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Influence of Drug Concentration on *In Vitro* Release of Salicylic Acid from Ointment Bases

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Abstract □ The effect of drug concentration on *in vitro* release of salicylic acid from a series of ointment bases was investigated. The bases were commercially available vehicles containing lanolin and/or lanolin derivatives and formed stable water-in-oil or oil-in-water emulsions. Release tests were performed both with the anhydrous and with the emulsion forms of the bases, at varying salicylic acid concentrations (0.5–5.0% w/v), and involved the use of silicone rubber membranes. The release of salicylic acid from the bases was in agreement with a reported diffusional model. A linear relationship between release rate, $q/\sqrt{t}$, and drug concentration in ointments existed when the drug was completely dissolved in the vehicles. The method reported is of potential utility for the determination of drug solubility in ointments and for the evaluation of the optimal drug concentration in topical vehicles. The relationships among type of vehicle, drug concentration, drug solubility, and release rate are discussed.

Keyphrases □ Vehicles (lanolin and lanolin derivatives)—*in vitro* release of salicylic acid, influence of drug concentration □ Ointment bases—influence of drug concentration on *in vitro* release of salicylic acid □ Drug concentration—influence on *in vitro* release of salicylic acid from ointment bases □ Lanolin and derivatives as ointment vehicles—influence of drug concentration on *in vitro* release of salicylic acid

It is generally recognized that a topical vehicle or base may affect drug penetration by modifying the permeability of the skin barrier phase and by releasing the drug to the skin in adequate amounts at a sufficient rate (1–3). A series of physicochemical factors, both pertaining to the drug and to the vehicle, appear to be involved in the latter process (4–6). Although several investigations have been directed toward determining these factors and elucidating their role in release, many unexplored points still exist whose study might prove profitable. The present paper is concerned with an *in vitro* study of the influence of drug concentration in different topical vehicles on release.

THEORETICAL

In the case of a membrane separating the donor and receptor phases, the release process may obey two different kinetic laws, depending on the resistance offered by the membrane to drug penetration. The relevant mathematical relationships have been developed and mainly investigated by T. Higuchi, W. I. Higuchi, and their coworkers (7–11). When the membrane offers little resistance to drug penetration (as may occur with injured skin or with some artificial membranes), large concentration gradients develop in the donor phase, and diffusional migration of the drug within the vehicle constitutes the slowest step in the release process. The following equations, derived from Fick's law, have been found to describe adequately the rate of release of drugs from ointment bases under these conditions (7, 10). The first equation refers to uniform solutions of drugs in ointments:

$$Q = q/A = 2C\sqrt{Dt/\pi} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug (q) released to the sink at time t per unit area (A) of contact, D is the diffusion coefficient of drug in the vehicle, and C is the initial concentration of drug in the vehicle, expressed in units per milliliter. The second equation refers to suspension-type ointments:

$$Q = q/A = \sqrt{Dt(2C - Cs)Cs} \qquad \text{(Eq. 2)}$$

where C is the total drug concentration, and Cs is the solubility of drug in ointment; both values are expressed in units per milliliter. Equations 1 and 2 predict that plots of the amounts of drug released with $\sqrt{t}$ will give straight lines passing through the origin. The origin as intercept may not be observed in some cases because of the lag time phenomenon (12).

The preceding model is based on a series of simplifying assumptions: *(a)* only a single drug species is important in the base; *(b)* the diffusion coefficient is constant with respect to both time and position in the base; *(c)* the drug alone is allowed to diffuse out of the base; *(d)* the drug is rapidly removed upon reaching the base–membrane interface, and the receiving phase is a "perfect sink"; *(e)* the percent drug released is not too large (<30%) in the case of solutions; and *(f)* C is substantially greater than Cs in the case of suspensions.

The assumption that D must be constant with respect to both time and position is a serious limitation, because in many situa-

tions involving emulsions the diffusion coefficient is not constant but varies with concentration. Koizumi and Higuchi (12) were able to show that even if D is concentration dependent the release pattern is the same as where D is constant. The equation for the amount of drug released becomes:

$$Q = 2a\sqrt{t} \qquad \text{(Eq. 3)}$$

where a is a constant, dependent on the initial drug concentration and on a function describing the change of D.

