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Examination of Biodegradability of Poly(ethylene carbonate) and Poly(propylene carbonate) in the Peritoneal Cavity in Rats

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The biodegradability of poly(ethylene carbonate) and poly(propylene carbonate), synthesized from carbon dioxide and alkylene epoxides, was investigated. The biodegradation of poly(ethylene carbonate) pellets in the peritoneal cavity in rats was observable 2 d after implantation and was nearly completed within 2 weeks. The degradation of poly(propylene carbonate) pellets was not measurable after 2 months. The degradation rate of the pellets made of mixtures of the two types of polycarbonates decreased with increase in poly(propylene carbonate) content. No retardation in body weight gain was observed in polycarbonate-implanted rats. No visible undesirable reaction was observed at the implanted sites.

Keywords——biodegradation; poly(ethylene carbonate); poly(propylene carbonate); pellets; peritoneal cavity; implantation; retardation in growth; inflammatory reaction

In recent years, there has been increasing interest in the design of biodegradable polymers for specialized applications such as controlled-release formulations of drugs,[1] sutures, and surgical implant materials. Although nonbiodegradable polymers made from a variety of synthetic and natural materials have been available for such purposes for a number of years, only a few polymers have been demonstrated to be suitable for use as implant materials as regards biodegradability and biocompatibility.[2]

Poly(lactic acid)[3] and poly(glycolic acid)[4] have been recognized as biodegradable synthetic polymers. The degradation rates of these polymers were, however, found to be relatively inflexible, with a half-life in the implant site of between 5 and 7 months.[4] These periods are satisfactory if the polymers are to be utilized for bone fracture repair but may be too long if the polymers are required as a substitute for soft tissues or for use as matrices in controlled-release formulations of drugs. This limitation has partly been overcome by the use of copolymers of lactide and glycolide.[5]

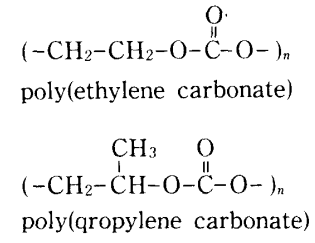

Chart 1. Chemical Structures of Polycarbonates

A new series of copolymers (Chart 1) has been synthesized from carbon dioxide and various alkylene epoxides.[6] Copolymerization of carbon dioxide and epoxides in the presence of organometallic compounds has been found to yield the corresponding polycarbonates. Since the chemical structure, *i.e.* the carbonate linkage, may be liable to hydrolysis, their biodegradability has been predicted.[7] In this study, pellets of poly(ethylene carbonate) and poly(propylene carbonate) or pellets made of mixtures of the two copolymers were implanted into the peritoneal cavity of rats, in order to examine the biodegradability of these polymers.

Experimental

Materials——Poly(ethylene carbonate) and poly(propylene carbonate) were prepared according to the procedures reported earlier.[6] Their intrinsic viscosity values were 0.34 and 0.56 dl/g, respectively, in dioxane at 25°C. Dioxane (400 ml) was purified by passing it through an activated alumina (160 g) column, adding concentrated hydrochloric acid (3 drops), stirring for 3 h, leaving for 24 h, and distilling. It was then used for dissolving the polymers for viscosity measurements. The above chemicals were obtained from Wako Pure Chemical Ind., Osaka. Mixtures of poly(ethylene carbonate) and poly(propylene carbonate) in w/w ratios of 95 : 5, 90 : 10, 80 : 20, and 50 : 50 were prepared by first dissolving both polycarbonates in methylene chloride (Wako Pure Chemical Ind.) and then evaporating the solvent. A small amount of a lipophilic dye (Sudan blue, Tokyo Kasei Kogyo Co., Tokyo) was added to the polymer to facilitate location of the implanted pellets in the peritoneal cavity of rats. Polycarbonate pellets were molded by melt pressing in a test presser (SA-302, Tester Sangyo Co., Tokyo) at 120°C under a pressure of 10 kg/cm^2.

Male Wistar rats weighing between 250 and 300 g were used.

Determination of Viscosity——The intrinsic viscosity values of the polymer solutions were estimated by plotting the ratio of specific viscosity to polymer concentration against polymer concentration for a series of solutions and extrapolating to zero concentration. A glass capillary Cannon–Fenske viscometer was employed.

Examination of Biodegradation——Matrices of polycarbonates weighing 200 mg were molded in the form of circular pellets; 20 mm in diameter and 0.6 mm in thickness. The pellets (one per rat) were implanted into the rat peritoneal cavity after surgical opening of the cavity under ether anesthesia. The opening was closed after sterilization with 80% ethyl alcohol solution. The operated rats were maintained on a normal diet, housed in separate cages and sacrificed at 1 to 60 d after implantation. At the time of sacrifice, the body weight of each rat was measured and the implanted pellets were recovered. The recovered pellets were carefully washed and dried *in vacuo* and their weights were measured. All experiments were done in duplicate.

