Release, Uptake, and Permeation Behavior of Salicylic Acid in Ointment Bases

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Abstract □ *In vitro* release of salicylic acid from ointments was investigated by a diffusion technique employing a silicone rubber membrane. The advantages of this membrane over a cellophane membrane are discussed. Release of salicylic acid from five ointment bases indicated that emulsion-type ointment bases are superior to oleaginous and polyethylene glycol ointment bases. Uptake of salicylic acid by polyethylene glycol ointment from the solution was much faster than that by others, indicating a fairly strong affinity of this drug for the polyethylene glycol base. The permeation of salicylic acid from the aqueous solution through ointment bases to another aqueous solution was studied with a three-compartment diffusion cell to examine the relative importance of the factors involved in the process. Dimethyl sulfoxide and dimethylacetamide facilitated the release of salicylic acid from the ointments. Di-*n*-butylpropionamide was found to increase both the release of salicylic acid from the ointment and permeation through the ointment base. The *in vitro* release pattern from various bases is in agreement with the *in vivo* data reported in the literature.

Keyphrases □ Ointment bases—salicylic acid □ Salicylic acid in ointment—release, uptake, permeation □ Release rates—salicylic acid, ointment bases □ Silicone rubber membrane—salicylic acid transfer □ UV spectrophotometry—analysis

Physiological availability of a topically applied drug depends on both the rate of release from the vehicle and the permeability through the skin. The former is physicochemical in nature, whereas the latter may be called physiological. The role of the physicochemical factor in the overall availability of a drug has not been fully understood. To explore this point, the behavior of a drug in ointment bases was examined with a diffusion cell and a silicone rubber membrane instead of the commonly used cellophane membranes (1, 2). Since an *in vitro* study using an excised skin (3) and a number of *in vivo* studies (4–6) deal with salicylic acid, this agent was selected for the present study.

Some of the special features and objectives of the present work are as follows. (*a*) The feasibility of the use of silicone rubber membranes in availability studies *in vitro* was investigated. (*b*) The very slow rate of release of salicylic acid from polyethylene glycol ointment prompted the authors to investigate the affinity or interactive nature of the drug for the ointment base by measuring the uptake of the drug from the solution by the ointment base. (*c*) To ascertain whether the diffusivity of the drug through the ointment or the solubility of the drug in the ointment base (7) plays the major role in the release characteristics of salicylic acid, the rate of permeation[1] of the drug from the solution to another solution through an ointment-base layer was determined with the use of a three-compartment cell. (*d*)

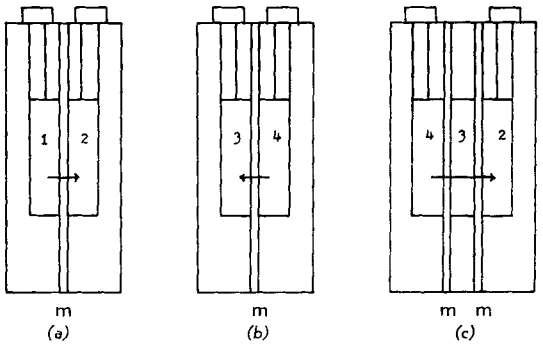

Figure 1—*Diagrams of apparatus used in:* (a) *release study*, (*b*) *uptake study, and* (c) *permeation study. Key:* **1.** *salicylic acid incorporated in an ointment base;* **2.** *sodium hydroxide solution;* **3.** *ointment base;* **4.** *salicylic acid solution; and* m, *dimethyl polysiloxane membrane. An arrow indicates direction of transfer of salicylic acid.*

The effect of dimethyl sulfoxide and two amides on the release and permeation of the drug was also investigated, since these organic solvents have received considerable attention with regard to their effect on membrane permeability (8).

EXPERIMENTAL

Materials—Reagent grade salicylic acid[2] was used throughout. Dimethyl polysiloxane[3] sheeting in a labeled thickness of 5 mil was used. Dimethyl sulfoxide,[4] *N,N*-dimethylacetamide,[5] and *N,N*-di-*n*-butylpropionamide[5] were used without further purification. Polyethylene glycol ointment, hydrophilic petrolatum, and hydrophilic ointment were prepared according to USP XVII. Water-in-oil and oil-in-water bases were prepared according to the method of Whitworth (9).