Rearranging Eq. 1:

$$q/\sqrt{t} = 2AC\sqrt{D/\pi} \qquad \text{(Eq. 4)}$$

shows the relationship existing between the release rate, $q/\sqrt{t}$, and C, the overall concentration of drug dissolved in ointment. According to Eq. 4, plots of release rates observed at different drug concentrations against the corresponding concentrations should be linear, with zero intercept and slope = $2A\sqrt{D/\pi}$. Such a linear relationship should hold until C exceeds the effective solubility, Cs. In the presence of suspended drug, release conditions described by Eq. 2 should prevail; accordingly, a different relationship between overall drug concentration and release rate might be observed. One main purpose of the present study was to test the scope and usefulness of Eq. 4 in a series of practical cases.

EXPERIMENTAL

Materials—Finely powdered, reagent grade salicylic acid[1] was used. Hydrophilic ointment and hydrophilic petrolatum, used as reference bases, were prepared according to USP XVIII. Dimethyl polysiloxane[2] (silicone rubber) sheeting, in a labeled thickness of 5 mil, was used as a membrane material. More than 40 commercial ointment bases, containing lanolin and/or lanolin derivatives, were submitted to a preliminary screening aimed at selecting the bases forming stable emulsions on admixture with an equal weight of water. An emulsion was considered stable if it showed no phase separation after storage at 40° for 30 days. The following bases were selected.

A. A mixture of sterols and sterol esters derived from wool grease and refined lanolin[3,4].

B. A balanced blend of cosmetic grade, anhydrous lanolin USP reacted with ethylene oxide plus *p*-oxybenzoates and antioxidants[3,5].

C. A mixture of pure, natural lanolin sterols in free alcohol form, free of fatty acids and esters and of preservatives[3,6].

D. A blend of sterols, fatty alcohols, and partial esters of fatty alcohols, waxes, and mineral oils[3,7].

E. A mixture of 30- and 75-mole ethoxylated lanolin (about 30% of total) plus hydrocarbon oils and cetyl and stearyl alcohols[3,8].

F. A mixture of cholesterol, alcohols, and esters obtained from lanolin (60% of total) in an oily vehicle analogous to human sebum[3,9].

Apparatus—The release of salicylic acid through silicone rubber membranes was investigated using a specially designed stainless steel cell (Fig. 1). The capacity of the cell was 5.0 ml, and the diameter of the available area for diffusion was 50 mm. For use, the filled cell was placed in a jacketed beaker (internal height 11.0 cm, internal diameter 10.0 cm) connected with a constant-temperature bath and circulator. The solution external to the cell was stirred using a 300-rpm synchronous motor[10]. The system was designed to produce reasonably fast release rates and to avoid absorption of salicylic acid by the cell material.

Preparation of Ointments—Emulsions were prepared by slowly adding distilled water, heated at 70°, to an equal weight of base, heated at the same temperature, while stirring. After cooling to room temperature, the emulsions were roll milled[11] twice. They are

