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Examination of Natural Gums as Matrices for Sustained Release of Theophylline

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Release patterns of theophylline from compressed tablets prepared from theophylline and various natural gums were examined. Carrageenan, locust bean gum, guar gum, gum tragacanth, and sodium alginate were tested. Release patterns of the drug from tablets prepared from a mixture of carrageenan and locust bean gum were more sustained than those from carrageenan tablets. Changes in release rates caused by changing the gum contents or drug-to-gum ratios were also examined.

Keywords—natural gum; carrageenan; locust bean gum; guar gum; gum tragacanth; sodium alginate; sustained release tablet; theophylline; carrageenan-locust bean gum mixture

Since various kinds of natural gums are used in the food industry and are regarded as safe for human consumption, they may be useful in dosage form design. Agar in the form of beads and konjac in the form cylinders have been examined as matrices for sustained release of drugs.¹⁻⁷⁾ When natural gums in the form of compressed tablets are placed in water, they are expected to absorb water from the medium and form a gel before they dissolve in the medium.^{8,9)} If a drug is contained in the tablet, it is expected to be released through the gel layer, and sustained release may be achieved.

In the present study, five natural gums¹⁰⁾ were examined. Carrageenan consists of sulfated linear polysaccharides of D-galactose and 3,6-anhydro-D-galactose. Locust bean gum is a linear chain of β -D-mannopyranosyl units with non-uniformly spaced side branches. Guar gum is similar to locust bean gum chemically, except that the side branches are spaced uniformly. Gum tragacanth is a mixture of a water-swelling major component, bassorin, and a water-soluble component, tragacanthin. The former contains tragacanthic acid while the latter is considered to be essentially a neutral polysaccharide. Sodium alginate is composed of polymannuronic acid, polyguluronic acid and alternating segments of the two uronic acids.

Theophylline was employed as a representative drug because sustained release formulations are desirable due to the short elimination half-life of theophylline, especially in children.¹¹⁾ Sustained release of theophylline from hydroxypropylcellulose tablets has been reported.¹²⁾

Experimental

Materials—Carrageenan from Tokyo Kasei Kogyo, Tokyo, locust bean gum and guar gum from Sigma Chemical Co., St. Louis, and gum tragacanth, sodium alginate, and theophylline (anhydrous) from Wako Pure Chemical Ind., Osaka, were used without further purification. Other chemicals were of reagent grade.

Preparation of Tablets—Flat-faced tablets, 13 mm in diameter, were prepared by compressing mixtures of theophylline and a natural gum directly under 150 kg/cm² for 60 s employing a die and a hydraulic press for potassium bromide tablets (Shimadzu KBr press, Shimadzu Manufacturing Co., Kyoto).

Release Studies—A tablet was suspended in 200 ml of release medium in a wide-mouthed bottle by means of a

polyethylene net. JP X Disintegration Test Medium No. 1, pH 1.2, was used as a release medium. In certain studies, the tablet in the net was taken out of the medium at pH 1.2 at 2 h and was placed in Disintegration Test Medium No. 2, pH 6.8. Each medium was kept at 37°C by means of a thermostated water-bath and stirred with a magnetic stirring bar. At predetermined intervals, a 1-ml portion of the medium was pipetted through a cotton plug for spectrophotometric determination of theophylline concentration at 272 nm after suitable dilution with 0.2 M acetate buffer, pH 5.0. Since reproducibility between identical experiments was good, each system was studied twice and average values are shown in each figure.

Results and Discussion

Release Profiles

Release profiles of theophylline from tablets prepared from 250 mg of the drug and 250 mg of the gum are given in Figs. 1 and 2. In comparison with the fast dissolution of

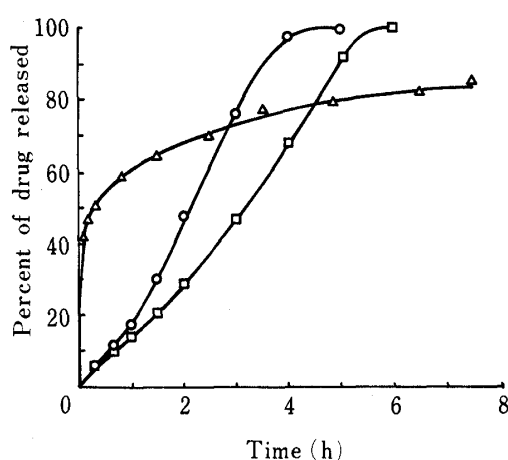


Fig. 1. Release Patterns of Theophylline from Tablets Prepared from 250 mg of Theophylline and 250 mg of Carrageenan (O), Locust Bean Gum (Δ), or a 2:1 Mixture of Carrageenan and Locust Bean Gum (\square) in Release Medium at pH 1.2

