Solubilization of Weakly Acidic and Basic Drugs by Aqueous Solutions of Polysorbate 80

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The relationship of apparent solubility of weakly acidic and basic drugs to pH and surfactant concentration has been established. Equations are presented which enable calculation of the total solubility of such drugs as represented by methylprednisolone hemiesters and procaine. The fraction of drug in the various solvated states can be computed readily.

NONIONIC SURFACTANTS have been studied by various workers (1–7) and found to solubilize effectively drugs which possess low water solubilities. In particular, Guttman *et al.* (8) and Hall (9) have presented data on the relationship of surfactant concentration to the degree of solubilization for anti inflammatory steroids and salicylic acid, respectively. Solubilization may take place by several mechanisms, *i.e.*, shallow or deep penetration of the micelles or simply by surface adsorption.

The present study was undertaken to define the relationship of apparent solubility of weakly acidic and basic drugs in aqueous systems to both pH and surfactant concentration. Accordingly, equations are presented which enable calculation of total solubility at any given pH and surfactant concentration and of the fraction of material present in the various solvated states. Three methylprednisolone-21-hemiesters and procaine have been investigated in aqueous solutions of polysorbate 80.

THEORY

Consider the case of a sparingly soluble drug possessing a single acidic functional group capable of salt formation. The total solubility of drug can be expressed as the sum of the various species present.

$$(D)_T = (D) + (D^-) + [D] + [D^-] \quad \text{(Eq. 1)}$$

where $(D)_T$ = total drug concentration, (D) = free acid not in micelle, (D^-) = ionized acid not in micelle, $[D]$ = free acid in micelle, $[D^-]$ = ionized acid in micelle, and concentration is expressed in terms of total volume.

If it is assumed that solubilization occurs by partitioning of the drug into micelles formed by the surfactant, partition coefficients can be defined for the free and ionized acid as $K' = \frac{[D]_0}{(D)_0}$ = partition coefficient of free acid into micelles and $K'' = \frac{[D^-]_0}{(D^-)_0}$ = partition coefficient of ionized acid into micelles. The subscript 0 denotes concentrations expressed in terms of the individual phase volumes rather than total volume. These constants may also be expressed in terms of total volume for convenience in computation and measurement.

$$K' = \frac{[D][1-(M)]}{(D)(M)} \qquad K'' = \frac{[D^-][1-(M)]}{(D^-)(M)}$$

Micelle concentration (M) is considered equal to volume fraction surfactant, neglecting that which is present in true solution. Where (M) is relatively small, the term $1-(M)$ can be neglected and the following equations used as a good approximation:

$$[D] = K'(D)(M) \quad \text{(Eq. 2)}$$

$$[D^-] = K''(D^-)(M) \quad \text{(Eq. 3)}$$

Substituting Eqs. 2 and 3 into Eq. 1

$$(D)_T = (D)[1 + K'(M)] + (D^-)[1 + K''(M)] \quad \text{(Eq. 4)}$$

The fraction, X, of drug unionized in the aqueous phase is

$$X = \frac{(D)}{(D^-) + (D)} = \frac{(H^+)}{Ka + (H^+)} \quad \text{(Eq. 5)}$$

where Ka is the acid dissociation constant of the drug.

Let $(D)_T^* = (D) + (D^-)$ = total drug solubility at a given pH in the absence of surfactant. Since from Eq. 5

$$(D) = (D)_T^*\left[\frac{(H^+)}{Ka + (H^+)}\right] \text{ and}$$

$$(D^-) = (D)_T^*\left[\frac{Ka}{Ka + (H^+)}\right]$$

then

$$(D)_T = (D)_T^*\left\{\left[\frac{H^+}{Ka + (H^+)}\right][1 + K'(M)] + \left[\frac{Ka}{Ka + (H^+)}\right][1 + K''(M)]\right\} \therefore$$

$$\frac{(D)_T}{(D)_T^*} = 1 + (M)\left[\frac{(H^+)K' + KaK''}{Ka + (H^+)}\right] \quad \text{(Eq. 6)}$$