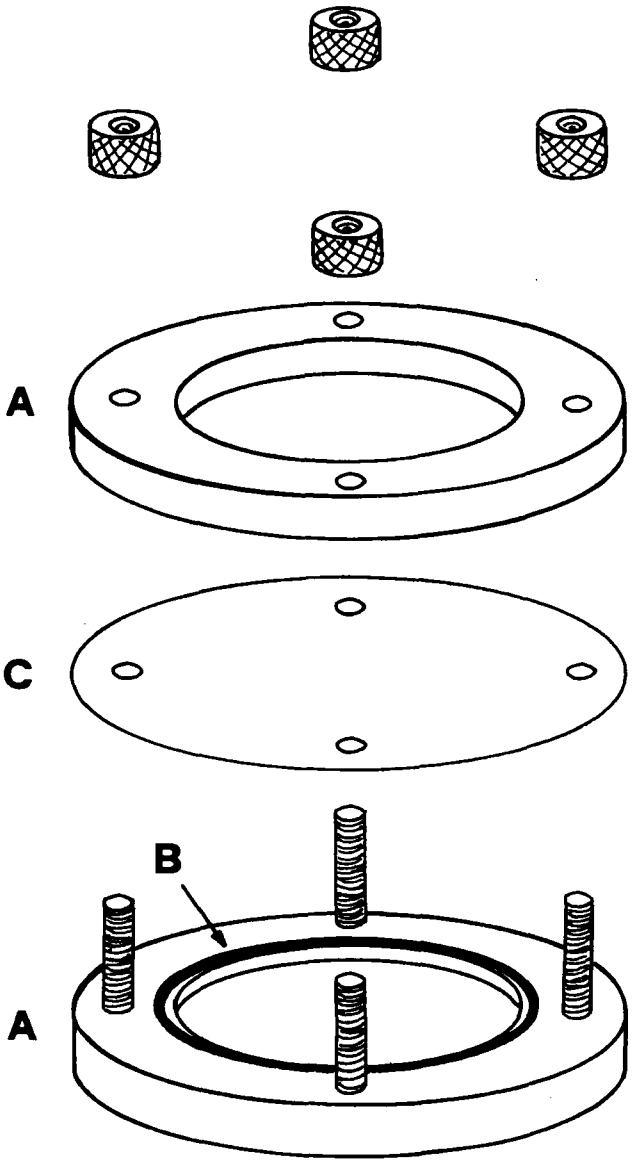

Figure 1—*Diffusion cell used for release experiments. Key: A, stainless steel cell body and plate; B, O-ring gasket; and C, silicone rubber membrane.*

indicated as X/H_2O, where X is the symbol of the anhydrous base. Salicylic acid (final concentrations of 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 5.0 w/v) was incorporated in anhydrous and emulsion bases by levigation, using a mortar and pestle. The resulting ointments were roll milled twice and stored at room temperature. Prior to use, each ointment was kept 2 days at 30°.

Solubility of Salicylic Acid in Anhydrous Bases—The method described by Mayer and Kedvessy (13) was followed with minor modifications. Finely powdered salicylic acid was stirred into each base at 80° in a series of concentrations ranging from 0.5 to 7.0% (w/v), with 0.2-g increments up to 3.0% and 0.5-g increments up to the maximum concentration of 7.0%. After cooling to room temperature, the ointments were roll milled twice and stored in a thermostatic oven at 30 ± 0.1°. After 30 days, they were examined using a 40× microscope[12] for the presence of suspended particles. The solubility value, Cs, was taken as the highest concentration at which no suspended crystals were visible.

Release from Ointments—The cell was filled with an ointment; the excess was removed with a spatula to produce an even surface; and the membrane, which had been presoaked in water for at least 12 hr, was carefully placed and pressed on the ointment. A

[1] Carlo Erba, Milano, Italy.
[2] Silastic, Medical Products Division, Dow Corning Corp., Midland, Mich.
[3] List of main components as given by the technical literature.
[4] Falba, Pfaltz & Bauer, Inc., Flushing, N.Y.
[5] Lanobase S. E., Lanaetex Products, Inc., Elizabeth, N.J.
[6] Nimcolan 11, Malmstrom Chemical Corp., Linden, N.J.
[7] Protegin X, Th. Goldschmidt A. G., Essen, West Germany.
[8] Sebase, Westbrook Lanolin Co., Bradford, England.
[9] Sebolan, Croda Ltd., London, England.
[10] Crouzet S. A., Paris, France.
[11] Erweka GmbH, Frankfurt am Main, West Germany.
[12] Zeiss Zoom III Stereomicroscope.

new membrane was used for each release run. The upper part of the cell was then assembled, thus securing the membrane in place. Prewarmed 0.01 *N* NaOH (200 ml) was introduced into the jacketed beaker, into which the cell was immediately placed, and stirring was initiated. At intervals, 100-ml portions of the solution were removed and replaced at once with an equal amount of prewarmed 0.01 *N* NaOH. This procedure allowed a direct spectrophotometric[13] determination (297 nm) of salicylic acid in the samples, thus simplifying the calculations. Sodium hydroxide was added to avoid retrodiffusion of the drug into the membrane, although the periodic removal of solution was sufficient to ensure sink conditions. Blank runs, performed on all bases, demonstrated the absence of diffusable substances, which might interfere with the measurements.

