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The Use of Chitin and Chitosan as Drug Carriers[1)]

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The suitability of chitin and chitosan for use as vehicles for the sustained release of drugs was examined. Indomethacin and papaverine hydrochloride were used as model drugs in this evaluation. Sustained release of the drugs from the dried gels was obtained. Drugs dispersed in the chitosan gels were released at a constant rate (zero order). Chitin and chitosan could be useful vehicles for the sustained release of drugs.

Keywords——chitin; chitosan; drug carrier; sustained release; papaverine hydrochloride; indomethacin

The applicability of natural polysaccharides such as agar,[3)] konjac,[4)] and pectin[5)] in the design of dosage forms for sustained release has been examined.

Chitin [a (1→4)-2-acetamido-2-deoxy-β-D-glucan], a structural polysaccharide, is distributed widely in nature, and chitosan [a (1→4)-2-amino-2-deoxy-β-D-glucan] is easily prepared from chitin by N-deacetylation with alkali.

Chitin and chitosan have been reported to have some useful medical applications.[6)] For example, chitin has been used as a blood anticoagulant,[7)] a wound-healing accelerator,[8)] and a surgical suture.[9)] Chitosan membrane has also been proposed as an artificial kidney membrane.[10)] Despite these medical applications, chitin and chitosan are still little utilized in the pharmaceutical field.[11)] It is known that low molecular weight compounds (MW< 2900) pass through membranes derived from chitosan.[12)] This suggests that most low molecular weight drugs might also pass through the membranes.

Since chitin and chitosan do not present any biological hazard, and since they are inexpensive, these polymers might be suitable for use in the preparation of dosage forms of commercial drugs. In this work, the suitability of chitin and chitosan as vehicles for the sustained release of drugs was examined. Indomethacin and papaverine hydrochloride, which are formulated as sustained release forms, were used as model drugs in this examination.

Experimental

Materials——A highly purified chitin of crab shell (Taraba crab) was obtained from Seikagaku Kogyo Co., Tokyo. Chitosan, Flonac N®, was obtained from Kyowa Yushi Co., Tokyo, and used after passage through a 42 mesh screen. Indomethacin and papaverine hydrochloride were obtained from Sigma Chemical Co., St. Louis, and Hoei Yakko Co., Tokyo, respectively. Hexafluoro-2-propanol was purchased from Aldrich Chemical Inc., Milwaukee. All other materials were of reagent grade, and were used without further purification.

Preparation of Dried Chitin Gel——Weighed samples of chitin (200 mg) were dissolved in hexafluoro-2-propanol (8 ml)[9,13)] by ultrasonic irradiation (Model 13, Ultrasonics, New York) at 200 W for 1 h and the solution was allowed to stand at room temperature overnight. A drug (100 mg each) was dissolved in 2 ml of solvent. The drug and chitin solutions were combined as homogeneously as possible by vigorous mixing. About 3 ml of the mixture was placed in a weighed bottle (1.5 cm in diameter and 2 cm in length) and the solvent was allowed to evaporate at 60°C for 5 h in order to afford a gelled mass, in which the drug was embedded. The whole mass was dried overnight at room temperature *in vacuo*. The final circular chitin gel was 1.1 cm in diameter and 0.1 cm in thickness.

The drug content of the gels was determined by measuring the drug concentration of the release medium after drug release from the gels (48 h).

Preparation of Dried Chitosan Gel——A drug (100 mg) was dissolved in 10% acetic acid (10 ml), and chitosan (500 mg) was dissolved in the drug solution with sonication for 1 h.[14)] After standing at room

temperature for 4—5 h, the mixture was treated in the same way as for the preparation of chitin gel. The final circular chitosan gel was 1.2 cm in diameter and 0.2 cm in thickness.

Measurement of the Amount of the Drug released——A gel containing the drug was added to 200 ml of release medium at 37°C in a 300 ml Erlenmeyer flask in a shaker bath. The flask was shaken horizontally at a rate of 60 strokes/min. At predetermined intervals, a 1 ml portion of the medium was taken and filtered through a Millipore filter (0.45 μm), and the filtrate was assayed for the drug spectrophotometrically.

Results and Discussion

Release profiles as well as dissolution profiles of indomethacin in pH 7.4 phosphate buffer are shown in Figs. 1 and 2. The average values are plotted in the figure. The reproducibility in triplicate runs was good. In contrast with the rapid dissolution of indomethacin in powdered form, sustained release was obtained from the chitin and the chitosan gels. Sustained but almost complete release from the chitin gel was observed (Fig. 1). A plot of the cumulative amount of the drug released from the chitosan gel against time was linear, and the drug was released from the gel at an almost constant rate for 5 h (Fig. 2). Chitin and chitosan gels were thus demonstrated to serve as barriers to the liberation of indomethacin.

The release patterns of papaverine hydrochloride from the chitin and the chitosan gels are compared with the dissolution patterns of the drug powder in an acid medium in Figs. 3 and 4, respectively. Only small differences were observed between the release pattern of the basic drug from the chitin gel and the dissolution pattern of the drug powder (Fig. 3). Sustained release was obtained from the chitosan gel, whereas the drug powder dissolved completely within 20 min (Fig. 4). Thus, the chitosan gel might be useful as a vehicle for a sustained release preparation of papaverine hydrochloride.

The above preliminary results suggest that chitin and chitosan are useful for the preparation of gels that exhibit sustained release of drugs. Although the advantages of chitin and chitosan have been discussed elsewhere, one major advantage from a commercial point of view is their low cost, since commercial sustained release preparations are more expensive than ordinary dosage forms.