Apparatus—The polymethyl methacrylate[6] diffusion cell described by Patel and Foss (11) was used. The diameter of the available area for diffusion was 34 mm. A three-compartment cell designed for permeation studies consisted of the mentioned diffusion components and a thin plastic[6] plate (1.8 mm. in thickness) with a central opening, 34 mm. in diameter.

Procedure—Finely powdered salicylic acid (final concentration = 3%) was levigated with 10 drops of liquid petrolatum and incorporated into an ointment base by means of a mortar and pestle. Organic solvent (final concentration = 5%) was blended with the ointment base using a mortar and pestle prior to incorporation of the drug.

Three types of experiments performed in the present investigation: (*a*) release, (*b*) uptake, and (*c*) permeation, are illustrated diagrammatically (not to scale) in Fig. 1 and the procedure is given for each experiment.

Release from Ointment—One compartment of the diffusion cell was filled with an ointment and the excess was removed with the edge of a spatula to produce an even surface. The silicone rubber

[1] In this communication the following terminology is used. Diffusion is designated as the transport of a material within a medium, whereas permeation is defined as the transport of a material from one aqueous medium to another aqueous medium through a semisolid phase which separates the two aqueous media, since in the latter both diffusion and partition take place.

[2] General Chemical Division, Allied Chemical Corp., New York, N. Y.

[3] Supplied by Medical Products Division, Dow Corning Corp., Midland, Mich.

[4] Chemical Manufacturing Division, Fisher Scientific Co., Fair Lawn, N. J.

[5] Distillation Products Industries, Division of Eastman Kodak Co., Rochester, N. Y.

[6] Plexiglas, Rohm & Haas Co., Philadelphia, Pa. This material has recently been shown to absorb some nonelectrolytes from the solution (10). Salicylic acid may also be absorbed to a certain extent.

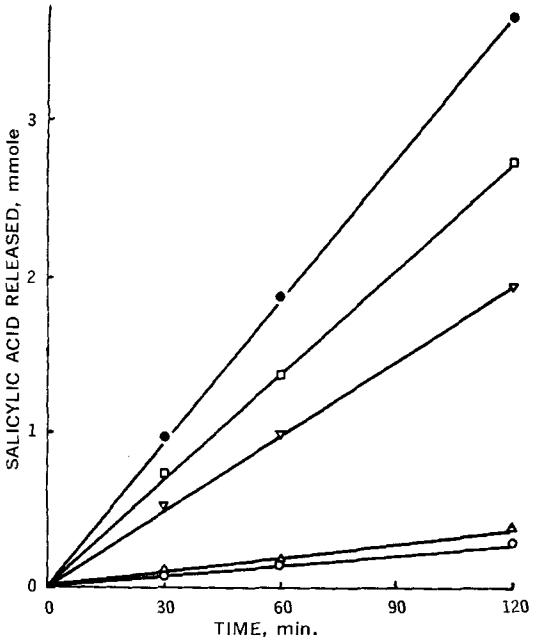

Figure 2—*Release of salicylic acid from ointments at 30°. Key: ●, oil-in-water ointment; □, hydrophilic ointment; ▽, water-in-oil ointment; △, hydrophilic petrolatum; and ○, polyethylene glycol ointment.*

membrane was then placed on it and carefully pressed to ensure complete contact of the membrane with the ointment. The other compartment of the cell was then placed on the membrane. The cell was assembled and tightly secured with bolts and wing nuts. The unit was brought up to a temperature of 30° by keeping it in a constant-temperature incubator.[7] A 10-ml. portion of prewarmed 0.01 *N* NaOH was placed in the empty compartment. Sodium hydroxide was added to maintain the effective concentration of permeable species to a value of zero in solution. The entire assembly was agitated on a shaker[8] in the incubator at a constant temperature of 30°. A 0.5-ml. aliquot of the aqueous solution was withdrawn at a definite interval and diluted to 10 ml. with 0.02 *N* HCl to suppress the dissociation of salicylic acid. The concentration of salicylic acid was determined spectrophotometrically[9] at 302 mμ.

