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Use of Fibrin Film as a Carrier for Drug Delivery: *In Vitro* Drug Permeabilities of Fibrin Film

Shozo Miyazaki and Tanekazu Nadai

Faculty of Pharmaceutical Sciences, Josai University[1]

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Fibrin film prepared from human plasma was evaluated as a new biodegradable carrier for drug delivery. Two steroidal compounds, prednisolone and prednisone, were used in this evaluation. The drug permeability of the fibrin film and the release characteristics of the drug/fibrin film system were investigated using *in vitro* test models. The high permeability of the fibrin film to drugs suggests that it may be available as a unique vehicle for drug delivery. The possible use of fibrin film in the control of drug release is also discussed.

Keywords——fibrin film; drug delivery; permeability; drug release; prednisolone; prednisone

Recently, considerable attention has been focused on the use of polymeric materials to control the release of drugs. Much of the previous work on controlled-release drug delivery has utilized polydimethylsiloxane (silicone rubber).[2] A nonallergenic, sterilizable, flexible, drug-bearing, and soluble material would be ideal for such a drug delivery system.

More recently, the application of collagen as a biodegradable carrier for drug delivery was studied.[3] Polylactic acid[4] and copolymers of lactic and glycolic acids[5] have also been evaluated as biodegradable vehicles for the controlled delivery of drugs.

In the present study, the potential use of fibrin film as a new biodegradable drug delivery carrier was investigated. Since the fibrin film is a bioplastic[6] prepared from human plasma, and since it offers good adaptability to the body, low antigenicity, and digestability in the body,[7] exploratory studies on its use as a carrier for drugs seemed useful. In addition to the possible use of fibrin film in neurosurgery,[8] the film is used to make an absorbable artificial skin.[9]

The drug permeability of the fibrin film was examined first to determine its usefulness as a drug delivery device. Two steroidal compounds, prednisolone and prednisone, were used in this examination.

Experimental

Materials——Commercial fibrin films were obtained from Green Cross Co., Osaka. They were delivered to the laboratory in the usual packing, *i.e.*, sealed in glass bottles containing sterile physiological saline.

1) Location: *1-1 Keyakidai, Sakado, Saitama 350-02, Japan.*
2) J. Folkman and D.M. Long, *J. Surg. Res.*, **4**, 139 (1964).
3) *a*) A.L. Rubin, K.H. Stenzel, T. Miyata, M.J. White, and M. Dunn, *J. Clin. Pharmacol.*, **13**, 309 (1973); *b*) M. Nakano, A. Kuchiki, and T. Arita, *Chem. Pharm. Bull.*, **24**, 2345 (1976).
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7) *a*) J.D. Ferry and P.R. Morrison, *J. Clin. Invest.*, **23**, 566 (1944); *b*) P.R. Morrison and M. Singer, *ibid.*, **23**, 573 (1944).
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The wet fibrin films had a stated thickness of 0.15 ± 0.05 mm and a fibrin content of 50% or more. Water content in the film, determined from the weight loss, was about 58%. The films were rinsed with distilled water to remove surface contaminants and then immersed in a large volume of water and allowed to equilibrate for 24 hr at room temperature before use.

Prednisolone and prednisone were obtained from Merck, Darmstadt and were used without further purification.

Permeation Studies——Permeation rates through the fibrin film were determined using plastic dialysis cells as described by Bahal and Kostenbauder.[10] Each dialysis cell consisted of two Plexiglas blocks, $6.3 \times 6.3 \times 2.7$ cm, each half having a cavity with a capacity of 20 ml. The film was clamped centrally between the two halves of the cell. The area available for permeation was 11.94 cm^2.

The cell was initially equilibrated overnight in a shaker bath maintained at 37° with 20 ml of distilled water in both compartments. The water was then removed by suction and 20 ml of fresh water was added to one compartment and an equal volume of a drug-saturated solution or suspension was placed in the other. All solutions were warmed to 37° before being placed in the cell. Caps were placed over both openings of the cell and the cell was mechanically shaken horizontally at a rate of 60 strokes/min. The sample solutions were withdrawn periodically, and the solution in the compartment was flushed out and replaced with fresh water. This procedure was used to maintain a sink condition with respect to the permeable species in the receptor solution.

Under the experimental conditions used, the permeability coefficients of the drugs in solution or suspension can be obtained from the following simplified steady state treatment.[11]

$$Q = \frac{P \cdot A \cdot C \cdot t}{h} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug permeated in time, t, C is the concentration of the drug in the donor solution, h is the thickness of the film, and A is the area of the film. The permeability coefficient, P, can be obtained from the linear portion of a plot of Q *vs.* t.

