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Percutaneous absorption of parachlorometaxylenol

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Abstract

The in vitro percutaneous absorption of *p*-chlorometaxylenol (PCMX), a topical antiseptic, was investigated using pig skin. Solubility studies in aqueous Tween 80 solutions were performed to develop a surfactant solubilized formulation. In vitro diffusion studies were carried out using side-by-side diffusion cells and pig skin. The diffusion of PCMX through pig skin followed a steady-state flux model. The total permeation coefficient of PCMX through pig skin was found to be $2.97 \times 10^{-4} \pm 9.61 \times 10^{-5}$ cm/min. It was observed that $18.1 \pm 0.98\%$ of the initial amount of PCMX was extracted from the skin.

Keywords: Percutaneous absorption; *p*-Chlorometaxylenol; Steady-state diffusion; Total permeability coefficient

1. Introduction

Percutaneous absorption is a complex process involving the diffusion of molecules through multiple layers of the skin and absorption to the systemic circulation. The diffusion of molecules through the lipophilic stratum corneum is related to the lipophilicity of the molecules, whereas the penetration of the molecules through aqueous epidermal and dermal regions of the skin is related to their aqueous solubility. For sparingly soluble molecules like *p*-chlorometaxylenol (PCMX), solubility can be increased by cosolvent solubilization or surfactant solubilization. However, surfactants and cosolvents may also act as skin penetration enhancers and may increase the diffusion rate through the lipophilic stratum corneum. In such formulations, percutaneous absorption may be solubility limited leading to depot formation. Therefore, it is necessary to determine whether there is any depot formation and/or association of PCMX in the skin. This is an important consideration in order to determine if potentially high toxic levels of PCMX may be reached on repeated use of preparations containing PCMX.

The objectives of the present study were to propose a model for in vitro percutaneous absorption of PCMX in pig skin, and to determine the amount extracted from the skin at the end of each experiment.

2. Experimental

PCMX was obtained from Dexide Inc. (Fort Worth, TX) and was recrystallized from ether

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before use. Tween 80 was purchased from ICI Ltd. Frozen pig skin (0.1–0.2 mm thick) was obtained from Genetic Laboratories and was thawed before use. Side-by-side diffusion cells (11 mm diameter) were obtained from Crown Glass Co. Ethanol, propylene glycol and sodium hydroxide were of analytical grade and were used as received. Distilled deionized water was used for making solutions.

2.1. Surfactant solubilization

3 ml each of aqueous Tween 80 solutions (1–5% w/w) were taken into separate stoppered glass vials. Excess PCMX was added to each vial. The vials were incubated by shaking in a water bath maintained at 25°C for 36 h. Equilibrium solubility concentrations at 25°C were determined at 280 nm using an ultraviolet spectrophotometer.

2.2. In vitro skin permeation

The in vitro skin permeation experiments were conducted using side-by-side diffusion cells and pig skin. 3 ml of a solution containing 2400 μg/ml of PCMX was placed in the donor cell and 3 ml of an isotonic phosphate buffer (0.05 M) was placed in the receptor cell. The donor solution was prepared by diluting 1 ml of a stock solution containing 4.8% (w/v) PCMX and 4.0% (w/w) Tween 80 to 20 ml with water. This yields a solution containing 2400 μg/ml of PCMX which is similar to the concentration obtained following the dilution indications in the label of a commercially available 4.8% w/v of PCMX solution (Dettol®) which states that the Dettol® solution be diluted 20 times prior to use. The circulating water in the jacketed cells was maintained at 37°C. 100-μl samples were withdrawn from the receptor cell at regular intervals, replacing with equal volume of buffer at each time. The experiment was stopped when the concentration of PCMX in the receptor solution approached about 38% of its saturation solubility. This value is the average value achieved at steady state. At the end of the experiment, the pig skin was removed, washed, and extracted with 0.1 N NaOH by homogenization and centrifugation. The membrane extract, the donor cell solution at the end of the experiment, and the periodic samples were analyzed using ultraviolet spectrophotometry at 280 nm.

3. Results and discussion

Percutaneous absorption of drugs from topical preparations is controlled by the rate of diffusion of the drug through multiple barriers of the skin and absorption into the systemic circulation. Permeability through the stratum corneum increases with solute lipophilicity, whereas permeability through the epidermal layers is proportional to water solubility of the permeant. For drugs whose aqueous solubility is very low, solubility can be increased by complexation, derivatization, cosolvent solubilization, or surfactant solubilization (Kreilgard et al., 1975; Repta and Hinchel, 1980; Yalkowsky, 1981; Gould and Goodman, 1983). The two most commonly used methods are using cosolvents or surfactants as solubilizing agents. Many cosolvents and surfactants may also act as skin penetration enhancers. The diffusion rates of such formulations of the sparingly soluble drugs will probably be greater in the lipophilic layers than in the aqueous layers of the skin. This may result in depot formation and/or association of the drug with the skin. In the present study using PCMX as a model drug, surfactant solubilization was used to develop formulations of PCMX. Diffusion studies through pig skin were performed using these formulations to characterize the in vitro percutaneous absorption of PCMX.

