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Effect of Additives on the Diffusion of Ketoprofen Through Human Skin

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ABSTRACT

The influence of Carbopol® polymer, types C-934P and C-940, and the penetration enhancer oleic acid on transdermal permeation of ketoprofen through a full-thickness human skin was investigated. Ketoprofen patches were fabricated; and permeation parameters such as the flux, permeability coefficient, enhancement ratio, lag time, and partition coefficients were determined. The results indicated a maximum flux of 7.778 μg/cm²/hr from the patches made with C-934P when the oleic acid concentration was 35%. The enhancement ratio was 22.8. The maximum flux value for patches made from C-940 was obtained with 10% oleic acid. The corresponding enhancement ratio was 34.25. The results indicated that the concentration of oleic acid needed for maximum flux depends upon the type of Carbopol polymer selected for the study. Further, ketoprofen transdermal drug delivery systems can be fabricated to obtain a zero-order release through human skin.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are designed to support the passage of drug substances from the surface of skin, through its various layers, into the systemic circulation. Their advantages over conventional dosage forms include improved patient compliance, avoidance of gastric irritation and first-pass effect, and controlled therapeutic responses. Technologically, TDDS may be categorized as either monolithic or membrane controlled. The membrane-controlled TDDS are designed to contain a drug reservoir in the form of a gel, a rate-controlling membrane, a backing layer, adhesive layer, and a protective layer. Since Carbopol®

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polymers are known to form hydrophilic gels, diffusion-controlled TDDS can be prepared with these polymers (1,2).

Ketoprofen (KP), a nonsteroidal anti-inflammatory drug, can be used as a suitable model to develop TDDS because of its short half-life of about 2 hr and gastrointestinal side effects (3). However, because of its ionization at the pH of skin and high dose requirements of 150–300 mg daily, the flux values need considerable improvement before a successful TDDS can be developed. Preliminary experiments with KP gels containing penetration enhancers such as oleic acid (OA), linoleic acid, propylene glycol, and polyethylene glycol 400 indicated that OA provides a greater flux through a polymeric membrane in phosphate buffer (pH 7.4) when Franz diffusion cells were used. The present investigation reports the effect of two grades of Carbopols, C-934P and C-940, in KP gels containing 5% and 10% drug, and the effect of different levels of the permeation enhancer OA on the flux in phosphate buffer saline (PBS) through full-thickness cadaver skin in Franz diffusion cells.

MATERIALS AND METHODS

Materials

KP was purchased from Sigma Chemical Co. (USA); Carbopols® C-934P and C-940 were gifts from BF Goodrich Co. (USA); full-thickness cadaver skin was purchased from Ohio Skin Valley Inc. (USA); heat-sealable foil backing (Cotran™ No. 1009), ethylvinyl acetate film (Cotran No. 9702), and transfer adhesive (Cotran No. 9871) were provided by the 3M Company (USA). All other reagents were of analytical grade.

Preparation of Ketoprofen Gels

Powdered Carbopol® C-934P or C-940 2% w/w, was dispersed into a mixture of water and OA with 5/10% of KP, and stirred at 800–1000 rpm using an open blade impeller. In the case of control there was no enhancer. The dispersions were neutralized and made viscous by the addition of a 10% solution of Tris amino® dropwise. The gels were mixed until a uniform preparation was obtained and left overnight to remove the entrapped air.

Coating of the Gels

A level draw-down machine or bird applicator was stroked end to end to give a uniform coating of 10 g of the weighed gel on an evenly clamped strip of the polyester heat-sealable foil backing material. This coating was then allowed to air dry for 2–6 hr.

Fabrication of the Patches

Patches were made prior to the permeation experiments. The dried coat was layered with the ethylvinyl acetate film and the adhesive strip. These were then heat sealed using a custom die of 2.2 cm diameter. Several patches were die cut with a hammer. Each patch was checked for leakage and labeled. Content uniformity of the patches was determined.

Analytical Method

KP was assayed by a high-performance liquid chromatographic (HPLC) procedure employing a Novapak C-18, 15 cm × 3.9 mm column with a particle size of 4 μm. The equipment was an ISCO isocratic pump (model 2350) with an ISIS autosampler, an autoinjector with a valco valve, an ultraviolet (UV) detector (Waters, model 484) at 260 nm, and an integrator (Shimadzu, CR-501). The mobile phase was a 4:3:3 mixture of acetic acid, acetonitrile, and methanol, respectively. A flow rate of 1 ml/m and an injection volume of 10 μl were used. The detector sensitivity was set at 1 AUFS. The retention time of KP was found to be 2.36 min. The peak area was plotted against different drug concentrations to construct the standard curve. Linearity was observed over the concentration range of 0.1 to 2 μg/ml.

Release Studies

The human skin samples from the abdomen of an adult male were stored at −30°C as soon as they were received from the supplier. At the time of experiments, they were thawed and soaked in PBS for 30 min and carefully checked for macroscopic damage by using a magnifying glass. A square section of the skin (3 cm^2) was positioned between the cell half of a Franz cell with the stratum corneum side facing upward into the donor compartment. A clean TDDS was placed with the releasing surface in contact with the skin. After carefully mounting the patch, the cells were held together, water tight, using a clamp. The excess skin was trimmed using a scissor. The receptor was filled with PBS and maintained at an ambient temperature of 25°C. Samples were withdrawn at predetermined time intervals and

were replaced by fresh buffer solutions. All the samples were analyzed by the HPLC method described above.

