Effect of Various Liquids on the Diffusion of Salicylic Acid from Ointment Bases

By CLYDE W. WHITWORTH

Water, alcohol, and dimethyl sulfoxide were each incorporated at 1, 2, and 5 percent concentrations into four ointment bases containing salicylic acid. The bases tested were white petrolatum, a hydrogenated cottonseed oil base, a water-in-oil emulsion base and an oil-in-water base. The diffusion of salicylic acid from five samples of each mixture was determined at 20-min. intervals for a period of 2 hr. All three liquids enhanced diffusion from the white petrolatum base and the water-in-oil base but tended to inhibit diffusion from the cottonseed oil base and the oil-in-water formula. In some instances the concentration of liquid appears to have an effect. Statistical analyses of data point out significance of differences.

THE TRANSFER ability of the skin is probably very strongly influenced by the presence of moisture as suggested by Higuchi (1). He showed that near 100% relative humidity the permeability of glyceryl monostearate was dependent on water activity. Wurster and Kramer (2) showed an increase in absorption of three salicylate esters accompanied increased moisture conditioning. Shelmire (3) has stated that hydration of the stratum corneum appears to increase the rate of passage of all substances which penetrate the skin.

Since moisture greatly influences percutaneous absorption, it was decided that a study of drug release from different ointment bases as influenced by various liquids might yield useful information. It is recognized that *in vitro* drug release measurements may be difficult to correlate with *in vivo* results; however, such studies may be useful in discovering and observing interactions between drugs and vehicles which in turn influence drug absorption. Diffusion techniques have been extensively employed to measure drug release especially from heterogeneous preparations such as ointments (4) and emulsions (5).

EXPERIMENTAL

Three liquids, water, alcohol, and dimethyl sulfoxide, were incorporated at 1, 2, and 5% concentrations into four different ointment bases. The bases consisted of:

(*a*)	White petrolatum USP (Standard Oil Co.)	
(*b*)	Water-in-oil base:	
	White petrolatum USP	64%
	Sorbitan monooleate[1]	6%
	Distilled water	30%
(*c*)	Oil-in-water base:	
	Stearyl alcohol[2]	25%
	White petrolatum USP	25%
	Glycerin[2]	12%
	Polysorbate 80[3]	5%
	Distilled water	33%
(*d*)	Partially hydrogenated cottonseed oil[4]	90%
	Completely hydrogenated cottonseed oil[5]	10%

The bases were prepared by fusion at low temperatures. The salicylic acid was added to the warm base and the mixture stirred until it cooled in order to achieve homogeneity. The liquids were mixed with the ointments just prior to use in order to minimize loss by evaporation.

Five samples of each ointment were packed into hollow plastic stoppers which had a top (open end) diameter of 40 mm., a bottom diameter of 30 mm., and a depth of 25 mm. The open end was then covered by a membrane (supplied by Young Drug Co.) and sealed by a rubber band so that the entire exposed surface of the ointment was brought into contact with the membrane. The containers were then inverted in 60 ml. of distilled water contained in 4-oz. ointment jars and the tops put on the jars to prevent evaporation of the diffusion media. The jars were then placed in a constant-temperature shaker-type water bath at 37.5°. At 20-min. intervals for 2 hr. the diffusion medium of each sample was assayed for salicylic acid content by reading absorbance on a Beckman DU spectrophotometer at 297 mμ. The assay samples were returned to the diffusion media each time in order to maintain volume.

Controls consisted of the base and the salicylic acid without additional liquids. All bases contained 2% by weight of salicylic acid except the oil-in-water base which contained 1% due to the rapid rate of diffusion from this vehicle.

Figures 1–12 are plots of the concentration of salicylic acid in the diffusion media against time. Each point represents the average of five samples.

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[1] Trademarked as Arlacel 80, Atlas Chemical Industries, Inc., Wilmington, Del.

[2] Fisher Scientific Co.

[3] Trademarked as Tween 80, Atlas Chemical Industries, Inc., Wilmington, Del.

[4] Trademarked as Cotmar, Procter and Gamble Co., Cincinnati, Ohio.

[5] Trademarked as Cotoflakes, Procter and Gamble Co., Cincinnati, Ohio.

