Significance of Vehicle Composition II: Prediction of Optimal Vehicle Composition

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Abstract □ Terms from the flux equation describing the passive transport of two steroids across a membrane were shown to be useful in predicting the optimal vehicle composition of gels. Calculations based on the increase in lag time for steady-state penetration with vehicle composition were made to explore the possible effects of vehicle composition on barrier permeability and drug binding within the barrier. Additional penetration studies were done to determine solvent effects on barrier permeability. These combined results indicated that the variation in barrier permeability was associated with a vehicle effect rather than binding.

Keyphrases □ Permeability, membrane—propylene glycol solvent effects □ Membrane permeability, fluocinolone acetonide and fluocinonide topical gels—predicting optimal vehicle composition □ Topical gels—optimal vehicle composition, theoretical □ Vehicle composition, membrane permeability—steroidal topical gels

A previous report (1) demonstrated that, for normal skin, the clinical efficacy of a series of topical gels containing fluocinolone acetonide or its 21-acetate ester (fluocinonide) was directly dependent on the ability of the drug to penetrate the stratum corneum. In turn, the penetrability was shown to be highly dependent upon the composition of the propylene glycol–water gels studied. This report: (*a*) illustrates the predictability of vehicle efficacy based on the physical parameters used to describe the diffusion of drugs across the stratum corneum, and (*b*) explores the possible effects of vehicle composition on barrier permeability and drug binding within the barrier.

Applicable theoretical considerations were described in the first paper of this series (1), where the terms in the following two equations were defined:

$$\frac{dQ}{dt} = \frac{D(PC)C_v}{h} \qquad \text{(Eq. 1)}$$

$$L = \frac{h^2}{6D} \qquad \text{(Eq. 2)}$$

Equation 1 suggests that the ability of a drug to penetrate the stratum corneum can be predicted by the term $D(PC)C_v$. If Eq. 2 is applicable, the term $(PC)C_v/L$ is equally useful. If barrier permeability is not altered by vehicle composition, then penetration should be proportional to $(PC)C_v$ for various vehicle compositions.

Equation 2 is valid only if the penetrant does not bind to components of the barrier. If binding occurs, L can be defined approximately by Eq. 3 (2):

$$L = \frac{h^2}{4D} + \frac{h^2 A_b}{2D(PC)C_v} \qquad \text{(Eq. 3)}$$

where A_b is the amount of drug bound per unit volume of barrier. Equation 3 gives reasonable estimates of L only when the degree of binding is significant. If the term A_b is small, however, Eq. 3 gives $L \simeq h^2/4D$, which differs substantially from the theoretical value $(L = h^2/6D)$.

Table I—Individual and Average Steady-State Penetration Rate(s) (mg./cm.^{2}/hr. × 10^6)[a]

Propylene Glycol, %	1	2	3	4	Av. ± $\bar{\sigma}_x$
Fluocinolone Acetonide[b]					
5	38.3	4.3	23.4	31.2	24.3 ± 7.3
10	19.2	2.8	19.1	27.0	17.0 ± 5.1
15	12.8	3.8	22.7	—	13.1 ± 5.5
20	14.9	2.1	24.1	22.7	16.0 ± 5.0
25	27.0	4.2	32.6	28.4	23.1 ± 6.4
30	26.2	3.5	34.8	39.7	26.1 ± 8.0
50	17.0	3.6	18.4	9.2	12.1 ± 3.5
100	12.1	1.8	5.0	2.8	5.4 ± 4.3
Fluocinonide[b]					
40	5.0	1.0	3.1	2.8	3.0 ± 0.8
60	7.8	1.4	6.5	2.5	4.6 ± 1.5
70	10.6	2.3	7.2	4.3	6.1 ± 1.8
75	31.9	5.4	15.4	6.2	14.7 ± 6.2
80	27.0	6.6	20.0	3.1	14.2 ± 5.6
90	27.7	4.5	7.7	4.3	11.1 ± 5.6
100	19.9	5.7	6.5	2.8	8.7 ± 3.8

[a] Whole abdominal skin, room temperature. [b] The standard errors, $\bar{\sigma}_x$, give the variation between skins and do not necessarily reflect the significance of differences for penetration rates at different compositions. For this reason, standard errors are not indicated in Fig. 1.