Examination of Degradation *in Vitro*——Possible degradation of pellets identical to those used in the animal studies was examined *in vitro*. Each pellet was placed in an Erlenmeyer flask containing 0.2 M phosphate buffer at pH 7.4 and incubated at 37°C in a reciprocal shaking bath (Personal H, Taiyo Scientific Ind. Co., Tokyo). The weight of each pellet after incubation for a suitable period was measured following drying of the pellet *in vacuo*.

Examination of Toxicity——To examine the possible toxicity of polycarbonates and their degraded products, body weight gain of rats and possible local reaction in the implanted sites were examined. Rats were weighed prior to and after predetermined days of implantation. Implanted sites were visually examined for inflammation and other indications of incompatibility when they were surgically opened for examination of implants.

Results and Discussion

Biodegradation

The percentages of the initial weight of implants remaining following implantation of pellets made of one of the two polycarbonates are shown in Fig. 1. Weight loss of poly(ethylene carbonate) pellets was observed 2 d after implantation and the pellets had disappeared within about 2 weeks. On the other hand, weight loss of the poly(propylene carbonate) pellets was not measurable even after 2 months under the same conditions.

Weight losses of pellets made of mixtures of the two copolymers are shown in Fig. 2. With increase in the poly(propylene carbonate) content, the disappearance rate of pellets decreased. For a 95% poly(ethylene carbonate): 5% poly(propylene carbonate) pellet, the half-life of disappearance was about 7 d; no pellet remained after 24 d, probably because of disintegration of the poly(propylene carbonate) network rather than dissolution of the polymer following degradation of poly(ethylene carbonate). For a 90% poly(ethylene carbonate): 10% poly(propylene carbonate) pellet, the half-life of disappearance was about 8 d. With a 80% poly(ethylene carbonate): 20% poly(propylene carbonate) pellet, degradation proceeded smoothly to 65% of the original weight, but after that the disappearance rate was reduced. Only 40% weight loss was observed after 4 weeks, in spite of the fact that the poly(ethylene carbonate) content of the pellet was 80%. The above phenomenon may be

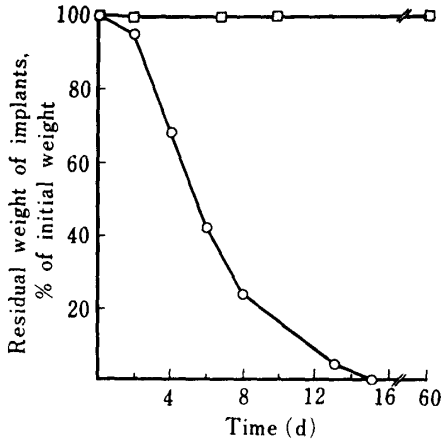

Fig. 1. Biodegradation Profiles of Poly (propylene carbonate) (□) and Poly (ethylene carbonate) (○) in the Rat Peritoneal Cavity

Data are averages of two experiments.

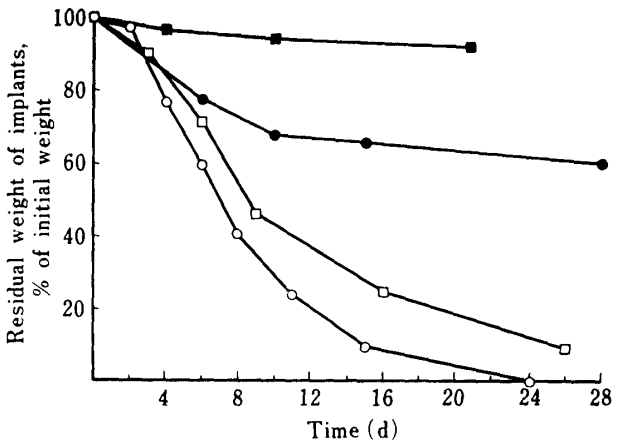

Fig. 2. Biodegradation Profiles of Polycarbonate Mixtures in the Rat Peritoneal Cavity

Data are averages of two experiments. Poly(ethylene carbonate) contents in the mixtures: ■, 50%; ●, 80%; □, 90%; ○, 95%.

rationalized in the following way; at first poly(ethylene carbonate) at the pellet surface suffers enzymatic degradation, but as the degradation proceeds, networks of nondegradable poly(propylene carbonate) prevent enzyme molecules from reaching poly(ethylene carbonate) in the inner portion.

Resistance to Degradation *in Vitro*

When pellets made of one of the two kinds of polycarbonates were incubated in phosphate buffer at pH 7.4 at 37°C, their weight was unchanged even after 40 d. This observation suggests that the weight loss of poly(ethylene carbonate) pellets in the rat peritoneal cavity may be attributed to dissolution of the copolymer due to enzymatic degradation.

Toxicity

Little difference in body weight gain was observed in polycarbonate-implanted rats compared to control rats. Therefore neither the polycarbonates nor their degradation products seem to have serious systemic effects retarding weight gain. No visible inflammatory reaction was noted at the implantation sites.

Other Factors

Since a thinner pellet will disappear faster than a thicker one, the dimensions as well as the composition of pellets may be important in controlling the disappearance rates of implants in the body. In addition, enzymatic activity may be variable among tissue locations and animal species, and this aspect should be examined in further studies.

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