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Effect of Small-Scale Preparation Techniques on Diffusion of Salicylic Acid from Various Ointment Bases

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Abstract □ The effect of small-scale preparation techniques on the diffusion of salicylic acid from ointment bases was studied. The method of mechanical incorporation of the drug in cold petrolatum base, using a spatula, appeared to result in higher rates of salicylic acid diffusion than those encountered with ointments prepared by fusion, regardless of drug concentration and the presence or absence of a surfactant. A similar effect was produced in the case of a 10% salicylic acid ointment made with a water-in-oil emulsion base.

Keyphrases □ Ointments—effect of small-scale preparation techniques on salicylic acid diffusion, petrolatum bases with and without surfactant and water-in-oil emulsion base □ Salicylic acid—diffusion from bases, effect of small-scale ointment preparation techniques □ Diffusion—salicylic acid from ointment bases prepared by small-scale techniques

The effect of various liquids on the diffusion of salicylic acid from ointments was reported previously (1). A literature review revealed that several reports have been published on the influence of numerous additives on the diffusion and absorption of drugs from ointments (2–7). However, it appears that little or no attention has been paid to the effect of preparation methods of ointments on the diffusion of the incorporated drug.

The aim of this investigation was to study the effect of small-scale preparation techniques of ointments on the diffusion of salicylic acid from some ointment bases. Mechanical incorporation of the drug using a spatula and the fusion process were investigated.

EXPERIMENTAL

Materials—Salicylic acid[1] USP, white petrolatum[2] USP, and sorbitan monooleate[3] were used as supplied. Other ingredients were official or analytical grades.

Preparation of Ointments—The bases used were white petrolatum, white petrolatum containing 2% sorbitan monooleate, white petrolatum containing 5% sorbitan monooleate, and a water-in-oil base consisting of 64% white petrolatum, 6% sorbitan monooleate, and 30% distilled water.

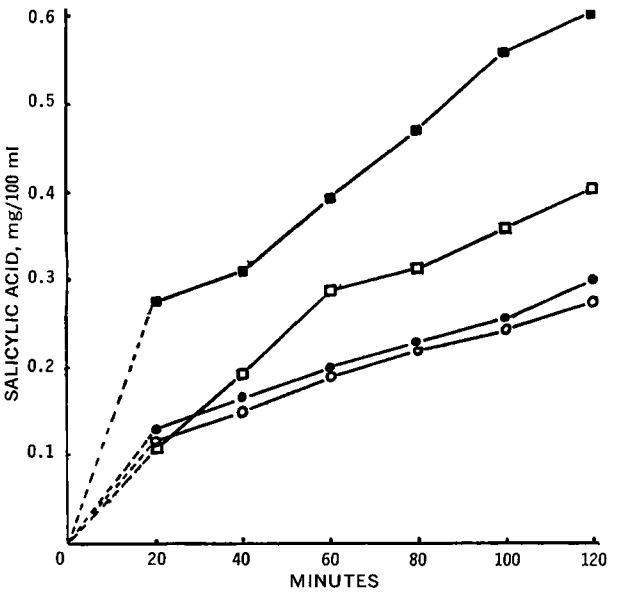

Figure 1—*Diffusion of salicylic acid from white petrolatum. Key: ■, 10% prepared by mechanical incorporation; □, 10% prepared by fusion; ●, 5% prepared by mechanical incorporation; and ○, 5% prepared by fusion.*

Mechanical Incorporation—The salicylic acid as supplied in fine powder was triturated with 150 g of the base on a glass slab using a spatula until a smooth homogeneous ointment was obtained.

Fusion—Each oleaginous base was first melted on a water bath at 70°. Salicylic acid was then gradually added to the molten material and stirred constantly until the ointment cooled to room temperature. In case of the ointments prepared with the water-in-oil base, white petrolatum and sorbitan monooleate were mixed and melted on a water bath at 70°. Salicylic acid was then added and dispersed in this fatty base at 70°. The distilled water, previously heated to 70°, was incorporated while stirring was maintained until the ointment cooled to room temperature.

Diffusion—The techniques used were the same as described previously (1). The amount of salicylic acid diffused into 100 ml of distilled water was determined by measuring the absorbance on a spectrophotometer[4] at 297 nm.

[1] Fisher Scientific Co.
[2] Oils Inc., Patterson, N.J.
[3] Span 80, Atlas Chemical Industries, Wilmington, Del.

[4] Cary model 118 recording spectrophotometer.

