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Research Article

Theoretical Analysis of Drug Dissolution: I. Solubility and Intrinsic Dissolution Rate

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ABSTRACT

The first-principles approach presented in this work combines surface kinetics and convective diffusion modeling applied to compounds with pH-dependent solubility and in different dissolution media. This analysis is based on experimental data available for approximately 100 compounds of pharmaceutical interest. Overall, there is a linear relationship between the drug solubility and intrinsic dissolution rate expressed through the total kinetic coefficient of dissolution and dimensionless numbers defining the mass transfer regime. The contribution of surface kinetics appears to be significant constituting on average ~20% resistance to the dissolution flux in the compendial rotating disk apparatus at 100 rpm. The surface kinetics contribution becomes more dominant under conditions of fast laminar or turbulent flows or in cases when the surface kinetic coefficient may decrease as a function of solution composition or pH. Limitations of the well-known convective diffusion equation for rotating disk by Levich are examined using direct computational modeling with simultaneous dissociation and acid–base reactions in which intrinsic dissolution rate is strongly dependent on pH profile and solution ionic strength. It is shown that concept of diffusion boundary layer does not strictly apply for reacting/interacting species and that thin-film diffusion models cannot be used quantitatively in general case.

Introduction

Dissolution plays a key role in defining bioavailability of the solid dosage forms, in particular those comprising drug substances of low aqueous solubility. It is therefore an integral part of preclinical and clinical development that includes screening and physicochemical characterization of active pharmaceutical ingredients (APIs) and product formulation work ideally resulting in the establishment of an *in vivo–in vitro* correlation.[1] Dissolution modeling is often used for *ab initio* biopharmaceutical evaluations[2] and in experimental gastrointestinal models[1,3] to rationalize selection of formulation and dosage strengths. Dissolution testing also constitutes one of the most important analytical tools in the pharmaceutical industrial quality control (QC) laboratory. The analytical method development typically involves selection of dissolution apparatus, optimizing dissolution media and hydrodynamic conditions (e.g., stirring or flow rate) with the aim to provide sufficient reproducibility and sensitivity or discriminatory power, and defining appropriate dissolution specifications for the drug products. It is therefore highly beneficial to generate reliable dissolution models that can streamline all these activities by taking into account both the inherent properties of different APIs or dosage forms and specific conditions during dissolution measurements.

The very fundamental principles of dissolution concern the role of surface kinetics and mechanisms of mass transfer on the solid–liquid interfaces. Not only do these processes directly relate to the intrinsic dissolution rate measurements routinely performed for drug substances, but they are also necessary to create meaningful dissolution models for any particulate, disintegrating, or matrix dosage forms. In what is probably the most cited article in dissolution literature, Noyes and Whitney[4] describe their dissolution model as follows: “the rate at which a solid substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution, … the phenomenon may be considered as simply a process of diffusion… We can imagine solid substances surrounded by an indefinitely thin film of saturated solution, from which diffusion takes place into all portions of the solvent…” This is a thin-film diffusion model, which was later modified by Nernst and Brunner[5,6] by incorporating the diffusion coefficient and static

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Nomenclature and Units

c	bulk solution concentration [mg/cm^3], [mol/cm^3], [M]
c_i	bulk concentration of species i [mg/cm^3], [mol/cm^3], [M]
c_0	equilibrium concentration (solubility) [mg/cm^3], [mol/cm^3], [M]
c_{0i}	bulk equilibrium concentration of species i [mg/cm^3], [mol/cm^3], [M]
c_s	surface solution concentration [mg/cm^3], [mol/cm^3], [M]
c_{0s}	surface equilibrium concentration [mg/cm^3], [mol/cm^3], [M]
D	diffusion coefficient of unionized solute [cm^2/s]
D_i	diffusion coefficient of species i [cm^2/s]
J	dissolution flux or intrinsic dissolution rate [mg/cm^2/s], [mol/cm^2/s]
J_0	$= \beta_0 c_{0s}$, intrinsic dissolution rate in the kinetic regime [mg/cm^2/s], [mol/cm^2/s]
J_D	$= \beta_D c_{0s}$, intrinsic dissolution rate in the diffusion regime [mg/cm^2/s], [mol/cm^2/s]
J_i	surface diffusion flux of nonreacting species i according to Equation 9 [mg/cm^2/s], [mol/cm^2/s]
J_i'	surface diffusion flux of reacting species i [mg/cm^2/s], [mol/cm^2/s]
i	designation for ionic species (e.g., HA, H^+, A^-, HB, B^-)
I	solution ionic strength [M]
k_i	ratio (J_i'/J_i)
K_a	acidity constant [mg/cm^3], [mol/cm^3], [M]
Re	Reynolds number
Re_c	critical Reynolds number of transition between laminar and turbulent flows
T	temperature [K], [°C]
β_0	surface kinetic coefficient [cm/s]
β_D	diffusion kinetic coefficient [cm/s]
$\overline{\beta}$	$=\beta_0\beta_D/(\beta_0+\beta_D)$, the total coefficient of dissolution [cm/s]
δ	thickness of diffusion boundary layer [cm], [μm]
δ_i	thickness of diffusion boundary layer of nonreacting species i according to Equation 9 [cm], [μm]
δ_i'	thickness of diffusion boundary layer of reacting species i according to Equation 10 [cm], [μm]
ν	kinematic viscosity of solution [cm^2/s]
σ	surface solution undersaturation
ω	disk rotating speed (angular velocity) [rpm], [rad/s]

