# External Control of Drug Release. IV.[1] Controlled Release of 5-Fluorouracil from a Hydrophilic Polymer Matrix by Microwave Irradiation

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**A polymeric system capable of delivering 5-fluorouracil (5-FU) at increased rates on demand by external microwave irradiation was developed. Sustained-release systems were made by incorporating 5-FU into an ethylene-vinyl alcohol copolymer. When exposed to release medium, the delivery systems released the drug slowly and continuously. Upon exposure to microwave irradiation, the drug was released at a much higher rate. Release rates returned to base line levels when the microwave irradiation was discontinued.**

**This study demonstrated that release rates of 5-FU from a polymer matrix can be increased at desired times by external microwave irradiation.**

**Keywords** drug delivery systems; matrix; controlled release; microwave irradiation; ethylene-vinyl alcohol copolymer; 5-fluorouracil

Many techniques have been utilized to develop implantable controlled-release drug delivery systems. Usually, the release rate of a drug from polymer systems may be controlled by variations of the dimensional parameters, the drug content, and the polymer system. A wide range of release rates for drugs can be obtained by simple modification of a polymer system. We have reported that the release rate of 5-fluorouracil (5-FU) could be controlled by modifying the monomer ratio in implantable polymers such as an ethylene-vinyl alcohol (EVAl) copolymer.[2-5]

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, the release rates of drugs are either constant or decay with time in all sustained-release system. There has been no way to change the release rate on demand, once release has started.

Recently, a system containing small magnetic beads has been developed in which the release rate can be controlled by applying an oscillating magnetic field.[6] When exposed to the magnetic field, the polymer matrices released up to 30 times more drug; release rates returned to normal when the magnetic field was discontinued.

In the previous paper,[7] it was demonstrated that release rates of 5-FU from a hydrophilic EVAl copolymer can be increased at desired times by external ultrasound irradiation. In this paper, we report the use of microwave irradiation as an external means of delivering drugs at increased rates at desired times. The 5-FU–EVAl copolymer systems developed earlier were utilized for *in vitro* drug release studies in the present investigation.

## Experimental

**Materials** An EVAl copolymer with 32 mol% of ethylene unit was a gift from Kuraray Co., Tokyo, 5-FU was obtained from Sigma Chemical Co., ST. Louis.

**Preparation of EVAl Copolymer Matrices** Sustained release EVAl copolymer matrices containing 5-FU were prepared by the incorporation of the drug into an EVAl copolymer, as described previously.[5] The matrices consisted of 9 mg of drug entrapped in an EVAl copolymer with 32 mol% ethylene content. They were fabricated in the shape of a disk (12 mm in diameter and 0.8 mm in thickness) with a small pocket for placing a temperature coupler, bonded with a cyanoacrylate adhesive. One surface of the matrices was covered with Scotch®(3M) alumi-tape. Only the exposed surface (1.13 $cm^2$) was available for release.

**Measurement of Release Rate** A schematic diagram of the release test apparatus used in the present study is shown in Fig. 1. The 5-FU–EVAl copolymer matrix(A) was placed in 40 ml of distilled water maintained at 37 °C in a water-jacketed beaker(C). The medium was gently agitated by means of a magnetic stirrer bar (D, 2 cm in length) and irradiated with a 2450 MHz microwave generator (G, Microtizer MT-300N, Minato Medical Science Co., Osaka) at 100 W or 200 W from a distance of 20 cm for 30 min followed by the same periods without irradiation. The distance between the surface of the medium and the matrix was maintained at 1 cm during the test. The sample solution was periodically withdrawn, and the solution in the beaker was flushed out and replaced with fresh water. The 5-FU concentration in the solution was determined spectrophotometrically by measuring the absorption at 266 nm. All experiments were carried out in triplicate and average values were plotted.

The temperature of the matrix was measured by insertion of a temperature coupler (Takara SZL-64) into the pocket of the device, and the temperature was read on a Takara thermister (F, D613).

Prior to an experiment the matrices were placed in 40 ml of distilled water for 1 h and allowed to hydrate. 5-FU that might have adhered to their surface could diffuse away.

## Results

**Effect of Microwave Irradiation on the Temperature of the Matrices** The benefits derived from therapeutic microwave irradiation are due only to thermal effects.[8] Exposure of the sample to microwave irradiation would increase the temperature inside the polymer delivery systems, which may facilitate the drug diffusion. Initially, therefore, the effect of microwave irradiation on the temperature of the matrix was determined. The matrices were irradiated at different power levels and the temperature change was measured.

