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Controlled Release Behavior of Spontaneously Cross-Linked Hydrogel Composed of Phospholipid Copolymers

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Physically cross-linked spontaneously formed hydrogel had been investigated in order to make use of oral delivery carrier. In this study, the 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer hydrogel was prepared from aqueous solutions containing water-soluble poly[MPC-*co*-methacrylic acid (MA)] (PMA) and poly[MPC-*co*-*n*-butyl methacrylate (BMA)] (PMB), and the physical properties of the hydrogels in terms of release behavior were examined by changing 4 factors (molecular weight of the copolymers, PMA/PMB feed ratio, water concentration inside the hydrogel, loaded model drugs) in neutral conditions. The affect of the erosion was the larger than diffusion for the release of the model drugs. The release was well in match with dissociation and followed non-Fickian case for all, but the diffusion coefficient *n* was changed according to the A/B feed ratio, water concentration, and the loaded model drugs. The release was not altered by the different kinds of the loaded model drugs, but by the condition of the hydrogels. The release was suppressed during swelling in neutral condition, while release was accelerated during dissociation.
Key words: phospholipid hydrogel, spontaneous gelation, non-Fickian diffusion, controlled release.

1. Introduction

The controlled release behavior of hydrogel is very important in the aspect of pharmacology. When, where, what and how to release the drug should be decided carefully in order to deliver the right drug in right carrier to the right position in right time. So far, the methods to deliver the drug, especially polypeptide drug, had been investigated world widely. Most convenient route for the delivery of the drug is known to be gastrointestinal (GI) tract. However, this route has a major drawback. The drug-loaded carrier would have to pass through acidic condition and although the carrier had passed the acidic condition safely, the carrier faces the preoteolytic enzymes and intestinal barrier.

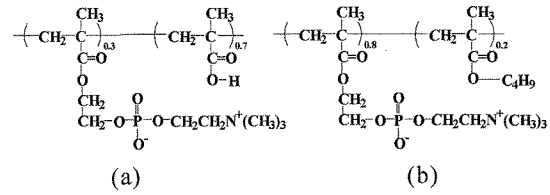
In order to develop the base material for the drug carrier, the material should be biocompatible. And in case of hydrogel, there can be three major ways to release the drug; 1) diffuse the drug out from the hydrogel, 2) degrade in the intestine or 3) erode in the intestine. The first one belongs to chemically cross-linked hydrogel, and others belong to physically cross-linked hydrogel. In case of chemical hydrogel, there is one very big disadvantage that the cross-linker is required. But in case of physical hydrogel, this is not needed. The term degrade indicates the chain scission process and the erosion indicates the loss of material from the hydrogel either by bulk or surface.

Our recent study showed that the polymer based on phospholipid shows spontaneous formation of the hydrogel caused hydrogen bonds between PMA in the hydrophobic domain provided by PMB [1]. This hydrogel posseses excellent biocompatibility and we had been studying in order to make use of this hydrogel as an oral delivery carrier [2] for this hydrogel is very clean, spontaneously forming, and has very high loading efficiency. In this study, we had executed the experiment on release behavior in neutral condition.

2. Materials and method

2.1 Preparation of the hydrogels

Two kinds of water-soluble phospholipid polymer PMA (MPC mole fraction: 0.3) and PMB (MPC mole fraction: 0.8) 5wt% aqueous solution that had been provided by NOF Corporation (Tokyo, Japan) was chosen for preparation of the hydrogel. The chemical structures of these MPC copolymers are shown in Figure 1. To make a 5wt% hydrogel, 5wt% PMA and PMB aqueous solution were put into a vial and mixed vigorously for 10 seconds.



(a) (b)

Figure 1. The chemical structure of the (a) PMA and (b) PMB.

Methyl orange (Mw. 327) (MO), fluorescein (Mw. 332) (FITC) was loaded into PMB 5wt% phosphate buffer solution (PBS). Then PMA

5wt% aqueous solutions were added and mixed as written above. Fluoroscein–4-isothiocyanate (FITC)-labeled insulin (1.1mol/mol FITC content, Mw. 5,500) (Ins), cytochrome *c* (Mw. 12,200) (Cyc), albumin (Mw. 65,000) (BSA), and γ-globulin (Mw. 160,000) (BγG), loaded hydrogels were prepared by the same method. These hydrogels were used to investigate the difference between the molecular weight and the hydrophilicity of the loaded drugs.

