J. Pharm. Pharmac., 1975, **27**, 599–605 *Received November* 20, 1974

The percutaneous absorption of phenolic compounds: the effect of vehicles on the penetration of phenol

M. S. ROBERTS AND R. A. ANDERSON

Department of Pharmacy, University of Sydney, N.S.W. 2006, Australia

The effects of interactions between drug and skin, drug and vehicle, and vehicle and skin on the overall penetration rate of a drug through the skin may be evaluated by comparison of penetration rates through excised skin and an inert reference membrane such as polyethylene. Dimethyl sulphoxide, dimethyl formamide, ethanol and water increase the permeability of the skin but because of reduced thermodynamic activities in the vehicles low penetration rates are observed.

The effect of vehicles on the percutaneous absorption of phenol *in vivo* has been examined by several authors. Freystadtl (1938) compared the local effects of phenol in several vehicles and found the anaesthetic effect of a 20% solution in glycerol to be similar to a 2% aqueous solution. At lower concentrations phenol is more toxic in liquid paraffin than in water, although the toxicity may be reduced by the addition of camphor to the liquid paraffin (Deichman, Miller & Roberts, 1950).

Effects of pharmaceutical formulation on drug activity have been reviewed by Hadgraft (1972), Katz & Poulsen (1971) and Poulsen (1973). Hadgraft (1972) concluded that vehicle effects should be considered in the clinical assessment of a topical agent, particularly any effect influencing its release and activity. Penetration has been shown to be optimal when the agent is present at its maximal solubility concentration.

The rate may also be influenced by interaction either between the vehicle and the skin or between the drug and the skin (Anderson & Roberts, 1974). The ability of dimethyl sulphoxide and dimethyl formamide to increase the penetration of substances by altering the permeability of the skin is well recognized (Katz & Poulsen, 1971). Roberts, Shorey & others (1974) reported that damage to the skin by the solute may lead to increased penetration rates.

Evaluation of the extent of drug-skin, drug-vehicle, and vehicle-skin interactions and their contribution to the observed penetration rate may be difficult. In the present work, we have examined the effects of various vehicles on the penetration rates of phenol by comparing the rate through excised rat skin to that through an inert polyethylene membrane.

MATERIALS AND METHODS

Materials

Light liquid paraffin (B.P.C.), arachis oil (B.P.), glycerol (B.P.), and ethanol (dehydrated alcohol, B.P.) were used. Dimethyl sulphoxide and dimethyl formamide were of laboratory reagent grade; phenol was of analytical reagent grade. High

density polyethylene film (grade 2101, thickness 0·0015 inch, supplied by Union Carbide Ltd., Sydney) and excised rat skin from the mid-dorsal region of 250–300 g male Wistar rats (Roberts & others, 1974) were used in this study.

Partition coefficients

Partition coefficients of phenol were estimated for arachis oil–water, light liquid paraffin–water, ethanol–light liquid paraffin, dimethyl sulphoxide–light liquid paraffin and dimethyl formamide–light liquid paraffin systems. These systems were allowed to equilibrate at 37°; the phases were then separated and the phenol in each phase was assayed spectrophotometrically. Each system was studied using several concentrations of phenol.

Permeation studies

Permeation studies of phenol in various vehicles through rat skin and polyethylene film were conducted at 37° by the procedures described by Roberts & others (1974). Penetration fluxes were estimated from the cumulative amount of solute penetrating through the membrane into an aqueous compartment per unit time.

The effect of damaging concentrations of phenol on the permeability of the skin was assessed by comparing the fluxes of phenol (at a non-damaging concentration) through the same sample of skin before and after damage. The skin was placed in contact with the damaging solution of phenol for 3 h. Fluxes after damage were measured following the desorption of the residual phenol.

