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Extraction coefficients and facilitated transport: The effect of absorption enhancers

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Summary

A theoretical model of the extraction coefficients of weak acids has been developed to account for the variation in partition dependent upon pK_a using the partition coefficients of the ionised and unionised species (P_i, P_u). The effect of these variables on the plots of both the extraction ratios and the relative changes, as indicated by the ratio of these coefficients, is illustrated. The model has been applied to the distribution of salicylic acid, as a function of pH, between an aqueous phase and isopropyl myristate containing tertiary amide enhancers of percutaneous absorption. The extraction coefficients determined are consistent with the model and show that ion-pairing between the ion and enhancer need not be invoked to explain the behaviour of the system.

Introduction

The factors which control the rates of percutaneous absorption and moderate topical delivery of medicinal agents are under intensive study (Barry, 1983; Bronaugh and Maibach, 1989; Hadgraft and Guy, 1989). The rate-limiting nature of the stratum corneum in healthy skin is well-recognised and strategies are being developed to enhance the frequently low delivery rates of topical drugs. These approaches include the use of absorption enhancers such as Azone (Stoughton, 1983; Stoughton and McClure, 1983) or alkyl methyl sulphoxides (Sekura and Scala, 1972), the design of facilitated absorption systems which involve ion-pair enhancement of delivery profiles (Barker and Hadgraft, 1981; Barker et al., 1984) and the use of iontophoresis to drive a flux of ionic or neutral compounds across the skin under the influence of an electric potential (Tyle and Kari, 1988).

It has been observed that the transport of salicylate across an isopropyl myristate membrane using a rotating diffusion cell (Albery et al., 1976; Guy and Fleming, 1979) is enhanced in the presence of Azone (Hadgraft et al., 1985). It was suggested that this effect was due to the formation of ion-pairs between Azone and salicylate anion which enhanced delivery rates of salicylate by means of a facilitated transport mechanism. The effect of Azone on the extraction coefficients of salicylate as a function of pH was determined and was interpreted as supporting this phe-

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nomenon. In particular, a maximum in the plot of the ratios of extraction coefficients determined with and without enhancer, as a function of pH, was seen to indicate optimum conditions for ion-pairing. Such conclusions have now reached the review literature (Neubert, 1989). While these ion-pair interactions may not be totally excluded, particularly in the low-polarity solvents used, this paper is presented to show that an enhancement of salicylate partition is caused by amide additives to the organic phase and that this effect may be explained solely on the basis of partition and ionisation equilibria without recourse to ion-pair formation.

Materials and Methods

Materials

Aqueous buffer solutions were prepared over the pH range 2.0–8.0 using McIlvaine's citrate-phosphate system (Elving et al., 1956). All buffer solutions were preserved using 0.002% phenylmercuric nitrate. Final pH values were measured using a Gallenkamp refillable general-purpose combination glass electrode attached to a Phillips PW 9409 digital pH meter. Values were adjusted as nearly as possible to pH 2.10, 2.37, 2.75, 3.15, 3.53, 3.96, 4.35, 4.75, 5.13, 5.48, 5.85 and 8.17. Reagents used were isopropyl myristate (Croda), sodium salicylate (BDH), lauric acid *N,N*-dimethylamide (Sigma), caproic acid *N,N*-dimethylamide (Sigma) and Azone^R (Nelson Research). All HPLC solvents were of Hypersolv grade. Analyses were undertaken using an HPLC system constructed from a Pye Unicam 010 dual-head reciprocating pump, a Rheodyne 7125 injection valve fitted with a 20 μl loop, a stainless-steel column (10 cm $\times$ 4.6 mm i.d.) containing Spherisorb S5 ODS (5 μm) stationary phase and a Pye Unicam PU 4020 UV detector equipped with an 8 μl flow cell. The detector was operated at a wavelength of 0.08 AUFS and results were analysed using a Trivector Trio Chromatography computing integrator. The mobile phase, comprising methanol/water/tetrahydrofuran/orthophosphoric acid (50:47:3:0.01), was degassed in an ultrasonic bath immediately prior to use and was delivered at a flow rate of 1 ml min^{-1}. The retention time of salicylic acid under these conditions was 3.87 min.

