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The effect of physicochemical properties on the in vitro diffusion of drug through synthetic membranes and pigskin. I. Methyl salicylate

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Summary

The in vitro diffusion of methyl salicylate (11.6% w/w) from solutions and emulsions across different synthetic membranes and pigskin was examined. Diffusion studies were performed in a two-compartment glass diffusion cell. The membranes studied included cellulose, dimethyl polysiloxane, polyethylene, polycaprolactam (nylon) and pigskin. Methyl salicylate solutions and emulsions were prepared with derivatives of lanolin and methyl glucoside. Except for one solution and one emulsion, the diffusion profiles exhibited the same rank order of membrane penetration: dimethyl polysiloxane > cellulose > polyethylene, pigskin. Attempts were made to relate the differences in the permeability coefficient with membrane type, physicochemical properties of the drug and vehicle, dielectric constant, aqueous solubility and viscosity.

Introduction

The release rate of drugs from topical preparations depends directly on the physical and chemical properties of the vehicle and drug employed. The physiological availability of topically applied drugs is dependent on both the release rate from the vehicle and the permeability through the skin.

The type of membrane utilized for the in vitro evaluation of drug release is of primary significance since permeability depends on the nature of membrane materials. Synthetic membranes are commonly employed for in vitro diffusion studies due to their accessibility and reproducibility, although many investigators use excised skin to measure permeability.

A limited list of key in vitro diffusion studies across cellulose, dimethyl polysiloxane and polyethylene membranes reported from 1960 to 1982 is contained in Table 1. The variety of compounds examined illustrates the scope of in vitro diffusion studies through synthetic membranes. Although many diffusion experiments have been performed, few studies have correlated the results with the physical and chemical parameters involved. Ex-

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TABLE 1

Key in vitro diffusion studies using synthetic membranes (1960–1982)

Cellulose	Dimethyl polysiloxane	Polyethylene
Acetyl salicylic acid (Barzegar-Jalali and Richards, 1979)	*p*-Aminobenzoate esters (Flynn and Yalkowsky, 1972)	Acetophenone
		Benzaldehyde
Benzocaine (Ayers and Laskar, 1974)	Benzocaine (Di Colo et al., 1980) (Bottari et al., 1978)	Benzoic acid
Caffeine (Kislalioglu et al., 1980)	(Bottari et al., 1979)	Benzyl alcohol
	Butamben (Juni et al., 1979)	4-Methylacetophenone
Flavonoids (Crevoisier et al., 1974)		4-Methylbenzaldehyde (Gonzales et al., 1967)
	Chlorpromazine (Bottari et al., 1974)	
Hydrocortisone (Papadimitriou and Sheth, 1980)		
	Salicylic acid (Nakano and Pater, 1970) (Bottari et al., 1974)	Salicylic acid (Whitworth and Elsabbagh, 1978)
Methyl salicylate (Plakogiannis and Yaakob, 1977)		
Nitrofurantoin (Papadimitriou and Sheth, 1980)	Steroidal compounds (Friedman et al., 1980) (Kincl et al., 1968)	
Salicylic acid (Borodkin and Tucker, 1974) (Donbrow and Samuelov, 1980) (Samuelov et al., 1979)		

periments that examine the diffusion of drug across a membrane frequently ignore the effect of membrane type on the drug's diffusion rate. The present report describes the differences observed in methyl salicylate diffusion across synthetic membranes and pigskin.

The effect of physicochemical parameters such as dielectric constant, solubility, partition coefficient and viscosity on the in vivo and in vitro diffusion of drugs has been reported.

The dielectric constant of several polyethylene glycol bases and an aqueous solution was shown to correlate with the rectal absorption of acetaminophen (Stavchansky et al., 1979; Pagay et al., 1974). The authors observed that the release of acetaminophen from the different formulations could be related to the drug's solubility–dielectric constant profile, and as the vehicles' dielectric constant varied from that of acetaminophen, the release of drug increased.

The dielectric constant of a solvent or solvent blend has been shown by other investigators to influence the solubility of compounds in that solvent system. Paruta and coworkers (Paruta, 1964; Lordi et al., 1964; Paruta et al., 1962; Paruta and Irani, 1966) have extensively examined the relationship between the dielectric constant and composition of a solvent or solvent blend and the solubility of compounds in these systems.

Additionally, the relationship between drug solubility and the in vitro drug permeability has been demonstrated by several investigators (Bottari et al., 1974; DiColo et al., 1980; Takizawa et al., 1980; Whitworth and Elsabbagh, 1978; Khalil and Martin, 1967; Poulsen et al., 1968).

The relative lipid–water solubility, or apparent partition coefficient, of a drug is an important physical property in determining the rate of penetration through synthetic and biological membrane barriers. The partition coefficient can also provide a measure of a compound's hydrophilic and lipophilic properties and its affinity for the

vehicle and the stratum corneum. Several in vitro diffusion studies (Flynn and Yalkowsky, 1972; Doluisio and Swintosky, 1965; Bronaugh et al., 1981; Schoenwald and Ward, 1978) examined the influence of partition coefficient on in vitro drug permeability.