EXPERIMENTAL

The experimental results pertaining to this work were reported previously (1).

RESULTS AND DISCUSSION

The steady-state penetration rates for 0.025% fluocinolone acetonide and 0.025% fluocinonide in various propylene glycol–water gels are given in Table I. The average rates are also given in Table I. Each set of gels was studied in four different abdominal human skin sections. A plot of average penetration rate *versus* percent glycol is given in Fig. 1 to show the dependence of penetrability on vehicle composition[1]. Figure 1 includes three data points for fluocinonide penetration (1, 5, and 10% glycol) which are not included in Table I. These data were obtained on a fifth skin specimen, and the data were normalized to make the rates comparable[2].

The data in Table I were analyzed statistically *via* a repeated measurement design (3) in the same manner as in the first paper of this series (1). Significant differences were shown for the penetration data for both fluocinolone acetonide ($p < 0.01$) and fluocinonide ($p < 0.05$). The maximum penetration rate for fluocinolone acetonide (30% gel) was shown to be significantly different at the 5% level from the 15, 50, and 100% gels. For fluocinonide, that

[1] As may be ascertained from Table I, similar profiles can be obtained utilizing data from any single experimental set.

[2] The steady-state penetration rates for these three gels were 2.4, 1.2, and 0.9 mg. cm.$^{-2}$ hr.$^{-1}$ (× 10^{-6}) for the 1, 5, and 10% gels, respectively. To make these data comparable to those for the other compositions, the data for four controls (40, 70, 75, and 100% gels) on the same single specimen were compared to the average values obtained for the four other specimens at these gel compositions. Proportionality factors were calculated at each of the four compositions, and the average was used to normalize the single values for the 1, 5, and 10% gels. The resultant normalized values were 3.5, 1.7, and 1.4 mg. cm.$^{-2}$ hr.$^{-1}$ (× 10^{-6}) for the 1, 5, and 10% gels, respectively.

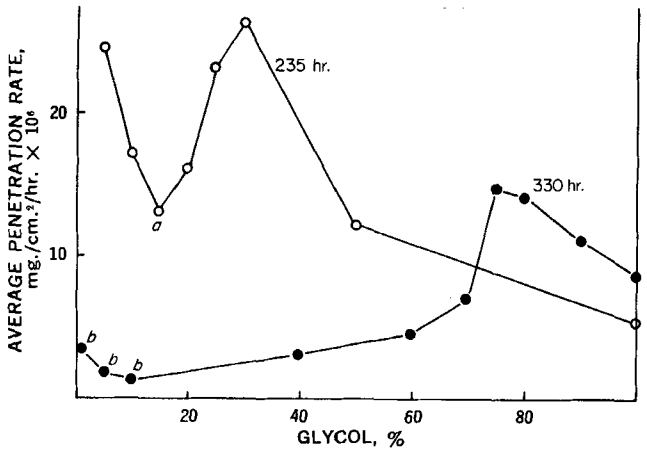

Figure 1—*Average penetration rate at RT as a function of vehicle composition (human abdominal skin). Key:* O, *fluocinolone acetonide; and* ●, *fluocinonide.* a = *average of three data points.* b = *normalized data points from a single experiment (see text).*

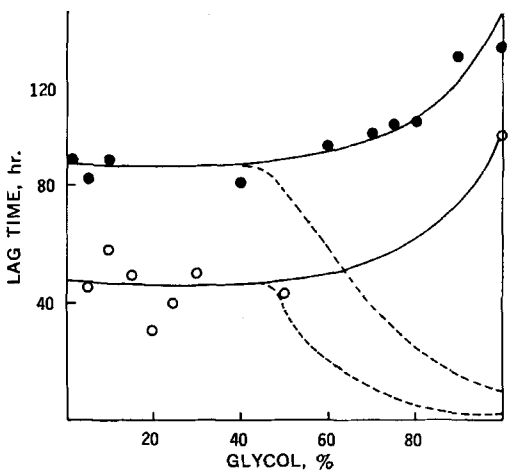

Figure 2—*Experimental* (——) *and calculated* (- - -) *lag times as a function of gel composition. Key:* O, *fluocinolone acetonide; and* ●, *fluocinonide.*

maximum penetration (75% gel) was significantly different at the 5% level from compositions with 70% or less glycol. This analysis supports the existence of real maxima for the dependence of penetration on composition. An equally significant result is that the data obtained on each skin specimen give similar profiles.

