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Caffeine Complexes with Low Water Solubility: Synthesis and Dissolution Rates of 1:1 and 1:2 Caffeine–Gentisic Acid Complexes

T. HIGUCHI and IAN H. PITMAN▲

Abstract □ The syntheses of 1:1 and 1:2 molecular complexes of caffeine with gentisic acid are described, and their rates of dissolution are reported and compared with that of caffeine. Both complexes were less soluble in water than caffeine, and their rates of dissolution in 0.1 *N* hydrochloric acid and in a phosphate buffer at pH 7.5 were less than that of caffeine. These complexes thus present a potentially useful way of formulating caffeine in dosage forms such as chewable tablets that are intended to linger in the mouth. Such dosage forms would only release caffeine slowly and should, consequently, have an improved taste factor over ones containing pure caffeine. The rates of dissolution of the complexes were close to those predicted by equations that take into account both the diffusional and chemical equilibrium processes occurring. These equations are shown to be useful in the selection of a complex to achieve a specific dissolution rate.

Keyphrases □ Caffeine complexes with gentisic acid—synthesis, characterization, solubility, dissolution rate, compared to caffeine dissolution rate □ Dissolution rates of caffeine–gentisic acid complexes—determination, compared to caffeine dissolution rate □ Complexes, caffeine–gentisic acid—synthesis, characterization, solubility, dissolution rate □ Tablets, chewable, potential—caffeine–gentisic acid complexes

Molecular complexes of drugs with other chemicals have frequently been proposed[1] for inclusion in dosage forms to enhance the solubility, chemical stability, and absorption characteristics of the drugs. The present report describes the results of a search for molecular complexes of caffeine that would dissolve less rapidly in aqueous solutions than caffeine. The complexes that were prepared and studied had the stoichiometry of 1 : 1 and 1 : 2 caffeine–gentisic acid. It is believed that caffeine complexes that dissolve less rapidly in water than caffeine provide a useful alternative means of formulating caffeine in chewable tablets and other dosage forms which linger in the mouth. Such dosage forms should have an enhanced taste factor over ones containing pure caffeine, because their caffeine would be released more slowly and, consequently, the intensity of the extremely bitter taste produced by caffeine should be reduced.

The principles involved in this mechanism of taste masking are similar to those involved in the use of ion-exchange absorbates (2) to mask taste.

It has long been recognized that caffeine and other xanthines form molecular complexes with organic acids and organic acid anions (3). The latter type of complex is generally more soluble than the xanthine (soluble complex), while the former is commonly less soluble (insoluble complex). The present report concerns the properties of two insoluble complexes.

EXPERIMENTAL

Chemicals—Caffeine was recrystallized from water, dried under vacuum at 80°, and stored in a desiccator (m.p. 238–238.5°). Gentisic acid was boiled in an aqueous suspension of charcoal and

[1] This subject is reviewed in *Reference 1*.

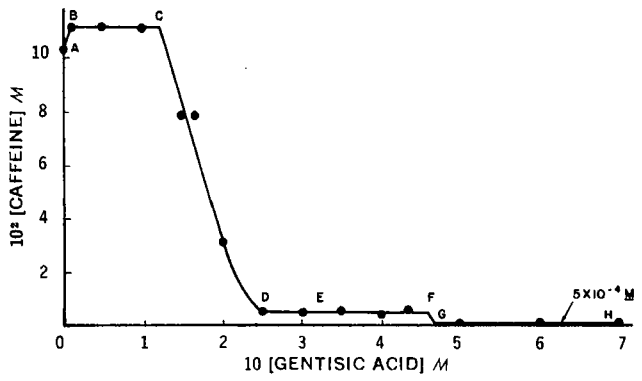

Figure 1—*Plot against* $[gentisic\ acid]_{added}$ *of the total concentration of caffeine (free and complexed).*

then recrystallized from water (m.p. 205°). All other chemicals were of analytical reagent grade and were used without further purification. The water used in all experiments was distilled from aqueous acidified potassium permanganate solutions and stored in Pyrex glass containers.

