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Rate constants for drug release from micellar solutions of non-ionic surfactants

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The release of a weak acid from micellar solutions containing different concentrations of two structurally related non-ionic surfactants was estimated using a dynamic dialysis apparatus. In all cases the effect of the surfactant was to reduce the amount of weak acid transferred. The data have been subjected to compartmental analysis using non-linear regression analysis. Rate constants for exchange across the dialysis membrane were independent of surfactant concentration. As surfactant concentration increased the rate constants for transfer from the non-micellar region did not show a marked change.

Non-ionic surface-active agents are known to have the general property of enhancing the solubility of non-ionic organic compounds in aqueous solution (Schick 1967). For example, the solubility of salicylic acid in 0·1 M hydrochloric acid is increased four-fold by the inclusion of micellar concentrations of polysorbates (Collett & Withington 1972). The mechanism of solubilization is generally assumed to be attributable to an interaction between the organic compound and the surface-active agent orientated in the micellar configuration. While bearing in mind (a) the question of whether or not micelles constitute a thermodynamically distinct and separate phase, and (b) the instability of micelles, it has become established practice to regard the solubilizable compound as partitioning dynamically between micellar and non-micellar regions of the solution.

For some 15 years chemical relaxation techniques (Lang et al 1975), stopped flow (Takeda 1974), n.m.r. (Nakagawa 1974) and e.p.r. (Nakagawa 1974; Nakagawa & Jizimoto 1972) have been extensively used to study the kinetics of fast processes occurring in micellar solutions. In the present work, the experimental technique involves continuous monitoring of the gradual removal of salicylic acid from aqueous polysorbate solutions by dialysis; the kinetic analysis is on a time scale that is several orders of magnitude greater than used previously. The aim of the work is to examine the data in terms of compartmental analysis as a means of estimating rate constants for exchange of salicylic acid between (a) solutions, separated by a dialysis membrane, that do and do not contain polysorbates, (b) proposed micellar and non-micellar regions within polysorbate solutions.

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MATERIALS AND METHODS

Materials

Salicylic acid A.R. (BDH) was used. The two surfactants were polyoxyethylene (20) sorbitan monolaurate and polyoxyethylene (20) sorbitan monooleate. They were characterized by their mass spectra and proton magnetic resonance spectra (Crooks et al 1974). Cellophane dialysis tubing (Visking) was washed and cut to size.

Methods

The procedures used and the design of the dialysis cell have been described previously (Withington & Collett 1973). In brief, the main features are as follows. The experimental procedures involved placing 100 ml of 0·1 M hydrochloric acid solution, the recipient solution, in one half cell. This solution was circulated by a peristaltic pump (Watson–Marlow H.R. flow inducer, Type N.R.E. 200) through a 1·0 mm path quartz cell in a Pye Unicam SP500 spectrophotometer and assayed for salicylic acid. 100 ml of donor solution was placed in the other half cell of the dialysis apparatus; 18·9 cm^2 of membrane surface was in contact with each solution.

THEORY

Kinetic representation of micellar solubilization by compartment models

It is thought that solutions of surface-active agents, that are not very dilute, contain regions having high concentrations of surface-active molecules. The local regions are usually regarded as temporary aggregates known as micelles that have, in one solution, a

narrow range of sizes. Individual surface-active molecules are thought to be continuously in a state of dynamic exchange between the micellar and non-micellar states, but while in the micellar state, the surface-active molecules are presumed to be orientated in such a way that lipophile–water interactions are minimized and hydrophile–water interactions are maximized. In addition, it is thought that the micelles rapidly disintegrate and equivalent ones reform concurrently giving rise to the concept of 'flickering micelles' by analogy with 'flickering clusters' within water (Nemethy & Scheraga 1962). Nevertheless, in attempting a kinetic analysis, it is thought reasonable to postulate on a time-averaged basis that a diffuse region of micelles is present within the aqueous solution of surface-active agents. Consequently, the dynamic partitioning of salicylic acid can be considered firstly between two distinct solutions divided by the dialysis membrane, that is between solutions that do and do not contain surface-active agent, and secondly between the postulated micellar and non-micellar regions within the solution of surface-active agent.

