Study of Diffusion of Two Sulfonamides from Ointment Bases

By CLYDE W. WHITWORTH* and CHARLES H. BECKER

Two sulfonamides of widely different solubilities were incorporated at two concentrations into ointment bases and their diffusion through a membrane into distilled water determined over a 6-hr. period. A lipophilic surfactant appeared to increase the diffusion of sulfacetamide from petrolatum and from the hydrogenated cottonseed oil base. The surfactant increased the diffusion of sulfathiazole from the vegetable oil base but appeared to retard the process when petrolatum was utilized as the base. A reduction of the water–oil ratio in the emulsion bases tended to slow diffusion of both drugs. The results were analyzed statistically using the Student *t* test.

THE USE OF FATS and oils as vehicles for cosmetics and drugs dates back to the ancient Babylonian and Egyptian civilizations (1). When one considers the staggering numbers of cosmetics and medicinal creams, ointments, and similar preparations daily applied to the human skin, it would seem imperative that we understand thoroughly the factors involved in this route of absorption.

Possibly the physical-chemical properties of a drug influence its absorption through the skin more than any other factor. Some of the characteristics of the medicament believed to exert an influence are the thermodynamic activity of the drug in the vehicle and the skin barrier phase and the diffusion coefficient of the drug in the vehicle and skin barrier phase (2).

A limited amount of evidence has been uncovered recently indicating that oil-soluble compounds are absorbed more easily externally than those which are more water soluble (3).

A great deal of work has been performed to determine the effect of the vehicle on percutaneous absorption. The general belief seems to be that the bases modify the absorption of substances but do not bring about absorption (4). Although much of the research in this area has been empirical, the theoretical considerations by Higuchi (2), Shelmire (5), and Wagner (6) have contributed much to our understanding of many of the findings. Excellent reviews on percutaneous absorption have been presented by Barr (7) and Wagner (6).

The purpose of this study was to observe the effect of certain solubility factors on the diffusion of some sulfonamides from various bases. Both the water solubility of the drugs and their solubility in the bases were considered. The sulfonamides chosen have widely differing water solubilities; sulfacetamide is soluble 1 in 150 at 20° and a pH of 3.8 and sulfathiazole 1 in 1667 at 26° and pH of 6.0.

Sorbitan sesquioleate (Arlacel 83), a lipophilic surfactant, was incorporated into two of the bases at various concentrations to observe its effect on diffusion.

One of the bases was composed of 10% Cotoflakes[1] and 90% Cotmar.[1] Cotoflakes, completely hydrogenated cottonseed oil, has a melting range of 58 to 68° and an iodine number of about 6. Cotmar, partially hydrogenated cottonseed oil, has a melting point of about 34° and an iodine number of approximately 70. This mixture will be referred to as cottonseed oil base throughout this report.

EXPERIMENTAL

Materials.—More than 100 ointment bases, varying in some constituents, were screened, using single samples of each to determine their effect on the diffusion of the sulfonamides. Those bases showing the greatest effect were studied in detail, each utilizing 10 samples. Table I shows the formulas for the bases. Table II shows the source and grade or lot number of the constituents of the ointments and also includes the reagents used.

The hollow polyethylene stoppers used in the experiment were purchased from Pioneer Plastics, Jacksonville, Fla. The stoppers had a top diameter of 20 mm. a bottom diameter of 12 mm. and a depth of 25 mm. The membranes employed were of animal origin, furnished by Young Rubber Corp. These membranes are obtained from the appendix region of the lamb and are subjected to light density tests to ascertain their uniform thickness and character.

Wide-mouth glass bottles of about 60-ml. capacity, having ground-glass stoppers, were utilized to contain the water into which the diffusion proceeded.

Preparation of Ointments.—The sulfonamides which were microcrystalline in form were levigated

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[1] Supplied by Proctor and Gamble Co.

Table I.—Formulas for Ointment Bases

Base No.	Constituents
1	White petrolatum U.S.P. incorporated with 1, 5, and 10% Arlacel 83
2	Cottonseed oil base incorporated with 1, 5, and 10% Arlacel 83
3	White petrolatum, 64% Arlacel 83, 6% Distilled water, 30%

carefully into the bases to insure homogeneity. In the bases containing Arlacel 83, the surfactant was used as a levigating agent to aid dispersion.

The emulsion base was prepared by heating the distilled water to 67°, the mixture of Arlacel 83 and petrolatum to 65°, and adding the former to the latter with stirring. The sulfonamides were incorporated into these bases without using a solvent.

