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means that it is possible to apply a large amount of this fraction to the paper.

Codeine and quinine are extracted by chloroform from the residue of tablet fragments after addition of alkali. These two alkaloids are clearly resolved on CT30 paper in about 20 minutes. Some quinine is also present in the initial chloroform extract of the tablets but is removed from the "neutral" fraction by washing with dilute acid.

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Diffusion of Sodium Salicylate and Salicylic Acid within Hydrophilic Ointments

Measurement with a New Diffusion Cell

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A cell has been designed to measure diffusion of medicaments within dermatologic vehicles to eliminate the influence of an external medium which differs from the vehicle. The cell consisted of two Lucite plastic compartments separated by a cellophane membrane. A medium containing a medicament was placed in one compartment and diffusion occurred into the other compartment which contained the same vehicle without the medication. The cell was used in a study of the diffusion of sodium salicylate and salicylic acid in various components of hydrophilic ointments made with three nonionic surface-active agents: Tween 40, Atlas G-7596-J, and Brij 35.

IN VITRO investigations of the efficiency of medicated dermatologic vehicles have usually utilized a system in which the drug diffuses from the vehicle into a dissimilar medium. Events which occur in this external medium provide the data for the evaluation of the vehicle. Workers in this field have noted the desirability for additional knowledge of diffusion within the base and its physicochemical properties (1–3). It is possible that in many reported experiments the results obtained have been more dependent upon the rate of diffusion in the external medium than upon the rate of diffusion in the vehicle being tested. Fuller, *et al.* (1), suggested that the rate of absorption of a drug from a locally applied vehicle will depend on the rate of the slowest of the processes involved in the transfer of medicament to the tissue fluids. Thus,

in vitro, the limiting influence could occur in the external medium, at the interface, or in the preparation containing the medicament. One significant physical property is diffusion of drug molecules within the vehicle.

A cell has been developed which makes possible the measurement of diffusion of a drug within its vehicle and it has been applied to diffusion measurements of salicylic acid and sodium salicylate in hydrophilic ointments prepared with three different emulsifiers. Studies involved media of increasing complexity from simple aqueous solutions to fluid emulsions to semisolid hydrophilic ointments.

EXPERIMENTAL

The Diffusion Cell.—Since free diffusion studies in liquid media require rather elaborate methods to avoid boundary disturbances due to the effect of convection currents, vibration, and gross movement of the apparatus, Geddes (4) suggested separation of the phases by a porous diaphragm to eliminate practically all boundary disturbance. Preliminary studies indicated that methods which brought
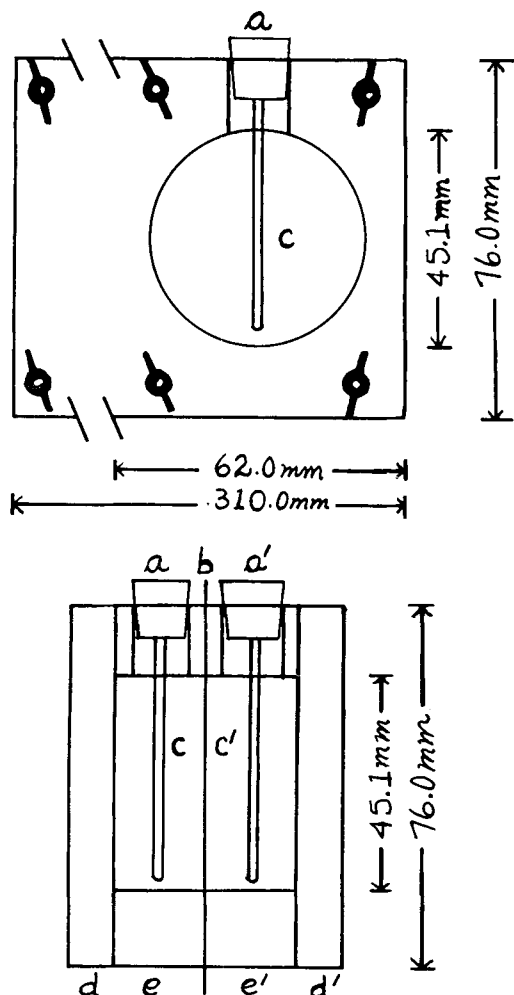
Fig. 1.—One section of the five-cell Lucite diffusion unit showing side view (top) and end view (bottom). d,d' is $^3/_8$ inch clear Lucite and e,e' is $^3/_4$ inch clear Lucite.

