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DISSOLUTION KINETICS AND RATE-CONTROLLING MECHANISMS

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SUMMARY

The kinetics and mechanisms of dissolution in a newly designed diffusion cell were investigated. It was found that benzoic acid is an ideal compound to calibrate the fluid hydrodynamics in the diffusion cell when the mass transfer at the boundary layer is the primary contributor for its dissolution process. The dissolution of a very lipophilic drug, progesterone was also studied and the mechanisms of its dissolution process appear to be diffusion controlled. Using the dimensionless Sh-Re-Sc relationship developed earlier, it became possible to study the kinetics and mechanisms of dissolution of a solid drug. A reciprocal plot was established to obtain the kinetic constant of dissolution at the interface. This approach could be applied to investigate the kinetics of dissolution and diffusional resistance of other drugs.

INTRODUCTION

Dissolution has been defined as a process in which diffusant molecules are dissociating from the solid matrix and subsequently diffusing into

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the elution medium. The kinetics of dissolution is usually considered to be a first-order rate process with the assumption that the diffusant is leaving from the solid phase into the surrounding solution phase in the form of solute molecules rather than aggregates. Several mechanisms of dissolution have been postulated by a number of researchers; they are: diffusion control, eddy current control and surface energy barrier control (1).

The intrinsic dissolution rate, which is defined as the mass dissolved in a system with a constant area (2) and is often expressed in mg/time/cm^2, has been used to compare the dissolution characteristics of various drugs. It was suggested that a drug compound with an intrinsic dissolution rate of greater than 1 mg/min/cm^2 usually produces negligible dissolution problems, while the drug with a rate below 0.1 mg/min/cm^2 might have some dissolution problems (2).

Among the three possible dissolution mechanisms discussed by Higuchi (1), the diffusion layer model is the most popular one and has been applied extensively in both conventional dosage forms and controlled-release drug delivery systems. However, one of the dissolution concepts, which has not been clearly defined, is that to what extent does the diffusion boundary layer play a rate-limiting role in the dissolution process? And, when does the interfacial energy barrier contribute significantly in the partitioning? Furthermore, how does the flow patterns of the dissolution fluid affect the diffusion boundary layer?

Recently, the effect of fluid hydrodynamics in a diffusion cell on the release profiles of a drug has received a great deal of attention. Experimental results have demonstrated that a diffusion cell should be calibrated in advance to correct the possible variation in drug release profiles arising from the effort of hydrodynamics on the release and perme-

ation profiles so that the boundary layer effect of a very lipophilic drug such as progesterone can be corrected (3). Although the concept has long been established, a survey of literature has suggested that no investigation has been conducted to qualify benzoic acid as the representative for studying the dissolution or release profiles of various drug molecules. In other words, whether or not the effect of the physicochemical properties of a drug should be taken into consideration.

The objective of this investigation is to evaluate the effect of drug lipophilicity on the dissolution pattern. Three drugs with physicochemical properties ranging from hydrophilic to lipophilic: benzoic acid, desoxycorticosterone and progesterone were studied. Shear rate and mass transfer properties were varied by changing the viscosity and the density of the dissolution medium as well as the rotation speed in the dissolution cell. The results were analyzed by mathematical treatment and the potential in pharmaceutical applications were also elucidated.

EXPERIMENTAL

Materials

Progesterone[1], desoxycorticosterone[1], benzoic acid[2] and polyethylene glycol (PEG) 400[2] were used as obtained.

Preparation of Drug Discs

The discs in cylinder-shaped, of various drug compounds (250 mg) were prepared directly in a specially-designed disc holder (Figure 1) using a hydraulic press. The surface of the discs was found to be smooth with minimum defects.