Diffusion.—Ten samples of each ointment were packed into the hollow polyethylene stoppers, and the open end was covered by the membrane, held in place by a rubber band. Care was taken to bring the entire exposed surface of the ointment into contact with the membrane. The containers were placed in 30 ml. of distilled water contained in wide-mouth glass bottles with ground-glass stoppers. The bottles then were placed in a water bath at 37.5 ± 1°; at 1-hr. intervals, samples of the water extracts were withdrawn and analyzed for their sulfonamide content by the Bratton-Marshall colorimetric assay. A Klett-Summerson colorimeter with a No. 54 filter was employed to determine the color intensity, which was compared to that of standard solutions.

The diffusion of sulfathiazole from two solutions of widely different pH's, 8.1 and 2.1, was observed to determine the effect of ionization on passage of the drugs through the membrane.

Solubility Determinations.—To study the effect of the surfactant on the solubility of each drug in the base, liquid petrolatum and cottonseed oil were substituted for the petrolatum and hydrogenated cottonseed oil bases, respectively.

A saturated solution of each of the sulfonamides in these oils was made and filtered carefully at a constant temperature to remove all suspended particles. A 5-ml. portion of each solution was shaken for 4 hr. with 10 ml. of ethyl alcohol. The alcoholic layer was centrifuged for 30 min. Aliquot portions of the alcoholic solutions were allowed to evaporate to dryness, the trichloroacetic acid solution added, and subsequently the Marshall reagents. From the intensity of the colors developed, it was possible to determine the amount of each drug extracted by the process utilized. Table III shows the results of the solubility determinations.

Statistical Analysis of Data.—The Student-Fisher t test was used to determine significance of differences between mean milligram per cent of drugs diffused from controls and from other bases at the end of 6 hr. The probability level used for acceptance or rejection of the null hypothesis was 0.05.

RESULTS AND DISCUSSION

Diffusion of Sulfathiazole from Solution

The results of the diffusion of sulfathiazole from solutions at two widely different pH's, 8.1 and 2.1, were almost identical, as shown in Fig. 1. Using the Student-Fisher t distribution at a 95% confidence level to determine the significance of any difference between two means, it was found that there was no significant difference between the mean milligram per cent of the drug which had diffused through the membrane from the two solutions at the end of 6 hr. It was reasonable to assume that both ions and molecules passed through the membrane with roughly the same degree of ease.

Diffusion of Sulfacetamide

From White Petrolatum.—In the solubility tests utilizing liquid petrolatum to simulate white petrolatum, it appeared that the sulfacetamide was more soluble in the mixtures of liquid petrolatum and Arlacel 83 than in the mineral oil alone. The apparent solubility increased with each increase in concentration of Arlacel 83.

Figure 2 shows that in the diffusion tests using the 1% ointments the pattern of diffusion seemed to parallel the results obtained in the solubility tests. The presence of Arlacel 83 increased the amount of sulfacetamide passing through the membrane, and each increase in concentration of Arlacel 83 resulted in an increase in the quantity of drug passing through the membrane. The differences between all bases containing surfactant and the controls were significant at 6 hr.

In general, the ointments containing 5% sulfacetamide (Fig. 2) gave results similar to those containing 1% of the drug. The presence of 1% Arlacel 83 in the base did not alter significantly the diffusion process from that observed with white

Table II.—Materials

Name	Supplier	Grade or Lot No.
Constituents of Ointments		
White petrolatum	Fisher Scientific Co.	U.S.P.
Arlacel 83	Atlas Powder Co.	129
Sulfacetamide	Ruger Chemical Co., Inc.	N.F.
Sulfathiazole	Eli Lilly and Co.	N.F.
Reagents		
Ammonium sulfamate	W. H. Curtin and Co.	27
N-(1-Naphthyl)-ethylenediamine dihydrochloride	W. H. Curtin and Co.	60
Sodium nitrite	Fisher Scientific Co.	701037
Trichloroacetic acid	J. T. Baker Chemical Co.	0414

