Release Rates of Solid Drug Mixtures Dispersed in Inert Matrices I

Noninteracting Drug Mixtures

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The theory for the simultaneous release of a mixture of two noninteracting drugs dispersed in an inert plastic matrix has been developed. Quantitative relationships based on a physical model were derived that express the diffusion-controlled rates of release of both drugs as functions of the amounts of each drug, the solubilities of the drugs, their diffusional coefficients, and the porosities and tortuosities of the tablet. The theoretical relationships were applied to the salicylic acid–benzoic acid–plastic mixture. The experimental data were found to be in close agreement with the theoretically calculated values.

RECENTLY the drug release rate of a single species dispersed in inert plastic matrices has been extensively investigated (1–4). It was felt that it would be of interest to explore the more complex situation in which more than one drug is present in the tablet matrix. This report is involved with matrices containing an ideal mixture of drugs where the presence of one drug species does not alter the physicochemical properties of the other. The salicylic acid–benzoic acid mixture was chosen to represent the nonreactive case. A subsequent paper will report the results of the benzocaine–caffeine mixture representing the reactive system.

A physical model for the simultaneous release of a mixture of two drugs embedded in an insoluble matrix is developed and theoretical equations derived from it. The equations permit the independent quantitative description of the release rates of both drugs. All the parameters operative in these equations were independently determined, and after substitution into the appropriate theory, the theoretical release rates were obtained. These were then compared with the experimentally determined release rates to test the validity of the proposed model.

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THEORETICAL MODEL

The diffusion-controlled model used to develop the mixture release equations derived under the *Appendix* is shown in Fig. 1. Figure 1(a) depicts initial conditions, *i.e.*, no solvent penetration, and both drugs exist solely as solids embedded in the matrix, region 3. Figure 1(b) depicts the conditions existing at a finite time, t. The boundary of the matrix solvent interface is at $x = 0$ and separates region 0 (solvent) and region 1 which corresponds to the completely leached portion of the matrix. The solid–liquid boundary of the slower moving drug is at $x = s_1$ and separates region 1 and region 2 which contains solid drug A in equilibrium with its saturated solution and drug B solely in solution. Finally the solid–liquid boundary of the faster

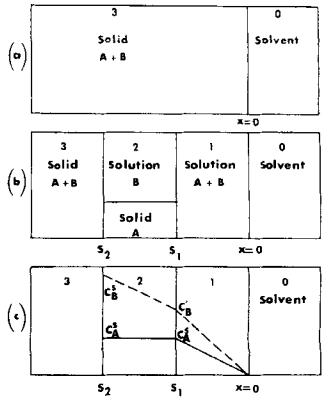

Fig. 1—The physical model that describes the release of a mixture of two noninteracting drugs from an inert matrix. Key: (a) *conditions existing at time* t = 0; (b) *conditions existing at finite time,* t; (c) *an illustration of the concentration gradients for all species.*

moving drug is at $x = s_2$ and separates region 2 and region 3 (solid drugs only). The concentration gradients of drugs A and B are shown in Fig. 1(c).

The relative boundary movement of drugs A and B will be a function of their solubilities, diffusion coefficients, and concentration of their solids in the matrix. If both drugs are present in equal concentrations and have equal diffusion coefficients, the more soluble drug will have the faster moving boundary. If both drugs have equal solubilities and are present in equal concentrations, the drug with the larger diffusion coefficient will move faster. Finally, if both drugs have equal solubilities and diffusion coefficients, the drug present in the smaller amount will have a faster moving boundary. It is evident from the above that the slower moving drug can be made to have a faster moving boundary by sufficiently decreasing its concentration in the matrix.

Inspection of Fig. 1 shows that the porosity and tortuosity of region 1 and region 2 will differ due to the presence of solid A in region 2 but not in region 1. The porosity of region 1 is given by the sum of the porosities due to the presence of drug A, drug B, and residual air in the matrix. The porosity of region 2, on the other hand, is given by the sum of porosity contributions of only drug B and residual air. In addition, the presence of solid drug A in region 2 will cause its tortuosity to be equal to or greater than that of region 1.

