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Experimental determination of the diffusion boundary layer width of micron and submicron particles

C. Galli *

Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, United States

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Abstract

Powder dissolution kinetics have shown that for particles in the so called "large" size regime (more than about 50 μm), the dissolution rate scales as the specific surface area, i.e. rate proportional to d^{-1} where d is the particle diameter. This is consistent with an effective diffusion boundary layer width h_{EFF} that is constant with respect to particle size. However, for particles in the so called "small" size regime (d less than about 50 μm), the dissolution rate has a stronger dependence than proportional to d^{-1} [Bisrat, M., Anderberg, E.K., Barnett, M.I., Nystroem, C., 1992. Physicochemical aspects of drug release. XV. Investigation of diffusional transport in dissolution of suspended, sparingly soluble drugs. Int. J. Pharm., 80, 191–201; Mosharraf, M., Nystroem, C., 1995. The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. Int. J. Pharm., 122, 35–47]. In this regime, Prandtl boundary layer theory predicts an h_{EFF} approximately equal to the particle radius or diameter. This paper presents the first experimental determination of h_{EFF} for particles less than about 2 μm. The powder dissolution kinetics of six suspensions over the particle diameter range of 5.9 ± 0.1 to 0.53 ± 0.05 μm are analyzed to yield h_{EFF} values of 8.5 ± 1.9 to 0.34 ± 0.14 μm. The theoretical expectation for mass transport, dissolution time proportional to $d^{2.0}$, is in good agreement with the experimental results of dissolution time proportional to $d^{2.3}$. An understanding of these mass transfer mechanisms allows pharmaceutical scientists to achieve targeted release rates with minimum ensemble instability.

Keywords: Hydrodynamic boundary layer; Nanoparticles; Powder dissolution; Solubility limited; Prandtl boundary layer theory; Diffusion limited

1. Introduction

Understanding mass transfer mechanisms at solid–liquid interfaces is central to the design, control, and performance of numerous processes important in the pharmaceutical industry, including chemical crystallizations to synthesize drug substances, and "decrystallization" processes such as in vivo dissolution following bioadministration. As the modern pharmaceutical industry develops microvolume control of wet processes via arrested precipitation, impinging jet crystallization, and nanoparticle formation (Liversidge and Cundy, 1995; Grau et al., 2000; Muller et al., 2001; Merisko-Liversidge et al., 2003; Rasenack and Mueller, 2005; Vaughn et al., 2005), the length scale of required models decreases into the submicron region and below. For rational design of pharmaceutical formulations and processes, a thorough understanding of mass transport mechanics and associated transport distances is essential.

Mass transport between particulate and fluid phases is largely an expression of the spatial distribution of fluid momenta surrounding the solid particle. While a solid suspended in a liquid may be gaining mass via ripening, crystallization, or precipitation, maintaining mass if in phase equilibrium, or losing mass via dissolution, dispersions under agitation have similar interfacial structure. A fluid velocity gradient exists along the solid normal, with the maximum value, the free stream velocity, far from the interfacial region. For particles in the no slip limit, the velocity gradient decreases to a minimum near zero at the solid "wall" (Schlichting, 1955; Bird et al., 1960). Within this hydrodynamic boundary layer formed by the velocity gradient, there is a region along the solid–liquid wall where the fluid velocity is sufficiently low such that mass transfer is dominated by diffusion (Schlichting, 1955; Grijseels et al., 1981). It is this latter region, the "stagnant film" or effective diffusion boundary layer h_{EFF}, which is the subject of this paper.

* Present address: TransForm Pharmaceuticals, Inc., 29 Hartwell Avenue Lexington, MA 02421, United States. Tel.: +1 781 674 7863; fax: +1 781 863 7247.
E-mail address: cgalli@transformpharma.com.

