Short communication

Ostwald–Freundlich diffusion-limited dissolution kinetics of nanoparticles

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ABSTRACT

For many years, nanoparticles have garnered increasing interest in pharmaceutical investigations. It is well known that the solubility of nanoparticles increases with decreasing size due to the Gibbs–Thomson effect. However, there are currently no analytical models to describe the kinetics of nanoparticle dissolution. The purpose of this article is to provide a Thermodynamics-based description of the kinetics of nanoparticle dissolution. In particular, the Ostwald–Freundlich relation is used to correct dissolution times for small particles, which have higher solubilities than larger particles. The developed model is an extension of the Hixson–Crowell cube root law in which the total normalized dissolution time is corrected by a "solubility size factor" that approaches unity for increasing initial particle size. This model enables rapid estimation of the total dissolution time of spherical nanoparticles in a gently agitated, zero solute concentration reservoir. The total dissolution time predicted differs from Hixson–Crowell by nearly 10% for initial particle sizes fifty times larger than the characteristic particle size, and increases to more than a factor of six at the characteristic particle size. This work provides a physics-based description of the nanoparticle dissolution kinetics and details the reaches and limitations of the developed model. The theoretical framework provided herein is valid for a wide range of dissolution processes and size scales affording it a high level of practicality.

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1. Introduction

The low aqueous solubility of new chemical entities is one of the major hurdles pharmaceutical scientists have been facing for more than thirty years. The solubility and the dissolution rate of drug particles are relevant to the bioavailability of oral solid dosage forms [1], because most drugs need to be dissolved in order to enter the body [2]. The improvement of the solubility and dissolution rate has been the focus of a tremendous amount of pharmaceutical research for several years [3,4].

Drug nanosizing is one common strategy [5] in particular because it increases the drug solubility. Although numerical methods have been used to successfully model the dissolution kinetics of nanoparticles [6], analytical models that capture the size effects on the rate of dissolution remain unavailable. In this context, the present article defines an analytical description to describe the dissolution kinetics of nanoparticles. Specifically, the Ostwald–Freundlich law is integrated with the Hixson–Crowell law to describe the dissolution kinetics of nanometer scale particles. In contrast to numerical techniques such as those described by Johnson [6], the model developed herein may be used to rapidly estimate dissolution times for different sized particles and predict

whether the Gibbs–Thomson effect will significantly contribute to enhanced dissolution times.

In 1904, E. Brunner [7], a former student of W. Nernst, published the derivation of the well known Nernst–Brunner law with Nernst's blessing [8] making use of A. Noyes's and W. Whitney's static diffusion layer concept [9]. Noyes and Whitney proposed that a static diffusion layer of thickness δ subjected to an equilibrium concentration, c_s, at the surface of an object in a mixing fluid [9] (See Fig. 1). Thus, the dissolution occurs at steady state through diffusion across the diffusion layer. For a diffusion-limited system, the rate of dissolution is thus obtained by solving Fick's laws for the boundary conditions shown in Fig. 1, which yields the Nernst–Brunner law [7,8]:

$$\frac{dm}{dt} = \frac{DA}{\delta}(c_s - c).$$ (1)

Here, dm/dt is the rate at which mass leaves the surface of the particle, D is the diffusivity, and A is the surface area of the solute exposed to the solvent.