Figure 1 not only demonstrates the importance of vehicle composition but also that the effect of vehicle composition is dependent on the nature of the drug, as indicated by the difference in the profiles for the two steroids. A previous report (1) illustrated the similarity of the profile in Fig. 1 to that for the dependence of *in vivo* vasoconstrictor response on composition.

The lag times for penetration were estimated by extrapolation of the pseudo-steady-state portion in plots of amounts penetrated *versus* time to the time axis. The average lag time in hours as a function of gel composition is given in Fig. 2 for both steroids (solid line). The data points corresponding to the 1, 5, and 10% gel compositions were normalized in the same manner described for penetration rates. For both steroids, the lag times are invariant at gel compositions containing less than about 50% propylene glycol and increase substantially as this percentage approaches 100. Since the diffusivity (D) of the drug within the barrier is inversely related to the lag time (Eq. 2), this result suggests that the permeability of the barrier decreased at high proportions of glycol.

From Eq. 1, it can be predicted that the ability of a drug to penetrate a barrier is proportional to $(PC)DC_v$ or, perhaps, $(PC)C_v/L$. The physical parameters PC, C_v, and D all may be altered by vehicle composition so as to facilitate skin penetration. The quantity $D_p(PC)C_v$ was calculated at each gel composition, using experimental data previously reported (1). D_p refers to the diffusion coefficient calculated by Eq. 2 (no binding). Experimental values for C_v were used directly, and values for PC and D_p were obtained by interpolation from plots of PC or D_p *versus* glycol content. The partition coefficient data were obtained by partitioning the steroids between various glycol–water mixtures and isopropyl myristate. The relationship between the quantity $D(PC)C_v$ and vehicle composition is given in Fig. 3 for both steroids. Figure 3 also includes the relationship between $(PC)C_v$ and composition (broken lines) to demonstrate the usefulness of this approximation in the event that L values for the calculation of D_p are not available. The similarity between the calculated profile and that for penetration rates (and *in vivo* responses) demonstrates the predictive nature of the terms $(PC)C_v/L$ and $(PC)C_v$. Since the PC terms used in the calculations were not the true values, deviations in the calculated profile are understandable. Other partitioning systems could accentuate the profile for the calculated values of $D(PC)C_v$ at either low or high proportions of glycol in the gel, depending on the relative shift in the partition coefficient scale for these other systems. Ideally, partition coefficients between the stratum corneum and the vehicle are required.

By examining the dependence of the parameters PC, C_v, and D (or L) on gel composition, the shape of the profile for both steroids in Fig. 3 can be interpreted. At proportions of glycol from 0 to 50%, D is essentially constant for both steroids, so the nature of the profile can be attributed to the terms PC and C_v. In the case of fluocinolone acetonide, at proportions of glycol less than 10%, PC is decreasing faster than C_v is increasing to produce a negative slope; at glycol proportions between 10 and 30%, the converse relationship exists to give a positive slope. Above 30% glycol, all of the steroid is in solution, C_v remains constant, and the term $D(PC)C_v$ decreases markedly, mainly due to a decreasing PC. Above 50% glycol, some of the decrease in $D(PC)C_v$ may also be attributed to an apparent decrease in permeability. In the case of fluocinonide, the profile can be interpreted in the same manner, the only difference being that the maximum occurs at a higher proportion of glycol due to the poorer solubility of this steroid in these vehicles. That is, at proportions of glycol from 0 to 50%, C_v is increasing faster than PC is decreasing; from 50 to 75% glycol, C_v is increasing faster than PC and D combined are decreasing. At 75% glycol, all of the steroid is in solution, C_v remains constant, and the term $D(PC)C_v$ decreases, mainly due to a decreasing PC.

