Effect of Three Liquid Additives on Diffusion of Atropine from Ointment Bases

CLYDE W. WHITWORTH and ROBERT E. STEPHENSON*

Abstract □ Water, alcohol, and dimethyl sulfoxide were each incorporated at 1, 2, and 5% concentrations into four ointment bases containing atropine. The diffusion of drug from five samples of each base was determined at 20-min. intervals for 2 hr. The diffusion process was zero order after 20 min. In the majority of instances, diffusion was significantly enhanced by the presence of the liquids. The concentration of liquid additive had significant effect in some instances; however, this effect was dependent on the type of base. Rate constants were calculated, and data were subjected to statistical analyses. The viscosity of each mixture was determined and, in some instances, appeared to correlate with the diffusion rates.

Keyphrases □ Atropine diffusion—ointment bases □ Ointments, atropine diffusion—water, alcohol, dimethyl sulfoxide effects □ Membrane permeation—atropine from ointments □ UV spectrophotometry—analysis

Percutaneous absorption of drugs from lotions, creams, and ointments is of considerable importance from the standpoint of toxicity, sensitivity, and effectiveness. The widespread use of such external preparations has led to increased interest in factors that may influence absorption through the skin. *In vitro* experiments usually involve the measurement of drug release from bases. Such measurements of drug release may detect interactions between drugs and vehicles which, in turn, may influence drug absorption through the skin.

It was previously found that the diffusion of salicylic acid from various ointment bases was influenced by the presence of low concentrations of certain liquids (1). It was subsequently suggested that other drugs be tried, and the weak base atropine was selected. This drug is extensively used in ophthalmic ointments. Coincidentally the water solubility of atropine is very near that of salicylic acid. Diffusion techniques have been used extensively to measure drug release from heterogeneous preparations such as ointments (2) and emulsions (3). The absorption of atropine from ophthalmic ointments probably involves the diffusion of the drug from the base into tear fluid.

Table I—Bases Used in This Study

Base	Percent
Water-in-oil base	
White petrolatum USP	64
Sorbitan monostearate[a]	6
Distilled water	30
Oil-in-water base	
Stearyl alcohol	25
White petrolatum	25
Glycerin	12
Polyoxyethylene (20) sorbitan monooleate[b]	5
Distilled water	33
Hydrogenated cottonseed oil base	
Partially hydrogenated cottonseed oil[c]	80
Completely hydrogenated cottonseed oil[d]	15
Sorbitan monooleate[e]	5
PEG base	
PGE 400	40
PEG 4000	40
Stearyl alcohol	20

[a,b] Trademarked as Span-60 and Tween-80, respectively, by Atlas Chemical Industries, Wilmington, Del. [c,d] Trademarked as Cotmar and Cotoflakes, respectively, by Proctor and Gamble Co., Cincinnati, Ohio. [e] Trademarked as Span-80 by Atlas Chemical Industries, Wilmington, Del.

Table II—Diffusion Rate Constants, K, for Atropine in moles/l./min. and Viscosity, N, of Ointments in Brookfield Viscometer Units

Additives	K	N	K	N
	Water-in-Oil		**Oil-in-Water**	
None	0.019	12.0	0.042	24.0
1% Alcohol	0.025	13.5	0.049	22.6
2% Alcohol	0.033	12.4	0.048	22.5
5% Alcohol	0.036	11.4	0.057	20.2
1% Water	0.037	19.0	0.055	24.0
2% Water	0.034	19.0	0.067	22.0
5% Water	0.044	14.5	0.069	20.6
1% DMSO	0.047	11.0	0.081	21.4
2% DMSO	0.042	9.5	0.066	20.6
5% DMSO	0.041	9.2	0.054	15.5
	Cottonseed Oil		**PEG**	
None	0.030	4.4	0.056	100+
1% Alcohol	0.035	4.5	0.067	100+
2% Alcohol	0.051	4.2	0.074	98.0
5% Alcohol	0.044	5.0	0.076	73.4
1% Water	0.053	5.7	0.069	100+
2% Water	0.037	3.2	0.073	100+
5% Water	0.035	4.5	0.075	86.0
1% DMSO	0.039	4.5	0.060	98.7
2% DMSO	0.038	3.7	0.066	89.8
5% DMSO	0.035	3.2	0.069	63.7

EXPERIMENTAL

Three liquids—water, alcohol, and dimethyl sulfoxide (DMSO)—were incorporated at 1, 2, and 5% concentrations into four different ointment bases. Two of the bases used in this study differ from those used in the previous investigation (1). The petrolatum base and the hydrogenated cottonseed oil base used in the first study did not release atropine. Consequently, a polyethylene glycol (PEG)