It has been reported that vehicle viscosity can influence the in vitro diffusion of drugs (DiColo et al., 1980; Whitworth and Elsabbagh, 1978; Barzegar-Jalali and Richards, 1979). In each of these studies an inverse relationship between viscosity and the diffusion rate was observed in most cases.

The present report examines the relationship between in vitro diffusion profiles of methyl salicylate through synthetic membranes and pigskin and the physicochemical properties of the pharmaceutical vehicles and the drug.

Materials and Methods

In vitro diffusion studies

Methyl salicylate [1] was used in the in vitro diffusion studies. Diffusion studies were performed in a glass, two-compartment diffusion cell [2]. The compartments were separated by a semipermeable membrane. Both compartments were equipped with a magnetic Teflon stirring rod and a sampling port. Due to the viscosity of some of the vehicles, constant stirring rates could not be achieved with magnetic stirrers, so the stirrers were attached to variable speed units and the stirring rate was controlled throughout the study at 150 rpm. Diffusion experiments were conducted in a diffusion cell with a 425 ml capacity per compartment, and a membrane surface area of 63.617 cm^2.

The membrane that separated the diffusion cell compartments was prepared according to type. The cellulose membrane [3] was hydrated for 15 min prior to the beginning of each experiment. Both the dimethyl polysiloxane membrane [4] and polyethylene membrane [5] were rinsed with deionized water and blotted lightly before each study. The polycaprolactam membrane [6] was hydrated in several changes of deionized water for 24 h prior to the start of the experiment. The thickness of each membrane type was as follows: cellulose 5.33×10^{-3} cm; dimethyl polysiloxane 2.54×10^{-2} cm; polyethylene 1.461×10^{-2} cm; polycaprolactam 1.52×10^{-3} cm and pigskin [7] 3.81×10^{-2} cm. The pigskin thickness includes most of the epidermal/dermal layer. Therefore, only the estimated thickness of the stratum corneum (1×10^{-3} cm) was used in the calculation of the normalized diffusion coefficient. After the membrane was hydrated, it was positioned and secured between the two compartments. The pigskin, which was split and then rinsed in an iodine solution to prevent bacterial growth, was kept frozen until 5 min prior to the start of the study.

Derivatives of lanolin and methyl glucoside with different dielectric constants were used as vehicles (donor phase). The lanolin derivatives included lanolin alcohol (Amerchol L-101) [8], laneth-9 acetate (Solulan 97) [8] and laneth-10 acetate (Solulan 98) [8]. The methyl glucoside derivatives included methyl gluceth-10 (Glucam E-10) [8] and methyl glucose ether (Glucam P-10) [8]. The dielectric constants of the vehicles were determined using a chemical oscillometer [9] equipped with a 100 ml sample cell.

An 11.6% w/w solution of methyl salicylate and vehicle was prepared prior to each diffusion study. The drug and vehicle mixtures were stirred on magnetic plates until solution was achieved. It was necessary to slightly warm the mixtures that contained methyl glucoside derivatives, since the viscosity of these liquids prevented effective stirring at ambient temperature. The receptor phase was composed of polyethylene glycol 400/water (1 : 1 w/w).

The methyl salicylate emulsions (o/w) were prepared with lanolin alcohol and laneth-10 acetate

[1] Matheson Coleman & Bell, Norwood, OH 45212, U.S.A.
[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] Gulf Oil Corp., Orange, TX 77630, U.S.A.
[6] Allied Chemical Corp., Morristown, NJ 07960, U.S.A.
[7] Genetic Laboratories, St. Paul, MN 55113, U.S.A.
[8] Amerchol Corp., Edison, NJ 08817, U.S.A.
[9] Sargent-Welch Scientific Co., Skokie, IL 60079, U.S.A.

as the oil phases. The composition of the emulsions was as follows:

Emulsion 1		
Methyl Salicylate	45.0 ml	11.6%
Lanolin Alcohol	124.0 g	27.2%
Water	265.0 ml	58.2%
Promulgen D[8] (Emulsifier)	13.5 g	3.0%
Emulsion 2		
Methyl Salicylate	46.5 ml	11.6%
Laneth-10 Acetate	126.0 g	26.7%
Water	278.0 ml	58.8%
Promulgen D[8] (Emulsifier)	13.5 g	2.9%

The lanolin derivative and emulsifying agent (Promulgen D, a combination of cetearyl alcohol and ceteareth-20) were weighed and placed in a 500 ml amber glass bottle. The bottle was placed in a silicone oil bath that was maintained at 70°C. After 20 min, when the emulsifying agent had dissolved, the container was removed from the oil bath, methyl salicylate was added and the contents were shaken for 30 s by hand. Water at 70°C was added and the mixture was secured in a mechanical shaker [10] until it reached room temperature, in approximately 1.5 h.

