Release Rates of Solid Drug Mixtures Dispersed in Inert Matrices II

Mutually Interacting Drug Mixtures

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The equations developed to describe the release from a mixture of two noninteracting drugs was further extended to cover the case where the two drugs mutually interact with each other. All the parameters were independently determined and evaluated as before. Complexation studies were carried out and their effects on the solubilities and diffusion coefficients were also considered in the theoretical equations. The different regions existing in the tablet matrix were independently analyzed. The theoretical equations for the drug release rates were seen to predict the experimental data extremely well.

In a previous communication, the release behavior of a mixture of two noninteracting drugs dispersed in an inert, insoluble matrix has been discussed (1). As a continuation of the same work, it was decided to study the somewhat more complex system where the two drugs incorporated in the matrix mutually interact. The benzocaine–caffeine mixture provided an interesting system since solution interactions between the two drugs lead to a mutual increase of their solubilities.

The diffusion-controlled model that will be utilized is essentially similar to the one used in the salicylic acid–benzoic acid mixture study. In this system, however, solution interactions of the two drugs require equations of a different form.

The model is schematically shown in Fig. 1. Figure 1(a) shows that benzocaine and caffeine are transported both as free drugs and as complex species through region 1. In region 2, however, the slower moving drug, caffeine, is transported solely as complexes, as the entire region is saturated with respect to free caffeine. Figures 1(b) and (c) show the appropriate boundary conditions at s_1 and s_2 and the resulting concentration gradients which are fully discussed under the *Appendix*.

Mutual interactions were included in the model by utilizing the appropriate stability expressions for the three complexes, B·C, B·C$_2$, and B·C$_3$. An adequate discussion of the release parameters, tortuosity, τ, and porosity, ϵ, was given in the previous paper (1) and the same terminology is applicable here.

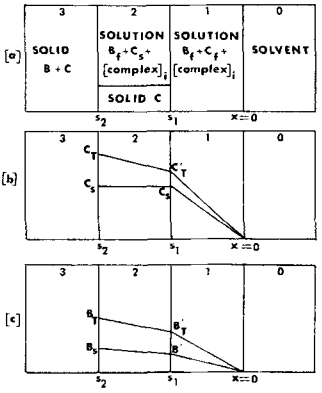

Fig. 1—The physical model that describes the simultaneous release of a mixture of two interacting drugs from an inert matrix. Key: (a) *conditions existing at finite time,* t; (b) *concentration gradients for the drug having the slower moving boundary;* (c) *concentration gradients for the drug having the faster moving boundary.*

The resulting equations are:

$$Q_B = A_B \cdot \gamma t^{1/2} \qquad \text{(Eq. 1)}$$

and

$$Q_C = \left[A_C \cdot \beta + A_B(\gamma - \beta)\left(\frac{\delta}{\alpha}\right)\right] t^{1/2} \qquad \text{(Eq. 2)}$$

where

$$\gamma = \frac{2\epsilon_1\epsilon_2 B_s \alpha}{A_B(\tau_2\epsilon_1\gamma - \tau_2\epsilon_1\beta + \tau_1\epsilon_2\beta)}$$

$$\beta = \left[\frac{2\epsilon_1 D_C C_s \alpha}{\tau_1(A_C\alpha - A_B\delta)}\right]^{1/2}$$

$$\alpha = D_B + D_{BC}K_1C_s + D_{BC_2}K_1K_2C_s^2 + D_{BC_3}K_1K_2K_3C_s^3$$

$$\delta = D_{BC}K_1C_s + 2D_{BC_2}K_1K_2C_s^2 + 3D_{BC_3}K_1K_2K_3C_s^3$$

A_i = concentration of drug i in the matrix,

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Q_i = total amount of drug i released per unit area,
D_i = diffusion coefficient of drug i,
K_i = stability constant of complex i,
C_s = solubility of uncomplexed caffeine,
B_s = solubility of uncomplexed benzocaine,
ϵ_j = porosity of region j,
τ_j = tortuosity of region j.

It should be emphasized that these equations are restricted to a system in which benzocaine exhibits the faster moving boundary. In this system the concentrations of all species are directly proportional to the concentration of free benzocaine in solution. In the reverse situation, however, the concentrations of all species must be expressed in terms of a polynomial involving the free caffeine solution concentration. This requires the solution of a cubic equation and results in a very lengthy and much more complicated set of equations.

EXPERIMENTAL

The matrix system used in these studies was a mixture of polyvinylchloride (PVC) and polyethylene in a 7:3 weight-to-weight ratio. This matrix was chosen for the study of drug release from mixtures of two drugs for reasons described previously (1).

A direct assay in the ultraviolet region for the simultaneous release of both drugs in the presence of each other was not utilized because of the strong mutual absorption at their respective maximum absorption wavelengths. Benzocaine was independently assayed using a colorimetric assay procedure involving a diazotization reaction (2), and recording its absorption at 550 mμ. The total absorption, however, due to both caffeine and benzocaine was determined at 273 mμ. The contribution from benzocaine adsorption at 273 mμ was then accounted for, allowing the determination of the caffeine concentration.

The diffusion coefficients of the pure drugs were determined experimentally by the method described earlier (3), modified by the use of a Gelman[1] Versapor filter in place of a sintered-glass disk.

