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Pluronic F-127 Gels as a Vehicle for Topical Administration of Anticancer Agents^{1,2)}

SHOZO MIYAZAKI,* SHIGEMI TAKEUCHI, CHIZUKO YOKOUCHI,
and MASAHICO TAKADA

*Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University,
Ishikari-Tohbetu, Hokkaido 061-02, Japan*

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Pluronic F-127 (a polyoxyethylene-polyoxypropylene surface-active block copolymer) was evaluated as a vehicle substance for topical administration of anticancer agents. 5-Fluorouracil and adriamycin were used in this evaluation. The effects of the concentration of Pluronic F-127, temperature, and the drug concentration on the release were studied by means of an *in vitro* release method using a cellulose membrane. With increasing concentration of Pluronic F-127 in the vehicle a corresponding decrease in the apparent release rate of the anticancer agents occurred. The apparent release rate increased with increasing temperature from 30 to 44 °C. Increase in drug concentration increased the drug release rate. The Pluronic F-127 gels appeared to have good potential for use in topical drug delivery systems since they exhibit reverse thermal gelation behavior and have good drug release characteristics and low toxicity.

Keywords—Pluronic F-127; drug vehicle; drug delivery system; 5-fluorouracil; adriamycin; topical administration

Surface-active block copolymers of polyoxyethylene-polypropylene (Pluronics®) are widely used in medical, pharmaceutical, and cosmetic systems.^{3,4)} The toxicity data for this series of block copolymers indicate that Pluronic F-127 is one of the least toxic of the block copolymers.⁵⁾ Pluronic F-127 consists by weight of approximately 70% ethylene oxide and 30% propylene oxide with an average molecular weight of 11500.⁶⁾ The unique characteristics of this copolymer is reverse thermal gelation; concentrated solutions (20–30% w/w) of the copolymer are fluid at refrigerator temperature (4–5 °C), but are soft gels at body temperature.⁵⁾ This suggests that when poured onto the skin or injected into a body cavity, the preparation will form a solid artificial barrier and sustained release depot. Pluronic F-127 shows good biocompatibility and should be useful as a drug vehicle for topical drug delivery systems.

Few studies have yet been done on the usefulness of Pluronic F-127 gels as topical drug delivery systems,^{5,7,8)} and no report has dealt with the release of anticancer agents from the gels. The present investigation was undertaken to determine by means of *in vitro* experiments the amounts of potent anticancer agents, 5-fluorouracil (5-FU) and adriamycin, released from Pluronic F-127 gels. The effects of temperature, concentration of Pluronic F-127, and drug concentration on the release were evaluated.

Experimental

Materials—Pluronic F-127 was a gift from Asahi Denka Kogyo Co. and was used as received. 5-Fluorouracil (5-FU) and adriamycin hydrochloride were obtained from Sigma Chemical Co. and Kyowa Hakko Kogyo Co., respectively.

Preparation of Pluronic F-127 Gels—Pluronic F-127 gels, 20, 25, and 30% w/w, were prepared by the cold method described by Schmolka.⁵⁾ A weighed amount of Pluronic F-127 was slowly added to cold water (5–10 °C) in

a vial containing a magnetic stirring bar, with gentle mixing. The container was left overnight in a refrigerator to ensure complete dissolution. Eventually, a clear, viscous solution formed. These gels exhibit reverse thermal behavior and are therefore fluid at refrigerator temperature (4–5 °C). An appropriate amount of 5-FU or adriamycin was then added to the cold solutions. Dissolution of the drugs was promoted by incubation of the mixture at 30 °C.

Measurement of Release Rate from Pluronic F-127 Gels—Release rates were measured by using plastic dialysis cells similar to that described previously.⁹ The capacity of each half cell was 1 ml (adriamycin) or 4 ml (5-FU) and the surface area of the membrane was 2.84 or 3.14 cm², respectively. An aqueous formulation was placed in the donor compartment and an equal volume of water in the receptor compartment. The gel donor phase and aqueous receptor phase were separated by a cellulose membrane (Visking Co., Type 36/32).¹⁰ The assembled cell was shaken horizontally at the rate of 60 strokes/min in an incubator maintained at 30 °C. The total volume of the receptor solution was removed at certain intervals and replaced by fresh water. The drug concentration of the samples was determined with a spectrophotometer at 266 nm for 5-FU and 233 nm for adriamycin. All experiments were carried out in duplicate (adriamycin) or triplicate (5-FU) and the average values were plotted.

Results

Effect of Pluronic F-127 Concentration on Drug Release

For studying the effect of Pluronic F-127 concentration on the drug release kinetics, the release of anticancer agents dissolved in vehicles composed of different concentrations of Pluronic F-127 was investigated. In this study, both the initial concentration of drug in the vehicle (0.5% w/v) and the temperature (30 °C) were held constant, while the concentration of Pluronic F-127 was varied (20, 25, and 30% w/w).

