Electric Current-Sensitive Drug Delivery Systems Using Sodium Alginate/Polyacrylic Acid Composites

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INTRODUCTION

External stimulus-sensitive polymer systems using polyelectrolyte gels can be swollen discretely and reversibly by changes in temperature, solvent composition, pH, concentration of added salts, or electric field. This swelling property can be explained in terms of the phase transition of the gel system consisting of a charged polymer network, ions in the network, and fluid (1). It can be utilized in drug delivery controlled by gel swelling by an external stimulus. The swelling of the gel network by electric field, the electrically modulated solute transport, and the design of a drug delivery system controlled by electric current have been reported (2–6).

In this study, hydrocortisone-dispersed monolithic devices composed of sodium alginate and polyacrylic acid were prepared and characterized. It was possible to obtain a pulsatile drug release pattern under the electric stimulus using the prepared monolithic devices.

MATERIALS AND METHODS

Materials

Sodium alginate (chemical grade) was purchased from Junsei Chemical Co. (Japan). Calcium chloride and sodium chloride (chemical grade) were purchased from Shinyo Chemical Co. (Japan). Polyacrylic acid aqueous solution (25 wt%, MW 90,000) and hydrocortisone were purchased from Sigma Chemical Co. (St. Louis, MO).

Preparation of Hydrocortisone-Dispersed Monolithic Devices

Three kinds of monolithic devices were prepared using sodium alginate and a sodium alginate/polyacrylic acid composite. The known amounts of 2 wt% sodium alginate aqueous solution and 25 wt% polyacrylic acid aqueous solution were mixed thoroughly with hydrocortisone using a homogenizer (Bodline Electronic Co.). A 5 wt% calcium chloride solution was poured gently onto the surface of polymer solution mixture. The calcium chloride solution used was twice the volume of the polymer solution mixture. The gel matrix was formed from the surface. The mixture of sodium alginate/polyacrylic acid solution was completely converted to the gel matrix of calcium alginate/polyacrylic acid composite (CPC) within 1 hr. The CPC gel matrix was immersed in distilled water for 3 hr to remove unreacted calcium chloride. Although hydrocortisone was also released from the CPC gel matrix during the purification of gel, the amount released was within the range of 10 wt% of the total dispersed hydrocortisone. The swollen CPC gel matrix was cut into hexahedrons ($2 \times 2 \times 2$ and $2 \times 4 \times 2$ cm^3 in size) and stored in sealed bottles to maintain the swollen state of the gel matrix until use. The drug loading amount was 20 wt% after purification.

Swelling Measurement

The swelling of the gel matrix was measured in 0.9% NaCl solution at two pH values (pH = 2 and 6). To simulate the experimental condition under electric stimulus, the pH of the 0.9% NaCl solution was controlled by the addition of 0.1 *N* HCl. Water uptake was measured by weighing the gel matrix after wiping off excess water on the surface at each time point. The swelling was defined as the weight of water uptake per unit weight of dried polymer.

Release Experiment

Two kinds of apparatus were designed for hydrocortisone release experiment as shown in Fig. 1.

In the case of the noncontacting device, the monolithic device was placed between positive and negative electrodes in a 0.9% NaCl solution. The distance between two electrodes was 3 cm and the voltage between the electrodes was 9 V. The applied electric current was 32 mA as measured with a Volt-Ohm-Milliammeter (Shimpson Electric Co.).

In the case of the contacting device, the monolithic device was placed in a 0.9% NaCl solution and the electrodes were inserted directly into the polymer matrix. The distance between the two electrodes was 3 cm and the voltage between the electrodes was 9 V. The applied electric current was 6 mA. The electric currents used in both cases were almost constant during the experiments. The amount of released drug was measured by taking 1 ml of the release medium at specific time points, replacing the total release medium (50 ml) with fresh NaCl solution to maintain sink conditions and assaying the drug concentration at 248 nm using a UV spectrophotometer (Shimadzu, Japan).