Fresh solutions and/or emulsions were prepared for each in vitro diffusion study. After the hydrated membrane was secured between the compartments, equivalent volumes of the receptor and donor solutions were carefully poured simultaneously into the appropriate cell to prevent stretching of the membrane. Sampling, with replacement, from the receptor phase, varied with the type of membrane and vehicle employed. Each sample (1.1 ml) was removed with a glass pipette and stored in a glass conical tube with Teflon-lined caps at room temperature and analyzed within 4–6 h.

Analysis

Samples of the diffusion medium were assayed by ultraviolet spectrophotometry using a Beckman Model 35 double-beam UV-visible spectrophotometer [11]. Standard curves of methyl salicylate in PEG 400/H_2O (1 : 1 w/w) exhibited absorption maxima at 238.5 nm. Methyl salicylate standard solutions (2.36–23.6 μg/ml) were prepared with the receptor phase solution. Ultraviolet scans were recorded each time to ensure that there was no interference from the diffusion of vehicles into the diffusion media at the absorption maximum of the drug. Each sample was specifically examined at the absorption maximum for salicylic acid (304 nm) since methyl salicylate may be hydrolyzed to salicylic acid. No salicylic acid was found in any of the samples, which may indicate that methyl salicylate remained intact.

Dielectric constant determinations

Dielectric properties were measured with a Sargent-Welch chemical oscillometer [9]. Acetone [1], carbon tetrachloride [1], cyclohexane [12] and double-distilled deionized water were used as standards to calculate the oscillometer constants.

Samples of 100 ml were used throughout the experiment. The dielectric constants of the lanolin and methyl glucoside derivatives were calculated from the following equation, developed by Adjei (1977):

$$\epsilon = C_g + S(C_g/C_0) + 1/C_g - S(C_0/C_g + 1) \qquad (1)$$

where ϵ is the dielectric constant, C_g and C_0 are oscillometer constants and S is the scale value reading from the oscillometer.

Viscosity determinations

The viscosities of the lanolin and methyl glucoside derivatives were determined using a Haake Rotovisco RV2 [13] with a MV III rotor. All of the samples were read at 25°C. Fluid 500 [14], a viscosity standard, was used to establish the accuracy of the scale readings. Viscosity measurements were read at several rpm's.

[10] Precision Scientific Corp., Chicago, IL, U.S.A.

[11] Beckman Instruments, Irvine, CA 92713, U.S.A.

[12] Fisher Scientific Co., Fair Lawn, NJ 07410, U.S.A.

[13] Haake Instruments, Saddle Brook, NJ 07662, U.S.A.

[14] Brookfield Engineering Labs, Inc. Stroughton, MS 02072, U.S.A.

The viscosity of the lanolin or methyl glucoside sample was calculated using the following equation:

$$\eta = G \cdot S/n \quad (2)$$

where η = viscosity in centipoise; G = a constant for the rotor; S = the scale value; and n = the revolutions per minute.

The viscosities ranged from 34.63 centipoise (cps) (lanolin alcohol) to 3450 cps (methyl glucose ether). All viscosity measurements were performed in duplicate and were reproducible within 2–8%.

Permeability and diffusion coefficient calculations

The zero-order transfer of salicylate can be represented by a two-compartment system where the compartments are separated by a semipermeable membrane. Compartment 1 represents the donor phase while compartment 2 serves as the receptor phase.

The diffusion rate of drug across the membrane can be described by Fick's first law:

$$J = -D(dC_m/dx)$$

where J = flux per exposed surface area (mg/s · cm^2); D = diffusion coefficient (cm^2/s); C_m = concentration in the membrane (mg/cm^3); x = distance into the membrane (cm); and dC_m/dx = concentration gradient within the membrane.

Another parameter that can be calculated using Fick's law is the permeability coefficient, P:

$$P = J/C$$

where C = the concentration differential across the membrane, which is taken to be equal to the donor phase concentration (mg).

The release data from the methyl salicylate emulsion systems followed a Q versus the square-root of time relationship. Koizumi and Higuchi's (1968) method for calculating diffusion coefficients for emulsion systems was utilized for the calculation of the methyl salicylate diffusion coefficients for the emulsions studied. The permeability values for the emulsion systems were calculated using the diffusion coefficients derived using this equation.

Apparent partition coefficient determinations

The octanol/water partition coefficient was determined for methyl salicylate. A specified amount of drug was added to a glass test tube with Teflon-lined caps (590 and 1180 μg methyl salicylate) for a final volume of 5 ml *n*-octanol [12] and 5 ml distilled deionized water. The tubes were equilibrated for at least 24 h on an aliquot mixer [15], model 4651. The mixtures were spun down in a Beckman centrifuge [16], model J-21C at 18,000 rpm at 10°C for 20 min. Both the aqueous and *n*-octanol phases were analyzed spectrophotometrically for drug content. The methyl salicylate in each portion was used to determine the apparent partition coefficient:

$$PC = \frac{[n\text{-octanol}]_{ms}}{[\text{water}]_{ms}} \quad (3)$$

where PC = partition coefficient; $[n\text{-octanol}]_{ms}$ = concentration of methyl salicylate in *n*-octanol portion; and [water] = concentration of methyl salicylate in water portion.