Methods

Partition coefficients of salicylic acid and isopropyl myristate were obtained with and without the presence of added enhancer over the pH range 2.1–8.2. Organic phases comprising isopropyl myristate (IPM), 0.1 and 0.5 M lauric acid *N,N*-dimethylamide (LDA) in IPM, 0.1 and 0.5 M caproic acid *N,N*-dimethylamide (CDA) in IPM and 0.1 M Azone^R in IPM were prepared and presaturated with the range of buffer solutions. Aqueous buffer phases were also presaturated with the appropriate organic phase and were prepared to contain sodium salicylate (approx. 2 mg ml^{-1}). Aliquots of the aqueous phases (15 ml) were pipetted into 25 ml volumetric flasks which were then made up to volume with the organic phase. Flasks were maintained at 25 °C and were stored, with stirring, for 2 days. Aqueous phases were removed using a glass syringe, centrifuged twice to remove any residual organic phase and were then diluted appropriately and assayed by HPLC. A calibration curve over the range 4×10^{-3}–2×10^{-2} mg ml^{-1} was prepared and residual concentrations were obtained by interpolation after appropriate dilution dependent upon pH. Extraction ratios were calculated according to Eqn 2 and were modelled theoretically using an IBM PC computer simulation based upon Eqns 11 and 12.

Theoretical

The extraction ratio is a measure of the partitioning behaviour of species between two immiscible solvents. It may be defined as the ratio of material extracted by an immiscible solvent to the original amount of material present. If the initial aqueous solution has a concentration of solute C_1 in a volume V_w and, after extraction with an immiscible solvent of volume V_o, the aqueous concentration of solute is C_2, the extraction ratio (ER′) is given by:

$$ER' = \frac{C_1 - C_2}{C_1} \quad (1)$$

As such, these values are dependent upon the phase volume ratio. An alternative expression which defines the extraction ratio (ER) as a volume-independent parameter is:

$$\mathrm{ER} = \frac{C_1V - C_2V}{C_1V - C_2V + C_2} \tag{2}$$

where the phase volume ratio $V = V_w/V_o$. When equal volumes of aqueous and organic phases are used ($V = 1$) this expression reduces to Eqn 1.

For an ionisable molecule the value of the extraction coefficient depends upon the partition coefficients of the molecule and ion, and upon the dissociation constant of the acid. This may be shown as follows for a weak acid (HA) partitioning between aqueous and oil phases and undergoing ionisation.

$$\underset{\text{oil}}{HA_o} \overset{K_2}{\rightleftharpoons} \underset{\text{water}}{HA_w} \overset{K_1}{\rightleftharpoons} H^+ + A_w^- \overset{K_3}{\rightleftharpoons} \underset{\text{oil}}{A_o^-}$$

where subscripts o and w refer to oil and water phases, K_1 is the acid dissociation constant and K_2 and K_3 are the partition coefficients of the neutral molecule and anion respectively.

The equilibria may be defined as:

$$K_1 = \frac{[H^+][A_w^-]}{[HA_w]} \tag{3}$$

$$K_2 = \frac{[HA_o]}{[HA_w]} \tag{4}$$

$$K_3 = \frac{[A_o^-]}{[A_w]} \tag{5}$$

The total acid in the system (HA_T) is given by:

$$HA_T = [HA_w]V_w + [A_w^-]V_w + [HA_o]V_o + [A_o^-]V_o$$

and expressing this in terms of the initial aqueous concentration ($[HA]_T = HA_T/V_w$) leads to:

$$[HA]_T = [HA_w] + [A_w^-] + [HA_o]/V + [A_o^-]/V$$

Substitution for $[A_w^-]$, $[HA_o]$ and $[A_o^-]$ using transformations of Eqns 3–5 leads to a solution for $[HA]_T$ as a function of $[HA_w]$:

$$[HA]_T = [HA_w]\left(\frac{[H^+]V + K_1V + K_2[H^+] + K_1K_3}{[H^+]V}\right) \tag{6}$$