RESULTS AND DISCUSSION

The effect of vehicles on the availability of some solutes for percutaneous absorption has been evaluated using oil–water partition coefficients (Nogami & Hanano, 1958; Ostrenga, Steinmetz & Poulsen, 1971; Poulsen, 1973). Light liquid paraffin-vehicle partition coefficients have been studied (Table 1) and were found to be independent of concentration up to at least half saturation. However they are only of limited use, since partial miscibility of the oil and the vehicle (e.g. ethanol) and/or association of solute in the oil may occur. Three phases are observed for high concentrations of phenol in arachis oil–water and light liquid paraffin–water systems. Similarly stratum corneum-vehicle partition coefficients can be determined directly but should be viewed with caution because of problems which may arise from adsorption of solute or differing hydration of the corneum (Poulsen, 1973).

Table 1. *Light liquid paraffin/vehicle partition coefficients of phenol.*

Vehicle	Light liquid paraffin/vehicle partition coefficient
Water	0·12
Arachis oil	0·034[1]
Ethanol	0·030
Glycerol	0·015
Dimethyl formamide	0·008
Dimethyl sulphoxide	0·003

[1] Obtained by dividing the arachis oil/water partition coefficient by the light liquid paraffin/water partition coefficient.

To overcome these limitations, availability has been assessed using polyethylene in the form of a membrane to permit a kinetic approach. The penetration flux of phenol through polyethylene is proportional to concentration from dimethyl sulphoxide, dimethyl formamide and ethanol (Fig. 1). Slight deviations from proportionality above half the saturation solubility are observed for glycerol, arachis oil and light liquid paraffin. Association of phenol in these vehicles has probably led to a decreased permeation rate at high concentrations. No interaction between phenol or the vehicles used and polyethylene was apparent.

When 3% of water is dissolved in the arachis oil–phenol system, the permeation rate through polyethylene is reduced. These results may have arisen from the increased solubility of phenol in the vehicle and hence decreased thermodynamic activity. Small amounts of moisture (from perspiration or the atmosphere) may therefore decrease the availability of phenol in a phenol–arachis oil system.

Differences in the fluxes of phenol from a vehicle through skin and polyethylene may be attributed to drug-vehicle, drug-skin or vehicle-skin interactions. The contribution of each effect to the overall penetration rate through skin may be assessed by comparing the rates of penetration through polyethylene and excised skin.

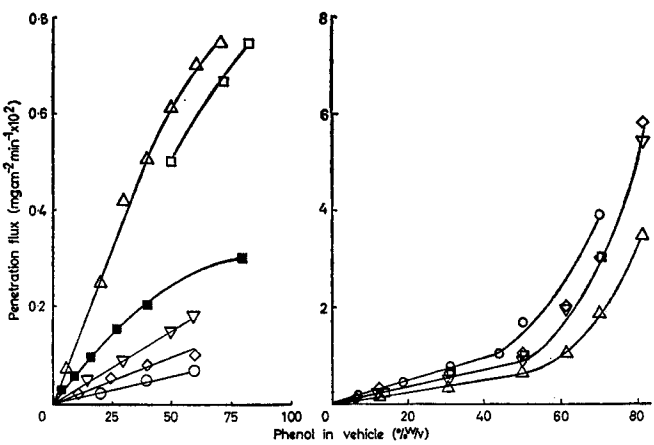

FIG. 1. Effect of concentration of phenol on its penetration through polyethylene film from various vehicles. ○—○ Dimethyl sulphoxide, ◇—◇ dimethyl formamide, ▽—▽ ethanol, ■—■ glycerol, □—□ arachis oil + water (3% w/w), △—△ arachis oil.

FIG. 2. Effect of concentration of phenol on its penetration from various vehicles through skin. △—△ Glycerol, ▽—▽ ethanol, □—□ dimethyl sulphoxide, ◇—◇ dimethyl formamide, ○—○ arachis oil.

Interactions between the vehicle and the skin

Idson (1971) expressed the penetration flux (J_m) of a solute through a membrane by:

$$J_m = \frac{Q}{A.t} = \frac{K_m.D.C_v}{h} \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where Q is the amount of solute which diffuses across area A in time t; K_m is the membrane-vehicle partition coefficient of the solute; D is the diffusion coefficient of the solute in the membrane of thickness h, and C_v is the concentration of solute in the vehicle.

The permeability coefficient (k_p) is given by J_m/C_v (Scheuplein, 1972).

