Analysis of Diffusion-Controlled Dissolution from Polydisperse Collections of Drug Particles with an Assessed Mathematical Model

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ABSTRACT: We introduce a "hierarchical" modeling strategy designed to be systematically extensible to increase the detail of dissolution predictions from polydisperse collections of drug particles and to be placed on firm mathematical and physical foundations with diffusion-dominated dissolution at its core to predict dissolution and the evolution of particle size distribution. We assess the model with experimental data and demonstrate higher accuracy by treating the polydisperse nature of dissolution. A level in the hierarchy is applied to study elements of diffusion-driven dissolution, in particular the role of particle-size distribution width with varying dose level and the influences of "confinement" on the process of dissolution. Confinement influences surface molecular flux, directly by the increase in bulk concentration and indirectly by the relative volume of particles to container. We find that the dissolution process can be broadly categorized within three "regimes" defined by the ratio of total concentration C_{tot} to solubility C_S. Sink conditions apply in the first regime, when $C_{tot}/C_S <\sim 0.1$. When $C_{tot}/C_S >\sim 5$ (regime 3) dissolution is dominated by confinement and normalized saturation time follows a simple power law relationship. Regime 2 is characterized by a "saturation singularity" where dissolution is sensitive to both initial particle size distribution and confinement. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2998–3017, 2015
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INTRODUCTION, MOTIVATIONS, AND BACKGROUND

Dissolution is a central element in the absorption of pharmaceuticals in the gastro-intestinal tract, beginning with gastric emptying and followed by the transport of drug particles along the gut, radial mixing within the gut, and the delivery of pharmaceutical molecules to the epithelium in preparation for trans-epithelial transport into the blood stream. For low solubility drugs, dissolution can be the rate-controlling step in this process. Furthermore, *in vitro* dissolution testing plays an important role in regulatory approval of new or changed products, and dissolution models are in the core of commercial systems-level software environments such as GastroPlus®, PK-Sim®, and Simcyp®. For these reasons, there is value in developing deeper levels of understanding of the dissolution process and its control, as well as in the development of more accurate mathematical models and methods to predict rates of dissolution. Given the small size of typical drug particles (<100 μm), and the frequent use of micronization of low solubility drugs, a dissolution model needs, at its core, an accurate diffusion-based model for dissolution from single drug particles.

In this paper, we build on a previous study that critically examined the accuracy of basic mathematical models built on solutions of the diffusion equation (i.e., "first principles" models) designed to predict the details of diffusion-dominated dissolution from single confined drug particles. Wang et al.,[1] referred to as W12 in what follows, quantified and contrasted the accuracy level of physics-based mathematical models of diffusion-dominated single-particle dissolution in order to identify a first-principles model that balances accuracy with practicality of use. They found that a relatively simple "quasi-steady state" model (QSM) predicts both the increase in bulk concentration and the surface flux with high-level of accuracy beyond a short initial transient so long as effects of confinement are carefully included in the prediction. The QSM further provides an analytic expression for what W12 refer to as the "γ confinement effect," one of two "confinement effects" discussed in detail in the current study. W12 show that this mathematical expression is accurate to within a few percent even with large relative γ confinement effect.

Since the QSM was found to be both practical and highly accurate for most applications, we place the QSM at the core of a strategy to predict dissolution from polydisperse collections of small drug particles of different size, as well as the change in particle size distribution with time for complete dissolution or saturation ("polydisperse model"). Accurate accounting for the confinement of dissolved concentrations of molecules by boundaries is treated with care. We present our polydisperse model strategy as the lowest level within a hierarchical building block framework in which the core physics-based model for normalized flux of drug molecules from particle surfaces ("Sherwood number," *Sh*) can be generalized to include hydrodynamic enhancements, surface chemistry, particle geometry influences, and so on. The hierarchical formulation is developed in the next section preceding the mathematical formulation for the polydisperse model for diffusion-based dissolution from confined polydisperse collections of drug particles. The approximations made in the model are presented along with potential enhancements for future increases in complexity and generality.

We validate the model by comparing with experimental data and demonstrate the increased accuracy in predictions afforded by treating the polydisperse nature of particle sizes in contrast

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with a monodisperse representation. After validation, we apply the model in a detailed study of dissolution from polydisperse collections of drug particles in order to characterize the influence of the range of particle sizes on the dissolution process. We further evaluate and characterize the roles of confinement on dissolution and discover that the dissolution process, sensitivity to distribution width, and the role of confinement are characterized differently within three regimes that are defined by the nondimensional parameters C_{tot}/C_S and $\upsilon_m C_S$, where C_{tot} is total concentration, C_S is solubility, and υ_m is the molar volume of the drug particles. We further show that by quantifying data from dissolution experiments in nondimensional form with specific nondimensional variables, the data can be generalized to describe multiple drugs.