Figure 1 shows plots of the data, expressed as the cumulative amount of 5-FU released against the time in h. In all experiments, there appeared to be two release phases; an initial period of rapid release of the drug (*i.e.*, burst effect) and a period when release was approximately linear with respect to time. The apparent release rate of each experiment was determined by measuring the slopes of the lines in mg/h by the least-squares method. The values for the vehicles with 20, 25, and 30% w/w Pluronic F-127 concentrations were 0.83, 0.51, and 0.46 mg/h, respectively.

The release patterns of adriamycin from Pluronic F-127 gels are shown in Fig. 2. The burst effect observed in the case of 5-FU release from the gels was not observed in the case of adriamycin release. The release rate of adriamycin decreased, as did that of 5-FU, as the concentration of Pluronic F-127 in the vehicle increased. The release rates for the vehicles with 20, 25, and 30% w/w Pluronic F-127 were 0.27, 0.14, and 0.09 mg/h, respectively.

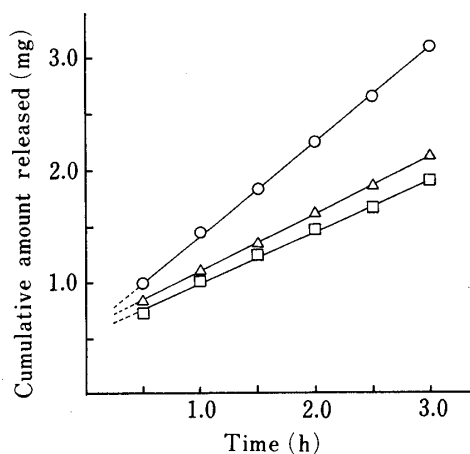


Fig. 1. Effect of Pluronic F-127 Concentration on 5-FU Release at 30 °C

Symbols: ○, 20%; △, 25%; □, 30% w/w Pluronic F-127 gels.
The concentration of 5-FU was 0.5% w/v.

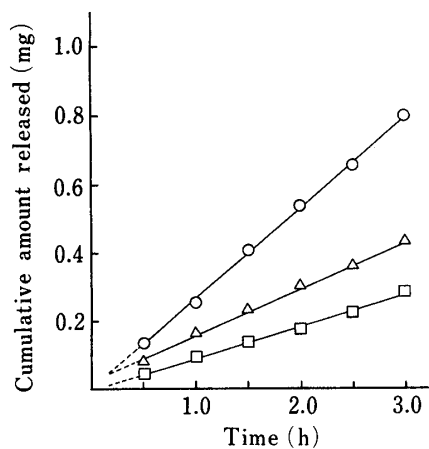


Fig. 2. Effect of Pluronic F-127 Concentration on Adriamycin Release at 30 °C

Symbols: see Fig. 1.
The concentration of adriamycin was 0.5% w/v.

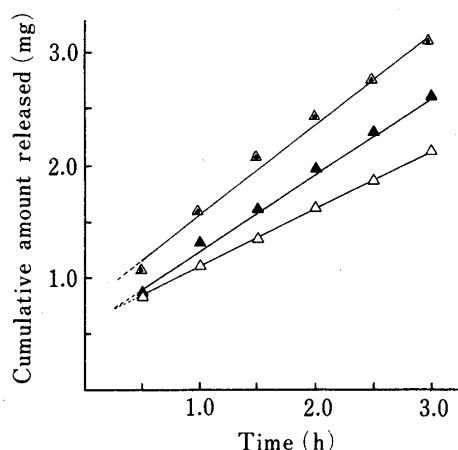


Fig. 3. Effect of Temperature on 5-FU Release from 25% w/w Pluronic F-127 Gels

Symbols: \triangle , 30°; \blacktriangle , 37°; \blacktriangle , 44°C.
The concentration of 5-FU was 0.5% w/v.

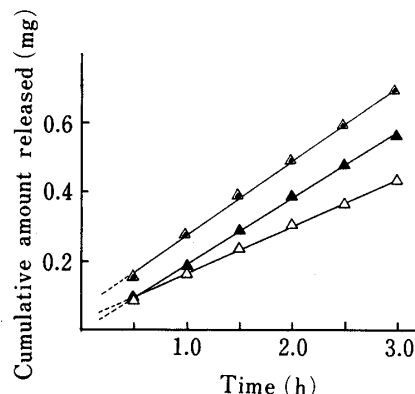


Fig. 4. Effect of Temperature on Adriamycin Release from 25% w/w Pluronic F-127 Gels

Symbols: see Fig. 3.
The concentration of adriamycin was 0.5% w/v.

