

mg) at 20° and 1 atm for 90 min. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to leave $14 \cdot \text{HClO}_4$ (460 mg, 100%), mp 158—163°, which was dissolved in H_2O (20 ml). The aqueous solution was made basic with anhyd. K_2CO_3 and extracted with ether. The ethereal solution was dried over anhyd. K_2CO_3 and evaporated *in vacuo*, leaving the free base **14** (344 mg, 95%) as a yellow, unstable oil, IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 2805, 2760 (*trans*-quinolizidine), 1730 (ester CO); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 2805, 2760 (*trans*-quinolizidine), 1722 (ester CO); NMR (CDCl_3) δ : 0.91 (3H, t, $J=7$ Hz, CCH_2Me), 1.28 (3H, t, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 3.88 (6H, s, two MeO's), 4.20 (2H, q, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 6.60 and 6.72 (1H each, s, aromatic protons).

The Perchlorate of **14**: Colorless minute needles (from EtOH), mp 163—164°; IR $\nu_{\text{max}}^{\text{Nujol}}$ 1720 cm^{-1} (ester CO). *Anal.* Calcd. for $\text{C}_{21}\text{H}_{32}\text{ClNO}_8$: C, 54.60; H, 6.98; N, 3.03. Found: C, 54.86; H, 7.01; N, 2.95.

The Hydriodide of **14**: A small portion of $14 \cdot \text{HClO}_4$ was dissolved in hot EtOH and an equimolar amount of KI was added. The resulting precipitate was filtered off and the filtrate was concentrated *in vacuo*, leaving a solid of mp 208—211°. Recrystallization of the solid from EtOH-ether (1:1, v/v) produced $14 \cdot \text{HI}$ as faintly yellow needles, mp 211—212° (lit.^{4b}) mp 214.5—216.5°; mp 210—212°^{4d}).

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Sustained Release of Dibucaine from Konjac Gels after Rectal Administration to Rats¹⁾

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The use of konjac gels as a vehicle for sustained drug release in the form of a rectal suppository was examined in rats. Dibucaine dispersed in the konjac gels was released in the rectum at a rate predictable from *in vitro* release studies. No observable destruction of rectal mucosa was noted on microscopic observation, even after two 24 hr contacts (3-week interval) with drug-free gels.

Keywords—hydrogel; konjac gel; elastic gel; sustained release; suppository; rectal administration; dibucaine; local anesthetic

The properties of konjac gels have been studied to investigate their suitability as vehicles for the sustained release of drugs. Sustained release of dibucaine, a local anesthetic, has been obtained from konjac gels in which dibucaine base had been dispersed in the form of fine crystals.³⁾ A linear relationship was obtained when the cumulative amount of the drug released was plotted against the square root of time, and the release profile was in agreement with that expected from the theoretical equation.^{4,5)} In the present study the suitability of konjac gels for use as a rectal suppository was examined in comparison with glycerinated gelatin suppositories, whose elasticity is similar to that of the konjac gels.

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Experimental

Materials—Konjac flour, New Mannan Gold®, with a total sugar content of 82.7%, was a gift from Tsuruta Shokuhin and Co., Tomioka. Dibucaine hydrochloride was of J.P.IX grade from Teikoku Kagaku-sangyo, Osaka, and dibucaine base was prepared from the hydrochloride according to the identification procedure for dibucaine hydrochloride in J.P.IX. Borax (reagent grade), urethan (ethyl carbamate), and glycerin were from Koso Chemical Co., Tokyo. Cyclohexane, sodium hydroxide, sodium acetate, sodium chloride, and acetic acid were of reagent grade from Wako Pure Chemical Industries, Osaka, while gelatin (test No. 48G123042) was from Kanto Chemical Co., Tokyo. These materials were used without further purification.

Preparation of the Konjac Gels—Large konjac gel cylinders (1.3 cm in diameter and 4 cm in length), in which dibucaine base was dispersed, were prepared by the procedure described previously.³⁾ The gel was sucked into a plastic syringe and extruded into a glass tube (0.3 cm in inside diameter). By cutting the gel to lengths of 1 cm, small gel cylinders suitable for rectal administration were obtained. The concentrations of the drug, konjac flour, and borax were 1% as dibucaine hydrochloride, 4%, and 0.03 N, respectively. Glycerinated gelatin suppositories with the same drug content and of the same size were prepared according to the U.S.P. procedure⁶⁾ in glass tubes (0.3 cm in inside diameter).

Rectal Administration—Male Wistar rats weighing 180–220 g were used for all experiments. Prior to the experiment the fecal content in the rectal canal was reduced by fasting for 48 hr.⁷⁾ The rats were anesthetized with urethan by intraperitoneal injection at a dose level of 100–150 mg per 100 g body weight, then the konjac gel or the glycerinated gelatin suppository was inserted into the rectum with a glass injector. The leakage of rectal contents was prevented by means of a stopper or a clip.

Measurements of the Amount of the Drug released—The amount of the drug released was calculated from the amount of the drug remaining in the gels. At a selected time, the konjac gel was removed from the rectum and placed in 10 ml of 0.2 M acetate buffer, pH 5.0, in a test tube with a glass-stopper. On shaking the content in the test tube for 2 hr, all of the drug remaining in the gel was completely released. Since the glycerinated gelatin suppository dissolved in the secreted fluid in the rectum, the following method was employed to collect the drug remaining in the rectum. Glass cannulae were inserted into the anus and the lower part of the colon. The contents of the rectum were washed out with about 2 ml of saline as far as 6 cm from the anus, and 0.2 M acetate buffer, pH 5.0, was then added to the washing solution to give a volume of 10 ml. The drug solution was then made alkaline by the addition of 0.1 N NaOH, and the drug in unionized form was extracted with 6 ml of cyclohexane. The cyclohexane layer was assayed for the drug spectrophotometrically at 330 nm employing a digital spectrophotometer (model 200-20, Hitachi Manufacturing Co., Tokyo). The drug content of samples prepared at the same time as those administered was measured in the same manner (except for the administration and recovery procedures) and the percent of the drug released *in vivo* was calculated relative to this value.