The pH change of release medium caused by the application of electric current was measured by taking 1 ml of release medium under the application of electric current for 10 min. The sampled release medium was diluted 10 times with fresh NaCl solution to obtain a sufficient volume for pH measurement and assayed with a pH-meter 245 (Corning). In the case of the contacting device, the release medium was taken directly from the gel matrix–electrode interface using a syringe. In the case of the noncontacting device, the release medium was taken from three points in the release experimental vessel (i.e., points near the positive and negative

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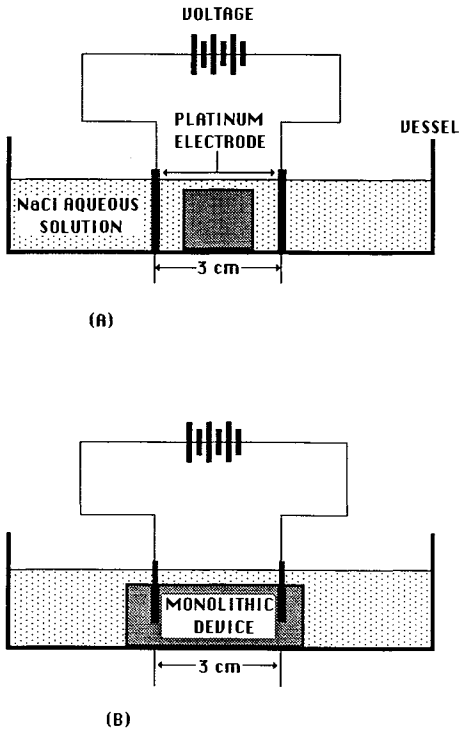

Fig. 1. Schematic diagram for apparatus used in drug release experiment.

electrodes and a point between these two). The pH profiles in the release experimental vessel were reproducible.

RESULTS AND DISCUSSION

Calcium alginate/polyacrylic acid composite (CPC) was used as a gel matrix for the hydrocortisone-dispersed monolithic device. Sodium alginate is easily converted to a gel matrix in the presence of divalent ions at a concentration of >0.1% (w/w) (7). Based on this property of sodium alginate, the solution mixture of sodium alginate and polyacrylic acid was treated with calcium chloride solution to form a CPC gel matrix. It could be expected that sodium alginate formed a gel matrix (calcium alginate) and polyacrylic acid chains entangled through the calcium alginate gel matrix, resulting in semi-interpenetrating networks (semi-IPNs). One of the prepared gel matrices, a (5/5, w/w) calcium alginate/polyacrylic acid composite, was stored in distilled water for 1 month and the pH change of the aqueous medium was measured to observe polyacrylic acid leaking from the CPC gel matrix. The lack of pH change of the aqueous medium indicates minimal leakage of polyacrylic acid from the CPC gel matrix. [The pH of the 0.5% (w/w) aqueous solution of polyacrylic acid was 3.22.]

In the electric current-sensitive drug delivery system, the key factor for controlling the release rate is the matrix swelling, which is affected by the surrounding pH. Therefore, the matrix swelling as a function of the pH of the NaCl solution was measured to assess the feasibility of electric current-sensitive drug release using the prepared monolithic device.

Figure 2 shows the pH-dependent swelling changes of CPC gel matrices. Under acidic conditions (pH = 2), carboxylic groups were protonated and the gel matrix deswelled. As the pH of the aqueous medium was increased from 2, the concentration of negatively charged carboxylic groups in the CPC gel matrix increased. This resulted in a drastic increase in swelling. This phenomenon was reversible and the range of swelling increased with increasing polyacrylic acid content in the CPC gel matrix. In the gel formation of sodium alginate in the calcium chloride solution, specific intermolecular cooperative interaction occurs between calcium ion and G blocks owing to the buckled ribbon structure of the polyguluronic acid moiety in sodium alginate leaving free carboxylic groups (7). The pH dependence of swelling and the electric current-sensitive hydrocortisone release from 100% sodium alginate matrix were attributed to these free carboxylic groups in the gel matrix. To increase the pH and electric-current sensitivities of the gel matrix, polyacrylic acid, which had a higher concentration of carboxylic groups than sodium alginate, was used to form the CPC gel matrix. As shown in Fig. 2, the pH-sensitive swelling change of the gel matrix for electric current-sensitive drug release was regulated by the polyacrylic acid content in the CPC gel matrix.

