Drug Development and Industrial Pharmacy, 25(11), 1209–1213 (1999)

COMMUNICATION

Percutaneous Transport of Diclofenac Sodium from Mixtures of Fatty Alcohol (or Fatty Acid) and Propylene Glycol Through the Rabbit Abdominal Skin

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ABSTRACT

Diclofenac sodium is a nonsteroidal anti-inflammatory drug with analgesic, antipyretic, and anti-inflammatory activity. When used in a topical application, diclofenac can diffuse through the skin and into the subcutaneous tissue to effect the anti-inflammatory action. In this study, in vitro evaluations of the percutaneous transport of diclofenac sodium in various bases containing fatty alcohols/propylene glycol or fatty acid/propylene glycol mixtures through the abdominal skin of the rabbit were investigated. Results show that the transdermal flux of diclofenac sodium in the fatty alcohol/propylene glycol bases of the same ratio is affected by the chain length of the fatty alcohol, and its effect is in the order of $C_{10} > C_{12} > C_{14} > C_{18}$*. However, the transdermal flux of diclofenac sodium in the fatty acid/propylene glycol bases of the same ratio is also affected by the chain length of the fatty acid, but no absolute relationship was found. For the same chain length of fatty acid and fatty alcohol used in the formulation base that was otherwise the same, the transdermal flux of diclofenac sodium is higher in the formula containing fatty alcohol than that containing fatty acid.*

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INTRODUCTION

Diclofenac sodium is a water-soluble, nonsteroidal, anti-inflammatory drug that is used primarily in the treatment of localized nonarticular rheumatism and inflammations of tendons, ligaments, muscles, and joints arising from trauma. It was reported by Koichi et al. that diclofenac and diclofenac sodium have different pathways in membrane penetration (1). Diclofenac can penetrate through the ethylene–vinyl acetate membrane (i.e., lipoidal model membrane), but diclofenac sodium cannot. However, Mutsuo et al. suggested that some water-soluble drugs with low molecular weight can also be candidates for transdermal drug delivery (2). In this study, diclofenac sodium was chosen as a model drug in this respect.

The fatty alcohol/propylene glycol base is a gel-like mixture with a crystalline network; it was reported to have some significant advantages over the traditional ointment and cream dosage forms (3).

In Katz and Neiman's patent (4), it was indicated that incorporation of suitable coupling agents, such as saturated fatty acids, amides of fatty acids, or esters of fatty acids, in the formulations based on propylene glycol can prevent propylene glycol from separating in the vehicle (i.e., bleeding) during storage. Therefore, in this study, fatty acids of various chain lengths were also used in addition to the fatty alcohols.

It was the purpose of this study to evaluate the in vitro percutaneous transport of diclofenac sodium through the rabbit skin from various formulations containing 1% diclofenac sodium in fatty alcohol/propylene glycol or fatty acid/propylene glycol bases. The information derived from this study will provide valuable information for further in vivo studies.

EXPERIMENTAL

Materials

The following materials were purchased from Sigma Company (St. Louis, MO): steric alcohol (C_{18}-ol, lot 24H1025), stearic acid (C_{18}-acid, lot 14H3423), myristic alcohol (C_{14}-ol, lot 92H0687), myristic acid (C_{14}-acid, lot 80H0527), lauryl alcohol (C_{12}-ol, lot 123H3434), lauric acid (C_{12}-acid, lot 54H0251), 1-decanol (C_{10}-ol, lot 23H3456), 1-decanoic acid (C_{10}-acid, lot 113H2507), and piroxicam (lot 54H4030). Cetyl alcohol (lot 9A015080) was purchased from Kanto Chemical Company, Incorporated, Japan. Sodium chloride solution 0.9% (lot 98309063) was purchased from Chi Sheng Chemical Company (Taiwan, R.O.C.). Acetonitrile (lot 3713340T) and methanol (lot L607702) were purchased from BDH, England. Propylene glycol (lot 44910) was purchased from Dow (United States). Diclofenac sodium (lot 90302) was obtained from Zheng Feng Chemical Company (Taiwan, R.O.C.).

