Effects of Natural Polysaccharide Addition on Drug Release from Calcium-Induced Alginate Gel Beads

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Calcium-induced alginate gel beads (Alg-Ca) containing various polysaccharides, including an alginate hydrolysate, were prepared and the drug release profiles were investigated. Hydrocortisone (HC) was gradually released from Alg-Ca into the mimic gastric fluid, while in intestinal fluid, it was quickly released with the dissolution of Alg-Ca. However, with Alg-Ca containing 5% chitin (CT), dissolution of Alg-Ca was not observed, and release of HC showed apparent zero-order kinetics. Furthermore, addition of the alginate hydrolysate altered the HC-release profile for Alg-Ca.

Key words alginate gel bead; chitin; alginic acid; hydrocortisone

Natural polysaccharides have been utilized as additives for oral dosage forms of various medications. Chitosan (CS) has recently been studied as an excellent vehicle for drug delivery because of its biocompatibility and biodegradability.[1—3] CS has polycationic properties and forms a film-like complex with polyanionic compounds.[4] Therefore, CS acts as an anion exchange resin, and the influence of CS intake on the human body has been studied.[5] In contrast, chitin (CT) has not been used as an additive, although it is both abundant and is the source of CS.[6] One of the reasons for this is that CT scarcely dissolves in most organic or inorganic solvents.

Alginic acid is an anionic polysaccharide, which consists of α-L-guluronic acid (G) and β-D-mannuronic acid (M) subunits. Sodium alginate is administered to treat gastric ulcers by reducing gastric acid irritation. Alginate solution quickly forms a gel matrix in the presence of a divalent cation such as Ca^{2+} and this gelation is known to arise primarily at junctions ("egg–box junctions") in G–G-sequence rich chain regions (G-blocks), rather than M-blocks. Alg-Ca is expected to be used as a vehicle for drug delivery because Alg-Ca is able to incorporate drugs or other polysaccharides within the matrix, and the relationship between drug release and alginate gel bead erosion has been investigated.[7]

Colon targeting has recently been studied for drug delivery to the topical region. The release profile of an anti-inflammatory drug such as a steroid from orally administered forms in the gastrointestinal tract may affect the treatment of inflammatory bowel diseases such as Crohn's disease.[8] In the present study, we attempted to prepare Alg-Ca containing polysaccharides, including an alginate hydrolysate, and investigated the effects on the drug release profiles of Alg-Ca under mimic gastrointestinal conditions.

Experimental

Chemicals A model drug, hydrocortisone (HC), was purchased from Wako Pure Chemical Ind. (Osaka, Japan). Sodium alginate (degree of polymerization; 450) was obtained from Nacalai Tesque (Kyoto, Japan), and alginic acid (non-swelling, NS) was obtained from Wako. CT and CS were obtained from Kimitsu Chem. Ind. (Tokyo, Japan) and agar (UP-16) was obtained from Ina Food Co. (Nagano, Japan). All other reagents used were of analytical grade.

Viscosity of Alginate Solution Containing Polysaccharide Each polysaccharide was added to 1% sodium alginate solution and well stirred, and then the viscosity of the solution was measured with a Brookfield viscometer 5 times at room temperature (25 °C).

Hydrolysis of NS NS was partially hydrolyzed (0.3 M HCl, 2 h, 100 °C) and the G- and M-blocks were separated by the method of Haug *et al.*[9] Solutions containing each block were precipitated with ethanol after neutralization and centrifuged (3000 rpm, 10 min). The pellet was then washed with ethanol, and dried *in vacuo* over P_2O_5.

Preparation of Modified Alg-Ca Alg-Ca was prepared as follows: One percent sodium alginate was dissolved in distilled and demineralized water with agitation. Polysaccharide and model drug were added to the solution, and 2 g of solution was dropped into 0.1 M $CaCl_2$ solution using the method described previously.[10] Hydrogel beads were washed with 50 ml distilled water twice and dried first at 30 °C for 8 h on a culture dish, and then under reduced pressure in a desiccator in the presence of P_2O_5.

