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# Release Profiles of 5-Fluorouracil and Its Derivatives from Polycarbonate Matrices *in Vitro*

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Release profiles of 5-fluorouracil (5-FU), 1-(tetrahydro-2-furanyl)-5-fluorouracil (ftorafur, tegafur) and 1,3-bis-(tetrahydro-2-furanyl)-5-fluorouracil (FD-1) from poly(ethylene carbonate) and poly(propylene carbonate) pellets were examined *in vitro*. Because of poor compatibility of 5-FU with polycarbonates, 5-FU was quickly released from the pellets. Release of ftorafur from pellets of both polycarbonates was sustained. Release profiles of FD-1 from polycarbonate pellets were complex but extended. Release of ftorafur and FD-1 from pellets of a 9:1 mixture of poly(ethylene carbonate) and poly(propylene carbonate) was less sustained than those from the individual polymers.

**Keywords**——5-fluorouracil; ftorafur; tegafur; FD-1; 1,3-bis-(tetrahydro-2-furanyl)-5-fluorouracil; antimetabolites; poly(ethylene carbonate); poly(propylene carbonate); pellets; sustained release

5-Fluorouracil (5-FU) is the first of a series of pyrimidine antimetabolites possessing a growth inhibitory effect on tumors of the gastrointestinal tract, liver, pancreas, and ovary.[1] The clinical efficacy of 5-FU has been limited because of the difficulty in maintaining effective serum levels of the drug due to its rapid elimination from the body. A number of attempts have been made to synthesize pro-drugs of 5-FU, in order to counteract its rapid elimination. 1-(Tetrahydro-2-furanyl)-5-fluorouracil (ftorafur, tegafur) has been used clinically because of its ability to form 5-FU *in vivo* for a long time.[2] 1,3-Bis(tetrahydro-2-furanyl)-5-fluorouracil has been examined as a more lipophilic derivative of 5-FU.[3] However, an adverse effect on the central nervous system that may be attributable to high lipophilicity of these derivatives has been observed. Thus, complex dosage schedules including continuous *i.v.* infusion have been used.

In recent years, the use of synthetic membranes for controlling the release of anti-cancer agents has been examined in order to prolong the drug action and to prevent toxic manifestations due to overdose. A topical dosage form that contains 5-FU in hydroxypropylcellulose and carboxypolymethylene has been reported for the treatment of uterine cancers in an attempt to improve the topical effectiveness and reduce the side effect of 5-FU.[4] Sustained release of 5-FU from microcapsules prepared by phase-separation has been described recently.[5]

Poly(ethylene carbonate) and poly(propylene carbonate), newly synthesized from carbon dioxide and the corresponding epoxides,[6] were selected for the present study to control the release of 5-FU, ftorafur, and FD-1. In a separate report, we demonstrated the biodegradability of poly(ethylene carbonate) in the peritoneal cavity in rats and the biocompatibility of both polycarbonates.[7]

In this study, release profiles of the drugs from polycarbonate pellets in monolithic systems were examined. The effects of the drug contents in the pellets on the release rate were studied. The effects of the tetrahydrofuryl moiety in ftorafur and FD-1 on the release characteristics are discussed.

## Experimental

**Materials**——Poly(ethylene carbonate) and poly(propylene carbonate) were prepared according to the procedures reported earlier.[8] Their molecular weights ranged from 50000 to 150000.

5-Fluorouracil was generously supplied by Kyowa Hakko Kogyo Co., Tokyo. Ftorafur and FD-1 were generous gifts from Taiho Pharmaceutical Co., Tokyo.

**Preparation of Polycarbonate Pellets**——Polymer matrices containing the drugs in the form of a monolithic system were prepared by dissolving the polycarbonate and the drug in methylene chloride and then evaporating off the solvent at room temperature. Polymer matrices containing the drug were crushed at −20°C and then polycarbonate pellets containing the drug in various contents were molded by melt pressing using a test presser (SA-302, Tester Sangyo Co., Tokyo) at 120°C under a pressure of 10 kg/cm². Pellets weighing 200 mg, 600 μm in thickness and 20 mm in diameter, were prepared.