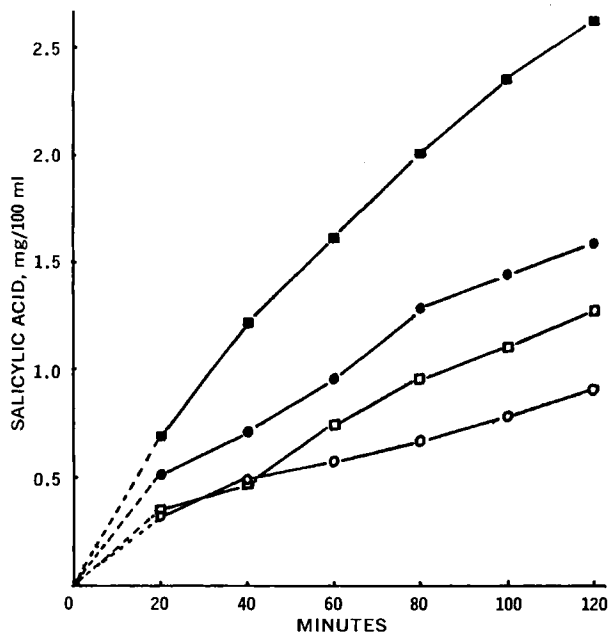

Figure 2—*Diffusion of salicylic acid from white petrolatum containing 5% sorbitan monooleate. Key: see Fig. 1.*

DISCUSSION AND CONCLUSIONS

The release characteristics of salicylic acid from the various ointment bases over 2 hr are illustrated in Figs. 1–3. The increase in concentration of the aqueous diffusion medium at varying time intervals is used to assess the rate of drug release from the ointments.

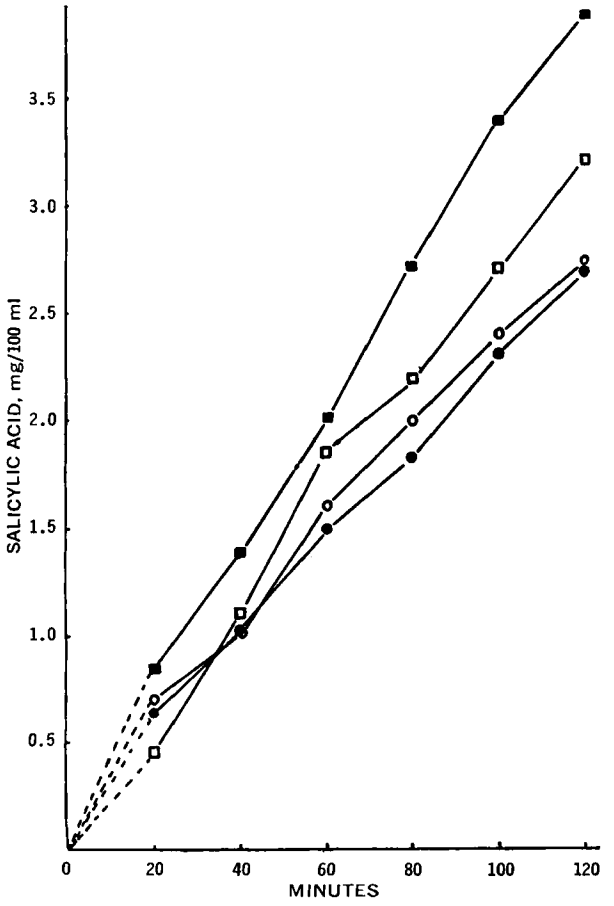

Figure 3—*Diffusion of salicylic acid from a water-in-oil base. Key: see Fig. 1.*

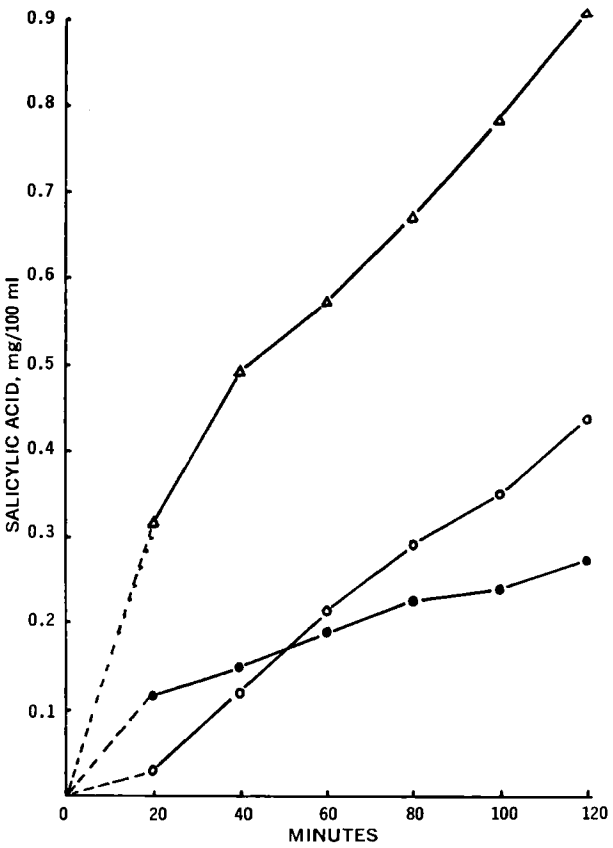

Figure 4—*Effect of sorbitan monooleate on the diffusion of salicylic acid from a 5% ointment in white petrolatum prepared by fusion. Key: ●, no surfactant; ○, 2% surfactant; and △, 5% surfactant.*