A plot of $(D)_T/(D)_T^*$ *versus* (M) should give a straight line with slope equal to $[(H^+)K' + KaK'']/[Ka + (H^+)]$. From Eq. 5

$$\text{Slope} = \frac{(H^+)K' + KaK''}{Ka + (H^+)} = XK' + (1 - X)K''$$

If the slope of $(D)_T/(D)_T^*$ *versus* (M) is plotted

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versus X, the intercept at $X = 0$ is K'', and at $X = 1$ is K'. K' and K'' as previously defined are the partition coefficients of the free and ionized acid, respectively. Given (D), Ka, K', and K''

$$(D)_T = (D)\left\{1 + K'(M) + \frac{Ka}{(H^+)}[1 + K''(M)]\right\}$$

may be used to calculate total drug solubility at any pH and surfactant concentration.

The following equations derived from preceding considerations are listed for information and hold at all concentrations of drug, at saturation or below, subject to the assumptions made previously.

$(D)/(D)_T$ = fraction of drug present as free acid

$$= \left\{1 + K'(M) + \frac{Ka}{(H^+)}[1 + K''(M)]\right\}^{-1}$$

$(D^-)/(D)_T$ = fraction of drug present as ionized acid

$$= \left\{1 + K''(M) + \frac{(H^+)}{Ka}[1 + K'(M)]\right\}^{-1}$$

$[D]/(D)_T$ = fraction of drug present as free acid in the micelles

$$= \left[1 + \frac{1}{K'(M)} + \frac{Ka}{K'(H^+)(M)} + \frac{K''Ka}{K'(H^+)}\right]^{-1}$$

$[D^-]/(D)_T$ = fraction of drug present as ionized acid in the micelles

$$= \left[1 + \frac{1}{K''(M)} + \frac{(H^+)}{K''Ka(M)} + \frac{K'(H^+)}{K''Ka}\right]^{-1}$$

The forms of the equations given above will remain essentially the same for the case of a drug having a single basic functional group. Consider the protonated base as analogous to the ionized acid discussed earlier and define K' and K'' as the partition coefficients of the free and protonated forms of the base, respectively. By substituting Kw/Kb for (H^+), and (H^+) for Ka in the previous equations, one obtains expressions peculiar to a basic drug with dissociation constant Kb.

EXPERIMENTAL

Materials.—Methylprednisolone hemi-β,β'-dimethylglutarate, methylprednisolone hemiglutarate, and methylprednisolone hemisuccinate were recrystallized from water-alcohol and micronized. Procaine hydrochloride U.S.P., procaine base (B. L. Lemke & Co., Inc.), and polysorbate 80 (Atlas Powder Co.) were used without purification.

Equilibration.—The apparent solubilities of three methylprednisolone hemiesters and procaine base in buffered aqueous solutions of polysorbate 80 have been studied by equilibration of the drugs with the solvent and subsequent analysis of total drug in solution. Solubilities of the steroids were determined by shaking an excess of the hemiesters with 5 ml. of buffer containing the surfactant. Equilibration was carried out in 6-ml. vials with butyl closures for periods of at least 48 hours. Procaine solubilities were determined in a similar manner, except that a 3-hour equilibration time was sufficient.

Temperatures were maintained ±0.01° in all cases. Solutions of steroid were buffered between pH's of 3 and 7 using a combination of 0.1 *M* tri-(hydroxy methyl)-aminomethane and 0.1 *M* β,β'-dimethylglutaric acid titrated to the desired pH with concentrated HCl or NaOH solution. Procaine solutions were studied in the pH range 8.5 to 9.4 with 0.5 *M* ammonium hydroxide - HCl buffers. Hydrolysis of polysorbate 80 was negligible under these conditions over the time intervals involved.

