and R. Robinson, Eds., Princeton University Press, Princeton, N. J., 1949, p. 973 ff.
(11) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **71,** 2124(1949).
(12) *Ibid.*, **72,** 2771(1950).
(13) *Ibid.*, **73,** 3172(1951).
(14) F. Moll, *Arch. Pharm.*, **301,** 272(1968).
(15) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed., Wiley, New York, N. Y., 1956, pp. 163–175.
(16) *Ibid.*, p. 573.
(17) L. Friedman and W. P. Wetter, *J. Chem. Soc., Sect. A*, **1967,** 36.
(18) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967.
(19) F. F. Blicke and W. A. Gould, *J. Org. Chem.*, **23,** 1102 (1958).
(20) R. G. Bates, "Determination of pH—Theory and Practice," Wiley, New York, N. Y., 1967.
(21) "Heterocyclic Compounds," R. C. Elderfield, Ed., Wiley, New York, N. Y., 1950, chap. 3.
(22) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, pp. 219–234.
(23) "Heterocyclic Compounds with Three- and Four-Membered Rings," part II, A. Weissberg, Ed., Interscience, New York, N. Y., 1964, chap. 7.
(24) S. S. Biechler and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **79,** 4927(1957).
(25) P. M. Mader, *ibid.*, **87,** 3191(1965).
(26) R. L. Schowen, H. Jayaraman, and L. Kershner, *ibid.*, **88,** 3373(1966).
(27) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, **20,** 1892 (1966).
(28) S. O. Eriksson and L. Bratt, *ibid.*, **21,** 1812(1967).
(29) M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, **83,** 4183(1961).
(30) M. I. Vinnik and Y. V. Moiseyev, *Tetrahedron*, **19,** 1441 (1963).
(31) R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, **92,** 5489 (1970).
(32) "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Eds., Princeton University Press, Princeton, N. J., 1949, p. 443.
(33) R. J. Washkuhn, Ph.D. thesis, University of Wisconsin, Madison, Wis., 1971.

ACKNOWLEDGMENTS AND ADDRESSES

Received January 4, 1971, from the *School of Pharmacy, University of Wisconsin, Madison, WI 53706*

Accepted for publication March 18, 1971.

* National Institutes of Health predoctoral fellow, 1967–1970 (5-F01-GM38494). Present address: Mead Johnson and Co., Evansville, Ind.

† To whom reprint requests and inquiries should be directed.

Significance of Vehicle Composition I: Relationship between Topical Vehicle Composition, Skin Penetrability, and Clinical Efficacy

JAMES OSTRENGA, CAROLYN STEINMETZ, and BOYD POULSEN

Abstract □ The penetration of two topical steroids, fluocinolone acetonide and fluocinonide, through human abdominal skin was investigated for various propylene glycol–water gels. Release, penetration, and *in vivo* data were compared as a function of vehicle composition. The similarity between the *in vivo* and *in vitro* composition profiles for both steroids suggested that clinical efficacy can be predicted from *in vitro* data and from the physical properties of the steroids. The correlations indicated that the *in vivo* results were directly dependent upon penetrability.

Keyphrases □ Fluocinolone acetonide, fluocinonide topical gels—skin penetration □ Topical gels, fluocinolone acetonide, fluocinonide—release, penetration, *in vivo*, *in vitro* data □ Vehicle composition profiles, *in vivo*, *in vitro*—fluocinolone acetonide, fluocinonide topical gels □ Pharmacokinetics, skin penetration—fluocinolone acetonide, fluocinonide topical gels, drug efficacy, vehicle and drug physical properties, effects

In the formulation of vehicles for topical drugs, the efficacy of such dosage forms is often dependent on the composition of the vehicle. The ability of a drug in a topical formulation to penetrate the skin and exert its effect is dependent on two consecutive physical events. The drug must first diffuse out of the vehicle to the skin surface, and then it must penetrate this natural barrier en route to the site of action. Many so-called "vehicle effects" reported in the literature are consequences of these two diffusional processes. Depending on which process proceeds slower, either event could determine the overall effectiveness of the topical dosage form. These two processes are intimately related, and both are dependent upon the physical properties of the drug, vehicle, and barrier.