It appears from Figs. 1 and 2 that in the case of the oleaginous petrolatum bases the mechanical incorporation techniques using a spatula gave a higher rate of drug release than that obtained with the fusion method, regardless of drug concentration and the presence or absence of a surfactant. This result may be due to the molten base possibly being much less viscous and more flowable than the nonfused base. Consequently, the molten base should be more effective in wetting, adhering to, and coating the incorporated salicylic acid particles, thus resulting in retardation of the diffusion rate of the drug. This was confirmed by a simple qualitative test whereby the comparative rapidity of coloration of the ointments with ferric chloride solution was noted. Two equal portions of the ointments prepared by the two techniques were filled into small plastic vial caps. One drop of ferric chloride solution was then added, and the rate of appearance of a blue color was followed. The development of a blue color appeared to be faster for ointments prepared by mechanical incorporation using a spatula than for ointments prepared by the fusion techniques.

It has been reported (8) that heating petrolatum to its melting point permits rearrangement of its crystal network so that it exhibits its initial thixotropic condition after cooling. Consequently, the difference in release patterns of salicylic acid from the ointments prepared by the two methods could not be attributed to a change in the crystalline structure of petrolatum as a result of fusion.

Figure 3 also shows that mechanical incorporation techniques using a spatula resulted in a higher rate of salicylic acid diffusion from a water-in-oil emulsion base containing 10% salicylic acid. However, with the 5% salicylic acid ointment, no significant difference could be noted. The reason might be that at the lower concentration of salicylic acid, the diffusion-retarding effect produced by the fusion method might have been balanced by the diffusion-enhancing effect demonstrated by the surfactant (Fig. 4). The solubi-

lizing effect of sorbitan monooleate on salicylic acid may account for its higher rate of diffusion from bases containing this surfactant (Figs. 2–4). However, at the higher drug concentration, a relatively greater proportion of salicylic acid particles could not be effectively surrounded by the nonfused base; therefore, the increase in diffusion rate was apparently due mainly to this factor, which would probably outweigh the surfactant effect.

Figures 1–3 also show that greater drug concentration produced higher rates of diffusion in both methods used to make the ointments. This is in agreement with the results obtained by Lockie and Sprowls (9) who found that the rate of diffusion of iodine and sulfathiazole from ointments increased with increasing drug concentration within a certain range. Undoubtedly, the solubility of a drug in an ointment base plays a major role in the diffusion or release of the drug from the base (10). The faster diffusion demonstrated by bases with higher concentrations of salicylic acid apparently reflects this solubility effect. The higher the concentration of salicylic acid, the more will be left undissolved and not effectively coated by the base.

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NOTES

Synthetic Procedures for Deuterium-Labeled Acetylcholine Perchlorates

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Abstract □ Synthetic procedures for selectively deuterated acetylcholine perchlorates are reported. Acetyl-d_3-choline perchlorate (I) was prepared *via* esterification of acetic acid-d_4 with ethylene bromohydrin followed by quaternization of the bromoester with trimethylamine and treatment with perchloric acid. N-$(CD_3)_3$-Acetylcholine perchlorate (II) was prepared by quaternization of ethanolamine with methyl-d_3 iodide, acetylation with acetic anhydride, and anion exchange using silver perchlorate. Lithium aluminum deuteride-d_4 reduction of ethyl bromoacetate gave 1,1-d_2-2-bromoethanol (VI), which was esterified with acetic acid followed by quaternization and anion exchange, as for I, to give acetylcholine-1,1-d_2 perchlorate (III). A similar sequence was used to prepare acetylcholine-2,2-d_2 perchlorate (IV) from 2,2-d_2-2-bromoethyl acetate (X).

Keyphrases □ Acetylcholine perchlorates, deuterium labeled—synthesis □ Deuterium-labeled acetylcholine perchlorates—synthesis

The enzyme acetylcholinesterase catalyzes the hydrolysis of the natural substrate acetylcholine in carrying out its central role in the function of the nervous system (1). Studies in this laboratory required the syntheses of four specifically labeled acetylcholine salts: $CD_3CO_2CH_2CH_2N^+(CH_3)_3ClO_4^-$, I; $CH_3CO_2CH_2CH_2N^+(CD_3)_3ClO_4^-$, II; $CH_3CO_2CD_2CH_2N^+(CH_3)_3ClO_4^-$, III; and $CH_3CO_2CH_2CD_2N^+(CH_3)_3ClO_4^-$, IV.

The syntheses of I and II, using reported procedures (2–4), are given in very limited detail (5) as are the syntheses of III and IV (5). Poor results were obtained in this group using many reported procedures, so modified procedures were developed and are reported here in detail. The compounds were isolated as their perchlorate salts since these have the distinct advantage of being nonhygroscopic as opposed to the halide salts (6). Compounds I and II could be obtained in relatively high yields, but the overall yields of III and IV could never be raised above a few percent due to the difficulties encountered in preparing the necessary labeled ethylene bromohydrins [$BrCH_2CD_2OH$ (VI) and $BrCD_2CH_2OH$ (IX)].

DISCUSSION

The two methods used for the preparation of the ethylene bromohydrins gave very low yields, even though the reactions were re-