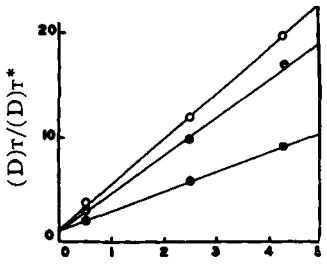

Fig. 1.—Plot of $(D)_T/(D)_T^*$ *vs.* per cent w/v polysorbate 80 for aqueous solutions of methylprednisolone DMG at 25°C. Key: ○, pH 3.0; ⊖, pH 4.8; ●, pH 6.9 in 0.1 *M* tris buffers.

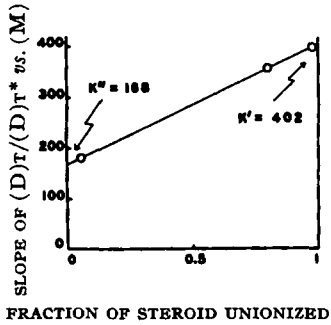

Fig. 2.—Graph showing the slopes of the lines of Fig. 1 plotted *vs.* the fraction of methylprednisolone DMG unionized. The intercepts are the partition coefficients of the free acid (K') and that of the ionized acid (K'').

Assay Procedure.—Filtered aliquots of the steroid solutions were diluted with 95% alcohol and analyzed for steroid content spectrophotometrically at 243 mμ. Procaine solutions were treated in the same way, except that absorption measurements were made at 271.5 and 288 mμ and the procaine content calculated by the method of Higuchi *et al.* (10). This method was employed since it was desired to avoid interference by *p*-aminobenzoic acid which is formed upon hydrolysis of procaine. Vials containing only the buffer and surfactant solutions, treated in the same way as the samples, served as blanks for both the steroid and procaine analyses. In no case was a shift in absorption maxima observed as a result of the presence of surfactant. All spectrophotometric determinations were made with a Beckman model DU spectrophotometer.

RESULTS AND DISCUSSION

Data were plotted in accordance with theory for methylprednisolone hemi-β,β'-dimethylglutarate, methylprednisolone hemiglutarate, methylprednisolone hemisuccinate, and procaine. Good agreement with theory was found in all cases. A typical plot of $(D)_T/(D)_T^*$ *versus* per cent w/v polysorbate 80 is shown in Fig. 1 for methylprednisolone hemi-β,β'-dimethylglutarate. Good linearity is evident over the pH range 3.0 to 6.9.

Figure 2 plots the slope of $[(D)_T/(D)_T^*$ *versus*

TABLE I.—PARTITION COEFFICIENTS IN BUFFERED AQUEOUS SOLUTIONS OF POLYSORBATE 80

Compd.	Temp., °C.	K'	K''
Methylprednisolone hemi-β,β'-dimethylglutarate	13.8	534	158
	25.0	402	168
	34.8	390	125
	45.2	358	102
	55.3	312	77
Methylprednisolone hemi-succinate[a]	25.0	400	22
Methylprednisolone hemi-glutarate[a]	25.0	680	43
Procaine	30.0	53	11

[a] Polysorbate 80 purified by the method of Malkemus and Swan (11).

TABLE II.—DISSOCIATION CONSTANTS IN AQUEOUS SOLUTIONS AT SATURATION

Compd.	Temp., °C.	Dissociation Constant
Methylprednisolone hemi-β,β'-dimethylglutarate[a]	25.0	4.0×10^{-6}
Methylprednisolone hemi-glutarate	25.0	2.7×10^{-5}
Methylprednisolone hemi-succinate	25.0	1.5×10^{-5}
Procaine	30.0	1.6×10^{-5}

[a] No change in the value observed at 25° was noted over the temperature range studied.