Dissolution Kinetics Studies

A well-calibrated Ghannam-Chien (G-C) diffusion system[3] with three pairs of water-jacketed half-cells was modified to study the kinetics

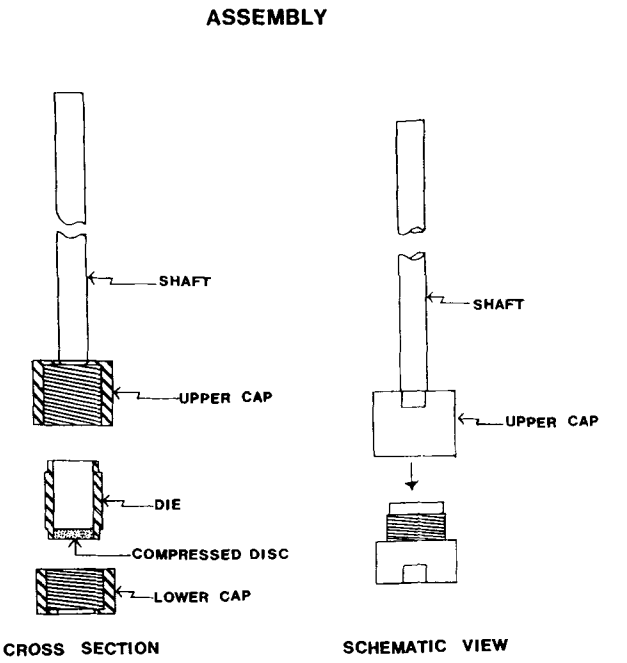

Figure 1: Diagrammatic illustration for the cross-section view of disc holder.

of dissolution from the discs. Each pair of half cells was made into two dissolution cells by partitioning an impermeable Teflon sheet in-between for duplicate studies. One hundred and seventy (170) milliliters of a dissolution medium containing 0-40% PEG 400, previously thermostated at 37°C, were charged into each dissolution cell and one unit of the modified disc holder assembly (Figure 1) was then inserted into the dissolution medium and held at a position which has a distance of 10 cm from the bottom (Figure 2). The magnets in the 6 units of dissolution cells were made to rotate at synchronized, constant speed, ranging from 125 to 900 rpm.

At predetermined intervals, 10 ml of sample was withdrawn from each of dissolution cell and immediately replaced with the same volume of drug-free elution medium to maintain a constant total volume. The samples were then analyzed by a UV/VIS spectrophotometer[4].

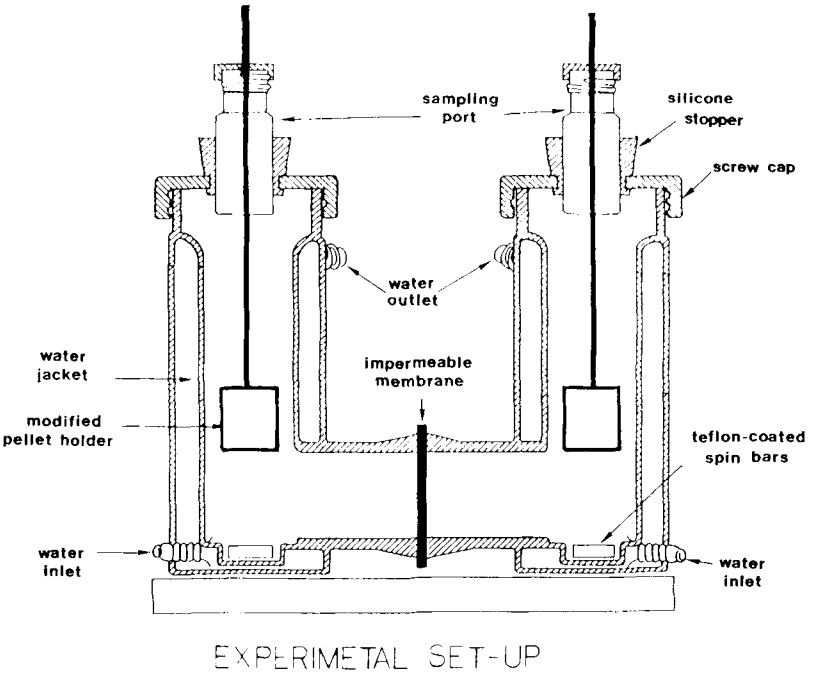

Figure 2: Diagrammatic illustration of one unit of modified G-C diffusion system for dissolution study.

