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CONTROLLED DRUG RELEASE BY ULTRASOUND IRRADIATION[1)]

Shozo Miyazaki,* Wei-Min Hou, and Masahiko Takada
Faculty of Pharmaceutical Sciences, Higashi-Nippon Gakuen University,
Ishikari-Tohbetsu, Hokkaido 061-02, Japan

Sustained release systems were made by incorporating 5-fluorouracil (5-FU) in an ethylene-vinyl alcohol copolymer. When exposed to aqueous medium, the delivery systems released the drug slowly and continuously. Upon exposure to ultrasound, the drug was released at a much higher rate. Release rates returned to base line levels when the ultrasound irradiation was discontinued. This study demonstrated that release rates of 5-FU from polymers can be increased at desired times by external ultrasound irradiation.

KEYWORDS —— drug delivery system; controlled release; ultrasound irradiation; ethylene-vinyl alcohol copolymer; 5-fluorouracil

In the field of cancer chemotherapy, sustainded release of therapeutic preparations into cancerous lesions has been used to try to maximize the effectiveness of the anticancer agents and to minimize toxic side effects. We reported that the release rate of 5-fluorouracil (5-FU) could be controlled by modifying monomer ratios in implantable polymers such as an ethylene-vinyl acetate (EVAc)[2-4)] and ethylene-vinyl alcohol (EVAl) copolymer.[5,6)] Sustained release and prolonged action of entrapped drugs was suggested for use in Ehrlich ascites carcinoma.[3,7,8)]

Unlike conventional routes of drug administration, sustained release systems that use implanted polymeric devices can deliver a steady quantity of drug to a target area over long periods of time. However, until recently the drug release rates have been either constant or decaying with time. There was no way to change the release rates on demand, once release had 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.[9)] When exposed to the magnetic field, the polymer matrices released up to 30 times more drugs; release rates returned to normal when the magnetic field was discontinued.

In this paper, we report the use of ultrasound as an external means of delivering drugs at increased rates and at desired times. Ultrasound in the frequency range 0.5-5 MHz has widespread used as a therapeutic agent in physical medicine.[10)]

The 5-FU-EVA1 system developed earlier[6-8] was utilized for drug release studies in the present investigation. These sustained release 5-FU matrices consisted of 26 mg of drug entrapped in an EVA1 copolymer with 60 mol% of ethylene content. They were fabricated in the form of films (15 x 20 x 0.35 mm). The 5-FU and EVA1 copolymer were mixed thoroughly in a mortar and passed through a 48-mesh screen. Matrix-type drug delivery systems were then prepared by the melt-press technique described previously.[11]

Reservior-type drug delivery systems were made with an EVA1 ring (14 mm in inner diameter, 20 mm in outer diameter, 0.6 mm in thickness) and two kinds of thickness of EVA1 films (0.014 mm and 0.6 mm), joined by a cyanoacrylate adhesive. Both the rings and films were made from a copolymer with 31 mol% ethylene content. Each device was filled with a 5-FU aqueous suspension. Only one surface, the thinner film side, was available for release in this type of device.

The drug-EVA1 copolymer device was placed in 10 ml of distilled water in a 40 x 30 x 10 mm release cell made from polystyrene. The assembled cell was placed in a constant temperature (37°C) bath and irradiated with a 1 MHz ultrasound generator (Model AU-1, Asahi Denshi Kogyo Co., Osaka) for 15 min (matrix-system) or 30 min (reservior-system) 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 water. The 5-FU concentration in the solution was analyzed spectrophotometrically. Release studies were made in triplicate and the average values were plotted.

Initially, the effect of ultrasound irradiation on the release rates of 5-FU was determined using the matrix-type delivery systems. The mean hourly release rate from the polymeric matrix is shown in Fig. 1. Upon exposure to aqueous media, the drug was released in a fashion typical of diffusion-controlled matrix systems. After an initial burst, the matrix system released the 5-FU slowly and continuously. Upon exposure to ultrasound irradiation, however, the drug was released at a much higher rate. Release rate returned to baseline levels when ultrasound irradiation was discontinued. For example, the first 15-min exposure period showed an average release rate of 432 μg/h compared to the 16 μg/h in the following 15-min of no irradiation. The rate decreased progressively with increasing time. With each exposure to ultrasound irradiation the release rates increased greatly throughout the course of this test. Although the first test experiment was conducted for 4.25 h, only 9 % of the total drug was released, indicating that this polymer matrix system would be capable of releasing drugs for longer periods of time.

