REFERENCES

(1) C. R. Szalkowski and W. J. Mader, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 613(1956).

(2) R. P. Haycock and W. J. Mader, *ibid.*, **46**, 744(1957).

(3) D. Banes, *ibid.*, **46**, 601(1957).

(4) R. P. Haycock, P. B. Sheth, T. Higuchi, W. J. Mader, and G. J. Papariello, *J. Pharm. Sci.*, **55**, 826(1966).

(5) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965.

(6) "National Formulary," 12th ed., Mack Publishing Co., Easton, Pa., 1965.

(7) W. J. Mader, R. P. Haycock, P. B. Sheth, and R. J. Connolly, *J. Assoc. Offic. Agr. Chemists*, **44**, 13(1961).

(8) W. J. Mader, G. J. Papariello, and P. B. Sheth, *ibid.*, **45**, 589(1962).

(9) K. B. Wrightman and W. W. Holl, *Ann. N. Y. Acad. Sci.*, **130**, 316(1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 28, 1969 from *E. R. Squibb & Sons, Inc., New Brunswick, NJ 08903*

Accepted for publication June 13, 1969.

Presented on June 6, 1969 at the Technicon International Congress on Automated Analysis, Chicago, Ill.

NOTES

Hydrophile-Lipophile Balance and Micelle Formation of Nonionic Surfactants

HANS SCHOTT

Abstract □ Comparison of the hydrophile-lipophile balance (HLB) values according to the two prevailing systems was made for two classes of nonionic surfactants, namely, ethylene oxide adducts of *n*-dodecanol and of branched nonylphenol with increasing degrees of polyoxyethylation. The two systems were shown to differ fundamentally because only one treats the HLB values as constitutive and additive. For both HLB systems, simple relationships were found between the HLB values of each class of surfactants and their critical micelle concentrations. These relationships had different forms for the two systems and, within the same system, different numerical values for the two classes of surfactants.

Keyphrases □ Hydrophile-lipophile balance—nonionic surfactants □ Nonionic surfactants, HLB balance—Davies, Griffin methods compared □ CMC-HLB relationships—nonionic surfactants □ Surface activity—CMC-HLB relationship

The hydrophile-lipophile balance (HLB) is a useful index for rating and selecting emulsifying agents. Griffin determined experimentally the HLB values of different surfactants (1) and derived equations which permit one to calculate the HLB value of a surfactant based on its composition (2). Davies assigned HLB group numbers to the various functional groups which make up surfactant molecules, giving positive values to the hydrophilic groups and negative values to the lipophilic ones. The summation of the products of group numbers times group frequencies gives the HLB (3). He also correlated HLB values with coalescence rates of emulsions. The statement (3) that the HLB values calculated from Davies' group numbers are in good agreement with those determined by Griffin is not correct in the case of most surfactants which are ethylene oxide adducts; this is shown below.

Correlation of the empirical HLB values with physicochemical parameters of the surfactants are rare, despite the practical value of the HLB rating system. In one of the few successful studies, HLB values were correlated with the spreading coefficient of the disperse liquid phase of an emulsion on the surface of the continuous liquid phase containing the dissolved emulsifying agent (4).

One of the surfactant properties which should be related to the HLB is the readiness with which the surfactant molecules associate into micelles, namely, the critical micelle concentration (CMC). One would expect such a relationship to exist because the more hydrophilic a surfactant is or the larger its HLB value, the lesser the tendency to form micelles and the higher its CMC. Furthermore, like the HLB, the CMC is a function of composition, at least within a homologous series of surfactants. The obvious limitation of this approach is that it can only be applied to those surfactants whose solubility in water exceeds their CMC. Surfactants used as wetting agents, detergents, solubilizing agents, and o/w emulsifying agents can be included, but not surfactants of low HLB values such as w/o emulsifiers.