Results and Discussion

The physical and chemical properties of both the drug and the vehicles were examined to determine the formulation parameter(s) which influence the release rates of drug from the vehicles through synthetic membranes and pigskin.

Dielectric constant determinations

The dielectric constants of the lanolin and methyl glucoside derivatives, determined using a chemical oscillometer, are listed in Table 2. The dielectric constants of lanolin derivatives, which were either insoluble or only slightly soluble with water ranged from 2.17 to 10.00. The water-soluble methyl gluceth-10 and methyl glucose ether had dielectric constants of 13.74 and 7.53, respectively.

Viscosity determinations

The lanolin and methyl glucoside derivatives exhibited large differences in viscosities. The

[15] Ames Co., Elkhart, IN 46515, U.S.A.

[16] Brinkman Instruments, Inc., Westbury, NY 11590, U.S.A.

TABLE 2

Physical properties of lanolin and methyl glucoside derivatives

	Dielectric constant	Miscibility with PEG 400	Water solubility	Viscosity (η) at 25°C (cps)
Laneth-9 acetate (Solulan 97)	10.00	+	1%	308.26
Laneth-10 acetate (Solulan 98)	9.06	+	10%	319.73
Lanolin alcohol (Amerchol L-101)	2.17	−	Insoluble	34.92
Methyl gluceth-10 (Glucam E-10)	13.74	+	Very soluble	3454.67
Methyl glucose ether (Glucam P-10)	7.53	+	Miscible	2037.89

+ = miscible; − = not miscible.

viscosities of the vehicles at 25°C are listed in Table 2. The lanolin alcohol was the least viscous vehicle (34.92 cps) while the methyl gluceth-10 exhibited the greatest viscosity (3454.67 cps).

Apparent partition coefficient

The octanol/water partition coefficient for methyl salicylate was 50.1 ± 1.8. Two different amounts of drug were equilibrated in triplicate to obtain the mean apparent partition coefficients. Since the rate of drug penetration is dependent on the concentration gradient and the drug's partition coefficient it is important to have a sufficiently large partition coefficient. Moderate aqueous solubility is necessary for penetration through the epidermis and the subsequent dissolution in tissue fluids.

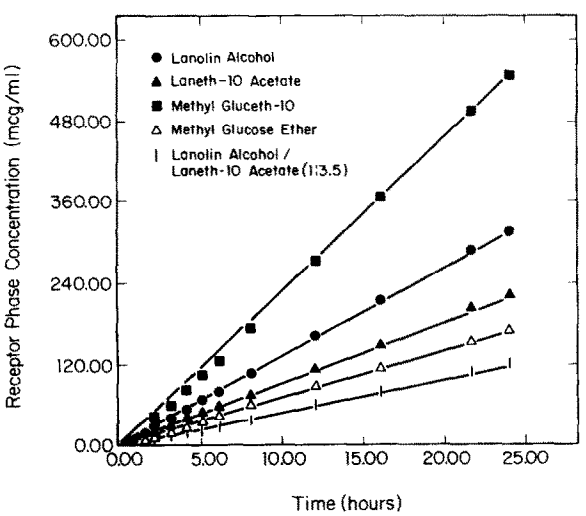

Fig. 1. In vitro diffusion of methyl salicylate across cellulose into aqueous glycol.

In vitro diffusion studies

The in vitro diffusion profiles of methyl salicylate (11.6% w/w) across synthetic and biological membranes into aqueous glycol resulted in linear relationships over the sampling period. This suggests that either the membranes are rate-controlling barriers or the vehicles are controlling drug penetration by a zero-order release process in accordance with Fick's first law. The permeability and diffusion coefficients for each methyl salicylate diffusion system are listed in Table 3. Comparison of these coefficients yields a good indication of the relative permeabilities since the differences in membrane thickness are considered.

The diffusion of methyl salicylate from lanolin and methyl glucoside derivatives across a cellulose membrane into an aqueous glycol receptor phase (PEG 400/water, 1:1 w/w) is shown in Fig. 1. The diffusion profiles appeared to be related to the dielectric constant of the vehicle (Fig. 2). The dielectric constant of methyl salicylate has been reported as 9.41 (Weast, 1974). As predicted by a dielectric relationship, laneth-10 acetate with a dielectric constant of 9.06 produced the slowest diffusion rate of methyl salicylate. Faster diffusion rates and permeabilities were seen with the vehicles whose dielectric constant varied from that of methyl salicylate. The lanolin alcohol ($\epsilon = 2.17$) and methyl gluceth-10 ($\epsilon = 13.74$) vehicles pro-

TABLE 3

Permeability coefficients for membranes – methyl salicylate solutions and emulsions

