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Migration of ephedrine and salicylic acid from lipid mixtures containing isopropyl myristate

N. Anthony Armstrong, Hazel-Anne Griffiths * and Kenneth C. James

Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cardiff (U.K.)

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Summary

The migration rates of ephedrine and salicylic acid from white soft paraffin–isopropyl myristate mixtures into water have been measured using a previously described procedure. The rates for ephedrine decreased progressively with increasing isopropyl myristate concentration, and this was attributed to the observed accompanying increase in solubility, which decreased the activity of the solute in the solution. Solubility and partition coefficient determinations established that the improved solubility resulted from complexation between ephedrine and isopropyl myristate. In contrast, migration rates of salicylic acid in white soft paraffin–isopropyl myristate mixtures increased with increasing isopropyl myristate concentration up to 50% isopropyl myristate, and then declined. Solubility and partition coefficient determinations indicated that salicylic acid dimerised and also complexed with isopropyl myristate in the lipid mixtures. The diffusion rate profile was attributed to a balance between declining solute–solute and increasing solute–solvent complexation with increasing isopropyl myristate concentration. This mechanism was supported by the behaviour of salicylic acid in Witepsol H15–isopropyl myristate mixtures.

Introduction

An apparatus which simulates release from a lipophilic base through a film of occluded moisture on the skin has been described (Armstrong et al., 1988). Salicylic acid was used as substrate, and the results were treated mathematically in 3 ways. The method of Frost and Pearson (1961) for opposing first-order kinetics, in which the data are fitted to Eqn. 1, was found to be the most suitable.

$$\ln \frac{Q_0 - Q_e}{Q_t - Q_e} = K \cdot t \qquad (1)$$

where Q_0, Q_e and Q_t are the quantities of drug present in the base at zero time, equilibrium and time t respectively.

In this publication, the procedure is used to investigate the influence of the nature of the base on rate of release.

* *Present address*: Beecham Research Laboratories, Worthing, U.K.

Correspondence: K.C. James, Welsh School of Pharmacy, University of Wales Institute of Science and Technology, P.O. Box 13, Cardiff CF1 3XF, U.K.

Materials and Methods

Materials

Liquid paraffin and soft paraffin (Macarthy, Romford, U.K.) and salicylic acid (Hopkin and Williams, Chadwell Heath, U.K.) were of B.P. quality. Isopropyl myristate (95% pure) was obtained from Fluka, Buchs, Switzerland, anhydrous ephedrine (98% pure) from Sigma Chemical Company, Poole, U.K. and Witepsol H15 from Dynamit Nobel, Witten, F.R.G. All were used without further purification.

U.V. determinations

The approximate wavelength of maximum absorbance was determined using a Cecil CE 5095 scanning spectrophotometer, and located precisely with a Cecil CE 292 manual instrument. All solutes obeyed Beer's law at the maximum in the solvents examined.

Solubility determinations

In liquids. An excess of solute was added to about 20 ml of solvent, and the resulting suspension was sonicated and left to equilibrate for 2 days at the required temperature $\pm 1°$ C. Excess solute was then removed by filtration through a 0.45 μm Millipore filter under vacuum, maintaining the receiving flask at the same temperature. Samples of solutions were diluted with water or cyclohexane, and assayed by UV absorption. Each determination was carried out in triplicate.

In semi solids. The basic methodology has been used by other workers (e.g. Bottari et al., 1974). The required quantities of solute and base were weighed into an ointment jar, which was maintained in a constant temperature bath at 60° C until all the solute had dissolved. The capped jar was then kept at $30 \pm 1°$ C. Samples were removed after 2 days, 1 week, 3 weeks, 3 months and 6 months, and examined under an optical microscope ($\times 40$), using polarized light. Solubility was taken as the highest concentration at which no crystals were visible in any of the samples examined. Determinations were carried out in quadruplicate, and the results are shown in Table 1.