Figure 2 shows the temperature change of the matrix during microwave irradiation for 10 min. Application of microwave irradiation increased the temperature of the matrix proportionally to the microwave power; the temperature returned to the baseline level when the microwave irradiation was discontinued.

Variations of the microwave intensities were also obtained by changing the distance between the microwave source and the matrix. The temperature after irradiation for 10 min was plotted in Fig. 3. The most marked increase in the temperature was observed at a distance of 20 cm from the microwave generator.

**Effect of Microwave Irradiation on the Release Kinetics** The mean hourly release rate of 5-FU from the polymeric matrix is shown in Fig. 4. In the absence of

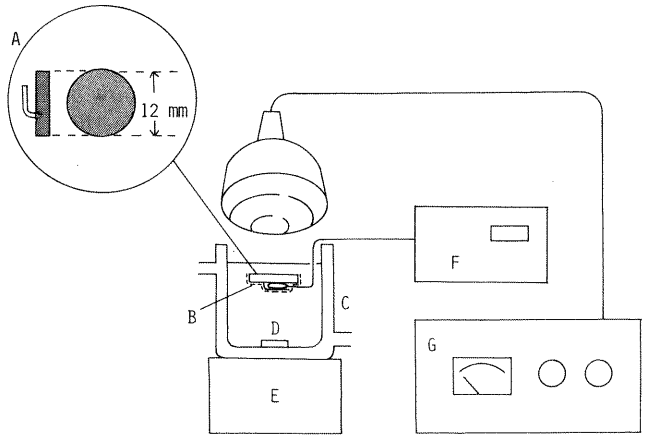


Fig. 1. Schematic Diagram of the Apparatus for Determination of the Effect of Microwave Irradiation on Release Rate

A, polymer matrix; B, alumi-tape; C, water-jacketed beaker; D, magnetic stirrer bar; E, magnetic stirrer; F, thermister; G, microwave generator.

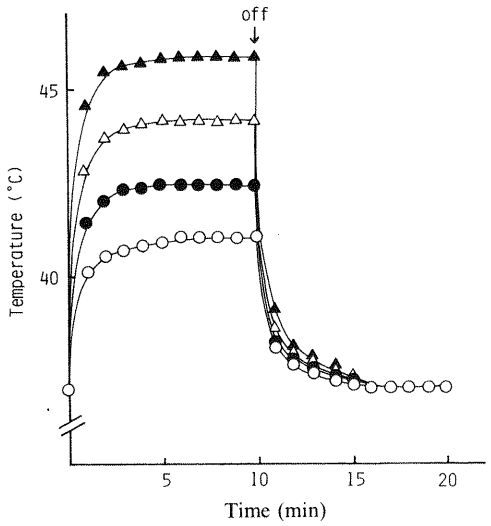


Fig. 2. Effect of Microwave Irradiation on the Temperature of the Polymer Matrix

Each matrix was irradiated with 2450 MHz microwaves from a distance of 20 cm for 10-min periods alternating with 10-min non-irradiation periods at the power levels of 50 (○), 100 (●), 150 (△), and 200 (▲) W.

microwave irradiation, 5-FU release was slow and constant, in a mode typical of diffusion-controlled matrix systems. Although the first preliminary experiment was conducted for 5 h, only 5.8% and 6.7% of the total drug was released at the power levels of 100 and 200 W, respectively, indicating that this polymer matrix system would be capable of releasing drugs for long periods of time.

During exposure to microwave irradiation, 5-FU was released at a much higher rate than during non-irradiation period (Fig. 4). The release rate returned to the baseline level when microwave irradiation was discontinued. For example (Fig. 4B), the first 30-min exposure period at 200 W showed an average release rate of 210.3 μg/h compared to the 91.6 μg/h in the following 30 min of no irradiation. The differential decreased with increasing time, but was still significant at the end of the experiment (120.2 μg/h *versus* 78.5 μg/h).

