

Relative Damköhler Numbers Approximate the Convection–Diffusion–Reaction Model for Diffusion-Limited Dissolution

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ABSTRACT: Diffusion-limited dissolution in reactive media was investigated with the convection-diffusion-reaction (CDR) model using monoprotic weak base and acid dissolution in unbuffered media in the rotating disk setup as an example. It was found that the typical film-based approaches are inaccurate in calculating surface pH and dissolution flux values. However, simple equations that accurately approximate the CDR model can be derived in the form of a relative Damköhler number (RDa) for a reversible reaction. As a result, general equations were developed for dissolution impacted by three different reversible reaction scheme examples. Those equations, actually, represent analytical solutions to the CDR equation for the asymptotic regime of infinitely high reversible reaction rates. The contrast between CDR-based and stagnant film-based models contradicts the commonly held notion of the thermodynamic driving force at the interface during diffusion-limited dissolution being independent of hydrodynamic and geometric factors.

$$\frac{\partial C_i}{\partial t} + v_x \frac{\partial C_i}{\partial x} = D_i \frac{\partial^2 C_i}{\partial x^2} + \sum R_{ij}$$

$$\frac{is_A [B]_{0,ss}}{([B]_{bulk} - [B]_{0,ss})K_{eq}} \left(\frac{D_L}{D_B} \right)^{2/3} = 1$$

$A_{(s)} = A_{(aq)} + B_{(aq)} + C_{(aq)}$

1. INTRODUCTION

Dissolution is one of the most common phenomena encountered in the context of mass transport with countless industrial, biological, geological, and other applications. Since the publication of the work of Nernst and Brunner in 1904,^{1,2} the stagnant film approach has dominated dissolution modeling. While Nernst and Brunner envisaged dissolution as a solely diffusion-driven process, subsequent research recognized the significance of reaction processes alongside convection and shear.

Based on the relative diffusional and reactional rates, dissolution processes have been broadly classified as diffusion rate-controlled and reaction rate-controlled. One of the most ubiquitous examples of diffusion-controlled dissolution in reactive media is the dissolution of acidic and basic solutes in basic and acidic solutions, respectively. The proton transfer reactions involved are extremely rapid. To model dissolution coupled to such extremely rapid reversible reactions, the dominant approach was to eliminate reaction terms through mass-balance considerations and assume equilibrium throughout the system, as first proposed by Higuchi et al. and Olander.^{3,4} The boundary layer in the system is typically assumed to behave as a stagnant film.

While this approach has proven useful over the past decades, it is not free of limitations. In most cases, a stagnant film assumption is made which can be problematic in cases where there are large diffusivity gaps between the reacting species. In addition, the equilibrium assumption, while useful, is not physically true. The very rapid nature of those reactions will probably give concentration profiles that are very close to the

equilibrium situation, but they will still not be exactly at equilibrium. Assuming them to be exactly at equilibrium in a stagnant film will lead to unphysical boundary conditions.⁵ In addition, with few exceptions, it is typical to assume an instantaneous steady state and to ignore the effects of electrical potential gradients during dissolution.

In 2022, Uekusa et al.⁶ concluded that the thermodynamic film models which assume the surface concentrations during dissolution to represent the composition of a saturated solution are misrepresentative of the actual situation when ionizable solids dissolve in unbuffered media. While a step forward, this was based on comparison with the paper's charge flux neutrality model, which also makes the stagnant film assumption and, as the authors state, is mathematically equivalent to the Mooney et al.⁷ approach from 1981 (which, as shown later, also misrepresents the situation at the interface). Therefore, that work does not address issues related to the stagnant film assumption itself. Over the past decade, the two-step chemical potential gradient approach introduced in 2015 by Paus et al. has been increasingly used and adapted to different scenarios.^{8–11} While constituting a welcome departure from the stagnant film assumption, these kinetic models are designed for fitting and analyzing

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dissolution data (with the possibility of fit-based predictions) rather than for *a priori* simulation based on physicochemical parameters with no previously available dissolution data.

Therefore, the first objective of this work was to investigate the dissolution of ionizable drug compounds in unbuffered aqueous media using the convection-diffusion-reaction (CDR) model with a minimal number of assumptions. The second was to develop a simple surrogate modeling approach that overcomes the limitations associated with the traditional film-based approaches and provides an accurate approximation of the comprehensive CDR model, which was achieved using Damköhler analysis. In addition to being a case example, dissolution in unbuffered media is of practical significance since it is the scenario pertaining to the dissolution of weakly basic drugs in gastric acid, and many industrial processes involve acid or base dissolution in sodium/potassium hydroxide or hydrochloric/sulfuric acid solutions.

To tackle these objectives, first the theoretical and mathematical basis of the CDR model and the Damköhler analysis is presented. Then the findings of the derived models are compared against experimental data obtained both from literature and in-house rotating disk experiments, and the Damköhler analysis is further expanded concurrently, thus ending up with simple algebraic models describing diffusion-limited dissolution impacted by three common reversible reactions schemes. The predictions of the proposed models are compared to those of important currently established ones showing that stagnant film models are inappropriate when the differences between the diffusivities of the major reacting species are large. Then the issue of background electrolyte and electrostatic potential gradients is addressed. Afterward potential extension to spherical geometry is discussed, where it is shown that, contrary to conventional wisdom, the thermodynamic driving force for diffusion-limited dissolution in reactive media is apparently not independent of hydrodynamic and geometric factors. Finally, the limitations and potential future research directions are discussed.

2. THEORETICAL SECTION

2.1. Physical Model

As seen in Figure 1, the modeled system is a rotating disk with axial fluid flow toward the solid surface. The un-ionized solute molecules move into the solution phase at the interface and react with the dissolved reactants resulting in a net outflux of both ionized and un-ionized solute molecules as well as of

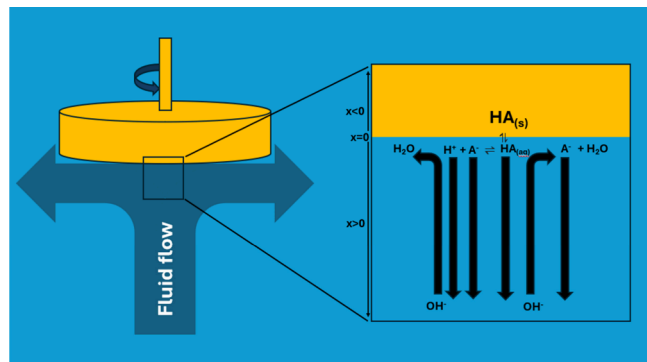


Figure 1. A representation of the physical model using the example of weak acid dissolution in unbuffered medium.

other produced species, while the consumed reactants get replenished from the bulk. For the case of a weakly acidic solute as an example, the physical model is summarized in Figure 1.

2.2. CDR Model

Mass transport processes during reactive dissolution can be described by the CDR equation

$$\frac{\partial C_i}{\partial t} + v_x \frac{\partial C_i}{\partial x} = -\frac{\partial J_i}{\partial x} + \sum_{j=1}^n R_{ij} \quad (1)$$

where C_i is the concentration of the i th species, v_x is the fluid velocity in the x direction, J_i the flux of the i th species and R_{ij} is the rate of the j th reaction of the i th species.

For ionizable species, the change of the flux with respect to the distance term is divided into a chemical potential gradient term and an electrical potential gradient term (Poisson–Nernst–Planck treatment) leading eq 1 to take the following form^{12–14}

$$\begin{aligned} \frac{\partial C_i}{\partial t} + v_x \frac{\partial C_i}{\partial x} = & D_i \frac{\partial^2 C_i}{\partial x^2} - z_i D_i \frac{\partial C_i}{\partial x} \frac{\sum_{i=1}^n z_i D_i \frac{\partial C_i}{\partial x}}{\sum_{i=1}^n z_i^2 D_i C_i} \\ & - \frac{z_i F^2 D_i}{\epsilon_r \epsilon_0 R T} C_i \sum_{i=1}^n z_i C_i + \sum_{j=1}^n R_{ij} \end{aligned} \quad (2)$$

where D_i is the diffusion coefficient of the i th species, z_i is the charge of the i th species, F is the Faraday constant, ϵ_r is the relative permittivity of water, ϵ_0 is the permittivity of vacuum, R is the gas constant and T is the absolute temperature.

Detailed information on the CDR model differential equations including their initial and boundary conditions is available in the Supporting Information. However, for later analysis, it needs to be kept in mind that all the chemical species involved except for the unchanged solute have no flux at the interface (i.e., at $x = 0$).

As for the fluid velocity, the theoretical simulations as well as the experiments were carried out in the rotating disk setup where the fluid velocity is rather well-defined according to the work of Levich¹⁵

$$v_x = -0.51 x^2 \sqrt{\frac{\omega^3}{\nu}} \quad (3)$$

where ω is the angular velocity of disk rotation, ν is the medium's kinematic viscosity, and the x -direction is the axial one.

Regarding the reactions, diffusion-limited second-order recombination rate constants for a base and a proton or an acid and a hydroxide were calculated using the Smoluchowski and (when both reactants are charged) Debye–Smoluchowski equations.¹⁶ The first-order dissociation rate constants were calculated using the recombination rate constants of their reverse and the equilibrium dissociation constants.¹⁶ For instance, for a base (B) reversibly reacting with a proton



the forward reaction (k_{rec}) is very fast diffusion-limited second-order recombination calculated using the Smoluchowski equation

$$k_{rec} = 4\pi D_{AB} R_c N \quad (5)$$

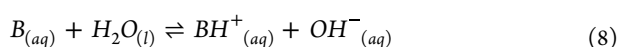
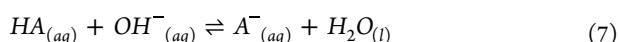
where k_{rec} is the recombination rate constant, D_{AB} is the mutual diffusion rate coefficient of the recombining acid and base, R_c is the critical reaction radius (i.e., the distance at which approaching molecules undergo recombination) and N is the Avogadro number. Eigen¹⁶ suggested multiplying the results of the Smoluchowski and Debye-Smoluchowski equations with a molecular symmetry factor (SF), which Weller¹⁷ proposed to represent the fractional solid angle within which the functional group is approached by the reactant to the critical distance. The backward reaction is a slower dissociation reaction which will be equal to the rate of the recombination multiplied by the equilibrium dissociation constant (K_a) of the protonated base.

Complete details on reaction rate constant determination including SF and R_c are available in the [Supporting Information](#). The extremely rapid nature of the recombination reactions means that all the reactions will be close to equilibrium throughout the system (the maximal deviation of a reaction quotient from equilibrium in the simulations presented in this manuscript was by a factor of 1.366). This makes rough approximations for the reaction rate constants sufficient.

The movement of undissociated solute molecules between solid and solution phases was assumed to be infinitely fast compared to the other processes, so the concentration of the un-ionized acid or base right at $x = 0$ is assumed to be equal to the intrinsic solubility throughout the process. Bulk volume is assumed to be sufficiently large for sink conditions to apply. Velocity profiles were assumed to reach their steady state instantaneously since momentum diffusivity is 2 orders of magnitude larger than mass diffusivity. Diffusion and activity coefficients were also assumed not to vary with time and space.

2.3. Relative Damköhler Number (RDa) Analysis: Recombination Case

A monoprotic acid and a monoprotic base will undergo the following reactions in unbuffered media



where HA is a generic monoprotic acid and B is a generic monoprotic base. With the concentration of the undissociated species at the interface being always equal to intrinsic solubility, the recombination reactions in eqs 7 and 9 will become pseudo-first-order ones. Those will compete with the dissociation reactions in eqs 6 and 8 (as well as with the reversible recombination of the protons and hydroxides to produce water). When the transport of incoming hydroxide/proton is substantially faster than that of outgoing proton/hydroxide, it means that direct recombination is the dominant reaction. Such a scenario is typically relevant at pH extremes.