***In Vitro* Release Studies**——Strips, 1.8×1.8 cm, were cut from the fibrin film using a microscope cover glass as a template. The strips of film were saturated with drugs by simple exposure of each strip to 5 ml of various concentrations of drug solutions overnight at 37°. After the drug exposure, they were rinsed and blotted with a filter paper. The fibrin films containing steroids were placed separately in 20 ml vials containing 5 ml of distilled water. The vials were closed tightly with caps. The release was followed with shaking at a rate of 60 strokes/min on a laboratory shaker at 37°. Each film was successively transferred to fresh vials containing 5 ml of water. Analysis of drugs released into each 5 ml fraction was carried out spectrophotometrically.

Results

The permeation properties of prednisolone and prednisone from saturated solutions and suspensions in water through the fibrin film are shown in Figs. 1 and 2, where the cumulative amount of the drug permeated into the receptor solution is plotted against time.

The fibrin film allowed the steroids to permeate in measureable quantities. When the saturated solutions and suspensions were placed in the donor compartment, the concentration of the steroids in the receptor solution increased linearly with time, since the concentration gradient was virtually constant under the conditions used. The average permeability of prednisolone (Fig. 1; $P = 4.79 \times 10^{-4}$ cm^2/hr from saturated solution and 4.87×10^{-4} cm^2/hr from suspension) was slightly smaller than that of prednisone (Fig. 2; $P = 5.14 \times 10^{-4}$ cm^2/hr from saturated solution and 5.29×10^{-4} cm^2/hr from suspension); permeability values were calculated from the slopes of the steady-state portion of the permeation curves, employing Eq. 1.

The amounts of steroids which can be released from the fibrin film into water were also determined by the methods described above. Figures 3 and 4 show plots of the data, expressed as the cumulative amount of steroids released, *versus* time. It is apparent that the release

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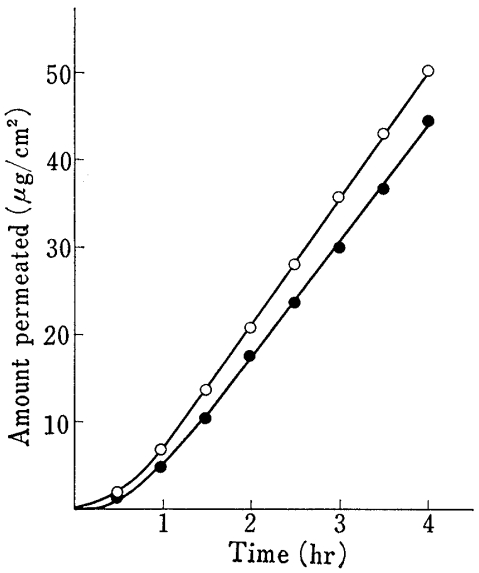

Fig. 1. Permeation Profiles of Prednisolone from Saturated Solution (○) and Suspension (●) through Fibrin Film at 37°

Each point represents the mean of three experiments.

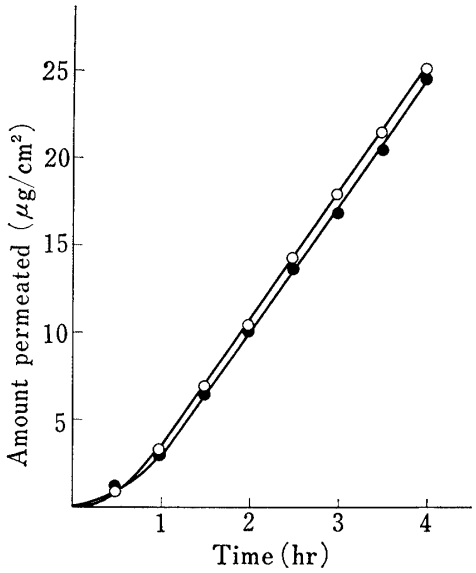

Fig. 2. Permeation Profiles of Prednisone from Saturated Solution (○) and Suspension (●) through Fibrin Film at 37°

Each point represents the mean of three experiments.

