International Journal of Cosmetic Science **6**, 123–130 (1984)

The interpretation of rate curves arising from membrane permeation studies

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Received 24 February 1981

Key words: rate curves, salicylic acid skin permeation, steady state, time lag, model zeolite/polystyrene membranes.

Synopsis

The evaluation of rate curves arising from the permeation of salicylic acid through human and pig skin is discussed. The approaches based upon steady state and time lag analyses are commented on in comparison with a more complete mathematical model.

Some model zeolite/polystyrene membranes are also discussed.

Interprétation des courbes découlant d'études de perméabilité des membranes

Résumé

La documentation liée à l'étude de la migration des espèces à travers les membranes est prolifique. La peau est toujours un sujet d'intérêt favori grâce aux connotations lointaines avec la cosmétique, le système d'absorption des produits pharmaceutiques et les recherches toxicologiques liées au maniement sans risque de substances potentiellement dangereuses. Cet exposé traite des méthodes d'interprétation utilisées pour analyser les courbes observées lorsque les ingrédients se déplacent à travers les membranes de la peau (*in vitro*) (par exemple les méthodes statiques et dynamiques.

Le but de la comparaison est d'examiner l'extention de ces analyses d'un système à un autre sans nier l'intérêt évident offert par ces simples approches – surtout pour des travaux comparatifs.

Ce manuscrit présente des données du mouvement de l'acide salicylique à travers les peaux et les membranes analysés par une 'constante' et par l'application de l'equation de Ash, Barrer et Plowman qui explique toute la courbe par un coefficient de diffusion.

Des comparaisons sont faites à diverses températures pour l'action de l'acide salicylique à travers deux membranes synthétiques composées de disques polysterene/zéolite pour lesquels le seul paramêtre qui varie est la charge du système zéolitique. Des expériences semblables étudient les peaux humaines et les peaux de porc. Des différences considérables dans les taux de calcul peuvent être observées entre les différentes méthodes d'analyse mathématique et ces désaccords sont discutés en relation avec les barrières d'energie observées dans la pénétration, ceci observé pour l'acide salicylique se déplaçant à travers les membranes typiques ainsi qu'à travers diverses peaux (humaine, peau de porc, peau entière, dermique et épidermique).

Des indications quant à la pratique des systèmes 'rapide' et 'lent' sont jointes.

INTRODUCTION

The literature associated with the measurements of the migration of species through membranes is vast. One particular area of study which has received a major proprtion of this

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interest is the penetration of materials through skin. This topic has obvious implications for cosmetic science and systemic drug absorption, and should be taken into consideration for the safe handling of, and exposure to, substances of a potentially hazardous nature.

Because of the inherent problems in carrying out *in vivo* experiments in man, many workers have used model materials and/or other skins to mimic human skin. This entirely reasonable approach raises the question as to the criteria whereby comparisons can be made between membranes (i.e. skin to skin, skin to model, etc.).

The first point for discussion arises from the interpretation of the rate curves commonly observed in a simple diffusion (permeation) cell whereby the migrating species is introduced into the donor side of a cell divided into two compartments by the membrane under examination.

Subsequent measurement of the variation of concentration of the species with time as it appears in the acceptor side (or as it diminishes in the donor side) gives rise to a penetration rate.

The rate curve observed from this approach is S shaped (if the process is allowed to proceed to near completion) as shown in Figure 1. The assumption of Fickian diffusion gives rise to an often-used simple evaluation of curves of this type via the equation:

$$J_s = DK/L\Delta C_s = K_p \Delta C_s \qquad \text{(i)}$$

where

J_s is the 'steady-state' rate of penetration,
D is a diffusion coefficient for the penetrant,
K is a partition coefficient of the penetrant between solvent and membrane,
L is the membrane thickness,
ΔC_s is the external concentration difference across the membrane, and
K_p is the permeability constant (where $K_p = DK/L$).

Values of K_p can be obtained by assuming that the S curve has a region of linearity, i.e. the 'steady state' (1).

Another method is to use the 'lag time' (T) (see Fig. 1) to calculate D from the equation (2),

$$T = L^2/6D \text{ or } T = L/6K_p, \qquad \text{(ii), (iii)}$$

assuming K to be the unity.