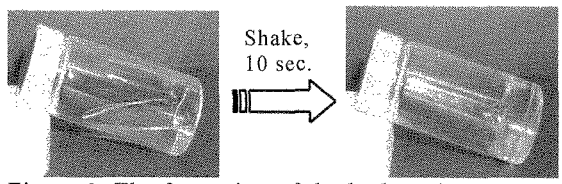


Figure 2. The formation of the hydrogel.

2.2 Determination of the release behavior

In order to observe the molecular effect of the polymers on the gelation, low molecular weight PMA (LPMA, Mn≈2.7×10^5, Mw≈6.8×10^5) and high molecular weight PMA (HPMA, Mn≈3.5×10^5, Mw≈1.0×10^6) were mixed with low molecular weight PMB (LPMB, Mn≈4.0×10^4, Mw≈8.7×10^4) and high molecular weight PMB (HPMB, Mn≈168k, Mw≈1.7×10^6) were mixed together to make LALB, HALB, HALB, and HAHB. All the prepared hydrogels were made with A/B feed ratio 5/5. The release of the FITC-labeled insulin (INS) and fluorescein (FITC) was measured every one hour with the fluoroscence spectrometer (λ_{EX}=490nm, λ_{EM}= 518nm for INS and λ_{EX}=493nm, λ_{EM}= 510nm for FITC). Measuring of methyl orange (MO), cytochrome *c* (Cyc), albumin (BSA), and γ-globulin (BγG) was executed by using UV spectrometer (λ=507nm for MO, λ=410nm for Cyc and λ=278nm for BSA and BγG).

To observe how the different feeding ratio of the MPC copolymers may effect the hydrogel for oral drug delivery carrier, feeding ratio was changed for preparing the hydrogel LPMA/HPMB (A/B feed ratio) = 1/9 to 9/1. Furthermore, the 5wt% and 10wt% hydrogels were prepared in order to find out how the hydrogel can be affected by the change of the water portion inside the hydrogel.

To observe the affect of water concentration, LPMA and HPMB aqueous solutions were lyophilized completely. And the water was added into LPMA and HPMB powder to make 20wt% hydrogel to 70wt%. The water and polymer mixture was stirred until the gelation broke out. All the hydrogel were made into A/B feed ratio 5/5.

3. Results and discussion

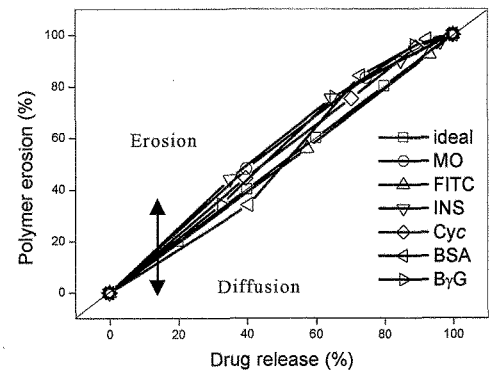
3.1 Relatioship between dissociation and release

Once the hydrogel is put into PBS, the hydrogel dissociates. The dissociation is different according to the parameters like PMA and PMB feed ratio, water concentration and molecular weight of the polymers [3]. Whether the release of the model drugs would be occurred by diffusion of the drugs or by erosion caused by chain disentanglement of the hydrogel had to be clearly explained. We could not find any proof for degradation, for the MPC polymers maintained its molecular weight after the dissociation.

Simple substantiation method by comparing release and dissolution behavior was executed [4]. By comparing the drug release and polymer erosion percentage, simple curve could be obtained (Figure 3). We could see that the release of the drug heavily depends on the erosion than diffusion and this tendency would become stronger for 10wt% hydrogels. The interesting point is that the release of the drugs was not depending on the solubility of the drugs. This implies that the release would not be changed by the alteration of the drugs but by alteration of the hydrogel.

3.2 Release behavior from the hydrogel

The release pattern for 5wt% and 10wt% hydrogel is sigmoidal, which is typical for cylindrical gel. The time term is very short, which last no longer than 4 hours. Generally, the release pattern resembles that of dissociation profile, but is not in exact match with it.



