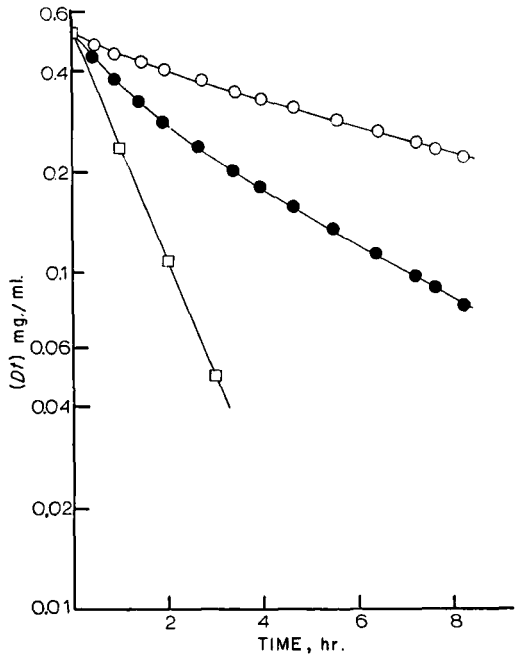

Fig. 3—The loss of methyl orange from inside a dialysis bag, in the presence and absence of BSA. The studies were run at pH 7.3 and 25°. Key: ○, 1.235% BSA; ●, 0.620% BSA; □, 0% BSA.

There is close agreement between data obtained by the two different techniques. The Scatchard plot was mathematically analyzed in terms of the fundamental binding parameters (n = number of sites in a class, k = intrinsic association constant characterizing the binding to a site) and was found to be consistent with an interaction involving two classes of sites on the protein molecule. Values for n and k are given in Table I where literature values are also shown. Figure 3 shows the dialytic behavior of methyl orange in the absence and presence of BSA. These data were analyzed in a similar manner. The binding parameters are shown in Table I and are seen to be in excellent agreement with values previously reported.

These preliminary results show the promise of this approach for studying protein binding. The relative ease and rapidity of the method, the minimum amount of sample preparation required, the convenient means of temperature control, and the economical utilization of protein are definite advantages of this approach. These factors become especially important when the supply of protein is limited or when a variety of experimental conditions such as pH or temperature are to be studied.

Studies are currently in progress to define the influences of viscosity, binding by the dialysis membrane, stirring rate, bag size, liquid volume, temperature, and other variables on rates of dialysis and the effects that these variables might have in applying this kinetic approach to the study of protein-small molecule interactions.

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M. C. Meyer
D. E. Guttman

Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Buffalo, NY 14214

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Keyphrases

Protein binding
Dialysis—protein binding determination
Diffusion—small molecules from protein containing compartment

Apparent Discrepancy Between Theory and Experimental Data for Dissolution from the Rotating Disk Under Stirred and Unstirred Conditions

Sir:

A recent article published by Gibaldi *et al.* (1), regarding the dissolution mechanism observed using a rotating disk, did not reach the same conclusions reported in our recent article (2). Their study indicated that the diffusion layer model was operative at 100 r.p.m., but could not reach a definite conclusion regarding the mechanism operative under static conditions. It is the purpose of this communication to show that their data can be used to confirm our conclusions, that the rotating disk model rather than the diffusion layer model is operative under stirred conditions and that the Danckwerts' model is operative under static conditions.

We believe that the excellent fit of their data to the diffusion layer model was intrinsic to the method used to calculate theoretical values for the mean micellar diffusion coefficient. It can be shown that the choice of models was arbitrary and that the diffusion layer model can be fitted equally well to static dissolution data. Figure 1 shows the result of using their approach to calculate a mean micellar diffusion coefficient (5.86×10^{-6} cm.^{2}/sec.) from their static rate data and assuming that the diffusion layer model is applicable. Equation 1 was used for this calculation along with their solubility data, and diffusion coefficient in water (1.2×10^{-5} cm.^{2}/sec.).

$$R = \frac{DC_s + D'C_s'}{DC_s} \qquad \text{(Eq. 1)}$$

D' is the diffusion coefficient of the micelle solubilized drug that must be calculated from the chosen model, and C_s' is the solubility increase due to micellar solubilization. D is the aqueous diffusion coefficient of the drug and C_s is the aqueous solubility of the drug. R is the ratio of the dissolution rate in surfactant solution to that in water. As expected, the diffusion layer model fits the static conditions, while the stirred data do not correspond to any of the represented models.