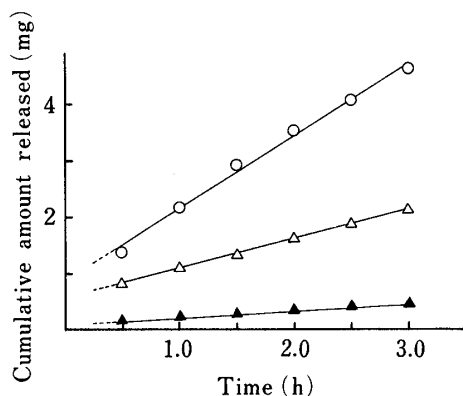


Fig. 5. Effect of Initial 5-FU Concentration on Release from 25% w/w Pluronic F-127 Gels at 30°C

Symbols: \blacktriangle , 0.1%; \triangle , 0.5%; \circ , 1.0% w/v.

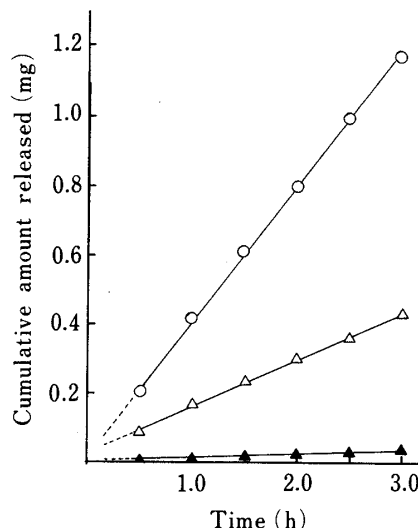


Fig. 6. Effect of Initial Adriamycin Concentration on Release from 25% w/w Pluronic F-127 Gels at 30°C

Symbols: see Fig. 5.

Effect of Temperature on Drug Release

The release patterns of 5-FU and adriamycin were measured at 30, 37 and 44 °C, and the results are shown in Figs. 3 and 4, respectively. In this study, both the initial concentration of drugs (0.5% w/v) in the vehicle and the Pluronic F-127 concentration (25% w/w) were held constant. It should be noted that the rate of drug release increased 1.6-fold when the temperature of the drug release system was raised from 30 to 44 °C.

Effect of Initial Drug Concentration on Release

The effect of initial drug concentration on the release pattern was tested using three drug concentrations (0.1, 0.5, and 1.0% w/v) and the results are shown in Figs. 5 and 6. It is evident that variation in the initial drug concentration in the vehicle affects the drug release. The smaller the drug concentration, the more slowly the drug was released. The particularly small release rate of 0.1% w/v adriamycin is due to adsorption of the drug on the cellulose membrane.

Discussion

Adriamycin and 5-FU have been used extensively in the treatment of a variety of malignant diseases. However, the clinical usefulness of these anticancer agents is severely restricted by the high toxicity. In order to maximize the effectiveness of anticancer agents and to minimize the toxic side effects, topical administration of the drugs on cancerous lesions has been attempted. The Pluronic F-127 gels appear to have potential application as topical drug delivery systems, since they exhibit reverse thermal gelation behavior, and have good drug release characteristics and low toxicity.

Since Pluronic F-127 gels are viscous isotropic liquid crystals consisting of micelles,^{8,11)} it is likely that the drug is released by diffusion through the extramolecular water channels of the gel matrix. Hence, the rate of drug release is determined by the micro-viscosity of the extramolecular fluid, the size of the water channels, and the drug equilibrium between the micellar phase and the external water phase.⁸⁾

In this work, we studied the release of 5-FU and adriamycin from aqueous gels of Pluronic F-127 by an *in vitro* release method using a cellulose membrane. With increasing concentration of Pluronic F-127 in the vehicle a corresponding decrease in apparent release rate of the two anticancer agents occurred. The reason for the decreased release rate may be a reduction in the size of the water channels and an increase in the micro-viscosity of the water channels of the gel. Schmolka⁵⁾ indicated that the higher the Pluronic F-127 concentration, the greater is the yield strength or rigidity of the gels.

Since Pluronic F-127 gels exhibit reverse thermal behavior, their viscosity increased as the temperature increased.⁸⁾ However, the apparent release rate for 5-FU and adriamycin increased with increasing temperature from 30 to 44 °C. Chen-Chow and Frank⁸⁾ suggested that the rate of drug release is determined by the micro-viscosity of the extramolecular fluid of the gel, rather than the macro-viscosity. The viscosity of water channels would be expected to decrease with increasing temperature. Recently, studies of the micellar properties of this compound have been carried out to gain insight into the gelation process.¹¹⁾ In order to elucidate the mechanism of drug release, one would also have to take into account the temperature dependence of micellar size.

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