Estimation of Dissolution Rate of Salicylamide in Complexing Media Using a Theoretical Diffusion Model

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Abstract □ Dissolution rates of salicylamide in water and caffeine solutions under perfect sink conditions were predicted by theoretical diffusion equations applicable to dissolution in complexing media. Experimental dissolution rates were measured using a compartmentalized rotating-basket apparatus under two sets of conditions. Agreement was found between experimental and predicted rates. Use of the theoretical equation for estimating dissolution rates involves simple calculations of diffusion coefficients and diffusion layer thickness under the operative dissolution conditions. The increase in dissolution rate caused by addition of the complexant can be calculated for diffusion-controlled dissolution directly if the stability constant and the drug solubility in water are known or measured.

Keyphrases □ Dissolution rates—salicylamide in water and caffeine solutions, estimated using theoretical diffusion model, compared to experimental results □ Salicylamide—dissolution rates in water and caffeine solutions, estimated using theoretical diffusion model, compared to experimental results □ Diffusion model, theoretical—used to estimate dissolution rates of salicylamide in water and caffeine solutions, compared to experimental results □ Complexes—salicylamide and caffeine, dissolution rates estimated using theoretical diffusion model, compared to experimental results

Dissolution rates of solid drug products in media containing substances capable of reaction with the drug have aroused much interest in view of their possible influence on bioavailability. Three main classes of interactions affecting dissolution have been recognized. The first, involving pH equilibria and their effects on the degree of drug ionization, has been investigated extensively, and theoretical treatments have been developed and tested (1–3). The second is the interaction between drugs and macromolecules, such as colloids or surfactant micelles, generally added as formulating agents; this area also has received considerable study (4–8).

Much less attention has been paid, however, to the third type, complex formation, which may occur between the drug and formulating agents, other drugs, food ingredients, enzymes, and toxins. Interaction of solid phase components was treated theoretically as one case of dissolution from polyphase mixtures, and the equations developed agreed with the dissolution behavior of caffeine–benzocaine disks (9). The initial dissolution rates of solid complexes of caffeine and gentisic acid were compared with those of caffeine using a simplified mathematical treatment (10). With regard to the interacting medium, the dissolution rate of 2-naphthol was studied in several complexing media. Experimental results were not reproducible, nor did they obey the Noyes–Whitney equation; a "concentration jump" extrapolation technique was developed to compare dissolution rates during individual experiments (11).

The purpose of the present studies was to determine whether a general diffusional mathematical treatment was applicable to prediction of dissolution rates over a range of complexant concentrations under experimental conditions used for *in vitro* testing. Such a treatment would permit theoretical estimation of dissolution rates in various complexing media since stability constants of many complexes are available or are easily measured; the necessary hydrodynamic parameters of the dissolution apparatus may be estimated for standard conditions.

THEORETICAL

The treatment used is based on the general theory previously developed (1) for the influence of bases on the dissolution of acidic solids undergoing diffusion-controlled transport through a liquid film. The complexation equilibrium replaces the ionization equilibrium, and the formation constant of the complex is the factor determining the activities of the free and complexed drug in the film and bulk medium. Complexation is considered to occur throughout a single liquid film at the solid interface through which there is a continuous concentration gradient rather than at a plane surface of contact somewhere within the film. Concentration gradients in the film need not be linear, but the chemical equilibrium must be rapid compared to transport. Diffusion coefficients are considered to be concentration independent. The treatment is based on the "unstirred" diffusion layer model.

In the test apparatus used in the present work (see *Experimental*), in which solvent flow occurs through a tube cut into a cylindrical block, the velocity gradient for streamline flow may be considered to be zero at the sides of the tube. In effect, the tube is bisected by the large flat compressed disk inserted in the center, which gives two hemispherical streamlined flows, with the velocity gradient approximated to zero over the disk surface. Equations for dealing with convective flow components were proposed previously (12–14) but are applicable to idealized model systems and are not valid for the apparatus used here. For the defined test apparatus, the film thickness is considered to be dependent on the stirring rate but independent of all other factors except viscosity.

