Release Rates of Solid Drug Mixtures Dispersed in Inert Matrixes IV: Binary Mixture of Amphoteric Drugs Released into Reactive Media

FAUZI SJUIB*, ANTHONY P. SIMONELLI†, and WILLIAM I. HIGUCHI▲

Abstract □ This study was a critical examination of the physical model approach to the understanding of release of interacting drug mixtures from an inert matrix into reactive media. The experimental system selected was the sulfapyridine–sulfadiazine mixture dispersed in a polyvinyl chloride matrix. Drug release rates in acetate, phosphate, and tromethamine buffers and in hydrochloric acid and sodium hydroxide solutions were investigated. The data were analyzed by appropriate models based upon the consideration of simultaneous equilibria and transport of all species in the system. The experimental results were generally found to be in good agreement with theory. A point of special interest was that it was necessary to consider the precipitation of drug in the matrix during drug release in alkaline buffers in order to obtain satisfactory agreement between experiment and theory.

Keyphrases □ Release rates of solid drug mixture (sulfapyridine–sulfadiazine) embedded in inert matrix—effect of reactive solvents, equations □ Sulfapyridine–sulfadiazine mixture—release from inert matrix, solvent effects, equations □ Drug mixtures, solid (sulfapyridine–sulfadiazine)—release from inert matrix, solvent effects, equations □ Binary drug systems—release from inert matrix, solvent effects, equations □ Amphoteric drug mixture (sulfapyridine–sulfadiazine)—release from inert matrix, solvent effects, equations

In a previous study the simultaneous release of two solids dispersed in an inert matrix into a solvent containing reactive constituents was investigated (1). Equations based on a diffusion-controlled model were derived which considered the simultaneous equilibria and transport of all species in the system. These experiments, involving the release of benzoic acid–salicylic acid mixtures dispersed in a polyethylene–polyvinyl chloride mixed matrix into phosphate buffers, were analyzed by means of the theory employing an approach involving the determination of a self-consistent set of physically meaningful parameters.

The purposes of the present study were to conduct a more critical test of the model and to generalize the problem to include a wider range of solvent and solute characteristics. The sulfadiazine–sulfapyridine–polyvinyl chloride system was selected because it offered the following advantages over the system described in the previous report (1):

1. Because of the low intrinsic solubilities of both drugs, large effects of buffers on the solubilities were expected. Therefore, a wide range of rates and a more substantial test of the theory were anticipated.

2. Also because both drugs are amphoteric, it was anticipated that the influences of the two pKa's of both drugs could be evaluated over a wide pH range.

3. The choice of 100% polyvinyl chloride provided a matrix that was expected to wet well (2, 3) and thereby yield good access of the solvent to the pores and not contribute to the uncertainties in the analysis.

It was decided to use a 1:1 w/w ratio of sulfadiazine and sulfapyridine where the total drugs represented 20% of the total tablet. This drug composition was such that a crossover behavior was predicted by the theory. That is, at low pH, sulfapyridine was expected to release faster than sulfadiazine; and at high pH, sulfadiazine was expected to release more rapidly than sulfapyridine.

The following four solvent systems were chosen because they represented limiting behavior with regard to release mechanisms:

1. Acetate buffer at pH 4.7, where only the diffusion of the neutral species was expected to be important.

2. Sodium hydroxide solution, where the hydroxide ion would indiscriminately react with whichever drug phase it encountered.

3. Hydrochloric acid, where the protonated species of drugs would significantly contribute to the overall release depending upon the first acid dissociation constants of the drugs.

4. Phosphate and tromethamine buffers, where the negatively charged species of the two drugs would contribute to the overall transport depending upon the second acid dissociation constants of the drugs and dissociation constants of the buffers.

THEORY

An amphoteric drug, HA, such as a sulfa in an aqueous solution, has the following equilibrium: $[H_2A^+] \rightleftharpoons [H^+] + [HA] \rightleftharpoons [H^+] + [A^-]$, where H_2A^+ is the protonated form and A^- is its negatively charged species. The ratio of the concentration of its species depends upon the pH of its solution. If the pH is much higher than its isoelectric point, the negatively charged species, A^-, is the principally charged species; at a pH much lower than the isoelectric point, the protonated form is predominant. However, if the pH of the solution is near the isoelectric point of the amphoteric drug, the drug involves an equilibrium of its neutral species, HA, with either the protonated or negatively charged species. At the isoelectric point, essentially all of the drug exists as the neutral species. Therefore, the species present in solution varies with the pH of its solvent, and the various solvent systems employed for these studies were expected to provide different drug release patterns.

The following discussion involves the theoretical analysis of the release of a sulfadiazine–sulfapyridine (1:1) mixture from a polyvinyl chloride matrix into four solvent systems. Equations were derived based on the species involved in each system.

Acetate Buffer, pH 4.7, as Solvent—Figure 1 shows the diffusion-controlled model in the acetate buffer case. According to the model, because the pH is near the isoelectric points for both drugs, only the diffusion of neutral species should be important. Figure 1*a* shows the initial conditions, in which both drugs exist solely as solids embedded in the matrix Region 3. Figure 1*b* shows the conditions existing after a finite time, t. Because of the lower intrinsic solubility of sulfadiazine (HSD), the sulfadiazine boundary, s_1, moves more slowly than the sulfapyridine boundary, s_2. Diffusion of sulfapyridine (HSP) occurs in both Regions 1 and 2, while diffusion of sulfadiazine, HSD, occurs only in Region 1.

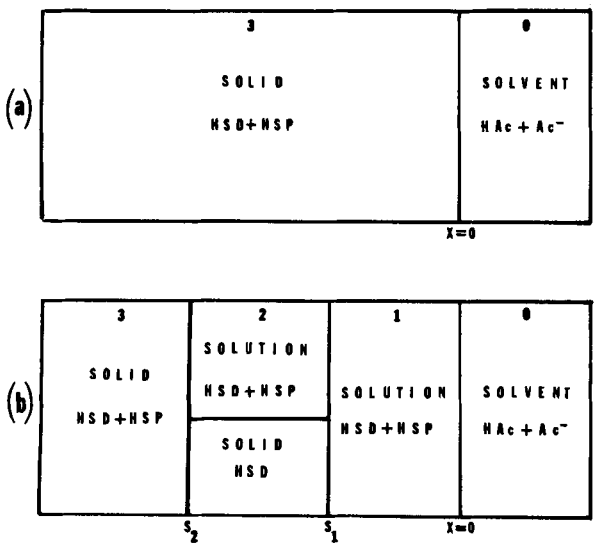

Figure 1—*Diffusion-controlled model for release of sulfadiazine-sulfapyridine (1:1) from an inert matrix into acetate buffer, pH 4.7. Key: (a), conditions existing at time* t = *0; and (b), conditions existing at finite time,* t.

For this situation the release of the components is governed by the equations previously derived (4), the only changes required being the physical parameters of the individual components, HSD and HSP for HS and HB. The resultant equations are:

$$\frac{Q_D}{t^{1/2}} = \left[D_S \frac{\epsilon_1}{\tau_1} \{2A_D - \epsilon_1(HSD)^*\}(HSD)^* \right]^{1/2} \quad \text{(Eq. 1)}$$

$$\frac{Q_P}{t^{1/2}} = \frac{2D_S(\epsilon_1/\tau_1)(\epsilon_2/\tau_2)(HSP)^*}{\left(\frac{Q_D/t^{1/2}}{A_D}\right)\left[\frac{\epsilon_2}{\tau_2} + \frac{\epsilon_1}{\tau_1}\left(\frac{A_D Q_P/t^{1/2}}{A_P Q_D/t^{1/2}} - 1\right)\right]} \quad \text{(Eq. 2)}$$

where D_S is equal to the diffusion coefficients for sulfadiazine and sulfapyridine, which were assumed to be equal; A_D and A_P are the solid concentrations of sulfadiazine and sulfapyridine in the tablet, respectively; (HSD)* and (HSP)* are the intrinsic solubilities of sulfadiazine and sulfapyridine, respectively; Q_D and Q_P are the amounts of sulfadiazine and sulfapyridine released after time t, respectively; ϵ_1 and ϵ_2 are the porosities in Regions 1 and 2, respectively; and τ_1 and τ_2 are the tortuosities in Regions 1 and 2, respectively.

