Letter to the Editor

To the Editor:

The recent paper "Dissolution of Ionizable Drugs in Buffered and Unbuffered Solution" by Ozturk *et al.* (1) purports to present a new model of transport and reaction of ionizable drugs across a boundary layer. Specifically, this presentation is differentiated from previous efforts (2–4) by the use of zero-flux boundary conditions at the dissolving surface. This letter examines the appropriateness of these conditions to represent the physical phenomena under consideration, their direct use in the solution of the differential equations that form the model, and the consistency of the boundary conditions with the actual results achieved. Here only the results for dissolution (as opposed to precipitation) of acidic drugs into unbuffered solution are examined. It is obvious that the discussion applies to the buffered media and basic drugs as well. In addition, the argument presented here is also directly pertinent to an additional publication by Ozturk *et al.* (5). All equations are numbered consistently with Ref. 1, as is the notation.

Zero-flux Conditions at a Dissolving Surface. Physically, several events occur at the surface of a dissolving ionizable solid as treated in this letter. Solid material undergoes a dissolution process that maintains an equilibrium concentration of both nonionized and ionized species at the surface in the aqueous phase. Both ionized and nonionized drug are free to diffuse away from this surface by random molecular motion, i.e., diffusion. While "the solid/liquid interface is open only to dissolving species (unionized drug)," this is irrelevant to the problem statement, which applies only to the liquid phase. Enough solid drug must dissolve to maintain the instantaneous ionization process at the surface. The assumption of equilibrium between ionized and nonionized species at the boundary demands that, for a given surface pH, essentially the boundary value concentrations are fixed and are the true boundary conditions for this model. The surface is the only source of drug in the problem, and the bulk is assumed to be free of drug. Therefore, there is a monotonic decrease in drug species across the boundary layer. Since a maximum occurs precisely at the surface, because of instantaneous ionization, and since there is *no other mechanism* to maintain a zero flux at the surface for these species, both H^+ and A^- must diffuse away from the solid, even at the boundary. By Fick's first law, since J is positive,

$$J_i = -D_i \frac{dCi}{dr} = 0, \qquad i = H^+, A^-$$

It follows that the derivatives at the wall are finite and nonzero. Clearly, there must be enough dissolution of solid material from the solid phase to maintain the ionic equilibrium and concomitant flux of ionic species, and the zero-flux condition is not appropriate to describe a system where it is assumed that *instantaneous* ionization can occur.

Use of Zero-Flux Boundary Conditions in the Solution of the Differential Equations. In the solution of the differential equations (14)–(19), the boundary conditions should be used to evaluate the constants C_1, C_2, C_3, and C_4. Yet C_1 and C_2 contain evaluations of A^- at the surface. Since no boundary condition (18)–(19) explicitly contains an evaluation of A^- at the surface, therefore, at the point equation (23) and Table I is presented, A^- at the surface is an unknown. Additional information, found in the form of the equilibria (26), is required to complete the solution. In previous efforts (2–4), which this solution, in reality, mirrors, another condition was also required, either an additional mass balance (2,3) or flux neutrality (4) (and clearly not stated in Ozturk's development). The question arises, Why three conditions to evaluate one constant, C_4? This question immediately raises doubts about the appropriateness of these conditions. It can be deduced that, contrary to the authors' assertion, the boundary conditions (19) are not sufficient for the complete solution. Therefore, the problem statement, Eqs. (14) through (20), is not a complete statement of the problem

Consistency of the Flux Boundary Conditions with the Presented Solution. Two essential elements of the solutions presented are Eqs. (23) and (26). That is, these expressions form the key result of the paper; each must be consistent with the problem statement, Eqs. (14) through (20).

By combining the solution equation (23),

$$D_{HA}[HA] + D_A\text{-}[A^-] = C_1 + C_{2/r} \tag{23}$$

with the first equilibrium expression (26),

$$[A^-] = K_a \frac{[HA]}{[H^+]} \tag{26}$$

an expression can be derived eliminating HA,

$$[A^-] = K_a(C_1 + C_2/r) \frac{(1)}{D_A\text{-}K_a + D_{HA}[H^+]}$$

The derivative of this expression with respect to r is

$$\frac{d(A^-)}{dr} = \frac{-K_aC_2/r}{D_A\text{-}K_a + D_{HA}[H^+]} - \frac{D_{HA}(C_1 + C_2/r)}{D_A - K_a + D_{HA}[H^+]^2} \cdot \frac{d(H^+)}{dr}$$

The authors contend that at $r = R$,

$$\frac{d[A^-]}{dr} = \frac{d[H^+]}{dr} = 0$$

Substituting into the above expression,

0724-8741/89/0500-0436$06.00/0

$$0 = \frac{1}{D_A - K_a + D_{HA}[H^+]} \frac{(-C_2)}{R^2} + 0$$

Therefore,

$$-C_2 = 0$$

is the only conclusion to be reached. From Table I,

$$C_2 = D_{HA}([HA]_{T,s} - [HA]_{T,B})R\left(\frac{R}{\delta} + 1\right) = 0$$

substituting in for the definitions of $[HA]_T$,

$$C_2 = D_{HA}[([HA]_s + \gamma[A^-]_s) - ([HA]_B + \gamma[A^-]_B)]R\left(\frac{R}{\delta} + 1\right) = 0$$

Note that the only way that these conditions can be met is that the sum of concentrations at the surface must equal the sum of concentrations in the bulk. Clearly, there is no net flux of drug under these conditions. Simply put, the requirement of equilibrium at the surface demands that, for mass transfer to occur of any of the species, they all must do so in lockstep. Differentiation of the equilibrium expression (26) shows that if the derivatives of H^+ and A^- are zero at the surface, so too must be the derivative of HA. An alternative demonstration of the inappropriateness of the boundary conditions can be found by examination of Fig. 2. Curves B, C, and D are those for which the authors assert that the derivatives of these curves are zero at $x = (r - R)/\delta = 0$. Clearly this is not the case. Had the authors presented a closed-form expression for H^+ concentration, which they had to derive and evaluate to provide Fig. 2, simple differentiation and evaluation at the surface would reveal quantitatively what is obvious visually: the derivative of H^+ in the solution provided is not zero at the surface.

Summing up, the zero-flux boundary conditions appear not to represent the physical phenomena described, are not sufficient for the solution of the differential equations, and are not consistent with the solutions presented.

REFERENCES

1. S. S. Ozturk, B. O. Palsson, and J. B. Dressman. *Pharm. Res.* 5:272–282 (1988).
2. K. G. Mooney, M. A. Mintun, K. J. Himmelstein, and V. J. Stella. *J. Pharm. Sci.* 70:13–21 (1981).
3. K. G. Mooney, M. A. Mintun, K. J. Himmelstein, and V. J. Stella. *J. Pharm. Sci.* 70:22–32 (1981).
4. J. G. Aunins, M. Z. Southard, R. A. Myers, K. J. Himmelstein, and V. J. Stella. *J. Pharm. Sci.* 74:1305–1316 (1985).
5. S. S. Ozturk, B. O. Palsson, B. Donohoe, and J. B. Dressman. *Pharm. Res.* 5:550–565 (1988).

Kenneth J. Himmelstein
64 Canyon Ridge
Irvine, California 92715