Uptake by Ointment Base—The general procedure is the same as just described with the exception that the ointment base was packed in one compartment and a 10-ml. portion of a 10 m*M* salicylic acid solution in 0.01 *N* HCl was placed in the opposite compartment. Decrease in the salicylic acid content of the aqueous phase was determined spectrophotometrically.

Permeation through Ointment Base—The plastic plate with a circular opening was placed on the silicone rubber membrane and the opening was filled with an ointment base. The second membrane was then placed on it and pressed down to ensure complete contact with the ointment base. This unit was then placed between the two halves of the diffusion cell and the cell was assembled. The cell was brought up to 30° by placing it in the incubator. A 10-ml. portion of prewarmed 0.01 *N* NaOH was placed in one compartment, and an equal amount of prewarmed 10 m*M* salicylic acid in 0.01 *N* HCl was pipeted into the opposite compartment. The cell was agitated at a constant temperature; the increase in the drug concentration of the alkaline solution at definite time intervals was followed spectrophotometrically.

RESULTS

Release of Salicylic Acid from Ointments—The release characteristic of salicylic acid from various ointment bases over a 2-hr. period is illustrated in Fig. 2. The increase in the drug concentration of the aqueous phase at varying time intervals was used to assess the rate of drug release from the ointments. The emulsion-type ointments were superior to either hydrophilic petrolatum or polyethylene glycol ointment bases in salicylic acid release. Among the emulsion-type bases investigated, the oil-in-water type bases gave a better release than the water-in-oil type. Although not shown in the figure, the rate of release of salicylic acid from white petrolatum was slower than that from hydrophilic petrolatum; whereas the drug release from Base II, a polyethylene glycol base containing cetyl alcohol (12), was comparable to that from the polyethylene glycol base. Results are in agreement with those published in the literature (4) with the exception of the release data from polyethylene glycol bases, which are in direct contrast with those reported earlier (13). A possible explanation is offered under *Discussion*. Three official ointment bases, *i.e.*, hydrophilic ointment (an emulsion base), hydrophilic petrolatum (an absorption base), and polyethylene glycol base (a water-soluble base), were further examined in the uptake and permeation studies.

Uptake of Salicylic Acid by Ointment Bases—The drug uptake from aqueous solution by the ointment bases, separated by the silicone rubber membrane, was measured to evaluate the relative affinity of the drug for the bases. The data for this part of the study are plotted in Fig. 3. The figure shows that only 8% of the drug remained in solution after a 24-hr. period in the case of polyethylene glycol base, thus demonstrating a comparatively rapid rate of uptake by this base. The uptake by hydrophilic ointment was fairly rapid, whereas it was very slow for hydrophilic petrolatum.

Permeation of Salicylic Acid through Ointment Bases—Figure 4 illustrates the permeation profile of salicylic acid from the acidic solution to the alkaline solution through various ointment bases. Here the drug concentration of the alkaline solution is plotted as a function of time. The permeation of salicylic acid through hydrophilic ointment was comparatively rapid, whereas very little drug permeated through polyethylene glycol base within a 10-hr. period, with hydrophilic petrolatum as an intermediate. Even though only a small fraction of salicylic acid permeated through polyethylene glycol base into the alkaline solution, there was a large decrease in the drug content of the acid solution, thus indicating a significant accumulation of salicylic acid in the base.

Effects of Some Organic Solvents on the Release and Permeation—The data on the influence of dimethyl sulfoxide and two amides for the release of salicylic acid from hydrophilic petrolatum are presented in Fig. 5. The rate of drug release was dependent upon the nature of the organic solvent. Di-*n*-butylpropionamide exhibited the greatest enhancing effect, followed by dimethylacetamide and dimethyl sulfoxide in decreasing order. Similar enhancing effects of these solvents were observed with polyethylene glycol and hydrophilic ointments.