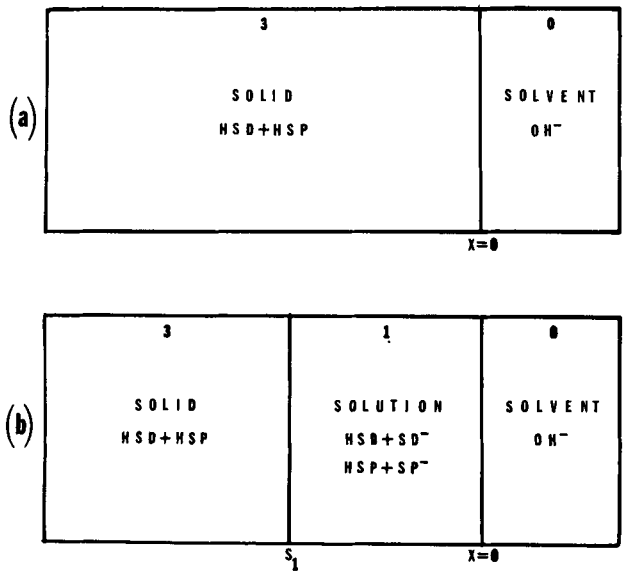

Figure 2—*Diffusion-controlled model for release of sulfadiazine-sulfapyridine (1:1) from an inert matrix into sodium hydroxide solution. Key: (a), conditions existing at time* t = *0; and (b), conditions existing at finite time,* t.

Sodium Hydroxide Solution as Solvent—Figure 2 describes the model when a sodium hydroxide solution is employed as the solvent. The hydroxide ion, OH^-, diffuses into the matrix and reacts completely with whichever drug species it encounters to form the negatively charged species of sulfadiazine, SD^-, and sulfapyridine, SP^-. There is no Region 2 in this case. From this model, differential equations were obtained which described the diffusional behavior of the various species involved in this system. Since the transport rate of hydroxide ion into the matrix must be equal to the sum of the diffusional rates of SD^- and SP^- out of the matrix, it follows that:

$$-D_{OH}\frac{\epsilon_1}{\tau_1}\frac{d(OH^-)}{dx} = D_S\frac{\epsilon_1}{\tau_1}\frac{d(SD^-)}{dx} + D_S\frac{\epsilon_1}{\tau_1}\frac{d(SP^-)}{dx} \quad \text{(Eq. 3)}$$

where D_{OH} is the diffusion coefficient of hydroxide ion in water; and D_S is, again, equal to the diffusion coefficients for sulfadiazine and sulfapyridine in either the neutral or ionized state. The total transport rates, G_D amd G_P, out of the matrix for sulfadiazine and sulfapyridine, respectively, are given by the following equations:

$$D_S\frac{\epsilon_1}{\tau_1}\frac{d(SD^-)}{dx} + D_S\frac{\epsilon_1}{\tau_1}\frac{d(HSD)}{dx} = G_D \quad \text{(Eq. 4)}$$

$$D_S\frac{\epsilon_1}{\tau_1}\frac{d(SP^-)}{dx} + D_S\frac{\epsilon_1}{\tau_1}\frac{d(HSP)}{dx} = G_P \quad \text{(Eq. 5)}$$

The requirement of mass balance dictates that the amount of drug released at time t is equal to the original amount of drug in the matrix less the amount of drug in the matrix at time t. This requirement is given by the following equation:

$$Q_D + Q_P = (A_D + A_P)s_1 - \frac{1}{2}\epsilon_1\{(HSD)^* + (SD^-)_1 + (HSP)^* + (SP^-)_1\}s_1 \quad \text{(Eq. 6)}$$

By definition:

$$G_P + G_D = \frac{d(Q_D + Q_P)}{dt} \quad \text{(Eq. 7)}$$

Integration of Eqs. 3–5 from $x = 0$ to $x = s_1$ and then solving the resultant equations simultaneously with Eqs. 6 and 7 yield the following equation:

$$Q_P + Q_D = \left\{\frac{\epsilon_1}{\tau_1}[D_{OH}(OH^-)_0 + D_S\{(HSD)^* + (HSP)^*\}] \times [2(A_D + A_P) - \epsilon_1\{(OH^-)_0 + (HSD)^* + (HSP)^*\}]t\right\}^{1/2} \quad \text{(Eq. 8)}$$

This equation was then used to analyze the experimental data for this system.

Hydrochloric Acid as Solvent—Figure 3 illustrates the case in which hydrochloric acid is the solvent. Figure 3*a* represents the initial condition ($t = 0$), and Fig. 3*b* shows the conditions existing at a finite time later, t. Hydrogen ion, H^+, diffuses into the matrix and interacts with the neutral species of the two drugs to produce the protonated species H_2SD^+ and H_2SP^+. The protonated species as well as the neutral species of both drugs in both Regions 1 and 2 are important in their total transport.

For the 1:1 drug mixture case, the sulfadiazine boundary, s_1, should move more slowly than the sulfapyridine boundary, s_2, because of two factors. First, the intrinsic solubility of sulfapyridine is larger than that of sulfadiazine. Second, the first acid dissociation constant for sulfapyridine is smaller than that of sulfadiazine.

From this model, differential equations were obtained which describe the diffusional behavior of the various species in Regions 1 and 2. For the equations to be developed in this section, D_H is the diffusion coefficient of hydrogen ion in 0.5 *M* NaCl solution, and D_S is the diffusion coefficient for either drug in the neutral and protonated forms.

Since the rate of hydrogen-ion transport into the matrix must be equal to the rate of transport of the protonated species H_2SD^+ and H_2SP^+ out of the matrix, it follows that:

$$-D_H\frac{\epsilon_1}{\tau_1}\frac{d(H^+)}{dx} = D_S\frac{\epsilon_1}{\tau_1}\frac{d(H_2SD^+)}{dx} + D_S\frac{\epsilon_1}{\tau_1}\frac{d(H_2SP^+)}{dx} \quad \text{(Eq. 9)}$$

The total transport rates, G_P and G_D, out of the matrix for sulfapyridine and sulfadiazine, respectively, are given by the following equations:

$$D_S \frac{\epsilon_1}{\tau_1} \frac{d(HSP)}{dx} + D_S \frac{\epsilon_1}{\tau_1} \frac{d(H_2SP^+)}{dx} = G_P \quad \text{(Eq. 10)}$$

$$D_S \frac{\epsilon_1}{\tau_1} \frac{d(HSD)}{dx} + D_S \frac{\epsilon_1}{\tau_1} \frac{d(H_2SD^+)}{dx} = G_D \quad \text{(Eq. 11)}$$

In the same manner, three similar equations can be obtained for Region 2:

$$-D_H \frac{\epsilon_2}{\tau_2} \frac{d(H^+)}{dx} = D_S \frac{\epsilon_2}{\tau_2} \frac{d(H_2SD^+)}{dx} + D_S \frac{\epsilon_2}{\tau_2} \frac{d(H_2SP^+)}{dx} \quad \text{(Eq. 12)}$$

$$D_S \frac{\epsilon_2}{\tau_2} \frac{d(HSP)}{dx} + D_S \frac{\epsilon_2}{\tau_2} \frac{d(H_2SP^+)}{dx} = G_P' = G_P \quad \text{(Eq. 13)}$$

$$D_S \frac{\epsilon_2}{\tau_2} \frac{d(HSD)}{dx} + D_S \frac{\epsilon_2}{\tau_2} \frac{d(H_2SD^+)}{dx} = G_D' \quad \text{(Eq. 14)}$$

where G_P' and G_D' are the total transport rates of sulfapyridine and sulfadiazine out of Region 2, respectively. The rate of total transport of the sulfapyridine species out of the matrix, G_P, is equal to the rate of transport out of Region 2, G_P', because Region 2 is rate controlling. G_D', however, is not equal to G_D because Region 1 is rate controlling.