Determination of partition coefficients

The required quantity of white soft paraffin or Witepsol H15 was weighed into a 250-ml quick-fit flask. The required volume of a standard solution of solute in isopropyl myristate was pipetted into the flask and the mixture was melted and mixed at 60° C. After cooling, 20 ml of distilled water, previously equilibrated with isopropyl myristate, was added. The mixture was left at $30 \pm 1°$ C for 1 week, sonicating in an ultrasonic bath for 10 s on the third and fifth days. Aliquots of the aqueous phase were removed, centrifuged, and the supernatants analysed spectrophotometrically, using blank samples as reference. Each determination was carried out in quadruplicate, and found to give consistent results.

Release determinations

The procedures used have been described previously (Armstrong et al., 1988).

Results and Discussion

Ephedrine was used in this investigation because it was found to have a similar solubility profile to salicylic acid in blends of white soft paraffin and isopropyl myristate. Release constants from a series of isopropyl myristate–white soft paraffin blends are plotted against percentage isopropyl myristate in Fig. 1, and show a uniform decline with increasing isopropyl myristate con-

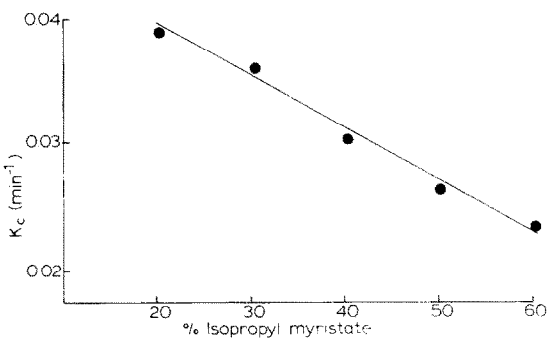


Fig. 1. The release constant (k_c) of ephedrine from white soft paraffin containing a range of concentrations of isopropyl myristate.

TABLE 1

Solubility of ephedrine and salicylic acid in white soft paraffin at 30 °C

Ephedrine		Salicylic acid	
% w/w in base	Observation of crystals	% w/w in base	Observation of crystals
1.6	–	0.050	–
1.7	–	0.055	–
1.8	+	0.060	+
1.9	+	0.065	+

centration. Rate of migration is related to the activity of the substrate, rather than its concentration, and is calculated approximately as the concentration divided by solubility (Ferguson, 1939). As shown in Table 1, a clear solution was obtained when 1.7% w/w ephedrine was added to white soft paraffin at 30 °C, but crystals separated at a concentration of 1.8%. The inferred solubility of between 1.7 and 1.8% was in good agreement with the solubility of 1.88% w/w measured in liquid paraffin at the same temperature. Solubilities of ephedrine in isopropyl myristate–white soft paraffin mixtures are plotted against the concentration of isopropyl myristate in the solvent mixture in Fig. 2. Solubilities increased, and therefore activities decreased, with increasing isopropyl myristate concentration, thereby accounting for the observed release behaviour shown in Fig. 1.

Water–oil partition coefficients are also plotted in Fig. 2. These were independent of solute concentration. For 1 : 1 complexation to occur exclusively between ephedrine (E) and isopropyl myristate (I) to give complex (EI), the solubility plot in Fig. 2 would have to be rectilinear, and the fact that it is not indicates that higher complexes are present. Uni-uni ($K_{1,1}$) and uni-bi ($K_{1,2}$) association constants, as defined by Eqns. 2 and 3, can be