Preparation of Caffeine Complexes—*1:1 Caffeine–Gentisic Acid Complex*—Gentisic acid, 15.41 g. (0.11 mole), dissolved in 100 ml. of hot water was mixed with 19.42 g. (0.1 mole) of caffeine dissolved in 100 ml. of hot water and the mixture cooled rapidly. The complex precipitated as a microcrystalline powder which, after washing with water and drying under vacuum at 80°, had a melting point of 209.5–210°. Titration of a solution of the powder with standard sodium hydroxide to the phenolphthalein end-point showed that it had a molecular weight of 348 ± 1 g. This powder thus corresponded to the 1:1 caffeine–gentisic acid complex which has a molecular weight of 348.31 g.

1:2 Caffeine–Gentisic Acid Complex—Caffeine, 19.4 g. (0.1 mole), dissolved in 600 ml. of hot water and 33.9 (0.22 mole) of gentisic acid dissolved in 600 ml. of hot 3×10^{-3} *M* hydrochloric acid were mixed, allowed to cool slowly, and shaken at room temperature for 12 hr. After filtration, washing with water, and drying at 80° under vacuum, the microcrystalline precipitate had a melting point of 194–196°. The molecular weight of the complex was shown by titration to be 502 ± 1 g. The molecular weight of the 1:2 complex would be 502.43 g.

Phase Solubility Study—Caffeine, 0.45 g. (2.317×10^{-3} mole), and 10 ml. of water or a standardized gentisic acid solution were added to screw-cap vials, which were then sealed and rotated in a water bath at 25 ± 0.1° for 24 hr. Preliminary experiments had shown that the solutions reached equilibrium after this time. The total amount of caffeine in each equilibrated solution was determined by filtering the solution, measuring out 1-ml. aliquots, adding sufficient sodium bicarbonate to bring them to pH 7, extracting with 4×10 ml. of chloroform, and measuring the absorbance of a solution made by combining the chloroform extracts and making them up to an appropriate volume with chloroform. Absorbance values were converted to concentrations of dissolved caffeine using a previously constructed Beer's law plot (Fig. 1).

Dissolution Rate Studies—The solid whose dissolution rate was to be measured was reduced to a uniform particle size by sifting it through a 40-mesh sieve and collecting it in a 60-mesh sieve. It was then compressed into tablets in an evacuable KBr die[2] at 5000 p.s.i. for 2 min. using a laboratory press[3]. A vacuum was applied during the compression. The tablets had a diameter of 13 mm. and a thickness of 3 mm. (400-mg. tablet).

The dissolution medium was either a 0.1 *N* solution of hydrochloric acid or a pH 7.5 buffer solution, which was made by mixing 50 ml. 0.1 *M* potassium dihydrogen phosphate with 40.8 ml. 0.1 *M* sodium hydroxide and 9.2 ml. of distilled water.

The method of obtaining absorbance against time data during the dissolution process was essentially the same as that described in an earlier publication from this laboratory (4). The stirring rate was maintained at 45 ± 1 r.p.m. The dissolution of caffeine was followed at either 290 or 297 nm. and that of the complexes was followed at wavelengths (330, 347, 350, and 355 nm.) where the gentisic acid was the main absorbing species.

Plots of absorbance against time during the dissolution were linear initially, but their gradients then decreased continually with time. A typical plot is displayed in Fig. 2. Initial rates of change in absorbance at the analytical wavelength $(dD/dt)_0$ were taken to be the gradient of the initial linear portion of the curve. Values of $(dD/dt)_0$ were converted to rates of increase in concentration by using the identity:

$$\left(\frac{dD}{dt}\right)_0 = E_C\left(\frac{d[C]}{dt}\right)_0 + E_G\left(\frac{d[G]}{dt}\right)_0 \qquad \text{(Eq. 1)}$$

