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이온성 고분자 겔(II) : pH에 민감한 약물전달 체계로의 응용

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Polyelectrolyte Gels(II) : Application as a pH-Sensitive Drug Delivery System

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요 약 : 본 연구에서는 이온성 고분자 겔의 pH에 민감한 약물전달 체계로서의 응용 가능성을 조사하였다. 2-Acrylamido-2-methyl-1-propane sulfonic acid와 Butyl methacrylate의 불규칙 공중합체 겔 네트워크 및 Acrylamide과 2-Acrylamido-2-methyl-1-propane sulfonic acid의 IPNs 겔 네트워크을 이용하였다. 모델 약물로 사용한 하이드로 코티손과 염화에드로포니움은 분산 및 이온교환 수지 방법을 사용하여 겔 네크워에 충진하였다. 약물 방출 형태는 약물이 충진되어 있는 겔 네트워크의 pH에 의존하는 수팽윤 형태와 약물이 겔 네트워에 충진되어 있는 형태에 밀접한 상관관계를 나타내었다.

Abstract : In this study, the feasibility of the application of polyelectrolyte gel network as a pH-sensitive drug delivery system was examined. Copolymer of 2-acrylamido-2-methyl-1-propane sulfonic acid (AMPSA) and butyl methacrylate(BMA) was prepared as random copolymer network(RCN) and that of acrylamide(AAm) and AMPSA was prepared as interpenetrating networks(IPNs). Hydrocortisone and edrophonium chloride were used as model drugs and were loaded into gel networks using dispersion and ion exchange methods, respectively. The drug release patterns were closely related to the pH-dependent swelling behaviors of gel networks and the mode of drug loading.

INTRODUCTION

Much interest has been focused on the properties of polyelectrolytes because of their scientific interest and technological importance.[1~9] In particular, stimulisensitive polyelectrolytes have a potential application in the area of swelling-controlled drug delivery system because these polyelectrolytes not only respond to external stimulus but also control the release rate of solute loaded in the polyelectrolyte network.

In this study, polyelectrolyte gel networks were prepared as model polymer networks in an attempt to investigate the feasibility of application as

a pH-sensitive drug delivery system. Two polymer systems, random copolymer network(RCN) and interpenetrating networks(IPNs), were prepared as model gel networks for pH-sensitive drug delivery systems. Copolymer of 2-acrylamido-2-methyl-1-propane sulfonic acid(AMPSA) and butyl methacrylate(BMA) was prepared as a model network for RCN and that of acrylamide(AAm) and AMPSA was prepared as a model network for INPs. Hydrocortisone and edrophonium chloride were used as model drugs and were loaded into gel networks using dispersion and ion exchange methods, respectively. Drug release patterns in response to the environmental pH change were observed in the view points of the swelling behaviors of gel networks and the mode of drug loading.

MATERIALS AND METHODS

Materials. AAm monomer was purchased from Junsei chemical.(Japan) N,N'-methylenebisacrylamide(NMBAAm), ammonium persulfate(APS), sodium pyrosulfite(SPS), ethyleneglycol dimethacrylate(EGDMA), AMPSA, BMA, and poly AMPSA aqueous solution(10 wt %) were purchased from Aldrich Chemical Co.(USA) Azobisisobutyronitrile(AIBN), hydrocortisone, edrophonium chloride were purchased from Sigma Chemical Co. (USA) BMA was purified by distillation with reduced pressure under nitrogen and all other chemicals were used without further purification.

Preparation of Drug-Loaded Gel Networks. For release experiments, two model drugs were loaded into RCNs and IPNs using dispersion or ion exchange methods. The preparation methods of RCN and IPNs were presented elsewhere.[4,10] After preparation of gel networks, the swollen gel was cut into disk(diameter : 2.5 cm and thickness : 0.5cm) and stored in the sealed bottle to maintain the swollen state of gel network until use.

For the preparation of hydrocortisone-loaded RCN, swollen gel(the weight of dried gel : 70 mg) was placed in 50 ml of a saturated solution of hydrocortisone for 3 days. The loading amount was approximately 20 weight %.