Figure 6 illustrates the effects of the solvents on the rate of drug permeation through hydrophilic petrolatum. Permeation through the vehicle was accelerated in the presence of di-*n*-butylpropionamide, but the effect due to dimethylacetamide was not very pronounced. Polyethylene glycol ointment showed a similar behavior with the solvents; however, the magnitude of acceleration was less

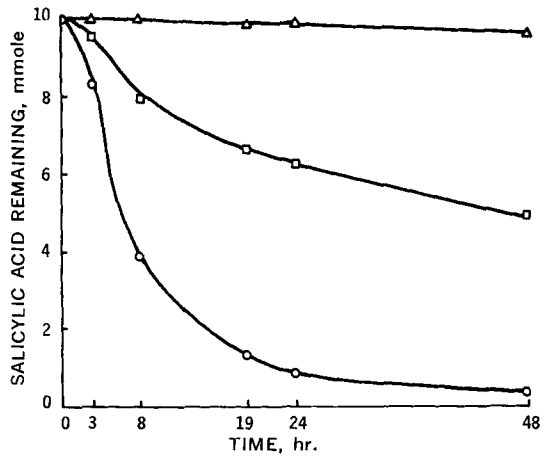

Figure 3—*Uptake of salicylic acid by ointment bases at 30°. Key: △, hydrophilic petrolatum; □, hydrophilic ointment; and ○, polyethylene glycol ointment.*

[7] Model 82, Fisher Scientific Co., Pittsburgh, Pa.
[8] Lab-Tek aliquot shaker, Ames Lab-Tek, Inc., Westmont, Ill.
[9] Model DB, Beckman Instruments, Inc., Fullerton, Calif.

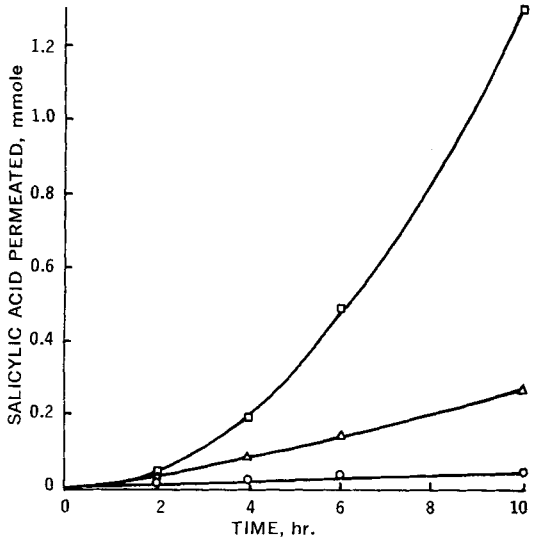

Figure 4—*Permeation of salicylic acid through ointment bases at 30°. Key: □, hydrophilic ointment; △, hydrophilic petrolatum; and ○, polyethylene glycol ointment.*

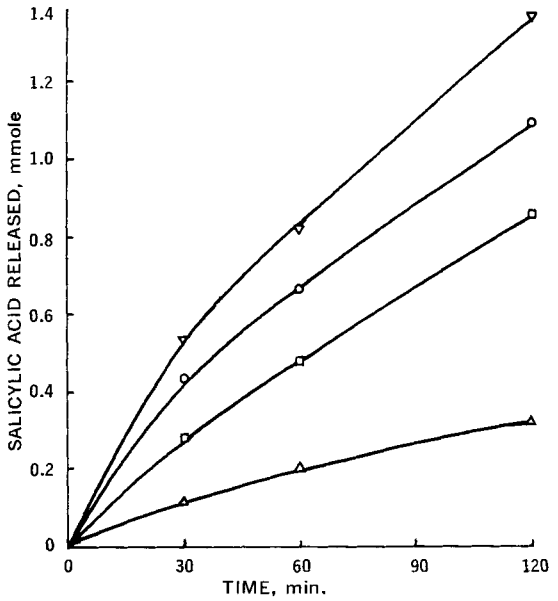

Figure 5—*Effect of dimethyl sulfoxide and amides on the rate of release of salicylic acid from hydrophilic petrolatum at 30°. Key: ▽, with di-n-butylpropionamide; ○, with dimethylacetamide; □, with dimethyl sulfoxide; and △, without organic solvent.*

marked. These solvents had little effect on the permeation of the drug through hydrophilic ointment.

