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The effect of physicochemical properties on the in vitro diffusion of drug through synthetic membranes and pigskin. II. Salicylic acid

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Summary

The effect of membrane type and receptor phase composition on the in vitro diffusion of salicylic acid was studied. Salicylic acid solutions (5% w/w) containing either lanolin or methyl glucoside derivatives were diffused across cellulose, dimethyl polysiloxane and pigskin into a receptor phase of aqueous glycol, water or a buffered solution. The permeabilities and diffusion profiles were unique for each membrane type that was examined and the salicylic acid solutions demonstrated the same rank order of membrane penetration (with one exception): pigskin > cellulose > dimethyl polysiloxane. Diffusion of salicylic acid into buffer solutions (pH 2.2–7.4) yielded patterns that were predicted by the pH partition hypothesis. The salicylic acid diffusion was decreased as the receptor phase pH was lowered.

Introduction

The in vitro diffusion of compounds can be significantly influenced not only by the vehicle and drug's physicochemical properties but also by the experimental parameters. It was demonstrated previously that the membrane type (Nagy et al., 1980; Nakano, 1979) and receptor phase composition (Walkow and McGinity, 1987) can alter the diffusion profile. The diffusion of methyl salicylate was significantly dependent on the membrane type employed (Walkow and McGinity, 1987).

The effects of vehicle membrane type and receptor phase on the in vitro diffusion of salicylic acid are examined in the present report. Comparison with the methyl salicylate in vitro study results in the examination of two chemically similar compounds that frequently exhibit different diffusional behavior.

Materials and Methods

In vitro diffusion studies

Salicylic acid, U.S.P. [1] was used in the in vitro

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diffusion studies. A mass spectrometry analysis was performed on salicylic acid to insure purity. Diffusion studies were performed in a glass, two compartment diffusion cell system described previously (Walkow and McGinity, 1987). The diffusion cells [2] had a 140 ml capacity per compartment and a membrane surface area of 17.429 cm^2.

The membrane types utilized in the diffusion studies included cellulose [3], dimethyl polysiloxane [4] and pigskin [5]. The preparation technique for the different membranes has been described (Walkow and McGinity, 1987).

The vehicles (donor phase) consisted of lanolin and methyl glucoside derivatives with different dielectric constants. The lanolin derivatives included laneth-9 acetate (Solulan 97) [6] and laneth-10 acetate (Solulan 98) [6]. The methyl glucoside derivatives included methyl gluceth-10 (Glucam E-10) [6] and methyl glucose ether (Glucam P-10) [6].

A 5% w/w solution of salicylic acid and vehicle was prepared for each diffusion study. The receptor phase was composed of polyethylene glycol 400 [7]/water, deionized water or a citrate–phosphate buffer solution.

The sampling, with replacement, from the receptor phase was determined by the type of membrane, vehicle and receptor phase employed. Samples (1.1 ml) were removed with a glass pipette and stored in glass conical tubes with Teflon-lined caps until assayed.

Analysis

Samples of the receptor phase were assayed using a Beckman Model 35 double-beam UV-visible spectrophotometer [8]. Salicylic acid standard solutions (2.5–60.0 μg/ml), prepared with the different receptor phases, exhibited absorption maxima between 297 nm and 300 nm. UV scans were recorded for samples from each diffusion study to ensure that there was no interference from the diffusion of vehicles into the diffusion media at the λ_{max} of the drug.

Dielectric constant, viscosity and apparent partition coefficient determinations

The methods utilized to determine the dielectric constant and the viscosity of the vehicles, and the octanol/water partition coefficient were previously reported by the authors (Walkow and McGinity, 1987).

Results and Discussion

The in vitro diffusion of salicylic acid through synthetic and biological membranes into a receptor phase composed of either aqueous glycol or water was examined. These studies allowed the diffusion properties of salicylic acid to be studied on the basis of both the membrane type and receptor phase employed.

The saturation solubilities of salicylic acid in the donor and receptor phase media are listed in Table 1. The permeability coefficients for each salicylic acid diffusion system are listed in Table 2. These coefficients were calculated using the equations described previously (Walkow and McGinity, 1987).