For dissolution of a solid unionized substrate, S, in the presence of an unionized complexant molecule, C, with which it forms complexes in solution by the Scheme I reactions:

$$S + C \rightleftarrows SC$$

$$S + 2C \rightleftarrows SC_2, \textit{ etc.}$$

Scheme I

the thermodynamic stability constants $K_{a(1:1)}$, $K_{a(1:2)}$, *etc.*, are given by:

$$K_{a(1:1)} = (SC)/(S)(C) \qquad \text{(Eq. 1}a\text{)}$$

$$K_{a(1:1)} = K_{c(1:1)}\,\gamma_{SC}/\gamma_S\gamma_C \qquad \text{(Eq. 1}b\text{)}$$

$$K_{a(1:2)} = (SC_2)/(S)(C)^2 \qquad \text{(Eq. 1}c\text{)}$$

$$K_{a(1:2)} = K_{c(1:2)}\,\gamma_{SC_2}/\gamma_S\gamma_C{}^2 \qquad \text{(Eq. 1}d\text{)}$$

where parentheses represent activities and γ activity coefficients of the various species and K_c is the concentration equilibrium constant. Concentrations and concentration stability constants are applicable to dilute aqueous solutions of nonelectrolytes, for which $\gamma \rightarrow 1$, and are used here.

With Olander's treatment (15), the solution rate of S is given by the fluxes of all species containing S—*viz.*, S, SC_2, . . . , SC_n. The concentration of each species SC_n formed can be evaluated, in principle, if the individual $K_{1:n}$ constants are known and used in conjunction with the appropriate diffusion coefficient of the species to write a flux equation. For weak complexes formed at low concentrations in water, measured K values are generally overall values or represent the dominant complex.

By designating steady-state concentrations at the solid–liquid interface with the subscript 0 and in the bulk solution with the subscript h, the

Table I—Estimated Diffusion Coefficients of Salicylamide, Caffeine, and Their 1:1 Complexes at 25 and 37°

Species	Partial Molal Volume, v, cm³/mole[a]	Diffusion Coefficient, D, cm²/sec × 10⁵[b] 25°	37°
Salicylamide	100	1.06	1.42
Caffeine	127	0.978	1.31
1:1 Complex	228	0.806	1.08

[a] The v values were calculated using data from Ref. 22. [b] The D values were calculated by means of Eq. 11.

concentrations of the components on the two sides of a film of thickness h (considered as one dimensional) are given by: $[S]_0$, $[C]_0$, and $[SC]_0$ and $[S]_h$, $[C]_h$, and $[SC]_h$, respectively. Application of Fick's second law (16) and Higuchi's treatment (1) to the steady-state condition leads to:

$$V_D = \frac{D_S([S]_0 - [S]_h)}{h} + \frac{D_C D_{SC} K([S]_0 - [S]_h)(D_{SC}[SC]_h + D_C[C]_h)}{h(D_{SC}[S]_0 K + D_C)(D_{SC}[S]_h K + D_C)} \quad \text{(Eq. 2)}$$

where V_D is the dissolution rate per unit area of substrate in the complexant solution in which a 1:1 complex of stability constant K is formed; D_S, D_C, and D_{SC} are the diffusion coefficients of the respective species. This equation is parallel to that developed for a nonionic acid–base equilibrium (1). Equation 2 may be simplified by using Eq. 1 to eliminate $[SC]_h$, giving:

$$V_D = \frac{D_S([S]_0 - [S]_h)}{h} + \frac{D_C D_{SC} K[C]_h([S]_0 - [S]_h)}{h(D_{SC}K[S]_0 + D_C)} \quad \text{(Eq. 3)}$$

When K is very small, Eq. 3 reduces to the usual Noyes–Whitney equation for dissolution of the pure solid:

$$V_D = \frac{D_S}{h}([S]_0 - [S]_h) \quad \text{(Eq. 4)}$$

When K is very large, Eq. 3 takes the form:

$$V_D = \frac{D_S}{h}([S]_0 - [S]_h) + \frac{D_C}{h}[C]_h \quad \text{(Eq. 5)}$$

Further simplifications of the general equation may be made under zero sink conditions when $(S)_h = (SC)_h = 0$. Equation 3 then reduces to:

$$V_D = \frac{[S]_0}{h}\left(D_S + \frac{D_C D_{SC} K[C]_h}{D_{SC}K[S]_0 + D_C}\right) \quad \text{(Eq. 6)}$$

or:

$$V_D = L_1 + L_2[C]_h \quad \text{(Eq. 7)}$$

where $L_1 = ([S]_0 D_S)/h$ and $L_2 = ([S]_0 D_C D_{SC} K)/h(D_{SC}K[S]_0 + D_C)$. Equation 7 predicts a linear increase of the dissolution rate with the complexant concentration, $[C]_h$.