As for the mass transport coefficient (β) at steady state, this can be defined as follows (for a rotating disk)^{15,18}

$$Sh = \beta \frac{r}{D} = 0.62 Re^{1/2} Sc^{1/3} \quad (10)$$

$$Re = \omega \frac{r^2}{\nu} \quad (11)$$

$$Sc = \frac{\nu}{D} \quad (12)$$

where Sh is the Sherwood number, Sc is the Schmidt number, Re is the Reynolds number and r is the disk radius. Multiplying the difference between interfacial and bulk concentrations with β will give the steady state flux (in the absence of reaction) in accordance with Levich's analytical solution to the convection-diffusion equation for a rotating disk^{15,18}

$$J = \beta(C_0 - C_{bulk}) \quad (13)$$

where J is the flux (and all the J terms in this paper's equations represent steady state fluxes of the subscripted species at the interface (i.e., at $x = 0$) unless stated otherwise). This will allow applying Damköhler analysis based on Damköhler numbers (Da), which represent the ratio of a characteristic reaction rate to that of a characteristic mass transport rate. Here, the example of the direct recombination of a dissolving base with H^+ being by far the dominant dissolution-impacting reaction (allowing other reactions to be ignored) is explained. The outlined principles can easily be extrapolated to the other reaction cases presented later in the manuscript.

The starting point is identifying the relevant mass transport terms by taking a look at the solute flux. Given that the reactions producing B are the same ones consuming BH^+ and vice versa, then, at steady state (assuming there is enough background electrolyte to ignore the electrostatic terms):

$$D_B \frac{\partial^2[B]}{\partial x^2} + D_{BH^+} \frac{\partial^2[BH^+]}{\partial x^2} = v_x \frac{\partial[B]}{\partial x} + v_x \frac{\partial[BH^+]}{\partial x} \quad (14)$$

With the nonlinear second order reaction terms gone, superposition can be applied when integrating. This means that the sum of the fluxes of B and BH^+ at the interface will be equal to their sum as if only convection and diffusion were involved in their transport. Thus, applying Levich's solution^{15,18} of the convection-diffusion equation (details in [Supporting Information](#))

$$J_{solute, total} = \beta_B[B]_{0,ss} + \beta_{BH^+}[BH^+]_{0,ss} = \beta_B is + \beta_{BH^+}[BH^+]_{0,ss} \quad (15)$$

where the ss in the subscripts signifies the establishment of the steady state and the " is " term is the intrinsic solubility. However, according to the CDR model, the only species having nonzero flux at the interface is the un-ionized solute with a no flux boundary condition existing for both the reactant(s) and the ionized reaction product(s) (See [Supporting Information](#)), which is a "natural" boundary condition. This means (assuming sink conditions):

$$J_{solute, total} = J_B = \beta_B is + \beta_{BH^+}[BH^+]_{0,ss} \quad (16)$$

The $\beta_B is$ term of the right-hand side represents the interfacial flux of B had there been no reaction, and the $\beta_{BH^+}[BH^+]_{0,ss}$ term represents the un-ionized solute's interfacial flux enhancement brought about by the net reaction. This enhancement term is also equal to the total mass transport of the reaction product into the bulk (i.e., at $x = \infty$) per unit area.

Another way to eliminate the reaction terms would be taking into account that the reactions consuming and producing B and protons are the same ones:

$$D_B \frac{\partial^2 [B]}{\partial x^2} - D_{H^+} \frac{\partial^2 [H^+]}{\partial x^2} = v_x \frac{\partial [B]}{\partial x} - v_x \frac{\partial [H^+]}{\partial x} \quad (17)$$

This would mean that the sum of the base outflux and proton influx will be equal to the sum of their Levich-based expressions

$$J_B - J_{H^+} = \beta_B is + \beta_{H^+} ([H^+]_{bulk} - [H^+]_{0,ss}) \quad (18)$$

and again, with B being the only species with nonzero flux at the interface

$$J_B = \beta_B is + \beta_{H^+} ([H^+]_{bulk} - [H^+]_{0,ss}) \quad (19)$$

which means that the mass transport term for H^+ also represents the flux enhancement and thus representing the total mass transport of the reactant from the bulk per unit area. This is physically in line with mass-balance considerations, which state that the net transport of the product out of the system should equal the net transport of the reactant into the system for a 1:1 reaction stoichiometry. In other words (combining eqs 16 and (19)),

$$\beta_{BH^+} [BH^+]_{0,ss} = \beta_{H^+} ([H^+]_{bulk} - [H^+]_{0,ss}) \quad (20)$$

Substituting eq 10 into eq 20 and rearranging gives

$$D_{BH^+}^{2/3} [BH^+]_{0,ss} = D_{H^+}^{2/3} ([H^+]_{bulk} - [H^+]_{0,ss}) \quad (21)$$

Very near to equilibrium, the above expression can easily be solved for $[H^+]_{0,ss}$. A more detailed analysis shows that this expression is actually a rearrangement of a Damköhler number, as shown below.

Da values for the forward and reverse reactions and a relative Damköhler number (RDa) for them (using weak base dissolution under sink conditions as an example) can be defined in this case as follows (taking into account that the first order dissociation constant of the protonated base is equal to the product of the forward recombination rate constant and the equilibrium dissociation constant)

$$\begin{aligned} Da_{forward} &= \frac{\text{forward reaction rate}}{\text{reactant mass transport rate}} \\ &= \frac{k_{rec} is [H^+]_{0,ss}}{\beta_{H^+} ([H^+]_{bulk} - [H^+]_{0,ss}) \left(\frac{\nu}{\omega} \right)^{-1/2}} \\ &= \frac{k_{rec} is [H^+]_{0,ss}}{D_{H^+} Sh_{H^+} r^{-1} \left(\frac{\nu}{\omega} \right)^{-1/2} ([H^+]_{bulk} - [H^+]_{0,ss})} \end{aligned} \quad (22)$$

and

$$\begin{aligned} Da_{backward} &= \frac{\text{backward reaction rate}}{\text{product mass transport rate}} \\ &= \frac{k_{rec} K_a^{BH^+} [BH^+]_{0,ss}}{\beta_{BH^+} [BH^+]_{0,ss} \left(\frac{\nu}{\omega} \right)^{-1/2}} = \frac{k_{rec} K_a^{BH^+}}{D_{BH^+} Sh_{BH^+} r^{-1} \left(\frac{\nu}{\omega} \right)^{-1/2}} \end{aligned} \quad (23)$$

where k_{rec} is the recombination rate constant, $\left(\frac{\nu}{\omega} \right)^{1/2}$ represents a characteristic axial length in the rotating disk setup, and $K_a^{BH^+}$ is the equilibrium dissociation constant for the protonated base, and the ss subscript signifies the establishment of a steady state. Substituting eq 10 into both equations

and then dividing (22) by (23) gives the RDa for the forward and backward reactions:

$$\begin{aligned} RDa &= \frac{Da_{forward}}{Da_{backward}} \\ &= \frac{is [H^+]_{0,ss}}{([H^+]_{bulk} - [H^+]_{0,ss}) K_a^{BH^+}} \left(\frac{D_{BH^+}}{D_{H^+}} \right)^{2/3} \end{aligned} \quad (24)$$

For very rapid reactions, it can be assumed that the concentrations of all species are very close to equilibrium values. In this context, given the presence of a quasi-equilibrium, the consumption of the reactant (forward reaction rate) within the time frame of its mass transport will equal its back-production from the product (backward reaction rate) within the time frame of an equal mass transport rate. And since, according to eq 20, the denominators of (22) and (23) are equal (both representing the same reaction-driven dissolution enhancement), RDa should be equal to 1 when all species are practically at equilibrium. Consequently, setting eq 24 equal to 1 and solving for $[H^+]_{0,ss}$ will give the proton molarity at the surface. The dissolution flux can then be calculated by eq 19.

When eq 24 is set equal to 1 and both sides are multiplied by $D_{H^+}^{2/3} ([H^+]_{bulk} - [H^+]_{0,ss})$, the following expression arises:

$$D_{BH^+}^{2/3} is \frac{[H^+]_{0,ss}}{K_a^{BH^+}} = D_{H^+}^{2/3} ([H^+]_{bulk} - [H^+]_{0,ss}) \quad (25)$$

Equation 25 is equivalent to eq 21 since $is \frac{[H^+]_{0,ss}}{K_a^{BH^+}}$ would be equal to $[BH^+]_{0,ss}$ at equilibrium (by virtue of the traditional definition of a dissociation equilibrium constant). This makes the mass balance in eq 21 a rearranged expression of a (relative) Damköhler number the value of which is preknown (one) when the reactions are at (quasi-)equilibrium.

Applying similar logic for a weak acid, the following expression can be derived and used for the dissolution of a weak acid in alkaline solutions when direct recombination with hydroxide is the only significant dissolution-enhancing reaction

$$RDa = \frac{is [OH^-]_{0,ss}}{([OH^-]_{bulk} - [OH^-]_{0,ss}) K_b^{A^-}} \left(\frac{D_{A^-}}{D_{OH^-}} \right)^{2/3} \quad (26)$$

$$J_{HA} = \beta_{HA} is + \beta_{OH^-} ([OH^-]_{bulk} - [OH^-]_{0,ss}) \quad (27)$$

where $K_b^{A^-}$ is the dissociation equilibrium constant of the solute's conjugate base. Assuming near-equilibrium, hydroxide molarity can be connected to proton molarity by the dissociation product of water (K_w) despite the negligible impact of the reversible water dissociation reaction on dissolution in this scenario.

This approach essentially provides a simple and accurate approximation of the solution of the CDR equation with three additional assumptions:

- 1) All reactions are practically at equilibrium.
- 2) The steady state is reached instantaneously.
- 3) There is sufficient background electrolyte to suppress electrostatic potential gradients and allow ions to diffuse in accordance with their native diffusion coefficients throughout the system.



Figure 2. A flowchart summarizing model development in this manuscript.

- Levich solution^{15,18} to the convection-diffusion equation for a rotating disk is 100% exact.

The use of the Damköhler numbers of the forward and backward reactions to calculate equilibrium concentrations during mass transport is not entirely new. Deen¹⁹ outlined an example of the use of such two numbers to calculate equilibrium concentrations during diffusion in a stagnant liquid film with a reversible homogeneous reaction, where they also end up being divided in the final expression. However, defining those numbers in manner that their mass transport terms are bound to be equal by mass-balance considerations, thus enabling to define chemical equilibrium by their ratio being equal to 1 is, to the best of our knowledge, a novel concept. Since the mass transport of incoming reactant and outgoing product molecules into and out of the bulk is convective (being at $x = \infty$), the involved Damköhler numbers are first Damköhler numbers.

2.4. Mathematical Summary of the CDR Model and the RDa Analysis

2.4.1. Numerical CDR Model. The assumptions can again be summarized as follows:

- The movement of undissociated solute molecules between solid and solution phases is assumed to be infinitely fast compared to the other processes.
- Only the undissociated solute molecules move between the solid and solution phases.
- Bulk volume is assumed to be sufficiently large for sink conditions to apply.
- Velocity profiles are assumed to reach steady state instantaneously since momentum diffusivity is 2 orders of magnitude larger than mass diffusivity.
- Diffusion and activity coefficients are assumed not to vary with time and space.

Mathematically, this model essentially consists of adapting eq 2 to each species involved, thus generating the systems of differential equations outlined in the Supporting Information.

The v_x term is defined by eq 3. The accompanying initial and boundary conditions are expressions of the first, second and third assumptions. The initial conditions can be summarized as follows (with the corresponding mathematical equations provided in the Supporting Information):

- The initial value of the unprotonated solute is zero everywhere except at $x = 0$ (i.e., at the surface) where it is equal to its intrinsic solubility which is in line with assumption 1.
- The initial concentrations of the other species throughout the system are equal to their stated initial bulk concentrations, which is in line of assumption 1. For the ionized solute species, those concentrations are always zero.

As for the boundary conditions at the surface ($x = 0$), those can be summarized as follows (with the corresponding mathematical equations provided in the Supporting Information):

- The value of the un-ionized solute concentration is equal to the intrinsic solubility.
- No flux conditions for all the other species, which is in line with assumption 2.