By assuming that the concentration of all drugs is zero in the bulk solution at all times, that is, by assuming a perfect sink situation, Eqs. 9-11 can be integrated from $x = 0$ to $x = s_1$ to give:

$$D_H\{(H^+)_0 - (H^+)_1\} = D_S\{(H_2SD^+)_1 + (H_2SP^+)_1\} \quad \text{(Eq. 15)}$$

$$D_S \frac{\epsilon_1}{\tau_1} \{(H_2SP^+)_1 + (HSP)_1\} = G_P s_1 \quad \text{(Eq. 16)}$$

$$D_S \frac{\epsilon_1}{\tau_1} \{(H_2SD^+)_1 + (HSD)_1\} = G_D s_1 \quad \text{(Eq. 17)}$$

Equations 12–14 can also be integrated from $x = s_1$ to $x = s_2$:

$$D_H\{(H^+)_1 - (H^+)_2\} = D_S\{(H_2SD^+)_2 - (H_2SD^+)_1 + (H_2SP^+)_2 - (H_2SP^+)_1\} \quad \text{(Eq. 18)}$$

$$D_S \frac{\epsilon_2}{\tau_2} \{(H_2SP^+)_2 - (H_2SP^+)_1 + (HSP)_2 - (HSP)_1\} = G_P(s_2 - s_1) \quad \text{(Eq. 19)}$$

$$D_S \frac{\epsilon_2}{\tau_2} \{(H_2SD^+)_2 - (H_2SD^+)_1 + (HSD)_2 - (HSD)_1\} = G_D'(s_2 - s_1) \quad \text{(Eq. 20)}$$

The subscripts 0, 1, and 2 denote the concentrations of the respective species at $x = 0$, $x = s_1$, and $x = s_2$.

It was assumed that the following equilibria exist in all regions: $HSD + H^+ \rightleftarrows H_2SD^+$ and $HSP + H^+ \rightleftarrows H_2SP^+$, and therefore obey the following relationships:

$$K_{1SD} = \frac{(H^+)(HSD)}{(H_2SD^+)} \quad \text{(Eq. 21)}$$

$$K_{1SP} = \frac{(H^+)(HSP)}{(H_2SP^+)} \quad \text{(Eq. 22)}$$

where K_{1SD} and K_{1SP} are the first acid dissociation constants of sulfadiazine and sulfapyridine, respectively. The principal equilibrium governing the system obtained from the above equilibria is given by $HSP + H_2SD^+ \rightleftarrows H_2SP^+ + HSD$.

The above equilibrium indicates that the protonated sulfadiazine, H_2SD^+, is converted to neutral species in Region 2, because K_{1SP} is smaller than K_{1SD}. In addition, the presence of solid HSD in Region 2 may dictate that the concentration of HSD in Region 2 should be equal to its intrinsic solubility. However, since the protonated form of sulfadiazine, H_2SD^+, is being converted to the neutral species, HSD, there are two physically reasonable or possible cases in this region: either precipitation of HSD somewhere in Region 2 might occur or Region 2 might become supersaturated with respect to HSD.

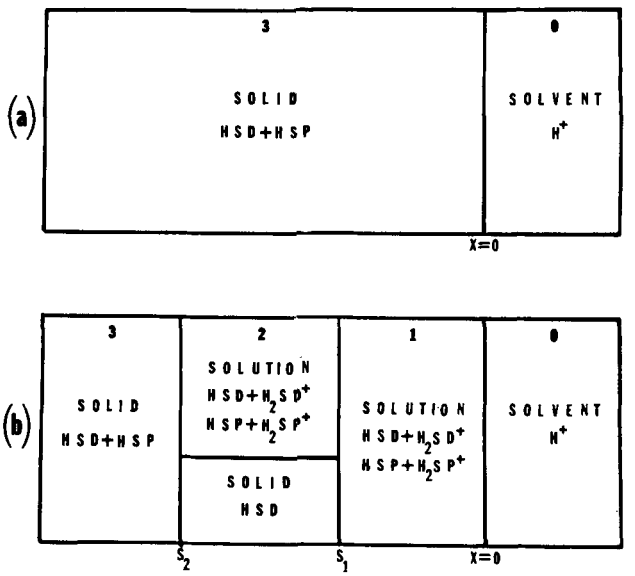

Figure 3—*Diffusion-controlled model for release of sulfadiazine–sulfapyridine (1:1) from an inert matrix into hydrochloric acid solution. Key: (a), conditions existing at time* t = *0; and (b), conditions existing at finite time*, t.

Case I (Precipitation in Region 2 Allowed)—A suitable set of boundary conditions can be specified for the case in which precipitation of HSD in Region 2 is permitted. If the rate of precipitation is sufficiently rapid, it may be assumed that the concentration of HSD in solution in Region 2 is equal to its intrinsic solubility; therefore, the following boundary conditions exist for HSD: $(HSD)_1 = (HSD)^*$ and $(HSD)_2 = (HSD)^*$. The absence of solid (HSP) in Region 2, however, means that the concentration of (HSP) in Region 2 is less than its intrinsic solubility; therefore, a saturated solution of HSP exists only at the boundary s_2, *i.e.*, $(HSP)_2 = (HSP)^*$, where $(HSP)^*$ is the intrinsic solubility for sulfapyridine. It should be emphasized that these boundary conditions are consistent with the assumptions that the processes are all diffusion controlled and that rapid equilibria among species and phases exist at any coordinate, x. Because of this precipitation, the net transport rate of total sulfadiazine species in Region 2, G_D', may not be zero.

By simultaneously solving Eqs. 15–20, equations were obtained which could be used to describe the drug release as a function of time. To test the model, these equations were solved to obtain expressions which could be used to analyze experimental data. The following expression involving the transport rate of total sulfapyridine (all species) was obtained by analysis of Region 2 equations:

$$G_P s_2 = D_S \frac{\epsilon_2}{\tau_2} \left[(HSP)^* + \frac{(HSP)^*(H^+)_2}{K_{1SP}}\right] + G_P s_1 \left[1 - \frac{\epsilon_2 \tau_1}{\epsilon_1 \tau_2}\right] \quad \text{(Eq. 23)}$$

In addition, an expression involving the rate of total sulfapyridine obtained by analysis of Region 1 equations was found to be given by:

$$G_P s_1 = D_S \frac{\epsilon_1}{\tau_1} \left\{(HSP)_1 + \frac{(HSP)_1(H^+)_1}{K_{1SP}}\right\} \quad \text{(Eq. 24)}$$

For convenience of analysis, as will later be seen, the expression was not solved explicitly for G_P. In Eqs. 23 and 24, the quantities $(HSP)_1$, $(H^+)_1$, and $(H^+)_2$ cannot be experimentally measured but the following expressions containing measurable quantities may be substituted for them:

$$(HSP)_1 = \frac{\frac{D_H}{D_S}(H^+)_0 K_{1SP}}{(H^+)_1} - \frac{D_H K_{1SP}}{D_S} - \frac{K_{1SP}(HSD)^*}{K_{1SD}} \quad \text{(Eq. 25)}$$

$$(H^+)_1 = \frac{K_{1SD}}{(HSD)^*} \left[\frac{G_D s_1}{D_S \frac{\epsilon_1}{\tau_1}} - (HSD)^*\right] \quad \text{(Eq. 26)}$$

$$(H^+)_2 = \frac{\frac{D_H}{D_S}(H^+)_0 K_{1SP} K_{1SD}}{(HSD)^* K_{1SP} + (HSP)^* K_{1SD} + \frac{D_H}{D_S} K_{1SP} K_{1SD}} \quad \text{(Eq. 27)}$$

Case II (Supersaturation in Region 2)—This case is probably the less likely one, since it is expected that it would be difficult to maintain a supersaturated solution of HSD in the presence of its solid phase. This case involves the following boundary conditions: $G_D' = 0$, $(HSD)_1 = (HSD)^*$, and $(HSP)_2 = (HSP)^*$. In this case, $(HSD)_2 \neq (HSD)^*$.

Although the slopes of the concentration profiles of both species, HSD and H_2SD^+, are not zero in Region 2, the total concentration of both species remains constant since the slopes are equal in magnitude but opposite in sign. Therefore, no net movement of the sulfadiazine species occurs in Region 2. For this case, the solution of Eqs. 15–20 yields the same four equations, Eqs. 23–26, as in the precipitation case. However, the expression for $(H^+)_2$ is changed and is given by the following equation:

$$(H^+)_2 = \frac{-Y + \sqrt{Y^2 - 4XZ}}{2X} \quad \text{(Eq. 28)}$$

where:

$$X = \frac{D_{H^+}}{D_S} + \frac{(HSP)^*}{K_{1SP}}$$

$$Y = \frac{D_{H^+}}{D_S} + (HSD)^* + \frac{(HSD)^*(H^+)_1}{K_{1SD}} - \frac{D_{H^+}}{D_S}(H^+)_0 + \frac{K_{1SD}(HSP)^*}{K_{1SP}}$$

$$Z = \frac{D_{H^+}}{D_S}(H^+)_0 K_{1SD}$$

Dipotassium Phosphate Solution or Tromethamine Solution as Solvent—Figure 4 illustrates the model predictions when dipotassium phosphate solution or tromethamine solution is the solvent. In the phosphate case, HP^{-2} diffuses into the matrix and interacts with the neutral species, HSD and HSP, to form the negatively charged forms, SD^- and SP^-. The negatively charged forms and the neutral species of both drugs are important in transport. The release of the drugs then depends upon the various equilibria involving the species (Fig. 4).