where E_C and E_G were the molar absorptivities of caffeine and gentisic acid, respectively, at the particular wavelengths; and $[C]$ and $[G]$ were the corresponding concentrations of these species, respectively. Preliminary experiments had shown that the dissolved complex was essentially completely dissociated into caffeine and gentisic acid during the initial period of the dissolution process. Because $E_C \simeq 0$ at the wavelengths at which the dissolution of the complexes was followed, the term $E_C(d[C]/dt)_0$ could be excluded from Eq. 1 in these experiments and $(d[G]/dt)_0$ could be calculated directly from the absorbance changes. The absorptivities of each species at the appropriate wavelength were calculated from independent determinations and are believed to be accurate to within ±5%. Results are included in Table I.

RESULTS AND DISCUSSION

Selection of a Molecular Complex of a Drug that Has the Desired Dissolution Characteristics—The rate at which the total *A* component in a molecular complex AB_n will dissolve is given by the flux of all forms of *A* (*i.e.*, AB_n, AB_{n-1}, . . . , *A*) from the solid–liquid interface into the bulk of the solution. In the following discussion this flux will be referred to as the rate of dissolution of the complex AB_n.

To select rationally a particular molecular complex of a drug which will dissolve either faster, slower, or at the same rate as the uncomplexed drug, it is useful to be able to predict the relative rates of dissolution of these two species. This type of prediction can be satisfactorily made in the following manner by using a film theory of mass transport.

Rate of Dissolution of Pure *A*—The Noyes–Whitney (5) equation, which is based on a film theory of mass transport, states that in a nonreacting medium that is being agitated in a constant manner:

$$\text{rate of dissolution of pure } A \text{ at time } t = kD_A(S_A - [A]_t) \qquad \text{(Eq. 2)}$$

In this equation, D_A is the diffusion coefficient of *A* in the dissolu-

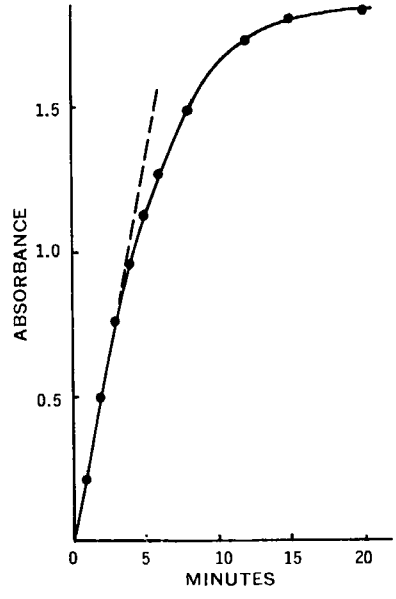

Figure 2—*Plot against time of the absorbance changes at 297 nm. which accompanied the dissolution of caffeine (400-mg. tablet) in 100 ml. of phosphate buffer at pH 7.5. Stirring speed = 45 r.p.m.*

[2] Research and Industrial Instruments Co., London, England.
[3] Fred S. Carver Inc., Summit, N. J.

Table I—Rates[a] of Appearance of Caffeine $(d[C]/dt)_0$ and Gentisic Acid $(d[G]/dt)_0$ in Solution during the Dissolution at 25° of Caffeine and Its 1:1 and 1:2 Complexes with Gentisic Acid

Compound	pH	$\lambda_{analytical}$, nm.	$\left(\frac{dD}{dt}\right)_0$, min.$^{-1}$	$\left(\frac{dG}{dt}\right)_0$, M min.$^{-1}$	Rate of Dissolution of the Solid, M min.$^{-1}$
Caffeine (400 mg.)	7.5	297[b]	1.12	—	2.1×10^{-3}
1:1 complex (400 mg.)	7.5	347[c]	0.83	8.8×10^{-4}	8.8×10^{-4}
1:2 complex (400 mg.)	7.5	350[d]	0.61	9.4×10^{-4}	4.7×10^{-4}
Caffeine (400 mg.)	1.0	297[b]	1.05	—	2.0×10^{-3}
1:1 complex (400 mg.)	1.0	350[e]	0.43	2.1×10^{-4}	2.1×10^{-4}
1:2 complex (400 mg.)	1.0	355[f]	0.21	1.7×10^{-4}	8.5×10^{-5}