As for the boundary conditions in the bulk ($x = \infty$), those can be summarized by a single sentence (with the corresponding mathematical equations provided in the Supporting Information):

- The initial bulk concentrations remain unchanged with time, which is in line with assumption 3.

2.4.2. RDa Analysis. As stated before, in addition to the assumptions of the numerical CDR model, the following are made for the RDa analysis:

- All reactions are practically at equilibrium (the reactions are infinitely fast relative to diffusion and convection).
- The steady state is reached instantaneously
- There is sufficient background electrolyte to suppress electrostatic potential gradients and allow ions to diffuse in accordance with their native diffusion coefficients throughout the system.
- Levich solution^{15,18} to the convection-diffusion equation for a rotating disk is 100% exact.

The final equations for the recombination dominance case of the RDa approach can be summarized as follows:

For a dissolving acid when recombination with hydroxide is by far the dominant reaction, the hydroxide molarity at the surface can be calculated by making eq 26 equal to 1:

$$\frac{is[OH^-]_{0,ss}}{([OH^-]_{bulk} - [OH^-]_{0,ss})K_b^{A^-}} \left(\frac{D_{A^-}}{D_{OH^-}} \right)^{2/3} = 1 \quad (28)$$

Then this surface hydroxide molarity can be used to calculate the total dissolution flux using eq 27. The β term is defined by eq 10. For a dissolving base when recombination with protons is by far the dominant reaction, first the proton molarity at the surface can be calculated by making eq 24 equal to 1:

$$\frac{is[H^+]_{0,ss}}{([H^+]_{bulk} - [H^+]_{0,ss})K_a^{BH^+}} \left(\frac{D_{BH^+}}{D_{H^+}} \right)^{2/3} = 1 \quad (29)$$

Then this surface proton molarity can be used to calculate the total dissolution flux using eq 19.

The other cases where other reversible reaction schemes are impacting dissolution are presented in section 4, where the model further evolves, with a final summary in section 4.5. In addition, section 4.8 includes applying the RDa approach at zero background electrolyte level by assuming ion coupling. A flowchart of this model development process is presented in Figure 2.

2.5. Film-Based Models

For comparison, simulations were also performed using two traditional stagnant film models. In the first one, the interfacial concentrations were assumed to reflect the concentrations at saturation solubility (referred to as thermodynamic model or

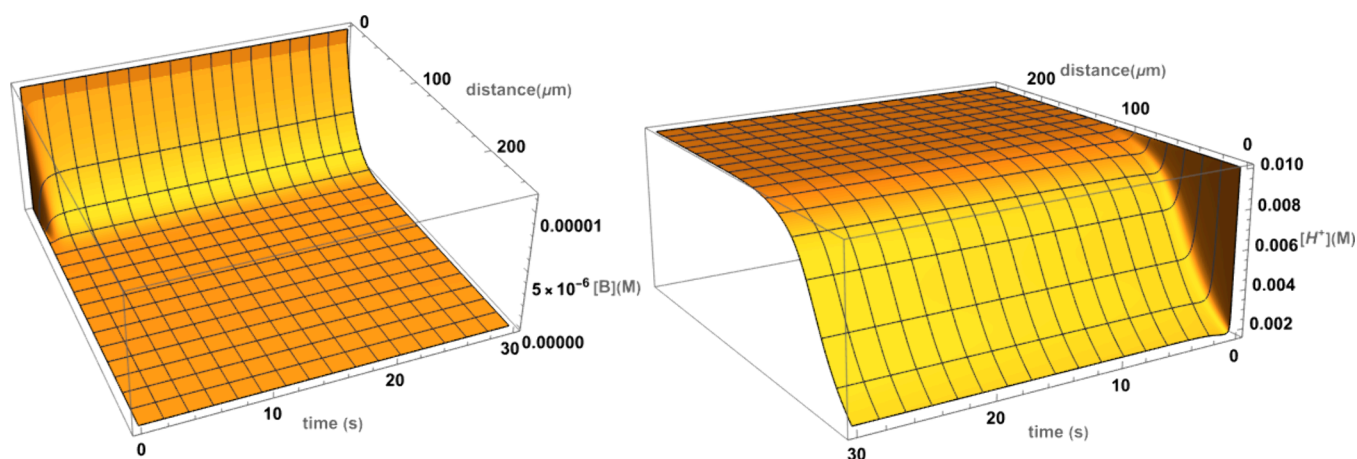


Figure 3. Simulated (CDR model) spatiotemporal profiles of the un-ionized solute (left) and proton (right) molarities during rotating disk dissolution of dipyrindamole in a solution of 0.01 M HCl at 100 rpm. Zero distance represents the interface.

“Thermo”).^{6,14} In the second one, a mass flux balance was used to calculate the surface pH and is referred to as the Mooney model.⁷ Surface pH values were used to calculate the total drug solubility at the surface, which was then used to estimate the interfacial flux assuming a stagnant film with a thickness equivalent to r/Sh_{solute} .

2.6. Simulations

Papaverine and dipyrindamole were used as model bases while 2-naphthoic acid was used as a model acid. For comparison with simulations, experimental data for papaverine and 2-naphthoic acid were obtained from literature.^{7,20} For dipyrindamole, rotating disk experiments were conducted at pH 2 and literature data was used for pH 5.²¹ All the simulations were performed using Wolfram Mathematica version 14.0 (Wolfram Research, Champaign, IL, USA). Detailed information on the simulation parameters is available in the Supporting Information.

3. EXPERIMENTAL SECTION

3.1. Materials

Dipyrindamole was obtained from Thermo Scientific Chemicals (UK). All other materials used were of analytical grade.

3.2. Methods

Intrinsic dissolution experiments were performed for dipyrindamole in the rotating disk setup using the μ Diss Profiler (Pion Inc., UK) in 0.01 M HCl at three different background electrolyte, in this case NaCl, molarities (0, 0.01, and 0.09 M). The disks had a diameter of 0.0707 cm² and were compressed with 50 kg force for 5 min. The dissolution experiments were performed at a rotation speed of 100 rpm and temperature of 37 ± 1 °C in triplicate for 0 and 0.09 M NaCl and duplicate for 0.01 M NaCl.

4. RESULTS AND DISCUSSION

4.1. CDR Model Numerical Solution Output

In general, as exemplified by Figure 3, a steady state was reached very quickly. Taking into account the no flux boundary conditions at the interface for all species save for the unchanged solute, the dissolution flux can be obtained by the following equations for a weakly acidic and a weakly basic solute respectively:

$$J_{HA} = -D_{HA} \left(\frac{\partial [HA]}{\partial x} \right)_{0,ss} \quad (30)$$

$$J_B = -D_B \left(\frac{\partial [B]}{\partial x} \right)_{0,ss} \quad (31)$$

4.2. Dipyrindamole and Papaverine

The closeness of the predictions of the simple RDa approach to those of the numerical CDR model is striking (Figures 4 and 5). Both the CDR and the RDa model predicted the available experimental data very well. The thermodynamic model tended to strongly underestimate the flux while the Mooney model tended to overestimate it except under conditions where reaction extent is limited (i.e. bulk pH > pK_a). The film models are going to be discussed further in section 4.6.

The RDa model surface pH predictions diverge from those of the CDR model at high bulk pH values where the proton molarity is too low for recombination dominance. The flux calculations were, however, not affected because the reactional flux enhancement is very low in this range anyway. Modeling the behavior at those high bulk pH values will be addressed in section 4.4.

4.3. 2-Naphthoic Acid: Dissociation Also Important

As shown in Figure 6, the numerical CDR model provided very good predictions for 2-naphthoic acid fluxes. The Mooney and Thermo models over- or under-predict flux except for the original Mooney model below pH ~ 4 (i.e., below the drug pK_a where reaction is limited) or the Thermo model below pH ~ 3. The RDa equation became close to the CDR model above a bulk pH of 10. Below this threshold, dissociation (eq 6) becomes more significant. The reason the dissociation impact is pronounced here but weak in the two previous examples, is because 2-naphthoic acid is stronger as an acid than dipyrindamole and papaverine are as bases.

When dissociation is the main reversible reaction in play, the reactions consuming the solute are the same ones producing protons (for weak acid dissolution) and also the same ones producing the ionized form of the solute and vice versa. Accordingly, at steady state (assuming high levels of background electrolyte):

$$D_{HA} \frac{\partial^2 [HA]}{\partial x^2} + D_{A^-} \frac{\partial^2 [A^-]}{\partial x^2} = v_x \frac{\partial [HA]}{\partial x} + v_x \frac{\partial [A^-]}{\partial x} \quad (32)$$

and

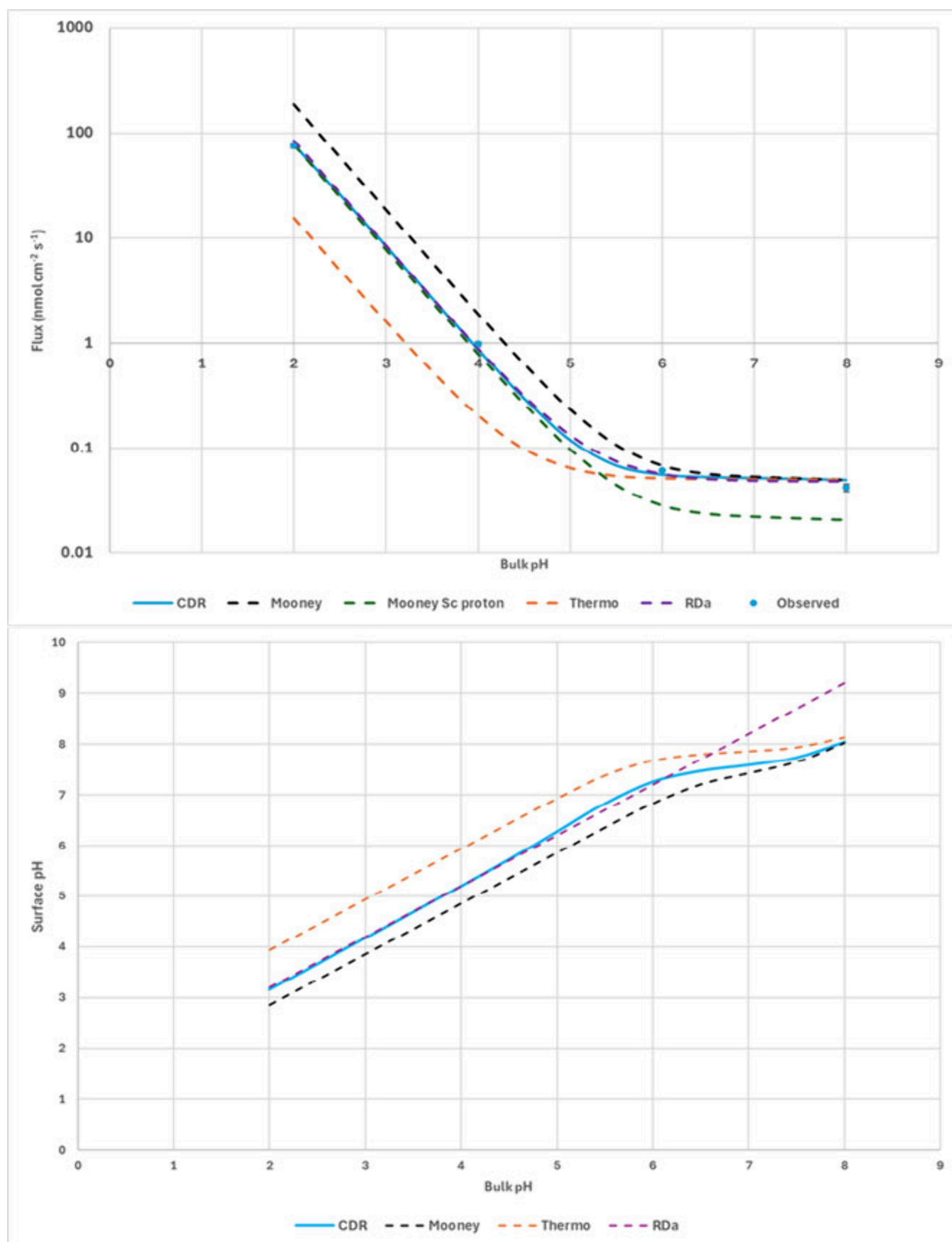


Figure 4. Simulated and experimental (McNamara and Amidon²⁰) flux (top) and simulated surface pH values (bottom) of papaverine as a function of bulk pH at 25 °C, 100 rpm and 0.1 M KCl. Sc proton means using the proton Sc to calculate flux from surface pH. Error bars represent one standard deviation.