	Membrane	$P \times 10^4$ (cm/h)
Solutions		
Lanolin alcohol	Cellulose	8.72
Methyl gluceth-10		15.68
Methyl glucose ether		6.25
Laneth-10 acetate		4.89
Lanolin alcohol /Laneth-10 acetate		4.18
	Dimethyl	
Lanolin alcohol	polysiloxane	32.81
Methyl gluceth-10		10.62
Methyl glucose ether		9.44
Laneth-10 acetate		13.86
Lanolin alcohol	Polyethylene	2.22
Methyl gluceth-10		0.96
Methyl glucose ether		0.52
Laneth-10 acetate		0.74
Lanolin alcohol	Pigskin	0.22
Methyl gluceth-10		390.10
Methyl glucose ether		1.18
Laneth-10 acetate		28.39
Emulsions		
Lanolin alcohol	Cellulose	0.0167
Laneth-10 acetate		0.1012
	Dimethyl	
Lanolin alcohol	polysiloxane	0.0079
Laneth-10 acetate		0.1314
Lanolin alcohol	Polyethylene	0.01166
Laneth-10 acetate		0.01179
Lanolin alcohol	Pigskin	0.0120
Laneth-10 acetate		0.0290

duced the highest permeability coefficients.

A mixture of lanolin alcohol (22.15%) and laneth-10 acetate (77.85%) was utilized as a vehicle in a subsequent diffusion study. The dielectric constant of the vehicle blend was 7.53, the same as methyl glucose ether. However, the in vitro diffusion profile of the vehicle combination did not duplicate the pattern of methyl salicylate diffusion from methyl glucose ether, but was very similar to the graph of laneth-10 acetate. These data suggest that although the diffusion of methyl salicylate

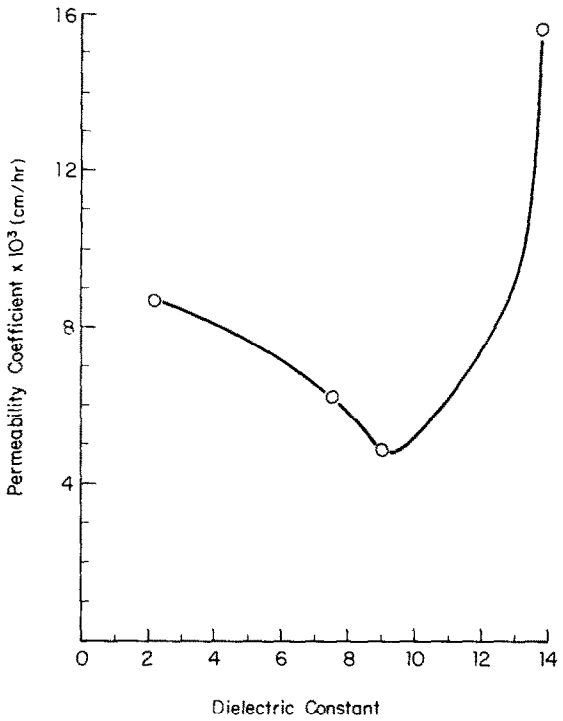

Fig. 2. Relationship between dielectric constant and the permeability coefficient of methyl salicylate.

across cellulose was dependent on the vehicle's dielectric constant, any modification or blend of the vehicles may change the physical or chemical properties related to the release of the drug.

The concept of changes in physicochemical properties of the vehicles resulting from vehicle alteration was supported by the diffusion of methyl salicylate through the cellulose membrane from the emulsion systems (Fig. 3). The addition of water and an emulsifying agent to form an emulsion modified the diffusion pattern in two ways. Initially, the diffusion of methyl salicylate from the emulsions resulted in a square-root relationship with respect to time instead of a zero-order mechanism that was observed for the solutions. In addition, the rank order of the permeability coefficient was changed when the emulsions were studied. The o/w emulsion serves as a reservoir for lipophilic drugs such as methyl salicylate, which may alter the diffusion of drug and

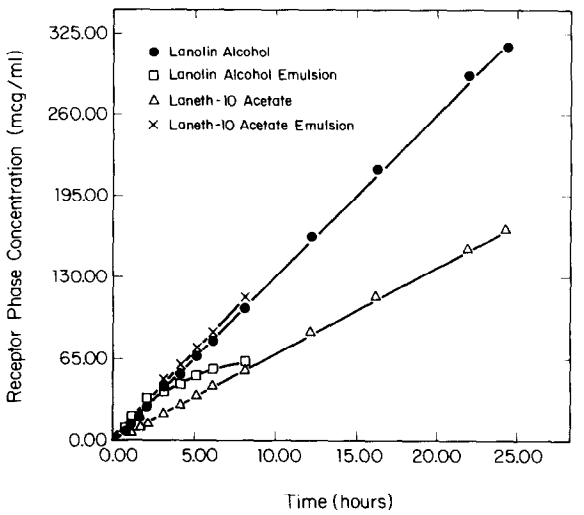

Fig. 3. In vitro diffusion of methyl salicylate from solutions and emulsions across cellulose into aqueous glycol.

