Cotrolled Release of Dibucaine from Konjac Gels

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Synopsis: A possible use of konjac gel for sustained release of drugs was examined in two types of systems containing dibucaine, a local anesthetic. The relationships between the cumulative amount of the drug released and time were in agreement with those expected from the theoretical equations in both monolithic and depot systems.

(Received Dec. 26, 1977)

Synthetic membranes have been successfully employed as release-controlling barriers in therapeutic systems.¹⁾

Because of essential lack of antigenicity in most polysaccharides, these biopolymers, if properly formulated, may be employed as release rate-controlling barrier for clinical use. Since konjac is a popular article of food in Japan, it may be considered that this polymer may be employed internally as a part of dosage forms. Therefore a possible use of konjac gel for sustained release of drugs was examined.

Konjac flour, New Mannan Gold®, total sugar content of 82.7%, was a gift from Tsuruta Shokuhin & Co., Tomioka. Dibucaine hydrochloride, a local anesthetic, JPIX grade, Teikoku Kagakusangyo, was used as a model drug without further purification. Dibucaine base was prepared according to the identification procedure of dibucaine hydrochloride in JPIX. An elastic konjac gel cylinder (about 4cm in length) was formed by warming swollen konjac flour at 60° in a glass tube (1.3cm in inside diameter) for 15min after the addition of borax ($\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$) solution (resultant concentration, 0.03-0.05N, pH9) to it and insertion of a glass suspender (0.3 cm in diameter). For a monolithic system, after konjac flour was swollen with dibucaine hydrochloride solution, the gel was prepared in which dibucaine base was dispersed in the form of fine crystals by the addition of borax solution. A depot system was prepared by covering a core gel which contained solid dibucaine base within the gel with a solid drug-free gel. It may be considered

that the decomposition of the drug during the gelation process was negligible.²⁾ The amount of the drug released under a sink condition (where effective concentration of the drug in the elution medium was maintained at a negligible level) was determined as follows. Twenty-five milliliters of 0.1M phosphate buffer, pH7.4 (elution medium) was placed in a graduated cylinder which was

Fig. 1 Release pattern of dibucaine from the konjac gel in the monolithic system at 37° under the sink condition, pH7.4 (45.2 mg of dibucaine base in a preparation)

Fig. 2 Release patterns of dibucaine from the konjac gels in the monolithic system (Δ) and the depot system ($\circ$) at 37° , under the sink condition, pH7.4 (18.1 mg of dibucainebase in each system)

immersed in a water bath maintained at 37° . The cylindrical gel was suspended in the elution medium which was agitated by a magnetic stirring button (1.5cm in diameter). At suitable time intervals, the whole elution medium was replaced together with the container, a portion of the elution medium was filtered through a sintered-glass disk, and an aliquot of the filtrate was assayed for the drug spectrophotometrically at 327nm after appropriate dilution with 0.2M acetate buffer, pH 5.0. The dissolution rate of dibucaine from the base powder and the amount released from the konjac gel under a non-sink condition were determined in the same way as above, except that the elution medium was not replaced and 1ml of sample was pipetted from the medium through a cotton plug.

In contrast with rapid dissolution rate of dibucaine in suspensions of dibucaine base at pH7.4, sustained release was obtained in the release profile from the konjac gel (not shown). Although release profile of the drug even under the sink condition was not linear when the cumulative amount of the drug released was plotted

against time (Fig. 1), a straight line relationship was obtained when the cumulative amount was plotted against the square root of time³⁾ (Fig. 1 Inset). On the other hand, in the depot system the cumulative amount of the drug released was linear when plotted against time (Fig. 2). It was shown that the drug was released continuously at almost constant rate for about 3 days. These release patterns were in agreement with those expected from the theoretical equations.¹⁾ Therefore the release rate may be estimated by determination of various parameters. Thus it is expected that the release rate may be controlled by the change of the parameters which govern the release rates, such as surface area of the cylinder, thickness of the outer layer, and the physico-chemical properties of the gel.

References

- 1) Baker, R. W. and H. K. Lonsdale: *Chem. Tech.*, **5**, 668 (1975).
- 2) Büchi, J., et al.: *Pharm. Acta Helv.*, **48**, 486 (1966).
- 3) Roseman, T. J.: *J. Pharm. Sci.*, **61**, 46 (1972).