The diffusion profiles of salicylic acid (5% w/w)

TABLE 1

Saturation solubility of salicylic acid in different media (n = 3)

Media	Mean saturation solubility ± S.D. (mg/ml)
Vehicles	
Laneth-9 acetate	199.5 ± 0.6
Laneth-10 acetate	212.0 ± 7.0
Methyl gluceth-10	254.6 ± 0.1
Methyl glucose ether	81.7 ± 8.0
Receptor Phases	
PEG 400/water (1 : 1 w/w)	25.7 ± 0.2
Water	2.2 ± 0.3
Citrate-phosphate buffers	
pH 2.2	2.0 ± 0.7
pH 3.0	2.6 ± 0.4
pH 4.5	6.9 ± 0.5
pH 7.4	21.9 ± 0.5

[2] Bellco Glass, Vineland, NJ 08360, U.S.A.
[3] Spectrum Industries, Los Angeles, CA 90054, U.S.A.
[4] Dow Corning Corp., Midland, MI 48640, U.S.A.
[5] Genetic Labs, St. Paul, MN 55113, U.S.A.
[6] Amerchol Corp., Edison, NJ 08817, U.S.A.
[7] Matheson Coleman & Bell, Norwood, OH 45212, U.S.A.
[8] Beckman Instruments, Irvine, CA 92713, U.S.A.

TABLE 2

Permeability coefficients for membranes — salicylic acid in aqueous glycol and water

Vehicle	Receptor phase	Membrane	$P \times 10^4$ (cm/h)
Methyl gluceth-10	Aqueous glycol	Cellulose	14.89
	Water		56.45
Methyl glucose ether	Aqueous glycol		7.27
	Water		35.95
Laneth-9 acetate	Aqueous glycol		6.09
	Water		16.23
Laneth-10 acetate	Aqueous glycol		6.74
	Water		12.75
Methyl gluceth-10 / Methyl glucose ether	(1) / (2) Aqueous glycol		10.42
	(2) / (1) Aqueous glycol		8.36
Methyl gluceth-10	Aqueous glycol	Dimethyl polysiloxane	0.24
	Water		0.23
Methyl glucose ether	Aqueous glycol		0.21
	Water		0.20
Laneth-9 acetate	Aqueous glycol		0.61
	Water		0.58
Laneth-10 acetate	Aqueous glycol		0.79
	Water		1.33
Methyl gluceth-10	Aqueous glycol	Pigskin	9.91
Methyl glucose ether			99.55
Laneth-9 acetate			50.75
Laneth-10 acetate			116.80
	pH	Membrane	$P \times 10^4$ (cm/h)
Methyl glucose ether	2.2	Cellulose	29.08
	3.0		36.77
	4.5		49.02
	7.4		74.28
Laneth-10 acetate	2.2		10.34
	3.0		13.55
	4.5		23.65
	7.4		37.75

TABLE 2 (continued)

Vehicle	Receptor phase	Membrane	$P \times 10^4$ (cm/h)
Methyl glucose ether	2.2	Dimethyl polysiloxane	0.2121
	3.0		0.2237
	4.5		0.2518
	7.4		0.2237
Laneth-10 acetate	2.2		0.7409
	3.0		0.8571
	4.5		0.8770
	7.4		0.9035

from lanolin and methyl glucoside derivatives through a cellulose membrane into aqueous glycol and water are shown in Figs. 1 and 2, respectively. The diffusion of a salicylic acid from the vehicles occurred in the same relative rank order in both cases (methyl gluceth-10, methyl ether, laneth-10 acetate, laneth-9 acetate) though the diffusion into water occurred more readily which may be due to differences in boundary layer thickness. The possibility of boundary layer effects was not confirmed through experimentation. The rank order of diffusion for salicylic acid was practically identical to the diffusion of methyl salicylate through cellulose into aqueous glycol (Walkow and McGinity, 1987). Due to the insolubility of salicylic acid in lanolin

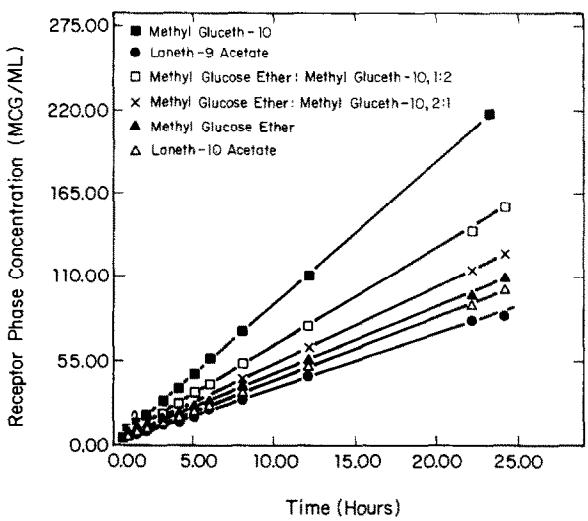

Fig. 1. In vitro diffusion of salicylic acid across cellulose into aqueous glycol.

