Effect of Formulation and Processing Techniques on Release of Salicylic Acid from Ointments

A. F. ASKER * and C. W. WHITWORTH ˣ

Abstract □ The effects of variation of drug particle size, fusion temperature of the base, and ointment milling on the release of salicylic acid were investigated. The larger the drug particle size, the higher was the amount of salicylic acid released from petrolatum base. The fusion temperature of the base also appeared to influence the rate of drug release, suggesting an optimum temperature to be considered. Ointments prepared by fusion at 70 or 90° demonstrated lower rates of drug release than those produced by mechanical incorporation. Moreover, salicylic acid was found to sublime during the ointment preparation by fusion at 90°. Homogenization of the ointment in a three-roller mill enhanced the rate of drug release from emulsion bases but not from petrolatum base.

Keyphrases □ Salicylic acid release from ointments—effects of drug particle size, temperature of fusion of the base, and milling process □ Ointments, salicylic acid—effects of drug particle size, temperature of fusion of the base, and milling process on drug release □ Drug release, salicylic acid from ointments—effects of drug particle size, temperature of fusion of the base, and milling process

From the standpoint of therapeutics, one important attribute of an ointment is its ability to release its active ingredient. Studies on the effect of various additives on drug release from different ointment bases have been reported (1–7). However, it appears from literature reports that the manufacture of ointments is generally carried out on an empirical basis following traditional techniques, and that no attempt has been made to study the effect of the variables encountered in formulating and processing ointments on the release of the incorporated drug.

A previous report (8) indicated that there was a significant difference in the release of salicylic acid from ointments prepared by fusion and mechanical incorporation using a spatula. The aim of this study was to investigate the effect of variation of drug particle size, fusion temperature of the base, and ointment milling on the release of salicylic acid.

EXPERIMENTAL

Materials—Salicylic acid[1], cetyl alcohol[1], white petrolatum USP[2], sorbitan monostearate[3], and polyethylene sorbitan monooleate[4] were obtained from commercial sources. Chloroform[5] was spectrograde. Other materials were official or analytical grades.

Drug Release Studies—Diffusion techniques have been extensively employed to measure drug release from heterogeneous preparations such as ointments (9) and emulsions (10). The techniques used in this study were the same as those described previously (1). The amount of salicylic acid diffused into 40 ml of distilled water at room temperature was determined by measuring the absorbance on a spectrophotometer[6] at 297 nm.

Assay of Salicylic Acid Ointments Made with Petrolatum Base—About 100 mg of the ointment was dissolved in chloroform, and the mixture was transferred into a 100-ml volumetric flask and diluted to volume with chloroform. Salicylic acid was determined by measuring the absorbance of this solution at 308 nm against an appropriate blank.

Effect of Particle Size of Salicylic Acid on Its Diffusion from White Petrolatum—Salicylic acid powder was classified using a set of standard sieves. Particles of 68-, 90-, and 127-μm average size were separated and used.

Three batches, each of 1 kg of 2% salicylic acid ointment, were made from the three portions of salicylic acid powder having different particle size. White petrolatum was first fused at 50° in the bowl of a laboratory model planetary, power-driven, kitchen aid