RESULTS AND DISCUSSION

Several mechanisms have been proposed to describe the kinetics and rate of dissolution (3), among which the film-controlled theory is the most popular one and is defined as:

$$J = (dC/dt)(V/A) = (D/h)\ (C_s - C) = k_m\ (C_s - C) \qquad (1)$$

where J represents the flux or rate of dissolution; D is the diffusion coefficient of drug molecules in the elution medium; h is the thickness of diffusion boundary layer, C_s and C are drug concentrations at solid surface and bulk respectively, and k_m (=D/h) is the mass transfer coefficient. A dimensionless Sherwood-Reynolds-Schmidt (Sh-Re-Sc) relationship (4), defined as:

$$Sh = \text{const.}\ Re^m Sc^n \qquad (2)$$

can be correlated with the dissolution process (which is known as a mass transfer phenomenon) with the assumption that diffusion boundary layer is the predominant resistance during the dissolution process. The Sherwood number is defined as (k_m d/D), the Reynolds number as ($d\mu\rho/\eta$) and the Schmidt number as (η/ρ d), where d, a characteristic length of the magnets used; μ, a characteristic velocity of the fluid; ρ, the density of the fluid and η, the viscosity of the fluid.

The dissolution profiles of benzoic acid and progesterone in the dissolution media of 0-40% PEG 400 at a rotation speed of 425 rpm are shown in Figure 3, which clearly demonstrated the significant difference in dissolution kinetics of these two drug compounds. By plotting log $(C_s-C_o)/(C_s-C)$ against (A/V)t, linear relationship was established (Figure 4), as expected from the following equation resulting from the integral of Equation (1):

$$\log (C_s-C_o)/(C_s-C) = (A/V)(k_m)t \quad (3)$$

The mass transfer coefficient (k_m) can be directly obtained from the slope, from which the Sherwood number is calculated.

The Sh-Re-Sc relationship (Eqn. 2) was applied successfully to predict the rate of dissolution, the diffusion boundary layer and its effect on the rate of membrane permeation (4). The linear $Sh/Sc^{1/3}$ vs. Re relationship was also observed (Figure 5) for the dissolution of benzoic acid discs in this dissolution system, which can be described as

$$Sh/Sc^{13} = 0.06\ Re^{0.72} \quad (4)$$

with a correlation coefficient of 0.9666. Similar linearity was observed for progesterone as well (Figure 6), which is described by:

$$Sh/Sc^{1/3} = 0.107\ Re^{0.72} \quad (5)$$

with a correlation coefficient of 0.9738.

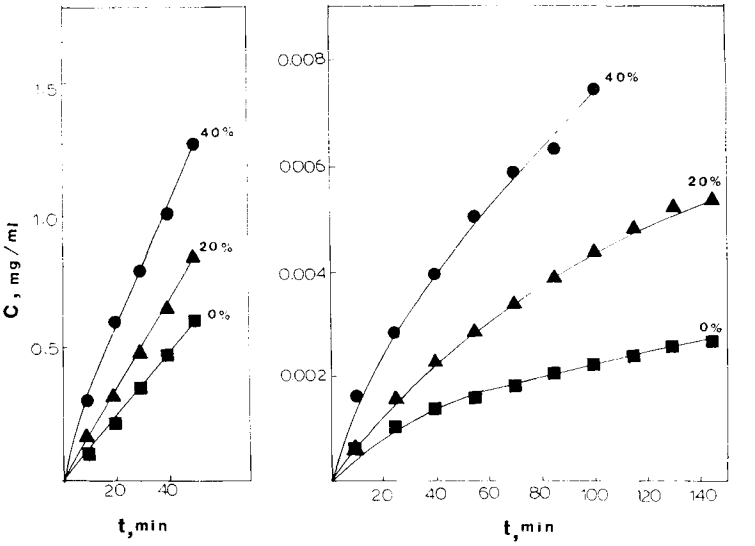

Figure 3: Dissolution profiles of benzoic acid (A) and progesterone (B) in aqueous PEG 400 solutions: (■) 0%, (▲) 20% and (●) 40%.