DISCUSSION

As illustrated in Fig. 2, the release characteristics of salicylic acid from five physically different ointment bases through a silicone rubber membrane over a period of 2 hr., indicate that the membrane of a thickness of 5 mil provides reasonably fast rates of release to be of practical use for investigations of release of drugs from ointments. The linearity of the plots appears to indicate that the release of salicylic acid follows apparent zero-order kinetics, although this is not always the case (Fig. 5). The release pattern obtained using a silicone rubber membrane is in agreement with the *in vivo* data of Stolar *et al.* (4). Their ranking of the ointment bases for percutaneous absorption of salicylic acid was: hydrophilic ointment > hydrophilic petrolatum > polyethylene glycol.

Billups and Patel reported that cellophane membrane gave unusually rapid release of salicylic acid from the polyethylene glycol–cetyl alcohol base (Base II), although it was satisfactory for emulsion- and oleaginous-type bases (13). This is in direct contrast to the poor percutaneous absorption of salicylic acid from polyethylene glycol base (4). Cellophane membrane is freely permeable to water. In the case of an ointment base with high affinity for water, such as polyethylene glycol, the base attracts water, thus forming a solution and thereafter allowing the drug to permeate from the aqueous solution rather than from the base.

The mechanism of transfer of salicylic acid through the silicone rubber membrane is possibly governed by the partitioning of the drug into and diffusion through the membrane (14). The partition coefficient of the drug between the membrane and the ointment base thus plays an important role. In overall availability, this factor may be desirable because of the similarities in the physical properties of the membrane with those of skin. The skin barrier is generally considered to be lipoid in nature, although the exact mechanism of percutaneous absorption is not fully understood (15). Silicone rubber membranes are known to be permeable to nonionic drug molecules; and because of their lipidlike properties, they are claimed to be of value in the investigation of the drug transport through lipoid barriers (14, 16, 17). Based on the agreement of *in vitro* release pattern with *in vivo* data (4), a silicone membrane appears to be ideal for investigating drug release from diverse bases.

The very slow release of salicylic acid from polyethylene glycol ointment observed in this study was also noted by Loveday using excised pig skin (3) and by Stolar *et al.* from the measurement of the blood level in the rabbit (4). This slow release is most likely due to the affinity of salicylic acid for polyethylene glycol. This was demonstrated by the fairly rapid uptake of salicylic acid by the polyethylene glycol base from the solution (Fig. 3) and the drug accumulation within the ointment base in the permeation studies (Fig. 4). Hydroxybenzoic acids and phenols form molecular complexes with polyethylene glycol (18, 19) through hydrogen bonding. Due to complexation, salicylic acid is held up by the vehicle, thus retarding its release. Drugs which do not complex with polyethylene glycol would be expected to show better drug release than the acid. Loveday observed superior release of methyl salicylate from polyethylene glycol ointment (3). Methyl salicylate would not be expected to complex with polyethylene glycol because of the lack of the carboxylic acid group and involvement of the hydroxy group in intramolecular hydrogen bonding.

For diffusion to occur, the medicinals should be dissolved in the ointment base; this factor is of considerable importance for poorly soluble drugs. The three-compartment cell was used to examine the permeability characteristics of the drug in each ointment base without complications from the difference in the solubilities of the drug in various bases. In this experiment the initial concentration of salicylic acid in one compartment was kept constant, and the drug was allowed to permeate through varied bases into another

