Mechanisms of Interphase Transport I

Theoretical Considerations of Diffusion and Interfacial Barriers in Transport of Solubilized Systems

By A. H. GOLDBERG, W. I. HIGUCHI, N. F. H. HO, and G. ZOGRAFI

Based on first principles of diffusion, equations were derived to predict transport rates of micelle-solubilized drug from its aqueous environment to an oil phase. The basic equations also take into account the possible effects of an electrical barrier between the micelle and the charged oil–water interface. These processes may be considered as being analogous to absorption of water insoluble–bile soluble drugs, and may be used to evaluate the mechanism of transport in such situations. The physical model includes the effects of the free drug-solubilized drug equilibrium, the diffusion coefficients of both free and solubilized drug, ionic strength of the aqueous medium, and the micelle size. A novel experimental approach based on the use of emulsion droplets as the "sink" is described.

MUCH RESEARCH has been carried out, particularly in the last two decades, on the mechanisms of drug absorption. These studies have led to now well-established physicochemical concepts such as the importance of the oil–water partition coefficient, and the acid-base nature of the drug.

What appears to be conspicuously absent is an attempt to study the basic diffusional processes, both theoretically and experimentally with well-defined models. Such a study should provide a unified approach for explaining some of the discrepancies in the existing qualitative theories, and also suggest new rate-determining mechanisms for drug absorption. The authors are not so naive as to think that the simple laws of physical chemistry can generally describe so complex a subject as drug absorption. What is contended, however, is that where qualitative physicochemical relationships are established or expected, it is more than worthwhile to attempt to describe them on mechanistically quantitative bases.

DISCUSSION

The present communication is related to an aspect of drug absorption that has recently attracted some interest (1–4), *viz.*, the role of micellar solubilization. The theory governing the diffusion of both the solubilized and the free drug from an aqueous environment to a lipoidal interface is presented. The various interfacial boundary conditions influencing the rate of transport between phases have been considered. In order to study the transport rate theory, a novel experimental technique, which is based on the use of micron-sized oil emulsion droplets as a lipoidal "sink," has been developed.

Past Studies on Micellar Solubilization and Drug Absorption

The earliest studies involving micellar solubilization and biological availability were concerned with the activity of germicides in soap solutions (4–6). Allawala and Riegelman (7, 8) postulated that the thermodynamic activity of the free drug is the driving force behind the effectiveness of germicides dissolved in surfactant solutions.

Based on such studies, one would expect that if a surfactant is added to a solution of a drug in a concentration high enough to exceed its CMC, the drug's thermodynamic activity would be reduced. We would, therefore, expect a decrease in rate of transport because of a reduced driving force. This was shown by Levy *et al.* (1), who measured the absorption rates of secobarbital by goldfish in the presence of polysorbate 80 solutions.

To evaluate the effect of increasing surfactant concentration on the rate of transport of a solubilized drug, Matsumoto *et al.* (2, 3) used a cellulose membrane dialysis technique. These workers mathematically derived an equation for transport, based on the laws of diffusion and the concentration of free drug. Their experimental values matched their theoretical values only when no great interaction between the drug and the surfactant was observed. The degree of interaction was independently measured, and was classified as the ratio (r) of *total drug in solution* to *free drug*. When the values of r were four or greater,[1] the rates of transport exceeded the rates predicted. They postulated that this discrepancy was due to the transport of drug directly from the micelle. In these studies, it had been initially assumed that the micelles containing drug did not contribute to the transport phenomena. Matsumoto *et al.* (2, 3) eventually considered this a possibility, but only at high r values. According to their interpretation, however, it was not due to diffusion of the micelles, but rather to the coalescence of the micelles with the membrane. What was not considered was an enhanced flux that can be attributed to the diffusion of drug-containing micelles.

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[1] In these experiments, the r value of the drug used is about 800, at a 1% polysorbate 80 concentration.

