DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(5), 617-626 (1992)



# DESIGN AND EVALUATION OF TRANSDERMAL FLUFENAMIC ACID DELIVERY SYSTEM

Meenu Madhavan and George Chiaw-Chi Hwang
College of Pharmacy and Allied Health Professions
Northeastern University, Boston, MA 02115

## ABSTRACT

Monolithic-type transdermal flufenamic acid (FA) delivery systems were prepared using an acrylate pressure sensitive adhesive (PSA) which contained 3, 6 and 9% (w/w) of FA. The in vitro release profiles of these systems were examined using modified Franz diffusion cells and observed that FA is molecularly dissolved in the acrylate PSA matrix and the drug released via a solution-diffusion mechanism. Permeation studies through excised hairless mouse skin revealed that the system containing 9% of FA showed the highest flux. The 9% system was further evaluated for its anti-inflammatory effect by applying the system on carrageenan-induced paw edema in mice and concluded that significant inhibition of swelling was produced as compared to the placebo system.

## INTRODUCTION

Flufenamic acid (FA), a nonsteroidal anti-inflammatory drug has been used as an analgesic and anti-inflammatory agent for the treatment of certain rheumatic disorders[1]. Untoward side effects have been reported after oral intake which include diarrhea, nausea, gastrointestinal ulcerations and in some cases haemopoietic toxicity[2]. In order to avoid the systemic side effects and to overcome the drawbacks offered by ointment formulation[3,4], a transdermal system of FA was developed and its effects on carrageenan-induced paw edema in mice were tested.

Selection of an appropriate pressure sensitive adhesive (PSA) is critical during the development of the transdermal system. Since acrylate polymers are saturated polymers, they are highly resistant to oxidation and do not require the addition of stabilizers which can potentially cause biocompatibility problems[5]. Polymers are also moderately polar, due to their acrylate ester structure and thus have a degree of moisture permeability. Hence, acrylate PSA was chosen in our study in which drug was dispersed.

## MATERIALS AND METHODS

System Design: The components of the transdermal system include a backing membrane and the drug reservoir. The

backing membrane is a stretchable polyester film (3M Co.) and serves as a carrier for the drug reservoir. The drug reservoir is a thin elastic layer (150 um) of FA dissolved in the PSA that provides contact of the system with the skin. Three monolithic systems were prepared using an acrylate PSA (GELVA 737, Monsanto Co.) containing various concentrations of FA ranging from 3, 6 and 9% by weight.

Release Study: The in vitro release kinetics of FA from the transdermal system were examined by using the modified Franz diffusion cell. A unit of transdermal system was clamped between the cell cap and receptor cell. The adhesive layer of the system was in contact with 0.05M phosphate buffer saline solution (pH 7.4) maintained at 37$^{o}$C. At predetermined time intervals, the receptor fluid was removed for analysis and replaced with the same volume of fresh receptor fluid. The concentration of FA in the receptor fluid was determined by a UV-VIS spectrophotometer at a wavelength of 285 nm.

Skin Permeation Studies: Full thickness abdominal skins were excised from hairless mouse ( female HRS/J strain, 6-8 weeks old). The transdermal system of surface area 0.71 cm$^2$ was applied to the stratum corneum side of the freshly excised skin and then mounted to the diffusion cell with the dermal side of the skin in contact with the receptor fluid. The receptor fluid consisted of

0.1% formaldehyde in 0.05M phosphate buffer saline solution (pH 7.4) and was maintained at 37°C through out the study. The receptor fluid was removed regularly and analysed by HPLC.

HPLC Analysis: The HPLC system consisted of a pump (model 510, Waters), an autosampler (AS-2000, Hitachi) and a variable wavelength detector (model 440, Waters). A $C_{18}$ column (LiChrocart 5 um 125-4, E. Merck) with guard cartridge was used. The mobile phase of methanol: 0.025M phosphate buffer (pH 7.4) (65:35) was used at the flow rate of 1 ml/min and the UV detector at 285 nm.

