A NOVEL METHOD FOR THE PREPARATION OF CONTROLLED-RELEASE THEOPHYLLINE CAPSULES COATED WITH A POLYELECTROLYTE COMPLEX OF κ-CARRAGEENAN AND CHITOSAN

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A novel method for the preparation of κ-carrageenan/chitosan polyelectrolyte complex (PEC) membrane capsules containing theophylline as a model drug was developed. The theophylline release from the capsules followed zero-order kinetics, and the release rates were independent of pH of the dissolution medium, suggesting that κ-carrageenan/chitosan PEC capsules could be a useful vehicle for controlled-release drug delivery.

KEYWORDS polyelectrolyte complex membrane capsule; theophylline; controlled-release; κ-carrageenan; chitosan; drug delivery system

In addition to the ability to form cation-induced gels, some anionic polysaccharides can crosslink with high molecular weight polycations to form water-insoluble polyelectrolyte complexes (PEC).[1,2] The applications of PEC membrane in the preparation of durable and semipermeable membrane capsules for the immobilization of living cells and enzymes have been described in several studies.[3-6] For example, Beaumont and Knorr[5] and Yoshioka *et al.* [6] prepared κ-carrageenan/chitosan or carboxymethylcellulose/chitosan PEC membrane capsules by dropping the respective anionic polysaccharide solution into a negatively charged chitosan solution. Capsule walls thus prepared were very thin, being 3–4 μm in wet state and 0.3 μm in dry state,[4,6] since the interphasic membrane that formed immediately around the droplet acted as a barrier and prevented crosslinking-polymers from producing additional PEC layers. In spite of the thin membrane, the PEC capsules were found to be impermeable to relatively high molecular weight compounds such as bovine serum albumin and hemoglobin.[4] The pore size of the capsule membrane may decrease as the membrane thickness increases. Therefore, PEC capsules with much thicker capsule membranes are expected to be used for a controlled-release system of low molecular weight drugs.[7] However, little information has been published on the possible applicability of PEC membranes or matrices as a controlled-release system.[8,9] In this communication, we report a novel method for the preparation of theophylline-loaded κ-carrageenan/chitosan PEC capsules which could be used for zero-order and pH-independent release of the drug. κ-Carrageenan and chitosan are employed in this study, because they are non-toxic when taken orally,[10,11] and their PEC membranes are stable in acidic and alkaline solution.

MATERIALS AND METHODS κ-Carrageenan (Fluka Chemie, Buchs, Switzerland) with sulfate ester content of 19.8% and MW 430,000, and pullulan (Tokyo Kasei Kogyo, Tokyo) with MW 200,000 were used as received. Chitosan (Kimitsu Chem. Ind., Tokyo) with 75.7% deacetylation and MW 610,000 was ground to pass through a 200-mesh sieve. Theophylline (solubility in water 5.8 mg/ml at 25 °C, Wako Pure Chem. Ind., Osaka) and wheat starch (Kishida Chem. Co., Osaka) were used after screening with a 120-mesh sieve. Spherical κ-carrageenan–chitosan PEC membrane capsules containing theophylline were prepared using a novel two-step process. In the first step, potassium-induced κ-carrageenan gel capsules were prepared in a way similar to that described previously.[12] In this experiment, however, theophylline (3 g) and wheat starch (7 g, used as an excipient) were dispersed homogeneously in the aqueous solution (10 g) comprising 0.4 M KCl and 2% pullulan (used as an agent to modulate the viscosity of dispersion), and this dispersion was dropped into 1% κ-carrageenan solution (pH about 9) containing

1% chitosan powder. A capsule membrane containing chitosan powder formed instantly around each droplet due to the ionotropic gelation of κ-carrageenan by potassium ions. After 20 min coating, the resulting capsules (for example, about 7.2 mm in diameter and 1 mm in coat thickness under the condition of 1% chitosan) were separated and briefly washed in distilled water. In the second step, these capsules were incubated in an aqueous solution (pH 2.1) containing 0.2 M citric acid and 0.1 M KCl for 10 min. During this treatment, the chitosan powder that was uniformly embedded in the coating gel membrane dissolved due to the ionization of amino groups (pKa 6.3[8]), and the chitosan molecules instantly crosslinked with the strongly ionized κ-carrageenan polyanions in the gel membrane to form κ-carrageenan/chitosan PEC membrane. After being rinsed with distilled water, the resulting PEC capsules were air-dried for 12 h and then vacuum-dried at 40 °C for 2 h. The theophylline release experiments were performed by the paddle method using a JP XII dissolution test apparatus (100 rpm, 500 ml, 37±0.5 °C). The theophylline concentration in the release solution was measured spectrophotometrically at 271 nm. Release studies were done in duplicate.

RESULTS AND DISCUSSION In this method, κ-carrageenan served as both a template and a crosslinking agent to lead to formation of spherical κ-carrageenan/chitosan PEC capsules containing theophylline and wheat starch. Scanning electron microphotographs of the cross-section of the PEC capsules showed that the capsule core was uniformly coated with a dense PEC layer of about 300 μm in thickness.