The difficulties arising from these simple interpretations are well known and many more complex evaluations have been suggested (3). Earlier papers from these laboratories made use of an equation developed by Ash, Barrer and Plowman (4, 5) to effect a complete solution for the measurement of a diffusional parameter, so avoiding the tacit assumptions in the 'time-lag' and 'steady-state' methods (i.e. the ascribing of a straight line portion to the S curve which is rarely justifiable – see Fig. 1).

The equation is

$$\Phi_2(t) = \alpha_1 CG_o/(\alpha_1^2 + 2\alpha_1) + 2 \sum_{u=1}^{\infty} \alpha_1 CG_o EE/ZZ \qquad \text{(iv)}$$

Where

$\Phi_2(t)$ = activity in acceptor cell at time t,
α_1 = ALK/V_1,
A = membrane surface area,

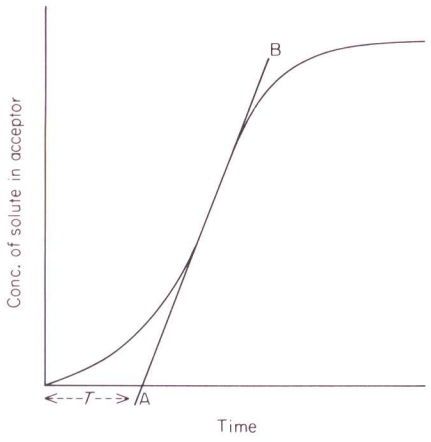

Figure 1. Sketch of rate curve for the penetration of a migrating species through a membrane. T = lag time.

V_1 = volume of acceptor cell,
D^* = self-diffusion coefficient,
$EE = \exp(-\beta_u^2 D^* t/L^2)$, (v)
$ZZ = xx - yy$, (vi)
$xx = (\alpha_1^2 - \beta_u^2)\cos\beta_u$, and (vii)
$yy = [1 + \alpha^2/\beta_u^2 + 2\alpha_1]\,\beta_u \sin\beta_u$. (viii)

β_u are the positive roots of

$$\beta^2 - 2\alpha_1\beta\cot\beta - \alpha_1^2 = 0 \qquad \text{(ix)}$$

Obviously the method of interpretation chosen by any one investigator must be subjective and it is not the purpose of this publication to detract from simple experimental approaches which, by measuring T or K_p, provide useful comparisons for in-house purposes.

The true problem of comparison becomes evident when extrapolations are made without due regard to the variables of temperature, skin type, experimental arrangements and partition coefficients. When temperature variation is considered, a common approach is the assumption of a passive diffusion mechanism followed by the assumption of an Arrhenius equation:

$$D^* = D_0\, e^{-E_a/RT} \qquad \text{(x)}$$

so that the energy barrier (E_a) experienced by the penetrant moving through the membrane can be calculated (a similar approach uses K_p values).

Hence a thermodynamic parameter appears which can provide a comparison between systems apparently divorced from the problems faced when comparing D, D^* or K_p values obtained at one temperature.

Further thermodynamic interpretation gives values for ΔS^* and ΔG^*, respectively the entropy and free energy of the activated diffusion (permeation) step. These parameters can also provide useful comparative data (4, 5), and studies over a suitable temperature range should enable the other variables (skin type, effect of vehicle, etc.) to be studied.

This paper presents data for the movement of salicylic acid through skins and model systems analysed via a steady-state (SS) approach and by the application of the Ash, Barrer and Plowman (ABP) equation.

EXPERIMENTAL PROCEDURE

Steady-state method (7): this preferred the use of root time plots to that of the more usual K_p interpretations, as they were easier to make 'best fit' to linearity curves, to calculate D^*.

The use of the ABP equation necessitated the development of a sophisticated computer analysis (6), based upon equation (iv). The analysis of data was by a FORTRAN computer program run on the I.C.L. 1906 A/CDC 7600 joint system at the University of Manchester Regional Computer Centre. The parameters $\Phi_2(t)$ and t of diffusion curves were input and calculated curves were generated on a solution to the ABP equation. The program then compared observed with calculated curves and so minimized the residual differences between these using a combination of simplex and variable metric 'migrad' algorithms. D^* and K were used as variable parameters.

RESULTS

Examples of the experimental data analysed are in Figures 2-4, and further experimental plots can be found in references 4-7.

Table I illustrates the calculation of D^* values for salicylic acid migration through synthetic zeolite/polystyrene membranes. Table II presents similar data for pig dermis and full-thickness pig skin. Table III shows derived thermodynamic parameters based upon D^* values calculated for the systems shown by the two alternative methods.