TABLE III.—SOLUBILITY DETERMINATIONS

Solvent	Solubility, mg. %
Sulfacetamide	
Liquid petrolatum	0.089
Liquid petrolatum with 1% Arlacel 83	0.150
Liquid petrolatum with 5% Arlacel 83	0.906
Liquid petrolatum with 10% Arlacel 83	1.761
Cottonseed oil	4.734
Cottonseed oil with 1% Arlacel 83	5.675
Cottonseed oil with 5% Arlacel 83	6.950
Cottonseed oil with 10% Arlacel 83	8.45
Sulfathiazole	
Liquid petrolatum	Negligible
Liquid petrolatum with 1% Arlacel 83	2.178
Liquid petrolatum with 5% Arlacel 83	2.272
Liquid petrolatum with 10% Arlacel 83	17.136
Cottonseed oil	0.863
Cottonseed oil with 1% Arlacel 83	0.798
Cottonseed oil with 5% Arlacel 83	8.098
Cottonseed oil with 10% Arlacel 83	19.953

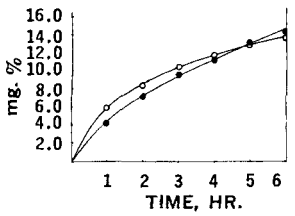

Fig. 1.—Diffusion of 0.2% sulfathiazole solutions at: ○, pH 8.1 and ●, pH 2.1.

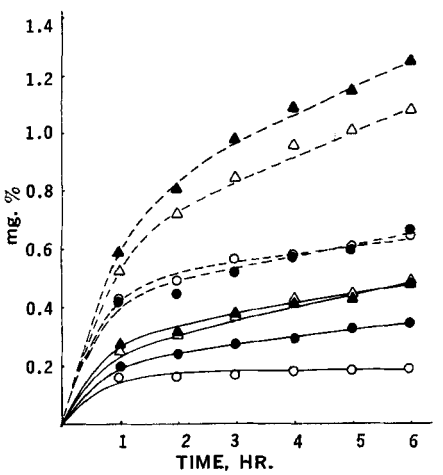

Fig. 2.—Diffusion of sulfacetamide in concentrations of 1% (——) and 5% (---) from bases composed of: ○, petrolatum; ●, petrolatum with 1% Arlacel 83; △, petrolatum with 5% Arlacel 83; and ▲, petrolatum with 10% Arlacel 83.

petrolatum alone. All other differences were significant at the final readings.

Of the three concentrations tested, it appeared that a 5% concentration of Arlacel 83 was the most practical in increasing the diffusion of sulfacetamide from white petrolatum.

From Hydrogenated Cottonseed Oil.—The solubility of sulfacetamide in cottonseed oil was determined to see if the results might help to clarify observations from the diffusion of the drug from a base composed of hydrogenated cottonseed oil. It was found that the sulfonamide was more soluble in mixtures containing Arlacel 83 than in the oil alone, and each increase in concentration of the surfactant resulted in an apparent increase in solubility.

The diffusion of sulfacetamide from the hydrogenated cottonseed oil base was increased by the addition of Arlacel 83 to the base. This was true for both the 1 and 5% concentrations of the sulfonamide, as seen in Fig. 3. As was the case with the petrolatum base, it appeared that the presence of 5% Arlacel 83 was the most desirable in enhancing the release of sulfacetamide from a hydrogenated cottonseed oil base. All differences between means at 6 hr. were significant.

Effect of a Change in the Water-Oil Ratio of the Emulsion Base.—The curves in Fig. 4 show that the diffusion of 5% sulfacetamide from the water-in-oil emulsion base used was retarded as the water/oil ratio was reduced. The difference between all means at 6 hr. was significant.

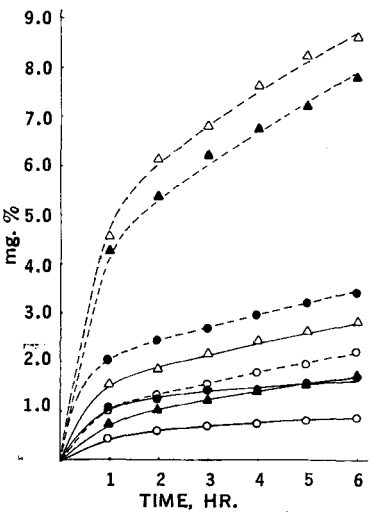

Fig. 3.—Diffusion of sulfacetamide in concentrations of 1% (——) and 5% (---), from bases composed of: ○, hydrogenated cottonseed oil; ●, hydrogenated cottonseed oil with 1% Arlacel 83; △, hydrogenated cottonseed oil with 5% Arlacel 83; and ▲, hydrogenated cottonseed oil with 10% Arlacel 83.

