Effect of Complex Formation on Dissolution Kinetics of *m*-Aminobenzoic Acid

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The dissolution kinetics of *m*-aminobenzoic acid have been studied in the presence of certain complexing agents. By the addition of creatinine, tartaric acid, malic acid, or succinic acid to the dissolution medium, the apparent saturation solubility of *m*-aminobenzoic acid was increased. By analysis of the dissolution rate as a function of solubility, the participation of the interfacial reaction and diffusion in the over-all control of dissolution was elucidated.

In 1904, Nernst (1) proposed a theory of heterogeneous reaction which has been the subject of extensive investigation. In this theory certain assumptions are made as to the physical and chemical factors involved in the reaction at the liquid–solid interface. They involve: (*a*) a stationary liquid film is assumed to exist through which diffusion into the main body of the stirred liquid takes place; and (*b*) the reaction at the liquid–solid interface is supposed to be infinitely rapid, thereby maintaining a saturated layer at this interface. This latter assumption has led investigators to refer to diffusion control of the dissolution process.

As the number of poorly soluble, pharmaceutically important compounds increase, it becomes increasingly important to understand more thoroughly the true mechanism of the dissolution process. The present investigation was therefore undertaken to study further the factors regulating the dissolution process, particularly with respect to complex formation and the reaction at the solid–liquid interface.

PLAN OF STUDY

In the reaction between two phases, two factors determine the over-all measured rate of reaction. The first is the rate of reaction at the interface; the second is the rate of transport of reactant, or product of reaction, to or from the interface. Either of these may be rate-determining or, if both rates are of the same order of magnitude, the over-all rate may be a function of both processes. If the interfacial or surface reaction is involved in the rate-determining step, the correct kinetic description would be expected to differ from that expressed by Noyes and Whitney (2).

In general, the dissolution rate ($-dw/dt$) is controlled by the following two expressions

$$\frac{-dw}{dt} = k_R(C_s - C_i) \qquad \text{(Eq. 1)}$$

where k_R is the rate constant for the interfacial reaction, C_s the saturation concentration, and C_i the effective concentration (less than saturation) existing at the interface. The existence of the intermediate concentration, C_i, was first proposed by Berthoud (3). The over-all rate is also a function of diffusion away from the interface, or

$$\frac{-dw}{dt} = k_D(C_i - C) \qquad \text{(Eq. 2)}$$

where k_D is the diffusion rate constant and C the concentration in the bulk solution.

If, initially, the interfacial reaction is the slow or rate-determining step, a steady-state condition should exist for C_i. This implies that if k_D is constant, the diffusional rate remains constant and under appropriate conditions the interfacial rate may increase until these two are equal, or

$$k_R(C_s - C_i) = k_D(C_i - C) \qquad \text{(Eq. 3)}$$

from which is obtained

$$C_i = \frac{k_R C_s + k_D C}{k_R + k_D} \qquad \text{(Eq. 4)}$$

Equation 4 may then be substituted into Eq. 1 or Eq. 2 for C_i to give the following general expression

$$\frac{-dw}{dt} = \frac{k_R k_D}{k_R + k_D}(C_s - C) \qquad \text{(Eq. 5)}$$

In order to investigate the extent of participation of the surface reaction in the over-all measured rate of the dissolution process, it was deemed desirable to extend the solubility range of the dissolving compound. When expressed in terms of Noyes-Whitney kinetics, the concentration gradient at the liquid–solid interface can be represented by $(C_s - C)/h$, where h is the controversial diffusion layer thickness. If h is considered constant under existing conditions, an increase in the dissolution rate would result if C_s were increased. In order to accomplish this increase in solubility, the phenomenon of complex formation was utilized. This has been defined as follows (4). A and B are complexed when there are more A species around and/or closer to B species than a random distribution of A's and B's would bring about. This approach is unencumbered by mechanism. By appropriate selection of complexing agents, it would be possible to obtain a wide range of saturation solubilities for the compound under investigation.

EXPERIMENTAL

Apparatus and Procedure.—The general experimental procedure for determining the dissolution

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rate, except for minor alterations, was similar to that used in a previous investigation (5) in this laboratory.

The tablets used in this work were compressed with the aid of a Carver laboratory press, model B,[1] using $^3/_8$-in. spherical punches under a force of 10,000 lb. At high compressional force the apparent density of a tablet effectively remains constant or approaches its true density (6, 7). As the force of compression was effectively constant in this investigation, it was assumed that the density of the tablets did not vary significantly. Because of the bulkiness of the *m*-aminobenzoic acid powder, it was first slugged under a force of 9000 lb.