When the diffusion coefficients have similar values, as with interactants differing in molecular weight by a factor of less than three (10), Eqs. 3–7 may be further simplified. Equation 6, for example, gives:

$$V_D = \frac{[S]_0 D}{h}\left(1 + \frac{K[C]_h}{K[S]_0 + 1}\right) \quad \text{(Eq. 8a)}$$

$$V_D = \frac{[S]_0 D}{h}\left(1 + \frac{[C]_h}{[S]_0 + 1/K}\right) \quad \text{(Eq. 8b)}$$

By rearrangement and substitution of $(K[S]_0[C]_h)/(K[S]_0 + 1)$ by $[SC]_0$[1], Eq. 8a approximates:

$$V_D = \frac{D}{h}([S]_0 + [SC]_0) = \frac{D}{h}c_S \quad \text{(Eq. 9)}$$

where c_S is the apparent salicylamide solubility; *i.e.*, $c_S = [S]_0 + [SC]_0$.

By using this relation, the ratio, R, of the dissolution rates in the caffeine solutions to those in water (Eq. 4 with $[S]_h = 0$) are given, under these limitations, by:

$$R = c_S/[S]_0 \quad \text{(Eq. 10)}$$

Table II—Diffusion Layer Thickness (h) at 25° and 48 rpm and at 37° and 90 rpm

Caffeine Concentration, $M \times 10^2$	Salicylamide Solubility, $M \times 10^2$	f_S/f_{SC}	D_m, cm²/sec × 10⁵[a]	h, cm × 10²[b]
		37° and 90 rpm		
1.00	—	—	—	—
2.90	4.50	2.11/1	1.31	0.87
3.00	—	—	—	—
5.00	—	—	—	—
5.75	6.07	1.07/1	1.25	0.97
8.12	7.38	1/1.32	1.22	1.03
		25° and 48 rpm		
2.25	—	—	—	—
2.90	2.85	1.02/1	0.93	1.35
3.50	—	—	—	—
4.00	3.36	1/1.25	0.92	1.36
8.12	5.27	1/2.74	0.87	1.34

[a] Calculated by means of Eq. 13. [b] Calculated by means of Eq. 12. The values of h for this apparatus estimated from benzoic acid dissolution rates were 0.82×10^{-2} at 37° and 90 rpm and 1.73×10^{-2} cm at 25° and 48 rpm.

EXPERIMENTAL

Materials—Salicylamide[2] and caffeine[3] were NF grade.

Viscosity and Density—The viscosity of filtered solutions containing mixtures of salicylamide and salicylamide–caffeine complex, prepared by saturation with salicylamide at the various caffeine concentrations, was measured at 25 and 37° using a capillary viscometer[4]. The densities of these solutions were measured at 25 and 37° pycnometrically.

Solubility of Salicylamide—The solubilities of salicylamide in water at 25 and 37° and the stability constants of its complex with caffeine were obtained by the solubility method. Experimental conditions and phase diagrams were reported elsewhere (18).

Dissolution Rate Determinations—Salicylamide was compressed into cylindrical tablets (diameter, 13.1 mm; thickness, 2.9 mm; and weight, 493 mg ± 1.5%) in a vacuum potassium bromide die with a laboratory press at high pressure[5]. Release of the drug was measured using a rotating-disk dissolution apparatus (19) in 1 liter of dissolution medium containing increasing concentrations of caffeine. Experiments were run at 48 rpm and 25° and at 90 rpm and 37° over 3 hr. Samples were assayed for total salicylamide content spectrophotometrically at λ_{max} 525 nm using a modified Trinder's reagent (18).