For the preparation of hydrocortisone-loaded IPNs, polymerization for the preparation of IPNs was performed with hydrocortisone contained in the reaction mixture. The reaction mixture was consisted of AAm, NMBAAm as a crosslinker, hydrocortisone, and poly AMPSA dissolved in distilled water. Redox initiators were added to the reaction mixture to initiate the polymerization. The aqueous solutions of SPS(3.5 g/25 ml) and APS(10 g/25 ml) were used as redox initiators and 0.25 ml of each component of redox initiators was added to reaction mixture. Because of the limited solubility in water(0.28 mg/ml),[10] hydrocortisone was most likely dispersed in the reaction mixture. The reaction mixture was mixed thoroughly using sonicator(Sonics & Materials INC, USA) at 60 W for 1 minute before the addition of initiators. Polymerization was performed between the two Mylar® sheet separated by a silicone rubber gasket and backed by glass plates at 40℃ for 12 hours. After polymerization, the gel network was removed from the mold and immersed in distilled water for 3 hours to remove the unreacted compound. Although hydrocortisone was released from the gel network during the purification, the release amount was within the range of 10 wt % of the total dispersed hydrocortisone. The loading amount was approximately 23 weight %.

Edrophonium chloride was loaded in salt form into the gel network by an ion exchange method which was described elsewhere.[4] The ion exchange method will be discussed briefly. The swollen gel(the weight of dried gel : 50 mg of RCN or IPNs) was equilibrated for 1 day in 300 ml of 0.5 N NaOH aqueous solution to convert SO_3D(where DCl is edrophonium chloride). Physically entrapped solute was washed out completely by soaking in distilled-deionized water. The loading amount in RCN was approximately 12 wt % and that in IPNs was 25 wt % after purification. The feed composition for the gel network used in this study is shown in Table 1.

Release Experiment. Solute release experiments

Table 1. Feed Composition for Polyelectrolyte Gel Networks

(unit : g)

Category	Sample code	Composition								
		AAm	PolyAMPSA	AMPSA	BMA	NMBAAm	EGDMA	AIBN	WATER	DMF
RCN	AMPSA/BMA	–	–	1.46	3.94	–	0.01	0.01	–	10
IPNs	AMPSA/AAm	3.88	1.16	–	–	0.12	–	–	40	–

were performed at two pH conditions(pH=1 and 7)(Temperature : 37.5℃). The pH of release media was controlled by the addition of HCl. The total ionic strength of each aqueous media was adjusted to 0.1 M with a calculated amount of NaCl.

The solute release experiment with a pulsatile pH change of aqueous media was carried out to observe an on-off pulsation of drug from the gel network.

The amount of released drug was measured by taking 1 ml of the release media at specific time points, replacing the total release media(20 ml) with fresh one to maintain sink condition. The drug concentration was assayed at 248 nm for hydrocortisone and 273 nm for edrophonium chloride using a UV spectrophotometer(Shimadzu, Japan).

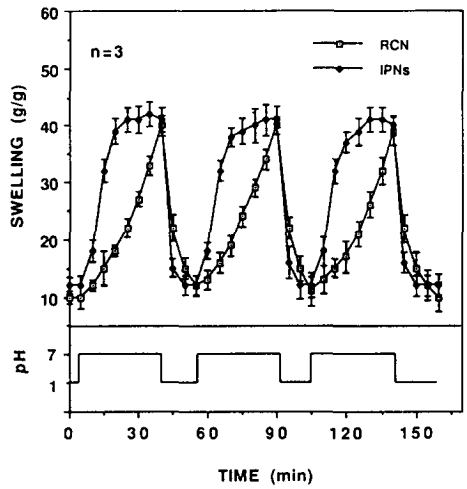

Fig. 1. Reversible swelling change of polyelectrolyte gel networks in response to pulsatile pH change. RCN (□) IPNs (◆).

RESULTS AND DISCUSSION

For the study on the pH-dependent drug release experiment, hydrocortisone and edrophonium chloride were used as model drugs and loaded in the gel network using different modes of drug loading. Neutral drug, hydrocortisone, was physically entrapped inside the gel network using dispersion method and ionic drug, edrophonium chloride, was ionically bound inside the gel network using ion-exchange method.