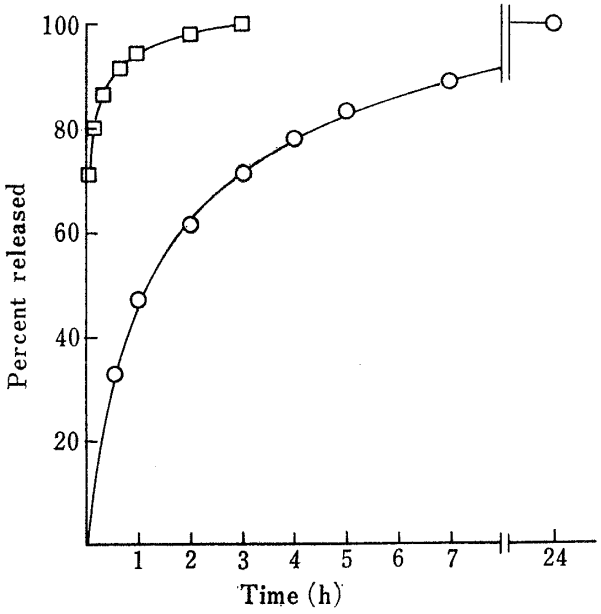

Fig. 1. Release Pattern of Indomethacin from Chitin Gel (○) and Dissolution Pattern of the Drug Powder (□) in pH 7.4 Phosphate Buffer

Each preparation contained 24.3 mg of the drug.

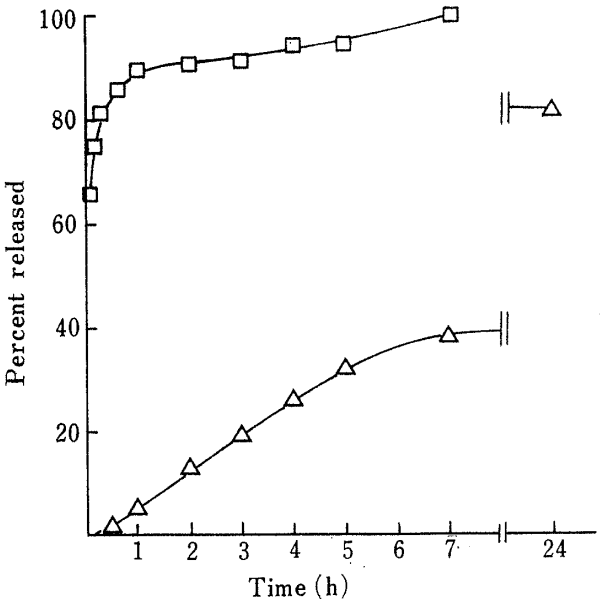

Fig. 2. Release Pattern of Indomethacin from Chitosan Gel (△) and Dissolution Pattern of the Drug Powder (□) in pH 7.4 Phosphate Buffer

Each preparation contained 18.6 mg of the drug.

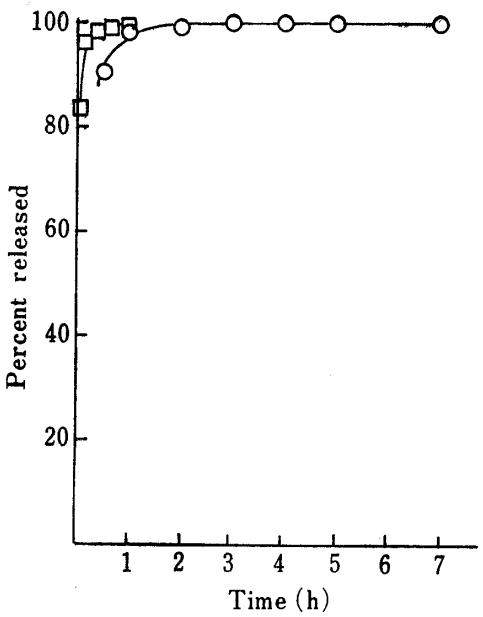

Fig. 3. Release Pattern of Papaverine Hydrochloride from Chitin Gel (○) and Dissolution Pattern of the Drug Powder (□) in 0.1 N HCl

Each preparation contained 21.0 mg of the drug.

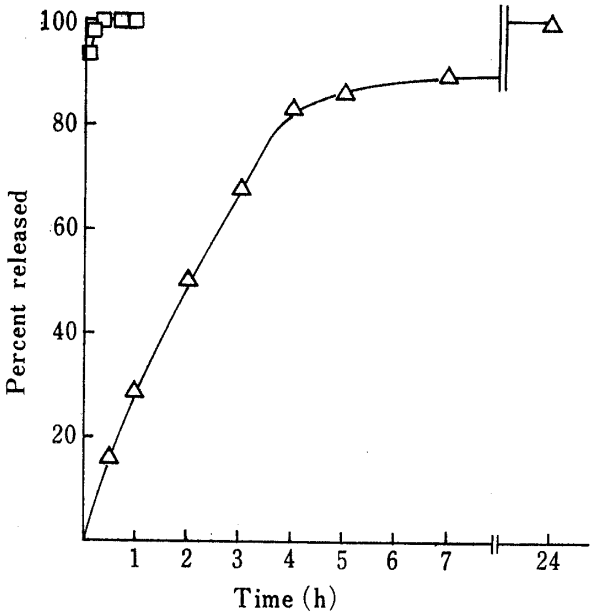

Fig. 4. Release Pattern of Papaverine Hydrochloride from Chitosan Gel (△) and Dissolution Pattern of the Drug Powder (□) in 0.1 N HCl

Each preparation contained 16.4 mg of the drug.

References and Notes

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