Two kinds of interaction studies were carried out. In the first case, an excess amount of benzocaine (0.4 Gm.) was weighed into a series of Teflon-stoppered culture tubes and known but varying amounts of caffeine were added to them. Then, 20 ml. of distilled water was added to each tube. The samples were equilibrated in a constant-temperature tumbling water bath for 24 hr. They were then filtered through a Millipore[2] filter (0.45-μ pore size) and the samples prepared for spectrophotometric assay. In the other study, the reverse experiment was carried out where an excess amount of caffeine (1.6 Gm.) was weighed into each culture tube and known but varying amounts of benzocaine added. The samples were then equilibrated, filtered, and assayed.

RESULTS AND DISCUSSON

Interaction Studies—The results of the complexation-solubility experiments are presented in Figs. 2 and 3. As can be seen, when caffeine was added to excess solid benzocaine the total solubility of benzocaine, B_T, increased more rapidly than linearly with added caffeine (Fig. 2). In those experiments where benzocaine was added to excess solid caffeine, the total solubility of caffeine, C_T, was found to be essentially linear with total benzocaine added.

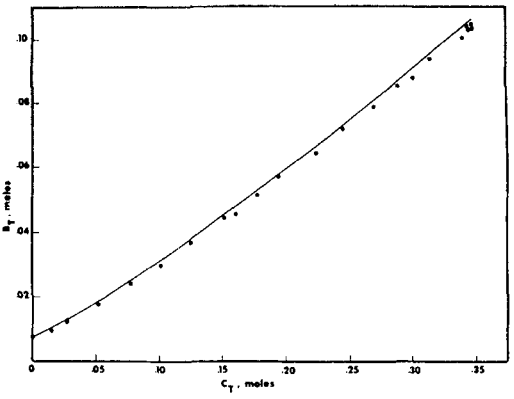

Fig. 2—Interaction study between benzocaine and caffeine using an excess of solid benzocaine and varying amounts of caffeine. The smooth curve represents the theoretical curve based on Eqs. 6 and 7 and the points represent experimental data. (See text for discussion.)

These data indicate that (*a*) for the Fig. 2 experiments, while only the 1:1 complex is important at low caffeine concentrations, there are other complexes contributing significantly to the B_T at the higher caffeine concentrations, and (*b*) in all of the complexes benzocaine probably occurs singly, *i.e.*, BC, BC_2, BC_3, BC_4, *etc.*, as suggested by the linear relationship (Fig. 3). In addition, the average stoichiometry of the complexes at the invariant point (saturation point for both phases) was found to be 2.17 with both sets of experiments. This showed that at least three complexes, the 1:1, the 1:2, and the 1:3 benzocaine–caffeine should be considered in a thermodynamic treatment of all of the data.

Thus, it was assumed that the following solution equilibria were present:[3]

$$B + C \overset{K_1}{\rightleftarrows} B\cdot C \qquad \text{(Eq. 3)}$$

$$B\cdot C + C \overset{K_2}{\rightleftarrows} B\cdot C_2 \qquad \text{(Eq. 4)}$$

$$B\cdot C_2 + C \overset{K_3}{\rightleftarrows} B\cdot C_3 \qquad \text{(Eq. 5)}$$

The stability constants were then evaluated in the following manner.

For the saturated-benzocaine experiment (Fig. 2), the total concentration of caffeine and benzocaine can be given by:

$$C_T = C_{\text{free}} + C_{\text{complexes}}$$
$$= C_i + K_1 B_s C_i + 2K_1K_2 B_s C_i^2 + 3K_1K_2K_3 B_s C_i^3 \qquad \text{(Eq. 6)}$$

and

[1] Gelman Instrument Co., Ann Arbor, Mich.
[2] Millipore Filter Corp., Bedford, Mass.
[3] The possibility is ignored that caffeine may self-associate at high caffeine concentrations as is suggested by the data of Guttman and Higuchi (4).

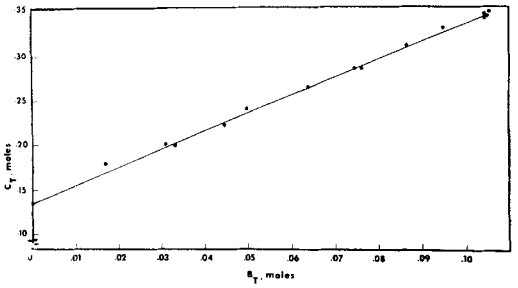

Fig. 3—Interaction study between benzocaine and caffeine using an excess of solid caffeine and varying amounts of benzocaine. The smooth curve represents the theoretical curve based on Eqs. 8 and 9 and the points represent experimental data. (See text for discussion.)

$$B_T = B_{\text{free}} + B_{\text{complexes}}$$

$$= B_s + K_1B_sC_i + K_1K_2B_sC_i^2 + K_1K_2K_3B_sC_i^3 \quad \text{(Eq. 7)}$$

For the saturated-caffeine experiments (Fig. 3) the corresponding expressions will be:

$$C_T = C_s + K_1B_iC_s + 2K_1K_2B_iC_s^2 + 3K_1K_2K_3B_iC_s^3 \quad \text{(Eq. 8)}$$

and

$$B_T = B_i + K_1B_iC_s + K_1K_2B_iC_s^2 + K_1K_2K_3B_iC_s^3 \quad \text{(Eq. 9)}$$

For the saturated-caffeine experiments (Fig. 3) where a straight line is obtained we have:

$$C_T = \text{slope} \times (B_T) + \text{intercept}$$

Then, using Eq. 8 and Eq. 9, we obtain:

$$K_2K_3 = \frac{2 + K_1C_s}{K_1C_s^3} \quad \text{(Eq. 10)}$$

Now K_1 may be determined from the initial slope of the Fig. 2 data. Then K_2 and K_3 can be solved by using Eq. 6 and Eq. 7. The calculated values for K_1, K_2, and K_3 were found to be 34.4, 3.2, and 24.1, respectively.