Corrections were applied for cumulative dilution caused by replacement of samples by equal volumes of the original medium. Two tablets were used per test; experiments were run in duplicate and the results were averaged. Reproducibility was within ±3%. The data were treated by means of the Hixson–Crowell equation (20), and dissolution rates ($3K'$) were obtained from the slopes ($K'a$) of $(W_0^{1/3} - W^{1/3})$ against time[6], which were linear throughout each experiment. The tablets maintained a constant shape throughout the measurements.

RESULTS AND DISCUSSION

Dissolution rates were predicted by Eq. 6, with perfect sink conditions prevailing throughout the measurements. The values used for $[S]_0$, the solubility of salicylamide in water, were 1.50×10^{-2} M at 25° and 2.90×10^{-2} M at 37°; the stability constants, K, at these temperatures were 57.9 and 44.1 M^{-1}, respectively (18). The diffusion coefficients (Table I) of the species S, C, and SC were calculated by the Stokes–Einstein equation (Eq. 11) (22):

$$D = \frac{RT}{4\pi\eta N}\left(\frac{4\pi N}{3v}\right)^{1/3} \quad \text{(Eq. 11)}$$

where R is the molar gas constant, T is the absolute temperature, η is the viscosity of the solvent, N is Avogadro's number, and v is the partial molal volume.

For the apparatus used in the present work, calculation of the apparent diffusion layer thickness, h, involved hydrodynamic properties, which are not readily definable. Therefore, this parameter was estimated experimentally by using compressed disks of a model solute, benzoic acid, reported to give diffusion-controlled dissolution (23).

[1] Here, $[SC] = Sl[C]_h$ and $Sl = K[S]_0/(1 + K[S]_0)$, where Sl is the slope of substrate solubility *versus* ligand concentration in the phase diagram (17).
[2] Sigma Chemical Co., St. Louis, Mo.
[3] Merck, Darmstadt, West Germany.
[4] Ostwald type U tube, A. Gallenkamp & Co., London, England.
[5] Research and Industrial Instruments Co., London, England.
[6] The notation used is that of Parrott *et al.* (21), except that K' replaces K.

Table III—Dissolution Rate, Experimental and Estimated Data

Caffeine Concentration, $M \times 10^2$	Salicylamide Concentration, c_S, $M \times 10^2$	Dissolution Rate, moles $cm^{-2}/sec \times 10^8$ [a]		Dissolution Rate Ratio[b]			
		Experimental	Estimated	R_1	R_2	R_3	R_4
		25° and 48 rpm					
0	1.50	0.98	1.09	—	—	—	—
0.26	1.62	1.09	1.12	1.11	1.14	1.02	1.08
0.47	1.72	1.22	1.23	1.24	1.26	1.12	1.14
0.94	1.92	1.34	1.36	1.37	1.39	1.24	1.28
2.00	2.43	1.66	1.66	1.70	1.70	1.31	1.62
2.90	2.85	1.96	1.92	2.00	1.96	1.75	1.90
4.70	3.68	2.39	2.43	2.44	2.48	2.21	2.45
8.12	5.27	3.43	3.40	3.50	3.47	3.09	3.47
		37° and 90 rpm					
0	2.90	4.25	4.11	—	—	—	—
1.99	4.00	6.38	5.44	1.50	1.28	1.32	1.37
3.26	4.70	6.86	6.30	1.61	1.48	1.53	1.62
4.08	5.15	7.23	6.86	1.69	1.61	1.66	1.76
5.57	5.97	7.75	7.85	1.82	1.84	1.90	2.06
7.42	6.99	8.50	8.63	2.00	2.00	2.10	2.41

[a] Slope of dissolution rate against caffeine concentration. At 25° and 48 rpm: experimental = 2.95×10^{-4} ($r = 0.998$), and predicted = 2.89×10^{-4} ($r = 0.999$). At 37° and 90 rpm, experimental = 5.36×10^{-4} ($r = 0.962$), and predicted = 6.21×10^{-4} ($r = 0.999$). Slope units are centimeters per second. [b] Ratio of dissolution rate in caffeine solution to that in water: R_1, both from experimental data; R_2, predicted values from Eq. 6 for caffeine solutions and experimental data for water; R_3, both predicted from Eq. 6; and R_4, predicted from Eq. 10.