Present Considerations

In the transport of a drug from an aqueous solubilized system to an oil phase, the flux consists of the transport of the free drug and that of the solubilized drug (9). The solubilized drug may be considered as an interaction product between the drug and the surfactant. In order for the solubilized drug to pass from the aqueous phase to the oil phase, it must diffuse to some point close to the oil, and then leave the micelle, unless the micelle itself enters the oil. The greater the drug–surfactant interaction, the greater is the role played by the drug-containing micelle in the transport process.

There are several mechanisms by which a drug can leave a micelle. In the simplest case, where a nonionic drug is solubilized by a nonionic surfactant, we postulate that it is simply diffusion from the micelle, close to the oil "sink." In the case of drug in a charged micelle approaching a charged surface, there may be a strong electrical effect, either repulsive or attractive.

To study these ideas a procedure was conceived which involves the use of micron-sized oil emulsion droplets as a sink for the drug. There are a number of advantages, both theoretical and experimental, in employing such a system instead of one involving two or more bulk phases as has been done by some investigators (10). First, even when the rates of interphase transfer are purely diffusion controlled in the external (aqueous) phase, the results are relatively insensitive to the rate of agitation of the medium over a wide range of shear rates, and the infinite-sink, steady-state mathematics may be applied to the data. This is to be expected from hydrodynamic considerations and from the theory of diffusion involving small spheres. As a result, the data may be directly evaluated with diffusion theory without invoking the empirical "effective" diffusion layer thickness ideas which have been the major cause of difficulties in past studies (10). Another advantage is that, because droplet distortion is likely to be negligible for such small droplets, it is safe to assume in most instances that surface-active agents will not alter the effective surface area of the droplets as they frequently do in the case of large interfaces. Finally, it can be shown that rate experiments with small droplets are much more sensitive to interfacial resistances. Based on the estimated diffusion layer thickness of 200 to 400 μ from the studies of Rosano *et al.* (10), experiments with sinks consisting of micron-sized oil droplets should be more than a hundred times more sensitive to interfacial resistances.

Case A—*Simple Diffusion*—For the first case to be considered, that of diffusion of a nonionic drug from a nonionic surfactant, a planar model will be presented first, and then rederived for the case of spherically symmetric transport to an oil droplet. This derivation is based solely upon the principles of diffusion. A graphical representation for the planar diffusion case is shown in Fig. 1.

If the transport rate of the drug is diffusion controlled, then the rate of uptake by the oil is equal to the rate of transport through the aqueous phase. The steady-state rate of diffusion in the aqueous phase can be denoted by:

$$G = \left(A\, D_d \frac{dC_d}{dl} + A\, D_{dm} \frac{dC_{dm}}{dl}\right) \qquad \text{(Eq. 1)}$$

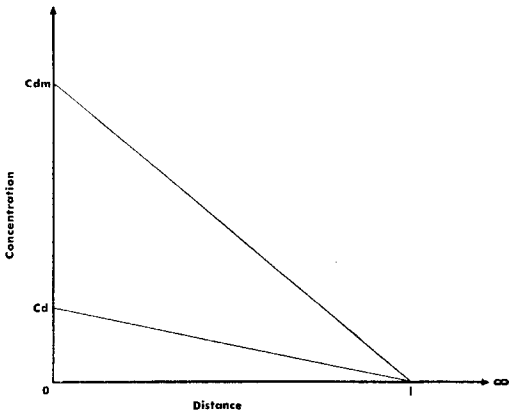

Fig. 1—Illustration of the planar model of diffusion. Key: C_{dm} *= concentration of drug in the micelles;* C_d *= concentration of free drug* l *= diffusion layer thickness.*