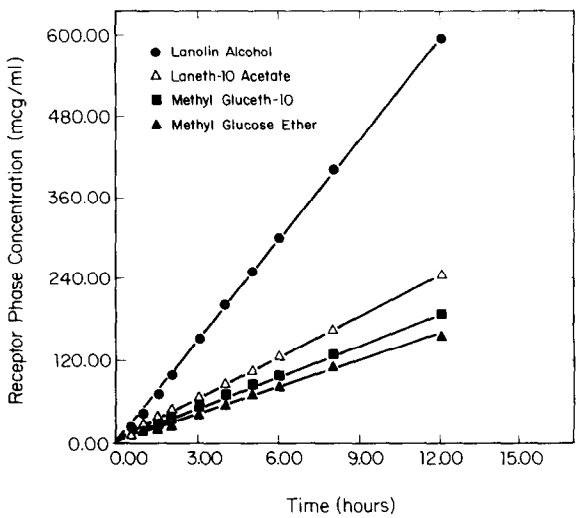

Fig. 4. In vitro diffusion of methyl salicylate across dimethyl polysiloxane into aqueous glycol.

result in a square-root relationship with respect to time as compared to zero-order diffusion from the solutions. For an o/w emulsion containing a lipophilic drug, some of the drug partitions into the aqueous phase. As the drug concentration in the aqueous phase is depleted, it is compensated by the partitioning of methyl salicylate from the oil phase. A driving force is created for the release and subsequent diffusion of the drug.

The limited water solubility of the laneth-10 acetate may contribute to the enhancement of methyl salicylate's diffusion from this vehicle (Plakogiannis and Yaakob, 1977). The solubilization of the vehicle may subsequently render more methyl salicylate in the aqueous phase than would be present if the vehicle had been completely water-insoluble as was the case with lanolin alcohol.

The in vitro diffusion of methyl salicylate across a dimethyl polysiloxane membrane into aqueous glycol is displayed in Fig. 4. Comparison with patterns of methyl salicylate diffusion across a cellulose membrane yielded several differences. Diffusion from the lanolin alcohol was the fastest across the dimethyl polysiloxane membrane, whereas the methyl gluceth-10 vehicle produced the most rapid diffusion across cellulose. For the dimethyl polysiloxane membrane, methyl gluceth-10 yielded one of the slowest diffusion rates. The diffusion across dimethyl polysiloxane was also a zero-order process; however, after 12 h the methyl salicylate concentration in the receptor phase was approximately equivalent to the levels achieved after 24 h in the studies employing cellulose.

The shift in the rank order of methyl salicylate diffusion across dimethyl polysiloxane versus cellulose indicated that the dielectric constant relationship does not apply to all in vitro diffusion systems. The diffusion across dimethyl polysiloxane instead may be inversely related to another physical property, the viscosity. The lanolin alcohol was the least viscous vehicle, followed by laneth-10 acetate and the methyl glucoside derivatives. Several published reports (DiColo et al., 1980; Whitworth and Elsabbagh, 1978; Garrett and Chemburkar, 1968) have noted an inverse relationship between viscosity and the diffusion rate. Although this relationship would not be expected in a system where the compartments are stirred, it is possible that a thin barrier layer was formed on the donor side of the membrane which may have resulted in a dependency on the vehicle viscosity.

As was the case with the cellulose membrane studies, the diffusion of methyl salicylate from emulsions across a dimethyl polysiloxane mem-

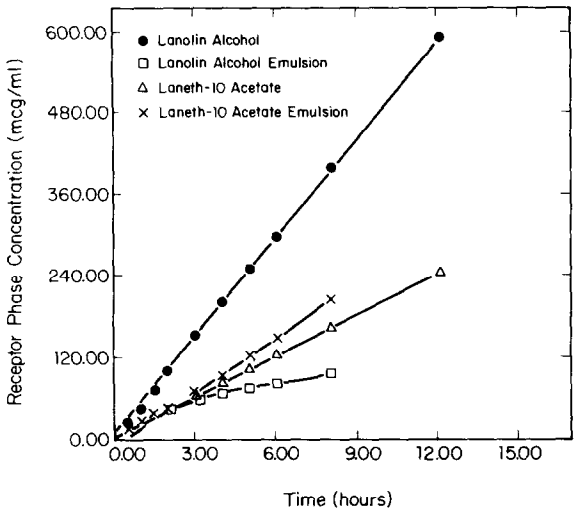

Fig. 5. In vitro diffusion of methyl salicylate from solutions and emulsions across dimethyl polysiloxane into aqueous glycol.

brane produced curves which followed a square-root relationship with respect to time (Fig. 5). A more rapid diffusion profile also resulted from the emulsion prepared with the laneth-10 acetate vehicle than from the lanolin alcohol.

