Effects of Polyoxypropylene 15 Stearyl Ether and Propylene Glycol on Percutaneous Penetration Rate of Diflorasone Diacetate

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Abstract □ Theoretical models for percutaneous penetration are described, and a diffusion apparatus useful in the evaluation of transport kinetics of drugs applied to skin is discussed. Experimental data are presented for: (*a*) the flux of diflorasone diacetate through hairless mouse skin, (*b*) the percutaneous penetration profile of propylene glycol, (*c*) the effects of vehicle concentrations of polyoxypropylene 15 stearyl ether and propylene glycol on the percutaneous flux of diflorasone diacetate, (*d*) skin-vehicle partition coefficients of diflorasone diacetate, (*e*) the solubility profile of diflorasone diacetate as a function of solvent concentration, and (*f*) the alteration of the skin's resistance to the penetration of diflorasone diacetate due to propylene glycol. Excess solvent in a vehicle caused a decrease in the percutaneous flux of diflorasone diacetate. Formulations containing 0.05 and 0.1% diflorasone diacetate had similar penetration rates when the solvent concentration was optimized for each percentage of diflorasone diacetate.

Keyphrases □ Diflorasone diacetate—percutaneous absorption rate, effect of polyoxypropylene 15 stearyl ether and propylene glycol □ Absorption, percutaneous—diflorasone diacetate, effect of polyoxypropylene 15 stearyl ether and propylene glycol □ Vehicles—polyoxypropylene 15 stearyl ether and propylene glycol, effect on percutaneous absorption rate of diflorasone diacetate □ Anti-inflammatory agents—diflorasone diacetate, percutaneous absorption rate, effect of polyoxypropylene 15 stearyl ether and propylene glycol

Various theoretical relationships (1–11) as well as experimental findings (12–27) concerning the diffusion of substances through heterogeneous barriers, such as skin, have been published. Three potential rate-determining barriers to percutaneous penetration are: (*a*) the dissolution rate of the drug in the vehicle, (*b*) the diffusion rate of solubilized drug through the vehicle to the skin, and (*c*) the permeation rate of drug through the stratum corneum. The slowest step determines the percutaneous penetration rate of the drug.

In the design of topical formulations, it is usually simple to eliminate the dissolution rate of the drug in a vehicle as a potential barrier through the incorporation of a suitable solvent. Factors such as vehicle ingredients, the chemical structure of the active component, and the condition of the skin determine if the rate-limiting step is in the vehicle diffusion layer or in permeation through the stratum corneum.

The importance of the vehicle in determining topical bioavailability is well documented (17–19, 21–23, 27). Nevertheless, vehicle design is often ignored in the biological evaluation of series of related compounds, in dose–response studies of a given drug, and, eventually, in marketed products. It is not generally recognized that the improper selection of the vehicle leads to biased biological results, because the chosen vehicle can have a different influence on each drug and even on different concentrations of a given drug.

In this study, the influence of propylene glycol in an aqueous base and polyoxypropylene 15 stearyl ether[1] in a mineral oil base on the percutaneous penetration rate of diflorasone diacetate (6α,9α-difluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-diacetate) was investigated.

Table I—Buffered Balanced Salt Solution

Ingredient	Percent (w/v)
Sodium chloride	0.8
Potassium chloride	0.04
Magnesium chloride	0.0075
Dibasic sodium phosphate	0.0154
Monobasic potassium phosphate	0.015
Glucose	0.11
Thimerosal	0.02
Sodium hydroxide *qs ad*	pH 7.0
Deionized water *qs ad*	100.00

THEORETICAL

The important physical factors in the penetration of a substance through a membrane are the concentration of dissolved drug in the vehicle, the partition coefficient of the drug between the skin and the vehicle, and the diffusion coefficients of the drug in the various barriers. The concentration of dissolved drug is important, because the percutaneous penetration rate is directly proportional to the concentration. The partition coefficient is an index of the relative affinity of the drug for the vehicle and the skin. The diffusion coefficient is an indication of the resistance to movement through a barrier. The relative magnitude of the

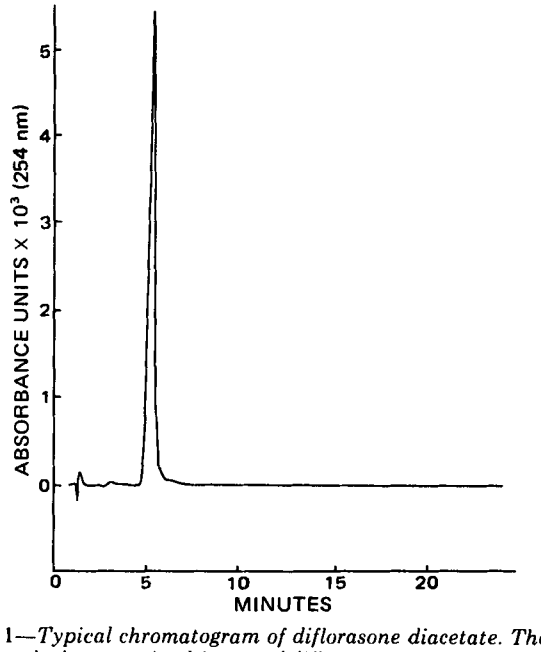

Figure 1—*Typical chromatogram of diflorasone diacetate. The acetonitrile solution contained 0.1 mg of diflorasone diacetate/ml.*

[1] ICI United States.

