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RESEARCH ARTICLES

Release of Corticoids from Oleaginous Ointment Bases Containing Drug in Suspension

Z. T. CHOWHAN [x] and R. PRITCHARD

Abstract □ Simplified methods for studying the release of drugs suspended in oleaginous ointment bases were developed. These procedures were used in studying the release rates of two corticoids, fluocinonide and flucloronide, from white petrolatum and petrolatum containing various adjuvants. A practical method for measuring drug solubilities was developed and used in determining solubilities of these corticoids in ointment bases. When using physical data obtained from model ointments, the release rates of drugs from modified ointment bases were predicted. Comparisons of the observed and predicted rates from ointments containing hydrophobic adjuvants indicated the usefulness of the physical model approach in predicting the release rates. For ointments containing emulsifying agents, the simple model used did not provide useful predictions.

Keyphrases □ Fluocinonide—suspension, release from oleaginous ointment bases containing various adjuvants, model predictions □ Flucloronide—suspension, release from oleaginous ointment bases containing various adjuvants, model predictions □ Ointment bases—release of corticoids in suspension □ Release rates—corticoid suspensions from oleaginous ointment bases containing various adjuvants

Percutaneous absorption involves two consecutive steps: the release of the drug from the vehicle and its subsequent penetration through the skin barrier. Generally, the latter step controls percutaneous absorption, because it is the slower of the two events. The release of the drug from the vehicle may play an important role in percutaneous absorption when the drug solubility and its diffusion constant in the vehicle are very small. When the skin barrier is in a damaged state due to disease or injury, drug release from the vehicle then controls percutaneous absorption.

Simplified equations describing the drug release from suspension- (1) and solution- (2) type vehicles have been in the literature for more than a decade. Numerous studies also have attempted to relate vehicle composition to observed changes in the *in vitro* release rate (3–9). Relatively little quantitative information appears in the literature correlating drug release data with variations in physical parameters produced by compositional changes in the formulations. In some cases, the drug release from the vehicles has been complicated by the use of a membrane barrier to separate the donor phase from the receptor phase. The use of dialysis membranes (3), filter membranes (4), membranes of animal origin (5, 6, 8), and dimethyl polysiloxane membranes (7) has been reported.

When a membrane is used in the *in vitro* release experiment, it may be difficult to explain the data using simple physical relationships. The membrane might alter the release rate profiles due to physical interactions with the drug molecule.

The purpose of this investigation was to develop relatively simple experimental procedures for studying the drug release from ointments. The solubility of the drugs in ointment bases was determined using data from the effective ointment–water partitioning experiments. The physical parameters determined for model ointments were used to predict the release rates of the modified ointments. Comparisons of the observed and predicted rates were expected to elucidate understanding the physical processes important in the release of drugs from ointments.

EXPERIMENTAL

Materials—Materials for the preparation of ointments were used as received from the manufacturers. The ointment base was white petrolatum[1], base number six (USP). The adjuvants were Amerchol CAB[2], glyceryl stearate[3], beeswax[4], cetyl alcohol[5], stearyl alcohol[5], coconut fatty acid[6], glycerol monolaurate[6], glycerol monostearate[7], hexadecyl alcohol[8] (cosmetic grade), hexadecyl stearate[9] (cosmetic grade), lecithin[10], polysorbate 60[11], sorbitan monostearate[12], soya fatty acid[6], stearic acid[6], and wool alcohol[13] (lanolin, anhydrous, USP). The solvents used were reagent grade chloroform[14] and methylene chloride[15] and spectrograde anhydrous methanol[14] and dioxane[16].

Procedures—*Preparation of Ointments*—Several methods for making ointments where the drug is uniformly suspended in the form of fine particles in the external phase were considered. The most commonly used procedure, in which the ointment ingredients were mixed together and the melt was cooled while mixing, produced a supersaturated solution of the drug in the ointment base. Approaching equilibrium solubilities from a supersaturated solution of corticoids in ointments was found to be a slow process. Besides supersaturation, heating produced some degradation of the corticoids unless the conditions were carefully controlled. Mechanical incorporation of the corticoid in the ointment base was also tried. The small quantities of the ointments needed for these experiments and the low drug concentration (50 μg/g) made it difficult mechanically to incorporate the drug uniformly.

