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Commentary

On the Use of the Quasi-Equilibrium Assumption for Drug Dissolution

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The quasi-equilibrium assumption is often used to simplify the analysis of reaction diffusion problems, including those that arise in drug dissolution and ionization processes. This approximation often makes the governing equations tractable, and analytical solutions may then be obtained. However, the application of the quasi-equilibrium assumption may lead to simplified solutions that (1) are apparently inconsistent with stated boundary conditions and (2) have a physical interpretation that is different from those of the original problem statement. Herein we discuss these two issues as they arise in the modeling of drug dissolution processes. In spite of the different conceptualizations, the concentration profiles and dissolution fluxes obtained from the full and approximate solutions converge as the reaction response times exceed those of diffusion, thus supporting the applicability of the quasi-equilibrium assumption for ionized drug dissolution processes.

KEY WORDS: modeling; drug dissolution; quasi-equilibrium; diffusion; instantaneous reaction.

INTRODUCTION

The application of simplifying kinetic assumptions is quite frequent. The two most commonly used simplifying assumptions are the quasi-equilibrium assumption and the quasi-steady-state assumption. Both are applied to spatially homogeneous and heterogeneous systems. The ramifications of using these assumptions and the parameter values under which they are applicable are not always apparent. For instance, the applicability of these assumptions to the classical Michaelis–Menten reaction mechanism has been extensively studied over most of this century (e.g., see review in Ref. 1). The parameter regions of the applicability for this mechanism have recently been mapped out using scaling and comparative time constant analysis (2,3).

Recently, similar concerns have risen in the pharmaceutical literature over the applicability of the quasi-equilibrium assumption to the modeling of dissolution of drugs (4,5). Intuitive arguments against its use state that the physically realistic boundary conditions are violated. Mathematically, imposition of quasi-equilibrium assumptions reduces the number of degrees of freedom in the model equations. Some variables that were independent in the original problem statement become dependent on other variables through the quasi-equilibrium relationships. The dependent variables that are eliminated by the use of the simplifying assumptions typically are those that maybe considered fast relative to some other variables that move slowly and/or are experimentally measurable. Since one cannot impose an independent boundary condition on a dependent variable, this procedure leads to a corresponding reduction in the number of independent boundary conditions necessary to solve the problem. Frequently, the simplified solution is inconsistent with the original problem statement or physical intuition. We first use a familiar example from enzyme kinetics to illustrate the main points and then show how analogous issues arise when one uses the quasi-equilibrium assumption for solving mathematical models of the drug dissolution process.

AN EXAMPLE FROM ENZYME KINETICS

Michaelis-Menten Kinetics. The simplest enzymatic reaction mechanism, first proposed by Henri in 1903 (6) but named after Michaelis and Menten (7), is

$$\underset{(s)}{S} + \underset{(e)}{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(x)}{X} \xrightarrow{k_2} E + \underset{(p)}{P} \qquad (1)$$

where a substrate S binds reversibly to the enzyme E to form the intermediate X, which can break down to give the product P and regenerate the enzyme. There are four chemical species in this mechanism which are constrained by two mass balances

$$e_0 = e + x \quad \text{and} \quad s_0 = s + x + p \qquad (2)$$

and consequently, there are two degrees of freedom. The lowercase letters represent the concentration of the chemical species denoted by the corresponding uppercase letter.

The two independent variables that are traditionally used are the substrate (s) and the intermediate complex (x) concentrations. The reaction dynamics are described by two differential equations:

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$$\frac{ds}{dt} = -k_1 e_0 s + k_{-1} x + k_1 s x, \qquad s(t = 0) = s_0 \tag{3}$$

$$\frac{dx}{dt} = k_1 e_0 s - (k_{-1} + k_2) x - k_1 s x, \qquad x(t = 0) = 0 \tag{4}$$

A typical concentration profile is sketched in Fig. 1, where the solid lines represent the solution of the full model. The substrate decays in time, whereas the intermediate complex initially rises rapidly and then decays. The initial rise of x typically is fast, leading to the use of simplifying kinetic assumptions.