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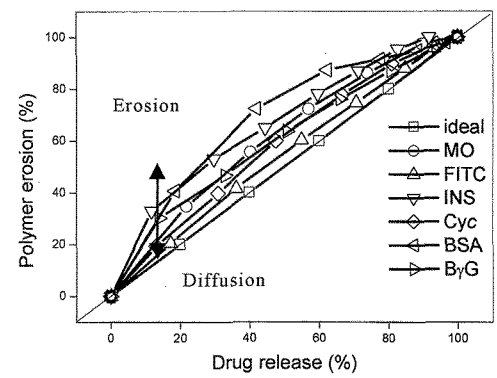
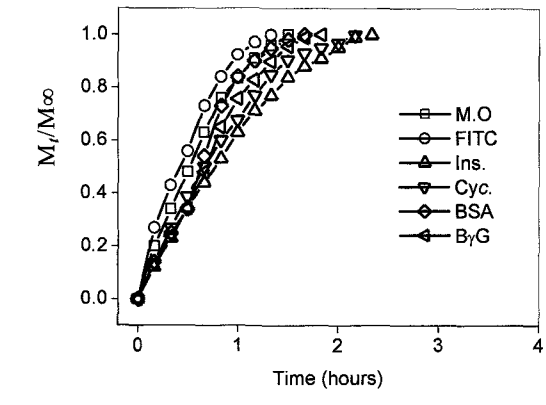
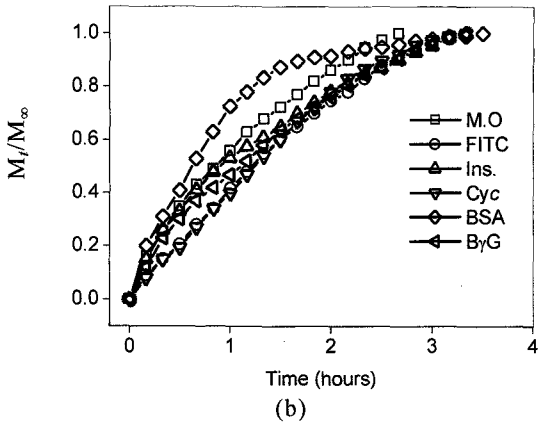


(b)

Figure 3. The erosion and release correlation curve of (a) 5wt% and (b) 10wt% hydrogels.



(a)



(b)

Figure 4. The release behavior of the model drugs loaded in (a) 5wt% and (b) 10wt% hydrogels.

Previously, we had mentioned that the surface erosion is going to occur [2-3]. The erosion mechanism is ruled by the dissolution of the polymer network that consist the hydrogel. When the polymer chains start disentangle out from the hydrogel, the drugs that is located would be revealed and diffuse out from the hydrogel. During this process, it is thought that the release of the model drugs would differ according to the loaded drugs, which have different diffusion coefficients, and the properties of the respective hydrogels. Furthermore, it can be thought that the location of the hydrophilic and hydrophobic model drugs is different. The hydrophobic drugs would be reservoir system while hydrophilic drugs would be matrix system.

The molecular weight of the adopted polymer changes the release behavior of the hydrogels. In the case of HPMB, the slower release was observed compared with LPMB. And for LPMB-adopted hydrogel, the release was too fast to measure the diffusion coefficient or exponent.

The diffusion exponent n was calculated using the power law equation written below [5];

$$M_t/M_\infty = kt^n \quad (1)$$

and for diffusion coefficient D [6];

$$M_t/M_\infty = 4(Dt/\pi l^2)^{1/2} \quad (2)$$

Where M_t/M_∞ is fractional release, k is kinetic constant, l is the height of the hydrogel matrix when $0 \le M_t/M_\infty \le 0.6$

The results suggested that release of drugs would be different among them. In general, the diffusion exponents laid between n=0.45-1.0, indicating that the release follow non-Fickian [6]. In several cases, which was hydrophilic model drug, showed that diffusion would be absolutely faster than chain relaxation or phase erosion.

The release of the cytochrome *c* and insulin was different according to the A/B feed ratio. As shown in Table I, the diffusion coefficient varied according to A/B feed ratio. When the ratio of PMA is higher than PMB, the diffusion coefficient is higher for insulin, but as the ratio of PMB increases, the diffusion coefficient decreases in case of insulin and increases for cytochrome *c*. This indicates that increment of hydrophobic domain would prohibit the fast diffusion of the insulin which would eventually bring fast release. On the other hand, cytochrome *c* has bigger molecular weight than insulin, which would slowly release the cytochrome *c*. The increase of diffusion coefficient for cytochrome *c* and decrease for insulin on the higher PMB ratio also implies that the relaxation of the polymer network would decrease, or have lesser network structure than the hydrogel with higher PMA ratio.

Table 1. The diffusion exponent of the hydrogels according to A/B feed ratio.