**Release Studies**——Twenty milliliters of 0.2 M phosphate buffer at pH 7.4 was placed in a vial which was immersed in a thermostated water bath maintained at 37°C. The pellet containing a drug was wrapped in glass wool in order to hold it in the elution medium, which was shaken horizontally. One half volume of the elution medium was removed at appropriate intervals (between 2 and 100 h) and replaced by 10 ml of fresh buffer. Thus, accumulation of the drug in the elution medium was avoided and a sink condition was maintained. Absorbance of the diluted sample was measured at 266 nm for 5-FU and at 270 nm for ftorafur. Because of the rapid degradation of FD-1 into ftorafur under the experimental conditions,[9] FD-1 released was measured at the isosbestic point of FD-1 and ftorafur (275.5 nm). The percentage of the drug released into the elution medium was plotted against time to obtain release profiles. Because of the good reproducibility of release profiles in experiments under identical conditions, plots of the mean values of two experimental runs are shown.

## Results and Discussion

### Release of 5-FU

A release profile of 5-FU from poly(propylene carbonate) pellets containing 20% 5-FU is shown in Fig. 1. In this system, about 20% of the 5-FU content was released within 2 h. After the initial fast release, however, the release rate became small and only 15% more of 5-FU was released during the following 1400 h period. This observation may be rationalized in the following way; during the initial period, 5-FU in the surface portion was released rapidly through the small pores, but 5-FU in the inner portion that was enclosed completely in the poly(propylene carbonate) matrices was released very slowly because of the small permeability

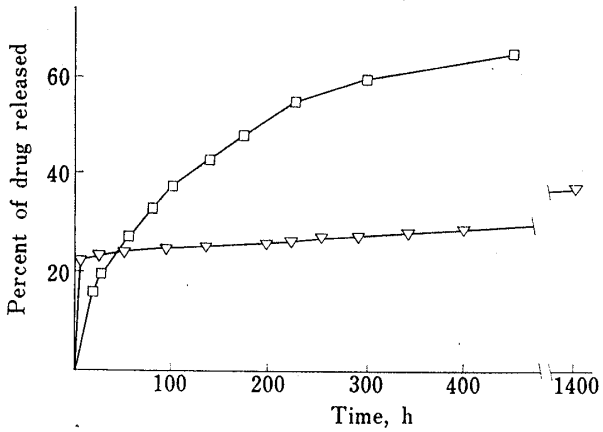


Fig. 1. Release Profiles of 5-FU(▽) and Ftorafur (□) from Monolithic Poly(propylene carbonate) Pellets containing 20% Drug into the Elution Medium at pH 7.4, 37°C

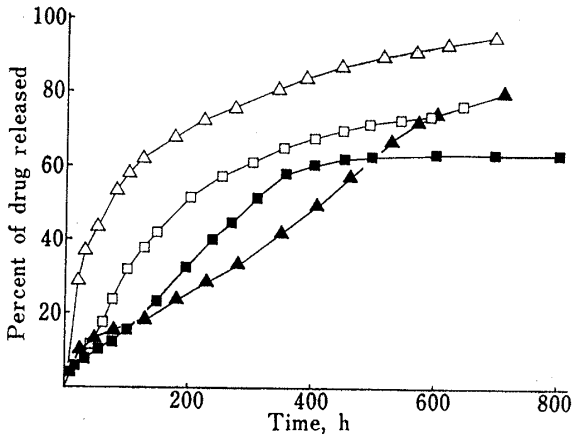


Fig. 2. Release Profiles of Ftorafur from Monolithic Poly(propylene carbonate) (□) and Poly(ethylene carbonate) (△) Pellets and of FD-1 from Monolithic Poly(propylene carbonate) (■) and Poly(ethylene carbonate) (▲) Pellets containing 40% Drug into the Elution Medium at pH 7.4, 37°C

of 5-FU through the poly(propylene carbonate) matrices.[10]

Since the compatibility of 5-FU with polycarbonates was rather poor, neither a poly(propylene carbonate) pellet containing over 25% 5-FU nor a poly(ethylene carbonate) pellet containing over 5% 5-FU could be prepared.

**Release of Ftorafur**

A release profile of ftorafur from poly(propylene carbonate) pellets containing 20% ftorafur is shown in Fig. 1. Because of the better compatibility of ftorafur with the matrix, no burst effect was observed. A linear relationship was obtained when the percentage of the drug released was plotted against the square root of time (not shown). This release profile was in agreement with that expected from theoretical equations[11,12] over 250 h.

A release profile of ftorafur from the poly(propylene carbonate) pellets containing 40% ftorafur is shown in Fig. 2. Sustained release was apparent in the release profiles over 250 h and 75% of the ftorafur content was released in 600 h. Poly(propylene carbonate) pellets containing 60% ftorafur were prepared, but the duration of the release was less than 20 h (not shown).