Figure 1 shows the release profiles of theophylline from the PEC capsules in different release media. The release media included JP XII disintegration test solutions No. 1 (HCl/NaCl solution, pH 1.2) and No. 2 (KH_2PO_4/NaOH buffer, pH 6.8), 0.05 M CH_3COOH/CH_3COONa buffer (pH 4.0), 0.05 M NaH_2PO_4/Na_2HPO_4 buffer (pH 8.0), distilled water and 0.9%(w/v) NaCl. It was found that the PEC capsules exhibited almost zero-order drug release up to the theophylline release percentage of 60-70, and that the release rates were much lower than the dissolution rate of theophylline from its powder (less than 20 min for complete dissolution[12]). Also, it is of interest to note that neither pH nor ionic strength of the release medium exerted any significant effect on the theophylline release from the PEC capsules, while the rates of drug release from gel matrices and through gel membranes of ionic polysaccharides depended greatly on pH of a release medium.[13,14] The swelling properties of the PEC capsules, which

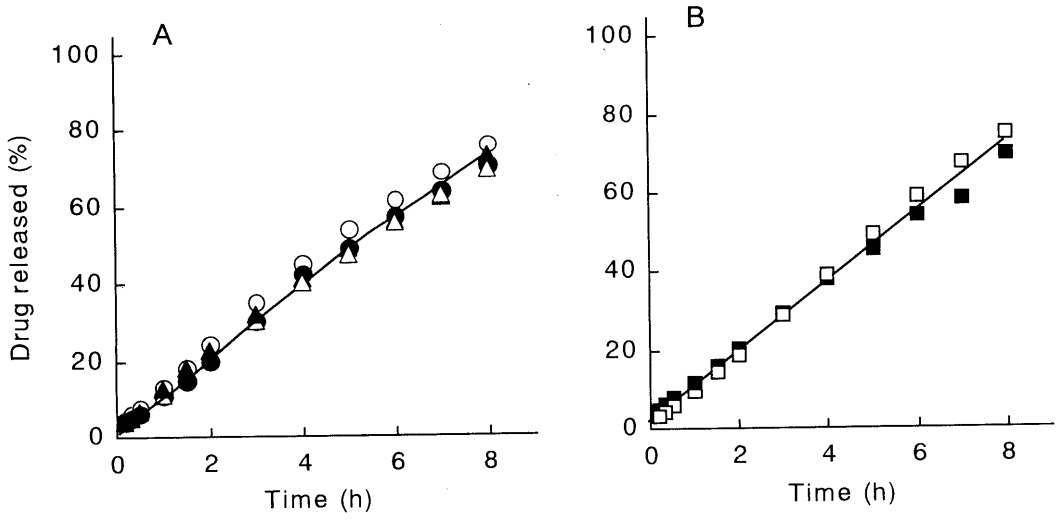

Fig. 1. Release Profiles of Theophylline from κ-Carrageenan/Chitosan PEC Capsules in Release Medium with Different pHs (A) and Ionic Strengths (B)

○, pH 1.2; ●, pH 4.0; △, pH 6.8; ▲, pH 8.0; □, distilled water; ■, 0.9%(w/v) NaCl.

are independent of the pH and ionic strength of the release media employed in this study, are considered to be responsible for the pH- and ionic strength-independent theophylline release rates.

Figure 2 shows the theophylline release profiles of PEC capsules prepared with varying chitosan concentrations in coating fluid. It is clear that as the chitosan concentration increased, the drug release rate decreased. On the other hand, the capsule diameter increased as the chitosan concentration increased, as depicted in Fig. 3. These results strongly suggest that the theophylline release rate of PEC capsules can be easily controlled by regulating the coat thickness.

Thus, unlike the previous encapsulation method in which PEC membranes were thin,[3-6] the present method rendered it possible to prepare PEC capsules with varying coat thickness and to modify drug release rates. Further studies are now in progress to elucidate the optimum conditions for preparing κ-carrageenan/chitosan PEC membrane capsules and to identify more effective polymers for the pH-independent and zero-order drug delivery vehicle.

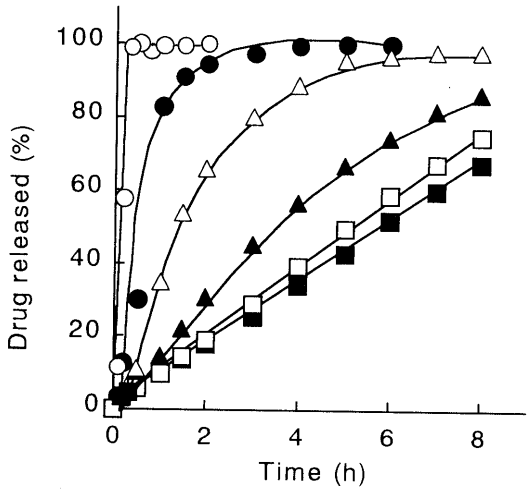

Fig. 2. Release Profiles of Theophylline from κ-Carrageenan/Chitosan PEC Capsules Prepared with Varying Chitosan Concentrations

Chitosan concentration (%): ○, 0; ●, 0.10; △, 0.25; ▲, 0.50; □, 1.00; ■, 1.50.

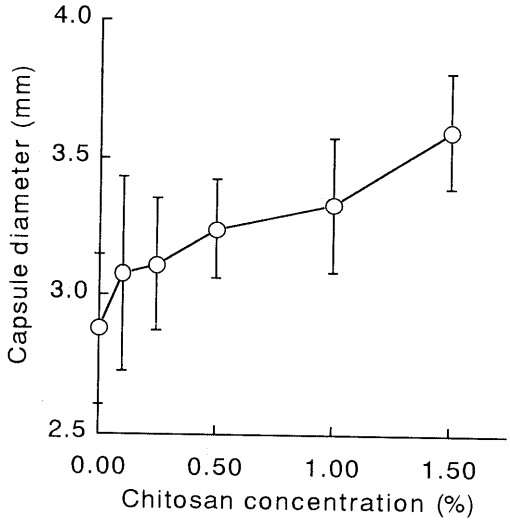

Fig. 3. Capsule Diameter as a Function of Chitosan Concentration in Coating Fluid

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