The apparent h value was obtained from the experimental dissolution rates and solubilities measured in 0.01 N HCl and substituted in Eq. 12 based on the Nernst theory (24):

$$h = \frac{Dc_S}{3K'} \qquad \text{(Eq. 12)}$$

The h values (Table II) were close to those calculated from the experimental parameters of the salicylamide–caffeine system, obtained using the same equation.

In calculating the thickness from dissolution rates corresponding to different forms of the diffusing substrate, D_m is the weighted mean diffusion coefficient—*viz.*:

$$D_m = f_S D_S + f_{SC} D_{SC} = \sum f_i D_i \qquad \text{(Eq. 13)}$$

where f_S and f_{SC} are the fractions of free and complexed salicylamide, respectively. These values were calculated from the complexation data (18) using the relations $f_S = 1/(K[C]_h + 1)$ and $f_{SC} = K[C]_h/(K[C]_h + 1)$, in which $[C]_h$ is the total caffeine concentration (Table II).

Estimated and experimental dissolution rates are given in Table III for caffeine concentrations used in the dissolution medium. At 25° and 48 rpm, the predicted and measured rates are virtually identical over the full concentration range.

There is reasonable agreement also at 37° and 90 rpm; the deviation of the first two points is the cause of the lower correlation coefficient, 0.962, of the experimental regression line; its source is apparently interfacial control of the dissolution process when the transport is largely of free salicylamide (25). There is evidence of a similar deviation of the initial point at 25 and 48 rpm, but it is small.

Participation of the interfacial control in the process is supported by point-to-point comparison of experimental and estimated ratios of the dissolution rates. Ratios of the dissolution rates in the caffeine solutions to those in water are included in Table III. When calculated with respect to the experimental dissolution rate in water at the respective temperature and agitation rate, the experimental ratios, R_1, and theoretical ratios, R_2, are in good agreement. However, when estimated with respect to the predicted dissolution rate of salicylamide in water, the predicted ratios, R_3, agree much less well with the experimental values.

Evidently, R_3 values based on rate equations that assume diffusion control for salicylamide dissolution in both caffeine solutions and water are incorrect for comparison with the experimental systems, so agreement is rather poor. However, the predicted ratios calculated with respect to the experimental rates in water, R_2, do take into account the initial interfacial control. Therefore, they become virtually identical with the experimental R_1 values as soon as the caffeine concentration is sufficient for the process to become diffusion controlled. The addition of the caffeine shifts the process from interfacial to diffusion control because of the increase of salicylamide concentration in the diffusion layer in the form of the complexed species.

Deviation from the linear diffusion model used in the present study might also be expected in three other cases: (*a*) where insoluble complexes are formed that coat the surface of the solid substrate, (*b*) where the complex contains more than one molecule of the ligand, and (*c*) where there is multiple complexation. In the first case, the dissolution rate–ligand concentration plot would exhibit a break; in the other cases, it would be curved since powers of $[C]_h$ would be involved. Ratios calculated in accordance with Eq. 10 (Table III, R_4) are also of the same order as the experimental ratios, R_1, the deviations presumably arising from the D approximation made. Thus, this simple equation yields a rapid estimate of the dissolution rate change obtained on complexation in these systems.

CONCLUSIONS

Complexation between the two drugs doubled the salicylamide dissolution rate at 37° and increased it fourfold at 25° over the range used. The experimental conditions selected covered substantial differences in K values, solubilities, and agitation rates. Therefore, since Eq. 6 and the estimated parameters correctly predicted the diffusion behavior during dissolution, they might afford a general procedure for estimating dissolution rates for a range of ligands without point-by-point experimental studies[7].

On the other hand, the dissolution rate of the substrate in water should always be measured since, should it differ appreciably from the predicted value, one would suspect interfacial control of dissolution rate to be present[8]. It would then be necessary to extend the experimental studies over a ligand concentration range sufficient to clarify the onset of diffusion control.

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[7] The procedure has not yet been tested with other types of dissolution apparatus, but further studies are underway.