For this situation, in contrast to the acetate and hydrochloric acid cases, the sulfapyridine boundary, s_1, is predicted to move more slowly than the sulfadiazine boundary. This is due to the influence

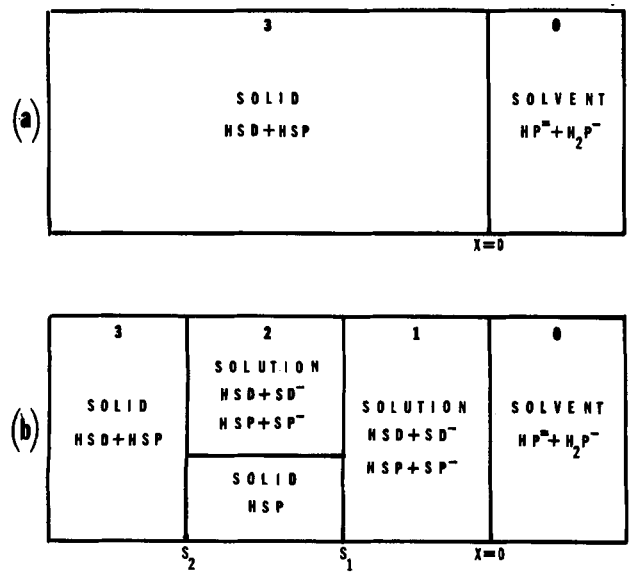

Figure 4—*Diffusion-controlled model for release of sulfadiazine-sulfapyridine (1:1) from an inert matrix into phosphate buffer. Key: (a), conditions existing at time* t = *0; and (b), conditions existing at finite time,* t.

of the smaller dissociation constant, K_{2SP}, of sulfapyridine, which more than offsets its greater intrinsic solubility.

This system is similar to the benzoic acid and salicylic acid mixture release into phosphate buffer (1). Therefore, the following equations can be written for the present situation to describe the diffusional behavior of all species. For Region 1:

$$D_P \frac{\epsilon_1}{\tau_1}\frac{d(HP^{-2})}{dx} + D_P \frac{\epsilon_1}{\tau_1}\frac{d(H_2P^-)}{dx} = 0 \quad \text{(Eq. 29)}$$

$$D_S \frac{\epsilon_1}{\tau_1}\frac{d(SD^-)}{dx} + D_S \frac{\epsilon_1}{\tau_1}\frac{d(SP^-)}{dx} = D_P \frac{\epsilon_1}{\tau_1}\frac{d(H_2P^-)}{dx} \quad \text{(Eq. 30)}$$

$$D_S \frac{\epsilon_1}{\tau_1}\frac{d(HSD)}{dx} + D_S \frac{\epsilon_1}{\tau_1}\frac{d(SD^-)}{dx} = G_D \quad \text{(Eq. 31)}$$

$$D_S \frac{\epsilon_1}{\tau_1}\frac{d(HSP)}{dx} + D_S \frac{\epsilon_1}{\tau_1}\frac{d(SP^-)}{dx} = G_P \quad \text{(Eq. 32)}$$

For Region 2:

$$D_P \frac{\epsilon_2}{\tau_2}\frac{d(HP^{-2})}{dx} + D_P \frac{\epsilon_2}{\tau_2}\frac{d(H_2P^-)}{dx} = 0 \quad \text{(Eq. 33)}$$

$$D_S \frac{\epsilon_2}{\tau_2}\frac{d(SD^-)}{dx} + D_S \frac{\epsilon_2}{\tau_2}\frac{d(SP^-)}{dx} = D_P \frac{\epsilon_2}{\tau_2}\frac{d(H_2P^-)}{dx} \quad \text{(Eq. 34)}$$

$$D_S \frac{\epsilon_2}{\tau_2}\frac{d(HSD)}{dx} + D_S \frac{\epsilon_2}{\tau_2}\frac{d(SD^-)}{dx} = G_D' = G_D \quad \text{(Eq. 35)}$$

$$D_S \frac{\epsilon_2}{\tau_2}\frac{d(HSP)}{dx} + D_S \frac{\epsilon_2}{\tau_2}\frac{d(SP^-)}{dx} = G_P' \quad \text{(Eq. 36)}$$

where D_P is the diffusion coefficient for all phosphate species, and D_S is the diffusion coefficient for all drug species.

Everywhere in the system, the following equilibria exist:

$$HSP + HP^{-2} \rightleftharpoons SP^- + H_2P^- \quad \text{(Eq. 37a)}$$

$$K_3 = \frac{(SP^-)(H_2P^-)}{(HSP)(HP^{-2})} = \frac{K_{2SP}}{K_{2P}} \quad \text{(Eq. 37b)}$$

$$HSD + HP^{-2} \rightleftharpoons SD^- + H_2P^- \quad \text{(Eq. 38a)}$$

$$K_4 = \frac{(SD^-)(H_2P^-)}{(HSD)(HP^{-2})} = \frac{K_{2SD}}{K_{2P}} \quad \text{(Eq. 38b)}$$

where K_{2SP} and K_{2SD} are the second acid dissociation constants of sulfapyridine and sulfadiazine, respectively; and K_{2P} is the second acid dissociation constant of phosphoric acid.

Equations 29–36 are similar to the benzoic acid–salicylic acid system; therefore, essentially the same method for data analysis may be used.

EXPERIMENTAL

Materials—Sulfadiazine was purified by recrystallization of sodium sulfadiazine USP[1] from 0.5 *M*, pH 4.7, acetate buffer (5). The crystals were filtered and dried at 100°. Sulfapyridine was purified by dissolving sulfapyridine USP[1] in an equimolar 1 *N* NaOH solution and then recrystallizing in 0.5 *M* acetate buffer at pH 4.7. It was then filtered and dried at 100°. A 1:1 mixture of sulfadiazine (particle size <80 mesh) and sulfapyridine (particle size <80 mesh) was dispersed in a polyvinyl chloride[2] matrix (particle size <80 mesh). The drugs represented 20% of the total tablet.

Tablets—Tablets were made in the same way as previously reported (1).

Solvents—Solvents used for this study were 0.05 *M* acetic acid[3]–sodium acetate[3] buffer at pH 4.7; 0.10, 0.04, and 0.02 *N* NaOH[4] solutions; 0.2, 0.05, and 0.01 *N* HCl solutions; 0.06, 0.015, and 0.04 *M* K_2HPO_4 solutions; and 0.10, 0.02, and 0.005 *M* tromethamine[5] solutions. All solvents also contained 0.5 *N* NaCl[6].

[1] Merck & Co., Inc., Rahway, N. J.
[2] Dow Chemical Co., Midland, Mich.
[3] J. T. Baker Chemical Co., Phillipsburg, N. J.
[4] Anachemia Chemicals, Ltd., Champlain, N. Y.
[5] Fisher Scientific Co., Pittsburgh, Pa.
[6] Mallinckrodt Chemical Works, St. Louis, Mo.

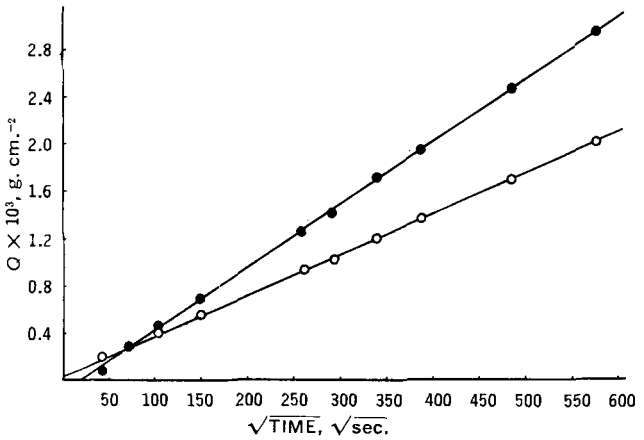

Figure 5—*Release of sulfadiazine and sulfapyridine from an inert matrix (polyvinyl chloride only) containing 20% of a sulfadiazine–sulfapyridine (1:1) mixture into 0.05* M *acetate buffer, pH 4.7. Key:* ●, *sulfapyridine; and* ○, *sulfadiazine.*

Release Rate—The experiments were conducted as described previously (1). The amount of drug released as a function of both sulfa drugs was determined by UV spectrophotometric analysis at 241 nm. in 10^{-3} *N* NaOH and at 300 nm. in 0.1 *N* HCl.