In the swelling-controlled drug delivery system, the swelling behaviors of polymer system in response to the environmental change is the major factor for understanding the drug release pattern. Fig. 1 shows the reversible swelling changes of RCN and IPNs. Under acidic conditions(pH=1.0), sulfonic groups were protonated and the gel network deswelled. As the pH of the aqueous media was increased from pH 1.0, the concentration of negatively charged sulfonic group increased resulting in a drastic increase in swelling. This phenomenon was reversible.

Fig. 2 and 3 show hydrocortisone release pattern from RCN and IPNs, respectively. The overall release rate increased with pH decrease of release media. Since hydrocortisone was physically entrapped inside the gel network, the release pattern was closely related to the swelling behaviors of gel network. As described previously,[10] the swelling of gel network decreased with the pH change of release media from pH 7 to 1. Therefore, the increase of release rate in response to pH change could be explained in terms of the bulk squeezing effect caused by the deswelling of gel network.

Although the degree of swelling variation in response to environmental pH change was almost

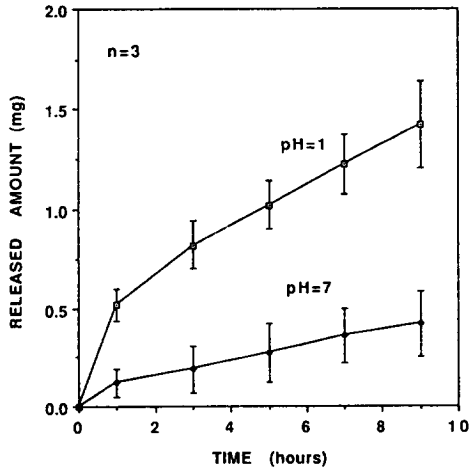

Fig. 2. Release of hydrocortisone from RCN at two pH conditions. pH=1 (□) pH=7 (◆).

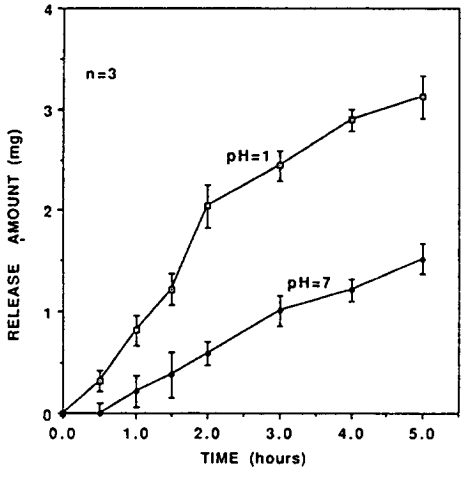

Fig. 3. Release of hydrocortisone from IPNs at two pH conditions. pH=1 (□) pH=7 (◆).

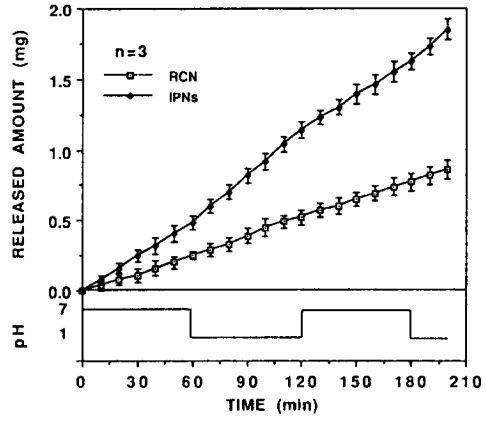

Fig. 4. Release of hydrocortisone from gel networks in response to the pulsatile pH change. RCN (□) IPNs (◆).

