Study on Drug Delivery Systems(II) — Synthesis of Stimule Sensitive Polymers for Intelligent Drug Delivery Systems —

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Abstract

The stimule-sensitive and responsive hydrogels were synthesized by radiation polymerization. The effects of copolymer composition, hydrolysis and crosslinking monomers on the electrical responsiveness were investigated and compared with those on the temperature responsiveness. It was observed that the content of electrolytic component strongly affected on the stimule responsiveness and the responses showed a maximum at a certain copolymer composition. It was suggested that the responsiveness had an optimum at a suitable polyelectrolyte in the hydrogels. However, the temperature responsiveness was realized in the absence of polyelectrolytic component, while the electrical responsiveness absolutely required the polyelectrolytic content. The on-off switching release of insulin from the hydrogel under electric field was also investigated.
Key word: intelligent drug delivery systems, insulin release, electrically responsive hydrogels, temperature responsive hydrogels, radiation polymerization.

1 Introduction

In the previous report,[1] the concept, purposes and kinds of administration forms in the drug delivery systems were generally reviewed and the trial of special intelligent delivery system consisting of biochipsensor and stimule responsive hydrogel with on-off switching release function was reported. In recent years, the research and development on drug delivery systems is becoming increasing active in the world. Especially, the interest for the intelligent drug delivery systems in which a signal recognized and responsive controlled release function is attached, is attracting many workers very recently. The most important component devices in the intelligent delivery system are the biochipsensor and the stimule-sensitive and responsive hydrogel[2,3] as a mechanochemical system. It is necessary to study and develop the practically useful hydrogels having an excellent electrical sensitiveness and responsiveness for this purpose. However, much fewer reports have been published on the electrically sensitive and responsive gels in comparison with the study on the temperature sensitive hydrogels.

In the series of studies on drug delivery sys-

tems, the authors want to clarify the relationship between the chemical structures and composition of polymers and the electrical responsiveness of the polymers more systematically and in details.

2 Experimentals

Monomers used are the extra pure grade reagents and were polymerized by the irradiation of gamma-ray or photo irradiation into hydrogels. The formed gels were cut into samples and put between the electrodes as shown in Fig.1. The amount of absorbed water under on and off electric field at intervals was measured by the weight. Hydrolysis of polymer was carried out with 0.1N NaOH solution at 20°C.

3 Results and Discussion

3.1 Effect of copolymer composition on the electrical responsiveness

Three kinds of monomers, isopropylacrylamide, acrylic acid or methacrylic acid and a crosslinker (polyfunctional monomer) such as 2G (diethyleneglycol dimethacrylate) and 14G (polyethyleneglycol dimethacrylate) were copolymerized as a hydrogel. It is expected that a suitable balance in copolymer composition would give the optimum hydrophilicity-hydrophobicity balance and electrolytic dissociation, resulting in the optimum electrical responsiveness. Fig.1 shows the electrical responsiveness of the hydrogel expressed by the weight change as the function of polyacrylic acid/ polyisopropylacrylamide ratio in the copolymers. According to the result in Fig. 1, the electrical response had a sharp maximum at the point of 10-20% polyacrylic acid content.

For the comparison, the temperature depending response of the same hydrogel was shown in Fig.2 as the function of polyacrylic acid/ polyisopropylacrylamide ratio. As shown in Fig. 2, the temperature response had a broad maximum at 10-20% polyacrylic acid content. However, polyisopropylacrylamide (0% polyacrylic acid) also showed a considerable temperature responsiveness, while it had no effectiveness for the electrical responsiveness (copolymerization with acrylic acid was necessary). As polyisopropylacrylamide is non-electrolyte, the introduction of polyelectrolyte component might be necessary for the effective electrical responses. Then, the effect of hydrolysis of the copolymer to introduce more carboxy group on the electrical responsiveness was investigated.

3.2 Effect of hydrolysis on the electrical responsiveness

The hydrolysis of copolymers with sodium hydroxide was carried out to introduce more electrolytic property. The effect of hydrolysis on the electrical responsiveness and also on the temperature responsiveness was investigated. The result is shown in Fig. 3 and 4. As shown in Fig.3, the composition range of effective electrical response was remarkably enlarged by the hydrolysis, that is, with the increase of electrolytic content. The polyacrylic acid content between 10-500% showed the electrical response, though there was a maximum still at the polyacrylic acid content 10-100% range for the copolymer hydrolyzed for 1 hr, and 10-250% range for the copolymer hydrolyzed for 4 hrs. The enlarging and broadening effect of hydrolysis on the effective electrical responses was larger with increase of hydrolysis time.