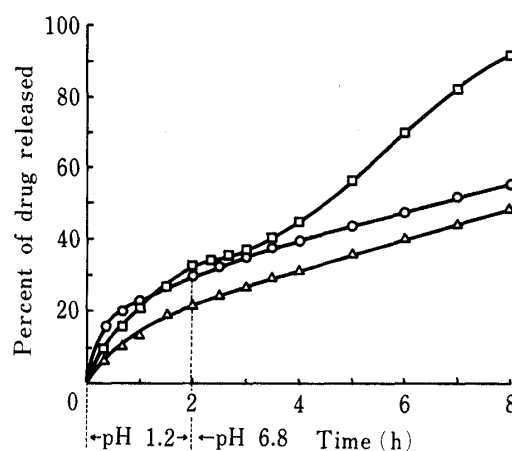


Fig. 2. Release Patterns of Theophylline from Tablets Prepared from 250 mg of Theophylline and 250 mg of Guar Gum (O), Gum Tragacanth (Δ), or Sodium Alginate (\square) in Release Medium at pH 1.2 for the First 2 h and Release Medium at pH 6.8 after 2 h

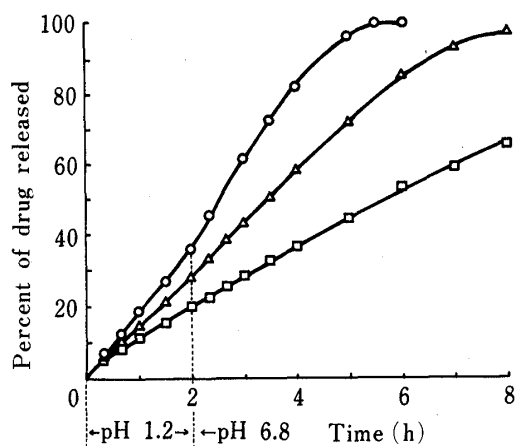


Fig. 3. Release Patterns of Theophylline from Tablets Prepared from 250 mg of Theophylline and 125 mg (O), 250 mg (Δ) or 670 mg (\square) of a 2:1 Mixture of Carrageenan and Locust Bean Gum in Release Medium at pH 1.2 for the First 2 h and Release Medium at pH 6.8 after 2 h

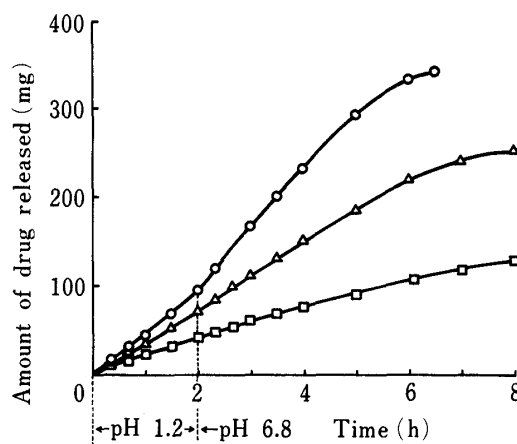


Fig. 4. Release Patterns of Theophylline from Tablets Prepared from 330 mg : 167 mg (O), 250 mg : 250 mg (Δ), or 125 mg : 375 mg (\square) of Theophylline and a 2:1 Mixture of Carrageenan and Locust Bean Gum in Release Medium at pH 1.2 for the First 2 h and Release Medium at pH 6.8 after 2 h

theophylline from its powder,³⁾ sustained release of the drug from tablets containing natural gums was observed. A sigmoidal release profile was obtained from a carrageenan tablet. From a locust bean gum tablet, about one-half of the drug was released very rapidly, but the rest was released slowly. The fast release was attributed to initial disintegration of the tablet, whereas the slow release was rationalized in terms of swelling of the undisintegrated part of the tablet and permeation of the drug through the resulting gel layer. Since locust bean gum is reported to enhance the gel strength of carrageenan,¹⁰⁾ a mixture of the two gums was also examined. The drug was released more slowly from a tablet prepared from a 2:1 mixture of carrageenan and locust bean gum than from the carrageenan tablet. Thus a synergistic interaction between the two gums was demonstrated.