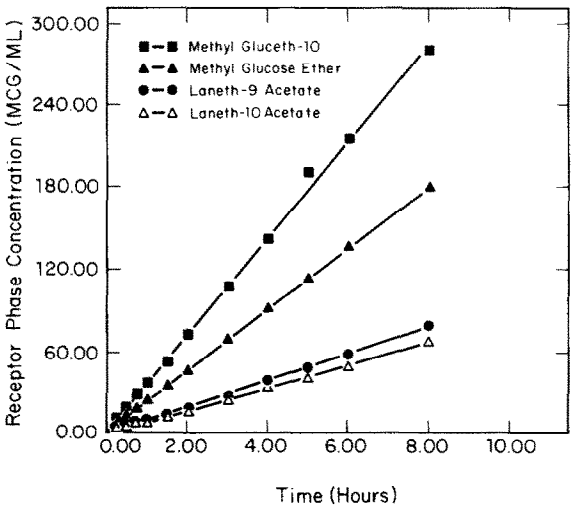

Fig. 2. In vitro diffusion of salicylic acid across cellulose into water.

alcohol, diffusion studies in that media could not be performed. The diffusion of methyl salicylate through the cellulose membrane was related to the dielectric constant of the vehicles and the drug. The dielectric constant of salicylic acid, calculated using Fedor's group analysis method, was found to be 15.53. This value is considerably larger than methyl salicylate's dielectric constant of 9.41, so the dielectric constant relationship with the diffusion rate did not apply to salicylic acid.

The salicylic acid appeared to be released more rapidly from the hydrophilic vehicles than from the more hydrophobic vehicles. In fact, the diffusion of salicylic acid decreased in relation to the vehicle's water solubility (Walkow and McGinity, 1987). This may be due to the permeability of water through the cellulose which may promote salicylic acid diffusion from the aqueous solution rather than from the vehicle.

Combinations of the methyl glucoside derivatives were prepared and employed in the study of salicylic acid diffusion through cellulose into aqueous glycol. As predicted from the water solubilities of the two derivatives, the methyl glucose ether : methyl gluceth-10 1 : 2 combination resulted in faster diffusion rates than the 2 : 1 mixture.

The diffusion of salicylic acid across a dimethyl polysiloxane membrane into aqueous glycol and water are exhibited in Figs. 3 and 4. The salicylic acid diffused much slower across the dimethyl polysiloxane than the cellulose membrane. Diffusion studies utilizing dimethyl polysiloxane were carried out for 72 h. The diffusion profiles were different than those observed with the cellulose membrane. With the dimethyl polysiloxane membrane, release from the lanolin derivatives was

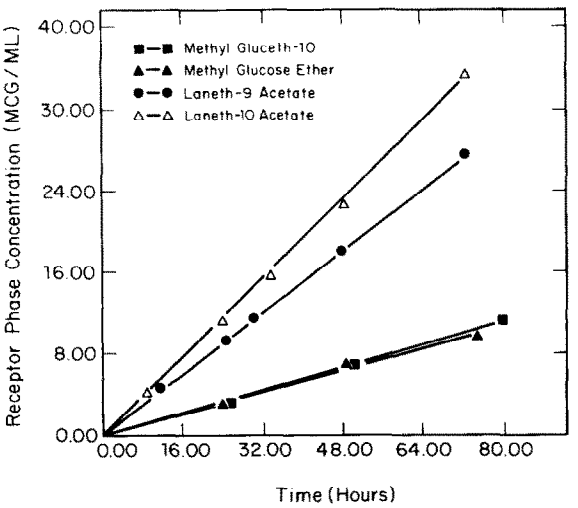

Fig. 3. In vitro diffusion of salicylic acid across dimethyl polysiloxane into aqueous glycol.