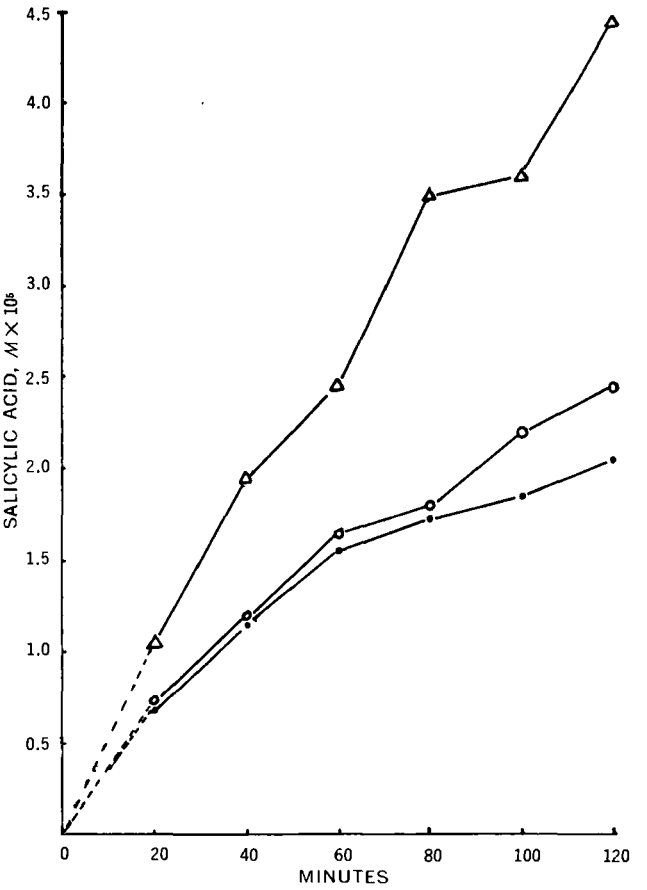

Figure 1—*Effect of particle size of salicylic acid on its diffusion from a 2% ointment in white petrolatum prepared by fusion at 50°. Key:* ●, *68 μm;* ○, *90 μm; and* △, *127 μm.*

[1] Fisher Scientific Co.
[2] Oils Inc., Paterson, N.J.
[3] Span 60, Atlas Chemical Industries, Wilmington, Del.
[4] Tween 80, Atlas Chemical Industries, Wilmington, Del.
[5] J. T. Baker Chemical Co.
[6] Cary model 118 recording spectrophotometer.

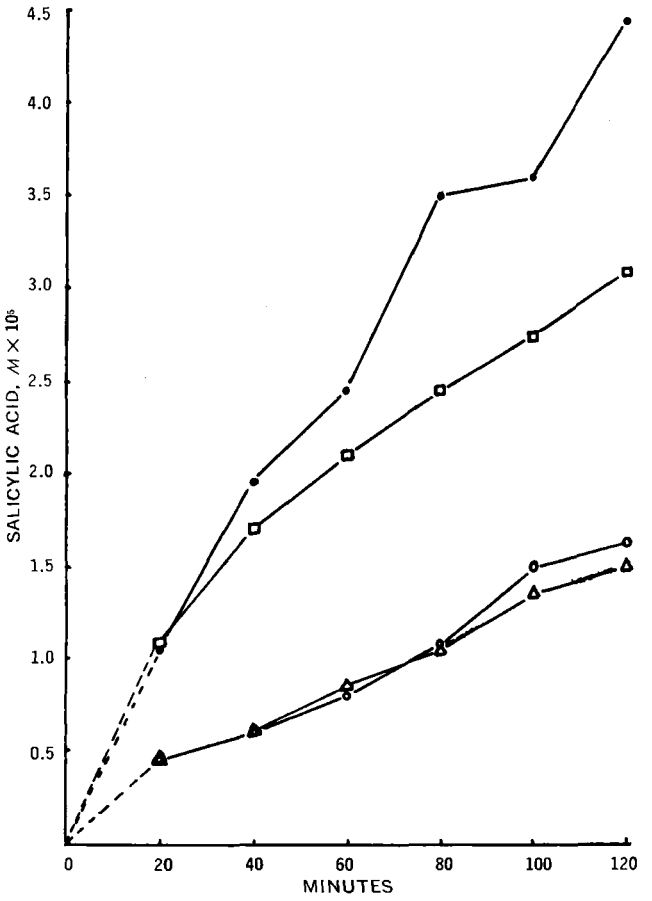

Figure 2—*Effect of fusion temperature of white petrolatum on the diffusion of salicylic acid. Key:* □, *control prepared by mechanical incorporation at room temperature;* ●, *50°;* ○, *70°; and* △, *90°.*

mixer[7]. Salicylic acid was then added while stirring was maintained at a fixed speed using the wire-type beater.

Heavier mixing blades were not utilized to avoid any change of particle size of the drug as a result of the grinding action produced by heavier blades. Stirring was continued until the ointment cooled to room temperature. Diffusion of salicylic acid from the three batches of ointment was determined the next day.

Effect of Variation of Temperature of Fusion of White Petrolatum on Diffusion of Salicylic Acid—Three batches of 2% salicylic acid ointment were prepared by fusing petrolatum at three different temperatures (50, 70, and 90°) in a manner similar to that already described. Diffusion of the salicylic acid from each batch was determined the next day.