It has been shown (3), however, that the rotating disk dissolution rate follows the Levich equation and hence should be applied to the stirred rate data. Using their same approach, the Levich equation was used to calculate a mean micellar diffusion coefficient (0.828×10^{-6} cm.^{2}/sec.) from their stirred data. The Levich equation can be represented by the following expression:

$$R = \frac{D_{\text{eff.}}^{2/3}C_t}{D^{2/3}C_s} = \frac{(D'C_s' + DC_s)^{2/3}\,(C_s + C_s')^{1/3}}{D^{2/3}C_s} \qquad \text{(Eq. 2)}$$

In this equation C_t is the total solubility of drug, which is $C_s + C_s'$, and $D_{\text{eff.}}$ is the effective diffusion coefficient which can be written as

$$D_{\text{eff.}} = \frac{DC_s + D'C_s'}{C_s + C_s'} \qquad \text{(Eq. 3)}$$

Using the calculated mean micellar diffusion coefficient, theoretical relative dissolution rates were again determined for the Danckwerts', rotating disk, and diffusion layer models. These theoretical plots are shown in Fig. 2 and shows that the Danckwerts' theory appears to fit the static data, while the rotating disk theory fits the stirred data, as expected. The diffusion layer theory predicts considerably lower relative rates than the experimental values.

An alternate approach was also utilized, whereby the Danckwerts' model was fitted to the static rate data in order to calculate another mean micellar diffusion coefficient (1.27×10^{-6} cm./sec.). The Danckwerts' model can be given as

$$R = \frac{D_{\text{eff.}}^{1/2}C_t}{D^{1/2}C_s} = \frac{(D'C_s' + DC_s)^{1/2}\,(C_s' + C_s)^{1/2}}{D^{1/2}C_s} \qquad \text{(Eq. 4)}$$

The theoretical plots for each model can be seen in Fig. 3 and yielded essentially the same agree-

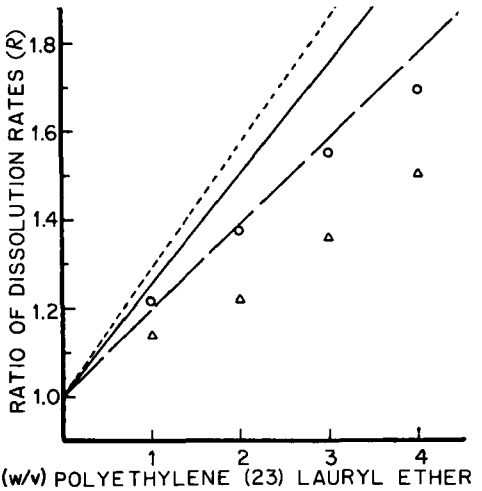

Fig. 1—Comparison of theoretical and experimental dissolution rate ratios assuming $D' = 5.86 \times 10^{-6}$ *cm.^{2}/sec., calculated from Eq. 1. Key: static, ○; 100 r.p.m., △; theoretical ratios predicted by Danckwerts' theory, ---; rotating disk theory, ——; diffusion layer theory, – – –.*

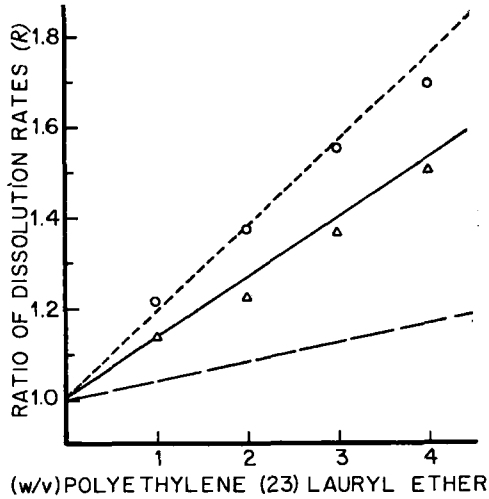

Fig. 2—Comparison of theoretical and experimental dissolution rate ratios assuming $D' = 0.828 \times 10^{-6}$ *cm.^{2}/sec., calculated from Eq. 2. Key: static, ○; 100 r.p.m., △; theoretical ratios predicted by Danckwerts' theory, ---; rotating disk theory, ——; diffusion layer theory, – – –.*