Statistical Evaluation of Data—The release results obtained with all bases and with the reference bases, containing 1.0 and 3.0% (w/v) salicylic acid, were compared to detect statistical differences between individual bases. Each experiment was repeated at least four times, and the average values obtained for each experimental point were used to draw the individual q *versus* $\sqrt{t}$ plots (*e.g.*, Figs. 2 and 3). For each experiment, statistical differences were assessed by employing the Student t test and comparing experimental points corresponding to identical values on the time axis. A significant difference between two bases was assumed to exist if all experimental points, except the first pair (1 hr), were significantly different at the 5% level.

RESULTS AND DISCUSSION

Release Rate Studies—The experiments of salicylic acid release from the bases investigated were carried out over 6 hr at concentrations ranging from 0.5 to 5.0% (w/v). In all cases, linear plots were obtained when the amount of salicylic acid released to the aqueous phase was plotted *versus* the square root of time. The release patterns obtained from the anhydrous and from the emulsion bases containing 1.0% salicylic acid are illustrated in Figs. 2 and 3, respectively. The data obtained with the reference bases are also included for comparison. In no case did the plots in Figs. 2 and 3 pass through the origin. Several examples reported in the literature also exhibit a lag time for the release of a drug across an artificial membrane (12, 14–17), and this phenomenon has been associated with the presence of the membrane separating the bulk phase and sink.

As indicated by Koizumi and Higuchi (12), two distinct lag times may be operative in similar cases; one is the classical lag time of Barrer (18), which is a measure of the time required for the absorption of drug by the membrane, and another results from a diffusion coefficient of the drug in the membrane smaller than that in the bulk phase. Steady-state diffusion experiments (not reported here) of salicylic acid in aqueous solution through a 5-mil silicone rubber membrane have shown Barrer's lag time to be of the order of a few seconds. The lag time observed in the present case, about 20 min, should, therefore, result from slow membrane diffusion[14]. The slower diffusivity of the permeant in the membrane is probably due to a greater rigidity of the polymeric units forming the silicone film, compared with the materials of the bulk, and to adsorption of the diffusant on the siliceous filler in the membrane. Indeed, the diffusion process is known to be slower when diffusion is accompanied by adsorption onto internal sites (19). The presence of a small but definite lag time probably indicates nonperfect sink conditions at the vehicle–membrane interface. However, even if this system does not comply exactly with the theoretical model, it should approximate the theoretical requirements, at least within the scope of the present investigation.

Release was faster from the emulsions than from the corresponding anhydrous bases, in agreement with other workers (1, 4, 20–23). Among emulsion bases, there was no clear trend to faster release from oil-in-water compared with water-in-oil types. This appears to confirm the reports of Barrett *et al.* (24) and of Sarkany *et al.* (25), who found no marked difference in skin penetration of methylnicotinate and of betamethasone valerate, respectively, from oil-in-water or water-in-oil creams. The anhydrous base, E, giving rise to a water-in-oil emulsion, showed the fastest release. It is possible that the absence of high hydrophilic–lipophilic balance emulsifiers, favoring formation of oil-in-water emulsions and endowed with a great interactive nature for salicylic acid (26–28), might have favored a faster release from this base. Release from

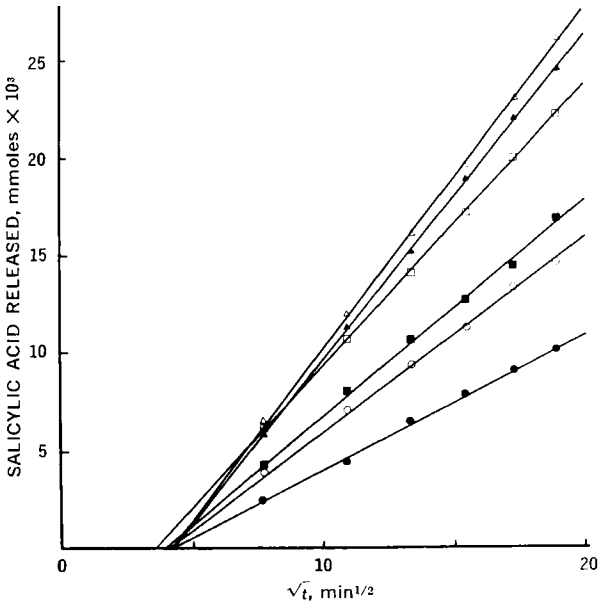

Figure 2—*Release of salicylic acid from anhydrous 1.0% (w/v) ointments at 30°. Key: △, D (and F, not shown for clarity of graph); ▲, hydrophilic petrolatum; □, A; ■, C; ○, E; and ●, B.*