diffusion layer thickness. Brunner's dissertation[5] also described experiments with benzoic acid, which included neutralization reaction through a "2-film" model, later developed by Higuchi et al.[7] The thin-film models are still the most prevalent approach in use today.[8,9] From the theoretical viewpoint, however, they present several issues. As it was emphasized by Levich,[10] the static diffusion layer cannot physically exist in stirred fluids, and in the absence of convection, the diffusion equations have no steady state solutions over large surfaces and infinite fluid volumes (i.e., under conditions usually applied to dissolving solid–fluid interface). It is well established that fluid convection extends very close to the surface ($<10^{-5}$ cm) and plays a key role in mass transfer. In film models, the thickness of diffusion layer cannot be obtained *ab priori*.

Limitations of the thin-film theories can be resolved by solving the convective diffusion equations directly as, for example, presented by Levich for a rotating disk.[10] This equation is often used to calculate the thickness of the diffusion boundary layer, δ, in intrinsic dissolution measurements. It should be emphasized, however, that this equation was derived for nondissociating, nonreacting species under conditions where such parameters as diffusion layer thickness, δ; the surface solution concentration, c_s; and dissolution flux, J, are all related in a simple manner and therefore can be calculated unambiguously. In many consequent articles, however, it was applied for electrolytes, acid–base reactions, and interacting species with different diffusion coefficients[11-17] without complete mathematical justification. The extension of the Levich equation to these more complex systems was typically accomplished using arguments similar to those for the thin-film theories, either by accepting the same value of δ for all species with the same "effective diffusion coefficient" or by considering independent diffusion of these species through layers of thicknesses δ_i assigned to each species i. All these assumptions have to be carefully examined because for dissociating and reacting compounds, the concept of diffusion boundary layer loses its clear physical meaning and may no longer be applicable.

Another critical point is that many heterogeneous processes are not diffusion controlled or at least not entirely controlled by diffusion, including some electrochemical reactions[10] and, very importantly, crystallization.[18] Both crystallization and dissolution involve the same molecular-level kinetic processes and thermodynamic considerations. The immediate conclusion therefore is that, at least for some hydrodynamic and kinetic conditions, there is a surface limitation on crystal dissolution. This is indeed accurately measured for acetaminophen using laser interferometry.[19] The possibility of surface-controlled dissolution was originally discussed by Higuchi,[20] but this point has largely escaped theoretical or experimental scrutiny. Over many years, the vast majority of dissolution data has been cited in support of the purely diffusion-controlled model. These data will be analyzed in detail in the following, but even at a glance, it often indicates a significant deviation from the diffusion-controlled mechanism as, for example, clearly seen for indomethacin,[11] ketanserin tartrate,[21] and josamycin[22] and, in particular, for several compounds measured by Nicklasson and Brodin,[23,24] where the experimental setup allowed for a more precise definition of dissolution rate at higher fluid velocities.

Application of intrinsic dissolution testing with a compendial rotating disk apparatus of Wood's type[25] resulted in accumulation of a large amount of data. Well-defined conditions for such measurements enable reliable data comparison from different laboratories. Although not intended to elucidate the relative contributions of surface kinetics and diffusion, these data nevertheless allow examining the fundamental relationship between dissolution rate and intrinsic solubility, distinguishing the cases where the surface kinetics can be of practical importance. In the present work, we use a more complete dissolution model incorporating both surface kinetics and convective diffusion. This work is not designed to be a review of existing approaches or concepts. All previous experimental results have been reanalyzed using a new theoretical framework, thus allowing for a different data interpretation and comparison with the previous models.

In what follows, we will start with formulating the surface kinetic equation for dissolution, the experimental methods to determine the surface kinetic coefficient, β_0. Next, the available