[a] Values represent the mean of three to four experiments under each condition. [b] $E_C = 527$. [c] $E_G = 945$. [d] $E_G = 647$. [e] $E_G = 2018$. [f] $E_G = 1252$.

tion medium, S_A is the solubility of A in the dissolution medium and is the concentration of A in solution at the solid–liquid interface, and $[A]_t$ is the concentration of A in the bulk of the solution at time t. The constant k is proportional to the surface area of the solid and inversely proportional to the thickness of a diffusional layer or film of liquid surrounding the solid. This equation has been well tested and yields acceptable estimates of the rate of dissolution of pure solids.

Rate of Dissolution of a Molecular Complex AB_n—If a molecular complex of a drug can dissociate in solution according to reactions such as:

$$AB_n \overset{K_{1:n}}{\rightleftharpoons} AB_{n-1} + B;\ \ldots;\ AB \overset{k_{1:1}}{\rightleftharpoons} A + B \qquad \text{(Eq. 3)}$$

it is necessary to use a rate equation that takes into account the effects of these dissociation reactions on the flux of AB_n. General equations of this type were developed by Olander (6) and he established that, for such a system, the flux of the total A component is equal to the sum of the fluxes of all species containing A. Hence:

$$\text{rate of dissolution of } AB_n \text{ at time } t = k' \{D_{AB_n}([AB_n]_0 - [AB_n]_t) + D_{AB_{n-1}}([AB_{n-1}]_0 - [AB_{n-1}]_t) + \ldots + D_A([A]_0 - [A]_t)\} \qquad \text{(Eq. 4)}$$

The symbols in this equation have similar meanings to those in Eq. 2, except that $[i]_0$ terms refer to the concentrations of the i species at the solid–liquid interface. If the restriction is imposed that the solid phase is composed entirely of AB_n and this is the only species that can reenter the interface, the value of $[AB_n]_0$ is the intrinsic solubility of AB_n in the dissolution medium, S_{AB_n}, and values of all other $[i]_0$ terms are less than the solubilities of these species.

In discussing the relative rates of dissolution of uncomplexed and complexed drugs, it is convenient to consider the initial rates of dissolution. These will be the rates of dissolution at times when the $[i]_t$ terms are very much smaller than the $[i]_0$ terms. Thus, if solid samples of species A and AB_n with equal surface areas are separately dissolving in identical solvents that are being agitated in the same manner (and hence the k and k' values in Eqs. 2 and 4 are equal), the ratios of their initial rates of dissolution are given by:

$$R = \frac{\text{initial rate of dissolution of } AB_n}{\text{initial rate of dissolution of } A} = \frac{D_{AB_n}S_{AB_n} + D_{AB_{n-1}}[AB_{n-1}]_0 + \ldots + D_A[A]_0}{D_AS_A} = \frac{(D_{AB_n}/D_A)S_{AB_n} + (D_{AB_{n-1}}/D_A)[AB_{n-1}]_0 + \ldots + [A]_0}{S_A} \qquad \text{(Eq. 5)}$$

In the special situation where the rates of the association and dissociation reactions are very fast compared to the diffusional processes, it can be assumed that equilibrium between all of the species containing A is maintained throughout the diffusional layer. This situation is believed to apply to the dissolution of caffeine–gentisic acid complexes because UV spectral observations suggest that they form and dissociate extremely rapidly. Hence, in the dissolution of these complexes, the total concentration at the solid–liquid interface of all species containing A would be the same as the total concentration of all species containing A that would pertain in a solution made by saturating the solvent used in the dissolution experiment with AB_n. This total concentration (A_T) would be given by:

$$A_T = S_{AB_n} - [AB_{n-1}]_0 + \ldots + [A]_0 \qquad \text{(Eq. 6)}$$

and is a property that can be rapidly determined for any complex.