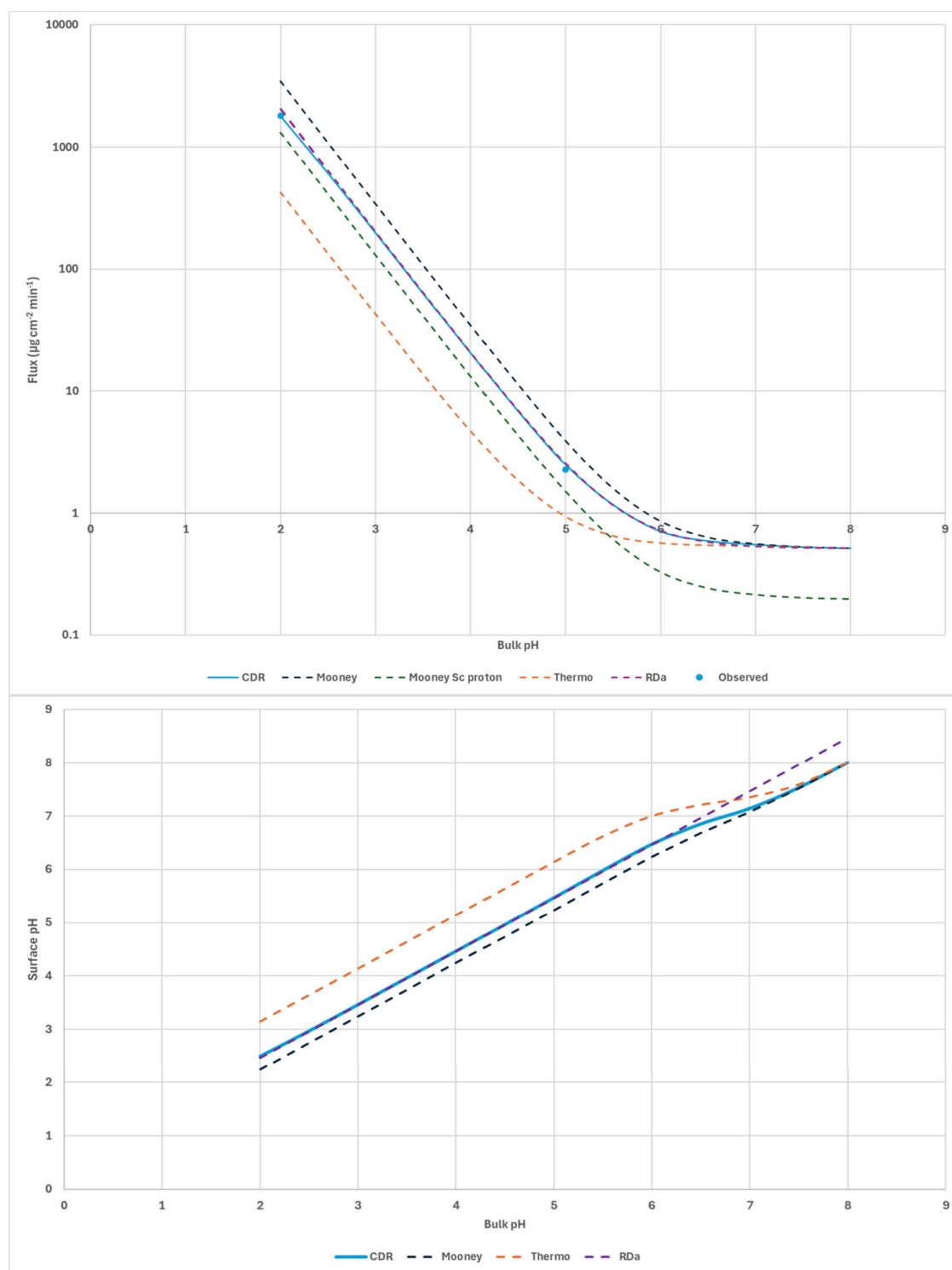


Figure 5. Simulated and experimental (in-house at pH 2 and McNamara et al.²¹ at pH 5) flux (top) and simulated surface pH values (bottom) of dipyradamole as a function of bulk pH at 37 °C, 100 rpm and 0.09 M NaCl (McNamara et al.²¹ used 0.15 M NaCl at pH 5, but the effect is negligible). Error bars represent one standard deviation.

$$D_{HA} \frac{\partial^2 [HA]}{\partial x^2} + D_{H^+} \frac{\partial^2 [H^+]}{\partial x^2} = v_x \frac{\partial [HA]}{\partial x} + v_x \frac{\partial [H^+]}{\partial x} \quad (33)$$

Applying similar steps as for the recombination case, and given that the dissociation first-order rate constant is the product of the second-order recombination rate constant of its

reverse reaction and the equilibrium dissociation constant, the relevant Damköhler numbers end up being

$$Da_{forward} = \frac{k_{rec} i s K_a^{HA}}{D_{H^+} Sh_{H^+} r^{-1} \left(\frac{\nu}{\omega} \right)^{-1/2} ([H^+]_{0,ss} - [H^+]_{bulk})} \quad (34)$$

and

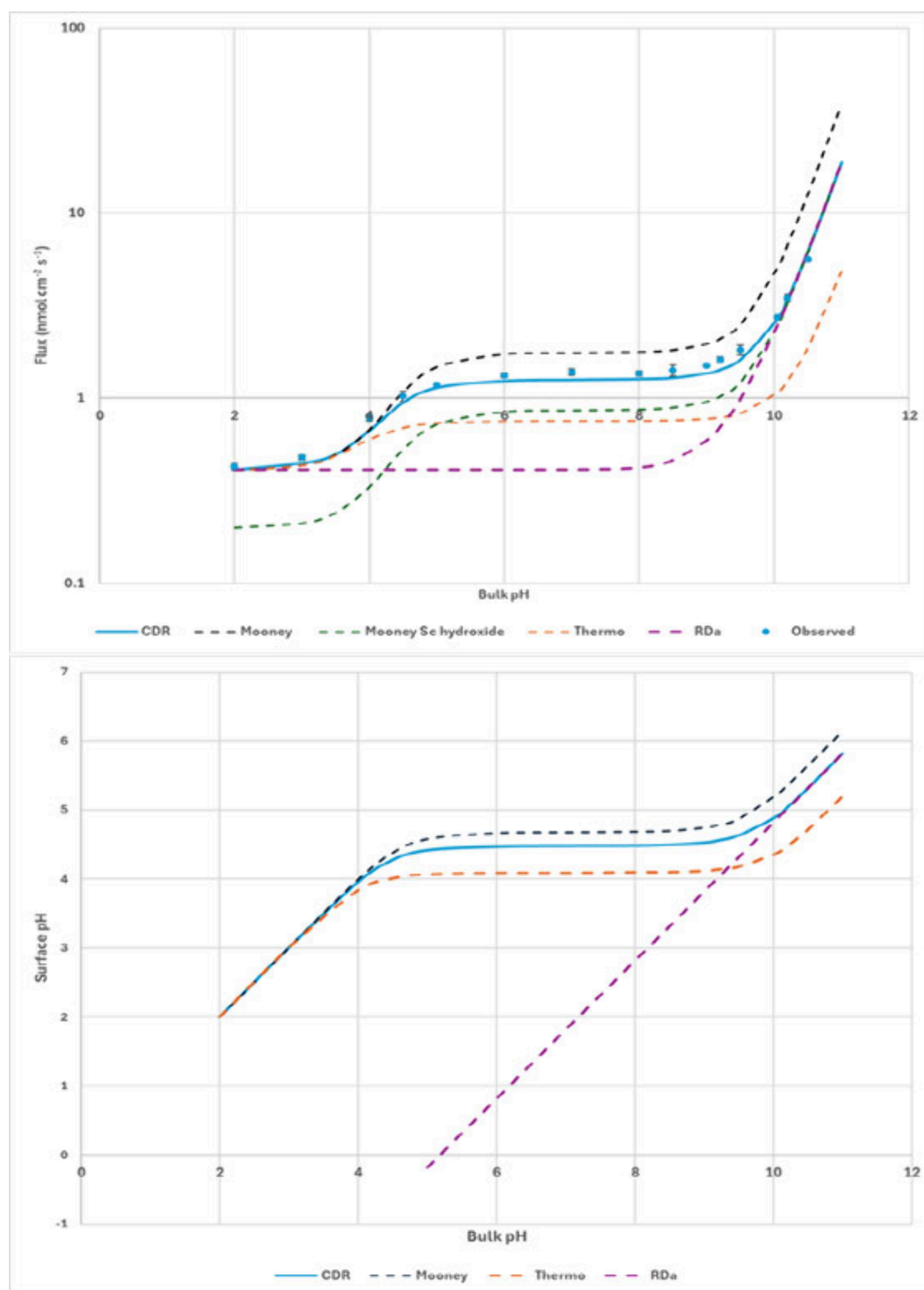


Figure 6. Simulated and experimental (Mooney et al.⁷) flux (top) and simulated surface pH values (bottom) of 2-naphthoic acid as a function of bulk pH at 25 °C, 450 rpm and 0.5 M KCl. Error bars represent one standard deviation.

$$Da_{backward} = \frac{k_{rec}[H^+]_{0,ss}[A^-]_{0,ss}}{D_A Sh_A r^{-1} \left(\frac{\nu}{\omega} \right)^{-1/2} ([A^-]_{0,ss} - [A^-]_{bulk})} \quad (35)$$

where K_a^{HA} is the equilibrium dissociation constant of the acid.

Applying sink conditions and substituting eq 10 for the Sh terms and dividing eq 34 by eq 35 will give

$$RDa = \frac{isK_a^{HA}}{([H^+]_{0,ss} - [H^+]_{bulk})[H^+]_{0,ss}} \left(\frac{D_A}{D_{H^+}} \right)^{2/3} \quad (36)$$

Setting eq 36 equal to 1 and solving for $[H^+]_{0,ss}$ gives the surface pH. The interfacial solute flux can be calculated as follows:

$$J_{HA} = \beta_{HA} is + \beta_{H^+} ([H^+]_{0,ss} - [H^+]_{bulk}) \quad (37)$$