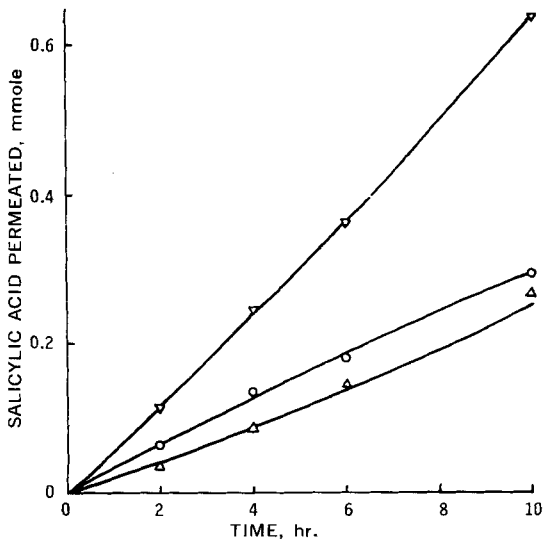

Figure 6—*Effect of amides on the rate of permeation of salicylic acid through hydrophilic petrolatum. Key: ▽, with di-n-butylpropionamide; ○, with dimethylacetamide; and △, without amide.*

compartment. Under these conditions the partition coefficient of the drug between the ointment base and membrane, as well as its diffusivity in the ointment base, would influence the rate of permeation and consequently the rate of release. The overall similarity of the release and permeation profile of the drug from hydrophilic ointment, hydrophilic petrolatum, and polyethylene glycol indicates that the solubility factor is not of overwhelming importance and the contribution from other factors, such as the diffusivity of the drug in the ointment base and possibly the partition characteristics of the drug between the base and the membrane, also have a significant bearing upon the release characteristics of the drug.

In the absence of specific interaction between the drug and the ointment base, as was the case with salicylic acid and polyethylene glycol ointment base, the base that takes up the drug fast appears to release the drug fast (Figs. 2 and 3). The rate of uptake of the acid by the ointment base from a solution through the silicone rubber membrane depends upon both the partition coefficient between the ointment base and the membrane and the diffusivity through the ointment base. Diffusivity through the ointment base may be the rate-limiting factor for ointments with poor drug release. This can be explained on the basis of uptake data for hydrophilic ointment and hydrophilic petrolatum. The greater uptake of drug by hydrophilic ointment than by hydrophilic petrolatum can be related to faster diffusion of salicylic acid through hydrophilic ointment. Water, being a continuous phase in hydrophilic ointment, is more mobile than the continuous oil phase of hydrophilic petrolatum and this, in turn, would favor diffusion of salicylic acid through hydrophilic ointment. The partition factor, on the other hand, should have a favorable effect upon hydrophilic petrolatum over hydrophilic ointment, since salicylic acid is roughly five times more soluble in oils and fats than in water (20).

Accelerated release of salicylic acid from white petrolatum and water-in-oil-type emulsion base in the presence of organic solvents has been reported by Whitworth (9). The results of the present study showed that the *in vitro* release of salicylic acid from hydrophilic petrolatum, polyethylene glycol base, and hydrophilic ointment was also increased in the presence of dimethyl sulfoxide and the amides. The reported increased percutaneous absorption of salicylic acid in the rabbit in the presence of dimethyl sulfoxide (21) may be attributed to the increased drug release from the ointment (Fig. 5) rather than merely to the change in the skin permeability by the sulfoxide. The increased solubility of salicylic acid in the ointment base containing organic solvents would be expected to increase the rate of release. The reason for attributing the increased release of salicylic acid mainly to the increased solubility of the drug in the base, rather than to change in membrane permeability, comes from the fact that the effect of dimethyl sulfoxide and dimethylacetamide on the rate of permeation was not so pronounced as that on the release rate. In addition, these two organic solvents have been shown not to partition to an appreciable extent into the silicone rubber membrane (22). These solvents, therefore, may not have a significant influence on the silicone rubber membrane itself, although the possibility of this effect may exist with biological membranes. The greater enhancing effect of di-*n*-butylpropionamide compared to dimethylacetamide may be due in part to the greater solubility of the former in the membrane. Di-*n*-butylpropionamide partitions into the membrane from the ointment, and it can form hydrogen bonds with salicylic acid which, in turn, facilitates the transfer of salicylic acid from the ointment into the membrane. This interaction is expected to accelerate the permeation of salicylic acid (22).

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