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Table II—^{3}H-Diflorasone Diacetate Topical Formulations [a]

Ingredient	Formulations												
	1	2	3	4	5	6	7	8	9	10	11	12	13
^{3}H-Diflorasone diacetate	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.10
Propylene glycol	10.0	30.0	50.0	70.0	99.95	—	—	—	—	—	—	—	—
Polyoxypropylene 15 stearyl ether	—	—	—	—	—	—	5	15	20	30	40	60	40
Mineral oil (85 viscosity)	—	—	—	—	—	99.95	94.95	84.95	79.95	69.95	59.95	39.95	59.95
Deionized water	89.95	69.95	49.95	29.95	—	—	—	—	—	—	—	—	—

[a] Values are percent (w/w).

diffusion coefficients in the vehicle and skin determines if penetration is rate limited by release from the vehicle or by the skin.

Relationships of these important parameters to drug transport were discussed previously (10). The influence of diffusion layer resistance and membrane resistance on the flux-determining properties of barrier and solute was quantified (10). The resistance to transport of a solute across a silicone membrane was shown to be not only within the membrane but also within the regions adjacent to its surface. The conditions needed for "membrane control of flux" and "diffusion layer control of flux" were explained (10).

The data obtained for the *in vitro* percutaneous penetration kinetics of diflorasone diacetate in vehicles consisting of propylene glycol–water and polyoxypropylene 15 stearyl ether–mineral oil suggest that the skin is the rate-determining barrier for this compound. In this case, the appropriate relationship is represented by:

$$\frac{-dC_F}{dt} = \frac{AK_sC_FD_s}{V_Fh_s} \qquad \text{(Eq. 1)}$$

where:

A = surface area of application (square centimeters)
C_F = concentration of dissolved diflorasone diacetate in the vehicle (micrograms per cubic centimeters)
D_s = diffusion coefficient of diflorasone diacetate through the skin (square centimeters per second)
h_s = thickness of the skin barrier (centimeters)
K_s = diflorasone diacetate skin–vehicle partition coefficient
V_F = volume of formulation applied (cubic centimeters)

The thickness of the skin barrier and the diffusion coefficient are combined and defined as a resistance, $R_s = h_s/D_s$. The resistance has units of time per length. Equation 1 can be simplified to:

$$\frac{-dC_F}{dt} = \frac{AK_sC_F}{V_FR_s} \qquad \text{(Eq. 2)}$$

The concentration of dissolved diflorasone diacetate, C_F, the partition coefficient, K_s, and, possibly, the resistance, R_s, are influenced by the quantity of solvent in a given vehicle. Under certain conditions, the solubility of a drug in a cosolvent system can be represented by the following expression (10):

$$C_F = C_0e^{\alpha(fs)} \qquad \text{(Eq. 3)}$$

where C_0 is the solubility of the drug in the formulation when the weight fraction of the solvent is zero, α is a constant, and fs is the weight fraction of the solvent.

In a similar manner, the partition coefficient of a drug between the skin and the vehicle can be expressed as:

$$K_s = K_{0}e^{-\beta(fs)} \qquad \text{(Eq. 4)}$$

where K_0 is the partition coefficient of the drug between the skin and the vehicle when the weight fraction of the solvent is zero and β is a constant. Inserting Eqs. 3 and 4 into Eq. 2 leads to the following expression:

$$\frac{-dC_F}{dt} = \frac{A[K_0e^{-\beta(fs)}][C_0e^{\alpha(fs)}]}{V_FR_s} \qquad \text{(Eq. 5)}$$

During the steady-state period of penetration, the following relationship is valid:

$$V_R\frac{dC_R}{dt} = \frac{-V_F\,dC_F}{dt} \qquad \text{(Eq. 6)}$$

where C_R is the concentration of diflorasone diacetate in the receptor compartment of the diffusion apparatus and V_R is the volume of the receptor compartment.

Equation 6 states that the amount of diflorasone diacetate leaving the vehicle per unit time is equal to the amount entering the receptor solution of the diffusion apparatus. With this relationship, Eq. 5 can be written as:

$$V_R\frac{dC_R}{dt} = \frac{a[K_0e^{-\beta(fs)}][C_0e^{\alpha(fs)}]}{R_s} \qquad \text{(Eq. 7)}$$

Integration of Eq. 7 yields:

$$Q_R = \frac{A}{R_s}[K_0e^{-\beta(fs)}][C_0e^{\alpha(fs)}]t \qquad \text{(Eq. 8)}$$

where Q_R is the amount of diflorasone diacetate in the receptor compartment at time t. Equation 8 predicts that the addition of a solvent to a formulation could increase, decrease, or have no effect on the amount of drug diffusing through the skin. The result depends on the magnitudes of α and β and whether or not the drug solution is saturated or unsaturated.