apparatus, the cellophane[1] (b) was placed at the center of the four components (Fig. 1, end view), and the unit was assembled by tightening the wing nuts on the bolts holding the unit together. The assembled unit, ready for use, was photographed for Fig. 2. The internal dimensions were such that when 28.5 ml. of liquid was placed in each side of the cell (c,c') and stirring rods positioned, the cell was completely filled to the bottom of the openings and the membrane (16 sq. cm.) was completely covered.
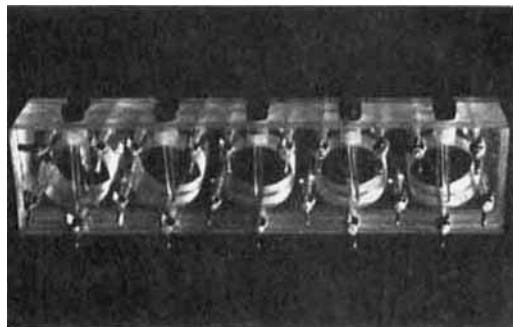

Fig. 2.—The assembled Lucite plastic diffusion cell unit.

For semisolid media the diffusion cell differed in only one respect from that used for the liquid systems; namely, the center components were constructed from $^3/_8$ inch Lucite. The depth of each half of the cell was thus $^3/_4$ inch instead of $^3/_4$ inch. Stirring rods were of no use, but openings to each cell compartment (6 mm. in diameter) were provided to permit the escape of ointment from the slightly overfilled cells. Slight overfilling with consequent pressure exerted on complete assembly was utilized to assure intimate contact between the ointment contained in each cell compartment and the cellophane membrane. The shallow-depth cell was used to facilitate chemical analysis because of the relatively short depth of penetration of medicament into the receptor ointment.

Diffusion Media.—Diffusion experiments were conducted on media which were variations of components of the terminal medium. The terminal medium was a modified form of hydrophilic ointment U.S.P. XV (5) of the following formula

	Quantity, Gm.
Surface-active agent[2]	5.0
Propylene glycol	12.0
Liquid petrolatum	25.0
Stearyl alcohol	25.0
Preserved water C.F. (6)	33.0

The simplest medium was preserved water C.F. (6), and other components of the formula were added to give media of increasing complexity until the hydrophilic ointment was formed. The quantities of ingredients in the simpler media were in the same ratio as in the terminal media. Three series of experiments were performed, differing only in the surface-active agent used as the emulsifier. Com-

medicated and nonmedicated portions of ointment (semisolid) into contact were suitable for visual observation of diffusion, but not suitable for removing samples for analysis. In order, therefore, to maintain stable boundary conditions in the liquid vehicles, and to permit separation of the two parts of the semisolid diffusion system, an intervening cellophane membrane was used. The vehicle was thus separated into two aliquots, one on each side of the membrane. At the beginning of each experiment, only one aliquot contained medicament. Samples could be removed at different time intervals for analysis to give the diffusion rate.

The diffusion apparatus consisted of a Lucite unit containing five diffusion cell compartments. Each cell was cylindrical in shape (Fig. 1) with an opening (12.5 mm. diameter) (a,a') in each section of the cylinder (c,c') for filling the cell and subsequently removing its contents. Stirring rods were inserted into rubber stoppers and installed in the openings (a,a'), serving both as stirring devices and as closures for the cells. To assemble the

TABLE I.—RATE OF DIFFUSION OF SODIUM SALICYLATE AND SALICYLIC ACID AND THE VISCOSITY OF THE DIFFUSION MEDIA

Sodium Salicylate Diffusion			Salicylic Acid Diffusion		
Diffusion Designation[a]	Diffusion, mg./cm.²/hr.	Viscosity of Diffusion Media, cps.	Diffusion Designation[a]	Diffusion, mg./cm.²/hr.	Viscosity of Diffusion Media, cps.
A	36.1	0.92	a	0.517	0.92
B	17.9	2.19	b	0.221	2.19
C1	27.5	2.08	c1	0.107	2.08
D1	15.0	3.67	d1	0.075	3.67
E1	5.55	22.5	e1	0.050	20.3
F1	0.29	26,000	f1	0.0020	26,000
C2	27.6	2.20	c2	0.083	2.15
D2	13.7	3.40	d2	0.068	3.49
E2	5.65	20.4	e2	0.067	20.7
F2	0.34	24,000	f2	0.0023	24,000
C3	24.1	3.59	c3	0.058	3.60
D3	12.7	5.60	d3	0.050	5.80
E3	5.40	30.0	e3	0.034	30
F3	0.25	30,000	f3	0.0018	30,000