The diffusion profiles of methyl salicylate across a polyethylene membrane into an aqueous glycol receptor phase, shown in Fig. 6, were similar to the diffusion across a dimethyl polysiloxane membrane. The rank order was not exactly the same, but in both studies the lanolin alcohol and the laneth-10 acetate emulsion produced the fastest diffusion of methyl salicylate while the diffusion of drug from methyl glucose ether was the slowest. However, the overall rates were approximately 20 times slower and the diffusion rate of methyl salicylate from the emulsions was zero-order across the polyethylene. The profiles of methyl salicylate diffusion across polyethylene indicated that a lag time of approximately 2 h occurred before there was any detectable amount of methyl salicylate in the receptor phase. In the studies that used cellulose and dimethyl polysiloxane membranes there was no apparent lag time. These results demonstrated the inherent differences in drug diffusion based on the type of membrane employed.

The in vitro diffusion of methyl salicylate across a polycaprolactam membrane did not yield detectable levels of the drug in the receptor phase after 72 h. Transfer across a non-porous membrane such as polycaprolactam involves the dissolution of solute in the membrane, resulting in longer times required for compounds to appear in the receptor phase (Kostenbauder et al., 1969).

The availability, easy preparation and reproducibility of synthetic membranes has in the past promoted their use for diffusional studies, al-

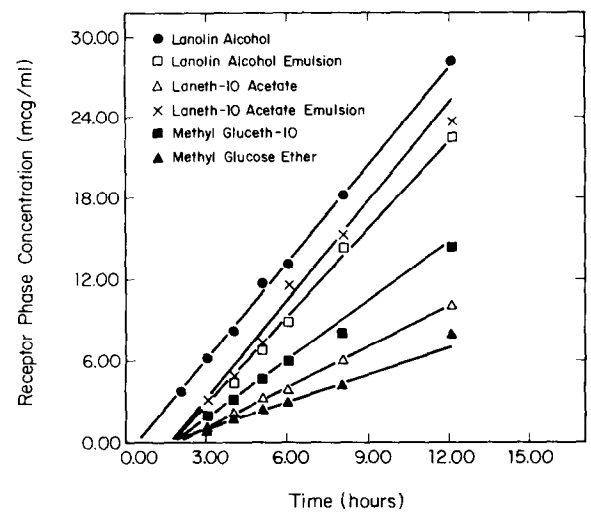

Fig. 6. In vitro diffusion of methyl salicylate from solutions and emulsions across polyethylene.

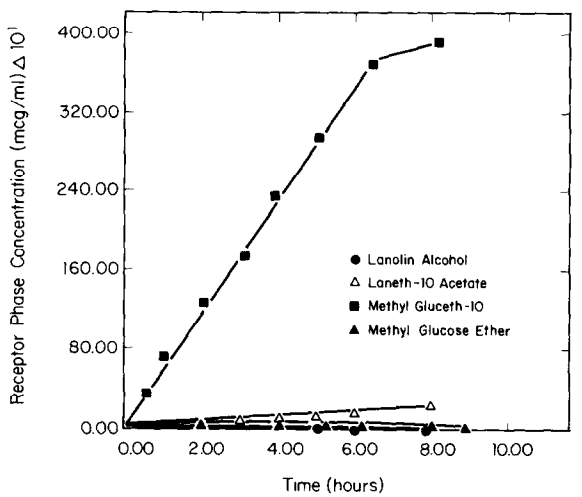

Fig. 7. In vitro diffusion of methyl salicylate across pigskin into aqueous glycol.

though a biological membrane may predict a drug's percutaneous absorption more accurately. The diffusion profile of methyl salicylate from the lanolin and methyl glucoside derivatives through pigskin are shown in Fig. 7. The appearance of methyl salicylate from the methyl gluceth-10 vehicle was nearly 10 times faster than the drug's release from any other vehicle. It appeared from the methyl gluceth-10 curve that the concentration of methyl salicylate was beginning to plateau. The concentration of methyl salicylate was approaching its saturation solubility in aqueous glycol, so that sink conditions did not apply. However, the profile demonstrated the quick diffusion across the pigskin and distinguished itself from the other curves.

Unlike the previous diffusion studies, the lanolin alcohol yielded the lowest methyl salicylate permeability coefficient with the pigskin membrane. The diffusion from the laneth-10 acetate solution had a lag time of 3 h. A plot of the diffusion from the lanolin solutions and emulsions in Fig. 8 revealed the same rank order of the lanolin emulsions, with release from the laneth-10 acetate exceeding that of the lanolin alcohol. The diffusion from the emulsions was found to fit better to the square-root relationship with respect to time (Figs. 9 and 10). The difficulty in evaluating the pigskin data is indicative of the complex nature of the skin itself.