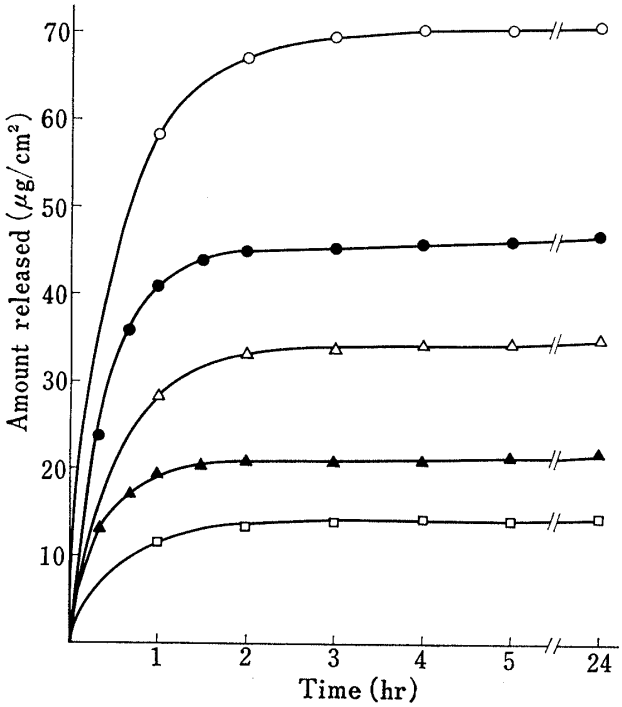

Fig. 3. *In Vitro* Release of Prednisolone from Fibrin Film saturated with 0.26 mM (□), 0.48 mM (▲), 0.62 mM (△), 0.97 mM (●), and 1.25 mM (○) Solutions at 37°

Each point represents the mean of three experiments.

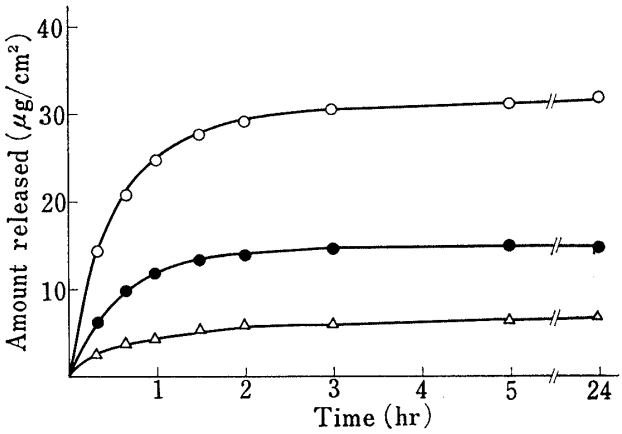

Fig. 4. *In Vitro* Release of Prednisone from Fibrin Film saturated with 0.11 mM (△), 0.26 mM (●), and 0.52 mM (○) Solutions at 37°

Each point represents the mean of four experiments.

of both prednisolone and prednisone proceeds more rapidly during the first 3 hours. In this period, about 90 to 98% of the total release of the steroids occurred.

The amount of the steroids released from these matrix systems was found to be dependent upon the concentration of the drugs incorporated; that is, the amount of the drugs in the matrix initially. The concentrations of prednisolone and prednisone used ranged from 0.26 mM to 1.25 mM (saturated solution) and from 0.11 mM to 0.52 mM (saturated solution), respectively.

These preliminary studies indicate that fibrin film is permeable to both steroids in water and that the steroids are readily released from the fibrin film.

Discussion

Fibrin film is prepared from human plasma by clotting a solution of human fibrinogen with thrombin. Fibrin film is a nontoxic, autoclavable, flexible, and absorbable material.[6-9] The safety and biocompatibility of the fibrin film are reflected in its use as a dural substitute and in the prevention of meningocerebral adhesions.[8] In addition, fibrin film is now available for use as an artificial skin.[9] It is known that diglycine passes through steam-sterilized fibrin film, whereas hemoglobin does not.[8b] This suggests that most low molecular weight drugs would also pass through the film. Fibrin film shows good biocompatibility and should be useful as a carrier for biomedical implanted, inserted, or surface-applied devices.

This preliminary *in vitro* study was done to determine the drug permeabilities of fibrin film. Prednisolone and prednisone were chosen for this initial study because they are middle molecular weight drugs, and because protective films containing steroids have used for dermatological and surgical applications.[12]

These preliminary results indicate that both steroids can permeate through the fibrin film; the film takes up and releases these steroidal compounds. This suggests that the fibrin film may represent a unique vehicle for drug delivery. Experiments are in progress to elucidate the mechanism of the passage of drugs through the fibrin film and the release characteristics in comparison with those of other carriers.

The data reported here also indicate that in the *in vitro* system tested (Figs. 3 and 4), steroids were released from the fibrin film in direct proportion to the amount of the drugs incorporated. The drug concentration in the film appears to govern the rate of drug release.

Drug release rates may be altered by varying the fibrin content, shape, and size of the films.[7a] Other fibrin devices, such as tubing and fibers, might also be worth investigating.

A biodegradable carrier also offers the possibility of controlling the rate of drug release in terms of the rate of carrier absorption in the body. The rate of absorption can be modified by suitable treatment of the films.[7b]

Further studies to evaluate the possible use of fibrin film in the control of drug release seem worthwhile.

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