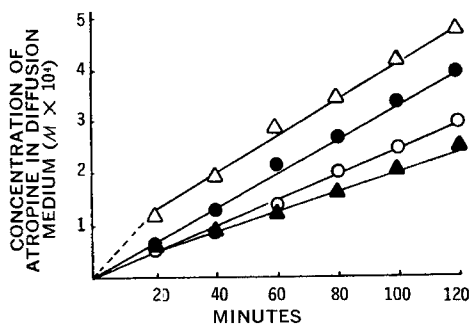

Figure 1—*Diffusion of 5% atropine from water-in-oil base* (▲) *and from water-in-oil base containing: 1% alcohol* (○), *2% alcohol* (●), *and 5% alcohol* (△).

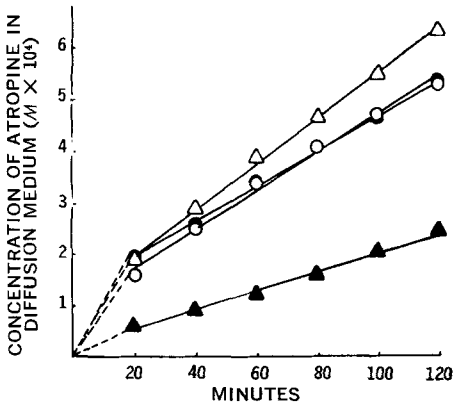

Figure 2—*Diffusion of 5% atropine from water-in-oil base* (▲) *and from water-in-oil base containing: 1% water* (○), *2% water* (●), *and 5% water* (△).

mixture was substituted for petrolatum, and 5% sorbitan monooleate was incorporated into the formula composed of hydrogenated cottonseed oil. The ingredients of the bases are given in Table I.

Atropine was incorporated into the emulsion bases by mixing it with the melted white petrolatum phase at low temperature prior to mixing the aqueous and oleaginous phases. For other ointments, the drug was added to the melted bases and stirred until the bases became firm. The concentration of atropine was 5% in all bases. To minimize evaporation, the liquids were each incorporated into the ointments just prior to use. All ointments including controls were thoroughly spatulated.

Five samples of each ointment were packed into uniform polyethylene cups which had a top (open end) diameter of 40 mm., a bottom diameter of 30 mm., and a depth of 25 mm. The open end was covered by a membrane[1] and sealed by a rubber band, so the entire exposed surface of the ointment was in contact with the membrane. The membranes used were of animal origin and during processing had been defatted and subjected to light density tests to ascertain their uniform character and thickness. The cups were then inverted in 60 ml. of distilled water contained in 4-oz. ointment jars, and the tops were replaced on the jars to prevent evaporation. The jars were then placed in a constant-temperature shaker-type bath at 37.5° for the diffusion to proceed. At 20-min. intervals for 2 hr., aliquots of the diffusion medium of each sample were assayed spectrophotometrically for drug content and returned to the container to maintain volume.

Diffusion of atropine from samples without additives was measured and taken as the control. A set of samples containing no drugs was run which furnished diffusion media for the reference cell. Atropine showed a spectrophotometric absorbance peak at 247.6 nm. Plots of concentration against absorbance showed conformity to Beer's law.

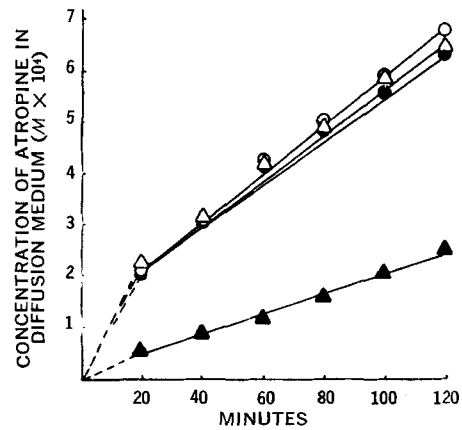

Figure 3—*Diffusion of 5% atropine from water-in-oil base* (▲) *and from water-in-oil base containing: 1% DMSO* (○), *2% DMSO* (●), *and 5% DMSO* (△).

[1] Supplied by Young Drug Co.