It is evident from the model that as neither solid A nor solid B is present in region 1, the release of the slower moving drug A can be described by the Higuchi equation (5):

$$\frac{dQ_A}{d(t^{1/2})} = \left[D_A \frac{\epsilon_1}{\tau_1} (2A_A - \epsilon_1 C_A^s) C_A^s \right]^{1/2} \quad \text{(Eq. 1)}$$

For the release of the faster moving drug, B, however, the following more complex equation must be utilized:

$$\frac{dQ_B}{d(t^{1/2})} = \frac{2D_B \epsilon_1}{\frac{k_A}{A_A}\tau_1} \left[\frac{\frac{\epsilon_2}{\tau_2} C_B^s}{\frac{\epsilon_2}{\tau_2} + \frac{\epsilon_1}{\tau_1}\left[\frac{\frac{k_B}{A_B} - \frac{k_A}{A_A}}{\frac{k_A}{A_A}} \right]} \right] \quad \text{(Eq. 2)}$$

Here, subscripts 1 and 2 symbolize parameters operative in regions 1 and 2, respectively, and subscripts A and B refer to the drugs A and B, respectively. The symbols used in the above equations are defined as follows: Q_i is the grams of drug i released per unit area of surface at time, t; D_i is the diffusion coefficient of the drug i in the release medium; A_i is the concentration of the drug i in the tablet; C_i^s is the solubility of the drug in the release medium; ϵ_j is the porosity of the region j and τ_j is the tortuosity of the region j. K_A is the slope of the Q_A *versus* $t^{1/2}$ plot (from Eq. 1) and K_B is the slope of the Q_B *versus* $t^{1/2}$ plot (from the *Appendix*).

The evaluation of these parameters and the application of these equations are discussed at length in later portions of the text.

EXPERIMENTAL

In previous papers the release behavior of drugs from polyethylene matrices as well as polyvinyl chloride (PVC) matrices were reported (3, 4). Both matrices provided nonideal release profiles using water as the release medium. It was found, however, that the inclusion of surfactant in the release medium provided ideal release profiles from polyethylene matrices but not for PVC matrices. The PVC matrices, on the other hand, provided ideal release profiles if previously subjected to vacuum treatment before introduction of solvent.

For these series of studies, both mutually interacting and noninteracting drug mixtures studies were anticipated. It would be highly undesirable, therefore, to include any surfactant in the release medium due to its possible direct or indirect interactions with the drug mixture systems. The use of vacuum techniques, on the other hand, always poses threats of technical difficulties.

Due to the possibility that a combination of these two plastics might lead to a matrix system that would eliminate the need for either of these treatments, a systematic series of matrices was studied in which the two plastics were mixed in different ratios from PVC: polyethylene ratios of 9:1 to 1:9 on a weight-to-weight basis. Both caffeine and potassium acid phthalate were separately used as drugs. In both instances the PVC–polyethylene ratio of 7:3 provided the most ideal matrix. The release rates in water, surfactant, and under vacuum conditions gave identical results for these drugs embedded in this matrix system. It was therefore decided to use this mixture as the inert matrix to investigate the release behavior for these series of drug mixtures.

The release rates from these matrices containing solid drug mixtures as well as solutions were studied using the techniques and the evaluation of parameters described previously (1, 2). The diffusion coefficients and solubilities of both drugs used in each mixture were determined individually as well as in the presence of each other.

For this study the simultaneous release of salicylic and benzoic acid from the above matrix was obtained by spectrophotometric assay of the release medium as a function of time at 302 mμ and 259 mμ and by solving the two simultaneous equations for their respective concentrations.

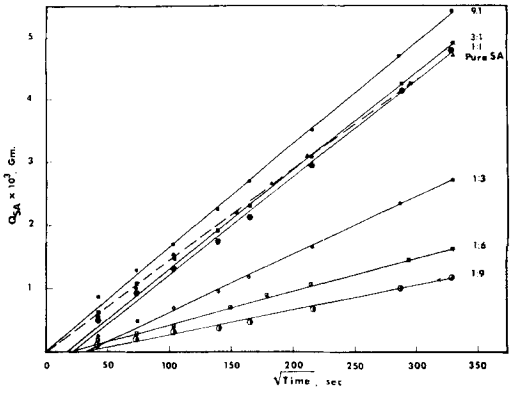

Fig. 2—Release of salicylic acid from matrices containing different ratios of salicylic acid-to-benzoic acid into 0.1 N HCl. The total amount of drug in all cases was 20% w/w, and the numbers indicate salicylic acid-to-benzoic acid ratios.