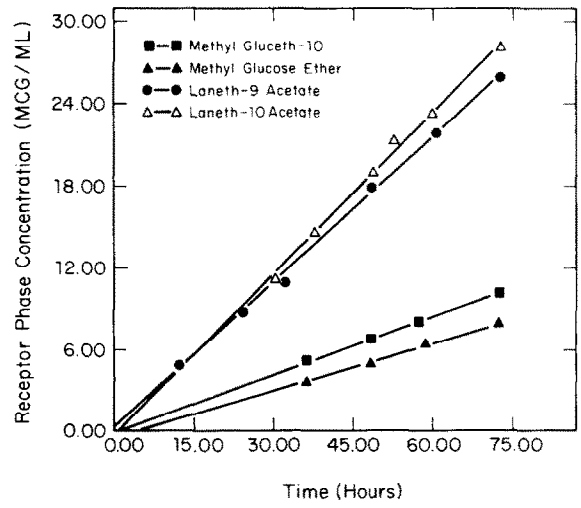

Fig. 4. In vitro diffusion of salicylic acid across dimethyl polysiloxane into water.

faster than from the methyl glucoside derivatives. These diffusion profiles were similar to the methyl salicylate profiles across the same membrane. As with the methyl salicylate diffusion studies, the diffusion of salicylic acid may be inversely related to the viscosity of the vehicle.

The penetration of salicylic acid through pigskin into aqueous glycol was studied (Fig. 5). The permeability of salicylic acid diffusion was approximately 10 times faster through the pigskin than the other membrane types. During the course of these diffusion studies, the receptor phase would become cloudy. Since this phenomenon did not occur when other drugs were diffused across pigskin, this cloudiness could be attributed to the salicylic acid. The considerable keratolytic action of salicylic acid confirmed the idea that the drug was probably breaking down components in the skin which were released into the aqueous glycol. The cloudiness may also be a result of an incompatibility of salicylic acid and the iodine wash solution.

The diffusion profiles across the pigskin did not resemble the salicylic acid patterns for the other membrane types. It was not possible to explain these profiles based on the limited physical and chemical properties that were examined. The inability to define the parameter(s) which influenced the diffusion rate across pigskin is due to the inherent complexities associated with the use of biological membranes for in vitro diffusion studies.

The diffusion profiles of salicylic acid across all of the membrane types for each formulation are shown in Figs. 6–9. From these graphs several trends in the salicylic acid diffusion rate were observed. The diffusion across the pigskin was the fastest followed by the cellulose membrane with every vehicle except the methyl gluceth-10. The penetration across the cellulose was the most rapid from methyl gluceth-10. All of the vehicles exhibited quicker diffusion across the cellulose into water versus an aqueous glycol receptor phase. The diffusion across dimethyl polysiloxane was the slowest for all of the vehicles and the receptor phase content did not alter the diffusion rate.

The influence of the receptor phase composition and membrane type on the rate of salicylic acid diffusion was more extensively examined utilizing different pH buffers as the receptor phase. Citrate–phosphate buffers of pH 2.2, 3.0, 4.5 and 7.4 were used as the receptors. The diffusion of salicylic acid from laneth-10 acetate and methyl glucose ether across cellulose and dimethyl polysiloxane into the pH buffer solutions was studied.

Salicylic acid diffusion across the cellulose

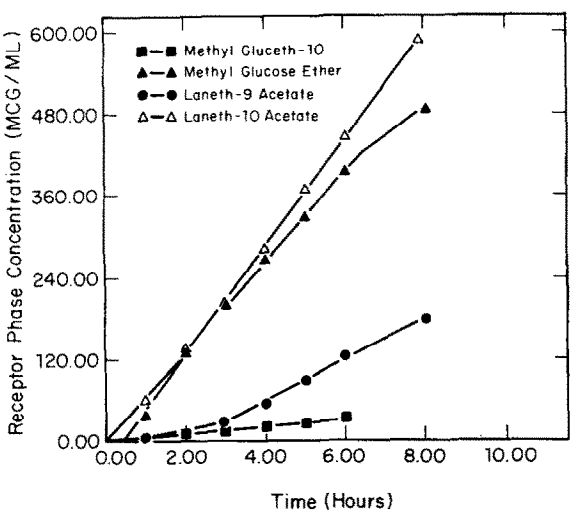

Fig. 5. In vitro diffusion of salicylic acid across pigskin into aqueous glycol.