The physical picture is one in which a single molecular species, the drug, experiences a changing environment as it diffuses out of the vehicle and across the skin. Poulsen *et al.* (1) reported on vehicle effects regarding the relative release characteristics of gels with varying compositions. The main objectives of this study were to explore the second process of diffusion, penetration of the drug through human skin, and to show that it is rate controlling when a topical dosage form is applied to normal skin. A more general objective was to provide insight into the manner in which the physical–chemical properties of drug and vehicle can be utilized to increase a formulation's effectiveness. Such information hopefully should aid in the intelligent design of topical dosage forms.

THEORETICAL CONSIDERATIONS

The transport of drugs across the skin barrier may be considered a process of passive diffusion. The flux, J (moles cm.$^{-2}$ sec.$^{-1}$), for

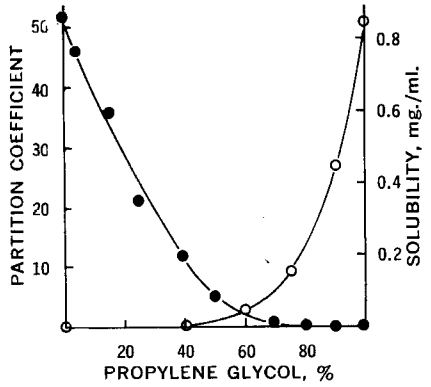

Figure 1—*Isopropyl myristate/propylene glycol–water partition coefficients* (●) *and propylene glycol–water solubilities* (○) *for fluocinonide.*

transport across a membrane is proportional to the product of force and concentration. That is,

$$J = \frac{DC}{RT}\left[\frac{-d\mu}{dx}\right] \quad \text{(Eq. 1)}$$

$$= -DC\frac{d\ln a}{dx}\ (\mu = \mu_0 + RT\ln a) \quad \text{(Eq. 2)}$$

$$= -DC\left[\frac{d\ln C}{dx} + \frac{d\ln\gamma}{dx}\right]\ (a = \gamma C) \quad \text{(Eq. 3)}$$

$$= -D\left[\frac{dC}{dx} + \frac{Cd\ln\gamma}{dx}\right] \quad \text{(Eq. 4)}$$

$$= \frac{-D\,dC}{dx}\ (\text{for a constant } \gamma) \quad \text{(Eq. 5)}$$

In Eqs. 1–5, D is the diffusion coefficient for the drug in the barrier, R is the gas constant, T is the absolute temperature, $d\mu/dx$ is the chemical potential gradient across the barrier, a is the thermodynamic activity, and γ is the activity coefficient. The rate of penetration, dQ/dt, then is given by:

$$\frac{dQ}{dt} = \frac{D(C_2 - C_1)}{h} \quad \text{(Eq. 6)}$$

where h is the effective thickness of the barrier, and Q is the amount penetrated per unit area. Since the concentration of drug in the membrane surface on the vehicle side, C_2, is related to the concentration in the vehicle, C_v, by $PC = C_2/C_v$, and if the concentration at the membrane surface on the opposite side, C_1, is maintained at zero concentration such that the concentration gradient for diffusion, dC/dx, is equal to the ratio of C_2 over the thickness of the membrane, C_2/h, then:

$$\frac{dQ}{dt} = \frac{D(PC)C_v}{h} \quad \text{(Eq. 7)}$$

In Eq. 7, the parameters that are alterable and may be modified by vehicle composition to facilitate skin penetration are D, PC, and C_v. The diffusion coefficient, D, of the drug in the barrier can be modified by the influence of the vehicle components on the nature of the barrier. The partition coefficient, PC, of the drug between the skin and the vehicle can be optimized by decreasing its solubility in the vehicle. The concentration of diffusible drug in the vehicle, C_v, for a given labeled strength can be optimized by ensuring that all of the drug is in solution. Experimentally, dQ/dt can be obtained from penetration studies by calculating the slope in the steady-state region from plots of amount of drug penetrated *versus* time. PC can be estimated by partitioning the drug between the vehicle and a phase thought to be representative of the barrier material. C_v either is known (if all of drug is in solution) or can be obtained by determining the solubility of the drug in the vehicle (if a fraction of drug is suspended). D can be obtained from Eq. 7 if the true partition coefficient is known, or it can be approximated indirectly from the lag time, L:

$$L = \frac{h^2}{6D} \quad \text{(Eq. 8)}$$

obtained by extrapolation of the pseudo-steady-state portion of a plot of amount of drug penetrated *versus* time to the time axis.

To characterize the relationships between a diffusing drug and its environment (vehicle and barrier), two steroids with substantially different physical properties were utilized. The steroids were fluocinolone acetonide[1] and its 21-acetate ester, fluocinonide[2].

EXPERIMENTAL

Materials—Propylene glycol[3], carboxypolymethylene[4], isopropyl myristate[5], diisopropanolamine[3], fluocinolone acetonide[1], and fluocinonide[2] were used as received. All other chemicals were of analytical reagent grade. The skin specimens were whole human abdominal sections obtained from autopsy and stored in the frozen state until utilized.

Solubility—The method employed was essentially the same as that reported previously (2). The solubility data correspond to the most stable polymorph at equilibrium (25°) for each solvent mixture.

Partition Coefficients—Isopropyl myristate and the various propylene glycol–water mixtures were saturated with respect to each other. Ten milliliters of the presaturated isopropyl myristate phases, containing approximately 0.02 mg./ml. of radioactive steroid (^{14}C) of known specific activity, was added to 10 ml. of the respective propylene glycol–water phases in a separator at room temperature. After equilibration, the phases were separated and assayed individually for steroid content. Partition coefficients were calculated as the ratio of steroid concentration in the isopropyl myristate phase to that in the propylene glycol–water phase.

Preparation of Vehicles—An appropriate amount of radioactive steroid (see *Release Rates* section) was dissolved in each propylene glycol–water mixture with the aid of heat and stirring. These solutions were gelled by first dispersing 1% carboxypolymethylene resin and then neutralizing to a pH of approximately 6.5 by adding a sufficient quantity of either diisopropanolamine or concentrated aqueous sodium hydroxide solution with proper mixing.

Release Rates—Initially, it was found that manufacturing difficulties caused a variation in release rates for different batches of the same gel composition. This variability was attributed to supersaturation effects during the heating step of manufacture. The problem was overcome by first preparing each gel with the steroid at saturation concentration in each propylene glycol–water solution for those preparations in which the solubility was less than 0.25 mg./ml. and then adding additional steroid (the insoluble portion) to the gelled preparation to give a final concentration of 0.025% (w/w). Release data were then obtained for each gel in a manner similar to that reported by Poulsen *et al.* (1) to verify a proper manufacturing technique.

Preparation of Membranes—Whole human abdominal skin, obtained at autopsy, was frozen on a glass plate with the epidermal surface flat in contact with the plate. Just prior to an experiment, the frozen skin was dislodged by warming the plate with water. A layer of skin, 0.076-cm. (0.030-in.) thick, was removed from the epidermal side with an Electro-Dermatome[6]. This procedure allowed removal of the subcutaneous fat without contamination of the intact epidermal surface. The epidermal surface was washed with hexachlorophene[7] and warm water; circular sections, having a diameter of 2.21 cm. (0.87 in.), were cut. Each section was then moistened with a few drops of distilled water and placed on a Whatman No. 1 filter paper of equal size with the dermal side in contact. The prepared sections were then positioned between the two Teflon disks of the diffusion cell. To ensure a good seal, the surfaces of both disks were coated

[1] 6α,9α-Difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide, Syntex Laboratories, Inc., Palo Alto, Calif.
[2] 6α,9α-Difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-acetate, Syntex Laboratories, Inc., Palo Alto, Calif.
[3] Union Carbide Co., New York, N. Y.
[4] Carbopol 934, B. F. Goodrich Co., Cleveland, Ohio.
[5] General Aniline & Film Corp., New York, N. Y.
[6] Model B, Padgett-Hood, Division of Kansas City Assemblage Co., Kansas City, MO 64111
[7] pHisohex.