The most simple kinetic model (Model I depicted in Fig. 1), that was considered to describe the data, involved the postulate that the rates of transfer

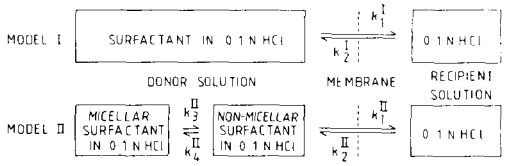

FIG. 1. Compartment models describing the release of salicylic acid from aqueous solution and from micellar solutions of a non-ionic surfactant.

between micellar and non-micellar regions would be sufficiently rapid for the processes to be apparently instantaneous within the limits of accuracy of the experimental methods employed. Thus the rate constants k_1^I and k_2^I for transfer of salicylic acid across the dialysis membrane are those that need to be considered in the kinetic description of the data. Since the system is closed only one differential equation is required to define effectively the two-compartment system.

$$\frac{dSA_R^I}{dt} = k_1^I SA_D^I - k_2^I SA_R^I \qquad \text{or}$$

$$\frac{dSA_D^I}{dt} = k_2^I SA_R^I - k_1^I SA_D^I$$

where SA_D^I and SA_R^I refer to amounts of salicylic acid in the donor and recipient cells respectively. In another model, (Model II depicted in Fig. 1), the micellar and non-micellar regions are considered to be separated into two kinetically distinguishable compartments. The differential equations for the three compartments are:

$$\frac{dSA_R}{dt} = k_1^{II} SA_{NM} - k_2^{II} SA_R$$

$$\frac{dSA_{NM}}{dt} = k_2^{II} SA_R + k_3^{II} SA_M - k_1^{II} SA_{NM} - k_4^{II} SA_{NM}$$

$$\frac{dSA_M}{dt} = k_4^{II} SA_{NM} - k_3^{II} SA_M$$

(where SA_R, SA_{NM} and SA_M refer to amounts of salicylic acid in the recipient solution, non-micellar region and micellar region of the donor solution respectively) although only two are required to define the system.

More complex models, for example, treating the membrane as a separate compartment were found to be not justified by the data reported here.

Computational details

The suitability of compartmental models, defined by differential equations, to describe quantitatively and account for changes of the amount of salicylic acid in the recipient cell as a function of time was tested by use of least squares regression analysis. The computer program employed a modified Gauss–Newton procedure (Draper & Smith 1966; Metzler et al 1974). The relative suitability of models was judged by comparing the total sums of squared deviations, in the case of a pair of models, by means of an F test at the 5% level of significance (Boxenbaum et al 1974).

RESULTS AND DISCUSSION

Fig. 2 shows a typical plot of amount of salicylic acid in the recipient solution when polysorbate was absent (Fig. 2a) and present (Fig. 2b). It can be seen that, while an apparent equilibrium was achieved after approximately 20 h when polysorbate was absent, the inclusion of polysorbate 20 in the donor solution at a concentration of 4% w/w caused the time required for a close approach to equilibrium exchange of salicylic acid across the dialysis membrane to be approximately doubled. In addition, the effect of the polysorbate was to reduce the fraction of salicylic acid transferred across the dialysis membrane. The least squares fits of the data of both

