Dissolution Kinetics in Micellar Solutions Under Nonsink Conditions

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Abstract □ It is shown that dissolution from constant-surface pellets into micellar solutions follows first-order kinetics in agreement with theory. A method to determine the apparent zero-order rate constant for dissolution from constant-surface preparations, which does not require maintenance of sink conditions, is suggested. Theoretical considerations and experimental data are presented to show that the difference between the dissolution rate of a drug in micellar solution and its dissolution rate in water does not represent the hypothetical dissolution rate of drug into the micellar pseudo phase.

Keyphrases □ Dissolution, tablets—micellar solution □ Micellar dissolution—nonsink conditions □ Polyoxyethylene lauryl ether—micellar solution □ Kinetic equations—micellar dissolution □ Salicylic acid, nondisintegrating tablets—test material

The influence of buildup of drug concentration in the dissolution medium on the apparent kinetics of dissolution has been discussed in a previous report (1). Data were presented to demonstrate that dissolution from a constant-surface pellet into a simple aqueous media follows apparent first-order kinetics. Upon introduction of an organic solvent layer above the dissolution medium, apparent zero-order dissolution was noted. Since the presence of a micellar pseudo phase in an aqueous medium also serves, in a sense, as a reservoir for dissolved drug, it was of interest to consider dissolution phenomenon in micellar solutions under nonsink conditions. The present report concerns the kinetics of dissolution of salicylic acid from constant-surface pellets in micellar solutions of polyoxyethylene [23] lauryl ether and clarifies an earlier communication (2) which incorrectly proposed the existence of a significant time lag before the occurrence of steady-state dissolution in micellar solutions.

THEORY

According to diffusion-layer theory, dissolution of a drug in water, under conditions of constant-surface area, may be described by the following equation,

$$dA/dt = D(A_s - A)/h \qquad \text{(Eq. 1)}$$

where A is the amount of drug dissolved at time t, A_s is the amount of drug soluble in the given volume of dissolution medium, D is the diffusion coefficient of the drug, and h is the effective thickness of the diffusion layer. Integration of Eq. 1 yields

$$A_s - A = A_s \exp(-Dt/h) \qquad \text{(Eq. 2)}$$

Dissolution of a drug in a solution of colloidal solubilizer, under conditions of constant-surface area, may be described by the following equation (3):

$$dA_t/dt = D(A_s - A)/h + D_M(A_M - A')/h \qquad \text{(Eq. 3)}$$

where D_M is the diffusion coefficient of the drug-micelle species, A_t is the amount of drug dissolved in the colloidal solution at time t, $A_M = (A_T - A_s)$, where A_T is the amount of drug soluble in the given volume of colloidal solution, and A and A' represent the amounts of drug dissolved in the nonmicellar and micellar phases, respectively, at time t. Therefore, $A + A' = A_t$. Assuming a constant phase-distribution coefficient, then $A_s/A_T = f_s$, $A_M/A_T = f_m$, $A/A_t = f_s$, and $A'/A_t = f_m$. Substitution into Eq. 3 yields

$$dA_t/dt = Df_s(A_T - A_t)/h + D_Mf_m(A_T - A_t)/h \qquad \text{(Eq. 4)}$$

Integration of Eq. 4 yields

$$A_T - A_t = A_T \exp[-(Df_s + D_Mf_m)t/h] \qquad \text{(Eq. 5)}$$

Hence, dissolution of a drug, under conditions of constant-surface area, in a micellar solution as well as in a simple aqueous media is predicted to follow first-order kinetics.

It is also of interest to note that the excess dissolution rate, *i.e.*, the difference in drug dissolution rates in micellar solution and in water, does not represent the dissolution rate of drug into the micellar pseudo phase as implied in a previous report (2).