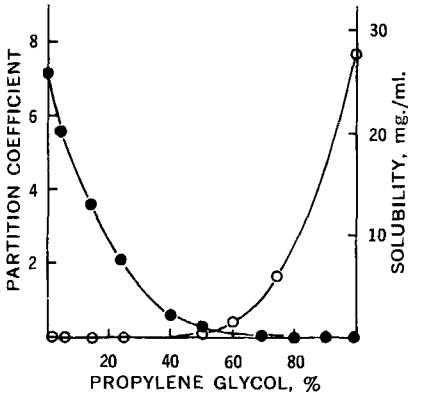

Figure 2—*Isopropyl myristate/propylene glycol–water partition coefficients* (●) *and propylene glycol–water solubilities* (○) *for fluocinolone acetonide.*

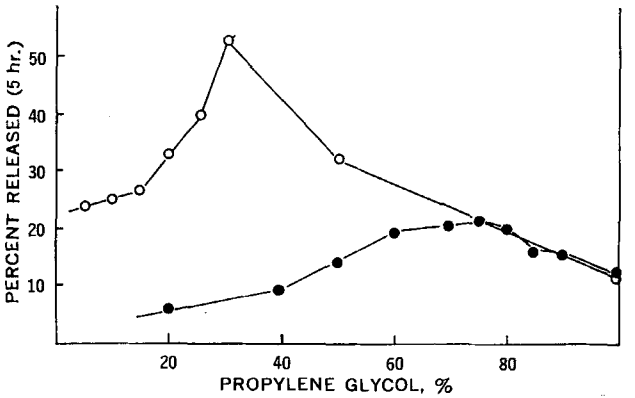

Figure 4—*Release profile for 0.025% fluocinolone acetonide* (○) *and 0.025% fluocinonide* (●) *at 25° (propylene glycol–water gels).*

with a thin film of silicone grease prior to positioning of the membrane.

Diffusion Cells—The cell design and operation were the same as these reported by Coldman *et al.* (3), except that the exposed area for penetration had a diameter of 1.33 cm. and an area of 1.41 cm.[2] The gels were applied to the epidermal surface, and the upper Teflon disk reservoir was filled completely. The surface of each gel was smoothed over with a spatula to make it flush with the disk surface. Each cell accommodated 0.83 g. of gel. To prevent evaporation, a glass coverslip was placed over the gel and sealed with silicone grease. A Teflon-coated stirring bar attached to a polyethylene sail provided efficient mixing in the sampling chamber, which contained 9–10 ml. of a 30% propylene glycol–water solution. The sampling arm was stoppered with a cork to prevent evaporation. One-milliliter samples were withdrawn for analysis at appropriate times over approximately 2 weeks (330–360 hr.).

Radiochemical Assays—A radiochemical assay using ^{14}C steroids was employed throughout the experimental work. The radiochemical purities of the steroids were checked by spotting an aliquot of each on a silica gel TLC plate, developing with CCl_4–dioxane–water (280:160:1), and scanning on a Vanguard model 880-D scanner. The resultant chromatograms indicated that the purity was ≥98% for both steroids. The radioactive steroids were prepared from solutions of high specific activity by diluting with nonradioactive steroid to about 2 μc./mg. and recrystallizing from ethanol and water. The analytical methodology was the same as that given previously (2).

***In Vivo* Assay**—Each gel was tested in an *in vivo* human assay procedure, a modified Stoughton–McKenzie assay (4), where the degree of blanching (vasoconstriction) of the skin was taken as a measure of efficacy or penetrability. Forty normal adult subjects (male and female) were employed in the study. All subjects had 3 mg. of each gel preparation applied to two sites on each forearm, so the total number of sites over all subjects was 160 per preparation.