EXPERIMENTAL

Diflorasone Diacetate Solubility—The solubility of diflorasone diacetate was determined in mixtures of polyoxypropylene 15 stearyl ether–mineral oil and propylene glycol–water at 23°. A reversed-phase high-performance liquid chromatographic (HPLC) procedure was used to analyze diflorasone diacetate in these mixtures.

A moderate excess of diflorasone diacetate and 10 ml of the appropriate mixtures were placed in 20-ml vials and shaken for 1 week with a wrist-action shaker. The samples were then filtered, and an appropriate amount of the filtrate was transferred to another vial, extracted, and analyzed by HPLC. The extraction system for the polyoxypropylene 15 stearyl ether–mineral oil mixtures was equal volumes of acetonitrile and hexane. It was not necessary to extract the diflorasone diacetate from the propylene glycol–water mixtures. These samples were diluted with acetonitrile[2] and analyzed.

Extraction Mixture—Acetonitrile and hexane[3], each saturated with the other, were used to extract diflorasone diacetate from the polyoxypropylene 15 stearyl ether–mineral oil mixtures.

Standard Solutions—Standard solutions containing 0.0002, 0.001, 0.002, 0.01, 0.1, and 0.5 mg of diflorasone diacetate/ml of acetonitrile were used to generate a calibration curve. The slope obtained with linear regression of the absorbance data was 0.057 (±0.00012 *SD*).

Sample Solution—An appropriate amount of the diflorasone diacetate polyoxypropylene 15 stearyl ether–mineral oil solution was weighed accurately into 20-ml vials, and 7.0 ml each of acetonitrile and hexane were added. The mixture was shaken for 20 min and centrifuged at 2000 rpm for 15 min. After centrifugation, a portion of the acetonitrile layer was transferred to another vial and held for assay. The diflorasone diacetate propylene glycol–water solutions were filtered, and an appropriate weight of the solubility solution was diluted with acetonitrile and held for assay.

HPLC Procedure—A high-performance liquid chromatograph[4], operated at ambient temperature, was equipped with a UV detector[5] for monitoring the column effluent at 254 nm. The stainless steel column, 30 cm × 3.9 mm (i.d.), was packed with a bonded-phase nonpolar surface[6]. A 20-μl loop injection valve[7] was used to introduce samples into the chromatographic system.

Mobile Phase—The mobile phase, deionized water–acetonitrile (45:55 v/v), was degassed prior to use.

Chromatography—A flow rate of 2.0 ml/min and a chart speed of 0.051 cm/min were used. The detector sensitivity was adjusted as needed

[2] Distilled in glass, Burdick and Jackson.
[3] Spectroquality, Matheson, Coleman & Bell.
[4] Altex model 110 solvent pump.
[5] Altex model 153.
[6] μBondapak C_{18}, Waters Associates.
[7] Rheodyne model 70-10.

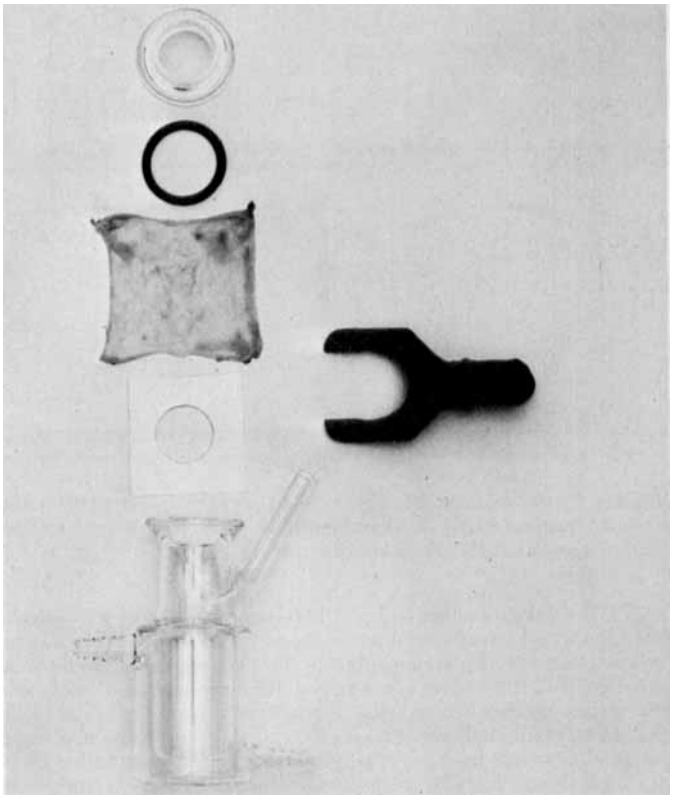

Figure 2—*Component parts of the percutaneous diffusion apparatus (bottom to top): the receptor compartment, waxed film gasket, clamp, hairless mouse skin section, rubber "O" ring, and donor compartment.*

for each sample. Aliquots of 20 μl of the sample solutions and standard solutions were injected, the absorbance (AU) was measured at 254 nm, and the solubility of diflorasone diacetate was calculated using:

$$S_{d.d.} = \frac{AU \times D.F.}{0.057 \times W} \qquad \text{(Eq. 9)}$$

where $S_{d.d.}$ is the solubility of diflorasone diacetate in milligrams per gram, $D.F.$ is the dilution factor, 0.057 is the slope of the calibration curve, and W is sample weight (grams) of solubility solution. A typical chromatogram is shown in Fig. 1.