Anti-Inflammatory Effects of the Transdermal System on Carrageenan-Induced Paw Edema: It has been suggested by Schrier et al.[6] that murine carrageenan-induced paw edema might be a useful model for development of novel topical anti-inflammatory agents. The paw edema was induced in male C57BL/6J mice (Jackson laboratories) by injecting 1% carrageenan solution as described by Levy[7]. The anti-inflammatory effect of transdermal FA delivery system was evaluated by applying a 0.5 $cm^2$ of the transdermal system containing 9% of FA on the right hind paw of the mouse. Placebo systems were similarly applied to a control group. After three hours, the transdermal systems were removed and the mice were injected intradermally in the right hind paw with 30 ul of 1% carrageenan solution and 30 ul of normal saline

solution in the left hind paw. Three hours after injection the mice were sacrificed and the paws were amputated at the joint and weighed on an analytical balance. Edema weight was calculated from the differences in weight between carrageenan and saline injected paws for each experimental group (at least six mice per group).

## RESULTS AND DISCUSSION

In Vitro Release Kinetics: The release kinetics of FA from the acrylate PSA matrix was evaluated by fitting the release data to the following equation[8]:

$$Q = 2C \left( Dt/\pi \right)^{1/2}$$

where the Q is the cumulative amount of drug released per unit area of matrix at time t, C is the concentration of drug in the matrix and D is the diffusion coefficient of drug in polymeric matrix. As shown in Figure 1, the cumulative amount of FA released is proportional to the square root of time and the slope of the regression line is directly proportional to the concentration of FA in the acrylate PSA matrix as predicted by the equation. The results suggest that FA is molecularly dissolved in the acrylate PSA matrix and the drug release via a solution-diffusion mechanism[8]. The system was further examined for the permeation characteristics through hairless mouse skin.

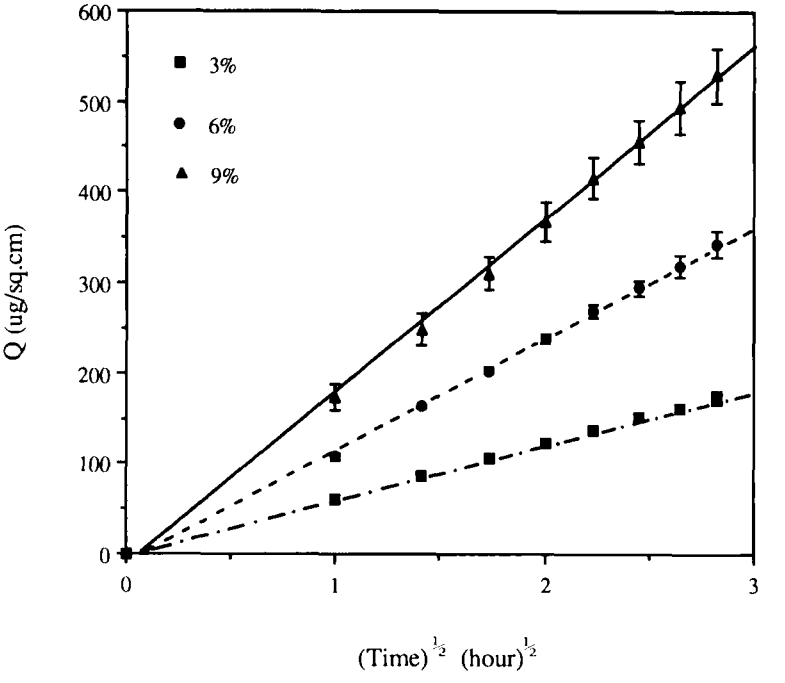


FIGURE 1

The cumulative amount of flufenamic acid released from transdermal systems versus square root of time. The symbols represent the observed release data of flufenamic acid from transdermal systems. The lines represent the best fit lines obtained by the linear regression procedure and can be represented by the following equations:

(-·-·-) $Q = (61.3)t^{1/2} - 0.45$, $r > 0.99$
(- - - -) $Q = (122.71)t^{1/2} - 7.32$, $r > 0.99$
(———) $Q = (189.52)t^{1/2} - 10.68$, $r > 0.99$