Where G = the steady-state rate of transport through the aqueous phase to the oil droplet, A = the area, D = the diffusion coefficients,[2] and dC/dl = the concentration gradients. If the area is maintained constant, Eq. 1 can be rearranged to:

$$\frac{G}{A}\, dl = D_d\, dC_d + D_{dm}\, dC_{dm} \qquad \text{(Eq. 2)}$$

Integration from $l = 1$ to $l = 0$ gives:

$$\frac{G}{A}\, l = D_d(\Delta C_d) + D_{dm}(\Delta C_{dm}) \qquad \text{(Eq. 3)}$$

Considering the transport from an aqueous phase to an oil phase which acts as a "perfect sink," (ΔC) can be denoted as (C^b-C^s), where C^b is the bulk aqueous concentration, and C^s is the concentration of the drug very close to the oil phase. The steady-state rate of diffusion is then finally denoted by:

$$G = \frac{A}{l}\left[D_d\,(C_d{}^b - C_d{}^s) + D_{dm}(C_{dm}{}^b - C_{dm}{}^s)\right] \qquad \text{(Eq. 4)}$$

The integral of this rate, with respect to time, should be equal to the uptake of the drug by the oil, and is expressed as:

$$\int G dt = C_{do} V \qquad \text{(Eq. 5)}$$

where C_{do} = the concentration of the drug in the oil, and V = the volume (ml./ml.) of the oil. Differentiation of both sides of Eq. 5 then expresses the rate of change of the concentration of the drug in the oil with respect to time, and is denoted by:

$$G = V \frac{dC_{do}}{dt} \qquad \text{(Eq. 6)}$$

Substitution for G from Eq. 4 gives:

$$\frac{A}{l}\left[D_d\,(C_d{}^b - C_d{}^s) + D_{dm}\,(C_{dm}{}^b - C_{dm}{}^s)\right] = V \frac{dC_{do}}{dt} \qquad \text{(Eq. 7)}$$

[2] Subscript d = free drug; subscript dm = drug in the micelles.

There are several relationships that can be used to reduce Eq. 7 to one equation with one unknown.

It has frequently been observed (11) that above the critical micelle concentration:

$$C_{dm} = KC_dC_{saa} \quad \text{(Eq. 8)}$$

where K = the pseudoequilibrium constant relating C_{dm} to C_d, and C_{saa} = the concentration of surfactant. If we assume that this relationship holds, then the substitution of Eq. 8 into Eq. 7 gives:

$$\frac{A}{l}\left[D_d\left(\frac{C_{dm}{}^b}{KC_{saa}} - \frac{C_{dm}{}^s}{KC_{saa}}\right) + D_{dm}(C_{dm}{}^b - C_{dm}{}^s)\right] = V\frac{dC_{do}}{dt} \quad \text{(Eq. 9)}$$

If the (KC_{saa}) terms in the denominator are factored, we can then factor $(C_{dm}{}^b\text{-}C_{dm}{}^s)$ to give:

$$\frac{A}{l}\left(\frac{D_d}{KC_{saa}} + D_{dm}\right)(C_{dm}{}^b - C_{dm}{}^s) = V\frac{dC_{do}}{dt} \quad \text{(Eq. 10)}$$

We now have only three concentration terms that are unknown.

We may base the analysis on a total emulsion volume of 1 ml. Then:

$$T = C_{do}V + C_{aq.}(1 - V) \quad \text{(Eq. 11)}$$

where T = the total amount of drug present and $C_{aq.}$ = the drug concentration in the aqueous phase. However, $C_{aq.}$ can be taken as $(C_{dm}{}^b + C_d{}^b)$. Inserting this into Eq. 11 and substituting for $C_d{}^b$ from Eq. 8, we arrive at:

$$T = C_{do}V + C_{dm}{}^b\left(1 + \frac{1}{KC_{saa}}\right)(1 - V) \quad \text{(Eq. 12)}$$

Rearrangement of Eq. 12 gives:

$$C_{dm}{}^b = \frac{T - C_{do}V}{\left(1 + \frac{1}{KC_{saa}}\right)(1 - V)} \quad \text{(Eq. 13)}$$

