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# Plasma Levels of Tegafur Following Implantation of Polycarbonate Pellets Containing Tegafur or FD-1 into Rats

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The possible use of poly(ethylene carbonate) and poly(propylene carbonate) pellets for sustained release of 5-fluorouracil derivatives (tegafur and FD-1) has been examined *in vivo*. Plasma levels of tegafur following implantation of the polycarbonate pellets into the rat peritoneal cavity were determined by high pressure liquid chromatography. Sustained release of the drug was obtained over 50 d following implantation of poly(propylene carbonate) pellets containing 40% FD-1. Plasma level profiles *in vivo* were compared with release profiles *in vitro*. Plasma level profiles with multiple peaks were observed following implantation of FD-1 in poly(propylene carbonate) pellets and tegafur in poly(ethylene carbonate) pellets.

**Keywords**——poly(ethylene carbonate); poly(propylene carbonate); pellets; tegafur; FD-1; rat; plasma level; peritoneal cavity; sustained release

5-Fluorouracil and its derivative, tegafur (ftorafur, 1-(tetrahydro-2-furanyl)-5-fluorouracil), have been widely used as antimetabolites having growth inhibitory effects on tumors of such organs as the stomach, ovary, liver, and pancreas. Another derivative, FD-1 (1,3-bis-(tetrahydro-2-furanyl)-5-fluorouracil) has been tested clinically. In conventional administration, the efficacies of these drugs have been limited due to gastrointestinal disturbance and myelic suppression, which are common side effects of anti-cancer agents. In addition, although the anti-tumor effects of antimetabolites are dependent on the retention in tumors, the elimination half-lives of the above compounds are rather short (11 min in 5-fluorouracil[1] and 6—10 h in tegafur)[2] after *i.v.* administration to humans. In order to prolong the duration of effective concentrations and to prevent side effects, dosage form design for controlling the release rate and selecting sites of administration of the drugs has been attempted recently.[3,4]

In the previous study, we examined a possible use of poly(ethylene carbonate) and poly(propylene carbonate) pellets for sustained release of drugs in monolithic systems containing 5-fluorouracil, tegafur, or FD-1.[5]

In the present work, we intended to investigate *in vivo* the effectiveness of these polycarbonate pellets containing tegafur and FD-1. The pellets, the release rate of which was adjusted to about 20 mg/kg/d *in vitro* at pH 7.4, were placed in the peritoneal cavity of rats after surgical opening. Although anticancer effects of tegafur and FD-1 are expected to be exhibited by 5-fluorouracil produced by hydrolysis from these prodrugs, plasma levels of tegafur were meaured in order to evaluate prolonged release of the drugs from the pellets *in vivo* following implantation, because plasma levels of 5-fluorouracil are expected to be too low[6] for assessment of the release patterns of drugs from the pellets.

### Experimental

**Materials**——Poly(ethylene carbonate) and poly(propylene carbonate) were prepared according to the procedures reported earlier.[7] Tegafur and FD-1 were generously supplied by Taiho Pharmaceutical Co., Tokyo. Caffeine and buffering agents (sodium dihydrogen phosphate, sodium acetate, and acetic acid) were all of reagent grade from Wako Pure Chemical Industries, Osaka, and Tokyo Kasei Kogyo Co., Tokyo. They were used without further purification.

Male Wistar rats weighing between 400 and 450 g were used.

**Methods**——Polycarbonate pellets containing 40% drug were prepared according to the method reported earlier.[5] In essence, a drug dispersion in a polycarbonate, produced by evaporation of the solvent from a solution of a polymer and a drug in methylene chloride, was molded in a melt press (SA-302, Tester Sangyo Co., Tokyo) to form a pellet.

Release rates of drugs were controlled by the diameter of the pellet (surface area) in proportion to the body weight of rats measured just before preparation of the pellet. The amount of drugs contained corresponds to a 20-d dose calculated at a release rate of 20 mg/kg/d. Typically a circular pellet 24 mm in diameter and 0.6 mm in thickness was administered to a rat weighing 400 g.

Pellets were implanted into the peritoneal cavity after surgical opening under ether anesthesia. The opening was closed after sterilization with 80% ethanol solution. The operated rats were maintained on a normal diet, housed in separate cages. One and a half milliliter blood samples were collected by heart puncture at 1 to 3 d intervals after implantation. The blood sample was centrifuged to obtain plasma, and stored in a refrigerator at $-20\,^{\circ}C$.