RESULTS AND DISCUSSION

Six different weight-to-weight ratios of salicylic acid and benzoic acid were homogeneously dispersed in the PVC–polyethylene 7:3 mixture and compressed. The total was maintained at 20% w/w. Release profiles were obtained in 0.1 *N* HCl to assure that both acids would exist primarily in their undissociated form. The results of these release studies are displayed in Figs. 2, 3, and 4. As predicted by the theoretical equations, a linear square root of time dependence is observed, both for the total as well as for the individual drugs when they are simultaneously released from the matrix.

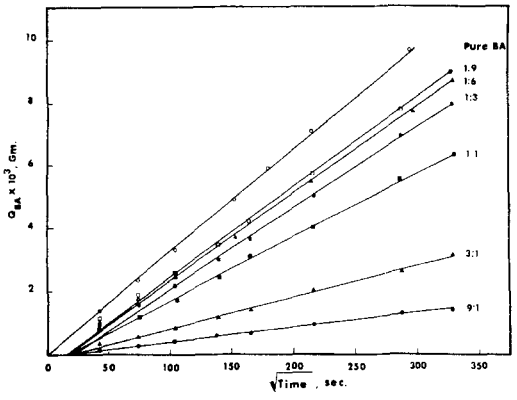

Fig. 3—Data showing benzoic acid release in the same experiments as in Fig. 2.

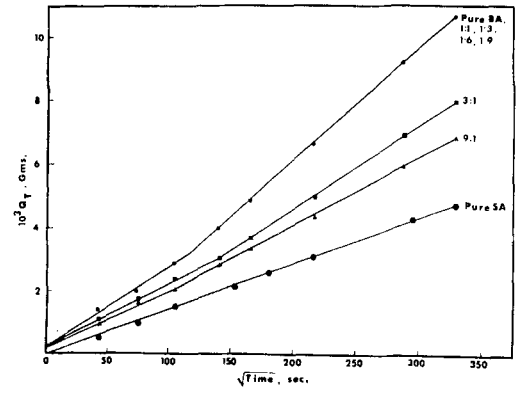

Fig. 4—The sum of the salicylic acid and benzoic acid release in the same experiments as in Figs. 2 and 3.

Examination of Fig. 1 indicates that the release profiles shown in Figs. 2 and 3 occur through region 1 for the slower moving drug and through region 2 for the faster moving drug. When $t = 0$, the relative rates of the two solid-liquid boundary movements can be given by the ratio of their respective release rates as indicated by Eq. 1; *i.e.*,

$$\frac{\text{salicylic acid boundary}}{\text{benzoic acid boundary}} = \frac{Q_{BA}/A_{BA}}{Q_{BA}/A_{BA}} = \left[\frac{D_{BA}C_{BA}A_{BA}}{D_{BA}C_{BA}A_{BA}}\right]^{1/2} \quad \text{(Eq. 3)}$$

All other factors in Eq. 1 are equal and cancel. The above indicates that both boundaries will move at an equal rate (no region 2) at a ratio of:

$$\frac{A_{SA}}{A_{BA}} = \frac{D_{BA}C_{BA}}{D_{BA}C_{BA}} = \frac{(1.16 \times 10^{-5})(2.0 \times 10^{-3})}{(1.22 \times 10^{-5})(3.6 \times 10^{-3})} = \frac{1}{1.9}$$

This analysis indicates that for ratios of salicylic to benzoic acid which are larger than 1:1.9, the benzoic acid drug–liquid boundary is moving more rapidly, but at ratios smaller than 1:1.9 it is moving more slowly.

ANALYSIS OF REGION 1 PARAMETERS

The previous discussion has indicated that Eq. 1 is valid for the release of the drug whose boundary is moving at a slower rate and therefore can be used to describe the salicylic acid release profile for drug ratios greater than 1:1.9 and for benzoic acid release at smaller ratios. The total porosity of the matrix (due to air and both drugs), the diffusion coefficient, solubility, and concentration in the matrix of the predicted slower moving drug were substituted in Eq. 1, and apparent tortuosity values, τ_1, for region 1 were calculated and tabulated in columns *7* and *8* of Table I. A similar treatment was used to calculate the tortuosity of region 1 using the parameters of the faster moving drug. Although Eq. 1 is not valid for the faster moving drug, these calculations were made only as a basis for comparison and are therefore listed in parentheses in Table I. An examination of columns *7* and *8* indicates that the bracketed values of τ are generally significantly higher when analyzing the extreme ratios and are in closer agreement as the ratio of drugs approaches the predicted ratio of equal boundary movement. This is reasonable because region 2 is relatively large at the extreme ratios and becomes smaller, completely disappearing when the boundaries move at an equal rate.