Subtracting Eq. 2 from Eq. 5 yields

$$A' = A_M - \{A_T \exp[-(Df_s + D_Mf_m)t/h] - A_s \exp(-Dt/h)\} \qquad \text{(Eq. 6)}$$

or

$$A_M - A' = A_T \exp[-(Df_s + D_Mf_m)t/h] - A_s \exp(-Dt/h) \qquad \text{(Eq. 7)}$$

Alternatively, assuming a constant phase-distribution coefficient,

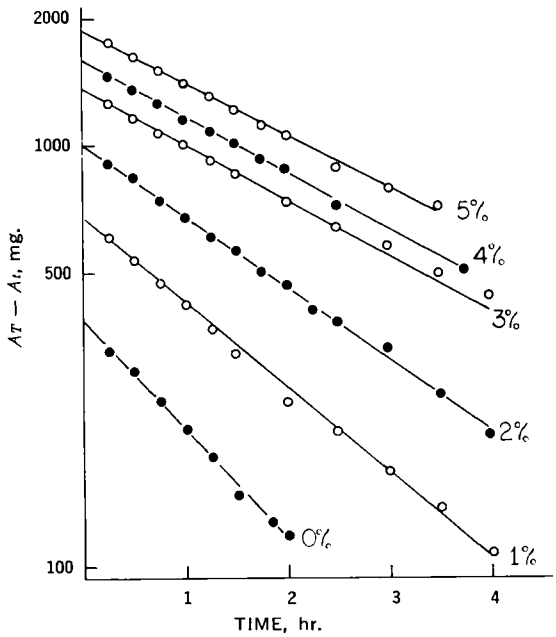

Figure 1—*Semilogarithmic plots of the amount of salicylic acid required to saturate the media* (A_T) *less the amount of drug dissolved to time* t (A_t) versus *time, for dissolution in 0.1* N *HCl (0%) and various concentrations (1–5%) of POE [23] lauryl ether in 0.1* N *HCl, using constant surface pellets.*

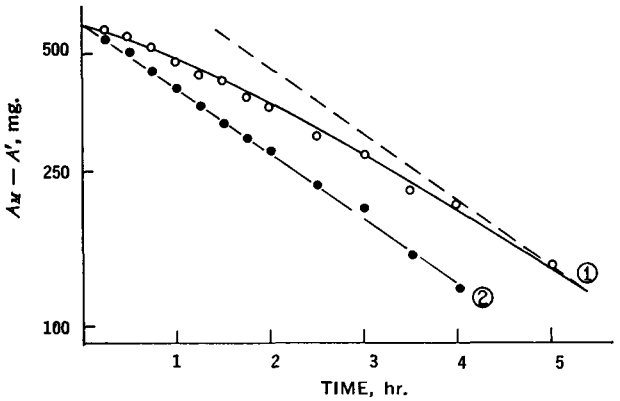

Figure 2—*Semilogarithmic plots of the amount of salicylic acid required to saturate the micellar pseudo phase of a 2% POE [23] lauryl ether solution in 0.1* N *HCl* (A_M) *less the amount of drug calculated to be dissolved in the pseudo phase to time* t (A′). *Values of* A′ *for Curve 1 were calculated by means of the following relationship:* $A_t - A = A'$. *The dashed line corresponds to the 2% plot in Fig. 1. Values of* A′ *for Curve 2 were calculated by means of the following relationship:* $f_m A_t = A'$.

independent of concentration, Eq. 5 may be written as

$$A_M - A' = A_M \exp[-(Df_s + D_M f_m)t/h] \qquad \text{(Eq. 8)}$$

Neither Eqs. 7 nor 8 are comparable to the anticipated equation for dissolution into a hypothetical pseudo phase, which may be expressed as

$$A_M - A' = A_M \exp(-D_M t/h) \qquad \text{(Eq. 9)}$$

EXPERIMENTAL

Nondisintegrating flat-faced tablets of pure drug were prepared by compressing 1.0 g. of salicylic acid at 10,000 psig. by means of a hydraulic press[1] equipped with 1.27-cm. (0.5-in.) diameter punch and die.

The dissolution assembly consisted of a 500-ml. three-neck round-bottom flask immersed in a constant-temperature bath adjusted to 37 ± 0.1°. A 7.62-cm. (3-in.) Teflon stirring blade and shaft attached to a stirring motor was inserted in the center neck. The motor was controlled by a constant torque unit[2] which also served to provide a direct readout of speed of rotation.