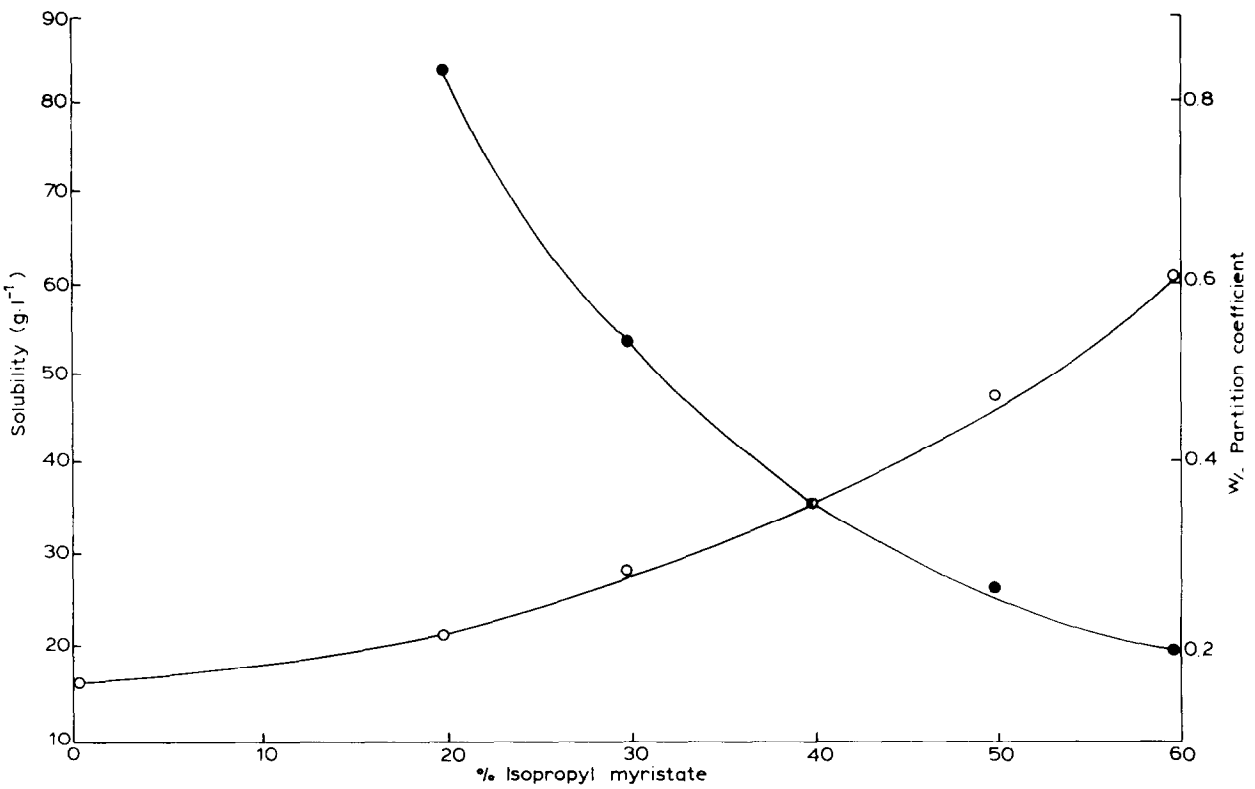


Fig. 2. Solubility (○) and water-oil partition coefficient (●) of ephedrine in mixtures of paraffin and isopropyl myristate.

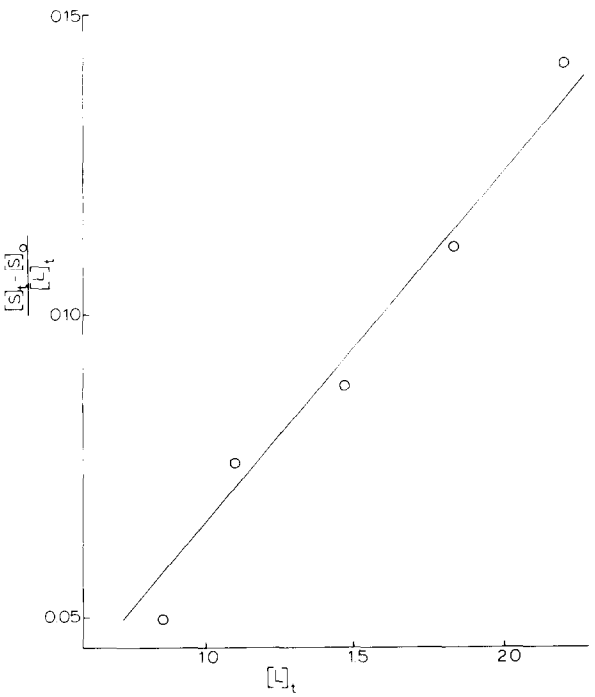


Fig. 3. Complexation plot for ephedrine in mixtures of paraffin and isopropyl myristate.