Using these calculated values for K_1, K_2, and K_3, both curves were reproduced theoretically and these results are given in Figs. 2 and 3 as the smooth curves. It can be seen that these calculated values for the stability constants give an extremely close fit to the experimental data and thereby confirm our hypothesis that, in the benzocaine–caffeine system, a consideration of these three complexes may adequately describe the system.

It should be pointed out that only this set of K_1, K_2, and K_3 values gave a good fit to the data. Thus, ignoring the terms involving K_3 did not give a satisfactory fit of the theory to the data.

Release Studies—The release profiles of benzocaine and caffeine as they are simultaneously released in water are presented in Figs. 4 and 5 for various weight-weight ratios of the two drugs in the tablet. Figure 6 shows the sum of benzocaine and caffeine release as a function of the square root of time. It is seen that the square root of time dependence, as

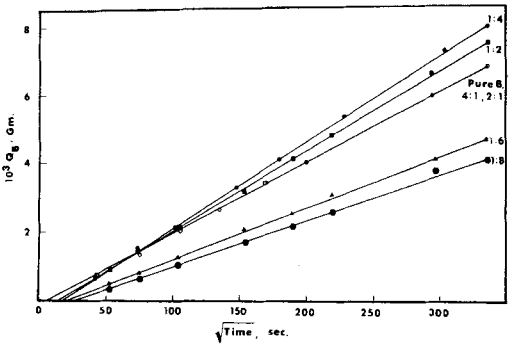

Fig. 4—Release of benzocaine from matrices containing different ratios of benzocaine to caffeine to water. The total amount of drug in all cases was 20% w/w, and the numbers indicate benzocaine-to-caffeine ratios.

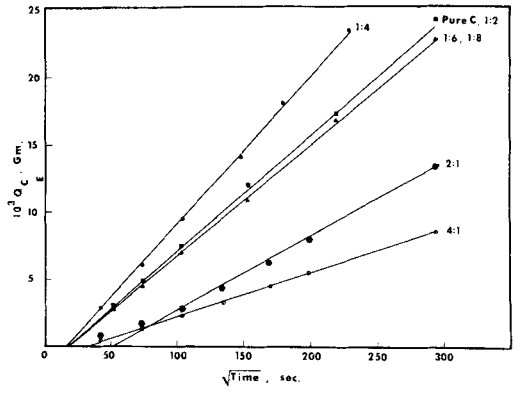

Fig. 5—Data showing caffeine release in the same experiments as in Fig. 4.

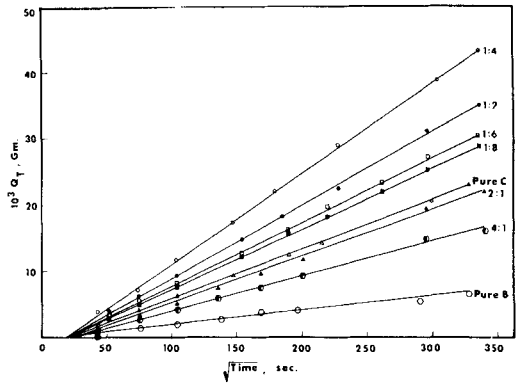

Fig. 6—The sum of the benzocaine and caffeine release in the same experiments as in Figs. 4 and 5.

predicted by the T. Higuchi equation (5), is observed in all cases. The data also show that for the total release as well as for the release of the individual drugs the 1:4 mixture ratio yields the highest release rate.

This 1:4 critical mixture ratio is in accordance with that predicted by the following relationship which is analogous to Eq. 3 of the previous com-

munication (1), and describes the relative rates of boundary movement for benzocaine and caffeine:

$$\frac{\text{boundary movement for caffeine}}{\text{boundary movement for benzocaine}} = \frac{Q_C/A_C}{Q_B/A_B} = \left[\frac{D_{C(eff.)}C_T A_B}{D_{B(eff.)}B_T A_C}\right]^{1/2}$$

assuming all other factors constant for both systems. Here, $D_{B(eff.)}$ and $D_{C(eff.)}$ are the effective diffusion coefficients for the total transport of benzocaine and caffeine, respectively, when diffusion of both solutes takes place from the solution saturated with respect to both drugs. Thus, when the two boundaries move at the same rate, the lefthand side of the above equation will be unity, and we have:

$$\frac{A_C}{A_B} = \frac{D_{C(eff.)}C_T}{D_{B(eff.)}B_T} = \frac{(6.94 \times 10^{-6})}{(7.08 \times 10^{-6})} \cdot \frac{(6.71 \times 10^{-2})}{(1.73 \times 10^{-2})} = 3.8$$

which is in close agreement with the experimental 1:4 ratio.