Partition Coefficient Determination—The partition coefficients between hairless mouse skin and the various vehicles were determined as follows. Skin sections, 1.35 cm in diameter, were placed in 20.0-ml vials and weighed. Then 10 ml of each vehicle containing ^{3}H-diflorasone diacetate[8] was added. The vials were shaken with a wrist-action shaker for 3 and 5 days, and the skin sections and vehicles were assayed for ^{3}H-diflorasone diacetate. The partition coefficients, K_s, were calculated using:

$$K_s = \frac{\text{dpm/mg of skin}}{\text{dpm/mg of vehicle}} \qquad \text{(Eq. 10)}$$

Equilibrium was reached in 3 days.

Percutaneous Transport Procedures—*Preparation of Hairless Mouse Skin*—Female hairless mice[9] were sacrificed, and the skin was removed just prior to use. The skin sections were assembled in the percutaneous diffusion apparatus shown in Figs. 2 and 3. The following procedure was used to assemble the percutaneous diffusion apparatus.

The lower portion (receptor compartment) of the glass diffusion cell was clamped over the magnetic stirring motors and connected to the water bath set at 37°. The degassed, buffered balanced salt solution (Table I) was added, and a waxed film[10] gasket was placed on the top of the receptor compartment. The skin section was placed over the gasket (care was taken to exclude air bubbles under the skin). Then a rubber "O" ring, coated with white wax, was placed over the skin section. The upper

[8] Synthesized by R. S. P. Hsi, The Upjohn Co.
[9] Jackson Laboratories, Bar Harbor, Me.
[10] Parafilm, American Can Co.

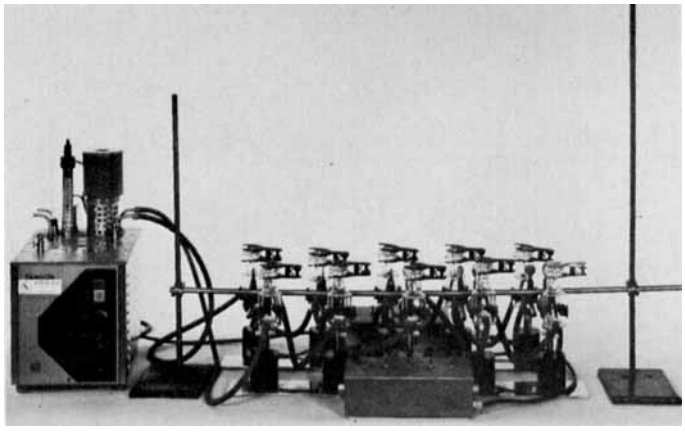

Figure 3—*Assembled percutaneous diffusion apparatus. Included are a water bath, 10 diffusion cells, and a magnetic stirrer.*

portion (donor compartment) of the glass diffusion cell was clamped in place, an additional 3 ml of buffered balanced salt solution was added through the side arm, and 1.0 ml of formulation was applied to the skin.

Receptor Compartment Analysis—At various times, 2.0 ml of the receptor solution was withdrawn and placed in scintillation vials. Scintillation cocktail[11], 15 ml, was added, and the samples were assayed using a liquid scintillation spectrometer[12]. Quench corrections were made with a calibration curve.

^{3}H-Diflorasone Diacetate Formulations—The formulations used in the transport experiments are shown in Table II.

RESULTS

An attempt was made to optimize diflorasone diacetate release from aqueous and lipid vehicle systems. Propylene glycol was selected as the