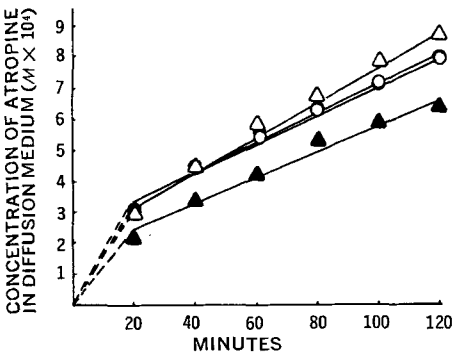

Figure 4—*Diffusion of 5% atropine from oil-in-water base* (▲) *and from oil-in-water base containing: 1% alcohol* (○), *2% alcohol* (●), *and 5% alcohol* (△).

Viscosity measurements were made with a Brookfield Synchro-Lectic viscometer model RVT mounted on a Helipath stand. A t-shaped spindle was used in all the measurements.

The influence of the additives on the permeability of the membrane was considered. It was determined that 1, 2, and 5% concentrations of alcohol or DMSO had no effect in 2 hr. on the passage of atropine through the membrane from aqueous solutions. This was found to be true with salicylic acid in the previous study (1). It was, therefore, assumed that the liquids used in this study exerted their influence on diffusion by means other than their action on the membrane.

Statistical methods were used to compare samples containing additives with controls. The *t* test at the 95% confidence level was employed (4).

The diffusion process was zero order between 20 and 120 min., with straight lines obtained when the concentration of the drug was plotted against time. Correlation coefficients confirmed these findings. All points on the graphs represent the average of five runs. The straight-line plots were calculated by the method of least squares. Rate constants were equal to the slopes of the lines and are shown in Table II along with viscosities.

RESULTS

Water-in-Oil Base—All liquids except 1% alcohol significantly increased the diffusion of atropine from this base. Figure 1 shows the effect of alcohol on diffusion. Although little effect was noted on viscosity (Table II), diffusion increased as the concentration of alcohol increased, as seen in the figure and in the rate constants of Table II.

In Fig. 2, water is seen to increase greatly the rate of diffusion of atropine from the water-in-oil base. It also increased the viscosity of the ointment over that of the control.

DMSO had the greatest effect in increasing the diffusion of atropine from this base (Fig. 3). Little difference was noted between

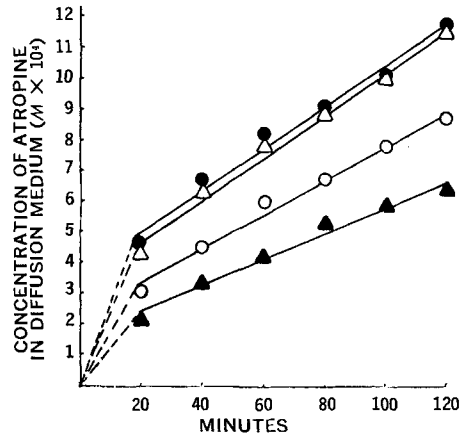

Figure 5—*Diffusion of 5% atropine from oil-in-water base* (▲) *and from oil-in-water base containing: 1% water* (○), *2% water* (●), *and 5% water* (△).

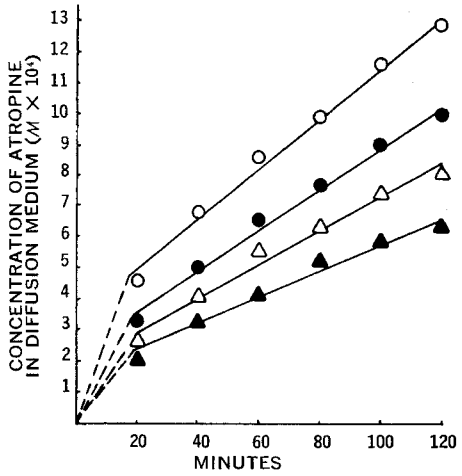

Figure 6—*Diffusion of 5% atropine from oil-in-water base* (▲) *and from oil-in-water base containing: 1% DMSO* (○), *2% DMSO* (●), *and 5% DMSO* (△).

the three concentrations of DMSO. The viscosities of the ointments containing DMSO were slightly lower than the viscosity of the control, but they do not vary greatly from each other.

Oil-in-Water Base—All concentrations of alcohol significantly increased the diffusion of atropine from the oil-in-water base (Fig. 4). Little difference was noted between 1 and 2% alcohol, either in effect on diffusion or on viscosity. The viscosity of this ointment was lowered slightly by all concentrations of alcohol, with the 5% giving the greatest reduction.

In Fig. 5, water is seen to increase the rate of diffusion of atropine from this base and a slight decrease in viscosity was observed. The diffusion results with 2 and 5% were almost identical.