The shape of the composition profiles for penetration and *in vivo* response, in the region where the gels are saturated with respect to steroid, deserves some comment. Theoretically, for all the gels with undissolved drug present, the driving force (chemical potential) for diffusion is the same. Consequently, one would predict, contrary to the experimental results, that the penetration rate would remain constant with composition in this region. This was not the case. The calculated profiles obtained from experimental solubilities and partition coefficients show a similar deviation. The discrepancy between theory and experimental results is particularly obvious with fluocinolone acetonide gels containing 0–30% glycol. The variation in rate is apparently not due

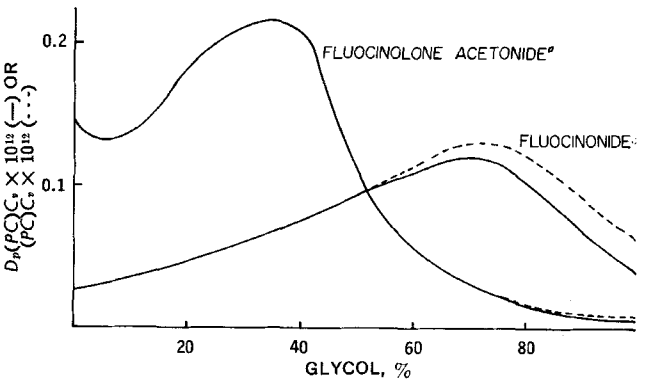

Figure 3—*Relationship between* $D_p(PC)C_v$ *and gel composition.* [a] *Values for* $D_p(PC)C_v$ *were divided by 2.21, which corresponds to the average* D *value for compositions with less than 50% glycol.* [b] *Values for* $D_p(PC)C_v$ *were divided by 1.20.*

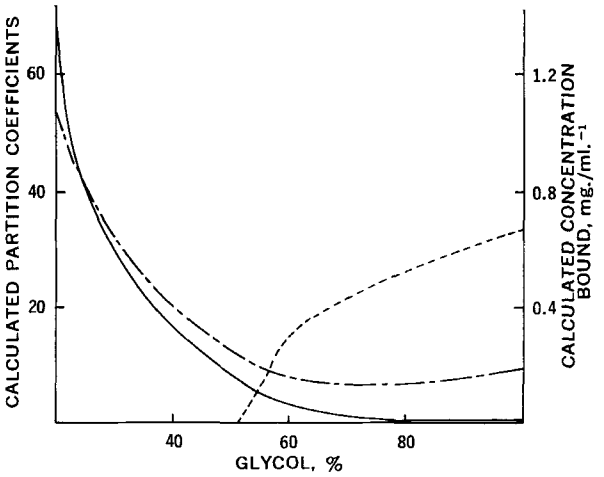

Figure 4—*Apparent partition coefficients* (- - -), *the theoretical partition coefficients* (——), *and fluocinolone acetonide concentration bound* (- - -) *as a function of gel composition.*

to the influence of the vehicle on D, since the lag time appears to be invariant in this composition range. One explanation is the possible alteration of barrier composition due to partial miscibility of the vehicle in the barrier lipid fraction without an alteration in barrier permeability (D remains the same). This would yield a barrier with varying composition as the glycol content varies. Such an alteration of barrier composition would then allow an effective drug concentration in the barrier different from the theoretical. In other words, the activity of the drug within the barrier may vary because of these barrier composition changes. Model systems which could include such an explanation have been discussed (4). Nonetheless, one can predict what the optimal vehicle composition for skin penetrability and clinical efficacy will be from a knowledge of drug solubilities and partition coefficients. Hopefully, these findings will be applicable to other topical vehicle types as well.