To determine the extent of complex formation on the increase in the apparent saturation solubility, an excess of *m*-aminobenzoic acid (200 mg.) was placed in vials of approximately 15-ml. capacity along with increasing amounts of the complexing agent. Ten milliliters of distilled water was added and the vials were then shaken vigorously in a constant-temperature water bath at 30 ± 0.1° for 24 hr. One-milliliter aliquots were taken and appropriate dilutions made using a borate buffer at pH 8.6. This pH was utilized to obtain maximum fluorescence. The solutions were analyzed using an Aminco-Bowman spectrophotofluorometer[2] with the activating light at 315 mμ and the fluorescence observed at 410 mμ (uncorrected). To elicit the effect of complex formation on dissolution kinetics, rates were determined in solutions containing varying amounts of the complexing agent. Approximately 1.3×10^{-3} moles of *m*-aminobenzoic acid was allowed to undergo dissolution in these solutions.

The chemicals used in this investigation were reagent grade or equivalent.

A Beckman model H-2 pH meter was used for pH determinations.

RESULTS AND DISCUSSION

Complex Formation.—The effect of the complexing agent on the apparent solubility of *m*-aminobenzoic acid is shown in Figs. 1 and 2. As these curves indicate, the solubility of *m*-aminobenzoic acid remains a linear function of the amount of complexing agent present. It would therefore be expected, from Noyes-Whitney kinetics, that the dissolution rate would also remain a linear function of the complexing agents concentration. The stability constants for these interactions, calculated from the equation, $K = S/(1 - S)$, where S is the slope, are presented in Table I. In this study no attempt was made to regulate the pH of the dissolution medium (Fig. 3). These changes, however, had no apparent effect on the solubility as shown by the linearity (except for creatinine lag) of the complexation curves.

Dissolution Studies in Distilled Water.—In order to apply special case 2 of the Hixon-Crowell general equation (8) to the data, it was necessary to restrict the amount of *m*-aminobenzoic acid that was dissolved in the solution. Plots of $W_0^{1/3} - W^{1/3}$ *versus* time (see *Reference 5*) showed linearity over the concentration range studied (1.3×10^{-3} moles/L.), thereby validating the use of the equation under these experimental conditions. In all

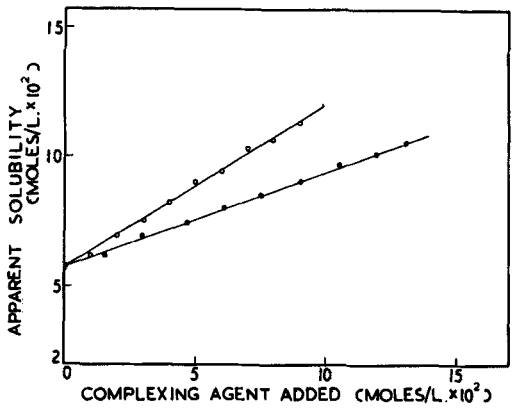

Fig. 1.—Effect of complex formation on the apparent solubility of *m*-aminobenzoic acid. Key: O, tartaric acid; ●, *d*, *l*-malic acid.

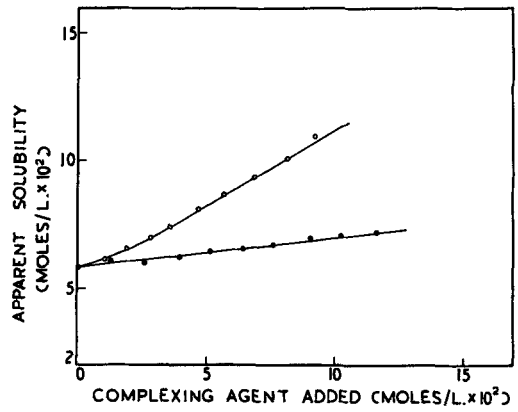

Fig. 2.—Effect of complex formation on the apparent solubility of *m*-aminobenzoic acid. Key: O, creatinine; ●, succinic acid.

subsequent experiments this concentration was not exceeded. The average dissolution rate was found to be 2.07 mg./cm.²/min.

Dissolution Studies in Succinic Acid Solutions.—The influence of succinic acid on the dissolution rate is shown in Fig. 4. Because of the linear relationship shown, it appears that Noyes-Whitney kinetics are followed. However, it may be seen from Table II that the increase in dissolution rate is not directly proportional to the increase in solubility. In considering the equation, $-dw/dt = DC_s/h$, where the terms are as previously defined, this deviation must be a function of either h or C_s. However, for dissolution in the succinic acid solutions investigated, the value of h remains effectively the same as for dissolution in distilled water (9).

TABLE I.—STABILITY CONSTANTS OF COMPLEXES FORMED WITH *m*-AMINOBENZOIC ACID

Complexing Agent	Slope	*K*stability
Succinic acid	0.114	0.129
Malic acid	0.367	0.580
Creatine	0.587[a]	1.421
Tartaric acid	0.630	1.703

[a] Slope taken from linear portion of the curve.