Eqns 3–5 and 6 lead to the following species concentrations as a function of the initial aqueous concentration of acid in the system $[HA]_T$:

$$[HA_w] = \frac{[HA]_T[H^+]V}{[H^+]V + K_1V + K_2[H^+] + K_1K_3} \tag{7}$$

$$[A_w^-] = \frac{[HA]_TK_1V}{[H^+]V + K_1V + K_2[H^+] + K_1K_3} \tag{8}$$

$$[HA_o] = \frac{[HA]_TK_2[H^+]V}{[H^+]V + K_1V + K_2[H^+] + K_1K_3} \tag{9}$$

$$[A_o^-] = \frac{[HA]_TK_1K_3V}{[H^+]V + K_1V + K_2[H^+] + K_1K_3} \tag{10}$$

When no significant ion partition occurs ($K_3 = 0$) or in the absence of partitioning ($K_2 = 0$, $K_3 = 0$) these expressions reduce to:

Species	No ion partition $K_3 = 0$	No partition $K_2 = 0$, $K_3 = 0$
$[HA_w]$	$\frac{[HA]_T[H^+]V}{[H^+]V + K_1V + K_2[H^+]}$	$\frac{[HA]_T[H^+]}{[H^+] + K_1}$
$[A_w^-]$	$\frac{[HA]_TK_1V}{[H^+]V + K_1V + K_2[H^+]}$	$\frac{[HA]_TK_1}{[H^+] + K_1}$
$[HA_o]$	$\frac{[HA]_TK_2[H^+]V}{[H^+]V + K_1V + K_2[H^+]}$	0
$[A_o^-]$	0	

Substitution of these values into Eqns 1 and 2, where $C_1 = [HA]_T$ and $C_2 = [HA_w] + [A_w^-]$, provides an estimate for the extraction coefficient of the system such that:

$$ER = \frac{K_2[H^+] + K_1K_3}{[H^+] + K_1 + K_2[H^+] + K_1K_3} \quad (11)$$

and

$$ER' = \frac{K_2[H^+] + K_1K_3}{[H^+]V + K_1V + K_2[H^+] + K_1K_3} \quad (12)$$

In systems where no significant ion partition is observed ($K_3 = 0$) this reduces to:

$$ER = \frac{K_2[H^+]}{[H^+] + K_1 + K_2[H^+]} \quad (13)$$

and

$$ER' = \frac{K_2[H^+]}{[H^+]V + K_1V + K_2[H^+]} \quad (14)$$

When no ionisation occurs ($K_1 = 0$, $K_3 = 0$) the extraction ratio is related to the partition coefficient (K_2, P) by:

$$ER = \frac{K_2}{K_2 + 1} \quad (15)$$

and

$$ER' = \frac{K_2}{K_2 + V} \quad (16)$$

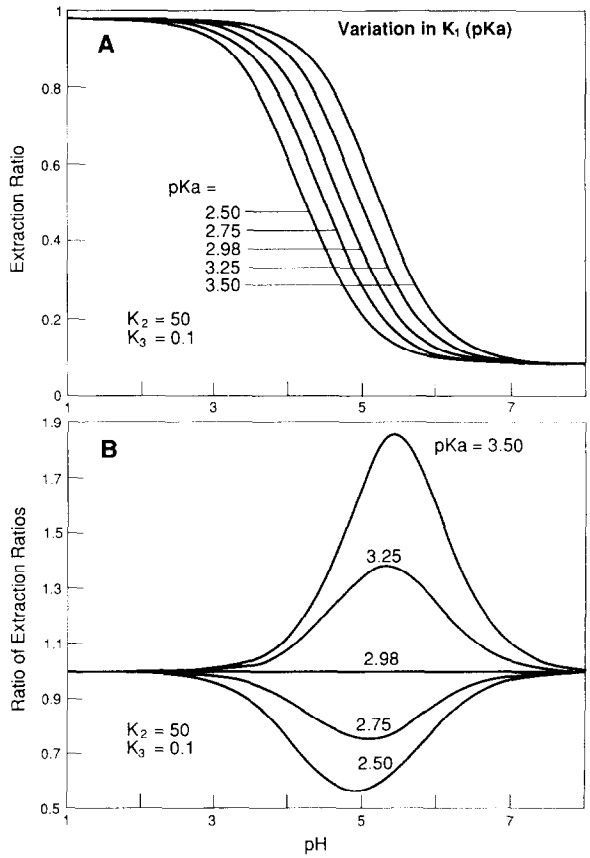

Fig. 1. Theoretical plots of the effect of pK_a (K_1) variation upon extraction ratios of a weak acid ($K_2 = 50$, $K_3 = 0.1$). Curve A illustrates the effect on the extraction ratio and curve B presents the ratios of extraction ratios. The centre, standard curve, with values of $pK_a = 2.98$, $K_2 = 50$ and $K_3 = 0.1$ was used as reference.

Results and Discussion

The consequences of Eqns 11 and 12 are illustrated in Figs 1–3 where the effects of a change in the system variables are examined as a function of pH. The ratios of the extraction ratios are also illustrated. Each curve is referenced to the $pK_a = 2.98$, $K_2 = 50$, $K_3 = 0.1$ data as this type of plot was used previously to indicate the pH of the maximum enhancement effect. Fig. 1A deals with the effects of a change in the pK_a of the acid over the range 2.5–3.5 pH units. This parameter could change during partition experiments involving added enhancer if the latter component is extracted to a significant level into the aqueous phase. In general, the strength of acids in mixed aqueous-organic solvents is less than in pure water, probably due to dielectric effects (Albert and Serjeant, 1984). It is noted that such an increase in pK_a causes curves to shift significantly to the right (higher pH) as more material is extracted at a particular pH due to reduced ionisation. The

ratio plot (Fig. 1B) shows this variation normalised to the $pK_a = 2.98$, $K_2 = 50$, $K_3 = 0.1$ data. No deviation from the reference curve is observed at either extreme of the ionisation profile but at intermediate values a maximum deviation develops. The direction of deviation depends only upon the relative magnitudes of the two pK_a values involved in the normalisation. Although changes in pK_a value produce profiles analogous to those sought, it is unlikely that this is responsible for the effect of Azone in the experimental system. Significant changes in pK_a require substantial concentrations of cosolvent. The highly lipophilic nature of Azone renders it only very sparingly water-soluble and it is unlikely that sufficient is in solution to modify ionisation to any measurable extent.

Addition of an amide percutaneous absorption enhancer to the largely lipoidal isopropyl myristate may increase the partition coefficient (K_2) of the undissociated salicylic acid. The effect of this variation over a range of $P_u = 10$–100 is illustrated in Fig. 2A where shifts in extraction ratios analogous to those recorded for pK_a variation are observed. In this example, the limiting extraction ratios at low pH values do not converge but the ratio plot (Fig. 2B) continues to show the same behaviour with a clear maximum deviation.

In contrast, variation in the partition coefficient of the ion (K_3) over the range $P_i = 0.01$–0.5, as shown in Fig. 3A, changes the relationship between the curves significantly. The extraction ratios at high pH are solely due to this variable and the ratio plots (Fig. 3B) are divergent. This trend is continued when simultaneous changes in K_1 and K_2 are modelled and only when the ion partition coefficients of both curves are close to equality are the ratio plots symmetrical and non-divergent.

To examine these conclusions experimentally, the partition coefficients of salicylic acid between an aqueous phase of variable pH and an isopropyl myristate phase containing an amide enhancer of percutaneous absorption were determined. Enhancers used were lauric acid *N*,*N*-dimethylamide (LDA), caproic acid *N*,*N*-dimethylamide (CDA) (Irwin et al., 1990a,b) and Azone

