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COMMUNICATIONS

External control of drug release: controlled release of insulin from a hydrophilic polymer implant by ultrasound irradiation in diabetic rats

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Abstract—The development of a polymeric system capable of delivering insulin in-vivo at increased rates on demand by an external ultrasound irradiation is reported. Implants composed of EVAl copolymer and insulin were placed subcutaneously in diabetic rats. When the diabetic rats receiving implants containing insulin were exposed to an ultrasound irradiation, a sharp drop in the blood glucose levels was observed after the irradiation, indicating a rapid rate of release of insulin in the implanted site.

Many biomedical polymers have been used to develop implantable drug delivery systems. We have reported that matrices composed of ethylene-vinyl alcohol (EVAl) copolymer could be useful vehicles for implanted delivery systems for anticancer agents (Miyazaki et al 1983a, b; 1985a, c). The unique characteristic of this copolymer is its hydrophilicity (Miyazaki et al 1983b). Sustained release systems that use implanted polymeric devices can deliver a steady quantity of drugs to a target area over long periods of time. However, release rates of drugs are either constant or decay with time in all sustained release systems. There has been no way to change the release rates on demand, once release has started.

We have previously shown (Miyazaki et al 1985b) that release rates of 5-fluorouracil from a hydrophilic EVAl copolymer can be increased at desired times by external ultrasound in-vitro. In this paper, we report the development of a polymeric system capable of delivering drug in-vivo at increased rates on demand by an external ultrasound irradiation. Insulin was used as a model drug in this examination.

Materials and methods

Materials. Bovine insulin (24 u mg^{-1}) was obtained from Sigma Chemical Co., St. Louis. Ethylene-vinyl alcohol (EVAl) copolymers with 32 mol% of ethylene unit were gifts from Kuraray Co., Tokyo.

Measurement of release rate. A schematic diagram of the release test apparatus used in the present study is shown in Fig. 1. The reservoir-type drug-EVAl copolymer systems (Fig. 1A) were prepared based on the method of Miyazaki et al (1985b). They were made with an EVAl ring (14 mm in inner diameter, 20 mm in outer diameter, 0·6 mm in thickness) and two kinds of thickness of EVAl films (0·020 and 0·6 mm), and the small pocket for placing a temperature coupler (TAKARA SZL-64), joined by a cyanoacrylate adhesive. Both the rings and films were made from a copolymer with 32 mol% ethylene content. Each device was filled with an insulin suspension in pH 7·0 phosphate buffer (2 mg/0·1 mL). Only one surface, the thinner film side, was available for release in this type of device.

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The insulin-EVAl copolymer device obtained was placed in 10 mL of phosphate buffer (pH 7·0) in a 40 × 30 × 10 mm release cell (B) made from polystyrene. The assembled cell was placed in a constant temperature (37°C) bath (C) and irradiated with a 1 MHz ultrasound generator (D, Model AU-1, Asahi Denshi Kogyo Co., Osaka) at 1 W cm^{-2} from a distance of 3 cm for 30 min followed by the same periods without irradiation. The sample solution was periodically withdrawn, and the solution in the cell was flushed out and replaced with fresh phosphate buffer. The insulin concentration in the solution was determined by the Lowry method (Lowry et al 1951). All experiments were carried out in triplicate and average values were plotted.

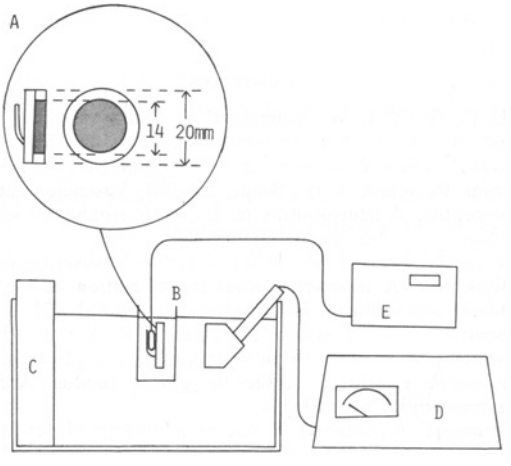

FIG. 1. Schematic diagram of the apparatus for determination the effect of ultrasound on release rate. A, reservoir type drug delivery system; B, release cell; C, water bath; D, ultrasound generator; E, thermistor.

Animal experiments. Male Wistar rats weighing 200–250 g were used. Each animal was made diabetic by an intravenous injection of freshly prepared alloxan solution (70 mg kg^{-1}). The rats were left untreated for 5 days and were then entered into the experimental design. The rats were anaesthetized with pentobarbitone and the devices were implanted subcutaneously in the lower abdomen of the animals, by means of a small incision on the skin. The skin incision was closed with adhesive for medical use. After spreading ultrasonic gel, the ultrasonicator was applied to the abdominal skin of rats. Two hours after implantation, ultrasound was exposed to the implanted site at 1 W cm^2 for 30 min. Blood samples were taken every 30 min after the irradiation and assayed for glucose using the glucose-oxidase method.

