in the kidney and liver, their physiological role remains to be elucidated. It has recently been reported[8] that the liver peroxisomes are capable of oxidizing palmitoyl-CoA and that treatment with clofibrate enhances the peroxisomal system of fatty acid oxidation. If this is also the case in kidney peroxisomes, increased activities of peroxisomal enzymes on sodium restriction may be associated with fatty acid metabolism, which is a major source of energy for renal processes. Further studies are required in this area.

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Sustained Release of Theophylline from Konjac Gels[1]

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The possible use of konjac gels to achieve sustained release of theophylline on oral administration was examined *in vitro*. Theophylline was trapped in the gels by soaking the gels in a hot drug solution and subsequently drying them. Sustained release of the drug from the dried konjac gels was obtained. No marked difference was observed in the release patterns in the range of pH values expected in the gastrointestinal tract, and the drug contained in the gels was completely released.

Keywords——hydrogel; konjac gel; theophylline; bronchodilator; sustained release; solubility; swelling rate

Theophylline, a bronchodilator, has been used for the management of chronic asthma for prophylactic purposes. Its plasma half-life ($t_{1/2\,\beta}$) has been reported to be 4.4—6.2 hr.[3-5] In order to obtain effective plasma theophylline concentrations, a dose of 200—300 mg of theophylline is administered three or four times daily. The rapid absorption and elimination characteristics of theophylline result in large variations in plasma theophylline concentration during dosing in patients receiving the chronic therapy. Therefore it has been suggested that sustained release preparations might decrease the variations in plasma concentration by slowing the rate of absorption.[6]

In an attempt to examine the applicability of hydrogels for sustained release preparations, the release of dibucaine, a local anesthetic, from konjac gels gelatinized with borax has been examined.[7] The results indicated that release of the drug dispersed in konjac gels was sustained. The release experiments *in vivo* following rectal administration of the gels

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showed a good correlation with *in vitro* data.[8] Since borax, the gelatinizing agent employed, is not suited to oral administration, konjac gels were prepared in the present study using the gelation procedure for food, and theophylline was then absorbed into the gels. The release patterns of theophylline trapped in the konjac gels were examined *in vitro*.

Experimental

Materials——Konjac flour, New Mannan Gold,® with a total sugar content of 82.7%, was a gift from Tsuruta Shokuhin and Co., Tomioka. Ammonia water, hydrochloric acid, acetic acid, potassium chloride, sodium acetate, sodium dihydrogen phosphate, disodium hydrogen phosphate (all of reagent grade), Nessler solution, and anhydrous theophylline were purchased from Wako Pure Chemical Industries, Osaka, while calcium hydroxide was from Koso Chemical Co., Tokyo. They were used without further purification.

Preparation of Dried Konjac Gels——Dried konjac gels, in which theophylline was dispersed in the form of fine crystals, were prepared by the following procedures. Konjac flour was fully swollen with distilled water to obtain a sol at a konjac level of 5% (w/w). The sol was sucked into a plastic syringe (4.6 mm inside diameter) and extruded into boiling water saturated with calcium hydroxide. After boiling for 30 min, an elastic gel cord (5 mm in diameter) was obtained. After removal of the alkali by washing the gel with water overnight, the elastic gel cord was cut into lengths of 5 mm. The gels were equilibrated with four times their volume of theophylline solution (5% in 0.01 N ammonia water) at 70° for 1 hr and then dried at $38\pm2°$ to a constant weight. Although they were prepared in 0.01 N ammonia water at 70° in order to load the gels with a highly concentrated drug solution, no decomposition of theophylline was observed spectrophotometrically. The amount of ammonia remaining in the dried gel was nearly at the limit of the detection by the Nessler method.