Salicylic acid has been reported to sublime at 76° (11). Gore *et al.* (12) found that the loss of salicylic acid by sublimation could occur even at moderately elevated temperatures of 40, 50, and 70°. Therefore, it was decided to investigate the possible loss of salicylic acid as a result of sublimation. This was done by preparing the ointment at the three temperatures in a bowl covered with aluminum foil. Any deposition of salicylic acid on the foil was taken as an indication of sublimation. Moreover, the ointment was assayed to determine the extent of loss of salicylic acid due to sublimation.

Effect of Milling—The effect of homogenization of 2% salicylic acid ointment prepared with various bases was studied. The bases used were: *(a)* white petrolatum; *(b)* a water-in-oil-base consisting of 64% white petrolatum, 6% sorbitan monostearate, and 30% distilled water; and *(c)* an oil-in-water base consisting of 25% cetyl alcohol, 25% petrolatum, 12% glycerin, 5% polyoxyethylene sorbitan monooleate, and 33% distilled water.

All ointments were prepared by mechanical incorporation of the drug in the base at room temperature. Half the quantity of each batch of ointment was milled by passing once through a three-roller mill[8] maintained at constant operating conditions. The second half of the ointment was not milled and served as a control for comparison. Diffusion of salicylic acid from each ointment was then determined.

DISCUSSION

An examination of many ointment formulas reveals that the fusion process is practically always used in the preparation of an ointment in large-scale manufacturing. Therefore, more emphasis was placed in this study on the effect of formulation on the diffusion of salicylic acid from ointments prepared by fusion.

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

It appears from Fig. 1 that the larger the particle size of salicylic acid, the higher was the amount of salicylic acid diffused from the petrolatum base. There was no appreciable difference in drug diffusion between particles of 68- and 90-μm average size, possibly due to the relatively narrower difference in particle size. The results may be explained by the gel-like structure of the base and its thixotropic properties (13), which would cause the smaller particles of salicylic acid to be entrapped more effectively within the crys-

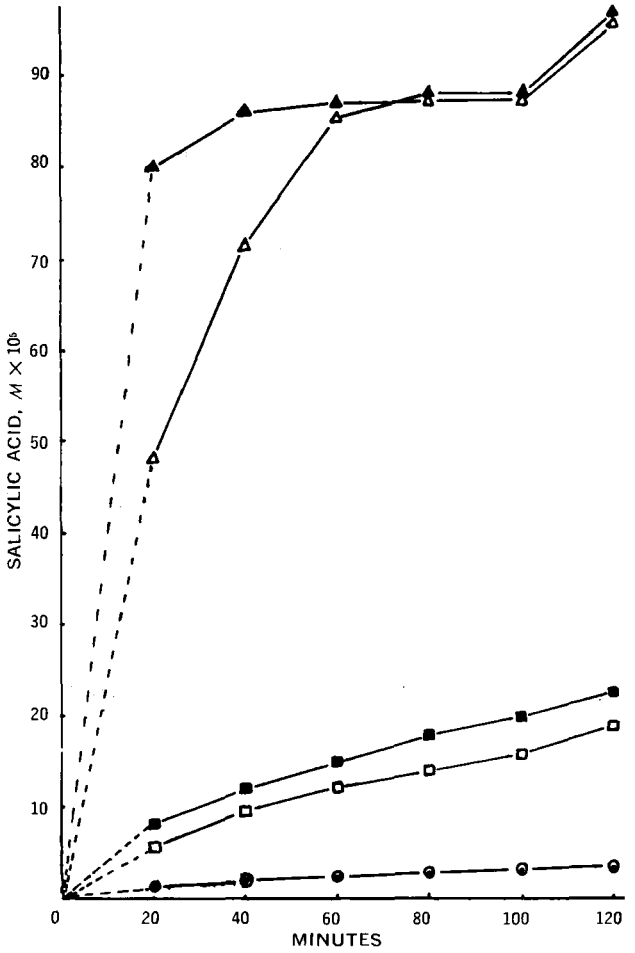

Figure 3—*Effect of milling on the diffusion of salicylic acid from various ointments prepared by mechanical incorporation. Open points represent the nonmilled ointments while the filled points represent the milled ointments. Key:* ▲, △, *oil-in-water base;* ■, □, *water-in-oil base; and* ●, ○, *white petrolatum base.*

[7] Hobart Manufacturing Co., Troy, Ohio.