An independent test of the tortuosity values of region 1 can be made by obtaining the release profile of the completely leached matrix resaturated with a drug solution. Tortuosity values obtained in this manner are shown in column *9* of Table I. It is seen that these tortuosity values are independent of the drug mixture ratio. This would be expected as both drugs have been leached from the matrix. In addition, these values are in close agreement with those calculated using Eq. 1 for the slower moving drug and confirm the previous analysis.

ANALYSIS OF REGION 2 PARAMETERS

The drug with the faster moving boundary must diffuse both through regions 1 and 2, and it is obvious that Eq. 2 (not Eq. 1) must be used to describe its release. The porosity of region 2 is due to air and the faster moving drug. All other parameters in Eq. 2 have been independently determined except the tortuosity, τ_2, and allow its calculation. These values are listed in column *5* of Table II. To verify the above tortuosity values, an independent study of these matrices was made by obtaining release profiles of salicylic acid using saturated benzoic acid solution as the release

TABLE I—CALCULATION OF THE TORTUOSITY OF REGION 1 AS DETERMINED BY THE SOLID AND LIQUID RELEASE EXPERIMENTS

SA/BA Ratio	1 ϵ^a Total	2 A_{SA}	3 A_{BA}	4 $10^5 Q_{SA}/t^{1/2}$ Solid Release	5 $10 Q_{BA}/t^{1/2}$ Solid Release	6 $10^5 Q/t^{1/2}$ Liquid Release	7 τ_{1SA}	8 τ_{1BA}	9 τ_1 Liquid Release
Pure BA	0.319	...	0.210	...	3.30	3.32	...	4.4	3.5
1:9	0.303	0.021	0.193	0.42	3.12	3.82	(14.5)[b]	4.2	2.8
1:6	0.295	0.031	0.186	0.54	2.84	3.76	(12.4)[b]	4.7	2.5
1:3	0.299	0.054	0.162	0.90	2.57	3.28	(4.0)[b]	5.1	3.7
1:1	0.268	0.107	0.107	1.60	2.00	5.36	4.5	(5.0)[b]	2.7
3:1	0.294	0.163	0.054	1.64	1.00	4.44	7.1	(11.0)[b]	3.6
9:1	0.286	0.197	0.055	1.70	0.53	3.36	7.8	(38.5)[b]	3.7
Pure SA	0.299	0.216	...	1.46	...	3.54	12.0	...	4.5

[a] ϵ total = $\epsilon_{SA} + \epsilon_{BA} + \epsilon_{air}$. [b] These tortuosity values are incorrect, but have been included for discussion purposes only.

TABLE II—CALCULATION OF THE TORTUOSITY OF REGION 2

SA/BA Ratio	1 $\epsilon_{BA + air}$	2 $\epsilon_{SA + air}$	3 $10^5 Q_{SA}/t^{1/2}$	4 τ_2 Expt. (Using Eq. 1)	5 τ_2 Calcd. from Eq. 2
1:9	0.288	0.150	0.18	41.1	31.7
1:6	0.274	0.148	0.27	24.6	34.4
1:3	0.262	0.171	0.34	32.5	17.5
1:1	0.194	0.183	...	...	7.9
3:1	0.180	0.251	...	...	10.0
9:1	0.151	0.245	...	...	9.8

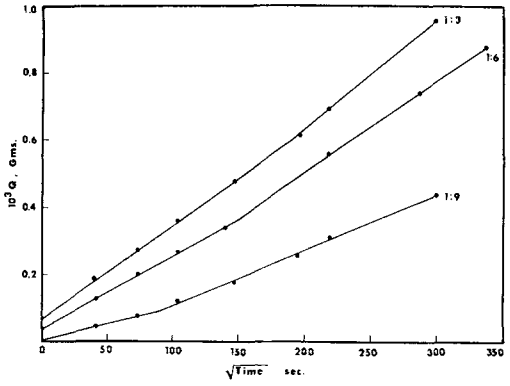

Fig. 5—Release of salicylic acid from matrices containing different ratios of salicylic acid to benzoic acid into saturated benzoic acid solutions containing 0.1 N HCl.

medium and are shown in Fig. 5. Since the benzoic acid embedded in the matrix is insoluble in this release medium, the conditions of region 2 are duplicated and permit its parameters to be determined using Eq. 1. The tortuosity values, τ_2, obtained in this manner are listed in column 4 in Table II and agree reasonably well with the values obtained using Eq. 2 and the release profiles in 0.1 *N* HCl.