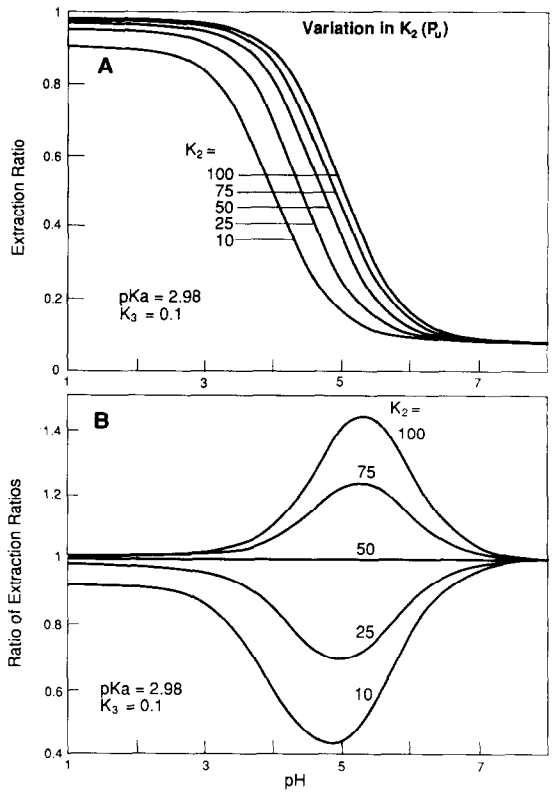

Fig. 2. Theoretical plots of the effects of partition coefficient (K_2) variation upon extraction ratios of a weak acid ($pK_a = 2.98$, $K_3 = 0.1$). Curve A illustrates the effect on the extraction ratio and curve B presents the ratios of extraction ratios. The centre, standard curve, with values of $pK_a = 2.98$, $K_2 = 50$ and $K_3 = 0.1$ was used as reference.

and data are recorded in Table 1. The partition coefficients measured at pH = 8.17 were taken as those of the ion (P_i, K_3) as this pH exceeds the pK_a value (2.98) by over 5 units and thus ensures virtually total ionisation. The phenolic ionisation of salicylic acid has a pK_a of 13.8, which is too far removed to play any part in the equilibria described here. The partition coefficients of the unionised molecule were calculated from the slope of the appropriate plots using the relationship (Tsuji et al., 1977; Irwin and Li Wan Po, 1979; Oakley and Swarbrick, 1978):

$$P_{app}\left(\frac{K_a + [H_3O^+]}{K_a}\right) = P_i + P_u\left(\frac{[H_3O^+]}{K_a}\right) \quad (17)$$

TABLE 1

Partition of salicylic acid between an aqueous phase of variable pH and an isopropyl myristate phase containing various tertiary amide additives

pH	Partition coefficient of salicylic acid into					
	IPM	CDA (0.1 M)	CDA (0.5 M)	LDA (0.1 M)	LDA (0.5 M)	Azone (0.1 M)
2.10	25.32			106.64	203.15	97.99
2.37	24.13	32.85		74.36	196.40	63.21
2.75	17.48	22.71	38.53	32.55	142.67	53.95
3.15	10.45	12.59	20.96	19.83	75.41	31.87
3.53	4.72	5.95	11.88	9.26	31.79	11.63
3.96	2.20	2.70	4.89	4.71	13.60	6.04
4.35	1.05	1.38	2.30	1.93	6.29	2.67
4.75	0.49	0.52	1.09	0.80	2.27	1.06
5.13	0.053		0.56	0.058		0.57
5.48			0.26		0.47	
5.85			0.11		0.20	
P_u	28.26	36.9	56.8	85.15	222.83	83.14
P_i	0.03403	0.0041	0.0178	0.00197	0.0052	0

IPM, isopropyl myristate; LDA, lauric acid dimethylamide; CDA, caproic acid dimethylamide.

and from nonlinear fitting (Metzler and Weiner, 1986; Irwin, 1990) to the alternative presentation:

$$P_{app} = \alpha P_i + (1 - \alpha) P_u \qquad (18)$$

where P_{app} is the apparent partition coefficient recorded in Table 1, P_i and P_u are the true partition coefficients of the ion and unionised molecule (K_3, K_2), respectively, and α is the fraction ionised. These values are also listed in Table 1.