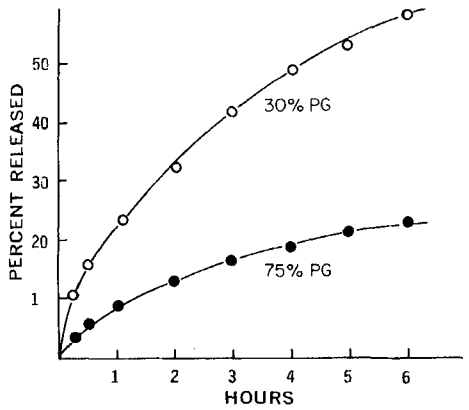

Figure 3—*Release for 0.025% fluocinolone acetonide* (○) *and 0.025% fluocinonide* (●) *from carboxypolymethylene gels (propylene gycol–water), giving maximum release at 25°.*

Each subject accommodated 32 sites per arm, and 16 gel preparations were studied in the same subject group at one time. The study was conducted under conditions of occlusion (6 hr.), and the number of sites showing vasoconstriction at 24 hr. was recorded.

RESULTS AND DISCUSSION

To demonstrate the significance of vehicle composition on both release and penetration, several carboxypolymethylene gels of propylene glycol–water mixtures in varying proportions, which contained either 0.025% fluocinolone acetonide or 0.025% fluocinonide separately, were evaluated. The physical constants of the two steroids applicable to this study are the solubilities of the steroids in the vehicles under consideration and the partition coefficients of the steroids between the barrier (stratum corneum) and these same vehicles. Isopropyl myristate was chosen to represent the barrier for the partition process[8]. The solubilities (25°) and partition coefficients (room temperature) for the two steroids are given in Figs. 1 and 2.

Although release data were reported previously (1), the rates of release into isopropyl myristate were obtained to ensure proper manufacturing of the gels as discussed in the *Experimental* section. Figure 3 gives the percent of drug released as a function of time for each

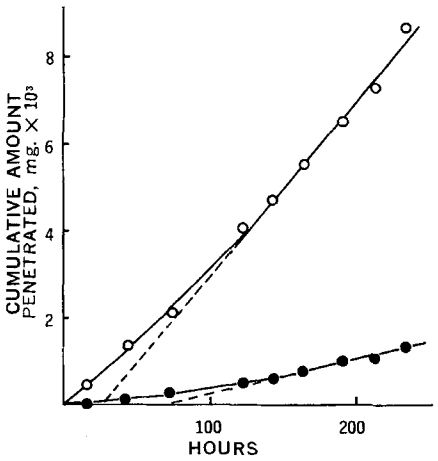

Figure 5—*Typical steroid penetration through human abdominal skin at RT (optimal vehicle). Key: ○, fluocinolone acetonide, 30% glycol; and ●, fluocinonide, 75% glycol.*

[8] Isopropyl myristate was arbitrarily chosen to represent the barrier since evidence has suggested that the barrier contains a lipid–protein matrix (5, 6) and that the lipid solubility of steroids is a significant factor in determining their penetrability (7).

Table I—Individual and Average Accumulative Amount(s) (mg. × 10^3) Penetrated[a]

Propylene Glycol, %	1	2	3	4	Av. ± $\bar{\sigma}_x$
			Fluocinolone Acetonide[b]		
5	11.80	1.55	4.65	7.60	6.40 ± 2.18
10	6.00	0.93	3.60	6.00	4.13 ± 1.21
15	4.05	1.05	5.70	—	3.60 ± 1.36
20	4.65	0.85	5.45	5.60	4.14 ± 1.12
25	7.85	1.90	8.25	7.70	6.43 ± 1.51
30	7.50	1.75	9.50	8.50	6.81 ± 1.74
50	4.65	1.35	4.25	2.50	3.19 ± 0.77
100	2.35	0.55	0.75	0.40	1.01 ± 0.45
			Fluocinonide[b]		
40	1.15	0.21	0.65	0.50	0.63 ± 0.20
60	1.90	0.18	1.30	0.46	0.96 ± 0.39
70	3.50	0.42	1.45	0.93	1.58 ± 0.68
75	4.05	0.61	2.05	1.31	2.01 ± 0.74
80	5.55	0.61	2.50	0.99	2.41 ± 1.12
90	4.95	0.48	0.95	0.82	1.80 ± 1.06
100	3.80	0.53	0.80	0.57	1.43 ± 0.79