Methods

Preparation of Skin Samples

Male New Zealand white rabbits weighing 1000 ± 100 g were euthanized by ether. After cleaning the abdominal hair with an electric clipper, the abdominal skin was scissored from the rabbit body and cut into pieces. The fresh skin samples were then mounted onto the Franz-type diffusion cell (Tong Hong Instruments, Taiwan, R.O.C.) for transdermal experiments.

In Vitro Transdermal Studies

In vitro transdermal studies were conducted using the upright Franz-type diffusion cells in which the jacketed cells were circulated with thermostated water maintained at 32°C ± 1.0°C. The receptor cell was then filled with normal saline solution, followed by mounting the freshly prepared rabbit skin between the donor and receptor cells. The test vehicle was then placed on the donor site to initiate the experiment. Samples of 0.5 ml from the receptor cell were withdrawn periodically for 24 hr and analyzed by high-performance liquid chromatography (HPLC). For each sample collection, an equal volume of normal saline solution was added to the receptor cell for volume replacement.

Preparation of 1% Diclofenac Sodium Test Vehicles

Formulations containing 1% diclofenac sodium in either fatty alcohol/propylene glycol or fatty acid/propylene glycol of various ratios were prepared according to the formulas described in Tables 1 and 2. The test vehicles were prepared by heating the fatty alcohols or fatty acids to 65°C ± 1°C, followed by the addition of diclofenac sodium in propylene glycol, previously heated to the same temperature. The mixture was then placed in a 0°C ice water bath and stirred until congealed.

High-Performance Liquid Chromatography Analysis

This HPLC system was equipped with an isocratic pump (model LC-6A, Shimadzu, Japan), a C_{18} column (Nova-Pak C_{18}, S-4 μm, Waters Associates, United States), an ultraviolet (UV) detector set at 276 nm (model SPD-6AV, Shimadzu, Japan), and an integrator (model

Table 1

In Vitro Transdermal Flux of Diclofenac Sodium from Various Formulas Containing 1% Diclofenac Sodium in Different Fatty Alcohol/Propylene Glycol Bases

Formula		C_{18}-ol		C_{14}-ol		C_{12}-ol		C_{10}-ol	
% Fatty Alcohol	Propylene Glycol	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)
0	99.00	34.4	0.110	34.4	0.110	34.4	0.110	34.4	0.110
9.90	89.10	355	0.203	27.5	0.842	30.5	26.854	33.4	30.728
24.75	74.25	535	0.551	41.3	1.234	27.5	29.360	24.6	38.756
39.60	59.40	766	1.079	204.0	7.602	24.6	35.342	19.7	39.279
49.50	49.50	184.0	1.662	142.0	6.783	22.6	30.316	16.7	43.746

C-R6A, Shimadzu). The mobile phase was composed of 45% (v/v) acetonitrile and 55% 0.75 M sodium acetate buffer at pH 5.0 and was delivered at a flow rate of 1.0 ml/min. The chromatogram from the injection of the diclofenac solution spiked with the internal standard, piroxicam, indicated a relative retention time of 6.2 min and 3.1 min for diclofenac sodium and piroxicam, respectively. The linearity for the diclofenac sodium in the concentration ranges 0.1 μg/ml to 150 μg/ml was determined to have a correlation coefficient of greater than 0.999.

RESULTS AND DISCUSSION

Effect of Fatty Alcohols on the Percutaneous Transport of Diclofenac Sodium

The results of in vitro transdermal studies of the 1% diclofenac sodium formulations containing fatty alcohols/propylene glycol of different ratios are shown in Table 1.