Since $K_m = a_m/a_v$ (where a_m and a_v are the activities of the solute in the membrane and the vehicle respectively), equation (1) is equivalent to the more fundamental relationship

$$J_m = \frac{a_m D}{h} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (2)$$

when $C_v = a_v$. Then the ratio of the fluxes or the permeability coefficients from the same solution through two membranes, m_1 and m_2 may be expressed as

$$\frac{J_{m_1}}{J_{m_2}} = \frac{k_{p_1}}{k_{p_2}} = \frac{a_{m_1} D_1 h_2}{a_{m_2} D_2 h_1} \quad .. \quad .. \quad .. \quad .. \quad (3)$$

and will be referred to as the penetration ratio. The penetration ratio is therefore independent of any effect the vehicle may have on the thermodynamic activity of the solute. This ratio should be constant for all vehicles unless the nature of the membrane is altered by either the solute or the vehicle. With polyethylene and excised skin similar ratios are observed for arachis oil, light liquid paraffin and glycerol as vehicles (Table 2). These vehicles are unlikely to interact with the skin and hence may be considered reference vehicles. According to equation 1, flux is proportional to concentration. This relationship is observed for the penetration of phenol through skin (Fig. 2) and polyethylene (Fig. 1) for most concentrations of phenol in the vehicle. Deviations which occur at high concentrations may be attributed to other effects and are discussed later.

The penetration ratios observed using water, dimethyl sulphoxide, dimethyl formamide and ethanol as vehicles are substantially different to the ratio observed for the reference vehicles. These results may be attributed to interaction between the vehicle and the skin since the parameters described in equation 3 are independent of any drug-vehicle interaction. Interaction between the vehicle and the skin usually decreases the diffusional resistance of the stratum corneum although alteration in the polarity or thickness of the stratum corneum may also occur.

The extent of hydration of the stratum corneum is significant in the penetration of most compounds through the skin. Hydration has been found to increase nominal diffusion constants in the human stratum corneum by 10 times and the thickness of the

Table 2. *Effect of vehicles on the penetration of phenol through polyethylene and excised skin.*

	Permeability coefficient[1] (cm $min^{-1} \times 10^3$)		Penetration ratio[2]
	Polyethylene	Skin	Skin: polyethylene
Light liquid paraffin	0·5	1·0	2
Water	0·044	0·19	4
Arachis oil	0·014	0·029	2
Glycerol	0·005	0·010	2
Ethanol	0·004	0·016	4
Dimethyl formamide	0·002	0·022	11
Dimethyl sulphoxide	0·001	0·018	18

[1] Average of five determinations.
[2] Estimated standard deviation 20% (approx.).

corneum three fold (Scheuplein, 1972). The increase in the penetration ratio observed for water as a vehicle compared to that for the reference vehicles (Table 2) may be attributed to this effect.

Many non-aqueous vehicles on application to the skin surface also alter the structure of the stratum corneum. Scheuplein & Blank (1973) have found that ethanol increases irreversibly the permeability of the skin about two fold. Dimethyl sulphoxide and dimethyl formamide have been used to increase the penetration of many compounds and it has been suggested that these changes result from increases in the permeability of the stratum corneum (Sekura & Scala, 1972). Use of the penetration ratios through polyethylene and skin confirm that ethanol, dimethyl sulphoxide and dimethyl formamide suppress to different extents the barrier resistance of the stratum corneum. Although penetration fluxes are low, very high penetration ratios are observed for these vehicles (Table 2).

Interactions between the solute and the vehicle

Interaction of solute and vehicle may affect availability of the solute. The reduced thermodynamic activity of a solute, which is reflected in decreased membrane-vehicle partition coefficients, results in slower penetration fluxes (eqn 2). The permeability coefficients of phenol from the vehicles used in this study differ markedly (Table 2).

Since the flux of a solute through excised skin is proportional to that through polyethylene for concentrations of phenol which do not result in skin damage, the flux of a solute through a polyethylene membrane can be used as a guide to the effect of the thermodynamic activity of a solute in a vehicle on its penetration flux through skin. Both the light liquid paraffin-vehicle partition coefficient (Table 1) and the permeability coefficient of phenol through polyethylene (Table 2) vary with the vehicle in a similar manner. Either of these parameters may reflect the thermodynamic activity of phenol in the vehicle.