[a] Whole abdominal human skin, 230 hr., room temperature. [b] The standard errors, $\bar{\sigma}_x$, give the variation between skins and do not necessarily reflect the significance of differences for amounts penetrated at different compositions. For this reason, standard errors are not indicated in Figs. 4–6.

steroid for the gel from which the corresponding release rate was maximal. Figure 4 gives the percent of drug released for each steroid after 5 hr. as a function of the percent glycol in the gel, and it clearly demonstrates the dependence of release on vehicle composition. In Fig. 4, a maximum is exhibited in the release profile for each steroid. These maxima correspond to that vehicle composition at which each steroid is completely solubilized and at its saturation concentration. Following each release profile from left to right, the increase in the amount released as the glycol content increases to the left of the maximum is due to an increase in the concentration of drug in solution, while the decrease in the amount released as the glycol content increases to the right of the maximum is due to a less favorable partition coefficient[9].

In Fig. 5, typical penetration curves (amount penetrated *versus* time) are shown for the same vehicle compositions that gave maximal release for each steroid. These penetration curves depict the usual behavior for passive diffusion through a membrane because there is a lag time before the penetration rate becomes constant. The amounts penetrated at 230 hr. for each steroid through four different skin specimens are given in Table I for the individual experiments as well as the average of these values. All 15 gel preparations were studied on each specimen, so the resultant data are comparable. The total number of gel preparations used in the penetration studies was limited to 15 initially because of the skin specimen size. Subsequently, however, it was thought advisable to obtain additional data points for the fluocinonide gels at low proportions of glycol. The penetration of fluocinonide from gels containing 1, 5, and 10% glycol was studied in a single and different skin specimen along with four gels from the original set. The results were normalized to make the data comparable[10].

The relationship between amount penetrated at a particular time (including the three normalized data points) and composition is shown in Fig. 6. There is an obvious dependence of penetrability on vehicle composition. As can be ascertained from Table I, comparable profiles can be obtained utilizing data from any single experimental set. Figure 6 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 drugs. The maximum for fluocinolone acetonide occurs at a gel composition of about 30% propylene glycol while the corresponding maximum for fluocinonide occurs at about 75%. These maxima correspond to that minimal glycol composition necessary to solubilize each steroid, as may be ascertained from the solubility data in Figs. 1 and 2.

The data in Table I were analyzed statistically *via* a repeated measurement design (8), which partitions out the variation due to people from the error term. The standard errors, $\bar{\sigma}_x$, given in Table I represent the skin-to-skin variation which has been partitioned out. Significant differences were shown for the amount penetrated for both fluocinolone acetonide ($p < 0.01$) and fluocinonide ($p < 0.05$). The maximum amount penetrated for fluocinolone acetonide (30% gel) was shown to be significantly different at the 5% level from all other compositions except 5 and 25%. For fluocinonide, the maximum amount penetrated (75% gel) was significantly different at the 5% level from compositions with 60% 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 specimens give similar profiles.