[1] Fred S. Carver, Inc., Summit, N. J.
[2] American Instrument Co., Silver Spring, Md.

This necessitates that the concentration gradient at the solid–liquid interface changes with the changing solubility of the dissolving substance. Because the effective concentration at the interface must then be less than saturation, it follows that the rate of the interfacial or surface reaction must affect the over-all rate of dissolution.

Dissolution Studies in d,l-Malic Acid, Tartaric Acid, and Creatinine.—The influence of malic acid, tartaric acid, and creatinine on the dissolution rate of *m*-aminobenzoic acid with increasing saturation solubility due to the addition of creatinine to the dissolution medium.

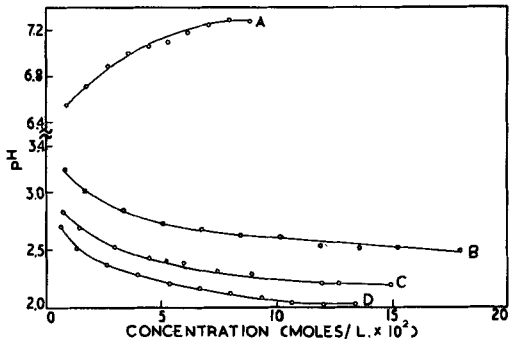

Fig. 3.—Change in the pH of the dissolution medium with increasing concentration of complexing agent. Key: curve A, creatinine; curve B, succinic acid; curve C, malic acid; curve D, tartaric acid.

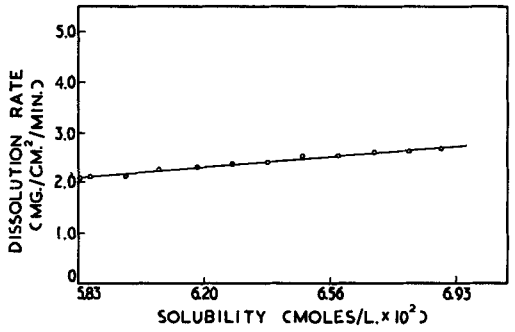

Fig. 4.—Change in the dissolution rate of *m*-aminobenzoic acid with increasing saturation solubility due to the addition of succinic acid to the dissolution medium.

TABLE II.—DISSOLUTION RATE OF *m*-AMINOBENZOIC ACID AS A FUNCTION OF ITS SOLUBILITY IN SUCCINIC ACID SOLUTIONS

Succinic Acid Concn., moles/L. × 10²	Solubility of *m*-Aminobenzoic Acid, moles/L. × 10²	Dissolution Rate, mg./cm.²/min.
0.00	5.83	2.07
0.85	5.87	2.13
1.69	5.97	2.18
2.54	6.07	2.23
3.39	6.18	2.29
4.23	6.28	2.35
5.08	6.38	2.41
5.93	6.48	2.47
6.77	6.58	2.53
7.62	6.69	2.58
8.47	6.79	2.65
9.31	6.88	2.70

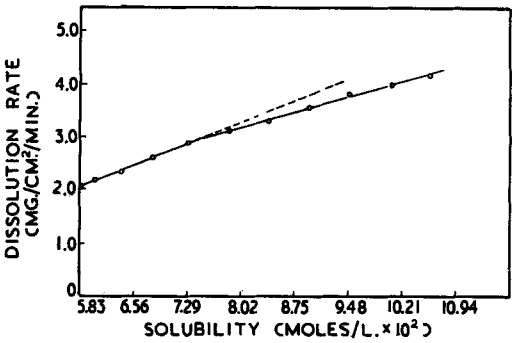

Fig. 5.—Change in the dissolution rate of *m*-aminobenzoic acid with increasing saturation solubility due to the addition of creatinine to the dissolution medium.

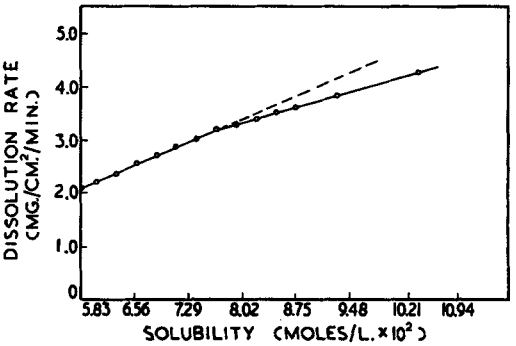

Fig. 6.—Change in the dissolution rate of *m*-aminobenzoic acid with increasing saturation solubility due to the addition of *d,l*-malic acid to the dissolution medium.