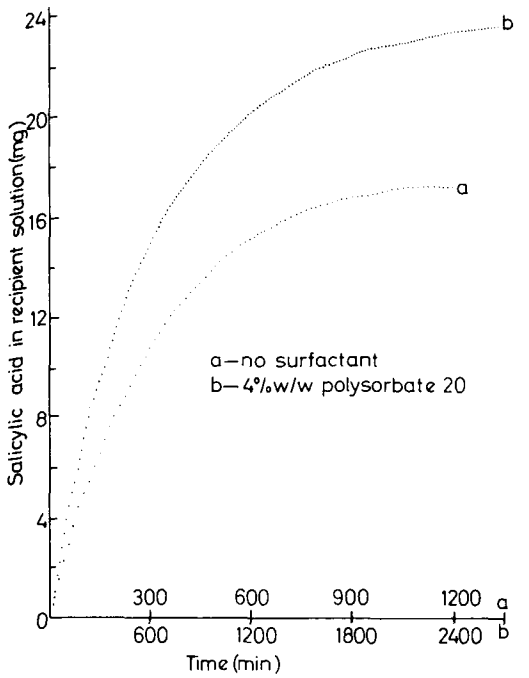

FIG. 2. Amounts of salicylic acid in recipient solution as a function of time

of the kinetic models depicted in Fig. 1 were generally very satisfactory. The question of whether the several primary postulates of least squares regression analysis (Draper & Smith 1966) were violated, centres particularly on the requirement that errors in the dependent variable (the estimates of salicylic acid in the recipient solution) should be normally distributed with constant variance. Some insight into this question, as well as the choice of preferred model, can be gained from an examination of residual (difference between observed and calculated value) plots, some examples of which are given in Fig. 3. It is concluded that the possible requirement for a weighting factor to correct for bias in the reliability of assessment of the dependent variable, salicylic acid, can be dismissed with a high degree of confidence.

From an inspection of the residual plots obtained when data were fitted by least squares regression to Model I, a typical example of which is shown in Fig. 3, it can be deduced that, while some systematic deviation of data from the fitted line is apparent, the correspondence is sufficiently great for the model to be worthy of consideration. In Table 1 are listed estimates of the rate constants of Model I when polysorbates 20 and 80 were present in the donor solution at concentrations of 0, 1, 4 and 5% w/w. It

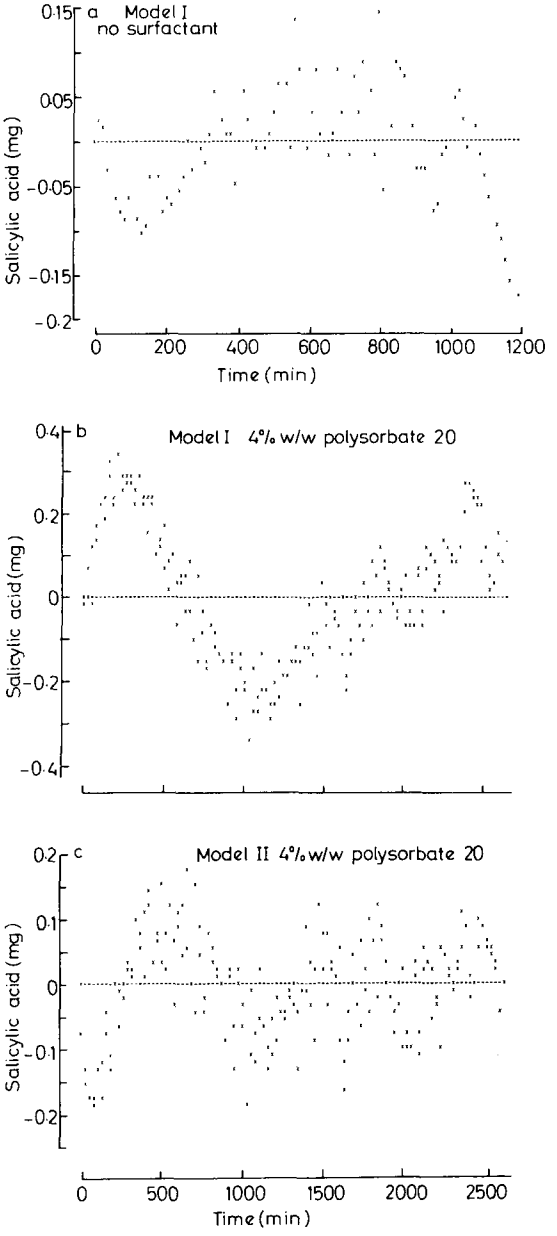

FIG. 3a, 3b, 3c. Examples of residual plots showing deviations of experimentally determined amounts of salicylic acid from calculated amounts.

can be seen that k_2^I, the rate constant for transfer into the polysorbate solutions, does not appear to depend systematically on the polysorbate type or concentration; in contrast k_1^I the rate constant transfer from the polysorbate solutions is affected by both the surfactant type and concentration. The rate constant k_1^I decreases as the concentration of each

surfactant increases and has lower values in the case of polysorbate 80 rather than polysorbate 20 at corresponding concentrations.