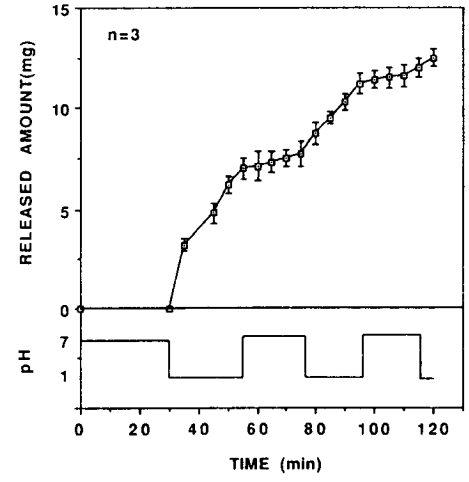

Fig. 5. Release of edrophonium chloride from RCN in response to the pulsatile pH change.

same,[10] the release amount of hydrocortisone from IPNs is two times larger than that from RCN. This might be attributed to the interaction between hydrocortisone and polymer networks. In other words, hydrophobic interaction between hydrocortisone and butyl methacrylate is dominant in RCN, therefore, the release of hydrocortisone from RCN was hindered by the hydrophobic interaction. However, the aforementioned interaction is not dominant in IPNs because IPNs do not have hydrophobic moiety in the gel network such as butyl methacrylate in RCN.

The release pattern of hydrocortisone with pulsatile pH change was observed, however, it did not show the significant pulsatile pattern as shown in Fig. 4. The marginal pulse might be attributed to the bulk squeezing caused by the pulsatile pH change.

Fig. 5 and 6 show the release pattern of edro-

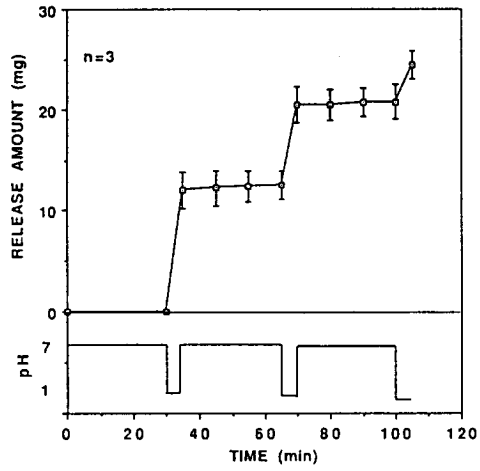

Fig. 6. Release of edrophonium chloride from IPNs in response to the pulsatile pH change.

phonium chloride from RCN and IPNs, respectively. The release of edrophonium chloride in response to the environmental pH shows an on-off pulsation. Since all physically entrapped solute was extracted by washing with distilled-deionized water, only ionically bound solutes exist inside the gel network. In the acidic condition, the ion exchange between a positively charged solute and hydrogen ion took place at the site of SO_3D group in the gel network. The freed drug caused by the ion exchange diffused out from the gel network and the diffusion of drug from the gel network was enhanced by the swelling decrease(bulk squeezing). Apparent on-off pulsation was observed in the release of edrophonium chloride from RCN (Fig. 5) comparing with that from IPNs(Fig. 6). This might be attributed to the differences in reversible swelling pattern of polymer networks in response to pulsatile pH change as shown in Fig. 1. Reversible swelling variation in response to pulsatile pH change was more significant in the case of IPNs(see Fig. 1).

From Figs 4, 5 and 6, pulsatile release pattern in response to pulsatile pH variation was observed in the release of edrophonium chloride and the marginal pulse was observed in the release of hydrocortisone. Because the release pattern of hydrocortisone could only be affected by swelling changes of gel network and pulsatile release of hydrocortisone was marginal, the effect of squeezing (bulk swelling change) on the pulsatile release was a minor factor. The squeezing could enhance the pulsatile release of freed drug as shown in the release of edrophonium chloride, which resulted in the complete on-off pulsation.

CONCLUSIONS

RCN and IPNs were prepared as model gel networks which showed pH-dependent swelling behaviors. Based on the character of model drugs, hydrocortisone and edrophonium chloride were loaded into the gel network using dispersion and ion exchange methods, respectively.

In the release of hydrocortisone, the release pattern was mainly regulated by the bulk squeezing effect caused by the deswelling of gel network but did not show the significant pulsatile release in response to the pulsatile pH change.

In the release of edrophonium chloride, the release pattern could be explained by two steps, the ion exchange between a positive charged solute bound ionically to sulfonic group and hydrogen ion in the acidic condition and the diffusion of freed drug. Because the release pattern of edrophonium chloride was enhanced by bulk squeezing caused by deswelling, it showed the pulsatile release pattern in response to pulsatile pH change.

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