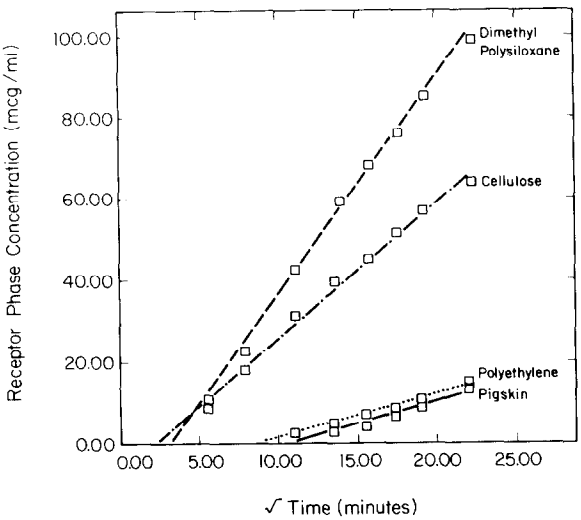

Fig. 9. In vitro diffusion of methyl salicylate from lanolin alcohol emulsions into aqueous glycol.

Comparison of the permeability coefficients yielded several observations. The permeability coefficients for the solutions across the synthetic membranes demonstrated the same rank order of membrane penetration without exception: dimethyl polysiloxane > cellulose > polyethylene. This il-

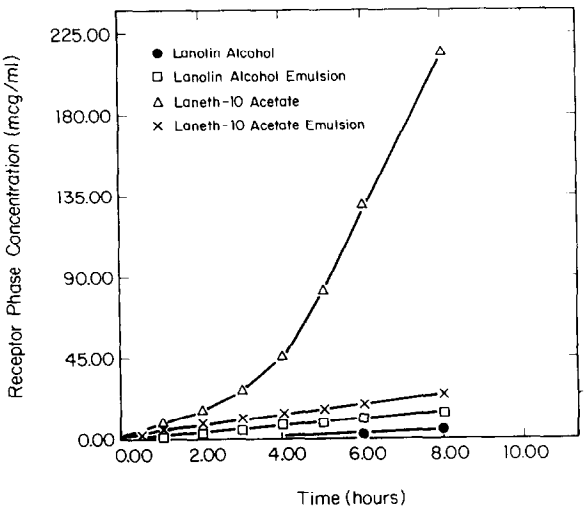

Fig. 8. In vitro diffusion of methyl salicylate from solutions and emulsions across pigskin into aqueous glycol.

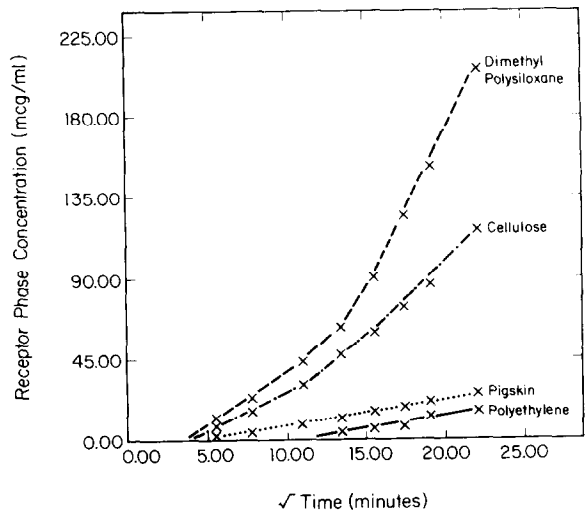

Fig. 10. In vitro diffusion of methyl salicylate from laneth-10 acetate emulsions into aqueous glycol.

lustrates the importance of membrane selection for in vitro diffusion experiments.

The importance of membrane type and vehicle composition is also evidenced in the change in rank order of the permeability coefficient for the methyl salicylate emulsions. The diffusion from the lanolin alcohol emulsion (Fig. 9) and the laneth-10 acetate emulsion (Fig. 10) are plotted as the receptor phase concentration versus the square-root of time. These plots support the previous observation that the diffusion from the laneth-10 acetate emulsions was consistently faster for each membrane type. The curves for the diffusion across the polyethylene membrane followed a zero-order release, as noted earlier.

The in vitro diffusion of methyl salicylate illustrated the differences that result from variations in the membrane systems. The diffusion profiles in certain cases exhibited direct relationships with physicochemical parameters including dielectric constant and viscosity. Large variations in diffusion rates and permeabilities were observed with the different membrane types and methyl salicylate.

The diffusion of methyl salicylate across the synthetic membranes did not parallel the diffusion across the pigskin membrane. Also, it was not possible to correlate any single physical or chemical property of either the drug or the vehicle with the resulting diffusion profiles. Instead, it appeared that a combination of factors were responsible for the unique diffusion of methyl salicylate across the membranes.

The extensive amount of investigation on single membrane systems utilized in permeability studies is evident in the scientific literature. However, only limited studies have examined and compared two or more membrane systems. It is necessary to compare the different synthetic and biological membranes that are used for in vitro testing to understand how the membrane type affects the diffusion profile of a compound and to determine if it represents what occurs in vivo. A future report will examine the percutaneous absorption of methyl salicylate from lanolin and methyl glucoside derivatives in human subjects. The in vivo results will be compared with the in vitro data in the present manuscript.

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