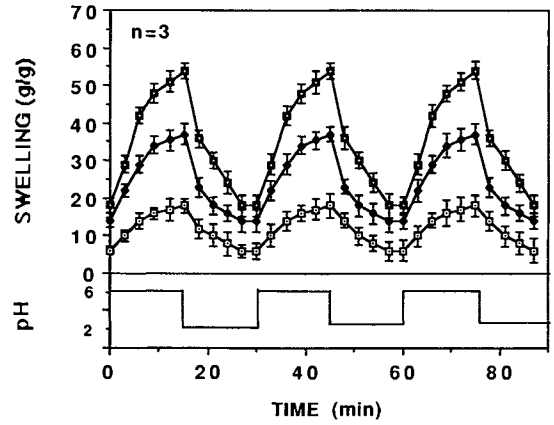

Fig. 2. Reversible swelling change depending on the pH of the 0.9% NaCl aqueous solution. (□) Calcium alginate monolithic device; (♦) (7/3, w/w) calcium alginate/polyacrylic acid composite monolithic device; (■) (5/5, w/w) calcium alginate/polyacrylic acid composite monolithic device.

In the external stimulus-sensitive drug delivery system, the swelling change in the drug delivery devices caused by external stimulus can be represented as surface swelling and bulk swelling changes (squeezing effect). In a thermosensitive drug delivery system, the major factor to control drug release from the device was the bulk swelling change (8) or the surface swelling change (9). In our study, two release patterns of hydrocortisone were observed by properly using one of these two swelling changes described previously. Two kinds of apparatus (contacting and noncontacting devices) were designed for our purpose. In the contacting device, the bulk swelling change was induced by inserting (contacting) the electrodes into the gel matrix. The release rate was increased by the application of electric current and it was possible to obtain a pulsatile drug release pattern as shown in Fig. 3. Under the application of electric current, the NaCl solution at the gel matrix-positive electrode interface became acidic (pH 2), therefore, the protonation of the

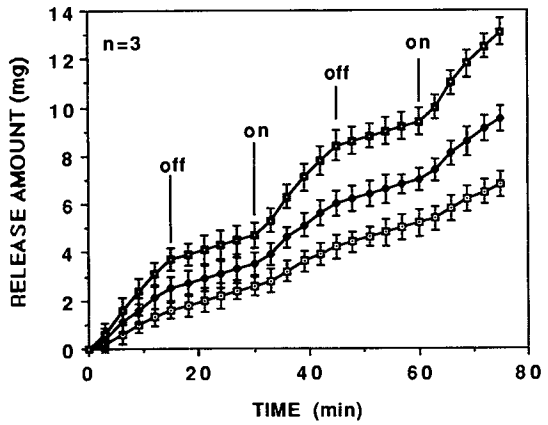

Fig. 3. Hydrocortisone release pattern using contacting device. (□) Calcium alginate monolithic device; (◆) (7/3, w/w) calcium alginate/polyacrylic acid composite monolithic device; (■) (5/5, w/w) calcium alginate/polyacrylic acid composite monolithic device.

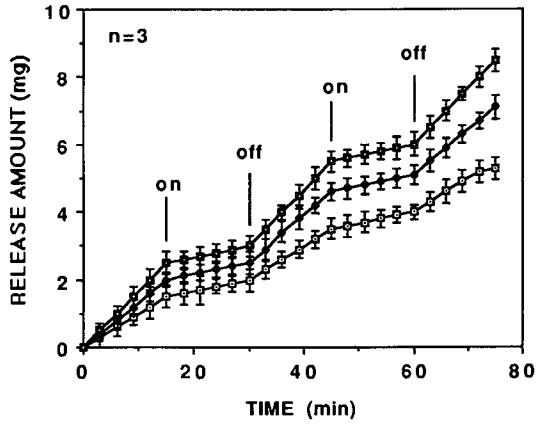

Fig. 4. Hydrocortisone release pattern using the noncontacting device. (□) Calcium alginate monolithic device; (◆) (7/3, w/w) calcium alginate/polyacrylic acid composite monolithic device; (■) (5/5, w/w) calcium alginate/polyacrylic acid composite monolithic device.