The data indicate that, for the same ratio composition of fatty alcohol/propylene glycol, the transdermal flux of

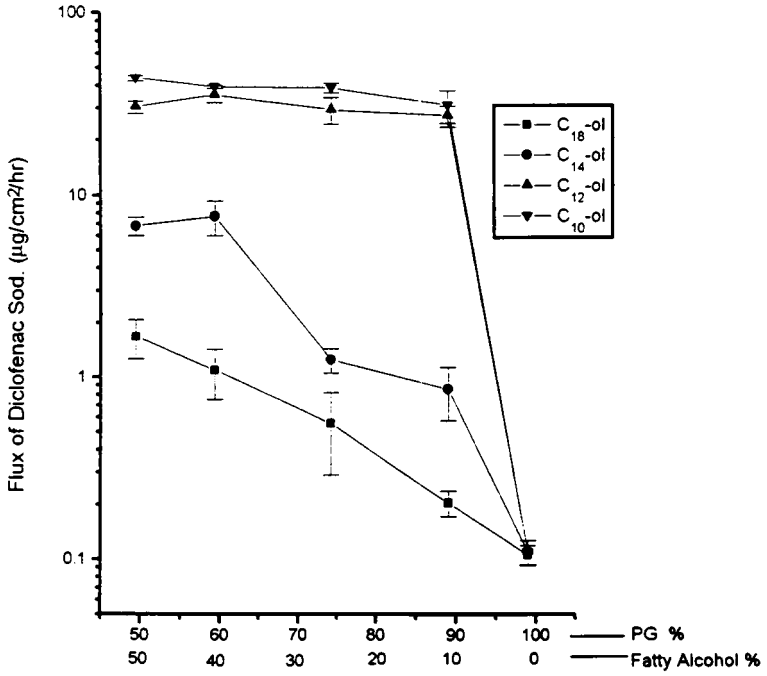

Figure 1. The logarithmic plot of diclofenac sodium flux versus percentage of polyethylene glycol and percentage of fatty alcohol.

Table 2

In Vitro Transdermal Flux of Diclofenac Sodium from Various Formulas Containing 1% Diclofenac Sodium in Different Fatty Acid/Propylene Glycol Bases

Formula		C_{18}-acid		C_{14}-acid		C_{12}-acid		C_{10}-acid	
% Fatty Alcohol	Propylene Glycol	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)
0	99.00	34.4	0.105	34.4	0.105	34.4	0.105	34.4	0.105
9.90	89.10	20.7	0.922	55.0	1.521	24.6	3.219	31.5	3.249
24.75	74.25	22.6	1.384	337.0	8.973	30.5	4.283	35.4	3.279
39.60	59.40	17.7	2.031	400.0	12.612	37.4	5.698	25.1	1.435
49.50	49.50	9.8	2.181	430.0	11.137	61.9	5.095	25.6	1.009

diclofenac sodium increased as the carbon chain length of the fatty alcohol decreased from C_{18}-ol to C_{10}-ol.

With this trend, the flux of diclofenac sodium in the cetyl alcohol (C_{16}-ol)/propylene glycol base could be estimated to be between the flux in the formulation with stearyl alcohol (C_{18}-ol) and the formulation with myristic alcohol (C_{14}-ol). For the formulations containing more than 24.75% fatty alcohols, it was also noted that, with the same fatty alcohol/propylene glycol composition, the transdermal flux of diclofenac sodium increased as the viscosity of the vehicle decreased, for which the Davis's theory applied (5). However, no absolute relationship could be established between the transdermal flux and the fatty alcohol concentration in the test vehicles.

In an article by Turi, Danielson, and Woltersom (6), it was indicated that propylene glycol can enhance the in vitro skin penetration of drugs due to the reduction of the diffusional resistance attributed to the propylene glycol. The addition of fatty alcohol in the propylene glycol vehicle increased the transdermal flux of diclofenac sodium (Fig. 1). The magnitude of increase in the flux is more significant in the fatty alcohols with short chain length (i.e., C_{10}-ol) than with long chain length (i.e., C_{18}-ol) in the same formulation. In the cases of the formulation containing fatty alcohol of C_{10}-ol, C_{12}-ol, and C_{14}-ol, the maximum flux was reached when the fatty alcohol concentration was increased to 50%, 40%, and 40%, respectively. In a study by Kaiho et al., propylene glycol from a fatty alcohol/propylene glycol base was absorbed through the rat skin into the systemic circulation (7). It was believed that the fatty alcohol and/or propylene glycol interacted with the lipid compartment in the stratum corneum of the skin and affected its permeability (1).