The temperature responsiveness of the hydrolyzed copolymers was shown in Fig. 4. As shown in Fig. 4, the temperature responses in the hydrolyzed copolymers increased the sensitivity than non-hydrolyzed copolymers showing larger swelling change and broader peak at lower temperatures. However, it was still the different characteristics that polyisopropylacrylamide (no polyacrylic acid content) showed a considerable temperature responsiveness. Therefore, it is con-

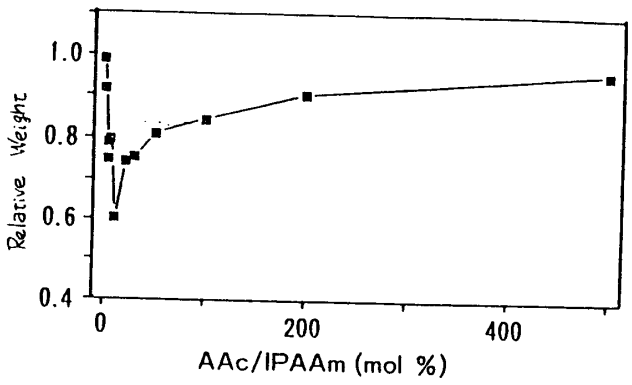

Fig. 1: Effect of copolymer composition on the electrical responsiveness of hydrogel. Electric field: 5V, Time of on-field: 5hrs. AAC/IPAAm: Ratio in mol% of acrylic acid to isopropylacrylamide.

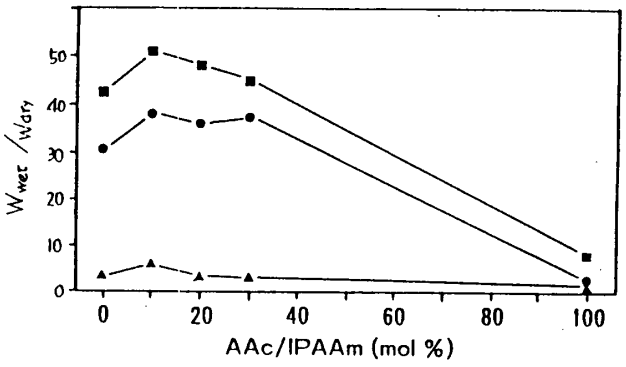

Fig. 2: Effect of copolymer composition on the temperature responsiveness of hydrogel. Temperature: ■ 10°C, ● 20°C, ▲ 30°C. W_{wet}/W_{dry}: Ratio of weight of swelled polymer to that of dried polymer. AAc/IPAAm: Same as in Fig. 1.

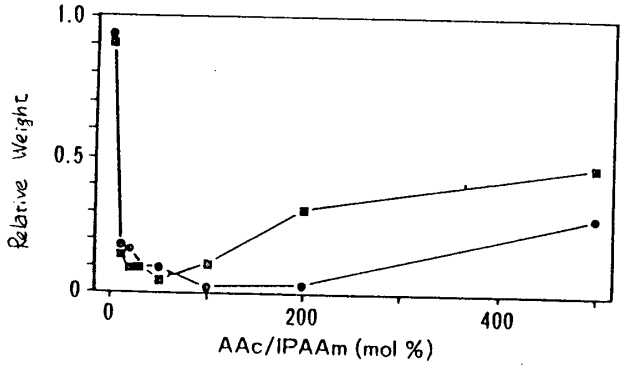

Fig 3: Effect of copolymer composition and hydrolysis time on the electrical responsiveness of hydrogel. Electric field: 5V, 5hrs. Hydrolysis time: ■ 1hr, ◐ 4hrs, AAc/IPAAm: Same as in Fig. 1.