The release rates from a guar gum tablet and a gum tragacanth tablet decreased with time. Although the release rates were comparable after 1 h, the initial release rate was greater in the former than the latter. A sigmoidal release profile was obtained from a sodium alginate tablet. The second rise in the release profile may be attributed to dissolution of alginate due to an increase in the solubility of the polymer in the neutral pH region as a result of ionization of carboxyl groups which had been protonated in the acidic pH region.

Since the release pattern of theophylline from the carrageenan-locust bean gum tablet was linear (Fig. 3) even if the pH value of the release medium was changed from 1.2 to 6.8, this gum mixture was examined further at various gum contents (125–670 mg) keeping the drug content constant (250 mg), and at various drug-to-gum ratios. Figure 3 shows release profiles of the drug from tablets prepared from 250 mg of theophylline and various amounts of 2:1 mixture of carrageenan and locust bean gum. As expected, the drug was released faster as the amount of gum was decreased. Thus changes in the amount of the gum in a tablet may be used to control the release rate of the drug.

Figure 4 shows release profiles of the drug from tablets prepared from the same total amount but at various drug-to-gum ratios. The release rate decreased with decrease in the drug contents in the tablets. Thus, the release rate of the drug can be modified by changing the drug-to-gum ratio even if the total weight of the tablet has to be kept constant.

General Discussion

Although carrageenan, locust bean gum, guar gum, and alginate have been examined by Bamba *et al.*^{8,9)} at various contents of each gum with a constant drug content, a mixture of carrageenan and locust bean gum, as well as gum tragacanth, was examined in the present study in addition to the above four gums. Tablets prepared at various drug-to-gum ratios, keeping the total weight of the tablet constant, were examined in addition to tablets prepared from a constant amount of the drug but various amounts of gum. It has been demonstrated that a mixture of carrageenan and locust bean gum can be used to design sustained release tablets, and variables such as gum content and drug content in the tablets can be controlled to achieve a desired release rate of a drug.

References and Notes

- 1) M. Nakano, Y. Nakamura, K. Takikawa, M. Kouketsu, and T. Arita, *J. Pharm. Pharmacol.*, **31**, 869 (1979).
- 2) M. Nakano, M. Kouketsu, Y. Nakamura, and K. Juni, *Chem. Pharm. Bull.*, **28**, 2905 (1980).
- 3) M. Nakano, Y. Nakamura, K. Juni, and T. Tomitsuka, *J. Pharm. Dyn.*, **3**, 702 (1980).
- 4) M. Nakano, K. Takikawa, and T. Arita, *Membrane*, **3**, 141 (1978).
- 5) M. Nakano, K. Takikawa, and T. Arita, *J. Biomed. Mater. Res.*, **13**, 811 (1979).
- 6) M. Nakano, K. Takikawa, and T. Arita, *Chem. Pharm. Bull.*, **27**, 2501 (1979).
- 7) M. Nakano, K. Takikawa, K. Juni, and T. Arita, *Chem. Pharm. Bull.*, **27**, 2834 (1979).
- 8) M. Bamba, F. Puisieux, J.-P. Marty, and J. T. Carstensen, *Int. J. Pharmaceut.*, **2**, 307 (1979).
- 9) M. Bamba, F. Puisieux, J.-P. Marty, and J. T. Carstensen, *Int. J. Pharmaceut.*, **3**, 87 (1979).

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- 10) R. L. Davidson (ed.), "Handbook of Water-Soluble Gums and Resins," McGraw-Hill, New York, 1980, pp. 2-1-4, 5-1-17, 6-1-4, 11-1-3, 14-1-3.
 - 11) D. E. Zaske, K. W. Mitler, E. L. Strem. S. Austrian, and P. B. Jonson, *J. Am. Med. Assoc.*, **237**, 1453 (1979).
 - 12) M. Nakano, N. Ohmori, A. Ogata, K. Sugimoto, Y. Tobino, R. Iwaoku, and K. Juni, *J. Pharm. Sci.*, **72**, 378 (1983).