To relate this approach to that adopted earlier (Hadgraft et al., 1985), the data were also expressed as extraction ratios using Eqn 2. The experimental values thus obtained were compared to those derived from the theoretical model in Eqn 12 using the appropriate estimates of K_1, K_2 and K_3 (K_a, P_u and P_i). Plots comparing the extraction ratio profiles for each system are shown in Figs 4–6 which also illustrate the degree of correspondence between the experimental and theoretical estimations.

Fig. 4 compares the data from IPM alone and systems including caproic acid *N,N*-dimethylamide. The partition follows the expected pH dependence with the salicylate showing little affinity for the organic phase as concentrations of the ionised form predominate. Fig. 4A also reveals that significant modification of the partition profile results from the inclusion of the tertiary amide enhancers of percutaneous absorption. The inclusion of 0.1 M CDA in the lipid phase causes an increase in P_u (K_2) of some 30% while a doubling is seen when the additive concentration is increased to 0.5 M. The coincidence of the theoretical lines and the values determined by experiment confirm the validity of the model. Fig. 4B displays the curves resulting from calculating the ratios of the extraction coefficients at corresponding pH values. The appearance is similar to that shown in Fig. 2B and shows clear maxima, increasing with cosolvent concentration confirming that this position is dependent upon the partition coefficient of the unionised species (P_u). No ion-pairing assumptions have been made in establishing this model and it seems unnecessary, therefore, to invoke their existence. The curves are somewhat distorted compared to the theoretical plots shown in Fig. 2. This is due to simultaneous variation in P_i (K_3) where it appears that the presence of the enhancers reduces the affinity for the anion resulting in a lowering of this parameter, an observation somewhat at variance with an ion-pairing phenomenon. Moreover,

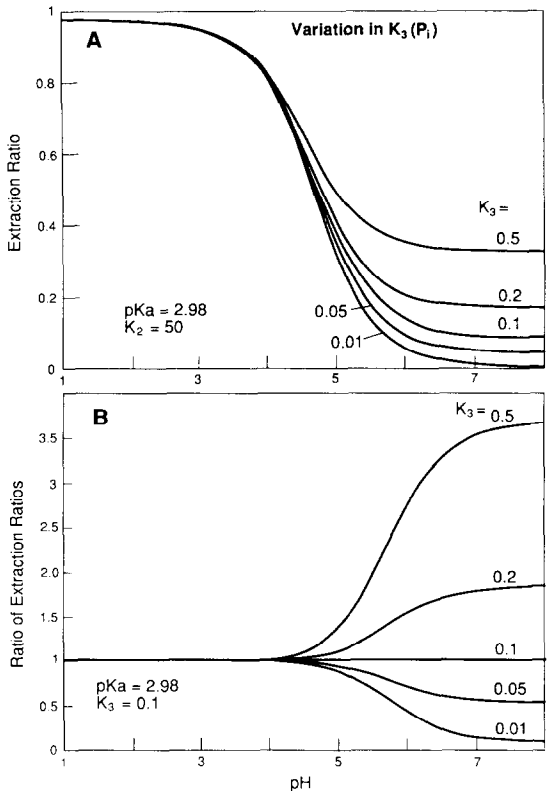

Fig. 3. Theoretical plots of the effect of ion partition coefficient (K_3) variation upon extraction ratios of a weak acid ($pK_a = 2.98$, $K_2 = 50$). Curve A illustrates the effect on the extraction ratio and curve B presents the ratios of extraction ratios. The centre, standard curve, with values of $pK_a = 2.98$, $K_2 = 50$ and $K_3 = 0.1$ was used as reference.

amides are not generally regarded as bases in aqueous systems and pK_a values of -0.7 for dimethylformamide and 0.1 for dimethylacetamide have been quoted (Adelman, 1964). Such values show little indication of significant ion-pairing potential.