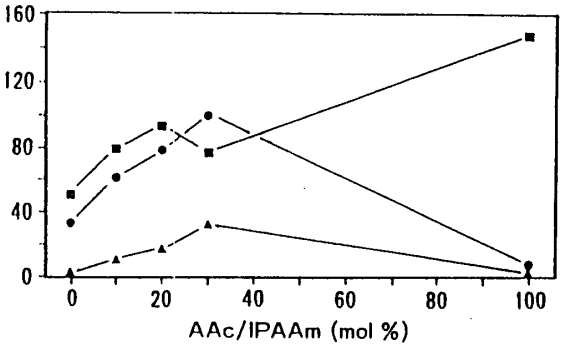

Fig 4: Effect of copolymer composition and hydrolysis time on the electrical responsiveness of hydrogel. Temperature: ■ 10°C, ● 20°C, ▲ 30°C, Hydrolysis: 1hr. W_{wet}/W_{dry}: Same as in Fig. 2.

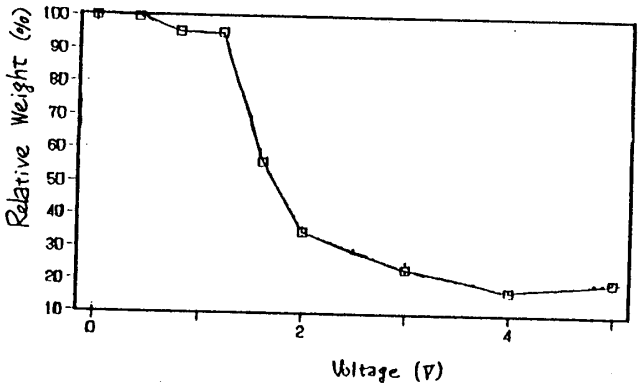

Fig. 5: Effect of voltage on the electrical responsiveness of hydrogel. Copolymer: Acrylic acid-isopropylacrylamide-diethylenglycol dimethacrylate. Hydrolysis: 18hrs.

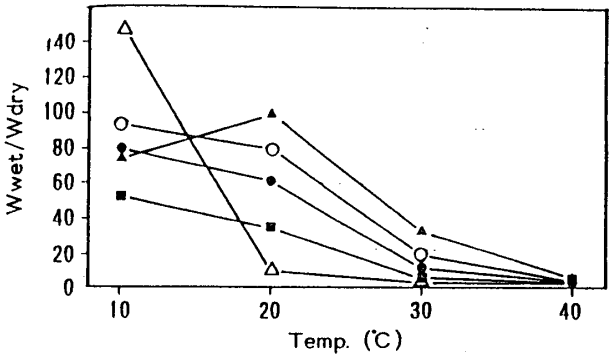

Fig. 6: Effect of temperature on the temperature responsiveness of hydrogel. AAc/IPAAm ratio(mol %): ■ 0%, ● 10%, ○ 20%, ▲ 30%, △ 100%. Hydrolysis: 4hrs.

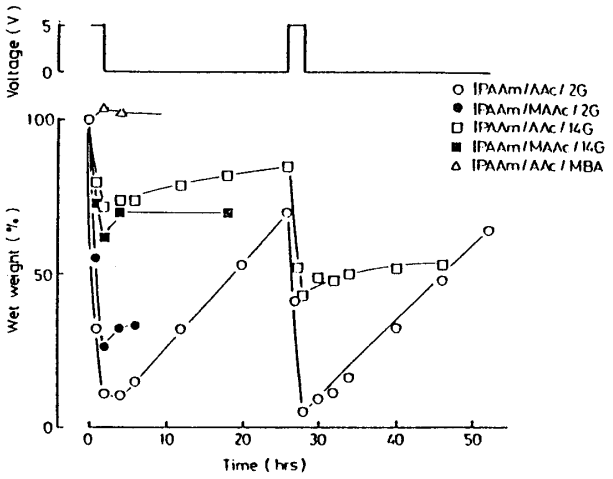

Fig. 7: Effect of crosslinking monomer on the electrical responsiveness of hydrogel. Crosslinking monomer: 2G (diethyleneglycol dimethacrylate), 14G (polyethyleneglycol dimethacrylate), MBA (methylene-bis-acrylamide)