3.1. Surfactant solubilization

A formulation of PCMX was developed from the solubility studies in 1–5% w/w aqueous Tween 80 solutions. Fig. 1 illustrates the plot of solubility of PCMX versus wt% of Tween 80. From these experiments, the optimum concentration of Tween 80 necessary to formulate 5% w/v solution of PCMX was found to be 4% w/w aqueous Tween 80. A 5% w/v solution of PCMX is desirable because a commercially available solution (Detol®) contains 4.8% w/v of PCMX.

3.2. In vitro diffusion of PCMX

Franz (1978) proposed that diffusion of substances across a membrane sandwiched between two cells containing well stirred solutions may exhibit three different phases, a lag phase, a nonlinear phase, and a linear phase (steady-state flux phase). The lag phase is characterized by solute movement through the membrane but no molecules appear in the receptor solution. During the nonlinear phase the solute concentration in the receptor solution begins to rise, slowly at first, but at an increasing rate. In the linear phase the rate of increase in solute concentration in the receptor solution is constant. The rate of absorption or flux is constant at its maximum value and steady-state conditions prevail. In the present study, the low aqueous solubility of PCMX may result in deviation from perfect sink conditions in the receptor solution, and a pseudo-steady-state condition may exist, where the rate of loss of PCMX from the donor solution is the same as the rate of gain of the drug in the receptor solution. However, correction for the solubility differences in the individual phases should be accounted for in the development of the model. This was done by incorporating the factor K', which is the ratio of the saturation solubilities of PCMX in the donor and receptor solutions.

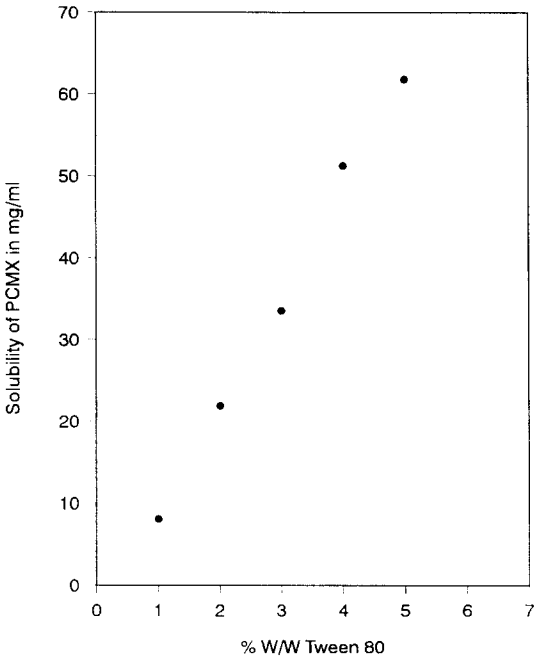

Fig. 1. Solubility plot of PCMX in aqueous Tween 80 solutions.

The following is the development of the equation for the steady state flux model which assumes a homogeneous membrane, and constant C_{Δ}, K (Yalkowsky, 1981) and C_R:

At steady state, the flux (J) is:

$$J = -1/A(\mathrm{d}Q_D/\mathrm{d}t) = 1/A(\mathrm{d}Q_R/\mathrm{d}t)$$

$$= P_T(C_D - K'C_R) = 1/A(V_R(\mathrm{d}C_R/\mathrm{d}t)) \quad (1)$$

where A represents the surface area of the membrane, $\mathrm{d}Q_D/\mathrm{d}t$ is the total or cumulative amount per time (rate) over the entire area for diffusion in the donor compartment, $\mathrm{d}Q_R/\mathrm{d}t$ denotes the total or cumulative amount per time (rate) over the entire area for diffusion in the receptor compartment, C_D is the concentration in the donor compartment, C_R represents the concentration in the receptor compartment, P_T is the total permeability coefficient of the membrane, V_R denotes the volume of the receptor compartment and, K' is the relative solubility of the drug in donor and receptor solutions. $K' = S_D/S_R$ where S_D and S_R are the saturation solubilities of PCMX in each solution.