DISCUSSION

It is evident from Table I that the two analytical methods can give extremely divergent results for the assessment of D^*. The exact reason for this is not clear, but it may be a function of either the incorrect assumption of the values used for K in the ABP equation *or* that the errors illustrate the dangers of applying the SS equation to a relatively fast diffusion process.

Consideration of Table II shows less divergence between the two methods. Nevertheless a practical assessment might be that, whereas the variation in estimating D^*_{293} may be tolerable when making comparisons at ambient temperatures, any attempt to extend comparisons to measurements made at higher temperatures (including physiological temperatures) would not be justifiable.

Of course this is just a recognition that different energy barriers are presented by human and pig skin to the migration of salicylic acid and when these are considered (Table III) the two methods give values which illustrate the misinterpretations which could arise if pig skin is used to model human skin.

Expressed another way, whereas it might seem that whole pig skin provides an adequate model for the penetration of salicylic acid through whole human skin if the rates

Table I. D^* values from SS and ABP analyses of rate curves for salicylic acid in zeolite/polystyrene membranes

	Zeolite X/polystyrene $D^* \times 10^{-13}$ m^2 s^{-1}			Zeolite Y/polystyrene $D^* \times 10^{-13}$ m^2 s^{-1}	
T (°K)	SS	ABP	T (°K)	SS	ABP
293	0.39	150	298	0.86	325
303	0.55	294	303	0.87	356
313	0.93	472	308	1.04	458
323	1.72	553	318	1.13	449
			324	1.25	603

Table II. D^* values from SS and ABP analyses of rate curves for salicylic acid in whole skins

	Human skin $D^* \times 10^{-13}$ m^2 s^{-1}		Pig skin $D^* \times 10^{-13}$ m^{2}s^{-1}	
T (°K)	SS	ABP	SS	ABP
293	6.0	1.8 (at 298)	5.3	3.8
303	7.1	2.4	11.4	6.0
308	14.0	3.7	16.8	8.4
313	15.3	6.3	24.9	10.1

Table III. Thermodynamic parameters for various systems based on D^* values obtained from SS and ABP† methods

Membrane	Analysis method	E_a (kJ mol^{-1})	ΔS^* (JK^{-1} mol^{-1})	ΔG^* (kJ mol^{-1})
Zeolite X/polystyrene	ABP	35	177	28
	SS	38 ± 4	−23	43
Zeolite Y/polystyrene	ABP	17	−40	26
	SS	12 ± 4	−106	41
Pig dermis	ABP	26	−10	27
	SS	31 ± 8	−22	35
Whole pig skin	ABP	49	30	38
	SS	72 ± 8	111	36
Human dermis	ABP	30	4	26
	SS	18 ± 2	−73	37
Whole human skin	ABP	65	78	42
	SS	42 ± 8	+12	36

† Errors estimated as ± 5%.

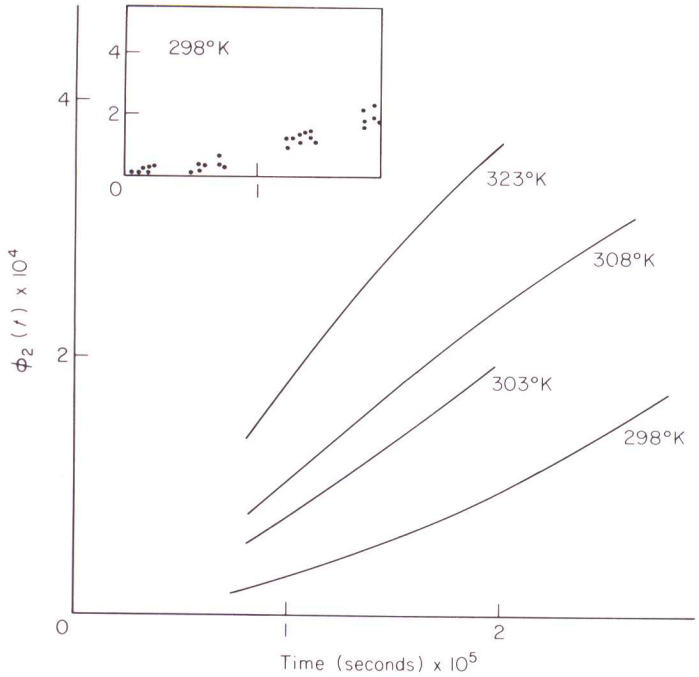

Figure 2. The rates of penetration of salicylic acid through full thickness human skin. Curves are computed from ABP and the insert illustrates the data points, used at 298°K to generate the curve, taken from three separate skin experiments.