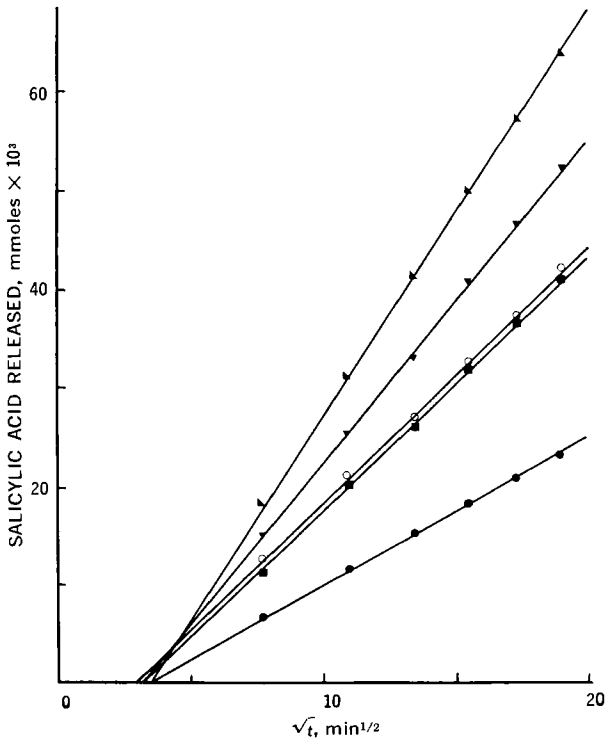

Figure 3—*Release of salicylic acid from 1.0% (w/v) emulsion-type ointments at 30°. Key: ▲, F–H_2O; ▼, hydrophilic ointment, A–H_2O, and D–H_2O (last two not shown for clarity of graph); ○, E–H_2O; ■, C–H_2O; and ●, B–H_2O.*

[13] Zeiss PMQ II spectrophotometer.

[14] The very small differences observed for the individual lag times probably originated from the different diffusion coefficients of the drug in the various bases. Slight modifications of the membrane by some ingredient of the bases might also contribute to the observed differences. Neither factor, however, should affect the validity of the experimental model. A study on membrane effects (drug transport through and partition with the membrane) in this model is now in progress.

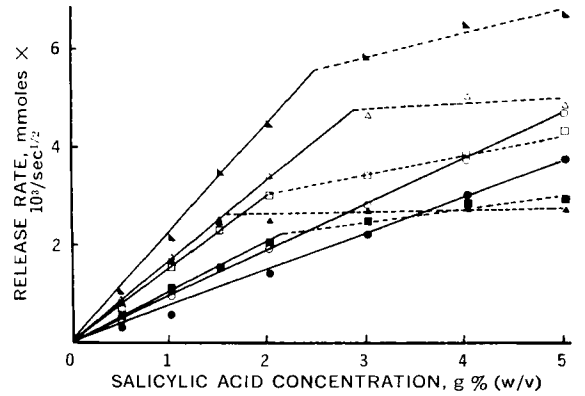

Figure 4—*Plot showing the effect on release rate of increasing concentration of salicylic acid in anhydrous ointments. Key: ▼, F; △, D; ○, E; □, A; ●, B; ■, C; and ▲, hydrophilic petrolatum.*

hydrophilic ointment was faster than from hydrophilic petrolatum, in agreement with *in vitro* (4) and *in vivo* (29) results.