Tegafur in blood samples was determined by a modification of the high pressure liquid chromatographic method reported by Sadee and his associates.[2,8] It was carried out with a Jasco TRIROTAR chromatograph equipped with a ultraviolet (UV) detector set at 270 nm and a column packed with Jascopak SS-10-ODS-B 4.60 × 250 mm. Caffeine was used as an internal standard.

Drug levels following administration of FD-1 pellets were measured in terms of tegafur levels because of the rapid degradation of FD-1 into tegafur under physiological conditions.[9] Namely FD-1 is hydrolyzed to tegafur with a half-life of 74 min at pH 7.4 and 37 °C. The rate constant for hydrolysis of tegafur to 5-fluorouracil is much smaller than that of FD-1 to tegafur.

## Results and Discussion

### Drug Concentrations in Plasma Following Administration of Poly(propylene carbonate) Pellets

Figure 1 shows concentrations of tegafur in plasma after implantation of poly(propylene carbonate) pellets containing 40% tegafur into rats. An average peak plasma level of 7.4 μg/ml was recorded on the third day and then the concentration decreased gradually to 1.9 μg/ml on the 20th day. Multiple peaks of the type observed in Figures 2—4 are not present in this figure. The plasma level curve, except for a shoulder on about the 18th day, was in good agreement with the release profile *in vitro*.[5]

Figure 2 shows the plasma levels of tegafur after implantation of poly(propylene carbonate) pellets containing 40% FD-1 into rats. In the previous study *in vitro*, a slow-down

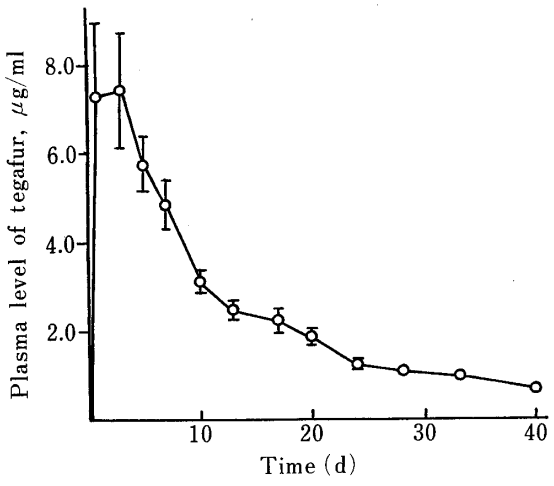


Fig. 1. Plasma Levels of Tegafur Following Implantation of Poly(propylene carbonate) Pellets Containing 40% Tegafur into Rats

Mean ± S.E.M., $n=5$.

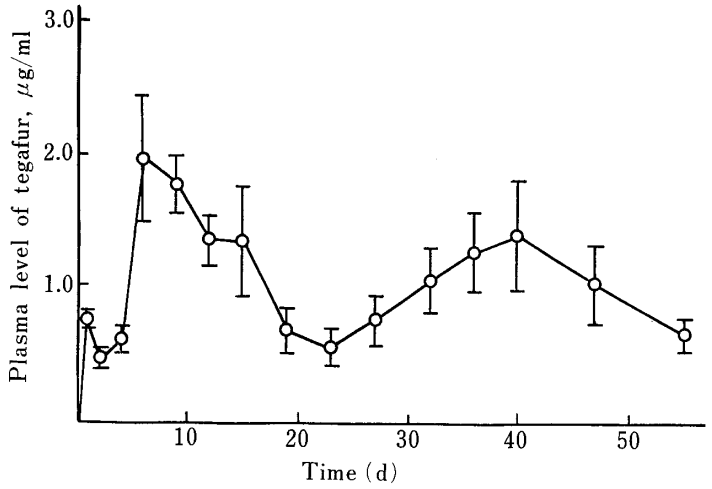


Fig. 2. Plasma Levels of Tegafur Following Implantation of Poly(propylene carbonate) Pellets Containing 40% FD-1 into Rats

Mean±S.E.M., $n=5$.