Solubility and Dissociation Constant—The intrinsic solubility of sulfadiazine and sulfapyridine was determined by equilibrating an excess of the solid sulfa drug in 0.05 *M* acetate buffer at pH 4.7 for 3 days and then determining the concentration of the sulfa drug in an aliquot solution. The first acid dissociation constants of sulfadiazine and sulfapyridine were estimated from their solubilities in different hydrochloric acid solutions. The second acid dissociation constants were estimated from their solubilities in different phosphate and tromethamine buffers. The dissociation constant of tromethamine was determined from the pH's of the different hydrochloric acid–tromethamine buffer solutions.

RESULTS

Figures 5–9 gives the experimental results in various solvent systems. As expected, a linear square root of time dependence was observed in all cases. Figures 5 and 6 show that, for the cases in which acetate buffer at pH 4.7 and hydrochloric acid are the solvents, sulfapyridine is released faster than sulfadiazine. With phosphate or tromethamine buffers as solvents (Figs. 7 and 8), sulfadiazine is released faster than sulfapyridine. When sodium hydroxide solution is used as the solvent (Fig. 9), both sulfa drugs are released at almost the same rate.

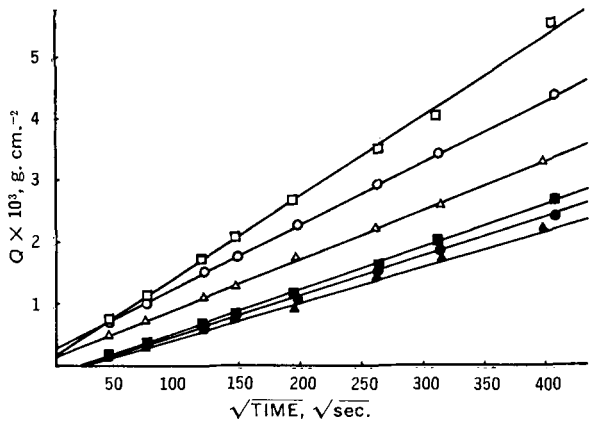

Figure 7—*Release of sulfadiazine and sulfapyridine from an inert matrix (polyvinyl chloride only) containing 20% of a sulfadiazine–sulfapyridine (1:1) mixture into dipotassium phosphate solution. Key: open data points (□, ○, △), release of sulfadiazine; closed data points (■, ●, ▲), release of sulfapyridine;* ■ *and* □, *0.06* M K_2HPO_4; ● *and* ○, *0.015* M K_2HPO_4; *and* ▲ *and* △, *0.004* M K_2HPO_4.

The release rate of both drugs is a function of the concentration of the reacting acid, base, or buffer in the solvent. Figures 6–9 show that the higher the reactant concentration in the solvent, the faster the release rate for both drugs.

TREATMENT OF EXPERIMENTAL DATA WITH EQUATIONS FROM MODEL

The same general approach used in the analysis of the benzoic acid–salicylic acid experiments previously presented (1) was employed in an effort to correlate the experimental results with theory. For each solvent system, a best set of τ_1, τ_2 values was determined using independently known or estimated values for all other parameters in the theory. Then the predictive ability of the theory using the best τ_1, τ_2 pair (or pairs) was used to determine the general validity and usefulness of the theory.

Table I tabulates the values for the various parameters used in the present treatment of the data.

Acetate Buffer Case—From the slope of Q_D *versus* $t^{1/2}$ with the use of Eq. 1 and the values in Table I, a value for $\tau_1 = 2.80$ was determined. Then from the slope of Q_P *versus* $t^{1/2}$ and Eq. 2, a τ_2 value of 6.0 was found.

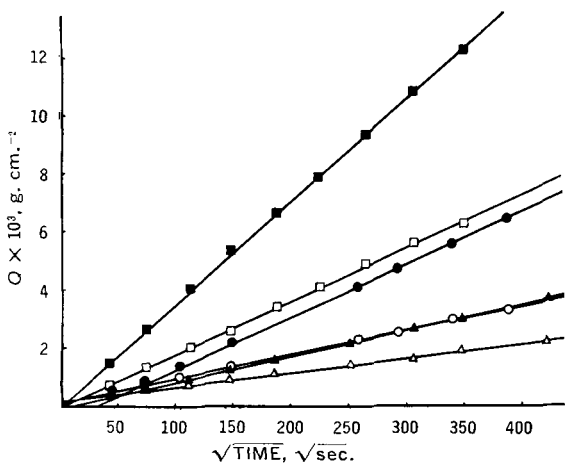

Figure 6—*Release of sulfadiazine and sulfapyridine from an inert matrix (polyvinyl chloride only) containing 20% of a sulfadiazine–sulfapyridine (1:1) mixture into hydrochloric acid solution. Key: open data points (□, ○, △), release of sulfadiazine; closed data points (■, ●, ▲), release of sulfapyridine;* ■ *and* □, *0.20* M *HCl;* ● *and* ○, *0.05* M *HCl; and* ▲ *and* △, *0.01* M *HCl.*

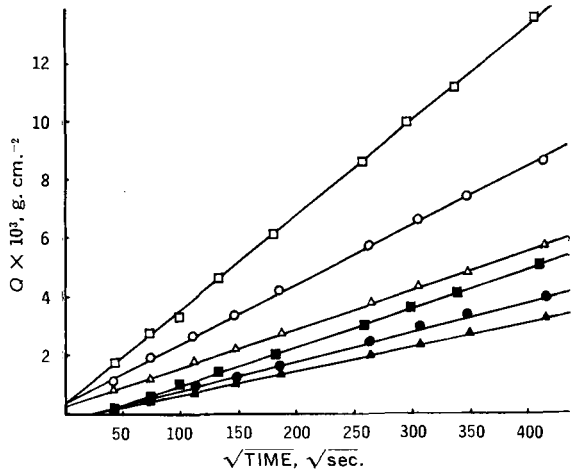

Figure 8—*Release of sulfadiazine and sulfapyridine from an inert matrix (polyvinyl chloride only) containing 20% of a sulfadiazine–sulfapyridine (1:1) mixture into tromethamine solution. Key: open data points (□, ○, △), release of sulfadiazine; closed data points (■, ●, ▲), release of sulfapyridine;* ■ *and* □, *0.10* M *tromethamine;* ● *and* ○, *0.02* M *tromethamine; and* ▲ *and* △, *0.005 M tromethamine.*

Table I—Parameters Used in the Present Treatment of the Data

Parameter[a]	Value	Note
K_{1SD}	8.10×10^{-3} mole/l.	
K_{2SD}	6.24×10^{-7} mole/l.	
K_{1SP}	4.40×10^{-3} mole/l.	
K_{2SP}	5.63×10^{-9} mole/l.	
K_{2P}	2.0×10^{-7} mole/l.	
$K_{tromethamine}$	1.0×10^{-8} mole/l.	
(HSD)*	3.08×10^{-4} mole/l.	
(HSP)*	1.2×10^{-3} mole/l.	
D_P	1.0×10^{-5} cm.²/sec.	
τ_1	0.344	
τ_2	0.258	Sulfadiazine is out front
	0.254	Sulfapyridine is out front
A_P	0.128 g. cm.$^{-3}$	
A_D	0.128 g. cm.$^{-3}$	
D_S	5.0×10^{-6} cm.²/sec.	Reference 7
D_{H^+}	1.0×10^{-4} cm.²/sec.	Reference 8
D_{OH}	2.75×10^{-5} cm.²/sec.	Reference 6

[a] The parameters with no reference indicated were determined independently in the laboratory.

Sodium Hydroxide Case—Equation 8 was used to calculate τ_1 of the matrix. Table II gives the values of τ_1 for the three different concentrations of sodium hydroxide solution.

Hydrochloric Acid Case—By employing a treatment similar to that used in the benzoic acid–salicylic acid studies[7], the experimental values for G_{DS_1} were used with the equations and the τ_1 and τ_2 values were adjusted so that the theoretical (calculated) G_{PS_2} and ratio of s_2/s_1 agreed satisfactorily with the experimental G_{PS_2} and s_2/s_1.