Again, DMSO (Fig. 6) showed the greatest ability to increase the diffusion of atropine. The 1% concentration of DMSO showed

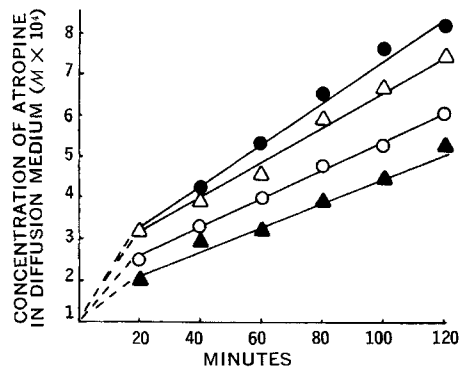

Figure 7—*Diffusion of 5% atropine from cottonseed oil base* (▲) *and from cottonseed oil base containing: 1% alcohol* (○), *2% alcohol* (●), *and 5% alcohol* (△).

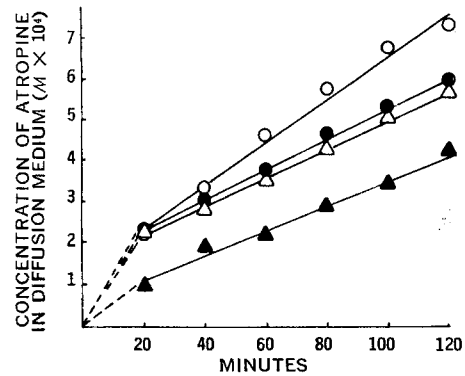

Figure 8—*Diffusion of 5% atropine from cottonseed oil base* (▲) *and from cottonseed oil base containing: 1% water* (○), *2% water* (●), *and 5% water* (△).

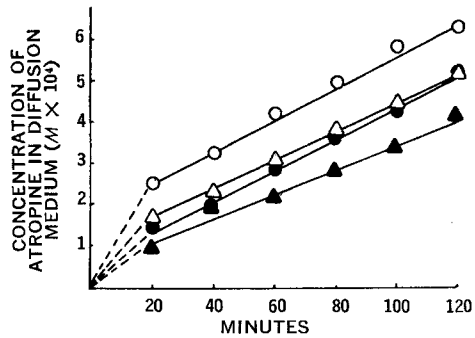

Figure 9—*Diffusion of 5% atropine from cottonseed oil base* (▲) *and from cottonseed oil base containing: 1% DMSO* (○), *2% DMSO* (●), *and 5% DMSO* (△).

the greatest effect followed by 2 and 5%, although the viscosities were reduced by increasing the concentration of DMSO.

Hydrogenated Cottonseed Oil Base—All liquids except 1% alcohol (Fig. 7) significantly increased the diffusion of atropine from the hydrogenated cottonseed oil base. The results with water (Fig. 8) and DMSO (Fig. 9) were very similar, with the greatest increase in diffusion produced by 1% concentrations of each. The viscosities were not changed greatly by the additives.

PEG Base—All liquids except 1% DMSO significantly increased the release of atropine from the PEG base (Figs. 10–12). Water had the greatest effect, as seen in Fig. 11; in general, an increase in concentration of liquid produced an increase in diffusion. Viscosity decreased with increasing concentrations of each liquid. The diffusion curves with this base are zero order in many instances over the entire 2-hr. period, indicating a constant rate of diffusion. This differed from the other bases which showed a greater rate during the first 20 min. and a steady rate thereafter.

DISCUSSION AND CONCLUSIONS

Higuchi (2) devised a modified mathematical statement of Fick's law to predict the amount of drug diffusing from certain types of ointment bases. The results, such as straight-line plots, of this study preclude the utilization of this equation. Certain assumptions are also made by Higuchi (2) that are not met by the conditions of this study.

Except in three instances involving 1% concentrations of liquids, the liquids increased the diffusion of atropine from the bases tested.

The PEG base gave the greatest release of atropine of the bases tested, both from the control and from the bases containing liquids. The average rate constant for the PEG base was 0.685. Next, in descending order, the average rate constants were: oil-in-water base, 0.588; cottonseed oil base, 0.397; and water-in-oil base, 0.358.

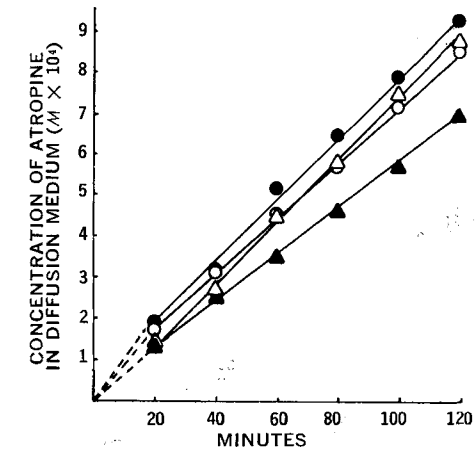

Figure 10—*Diffusion of 5% atropine from PEG base* (▲) *and from PEG base containing: 1% alcohol* (○), *2% alcohol* (●), *and 5% alcohol* (△).