The values for the effective diffusion coefficients $D_{B(eff.)}$ and $D_{C(eff.)}$ were estimated from the following equations:

$$D_{B(eff.)} = \frac{D_B(B_s) + D_{BC}(K_1B_sC_s) + D_{BC_2}(K_1K_2B_sC_s^2) + D_{BC_3}(K_1K_2K_3B_sC_s^3)}{B_s + K_1B_sC_s + K_1K_2B_sC_s^2 + K_1K_2K_3B_sC_s^3}$$

and

$$D_{C(eff.)} = \frac{D_C(C_s) + D_{BC}(K_1B_sC_s) + 2D_{BC_2}(K_1K_2B_sC_s^2) + 3D_{BC_3}(K_1K_2K_3B_sC_s^3)}{C_s + K_1B_sC_s + 2K_1K_2B_sC_s^2 + 3K_1K_2K_3B_sC_s^3}$$

The diffusion coefficients for benzocaine and caffeine and the stability constants were determined experimentally, and the diffusion coefficients for the complexes were estimated from the Stokes-Einstein relation (6). That the Stokes-Einstein estimations were reasonable was verified by an experimental determination of the effective diffusion coefficient for benzocaine which was done by diffusing a solution saturated with both caffeine and benzocaine into a solution saturated only with caffeine. (See Table I.)

Analysis of Region 1 Parameters—To test the proposed model, both region 1 and region 2 need to be independently analyzed. The tortuosity value of region 1 cannot be obtained from the experiments as was done in the salicylic acid–benzoic acid problem using the T. Higuchi equation (5) since the total solution concentrations of benzocaine and caffeine at the boundary s_1 are unknowns in this problem. For this reason, a different approach was used. Equation 8*a* (from the *Appendix*) is:

$$G_C = \frac{\epsilon_1}{\tau_1 s_1} D_C \cdot C_s + G_B \frac{\delta}{\alpha} \qquad \text{(Eq. 8a)}$$

s_1 can be substituted for by Eqs. 21*a* and 22*a*, G by $dQ/2t^{1/2}d(t^{1/2})$, and after rearrangement, τ_1 can be expressed as:

$$\tau_1 = \frac{2\alpha\epsilon_1 D_C C_s}{\beta[(Q_C/t^{1/2})\alpha - (Q_B/t^{1/2})\delta]} \qquad \text{(Eq. 11)}$$

Since this model only describes the case where caffeine has the slower moving boundary, the tortuosity values that can be obtained by this method are restricted to the data for benzocaine–caffeine ratios of 1:4, 1:6, and 1:8. These are presented in Table II.

Tortuosity values for region 1 have also been determined independently by liquid leaching experiments (7) and are listed in Table II. The agreement between the two sets of tortuosity values obtained by these separate experiments is generally good. These findings alone lend strong support to the validity of the proposed model.

Analysis of Region 2 Parameters—In order to evaluate the tortuosity factor in region 2, benzocaine release data (see Fig. 7) were obtained with the tablets in media saturated with caffeine, a procedure employed previously (1). The data then may be evaluated directly by means of the following equation:

$$Q_B = \left[\frac{2\epsilon_2 A_B}{\tau_2}(D_B B_s + D_{BC}K_1C_sB_s + D_{BC_2}K_1K_2B_sC_s^2 + D_{BC}K_1K_2K_3B_sC_s^3)t\right]^{1/2} \qquad \text{(Eq. 12)}$$

which was derived using Eq. 9*a* with the boundary conditions that $s_1 = 0$ for all t, and B = 0 and C = C_s at $x = 0$ for all t. The ϵ_2 entering in Eq. 12 is given by:

$$\epsilon_2 = \frac{A_B}{\rho_B} + A_B\frac{G_C'}{G_B\rho_C} + \epsilon_{air} \qquad \text{(Eq. 13)}$$

where ρ_B and ρ_C are the densities of benzocaine and caffeine and ϵ_{air} is the porosity contribution due to air. The second term of Eq. 13 represents the porosity contribution due to the caffeine loss from the tablet resulting from the diffusion of the complexes through the matrix and out of the tablet (see Eq. 10*a* under *Appendix*).

Table III gives the calculated ϵ's and τ_2 values obtained from the experiments (Fig. 7) in saturated caffeine solutions using Eqs. 12 and 13. The stability constants determined in the solubility studies and the diffusion coefficients given in Table I were used.

Test of the Model Using All Parameters—Having obtained all of the matrix parameters (ϵ_1, ϵ_2, τ_1, τ_2) and the interaction parameters (K_1, K_2, K_3, C_T, B_T, and the diffusion coefficients), it was then possible to carry out a composite test of the model proposed

Table I—Diffusion Coefficients of the Different Benzocaine and Caffeine Species Involved in This Study

Drug Species	Diff. Coeff. × 10^6 cm.²/sec.
Benzocaine	9.86[a]
Caffeine	7.53[a]
[B·C]	7.84[b]
[B·C_2]	6.85[b]
[B·C_3]	6.20[b]
Total benzocaine species $D_{B(eff.)}$	5.94[a]
$D_{BB(eff.)}$	7.08[b]
Total caffeine species $D_{C(eff.)}$	6.94[b]

[a] Experimental values. [b] Calculated values, based on the Stokes-Einstein relation.