To relate $C_{dm}{}^s$ to C_{do}, we can use the apparent partition coefficient. The true partition coefficient for a drug between oil and water is given by:

$$PC_{o/w} = \frac{C_{do}}{C_d{}^s} \quad \text{(Eq. 14)}$$

The apparent partition coefficient may be expressed as:

$$PC_{app.} = \frac{C_{do}}{C_{aq.}} = \frac{C_{do}}{C_d{}^s + C_{dm}{}^s} \quad \text{(Eq. 15)}$$

Taking the reciprocal of Eq. 15 gives:

$$\frac{1}{PC_{app.}} = \frac{1}{PC_{o/w}} + \frac{C_{dm}{}^s}{C_{do}} \quad \text{(Eq. 16)}$$

Equation 16 rearranges to:

$$C_{dm}{}^s = C_{do}\left[\frac{1}{PC_{app.}} - \frac{1}{PC_{o/w}}\right] \quad \text{(Eq. 17)}$$

Substitution of Eqs. 13 and 17 into Eq. 10 yields:

$$\frac{A}{l}\left\{\left(\frac{D_d}{KC_{saa}} + D_{dm}\right)\times\left(\frac{T - C_{do}V}{\left(1 + \frac{1}{KC_{saa}}\right)(1 - V)} - C_{do}\left[\frac{1}{PC_{app.}} - \frac{1}{PC_{o/w}}\right]\right)\right\} = V\frac{dC_{do}}{dt} \quad \text{(Eq. 18)}$$

The C_{do} terms can be factored to give:

$$\frac{A}{l}\left\{\left(\frac{D_d}{KC_{saa}} + D_{dm}\right)\times\left[\frac{T}{\left(1 + \frac{1}{KC_{saa}}\right)(1 - V)} - C_{do}\left(\frac{V}{\left(1 + \frac{1}{KC_{saa}}\right)(1 - V)} + \left(\frac{1}{PC_{app.}} - \frac{1}{PC_{o/w}}\right)\right)\right]\right\} = V\frac{dC_{do}}{dt} \quad \text{(Eq. 19)}$$

We can collect constants, and let:

$$\alpha = \frac{T}{\left(1 + \frac{1}{KC_{saa}}\right)(1 - V)} \quad \text{(Eq. 20)}$$

and

$$\beta = \frac{V}{\left(1 + \frac{1}{KC_{saa}}\right)(1 - V)} + \left(\frac{1}{PC_{app.}} - \frac{1}{PC_{o/w}}\right) \quad \text{(Eq. 21)}$$

Insertion of Eqs. 20 and 21 into Eq. 19 and rearrangement yields:

$$\frac{dC_{do}}{\alpha - \beta C_{do}} = \left(\frac{D_d}{KC_{saa}} + D_{dm}\right)\frac{A}{lV}\,dt \quad \text{(Eq. 22)}$$

Integration of t from 0 to t and of C_{do} from 0 to C_{do} gives:

$$\ln\left(\frac{\alpha}{\alpha - \beta C_{do}}\right) = \left(\frac{\beta A}{lV}\right)\left(\frac{D_d}{KC_{saa}} + D_{dm}\right)t \quad \text{(Eq. 23)}$$

A plot of the lefthand side of this function *versus* time should yield a straight line going through the origin, with a slope of $(\beta A/lV)\,(D_d/KC_{saa} + D_{dm})$.

If we now derive this equation for small spheres, we can graphically represent the model as in Fig. 2.