The results obtained when these same gels were tested in an *in vivo* human vasoconstrictor assay are shown in Fig. 7. The percent of sites responding 24 hr. after application is plotted as a function of gel composition. The similarity between the profiles for vasoconstriction and penetration is striking[11]. These data suggest that the rate-controlling step is in the skin barrier and that the efficacy of a topical preparation is directly related to the ability of a drug in that vehicle to penetrate the skin barrier. The results for both *in vitro* penetration and *in vivo* vasoconstriction in the case of fluocinolone acetonide (Figs. 6 and 7) show that the 5% glycol gel, which contained most of the steroid in suspension, performed as well as the 30% glycol gel where the steroid was just solubilized. This can be attributed to a very high partition coefficient of the 5% glycol gel offsetting the decrease in concentration of steroid in solution. Thus, it is possible that in certain instances a vehicle in which the drug is suspended will be most efficacious.

The results in Fig. 7 should not be interpreted to judge the relative potency of the two steroids. Although the *in vivo* data for the gels indicate that the steroids are nearly equivalent when comparing their optimum gels, fluocinonide releases and penetrates at about

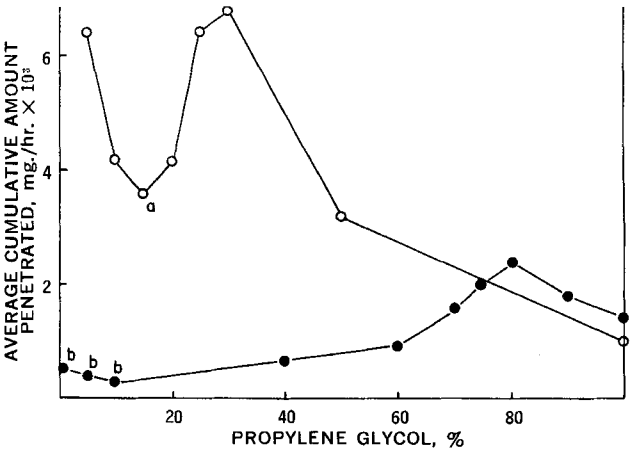

Figure 6—*Average cumulative amount penetrated at RT as a function of vehicle composition (human abdominal skin, 230 hr.). Key: ○, fluocinolone acetonide; and ●, fluocinonide.* a = *average of three data points.* b = *normalized data points from a single experiment (see text).*

[9] A change in partition coefficient may also be viewed as a change in thermodynamic activity. That is, the tendency of the drug to leave (partition from) the vehicle decreases as the glycol content increases.

[10] The amounts penetrated after 230 hr. for these three gels were 0.24, 0.21, and 0.13 mg. (× 10^{-3}) for the 1, 5, and 10% gels, respectively. To make these data comparable to those for the other compositions, the data for the 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 0.48, 0.42, and 0.26 mg. (× 10^{-3}) for the 1, 5, and 10% gels, respectively.

[11] Although it was suggested by the reviewer to make a linear correlation between the *in vivo* and *in vitro* data, this was not feasible since the two maxima in the composition profiles do not occur at exactly the same composition. The difference in the position of these maxima, however, can be rationalized on the basis that the gel during *in vitro* penetration may incorporate some water from the receptor, whereby a higher percentage of glycol is required to solubilize the drug, thus placing this profile to the right of the composition profile for *in vivo* response.

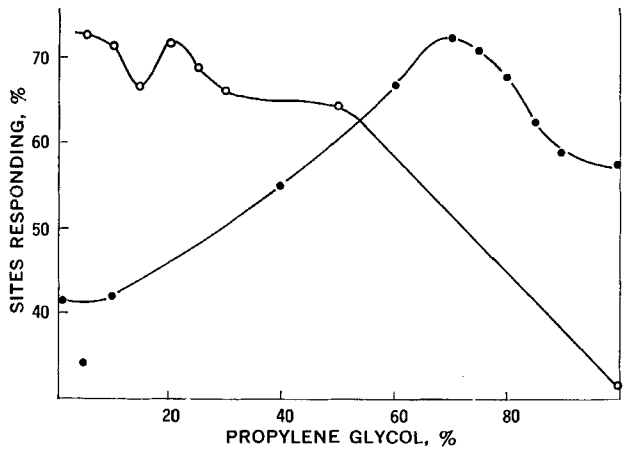

Figure 7—In vivo *response (24-hr. vasoconstriction) as a function of vehicle composition. Key:* ○, *fluocinolone acetonide; and* ●, *fluocinonide.*

one-third the rate of fluocinolone acetonide. One may conclude then that fluocinonide has an *intrinsic* potency three times that of fluocinolone acetonide. The relative potencies are also undoubtedly dependent on the vehicle type (gel, cream, ointment, *etc.*), and studies with other formulations could give different relative clinical efficacies.