TABLE II—PARAMETERS INVOLVED IN THE DETERMINATION OF TORTUOSITY OF THE OUTER REGION 1

B:C Ratio	ϵ_1[a]	$10^5 Q_B/t^{1/2}$ Solid Release	$10^5 Q_C/t^{1/2}$ Solid Release	$10^5 Q/t^{1/2}$ Liquid Release[b]	τ_1 from Solid Release (Eq. 11)	τ_1[b] from Liquid Release
Pure B	0.313	1.85	...	1.52	3.2	2.0
4:1	0.312	2.08	3.50	1.38	...	2.2
2:1	0.311	2.20	5.50	1.39	...	2.1
1:2	0.299	2.30	8.70	1.26	...	3.0
1:4	0.295	2.53	11.0	1.15	2.5	2.8
1:6	0.283	1.49	8.0	1.13	3.3	2.6
1:8	0.278	1.34	7.8	1.04	3.8	3.0
Pure C	0.289	...	8.25	1.04	3.0	3.2

$\epsilon_1 = \epsilon_{total} = \epsilon_{benz.} + \epsilon_{caff.} + \epsilon_{air}$. [b] For these experiments, C_0 = 2.6% caffeine solution (see *Reference 7*).

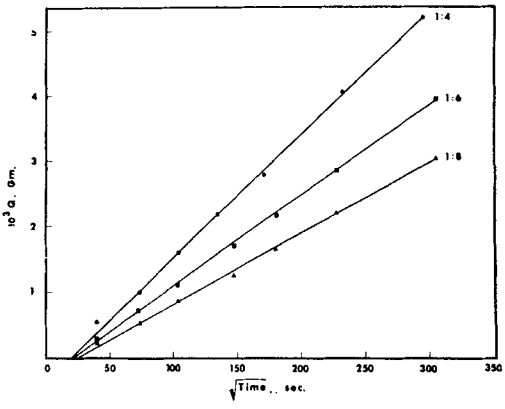

Fig. 7—Release of benzocaine from matrices containing different ratios of benzocaine to caffeine into saturated caffeine solutions.

tion of these equations is based on the model presented in Fig. 1 for the case when benzocaine has the faster moving solid–liquid drug boundary. Since the benzocaine–caffeine system forms more than one complex at stoichiometrically different ratios, the reverse situation of benzocaine having the slower boundary would require different equations.

It has been shown that benzocaine and caffeine interact to form three soluble complexes as represented below:

$$B + C \rightleftharpoons B\cdot C$$
$$B\cdot C + C \rightleftharpoons B\cdot C_2$$
$$B\cdot C_2 + C \rightleftharpoons B\cdot C_3$$

The corresponding stability constants are expressed as:

$$K_1 = \frac{(B\cdot C)}{(B)\,(C)}$$

TABLE III—PARAMETERS INVOLVED IN THE DETERMINATION OF TORTUOSITY OF THE INNER REGION 2

B:C Ratio	$\epsilon_{benz.}$	$\epsilon_{caff.}$[a]	ϵ_{air}	ϵ_2 (Eq. 13)	$10^5 Q/t^{1/2}$	τ_2
1:4	0.037	0.061	0.136	0.234	1.07	7.7
1:6	0.027	0.044	0.121	0.192	1.40	6.6
1:8	0.021	0.035	0.118	0.174	1.88	6.2

[a] $\epsilon_{caff.}$ value for the second term in Eq. 13.

TABLE IV—COMPARISON OF THE EXPERIMENTAL AND THEORETICAL RELEASE RATES

B:C Ratio	Exptl. $10^5 Q/t^{1/2}$ B	Exptl. $10^5 Q/t^{1/2}$ C	Theoret. $10^5 Q/t^{1/2}$ B	Theoret. $10^5 Q/t^{1/2}$ C
1:4	2.53	11.0	2.83	10.8
1:6	1.49	8.00	2.00	10.37
1:8	1.34	7.80	1.45	9.34

in this paper. This was done by substituting the values for all of these parameters into Eqs. 1 and 2, calculating the theoretical rates of drug release for both benzocaine and caffeine, and then comparing these to the experimental values.

Table IV shows the close agreement of experiment with theory for both drugs and for the three mixture ratios.

APPENDIX

Derivation of Theoretical Equations When Benzocaine is the Faster Moving Boundary—The derivation of these equations is based on the model presented in Fig. 1 for the case when benzocaine has the faster moving solid–liquid drug boundary. Since the benzocaine–caffeine system forms more than one complex at stoichiometrically different ratios, the reverse situation of benzocaine having the slower boundary would require different equations.

It has been shown that benzocaine and caffeine interact to form three soluble complexes as represented below:

$$B + C \rightleftharpoons B\cdot C$$
$$B\cdot C + C \rightleftharpoons B\cdot C_2$$
$$B\cdot C_2 + C \rightleftharpoons B\cdot C_3$$

The corresponding stability constants are expressed as:

$$K_1 = \frac{(B\cdot C)}{(B)\,(C)}$$

$$K_2 = \frac{(B\cdot C_2)}{(B\cdot C)\,(C)}$$

$$K_3 = \frac{(B\cdot C_3)}{(B\cdot C_2)\,(C)}$$

The boundary conditions for the two drugs at s_1 and s_2 can be given in terms of K_1, K_2, K_3, and uncomplexed drug concentrations.

At the boundary s_1, the concentration expressions are:

$$(C) = C_s$$
$$(B) = B'$$
$$(B\cdot C) = K_1 B' C_s$$
$$(B\cdot C_2) = K_1 K_2 B' C_s^2$$
$$(B\cdot C_3) = K_1 K_2 K_3 B' C_s^3$$

and at the boundary s_2, they are:

$$(C) = C_s$$
$$(B) = B_s$$

$$(B\cdot C) = K_1 B_s C_s$$
$$(B\cdot C_2) = K_1 K_2 B_s C_s^2$$
$$(B\cdot C_3) = K_1 K_2 K_3 B_s C_s^3$$

where B' is the concentration of benzocaine at the boundary s_1. The other parameters have been defined earlier.