Relationship to Previous Studies

A number of papers propose theoretical models to predict dissolution from polydisperse groupings of particles. Most of these apply a Noyes–Whitney type equation as a starting point, often generalized to include a specified "stagnant" or "diffusion layer" thickness. Dressman and Fleisher,[2] for example, developed a mixing-tank model for predicting dissolution controlled oral absorption for a monodisperse powder using this kind of dissolution model. One of the earliest attempts at polydisperse models was developed by Higuchi and Hiestand[3] using a simplistic approach with questionable assumptions such as fixed bulk concentration. The first true polydisperse model was developed by Hintz and Johnson[4] who modified the Dressman and Fleisher approach to take into account the accumulation of molecules in the bulk fluid. In this and subsequent work,[5–8] a diffusion-layer representation for single-particle dissolution was applied with an assumed form for diffusion-layer thickness.

The application of first-principle conservation laws to predict diffusion-layer thickness (in the form of Sherwood number) is central to the current work. A number of previous studies have applied Noyes–Whitney like models with diffusion layer thickness assumed to be constant, or heuristically specified with reference to experimental data. Examples include the studies by Simões et al.,[9] Almeida et al.,[10] Cartensen and Dali,[11] Wang and Flanagan,[12,13] Shan et al.,[14] Sheng et al.,[15] and Johnson and coworkers.[4–8] The latter works originate with Hintz and Johnson[4] where the diffusion layer thickness (h) is assumed proportional to particle radius up to a maximum value above which h is held fixed at h_{max}. There was no first-principles basis for this assumption and h_{max} has sometimes been chosen so as to maximize the fit between a prediction and a dissolution measurement.[5,6] In other studies, the diffusion layer thickness has been taken to be constant and independent of particle radius and/or time.[12,13]

An aim of the current study is to extend W12 to dissolution from polydisperse collections of particles in which diffusion thickness assumptions are replaced with an approach that has, at its core, the conservation law for diffusion dynamics, what is meant by "first-principles" modeling. As in W12, we argue that the treatments of "diffusion layer" thickness as a model constant should be avoided as this assumption is inconsistent with true dissolution physics. A difficulty has been lack of theoretical foundation built on first principles (i.e., the conservation laws)—a focus of the current hierarchical modeling strategy. Similarly, basic mechanisms surrounding the dissolution of polydisperse collections of drug particles are not well understood, another aim of the current work.

Another approach to modeling the evolution of polydisperse collections of particle sizes is the prediction of particle size distribution through a "population balance equation," the evolution equation for the particle size distribution function. The population-balance method was first proposed by Shapiro and Erickson[17] to model the combustion of sprays. This approach has been developed primarily in the chemical engineering literature in context with combustion processes. Examples include the work of Hulburt and Katz,[18] LeBlanc and Fogler,[19] Bhaskarwar,[20,21] Dabral et al.,[22] Giona et al.,[23] and Bhattacharya.[24] For most conditions, the theoretical solution does not exist and the population-balance equation must be solved numerically. At the core of the population-balance equation is the dissolution of single particles in the distribution, and therefore the same need to model diffusion-layer thickness arises.

We apply the population balance framework in the current study, but with the work of Wang et al.[1] at the center of a hierarchical modeling strategy built on first-principles dynamics. W12 derived an exact model for the details of diffusion-dominated dissolution from single confined particle and compared with a lower order QSM. They found the QSM to be highly accurate so long as confinement effects are properly taken into account. In the present work, we extend the single particle model developed in W12 and propose a new polydisperse model with the more accurate estimation of diffusion layer thickness.

MATHEMATICAL MODEL FORMULATIONS

A General Framework for Dissolution from Polydisperse Collections of Drug Particles

We develop a mathematical modeling framework for accurate predictions of dissolution from polydisperse collections of drug particles designed so that geometric, hydrodynamic, and chemical complexity can be progressively enhanced through a hierarchical modeling strategy in which complexity increases with level in the hierarchy, or where specific physical effects may be included or excluded depending on application. Because of the small size of typical drug particles and the current trend toward micronization, the mass flux from the particle surface is largely driven by molecular diffusion. Therefore, at its core, the framework contains an accurate model for diffusion-dominated dissolution from single spherical particles. The concept of a hierarchical framework is a modeling structure where the diffusion-based core can be systematically enhanced to include effects that alter diffusive transport from spherical particles. Relative motion between the particle and solvent, for example, increases surface flux by convection; pH surface chemistry can alter surface flux; nonspherical particle geometry, agglomeration, and deagglomeration can alter net dissolution rate relative to pure diffusive transport from a spherical particle.

Dissolution generally involves flux and dispersion of drug molecules from large collections of small particles of different size and shape. Our hierarchical strategy centers on progressive enhancement of a single-particle diffusion-dominated core within a generalized model for polydisperse collections of particles of different size. The mathematical structure of the polydisperse model predicts the change in the distribution of particle sizes over time from an initial specified particle size distribution. The central model assumption is that the particles, and the local bulk concentrations around the particles, are