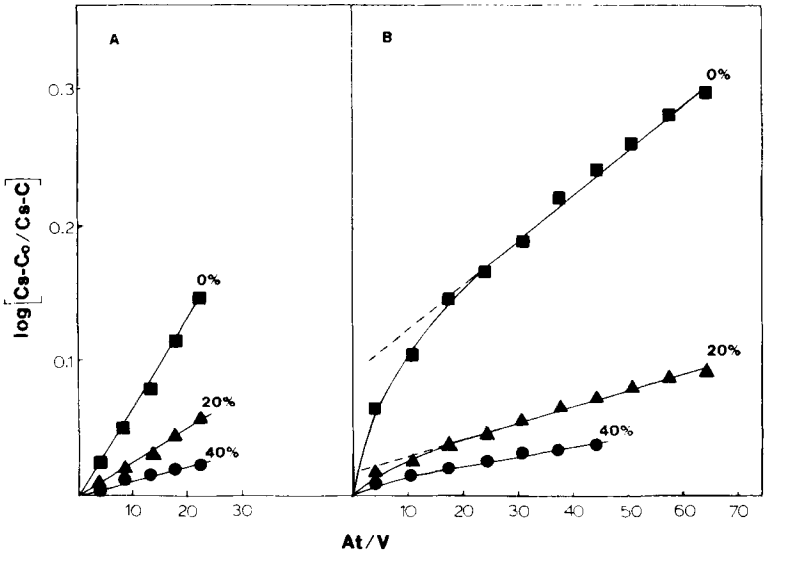

Figure 4: Linear-relationship between log $[C_s - C_0)/(C_s - C)]$ and (A/V)t of benzoic acid (A) and progesterone (B) in aqueous PEG solutions: (■) 0%, (▲) 20% and (●) 40%.

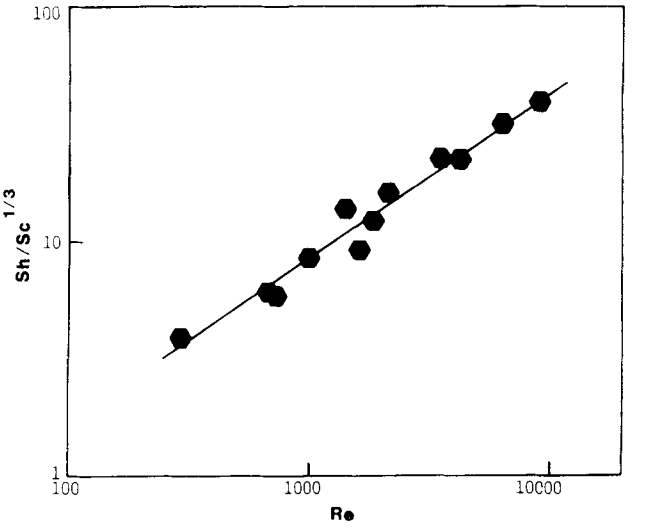

Figure 5: Linear $Sh/Sc^{1/3}$ vs. Re relationship for the dissolution of benzoic acid in the G-C modified dissolution system (Equation 4).