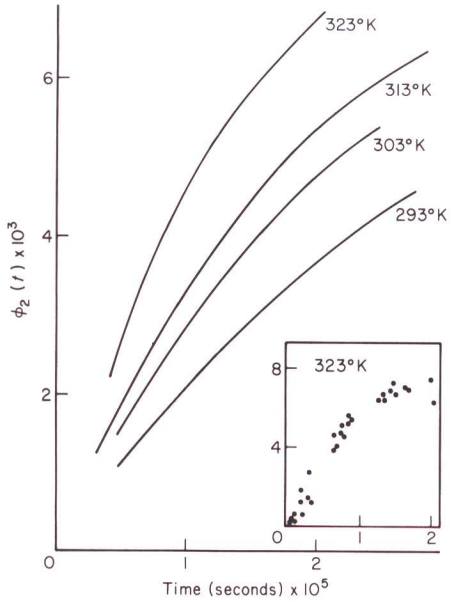

Figure 3. The rates of penetration of salicylic acid through human dermis. Curves are computed from ABP and the insert illustrates the data points, used at 323°K to generate the curve, taken from three separate skin experiments.

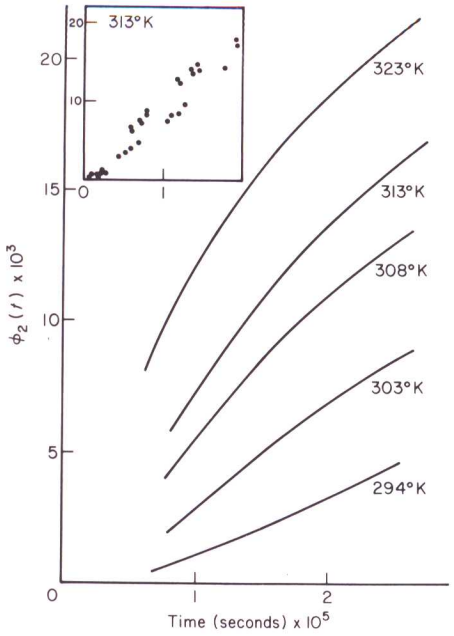

Figure 4. The rates of penetration of salicylic acid through full thickness pig skin. Curves are computed from ABP and the insert illustrates the data points, used at 313°K to generate the curve taken from three separate skin experiments.

of penetration at ambient temperatures alone are measured, the true situation is that this is largely fortuitous and the energy barriers are quite different (5). Similar results have been obtained for other penetrants and will be reported at a later date.

It can be seen also from Table III that the error in assuming a SS analysis seems to be least when the rate of penetration is more rapid. Again, this may be a function of the effect of the influence of K on the correct computation of D^*.

Practically this means that pig dermis seems a more suitable skin to act as a model for human dermis (see Table III).

Finally, it should be noted that it has not been the intention of this paper to explain the data from the skin experiments in terms of a physical model, as this has been done in earlier publications (4, 5, 7), but to emphasize the care which should be exercised in analysing rate curves from skin penetration studies.

Despite this it might be helpful here if some comments are included in the data quoted for the synthetic zeolite membranes. The results in Table III show the same trends regardless of computational method, namely that the energy barrier to the passage of salicylic acid drops as the charge on the zeolite framework is reduced (zeolite X has a Si/Al of 1.27 and that of Y is 2.60). Furthermore the change in entropy (ΔS^*) has a more positive value for X than for Y, reflecting the larger disturbance caused to the more ordered water molecules in X by the passage of salicylic acid through the structure. The ΔG^* values show that the same process is being monitored in both zeolites.

The prior publications (4, 5, 7) use this style of interpretation as their basis.

ACKNOWLEDGEMENTS

The work described herein is taken from the Ph.D. studies of Dr G. G. Hayes, supported by Nicholas International, and Dr J. G. Wilson, supported by S.R.C. Thanks to their financial sponsors are sincerely given. Professor R. M. Barrer (Imperial College) very kindly helped with the interpretation of his equation. We greatly appreciate the valuable support of Dr D. Wimbourne (Salford Royal Hospital) and the staff of Hope Hospital, Salford for skin samples.

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