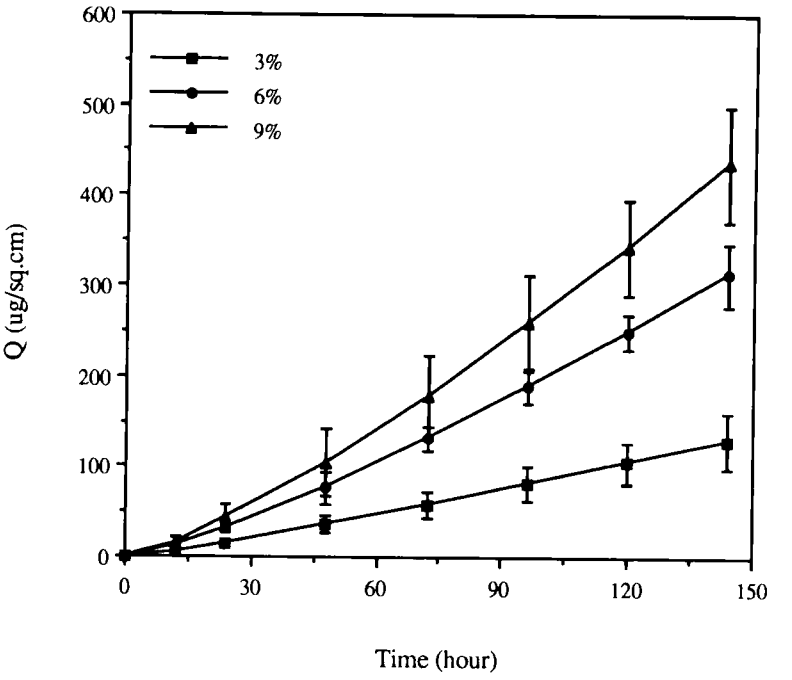


FIGURE 2

The cumulative amount of flufenamic acid permeated through hairless mouse skin versus time from transdermal systems.



Skin Permeation Study: Figure 2 shows the cumulative amounts of FA released from the three systems through the skin. Each data represents the average of three readings. During the initial stages there is a characteristic lag phase followed by steady state diffusion.

The apparent steady state fluxes across excised skin from the different systems containing 3, 6 and 9% (w/w) of FA were 0.94, 2.29 and 3.18 ug/hr/cm$^2$,

TABLE 1

Inhibitory Effect of Transdermal Flufenamic Acid Delivery System on Carrageenan-Induced Paw Edema

| | Edema Weight (g) | Inhibition (%) |
|---|---|---|
| Control (7) | 0.0317 ± 0.0098 | |
| Treatment (10) | 0.0210 ± 0.0053 | 33.8 |



respectively. Since the system containing 9% of FA showed the highest permeation rate through the skin, the system was further evaluated for the anti-inflammatory effect in an animal model.

Inhibitory Effect of Transdermal Flufenamic Acid Delivery System on Carrageenan-Induced Edema: The saline injected paws retained approximately the same weight through out the experiment and therefore the differences in weight between carrageenan and saline injected paws were tested as a measure of the inflammation caused by carrageenan. Statistical difference in edema weight between the experimental groups were determined by Student's t-test. Results were expressed as % inhibition of swelling in drug treated mice compared with placebo treated mice. Table 1 shows that the transdermal FA delivery system produced

significant inhibitory effect on carrageenan-induced paw edema (34% inhibition, $P<0.01$).

The results of the study show the possibility of formulating a transdermal FA delivery system which can produce significant local anti-inflammatory effect. The system might offer some advantages in terms of a clean, easy to use method of administration and overcome the drawbacks of ointment formulation such as inaccuracy of dosage, low patient compliance and frequency of application.



## ACKNOWLEDGMENTS

We thank 3M Co. (St. Paul, MN) and Monsanto Co. (St. Louis, MO) for supplying films and pressure sensitive adhesives.

## REFERENCE

1. H.G. Hamor in "Principles of Medicinal Chemistry", W.O Foye, eds., J.P.Lippincott, Philadelphia, 1985, p. 561.
Philadelphia, 1985, p.561.
2. W.M. O'Brien and G.F. Bagby, J. Rheumatol., 12, 13 (1985).
3. P. Panse, P. Zeiller and K.H. Sensch, Arzneim.-Forsch., 21, 1605, (1971).

4. P. Panse, P. Zeiller, and K.H. Sensch, Arzneim.-Forsch., 24, 1298, (1974).

5. C.M. Musolf, in "Transdermal Controlled Systemic Medications", Y.W. Chien, ed., Marcel Dekker, New York 1987, p. 93.

6. D.J. Schrier, S. Moniot, M.I. Gluckman and R.B. Gilbertsen, J. Pharm. Pharmacol., 39, 57, (1987).

7. L. Levy, Life Sci., 8, 601, (1969).

8. R.S. Langer and N.A. Peppas, Biomaterial., 2, 201, (1981).