Measurement of the Amount of the Drug Released——Twenty pieces of dried gel (about 143 mg) containing about 64 mg of theophylline were added to 100 ml of the release medium in a wide-mouthed bottle in water-jacketed beaker maintained at 37°. The following three media were employed: Clark and Lubs HCl–KCl solution at pH 1.0, 0.2 M acetate buffer at pH 5.0, and 0.1 M phosphate buffer at pH 7.4. The release medium was agitated with a magnetic stirring bar (4 cm in length) at a rate of about 185 rpm. At suitable intervals, 0.5 ml of the medium was taken with a pipette through a cotton plug and assayed for the drug spectrophotometrically at 272 nm, employing a digital spectrophotometer (model 200-20, Hitachi Manufacturing Co., Tokyo) after appropriate dilution with 0.2 M acetate buffer, pH 5.0. The volume of the release medium was kept constant throughout the release experiment by the addition of 0.5 ml of fresh release medium after each sampling.

Measurement of Solubility——An excess of theophylline was added to each medium in a test tube with a glass stopper. The suspension was equilibrated in a water-jacketed beaker maintained at 37° for 24 hr, mixing with a magnetic stirring bar (1 cm in length). A portion of the equilibrated suspension was filtered quickly through a sintered-glass disk. An aliquot of the filtrate was assayed for the drug in the same manner as in the release studies.

Differential Scanning Colorimetry and Thermal Gravimetric Analysis——Melting and dehydration properties of theophylline in the dried gel sample were examined with a thermal gravimetry-differential scanning colorimeter (Thermoflex model M 8085, Rigaku Denki, Tokyo). A heating rate of 5°/min was employed.

Measurement of the Sizes of the Konjac Gels——The sizes of the konjac gels were measured with slide calipers. The volumes of the gels were calculated from their diameters and lengths. The swelling pattern of the dried gels was determined by measuring their diameters and lengths at various stages of swelling (five gels at each sampling time).

Scanning Electron Microscopic Observation of the Dried Konjac Gel——Dried konjac gel was sliced with a razor, and the pieces were coated with gold employing an ion coater (model IB-3, Eiko Engineering Co., Tohkai). The preparation was observed with a scanning electron microscope (model S-430, Hitachi Manufacturing Co., Tokyo) and photomicrographs were taken.

Results and Discussion

In contrast with the very rapid dissolution of theophylline in powdered form, irrespective of the pH of the medium, sustained release was obtained in the release profile from the dried konjac gels (Fig. 1). The average values are plotted in the figure. The reproducibility in duplicate runs was good. Assuming that all of the drug contained in the dried gels is released when the concentration of the drug in the release medium reaches the equilibrium value,

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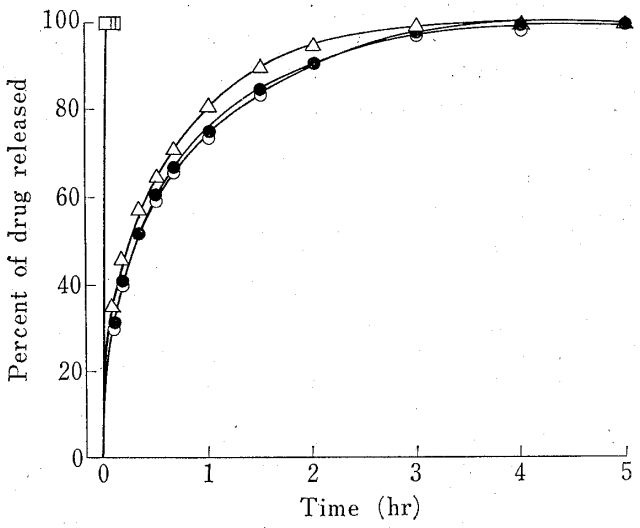

Fig. 1. Release Patterns of Theophylline from Dried Konjac Gels at pH 1.0(△), pH 5.0(○), and pH 7.4 (●) and Dissolution Patterns from Powders at the Three pH Values (□) at 37°

