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A quantitative approach to the *in vitro* availability of drugs from some non-ionic surfactant solutions

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Equations that can be used in calculating the theoretical dialysis rates of drugs from surfactant solutions have been derived. Theoretical dialysis rates for the dialysis of salicylic acid from polysorbate solutions at a range of pH levels are compared with those determined experimentally. At low pH levels there is good agreement between theoretical and experimental values. With increasing pH at each surfactant concentration the values diverge. A possible reason for this divergence is considered.

Surfactants may influence drug absorption by a variety of mechanisms of which solubilization is probably the most important (Gibaldi & Feldman, 1970). Several workers have investigated the *in vivo* absorption of weak electrolytes from surfactant solutions. They found that the increased amount of drug in solution in the presence of micellar concentrations of surfactants was not always reflected by an increased drug absorption. Equations relating the rate at which a drug was absorbed from surfactant solutions to the amount of drug solubilized have been described (Kakemi, Arita & Muranishi, 1965; Yamada & Yamamoto, 1965; Yamada, Ichihashi & others, 1966). In each case the usefulness of the equations was limited to systems where only the unionized form of the drug was solubilized. Consequently, the pH at which absorption experiments were carried out was restricted to levels at which only unionized drug was present. Equations that can be used at other pH levels, and for drugs that are solubilized in the ionized, as well as the unionized, form will be of great value in bioavailability studies.

In this report we have described the use of a dialysis model of drug absorption to study the influence of surfactants on the availability of salicylic acid at a range of pH levels. The aim of the work is to derive equations that can be used in the calculation of theoretical values of dialysis rate and to compare these values with experimentally obtained values. Such equations derived from data obtained in a physical system will be free from effects due to a biological system and may be useful in the prediction of the overall rate of drug absorption from surfactant solutions at different pH levels.

MATERIALS AND METHODS

The method of studying dialysis of salicylic acid (BDH Analytical reagent) from solutions of polysorbate 20 and polysorbate 80 (Honeywill Atlas) has been described (Withington & Collett, 1973).

Rate constants of dialysis are calculated using

$$\frac{dm}{dt} = K(C_d - C_r) \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where m is the amount of solution transferred by dialysis in time t, C_d and C_r are the

concentrations of solute in the donor and recipient dialysis cells respectively and K is the dialysis rate constant. The integrated form of equation 1 is

$$\log(C_d - C_r) = -Kt + \text{constant} \quad .. \quad .. \quad (2)$$

Dialysis rate constants are obtained from the slopes of plots of log $(C_d - C_r)$ against time. In the absence of surfactant the rate constant is denoted by K and in the presence of surfactant by K_{app}.

RESULTS AND DISCUSSION

(1) *Calculation of rate constants for dialysis from the aqueous phase of surfactant solutions*

If the initial concentration of solute in the aqueous phase of surfactant solutions is known and it is assumed that dialysis takes place from only the aqueous phase then the rate constant K_{aq} for dialysis from the aqueous phase can be calculated. Initial aqueous concentrations, C_a, of solute in surfactant solutions may be calculated from total solute concentrations using previously determined (Collett & Withington, 1972) micellar: aqueous partition coefficient as follows:—

$$P^o = \frac{C_m^o}{C_a^o} \quad .. \quad .. \quad .. \quad .. \quad (3)$$

describes the partition coefficient, P^o, of unionized solute molecules between surfactant micelles and water where subscripts a and m denote aqueous and micellar phases respectively. Substituting amounts, A, and volumes, V, for concentrations in equation (3) gives

$$P^o = \frac{A_m^o V_a}{A_a^o V_m} \quad .. \quad .. \quad .. \quad .. \quad (4)$$

Similarly the partition coefficient for ionized molecules is given by

$$P^- = \frac{A_m^- V_a}{A_a^- V_m} \quad .. \quad .. \quad .. \quad .. \quad (5)$$

The total amount, A_t, of solute in a micellar surfactant solution is given by

$$A_t = A_m^o + A_m^- + A_a^o + A_a^- \quad .. \quad .. \quad .. \quad (6)$$

re-arranging equation (5) gives

$$A_m^- = \frac{P^- A_a^- V_m}{V_a} \quad .. \quad .. \quad .. \quad .. \quad (7)$$

The ratio $\frac{V_m}{V_a}$ may be designated R.