A. Hixson and J. Crowell [10] extended the Nernst–Brunner concept to model the dissolution of an individual particle, by considering the time-dependence of the surface area during particle dissolution. This is done by writing the area, A, in Eq. (1) as a function of the remaining particle mass, m_R, and integrating. The Hixson–Crowell cube root law [10] relates the initial particle mass, m_o, and the remaining particle
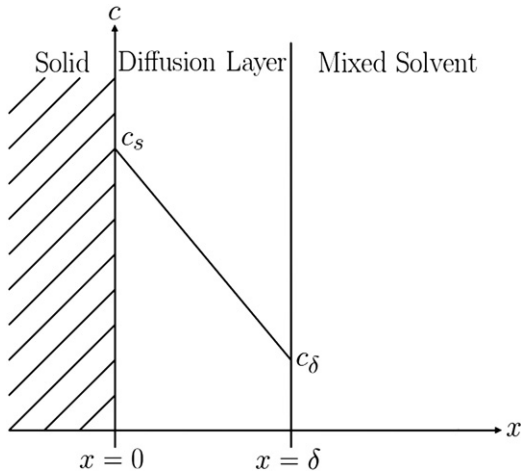
Fig. 1. Schematic of the diffusion layer proposed by Noyes and Whitney [9]. $x = 0$ represents the solid–liquid interface at the equilibrium concentration, c_s. The concentration in the diffusion layer drops to the solvent concentration, $c\delta$, at $x = \delta$, as shown by Brunner [7].

mass, m_R, to the dissolution time, t, via a proportionality constant, K_{HC}, which accounts for the effect of particle geometry and density on the mass transfer to the solvent:

$$m_o^{1/3} - m_R^{1/3} = K_{HC}t. \tag{2}$$

For spherical particles, $K_{HC} = D(c_s - c)\delta^{-1}(4\pi/3)^{1/3}\rho^{-2/3}$.

2. Results and discussion

2.1. Size dependence

In a binary system containing solvent atoms (A) and solute atoms (B), β-phase particles of pure B exist in equilibrium with the surrounding A-rich α-phase at the equilibrium concentration of B in A, that is, at the solubility limit, c_s. It is well-known that the equilibrium concentration of B atoms in the vicinity of β-phase particles increases with decreasing size of the β-phase particles [11–13]. In limit of ideal solutions, the relationship between solubility and particle size is given by the Ostwald–Freundlich equation, which is a special case of the Gibbs–Thomson effect [14–19]:

$$\frac{c_1}{c_2} = \exp\left[2\gamma_{sl}\frac{V_c}{RT}\left(\frac{1}{r_1} - \frac{1}{r_2}\right)\right] \tag{3}$$

where c_1 is the solubility of a spherical particle with radius, r_1, and c_2 is the solubility of a spherical particle with radius, r_2. For a large radius, r_2, the interface between the particle and solvent is comparatively flat, so $c_2 \approx c_s^\infty$ where c_s^∞ is the solubility of a flat surface, i.e., $r = \infty$, and thus

$$\hat{c}_s = \frac{c_s}{c_s^\infty} = \exp\left(\frac{2\gamma_{sl}V_c}{rRT}\right) \tag{4}$$

where $\hat{c}_s$ is the normalized solubility limit. This equation is analogous to equilibrium vapor pressure of a liquid droplet suspended in a gas of the same substance [20], which leads to analogous evaporation kinetics.

In terms of normalized radius, $\hat{r} = r/r'$ where $r' = 2\gamma_{sl}V_c/RT$, Eq. (4) is

$$\hat{c}_s = \exp\left(\frac{1}{\hat{r}}\right) \tag{5}$$

$r' = 2\gamma_{sl}V_c/RT$ is the critical size for nucleation [11] of a hypothetical substance with a Gibbs free energy of formation equal to RT/V_c.

The validity of the Ostwald–Freundlich relation has been challenged in recent years by G. Kaptay [21–23], who argues that Ostwald's equation [13] should be used in its original form in lieu of the modified form given by Freundlich [14]. In this context, G. Kaptay argues that the factor of 2 in Eqs. (3) and (4) should be changed to 3. Thus, the characteristic radius, r', would be $r' = 3\gamma_{sl}V_c/RT$. Such a value corresponds to the radius at which the Gibbs free energy of transformation is zero for a substance with a Gibbs free energy of formation equal to RT/V_c rather than the critical radius of nucleation. Such change is relatively minor, but this is noted herein.