The increase in lag time to achieve steady-state penetration for both steroids at gel compositions of glycol above 50% suggests that the change in vehicle composition may be associated with two phenomena. These are: (*a*) a change in membrane permeability (D) due to the direct effect of vehicle components on the disposition of the barrier, and/or (*b*) the binding of the steroid within the barrier during transport. It is conceivable, for example, that as the glycol content increases, the barrier tends to dehydrate and becomes less permeable. Upon completion of the penetration studies, it was observed that the membranes exposed to high concentrations of glycol had become less pliable[3]. Also, it is logical that incorporation of some glycol by the membrane would alter its barrier properties in addition to a dehydration effect. Alteration of the barrier by glycol could conceivably increase or decrease its permeability. If binding or adsorption of the steroid on polar sites within the barrier occurs, one would expect an increase in binding tendency as the polarity of the vehicle decreases, corresponding to less competition for binding sites by the solvent. With binding playing a role, the lag time would tend to increase as the propylene glycol content increases because a longer period of time would be required to establish a steady-state concentration gradient across the barrier.

Thus, one can take two approaches in examining the data to speculate on the significance of the varying lag time with composition.

Case I: No Binding—If no binding occurs, the interpretation is simple. For this case, $D_p = h^2/6L$ is valid, and D_p can be calculated at each gel composition. By using 15 μ as an estimate of the effective thickness of the barrier (stratum corneum), the calculated values for D_p fall in the range of $1.1\text{–}2.2 \times 10^{-12}$ cm.^{2} sec.$^{-1}$ for fluocinolone acetonide and $0.75\text{–}1.2 \times 10^{-12}$ cm.^{2} sec.$^{-1}$ for fluocinonide. These D_p values are in the range of those reported for other steroids (5). This simple interpretation suggests that the membrane becomes less permeable as the glycol content increases above 50%.

Case II: Binding—In this case, the increase in lag time can be caused by both binding and a permeability change. Equation 3 may be used to estimate the extent of binding (A). This, however, requires a knowledge of the diffusivity of the steroids in the barrier and the barrier/vehicle partition coefficient at the various gel compositions. Although barrier/vehicle partition coefficients were not determined, they can be estimated in the following manner. The expression $D = h^2/6L$ is applicable in this case for gel compositions with less than 50% glycol where the lag time is invariant. Substitution for D in the flux equation (Eq. 1) allows one to calculate apparent partition coefficients, PC_p, over the 0–50% glycol range. The PC_p values over the 50–100% range can be obtained in a similar manner for the case where binding is insignificant.

The solubilities of the steroids in the barrier can then be estimated from Eq. 4, utilizing PC_p values for the 0–50% range:

$$PC_p \simeq \frac{S_b}{S_v} \qquad \text{(Eq. 4)}$$

where S_b and S_v are the steroid solubilities in the barrier and vehicle, respectively. Equation 4 should provide fairly good estimates of S_b since the gels are at or near saturation in the 0–50% glycol range. With S_b and S_v known, Eq. 4 can then be used to calculate theoretical partition coefficients, PC_b, over the whole glycol range. This requires the assumption that the vehicle does not alter the steroid solubility in the barrier at high glycol concentrations. Values for PC_p and PC_b so calculated are given in Figs. 4 and 5 for fluocinolone acetonide and fluocinonide, respectively, where they are plotted as a function of glycol content. The calculated solubility of fluocinolone acetonide in the barrier ranged from 2.5 to 6.4 mg./ml., with an average value of 4.1. The calculated fluocinonide solubility ranged from 0.66 to 1.7 mg./ml., with an average value of 1.1. The finding that the calculated solubility of fluocinolone acetonide in the barrier is greater than that of fluocinonide agrees with solubility data reported previously (6). Yet the lipid/water partition coefficient of fluocinonide is larger. This result corresponds to the markedly reduced solubility of fluocinonide (relative to fluocinolone acetonide) in the polar phase.