By rewriting Eq. 1 and replacing the area (A) by the area of a sphere, Eq. 1 becomes:

$$G = 4\pi r^2\left(D_d\frac{dC_d}{dr} + D_{dm}\frac{dC_{dm}}{dr}\right) \quad \text{(Eq. 24)}$$

where $\frac{dC}{dr}$ = the concentration gradient as a function of the radius. Equation 24 rearranges to:

$$\frac{dr}{r^2} = \frac{4\pi}{G}(D_d\,dC_d + D_{dm}\,dC_{dm}) \quad \text{(Eq. 25)}$$

Integration from $r = \infty$ to $r = a$, gives:

$$\frac{1}{a} = \frac{4\pi}{G}(D_d\Delta C_d + D_{dm}\Delta C_{dm}) \quad \text{(Eq. 26)}$$

or, with rearrangement and insertion of the same

concentration notations as in Eq. 4, it becomes:

$$G = 4\pi a[D_d (C_d^b - C_d^s) + D_{dm} (C_{dm}^b - C_{dm}^s)] \quad \text{(Eq. 27)}$$

The $4\pi a$ term has come from the derivation for a single sphere; however, for an emulsion that has a narrow distribution of oil droplet sizes, this can be replaced by $n4\pi a$, where n is the number of droplets. Since in a dilute, stable emulsion this term is constant with time, we can assign it the constant value A.

If we now make the same substitutions as were made for the planar case, the final equation becomes:

$$\ln\left(\frac{\alpha}{\alpha - \beta C_{do}}\right) = \frac{\beta A}{V}\left(\frac{D_d}{KC_{saa}} + D_{dm}\right) t \quad \text{(Eq. 28)}$$

The only difference between this equation and Eq. 24 for the planar model is the disappearance of (l), the size of the diffusion layer.

Equation 28 may also be rewritten to give:

$$C_{do} = \frac{\alpha}{\beta}\left\{1 - \exp.\left[-\frac{\beta A}{V}\left(\frac{D_d}{KC_{saa}} + D_{dm}\right) t\right]\right\} \quad \text{(Eq. 29)}$$

Every term, excluding C_{do}, can be independently determined. From such data, C_{do} values can be predicted for any value of time, and can be compared to the C_{do} values experimentally obtained.

There have been several assumptions made in the derivation of these equations. The first is that there exists a K between C_{dm} and C_d that holds below, as well as at saturation. It also has been assumed that the apparent partition coefficient expression correctly represents the relationship between C_{do} and C_{dm}^s. Both these assumptions can be shown to be valid with appropriate experiments.

Case B—*Electrical Effects*—The second case, that of a charged micelle diffusing to a charged lipid interface, will be presented for spheres directly. This is illustrated in Fig. 3. The steady-state rate of diffusion now has an additional term added that considers the force field of the electrical barrier. The expression for the rate becomes:

$$G = 4\pi r^2 \times \left[D_d \frac{dC_d}{dr} + D_{dm} \frac{dC_{dm}}{dr} + \frac{D_{dm}}{kT} C_{dm} \frac{dV^o}{dr}\right] \quad \text{(Eq. 30)}$$

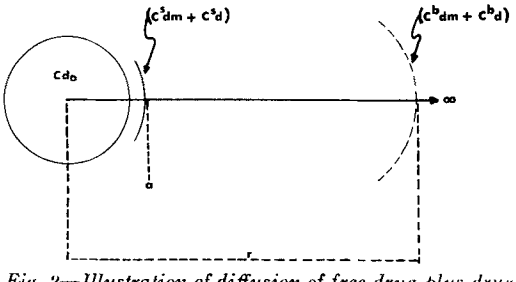

Fig. 2—Illustration of diffusion of free drug plus drug in the micelles from the aqueous phase to an oil droplet "sink." Key: C_{do} *= concentration of drug in the oil;* C^s_{dm} *= concentration of drug in the micelles, at some point* (a), *arbitrarily close to the oil droplet;* C^b_{dm} *= concentration of drug in the micelles at an infinite distance (the bulk) from the oil droplet;* C_d *= concentration of free drug.*

The last term in the equation gives the influence of the electrical interaction upon the rate. Here V^o is the potential energy of interaction of the micelle with the charged oil–water interface. The factor, $(D_{dm}/kT)(dV^o/dr)$, is the average micellar velocity contribution due to the force. The k and T are the Boltzmann constant and the absolute temperature.