The equations of continuity for region 1 yield the following relationships for the net movement of all species:

$$G_B = \frac{\epsilon_1}{\tau_1}\left[D_B\frac{d(B)}{dx} + D_{BC}\frac{d(BC)}{dx} + D_{BC_2}\frac{d(BC_2)}{dx} + D_{BC_3}\frac{d(BC_3)}{dx}\right] \quad \text{(Eq. 1}a\text{)}$$

and

$$G_C = \frac{\epsilon_1}{\tau_1}\left[D_C\frac{d(C)}{dx} + D_{BC}\frac{d(BC)}{dx} + 2D_{BC_2}\frac{d(BC_2)}{dx} + 3D_{BC_3}\frac{d(BC_3)}{dx}\right] \quad \text{(Eq. 2}a\text{)}$$

where G_i is the rate of movement of species i, D_i is the diffusion coefficient of species i, and di/dx is the concentration gradient for species i.

Integration of Eq. 1a from $x = 0$ to $x = s_1$ yields:

$$G_B\cdot s_1 = \frac{\epsilon_1}{\tau_1}B'\alpha \quad \text{(Eq. 3}a\text{)}$$

where

$$\alpha = (D_B + D_{BC}K_1C_s + D_{BC_2}K_1K_2C_s^2 + D_{BC_3}K_1K_2K_3C_s^3) \quad \text{(Eq. 4}a\text{)}$$

Rearrangement of Eq. 3a gives:

$$B' = \frac{G_B s_1 \tau_1}{\epsilon_1 \alpha} \quad \text{(Eq. 5}a\text{)}$$

Integration of Eq. 2a similarly yields:

$$G_C s_1 = \frac{\epsilon_1}{\tau_1}(D_C\cdot C_s) + \frac{\epsilon_1}{\tau_1}B'\delta \quad \text{(Eq. 6}a\text{)}$$

where

$$\delta = (D_{BC}K_1C_s + 2D_{BC_2}K_1K_2C_s^2 + 3D_{BC_3}K_1K_2K_3C_s^3) \quad \text{(Eq. 7}a\text{)}$$

On substituting for B' from Eq. 5a, Eq. 6a then becomes:

$$G_C = \frac{\epsilon_1}{\tau_1\cdot s_1}(D_C\cdot C_s) + G_B\frac{\delta}{\alpha} \quad \text{(Eq. 8}a\text{)}$$

The equations of continuity for region 2, on the other hand, are:

$$G_B = \frac{\epsilon_2}{\tau_2}\left[D_B\frac{d(B)}{dx} + D_{BC}\frac{d(BC)}{dx} + D_{BC_2}\frac{d(BC_2)}{dx} + D_{BC_3}\frac{d(BC_3)}{dx}\right] \quad \text{(Eq. 9}a\text{)}$$

and

$$G_C' = \frac{\epsilon_2}{\tau_1}\left[D_C\frac{d(C)}{dx} + D_{BC}\frac{d(BC)}{dx} + 2D_{BC_2}\frac{d(BC_2)}{dx} + 3D_{BC_3}\frac{d(BC_3)}{dx}\right] \quad \text{(Eq. 10}a\text{)}$$

It is to be noted that G_C' is equal to the rate of transport of total caffeine from region 2. Since region 2 contains a saturated solution with respect to free caffeine, this rate must only involve the movement of caffeine complexes and therefore is different from G_C which includes the diffusion of free caffeine as well as the complexes.

On integrating Eq. 9a from $x = s_1$ to $x = s_2$ one obtains:

$$G_B(s_2 - s_1) = \frac{\epsilon_2}{\tau_2}(B_s - B')\alpha \quad \text{(Eq. 11}a\text{)}$$

again, where α is given by Eq. 4a. Equation 5a is substituted for B', yielding:

$$G_B = \frac{\epsilon_2\alpha}{\tau_2(s_2 - s_1)}\left[B_s - \frac{G_B s_1 \tau_1}{\propto \epsilon_1}\right] \quad \text{(Eq. 12}a\text{)}$$

Integration of Eq. 10a, on the other hand, gives:

$$G_C' = \frac{\epsilon_2\cdot\delta}{\tau_2(s_2 - s_1)}(B_s - B') \quad \text{(Eq. 13}a\text{)}$$

where δ is given by Eq. 7a.

The above equations cannot be solved as there are more variables than equations. Another set of equations, however, can be obtained by considering the amount of each drug released, determined on the basis of the amount incorporated in the tablet matrix and both drug boundary movements. In this way equivalent expressions for G_B and G_C can be obtained. Examination of Fig. 1 shows that the total amount of drug B released, Q_B, is a function of the distance its boundary has moved out, and therefore,

$$Q_B = s_2\cdot A_B \quad \text{(Eq. 14}a\text{)}$$

neglecting the amount of drug remaining as solution in the matrix. This condition is met when $C_s <<< A$. Then, differentiating Eq. 14a,

$$G_B = \frac{dQ_B}{dt} = A_B\frac{ds_2}{dt} \quad \text{(Eq. 15}a\text{)}$$

The total amount of drug C released, Q_C, on the other hand, is a function of the distance both boundaries have moved and can be expressed as:

$$Q_C = s_1A_C + (s_2 - s_1)A_B\frac{G_C'}{G_B} \quad \text{(Eq. 16}a\text{)}$$

where s_1A_C describes the total amount of caffeine released from region 1, and the second term describes the total amount released from region 2. Since caffeine is released solely in the form of complexes from region 2, its amount will be directly proportional to the amount of benzocaine released from region 2 $[(s_2 - s_1)A_B]$. The proportionality constant obviously is given by the ratio of the caffeine and benzocaine rates of release from that region.