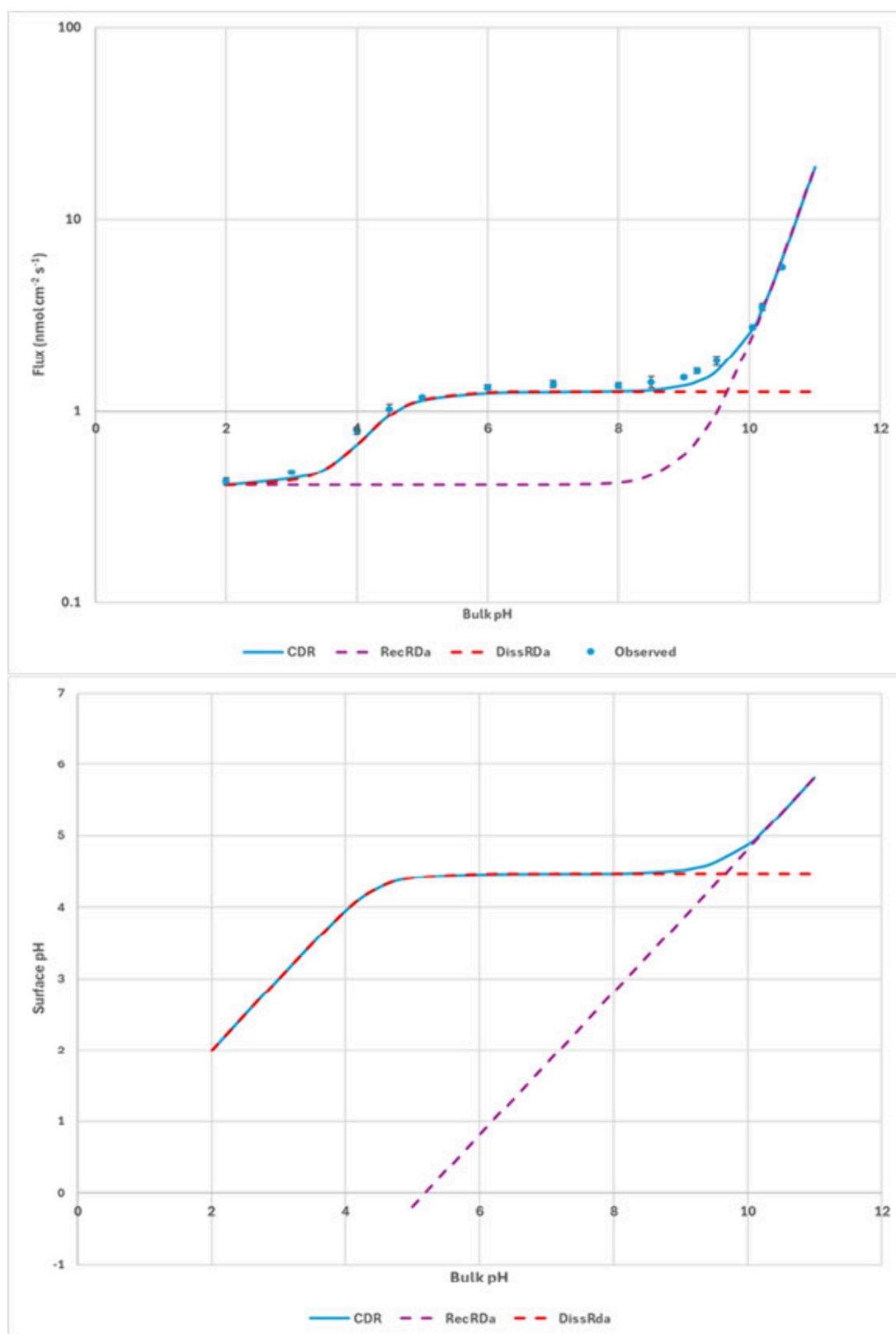


Figure 7. Simulated and experimental (Mooney et al.⁷) flux (top) and simulated surface pH values (bottom) of 2-naphthoic acid as a function of bulk pH at 25 °C, 450 rpm and 0.5 M KCl. RecRDa and DissRDa signify recombination- and dissociation-dominance based RDa equations, respectively. Error bars represent one standard deviation.

As can be seen in Figure 7, both the numerical CDR simulation and experimental results follow the limiting case of dissociation dominance until a bulk pH value of around 8.5,

and then, above a bulk pH value of ~ 10 , they follow the limiting case of recombination dominance. There is a transition regime between the bulk pH values of 8.5 and 10.

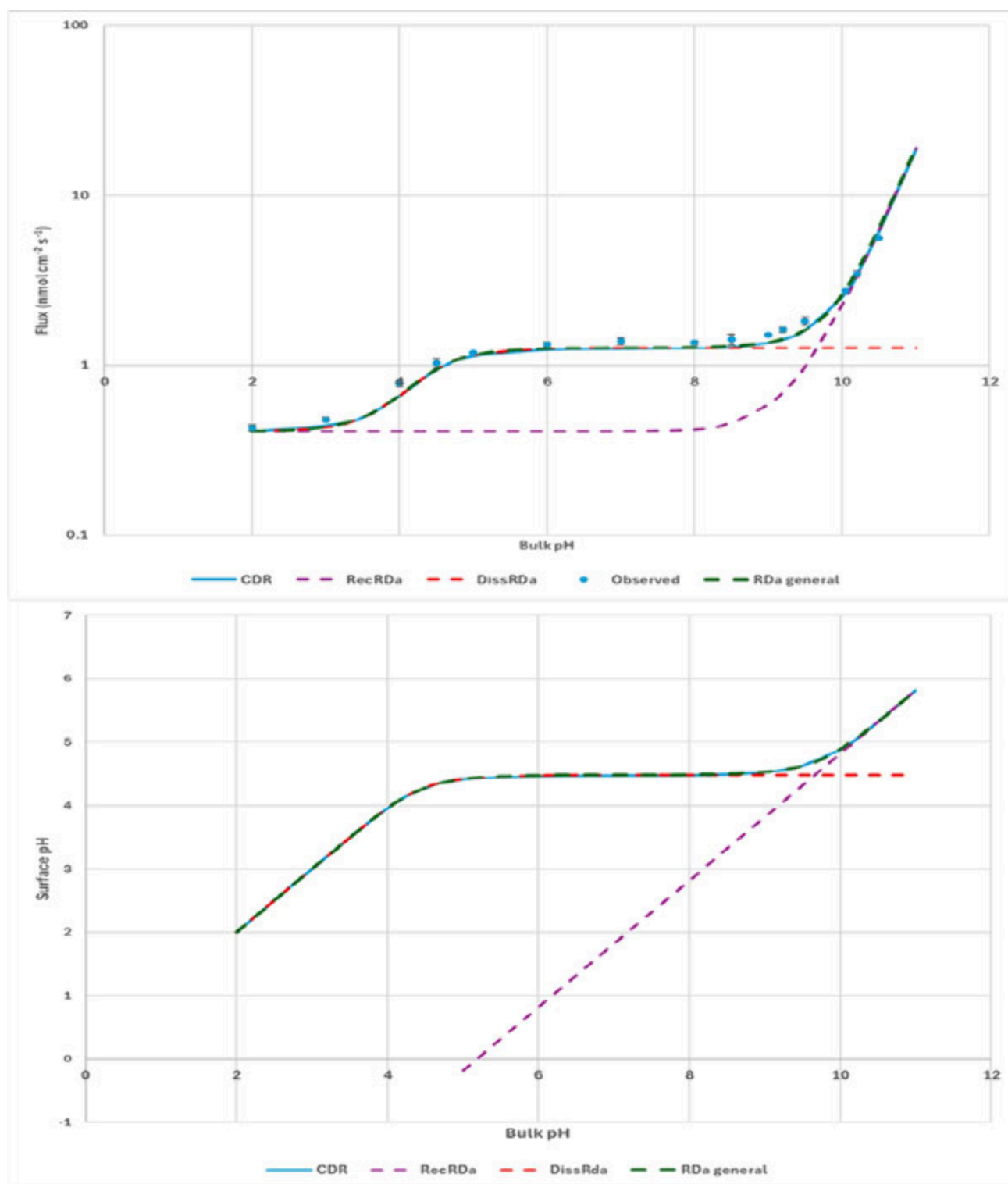


Figure 8. Simulated and experimental (Mooney et al.⁷) flux (top) and simulated surface pH values (bottom) of 2-naphthoic acid as a function of bulk pH at 25 °C, 450 rpm and 0.5 M KCl. Error bars represent one standard deviation.

Within this transitional regime, the reaction of H^+ with OH^- likely starts to significantly impact mass transport. Then when the direct recombination of OH^- with HA overtakes that with H^+ , direct recombination dominance sets in.

For a base stronger than the two examples here, where dissociation dominance can be significant, the RDa for the dissociation dominance regime would, along similar lines, be

$$RDa = \frac{isK_b^B}{([OH^-]_{0,ss} - [OH^-]_{bulk})[OH^-]_{0,ss}} \left(\frac{D_{BH^+}}{D_{OH^-}} \right)^{2/3} \quad (38)$$

and the interfacial flux

$$J_B = \beta_B is + \beta_{OH^-} ([OH^-]_{0,ss} - [OH^-]_{bulk}) \quad (39)$$

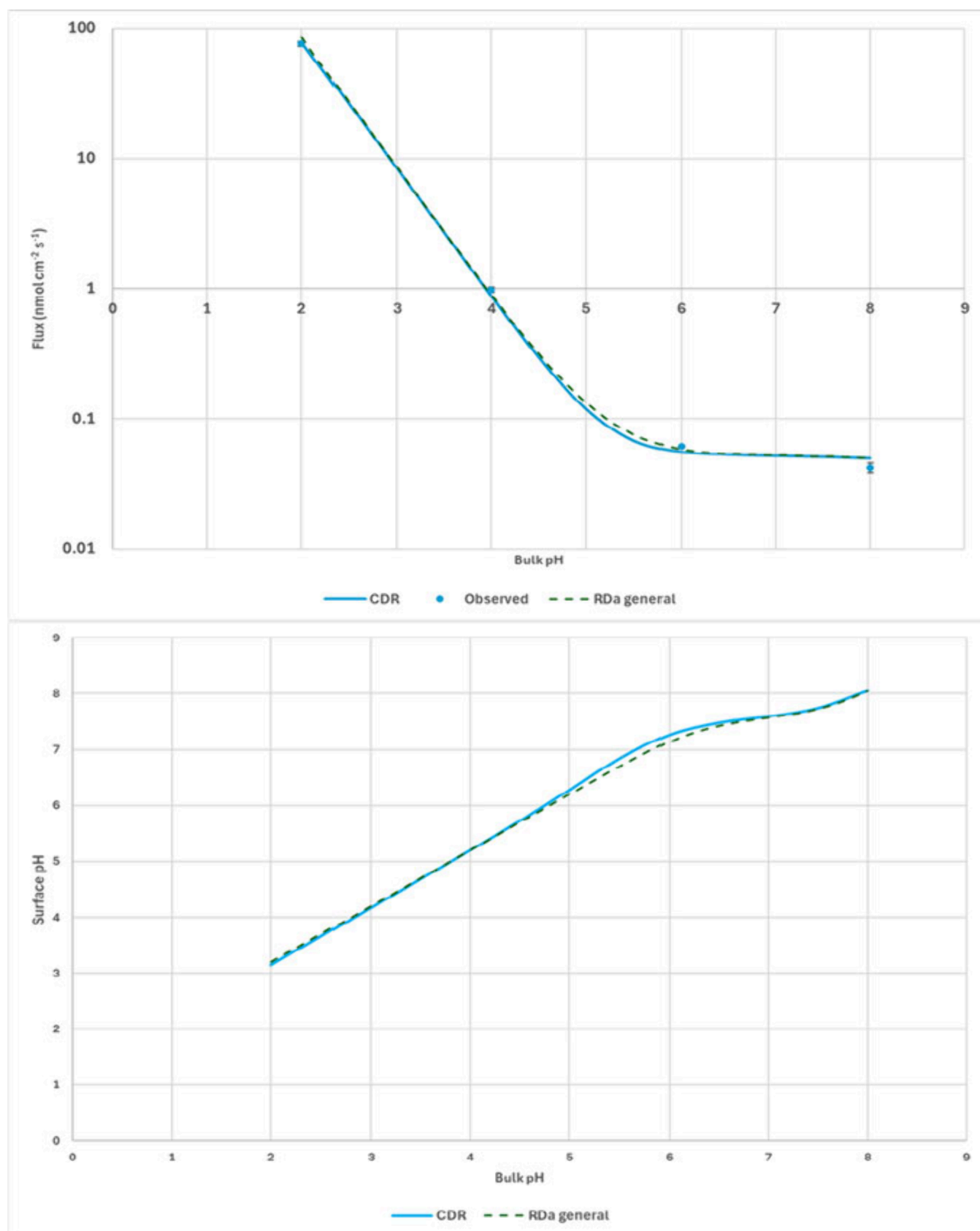


Figure 9. Simulated and experimental (McNamara and Amidon²⁰) flux (top) and simulated surface pH values (bottom) of papaverine as a function of bulk pH at 25 °C, 100 rpm and 0.1 M KCl. Error bars represent one standard deviation.

where K_b^B is the equilibrium dissociation constant of the base.