For obtaining uniform suspensions and attaining equilibrium solubilities without degrading the drug, the following procedure was developed and used throughout this investigation. The radioactive and cold fluocinonide[17] and flucloronide[18] were coprecipitated from methylene chloride in a polypropylene beaker[4]. Contact of the ointments with glass surfaces was avoided, because these steroids adsorb onto glass surfaces. One gram of white petrolatum and a sufficient quantity of chloroform were added to the coprecipitated mixture to dissolve the drug and the white petrolatum completely. The solvent was then removed under a stream of nitrogen gas.

[1] Pennsylvania Refining Co., Butler, Pa.
[2] American Cholesterol Products, Edison, N.J.
[3] Atmul 84, ICI.
[4] Van Waters & Rogers, Brisbane, Calif.
[5] Ashland Chemical Co., Division of Ashland Oil, Columbus, Ohio.
[6] Emery Industries, Fatty Acid Division, Los Angeles, Calif.
[7] Armour Industrial Chemical Co., Chicago, Ill.
[8] Enjay Chemical Co., New York, N.Y.
[9] Wilson, Martin, Division of Wilson and Co., Inc., Philadelphia, Pa.
[10] Reheis Chemical Co., Chicago, Ill.
[11] Tween 60, Atlas Chemical Industries.
[12] Span 60, Atlas Chemical Industries.
[13] Malmstrom Chemical Corp., Linden, N.J.
[14] Mallinckrodt Chemical Works, St. Louis, Mo.
[15] J. T. Baker Chemical Co., Phillipsburg, N.J.
[16] Matheson, Coleman and Bell, Los Angeles, Calif.
[17] 6α,9α-Difluoro-16α-hydroxyprednisolone 16α,17α-acetonide 21-acetate, Syntex Research, Palo Alto, Calif.
[18] 6α-Fluoro-9α,11β-dichloro-16α,17α,21-trihydroxypregna-1,4-diene-3, 20-dione 16,17-acetonide, Syntex Research, Palo Alto, Calif.

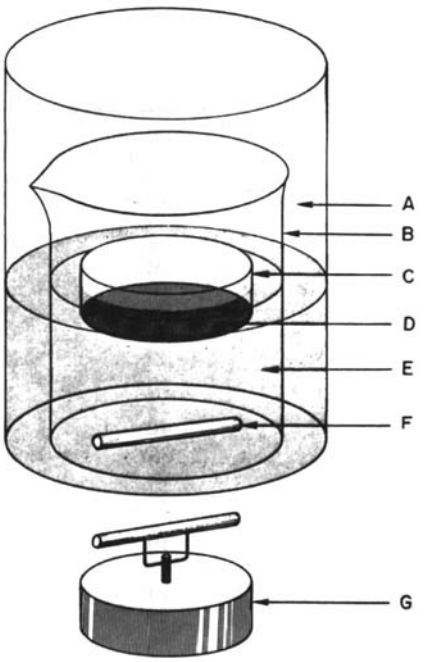

Figure 1—*Apparatus used in studying the release of drugs from an ointment layer containing suspended drug. Key: A, constant-temperature water bath; B, 250-ml beaker; C, Teflon dish; D, layer of ointment; E, sink; F, 5.0 × 0.9-cm (2 × 0.37-in.) magnetic stirring bar; and G, synchronous motor.*

All traces of solvent were removed by keeping the petrolatum stock suspension in vacuum for 5–7 days with occasional mixing by means of a spatula. The ointments were prepared from the petrolatum stock suspension and had the following composition: 0.05% corticoid, 5% adjuvant, and 95% white petrolatum. These ointments were well mixed with a spatula and allowed to equilibrate at room temperature before performing a release experiment.

Drug Release—The apparatus for studying drug release from ointments is shown in Fig. 1. It consisted of a Teflon dish [outer diameter 5.0 cm (2 in.)], which was allowed to float in 100 ml of distilled water in a 250-ml beaker. The water was stirred with a Teflon-coated magnetic stirring bar, which was driven by a synchronous motor at 60 rpm placed at the bottom of a water bath. The beaker was kept in a constant-temperature water bath maintained at 25°.

