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Theoretical Analysis of Drug Dissolution in Micellar Media

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ABSTRACT

A new theoretical approach combining convective diffusion and surface dissolution kinetics has been applied to micellar systems and tested on experimental data available for both rotating disk apparatus and particles. The micelles are shown to be in the state of dynamic equilibrium with solution for most systems but nanoparticles. For ionizable molecules, the variation of partition coefficient across diffusion boundary layer may affect the diffusivity. The intrinsic dissolution rate is generally a nonlinear function of the equilibrium concentration, c_0, in which the diffusion kinetic coefficient, β_D, surface kinetic coefficient, β_0, and total kinetic coefficient of dissolution, β, all typically decrease as functions of c_0 (or increasing micellar concentration, M_c). The observed absolute values of β_0 are usually in the order of 10^{-3}-10^{-2} cm/s and strongly dependent on the nature of surfactant and solute molecules. For dissolution of particles, the surface kinetics tend to become the rate-limiting step.

Introduction

Addition of surface-active molecules to dissolution media above their critical micellar concentration (CMC) results in micellar formation and, for the drugs with low aqueous solubility, may significantly increase both the equilibrium concentration and intrinsic dissolution rate. These micellar systems can be designed to represent physiologically relevant media such as fasted- and fed-state simulated intestinal fluids (FaSSIF and FeSSIF, respectively) consisting of phospholipid and bile salt mixtures of different concentrations. In the pharmaceutical quality control, different surfactants are usually added to facilitate the solubilization and wettability of dispersed solids, whereas a group of functional surfactants can be included in pharmaceutical formulations to enhance the drug absorption. All these phenomena are related to the same fundamental mechanism in which mass transfer of solute is mediated by diffusion of drug-saturated nanocarriers (micelles) that can also interact with the dissolving surface. Understanding of this mechanism is important not only for the data interpretation and establishing *in vitro–in vivo* correlations but also for the design and optimization of different dissolution systems and methods.

The prevailing theoretical approach in dissolution literature is based on the semiempirical Noyes–Whitney (or Nernst–Brunner) models,[1-7] in which the diffusion layer thickness for the rotating disk, δ, is usually calculated using the Levich equation[3-6] or, for particles, by invoking some phenomenological models relating δ to the particle diameter.[1,2,7] The unknown experimental parameters such as diffusivities are often determined using the same Levich equation or by applying a multivariate parameter fitting.[4,6] In addition to possible circular reasoning, such an approach leads to the following fundamental concerns:

a. The current experimental data and their interpretation are highly fragmented. Most importantly, many concepts lack complete theoretical justification. For example, the expression for the "effective diffusion coefficient," D_E, was proposed by Higuchi[8] based on considerations of Fickian diffusion through a thin film and further applied to the measurements in rotating diffusion membrane cell.[9] It will be shown in later sections that this expression can be derived from the general convective-diffusion equations under the conditions of dynamic equilibrium and linearity between concentrations in micellar solution. In other studies,[3-6] however, a different expression for D_M was applied, which can be traced to the concept of independent

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Nomenclature

c	total concentration in the micellar medium
c_0	equilibrium concentration (solubility)
c_f	solute concentration in the free state (bulk solution)
c_M	solute concentration in the micellar phase
c_s	surface solution concentration
d	particle diameter
D	diffusion coefficient of solute
D_M	diffusion coefficient of micelles
D_E	"effective" diffusion coefficient in micellar medium
D_i	diffusion coefficient of solute within micelles
f	$= c_f/c$, fraction of solute in the free state
J	intrinsic dissolution rate (dissolution flux)
J_0	maximum dissolution rate (in the kinetic regime)
J_D	dissolution rate in the diffusion regime
M_c	micellar concentration (volume fraction of micelles)
k	total mass transfer coefficient from/to micelles
k_i	internal mass transfer coefficient within micelles
k_s	mass transfer coefficient on micellar surface
k_D	diffusion mass transfer coefficient from/to micelles
r_M	micellar radius
Re	$= ud/\nu$, Reynolds number
Pe	$= ud/D_E$, Peclet number
Sh	$= \beta_D d/D_E$, Sherwood number
Sh_1	Sherwood number in blank solution ($f = 1$)
v_y	fluid velocity perpendicular to the rotating disk surface
u	slip velocity
α	dimensionless coefficients defining the hydrodynamic regime of dissolution
β_0	surface kinetic coefficient
β_{01}	surface kinetic coefficient in blank buffer solution ($f = 1$)
β_D	diffusion kinetic coefficient
β	total (combined) coefficient of dissolution
δ	thickness of the diffusion boundary layer
θ	equilibrium distribution (partition) coefficient of solute between the micelles and bulk solution
θ_s	equilibrium partition coefficient of solute in the absorption layer
ν	kinematic viscosity of solution
ξ	parameter describing the effect of pH gradient on parameter f
τ_D	characteristic time for micelles to diffuse through the boundary layer
τ_M	characteristic time of equilibration (solubilization) of micelles
φ	dissolution rate enhancement by micelles
φ_D	φ in the purely diffusion regime
χ	$= \beta_D/\beta_0$ (dimensionless ratio between diffusion and surface kinetic coefficients)
χ_1	$= \beta_D/\beta_{01}$ (χ in blank solution)
ω	disk rotating speed (angular velocity)