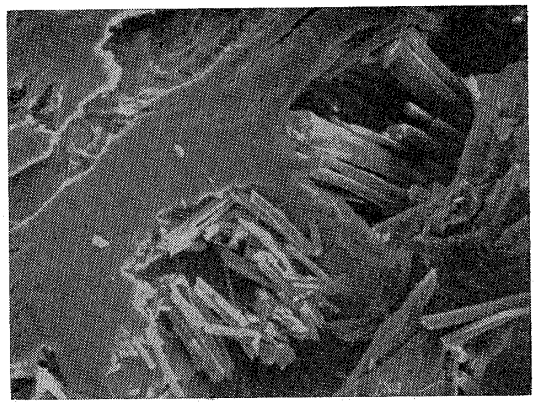

Fig. 2. Scanning Electron Photomicrograph of a Cross Section of a Dried Konjac Gel (×117)

the percentage of the drug released at each sampling time was calculated. The weight of 20 pieces of the dried gel was 142.8±1.7 mg (mean±S.D., n=8). The amount of the drug contained in the dried gels calculated from release studies was 44.6±0.8 mg/100 mg (n=6) and that calculated on the basis of drug equilibration between the gels and the drug solution during the drug-loading process of the preparation was 44.4 mg/100 mg. The good agreement between these values supports the validity of the above assumption that all of the drug is released from the gels. It was found that theophylline was in an anhydrous form in the dried konjac gel by differential scanning colorimetry and thermal gravimetric analysis. A scanning electron photomicrograph of the konjac gel (Fig. 2) shows that anhydrous theophylline crystals occupied cavities in the konjac gel network.

In conjunction with examination of the effect of the pH of the release medium on the release profile, the solubility of theophylline at each pH was determined (Table I). The release rate of theophylline was greater when the solubility of the drug in the release medium

Table I. Solubilities of Theophylline at Three pH Values at 37°

pH	Solubility, 10^{-2} M
1.1	7.3
5.1	5.5
7.3	5.9

Table II. Sizes of the Konjac Gels (Mean ± SD)

	Diameter, mm	Length, mm
Before drying	5.0±0.1 (n=20)	5.0±0.2 (n=20)
After drying	2.3±0.2 (n=20)	2.7±0.2 (n=20)
After swelling	3.0±0.2 (n=60)	3.2±0.2 (n=60)

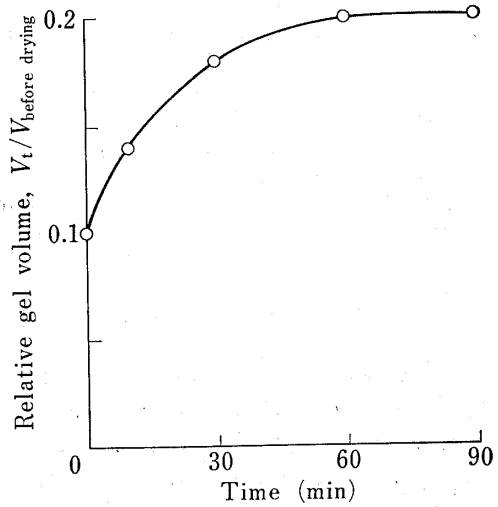

Fig. 3. Swelling Pattern of Dried Konjac Gel in Distilled Water at 37°

The mean of five determinations.

was greater. However no marked change was observed in the release profiles between pH 1.0 and pH 5.0. These pH values are expected to cover pH values where the solubility of theophylline exhibits the maximum and minimum values in the gastrointestinal tract. Therefore no sudden change in the release pattern is expected during passage of a gel through the gastrointestinal tract.[9]

The sizes of the gels before drying, after drying, and after swelling are given in Table II. The difference in size after swelling in three media was not significant, and thus the swelling is not significantly dependent on the pH of the medium. Fig. 3 shows the swelling pattern of the dried gels in distilled water at 37°. The volume of the dried gel was 10% of that before drying and increased to 20% at equilibrium. This observation suggests that the drying procedure not only helps to overcome such problems as degradation during storage and bulkiness, but also gives a more sustained release because of the denser gel structure after the drying process.

The significant difference between the dissolution rates of theophylline from powders and the release rates from dried konjac gels suggests that the drug absorption following oral administration of the gels may be prolonged, although the results of *in vitro* experiments may not be directly related to the *in vivo* situation. Furthermore, the complete release of the drug from the gels is noteworthy, since some commercial oral sustained release preparations reportedly fail to release all of the drug during their passage through the gastrointestinal tract.[6,10] It thus appears that oral administration of drugs trapped in konjac gels may be useful for the sustained release of the drugs. The release profiles of theophylline after oral administration of the gels will be examined shortly.

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