The above procedure was not duplicated for benzoic acid release into saturated salicylic acid solution because of the difficulties in accurately determining small concentrations of benzoic acid in the presence of relatively high concentrations of salicylic acid. Furthermore, it was felt that the agreement between the τ_2 values obtained for the 1:9, 1:6, and 1:3 drug ratio systems sufficiently established the validity of this approach.

COMPLEMENTARY SURFACTANT AND VACUUM STUDIES

It was interesting to note, however, that the apparent tortuosity values for region 1 listed in Table I indicate an apparent tendency to increase with an increasing ratio of salicylic acid to benzoic acid. In contrast they were lower and relatively constant when obtained using the solution saturated matrices as compared to matrices containing the solid drug. The tortuosity values for region 2, on the other hand, indicate an apparent tendency to decrease rather than increase with an increasing ratio of salicylic acid to benzoic acid. Furthermore, they are relatively high for the lower ratios.

Although the potassium acid phthalate and caffeine studies indicated that there would not be any surfactant or vacuum effect when using this matrix system, the above observations prompted the study of their effect in the salicylic acid–benzoic acid system.

The surfactant effect was determined by obtaining release rates of matrices containing 20% salicylic acid in 0.1 *N* HCl solution containing 0.1% dioctyl sodium sulfosuccinate[1] (AOT) and the vacuum effect with 0.1 *N* HCl as the release medium (3, 4).

The results of these studies are presented in Fig. 6. It is noted that the release rates are increased with either treatment. Since the surfactant effect provided the faster release rates and therefore the more ideal system, the matrices containing both salicylic and benzoic acid were similarly studied.

The salicylic acid–benzoic acid mixture ratios of 1:6 and 3:1 were selected for these studies to provide examples of both drugs functioning as the faster moving drug boundary. Salicylic acid functions as

[1] Marketed as Aerosol OT by the American Cyanamid Co., Wayne, N. J.

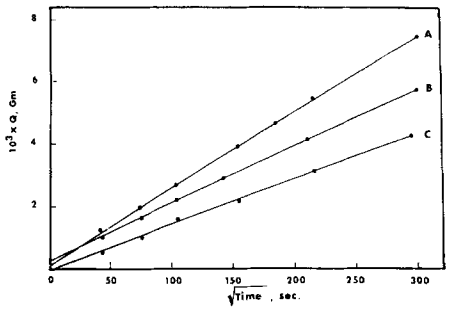

Fig. 6—Salicylic acid release experiments with matrices containing only 20% salicylic acid showing the influence of surfactant and of vacuum treatment. Key: A, *0.1* N *HCl/0.1% AOT as the release medium;* B, *0.1* N *HCl as the release medium and with vacuum treatment (4);* C, *0.1* N *HCl as the release medium.*

the faster moving boundary in the 1:6 mixture ratio but as the slower moving boundary in the 3:1 mixture ratio.

The results of these studies are reported in Table III. The presence of surfactant, as anticipated, increased all release rates. In addition the tortuosity values for region 1 were significantly decreased and remained constant for the four ratios of salicylic acid-to-benzoic acid mixtures indicating that its dependence on which drug was the slower moving boundary disappeared when surfactant was incorporated in the release medium.

The tortuosities of region 2 were also calculated using the surfactant release data for both mixture ratios by substituting the above tortuosities for region 1 in Eq. 2. They are listed in Table III and reveal that the tortuosities for region 2 are significantly decreased for the 1:6 and 3:1 mixture ratios from 34.4 and 10.0 to 6.1 and 8.4, respectively. Very significantly the tortuosity dependence on which drug is slower moving has again disappeared when surfactant is used as the two values are reasonably close.