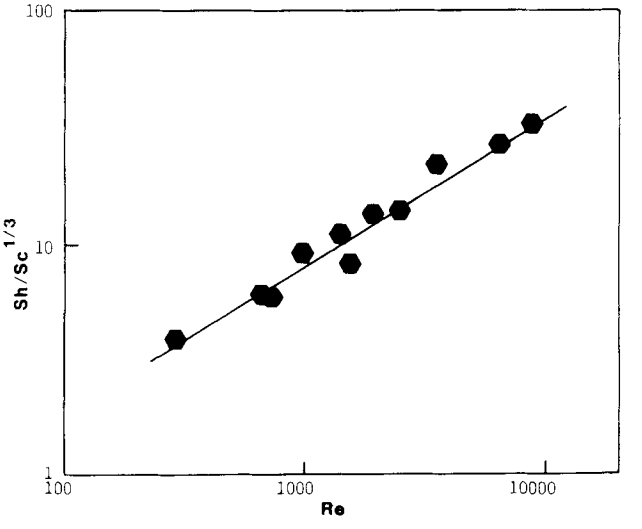

Figure 6: Linear $Sh/Sc^{1/3}$ vs. Re relationship for the dissolution of progesterone in the G-C modified dissolution system (Equation 5).

Table I: Physical Properties of Benzoic Acid and Progesterone

	PEG 400 (% V/V)	Benzoic Acid	Progesterone
Solubility	0	43.9	0.125
($\mu g/ml \times 10^2$)	20	153.6	0.48
	40	542.0	1.98
Log K*	0	1.87	3.87
Molar Volume (cm^3/ml)		104	269
Diffusivity ($cm^2/sec \times 10^6$)	0	14.5	7.0
	20	5.4	2.7
	40	2.2	1.0

*Partition Coefficient for octanol/water system.

It is interesting to observe that both benzoic acid and progesterone yield essentially the same $Sh/Sc^{1/3}$ vs. Re linearity (Equation 4 & 5), despite the great difference in their physical properties (Table I). By combining the data from benozic acid and progesterone the same $Sh/Sc^{1/3}$ vs. Re linearity was obtained:

$$Sh/Sc^{1/3} = 0.07\ Re^{0.68} \qquad (6)$$

with a correlation coefficient of 0.9800 (Figure 7). The observation suggested that the same hydrodynamic relationship are operated in the

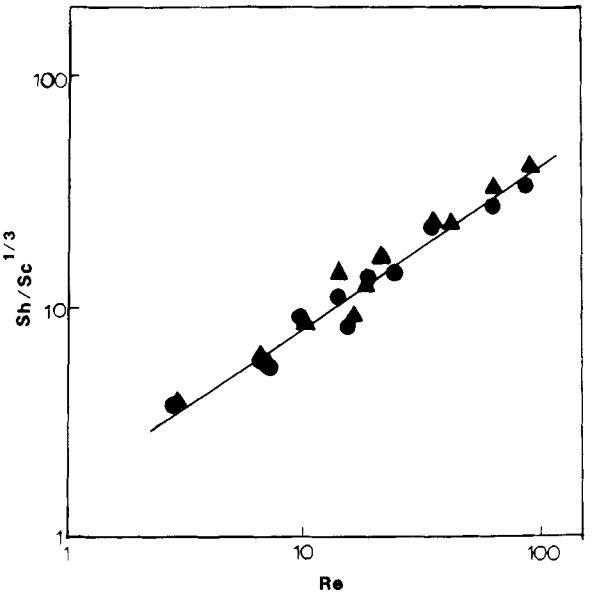

Figure 7: Linear $Sh/Sc^{1/3}$ vs. Re relationship for both (▲) benzoic acid and (●) progesterone.

G-C diffusion system for both benzoic acid, a water-soluble compound, and progesterone, a hydrophobic compound, as long as the system has been well calibrated hydrodynamically. The results also confirmed that the film theory is obeyed for the dissolution of both water-soluble and water-insoluble compounds.