Data Treatment

In the steady-state kinetics, Fick's second law of diffusion can be represented by the following equation:

$$Q/A = KLC_0 (D_t/L^2 - 1/6) \quad (1)$$

where Q represents the amount of drug appearing in the receptor compartment; A is the effective diffusion area; L is the thickness of the membrane/skin; C_0 is the drug concentration, which remains constant in the vehicle; D is the diffusion coefficient; and K is the partition coefficient. The flux, J, can be determined from the slope of the steady-state portion of Q/A versus time. The lag time values can be obtained from the x intercept of the slope at steady state. By Eq. (1), the flux can be expressed as:

$$J = C_0KD/L = C_0P_m \quad (2)$$

where P_m is the permeability coefficient. The enhancement ratio (ER) can be calculated by dividing the KP flux with enhancer with the KP flux without enhancer. The diffusion coefficients can be calculated by the equation $D = h^2/6t_L$ and the skin vehicle partition coefficient (K_m) can be calculated from the equation $K_m = P_mh/D$.

RESULTS AND DISCUSSION

The human skin permeation profiles of ketoprofen from patches containing different concentrations of OA and KP are shown for both C-934P and C-940 polymers in Fig. 1. The flux values, permeability coefficient, lag time, enhancement ratio, diffusion coefficient, and skin-vehicle partition coefficient were calculated from these profiles as explained under Data Treatment. The parameters are shown in Table 1.

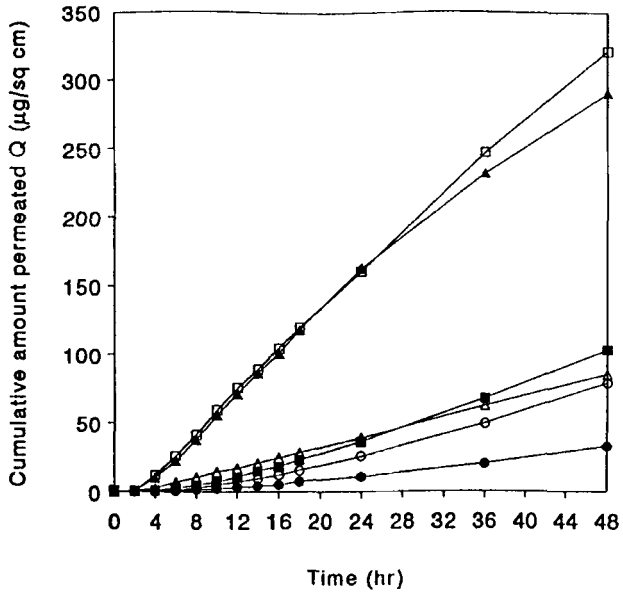

Figure 1. Cadaver skin permeation profiles of 5/10% ketoprofen (KP) patches of C-934P/C-940 with different concentrations of OA. With C-934P: ▲, 5% KP/35% OA; ●, 5% KP/10% OA; ■, 10% KP/10% OA. With C-940: Δ, 10% KP/10% OA; ○, 10% KP/35% OA; □, 5% KP/10% OA.

Table 1

Cadaver Skin Permeability Parameters of Ketoprofen (KP) from Various Patches

KP %	Type	O.A. concentration (%)	J	ER	T_L	P_m	D	K_m
5	934P	0	0.34	—	5	2.95×10^{-4}	4.08×10^{-5}	0.2524
10	934P	0	0.31	—	6.5	2.21×10^{-4}	3.14×10^{-5}	0.2461
5	934P	10	0.69	2.01	3.5	9.98×10^{-5}	5.83×10^{-5}	0.5985
5	934P	35	7.78	22.79	2.6	8.89×10^{-4}	7.85×10^{-5}	0.3961
10	934P	10	1.93	6.17	7.0	8.03×10^{-4}	2.92×10^{-5}	0.9635
5	940	0	0.21	—	21.25	3.95×10^{-5}	9.61×10^{-6}	0.1438
10	940	0	0.10	—	23.75	1.75×10^{-5}	4.29×10^{-4}	0.0143
5	940	10	7.09	34.25	2.5	3.87×10^{-4}	8.17×10^{-5}	0.1659
10	940	35	2.03	20.04	8.75	2.36×10^{-4}	2.33×10^{-5}	0.3533
10	940	10	1.86	18.40	2.1	3.20×10^{-4}	9.72×10^{-5}	0.1153

Note. OA = oleic acid; J = flux, in µg/cm²/hr; ER = enhancement ratio; T_L = lag time, in hr, P_m = permeability coefficient, in cm/hr, D = diffusion coefficient, in cm²/hr, K_m = partition coefficient.

The skin permeation experiments showed a linear relationship between Q and t, which indicates a zero-order rate of permeation. This relationship can be explained by Fick's law of diffusion under sink conditions, $Q = [(DAK)/h]C_d t$, where C_d is the concentration of drug in the donor side. The constancy of release and lack of specific trend in the change in flux with KP concentration indicates that there is no significant effect of KP concentration in the patches. From Table 1 it can be seen for KP patches made from C-934P that OA increased the flux as compared to the controls. The *ER* of OA by 5% KP patches reached a maximum at 35% and was reduced at 60%. This decrease in value may be due to the increased lipophilicity of the gel. Similar explanation was provided for the decreased permeation of piroxicam through rat skin (1). However, unlike the present investigation, Santoyo et al. (1) indicated the maximum flux at 5% OA levels. The difference may be attributed to the differences of the source of skin. In the case of C-940 patches, the maximum influence of OA was seen at 10% concentration. Results presented in Table 1 also suggests that OA exerts its effect by increasing both the D and K_m. This increase may be due to the interaction of OA with stratum corneum lipids, thereby disrupting the skin structure and increasing the fluidity (4). It can be concluded that OA considerably increases the flux value of KP, and that the concentration needed for maximum flux depends upon the type of Carbopol used. Further, the results obtained suggest the feasibility of designing a KP transdermal drug delivery system to provide a zero-order release through human skin.

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