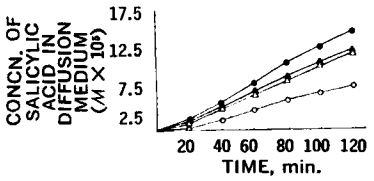

Fig. 1—Diffusion of 2% salicylic acid from white petrolatum (○), and from white petrolatum containing: 1% water (●), 2% water (△), and 5% water (▲).

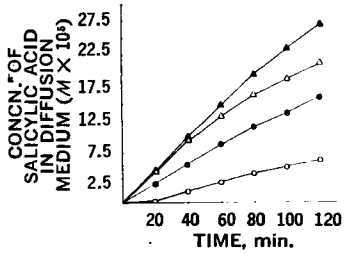

Fig. 2—Diffusion of 2% salicylic acid from white petrolatum (○), and from white petrolatum containing 1% ethanol (●), 2% ethanol (△), and 5% ethanol (▲).

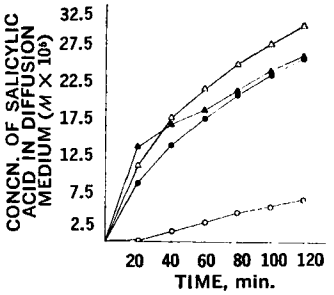

Fig. 3—Diffusion of 2% salicylic acid from white petrolatum (○), and from white petrolatum containing: 1% DMSO (●), 2% DMSO (△), and 5% DMSO (▲).

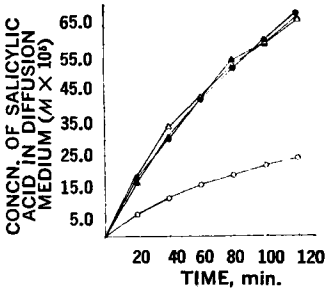

Fig. 4—Diffusion of 2% salicylic acid from a w/o base (○), and from a w/o base containing: 1% water (●), 2% water (△), and 5% water (▲).

RESULTS AND DISCUSSION

White Petrolatum Base—The diffusion of salicylic acid from white petrolatum base proceeded more slowly than from any of the other bases. All concentrations of all three liquids significantly increased the rate of diffusion of the drug, however, as seen in Figs. 1–3. Of the three liquids used water is

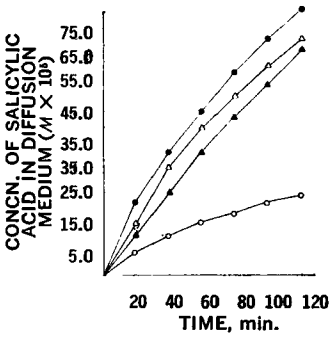

Fig. 5—Diffusion of 2% salicylic acid from a w/o base (○), and from a w/o base containing: 1% ethanol (●), 2% ethanol (△), and 5% ethanol (▲).

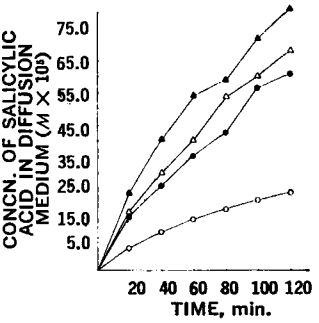

Fig. 6—Diffusion of 2% salicylic acid from a w/o base (○), and from a w/o base containing: 1% DMSO (●), 2% DMSO (△), and 5% DMSO (▲).

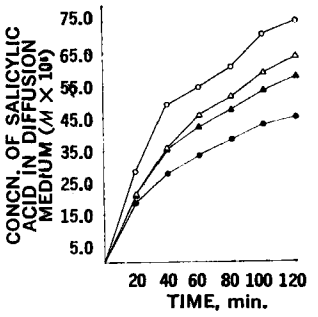

Fig. 7—Diffusion of 1% salicylic acid from an o/w base (○), and from an o/w base containing: 1% water (●), 2% water (△), and 5% water (▲).