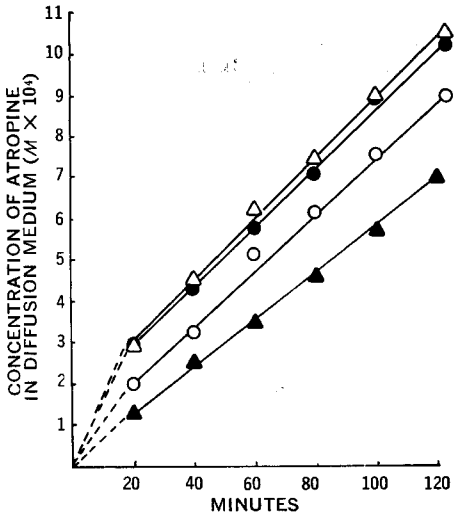

Figure 11—*Diffusion of 5% atropine from PEG base (▲) and from PEG base containing: 1% water (○), 2% water (●), and 5% water (△).*

Referring to the rate constants listed in Table II, one can see that DMSO was the most effective in increasing diffusion from both the water-in-oil and the oil-in-water bases followed by water and alcohol, respectively, in these bases.

The order was reversed in the case of the cottonseed oil base, with alcohol giving the greatest increase followed by water and DMSO.

The PEG base showed little difference between the results with alcohol and water. However, the rate constants for both of these were greater than those for DMSO.

The concentration of liquids had an effect on the diffusion patterns. As the concentration of DMSO was increased, the diffusion rates decreased for the water-in-oil, oil-in-water, and cottonseed oil bases and increased slightly for the PEG base.

As the concentration of both alcohol and water increased, the diffusion rate increased from all bases except dehydrogenated cottonseed oil which showed a decrease in the case of water and an increase and then a decrease as the alcohol concentration went from 1 to 2 to 5%.

In most cases, the viscosity of the ointments decreased, if only slightly, as the concentration of liquid was increased. With the exception of DMSO, this corresponded in most instances to an increase in diffusion.

The solubility of a drug in an ointment base undoubtedly plays a major role in its diffusion from that base. In other studies, liquids were used to simulate the single-component ointment bases and to correlate solubility with release (5) and *in vivo* absorption (6). It is not possible to determine accurately the solubility of drugs in the intact ointment base in studies in which the bases are composed of several components such as the emulsion bases. In some cases, it is possible to make assumptions and draw conclusions concerning solubility from the physical and chemical properties of both the drug and base. In this study the results of the diffusion measurements show no apparent correlation to the solubility that atropine might be assumed to have in the bases. The bases that

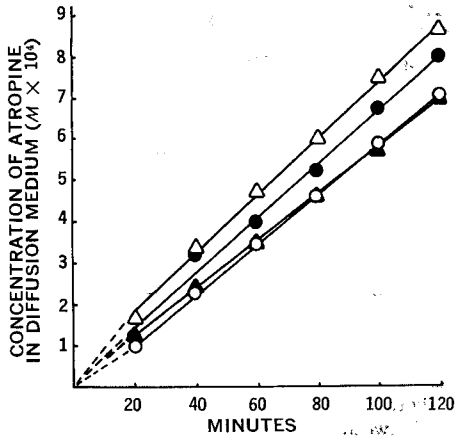

Figure 12—*Diffusion of 5% atropine from PEG base (▲) and from PEG base containing: 1% DMSO (○), 2% DMSO (●), and 5% DMSO (△).*

were more like the diffusion medium, *i.e.*, PEG and oil-in-water emulsion, gave the greatest release.

It is apparent that the incorporation of even small concentrations of certain liquids into certain types of ointment bases may increase the diffusion of some drugs from these bases. This is true for certain emulsion bases which themselves already contain appreciable amounts of water and oil. It should be remembered that the liquids were incorporated uniformly after the emulsion bases were prepared.

Some researchers have suggested that the rate of dissolution of suspended drugs in ointment bases as well as methods of preparation are quite likely to influence drug release. Some of these factors are currently under investigation in these laboratories.

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* Present address: U. S. Public Health Service, Indian Hospital, Tuba City, Ariz.