The more commonly used quasi-steady-state assumption assumes that the transients of x are fast and relaxing them, $dx/dt \approx 0$, results in

$$x_{qss} = \frac{e_0 s}{K_m + s} \tag{5}$$

where $K_m = (k_{-1} + k_2)/k_1$ is the well-known Michaelis constant. The important ramification is that x is no longer an independent variable and is calculated based on s. Substituting x_{qss} into the differential equation for the substrate, Eq. (3), gives the well-known Michaelis–Menten rate law

$$\frac{ds}{dt} = \frac{-k_2 e_0 s}{K_m + s} \tag{6}$$

The time profiles resulting from the reduced model are sketched by the dashed lines in Fig. 1. The important difference between the full and the reduced solution is that x no longer is zero at time zero but is immediately in a quasi-steady state with respect to s. Hence x has a finite value at time zero [$x_0 = e_0 s_0/(K_m + s_0)$] which is in *direct contradiction* with the physically realistic initial condition of $x_0 = 0$. Further, the initial rate of change of x has changed from being positive for the full solution to being negative for the reduced solution.

The violation of the initial condition by the reduced solution is clear in this example. Since the reduced solution for x is obtained directly from s we *cannot* impose independent initial conditions for x. It should be pointed out that the initial dynamics of the reaction are, in many cases, not important, and although the simplified solution has a different initial condition, it leads to a good approximation to the concentration profile for the longer time span of interest. Similar arguments apply for the use of the quasi-equilibrium assumption (2,3) and the parameter combinations under which they are applicable have been described (2,3).

This familiar and readily understandable example is intended to serve as an illustration. Parallel issues arise when one uses the quasi-equilibrium assumption for the simplification of mathematical descriptions of drug dissolution processes.

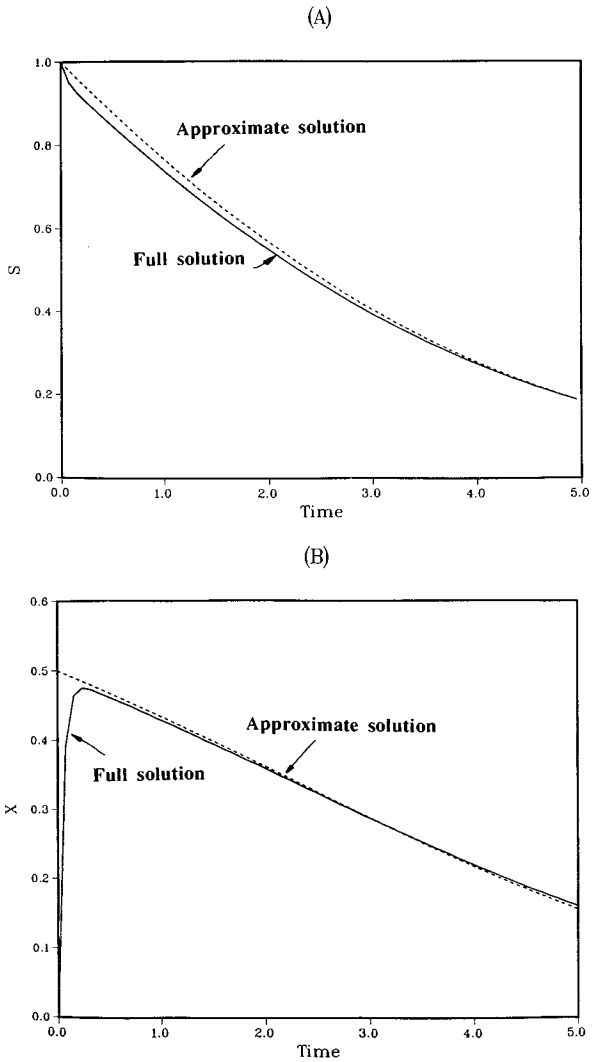

Fig. 1. Concentration profiles for the Michaelis–Menten reaction mechanism. Solid line, full solution; dashed line, solution after applying the steady-state assumption. (A) The concentration profile for the substance s. (B) The concentration profile for the intermediate complex concentration x.

MODELING DRUG DISSOLUTION

We now consider the situation where dissolution and subsequent reaction occurs. An analytical solution exists, for both the full and the simplified model, when the dissolution of compound A is followed by a conversion to compound B by a reversible reaction as

$$A_{solid} \rightarrow A_{aq} \rightleftarrows B_{aq}, \qquad r = k(C_A - KC_B)$$

where r represents the rate of the reaction. This example might be taken to represent the dissolution of an acidic drug molecule into a medium that is well buffered, with B representing the ionized form.

