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# 알진과 PAA 혼합물을 이용한 생분해성이 있고 pH에 민감한 약물전달체계

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# Biodegradable and pH-Sensitive Drug Delivery System Using Sodium Alginate and Polyacrylic Acid Composite

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요 약 : 생분해성이 있는 알진산 나트륨과 아크릴산의 복합체를 이용하여 구슬형 약물전달체계를 고안하여 제조하였다. 고안된 약물전달체계는 고농도의 초산기를 함유하고 있기 때문에 주위의 pH변화에 따라 약물방출 형태의 차이를 보인다. 중성조건에서의 약물방출속도는 주위의 액성이 산성화됨에 따라 현저히 저하되었고 액성이 중성화되면 원상태로 돌아가는 우수한 가역성을 보였다.

**Abstract** : Bead-type drug delivery system, which was biodegradable and pH-sensitive, was designed and characterized using sodium alginate and polyacrylic acid. The drug (hydrocortisone) release profile was measured as the functions of composition of sodium alginate/polyacrylic acid and environmental pH. The designed drug delivery system showed the reversible pH-sensitive drug release pattern.

## INTRODUCTION

Recently, much interest has been focused on the biodegradable drug carriers for prolonged and controlled delivery of therapeutic agents in biological system. A number of studies on different carrier systems using biodegradable polymer have been reported including synthetic lyposome, permeable polymeric microcapsules, and solid microsphere[1~3] and these carrier systems have been investigated for a variety of applications.

Nixon and Walker[4] reported the release of sulfadiazine from microcapsule formed by gelatin and Sugibayashi et al.,[5] reported the property of albumin microsphere in chemotherapy.

Poly($\beta$-hydroxybutyrate) and its copolymer with poly($b$-hydroxy valerate) have been examined as a potential drug carrier system in the form of microparticulate.[6]

In this study, bead-type drug delivery system, which was biodegradable and enviornmental pH-sensitive, was designed and characterized using

sodium alginate and its composite with polyacrylic acid. Drug release kinetics was measured as a function of sodium aliginate/polyacrylic acid composition and decoupling time at various pH conditions.

## EXPERIMENTALS

### Materials

Sodium alginate (chemical grade) was purchased from Junsei Chemical, Japan. Polyacrylic acid aqueous solution (25 weight %, M. W. : 90,000) and hydrocortisone (chemical grade) were purchased from Sigma. Calcium chloride and sodium acetate (chemical grade) were purchased from Shinyo Chemical, Japan.

### Preparation of Hydrocortisone-Entrapped Bead Composed of Sodium Alginate and Its Composite with Polyacrylic Acid

The known amounts of 2 weight % sodium alginate aqueous solution and 25 weight % polyacrylic acid aqueous solution were mixed thoroughly with hydrocortisone using homogenizer. Mixture was dropped into 5 weight % calcium chloride aqueous solution dropwisely for hardening (crosslinking) sodium alginate/polyacrylic acid mixture droplet which became bead-type calcium alginate/polyacrylic acid gel networks (diameter : 0.1~0.5cm). The drug loading amount was 25(w/w) %.

Calcium alginate was easily disintegrated into sodium alginate in EDTA and alkaline solution (decoupling). To control the crosslinking density of calcium alginate/polyacrylic acid gel, the gel was treated with 10 weight % sodium acetate aqueous solution. After the required decoupling time was passed, the gel was equilibrated with distilled water to remove the unreacted sodium acetate for 12 hours. Although hydrocortisone was released from the drug carriers during the purification of gel, the release amount was minimal compared to the total amount of entrapped hydrocortisone because the solubility of hydrocortisone in water was low (0.28 mg/ml). The prepared drug delivery system was stored at the sealed bottle to prevent the dryness of gel network before use.

### Swelling and Swelling Kinetics Measurements

Swelling was measured by the following equation.

$$\text{Swelling} = (Ws - Wo)/Wo \times 100 \quad (1)$$

where Ws is the weight of the swollen polymer and Wo is the weight of dehydrated polymer.

Swelling measurements were performed as a function of pH of surrounding aqueous media. The ionic strength and pH of surrounding aqueous media were controlled by the addition of NaCl and HCl, respectively.

For the pulsatile drug release depending on the environmental pH, reversible swelling kinetics with pulsatile pH variation of surrounding aqueous media was measured. The time course of swelling profile with pulsatile pH change was measured using tea-bag method. Tea-bag method can be explained briefly as follows. The kwown amount of bead-type drug carrier was enclosed in tea-bag. After tea-bag was immersed in surrounding aqueous media with constant time interval, tea-bag was withdrawn from the surrounding aqueous media. The weight difference of surrounding aqueous media between before and after withdrawing tea-bag was the swelling of bead-type drug carrier at given time.

### Drug Release Experiment

To investigate the drug release pattern from bead-type drug carrier system, the system entrapping hydrocortisone was placed in separate glass bottle. 30ml(pH=2 and 6) of water for release media was added to each and the ionic strength of release media was controlled by addition of NaCl. The release media was agitated gently using star-shapped magnetic stirring bar at 37℃.