Model I having been seen to give an approximate description of the data, a decision is needed on whether the refinements built into Model II are justified by the data available. The relative goodness of fit of the data to the two models can be judged qualitatively by reference to the residual plots and quantitatively by means of F tests. When Model I is used to describe data from experiments in which polysorbate is absent, the scatter of residuals around zero is apparently random almost independently of time. In contrast, in the presence of polysorbate, the residuals are first systematically biased towards positive values then correspondingly to negative values. In the typical example shown in Fig. 3b, the residuals range from +0·35 mg to −0·30 mg with a standard deviation of 0·16 mg. On the other hand, when the data are fitted to Model II the systematic trend of the residuals is largely eliminated. The residuals then range from ±0·15 mg with standard deviation 0·08 mg in the case of the example shown in Fig. 3c. The qualitative conclusion is that Model II rather than Model I gives the better representation of data when polysorbate is present. General quantitative support for this conclusion can be obtained from an examination of the calculated values of F listed in Table 2. It can be seen that in every case, a significant improvement in total sum of squares is obtained at the conventional 5% probability level ($F \simeq 3{\cdot}9$) by use of Model II rather than Model I. In conclusion, the preference for Model II is believed to be justified and consequently the concept of a micellar solution behaving as two kinetically distinguishable compartments is supported in the context of this work.

Table 1. Rate constants with standard deviations for Model I.

Surfactant Type	Concn (% w/w)	$k_1^{I} \times 10^4$ (min^{-1})	$k_2^{I} \times 10^4$ (min^{-1})
—	0	15·527 (0·047)	15·527 (0·047)
Polysorbate 20	1	7·275 (0.015)	15·059 (0·045)
	4	2·836 (0·008)	13·494 (0·051)
	5	2·446 (0·012)	13·741 (0·089)
Polysorbate 80	1	6·527 (0·017)	15·323 (0·057)
	4	2·515 (0·007)	14·408 (0·053)
	5	2·021 (0·009)	14·164 (0·079)

Rate constants for transfer of salicylic acid estimated on the basis of Model II are listed in Table 3. The rate constants k_1^{II} and k_2^{II} for exchange across the dialysis membrane are approximately independent of polysorbate type and concentration in the donor solution. Moreover, the values of these rate constants are close to those estimated from Model I when polysorbate is absent (Table 2). Consequently the function of the membrane is apparently not altered by polysorbate.

Table 2. Statistical comparison of Models I and II using F tests based on equation 1.

Surfactant type	Concn (%w/w)	$F_{cal.}$	$F_{tab.}$ ($P = 0{\cdot}05$)
Polysorbate 20	1	5·2	3·9
	4	132	3·9
	5	136	3·9
Polysorbate 80	1	71	3·9
	4	60	3·9
	5	101	3·9

Eqn. 1 $F_{cal.} = ((SS^{I} - SS^{II})/DF^{I} - DF^{II}))/(SS^{II}/DF^{II})$
SS is sum of squared deviations
DF is degrees of freedom

The correlation matrix of parameter estimates in the least squares analysis is such that the estimates of rate constants k_3^{II} and k_4^{II} for all sets of data are quite highly correlated and therefore deductions based upon their relative magnitudes are more reliable than those based upon their absolute values. The ratios k_4^{II}/k_3^{II} are listed in Table 3 and are, at a first approximation, directly proportional to polysorbate concentration; the proportionality constant has values of 0·9 and 1·2 in the case of polysorbates 20 and 80 respectively. When it is postulated that the relative magnitudes of the micellar and non-micellar regions determine both k_3^{II} and k_4^{II} as follows:

$$\frac{k_4^{II}/\text{mass of micellar region}}{k_3^{II}/\text{mass of non-micellar region}} = K$$

then K has the form of an apparent partition coefficient. Calculated values of K are listed in Table 3* and are consistently higher in the cases of polysorbate 80 rather than polysorbate 20 at equivalent concentrations. However, the trend shown in the cases of both polysorbates, whereby the value of K declines as the polysorbate concentration increases, is in contrast to the previous work (Collett & Withington 1972). The decline would not be expected if the distributions of sizes and shapes of micelles are unaffected by changes of the polysorbate concentration and it is to be expected that the average micellar aggregation number would depend on surfactant concentration to some degree (Lang et al 1975).

* The relative masses were estimated as the relative weight fractions of polysorbate and water in a system.

Table 3. Rate constants with standard deviations for Model II.

Surfactant	conc'n % w/w	$k_1^{II} \times 10^4 = k_2^{II} \times 10^4$ (min^{-1})	$k_3^{II} \times 10^4$ (min^{-1})	$k_4^{II} \times 10^4$ (min^{-1})	k_4^{II}/k_3^{II}	Partition ratio
Polysorbate 80	1	16·693 (0·063)	33·147 (1·615)	43·797 (2·223)	1·32	130·81
	4	16·387 (0·106)	14·293 (0·747)	66·917 (3·571)	4·68	112·36
	5	17·137 (0·123)	7·623 (0·295)	44·919 (1·807)	5·89	111·96
Polysorbate 20	1	15·709 (0·115)	79·919 (14·608)	85·131 (15·700)	1·07	105·46
	4	15·535 (0·052)	13·137 (0·333)	48·554 (1·275)	3·70	88·70
	5	16·754 (0·090)	7·619 (0·223)	34·074 (1·063)	4·47	84·967

A consideration of the absolute values of the rate constants k_3^{II} and k_4^{II}, being of the order of 10^{-3} to 10^{-4} min^{-1}, may lead one to the view that the magnitude of these estimates is significantly less than may be anticipated from previously reported studies of chemical relaxation of micellar equilibria (Lang 1975). Therefore it is concluded that the rate processes studied here differ from the related previous work in some general way. Clearly, in this work the process investigated is the definite physical separation of salicylic acid from an environment of polysorbate at micellar concentration. On the other hand, e.p.r. and chemical relaxation methods of estimating relaxation times follow a physical disturbance of a closed system. Consequently the consistency of results from these techniques, that is in producing estimates of the relaxation time for release of single components from micelles of approximately 10^6 s^{-1} or more, and the dissimilarity of the consistent results of the present work can be accounted for. The results obtained from the physical disturbance of the closed systems probably reflect a process other than the complete removal of components from a micellar region. For example, they may represent transfer either between the micellar core and periphery or between micelles and hydration layers (Aniannson 1978).

The significance of the temporary nature of the micelle has been ignored so far in the discussion of this work and in much of the other previous work on the kinetics of the interaction of solubilizates with micelles. However, it is worth noting (Muller 1976; Lang et al 1975) that the rate constant for the complete dissolution of a micelle is probably n^2 times less than for the consecutive dissociation of a single molecule from a micelle with the result that the two rate constants may differ by as much as three or four orders of magnitude (n is the micellar aggregation number). Therefore it is concluded that the values in this work for the rate constants for entry and exit of solute to and from the micelles are closer than previous estimates to the values of rate constants for complete micelle dissolution than to those for consecutive dissociation. In considering the mechanisms of solubilization and release it is inferred that micellar solubilizate is transferred to an aqueous environment as a result of the complete dissolution of a micelle and to a lesser extent as a result of diffusion from a micelle. Likewise it is likely that the presence of solubilizate in a micelle is due to diffusion into an existing micelle and to selective inclusion during the formation of a micelle. Thus, on dissolution of a micelle containing an enhanced concentration of solubilizate, excess solubilizate beyond that which can be retained under non-micellar conditions will with high probability appear in a micelle formed at a different site (Aniansson 1978).

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