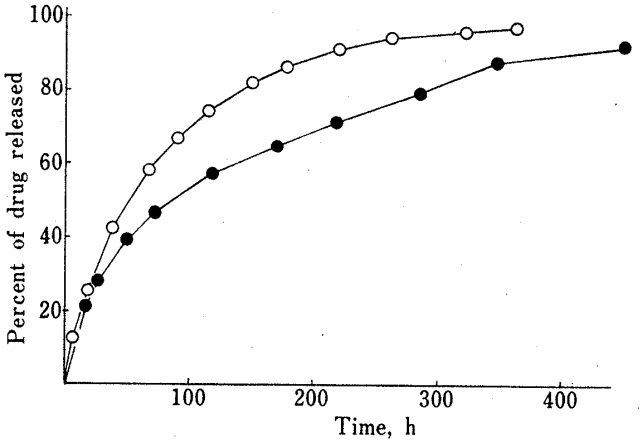


Fig. 3. Release Profiles of Ftorafur (○) and FD-1 (●) from Pellets made of a Mixture of Poly(ethylene carbonate) and Poly(propylene carbonate) in w/w Ratio of 9:1 containing 40% Drug into the Elution Medium at pH 7.4, 37°C

A release profile from poly(ethylene carbonate) pellets containing 40% ftorafur is shown in Fig. 2. The release rate up to 100 h was greater than that from the poly(propylene carbonate) system. However the release rate became small after that and cumulative amount of ftorafur released reached 95% at around 700 h. Since the biodegradability of poly(ethylene carbonate) has been demonstrated,[7] the release profile from the poly(ethylene carbonate) pellets containing the drugs *in vivo* may be different from that *in vitro*. *In vivo* release studies on these pellets have been carried out recently and the results will be published elsewhere.[13]

**Release of FD-1**

A release profile of FD-1 from poly(propylene carbonate) pellets containing 40% FD-1 is shown in Fig. 2. A decrease in FD-1 release rate was observed after the initial fast release. This slow release continued for about 100 h, and then the rate of FD-1 release increased again. Almost constant rate of release was obtained from 100 h to 350 h, and the cumulative amount of FD-1 released reached 60% of FD-1 content in 400 h. Little drug was released after that.

A release profile from poly(ethylene carbonate) pellets containing 40% FD-1 is shown in Fig. 2. Slow release was again observed after the initial fast release, and the second fast release was similar to that in the poly(propylene carbonate) pellet. The cumulative amount of FD-1 released was almost linear when plotted against time between 230 and 570 h, and the release rate of FD-1 levelled off after 600 h.

In the examination of the release patterns of polycarbonate pellets containing 20% FD-1 (not shown), a profile similar to that of the pellets containing 40% FD-1 was observed. These release profiles were not in good accord with those expected from theoretical equations.[11,12] The reason for the complex release profile is not clear at this time, but possible conversion

of FD-1 to ftorafur within the polymer matrices has to be considered because of the poor stability of FD-1 in the presence of moisture. *In vivo* release studies on pellets containing FD-1 have been carried out recently.[13]

**Release of Drugs from Pellets made of a Mixture of the Two Polycarbonates**

In the previous study, we demonstrated that the bioerosion rate in the body of pellets which were made of mixtures of the two polycarbonates decreased with increase in poly(propylene carbonate) content.[7] In order to design controlled release dosage forms with biodegradability, release profiles from pellets made of a mixture of the two polycarbonates were examined. Release profiles of drugs from pellets made of a mixture of poly(ethylene carbonate) and poly(propylene carbonate) in a w/w ratio of 9:1 containing 40% ftorafur or FD-1 are shown in Fig. 3. Release rates of the drugs from pellets made of the mixture were greater than those from pellets made of the individual polymers. The release profile from pellets of the polymer mixture containing 40% ftorafur was in accord with the monolithic release profile, and the duration (about 300 h) was one-half as long as that of the poly(ethylene carbonate) pellet (Fig. 2, about 600 h). The complex release profiles which were observed in monolithic polycarbonate pellets containing FD-1 (Fig. 2) did not appear in the case of pellets made of the mixture of the two polycarbonates.

These observations suggest that the crystallinity of polycarbonate matrices may be modified in the mixture of the two polycarbonates, and the release rate tended to be greater from the mixture.

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