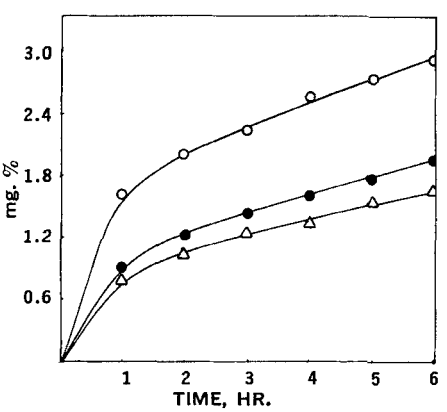

Fig. 4.—Diffusion of 5% sulfacetamide from a water-in-oil emulsion base with varying ratios of water/oil. Key: w/o ratio of base: ○, 40/49; ●, 30/59; and △, 20/69.

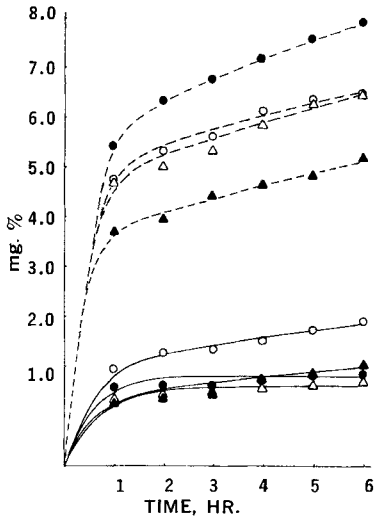

Fig. 5.—Diffusion of sulfathiazole in concentration of 1% (——) and 5% (---), from bases composed of: ○, petrolatum; ●, petrolatum with 1% Arlacel 83; △, petrolatum with 5% Arlacel 83; and ▲, petrolatum with 10% Arlacel 83.

Diffusion of Sulfathiazole

From White Petrolatum.—The solubility of sulfathiazole appeared to be greater in mixtures of liquid petrolatum and Arlacel 83 than in the mineral oil alone, increasing as the concentration of surfactant was increased. These differences in solubility were small compared to those observed with sulfacetamide.

However, the diffusion results (Fig. 5) differed from the pattern observed in the cash of sulfacetamide in that the presence of the surfactant seemed to retard diffusion rather than increase it. This was true in both the 1 and 5% ointments for all quantities of Arlacel 83, except the base containing 5% sulfathiazole and 1% Arlacel 83. All the differences between the control and the bases containing surfactants were significant in the 1% ointments. None of the other differences were significant.

From Hydrogenated Cottonseed Oil.—The solubility of sulfathiazole was greater in mixtures containing Arlacel 83 than in the oil alone. As in the previous cases, the solubility increased with each increase in concentration of the surfactant.

Figure 6 shows that, from both the 1 and 5% ointments containing surfactants, diffusion was greater than from the controls for all but one case. The differences were significant between all, except two pairs—the control and the base containing 1% Arlacel 83 and the control and base containing 10% Arlacel 83 for the 1% ointments. The 5% concentration of surfactant was most effective in increasing the rate of diffusion.

Effect of a Change in the Water-Oil Ratio of the Emulsion Base.—No significant difference was noted when the water-oil ratio was changed from 40/49 to 30/59, as seen in Fig. 7. A significant difference at 6 hr. was noted when the ratio was reduced further to 20/69, with an apparent decrease in the rate of diffusion resulting.

It appears that the solubility of a drug in an ointment base greatly influences the diffusion of that drug from the base. In this study, the surfactant apparently increased the solubility of both sulfonamides in petrolatum and in the cottonseed oil base. Except for sulfathiazole in petrolatum, an increase in diffusion from the bases was noted. It is evident that the optimum concentration of surfactant for increasing diffusion in this study is 5%.

It is hypothesized that solubilization of the drug in the base increases the drug mobility in the base, thereby enhancing saturation of the ointment with higher concentrations of the drug at the surface. This promotes drug diffusion from the base.

In view of the wide difference in the water solubilities of the two drugs used, it is somewhat surprising that the rates of diffusion of the two sulfonamides do not differ greatly. From the results with sulfathiazole, one might conclude that, for drugs of low water solubility, the effect of a lipophilic surfactant on diffusion is more dependent on the type of base than in the case of the more soluble drugs.