On the other hand, for those compounds of which the interfacial energy barrier might also play an important role in addition to the diffusional resistance discussed above in the dissolution process, the interfacial kinetics has to be considered:

$$J = (dC/dt)(V/A) = k'(C_s - C) \quad (7)$$

where k' is the interfacial rate constant for a first-order reaction. For instance, the linear $Sh/Sc^{1/3}$ vs. Re relationship for the dissolution

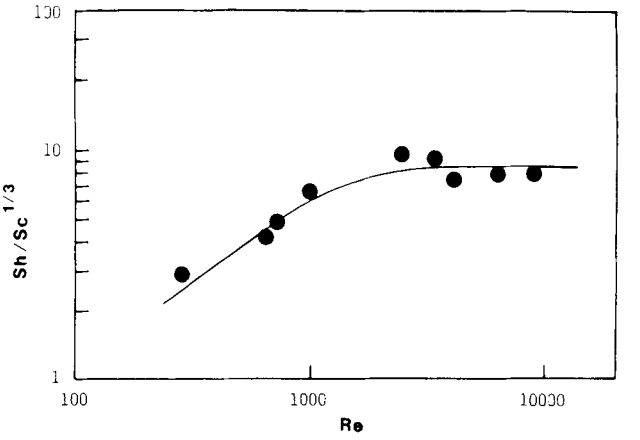

Figure 8: Sh-Re-Sc correlation for the dissolution of desoxycorticosterone.

of desoxycorticosterone can only be achieved with Reynolds number less than 1,000, i.e., at low rotation speed or in a high viscosity elution medium (Figure 8). Also, non-linearity was observed for the dissolution of desoxycorticosterone as compared to that for benzoic acid and progesterone when the apparent dissolution constant (k*, which consists of the diffusional resistance at hydrodynamic boundary layer and the kinetic resistance at the interfacial energy barrier) was plotted against rotation speed ranging from 0-900 rpm (Figure 9). The results suggest that the contribution from the interfacial barrier is more pronounced for desoxycorticosterone with the increase in the rotation speed.

The rationale of analyzing dissolution rate in conjunction with the kinetic resistance at the interfacial energy barrier is originated from the merger of diffusion boundary layer and interfacial energy barrier, which can be expressed mathematically as follows:

$$\text{Since } J = \frac{(D/h)(C_s - C)}{[1 + (D/h)(1/k')]} \qquad (8)$$

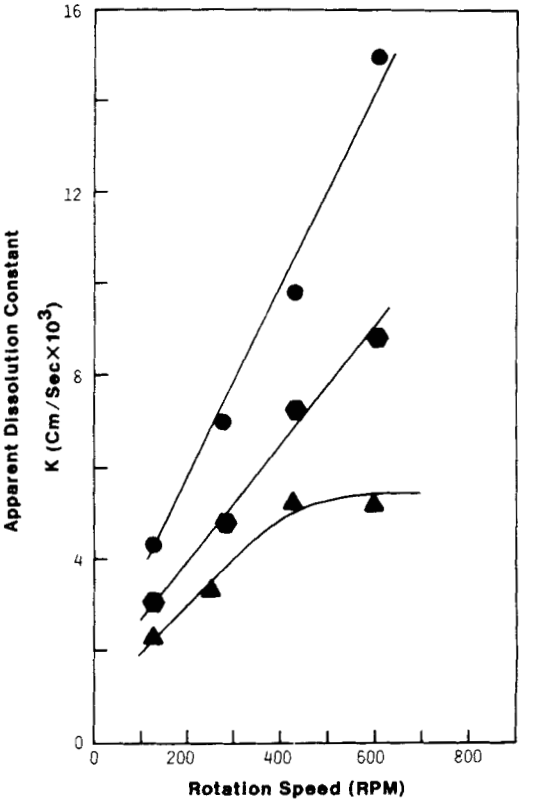

Figure 9: Effect of rotation speed on the apparent dissolution constant of: (●) benzoic acid, (●) progesterone and (▲) desoxycorticosterone in aqueous 40% PEG400 solution.