At the end of equilibration time, 300 mg of ointment was evenly spread in a thin layer at the bottom surface of a Teflon dish. Teflon served to hold the ointment layer because of similar surface properties. At zero time the dish was lowered onto the surface of water. This allowed direct contact between the donor ointment layer and the receptor phase. One-milliliter samples were withdrawn from the sink as a function of time and added to the liquid scintillation vials. To the latter, 15 ml of a liquid scintillation cocktail consisting of 50 mg of dimethyl 1,4-bis[2-(methyl-5-phenyloxazolyl)]benzene[19], 7 g of 2,5-diphenyloxazole[19], 50 g of naphthalene[15], 200 ml of methanol[14], and 800 ml of dioxane[16] was added. The radioactive counts were measured by a liquid scintillation counter[20]. The volume of the receptor phase was kept constant throughout the release run by replacing the removed sample with an equal volume of distilled water.

Partition Coefficient—For determining the ointment–water effective partition coefficient of the drug, the placebo ointments were prepared by melting the petrolatum and the adjuvant together and allowing them to cool to 25°. Exactly 2 g ointment was spread on the internal sides of a 50-ml polypropylene beaker. The radioactive drug was dissolved in distilled water, and 50 ml was added to the beaker. The aqueous solution was stirred with a Teflon-coated magnetic stirring bar, using a synchronous motor at 60 rpm placed under a water bath. The beaker was kept in a constant-

[19] Arapahoe Chemicals, Division of Syntex Corp., Boulder, Colo.
[20] Unilux II, Nuclear Chicago, Chicago, Ill.

Table I—Apparent Diffusion Constants of Fluocinonide and Flucloronide Calculated from Observed Release Rates and Apparent Solubilities after Equilibrating the Ointments for Different Times

Ointment Composition	Equilibrium Time, days	Apparent Diffusion Constant, $cm^2\ sec^{-1}$
Wool alcohol, 5%	9	2.2×10^{-11}
Petrolatum, 95%	23	2.3×10^{-11}
Fluocinonide, 0.05%	42	1.8×10^{-11}
Coconut fatty acid, 5%	9	6.86×10^{-11}
Petrolatum, 95%	23	5.75×10^{-11}
Fluocinonide, 0.05%	42	5.19×10^{-11}
Beeswax, 5%	9	0.77×10^{-11}
Petrolatum, 95%	23	0.88×10^{-11}
Fluocinonide, 0.05%	42	1.22×10^{-11}
Cetyl alcohol, 5%	9	1.1×10^{-11}
Petrolatum, 95%	23	1.4×10^{-11}
Fluocinonide, 0.05%	42	1.0×10^{-11}
Wool alcohol, 5%	5	0.15×10^{-9}
Petrolatum, 95%	19	0.18×10^{-9}
Flucloronide, 0.05%	33	0.15×10^{-9}
Coconut fatty acid, 5%	10	1.69×10^{-9}
Petrolatum, 95%	29	1.61×10^{-9}
Flucloronide, 0.05%	39	1.11×10^{-9}
Beeswax, 5%	5	0.68×10^{-9}
Petrolatum, 95%	19	0.72×10^{-9}
Flucloronide, 0.05%	33	0.74×10^{-9}
Cetyl alcohol, 5%	5	0.82×10^{-9}
Petrolatum, 95%	19	0.40×10^{-9}
Flucloronide, 0.05%	21	0.57×10^{-9}

temperature water bath at 25° until equilibrium was reached. One-milliliter samples were withdrawn from the aqueous phase and analyzed radiochemically.

THEORETICAL

An equation relating the amount of drug release from an ointment base containing drug in suspension to time and variables of the system was derived by Higuchi (1):

$$Q = \sqrt{2C_0DC_s^0t} \qquad \text{(Eq. 1)}$$

where Q equals the amount of drug released at time t per unit area of exposure, C_0 equals the concentration of drug expressed in units per cubic centimeter, C_s^0 equals the solubility of the drug as units per cubic centimeter in the external phase of the ointment, and D equals the diffusion constant of the drug molecule in the external phase.