calculated from solubility data (James, 1986).

$$K_{1,1} = \frac{[EI]}{[E][I]} \tag{2}$$

$$K_{1,2} = \frac{[EI_2]}{[E][I]^2} \tag{3}$$

If the complexes involved are only uni-uni and uni-bi, a plot of $([S]_t - [S]_0)/[L]_t$ against $[L]_t$ should be rectilinear with intercept $K_{1,1}[S]_0$ and slope $K_{1,1}K_{1,2}[S]_0$. $[S]_t$ represents the total concentration of solute (ephedrine) in solution, and $[S]_0$ the solubility when $[L]_t$, the concentration of isopropyl myristate, is zero. The plot is shown in Fig. 3. Regression analysis yielded Eqn. 4 which, since $[S]_0 = 0.108$ mol/kg, gave values of 0.07 kg/mol and 8.05 kg^2/mol^2 for $K_{1,1}$ and $K_{1,2}$, respectively.

$$\frac{[S]_t - [S]_0}{[L]_t} = 0.0579[L]_t + 0.00719$$

$$r = 0.996 \quad n = 5 \tag{4}$$

This confirms that solute–solvent interaction occurs, and the stoichiometry is in agreement with a hydrogen-bonded complex between two isopropyl myristate carbonyl oxygens and the hydrogens of the hydroxyl and amino groups of ephedrine.

Different behaviour was exhibited by salicylic acid. Release constants from isopropyl myristate/white soft paraffin mixtures, as shown in Fig. 4, increased with increasing isopropyl myristate concentration, and reached a maximum around 50% w/w isopropyl myristate. The solubility of salicylic acid in liquid paraffin at 30 °C was found to be 0.62 g/kg, in good agreement with the result for white soft paraffin, shown in Table 1. Liquid paraffin was therefore used as substitute for white soft paraffin in subsequent solubility determinations. Solubilities of salicylic acid in isopropyl myristate–liquid paraffin blends are plotted in Fig. 5. As with ephedrine, they increase with increasing isopropyl myristate concentration, but as a result, the relationship between Figs. 4 and 5 is in complete conflict with the theories advanced for ephedrine.

The release behaviour of salicylic acid from liquid paraffin–isopropyl myristate mixtures is attributed to solute–solute complexation. It is well known that carboxy acids dimerise in organic solvents. Dimerisation increases with increasing solute concentration, and can be accompanied by solute–solvent complexation in hydrogen-bonding solvents. Support for the existence of dimers in the

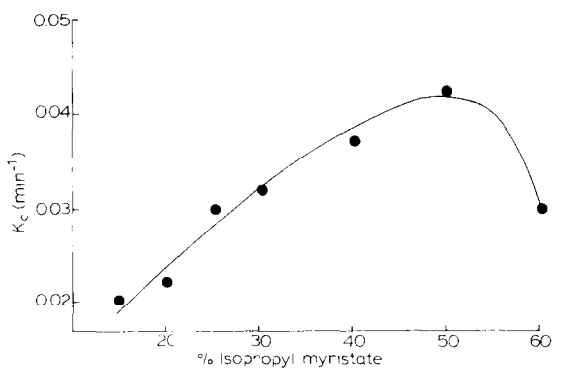


Fig. 4. The release constant (k_c) of salicylic acid from white soft paraffin containing a range of concentrations of isopropyl myristate.