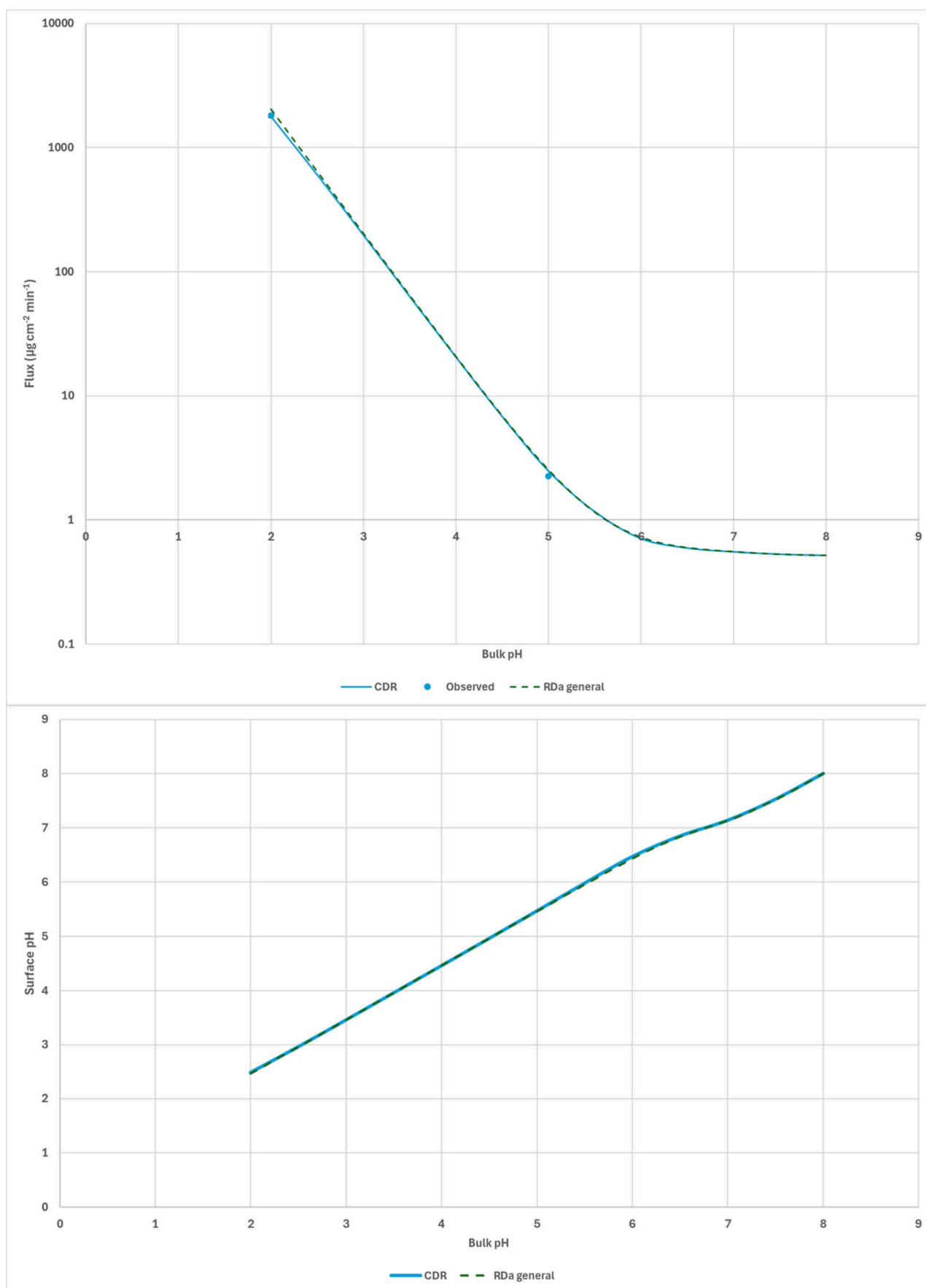


Figure 10. Simulated and experimental (in-house at pH 2 and McNamara et al.²¹ at pH 5) flux (top) and simulated surface pH values (bottom) of dipyrindamole as a function of bulk pH at 37 °C, 100 rpm and 0.09 M. Error bars represent one standard deviation.

4.4. Solving for the Transition Zone: General RDa Analysis

The above-mentioned transition zone between the two regimes experiences extensive reaction between protons and hydroxides. This means that a portion of the produced protons leads to considerable hydroxide influx. Accordingly, eq 33 needs to be modified:

$$D_{HA} \frac{\partial^2 [HA]}{\partial x^2} + D_{H^+} \frac{\partial^2 [H^+]}{\partial x^2} - D_{OH^-} \frac{\partial^2 [OH^-]}{\partial x^2} = v_x \frac{\partial [HA]}{\partial x} + v_x \frac{\partial [H^+]}{\partial x} - v_x \frac{\partial [OH^-]}{\partial x} \quad (40)$$

$$Da_{forward} = \frac{k_{rec} is K_a^{HA}}{D_{H^+} Sh_{H^+} r^{-1} \left(\frac{\nu}{\omega}\right)^{-1/2} ([H^+]_{0,ss} - [H^+]_{bulk}) + D_{OH^-} Sh_{OH^-} r^{-1} \left(\frac{\nu}{\omega}\right)^{-1/2} ([OH^-]_{bulk} - [OH^-]_{0,ss})} \quad (41)$$

and accordingly

$$RDa = \frac{is K_a^{HA}}{(D_{H^+})^{2/3} ([H^+]_{0,ss} - [H^+]_{bulk}) + D_{OH^-}^{2/3} ([OH^-]_{bulk} - [OH^-]_{0,ss}) [H^+]_{0,ss}} D_A^{2/3} \quad (42)$$

Applying similar steps for a weakly basic solute will give

$$RDa = \frac{is K_b^B}{(D_{H^+})^{2/3} ([H^+]_{bulk} - [H^+]_{0,ss}) + D_{OH^-}^{2/3} ([OH^-]_{0,ss} - [OH^-]_{bulk}) [OH^-]_{0,ss}} D_{BH^+}^{2/3} \quad (43)$$

Setting eqs 42 and 43 equal to 1 and solving for $[H^+]_{0,ss}$ gives the surface pH (hydroxide molarity is connected to the proton molarity by K_w). The interfacial solute flux can be calculated as follows:

$$J_{HA} = \beta_{HA} is + \beta_{H^+} ([H^+]_{0,ss} - [H^+]_{bulk}) + \beta_{OH^-} ([OH^-]_{bulk} - [OH^-]_{0,ss}) \quad (44)$$

$$J_B = \beta_B is + \beta_{OH^-} ([OH^-]_{0,ss} - [OH^-]_{bulk}) + \beta_{H^+} ([H^+]_{bulk} - [H^+]_{0,ss}) \quad (45)$$

As shown in Figures 8-10, these equations can predict the flux and surface pH over the entire bulk pH range, even in the region where recombination is dominant. Therefore, this RDa is henceforth referred to as $RDa_{general}$. The reason behind its ability to predict even the direct recombination region is that OH^- reacting with the H^+ produced by HA dissociation is in net effect equivalent to the direct recombination, the presence of which is covered by the very same mass balance expressed by eq 40. Therefore, provided all the reactions are very fast, $RDa_{general}$ will cover the entirety of the dissolution flux vs bulk pH profile. For a weakly basic solute, the same will happen just with the OH^- produced by the base reacting with protons from the bulk, which can concurrently undergo direct recombination with the basic solute. That is why this $RDa_{general}$ approach also managed to fill the gap in the surface pH predictions for papaverine and dipyrindamole at high bulk pH values.

4.5. Generalizing from Dissolution in Unbuffered Media

Based on the presented analyses, three diffusion-controlled dissolution scenarios impacted by reversible reactions can be

Therefore, Da for the forward reaction will be modified

solved by relatively simple expressions that approximate the solution of their respective systems of CDR equations (with A being the solute under sink conditions). Take note that A and B (as well as C, D and E) in the following equations refer to generic chemical species, so B here is not necessarily a base and A is not necessarily the conjugate base of an acid HA.

- 1) For the general case with the $A+B \rightleftharpoons C$ type reaction (Scenario 1):

Solve for $[B]_{0,ss}$ at the interface in

$$\frac{is_A [B]_{0,ss}}{([B]_{bulk} - [B]_{0,ss}) K_{eq}} \left(\frac{D_C}{D_B} \right)^{2/3} = 1 \quad (46)$$

and substitute the solution into

$$J_A = \beta_A is_A + \beta_B ([B]_{bulk} - [B]_{0,ss}) = \beta_A is_A + \beta_C ([C]_{0,ss} - [C]_{bulk}) \quad (47)$$

where K_{eq} is the equilibrium constant of the reverse dissociation.

- 2) For the general case with the $A \rightleftharpoons B+C$ reaction (Scenario 2):

Solve for $[B]_{0,ss}$ at the interface in

$$\frac{is_A K_{eq}}{([B]_{0,ss} - [B]_{bulk}) [B]_{0,ss}} \left(\frac{D_C}{D_B} \right)^{2/3} = 1 \quad (48)$$

and substitute the solution into

$$J_A = \beta_A is_A + \beta_B ([B]_{0,ss} - [B]_{bulk}) = \beta_A is_A + \beta_C ([C]_{0,ss} - [C]_{bulk}) \quad (49)$$

Table 1. Papaverine Flux Prediction Comparison of Stagnant Film vs Proposed Models at 25 °C, 100 rpm, and 0.1 M KCl

Bulk pH	Flux (nmol cm ⁻² s ⁻¹)					Observed		
	CDR	Mooney	Mooney Sc proton	Thermo	RDa _{general}	Mean	Standard deviation	Source
2.00	77.40	186.30	77.85	15.70	84.82	75.50	3.00	ref 20
4.00	0.88	1.91	0.80	0.21	0.90	0.98	0.05	
6.00	0.06	0.07	0.03	0.05	0.06	0.06	0.001	
8.00	0.05	0.05	0.02	0.05	0.05	0.04	0.003	

Table 2. Dipyrindamole Flux Prediction Comparison of Stagnant Film vs Proposed Models at 37 °C, 100 rpm, and 0.09 M NaCl at Bulk pH 2 and 0.15 M NaCl at Bulk pH 5

Bulk pH	Flux (μg cm ⁻² min ⁻¹)					Observed		
	CDR	Mooney	Mooney Sc proton	Thermo	RDa _{general}	Mean	Standard deviation	Source
2.00	1788.56	3438.35	1317.38	422.66	2040.25	1804.67	61.03	In-house
5.00	2.53	4.02	1.54	0.94	2.58	2.26	N/A ^a	ref 21

^aThe error bar was smaller than the plot marker in the cited reference.

Table 3. 2-Naphthoic Acid Flux Prediction Comparison of Stagnant Film vs Proposed Models at 25 °C, 450 rpm, and 0.5 M KCl

Bulk pH	Flux (nmol cm ⁻² s ⁻¹)					Observed		
	CDR	Mooney	Mooney Sc hydroxide	Thermo	RDa _{general}	Mean	Standard deviation	Source
2.00	0.41	0.41	0.20	0.41	0.41	0.43	0.02	ref 7
3.00	0.45	0.43	0.21	0.43	0.43	0.48	0.01	
4.00	0.66	0.68	0.33	0.60	0.66	0.78	0.03	
4.50	0.95	1.08	0.53	0.69	0.95	1.03	0.06	
5.00	1.14	1.48	0.72	0.73	1.15	1.19	0.02	
6.00	1.24	1.73	0.84	0.75	1.26	1.33	0.04	
7.00	1.26	1.76	0.86	0.75	1.27	1.38	0.06	
8.00	1.27	1.78	0.87	0.76	1.28	1.36	0.04	
8.50	1.29	1.83	0.89	0.76	1.30	1.42	0.10	
9.00	1.36	1.97	0.96	0.78	1.37	1.50	0.02	
9.20	1.43	2.10	1.02	0.79	1.43	1.62	0.06	
9.50	1.62	2.50	1.21	0.83	1.61	1.82	0.11	
10.05	2.68	5.08	2.47	1.08	2.80	2.74	0.07	
10.20	3.45	6.75	3.28	1.25	3.58	3.46	0.15	
10.50	6.22	12.63	6.14	1.88	6.40	5.62	0.09	

In this case C can well replace B in eqs 48 and 49 with no difference in complexity. Here K_{eq} signifies the forward dissociation equilibrium constant.