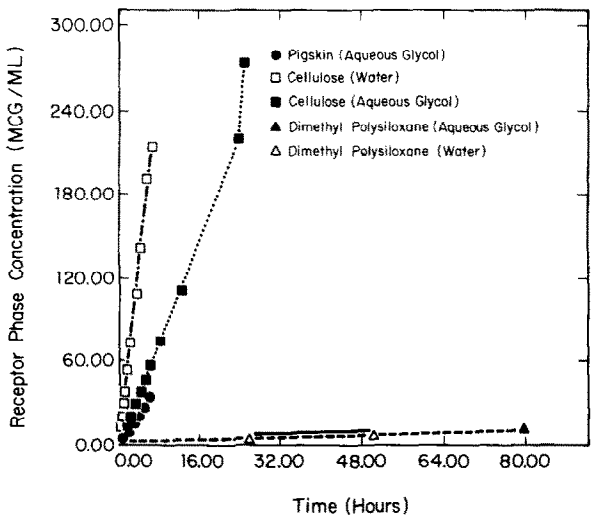

Fig. 6. In vitro diffusion of salicylic acid from methyl gluceth-10 into an aqueous glycol and an aqueous receptor phase.

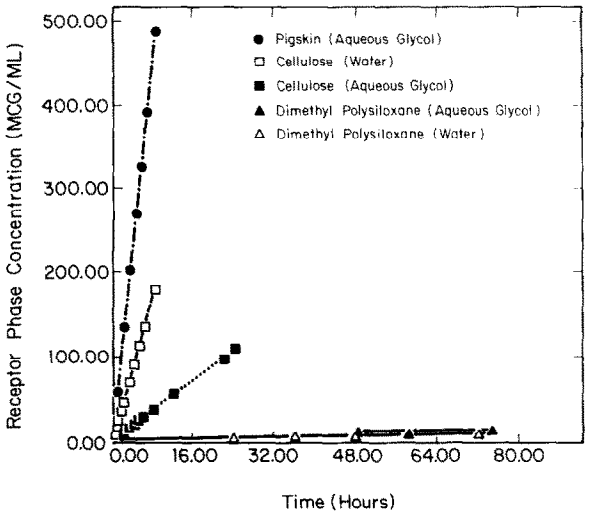

Fig. 7. In vitro diffusion of salicylic acid from methyl glucose ether into an aqueous glycol and an aqueous receptor phase.

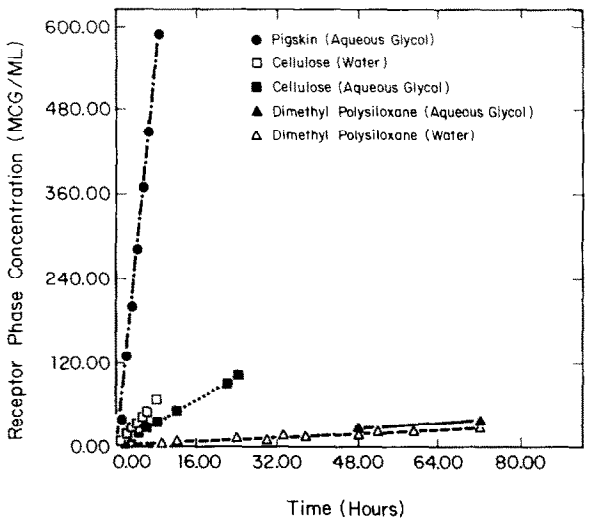

Fig. 9. In vitro diffusion of salicylic acid from laneth-10 acetate into an aqueous glycol and an aqueous receptor phase.

membrane into the different pH buffer solutions is shown in Fig. 10. The permeability coefficients for methyl glucose ether were approximately twice as large for any given pH buffer solution, yet the rank order of diffusion into the different pH buffer solutions was identical. The diffusion of salicylic acid was the fastest with the pH 7.4 buffer and the slowest with the pH 2.2 buffer solution, with the remaining pH buffer solutions in between the two extremes.

The diffusion of salicylic acid into the citrate–phosphate buffer solutions can be predicted by the pH partition hypothesis. Salicylic acid is a weak acid that can exist in solution as either the unionized (U) or ionized (I) form. The unionized species will cross a semipermeable mem-

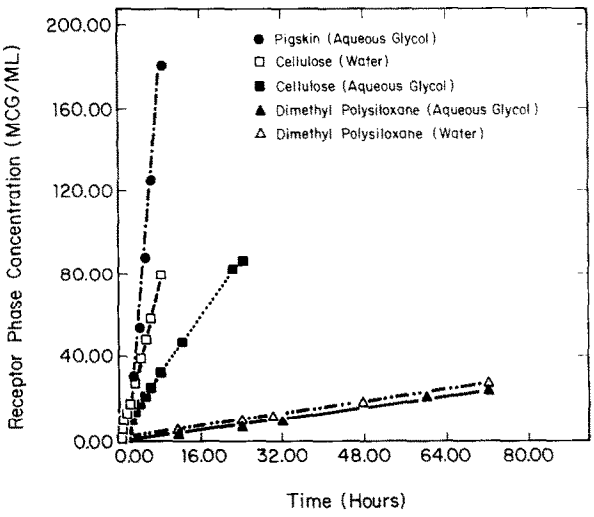

Fig. 8. In vitro diffusion of salicylic acid from laneth-9 acetate into an aqueous glycol and an aqueous receptor phase.