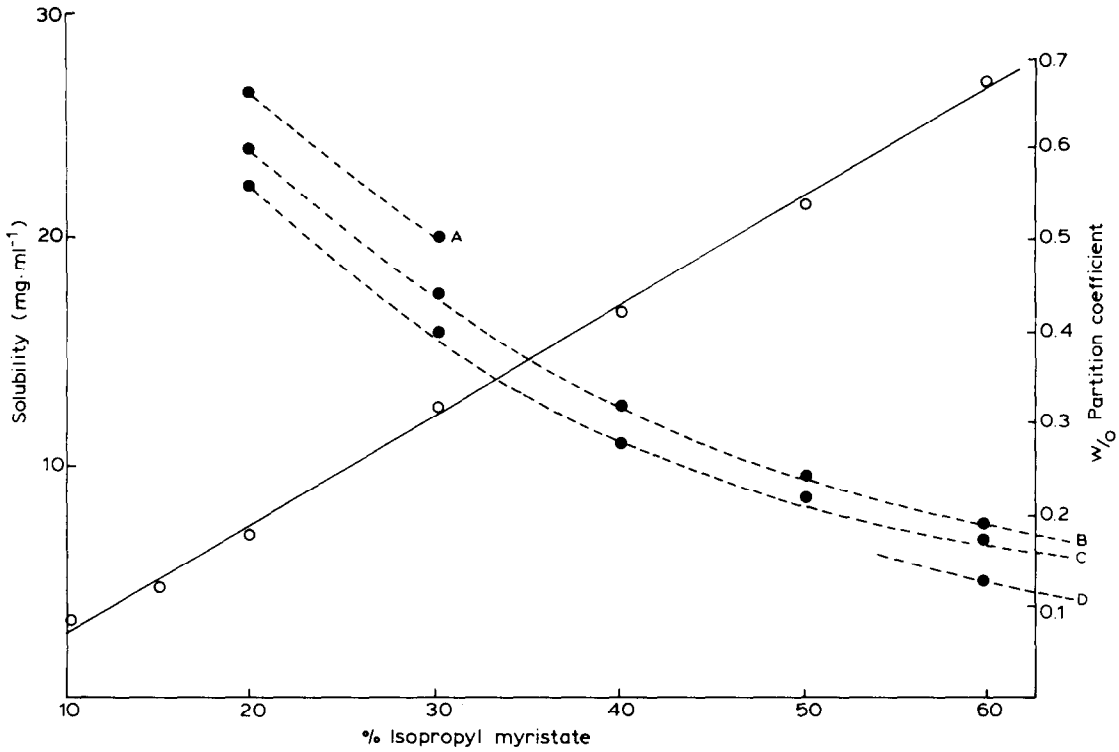


Fig. 5. Solubilities (○) and water-oil partition coefficients (●) of salicylic acid in mixtures of paraffin and isopropyl myristate. A = 0.69; B = 1.08; C = 1.61; D = 3.23 mg salicylic acid per ml base before mixing.

current systems is given in Fig. 5, in which the apparent partition coefficients between isopropyl myristate–white soft paraffin blends and water vary with salicylic acid concentration, indicative of solute–solute association. Davies and Hallam (1956) have shown that the apparent partition coefficient (K_d) is related to concentration in the aqueous phase (C_w) by Eqn. 5, in which a and b are constants and n is the number of monomers in the solute–solute complex.

$$K_d = aC_w^{n-1} + b \qquad (5)$$

The procedure is given in more detail elsewhere (James, 1986). Substitution of experimental results into Eqn. 5, placing n equal to 2, gave the approximately parallel rectilinear plots shown in Fig. 6, indicating dimerisation.

Water/oil partition coefficients are plotted against % w/w isopropyl myristate in Fig. 5. The lines all cross the solubility plot below 50% w/w isopropyl myristate, indicating that solute–solvent complexation occurs alongside solute–solute complexation, and that dimerisation persists up to at least 60% w/w isopropyl myristate. Solute–solvent complexation between the ester carbonyl of isopropyl myristate and solute hydroxyl groups has been demonstrated by James and Mehdizadeh (1981). These systems must therefore be considered in terms of solute dimerion, persisting at high isopropyl myristate concentrations, coupled with salicylic acid monomer–isopropyl myristate complexation. The reactions shown in scheme 1 (Eqns. 6 and 7) fit this situation.