seen in Fig. 1 to have the least effect, dimethyl sulfoxide (DMSO) the greatest effect, the results with alcohol falling in between. While it is evident that all three liquids increase diffusion, the influence of the concentration of each liquid on diffusion does not follow a similar pattern for all liquids. In the case of water a significant difference exists only between the results with 1 and 2% water. Other differences may be taken as due to chance. In Fig. 2 each increase in concentration of alcohol shows an increase in rate of diffusion. All differences are significant. As seen in Fig. 3, DMSO has a great effect on the diffusion process with the 2% concentration showing the greatest influence. All differences at 2 hr. are significant except between

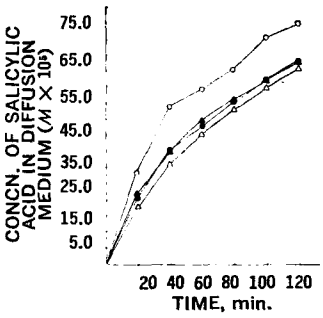

Fig. 8—Diffusion of 1% salicylic acid from an o/w base (○), and from an o/w base containing 1% ethanol (●), 2% ethanol (△), and 5% ethanol (▲).

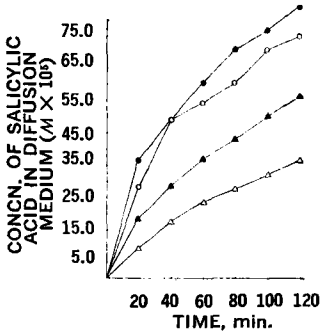

Fig. 9—Diffusion of 1% salicylic acid from an o/w base (○), and from an o/w base containing: 1% DMSO (●), 2% DMSO (△), and 5% DMSO (▲).

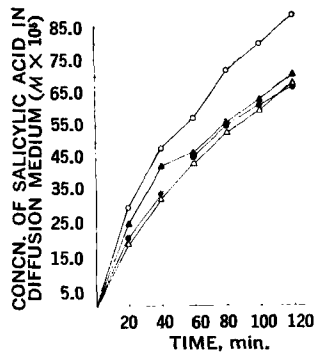

Fig. 10—Diffusion of 2% salicylic acid from a cottonseed oil base (○), and from a cottonseed oil base containing: 1% water (●), 2% water (△), and 5% water (▲).

1 and 5% amounts of DMSO. The crossover seen between the 2 and 5% DMSO is probably due to a lack of homogeneity of the mixture containing 5% DMSO, a condition which tends to diminish as the diffusion process proceeds.

Water-In-Oil Base—Figure 4 shows all three concentrations of water to significantly increase the diffusion of salicylic acid from the water-in-oil emulsion base by about the same amount. Comparisons by statistical analyses show no significant differences in the results from the treated bases at the 2-hr. mark.

Alcohol significantly increases the diffusion of the drug in all concentrations (Fig. 5). The diffusion rate, however, tends to decrease as the concentration of alcohol increases with the 1% concentration giving the greatest rate of passage. All differences are statistically significant.

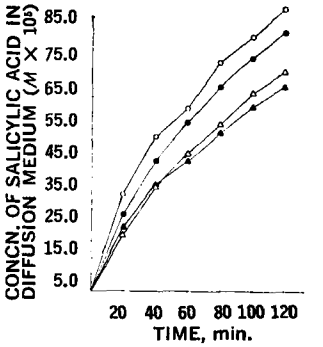

Fig. 11—Diffusion of 2% salicylic acid from a cottonseed oil base (○), and from a cottonseed oil base containing: 1% ethanol (●), 2% ethanol (△), and 5% ethanol (▲).

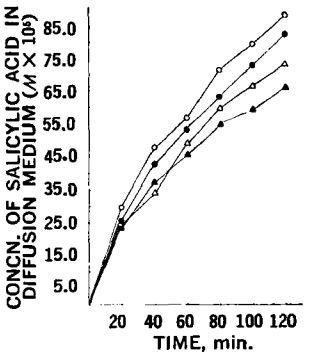

Fig. 12—Diffusion of 2% salicylic acid from a cottonseed oil base (○), and from a cottonseed oil base containing: 1% DMSO (●), 2% DMSO (△), 5% DMSO (▲).