Model Equations. Using a film model with Fick's law of diffusion in slab geometry, the differential equations describing this system are as follows.

(a) For compound A,

$$D_A \frac{d^2 C_A}{dx^2} = r = k(C_A - KC_B) \tag{7}$$

(b) For compound B

$$D_B \frac{d^2 C_B}{dx^2} = -r = -k(C_A - KC_B) \tag{8}$$

where C_A and C_B are the concentrations of A and B, D_A and D_B are the respective diffusion coefficients, x is the coordi-

nate measured from the surface, k is the reaction rate constant, and K is the equilibrium constant with $K = (C_A/C_B)_{eq}$.

Boundary Conditions. When a compound dissolves into water it must cross the phase boundary between the solid phase and the aqueous phase in which it will be dissolved. For drugs which are in the free acid or free base form in the solid state, any dissociation will occur *subsequent* to hydration. Regardless of the chemical kinetics involved and their rates, the ionized species are created *after* the molecules have left the solid phase. The flux of ionized drug must therefore be zero at the interface, while the flux of the dissolving molecule that crosses the phase boundary is nonzero.[4]

Based on these observations we state the following boundary conditions.

(a) At the surface, $x = 0$,

$$C_A = C_{Ai} \tag{9}$$

which is the intrinsic solubility of A. Since B, the product, is ionized it cannot penetrate the solid drug and we have

$$\frac{dC_B}{dx} = 0 \tag{10}$$

(b) At the bulk edge of the diffusion layer, $x = \delta$,

$$C_A = C_{AL} \quad \text{and} \quad C_B = C_{BL} \tag{11}$$

which are the values in the bulk. In most cases these values are zero (sink conditions). To simplify the ensuing mathematical expressions we take C_{AL} and C_{BL} to be zero (sink conditions).

Full Solution. The solution of the differential equations with the boundary conditions specified results in the following concentration profile for C_A (11):

$$C_A = \frac{(1 - z)C_{Ai}}{1 + (\gamma/\phi K)\tanh(\phi)} + \cosh(\phi z)\left[1 - \frac{1 + (\gamma/\phi K)\tanh(\phi z)}{1 + (\gamma/\phi K)\tanh(\phi)}\right] C_{Ai} \tag{12}$$

and

$$C_B = \frac{(1 - z)C_{Ai}/K}{1 + (\gamma/\phi K)\tanh(\phi)} - \cosh(\phi z)\left[1 - \frac{1 + (\gamma/\phi K)\tanh(\phi z)}{1 + (\gamma/\phi K)\tanh(\phi)}\right] \frac{C_{Ai}}{\gamma} \tag{13}$$

where $z = x/\delta$ is a dimensionless coordinate, $\gamma = D_B/D_A$, and ϕ is the Thiele modulus defined as

$$\phi^2 = k\delta^2(\gamma + K)/D_{A\gamma} \tag{14}$$

The Dissolution Flux. The dissolution flux of A is obtained from

$$J_A = -D_A\left(\frac{dC_A}{dx}\right)_{x=0} = \frac{D_A}{\delta} C_{Ai} \frac{\gamma + K}{[\tanh(\phi)/\phi] + K} \tag{15}$$

while J_B is zero. At this point we note that the flux of A is equal to the total rate of dissolution since the flux of B at the surface is zero:

$$J_A = -D_A\left(\frac{dC_A}{dx}\right)_{x=0} = -D_A\left(\frac{dC_T}{dx} - \gamma\frac{dC_B}{dx}\right)_{x=0} = -D_A\left(\frac{dC_T}{dx}\right)_{x=0} = J_T \tag{16}$$

where we define the "dynamic total concentration" of A as $C_T = C_A + \gamma C_B$.

QUASI-EQUILIBRIUM ASSUMPTION

The set of equations described above can be solved in terms of total concentrations. Combining Eqs. (7) and (8) we get

$$D_A\frac{d^2(C_A + \gamma C_B)}{dx^2} = D_A\frac{d^2C_T}{dx^2} = 0 \tag{17}$$

Integration and evaluation of the constants of integration using the boundary conditions $C_T = C_{Ai} + \gamma C_{Bi}$ at the surface and Eq. (11) lead to

$$C_T = (1 - z)C_{Ti} \text{ or } C_A + \gamma C_B = (1 - z)(C_{Ai} + \gamma C_{Bi}) \tag{18}$$