One hundred fifty milliliters of either 0.1 *N* HCl or various concentrations of POE [23] lauryl ether[3] dissolved in 0.1 *N* HCl was placed in the flask and permitted to equilibrate to 37°. The stirring blade was immersed in the dissolution medium to a constant depth and accurately centered by means of a guide. The stirrer was rotated at a speed of 50 r.p.m. and three salicylic acid tablets were placed in the medium by dropping them through the side neck. The tablets rested on the bottom of the flask, on one face, and remained in this position throughout the experiment.

One-milliliter samples of the dissolution medium were taken at appropriate intervals, diluted, and assayed spectrophotometrically at 302 mμ, using a spectrophotometer.[4] A volume of 0.1 *N* HCl or POE [23] lauryl ether in 0.1 *N* HCl (maintained at 37°) equal to the sample volume was added immediately after each sampling.

RESULTS AND DISCUSSION

According to Eq. 5, a semilogarithmic plot of the amount of drug required to saturate the micellar solution less the amount of drug dissolved to time *t versus* time will be linear with a *y*-intercept corresponding to the total solubility of the drug in the micellar solution. The experimental data plotted in Fig. 1 show excellent agreement with theoretical predictions. At each concentration of POE (23) lauryl ether, linearity was observed. For comparison, a plot of drug solubility in 0.1 *N* HCl less the amount of drug dissolved in 0.1 *N* HCl as a function of time is also shown in Fig. 1.

Treatment of dissolution data from constant-surface pellets in the manner described above also permits calculation of the apparent zero-order dissolution rate. Under sink conditions Eqs. 1 and 4 reduce to Eqs. 10 and 11, respectively.

$$dA/dt = DA_s/h = k_0 \qquad \text{(Eq. 10)}$$

and

$$dA_t/dt = A_T[(Df_s + D_M f_m)/h] = (k_0)_m \qquad \text{(Eq. 11)}$$

where k_0 and $(k_0)_m$ are the apparent zero-rate constants for dissolution in the aqueous and micellar media, respectively. Considering Eqs. 2 and 5 it is apparent that the product of the slope (k) of a semilogarithmic plot of ($A_T - A_t$) or ($A_s - A$) *versus* time and the solubility (*i.e.*, kA_T or kA_s) yields $(k_0)_m$ or k_0.

The relationship between k and k_0 is advantageous in that dissolution studies from constant-surface preparations need not be conducted under approximate sink conditions. Provided the surface area of solid is essentially constant, the influence of buildup of drug concentration in the medium on the dissolution rate may be corrected for by plotting the data on semilogarithmic coordinates and calculating k_0 as described above.

Figure 2 shows semilogarithmic plots of the amount of drug required to saturate the micellar pseudo phase of a 2% POE [23] lauryl ether solution in 0.1 *N* HCl (A_M), less the amount of drug calculated to be dissolved in the pseudo phase to time *t* (*A′*) *versus* time. The values of *A′* for constructing Curve 1 were calculated from the following relationship; $A_t - A = A'$, where A_t is the amount of drug dissolved in a micellar solution to time *t* and *A* is the amount of drug dissolved in water to an equivalent time. As predicted by Eq. 7 the curve is biexponential. Since $D/h > (Df_s + D_M f_m)/h$, the curve gradually approaches linearity. The linear segment may be described by Eq. 5.

Data similar to those shown for Curve 1 in Fig. 2 were presented in a preliminary report (2). However, contrary to the conclusions of the earlier communication the curvature in the log ($A_M - A'$) *versus* time plot is predicted by theory and does not suggest a presteady state phenomenon with respect to the micellar pseudo phase.

The values of *A′* for constructing Curve 2 in Fig. 2 were calculated from the following relationship: $f_m A_t = A'$, where f_m is A_M/A_T. As predicted by Eq. 8 a plot of log ($A_M - A'$) *versus* time is linear and parallels the log ($A_T - A_t$) *versus* time plot (shown as the dashed line in Fig. 2).

Dissolution phenomena in micellar solutions cannot be viewed as two dissolution processes occurring simultaneously into two isolated pseudo phases. Rather, the apparently instantaneous distribution between the two pseudo phases, results in a cooperative phenomenon and the rate of appearance of drug in each pseudo phase is identical.

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[1] Carver model B.
[2] Servodyne.
[3] Brij 35 SP, Atlas Chemical Industries, Wilmington, Del.
[4] Beckman model DB-G, Beckman Instruments, Inc., Fullerton, Calif.