If A_0 is the initial amount of the drug in the donor compartment at $t = 0$ and A_m is the amount in the membrane at steady state, then material balance equation at steady state is:

$$A_0 = V_D C_D + V_R C_R + A_m \quad (2)$$

Eq. 2 accounts for the material removed in sampling the receiver phase

Solving for C_D:

$$C_D = [((A_0 - A_m)/V_D) - (V_R C_R/V_D)] \quad (3)$$

Substituting Eq. 3 into Eq. 1 and solving for $\mathrm{d}C_R/\mathrm{d}t$ leads to Eq. 4:

$$\mathrm{d}C_R/\mathrm{d}t = (P_T A/V_R)[((A_0 - A_m)/V_D) - (K' + V_R/V_D)C_R)] \quad (4)$$

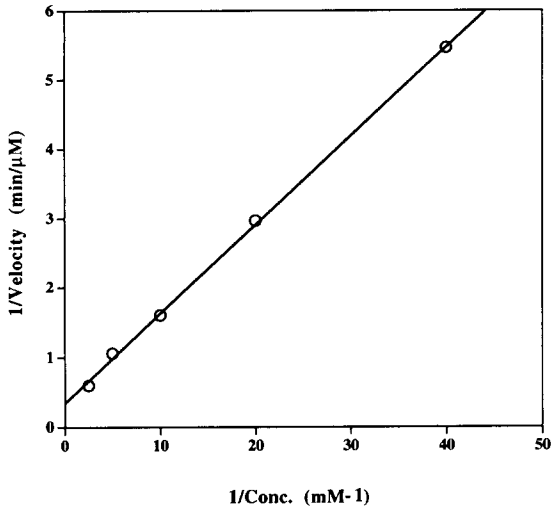

Fig. 2. Typical steady-state flux plot according to Eq. 6. Solid line represents nonlinear fit.

Let $a = (A_0 - A_m)/V_D$; $b = (K' + (V_R/V_D))$; $m = P_T A/V_R$, then:

$$dC_R/dt = m(a - bC_R) \quad (5)$$

Separating the variables and integrating from $C_R = 0$ to $C_R = C_R$ as t goes from 0 to t, leads to Eq. 6:

$$\ln((a - bC_R)/a) = -bmt \quad (6)$$

A plot of $\ln((a - bC_R)/a)$ vs t should give the estimate of the total permeability coefficient P_T.

Eq. 7 can be written in terms of C_R as:

$$C_R(t) = a/b(1 - \exp(-bmt)) \quad (7)$$

The parameters used in the diffusion model are presented in Table 1.

Fig. 2 represents a typical plot of the diffusion data according to Eq. 7. A linear relationship was observed between $\ln((a - bC_R)/a)$ and t. The estimate of the total permeability constant (P_T) was calculated from the slope of the linear regression line. The validity of the model was checked by fitting the experimental data to Eq. 7 using a non-linear regression program (Metzler and Weiner, 1992). Fig. 3 represents a typical non-linear fit according to Eq. 7. The estimate of the total permeability coefficient (P_T) was found to be $2.97 \times 10^{-4} \pm 9.61 \times 10^{-5}$ cm/min. The average amount of PCMX determined by extracting PCMX from the membrane was determined to be 1260 ± 130 μg. The average percent of initial dose of PCMX extracted from the membrane was found to be $18.1 \pm 0.98\%$.

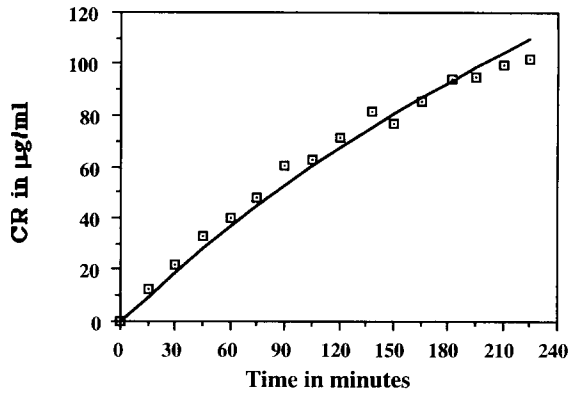

Fig. 3. Nonlin fit of the diflusion data according to Eq. 7. Solid line represents nonlinear fit.

4. Conclusions

In this study, *p*-chlorometaxylenol was used as a model drug to study percutaneous absorption of

Table 1
Parameters used in the diffusion model

Volume of the receptor solution	(V_R) = 3 ml
Volume of the donor solution	(V_D) = 3 ml
Solubility of PCMX in donor solution	(S_D) = 2.5 μg/ml
Solubility of PCMX in receptor solution	(S_R) = 0.33 μg/ml
Initial mount of PCMX in donor solution	(A_0) = 7,200 μg
Amount of PCMX in membrane at steady state	(A_M) = 1259.7 μg (129.9) [a]
Percent PCMX extracted from the membrane	18.1 (0.98) [a]
Total percent recovery of PCMX	96.2 (98) [a]

[a] Number in parentheses is the standard deviation; $n = 3$ experiments.

sparingly soluble drugs. The results of the in vitro diffusion studies of PCMX through pig skin using the surfactant solubilized formulation were fitted using a steady-state flux diffusion model. The experimental results indicated that $18.1 \pm 0.97\%$ of the initial amount of PCMX was extracted from the skin. The total permeability coefficient of PCMX through pig skin was found to be $2.97 \times 10^{-4} \pm 9.61 \times 10^{-5}$ cm/min. The fraction of PCMX associated with the skin is significant. Further studies are needed to determine if this amount of PCMX may cause local and/or systemic toxicity.

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