HLB AND CMC RELATIONSHIPS

Two homologous series of ethylene oxide adducts, for which surface and micellar properties (CMC, micellar molecular weight and radius) have been studied extensively (5–8), will be used. These

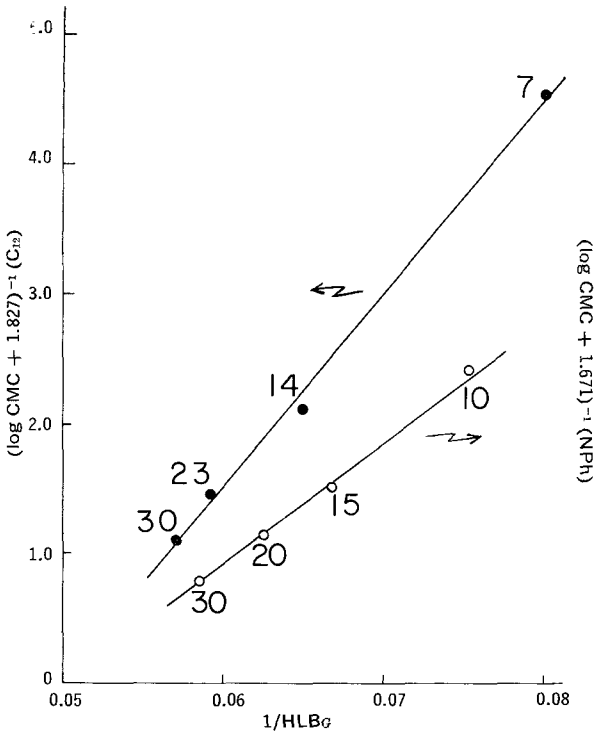


Figure 1—*Relation between Griffin HLB values and the CMC of polyoxyethylated surfactants. Key:* ●, *dodecanol adducts;* ○, *nonylphenol adducts.*

are the addition products of *n*-dodecanol (C_{12}) with 4, 7, 14, 23, and 30 ethylene oxide units, and of a branched nonylphenol (NPh) with 10, 15, 20, and 30 ethylene oxide units. Due to its random addition, the number of added ethylene oxide molecules per molecule of alcohol or phenol is an average value. All properties are given at 25°.

For ethylene oxide adducts of fatty alcohols and alkylphenols, the HLB according to Griffin (HLB_G) is

$$HLB_G = E/5 \qquad \text{(Eq. 1)}$$

where E is the weight percentage of ethylene oxide (2). According to Davies' data (3), one can express the HLB (HLB_D) by

$$HLB_D = 3.20 + 0.33n \qquad \text{(Eq. 2)}$$

for dodecanol adducts and by

$$HLB_D = 1.78 + 0.33n \qquad \text{(Eq. 3)}$$

for nonylphenol adducts; n is the number of ethylene oxide molecules per surfactant molecule.

According to Eq. 1, HLB values on the Griffin scale tend asymptotically to 20 as n increases. On the other hand, HLB values on the Davies scale increase linearly with n according to Eq. 2 and 3. For surfactants of commercial importance, the latter are smaller than the former. The Davies values reach the Griffin values at $C_{12}(EO)_{46}$ and at $NPh(EO)_{50}$ and surpass them at higher polyoxyethylene contents. Since

$$E = \frac{(100)(44.05)n}{M + (44.05)n}$$

where M is the molecular weight of dodecanol (186.3), or of nonylphenol (220.3), Eq. 1 for Griffin's HLB can be rewritten as

$$\frac{1}{HLB_G} = \frac{M}{881n} + 0.05 \qquad \text{(Eq. 4)}$$

For ethylene oxide adducts of dodecanol (6–8),

$$\log CMC = -1.827 + 0.0308n \qquad \text{(Eq. 5)}$$

and for polyoxyethylated nonylphenol (5, 7, 8)

$$\log CMC = -1.671 + 0.04304n \qquad \text{(Eq. 6)}$$

where CMC is given in g./l.