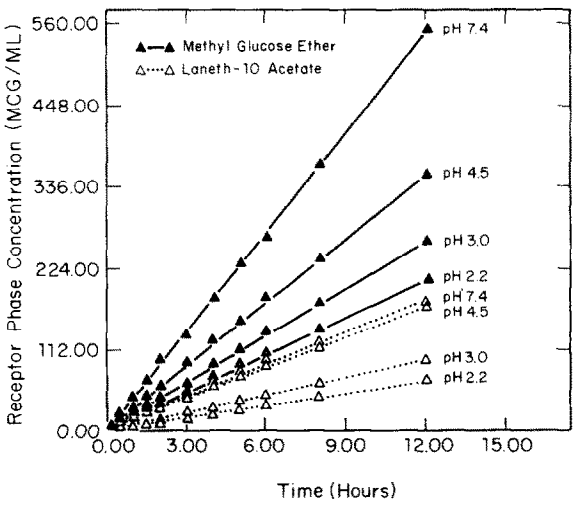

Fig. 10. In vitro diffusion of salicylic acid across cellulose into pH buffer solutions.

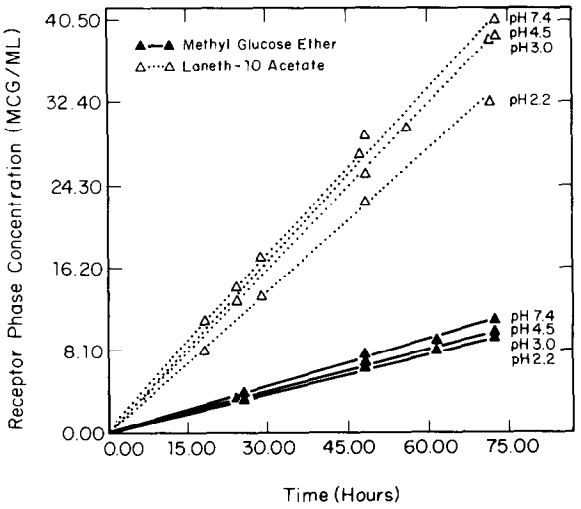

Fig. 11. In vitro diffusion of salicylic acid across dimethyl polysiloxane into pH buffer solutions. Note: the diffusion rate from methyl glucose ether into the pH 2.2 buffer solution = the diffusion rate into the pH 3.0 buffer solution.

brane, such as cellulose, to achieve an equilibrium concentration on both sides. The ratio of ionized to unionized drug (I/U) can be estimated by the Henderson-Hasselbalch equation for an acid:

$$pH - pK_a = \log(I/U)$$

The pK_a of salicylic acid is 3.0, so in a pH 7.4 buffer solution a ratio of approximately 25,000/1 (I/U) exists. The conversion of unionized drug to the ionized form in the receptor phase will provide a strong driving force for the diffusion of salicylic acid across the cellulose membrane. Little, if any, of the ionized form of the drug will cross the membrane into the donor compartment, since the donor phase is not an aqueous solution. As the pH of the buffer solution decreases, the I/U ratio is reduced and the driving force for the salicylic acid is diminished accordingly, resulting in a slower diffusion rate.

The diffusion of salicylic acid across the dimethyl polysiloxane membrane into the different pH buffer solutions was different from the diffusion across cellulose (Fig. 11). The dimethyl polysiloxane membrane is not a semipermeable membrane, so a strong driving force between the two compartments was not established. The results of these studies implied that the dimethyl polysiloxane membrane and not the receptor phase controlled the rate of salicylic acid diffusion. The diffusion profiles in Fig. 11 did not differ significantly for either vehicle, indicating a membrane-controlled diffusion process. These data emphasize the importance of membrane and vehicle selection in the design of diffusion experiments.

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