PMA/PMB	Drug type	
	Cytochrome *c*	Insulin
9/1	0.62±0.11	-
7/3	0.79±0.19	0.99±0.03
5/5	0.78±0.09	0.82±0.17
3/7	0.94±0.10	0.81±0.03
1/9	0.90±0.13	-

Table II. The diffusion exponent (n) and diffusion coefficient (D) of the 5/5 hydrogels.

Sample	n	D (mm^2/hr)	Remark
Methyl orange	0.68	0.79	
Fluorescein	1.02	0.44	
Insulin	0.82	0.72	
Cytochrome *c*	0.78	0.40	
BSA	0.83	1.30	
γ-globulin	0.63	0.56	
PVA / H_2O	0.53	0.45	Ref. (5)
PVA/NaCl/H_2O	0.44	2.64	Ref. (5)

The diffusion coefficient D of the hydrogels calculated using equation 2, show that the diffusion dependency is low and the relationship between hydrophilicity of the drugs would not be important (Table II). Release mechanism slightly differed according to the model drug in spite of almost overlapping dissociation profile. The release from the low molecular weight drug did not release the model drug faster then the high molecular weight model drugs in A/B feed ratio 5/5. The diffusion coefficient was lying between 0.6 and 1.0 indicating that the release would be controlled by relaxation and diffusion (non-Fickian). Rise of the diffusion coefficient and diffusion exponent with the molecular weight of the drug was not observed. S.J. de Jong et al, had mentioned that the diffusion exponent would increased with molecular weight of the drugs [7]. In this system, the rise did not occur due to complete independency from the diffusion. The release of the model drugs would be occurred by erosion. And the drug would be diffused out together with eroding PMA or PMB.

Change in the water concentration had also brought up the alternation of the release profile. The release of the model drugs for first 4 hours was suppressed as water concentration of the hydrogel decreased as shown in Figure 5. This is well in match with the dissociation profile [3]. We had found out that the swelling would occur for certain time and then would be dissociated. The swelling is occurred by the absorption of the water and when the hydrogel starts to absorb the water, the uncross-linked polymer would be leaking out. The swelling itself do not induce the release, for the higher swelling hydrogel showed lower release of the drugs. The release would be occurred together with leaking out of uncross-linked polymer. The released drug percentage was almost same with each other (≤10%) while swelling.

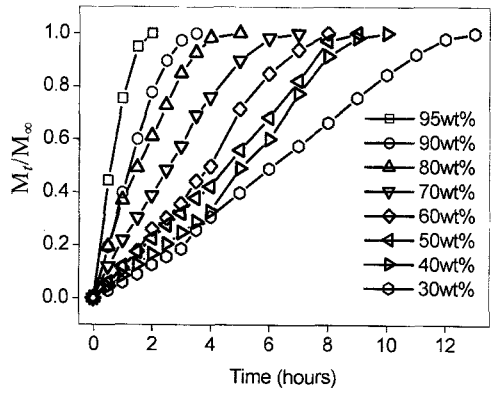


Figure 5. The release of cytochrome *c* from diverse water concentration.

4. Conclusions

The release property of the hydrogel showed different behavior as dissociation behavior did. The erosion of the hydrogel caused the release of the drugs. When the different drugs were loaded in the same hydrogels, the release pattern had not changed. However, the release pattern changed according the A/B feed ratio and water concentration within the hydrogel. The diffusion coefficient had decreased when the hydrophobic domain inside the hydrogel became abundant. It was opposite for the hydrophilic drugs. When the water concentration had changed, the release pattern had changed, too. As the hydrogel started to swell, the release was suppressed. And once the dissociation took place, the release suddenly accelerated. The same phenomenon could be seen in the in vitro release experiment. The release was suppressed in acidic condition, where the hydrogel is swelling, and the release was faster when the hydrogel was dissociating [2]. When the release of the model drugs were calculated by power-law equation, the release under 10wt% hydrogel was all following non-fickian, with few exceptions. This exception is thought to the due to hydrophobic interaction or hydrogen bonds between polymer chains and the drugs. The molecular weight specificity of the model drugs in neutral condition was not seen, for the release was mainly due to the surface erosion of the hydrogel.

By changing the several factors, we had achieved the changed release behavior of the hydrogel. This means that it is now possible to control the release of the drug in the right time, in the right position by adopting right drugs. Simply by changing the water concentration, molecular weight, or A/B feed ratio, it would be able to release the drug anywhere inside the GI tract without adding any other agents.

5. Acknowledgement

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