and the dissolution flux may be expressed as

$$J = k^*(C_s - C) \tag{9}$$

Comparing Equation (8) with Equation (9) yields the following relationship:

$$k^* = \frac{(D/h)}{[1 + (D/h)(1/k')]} \tag{10}$$

Rearranging the Equation (10) gives:

$$\frac{1}{k^*} = \frac{1}{(D/h)} + \frac{1}{k'} \tag{11}$$

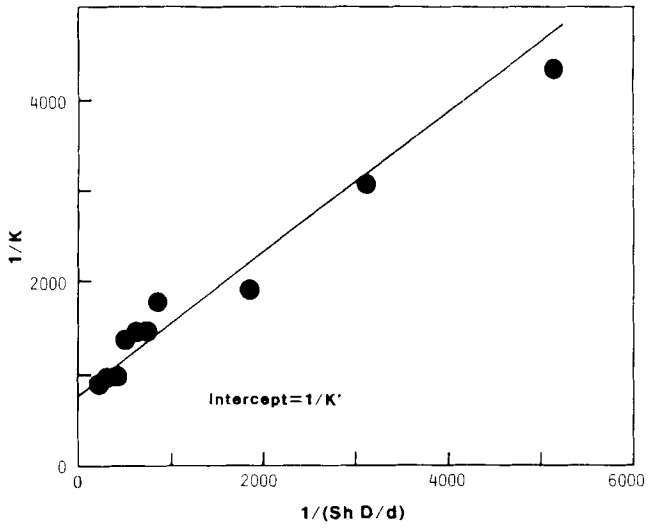

Figure 10: Linear 1/k* vs. 1/(Sh·D/d) relationship for desoxycorticosterone (Equation 12).

Equation (11) implies that the apparent dissolution constant (k*), approaches the interfacial rate constant (k') as the diffusional boundary layer (h) becomes infinitely thin, i.e., $h \tilde{=} o$.

Since $h = d/Sh$

Equation (11) becomes:

$$\frac{1}{k^*} = \frac{1}{k'} + \frac{1}{(Sh \cdot D/d)} \qquad (12)$$

The interfacial rate constant (k'), for a given drug under investigation can thus be obtained from the intercept of the linear 1/k* vs. 1/(Sh·D/d) plot, where Sherwood number can be calculated from Equation (6). A typical result is shown in Figure 10 for desoxycorticosterone. As expected, a fine linear relationship is established and the interfacial rate constant, as calculated from the reciprocal of intercept, is 0.001 cm/sec.

CONCLUSIONS

The results indicated that the applicability of the film theory in a dissolution process depends upon the relative contribution of the kinetic energy barrier at the solid-liquid interface of a compound. The rate of dissolution appears to be influenced by both the hydrodynamic diffusion layer and the interfacial energy barrier. It was concluded that the dissolution of a drug compound should be well characterized in terms of kinetics, mechanisms, and the conditions such as rotation speed and dissolution medium under which the mechanisms are essentially held.

FOOTNOTES

1. Sigma Chemical Company, St. Louis, Missouri.
2. Fisher Scientific Company, Fairlawn, New Jersey.
3. Bellco Glass Inc., Vineland, New Jersey.
4. Perkin Elmer, 559A UV/VIS Spectrophotometer, Perkin-Elmer, Elmwood Park, New Jersey.

REFERENCES

1. W. I. Higuchi, J. Pharm. Sc., 56, 315, (1967).
2. J. T. Cartensen, "Dissolution Technology", Washington: Industrial Pharmaceutical Technology, Section of the Academy of Pharmaceutical Science (1974).
3. K. Tojo, Y. Sun, M. M. Ghannam and Y. W. Chien, AIChE, 31, 741, (1985).
4. D. A. Frank-Kamenetskii, "Diffusion and Heat Transfer in Chemical Kinetics", Plenum press, New York, (1969).