[a] Upper case letters indicate sodium salicylate and lower case salicylic acid. Arabic numerals indicate the emulsifier used in each series: 1, Tween 40; 2, Atlas G-7596-J; 3, Brij 35; Aa, preserved water C.F.; Bb, same as A plus propylene glycol; Cc, same as A plus emulsifier; Dd, same as B plus emulsifier; Ee, same as D plus liquid petrolatum; Ff, same as E plus stearyl alcohol, a hydrophilic ointment.

ponents of each medium are indicated in Table I which presents the results.

Medicaments.—Sodium salicylate U.S.P. and salicylic acid U.S.P. were incorporated into the diffusion media to form the medicated preparations. Salicylic acid, a commonly used agent in dermatology, was selected for its low aqueous and higher lipid solubility and sodium salicylate for its reverse solubility characteristics. The concentration of medicament was arbitrarily set at 12% for sodium salicylate, and because of its low water-solubility, the salicylic acid concentration was 0.2% in the fluid preparations and 1% in the semisolid medicated preparations.

The Diffusion Procedure.—The diffusion procedure for liquid preparations was as follows: The cell unit was immersed almost to the top in a constant-temperature water bath at 30°. Exactly 28.5 ml. of diffusion medium was transferred to the receptor side of the first cell and the stopper and stirring rod were positioned without pressure. Exactly 28.5 ml. of medicated preparation were transferred to the donor side of the first cell, the time of completion noted, and the stopper and stirring rod positioned without pressure. The other cells were filled in succession in the same manner. At 15-minute intervals for sodium salicylate and 30-minute intervals for salicylic acid, the solution in each side of each cell was stirred 10 times. Sixty minutes after the sodium salicylate diffusion had started (120 minutes for salicylic acid), the two solutions were removed completely from each cell (donor and receptor), placed in appropriately labeled flasks, and reserved for analysis and examination. On completion of the analysis of the five receptor solutions, they were combined and the five donor solutions were combined. These two solutions, donor and receptor, were then subjected to determination of density, pH, surface tension, and viscosity.

For diffusion experiments involving the semisolid terminal media, the diffusion cell chambers were filled by the use of a spatula as the unit was assembled. Care was exercised to avoid air spaces in the material and between the ointment and the cello-

phane. After an appropriate diffusion period in an incubator at 30° (18 hours for sodium salicylate and 60 hours for salicylic acid), the preparations were carefully removed, weighed, and placed in suitable containers for analysis and examination.

Physical Properties.—Certain physical data were routinely compiled for each diffusion study. These were density, pH, surface tension, and viscosity. The solubility of the medicament in the vehicle (7) was also determined. The Brookfield UL adapter for use with the Brookfield Synchro-Lectric viscometer, Model LVT, for the measurement of ultra low viscosities, was used to determine the viscosities of all of the fluid preparations. Corrected apparent viscosities were calculated for the emulsified media according to Bowles' method (8). Approximate viscosities for the semisolid preparations were determined using the model RVT viscometer. Only viscosity values are recorded in the results since it was the only property paralleling the differences in diffusion rates.

Method of Analysis.—Salicylate concentrations were determined colorimetrically by measurement of color produced by the reaction of ferric chloride with salicylates. The readings were taken at 525 mμ with a Beckman model B spectrophotometer. The emulsion preparations could not be assayed by direct dilution because of the insoluble components. Preparations emulsified with Tween 40 and G-7596-J were broken down by heating with 2 N sodium hydroxide, thus permitting separation of the aqueous phase. Since Brij 35 was stable to alkaline hydrolysis, the aqueous phase was separated by saturation with sodium chloride.