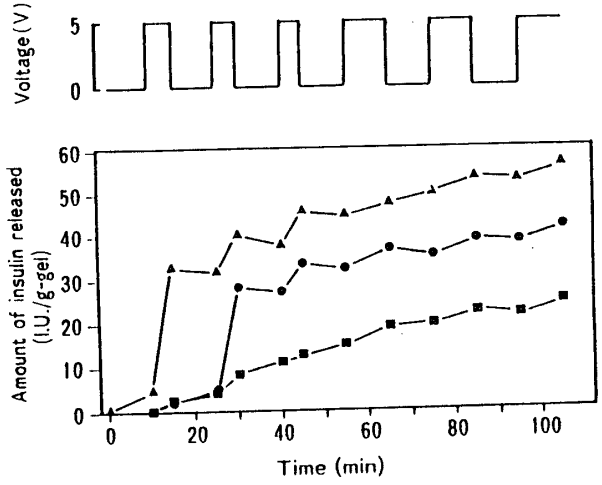

Fig. 8: On-off switching release of insulin from the electrically responsive hydrogels obtained by various hydrolysis times.
Hydrolysis time: ■ 0hr, ● 1hr, ▲ 4hrs, copolymer: Acrylic acid-isopropylacrylamide-diethyleneglycol dimethacrylate.

cluded that the electrical responsiveness requires the electrolytic component unit in the copolymer (polyacrylic acid unit or hydrolyzed polyisopropylacrylamide unit), while the temperature responsiveness needs no electrolytic unit, but absolutely needs polyisopropylacrylamide unit.

Fig. 5 and 6 showed the electrical responsiveness and the temperature responsiveness of the hydrolyzed copolymers as the function of voltage changes and temperature changes, respectively. At the present stage of sensitivity in the copolymers, 1-2 volts was necessary to realize the sufficient electrical response, and at least lower than 20°C was necessary for the temperature response. The specific responses of the gels were opposite in the two stimule responsiveness. The response is shrinkage in volume in the electrical responsiveness and it is expansion (swelling) in the temperature responsiveness. The further improvement of the sensitivities would be the future problem.

3.3 Effect of crosslinking on the electrical responsiveness

As the stimule sensitive responsivenesses are affected by the hydrophilicity and phase separation property of the gels, the kinds and amount of crosslinking agents (chemical structure and density of the crosslinking) would have the important effects on the responsiveness. From this point of view, the effects of crosslinking monomers on the electrical responses of polymers were investigated. The results are shown in Fig. 7. According to those results, the crosslinking monomers showed the effectiveness in the order of diethyleneglycol dimethacrylate, polyethyleneglycol dimethacrylate and methylene-bis-acrylamide, on the electrical sensitivity. Diethyleneglycol dimethacrylate (2G) showed the best effect on the sensitivity and response in the repeated uses under on-off switching of electric field. This result suggested the more effectiveness of shorter and hydrophobic crosslinked chain than the longer hydrophilic one. The further detailed studies would be done on the effects of amount and density of the crosslinking in the near future.

3.4 Entrapping and release of insulin in the electrical responsive hydrogels

The entrapping inclusion of insulin into the synthesized hydrogels was studies in relation to the electrically responsive controlled release. The hydrogels were put in an aqueous solution of insulin at pH 7.4, and absorbed insulin. Then the insulin release was measured in the water bath under the on- off switching of electric field. The result is shown in Fig. 8 There are several factors to be checked for the results. It was recognized that insulin was entrapped considerably and the release was repeated at intervals with the addition of electric field. However, automatic release during the off period was observed also in non-hydrolyzed copolymers. It was improved in the hydrolyzed gels. But, with the repetition of on-off switchings, the release amount of insulin decreased gradually, probably owing to the decrease in the entrapped amount of insulin. There was a burst of release in the initial stage. Therefore, the constancy, reproductivity and life length in the on-off switching release of insulin are the future problems to be improved. For this purpose, the simultaneous entrapping of insulin in the polymerization or the use of insulin reservoir (insulin layer) should be investigated to increase the amount of insulin and refine the release system as well as the improvement of hydrogel.

As described in the previous report, the hydrogel-insulin composite device was combined with a glucoseoxidase biochipsensor and tested for the stimule sensitive and responsive insulin releases with the on-off addition of glucose. It was proved that the whole system worked as a glucose recognizable and responsive insulin release system. However, the further improvements on the sensitivity, reproductivity, and life length would be important for the practical uses in the future.

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