Substituting Eq. 5 and 6 into 4 gives the following relations between the Griffin HLB values and the CMC: for dodecanol adducts,

$$\frac{1}{HLB_G} = \frac{0.006513}{\log CMC + 1.827} + 0.05 \qquad \text{(Eq. 7)}$$

and for nonylphenol adducts,

$$\frac{1}{HLB_G} = \frac{0.01076}{\log CMC + 1.671} + 0.05 \qquad \text{(Eq. 8)}$$

These relations are shown in Fig. 1, where the two straight lines represent Eq. 7 and 8 with the CMC values calculated according to Eq. 5 and 6, and the points are based on experimental CMC values; the numbers represent n. Eq. 8 can be rearranged to

$$HLB_G = \frac{\log CMC + 1.671}{0.05 \log CMC + 0.0943} \qquad \text{(Eq. 8}a\text{)}$$

Combining Eq. 2 with Eq. 5 results in the following relation between Davies' HLB and the CMC of dodecanol adducts:

$$HLB_D = 22.775 + 10.714 \log CMC \qquad \text{(Eq. 9)}$$

For nonylphenol adducts, the relation is

$$HLB_D = 14.592 + 7.667 \log CMC \qquad \text{(Eq. 10)}$$

These two relationships are shown in Fig. 2, where the numbers again refer to n.

While Davies treats HLB as an additive and constitutive property of a given surfactant molecule, neither the Griffin HLB nor the CMC are. Therefore, the lines in Figs. 1 and 2 for the dodecanol and nonylphenol derivatives are not parallel. The effect of an additional ethylene oxide unit on HLB_G and CMC of polyoxyethylated surfactants depends on the nature of the hydrocarbon moiety of their molecules.

APPENDIX

Correlation of HLB with Other Factors—There is no simple relationship between the HLB of these nonionic surfactants and the molecular weight or aggregation number of their micelles. This is not surprising since the latter two parameters are governed to some extent by geometrical factors.

There is a linear relation between the HLB value and the surface tension of surfactant solutions above the CMC (γ). Once the CMC is reached, γ decreases only very slightly with increasing surfactant concentration. For the dodecanol adducts, the relation is

$$HLB_G = 1.93 + 0.345\,\gamma \qquad \text{(Eq. 11)}$$

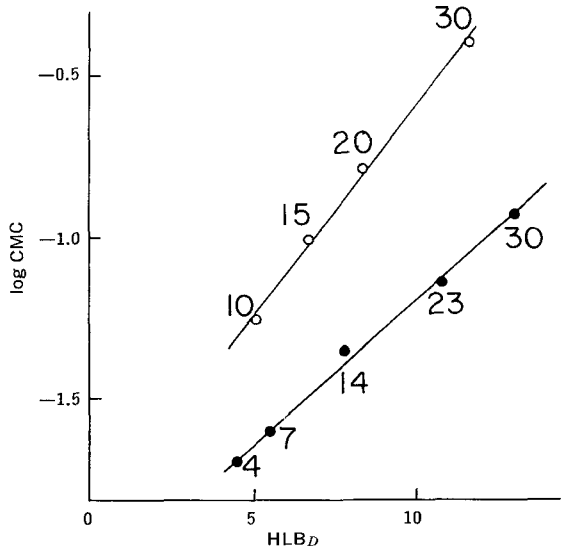


Figure 2—*Relation between Davies HLB values and the CMC of polyoxyethylated surfactants. Key:* ●, *dodecanol adducts;* ○, *nonylphenol adducts.*

and for nonylphenol adducts,

$$HLB_G = 1.55 + 0.380\,\gamma \qquad \text{(Eq. 12)}$$

The significance of these simple relations is questionable, however, in view of the different and varying behavior of the o/w interfacial tensions (9).

REFERENCES

(1) W. C. Griffin, *J. Soc. Cosmetic Chemists*, **1**, 311(1949).

(2) *Ibid.* **5**, 249(1954).

(3) J. T. Davies, *Proc. Intern. Congr. Surface Activity, 2nd, London*, **1**, 426(1957).

(4) S. Ross, E. S. Chen, P. Becher, and H. J. Ranauto, *J. Phys. Chem.*, **63**, 1681(1959).