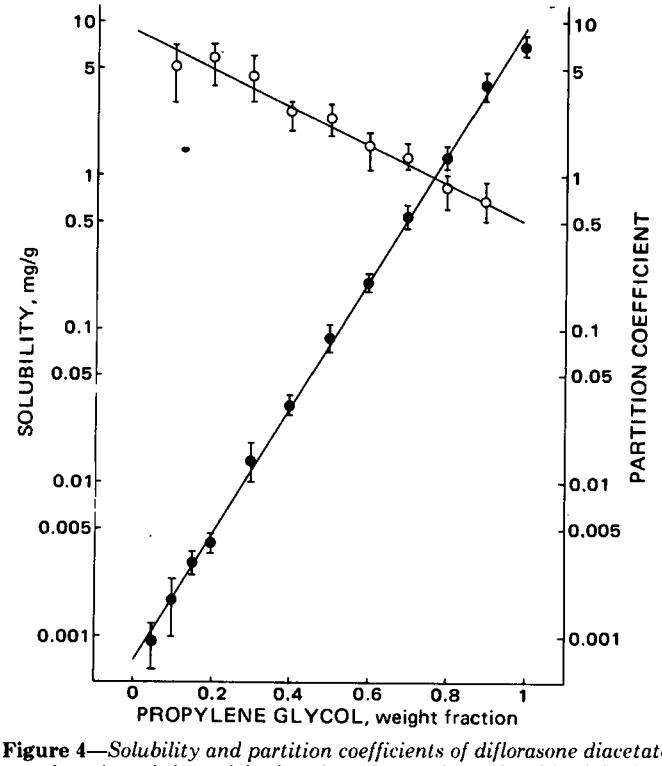

Figure 4—*Solubility and partition coefficients of diflorasone diacetate as a function of the weight fraction of propylene glycol in deionized water; average (± SD) of four determinations. Key: ●, solubility; and ○, partition coefficient.*

[11] PCS, Amersham/Searle.
[12] Searle Mark III.

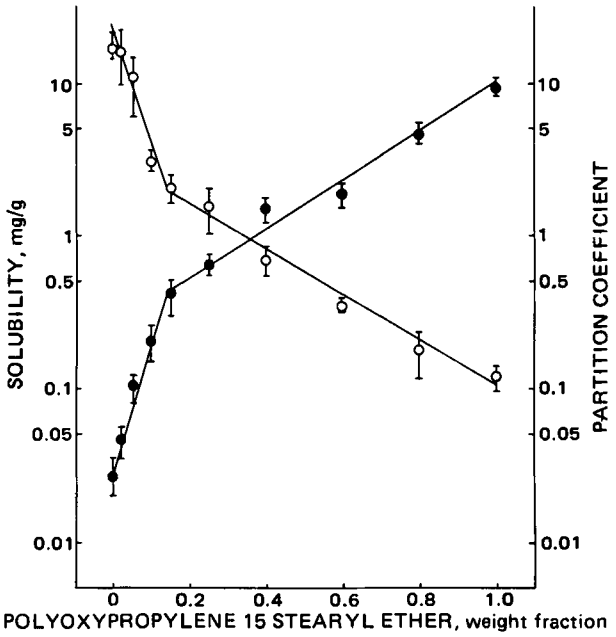

Figure 5—*Solubility and partition coefficients of diflorasone diacetate as a function of the weight fraction of polyoxypropylene 15 stearyl ether in mineral oil (85 viscosity); average* (± SD) *of four determinations. Key:* ●, *solubility; and* ○, *partition coefficient.*

aqueous miscible solvent since it is a satisfactory solvent for steroids and is commonly used in many topical steroid formulations. A fairly new solvent, polyoxypropylene 15 stearyl ether, also was selected because of its good solvent capacity for diflorasone diacetate. It is a nonirritating emollient miscible with mineral oil.

Solubility and Partition Coefficients of Diflorasone Diacetate in Propylene Glycol–Water Mixtures—The solubility and partition coefficients (defined by Eq. 10) of diflorasone diacetate, as a function of the weight fraction of propylene glycol, are shown in Fig. 4. The increase in solubility and the decrease in the partition coefficient as the weight fraction of propylene glycol is increased can be described by Eqs. 3 and 4, respectively. From these data, α and β were calculated to be 9.4 and 2.9, respectively. Since α is larger than β, Eq. 8 predicts that an increase in the percutaneous penetration rate of diflorasone diacetate should result when the weight fraction of propylene glycol is increased, provided a saturated solution is maintained.

Solubility and Partition Coefficients of Diflorasone Diacetate in Polyoxypropylene 15 Stearyl Ether–Mineral Oil Mixtures—The solubility and partition coefficients of diflorasone diacetate in the polyoxypropylene 15 stearyl ether–mineral oil solvent systems are shown in Fig. 5. Both the solubility and partition coefficient curves are biphasic with the transition at a point where the weight fraction of polyoxypropylene 15 stearyl ether is approximately 0.15. The reason for this biphasic solubility and partitioning is not known. However, each portion of these curves can be described by Eqs. 3 and 4. Since there are two slopes each for the solubility and partition coefficient, there are two α and two β values. For weight fractions of polyoxypropylene 15 stearyl ether up to 0.15, α and β are 20 and 17, respectively; for weight fractions larger than 0.15, α and β are 3.7 and 3.5, respectively.