- 3) For the general case with the $A \rightleftharpoons B + C$ reaction where C also undergoes the $C + D \rightleftharpoons E$ type reaction with E being the solvent (Scenario 3):

Solve for $[C]_{0,ss}$ at the interface in

$$\frac{i_A K_{eq1}}{\left(D_C^{2/3} ([C]_{0,ss} - [C]_{bulk}) + D_D^{2/3} \left([D]_{bulk} - \frac{K_{eq2}}{[C]_{0,ss}} \right) \right) [C]_{0,ss}} D_B^{2/3} = 1 \quad (50)$$

and substitute the solution and the appropriate equilibrium relationships into

$$\begin{aligned} J_A &= \beta_A i_A + \beta_C ([C]_{0,ss} - [C]_{bulk}) \\ &+ \beta_D ([D]_{bulk} - [D]_{0,ss}) = \beta_A i_A \\ &+ \beta_B ([B]_{0,ss} - [B]_{bulk}) \end{aligned} \quad (51)$$

where K_{eq1} is the equilibrium constant of the initial dissociation and K_{eq2} is that of the reverse of the subsequent recombination assuming a dilute solution (i.e., it is equal to the product of the C and D molarities at equilibrium).

The first scenario will give what essentially is a linear equation, the second quadratic and the third quadratic as well. When both the solute and a dissociation product undergo recombination with the same reactant coming from solvent dissociation, Scenario 3 will mathematically cover both reactions (with Scenario 3 converging to Scenario 2 at low recombining reactant concentrations and to Scenario 1 at high recombining reactant concentrations). With the RDa equations being, as shown in the theoretical section, expressions of the reactant-product mass balance at equilibrium, this analysis is, actually, a modified version of the Higuchi et al. and Olander approaches of eliminating reaction terms.^{3,4} The difference is that those works eliminated proper convection terms and assumed either a stagnant film or surface renewal, but the current approach, instead of simplifying by removing

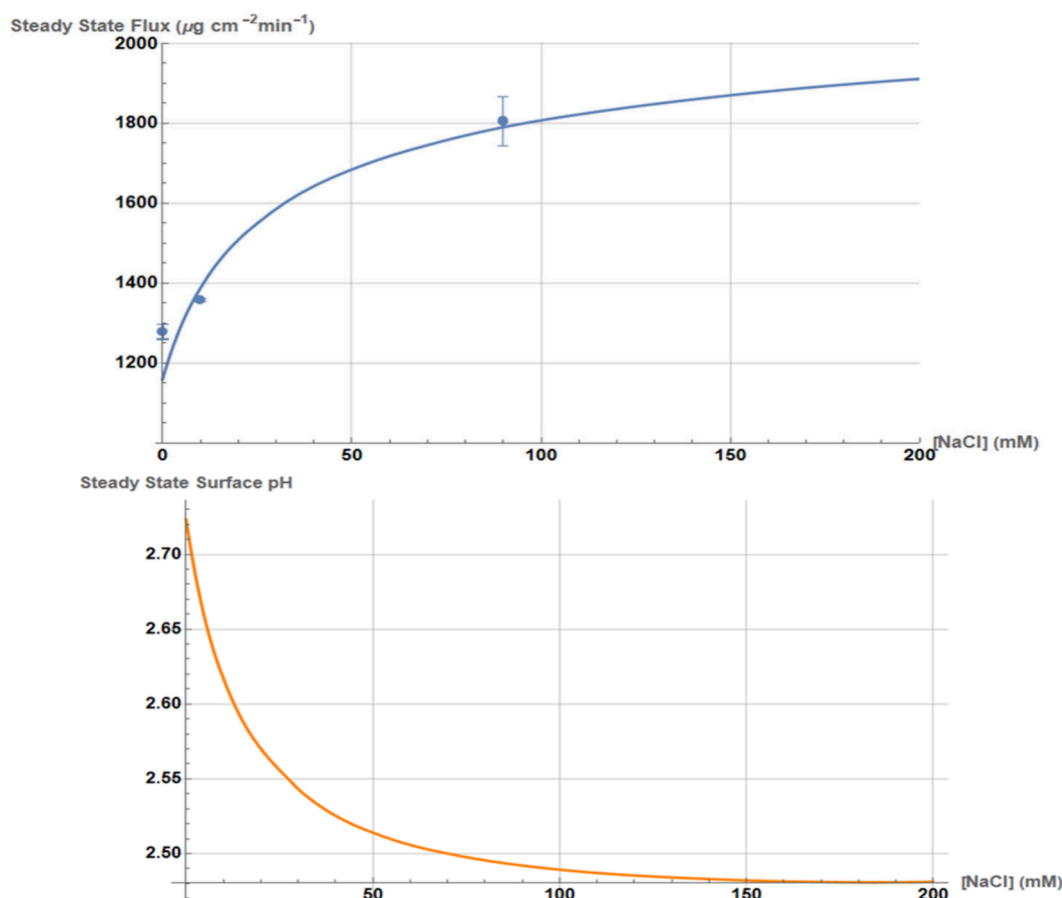


Figure 11. Effect of NaCl molarity on dipyrnidamole flux (top) and surface pH (bottom) in 0.01 M HCl at 37 °C and 100 rpm. The curves represent theoretical simulations (numerical CDR model) and the dots experimental flux data. Error bars represent one standard deviation.

convection terms, focuses only on the natural boundary conditions and the mass balances. This provides expressions that are both simple and accurate in approximating the CDR model (in reality, constituting analytical solutions for its asymptotic state at infinitely fast reaction kinetics, which is applicable when dissolution is completely diffusion-controlled with negligible reaction control).

4.6. Film Models

As shown in Tables 1–3, the conventional stagnant film models tend to result in high prediction errors when flux enhancement by the reactions is high. For flux predictions, the Mooney model could be improved at high acidities (for basic solutes) or alkalinities (for acidic solutes) by using the H^+ or OH^- diffusivities respectively instead of the traditionally employed solute diffusivity for calculating the Schmidt number value used to define the stagnant film thickness (corresponding also to the Mooney Sc proton and Mooney Sc hydroxide curves in Figures 4–6). This reflects the dissolution at those conditions being rate-limited by H^+/OH^- diffusion from bulk. Dipyrnidamole flux calculations get less accuracy enhancement from changing Sc for Mooney model probably because its combination of lower basicity/ionizability and intrinsic solubility leads to the reaction being more reversible. The higher reversibility makes it less accurate to discount the role of the diffusion of the protonated solute species away from the interface in controlling the dissolution.

However, changing the used Sc does not bring the surface pH results closer to those obtained by the CDR (and RDa)

approaches. This is because the surface pH calculated by the Mooney model is unaffected by the value of the stagnant film thickness. This means that even when flux prediction accuracy can be enhanced, surface pH predictions of the Mooney model remain off. This would be problematic, for example, when attempting to predict the possibility of the molarity product of BH^+ and Cl^- exceeding the K_{sp} of the BHCl salt creating potential for salt precipitation at the interface. The surface pH predictions of all models become equal only when the diffusivities of all ionic species are equal. This is significant also because it means that even when the dissolution process is diffusion-limited, the presence of convection can still influence the governing thermodynamic force as discussed later in section 4.9.

As for the thermodynamic model, changing the Sc does not improve accuracy but makes the flux predictions even worse (not shown). This result challenges the commonly made assumption of concentrations at the dissolving reacting solid surface being equal to those at saturation solubility when dissolution is diffusion-controlled as previously noted by Uekusa et al.⁶ This is because the discrepancies in diffusivities mean that product accumulation is not completely balanced by reactant depletion at the interface, which means that the mass balance applied at saturation solubility is not obeyed. However, the charge flux neutrality model proposed by the Uekusa et al. paper is not the best alternative, for its charge flux balance is essentially a form of Mooney's mass flux balance, thus giving identical results.

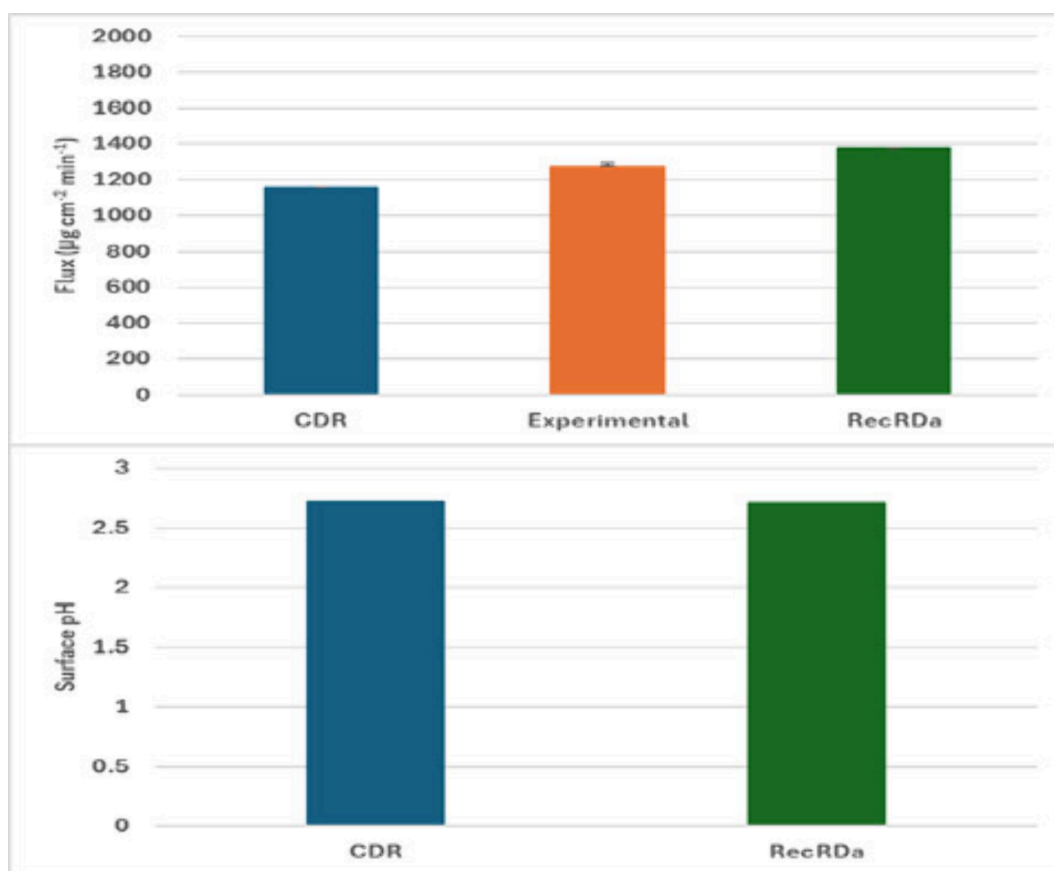


Figure 12. Simulated and experimental rotating disk flux and simulated surface pH values for dipyrindamole in 0.01 M HCl at 37 °C and 100 rpm in the absence of background electrolyte. The RecRDa model here assumes ion coupling. Error bars represent one standard deviation.

4.7. Comparison with the Two-Step Chemical Potential Gradient Approach

In 2015, Paus et al.⁸ published the two-step chemical potential gradient approach that does not include a stagnant film assumption. It is an extension of the nonequilibrium thermodynamics analysis of Lu et al.,²² which is based on the statistical rate theory work by Dejmek and Ward.²³ Since then, many adaptations of this model have appeared.^{9–11} This approach envisages dissolution as a kinetic process with two essentially first-order (with respect to chemical potential gradient) steps: Surface reaction (movement of molecules from the solid to an interfacial phase) followed by diffusion into the bulk.