Experimental G_{DS_1}, G_{PS_2}, and s_2/s_1 were calculated from the following equations:

$$G_{DS_1} = \frac{1}{2A_D}\left(\frac{Q_D}{t^{1/2}}\right)^2 \qquad \text{(Eq. 39)}$$

$$G_{PS_2} = \frac{1}{2A_P}\left(\frac{Q_P}{t^{1/2}}\right)^2 \qquad \text{(Eq. 40)}$$

$$\frac{s_2}{s_1} = \left(\frac{G_{PS_2} \cdot A_D}{G_{DS_1} \cdot A_P}\right)^{1/2} \qquad \text{(Eq. 41)}$$

where $Q_P/t^{1/2}$ and $Q_D/t^{1/2}$ are the slopes of plots of the experimental release of sulfapyridine and sulfadiazine against the square root of time, respectively.

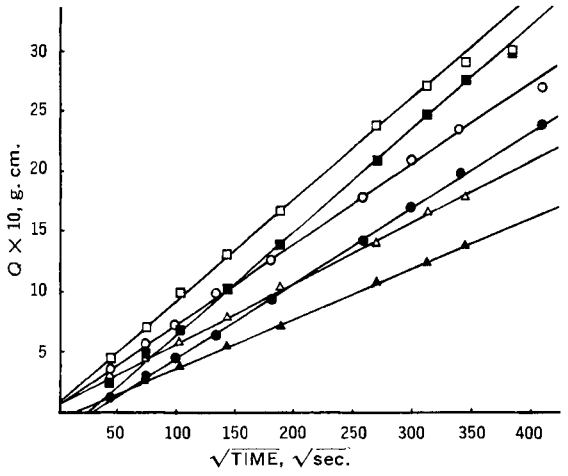

Figure 9—*Release of sulfadiazine and sulfapyridine from an inert matrix (polyvinyl chloride only) containing 20% of a sulfadiazine–sulfapyridine (1:1) mixture into sodium hydroxide solution. Key: open data points (□, ○, △), release of sulfapyridine; closed data points (■, ●, ▲), release of sulfadiazine; ■ and □, 0.10 M NaOH; ● and ○, 0.04 M NaOH; and ▲ and △, 0.02 M NaOH.*

[7] With the IBM 360 digital computer.

Table II—τ_1 in Sodium Hydroxide Case

Solvent	τ_1
0.1 *M* NaOH	3.45
0.04 *M* NaOH	2.67
0.02 *M* NaOH	2.97

Table III lists the combinations of τ_1 and τ_2 that gave the best simultaneous fits for the theoretical and experimental values of G_{PS_2} and s_2/s_1. Identical optimum values of τ_1 and τ_2 were obtained for both cases (the supersaturation and precipitation models) discussed in the theoretical part of this paper. This result was the opposite of that obtained using Cases I and II in the analysis of the benzoic acid–salicylic acid system. That there is no difference observed in this system can be attributed to the fact that K_{1SD} and K_{1SP} are of comparable magnitudes as opposed to the two dissociation constants for the benzoic acid–salicylic acid system.

Dipotassium Phosphate or Tromethamine Case—The method used to find τ_1 and τ_2 is the same used for the release of the mixture of benzoic acid–salicylic acid into phosphate buffers (1). In this case, the parameters appropriate for the sulfadiazine–sulfapyridine system were used in the computer program. Table IV gives the combinations of τ_1 and τ_2 that gave the best simultaneous fits for the theoretical and experimental values of $Q_D/t^{1/2}$ and s_2/s_1 with the first boundary conditions. For the second boundary conditions, combinations of τ_1 and τ_2 that gave good simultaneous fits for the theoretical and experimental values of $Q_D/t^{1/2}$ and s_2/s_1 could not be obtained. In this system, K_{2SD} is much higher than K_{2SP}; therefore, the precipitation model appears to be more reasonable and is favored by these results.

EXAMINATION OF MODELS

Meaning of τ_1 and τ_2 Values Using First Boundary Conditions—Tables II–IV and the results of release experiments with acetate buffer show that the τ_1 and τ_2 values determined were relatively independent of the solvents in all experiments. A τ_1 value of 2.8 ± 0.8 may be considered appropriate for all experiments. The τ_2 values appear to exhibit somewhat larger deviations. However,

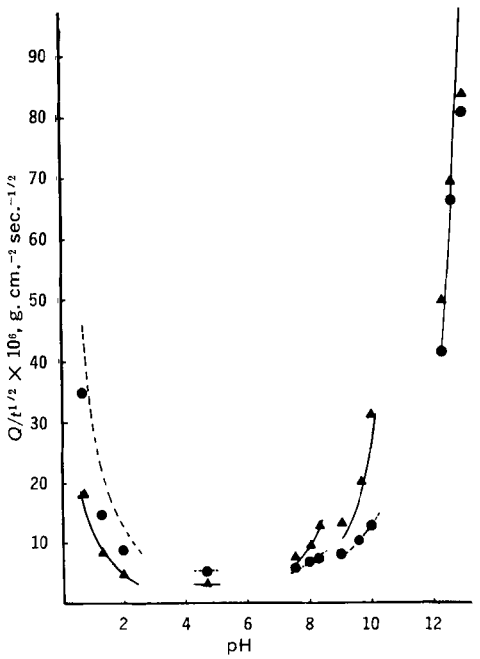

Figure 10—*Comparison of theoretical release rates based on the precipitation model with experimental data as a function of pH. Key: ——, theoretical sulfadiazine release; - - -, theoretical sulfapyridine release; ▲, experimental sulfadiazine release; and ●, experimental sulfapyridine release.*

Table III—τ_1 and τ_2 in Hydrochloric Acid Solutions[a]

Solvent	τ_1	τ_2	$\frac{Q_D}{t^{1/2}} \times 10^{6b}$	$\frac{Q_P}{t^{1/2}} \times 10^{6b}$ Calc.	$\frac{Q_P}{t^{1/2}} \times 10^{6b}$ Exp.	s_2/s_1 Calc.	s_2/s_1 Exp.
2.0×10^{-1} *M* HCl	2.554	5.50	18.2	34.9	34.9	1.92	1.92
5.0×10^{-2} *M* HCl	3.387	8.80	8.33	15.0	14.6	1.75	1.75
1.0×10^{-2} *M* HCl	3.250	6.00	4.75	8.72	8.85	1.86	1.86

[a] Identical results obtained for both cases. [b] g. cm.$^{-2}$ sec.$^{-1/2}$.

Table IV—τ_1 and τ_2 in Dipotassium Phosphate and Tromethamine Solution Cases with the First Boundary Conditions

Solvent	τ_1	τ_2	$\frac{Q_P}{t^{1/2}} \times 10^{6a}$	$Q_D/t^{1/2} \times 10^{6a}$ Calc.	$Q_D/t^{1/2} \times 10^{6a}$ Exp.	s_2/s_1 Calc.	s_2/s_1 Exp.
0.1 *M* Tromethamine	3.10	4.0	12.9	29.39	31.45	2.11	2.44
0.02 *M* Tromethamine	2.80	4.0	10.3	17.92	20.0	1.94	1.94
0.005 *M* Tromethamine	2.80	4.5	8.15	11.00	13.2	1.42	1.44
0.06 *M* K_2HPO_4	3.4	4.9	7.38	12.83	12.80	1.73	1.73
0.016 *M* K_2HPO_4	3.5	4.5	6.50	9.63	9.83	1.33	1.51
0.004 *M* K_2HPO_4	3.8	4.5	5.98	6.83	7.80	1.18	1.30

[a] g. cm.$^{-2}$ sec.$^{-1/2}$.

sulfapyridine is the drug phase in Region 2 (Figs. 1 and 2) for the hydrochloric acid and the acetate buffer cases. Therefore, τ_2 can be expected to be somewhat different for the two situations, while τ_1 should be constant since Region 1 is simply the matrix completely leached of both drugs. A τ_2 value of 4.5 ± 0.5 may be assigned to both the phosphate and the tromethamine buffer cases, and a τ_2 value of 6.0 ± 0.5 would be appropriate for the hydrochloric acid and acetate cases.

The τ_1 value of 2.8 is in good agreement with the work of Desai *et al.* (2), who found values varying from around 1.5 to 3.0 for several organic compounds with the polyvinyl chloride matrix. It is also a physically realistic value consistent with the theory for the effective diffusivity in a packed bed of spheres. The τ_2 values probably reflect the mobility, particle size, particle shapes, and plastic deformability of the drug phase remaining in Region 2.

Theoretical Calculations of Release Rates Using Appropriate τ_1 and τ_2 Values from First Boundary Conditions—The selected values for τ_1 and τ_2 were used with the previously derived theoretical relationships to generate rates of release profiles for the different solvent conditions.