In deriving the equation, it was assumed that: *(a)* the suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the applied layer; *(b)* the amount of drug, C_0, present per unit volume is substantially greater than C_s, the solubility of the drug per unit volume of the vehicle; and *(c)* the surface area to which the drug ointment is applied is immiscible with respect to the ointment and constitutes a perfect sink for the released drug.

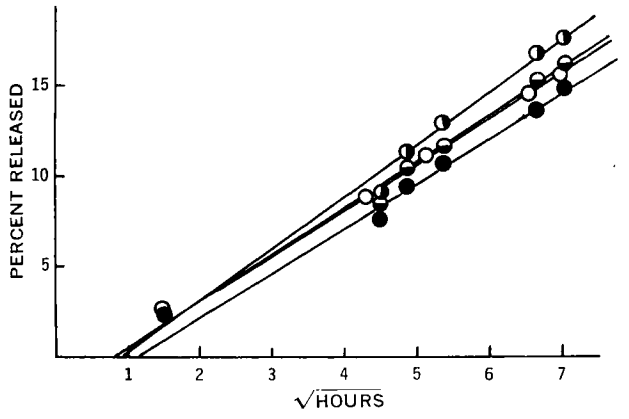

Figure 2—*Results of flucloronide release from oleaginous ointments prepared from white petrolatum. Key (in cm²/sec): ●, Batch I, run 1, D = 2.68 × 10⁻⁹; ◑, Batch I, run 2, D = 3.32 × 10⁻⁹; ◒, Batch I, run 3, D = 2.48 × 10⁻⁹; and ○, Batch II, run 1, D = 2.60 × 10⁻⁹.*

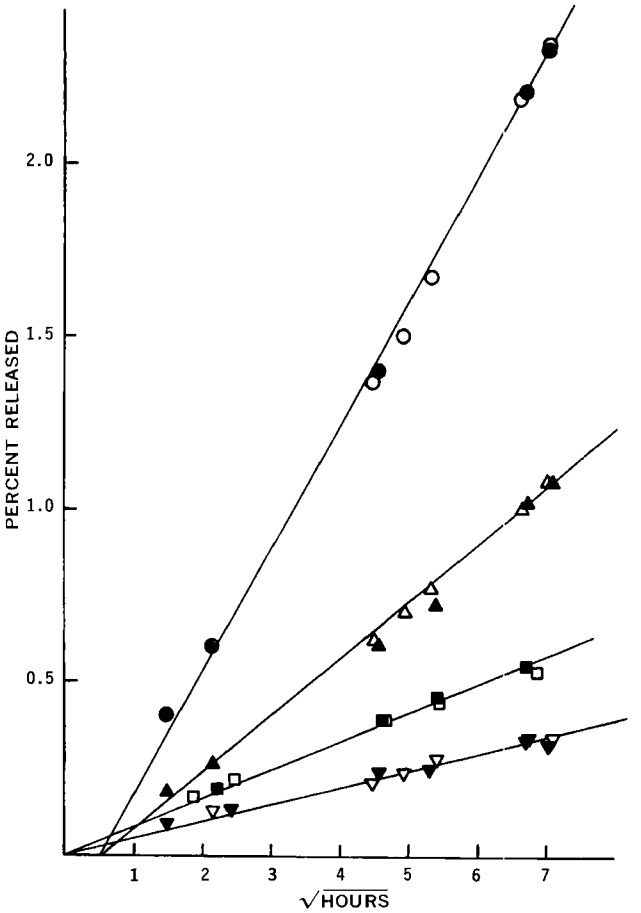

Figure 3—*Results of fluocinonide release from oleaginous ointments, showing the effect of the addition of various adjuvants to petrolatum. Empty and solid symbols represent data from two different runs. Key: ●, ○, 5% hexadecyl alcohol; ▲, △, 5% wool alcohol; ■, □, 5% Amerchol CAB; and ▼, ▽, 5% beeswax.*

Equation 1 may be rewritten to relate the percent drug release to time and variables of the system:

$$R = \sqrt{\frac{2 \times 10^4 DC_s^0t}{C_0h^2}} \qquad \text{(Eq. 2)}$$

where R is the percent drug release, and h is the thickness of the ointment layer.