For a dimensionless mass, $\hat{m} = m/m'$ where $m' = (4\pi\rho/3)r'^3$, and a dimensionless time, $\hat{t} = t/t'$ where $t' = 2\gamma_{sl}V_c\delta\rho/c_s^\infty DRT$, Eq. (1) reduces to:

$$\frac{d\hat{m}}{d\hat{t}} = \frac{3A(RT)^2}{16\pi\gamma_{sl}^2V_c^2}(\hat{c}_s - \hat{c}). \tag{6}$$

This is the dimensionless form of the Nernst–Brunner equation. Here, m' is the mass of a particle of radius r', and t' is the characteristic time. Physically, $t' = t_D\Gamma$, is the characteristic diffusion time, $t_D = \delta^2/4D$, across a distance, δ, multiplied by a dimensionless constant, $\Gamma = 8\gamma_{sl}V_c\rho/\delta c_s^\infty RT$. Eq. (6) shows that the dissolution rate increases as the square of the temperature and linearly with the thickness, δ, of the diffusion layer. Also, the dissolution rate is a quadratic function of the surface energy and has a great impact on the dissolution rate. Thus, surfactants are effective dissolution aids because they increase the wettability, which in turn increases the dissolution rate. In the Ostwald–Freundlich limit, solute dissolution is shut down entirely, i.e., $d\hat{m}/d\hat{t} = 0$, when $\hat{c} = \hat{c}_s$, and precipitation occurs at a rate $d\hat{m}/d\hat{t} < 0$ for supersaturated solutions when $\hat{c} > \hat{c}_s$.

Similarly, substituting $m_o = \hat{m}_o m'$, $m_R = \hat{m}_R m'$, $t = \hat{t}t'$, $c = \hat{c}c_s^\infty$, and $c_s = \hat{c}_s c_s^\infty$ into Eq. (2) yields the dimensionless form of the Hixson–Crowell cube root law upon expansion and rearrangement:

$$\hat{m}_o^{1/3} - \hat{m}_R^{1/3} = (\hat{c}_s - \hat{c})\hat{t}. \tag{7}$$

The solubility dependence on particle size directly impacts the dissolution rate of small particles due to the increased solubility predicted by the Ostwald–Freundlich equation (Eq. (4)). During dissolution, decreased particle size leads to an increased solubility with time and a shorter total dissolution time than that predicted by the Hixson–Crowell law (Eq. (2)).

The time dependence of the solubility is accounted for by expressing the Nernst–Brunner law (Eq. (1)) in terms of the remaining mass, m_R, and then substituting the Ostwald–Freundlich relation in place of the solubility. The rate of change of the remaining mass is the negative of the rate change of the mass dissolving, i.e., $d\hat{m}_R/d\hat{t} = -d\hat{m}/d\hat{t}$, and the surface area of a spherical particle in terms of m_R, $A = \alpha m_R^{2/3} = \alpha(m'\hat{m}_R)^{2/3}$ where $\alpha = (3/\rho)^{2/3}(4\pi)^{1/3}$. The Ostwald–Freundlich relation is expressed in terms of the dimensionless particle mass (assuming a spherical particle) by substituting $\hat{r} = \hat{m}_R^{1/3}$ into Eq. (5) to yield $\hat{c}_s = \exp\left(1/\hat{m}_R^{1/3}\right)$. Within the limits of a constant background solute concentration of $c = 0$ in the dissolution medium, the dissolution rate corrected for the size dependence of the solubility is

$$\frac{d\hat{m}_R}{d\hat{t}} = -3\hat{m}_R^{2/3}\exp\left(\frac{1}{\hat{m}_R^{1/3}}\right). \tag{8}$$

Eq. (8) is rearranged to solve for the dissolution time as:

$$\int \frac{d\hat{m}_R}{\hat{m}_R^{2/3}\exp\left(\frac{1}{\hat{m}_R^{1/3}}\right)} = -3\int d\hat{t} \tag{9}$$