Similar results are afforded with the longer chain enhancer lauric acid *N,N*-dimethylamide and representative plots are shown in Fig. 5. Analogous, but larger, increases in P_u (K_2) are seen with 0.1 M (3-fold increase) and 0.5 M (~ 8-fold increase) incorporation of the cosolvent. The ratio plots show effects comparable to those seen with CDA. The presence of 0.1 M Azone exerts an effect almost identical to that observed with 0.1 M LDA, as shown in Fig. 6, with P_u (K_2) increasing almost 3-fold in the presence of the enhancer. The values for P_i (K_3) are also suppressed and in our hands no ion-partition at all could be detected in this case. The ratio plots in Fig. 6B again follow the previous trend and indicate no evidence for processes other than simple partition and ionisation. It is of interest to note that the maximum of this plot occurs at pH 5.3, comparable to the value of 5.5 quoted earlier (Hadgraft et al., 1985). It is also noteworthy to observe the exquisite dependence of the shape of the ratio curves upon P_i (K_3) as a result of the low values observed. This effect is illustrated in Fig. 7 which shows the consequence of

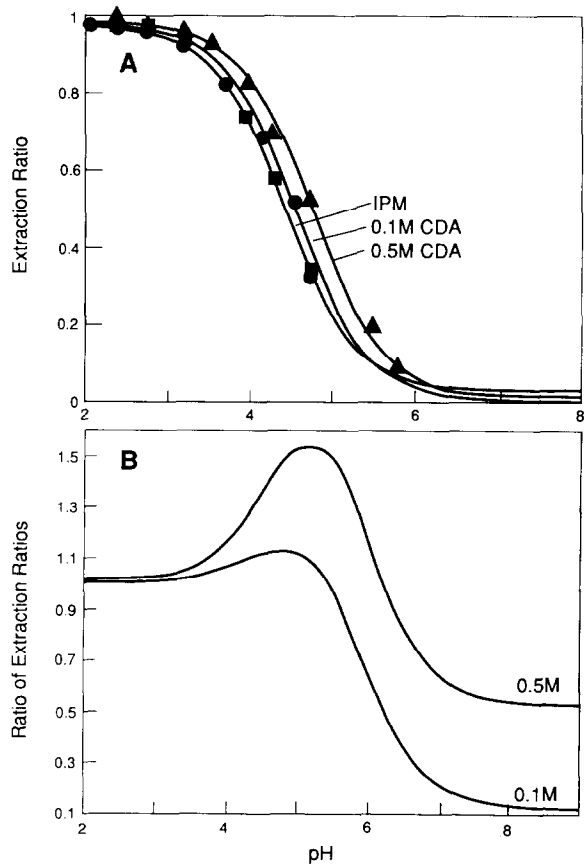

Fig. 4. Extraction ratios for the partition of salicylic acid between an aqueous phase of variable pH and an isopropyl myristate phase containing caproic acid *N,N*-dimethylamide (0.1 M, 0.5 M). (A) Extraction ratios; (B) ratio of extraction ratios using pure IPM as the reference; (●) IPM; (■) 0.1 M; (▲) 0.5 M.

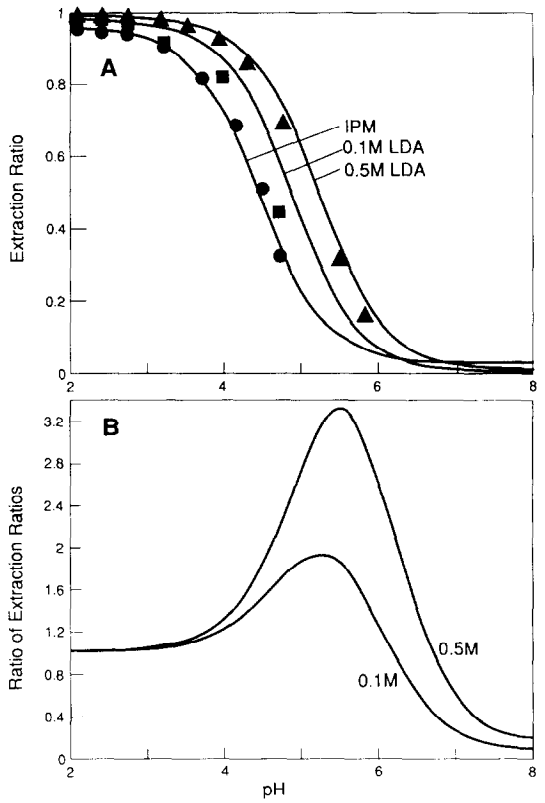

Fig. 5. Extraction ratios for the partition of salicylic acid between an aqueous phase of variable pH and an isopropyl myristate phase containing lauric acid *N,N*-dimethylamide (0.1 M, 0.5 M). (A) Extraction ratios; (B) ratio of extraction ratios using pure IPM as the reference; (●) IPM; (■) 0.1 M; (▲) 0.5 M.