As with previous studies the tortuosities of region 2 were confirmed by determining the release profile of a matrix containing the 1:6 salicylic acid–benzoic acid mixture into a saturated solution of benzoic acid containing 0.1 *N* HCl and 0.1% AOT. Using Eq. 1, the tortuosity was found to be 7.4 which agrees very well with the tortuosity previously calculated for region 2.

Previous work (3) has shown that the polyethylene matrix generally provides significantly higher drug release rates if surfactant is incorporated in the release medium. This was not true for the PVC matrices (4); the PVC, on the other hand, exhibited a more marked effect than the polyethylene matrix when pretreated by the vacuum technique.

Since the PVC–polyethylene matrix utilized in these studies demonstrated a markedly higher increase in the release rates when surfactant was included in the release medium as compared to the studies utilizing the vacuum treatment, it is strongly suggested that the polyethylene plastic is the controlling plastic in this matrix.

This indicates that in the compressional process the polyethylene plastic predominantly flows around the PVC plastic resulting in a discontinuous phase of PVC plastic surrounded by a continuous phase of polyethylene plastic. Comparison of the physical properties of both plastics indicates that the above is reasonable as polyethylene appears to be more plastic in nature and less rigid than the PVC plastic. In addition, the lower tortuosity values generally obtained in previous studies with the PVC matrices suggested that PVC existed as spheres in the compressed matrices, whereas polyethylene yielded higher tortuosity values in general indicating that it underwent considerable distortion with compression.

The results also indicate that salicylic acid is also predominantly surrounded by the polyethylene plastic under compression as indicated by the much higher tortuosity values obtained for region 2 when it participates as the faster moving drug in nonsurfactant solutions but exhibits a slightly lower tortuosity in the presence of surfactant. In addition, the tortuosity values of region 1 are higher when it participates as the slower moving drug in nonsurfactant solutions but not in the presence of surfactant. Finally the tortuosity of a matrix containing only salicylic acid showed a tortuosity of 12 in nonsurfactant solution but only 4.3 in the presence of surfactant.

Benzoic acid, on the other hand, exhibited consistently low tortuosities in all of the above situations, and this indicates that it is sufficiently distorted under compression to prevent it from being effectively coated in a similar manner.

APPENDIX

Derivation of Eq. 2—This derivation is based on the model previously described in Fig. 1. The equation for continuity at the boundary, s_1, is given by:

$$D_B \frac{\epsilon_1}{\tau_1}\left[\frac{dB}{dx}\right]_1 = D_B \frac{\epsilon_2}{\tau_2}\left[\frac{dB}{dx}\right]_2 \qquad \text{(Eq. 1}a\text{)}$$

Using the concentration gradients obtained from Fig. 1(c), the above yields:

TABLE III—CALCULATION OF THE TORTUOSITY OF REGION 1 AND REGION 2 USING SURFACTANT AS THE RELEASE MEDIUM

SA/BA Ratio	$10^5 Q_{SA}/t^{1/2}$ Solid Release	$10^5 Q_{BA}/t^{1/2}$ Solid Release	τ_{1SA}	τ_{1BA}	$10^5 Q_{SA}/t^{1/2}$[a]	τ_2 Exptl.	τ_2 Theoret.
Pure BA	...	3.90	...	3.2	...	...	...
1:6	0.70	3.10	...	4.0	0.27	7.4	6.1
3:1	2.07	1.16	4.5	...	0.50	...	8.4
Pure SA	2.45	...	4.3	...	...	...	...

[a] Slope of the release study when the salicylic acid–benzoic acid mixture tablet is released into saturated benzoic acid solution.

$$D_B \frac{\epsilon_1}{\tau_1} \frac{C_B'}{s_1} = D_B \frac{\epsilon_2}{\tau_2} \frac{(C_B^s - C_B')}{(s_2 - s_1)} \quad \text{(Eq. 2a)}$$

The concentration of drug B at the boundary s_1 can be obtained by rearrangement of Eq. 2a to give:

$$C_B' = \frac{\frac{\epsilon_2}{\tau_2} C_B^s}{\frac{\epsilon_2}{\tau_2} + \frac{\epsilon_1}{\tau_1} \frac{(s_2 - s_1)}{s_1}} \quad \text{(Eq. 3a)}$$