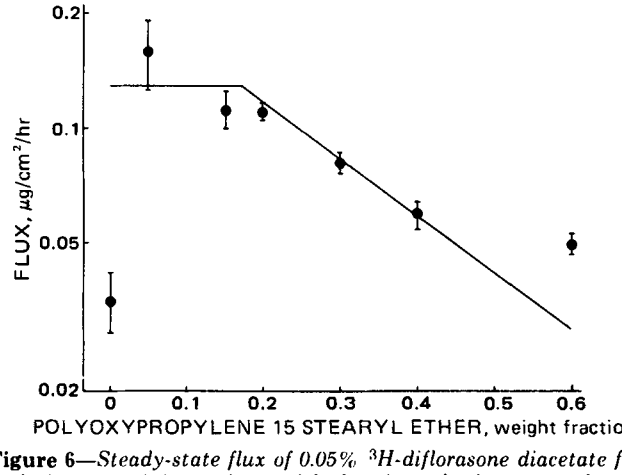

Figure 6—*Steady-state flux of 0.05% ^{3}H-diflorasone diacetate formulations containing various weight fractions of polyoxypropylene 15 stearyl ether in mineral oil (85 viscosity). The solid line was generated using Eq. 8. The points are experimental values obtained from penetration studies.*

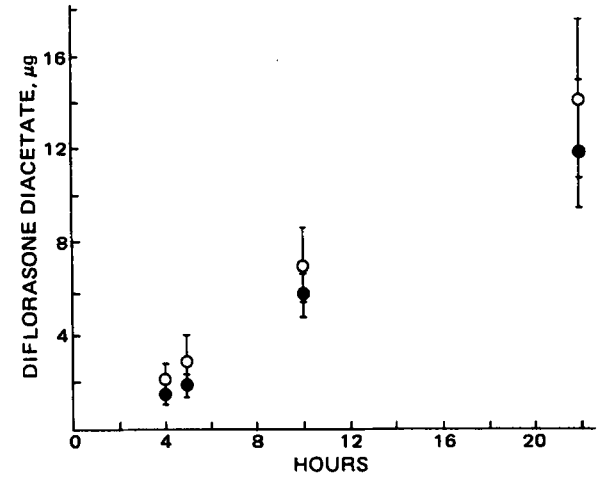

Figure 7—*Cumulative amount of ^{3}H-diflorasone diacetate diffusing through hairless mouse skin as a function of time. Key:* ●, *0.05% (Formula 9); and* ○, *0.1% (Formula 13).*

Since α and β are comparable in both cases, the percutaneous penetration rate of diflorasone diacetate should be independent of the weight fraction of polyoxypropylene 15 stearyl ether, as predicted by Eq. 8. This hypothesis should be true, provided a saturated solution of diflorasone diacetate is maintained and the solvent does not affect the barrier properties of the skin. An excess of solvent should result in a decreased flux since the partition coefficient declines while the concentration of dissolved drug remains constant.

Percutaneous Penetration of Diflorasone Diacetate Formulated in Polyoxypropylene 15 Stearyl Ether–Mineral Oil—The steady-state flux of ^{3}H-diflorasone diacetate as a function of the weight fraction of polyoxypropylene 15 stearyl ether is shown in Fig. 6. The solid line was generated using the theoretical Eq. 8. Experimental values for the solubility and partition coefficients and a skin resistance of 6666 hr/cm were

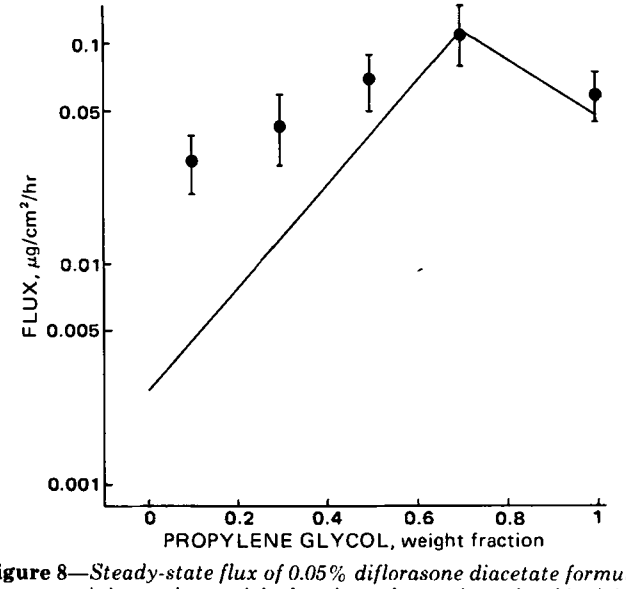

Figure 8—*Steady-state flux of 0.05% diflorasone diacetate formulations containing various weight fractions of propylene glycol in deionized water. The solid line was generated using Eq. 8. The points are experimental values obtained from penetration studies.*

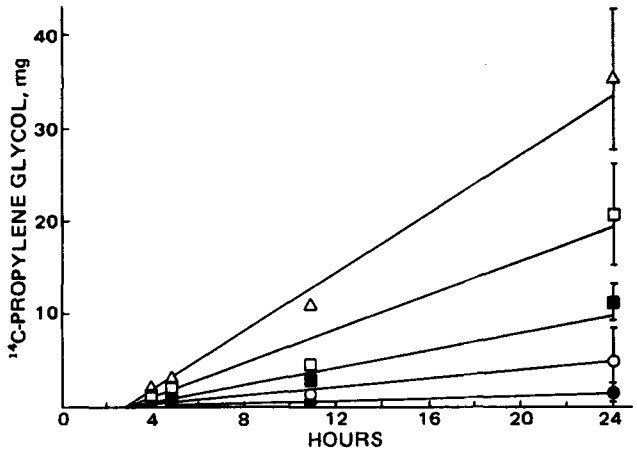

Figure 9—*Cumulative amount of ^{14}C-propylene glycol diffusing through hairless mouse skin as a function of time. Key (^{14}C-propylene glycol in deionized water): ●, 10%; ○, 30%; ■, 50%; □, 70%; and △, 90%.*