(5) L. Hsiao, H. N. Dunning, and P. B. Lorenz, *ibid.*, **60**, 657 (1956).

(6) M. J. Schick, S. M. Atlas, and F. R. Eirich, *ibid.*, **66**, 1326 (1962).

(7) M. J. Schick, *J. Colloid Sci.*, **17**, 801(1962).

(8) H. Schott, *J. Phys. Chem.*, **68**, 3612(1964), **70**, 2966(1966).

(9) P. Becher, *J. Colloid Sci.*, **18**, 665(1963).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 14, 1969 from the *School of Pharmacy, Temple University, Philadelphia, PA 19140*

Accepted for publication April 17, 1969.

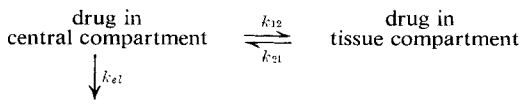
Estimation of the Pharmacokinetic Parameters of the Two-Compartment Open Model from Post-Infusion Plasma Concentration Data

MILO GIBALDI

Abstract □ A model is presented which can serve as a means for obtaining the pharmacokinetic parameters of the two-compartment open system for drugs which are too poorly soluble or too irritating to be administered by rapid intravenous injection. Experimentally, this method involves administering the drug by a constant rate intravenous infusion, until the attainment of infusion equilibrium, and determining the plasma concentrations of drug in the postinfusion period. This approach has been applied to literature data and has resulted in the evaluation of the two-compartment pharmacokinetics of oxacillin.

Keyphrases □ Pharmacokinetic parameters—two-compartment open model □ Infusion equilibrium—i.v. administration □ Post-infusion period—plasma concentration

The kinetics of distribution and elimination of a number of drugs may be described adequately by the two-compartment open model shown in Scheme I (1, 2).



Scheme I

The usual method of calculating the rate constants is to first determine the parameters A, B, α, and β (see Fig. 1 in *Reference 3*) from the plasma concentration of drug *versus* time plot obtained after rapid intravenous injection of the drug and to use these values for calculating the rate constants k_{12}, k_{21}, and k_{el}. However, a number of drugs are too poorly soluble, irritating, or acutely toxic to be injected rapidly. In these cases it is difficult or impossible to obtain the parameters of Scheme I. A method is presented here for determining the rate constants of the two-compartment open model which does not require rapid intravenous injection.

Often, drugs which cannot be administered as a rapid intravenous injection may nevertheless be introduced to the body in the form of a slow intravenous infusion of a dilute solution of the drug. When the drug is infused at a constant rate and is eliminated by first-order kinetics, drug levels in both the central and tissue compartments asymptotically approach, with time, a constant value and infusion equilibrium occurs. The present method is based on evaluation of plasma concentration of drug with time after attainment of infusion equilibrium. Where a drug is eliminated very slowly, then the infusion should be preceded by an intravenous loading dose (administered as rapidly as

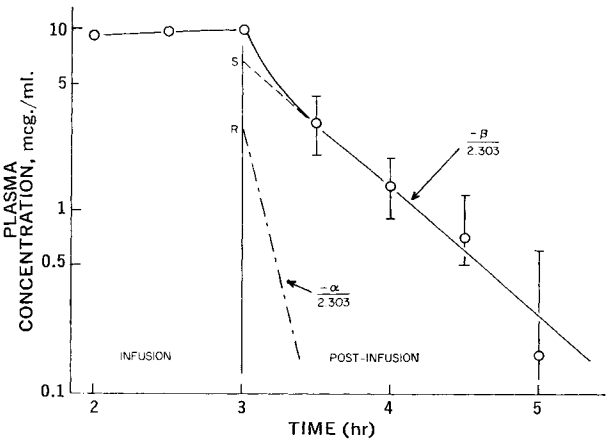


Figure 1—*Average plasma concentrations of oxacillin in four healthy subjects receiving a constant rate (0.25 g./hr.) intravenous infusion of drug for 3 hr. Experimental data* (O) *from* Reference *5. Solid curve represents nonlinear least-squares regression fit to the data.*