Now we assume that A and B are always at equilibrium, i.e.,

$$C_B = C_A/K \tag{19}$$

We may now obtain the concentration profile for A by using Eq. (19) in Eq. (18):

$$C_A = (1 - z)C_{Ai} = \left(\frac{K}{\gamma + K}\right) C_{Ti} \tag{20}$$

and C_B can be calculated from the equilibrium relationship. The dissolution fluxes of A and B are simply given by

$$J_A = \frac{D_A}{\delta} C_{Ai} \quad \text{and} \quad J_B = \frac{D_A}{\delta}\frac{\gamma}{K} C_{Ai} \tag{21}$$

while the total rate of dissolution, obtained from Eq. (18), is

$$J_T = \frac{D_A}{\delta}\left(1 + \frac{\gamma}{K}\right) C_{Ai} \tag{22}$$

This quasi equilibrium solution, of course, assumes that the reaction is infinitely fast, hence no rate constants (ϕ) appear in the solution. A comparison of the results from full and approximate solutions can be made only in the limiting case of infinitely large reaction rate constants. However, an important difference is immediately seen irrespective of the rate constant. The difference of course is that the rate of dissolution of B *is now finite*. This result is in direct contradiction with the original problem statement and is a con-

[4] An analogous situation occurs when a molecule in the gaseous state dissolves in a liquid—a situation of which numerous treatments are found in the gas/liquid dissolution (absorption) literature (8–10). Even if the ionized species could penetrate the solid, the rate of diffusion would be five to seven orders of magnitude slower in the solid than the liquid, making the flux into the solid negligible.

sequence of imposing the quasi-equilibrium assumption. Since C_B has been eliminated as an independent variable—it depends now directly on C_A through Eq. (19)—we can no longer impose an independent boundary condition on C_B, hence the solution obtained under the quasi-equilibrium assumption is inconsistent with the original problem statement.

This limitation of quasi-equilibrium assumption is inevitable, as this approach does not have an independent evaluation of concentration profiles for individual species. Rather, the total concentration profile is evaluated first. Then the equilibrium is assumed to relate the total concentration to the individual ones (5). Hence, we cannot recover the independent boundary condition assigned for B when it was an independent variable. Once B becomes dependent, its behavior at the boundary, or the boundary conditions, also becomes dependent, and obviously the independent and dependent boundary conditions do not match.

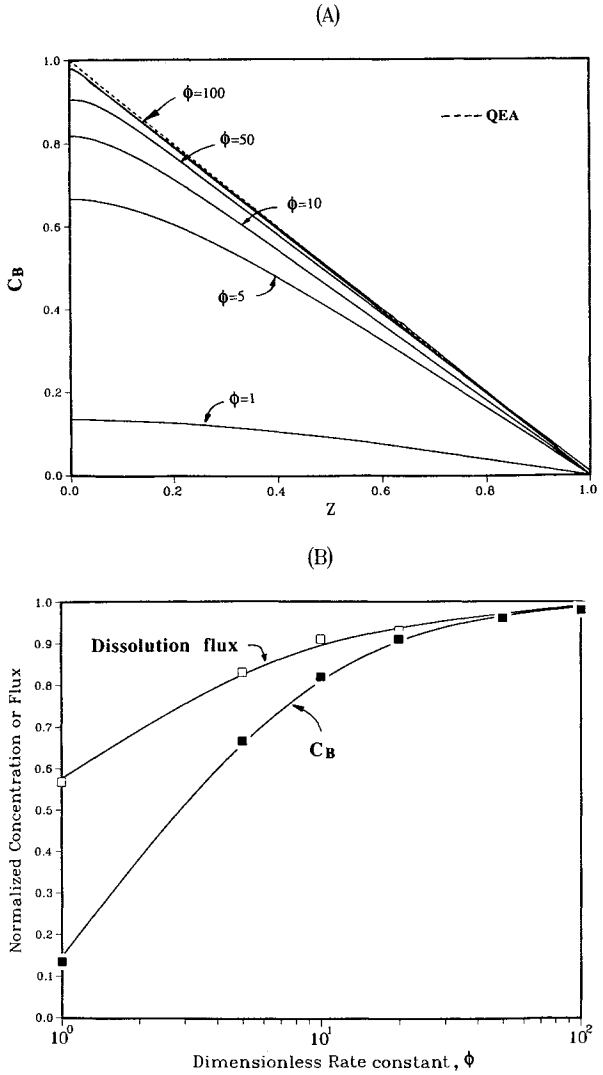

Fig. 2. (A) Concentration profiles for B in the boundary layer, for sink conditions, $K = 1$, and $\gamma = 1$. The full solution is represented by the solid line, and the quasi-steady-state assumption solution by the dashed line. (B) The dissolution flux (open squares) and the concentration of B at the solid surface (filled squares) as a function of rate constant. The values are normalized to the quasi-equilibrium solution.