The mechanism by which microwave irradiation increases the release rate is the thermal effect. Exposure of the

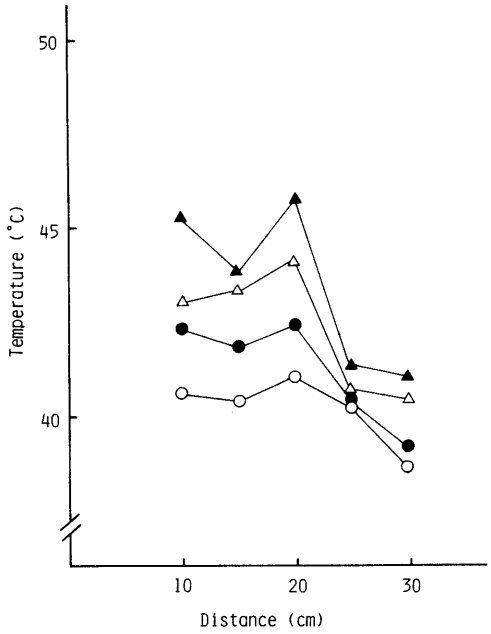


Fig. 3. Effect of Microwave Power on the Temperature of the Polymer Matrix

Each matrix was irradiated with 2450 MHz microwaves with various distances between the microwave source and the matrix at the power levels of 50 (○), 100 (●), 150 (△), and 200 (▲) W. The temperature after irradiation for 10 min was plotted.

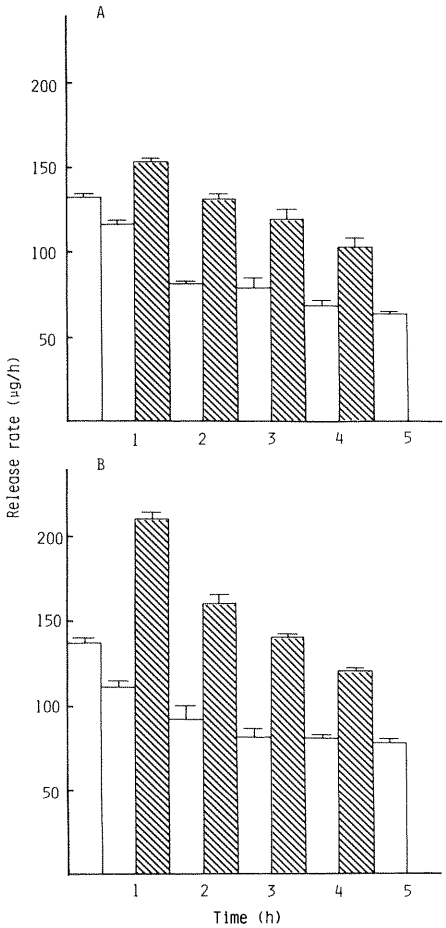


Fig. 4. Effect of Microwave Irradiation at 100 (A) and 200 (B) W on the Release Rates of 5-FU from the Polymer Matrix at 37 °C

Each matrix was irradiated with 2450 MHz microwaves from a distance of 20 cm for 30-min periods ( ▨ ) alternating with 30-min non-irradiation periods ( □ ). Each value is the mean ± S.E. of 3 experiments.

polymeric system to microwave irradiation would increase the temperature inside the polymer, as shown in Fig. 2. The temperature of the release medium was found to be constant at 37 °C during the experiment.

## Discussion

In the field of cancer chemotherapy, sustained release of therapeutic preparations into cancerous lesions has been used to maximize the effectiveness of the anticancer agents and to minimize toxic side effects. We reported that the release rate of 5-FU or adriamycin could be controlled by modifying monomer ratios in implantable polymers such as an ethylene-vinyl acetate[9,10] and EVAl[2-5] copolymers. Sustained release and prolonged action of entrapped drugs was suggested to be effective against Ehrlich ascites carcinoma.[4,5,10] However, little attention has been paid to designing systems where the rate of delivery can be controlled externally.

In the previous paper,[7] it was demonstrated that release rates of 5-FU from devices composed of hydrophilic EVAl copolymer can be increased at desired times by external ultrasound irradiation. The present study demonstrated that release rates of 5-FU from the polymeric matrix can be increased on demand by external microwave irradiation. Microwave irradiation causes an increase of temperature in the delivery systems, which may facilitate the drug diffusion.

The application of microwave irradiation in humans, both for diagnostic and therapeutic purposes, has been extensively studied and is considered a safe practice. In the field of cancer chemotherapy, microwave irradiation has been used to produce local hyperthermia.[8] Controlled-release systems employing microwaves as well as ultrasound could be potentially useful in cancer chemotherapy, and may have the added therapeutic value of inducing hyperthermia.

These delivery systems represent an important new concept in controlled-release technology, because they allow external control of drug release rates. The development of these systems with controlled release rates induced by microwave or ultrasound irradiation may prove useful in a variety of applications.

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