Drug Release Test The release of the drug incorporated in Alg-Ca (dried weight: 0.1—0.15 g) was determined in 500 ml of JP XIV 1st fluid (pH 1.2) for 2 h, followed by 2nd fluid (pH 6.8) for 4 h using JP XIV dissolution test apparatus (paddle method, 37±0.5 °C). In this experiment, 150 rpm was set as the rotation speed of paddle to avoid the adhesion of Alg-Ca to the vessel. A 4-ml aliquot of each solution was removed periodically for analysis, and 4 ml of test medium (37 °C) was added in order to maintain a constant volume. Absorbance of each sample was determined on a Hitachi 200-20 Spectrophotometer at 248 nm, after centrifugation (3000 rpm, 10 min), when necessary. Total amount of drug released from Alg-Ca was determined based on analysis of the solution in which Alg-Ca was further soaked for 24 h after the release test. All dissolution tests were performed in triplicate.

Results and Discussion

The viscosity of 1% sodium alginate (viscosity: 150 cp) changes by adding polysaccharide. Specifically, NS (5% addition) significantly increased the viscosity (6000 cp), although the beads did not swell in distilled water. It appears that this increase is due to a sodium-exchange reaction between alginate and NS. When 5% CT or 5% CS was added to the solution, the increase in viscosity was very small (230 cp or 250 cp, respectively) when compared to that of NS, and gel formation was not observed under these conditions.

Figure 1 shows the photograph of Alg-Ca containing 5% chitin. The diameter was 1.8±0.1 mm (30 granules) and the incorporation capability for HC in the bead was about 80%.[11] HC was gradually released from Alg-Ca in the 1st fluid (pH 1.2), and about 30% of HC was released over 120 min. However, in the 2nd fluid (pH 6.8), rapid dissolution could be clearly observed with the naked eye, and at the same time, HC was quickly released, as shown in Fig. 2. In the case of Alg-Ca containing 5% NS, the HC release profile was similar to that of Alg-Ca. The same release profile was seen when 5% agar was added to Alg-Ca. This means that

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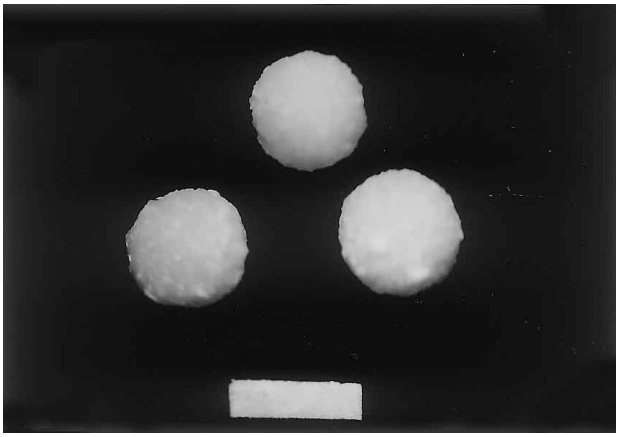

Fig. 1. Photograph of Alg-Ca Ccontaining 5% CT
Scale bar=2 mm.

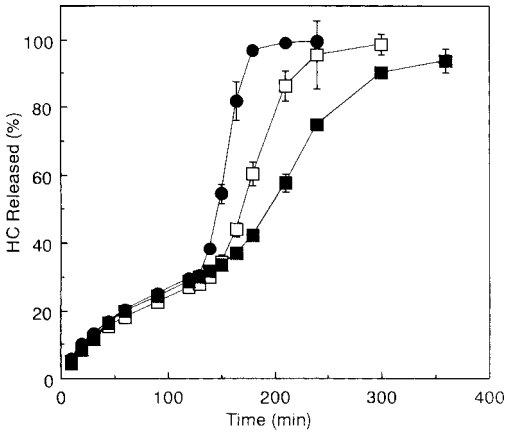

Fig. 3. HC-Release Curves from Alg-Ca Containing NS and CT
—●— 5% NS, —□— 0.5% NS, 3% CT, —■— 0.5% NS, 5% CT.