Drug Concentration-Release Rate Relationship—To test the validity of Eq. 4, the release rates, $q/\sqrt{t}$, of the ointments containing salicylic acid in the 0.5–5.0% (w/v) concentration range were plotted *versus* the corresponding concentrations (Figs. 4 and 5, anhydrous bases and emulsions, respectively). Linear plots with zero intercept, as predicted by Eq. 4, were obtained only from two bases (B and E). The solubility of salicylic acid in the anhydrous form of these bases exceeded 7.0% (w/v), and, in all probability, the drug was soluble in the corresponding emulsions up to the maximum concentration tested in the release experiments (5.0%). The $q/\sqrt{t}$ *versus* C graphs of all other anhydrous bases, in which a lower solubility of salicylic acid had been verified, showed a linear portion with zero intercept, followed by a sudden change in slope in correspondence to a point on the abscissa coinciding with the solubility limit of salicylic acid, determined visually (*cf.*, Table I). This finding also appears to agree with Eq. 4, which predicts a linear dependency of $q/\sqrt{t}$ on C when C is below the solubility of the drug in the ointment. The emulsions gave similar graphs, showing slope changes at lower drug concentration with respect to the corresponding anhydrous bases. It might be assumed that these changes also correspond to the maximum solubility, Cs, of the drug in the emulsions. These lower "saturation" values agree with the fact that solubility of salicylic acid in the emulsions ought to be lower than in the corresponding anhydrous bases because of the low solubility of the drug in water. The "solubility" values of salicylic acid in all ointments, in grams percent (w/v), obtained graphically from the plots are reported in Table I. The agreement between these values and those independently obtained for the anhydrous bases is quite satisfactory. The apparent diffusion coefficients, D', of salicylic acid in all ointments, calculated with Eq. 4 from the first portions of the $q/\sqrt{t}$ *versus* C plots, are also reported in Table I.

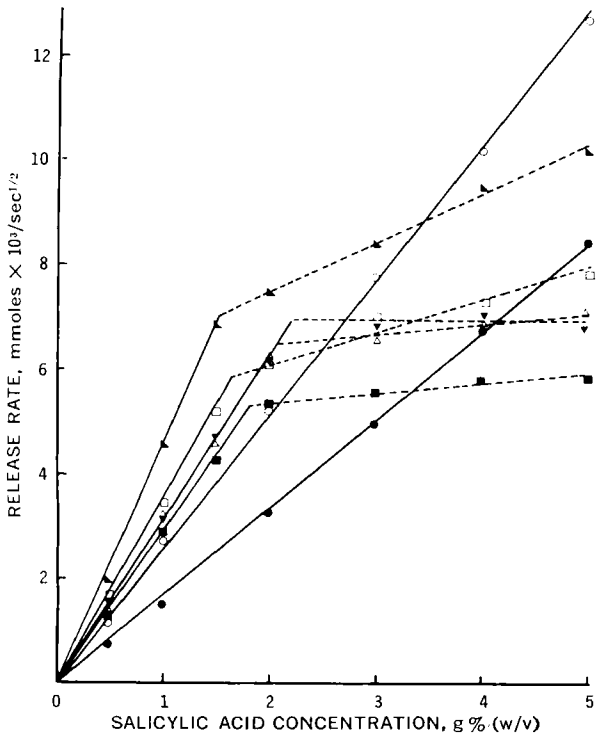

Figure 5—*Plot showing the effect on release rate of increasing concentration of salicylic acid in emulsion-type ointments. Key: ○, E–H₂O; ▲, F–H₂O; □, A–H₂O; △, D–H₂O; ▼, hydrophilic ointment; ■, C–H₂O; and ●, B–H₂O.*

Table I—Solubility and Apparent Diffusion Coefficients of Salicylic Acid in Ointments

Base (Emulsion Type)[a]	Solubility, g % (w/v)		Apparent Diffusion Coefficient, D', $cm^2\ sec^{-1} \times 10^6$
	Microscopic Data	Release Data	
A	2.00	2.00	0.89
A–H_2O (oil-in-water)	—	1.60	4.95
B	7.00	5.00	0.23
B–H_2O (oil-in-water)	—	5.00	1.09
C	2.00	2.15	0.42
C–H_2O (water-in-oil)	—	1.80	3.45
D	3.00	2.90	1.05
D–H_2O (water-in-oil)	—	2.05	4.00
E	7.00	5.00	0.33
E–H_2O (oil-in-water)	—	5.00	2.69
F	2.50	2.45	1.99
F–H_2O (water-in-oil)	—	1.50	8.53
Hydrophilic petrolatum	1.50	1.55	1.20
Hydrophilic ointment (oil-in-water)	—	2.20	4.10

[a] Determined by the electrical conductivity method.