Substitution of Eq. 6 in Eq. 5 leads to:

$$R = \frac{A_T + S_{AB_n}[(D_{AB_n}/D_A) - 1] + [AB_{n-1}]_0 + [(D_{AB_{n-1}}/D_A) - 1] + \ldots}{S_A} \qquad \text{(Eq. 7)}$$

Hence, it can be seen that in situations where the diffusion coefficients of all species have similar values, the relative rates of dissolution of complexed and uncomplexed drugs are simply given by:

$$R = \frac{A_T}{S_A} \qquad \text{(Eq. 8)}$$

Equation 8 is expected to give a good estimate of relative dissolution rates of caffeine–gentisic acid complexes and caffeine because the molecular weights of these species differ by less than a factor of 3 (molecular weights: 1:2 complex, 502; 1:1 complex, 384; and caffeine, 196). Hence, the diffusion coefficients of these substances are expected to be comparable because the diffusion coefficient is proportional to only the $^1/_2$ or $^1/_3$ power of the molecular weight (4).

Equation 8 is quite general for dissolution of substances that can undergo any rapid reversible reaction in the dissolution medium. Hence, as well as taking into account dissociation reactions, it also takes into account ionization reactions in the dissolution medium of any or all of the species.

Because the value of A_T is dependent on both the intrinsic solubility of the complex and the extent to which it dissociates or ionizes in solution, these factors will also affect the dissolution rate of the complex relative to the uncomplexed drug. Hence, the value of R for a particular complex can be increased or decreased by using a solvent that increases or represses, respectively, the intrinsic solubilities of the complex or uncomplexed drug, the dissociation reactions, or ionization reactions.

Synthesis and Characterization of Caffeine–Gentisic Acid Complexes—The initial evidence for formation of 1:1 and 1:2 caffeine–gentisic acid complexes was provided by the phase solubility diagram shown in Fig. 1. The portion A–D of this diagram is a typical B_s-type diagram (7). Based on arguments similar to those proposed by Higuchi and Connors (7), this portion of the diagram provides evidence for the formation of a 1:1 caffeine–gentisic acid complex with an approximate association constant of 100 M^{-1} and a solubility of the complex of 5×10^{-3} M. Insufficient data points were acquired for an accurate determination of the value of the association constant. Further evidence that a 1:1 complex was precipitating out in the C–D region was provided by the isolation of a pure solid 1:1 complex when 100 ml. of a 0.011 M solution of gentisic acid was mixed with 100 ml. of a 0.01 M solution of caffeine.

The D–H portion of this diagram is interpreted as providing evidence for the formation of a 1:2 caffeine–gentisic acid complex, because this portion is typical of the B_i diagram described by Higuchi and Connors (7). The solid phase in the D–F segment would be a mixture of 1:1 and 1:2 complexes and that in the G–H segment would be the 1:2 complex. Again, confirmation that this

Table II—Experimentally Determined and Predicted[a] Rates of Dissolution of 1:1 and 1:2 Caffeine-Gentisic Acid Complexes Relative to that of Caffeine

Solid	pH	A_T[b], M	R_{expt}[c]	R_{calc}[a]
1:1 complex	7.5	4.8×10^{-2}	4.2×10^{-1}	4.6×10^{-1}
1:2 complex	7.5	1.13×10^{-2}	2.2×10^{-1}	1.1×10^{-1}
1:1 complex	1.0	8.6×10^{-3}	1.1×10^{-1}	8.2×10^{-2}
1:2 complex	1.0	3.5×10^{-3}	4.3×10^{-2}	3.3×10^{-2}
Caffeine	1.0 or 7.5	1.05×10^{-1}	—	—

[a] Using Eq. 8. [b] As defined in Eq. 6. [c] Data from Table I.