Dimethyl sulfoxide (Fig. 6) significantly increases the diffusion of salicylic acid from this base. The 5% concentration has the greatest effect and all differences in the points of 2 hr. are significant except between 1 and 2%.

Oil-In-Water Base—In the case of the oil-in-water emulsion base it was necessary to reduce the concentration of salicylic acid from 2 to 1% because of the rapid rate of diffusion. In this base all concentrations of all liquids except 1% DMSO were found to be retard diffusion. The 1% concentration of water (Fig. 7) is seen to have the greatest effect in inhibiting the diffusion process. All differences at 2 hr. are significant except between 2 and 5%.

Alcohol in all three concentrations significantly retards diffusion (Fig. 8). However, there is no significant difference among the results from the different amounts of alcohol at the 2-hr. point.

Figure 9 shows 1% dimethyl sulfoxide to significantly increase the diffusion of drug from this base however the 2 and 5% concentrations significantly inhibit the process. The 2% quantity has the greatest effect of inhibition of the three concentrations used.

Cottonseed Oil Base—Results with the cotton-

seed oil base were similar to those with the oil-in-water emulsion in that all three liquids inhibited diffusion. Figure 10 shows the three concentrations of water to significantly retard diffusion. However, the results with water do not differ significantly from each other.

The results with alcohol differ significantly from the control (Fig. 11). As the concentration of alcohol is increased, the retardation of diffusion becomes more pronounced. However, the results with the 2 and 5% do not differ significantly.

The results with DMSO and this base (Fig. 12) are very similar to those obtained with alcohol. All differ significantly from the control. As with the alcohol and this base the difference in results between 2 and 5% DMSO may be taken as due to chance and is not significant. Again as the concentration of liquid is increased inhibition of diffusion becomes more pronounced.

CONCLUSIONS

Undoubtedly the solubility of a drug in an ointment base plays a major part in the diffusion or release of the drug from that base (6). For the most part the solubility of a drug in an intact ointment base is impossible to determine with any degree of confidence due to the fact that one is working with a solid and perhaps a heterogeneous or multiphase system.

Factors which also may influence diffusion in such instances are those of viscosity and the nature of the diffusion membrane. In preliminary experiments alcohol and DMSO in 1, 2, and 5% concentrations did not appreciably influence the passage of salicylic acid from aqueous solutions through the membrane used in this study. From this it is assumed that the liquids used in this study exerted their influence on diffusion by means other than their action on the membrane. Although viscosity measurements were not taken on the ointments, the quantities of liquids added to the various bases were so small that their influence on viscosity would be negligible. If viscosity changes were a great factor in this study, one would expect to get results all going in one direction, probably toward increased diffusion rate, rather than results shown in these experiments, *i.e.*, increased diffusion from two bases and decreased release from the other two.

It is apparent that from this study no general explanation is sufficient to cover all the results. The results indicate that diffusion from ointment bases is greatly influenced by the inclusion of liquids. The characteristics of the base probably determine whether the diffusion process is enhanced or retarded.

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Keyphrases

Salicylic acid diffusion—ointment bases
DMSO, alcohol, water—diffusion effect
Diffusion—ointment base effect
UV spectrophotometry—analysis

Effect of β-Adrenergic Blockade on the Toxicity of Bronchoconstricters in Guinea Pigs

By F. P. LUDUENA and W. B. McKEON, JR.

Propranolol (10 mg./kg.) greatly increased the intravenous toxicity of serotonin, oxotremorine, histamine, and nicotine in guinea pigs. In the case of serotonin, the LD_{50} in the controls was more than 100 times larger than in the propranolol-treated animals. In both groups, bronchoconstriction was the cause of death following the injection of histamine, serotonin, and oxotremorine. In the case of nicotine, lethal bronchoconstriction was produced only in the propranolol-treated animals. The presence or absence of bronchoconstriction was determined by *in vitro* perfusion of the lungs, excised immediately after death.

It has been reported recently that β-adrenergic blockade increases the sensitivity of guinea pigs (1–5) and man (6, 7) to bronchoconstrictors. This potentiation has been attributed to an antagonism of the bronchodilator effect of catecholamines, released as a result of the action of bronchoconstrictors. This suggested that the LD_{50} values of histamine, serotonin, and a cholin-

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