carboxylic groups led to the irreversible shrinkage (collapse) of the gel matrix (bulk squeezing). The shrinkage of the gel matrix around the positive electrode could be observed visually, while no shrinkage was found around the negative electrode. The release pattern was observed as a function of the polyacrylic acid content in the monolithic device. As the polyacrylic acid content increased, the pulsatile release pattern became more apparent due to the increase in the magnitude of swelling change as shown in Fig. 2. In the noncontacting device, the surface swelling change played a major role in regulating the pulsatile drug release pattern. The pH of the release medium under electric stimulus was measured at three points in the release experimental vessel. The pH of the release medium was approximately 2.1 around the positive electrode, 7.9 around the negative electrode, and 3.8 between two electrodes. H^+ ions generated around the positive electrode protonated the carboxylic groups mostly at the surface of the monolithic device and the surface deswelling caused by protonation retarded the solute release from the monolithic device. With the application of electric current, the amount of solute released decreased as a result of the surface deswelling; this is contrary to the results in the case of the contacting device (Fig. 4). The change in drug release rate was also observed with variation of the polyacrylic acid content in the CPC gel matrix and the results showed the similar trend in the case of the contacting device.

The release rate from the noncontacting device without electric current, even though its size was smaller than the contacting device, was faster (Figs. 3 and 4). In the contacting device, the collapse of the gel matrix occurred with the application of electric current as mentioned previously. The release rate of hydrocortisone from the contacting device might be hindered by the formation of a collapsed gel matrix.

No pulsatile release pattern of hydrocortisone was observed using the noncontacting device in distilled water, indicating that drug release from the devices was electric current sensitive. Although the pulsatile release pattern was observed using contacting devices in distilled water, the sharpness of the pulsatile release pattern decreased compared to that in NaCl solution.

CONCLUSIONS

Monolithic devices composed of sodium alginate and polyacrylic acid were prepared. A pulsatile drug release pattern was observed upon application of electric current using the prepared monolithic devices. Two release patterns of hydrocortisone were achieved by the proper design of the drug delivery devices, and the experimental results demonstrated the feasibility of achieving a pulsatile drug delivery system depending on the environmental conditions.

REFERENCES

1. T. Tanaka, I. Nishio, S. Sun, and S. Ueno-Nishio. Collapse of gels in an electric field. *Science* 218:467–469 (1982).
2. Y. Osada, K. Umezawa, and A. Yamauchi. Oscillation of electrical current in water-swollen polyelectrolyte gel. *Makromol. Chem.* 89:597–605 (1988).
3. D. De Rossi, P. Parrini, P. Chiarelli, and G. Buzzigoli. Electrically induced contractile phenomena in charged polymer networks: Preliminary study on the feasibility of muscle-like structure. *Trans. Am. Soc. Artif. Intern. Organ* 31:60–65 (1985).
4. A. J. Grodzinsky and A. M. Weiss. Electric field control of membrane transport and separations. Separation and *Purificat. Methods* 14:1–38 (1985).
5. I. C. Kwon, Y. H. Bae, T. Okano, B. Berner, and S. W. Kim. Stimulus sensitive polymers for drug delivery system. *IUPAC Int. Symp. Preprint,* 1989, pp. 275–276.
6. K. Sawahata, M. Hara, H. Yasunaga, and Y. Osada. Electrically controlled drug delivery system using polyelectrolyte gels. *J. Control. Release* 14:253–262 (1990).
7. M. Yalpani. Gelation properties. In M. Yalpani (ed.), *Polysaccharide,* Elsevier, New York, 1988, pp. 107–114.
8. A. S. Hoffman, A. Afrassiabi, and L. C. Dong. Thermally reversible hydrogel. II. Delivery to and selective removal of substances from aqueous solution. *J. Control. Release* 4:213–222 (1986).
9. Y. H. Bae, T. Okano, and S. W. Kim. Thermo-sensitive polymers as on-off switches for drug release. *Makromol. Chem. Rapid Commun.* 8:481–485 (1987).