latter conclusion was correct came from the fact that an essentially pure solid sample of the 1:2 complex precipitated when solutions of gentisic acid and caffeine with the molar concentration ratio of 2.2:1 were mixed. Although it was not possible to estimate the value of the 1:2 association constant because of the lack of precise data points, this portion of the diagram does provide an estimate of the solubility of the 1:2 complex. Thus, the maximum value of the solubility of the 1:2 complex can be seen from the value of the G–H plateau region to be 5×10^{-4} M. The caffeine in solution in this region could come from the dissolved 1:2 complex and any dissolved 1:1 complex or free caffeine that resulted from its dissociation. However, the fact that the concentration of caffeine in solution does not decrease with increasing gentisic acid concentration in this region suggests that the excess gentisic acid is effectively repressing the dissociation of the complex, and 5×10^{-4} M is consequently its solubility. This argument would not be valid if a 1:3 or higher order caffeine–gentisic acid complex was precipitating in this region but no evidence was found for this occurrence.

The total amounts (in M units) of the 1:1 and 1:2 complexes that would dissolve in aqueous 0.1 M HCl and a phosphate buffer at pH 7.5 were calculated from the amount of caffeine that could be extracted from aliquots of the supernatant liquids over their saturated solutions. The results are the A_T values referred to in Eq. 8, and they are included in Table II.

Comparison of Measured and Predicted Initial Dissolution Rates of 1:1 and 1:2 Caffeine–Gentisic Acid Complexes and Caffeine—The initial rates of dissolution of caffeine and its 1:1 and 1:2 gentisic acid complexes were calculated from the results of experiments carried out as described in the *Experimental* section. The initial rates of appearance of caffeine or gentisic acid in the bulk of the solution are listed in Table I.

During the initial stages of the dissolution of the 1:1 and 1:2 complexes (*i.e.*, when the concentrations of solute in the bulk of the solution were extremely small), the complexes were essentially totally dissociated in the bulk of the solution. Hence, the rate of dissolution of the complex was the same as the rate of appearance of gentisic acid in the solution in the case of the 1:1 complex and was half the rate of appearance of the gentisic acid in the case of the 1:2 complex. In all experiments, the dissolving tablets had the same dimensions (diameter, thickness, and particle size of the powder) and it was assumed that the surface area of the dissolving solid was identical. Stirring rate and temperature were also kept constant in each experiment. The rates of dissolution of the complexes relative to that of caffeine are listed in Table II together with the values of these ratios that were calculated using Eq. 8. It can be seen that Eq. 8 provides a useful way of predicting the rate of dissolution of a molecular complex of caffeine relative to pure caffeine. The fact that the complexes dissolve much faster in a buffer at pH 7.5 than in 0.1 M HCl is almost certainly because both the complexes and gentisic acid ionize in this medium. It is important to remember that while the bulk solvent in the experiments in phosphate buffer initially has a pH of 7.5, the pH at the solid–liquid interface, where the solvent is saturated with acidic species such as gentisic acid and its complexes, is much less.

The rates of dissolution of the complexes in saliva (pH 6.7–7.3) were not measured, but they are expected to approach the rates of dissolution in the phosphate buffer. Hence, they would just be marginally less than the rate of dissolution of pure caffeine. However, in an actual formulation it should be possible to reduce the dissolution rate of the complexes in saliva by including excess gentisic acid in the formulation. Dissolution of the excess gentisic acid would have the effects of both lowering the pH of the dissolution medium (addition of 1 ml. 0.1 M gentisic acid to 3 ml. of saliva lowers its pH from 6.7 to 3.2) and repressing the dissociation of the complexes. Both these effects would be expected, from Eq. 8, to lower the rate of dissolution. Evidence that this approach is valid comes from the observation that when 200 mg. of powdered 1:1 complex was stirred in water, it took 8 min. for the concentration of dissolved caffeine to reach 1.15×10^{-3} M, whereas the same concentration of caffeine was only attained after 113 min. when the dissolution medium contained 1×10^{-2} M gentisic acid.

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