Upon sampling, the entire release medium was replaced with fresh one to simulate sink condition. The release amount of hydrocortisone was assayed by U. V. spectrophotometer at 248 nm(Shimadzu, Japan).

## RESULTS AND DISCUSSIONS

Fig. 1 shows the swelling behaviors of drug carriers composed of calcium alginate and polyacrylic acid as a function of their composition.

It is well known that specific intermolecular cooperative interactions occur between calcium and G block owing to the buckled ribbon structure of polyguluronic acid, the major part of sodium alginate.[7] In the preparation of drug carriers, sodium alginate forms a gel network(calcium alginate) in the presence of divalent cation($Ca^{++}$) and polyacrylic acid entangles along calcium alginate gel network which results in interpenetrating networks(IPNs).

In general, it is acceptable that the swelling power of polyacrylic acid gel (crosslinked one) is higher than that of calcium alginate gel due to the higher concentration of carboxylic group in polyacrylic acid gel, therefore, the swelling of drug carrier increases as the content of polyacrylic acid increases.

To investigate pH-sensitivity of drug carriers, the swelling behaviors of drug carrier (calcium alginate/polyacrylic acid composite(CPC)) was observed with pH variation of surrouding aqueous media. Fig. 2 shows that CPC drug carrier systems exhibit sharp swelling change around pH=4 indicating the good pH-sensitivity. As the content of polyacrylic acid in the CPC gel network increases, the range of swelling change increases indicating the feasibility of regulation of swelling range by the control of the content of polyacrylic acid in CPC gel network. At acidic condition (pH=2), carboxylic groups are protonated and the protonated carboxylic groups lose their swelling power. As the pH of aqueous media is increased from pH=2, the increasing concentration of negatively charged carboxylic group in the CPC network is accompanied by a drastic increase in swelling.

In EDTA or alkaline aqueous solution, calcium alginate network is easily disintegrated into sodium alginate(decoupling or gel collapse). Therefore, the crosslinking density in CPC network can be regulated by the control of decoupling time. Sodium acetate was used as the decoupling agent in this study. Fig. 3 shows that the swelling of CPC gel network increases as the decoupling time increases. This is due to the fact that the expansion of gel network caused by swelling becomes more favorable, since the degree of freedom (mobility) of polyacrylic acid chain strictly entangled in CPC network increases by decreasing the crosslinking density of CPC gel network. From the experimental result from Fig. 3, the optimal decoupling time is fixed as 1 hour. Although the swelling of drug

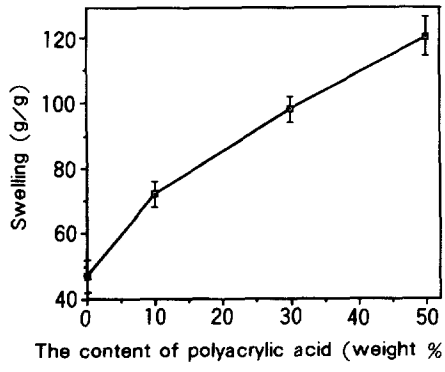


**Fig. 1.** The swelling behavior of calcium alginate/polyacrylic acid composite as a function of the content of polyacrylic acid.

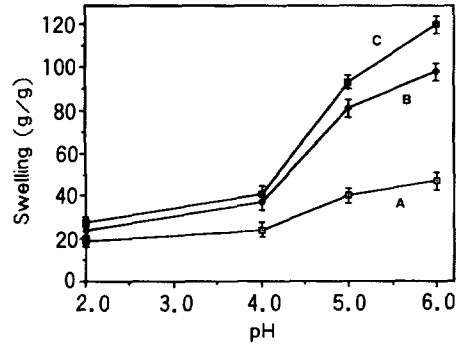


**Fig. 2.** The swelling behavior of CPC gel network as a function of environmental pH : (A) (100/0)(w/w) CPC gel network, (B) (70/30)(w/w) CPC gel network, (C) (50/50)(w/w) CPC gel network.

carrier increases with the increase of decoupling time, the drug carrier system starts to collapse around 2 hours of decoupling time due to the disintegration of CPC gel network.

The reversible swelling kinetics of CPC gel network for pulsatile drug delivery depending on pH variation of surrounding aqueous media was measured as shown in Fig. 4. CPC gel network (The content of polyacrylic acid is 30 weight % and the decoupling time is 1 hour.) shows the drastic swelling change by pH variation of surrounding aqueous media from 2 to 6 and vice versa indicating the good swelling reversibility of CPC drug carrier. This characteristic swelling bebavior of

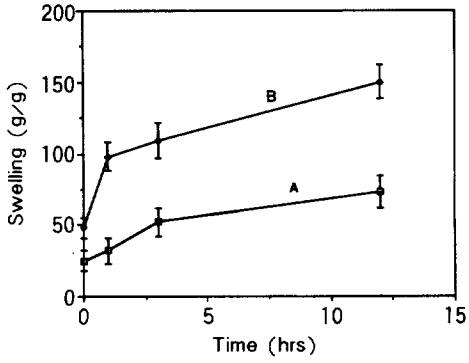


**Fig. 3.** The swelling behavior of CPC gel network as a function of decoupling time : (A) (100/0)(w/w) CPC gel network, (B) (70/30)(w/w) CPC gel network.