The equation of continuity dictates that the rate of release of drug B, G_B, must be equal to its rate of diffusion in region 1, *i.e.*,

$$G_B = \frac{dQ_B}{dt} = D_B \frac{\epsilon_1}{\tau_1} \frac{C_B'}{s_1} \quad \text{(Eq. 4a)}$$

Rearrangement of Eq. 4a yields a second relationship for the concentration for drug B at the boundary s_1:

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

By equating Eqs. 3a and 5a one obtains:

$$G_B = \frac{dQ_B}{dt} = D_B \frac{\epsilon_2}{\tau_1 s_1} \left[\frac{\frac{\epsilon_2}{\tau_2} C_B^s}{\frac{\epsilon_2}{\tau_2} + \frac{\epsilon_1}{\tau_1} \frac{(s_2 - s_1)}{s_1}} \right] \quad \text{(Eq. 6a)}$$

Since s_1 and s_2 do not readily lend themselves to experimental determination, it would be advantageous to replace them with functions of measurable variables.

If the amount of dissolved drug remaining in the pores is assumed negligible, as compared to the amount of drug released (true for poorly soluble drugs), then:

$$Q_A = s_1 \cdot A_A$$

For the slower moving drug, Q_A is also given by Eq. 1, and its substitution in the above equation yields the following:

$$s_1 = \frac{K_A}{A_A} t^{1/2} \quad \text{(Eq. 7a)}$$

where K_A is given by the slope of the corresponding Q_A *versus* $t^{1/2}$ plot. It would be desirable if a similar relationship could be obtained for s_2 which would then permit the integration of Eq. 6a as all parameters could then be experimentally determined.

Equation 1 cannot be used to obtain a similar expression for s_2 as it involves both regions 1 and 2 as shown in Fig. 1. It can be shown, however, that Q_B is also proportional to $t^{1/2}$. If the ratio of $(s_2 - s_1)/s_1$ is invariant and Eq. 7a is used to substitute for s_1, Eq. 6a shows that G_B is inversely proportional to the square root of time, and therefore Q_B is directly proportional to the square root of time, *i.e.*,

$$Q_B = K_1 t^{1/2} \quad \text{(Eq. 8a)}$$

where K_1 is the integration constant.

The ratio of $(s_2 - s_1)/s_1$ can be shown to be invariant by the following analysis. The equation of continuity, Eq. 2a, dictates that:

$$\frac{C_B^s - C_B'}{s_2 - s_1} = K_2 \frac{C_B'}{s_1} \quad \text{(Eq. 9a)}$$

where K_2 is a function of the porosities and tortuosities of the two regions. s_1 describes the position of the slower moving drug boundary as it moves from the matrix surface and must increase with time. Since s_2 describes the position of the faster moving drug boundary, the value of $s_2 - s_1$ must also increase with time. If C_B' increases, $C_B^s - C_B'$ would correspondingly decrease. Equation 9a, however, would then require $s_2 - s_1$ to correspondingly decrease relative to s_1 and would require the impossible situation of the supposedly slower moving boundary to be the faster one. C_B', on the other hand, cannot decrease as $C_B^s - C_B'$ would correspondingly increase and would require a positive acceleration of the movement of s_2 relative to s_1; yet its maximum acceleration must occur at $t = 0$. Since C_B' must be invariant, rearrangement of Eq. 9a shows that the ratio of $(s_2 - s_1)/s_1$ is indeed invariant and that Eq. 8a is therefore valid.

Its substitution in $Q_B = s_2 A_B$ shows that s_2 is directly proportional to the square root of time and is equal to $K_B t^{1/2}/A_B$ where K_B is the slope of the corresponding Q_B *versus* $t^{1/2}$ plot.

Substituting for s_1 and s_2 into Eq. 6a yields the desired relationship:

$$\frac{dQ_B}{d(t^{1/2})} = 2\left[\frac{dQ_B}{dt}\right] t^{1/2} = \frac{2D_B \epsilon_1}{\tau_1 \frac{K_A}{A_A}} \times \left[\frac{\frac{\epsilon_2}{\tau_2} C_B^s}{\frac{\epsilon_2}{\tau_2} + \frac{\epsilon_1}{\tau_1} \left(\frac{K_B/A_B - K_A/A_A}{K_A/A_A} \right)} \right] \quad \text{(Eq. 10a)}$$

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