The effect of glycerol on the permeation rate of phenol through excised rat skin and polyethylene is shown in Fig. 3. The inclusion of glycerol in an aqueous system leads to reduced penetration fluxes as a result of increased solubility of phenol in the system (with reduced thermodynamic activity of phenol in the vehicle). Similar

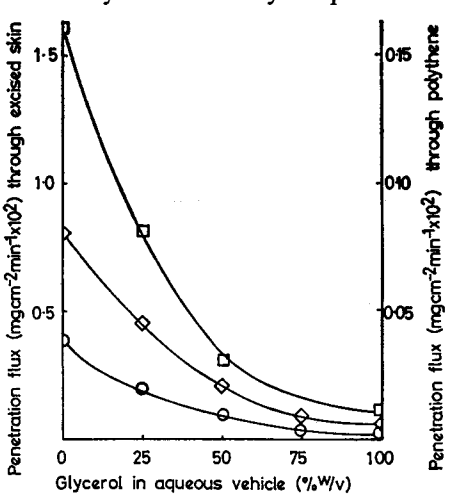

FIG. 3. Penetration of phenol from glycerol–water mixtures through skin and polyethylene film. □—□ phenol 5% w/v, skin; ◇—◇ phenol 2% w/v, polyethylene; ○—○ phenol 2% w/v, skin.

results are observed for dimethyl sulphoxide, ethanol and dimethyl formamide through excised skin and polyethylene (Fig. 4). Reduction in the penetration rates may also be caused to some extent by the partial dehydration of the stratum corneum as a result of the application of glycerol and ethanol. It is to be noted that although concentrations in excess of 50% of dimethyl sulphoxide increase the penetration of some solutes appreciably (Sekura & Scala, 1972), this effect is not apparent in this study. Schulze (1968) reported reduced penetration rates of phenol and salicylic acid for increasing concentrations of dimethyl sulphoxide in the vehicle, although the rate of penetration of dimethyl sulphoxide itself increases. Very strong interaction between phenol and dimethyl sulphoxide (Szmart, 1971) has led to marked reductions in the availability of phenol and its permeability coefficient (cf. water) in spite of the increased diffusivity of the solute in the stratum corneum (Table 2).

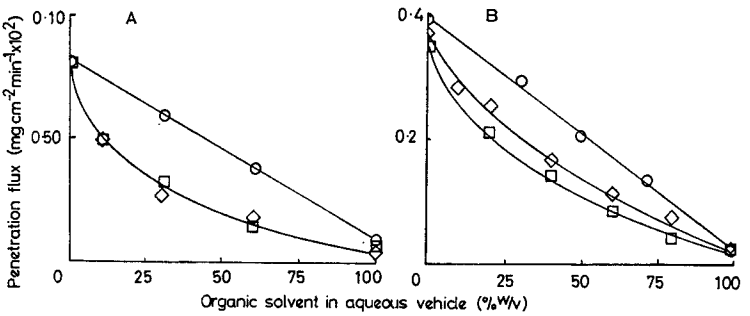

FIG. 4. Effect of vehicle composition on the penetration of phenol (2% w/v) through (A) polyethylene film and (B) skin. □—□ dimethyl formamide–water, ◇—◇ dimethyl sulphoxide–water, ○—○ ethanol–water.

Nogami & Hanano (1958) used benzene–vehicle partition coefficients to correlate vehicle effects to *in vivo* percutaneous absorption of salicylic acid, and found that viscosity of the vehicle had no effect on the absorption. Jordan & Polack (1972) attributed the reduction of the permeation rate of nitrobenzene from glycerol–water mixtures through polyethylene to changes in partition coefficients and not to changes in viscosity. The variability in the permeability coefficients observed in this study is probably not influenced by the viscosity of the vehicle to any significant extent.