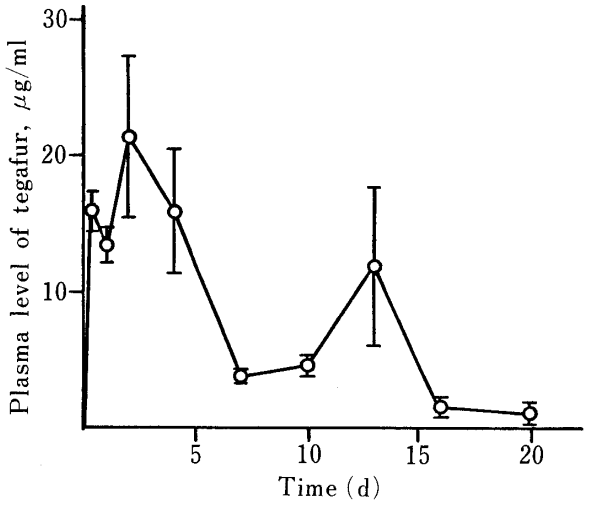


Fig. 3. Plasma Levels of Tegafur Following Implantation of Poly(ethylene carbonate) Pellets Containing 40% Tegafur into Rats

Mean±S.E.M., $n=3$.

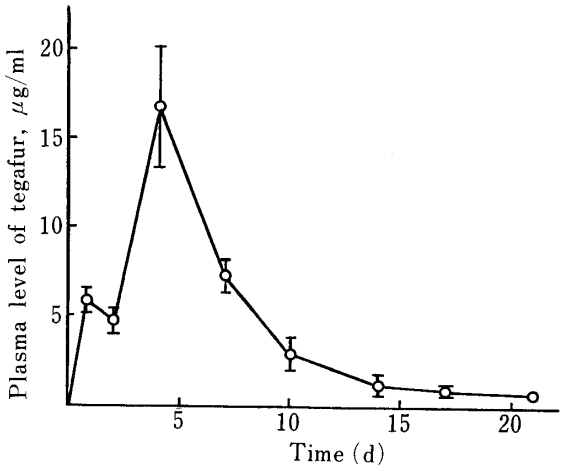


Fig. 4. Plasma Levels of Tegafur Following Implantation of Poly(ethylene carbonate) Pellets Containing 40% FD-1 into Rats

Mean±S.E.M., $n=5$.

in the release rate after the initial burst was observed in the release profile from the pellet.[5] In the present study, a decrease in plasma concentration was also observed during the 2nd and 4th days after implantation. The second peak plasma level was 2.0 μg/ml on the 6th day and the concentration decreased gradually until the 23rd day. Thus, the plasma level curve for 20 d after implantation was in good agreement with the release profile *in vitro*, indicating predictability of the *in vivo* release. However, after the 23rd day, the plasma drug concentration increased again, and a third peak plasma level (1.4 μg/ml) was observed on the 40th day; this could not have been predicted from the release profile *in vitro*. The cause of the third peak is not clear. Although no biodegradation of poly(propylene carbonate) pellets was observed in terms of weight loss of pellets in rat peritoneal cavity,[10] possible loosening of the polymer matrix with leaching of the drug molecules and possible collapse of the pellet have to be considered in the case of the pellets containing FD-1.

**Drug Concentration in Plasma Following Administration of Poly(ethylene carbonate) Pellets**

In a separate study,[10] biodegradation of poly(ethylene carbonate) pellets was demonstrated in the rat peritoneal cavity, whereas no observable biodegradation took place with poly(propylene carbonate) pellets. Thus, when a poly(ethylene carbonate) pellet containing a drug is implanted in rat peritoneal cavity, the release of the drug may be governed both by diffusion of the drug through the poly(ethylene carbonate) matrix and dissolution of the polymer matrix.

Figure 3 shows the plasma levels after implantation of poly(ethylene carbonate) pellets containing 40% tegafur into rats. The plasma level after 6 h was 16.5 μg/ml and that after 24 h was reduced to 13.5 μg/ml, but the concentration increased again, and the maximum plasma level of 21.5 μg/ml was recorded on the second day. This phenomenon may be attributable to additional drug release caused by polymer matrix degradation. According to a previous study,[10] polymer degradation could have occurred at a constant rate in the rat peritoneal cavity. On the other hand, the plasma level curve showed a trough (low plasma level area) between the 5th and 10th day and a third peak on the 13th day. This observation may be rationalized in the following way; the trough may reflect a period of possible degradation of a polymer matrix from which the drug contained has already been released by diffusion, and the third peak may reflect a period of possible degradation of the inner matrix containing the larger part of the drug which has not been released yet.

Figure 4 shows the plasma tegafur levels after implantation of poly(ethylene carbonate) pellets containing 40% FD-1 into rats. In this preparation, the peak plasma level was 16 μg/ml on the 4th day and the duration of drug release was shorter than that from the tegafur preparation. This observation suggests that the release rate of FD-1 by diffusion may be greatly affected by polymer matrix degradation.

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