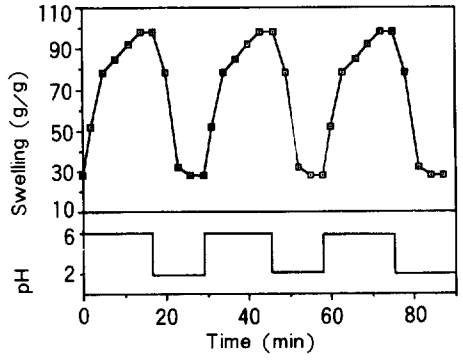


**Fig. 4.** The reversible swelling kinetics of (70/30) (w/w) CPC gel network depending on the environmental pH.

CPC gel network can be utilized for the pulsatile drug delivery depending on the enviornmental pH.

The release kinetics of loaded hydrocortisone from the CPC drug carrier (The contents of polyacrylic acid are 0 and 30 weight % and the decoupling time is 1 hour.) at pH=2 and 6 of surrounding aqueous media were measured as shown in Fig. 5. At pH=2, the release rate(or amount) is lower than that at pH=6.

The release of drug from CPC drug carrier is controlled by passive diffusion. Two mechanisms are proposed for the solute diffusion through polymer network (or polymer membrane).[8] The one is pore mechanism and the other is partition mechanism. If polymer network-drug interaction is dominant in diffusion process, the partition is a major factor to control the diffusion of drug through polymer network. CPC gel network is composed of hydrophilic polymer and the drug loaded in CPC drug carrier is hydrophobic steroid drug, hydrocortisone. In this case, polymer network-drug interaction is minimal. Therefore, the drug release from CPC drug carrier can be explained in terms of pore mechanism. In the release of hydrocortisone from CPC drug carrier, loaded hydrocortisone diffuses through water-filled pores in CPC

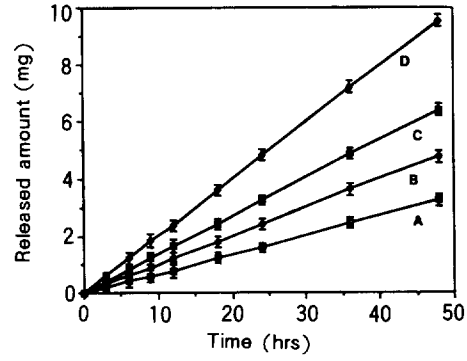


**Fig. 5.** The release amount of hydrocortisone from CPC drug carriers : (A) (100/0)(w/w) CPC drug carrier at pH=2, (B) (70/30)(w/w) CPC drug carrier at pH=2, (C) (100/0)(w/w) CPC drug carrier at pH=6, (D) (70/30)(w/w) CPC drug carrier at pH=6.

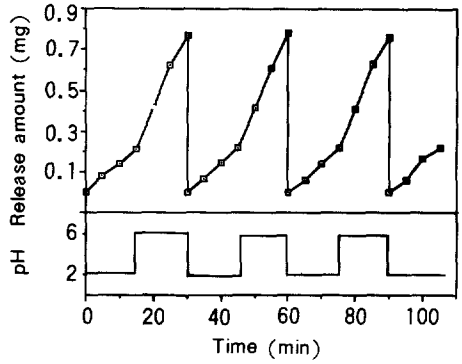


**Fig. 6.** The reversible kinetics of hydrocortisone release from (70/30)(w/w) CPC drug carrier depending on the environmental pH.

gel network.

The protonation of carboxylic groups in CPC gel network at pH=2 causes the swelling decrease accompanying the shrinkage of CPC gel network, which results in blocking the pores in CPC gel network. As the pH of surrounding aqueous media is increased from pH=2, the concentration of negatively charged carboxylic groups in CPC gel network increases with the drastic increase in swelling. Therefore, the pores in the gel network become larger and the activation energy for the diffusion of hydrocortisone through CPC gel network decrease. (Hydrocortisone can diffuse more easily through CPC gel network.)

The pulsatile drug release kinetics depending on pH variation of surrounding aqueous media was measured as shown in Fig. 6. The release amount of hydrocortisone increases drastically with the increase of enviornmental pH. This pulsatile release under pH variation of surrounding aqueous media is attributed to the reversible swelling change caused by pH variation.

## CONCLUSIONS

pH-sensitive drug delivery system was designed and characterized using biodegradable sodium alginate and polyacrylic acid. The proposed drug delivery system in our study shows pulsatile drug release kinetics with pH variation of surrounding aqueous media and can be utilized as external stimulus sensitive drug carrier systems.

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