Results and discussion

The effect of ultrasound irradiation on the release kinetics of insulin was determined using the reservoir-type drug delivery systems. Prior to experiment the systems were placed in 10 mL of buffer for 1 h and allowed to hydrate. Fig. 2B shows the release rate from the polymeric device with zero order kinetics. In the absence of ultrasound irradiation, insulin release was fairly slow and constant. Upon exposure to ultrasound irradiation, however, insulin was released at a much higher rate. Release rate returned to baseline levels when ultrasound irradiation was discontinued. For example, the first 30-min exposure period showed an average release rate of 13·77 $\mu g\ h^{-1}$ compared with the 5·10 $\mu g\ h^{-1}$ in the following 30 min of no irradiation. With each exposure to ultrasound irradiation the release rates increased about 2 times throughout the course of this test.

The mechanism by which the ultrasound irradiation increases release rates is not well understood. Exposure of the polymeric system to ultrasound would increase the temperature inside the polymer. Fig. 2A shows the temperature increase of the device while exposed to ultrasound. These results suggest that the irradiation causes increasing temperature in the delivery systems, which may facilitate the drug diffusion. Other studies demonstrated a marked effect of temperature on the release kinetics: that is, the release rate increased with an increase in temperature.

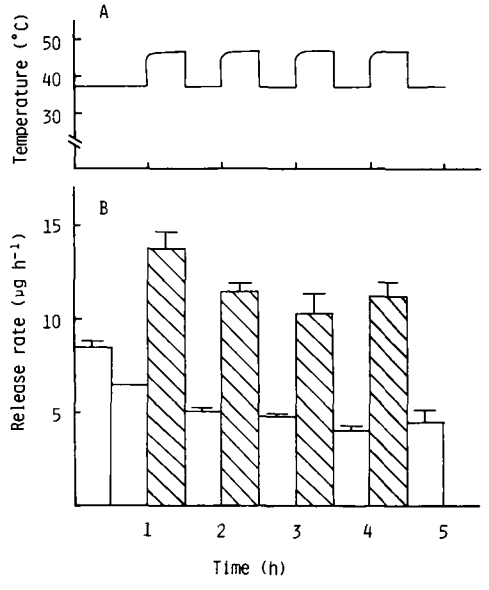

FIG. 2. Effect of ultrasound irradiations on the temperature of the drug delivery system (A) and the release of insulin from the system (B). Each system was irradiated with 1 MHz ultrasound (1 $W\ cm^{-2}$) from a distance of 3 cm for 30-min periods (hatched columns) alternating with 30 min non-irradiation periods (open columns). Each value is the mean ± s.e.m. of 3 experiments.

Implant composed of EVAl copolymer and insulin were placed subcutaneously in diabetic rats. After implantation the blood glucose levels were not affected at the first 2 h.

When the diabetic rats receiving implants containing insulin were exposed to an ultrasound irradiation, a sharp drop in the blood glucose levels was observed after the irradiation (Fig. 3), indicating a rapid rate of release of insulin in the implanted site. The hypoglycaemic effect was observed at 0·5 h and continued for the test period. This phenomenon was not observed in diabetic rats receiving implants with an ultrasound irradiation but without insulin. The rectal temperature of rats was found to be constant at 35°C during the experiment.

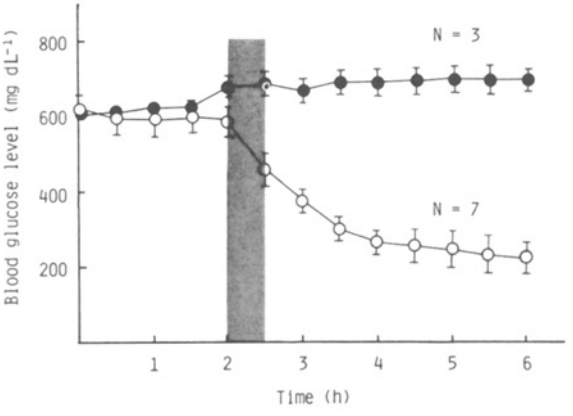

FIG. 3. Effect of an ultrasound irradiation on the blood glucose levels of diabetic rats receiving a drug delivery system without (●) or with (○) insulin (2 mg). The shaded area covers the periods in which the device was exposed to ultrasound. Each value is the mean ± s.e.m. of 3 or 7 experiments.

The present study demonstrated that release rates of insulin from a polymer implant can be increased and the blood glucose levels are decreased on demand by an external ultrasound irradiation. Ultrasound controlled release systems may ultimately improve the release pattern of insulin in human. For example, it could be used to increase insulin delivery at desired times, such as after a meal.

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