fluxes for all species, not consistent with the equilibrium model. Similarly, a major assumption,[10] that non−micellar mass transport is negligible because of very low drug aqueous solubility, is also inconsistent with the equilibrium model and can be challenged for many systems. Such contradictions call for better defined limits to the convective-diffusion mechanism.

b. The impact of surface kinetics is ignored in most treatments of dissolution data. This is true both for the micellar systems considered here[1-7,12] and for homogeneous solutions discussed previously.[11] Nevertheless, the surface kinetic coefficient may exercise a significant influence,[11] especially in the case of particles where the surface kinetics can be the rate-controlling step. This discrepancy between the diffusion models and experimental data has been noticed[2] but not explained. In the micellar solubilization model,[10,13,14] the kinetic coefficient, responsible for incorporation of drug into micelles on the solid−liquid interface followed by desorption of micelles, is formally incorporated into the overall kinetic equation for dissolution rate. Although this "interfacial reaction" step can be a contributing factor in some cases, such interpretation is fundamentally different from the surface kinetic coefficient, β_0, as discussed here. This coefficient corresponds to the maximum rate of dissolution under ideal hydrodynamic conditions (kinetic regime, $\delta \to 0$) and describes any molecular-level dissolution process on the solid−liquid interface, with or without direct interactions with micelles. For example, β_0 can be sufficiently small and affect dissolution in pure water, buffers, or other solvents without surfactant[11] or in surfactant/micellar systems where there is no direct surface contact with the micelles (e.g., due to electrostatic repulsion[15]).

c. Finally, the diffusion boundary layer thickness becomes an ambiguous quantity for systems with reactions or conversions between different species, for example, in the pH-dependent dissolution of ionizable drugs.[11] For such systems, the classic Levich equation[16] may show significant deviations with the results directly computed from the equations of convective diffusion. Thus, the effects of ionization and pH have to be considered in conjunction with the micellar solubilization. It should be noted that from the methodologic viewpoint, the diffusion layer thickness is the parameter necessary only in the thin-layer theories. In terms of the convective-diffusion theory, this thickness is a secondary quantity which can be derived from the concentration profile or from the dependence of dissolution rate on surface concentration, but it has no principal role in computations.

The present work proposes a generalized approach to convective diffusion and surface kinetics in micellar systems and applies it to the experimental data obtained elsewhere.[1-7,10,12-14] These data were completely reanalyzed, whereas the presented interpretations or conclusions may differ from those originally proposed by the authors. Most of these experimental studies were not designed to elucidate the current theory and therefore were supplemented by data from different sources, for example, values of the micellar self-diffusion coefficients for sodium lauryl sulfate (SLS, or SDS),[17,18] time constants for micellar solubilization,[19,20] or numerical values for the surface kinetic coefficients.[11,21,22] Measurements of the particle dissolution introduce new challenges for data evaluation mostly related to the fact that the powder specific surface area is very rarely measured directly, leaving a less accurate estimate based on the mean particle diameter. In addition, there are usually insufficient data points for the most important initial dissolution stage, whereas the hydrodynamic conditions are always less defined than for the rotating disk apparatus. Thus, although much more literature is available on the dissolution with micelles, only a limited number of experimental studies offer sufficient information to compute the kinetic coefficients. The present work continues studies of intrinsic