The ratio of Eqs. 11a and 13a yield:

$$\frac{G'_C}{G_B} = \frac{\delta}{\alpha}$$

Substitution of the above in Eq. 16a and differentiating provides another expression for G_C:

$$G_C = A_C\frac{ds_1}{dt} + A_B\frac{\delta}{\alpha}\left[\frac{ds_2}{dt} - \frac{ds_1}{dt}\right] \quad \text{(Eq. 17}a\text{)}$$

Equating the expressions for G_C, given by Eqs. 8a and 17a:

$$A_C\frac{ds_1}{dt} + A_B\frac{\delta}{\alpha}\left[\frac{ds_2}{dt} - \frac{ds_1}{dt}\right] = \frac{\epsilon_1}{\tau_1 s_1}(D_C \cdot C_s) + G_B\frac{\delta}{\alpha} \quad \text{(Eq. 18a)}$$

Substituting for G_B from Eq. 15a gives:

$$A_C\frac{ds_1}{dt} - A_B\frac{\delta}{\alpha}\frac{ds_1}{dt} = \frac{\epsilon_1 D_C C_s}{\tau_1 s_1} \quad \text{(Eq. 19a)}$$

or

$$s_1\frac{ds_1}{dt} = \frac{\epsilon_1 \cdot D_C \cdot C_s}{\tau_1(A_C - \frac{\delta}{\alpha}A_B)} \quad \text{(Eq. 20a)}$$

Equation 20a can be integrated to yield:

$$s_1 = \beta t^{1/2} \quad \text{(Eq. 21a)}$$

where

$$\beta = \left[\frac{2\epsilon_1 D_C C_s \alpha}{\tau_1(A_C\alpha - A_B\delta)}\right]^{1/2} \quad \text{(Eq. 22a)}$$

As expected, the movement of boundary s_1 has a square root of time dependence.

Similarly, Eqs. 12a and 15a for G_B can be equated. After rearranging, the following expression is obtained:

$$G_B = A_B\frac{ds_2}{dt} = \frac{\epsilon_1\epsilon_2 B_s \alpha}{\tau_2\epsilon_1(s_2 - s_1) + \epsilon_2 s_1 \tau_1}$$

and

$$\frac{ds_2}{dt} = \frac{\epsilon_1\epsilon_2 B_s \alpha}{A_B s_1\left[\tau_2\epsilon_1\frac{(s_2 - s_1)}{s_1} + \epsilon_2\tau_1\right]} \quad \text{(Eq. 23a)}$$

The ratio of $(s_2 - s_1)/s_1$ has been shown to be invariant (1). Equation 21a can be substituted for s_1. Integration of Eq. 23a then shows that:

$$s_2 = \gamma\, t^{1/2} \quad \text{(Eq. 24a)}$$

$$\gamma = \frac{2\epsilon_1\epsilon_2 B_s \alpha}{A_B(\tau_2\epsilon_1\gamma - \tau_2\epsilon_1\beta + \tau_1\epsilon_2\beta)} \quad \text{(Eq. 25b)}$$

Equations When Both Boundaries Move at the Same Rate—It can be seen from Eqs. 3a and 6a that when both boundaries recede at the same rate, we may write:

$$G_B \cdot s_1 = \frac{\epsilon_1}{\tau_1}B_s\alpha \quad \text{(Eq. 26a)}$$

and

$$G_C \cdot s_1 = \frac{\epsilon_1}{\tau_1}D_C \cdot C_s + \frac{\epsilon_1}{\tau_1}B_s\delta \quad \text{(Eq. 27a)}$$

As, for this case, $s_1 = s_2$:

$$G_B = A_B\frac{ds_1}{dt} \quad \text{(Eq. 28a)}$$

and

$$G_C = A_C\frac{ds_1}{dt} \quad \text{(Eq. 29a)}$$

Then these equations may be solved as before to give:

$$Q_B = \left[\frac{2\epsilon_1 A_B}{\tau_1}(D_B B_s + D_{BC}K_1 C_s B_s + D_{BC_2}K_1K_2B_sC_s^2 + D_{BC_3}K_1K_2K_3B_sC_s^3)t\right]^{1/2} \quad \text{(Eq. 30a)}$$

and

$$Q_C = \left[\frac{2\epsilon_1}{\tau_1}A_C(D_C C_s + D_{BC}K_1C_sB_s + 2D_{BC_2}K_1K_2B_sC_s^2 + 3D_{BC_3}K_1K_2K_3B_sC_s^3)t\right]^{1/2} \quad \text{(Eq. 31a)}$$

These equations may also be written as:

$$Q_B = \left[\frac{2\epsilon_1 A_B D_{B(\text{eff.})} B_T t}{\tau_1}\right]^{1/2} \quad \text{(Eq. 32a)}$$

and

$$Q_C = \left[\frac{2\epsilon_1 A_C D_{C(\text{eff.})} C_T t}{\tau_1}\right]^{1/2} \quad \text{(Eq. 33a)}$$

where $D_{B(\text{eff.})}$ and $D_{C(\text{eff.})}$ are the effective diffusion coefficients for the total transport rates of benzocaine and caffeine, respectively.