Using the values for PC_b, one can now calculate theoretical D values (D_b) over the entire glycol range using Eq. 1, assuming

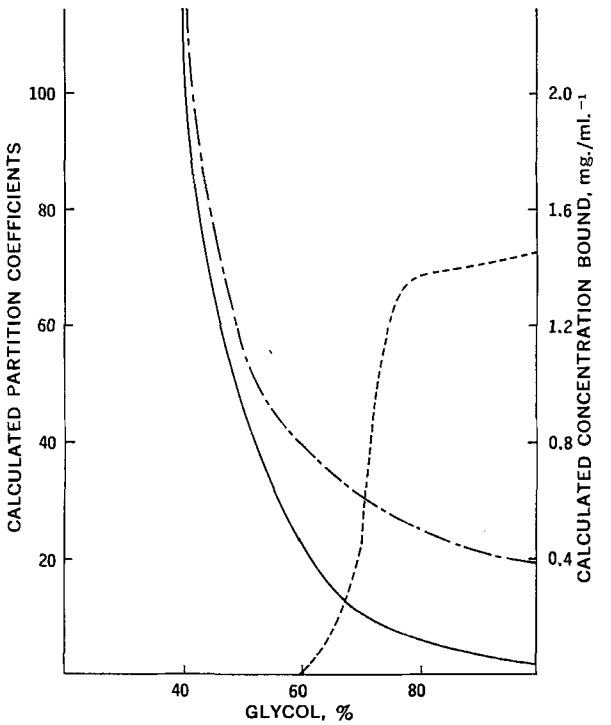

Figure 5—*Apparent partition coefficients* (- - -), *theoretical partition coefficients* (——), *and fluocinonide concentration bound* (- - -) *as a function of gel composition.*

[3] A decrease in pliability need not necessarily mean the membrane became less permeable. Other investigators (4) reported that dimethyl sulfoxide causes a hardening of skin and yet dimethyl sulfoxide is known to increase skin permeability.

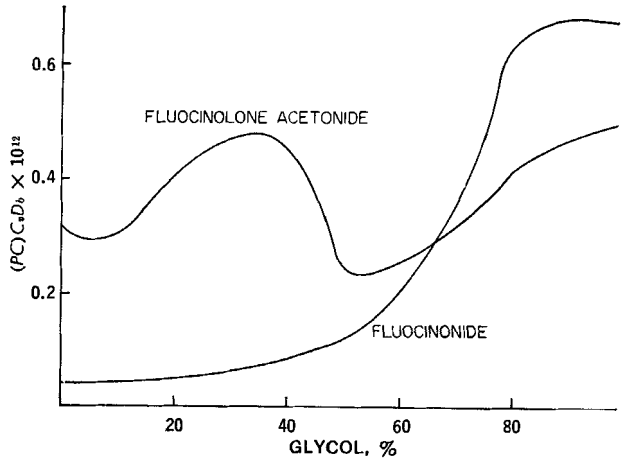

Figure 6—*Profile for the prediction of penetrability for steroid binding within the barrier.*

that binding does not affect diffusivity. Subsequently, lag times calculated from Eq. 2 using these D_b values will give estimates of L that correspond to the hypothetical situation where no binding occurs. The L values as a function of composition are given in Fig. 2 (dashed lines). The difference between experimental and calculated lag times (or D_p and D_b values) is actually a reflection of the difference between apparent and theoretical partition coefficients. Figure 2 indicates that glycol concentrations above 50% actually increase the permeability of the barrier (decreased lag time) and that the increase in experimental lag times for glycol concentration above 50% corresponds to a hypothetical binding phenomenon.

By using PC_b and D_b values calculated in the manner described and experimental L values, the hypothetical concentration of steroid bound to the barrier, A, was calculated using Eq. 3. A is plotted *versus* gel composition in Figs. 4 and 5. For each steroid, the hypothetical concentration of steroid bound is seen to increase rapidly at gel compositions above 50% glycol. For both steroids, the dependence of A on gel composition is linear above 75% glycol.

The extent of binding may be dependent on several factors. These include the steroid concentration in the barrier, the affinity of the steroid for the solvent mixture, and the relative affinity of the steroid and solvent mixture for the binding sites. The steroid concentration is directly related to the term $PC \times C_v$. The steroid affinity terms would be difficult to describe except that as the proportion of glycol increases, they increase. Also, different solvent compositions most likely change the nature of the barrier such that the number or type of binding sites varies.