The homogeneously dispersed drug particles should be in equilibrium with the drug in solution in the external phase of the ointment. Supersaturation or undersaturation of the drug in the external phase of the ointment might result, depending upon the manufacturing procedure. If the drug has not reached equilibrium within the ointment, different release profiles could result from the same ointment. When the initial concentration of the drug in the ointment is very low, changes in concentration due to nonhomogeneity or any other reason could also result in differences in release profiles. In light of these variables, release profiles showing the effect of adjuvants would have little meaning unless all of these factors have been accounted for.

Commonly used methods of determining the solubility of a drug in a liquid solvent cannot be used for solubility determinations in a semisolid ointment. For nonionic drugs that do not associate to form, for example, dimers in one of the two phases and for which the activity coefficients can be assumed to be unity in each phase,

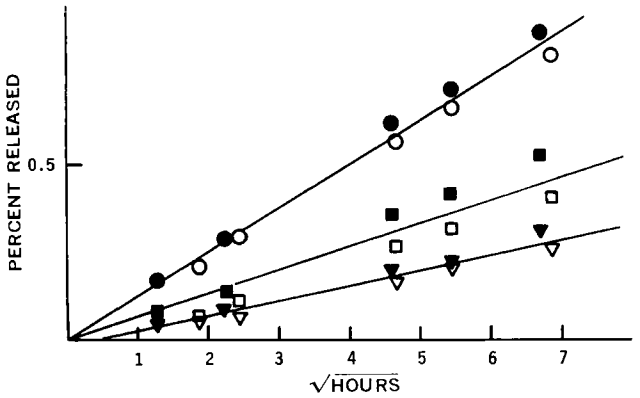

Figure 4—*Results of fluocinonide release from oleaginous ointments, showing the effect of the addition of various adjuvants to white petrolatum. Empty and solid symbols represent data from two different runs. Key: ●, ○, 5% coconut fatty acid; ■, □, 5% glyceryl stearate; and ▼, ▽, 5% glyceryl monostearate.*

the partitioning of the solute may be expressed in terms of the ratio of the concentrations in the two phases:

$$K = \frac{C_0}{C_a} \qquad \text{(Eq. 3)}$$

where K is the partition coefficient, and C_0 and C_a are the drug concentrations in the oil and aqueous phases, respectively.

When the amount of solute added is sufficiently small, the partition coefficient is relatively independent of the concentration. For solutes obeying Henry's law in each phase, changes in solute concentration would be expected to produce small changes in the partition coefficient. For these systems the effective partitioning of drugs near saturation between the two immiscible phases, such as ointment and water, can be expressed by:

$$K_e = \frac{A_0/W_0}{A_a/W_a} = \frac{(A_a^i - A_a)W_a}{A_a W_0} \qquad \text{(Eq. 4)}$$

where K_e is the effective partition coefficient; A_0 and A_a are the amounts of drug in the ointment and in the aqueous phase, respectively; A_a^i is the initial amount of drug in the water; and W_0 and W_a are the weights of the ointment and water, respectively.

Since the effective partition coefficient relates to the drug concentration in the two phases near saturation, the apparent solubility of the drug in an ointment can be determined from experimental drug solubility in water using:

$$C_s^0 = K_e C_s^w \qquad \text{(Eq. 5)}$$

where C_s^0 is the apparent solubility in the ointment, and C_s^w is the drug solubility in water.