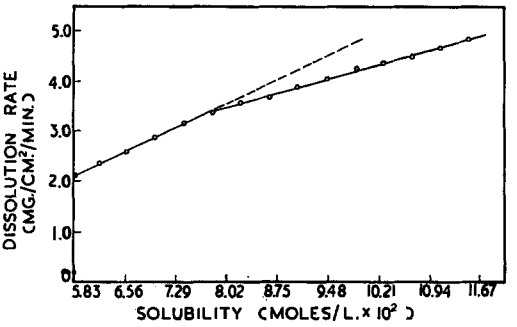

Fig. 7.—Change in the dissolution rate of *m*-aminobenzoic acid with increasing saturation solubility due to the addition of tartaric acid to the dissolution medium.

of *m*-aminobenzoic acid is shown in Figs. 5, 6, and 7. It would appear that these results cannot be explained solely on the basis of diffusion control of the dissolution process.

If initially the rate is determined by the interfacial reaction, steady-state conditions should exist for the concentration, C_i, and it remains essentially constant. It is then seen from Eq. 1 that if the interfacial layer were saturated, while the rate-determining step remained the same, the rate would be zero, *i.e.*, thermodynamic equilibrium has been

TABLE III.—APPROXIMATION OF EFFECTIVE INTERFACIAL CONCENTRATION AND CALCULATION OF DISSOLUTION RATE INCREASE

System	Extrapolated Value of C_i, moles/L. × 10^2	Calcd. Dissolution Rate Increase for 10% Solubility Increase, %	Experimentally Determined Increase, %
Succinic acid	2.36	16.8	16.3
Malic acid	2.33	15.5	15.5
Creatinine	2.11	14.8	14.6
Tartaric acid	2.65	16.8	16.6

TABLE IV.—RATE CHANGE WITH SOLUBILITY AND EXTRAPOLATION DATA FOR APPARENT DIFFUSION CONTROL

System	Intercept of Extrapolation to Zero Rate, moles/L. × 10^3	Change of Dissolution Rate with 10% Change in Solubility, %
Malic acid	−2.19	9.34
Creatinine	−1.09	9.75
Tartaric acid	−6.20	9.36

obtained and the driving force for transition from solid to solution has been satisfied. This occurs as C_s decreases and approaches C_i. An extrapolation of the initial slope to zero rate should therefore give the value of C_i. The value of these intercepts are shown in Table III. Furthermore, it will be noted that, as C_i is a number different from zero, the rate of increase or decrease of the dissolution rate will be greater than the corresponding rate of change of the solubility. Using the value of C_i obtained upon extrapolation, the rate of change of the dissolution rate with solubility has been calculated using Eq. 1. These data, along with the experimentally determined results, are presented in Table III.

Equation 5 predicts that when the interfacial rate becomes equal to the diffusional rate, the dissolution rate will be directly proportional to the saturation concentration C_s. This would indicate that apparent diffusion control of the process has now been achieved. The rate of change of the dissolution rate with solubility has been calculated and is shown in Table IV. The close agreement with predicted values indicates k_D remains essentially constant in the presence of those complexing agents used. The equation also predicts that if the concentration, C_s, were to decrease to zero concentration, and the limiting conditions for Eq. 5 still apply, the rate would also be zero. Therefore, the extrapolation of the second slope should pass through the origin. The intercepts of these extrapolations are shown in Table IV.

The value of C_i would certainly be expected to vary among different chemical compounds as it would be a function of the magnitude of the intermolecular forces present. As the interfacial and diffusional rates are different functions of C_i, their relative magnitudes will also vary with different compounds. For an individual compound, however, the dependence of the over-all rate on C_s should remain constant. That this is true is evidenced by the location of the change in rate control with respect to the saturation solubility C_s. For malic acid and tartaric acid, this change occurs at 7.66×10^{-2} moles/L. and for creatinine at 7.44×10^{-2} moles/L. This represents a difference of less than 3%. It can be seen that the initial slopes of all four compounds agree quite well, but that a deviation does not result in the case of the succinic acid system. Apparently this is because, over the range studied, the solubility of *m*-aminobenzoic acid does not reach 7.44×10^{-2} moles/L.

Oxalic acid was also employed in this study, but yielded precipitates with the *m*-aminobenzoic acid at all concentrations tested (0.17 to 1.42×10^{-2} moles/L.).

SUMMARY

Through the technique of complex formation, the influence of a changing saturation solubility on the dissolution rate of *m*-aminobenzoic acid has been investigated. The dissolution rate was determined in solutions of varying concentration of succinic acid, *d,l*-malic acid, tartaric acid, and creatinine, although experimental evidence indicated that for *m*-aminobenzoic acid at its normal solubility, the dissolution process is apparently controlled by the interfacial reaction; it was found that apparent diffusion control could be reached if the solubility of *m*-aminobenzoic acid was sufficiently increased. The kinetic expressions describing these processes are shown. The approximate concentration of molecules available from the solid phase and existing in solution at the interface was determined by extrapolation to zero rate.

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