We may substitute for C_{dm} from Eq. 8 into Eq. 30. This gives:

$$G = 4\pi r^2 \left[D_d \frac{dC_d}{dr} + D_{dm}KC_d \frac{dC_{saa}}{dr} + D_{dm}KC_{saa} \frac{dC_d}{dr} + \frac{KC_dD_{dm}}{kT} C_{saa} \frac{dV^o}{dr}\right] \quad \text{(Eq. 31)}$$

Taking the case where the transport rate of the surface-active agent itself is zero, we may write:

$$C_{saa} = C^b_{saa} \exp.(-V^o/kT) \quad \text{(Eq. 32)}$$

where C^b_{saa} is the surfactant concentration at infinity. Equation 32 states that the micelle distribution obeys the usual Boltzmann distribution.

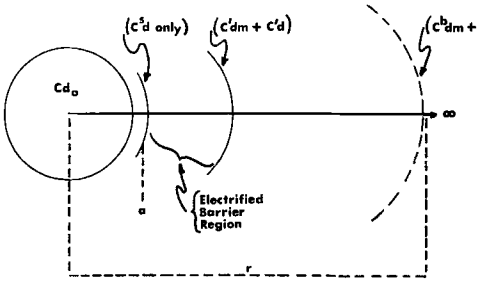

Fig. 3—Illustration of diffusion of free drug plus drug in the micelles freely diffusing to some distance from the oil droplet, where an electrical barrier permits only free drug to diffuse to some point (a), *arbitrarily close to the oil droplet. Key:* C_{do} *= concentration of drug in the oil;* C_d *= concentration of free drug;* C_{dm} *= concentration of drug in the micelles; superscript* s *= surface,* b *= bulk, and the prime = the concentration at the start of the electrical barrier region.*

We may now substitute Eq. 32 into Eq. 31 and obtain:

$$G = 4\pi r^2 \times [D_d + D_{dm}KC^b_{saa} \exp.(-V^o/kT)] \frac{dC_d}{dr} \quad \text{(Eq. 33)}$$

This may be integrated as was done previously, C_d from C_d^s to C_d^b and r from a to ∞, to give:

$$G = \frac{4\pi (C_d^b - C_d^s)}{\int_a^\infty \frac{dr}{r^2 [D_d + D_{dm}KC^b_{saa} \exp.(-V^o/kT)]}} \quad \text{(Eq. 34)}$$

The integral in the denominator of Eq. 34 may be evaluated numerically. As it is constant with respect to time, it can be identified as the constant, γ.

As before, the drug transported from the aqueous phase to the oil phase can be represented by Eq. 5.

As was done for case A, we may substitute for G from Eq. 34 to give:

$$\int_0^t \frac{4\pi}{\gamma}(C_d^b - C_d^s)\,dt = C_{do}V \qquad \text{(Eq. 35)}$$

Differentiation of both sides gives:

$$\frac{4\pi}{\gamma}(C_d^b - C_d^s) = V\frac{dC_{do}}{dt} \qquad \text{(Eq. 36)}$$

By means of Eqs. 12, 15, and 36 we obtain the following equation:

$$\frac{4\pi}{\gamma}\left\{\frac{\text{tot.}}{(1 + KC_{saa}^b)(1 - V)} - C_{do}\times\left[\frac{V}{(1 + KC_{saa}^b)(1 - V)} + \left(\frac{1}{PC_{app.}(1 + KC_{saa}^b)}\right)\right]\right\} = V\frac{dC_{do}}{dt} \qquad \text{(Eq. 37)}$$

We can collect constants, and let:

$$\delta = \frac{\text{tot.}}{(1 + KC_{saa}^b)(1 - V)} \qquad \text{(Eq. 38)}$$

and also,

$$\epsilon = \left[\frac{V}{(1 + KC_{saa}^b)(1 - V)} + \frac{1}{PC_{app.}(1 + KC_{saa}^b)}\right] \qquad \text{(Eq. 39)}$$