[8] The water experiment would also permit detection of surface area deviations (12). If the ligand possessed surface activity, it might influence the dissolution rate even before an appreciable amount of complex was formed. There is no evidence of such an effect with caffeine.

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Dihydroergotoxine: Separation and Determination of Four Components by High-Performance Liquid Chromatography

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Abstract □ The evaluation of a new high-performance liquid chromatographic method is described. It permits the separation and determination of the four components of dihydroergotoxine (dihydroergocristine, dihydroergocornine, dihydro-α-ergocryptine, and dihydro-β-ergocryptine) in a single step. On reversed-phase microparticles, complete baseline separation is possible with different mobile phases containing about 10^{-2} *M* base. The analysis of dihydroergotoxine mesylate drug substance or its dosage forms can be carried out in about 15 min. No reference substance is required for the determination of the proportions of the components. This method is simple and exhibits high accuracy, reproducibility, and selectivity. It permits the analytical control of dosage forms containing dihydroergotoxine mesylate to ensure that they comply with the specifications for the drug substance used in clinical and pharmacological studies.

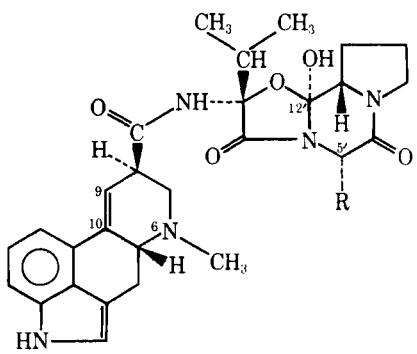
Keyphrases □ Dihydroergotoxine—high-performance liquid chromatographic analyses of four components in bulk drug and pharmaceutical formulations □ High-performance liquid chromatography—analyses, four components of dihydroergotoxine in bulk drug and pharmaceutical formulations □ Antiadrenergic agents—dihydroergotoxine, high-performance liquid chromatographic analyses of four components in bulk drug and pharmaceutical formulations

Ergotoxine is the name given to a particular group of ergot alkaloids derived from lysergic acid; they contain peptide moieties with similar chemical structures and have almost the same chemical and physical properties. These alkaloids are produced together by many strains of *Claviceps purpurea.*

Ergotoxine was believed to consist of three components: ergocristine (I), ergocornine (II), and ergocryptine (1, 2). In 1967, however, ergocryptine was shown to be composed of two isomers (3, 4), designated α-ergocryptine (III) and β-ergocryptine (IV) (5), differing only in one isomeric amino acid.

BACKGROUND

Ergotoxine, the actual product from *Claviceps,* is not used as such but in the form of the 9,10-dihydro derivative, generally called dihydroergotoxine (V–VIII). In the mesylate form, it is now widely used for the treatment of symptoms of impairment of mental function in the elderly.



I: R = $CH_2C_6H_5$
II: R = $CH(CH_3)_2$
III: R = $CH_2CH(CH_3)_2$
IV: R = $CH(CH_3)CH_2CH_3$
V: R = $CH_2C_6H_5$; 9,10-dihydro
VI: R = $CH(CH_3)_2$; 9,10-dihydro
VII: R = $CH_2CH(CH_3)_2$; 9,10-dihydro
VIII: R = $CH(CH_3)CH_2CH_3$; 9,10-dihydro

Proof of safety and efficacy was obtained with material[1] containing the four constituents in specified proportions, representing the amounts found in natural ergotoxine isolated from selected, cultivated strains of *C. purpurea.* This defined dihydroergotoxine mesylate[2] consists of equal amounts of the mesylates of dihydroergocristine (V), dihydroergocornine (VI) and dihydroergocryptine (both isomers taken together), the ratio of dihydro-α-ergocryptine (VII) to dihydro-β-ergocryptine (VIII) being 2:1.

An analytical method is required to check the compliance of active ingredient and dosage forms with these specifications[3]. No simultaneous

[1] Hydergine, Sandoz Ltd.
[2] Dergocrine, generic name proposed to WHO.
[3] The tolerance ranges are 30.3–36.3% for V and VI as well as for the sum of VII and VIII and 1.5:1–2.5:1 for the ratio of VII to VIII.