The similarity between the *in vitro* penetration and *in vivo* vasoconstriction profiles for each steroid suggests a working hypothesis which can be used to describe by *in vitro* techniques the relationship between clinical efficacy, penetrability, and physical parameters of the drug, vehicle, and skin. In this study, increasing the proportion of glycol increases the concentration of drug in solution but, at the same time, creates a less favorable partition coefficient. Consequently, a proper balance of PC, C_v, and D is required to obtain the optimal composition and thereby produce the best conditions to facilitate penetration and clinical response. Equation 1 predicts that the ability of a drug to penetrate a barrier is proportional to the term $(PC)DC_v$. A subsequent report (9) will deal with the relative significance of the physical parameters (PC, D, and C_v), the predictive capability of the term $(PC)DC_v$, and the possible changes in barrier properties due to vehicle composition.

SUMMARY

1. Data were obtained which illustrated the dependence of release rate, skin penetration, and *in vivo* vasoconstrictor response on vehicle composition for two steroids with significantly different physical properties. The vehicles studied were various propylene glycol–water gels.

2. The relationships between the physical properties of the drug, vehicle, and barrier were shown to correlate well with the nature of the profiles of release, penetration, and vasoconstriction. The efficacy of a topical preparation was shown to be directly related to the ability of a drug to penetrate the skin barrier.

3. The correlations have led to a working hypothesis for vehicle formulation which describes by *in vitro* experimentation the relationship between vehicle composition and clinical efficacy and may aid in the design of efficacious topical dosage forms.

4. In general, an efficacious topical gel preparation is one in which: (*a*) the concentration of diffusible drug in the vehicle, C_v, for a given labeled strength is optimized by ensuring that all of the drug is in solution, (*b*) the minimum amount of solvent is used to dissolve the drug completely and yet maintain a favorable partition coefficient, and (*c*) the vehicle components affect the permeability of the stratum corneum in a favorable manner.

REFERENCES

(1) B. J. Poulsen, E. Young, V. Coquilla, and M. Katz, *J. Pharm. Sci.*, **57**, 929(1968).

(2) J. A. Ostrenga and C. Steinmetz, *ibid.*, **59**, 414(1970).

(3) M. F. Coldman, B. J. Poulsen, and T. Higuchi, *ibid.*, **58**, 1098(1969).

(4) K. H. Burdick, B. J. Poulsen, and V. A. Place, *J. Amer. Med. Ass.*, **211**, 462(1970).

(5) I. J. Brody, *Ultrastruct. Res.*, **4**, 264(1960).

(6) A. G. Matoltsy and M. N. Matoltsy, *J. Invest. Dermatol.*, **46**, 127(1966).

(7) R. J. Schueplein, I. H. Blank, G. J. Branner, and D. J. MacFarlane, *ibid.*, **52**, 65(1969).

(8) B. J. Winer, "Statistical Principles in Experimental Design," McGraw-Hill, New York, N. Y., 1962.

(9) J. Ostrenga, C. Steinmetz, B. Poulsen, and S. Yett, *J. Pharm. Sci.*, **60**, 1180(1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 17, 1970, from the *Institute of Pharmaceutical Sciences, Syntex Research, Stanford Industrial Park, Palo Alto, CA 94304*

Accepted for publication March 8, 1971.

The authors thank Dr. W. Hafferl and A. Hary, Institute of Organic Chemistry, Syntex Research, for preparation of the radiochemicals; the Institute of Clinical Medicine, Syntex Research, for conducting the *in vivo* assay; and Miss M. Hanks, for her assistance in the statistical analysis.