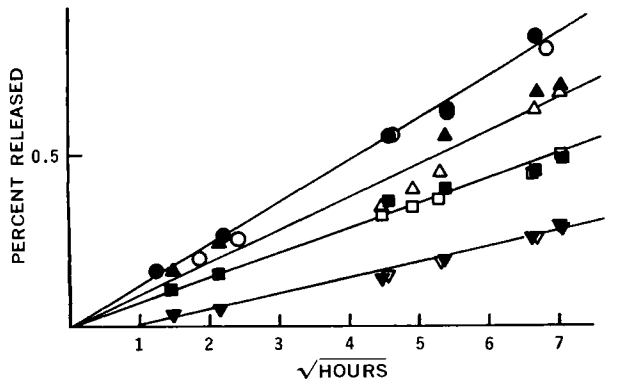

Figure 5—*Results of fluocinonide release from oleaginous ointments, showing the effect of the addition of various adjuvants to petrolatum. Empty and solid symbols represent data from two different runs. Key: ●, ○, 5% glyceryl monolaurate; ▲, △, 5% stearic acid; ■, □, 5% lecithin; and ▼, ▽, 5% cetyl alcohol.*

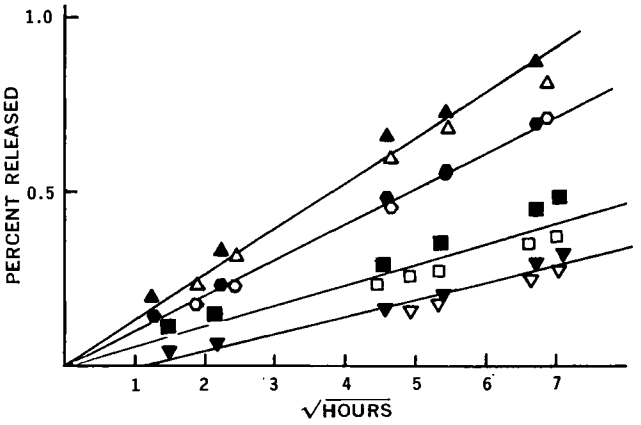

Figure 6—*Results of fluocinonide release from oleaginous ointments containing white petrolatum and adjuvants. Empty and solid symbols represent data from two different runs. Key: ▲, △, 5% Amerchol CAB + 2% sorbitan monostearate; ●, ○, 5% soya fatty acid; ■, □, petrolatum base six only; and ▼, ▽, 5% stearyl alcohol.*

RESULTS AND DISCUSSION

To determine the time required for reaching equilibrium solubilities of flucloronide and fluocinonide in different ointment bases, release runs were carried out after equilibrating the ointments for different time intervals. The apparent diffusion constants were calculated from the apparent drug solubilities in the ointments and the experimental release rates for each equilibrium time point. These data, given in Table I, indicate that the apparent solubility of the drugs had reached equilibrium as early as 5 days after preparation.

The results of flucloronide release from white petrolatum, showing the reproducibility of the experiment using the same ointment and using different ointments, are given in Fig. 2. These results indicate a lag time in all cases. Higuchi (1) pointed out that the initial lag time, L, corresponding to the time necessary for establish-

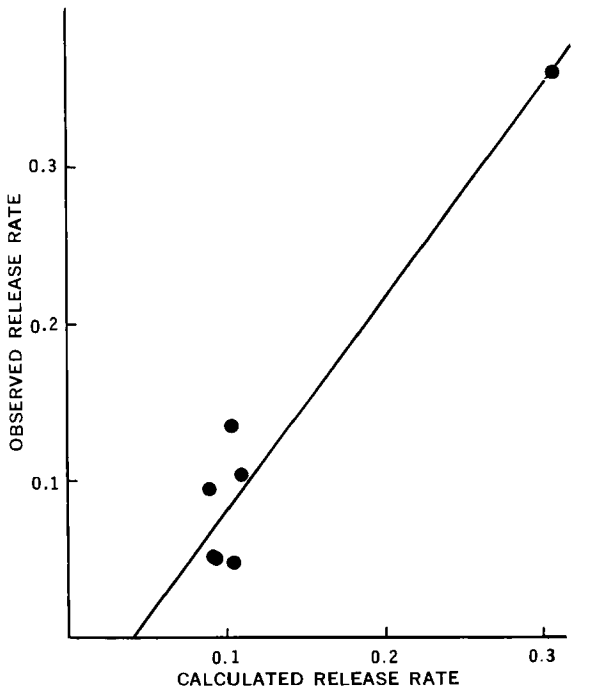

Figure 7—*Scatter diagram of the observed and calculated release rates of fluocinonide from Type I modified ointment bases. The line is the estimated regression line* $Y = 1.3461X - 0.0540$ *for solid circles.*