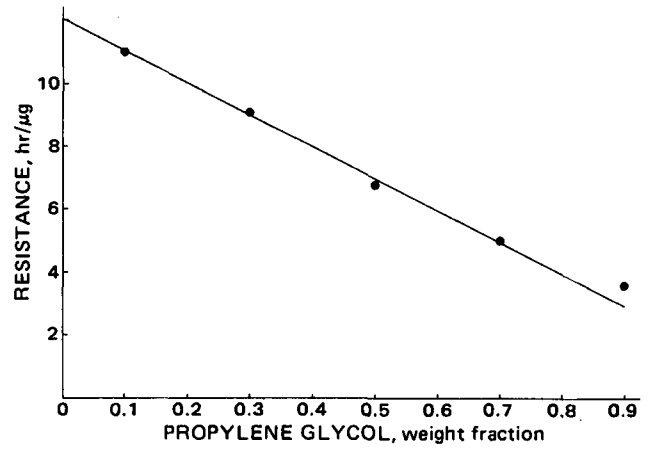

Figure 10—*Resistance of hairless mouse skin to the penetration of ^{14}C-propylene glycol as a function of the weight fraction ^{14}C-propylene glycol in deionized water.*

used in the calculations. The data points are the experimental values obtained from the penetration studies.

The low value obtained in the vehicle without polyoxypropylene 15 stearyl ether could be attributable to the low solubility and slow dissolution rate of diflorasone diacetate in mineral oil. The other data points agree with the theoretical line. The decrease in flux of the 0.05% diflorasone diacetate solutions obtained for vehicles containing greater than 0.15 weight fraction of polyoxypropylene 15 stearyl ether is expected. This result occurs because the partition coefficient is reduced while the concentration of dissolved diflorasone diacetate remains constant.

The theoretical model also predicts that the steady-state flux will be maintained as long as saturation of the drug in the vehicle exists. Therefore, increasing the amount of diflorasone diacetate in a formulation should not result in a greater steady-state flux. This will be true for a given period of time if the drug and solvent do not affect the skin barrier and if the vehicle is saturated with drug since the skin is the rate-limiting barrier. Figure 7 shows the comparison of two percentages of diflorasone diacetate in the polyoxypropylene 15 stearyl ether–mineral oil system. The steady-state penetration rates obtained with 0.05 and 0.1% diflorasone diacetate were similar. These data suggest that no additional therapeutic benefit will result from the use of a 0.1% formulation.

Percutaneous Penetration of Diflorasone Diacetate Formulated in Propylene Glycol–Water Mixture—The influence of propylene glycol on the penetration rate of 0.05% diflorasone diacetate formulations is shown in Fig. 8. The solid line was generated as described previously. The penetration rate should increase as the propylene glycol weight fraction is increased to 0.7 and should decrease beyond this point. The experimental values are greater than the predicted values according to the theoretical model. One feasible explanation for the deviation is supersaturation, which would result in larger penetration rates. These formulations were prepared by dissolving the diflorasone diacetate in propylene glycol and then adding water. Up to 5 days was required to reach equilibrium solubility when this method was used.

Differential scanning calorimetry of diflorasone diacetate crystals obtained from propylene glycol–water mixtures indicated a change in the polymorphic form, which might explain the prolonged equilibration time. These high experimental values could also be attributed to the loss of some water from the vehicle due to evaporation. Even though the donor compartment was sealed in these experiments, some water could evaporate and condense on the stopper, which would cause an increase in the weight fraction of solvent and result in a larger flux.

Percutaneous Penetration of ^{14}C-Propylene Glycol—Figure 9 shows the percutaneous penetration data of ^{14}C-propylene glycol[13] through hairless mouse skin. Propylene glycol penetrated the skin rather easily, and the skin resistance to propylene glycol decreased as the weight fraction of propylene glycol increased (Fig. 10). Further evidence that propylene glycol decreases the diffusional resistance of skin was obtained by pretreating skin sections in propylene glycol for 18 hr (Fig. 11). The skin sections treated with propylene glycol were very dry and without supple characteristics. The penetration rate of diflorasone diacetate through the propylene glycol-pretreated skin was twice the rate without pretreatment.

[13] ICN Isotope and Nuclear Division.

SUMMARY

An important factor affecting topical bioavailability is the release rate of the drug from the vehicle. The development of topical formulations should include the use of theoretical models and appropriate experimental procedures to quantify drug–vehicle interactions and topical bioavailability. This procedure should be used in early biological screening as well as in the design of final marketed products. In biological tests of topical drugs, the vehicle and its effects on the release rates of test compounds must be considered to avoid biased results due to vehicle–drug interactions.