[8] Erweka, West Germany.

talline hydrophobic structural network of the petroleum jelly. These findings are in agreement with those of Buckwalter and Dickison (14), who found that small particles of procaine penicillin G suspended in oily vehicles gelled with aluminum stearate were superior to large particles in delaying absorption. This finding was attributed to the reduction in rate of solution of the suspended solid from the thixotropic vehicle.

The effect of variation of fusion temperature of petrolatum on the diffusion of salicylic acid is illustrated in Fig. 2. It appears that white petrolatum fused at 50° before incorporation of the drug gave a higher rate of drug diffusion than that demonstrated when petrolatum was fused at 70 or 90°. This may be explained on the basis that, on heating petrolatum at temperatures higher than 50°, it became a more flowable and less viscous liquid that would more effectively wet, strongly adhere to, and coat the suspended drug particles. Such difference in diffusion rate could not be attributed to any changes in the crystalline structure of petrolatum produced as a result of the fusion process. This is based on the fact that heating petrolatum to its melting point permits a rearrangement of the crystal network, so that the product, after cooling, exhibits its initial thixotropic condition (13).

Ointments prepared by fusion at 50°, however, demonstrated higher rates of diffusion than those of the ointments prepared by mechanical incorporation at room temperature. The reason might be that the less viscous base maintained at 50° could have enhanced aggregation of salicylic acid particles. This would be expected to increase the diffusion rate due to an increase of particle size (Fig. 1). This effect, however, was not exhibited by the ointments prepared at the higher temperatures of 70 and 90°, probably due to better dispersion of the drug particles caused by the greatly reduced viscosity of the base. The slower release rates demonstrated by ointments made by fusion at 70°, as compared with those prepared by mechanical incorporation at room temperature, confirm the results previously reported for the effect of small-scale preparation techniques of ointments on the release of salicylic acid (8). It appears, therefore, that the optimum temperature of fusion should be considered in the preparation of ointments by fusion.

Salicylic acid was found to sublime and collect on the bowl cover as tiny crystalline needles in the case of ointments prepared at 90°. No sublimation was noted for ointments prepared at 50 or 70°. The loss of salicylic acid due to sublimation at 90° was 1.5%.

Figure 3 shows the effect of homogenization of salicylic acid ointment on its diffusion from the various bases. It is evident that milling enhanced the rate of drug diffusion from the emulsion bases, but no apparent difference in diffusion rate was noted for petrolatum base. This could be due to an increase in the degree of dispersion and/or solubility of salicylic acid in the emulsion phases as a result of homogenization.

It can be also seen that the emulsion-type ointments were superior to white petrolatum in salicylic acid release. The oil-in-water type base gave a better release than the water-in-oil type. These results are in agreement with those already published (3).

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Fluorocarbon Aerosol Propellants III: Effect of Water Vapor on Sensitivity of Electron-Capture Detector during GC Analysis

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Abstract □ The quantitative depressive effects of the presence of various amounts of water in samples injected onto a GC column on the detector response to three fluorocarbon aerosol propellants were investigated.

Keyphrases □ Propellants (fluorocarbon aerosol)—effect of water vapor on sensitivity of electron-capture detector, GC analysis □ Aerosols—fluorocarbon propellants, effect of water vapor on sensitivity of electron-capture detector, GC analysis □ Fluorocarbon aerosol propellants—effect of water vapor on sensitivity of electron-capture detector, GC analysis □ GC—effect of water vapor on sensitivity of electron-capture detector during analysis of fluorocarbon aerosol propellants

The presence of water vapor has been known to affect adversely the performance of ionization detectors in GC analysis. Lovelock (1) stated that the contamination of water in the carrier gas was objectionable. Although its presence could not be immediately detected, it could lead to a serious reduction in the detector sensitivity. It was shown (2) that the sensitivity of a macro-argon detector would be reduced 10-fold by a change in water vapor concentration from 30 to 1000 ppm (v/v). It was also shown (3) that