If Eqs. 38 and 39 are substituted into Eq. 37, then rearranged and integrated from $t = 0$ to $t = t$, $C_{do} = 0$ to $C_{do} = C_{do}$, then we find that:

$$\ln\left(\frac{\delta}{\delta - \epsilon C_{do}}\right) = \frac{4\pi\epsilon}{\gamma V}t \qquad \text{(Eq. 40)}$$

This can be rewritten to:

$$C_{do} = \frac{\delta}{\epsilon}\left[1 - \exp.\left(-\frac{4\pi\epsilon}{\gamma V}t\right)\right] \qquad \text{(Eq. 41)}$$

Here, as in case A, all terms other than C_{do} can be independently determined and can be compared to experimentally obtained C_{do} values.

Discussion—A complete examination of models such as those discussed here requires extensive complementary studies of such parameters as K, $PC_{app.}$, D_d, D_{dm}, particle size, and a of the emulsion droplets, and the surface potential (actually the ζ-potential). Such studies are underway for several systems.

Preliminary results have been obtained on the transport rate of 2,3-bis(paramethoxyphenyl indole), a drug with very low water solubility. Isopropyl myristate was the emulsion oil phase with polysorbate 80 as the surfactant.

Figure 4 shows the comparison of experimental transport data for this system compared with theory (Eq. 29). The constants K, C_{saa}, α, and β were known from other experiments. However, only an estimate of the particle size of the emulsion and the diffusion coefficients, D_d and D_{dm}, were available. Therefore, the relatively good agreement is being regarded as tentative. A forthcoming communication (12) will present a full test.

Aside from the uncertainties in some of the parameters, the deviations between the experiments and theory in Fig. 4 are believed to be due to (*a*) neglect of the effects of the nonsteady-state diffusion, (*b*) the heterodispersity of the emulsion droplets, and (*c*) the effect of neighboring particles upon the particles in question. These factors are also being investigated, and it appears that all of these effects may be accounted for satisfactorily.

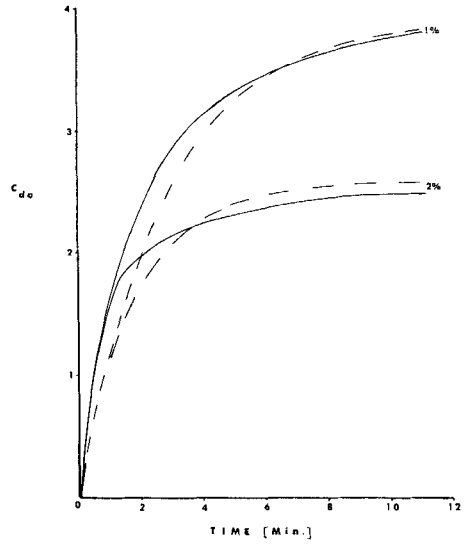

Fig. 4—Illustration of the correlation of predicted C_{do} *values to those experimentally found as a function of time. Key:* C_{do} *= concentration of drug in the oil; ——, experimental values; – – –, theoretical. The 1% and 2% refer to the concentration of polysorbate 80 present.*

Theoretical calculations of the integral in Eq. 34 have been carried out to estimate the expected electrical barrier effects upon G. The potential function, V^o, was taken to be:

$$V^o = V_A^o + V_R^o \qquad \text{(Eq. 42)}$$

where

$$V_A^o = -\frac{A}{6}\left[\frac{2a'(H + a')}{H(H + 2a')} - \ln\left(\frac{H - 2a'}{H}\right)\right] \qquad \text{(Eq. 43)}$$

is the Hamaker relation (13) for the attraction between a sphere and a plane. Here, a' is the radius of the micelle, and H is the closest distance of separation between the surface of the plane (oil droplet) and the surface of the sphere (micelle). A is the Hamaker constant, taken as 5×10^{-13} erg. V_R^o is given by:

$$V_R^o = \epsilon a'\psi_o^2 \ln\,[1 + \exp.\,(-KH)] \qquad \text{(Eq. 44)}$$

which is the electrical double layer repulsion between a sphere and a plane. ψ_o is the surface potential assumed to be the same for the micelle and the surface of the oil droplet, K is the Debye-Huckel κ, and ϵ is the dielectric constant of the medium. Equation 44 is strictly valid for the case in which $\psi_o \lesssim 25$ mv. and $a' \gg 1/K$. However, it is believed (14) to be a good approximation even for $a' \backsimeq 1/K$ and $\psi_o \backsimeq 50$ mv.

The calculations have shown that even for $\psi_o = 50$ mv., $a' = 50$ Å., and $1/K = 50$ Å., the interfacial electrical barriers may be great enough to significantly reduce G by a factor of two or more.

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Ultraviolet Spectrophotometric Determination of Chlorprothixene in Biologic Specimens

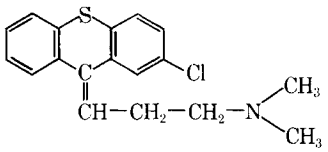
By JACK E. WALLACE

A rapid spectrophotometric method for determining chlorprothixene permits analysis of the drug in biologic specimens in the presence of its metabolites and other alkaline drugs without preliminary separation. The procedure is based upon the oxidation of chlorprothixene and its immediate metabolites to a mixture of reaction products by means of alkaline permanganate. In hexane the products have a characteristic ultraviolet absorption curve with a well-defined maximum at 233 mμ. The strong absorption at this wavelength is utilized as a basis for the analytical procedure. The method is sufficiently sensitive for the determination of chlorprothixene in urine 3 days after the ingestion of a single 50-mg. dose. Observations concerning the distribution of chlorprothixene in the rat and the excretion of the drug in man are presented.

CHLORPROTHIXENE,[1] *trans* isomer of 2-chloro-9-(13-dimethylaminopropylidene) thioxanthene, is a potent tranquilizing agent not only in acute and chronic schizophrenia but in severe psychoneuotic conditions. The chemical structure of chlorprothixene resembles that of the phenothiazines. Few methods for the determination of the drug are available in the scientific literature.

Ferrari and Toth (1) described a thin-layer chromatographic technique which identifies urinary metabolites of chlorpromazine, chlorprothixene, imipramine, and amitriptyline. Although the method is specific, it is time consuming and is not quantitative. Fluorometric procedures for determining chlorprothixene in blood and urine (2) are very sensitive, detecting 0.25-mcg. amounts of the drug, but they require the utilization of specialized analytical instruments.

Chlorprothixene strongly absorbs ultraviolet radiations, therefore, it can be determined spectrophotometrically in biologic extracts, but its strongest absorption is at 227 mμ. At that wavelength the spectral curve of the drug is often affected by background absorption and sulfoxide metabolites which induce a wide degree of variance in the ultraviolet absorbance curve, unless extensive purification of the drug extract is achieved. The method reported here is a specific spectrometric assay which requires no extensive purification procedure or no separation of unchanged drug and sulfoxides (3). The method permits a reliable evaluation of drug intake by patients treated with chlorprothixene.



Chlorprothixene

EXPERIMENTAL

Instrumentation—A Beckman DK-2A ratio recording spectrophotometer with linear presentation of the wavelength was used for the ultraviolet absorption measurements. The sample path was 10 mm. throughout. A Beckman IR-4 doublebeam infrared spectrophotometer was used for infrared spectral characterization of functional groups in the reaction products. Gas chromatographic analyses were performed by means of a Barber-Colman model 5000 gas chromatograph utilizing a 6-ft. U-shaped glass column containing 2% Carbowax 20 M on Gas-Chrom Q, 100–120 mesh. An F & M model

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[1] Marketed as Taractan by Hoffmann-LaRoche, Inc., Nutley, N. J.