In liquid paraffin alone, salicylic acid would exist in forms S_f and S_2, but as the concentration of isopropyl myristate (I) increased, S_2 would give way to SI. The concentrations of the complexed species in the scheme are given by Eqns. 8 and 9, in which $[S_f]$ represents the concentration of free

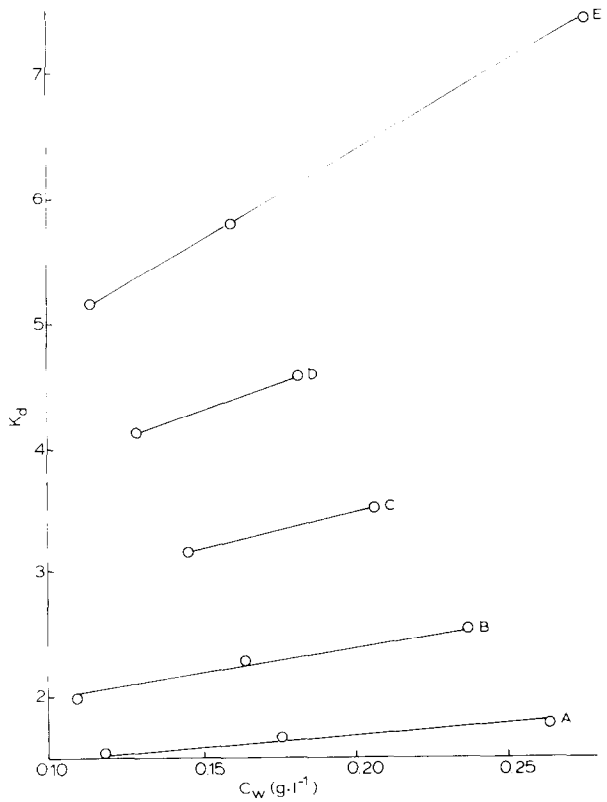
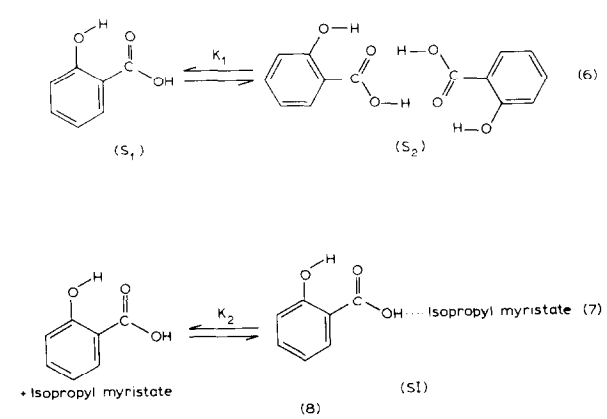


Fig. 6. The association and partition of salicylic acid between isopropyl myristate–paraffin mixtures and water (isopropyl myristate concentration: A, 20%; B, 30%; C, 40%; D, 50%; E, 60%). K_d = apparent partition coefficient, C_w = equilibrium salicylic acid concentration in the aqueous phase (g/liter).



Scheme 1.

salicylic acid, and K_1 and K_2 are equilibrium constants.

$$[S_2] = K_1[S_f]^2 \tag{8}$$

$$[SI] = K_2[S_f][I] \tag{9}$$

Thus the total salicylic acid concentration $[S_t]$ is given by Eqn. 10. The factor of 2 in the second term on the right hand side of Eqn. 10 is necessary to express dimer concentration in terms of salicylic acid.

$$[S_t] = [S_f] + 2K_1[S_f]^2 + K_2[S_f][I] \tag{10}$$

It is also well known that salicylic acid forms strong intramolecular hydrogen bonds between phenolic hydrogen and ester carbonyl oxygen, as shown in Eqns. 6 and 7. The fate of this bond in moving to the dimer is uncertain, but since oxygen atoms are able to take part in two hydrogen bonds, it is assumed that the intramolecular bond persists in the dimer, to give the species S_2.