For the hydrochloric acid case, Eq. 24 can be written as:

$$G_P s_1 = G_P s_2 \left(\frac{s_1}{s_2}\right) = \phi_1 \qquad \text{(Eq. 42)}$$

where:

$$\phi_1 = f(D_S, D_{H^+}, K_{1SP}, \epsilon_1, \tau_1, (HSD)^*, K_{1SD}, (H^+)_0, Q_D/t^{1/2})$$

Substitution of Eqs. 39–41 into Eq. 42 gives:

$$\left(\frac{Q_P}{t^{1/2}}\right) \cdot \left(\frac{Q_D}{t^{1/2}}\right) - 2A_D\phi_1 = 0 \qquad \text{(Eq. 43)}$$

$$\frac{1}{2A_P}\left(\frac{Q_P}{t^{1/2}}\right)^2 - \frac{1}{2A_D}\left(\frac{Q_P}{t^{1/2}}\right) \cdot \left(\frac{Q_D}{t^{1/2}}\right)\left[1 - \frac{\epsilon_2\tau_1}{\epsilon_1\tau_2}\right] - \phi_1 = 0 \qquad \text{(Eq. 44)}$$

where:

$$\phi_2 = f\left[D_S, D_{H^+}, \epsilon_1, \epsilon_2, \tau_1, \tau_2, (HSD)^*, (HSP)^*, K_{1SP}, K_{1SD}, (H^+)_0, \frac{Q_D}{t^{1/2}}\right]$$

It can be seen from Eqs. 43 and 44 that when τ_1 and τ_2 are known, $Q_D/t^{1/2}$ and $Q_P/t^{1/2}$ are the only two unknowns. Therefore, by taking the best pair of τ_1 and τ_2 values, one can calculate (predict) the release rates of two drugs.

For the cases using phosphate and tromethamine buffers, a similar procedure can be used to obtain two equations similar to Eqs. 43 and 44 from which the release rates for the two drugs may be calculated when τ_1 and τ_2 are known. For the acetate buffer and sodium hydroxide cases, on the other hand, the situations are simpler. Equations 1 and 2 for the acetate case and Eq. 8 for the sodium hydroxide case can be used directly.

Based upon the above procedures and the parameters given in Table I, the theoretical rates of release were calculated using τ_1 = 2.80 (all cases), τ_2 = 4.5 (when the sulfapyridine phase is in Region 2), and τ_2 = 6.0 (when sulfadiazine is in Region 2). These results are presented in Fig. 10 and compared to the experimental data.

As can be seen, the two-parameter fit of all data is very satisfactory. In view of the fact that both the τ_1 and τ_2 are physically reasonable, and because all other parameters were independently determined, the agreement may conservatively be considered physically significant at this point.

Analysis of Second Boundary Conditions (The Supersaturation Assumption)—Because the second boundary conditions did not yield satisfactory τ_1 and τ_2 values, meaningful calculations of the theoretical rates for the phosphate and tromethamine buffer cases were not possible according to the adopted procedure. This finding alone should argue against the supersaturation assumption. Figures 11 and 12 show the theoretical predictions based on the second

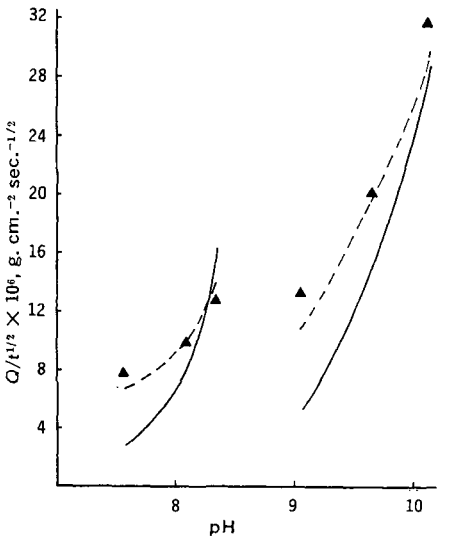

Figure 11—*Comparison of experimental release rates of sulfadiazine with theoretical release rates based on the precipitation model and the supersaturation model. Key: - - -, precipitation model; ——, supersaturation model; and ▲, experimental data.*

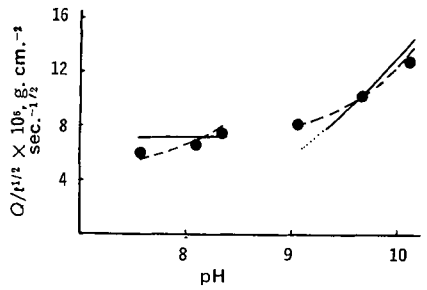

Figure 12—*Comparison of experimental release rates of sulfapyridine with theoretical release rates predicted by the precipitation model and supersaturation model. Key: - - -, precipitation model; ——, supersaturation model; . . ., region in which the supersaturation model yields no mathematical solutions; and ●, experimental data.*

boundary conditions using the τ_1 and τ_2 values obtained with the first boundary conditions. The exact meaning of this attempted correlation is unclear. However, the large deviations of the experimental results from the theoretical release rates for the phosphate and tromethamine cases are probably significant because the τ_1 and τ_2 values used in the calculations were expected to be close to the actual values. They are also consistent with the acetate case, which is independent of the two sets of boundary conditions. Other reasonable τ_2 values when used in the calculations did not improve the situation.

Concentration Profiles—Concentration profiles for each species of drug and solvent, in the case of the mixture of sulfadiazine–sulfapyridine (1:1) released into phosphate buffer, can be calculated in the following manner. First the concentrations of each species at $x = s_1$ and $x = s_2$ are found; then the concentrations of each species at any point $0 \leq x \leq s_2$ are calculated.

To obtain the concentrations of each species of drug and phosphate buffer at $x = s_1$ and $x = s_2$, Eqs. 29–32 may be integrated from $x = 0$ to $x = s_1$, and Eqs. 33–36 may be integrated from $x = s_1$ to $x = s_2$. These integrated equations may be solved simultaneously and evaluated at $x = s_1$ and $x = s_2$.

In the calculations, the experimental G_{PS_1} and G_{DS_2} and the best pair of τ_1 and τ_2 as found previously were used. The species concentration profiles in Region 1 were found by integrating Eqs. 29–32 from $x = 0$ to any point within the range $0 \leq x \leq s_1$. At these points the concentration of each species was calculated by using concentrations at $x = s_1$ and G_{DS_1} and G_{PS_1} values obtained earlier. The same procedure was used to find the concentration profiles in Region 2. Figure 13 shows the results of these theoretical calculations for the mixture of sulfadiazine and sulfapyridine released into 0.06 *M* K_2HPO_4. What is particularly noteworthy (Fig. 13) is the inward flux of the negatively ionized sulfapyridine which, according to this analysis, must precipitate in Region 2 at a rate equal to:

$$\text{rate} = D_S \frac{\epsilon_2}{\tau_2} \frac{d^2(SP^-)}{dx^2} \qquad \text{(Eq. 45)}$$

Further Examination of Precipitation Model—The preceding analysis of the data showed that the first boundary conditions model (precipitation case) is most likely the correct one. One should note, however, that equations based on this model did not include the effects of precipitation upon ϵ_2, τ_2, and A_p. The arguments presented below show that the changes in these quantities caused by the precipitation in Region 2 probably do not greatly affect the rates of release.

First, ϵ_2 would be about 0.255 ($\epsilon_{HSD} + \epsilon_{air}$) in the absence of precipitation. For the example given in Fig. 13, one can estimate that the inward concentration gradient of SP^- at $x = s_1$ is around 40–50% of the outward concentration gradient at $x = s_1$. Since ϵ_1/τ_1 is about twice as large as ϵ_2/τ_2, this means that the *inward* flux should be no more than about 15% of the total flux at $x = s_1$. Assuming that all of the inward flux may be equated to the rate of precipitation in Region 2, one finds that ϵ_2 should change from around 0.255 to 0.24. This is a relatively small change and probably would not be expected to alter significantly the rates of release.