The data presented demonstrate the effects of two solvents on the *in vitro* penetration rate of diflorasone diacetate. Incorporation of too much solvent in the vehicle resulted in a decreased penetration rate. In the polyoxypropylene 15 stearyl ether–mineral oil systems, it was possible to obtain similar penetration rates with 0.05 and 0.1% diflorasone diacetate formulations by selection of the optimum weight fraction of the solvent for the given percentage of diflorasone diacetate. Selection of a common vehicle with too high a solvent composition would have given a larger flux for the 0.1% formulation. Another observation was that the steady-state flux for both concentrations was maintained during the time

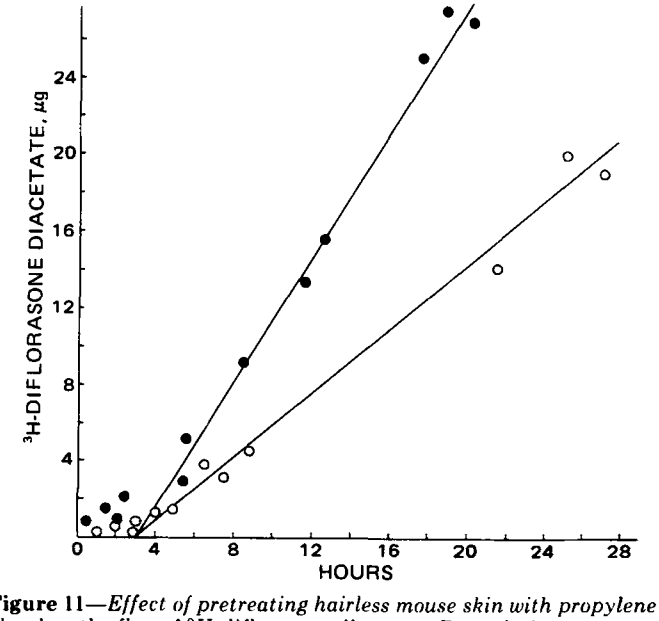

Figure 11—*Effect of pretreating hairless mouse skin with propylene glycol on the flux of ^{3}H-diflorasone diacetate. Formulation 8 was applied to the skin sections. Key: ●, skin pretreated with propylene glycol; and ○, untreated skin.*

of the experiment (approximately 24 hr).

Based on these results, one could hypothesize that one daily application would be sufficient for the optimal therapeutic effect, provided the formulation is not washed or rubbed off by the patient. The results also show that the formulation with 0.1% diflorasone diacetate offers no therapeutic advantage over the 0.05% formulation. Recent clinical studies comparing the therapeutic benefit of diflorasone diacetate 0.05 and 0.1% ointments (28) support this hypothesis.

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High-Pressure Liquid Chromatographic Assay of Benzoyl Peroxide in Dermatological Gels and Lotions

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Abstract □ A high-pressure liquid chromatographic method for the assay of benzoyl peroxide in dermatological preparations is described. Degradation products such as benzoic acid and perbenzoic acid do not interfere. The method is simple, precise, accurate, and stability indicating.

Keyphrases □ Benzoyl peroxide—high-pressure liquid chromatographic analysis in pharmaceutical preparations □ High-pressure liquid chromatography—analysis, benzoyl peroxide in pharmaceutical preparations □ Keratolytics—benzoyl peroxide, high-pressure liquid chromatographic analysis in pharmaceutical preparations

Benzoyl peroxide is inherently a very reactive compound, and its chemical stability has been studied extensively. Depending on the experimental conditions (temperature, pH, solvent, *etc.*), the degradation of benzoyl peroxide may lead to benzoic acid, biphenyl, phenyl benzoate, benzene, and carbon dioxide. In alcoholic solutions, the degradation products were carbon dioxide, benzoic acid, and alcohol esters of benzoic acid (1). In pharmaceutical lotions, benzoic acid was the significant product (2).

BACKGROUND

The existing stability assays for benzoyl peroxide in pharmaceutical preparations have used spectrophotometric, iodometric, polarographic, and TLC techniques (3–6). Controversial claims of superiority of one method over the others have been made. Gruber and Klein (4) reported that the polarographic method is superior to the spectrophotometric method which, in turn, is much better than the iodometric method. Simmons *et al.* (6) compared the iodometric method with a combination TLC–spectrophotometric method and reported good agreement in assay results, suggesting that the iodometric method is stability indicating.

Daly *et al.* (5) reported "fair agreement" between the assay results by the iodometric method and a combination TLC–iodometric method. Furthermore, the results were reported to be lower than the corresponding assay results by the iodometric and spectrophotometric methods of Gruber and Klein (4). From these observations, Daly *et al.* (5) concluded that the described iodometric method is a stability-indicating procedure. This iodometric procedure has been accepted as the USP method for benzoyl peroxide in lotions (7).

In evaluating the stability-indicating nature of the methods, one or both of the following criteria were used:

1. The results obtained by the method should agree with those obtained by a separate and inherently stability-indicating "reference" method (*e.g.*, chromatographic methods).
2. The results obtained by the method should be lower than those obtained by other methods.

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