There is no quantitative information in the literature regarding the dimerisation of salicylic acid at ambient temperature, or its complexation with isopropyl myristate. Pimental and McClellan (1960) quote dimerisation constants for benzoic acid in benzene from several sources. These vary considerably, but suggest that K_1 would be of the order of 1000. The same authors quote association constants between phenol and methyl acetate in *n*-heptane, which suggest that the value of K_2 would be around 10. Substitution of these values into Eqn. 10 indicates that in liquid paraffin, 90% of the salicylic acid will be dimerised, and that the proportion of dimer decreases progressively with increasing isopropyl myristate concentration to 4% in pure isopropyl myristate. At the same time, the proportion of the complex SI increases from zero to 94%. No matter what the values of K_1 and K_2 may be, dimer concentrations will decrease and SI concentrations increase with increasing isopropyl myristate concentration.

Since the dimer has double the mass of the monomer, it will diffuse more slowly. It is therefore probable that the increase in rate constant with increasing isopropyl myristate concentration,

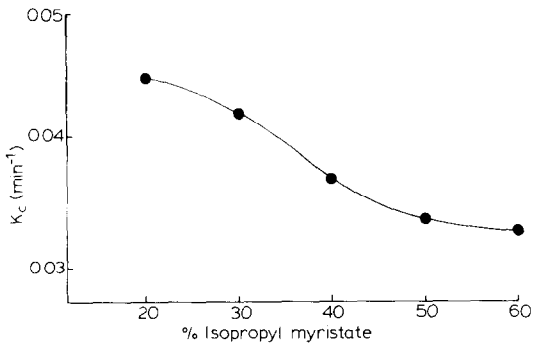


Fig. 7. The release constant (k_c) of salicylic acid from Witepsol containing a range of concentrations of isopropyl myristate.

shown in Fig. 4, represents the progressive decrease in dimer concentration. The SI complex also has a high molecular weight. However, since equilibrium represents a balance between continuously changing species, then when isopropyl myristate is in large excess, the migration of the complex can be considered as a transfer of salicylic acid monomer from one isopropyl myristate molecule to another. The resulting species will be more mobile and soluble than the dimer, and as its concentration increases it will reach a point when its influence is greater than that of the dimer, represented by the maximum in Fig. 4.

Final support for the suggestion that release of salicylic acid from isopropyl myristate/liquid paraffin mixtures is controlled by a balance between solute–solute and solute–solvent complexation is shown in Fig. 7, in which release constants from isopropyl myristate–Witepsol H15 mixtures decrease with increasing isopropyl myristate concentration. The solubility of salicylic acid in the Witepsol could not be determined because of the opacity of the solvent, but partition coefficients between isopropyl myristate–Witepsol H15 blends and water, shown in Table 2, indicate that salicylic acid is more soluble in isopropyl myristate than in Witepsol H15. Release rates of salicylic acid from these systems are therefore related to solubilities in the normally accepted manner, and come into line with the release pattern of ephedrine shown in Fig. 1. Witepsol H15 is a mixture of triglycerides which are esters, and therefore unlike liquid paraffin, are capable of hydrogen bonding with salicylic acid in the same way as isopropyl myristate. Dimer concentration can therefore be assumed to be small and reasonably constant throughout all the isopropyl myristate–Witepsol H15 combinations.

TABLE 2

Dependence of the apparent partition coefficient of salicylic acid between Witepsol bases and water on the percentage of isopropyl myristate (IPM) in the base

% (w/w) IPM in base	Partition coefficient at 30 °C
20	6.4
30	7.8
40	9.0
50	10.2
60	11.5

Summing up, theoretical prediction of release rates on the basis of solubility and partitioning data should be carried out with caution. It is particularly cogent to reflect that salicylic acid has been used more often than any other model compound in percutaneous absorption and bioavailability studies. Acceptance of data derived from its use as a model drug may be misleading unless possible solute–solute and solute–solvent interactions are given due consideration.

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