Figure 2 shows the result for reservior-type drug delivery systems with zero order kinetics. In the absence of ultrasound irradiation, the drug release was fairly constant; application of ultrasound increased the release rate directly proportional to the ultrasound strength.

The mechanism by which the ultrasound irradiation increases release rates has been investigated.[12] We speculate that the irradiation causes increasing temperature in the delivery systems, which may facilitate diffusion.

The present study demonstrated that release rates of 5-FU from polymers can be increased on demand by external ultrasound irradiation. Ultrasound controlled

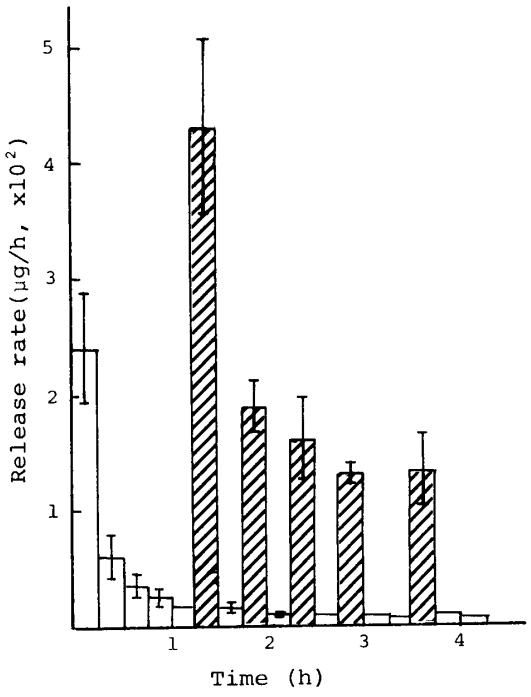

Fig. 1. Effect of Ultrasound Irradiation on the Release Rates of 5-FU from the Matrix-Type Drug Delivery System at 37°C

Each matrix was irradiated with 1 MHz ultrasound (5 W/cm^2) from a distance of 3 cm for 15-min periods (▨) alternating with 15-min non-irradiation periods (□). Data represent the average release rate per unit area of three matrix systems ± S.D.

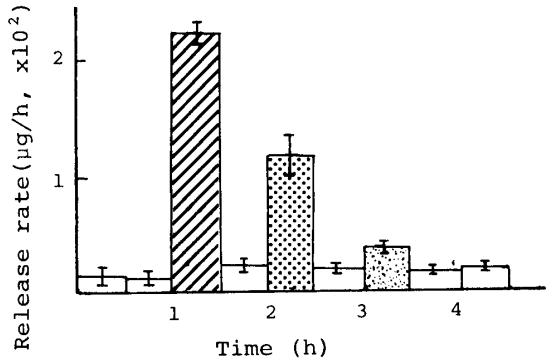

Fig. 2. Effect of Ultrasound Irradiation on the Release Rates of 5-FU from the Reservior-Type Drug Delivery System at 37°C

Each system was irradiated with 1 MHz ultrasound from a distance of 3 cm for 30-min periods at the strengths of 1 W/cm^2 (▩), 3 W/cm^2(▩), and 5 W/cm^2(▨) alternating with 30-min non-irradiation periods (□). Data represent the average release rate per unit area of three reservior systems ± S.D.

release systems could be potentially useful in cancer chemotherapy as a means of delivering the drug in relation to the status of the illness or the cell cycle.

In the field of cancer chemotherapy, ultrasound has been used to produce local hyperthermia.[10] Thus the ultrasound used to control drug delivery may have the added therapeutic value of inducing hyperthermia.

This delivery system represents an important new concept in controlled release technology, because it allows external control of drug release rates. The further development of systems with controlled release rates induced by ultrasound irradiation or other means(e.g., microwave) may prove useful in a variety of applications.

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