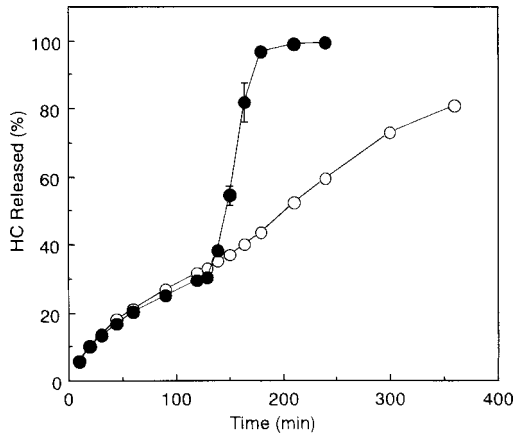

Fig. 2. HC-Release Curves from Alg-Ca Containing 5% Polysaccharide
—●— NS, —○— CT.

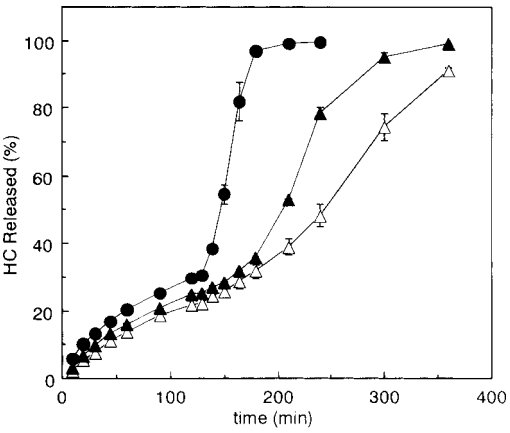

Fig. 4. HC-Release Curves from Alg-Ca Containing CT and Alginate Hydrolysate
—●— 5% NS, —△— 3% CT, 1% G-block, —▲— 3% CT, 1% M-block.

the structure of the alginate gel matrix responsible for drug release was unchanged by addition of these polysaccharides and that disintegration of the "egg–box junctions" occurred (probably by the ion-exchange between Ca^{2+} and K^{+}) when the pH of the medium rose to 6.8. In contrast, for Alg-Ca containing 5% CT, although the release rate in the 1st fluid was same as that of Alg-Ca, the dissolution in the 2nd fluid was not observed and HC release showed apparent zero-order kinetics (Fig. 2). The release rate constant was 0.215%/min (r^2=0.994), which was determined from the results of linear regression by fitting HC-release data within a range of 10 to 360 min. This phenomenon seems to be attributable to formation of a complex between the carboxyl group of alginate and an amino group, which is present in the CT molecule. Sustained release was recognized in the 2nd fluid when CS was added to Alg-Ca instead of CT.

When NS and chitin were both present in Alg-Ca, unique drug release profiles were obtained. In the case of Alg-Ca containing 0.5% NS and 3% CT, the gel matrix began to disintegrate after a lag time of about 30—45 min in the 2nd fluid, and it finished at 240 min. The drug release profile reflected the disintegration of Alg-Ca, as shown in Fig. 3.

The addition of the alginate hydrolysate also resulted in a change in the HC-release profile, as shown in Fig. 4. The release rate of HC in the 2nd fluid was controlled by addition 3% chitin and 1% G-blocks, and the release rate constant was 0.346%/min (180—360 min, r^2=0.991). The effect of G-blocks on the suppression of HC-release rate was larger than that of M-blocks. This may be the result of inhibition of gel disintegration by interaction between CT and G-blocks. This is supported by a report that calcium-induced gel matrix containing a G-rich alginate was more strongly reinforced after CS addition compared with one containing an M-rich alginate.[12]

In this paper, modification of Alg-Ca was investigated in order to develop an oral dosage form for treatment of inflammatory bowel diseases. If inflammation is spread through the whole small intestine, the drug must be released gradually throughout the region. If not, the drug must be released quickly at the affected site. These results demonstrate that the release profile of a steroid drug incorporated into Alg-Ca can be controlled by adding polysaccharides. Therefore, it may prove to be an excellent vehicle for drug delivery to inflamed regions in the intestinal tract.

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