RESULTS AND DISCUSSION

The rates of diffusion of sodium salicylate and salicylic acid in the various media and the viscosities of these media are shown in Table 1. The rates of diffusion are compared in Fig. 3.

The results of the investigation showed, as expected, that in water and solutions of propylene glycol in water, the rate of diffusion was very closely related to the viscosity of the medium. When
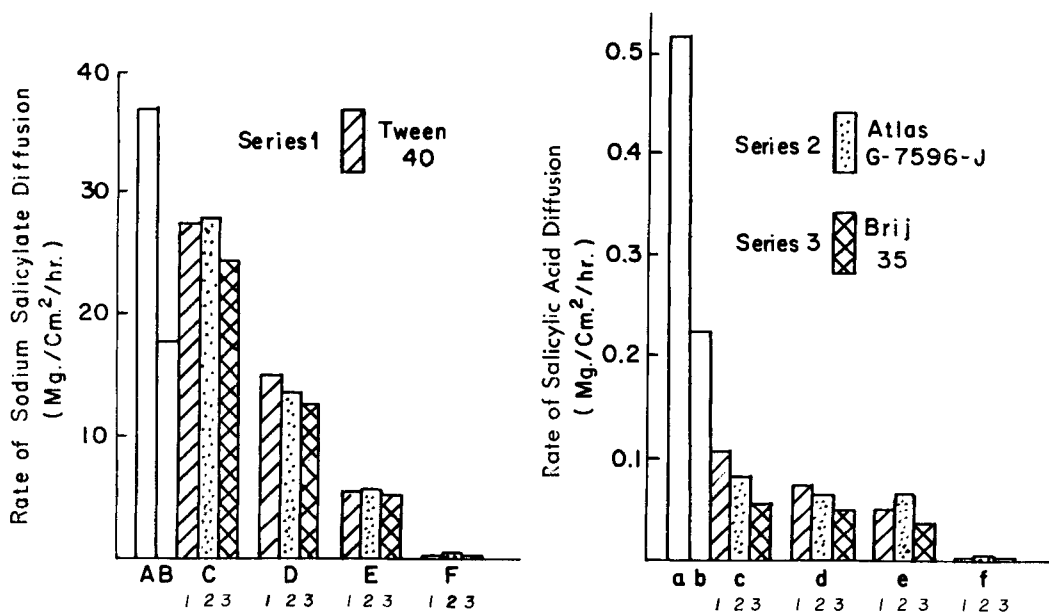
Fig. 3.—The effect on sodium salicylate and salicylic acid diffusion of adding each formula component in the three series and relating these to diffusion in Aa and Bb. Aa = Preserved water; Bb = A + propylene glycol; Cc = A + surfactant; Dd = C + propylene glycol; Ee = D + liquid petrolatum; Ff = E + stearyl alcohol.

a surface-active agent was added, the change in viscosity was similar to the change produced by the propylene glycol, but the reduction in the rate of diffusion resulting was only approximately half the reduction caused by propylene glycol. Since aqueous solutions of surface-active agents form micelles, these could be responsible for a measured viscosity which has less effect on a diffusing molecule or ion than the viscosity due to a substance like propylene glycol which does not form micelles. The bulk viscosity of propylene glycol solution, measured with the viscometer, approximates a microscopic viscosity. In the surface-active agent solutions containing micelles, a much greater difference exists between the bulk and microscopic viscosities. The fact that the diffusion effects of propylene glycol and a surface-active agent are additive only to a low degree also is probably related to the same phenomenon.

In contrast to the sodium salicylate diffusion system, once the surface-active agent is added to the salicylic acid diffusion system there is a marked reduction in the diffusion rate and only relatively small changes result from the additon of propylene glycol and liquid petrolatum. Since it can be shown that salicylic acid is solubilized by the micelles of surface-active agents, the presence of micelles in which salicylic acid is preferentially soluble would retard the diffusion process.

All components in each series which increased viscosity caused a reduction in the rate of diffusion from that in simple aqueous solution. The largest reduction was due to stearyl alcohol which transformed the media from liquid to semisolid with a consequent very large increase in viscosity. The effect due to differences in the surface-active agents were slight (see Fig. 3). It may be noted, however, that all preparations containing Brij 35 were somewhat more viscous than those containing the other two emulsifiers and, generally speaking, the rate of diffusion in media containing Brij 35 was slightly lower.

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