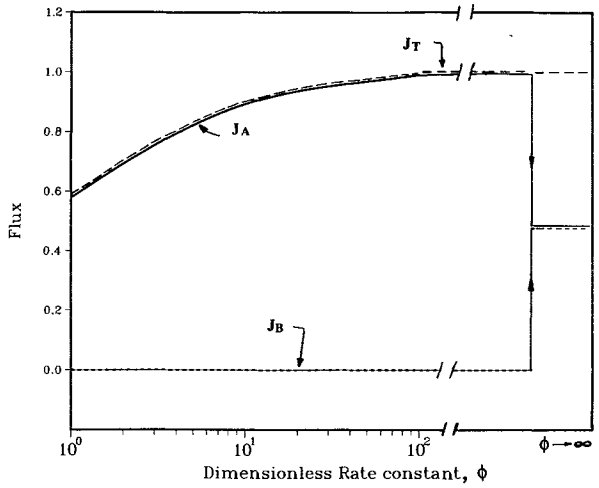

Fig. 3. Dissolution fluxes. The total rate of dissolution is represented by the dashed line, the rate of dissolution of A is represented by the solid line, and the rate of dissolution of B is represented by the dotted line.

COMPUTER SIMULATIONS

We have seen that the quasi-equilibrium assumption leads to a nonzero flux of B at the solid/liquid interface, in apparent contradiction to the original problem statement. Now let us examine solutions from full and quasi-equilibrium assumption approaches in predicting the dissolution fluxes and the concentration profiles in the boundary layer.

Figure 2A illustrates the concentration profile of B in the boundary layer for sink conditions with $K = 1$, $\gamma = 1$, predicted from the full model. The concentration of B is normalized to the concentration of A. The profiles from full and quasi-equilibrium assumption solutions differ at slow reaction rates (low ϕ). However, the concentration profiles for B approach the approximate solution obtained under the quasi-equilibrium assumption as ϕ increases. Figure 2B shows the concentration of B at the interface and the total dissolution flux as a function of the reaction rate constant. These values are normalized using the quasi-equilibrium assumption solution and we see that both values approach those obtained from the quasi-equilibrium assumption solution at high rate constants. Hence it is apparent from Fig. 2 that although the discrepancy arises in the boundary condition for C_B, the quasi-equilibrium solution closely approximates the full solution under the condition that $\phi \gg 1$.

The dissolution rate of B (directly proportional to the slope of the concentration profile at the interface) is always zero for the full solution, as dictated by the boundary conditions, Eq. (4). The slope for the quasi-equilibrium solution is, however, not zero, even though the concentration profiles converge as ϕ becomes large. The rates of dissolution for A and B are thus discontinuous in the instantaneous reaction rate limit ($\phi \to \infty$). The estimated total rates of dissolution for both the full and the approximate solutions, though, are numerically the same under these limiting

condition.[5] The solutions for the individual and total fluxes are shown in Fig. 3. This figure also illustrates the discontinuity in the limit $\phi \to \infty$.

If one considered only the solution obtained after imposing the quasi-equilibrium assumption, one would arrive at the physical interpretation that component B is actually crossing the solid/liquid interface. The analogous interpretation in the Michaelis–Menten example would be that there is a finite concentration of the intermediate substrate–enzyme complex at time zero. These misleading physical interpretations result from examining the solutions *after* the simplifying assumptions have been imposed. The appropriate point to establish the physical interpretation is in the initial statement of the problem. Regardless of the altered physical interpretation, the approximate solutions give the correct numerical values under the appropriate conditions (in the drug ionization example, when ϕ is large).

[5] This convergence is in fact clear if one notes that $\tanh(\phi)/\phi \to 0$ as $\phi \to \infty$; thus Eq. (15) becomes Eq. (22), and Eq. (12) becomes Eq. (20).

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