Microscopic Observation of the Rectal Tissue—The effects of the konjac gels on the rectal mucosa were checked by microscopic observation of the rectal tissue. Drug-free konjac gels were prepared and each gel was held in the rectum of a rat for 24 hr twice at an interval of 3 weeks. The tissue samples for microscopic observation were prepared by the standard procedure⁸⁾ and observed with a microscope (model BHB, Olympus, Tokyo).

Results and Discussions

In comparison with the release profile of dibucaine from glycerinated gelatin suppositories, sustained release was obtained in drug release from the konjac gels (Fig. 1). The drug contents of the konjac gels and the glycerinated gelatin suppositories were 0.64 ± 0.02 mg (mean \pm SEM, $n=4$) and 0.65 ± 0.03 mg ($n=3$), respectively.

As shown in Fig. 2, a linear *in vivo* release profile was obtained when the cumulative amount of the drug released was plotted against the square root of time. The calculated values based on the previously reported *in vitro* release profile of dibucaine from large konjac gels (1.3 cm in diameter and 4 cm in length) at pH 7.4³⁾ are also shown in Fig. 2. The surface area of the large gel was 17.5 times that of the small gel, and the drug content of the former was 70.6 times that of the latter. The expected percentages of the drug released from the small gels were calculated by multiplying the data for the large gels by 70.6/17.5. Since

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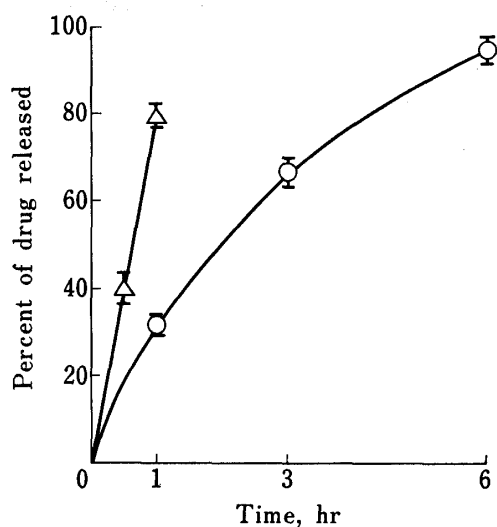


Fig. 1. Release Patterns of Dibucaine from the Konjac Gels (O) and Glycerinated Gelatin Suppositories (Δ) in Rat Recta

Mean \pm standard error of the mean, $n=3$.

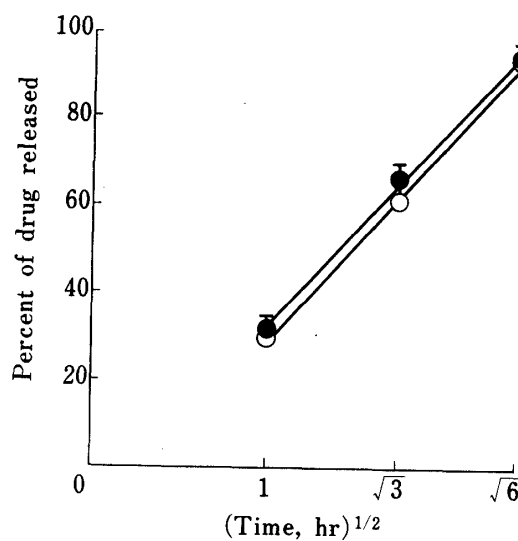


Fig. 2. *In Vivo* (●)—*In Vitro* (O) Comparison of Release Patterns of Dibucaine from Konjac Gels

The slopes of the *in vivo* and *in vitro* lines are 43.2 and 44.3, respectively.

a good correlation was obtained between the *in vivo* and *in vitro* release profiles, the *in vivo* release profiles may be estimated from measurements of the *in vitro* release rate.

No observable destruction of rectal mucosa was noted in the photomicrograph after 24 hr contact with the drug-free konjac gel (not shown) or two 24 hr contacts with the gel 3 weeks apart (Fig. 3).

Borax in the amount used for gelation in the present study is not expected to exhibit toxicity when administered topically.⁹⁾

The above results show that konjac gels are potentially useful for sustained drug release in the form of a suppository. Although this study was limited to rectal administration, it seems likely that the konjac gels will also be particularly suitable for vaginal administration because of their elastic properties.

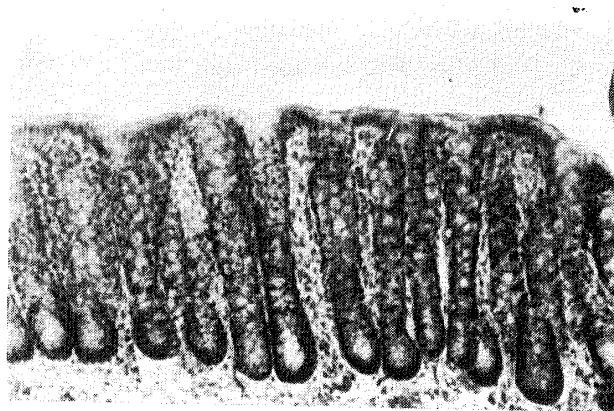


Fig. 3. Photomicrograph of the Rectal Mucosa of a Rat after Two 24 hr Contacts with Drug-free Konjac Gels 3 Weeks Apart

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