Table II—Parameter Values Determined from the Release and Partitioning Data of Fluocinonide for Ointments Prepared from Petrolatum and the Listed Adjuvants Using Eqs. 2 and 4

Adjuvant	K_e	C_s^0, μg/ml	Calculated Release Rate, %/$\sqrt{\text{hr}}$	Observed Release Rate, %/$\sqrt{\text{hr}}$
Type I				
Hexadecyl alcohol, 5%	10.61	4.46	0.308	0.360
Beeswax, 5%	1.01	0.42	0.094	0.049
Stearyl alcohol, 5%	0.96	0.40	0.092	0.050
Cetyl alcohol, 5%	1.25	0.52	0.105	0.047
Stearic acid, 5%	0.91	0.38	0.090	0.094
Hexadecyl stearate, 5%	1.26	0.53	0.106	—
Soya fatty acid, 5%	1.37	0.57	0.110	0.103
Coconut fatty acid, 5%	1.21	0.51	0.104	0.134
Type II				
Glyceryl monostearate, 5%	0.28	0.12	0.050	0.045
Glyceryl monolaurate, 5%	2.87	1.21	0.160	0.121
Wool alcohol, 5%	6.85	2.88	0.248	0.167
Amerchol CAB, 5%, + sorbitan monostearate, 2%	0.81	0.34	0.085	0.131
Amerchol CAB, 5%, + polysorbate 60, 2%	2.81	1.18	0.158	—
Lecithin, 5%	11.50	4.83	0.321	0.071
Glyceryl stearate, 5%	0.63	0.26	0.074	0.066
Amerchol CAB, 5%	0.86	0.36	0.087	0.083
None (petrolatum only)	0.39	0.16	—	0.058

ment of a quasistationary state would generally be less than:

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

where α is the mean distance between the suspended particles, D is the diffusion constant of the drug in the external phase of the ointment, and n is the order of 2 or 3. The derivation of Eq. 1 assumed the particulate distance to be extremely small for the model system relative to the layer thickness, and thus the lag time was expected to be very short in comparison to the depletion period. The lag time seen in the present study may be explained on the basis of this assumption. It could be primarily due to the experimental difficulty in producing a suspension of fine particles containing 0.05% drug. Since the steady-state flux is reflected in the slope, any lag time seen in this study was neglected.

The effective partition coefficient data and the apparent solubilities of fluocinonide in ointments containing different adjuvants are given in Table II. The plots of percent fluocinonide release *versus* square root of time are given in Figs. 3–6. Table II also gives the observed and calculated release rates of fluocinonide in various ointment bases. The calculated release rates were obtained from Eq. 2 using the apparent solubilities of the modified ointment bases and the diffusion constant of the drug molecule in pure petrolatum.

A comparison of the observed and calculated release rates for ointments containing hydrophobic adjuvants (Type I) is given in Fig. 7. The correlation between the two rates was very good (r = 0.96). However, an examination of the observed and calculated rates (Table II) for ointments containing mainly emulsifying agents (Type II) indicated that knowledge of the calculated release rates offers little help in predicting the observed rates (r = 0.34).

Table III gives the effective partition coefficient data and apparent solubilities of flucloronide in ointments containing various adjuvants. The observed and calculated release rates of flucloronide

Table III—Parameter Values Determined from the Release and Partitioning Data of Flucloronide for Ointments Prepared from Petrolatum and the Listed Adjuvants Using Eqs. 2 and 4