Substituting equation (7) into equation (6) gives

$$A_t = A_m^o + P^- A_a^- R + A_a^o + A_a^- \quad .. \quad .. \quad (8)$$

Using the Henderson–Hasselbach equation it can be shown that

$$\frac{C_a^o}{C_a^-} = \frac{A_a^o}{A_a^-} = \left(\frac{1}{f_i}\right) - 1 \quad .. \quad .. \quad .. \quad .. \quad (9)$$

where f_i is the fraction of ionized solute present and therefore

$$A_a^- = \frac{A_a^o}{(1/f_i) - 1} \quad .. \quad .. \quad .. \quad .. \quad (10)$$

The term $\frac{1}{[(1/f_i) - 1]}$ may be represented by F_i

Substituting for A_a^- in equation (8) gives

$$A_t = A_m^o + P^- A_a^o R F_i + A_a^o + A_a^o F_i \quad .. \quad .. \quad (11)$$

From equation (4)

$$A_m^o = P^o A_a^o R \quad .. \quad .. \quad .. \quad .. \quad .. \quad (12)$$

Substituting for A_m^o in equation (11) gives

$$A_t = P^o A_a^o R + P^- A_a^o R F_i + A_a^o + A_a^o F_i \quad .. \quad .. \quad (13)$$

Dividing equation (13) by A_a^o gives

$$\frac{A_t}{A_a^o} = P^o R + P^- R F_i + 1 + F_i \quad .. \quad .. \quad .. \quad .. \quad (14)$$

and, re-arranging gives

$$A_a^o = \frac{A_t}{P^o R + P^- R F_i + 1 + F_i} \quad .. \quad .. \quad .. \quad (15)$$

Converting to concentrations by dividing by V_a, and substituting $C_t V_t$ for A_t produces

$$C_a^o = \frac{C_t V_t}{[P^o R + P^- R F_i + 1 + F_i]V_a} \quad .. \quad .. \quad .. \quad (16)$$

Equation (9) can be used to calculate the concentration of ionized molecules from the concentration of unionized molecules:

$$C_a^- = C_a^o F_i \quad .. \quad .. \quad .. \quad .. \quad (17)$$

Substituting equation (16) into equation (17) gives

$$C_a^- = \frac{C_t V_t}{[P^o R + P^- R F_i + 1 + F_i]V_a} \times F_i \quad .. \quad .. \quad (18)$$

so the total aqueous concentration, C_a, of solute is given by the sum of equations (16) and (17)

$$C_a = \left[\frac{C_t V_t}{[P^o R + P^- R F_i + 1 + F_i]V_a}\right] + \left[\frac{C_t V_t}{[P^o R + P^- R F_i + 1 + F_i]V_a}\right] \times F_i \quad .. \quad .. \quad .. \quad (19)$$

which reduces to

$$C_a = C_t \left[\frac{V_t}{[P^o R + P^- R F_i + 1 + F_i]V_a}\right] \times [1 + F_i] \quad .. \quad .. \quad (20)$$

Values of C_a calculated using equation (20) are substituted for C_d in equation 2 and the aqueous concentration of solute across the dialysis membrane is obtained. Rate constants K_{aq} were determined and are reported in Table 1.

(ii) *Calculation of overall rate constants for dialysis from surfactant solutions*

Apparent rate constants, K_{app}, for dialysis from surfactant solutions have been determined from plots of $\log(C_d - C_r)$ against t.

If solute dialyses from only the aqueous phase of surfactant solutions then the concentration gradient term of equation 1 should represent the aqueous concentration gradient of the solute and may be written as

$$\frac{dm}{dt} = K\,F\,(C_d - C_r) \quad .. \quad .. \quad .. \quad .. \quad (21)$$

where F is a factor for converting total (micellar + aqueous) concentrations of solute in surfactant solutions to aqueous solute concentrations. Thus

$$K_{app} = K\,F \quad .. \quad .. \quad .. \quad .. \quad (22)$$

For a solute whose ionized and unionized molecules dialyse at different rates, the rate constant K is the sum of the rate constants for the individual species so that equation 22 can be written as

$$\frac{dm}{dt} = K^oF(C_d^o - C_r^o) + K^-F(C_d^- - C_r^-) \quad .. \quad (23)$$

where superscripts o and - denote unionized and ionized molecules respectively.

In terms of total solute concentrations

$$\frac{dm}{dt} = K^oF(1-f_i)\,(C_d - C_r) + K^-F\,f_i\,(C_d - C_r) \quad .. \quad (24)$$

Equation 24 reduces to

$$\frac{dm}{dt}\,(K^o(1-f_i) + K^-f_i\,F)\,(C_d - C_r) \quad .. \quad .. \quad .. \quad (25)$$

Comparing equation 25 with equation 21 shows that

$$K^o(1-f_i) + K^-f_i = K \quad .. \quad .. \quad .. \quad (26)$$

The factor F (equation 21), that is required to convert total solute concentrations in surfactant solutions to aqueous phase concentrations, is obtained from equation 20

$$F = \left[\frac{V_t}{[P^o\,R + P^-\,R\,F_i + 1 + F_i]V_a}\right] \times [1 + F_i] \quad .. \quad (27)$$

Combining equations 27 and 26 with equation 22 gives

$$K_{app} = K^o(1-f_i) + K^-f_i \times \left[\frac{V_t}{[P^o\,R + P^-\,R\,F_i + 1 + F_i]\,V_a}\right] \times [1 + F_i] \quad .. \quad (28)$$