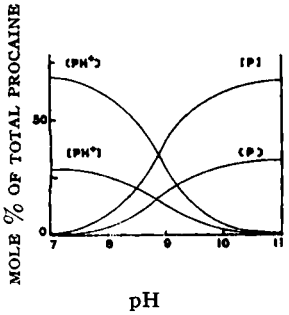

Fig. 3.—Graph showing the fraction of procaine present in various solvated states in 4% aqueous solutions of polysorbate 80. Calculations are for systems at 30°C. buffered with 0.5 *M* ammonium hydroxide–ammonium chloride. Key: (PH^+), protonated procaine in the bulk of the solution; (P), free procaine in the bulk of the solution; [PH^+], protonated procaine in the micelles; [P], free procaine in the micelles.

(M)] *versus* X, the fraction of drug unionized. Again, good linearity indicates close conformity with theory. Extrapolation of the curve to $X = 0$ and $X = 1$ gives the partition coefficients of ionized and free drug. K'' represents the partition coefficient of ionized acid for an acidic drug or protonated base in the case of a basic drug. Table I presents partition coefficients of procaine and the selected steroids between polysorbate 80 micelles and the bulk of the solutions.

In methylprednisolone hemi-β,β'-dimethylglutarate, determinations were made at several temperatures and the enthalpy of partitioning calculated. ΔH for the over-all process was −2.2 Kcal. per mole for the undissociated acid and −4.7 Kcal. per mole for the acid anion. The greater energy required for partitioning of the ionized acid may be due in part to the ion-dipole interaction with water which does not occur in the free acid. The lower consolute temperature of the water-polysorbate 80 system limits the temperatures over which these studies can be made. It has been reported (12) that the micelle weight increases exponentially with temperature at temperatures below the cloud point. This would indicate that the observed changes in the partition coefficients with temperature change may be partially due to the expected change in micelle size.

Acid dissociation constants of the steroid hemiesters and the base constant for procaine are given in Table II. Constants were derived from the pH dependency of solubility in the absence of surfactant. These values were used in calculation of the data presented in Table I.

A graphical representation of the procaine-polysorbate 80 system is shown in Fig. 3. The fraction of total procaine present in the indicated solvated states over the pH range 7 to 11 (4% polysorbate 80) was computed from data in Tables I and II. Similar plots can be made for systems comprising other combinations of drugs and surfactants. Such information can be useful in the determination of the relative stability of drugs within micelles and in product formulation.

CONCLUSIONS

The micellar solubilization of weakly basic and acidic compounds, represented by procaine and methylprednisolone hemiesters, can be described by equations based on the assumption that the drugs partition into the micelles.

Calculation of the concentrations of the several solvated species in solution is possible.

Given the partition coefficients and dissociation constants, total solubility can be predicted for a range of pH and surfactant concentrations.

REFERENCES

(1) Kern, C. J., and Antoshkiw, T., *Ind. Eng. Chem.*, **42**, 709(1950).
(2) Watanabe, A., *et al.*, *J. Pharm. Soc. Japan*, **75**, 1093 (1955).
(3) Mina, H., *Yakugaku Zasshi*, **78**, 983(1958).
(4) Nakagawa, T., *J. Pharm. Soc. Japan*, **74**, 858(1954).
(5) Ekwall, P., *Acta Chem. Scand.*, **7**, 347(1953).
(6) Johnson, R. H. (to The Upjohn Co.), U. S. pat. 2,880,130(1959).
(7) Johnson, R. H. (to The Upjohn Co.), U. S. pat. 2,880,138(1959).
(8) Guttman, D. E., *et al.*, THIS JOURNAL, **50**, 305(1961).
(9) Hall, N. A., *ibid.*, **52**, 189(1963).
(10) Higuchi, T., Havinga, A., and Busse, L. W., *ibid.*, **39**, 405(1950).
(11) Malkemus, J. D., and Swan, J. D., *J. Am. Oil Chemists' Soc.*, **34**, 342(1957).
(12) Balmbra, R. R., *et al.*, *Trans. Faraday Soc.*, **58**, 1661 (1962).