Adjuvant	K_e	C_s^0, μg/ml	Calculated Release Rate, %/$\sqrt{\text{hr}}$	Observed Release Rate, %/$\sqrt{\text{hr}}$
Type I				
Hexadecyl alcohol, 5%	8.29	19.90	5.10	3.93
Beeswax, 5%	2.53	6.07	2.81	1.28
Stearyl alcohol, 5%	2.79	6.70	2.96	1.40
Cetyl alcohol, 5%	2.72	6.53	2.92	1.17
Stearic acid, 5%	3.76	9.02	3.43	3.13
Hexadecyl stearate, 5%	5.35	12.84	4.09	2.69
Soya fatty acids, 5%	6.23	14.95	4.42	3.02
Coconut fatty acid, 5%	5.17	12.41	4.02	3.10
Type II				
Glyceryl monostearate, 5%	2.86	6.86	2.99	—
Glyceryl monolaurate, 5%	6.30	15.12	4.44	3.56
Wool alcohol, 5%	8.11	19.46	5.04	1.24
Amerchol CAB, 5%	4.20	10.08	3.63	0.72
Amerchol CAB, 5%, + sorbitan monostearate, 2%	3.71	8.90	3.41	1.43
Amerchol CAB, 5%, + polysorbate 60, 2%	7.02	16.84	4.69	2.79
Lecithin, 5%	14.05	33.72	6.63	2.98
Glyceryl stearate, 5%	4.55	10.92	3.78	2.98
None (petrolatum only)	2.07	4.97	—	2.55

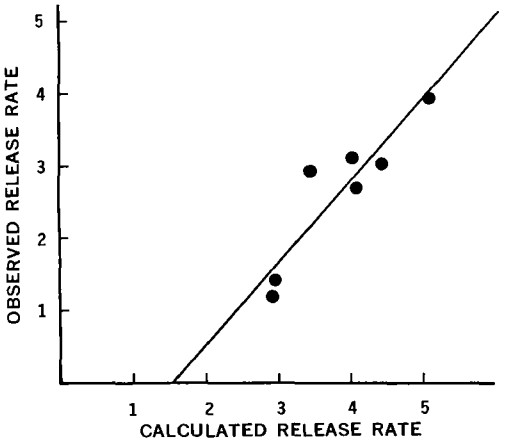

Figure 8—*Scatter diagram of the observed and calculated release rates of flucloronide from Type I modified ointment bases. The line is the estimated regression line* $Y = 1.1397X - 1.7732$ *for solid circles.*

are also given in Table III. For Type I adjuvants, these rates are plotted in Fig. 8. As in the case of fluocinonide, Fig. 8 indicates that the knowledge of calculated rates is helpful in predicting the release rates of flucloronide from ointments containing Type I adjuvants ($r = 0.90$). Type II adjuvants for flucloronide also gave a rather poor correlation between the observed and calculated rates ($r = 0.38$).

Negative intercepts were obtained in the observed *versus* calculated rate plots of Figs. 7 and 8. For the calculated rates, no association of the drug with the components of the ointment was assumed. If the drug has any tendency to bind with the ointment vehicle, the calculated rates would be higher than the observed rates. The negative Y intercept in Figs. 7 and 8 can thus be attributed to binding. In the calculations of release rates, it was also assumed that the diffusion constant remains constant when different adjuvants are added to petrolatum. Since the resistance to diffusion of drug molecules in the modified ointments is expected to vary depending on the adjuvant, some variations in the observed rates are expected due to changes in the diffusion constant of the modified vehicles.

Lack of correlation between the observed and calculated rates for Type II adjuvants indicates that the knowledge of calculated rates did not provide useful information in predicting the observed rates. Since Type II adjuvants are mainly emulsifying agents, during a release run the surfactant molecules are expected to orient at the ointment aqueous interface with their polar heads sticking in the aqueous phase and the hydrocarbon chain inside the ointment layer. Different surfactants are expected to dissolve and/or bind the drugs differently. Under these circumstances, the ointment–water interface and not the whole ointment layer may be the rate-determining step. The simple physical model used to calculate the release rates of drugs from ointment containing Type II adjuvants did not provide useful information in predicting the observed rates.

In summary, the results of this study show the usefulness of the physical model approach in helping to explain and predict the role of various factors in drug release from ointments containing suspended drug. In addition to drug solubility, initial drug concentration, and diffusion constant, drug release may be modified by unpredictable drug–excipient interactions. Surfactants are generally known to orient at the oil–water interface. The experimental observations of the ointment layer containing surface-active adjuvants before and after the release run indicated some changes in the ointment layer surface. Analysis of the data presented in this report has shown that the drug release from ointments containing surfactants as adjuvants cannot be explained solely by the simple equations used in this investigation.

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