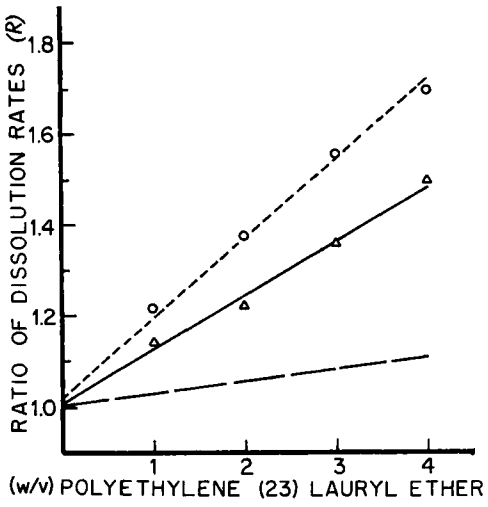

Fig. 3—Comparison of theoretical and experimental dissolution rate ratios assuming $D' = 1.27 \times 10^{-6}$ *cm.²/sec., calculated from Eq. 4. Key: static, ○; 100 r.p.m., △; theoretical ratios predicted by Danckwerts' theory, ---; rotating disk theory, ——; diffusion layer theory, – – –.*

ment between theory and experimental data as Fig. 2.

Despite this good agreement, one must be cautious when using this approach because of the assumption that the micellar diffusion coefficient remains constant with increasing surfactant concentration. Changes in viscosity, micelle interactions, micelle type, *etc.*, could significantly alter the micelle diffusion coefficient as surfactant concentration is changed. For these reasons, we feel that the approach utilized in our study should be used to clearly elucidate the specific dissolution mechanism operative under a given set of conditions, *i.e.*, the correlation of the relative dissolution rates with the corresponding effective diffusion coefficients, which are independently determined.

It also should be noted that the hydrodynamics associated with a rotating disk is such that the diffusion layer model *per se* is not applicable and the the Levich equation must be used. The rotating disk model represents one of the few instances of an exact mathematical solution to a classical hydrodynamic problem, while the diffusion layer model assumes a uniform one-dimensional diffusion layer. Therefore, this diffusion layer model cannot be applied to the diffusional flux from a rotating disk, which is influenced by both a centrifugal force and a concentration gradient. In view of this and the reasonable agreement of the Danckwerts' prediction to their static data, this analysis confirms our conclusions. Since they used a completely different drug-surfactant system from that used in our study, it appears that our conclusions are generally applicable to micellar transport systems.

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A. P. Simonelli
D. R. Flanagan
W. I. Higuchi

College of Pharmacy
The University of Michigan
Ann Arbor, MI 48104

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Keyphrases

Dissolution study—rotating disk method
Stirred conditions—diffusion layer model
Static conditions—Danckwerts' model

Books

REVIEWS

Rogers' Inorganic Pharmaceutical Chemistry. Eighth Edition. By Taito O. Soine and Charles O. Wilson. Lea & Febiger, 600 S. Washington Square, Philadelphia, PA 19106, 1967. xii + 704 pp. 15 × 23 cm. Price $12.00.

Readers familiar with previous editions of this well-known textbook will note that the most significant difference is in the discussion of the pharmacological action of the ions of each element considered. This portion of the text material has been extensively rewritten and expanded to include recent observations, to which literature references are supplied. Among these may be mentioned: lithium salts in the treatment of mania; the therapy of osteoporosis with sodium fluoride; hypopotassemia as a possible consequence of the administration of the thiazide diuretics; the internal and external action of the copper ion; silver nitrate in burn therapy; zinc compounds in wound healing and in atherosclerosis; and the mucosal block, active transport, and iron-chelate hypotheses for the absorption of