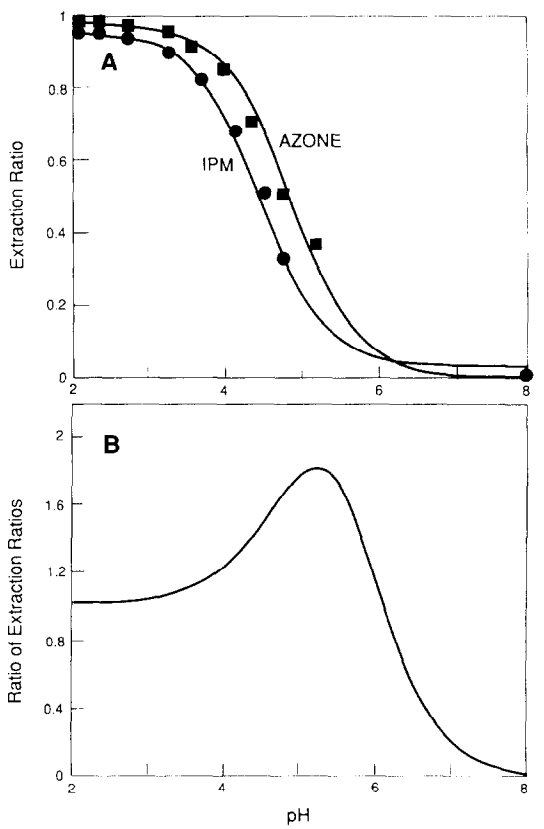

Fig. 6. Extraction ratios for the partition of salicylic acid between an aqueous phase of variable pH and an isopropyl myristate phase containing Azone (0.1 M). (A) Extraction ratios; (B) ratio of extraction ratios using pure IPM as the reference; (●) IPM; (■) 0.1 M Azone.

varying P_i from zero, the measured value, to 0.2, which represents a value of less than 0.25% of P_u. Over this range, the maximum entirely disappears and is replaced by a sigmoid curve as P_i in the cosolvent system progressively exceeds that in the pure solvent reference. The low values of P_i make their determination with any degree of precision difficult and the high dependence of the ratio profile on this parameter suggests that this mode of data analysis is unreliable as a guide to mechanistic events.

Partition studies as a function of concentration and pH have shown that carboxylic acids, including salicylic acid, show some association in the organic phase (Smith and White, 1929). This as-

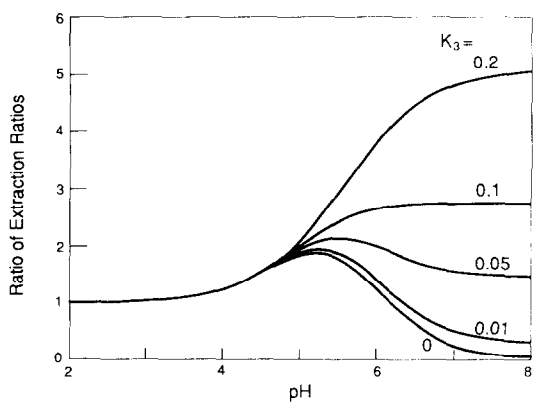

Fig. 7. Theoretical ratios of extraction ratios for the partition of salicylic acid between an aqueous phase of variable pH and an isopropyl myristate phase containing Azone (0.1 M) showing the effect of P_i on curve shape.

sociation is usually neglected in partitions determined to model topical delivery and, although expressions analogous to Eqns 11 and 12 may be derived which model association in the organic phase, the system described here fits the derived model well indicating that this modification is not required in this instance.

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