Rather than predicting dissolution fluxes from physicochemical parameters, the model is used to fit dissolution data to obtain rate constants for the diffusion and surface reaction processes, analyze the dissolution mechanism, and determine which step is the rate-limiting one. These rate constants can be used to construct dissolution profiles under similar conditions or to be fitted over different conditions to get dissolution profiles under various conditions. This lack of ability to generate *a priori* simulations without pre-existing dissolution data is a major disadvantage compared to our mass transport approach. On the other hand, the lack of surface reaction with a finite molecular movement rate between phases is a limitation of our approach, so, as a future line of research, it would be interesting to incorporate surface reaction into the CDR model and compare the findings to those of such kinetic approaches.

4.8. Background Electrolyte

The data presented in previous subsections was obtained with background electrolyte levels sufficient to largely suppress electric potential gradients created because of the discrepancies between the diffusivities of diffusing ions (with H^+ and OH^- having much higher diffusivities than the rest due to the involvement of the Grotthuss mechanism).²⁴ When background electrolyte is below such levels, this influences dissolution (Figure 11). During weak base dissolution, for example, higher background electrolyte accelerates dissolution and lowers the surface pH. This is because, as the ions are freer to move in accordance with their native diffusivities, H^+ can be more effectively replenished at the surface by diffusion from bulk.

While the numerical solution of the CDR model can account for the impact of electrical potential gradients, the RDa solution cannot as ignoring electrostatic gradients is one of its assumptions. However, for the limiting case of zero background electrolyte, reasonable approximation can still be made using the RDa approach. For example, when a weak base dissolves under conditions of recombination dominance, the reaction can be thought of as HCl reacting with the free base B to form the salt BHCl because the ions are strongly coupled to each other. Effective diffusivities of HCl and BHCl can be calculated as the harmonic means of the component ion diffusivities.²⁵ Accordingly, the BH^+ and H^+ diffusivity terms in equation 24 will be replaced by the calculated BHCl and HCl diffusivity values respectively, thus enabling the use of the RDa approach. As shown in Figures 12 and 13, adding this ion

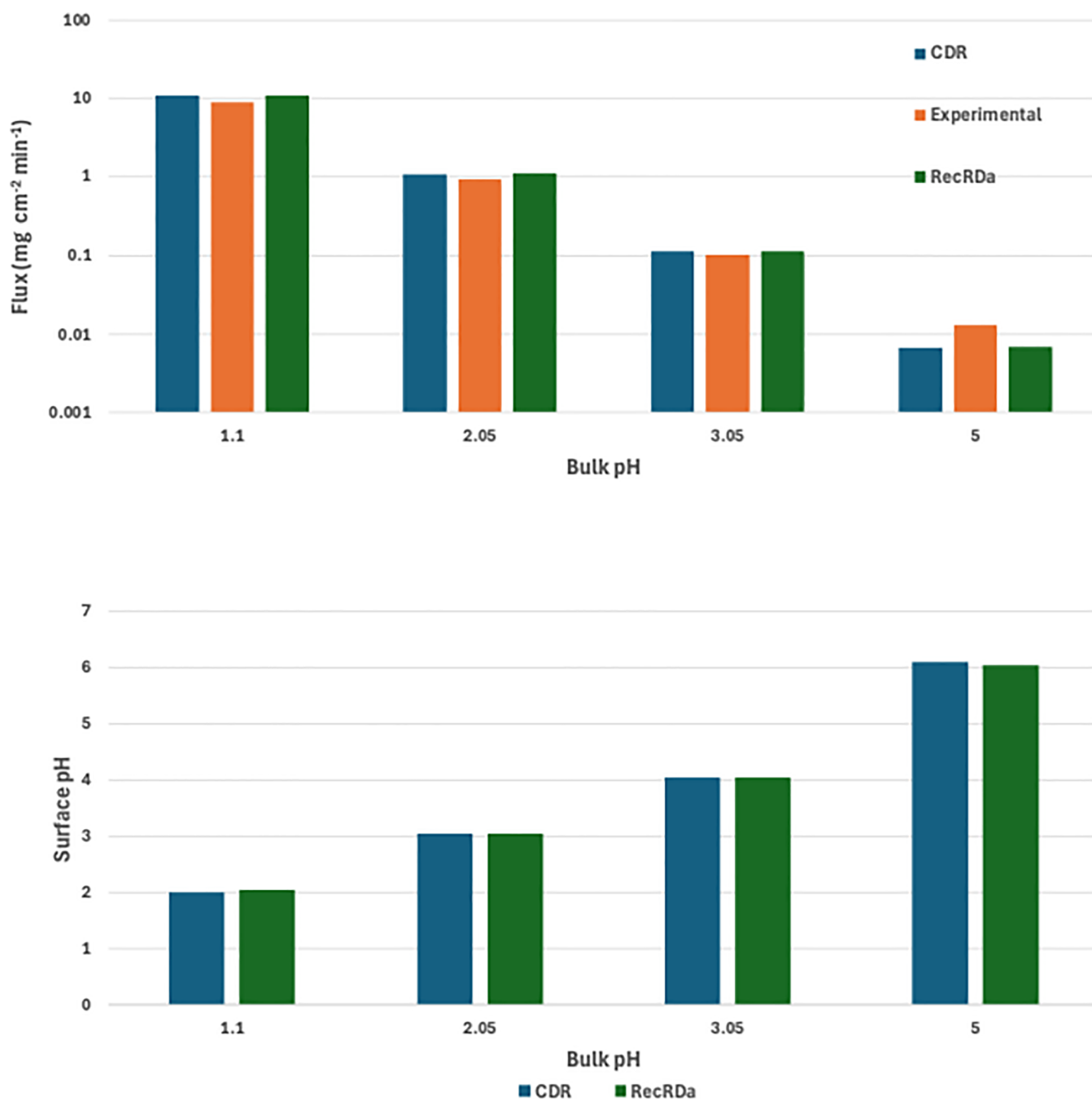


Figure 13. Simulated and experimental rotating disk dissolution and simulated surface pH values for phenazopyridine at 37 °C and 200 rpm in the absence of background electrolyte. The RecRDa model here assumes ion coupling. Fluxes are expressed as equivalent to the hydrochloride salt flux. Experimental data was obtained from Serajuddin and Jarowski.²⁶

coupling assumption results in good approximation of the numerical CDR results (and of experimental results as well).

4.9. What About Other Geometries?

For a rotating disk, the Sh expression contains neither addition nor subtraction, so the radius term gets eliminated upon applying it to calculate flux enhancement (which would be independent of the angular velocity). However, for other geometries, this is not necessarily the case. For example, for spherical particles, Sh expressions typically include an added constant term to account for curvature effects. When including such Sh expressions in the RDa equations, this would mean particle size- and agitation rate-dependence of the interfacial

reactant and product concentrations (and accordingly of the reaction-induced dissolution flux enhancement) even during diffusion-controlled dissolution. So, for example, the surface pH (and accordingly the governing thermodynamic driving force), during the dissolution of the particles of a base in a solution of hydrochloric acid, could become a function of the particle size and of the agitation rate. This can be shown by assuming the classical Ranz and Marshall correlation to provide an accurate approximation for the convection-diffusion equation's solution in the spherical geometry, which would transform eq. 25 into

$$\begin{aligned} \frac{D_{BH^+}}{d} is \frac{[H^+]_{0,ss}}{K_a^{BH^+}} (2 + 0.6Re^{1/2} Sc_{BH^+}^{1/3}) \\ = \frac{D_{H^+}}{d} ([H^+]_{bulk} - [H^+]_{0,ss}) (2 + 0.6Re^{1/2} Sc_{H^+}^{1/3}) \end{aligned} \quad (52)$$

where d is the particle diameter and the $2 + 0.6Re^{1/2} Sc^{1/3}$ terms are the species' Sherwood numbers according to the Ranz and Marshall correlation.

Substituting eq. 12 for Sc and assuming laminar flow around a sphere for Re , eq. 52 becomes

$$\begin{aligned} \frac{D_{BH^+}}{d} is \frac{[H^+]_{0,ss}}{K_a^{BH^+}} \left(2 + 0.6 \left(\frac{vd}{\nu} \right)^{1/2} \nu^{1/3} D_{BH^+}^{-1/3} \right) \\ = \frac{D_{H^+}}{d} ([H^+]_{bulk} - [H^+]_{0,ss}) (2 + 0.6(vd/\nu)^{1/2} \nu^{1/3} D_{H^+}^{-1/3}) \end{aligned} \quad (53)$$

where v is the fluid velocity around the particle.

Further algebraic manipulation gives

$$\begin{aligned} D_{BH^+} is \frac{[H^+]_{0,ss}}{K_a^{BH^+}} (2 + 0.6(vd)^{1/2} \nu^{-1/6} D_{BH^+}^{-1/3}) \\ = D_{H^+} ([H^+]_{bulk} - [H^+]_{0,ss}) (2 + 0.6(vd)^{1/2} \nu^{-1/6} D_{H^+}^{-1/3}) \end{aligned} \quad (54)$$

At very low Sh values when curvature effects dominate, eq. 54 will reduce to

$$D_{BH^+} is \frac{[H^+]_{0,ss}}{K_a^{BH^+}} = D_{H^+} ([H^+]_{bulk} - [H^+]_{0,ss}) \quad (55)$$

which corresponds to the stagnant film scenario.

And at very high Sh values where curvature effects are no longer significant, it will reduce back to equation 25.

Accordingly, the surface pH (and consequently the thermodynamic driving force) will vary as a function of the particle size, with small particle sizes approaching a stagnant film-like situation, and the large ones approaching a rotating disk-like situation. The exact particle size dependence will be a function of the agitation rate.

This warrants deeper investigation in the future as it contradicts the commonly held notion of the thermodynamic force driving diffusion-controlled dissolution being independent of hydrodynamic and geometric factors. It also emphasizes the need for Sh expressions that accurately approximate the solution of the convection-diffusion equation for a variety of particle geometries.

4.10. Limitations

The main limitations of the presented approach are

- 1) Assuming the molecular movement between solid and solution phases to be instantaneous. This would be problematic for substances with (relatively) slow surface reaction like $KAlum$.²³ As mentioned in section 4.7, an interesting future line of research would involve adding a surface reaction term to the CDR model to evaluate the significance of this step.
- 2) The model implicitly assumes a perfectly smooth interface. For the case of high flux enhancement by reaction, the steep gradient of the un-ionized solute near the interface could be affected by even small degrees of roughness. This should be investigated in the future.

- 3) The activity coefficients are assumed to remain constant in time and space, which could be especially problematic when dissolution processes involving steep concentration gradients of multivalent ions are modeled.
- 4) The ion coupling assumption presented in section 4.8 ignores possible "ternary effects",²⁵ where, for instance, BH^+ could slow down H^+ indirectly through slowing down Cl^- .

5. CONCLUSIONS

For diffusion-limited dissolution in reactive media, film-based approaches are rather poor approximations when the differences between the diffusion coefficients of the reacting species are large. This does not, however, mean that the impact of very rapid reversible reactions on dissolution can be modeled only by numerically solving the accurate but relatively complex CDR equation. For the limiting cases of either high or zero background electrolyte level, simple analytical solutions to the CDR model (or rather for its asymptotic behavior at infinitely fast reaction rates at steady state) in the rotating disk setup can be obtained when natural boundary conditions are accounted for in the mass balance. An important insight provided by this modeling work is that the widely held belief that the thermodynamic driving force at the interface during diffusion-limited dissolution is independent of hydrodynamic and geometric factors is apparently inaccurate.

■ ASSOCIATED CONTENT

Data Availability Statement

Data is available from the authors upon request.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.iecr.5c04739>.

List of all the relevant reactions, details of the differential equations, details on the application of the Smoluchowski and Debye-Smoluchowski equations, detailed simulation parameters, and the detailed derivation of eqs 15 from 14 (PDF)

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