SUMMARY

The diffusion of sulfacetamide and sulfathiazole from three ointment bases through a membrane into water has been studied. The effect of a lipophilic nonionic surfactant on the diffusion of the two sulfonamides has been shown. The solubility of the sulfonamides in the presence of the surfactant

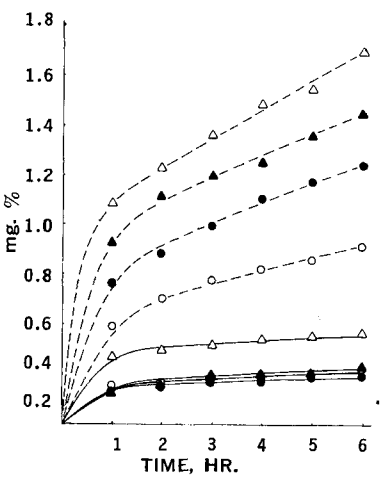

Fig. 6.—Diffusion of sulfathiazole in concentrations of 1% (——), and 5% (---), from bases composed of: ○, hydrogenated cottonseed oil; ●, hydrogenated cottonseed oil with 1% Arlacel 83; △, hydrogenated cottonseed oil with 5% Arlacel 83; and ▲, hydrogenated cottonseed oil with 10% Arlacel 83.

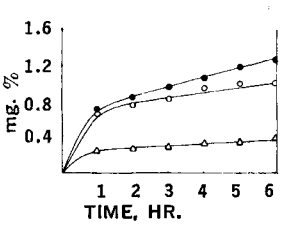

Fig. 7.—Diffusion of 5% sulfathiazole from a water-in-oil emulsion base with varying ratios of water/oil. Key: w/o ratio of base: ○, 40/49; ●, 30/59; and △, 20/69.

has been determined using liquids to simulate the ointment bases. A reduction of the water/oil ratio of an emulsion base tended to retard diffusion of the sulfonamides. A statistical evaluation of the results was made. In general, the surfactant increased the solubilities of the sulfonamides in the solvents used and in most of the determinations tended to increase diffusion from the ointment bases. The 5% concentration of surfactant appeared to be most effective.

The authors conducted a similar study utilizing the sodium salts of these two sulfonamides. These results will be submitted at a later date.

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Relationships Between the Surface Activity and Cholinesterase Inhibition of Carbamoylpiperidinoalkanes II

Variations in the Amide Function

By RONALD P. QUINTANA

The static surface tension of aqueous solutions of selected mono- and bis(carbamoylpiperidino)ethanes and -decanes has been determined and compared with the ability of these compounds to inhibit human plasma pseudo-cholinesterase. Parallels reported in a preceding communication were confirmed, and other relationships between surface-active properties and biochemical activity were explored.

IN A PREVIOUS communication (1), the relationships between surface activity and cholinesterase inhibition of a series of mono- and bis-[3 - (*N,N* - diethylcarbamoyl)piperidino]alkanes were reported. While a parallel was observed between the ability of mono[3-(*N,N*-diethylcarbamoyl)piperidino]alkanes to lower surface tension and their inhibition of isolated human plasma pseudo-cholinesterase, no such relationship was noted in the case of the corresponding bis-substituted alkanes. Subsequently, the influence of variation in the amide function of mono- and bis(carbamoylpiperidino)ethanes and -decanes upon inhibitory characteristics was studied (2), and a parallel between electric moments of *N*-alkyl substituted nicotinamides and cholinesterase inhibition of identically substituted 1-decylnipecotamides was observed (3).

In the present paper, parallels reported in the preceding paper (1) were confirmed, and additional relationships between surface activity and biochemical response were explored.

EXPERIMENTAL

Materials.—The chemistry and properties of the mono- and bis(carbamoylpiperidino)ethanes and -decanes employed in this study were described elsewhere (2, 4). All of the compounds used were of analytically pure grade.

Solutions.—For each of the monosubstituted decanes, surface tension measurements were made on aqueous solutions of the following concentrations: 0.00125, 0.001875, 0.0025, 0.00375, 0.005, 0.0075, and 0.01 *M*. For all other compounds, measurements were made on 0.005 and 0.01 *M* solutions, although the former are not reported.

Instrumentation and Methods.—The instrumentation and methods previously employed (1) were utilized without modification for the compounds discussed in this paper.

Solutions of most of the mono(carbamoylpiperidino)alkanes had pH values between 5.70 and 6.20, those of the bis(carbamoylpiperidino)-ethanes between 3.30 and 3.80, and those of the bis(carbamoylpiperidino)decanes between 5.50 and 5.90.

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