Equations When Caffeine Is the Faster Moving Boundary—As was done for the first case and considering the continuity relations at the boundaries we obtain the following equations that are analogous to Eqs. 3a, 6a, 11a, and 13a:

For region 1,

$$G_B s_1 = \frac{\epsilon_1}{\tau_1}[D_B B_s + D_{BC}K_1B_sC' + D_{BC_2}K_1K_2B_s(C')^2 + D_{BC_3}K_1K_2K_3B_s(C')^3] \quad \text{(Eq. 34a)}$$

and

$$G_C s_1 = \frac{\epsilon_1}{\tau_1}[D_C C_s + D_{BC}K_1B_sC' + 2D_{BC_2}K_1K_2B_s(C')^2 + 3D_{BC_3}K_1K_2K_3B_s(C')^3] \quad \text{(Eq. 35a)}$$

and, for region 2,

$$G_B'(s_2 - s_1) = \frac{\epsilon_2}{\tau_2}D_{BC}K_1B_s(C_s - C') + D_{BC_2}K_1K_2B_s[C_s^2 - (C')^2] + D_{BC_3}K_1K_2K_3B_s[C_s^3 - (C')^3] \quad \text{(Eq. 36a)}$$

and

$$G_C(s_2 - s_1) = \frac{\epsilon_2}{\tau_2}D_C(C_s - C') + D_{BC}K_1B_s(C_s - C') + 2D_{BC_2}K_1K_2B_s[C_s^2 - (C')^2] + 3D_{BC_3}K_1K_2K_3B_s[C_s^3 - (C')^3] \quad \text{(Eq. 37a)}$$

Here C' is the caffeine concentration and s_1 and G_B' represent the rate of benzocaine movement in region 2. All other symbols are the same as before.

In addition to these equations we have the relations,

$$G_C = \frac{dQ_C}{dt} = A_C\frac{ds_2}{dt} \quad \text{(Eq. 38a)}$$

and

$$G_B = \frac{dQ_B}{dt} = A_B\frac{ds_1}{dt} + A_C\frac{G_B'}{G_C}\left[\frac{ds_2}{dt} - \frac{ds_1}{dt}\right] \quad \text{(Eq. 39a)}$$

As in the first case we now have six equations in six unknowns—G_B', G_B, G_C, C', s_1, and s_2. While in principle the problem can therefore be solved, one finds that the algebra becomes extremely complicated due to the occurrence of an equation cubic in C'.

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Penicillin G Interactions with Deoxycholic Acid Polymer-Like Structures

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Conductivity, activity coefficient, and ultraviolet absorption data have shown that an interaction occurs between deoxycholate helical complexes (DCA) and sodium benzylpenicillin (P). The mechanism of this interaction is still unknown, but a merely electrostatic interpretation can be ruled out. Experimental data seem to be consistent with the stereospecific nature of this interaction. The presence of DCA helical complexes increases benzylpenicillin resistance to the hydrolytic activity of penicillinase. No interaction and therefore no decrease in the hydrolytic activity of penicillinase has been found with different derivatives, *i.e.*, dimethoxyphenyl- and α-aminobenzylpenicillin. At the same time dehydrocholic acid sodium salt (NaDHCA), which in no case forms helical complexes, shows no effect upon P, whereas sodium salt of cholic acid (NaCA) still exerts a protective action upon P but to a lesser degree.

THE FORMATION of a helical complex of macromolecular dimension from sodium deoxycholate has been previously described by Rich and Blow (1, 2). Under appropriate conditions sodium deoxycholate aggregates in solution to form a gel which behaves in many ways like a polymer of high molecular weight. The fibers, which can be drawn from the solutions, showed an X-ray diffraction pattern which is characteristic of a helical aggregate (2). In a previous work (3) the influence of cation dimensions, hydration, and hydrogen bonds on the thermal stability of deoxycholic acid (DCA) "polymer-like" structure was discussed. It was shown that the thermal stability of deoxycholate aggregates is cationic species dependent.

In this paper the possibility of an interaction between DCA or related molecules and antibiotics has been studied. Even if the micelle-forming properties of deoxycholate could account for some of the observed phenomena, the formation of huge micelles with a regular or "crystalline" (2) internal structure seems to be responsible for effects which occur only when a specific system of hydrogen bonding is established within the micelle.

Conductivity, activity coefficient, and ultraviolet absorption data gave evidence that a specific interaction takes place between DCA polymer-like structure and benzylpenicillin (P). The mechanism of this interaction is still unknown, but an interpretation of the experimental data on merely electrostatic grounds can be ruled out.

It seemed sound to suppose that this interaction should somehow affect the biological activity of P, namely, its resistance to the penicillinase hydrolytic activity.

An inclusion, already demonstrated in the case of fatty acids (4, 5), could be proposed as an explanation for the observed decrease of penicillinase activity which has been chosen as reference. At the same time it could be suggested that the other molecular species present in the solution during the formation of the complex, could be attached to the outside of the helical steroid core, as are amino acids and peptides (2).

It cannot be overlooked that the study of this kind of interaction can lead to a more detailed knowledge of the mechanism of action of this class of antibiotics at the level of biomembranes.

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