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Powder dissolution is a sensitive probe of both *interfacial* properties such as mass transfer rates across solid–liquid interfaces (Niebergall et al., 1963; Bisrat et al., 1992; Mosharraf and Nystroem, 1995) and *static* powder properties such as particle size and area (Hintz and Johnson, 1989), particle morphology (Kitamori and Iga, 1978; Lu et al., 1993; Dali and Carstensen, 1998), crystallinity/amorphous content (Hendriksen, 1990), and redispersibility (Galli et al., 2005). In the large particle regime of about 50 μm and above, the dissolution rate for a diffusion controlled process is proportional to the interfacial surface area: because the specific surface area is inversely proportional to diameter, the powder dissolution rate is proportional to d^{-1}, where d is the particle diameter (Niebergall et al., 1963). However, powder dissolution kinetics have shown that for particles size less than about 50 μm, the dissolution rate increases more sharply than d^{-1} (Bisrat et al., 1992; Mosharraf and Nystroem, 1995). This increased dependence of dissolution rate on diameter is typically ascribed to a decrease in the interfacial structure supported by small versus large particles. In the large particle regime, the effective diffusion boundary layer h_{EFF} is constant with respect to particle size, and typically about 30 μm (Hintz and Johnson, 1989). This value can be determined for a specific powder by modeling intrinsic dissolution results (Carstensen, 1977). Particles of diameter less than 50 μm, however, do not have sufficient surface area and associated frictive force to support a hydrodynamic boundary layer and diffusion boundary layer of this magnitude. Prandtl boundary layer theory has postulated that for particles less than 50 μm, the effective hydrodynamic boundary layer h_{EFF} is approximately equal to the particle radius or diameter (Schlichting, 1955; Niebergall et al., 1963; Mosharraf and Nystroem, 1995; Muller and Peters, 1998). It is worth noting that all drug powders go through this particle regime during the course of biodissolution.

The work described herein is the use of powder dissolution to determine the effective hydrodynamic boundary layer h_{EFF} as a function of particle size over the diameter range of approximately 6–0.5 μm. After demonstrating that the powder dissolution data is recording a mass transfer process that is diffusion limited, a diffusion equation containing h_{EFF} and the mass transfer rate $\dot{\mu}$ is introduced. This expression is then evaluated for h_{EFF}. The paper concludes with a short description of how this data can be used to target pK profiles via API size control.

2. Materials and methods

2.1. Suspension preparation, particle size distributions and surface area

The suspensions for this study were formed via ultrahigh pressure homogenization (Galli et al., 2005). The size reduction system and process are currently under review by both United States and international patent offices. A suspension series of decreasing particle size was obtained by sampling the homogenizer as a function of process time; this series was labelled suspensions A through F. The particle size distribution and surface area of the suspensions were determined by differential centrifugal sedimentation (CPS Instruments, Inc; DC18000)(Fitzpatrick, 1999). The spin fluid was a sucrose density gradient ranging from 0% to 10% by weight; a typical rotational frequency was 12,000 rpm, resulting in a run time of 8 min. The solid concentration in the suspension and the injection volume were controlled to ensure linearity and accuracy with respect to the experimental results of total mass and volume detected; four to seven injections of 50–200 μL were recorded for each suspension. The true density of the drug powder was determined via helium pyncnometry (Quantichrome Ultrapycnometer 1000).

The specific surface area of the solid material in the suspension was also measured via differential centrifugal sedimentation. The specific surface area for each differential centrifugal sedimentation injection was calculated by dividing the total surface area detected by the total mass detected.

2.2. Powder solubility

To determine the powder solubility, the suspension series A through F was incubated on a platform shaker at 37 °C for at least 24 h. Aliquots of the suspensions were clarified at 37 °C via 1 h ultracentifugation at 4.7e6 × g. The supernatants were collected; precipitation was quenched via 1:1 dilution with 50:50 water:methanol. Four to six trials were completed for each suspension. The resulting solutions were chemically analyzed for drug and degradates via HPLC. Two ensemble methods were also used as referee methods. After 24 h incubation on a platform shaker at 37 °C, the saturated suspension A was transferred to a 1 cm quartz cuvette, and maintained at the desired temperature (Cary Bio 300 with Cary/Varian Peltier temperature control). The amount of dissolved drug was quantitated using the response of a drug standard solution. The incubated suspension A was also filtered through a 0.22 μm filter, the supernatant was quantitatively diluted with 50:50 water:methanol, and the dissolved drug quantitated versus the standard solution. To determine the effect of polymer concentration on drug solubility (hydroxypropylcellulose), both the ensemble methods above were applied to suspension E in dissolution media of 1%, 3%, and 4.3% polymer at 37 °C.

2.3. Diffusion coefficient

The diffusion coefficient for the drug was measured by the method of stopped time (diffusive) migration (Terabe et al., 1991; Yao and Li, 1994). A 0.4 mg/mL sample plug was transported to the center of the capillary via an electric field of 20 kV, the electric field set to zero for an incubation time chosen by the user, then returned to 20 kV. The UV absorbance chromatogram was exported to a suitable computer program; a linear least squares fit to a Gaussian function determines the peak variance. At least three injections were recorded for each chosen stop time.

2.4. Dissolution media viscosity

The viscosities of the dissolution media containing 1%, 3%, and 4.3% polymer were determined by recording the shear stress over a shear rate range of 1–1000 s^{-1}. The temperature of the