. Biomaterials 1, 51–57.

Hopfenberg, H.B., 1976. In: Paul, D.R., Harris, F.W. (Eds.), 1976. Controlled Release Polymeric Formulations. ACS Symposium Series 33. American Chemical Society, Washington, DC, pp. 26–31.

Hörter, D., Dressman, J., 2001. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv. Drug Deliv. Rev. 46, 75–87.

Ishihara, K., Aragaki, R., Ueda, T., Watanabe, A., Nakabayashi, N., 1990. Reduced thrombogenicity of polymers having phospholipid polar groups. J. Biomed. Mater. Res. 24, 1069–1077.

Ishihara, K., Oshida, H., Endo, Y., Ueda, T., Watanabe, A., Nakabayashi, N., 1992. Hemocompatibility of human whole blood on polymers with a phospholipid polar groups and its mechanism. J. Biomed. Mater. Res. 26, 1543–1552.

Ju, R.T.C., Nixon, P.R., Patel, M.V., Tong, D.M., 1995a. Drug release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer. J. Pharm. Sci. 84, 1455–1463.

Ju, R.T.C., Nixon, P.R., Patel, M.V., Tong, D.M., 1995b. Drug release from hydrophilic matrices. 2. A mathematical model based on the polymer disentanglement concentration and the diffusion layer. J. Pharm. Sci. 84, 1464–1477.

Katzhendler, I., Hoffman, A., Goldberger, A., Friedman, M., 1997. Modeling of drug release from erodible tablets. J. Pharm. Sci. 86, 110–115.

Khare, A.R., Peppas, N.A., 1995. Swelling/deswelling of anionic copolymer gels. Biomaterials 16, 559–567.

Konar, N., Kim, C.-J., 1997. Water-soluble polycations as oral drug carriers (tablets). J. Pharm. Sci. 86, 1339–1344.

Konno, T., Kurita, K., Iwasaki, Y., Nakabayashi, N., Ishihara, K., 2001. Preparation of nanoparticles composed with bioinspired 2-methacryloyloxyethyl phosporylcholine polymer. Biomaterials 22, 1883–1889.

Nam, K., Watanabe, J., Ishihara, K., 2002a. Characterization of the spontaneously forming hydrogels composed of water-soluble phospholipid polymers. Biomacromolecules 3, 100–105.

Nam, K., Watanabe, J., Ishihara, K., 2002b. pH-modulated release of insulin entrapped in spontaneously formed hydrogel system composed of two water-soluble phospholipid polymers. J. Biomater. Sci. Polym. Edn. 11, 1259–1270.

Nam, K., Watanabe, J., Ishihara, K. The characteristics of spontaneously forming physically cross-linked hydrogel composed of two water-soluble phospholipid polymers for oral drug delivery carrier II: release behavior of diverse model drugs loaded in the hydrogels, Eur. J. Pharma. Sci., submitted for publication.

Narasimhan, B., 2000. Mathematical models describing polymer dissolution: consequences for drug delivery. Adv. Drug Deliv. Rev. 48, 195–210.

Park, K., Shalaby, W.S.W., Park, H., 1993. Physical gels. Biodegradable Hydrogels for Drug Delivery. Technomic Publishing Co., Lancaster, PA, USA, pp. 99–140.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.

Qu, X., Wirsen, A., Albertson, A.-C., 1999. Synthesis and characterization of pH-sensitive hydrogels based on chitosan and D,L-lactic acid. J. Appl. Polym. Sci. 74, 3186–3192.

Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release I. Fickian and anomalous release from swellable devices. J. Control. Release 5, 37–42.

Shaheen, S.M., Yamaura, K., 2002. Preparation of theophylline hydrogels of atatic poly(vinyl alcohol)/NaCl/H_2O system for drug delivery system. J. Control. Release 81, 367–377.

Siepmann, J., Göpfrerich, A., 2001. Mathematical modeling of bioerodible, polymeric drug delivery systems. Adv. Drug Deliv. Rev. 48, 229–247.

Siepmann, J., Kranz, H., Bodmeier, R., Peppas, N.A., 1999. HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling, and dissolution mechanism and predicting the release kinetics. Pharm. Res. 16, 1748–1756.

Sinclair, G.W., Peppas, N.A., 1984. Analysis of non-Fickian transport in polymers using simplified exponential expressions. J. Membr. Sci. 17, 329–331.

Ueda, T., Oshida, H., Kurita, K., Ishihara, K., Nakabayashi, N., 1992. Preparation of 2-methacryloyloxyethyl phosphorylcholine copolymers with alkyl methacrylate and their blood compatibility. Polym. J. 24, 1259–1269.

Van Krevelen, D.W., 1990. Properties of Polymers, vol. 3. Elsevier, New York, USA, pp. 535–584.

von Burkersroda, F., Schdl, L., Göpferich, A., 2002. Why degradable polymers undergo surface or bulk erosion. Biomaterials 23, 4221–4231.

Wang, C., Steward, R.J., Kopecek, J., 1999. Hybrid hydrogels assembled from synthetic polymers and coiled-coil protein domains. Nature 397, 417–420.

Watanabe, T., Ohtsuka, A., Murase, N., Barth, P., Gersonde, K., 1996. NMR studies on water and polymer diffusion in dextran gels. Influence of potassium ions on microstructure formation and gelation mechanism. Magn. Reson. Med. 35, 697–705.

Watanabe, J., Eriguchi, T., Ishihara, K., 2002. Cell adhesion and morphology in porous scaffold based on enantiomeric poly(lactic acid) graft-type phospholipid polymers. Biomacromolecules 3, 1375–1383.

Yasin, M., Tighe, B.J., 1993. Strategies for the design of biodegradable polymer systems: manipulation of polyhydroxybutyrate-based materials. Plastic Rubber Comp. Proc. Appl. 19, 15–27.

Yoneyama, T., Ishihara, K., Nakabayashi, N., Ito, M., Mishima, Y., 1998. Short-term in vivo evaluation of small-diameter vascular prosthesis composed of segmented poly(etherurethane)/2-methacryloyloxyethyl phosphorylchline polymer blend. J. Biomed. Mater. Res. (Appl. Biomater.) 43, 15–20.

Zuleger, S., Lippold, B.C., 2001. Polymer particle erosion controlling drug release. I. Factors influencing drug release and characterization of the release mechanism. Int. J. Pharm. 217, 139–152.