Because the change of ϵ_2 due to precipitation is small, τ_2 would also be expected to remain relatively insensitive to the amounts of

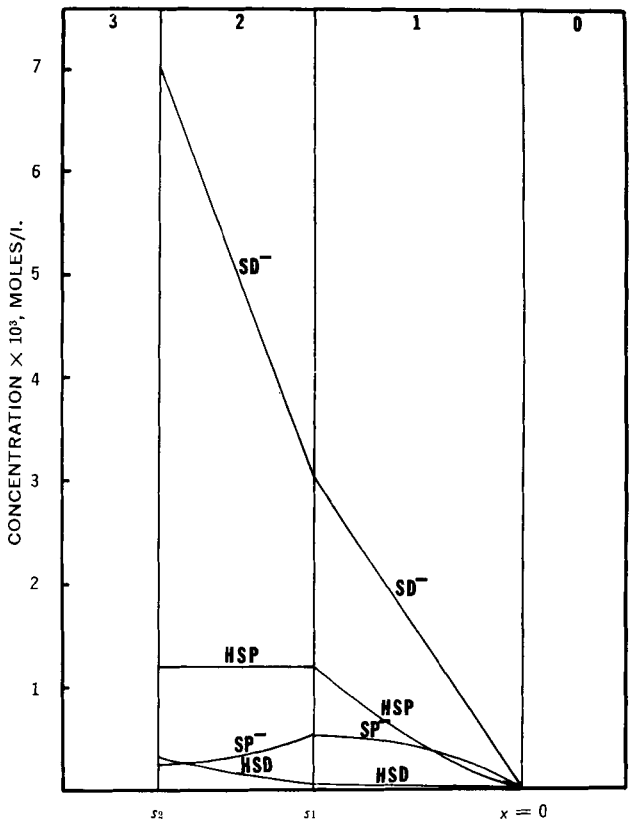

Figure 13—*Concentration gradients of all sulfadiazine and sulfapyridine species (0.06 M K_2HPO_4 solution as solvent).*

precipitation involved under the conditions given in Fig. 13.

The influence of precipitation on A_p (at $x = s_1$) is expected to be constant with time and around 15% for the example in Fig. 13. These conclusions were based on an analysis using arbitrary functions representing the solute and fluxes given by the concentration profiles in Fig. 13.

It can be seen, however, that the appropriate A_p to be used in calculation of G_{PS_1} is not the A_p corrected for precipitation only but that corrected for both precipitation effects and the inward flux effects. These two processes have a canceling tendency; therefore, the original A_p (without any precipitation considerations) is probably the most appropriate one. Thus, the treatment of the experimental data using the model that ignores precipitation is probably quite good, and the uncertainty in A_p is probably much better than 15%.

SUMMARY AND CONCLUSIONS

The results of this investigation and those of the previous study (1) showed that the physical model approach may be fruitfully utilized in mechanistically describing such complex drug release situations as those reported here. Virtually no problem exists that cannot be approached by these methods whether it is complicated by the presence of many interacting phases or many equilibria, both homogeneous and heterogeneous.

REFERENCES

(1) F. Sjuib, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **61**, 1374(1972).

(2) S. J. Desai, P. Singh, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **55**, 1235(1966).

(3) P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **57**, 217(1968).

(4) *Ibid.*, **56**, 1542(1967).

(5) "The United States Pharmacopeia," 15th rev., Mack Publishing Co., Easton, Pa., 1955, p. 690.

(6) W. I. Higuchi, E. L. Parrott, D. E. Wurster, and T. Higuchi, *J. Amer. Pharm. Ass., Sci. Ed.*, **47**, 376(1958).

(7) L. B. Holder and S. L. Hayes, *Mol. Pharmacol.*, **1**, 266(1965).
(8) J. R. Vinograd and J. W. McBain, *J. Amer. Chem. Soc.*, **63**, 2008(1941).

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Investigations of Hydrolytic Products of Butalbital

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Abstract □ Two pathways of cleavage of butalbital (5-allyl-5-isobutylbarbituric acid) were elucidated. Depending upon the reaction conditions, one or both routes might be operative. These proceed initially: (*a*) through 1,6-ring opening to the malonuric acid, and (*b*) *via* 1,2-cleavage of the barbiturate producing the diamide. Several intermediates were isolated and identified or characterized. At pH values around neutrality and a few units above, the hydrolysis takes place solely by means of the 1,6-solvolysis; at higher alkalinities (pH about 9.5), the 1,2-ring opening plays a role. Kinetics of acylureide breakdown at several hydrogen-ion concentrations and temperatures were studied. Data for the diamide and malonuric acid are reported. Ionic strength effects on the alkaline solvolysis of butalbital were examined. A positive relationship of the rate constant to the ionic strength was found, indicative of hydroxyl-ion attack on barbiturate monoanion as a mechanism of degradation.

Keyphrases □ Butalbital—intermediates, products of barbiturate-ring decomposition □ Barbituric acid derivatives—mechanism of butalbital degradation, ring cleavage □ Hydrolysis, butalbital—mechanism, intermediates, products □ Itobarbital—intermediates, products of barbiturate-ring decomposition

The kinetics of the degradation of butalbital[1] (itobarbital) were previously reported (1). However, nothing concerning the mode and products of the hydrolysis was available at that time.

This study pertains principally to the intermediates and final compounds related to decomposition of the barbiturate ring at pH > 7 because kinetics alone fail to illustrate the complete picture.

A review of barbiturate kinetics is available (2), as are several publications regarding decomposition products of barbiturates as their sodium salts (3–6). Conditions are variable between ambient (3) and reflux (4–6), with products dependent on structural considerations as well as pH. Little is available concerning the compounds formed by rupture of the pyrimidine ring as a function of changing pH.

The route of solvolysis of barbiturates has been postulated as passing through both 1,2- and 1,6-ring openings. In the case of butalbital, an investigation of the comparative importance of the two pathways was considered along with some kinetic aspects of the processes involved.

EXPERIMENTAL

Kinetic Procedures—A stock solution of sodium butalbital containing 542 mg. (0.0022 mole/100 ml.) was prepared using distilled water. Two-milliliter aliquots were placed in 200-ml. volumetric flasks, previously equilibrated at 80°, containing 198 ml. 0.05 *N* NaOH along with various quantities of sodium chloride. Ten-milliliter samples were withdrawn and read periodically against the appropriate blank at 240 nm. on a recording spectrophotometer[2] (1).

A stock solution of allylisobutylacetylurea containing 444 mg. (0.0022 mole/100 ml.) in ethanol or dioxane was prepared. Four-milliliter aliquots were placed in 200-ml. volumetric flasks, previously equilibrated at the specified temperatures. Samples were periodically withdrawn and read at 240 nm. against the appropriate blanks on the recording spectrophotometer.

The diamide was run in the same concentration as the acetylurea and barbiturate. It was followed spectrophotometrically at 240 nm.

A stock solution of allylisobutylmalonuric acid (10.6 mg./4 ml. ethanol) was prepared. Two milliliters was placed in 100 ml. of pH 7.0 phosphate and 9.2 borate buffer, μ = 0.10. Three-milliliter samples were withdrawn (adjusted to pH 11.5 with sodium hydroxide) and monitored periodically on the recording spectrophotometer at 240 nm.

Preparation of Hydrolytic Intermediates—*Allylisobutylacetylurea*—Ten grams of sodium butalbital was placed in 400 ml. phosphate buffer, giving a final measured pH of 8.5. The solution was heated at 80° for 48 hr., allowed to crystallize at room temperature, and filtered, yielding 2.3 g. (31.2%), m.p. 136–138° (3).

2-Allyl-2-isobutylmalonamide—One gram of sodium butalbital was heated for 24 hr. in 0.1 *N* NaOH, 80°, followed by extraction with 3 × 50 ml. portions of ether. The ether was allowed to evaporate slowly, yielding 15 mg., m.p. 213–215° (3).

Anal.—Calc. for $C_{10}H_{18}N_2O_2$: C, 60.6; H, 9.2; N, 14.1. Found: C, 60.3; H, 9.1; N, 13.8.

Allylisobutylmalonuric Acid—One gram of sodium butalbital was heated in pH 9 buffer for 48 hr. at 80°, allowed to cool, and filtered and the filtrate was made acidic, pH 4.5. The precipitate was collected after 3 days in the refrigerator, yielding 45 mg., m.p. 155–158°.

Anal.—Calc. for $C_{11}H_{18}N_2O_4$: C, 54.1; H, 7.5; N, 11.1. Found: C, 54.5; H, 7.5; N, 11.5.

Allylisobutylmalonic Acid—Fifty grams (0.16 mole) of barium hydroxide [$Ba(OH)_2 \cdot 8H_2O$] was dissolved in 300 ml. methanol and 96 ml. water with heating on a steam bath. The cloudy solution was

[1] Sandoptal.

[2] Cary 14.