Values of K_{app} for the dialysis of salicylic acid from polysorbate 20 and 80 solutions, have been calculated from previously determined micellar: aqueous partition coefficients and the dialysis rate constants of ionized and unionized salicylic acid molecules. Calculated values of K_{app} and K_{aq} are presented in Tables 1 and 2, together with the experimentally determined values. There is good agreement between theoretical and experimental K_{app} values excepting those at high pH levels where divergence is seen. Possible reasons for the divergence of experimental values of K_{app} from theoretical values with increasing pH may be obtained by examining equation 28 more closely. Each quantity in the equation excepting P^- (the micellar: aqueous partition

Table 1. *Rate constants for the dialysis of salicylic acid from polysorbate 20 solutions.*

pH		Rate constant $\times 10^3$ (cm^3 min^{-1}) Polysorbate 20 concentration (% w/v) 1 K_{aq}	1 K_{app}	2 K_{aq}	2 K_{app}	4 K_{aq}	4 K_{app}	5 K_{aq}	5 K_{app}
1	Experimental[a]	1·45	0·72	1·45	0·48	1·44	0·29	1·32	0·22
	Theoretical[b]	1·37	0·75	1·37	0·51	1·37	0·32	1·37	0·27
2	Experimental[a]	1·40	0·72	1·35	0·47	1·29	0·28	1·23	0·22
	Theoretical[b]	1·33	0·75	1·33	0·52	1·33	0·33	1·33	0·28
3	Experimental[a]	1·11	0·74	1·05	0·52	1·00	0·35	0·98	0·29
	Theoretical[b]	1·10	0·79	1·10	0·61	1·10	0·42	1·10	0·36
4	Experimental[a]	0·88	0·82	0·80	0·71	0·69	0·55	0·68	0·51
	Theoretical[b]	0·92	0·86	0·92	0·81	0·92	0·73	0·92	0·70
5	Experimental[a]	0·80	0·80	0·70	0·70	0·63	0·64	0·59	0·60
	Theoretical[b]	0·87	0·87	0·87	0·88	0·87	0·88	0·87	0·88

a. Experimental values of K_{aq} were calculated as described in the text.
b. Theoretical values of K_{aq} are the rate constants determined in the absence of surfactant, and theoretical values of K_{app} were calculated according to equation 28.

coefficient) is known with a high degree of certainty. P^- was found to be zero (Collett & Withington, 1972) for polysorbate 20 and 80 and was consequently omitted from equation 28 when calculating K_{app}. By substituting increasing values of P^- into equation 28 the effect of P^- on calculated values of K_{app} can be determined. Using this iterative technique it was found that for polysorbate 20 solutions, at pH 4·0 and 5·0, a value of 8·0 for P^- gave calculated values of K_{app} equal to the experimental values. The apparent failure of equation 28 to account for dialysis of salicylic acid from relatively high pH polysorbate solutions is probably the result of the use of incorrect P^- values. However, the close agreement between theoretical and experimental K_{app} values at other levels indicates the usefulness of equation 28 for predicting dialysis rates of drugs in the presence of surfactants. Equation 28 can be employed over a range of pH levels and surfactant concentrations, and for those drugs whose ionized, as well as unionized molecules partition into the surfactant micelles. These

Table 2. *Rate constants for the dialysis of salicylic acid from polysorbate 80 solutions.*

pH		Rate constant $\times 10^3$ (cm^3 min^{-1}) Polysorbate 80 concentration (% w/v) 1 K_{aq}	1 K_{app}	2 K_{aq}	2 K_{app}	4 K_{aq}	4 K_{app}	5 K_{aq}	5 K_{app}
1	Experimental[a]	1·41	0·67	1·52	0·40	1·40	0·22	1·34	—
	Theoretical[b]	1·37	0·66	1·37	0·43	1·37	0·26	1·37	—
2	Experimental[a]	1·37	0·67	1·45	0·43	1·40	0·24	1·35	—
	Theoretical[b]	1·33	0·66	1·33	0·44	1·33	0·27	1·33	—
3	Experimental[a]	1·06	0·65	1·04	0·46	0·99	0·28	0·99	0·24
	Theoretical[b]	1·10	0·72	1·10	0·53	1·10	0·35	1·10	0·30
4	Experimental[a]	0·86	0·79	0·82	0·70	0·80	0·58	0·72	0·50
	Theoretical[b]	0·92	0·84	0·92	0·78	0·92	0·68	0·92	0·64
5	Experimental[a]	0·84	0·84	0·81	0·81	0·78	0·78	0·69	0·69
	Theoretical[b]	0·87	0·87	0·87	0·87	0·87	0·87	0·87	0·87

a. Experimental values of K_{aq} were calculated as described in the text.
b. Theoretical values of K_{aq} are the rate constants determined in the absence of surfactant, and theoretical values of K_{app} were calculated according to equation 28.

features of the equation are in contrast to the limited scope of equations presented by other authors (Yamada & Yamamoto, 1965; Yamada & others, 1966).

The usefulness of equation 28 having been demonstrated in an *in vitro* model of drug absorption, the question arises of its usefulness in estimating the *in vivo* absorption rate of a weak rate of a weak electrolyte from non-ionic surfactant solutions with a knowledge of the physical parameters in equation 28.

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