Effect of Fatty Acid on the Percutaneous Transport of Diclofenac Sodium

The results of in vitro transdermal studies of the 1% diclofenac formulations containing fatty acids/propylene glycol of different ratios are shown in Table 2. The data indicated that, for the same composition ratio of fatty acid/propylene glycol, the transdermal flux increased to

Table 3

In Vitro Transdermal Flux of Diclofenac Sodium from Various Formulas Containing 1% Diclofenac Sodium in Different Fatty Acid/Fatty Alcohol/ Propylene Glycol Bases

Formula (% Weight)				
Diclofenac Sodium	C_{18}-acid	C_{10}-ol: Propylene Glycol (1:1)	Viscosity (cps)	Flux ($\mu g/cm^2/hr$)
1	0	99	16.7	43.41
1	1	98	19.6	44.00
1	3	96	29.5	12.13
1	5	94	354	5.70

a maximum as the carbon chain length of the fatty acid decreased and then the flux decreased as the carbon chain length further decreased. Examples of these observations are seen in the formulations with fatty acid/propylene glycol vehicles at 24.75/74.25, 39.60/59.40, and 49.50/49.50 weight ratios, for which the diclofenac sodium flux increased to a maximum as the chain length of the fatty acids decreased from C_{18}-acid to C_{14}-acid, but further decrease in the chain length from C_{14}-acid to C_{10}-acid decreased the diclofenac sodium flux. For the formulations with a fatty acid/propylene glycol ratio of 9.90/89.10, the diclofenac sodium flux appeared to increase as the chain length decreased from C_{18}-acid to C_{12}-acid and leveled off as the chain length further decreased to C_{10}-acid. For the formulation base containing the same fatty acid, the diclofenac flux increased as the fatty acid concentration increased to an optimal concentration (i.e., 49.5% for C_{18}-acid, 39.6% for C_{14}-acid, 39.6% for C_{12}-acid, and 24.75% for C_{10}-acid) and then started to decline as the fatty acid concentration further increased.

By comparing Tables 1 and 2, the degree of effect on the transdermal flux of diclofenac sodium from fatty alcohol and fatty acid with the same chain length in a formulation that was otherwise the same was found to be greater for the fatty alcohol than the fatty acid when the chain length was C_{10} and C_{12}, but was reversed when the chain length was C_{14} and C_{18}. Aungst, Rogers, and Shefter (8) and Komata et al. (9) reported that several fatty acids, such as lauric acid, myristic acid, and stearic acid, are capable of enhancing the percutaneous absorption of some coadministered drugs, which is consistent with the results of this study, in which the transdermal flux increased with the incorporation of fatty acid in the formulation base.

Effect of Fatty Acid and Fatty Alcohol on the Percutaneous Transport of Diclofenac Sodium

In this study, C_{18}-acid and C_{10}-ol were used as the model fatty acid and fatty alcohol, respectively. The results of in vitro transdermal studies on the 1% diclofenac formulations containing fatty acids/(fatty alcohol:propylene glycol) of different ratios are shown in Table 3. The data indicated that the addition of C_{18}-acid into the C_{10}-ol/propylene glycol base decreased the transdermal flux of diclofenac sodium. There was an insignificant effect of C_{18}-acid on the transdermal flux of diclofenac sodium when the C_{18}-acid concentration was at 1%, but a significant decrease of the diclofenac sodium flux was observed when the concentration of C_{18}-acid was increased from 1% to 5%. The trend was consistent with the observations of the viscosity of these formulations, for which the viscosity was increased only slightly when the fatty acid concentration was increased from 0% to 1%, but had significant increases when the C_{18}-acid concentration was increased from 1% to 5%.

ACKNOWLEDGMENT

We gratefully thank the National Science Council, Republic of China, for the financial support of this project (NSC 82-0420-B016-088 and NSC 84-233 1-B016-023).

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