Letter to the Editor

To the Editor:

In his letter to the editor, Dr. Himmelstein raises three issues with regard to the articles by Ozturk *et al.* (1,2). The discussion in Refs. 1 and 2 of the quasi-equilibrium assumptions used, their interpretation, and the consequences of their use is perhaps insufficient to avoid misinterpretation of the problem statement and the method of solution. The use of simplifying kinetic assumptions, such as the quasi-equilibrium assumption, often involves subtle changes in problem interpretation and the consistency of the simplified solution with the original problem statement, e.g., see Ref. 3. In many areas of analyses, the shortcoming of the use of simplifying kinetic assumptions is well known. Dr. Himmelstein's comments, however, suggest that an assessment should be made of how restrictive the quasi-equilibrium assumption is in the mathematical analysis of drug dissolution processes.

We now attempt to clarify the three points that Dr. Himmelstein raises in his letter. The equation numbers used herein correspond to those in Ref. 1.

Zero Flux at the Solid/Liquid Boundary. When a compound dissolves in water it must cross the phase boundary between the solid phase and the aqueous phase in which it will be dissolved. 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 (4–6). In either case, the flux of the dissolving molecule that crosses the phase boundary is nonzero. However, the flux of nonpenetrating components (i.e., those that cannot cross the boundary) is zero.

If the dissolving species is ionizable in the aqueous phase, as is the case for the drugs treated in Refs. 1 and 2, the molecule dissociates *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. There are no ionized species in the solid phase, therefore the drug cannot dissolve and cross the phase boundary as the ionized species. The flux of ionized drug *must* therefore be zero at the interface. Dr. Himmelstein agrees with this physical analysis but then argues that the drug must dissolve at a rate sufficient to maintain instantaneous ionization equilibrium.

When two processes occur in series, the slower step will be rate limiting. Only in the case where two processes occur in parallel will the faster process be rate determining, e.g., see a series of examples in Ref. 7. In the present case we have dissolution occurring prior to ionization. Therefore, according to the series process model, the rate of generation of ionized species, although instantaneous once drug has dissolved, is limited by the rate at which the drug dissolves. Since the drug is always nonionic in the solid (i.e., no efflux of ionized drug can occur), and drug is incapable of precipitating from solution as the ionic form (i.e., no influx of ionized drug is possible), the net flux of ionic species at the phase boundary must be zero. The differential equations, boundary conditions, flux expressions, and dissolution rates in the paper are derived based on this physical analysis of the system. A stepwise outline of the model development and solution procedure in Refs. 1 and 2 is given below:

(1) formulation of differential equations,
(2) statement of boundary conditions,
(3) combination of variables to eliminate the reaction rate terms,
(4) solution of differential equations in the combined form for combined variables,
(5) use of boundary conditions in the combined form to evaluate the integration constants,
(6) use of quasi-equilibrium assumption to calculate the surface pH, and
(7) use of this pH to calculate the individual concentrations.

Notice that the dissolution flux expression, Eq. (45), is derived before considering the rate of ionization and it is therefore a *general* solution. Dr. Himmelstein's comments, however, bring out some of the main shortcomings of the use of the quasi-equilibrium assumption (step 6), namely, the unrealistic physical interpretation that results from its use.

Use of Zero-Flux Boundary Conditions in the Solution of the Differential Equation. The concentration profiles for the combined variables ("dynamic concentrations") *can* be obtained directly using the boundary conditions stated in Eq. (14) though (17). However, as Dr. Himmelstein correctly points out and as stated explicitly in Refs. 1 and 2 further information is required to evaluate the concentration profiles of individual species—this is accomplished in Refs. 1 and 2, by imposing quasi-equilibrium assumptions. Equations (14) through (20) plus the quasi-equilibrium assumption form a complete statement of the problem. There are other methods which can be used to obtain the solution. Two of these, a mass balance and flux neutrality, were used in earlier analyses (8–10).

The value of C_4 is dictated by H^+, A^-, and OH^-. Since three variables are involved, it is completely reasonable to combine three conditions in the evaluation of C_4.

Consistency of the Flux Boundary Condition with the Presented Solution. Imposition of quasi-equilibrium assumptions (step 6 in the solution procedure) reduces the number of degrees of freedom in the problem statement. Thus, some variables that were previously independent become dependent on other variables through the quasi-equilibrium relationships. Since one cannot impose an independent boundary condition on a dependent variable, this procedure reduces the number of independent boundary conditions necessary to solve the problem. Solution for the

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concentration profiles obtained under the quasi-equilibrium assumption represents a correspondingly restricted set of solutions, relative to the general case stated in Eq. (45).

Dr. Himmelstein, in his letter, manipulates the mathematical expressions derived prior to and subsequent to imposition of the quasi-equilibrium assumption and he then compares the results. He, therefore, is comparing two different things, and it is not surprising that he obtains inconsistencies. The inconsistencies that he obtains simply reflect the restrictions imposed by the quasi-equilibrium assumption.

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