Whether the slope changes observed with the emulsions also correspond to the saturation of the vehicles by the drug might be open to some doubt. Indeed, an essential condition for the validity of Eq. 4 is the constancy of the diffusion coefficient, and this factor has been found to be concentration dependent in the case of some emulsions (12). However, the linearity of the plots within a definite concentration range and their zero intercept might indicate that D is sufficiently concentration independent in the present case to not interfere too seriously with the application of Eq. 4 or, at least, that there is a linear dependency of $2a$ (Eq. 3) on C. This point, however, might deserve further investigation. If it is assumed that the change in slope in the $q/\sqrt{t}$ *versus* C graphs is related to the saturation of the vehicles by the drug rather than to a sudden change of D with increasing concentration (particularly in the case of emulsions), application of Eq. 4 might yield useful information on the solubility of drugs in ointments in cases where visual methods for determining solubility are not applicable (emulsions or otherwise opaque vehicles) and might give direct insight on the effect on the release rate of drug concentration and solubility in vehicles.

Adherence to Eq. 2 of saturated ointments was not satisfactory in most cases. One essential condition for the validity of Eq. 2 is that the amount of drug present per unit volume, C, be substantially greater than the solubility, Cs; this condition was probably approximated only at the highest concentrations tested. An inadequate dissolution rate of the suspended particles (9, 15) might also be responsible for the unsatisfactory adherence to Eq. 2; this factor seems evidenced by the independence of release rate on drug concentration shown by many saturated ointments. An approximate zero-order dependence of release on drug concentration for saturated systems was observed by others (15).

Figures 4 and 5 clearly show that release proceeds most efficiently only within the solubility range; after saturation, a further increase of drug concentration may have little effect on the release rate. Therefore, the presence of excess undissolved drug in a vehi-

Table II—Groups of Bases Showing Release Rates Not Statistically Different at the 5% Probability Level

Salicylic Acid Concentration	
1.0% (w/v)	3.0% (w/v)
Hydrophilic ointment; D–H_2O	Hydrophilic ointment; D–H_2O; A–H_2O
C–H_2O; E–H_2O	B–H_2O; D
Hydrophilic petrolatum; D; B–H_2O	Hydrophilic petrolatum; E

cle may be wasteful in cases where the rate of release, rather than the total amount of released drug, is therapeutically important. The solubility factor assumes a paramount importance when release rates of different bases are compared. One base might show, with respect to a reference base in which the drug is more soluble, faster release rates at a low drug concentration and slower rates at a higher drug concentration. The release rate at 1% salicylic acid was faster for D–H_2O than for E–H_2O, while the opposite occurred at the 3% concentration. Thus, comparison of release properties made at a single drug concentration, with no concern for solubility, may offer only a partial view of the drug-releasing potentiality of different vehicles.

Statistical Evaluation of Data—Table II summarizes the results of the statistical tests. Only groups of bases giving release results that are not statistically different at the 5% level are indicated. One objective of the tests was to assess whether relative identities in release rates within groups would be maintained at different drug concentrations (1.0 and 3.0%). Only one pair of ointments [hydrophilic ointment–(D–H_2O)] released salicylic acid at relatively identical rates at both concentrations. Most bases in Table II showing release rates not statistically different at one concentration had dissimilar rates at the other, and vice versa. This effect, presumably due to saturation of the vehicle by the drug, was discussed in a previous section. At the 3% concentration, salicylic acid was not completely dissolved in most bases (*cf.*, Table I).

CONCLUSIONS

The present results, although needing further experimental support, are indicative of a practical method for obtaining information on the solubility of drugs in topical vehicles and on interactions between drugs and vehicles that might influence drug absorption. The results indicate that the solubility of a drug in the vehicle plays an important role in release and should be carefully considered when selecting or developing a base. Such knowledge may be essential for the selection of the most therapeutically effective base and for the determination of the most effective drug concentration in a given base.

During the present investigation, several commercial "lanolin" bases were examined, and their different release characteristics were pointed out. The different release rates observed at low drug concentration might possibly be rationalized in terms of different diffusivity of the drug in the various bases. An investigation on the correlations between the composition (and/or structure) of the bases and drug diffusivity within them was beyond the scope of the present work, but the problem might deserve further study.

Some bases showed particularly good release characteristics when compared with the standard vehicles, hydrophilic ointment and hydrophilic petrolatum. It is possible that the same bases might show a similar action *in vivo*, in analogy with other fatty substances (30) and water-in-oil emulsifiers (31) acting as "sorption promotors" (32). Further *in vivo* experiments have been planned to verify this hypothesis.

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