This analysis of the data, of course, does not necessarily tell one what actually happens during skin penetration. However, one can gain some insight into which of the two cases more closely corresponds to the experimental situation for skin penetration with these gel formulations. Case I gave D_p values based on the experimental lag times and the use of Eq. 2, while Case II gave D_b values based on a theoretical partition coefficient and the use of Eq. 1. $(PC)C_vD_b$ values were calculated using isopropyl myristate/glycol–water partition coefficients and vehicle solubilities. A plot of $(PC)C_vD_b$ *versus* percent glycol is given in Fig. 6. The profile using $(PC)C_vD_p$ is the same as that in Fig. 3. Since the profile generated by using D_p (or experimental lag times in Fig. 3) more closely resembles the penetration profile (Fig. 1) for both steroids, Case I is probably more representative of the experimental situation.

To help ascertain the significance of the apparent permeability changes at high glycol concentrations, the following penetration experiments were done. Five membranes were prepared from a single skin specimen and placed in diffusion cells in the same manner described for previous experiments (1). Three membranes were pretreated with water saturated with isopropyl myristate, and two membranes were pretreated with propylene glycol saturated with isopropyl myristate. The pretreatment procedure was simply immersion of the membranes in the solvents for 36 hr. One-half milliliter of a solution of 0.025% w/v fluocinolone acetonide in isopropyl myristate saturated with either water or propylene glycol was placed on the epidermal side of the membranes. Isopropyl myristate saturated with either water or propylene glycol was used as the receptor from which samples were withdrawn. The penetrant solution and receptor were saturated with water or propylene glycol to ensure that solvent extraction from the membrane would be minimal during the penetration experiments. The average rate of penetration for the membranes pretreated with water was 0.121 mg. cm.$^{-2}$ hr.$^{-1}$; for the membranes pretreated with propylene glycol, the average rate was 0.006 mg. cm.$^{-2}$ hr.$^{-1}$. The average lag times were 89 and 256 hr., respectively. Thus, propylene glycol does decrease the permeability of the barrier significantly. Compared to water, the rate was reduced 20-fold. This result, coupled with the finding that the term $D_p(PC)C_v$ [rather than $D_b(PC)C_v$] as a function of composition gave a profile more similar to that for penetration rates as a function of composition, strongly suggests that: (*a*) propylene glycol causes the barrier to become less permeable[4], and (*b*) there is little or no binding of the steroid within the barrier.

The observation that propylene glycol causes the barrier to become less pliable probably corresponds to a dehydration of the barrier by the vehicle. Since there appears to be no binding, the difference between the apparent and theoretical partition coefficients is apparently fictitious. The apparent partition coefficients are most likely real. This result implies that the vehicle affects the barrier to give partition coefficients that vary from predicted ones. This alteration of the barrier by the vehicle could involve incorporation of vehicle components by the barrier or extraction of barrier components by the vehicle at high proportions of glycol.

SUMMARY

The dependence of skin penetrability and *in vivo* response on vehicle composition was demonstrated for two topical steroids in propylene glycol–water gels. In this report, it was shown that the terms $(PC)C_v/L$ and $(PC)C_v$ from the diffusion equation had a similar dependence on vehicle composition and that these terms may be useful in predicting the optimal vehicle composition for vehicle and clinical efficacy of topical drugs. Calculations based on the increase in lag time with vehicle composition were made to explore the possible effects of vehicle composition on barrier permeability and steroid binding within the barrier. Additional penetration studies were also performed to determine the relative solvent effect of propylene glycol and water on barrier permeability. The combined results suggests that propylene glycol decreases the permeability of the barrier and that there is little or no binding of steroid within the barrier.

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[4] Permeability refers to the diffusivity of the steroid within the barrier. Penetration rates are not necessarily indicative of permeability, because partition coefficients usually vary from one set of experimental conditions to another. A change in barrier permeability implies an actual change in the nature of the barrier (*e.g.*, a swelling effect); the best measure of this for a particular penetrant is the diffusion coefficient, D.