Table 3. *Penetration fluxes of phenol through excised skin from vehicles following treatment with damaging concentrations of phenol.*

Vehicle	Glycerol	Water	Arachis oil	Light liquid paraffin
Damaging concentration (% w/v phenol)	80	7	67	1·4
Concentration of phenol (% w/v) in vehicle used for flux determinations	16	2	8	0·6
Flux of phenol before treatment (mg cm^{-2} min^{-1} × 10^2)	0·26	0·42	0·30	0·57
Flux of phenol after treatment (mg cm^{-2} min^{-1} × 10^2)	1·3	2·3	2·9	5·5

Interactions between the solute and skin

For aqueous solutions, Roberts & others (1974) observed that above a threshold concentration, phenol may interact with the skin to cause damage with an increase in

its permeability. Similar results are observed for the vehicles used in this study (Fig. 2). Threshold concentrations are related to the solubility of phenol in the vehicle. Damage is also reflected by an increase in the penetration ratio at this threshold concentration. (For vehicle-skin interactions, the penetration ratio is independent of the concentration of solute used).

The extent of damage may also be evaluated from the fluxes of a non-damaging concentration of phenol before and after treatment with a damaging concentration of phenol. The original flux increases if irreversible damage has occurred, and Table 3 shows that the flux may increase many fold as a result of severe damage.

In general, the toxicity and therapeutic effect of phenol applied to the skin in a particular vehicle is dependent on the availability of phenol from that vehicle. In addition interactions between the skin and vehicles may alter the permeability characteristics of the skin with consequent changes in penetration rate.

REFERENCES

ANDERSON, R. A. & ROBERTS, M. S. (1974). *Aust. J. pharm. Sci.*, **NS3**, 75–80.

DEICHMAN, W. B., MILLER, T. & ROBERTS, J. B. (1950). *Archs ind. Hyg.*, **2**, 454–461.

FREYSTADTL, B. (1938). *Derm. Wschr.*, **106**, 73–79.

HADGRAFT, J. W. (1972). *Br. J. Derm.*, **81**, 386–389.

IDSON, B. (1971). *J. Soc. Cosmet. Chem.*, **22**, 615–634.

JORDAN, D. O. & POLACK, A. E. (1972). *Aust. J. pharm. Sci.*, **NS1**, 82–87.

KATZ, M. & POULSEN, B. (1971). In *Handbook of Experimental Pharmacology:* Vol. XXVIII, *Concepts in Biochemical Pharmacology, Part* **1**, Editors: Brodie, B. B. & Gillette, J. R., pp. 107–174, New York: Springer.

NOGAMI, H. & HANANO, M. (1958). *Chem. Pharm. Bull.*, **6**, 249–255.

OSTRENGA, J., STEINMETZ, C. & POULSEN, B. (1971). *J. pharm. Sci.*, **60**, 1175–179.

POULSEN, B. J. (1973). In *Drug Design*, Vol. IV, pp. 149–192. Editor: Ariens, E. J., New York: Academic Press.

ROBERTS, M. S., SHOREY, C. D., ARNOLD, R. & ANDERSON, R. A. (1974). *Aust. J. pharm. Sci.*, **NS3**, 81–91.

SCHEUPLEIN, R. J. (1972). In *Advances in Biology of the Skin*, Vol. XII, *Pharmacology and the Skin*, pp. 125–152. Editors: Montagna, W., Van Scott, E. J. & Stroughton, R. B. New York: Appleton Century Crofts.

SCHEUPLEIN, R. J. & BLANK, I. H. (1973). *J. invest. Derm.*, **60**, 289–296.

SCHULZE, W. (1968). *Fette-Seifen-Anstrichmittel*, **70**, 663–667.

SEKURA, D. L. & SCALA, J. (1972). In *Advances in Biology of the Skin*, Vol. XII, *Pharmacology and the Skin*, pp. 257–269. Editors: Montagna, W., Van Scott, E. J. & Stroughton, R. B. New York: Appleton Century Crofts.

SZMART, H. H. (1971). In *Dimethyl Sulfoxide*, Vol. 1, *Basic Concepts of DMSO*, pp. 1–97. Editors: Jacob, S. W., Rosenbaum, E. E. & Wood, D. C. New York: Marcel Decker.