



Dissolution of a colloidal particle in an oscillatory flow



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ABSTRACT

Understanding dissolution kinetics of a colloidal particle in an aqueous solution is of great importance in many pharmaceutical and biochemical applications. We present theoretical analysis of low Reynolds number flow dynamics and mass transfer of a dissolving spherical particle in a unidirectional oscillatory flow field. The coupling of fluid flow and passive motion of the particle are solved analytically, and the transient mass transfer associated with the oscillation of the particle is computed numerically. The flow patterns, basic characteristics of mass transport, and the simplified long-time dissolution process under various saturation concentrations and relative flow conditions are discussed in details.

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1. Introduction

Better understanding of dissolution of a colloidal particle to the surrounding liquid environment is of great importance in broad industrial applications. There exist lots of relevant chemical processes in liquid–liquid, solid–liquid, and gas–liquid systems ranging from absorption, extraction, leaching, drying, crystallization, dissolution, to combustion of solid and liquid fuels [1–9]. In pharmaceutical sciences, investigations on the reconstitution of various pharmaceutical composition and dosage forms based on dissolution methods are essential for practical purposes [10–13]. Specifically, therapeutic molecules such as monoclonal antibodies are often highly concentrated to reduce the volume injected into the patient. The concentrated protein therapeutics are lyophilized or freeze-dried from a solution in a vial, producing a porous plug or cake in order to improve storage stability. Just prior to administration to the patient, the cake is reconstituted with sterile water or other aqueous diluent. However, reconstitution of these highly concentrated protein therapeutics is a challenge, due to unacceptably long and variable reconstitution times. The methods of reconstitution (i.e., the rate and location to add the sterile diluent, and the fluid flow mixing pattern) [14–17] are known to affect the time required for reconstitution. A typical and preferred method of mixing is by moving the vial with a horizontal orbital motion (Fig. 1a and b). An end-over-end or other vigorous shaking method is less often used due to the generation of fresh air/water interfaces at

which proteins may denature. Under the most common orbital shaking mode, a free surface wave driven by the gravity and centrifugal effects travels circumferentially, which introduces a locally periodic oscillation pattern within the fluid. Fig. 1c and d illustrate the linear approximation of the first two eigenmodes of the free surface wave and a typical oscillatory flow pattern beneath the wave, respectively. A suspending colloidal particle within the fluid thus will move passively by following the periodic flow while its mass is dissolving into the medium.

Quantitative analysis of dissolution mechanisms remains a great scientific challenge. Complicated dissolution scenario often involves disintegration of various drug dosage forms, transient flow field, and multiphase transport phenomena. The dissolving particle, particle clump, or cake interacts with the surrounding fluid medium, and the process can be further complicated by the physicochemical properties, size and shape, and packing density of the particles to be dissolved. The basic diffusive and convective transport phenomena therefore play important roles in dispersing the drugs and in determining the efficiency of reconstitution. However, both the primary and secondary flows involved in a more realistic, three-dimensional and periodic fluid motion is fairly complicated. Here we simplify the flow pattern to a unidirectional oscillatory flow in the low particle Reynolds number regime and focus on the investigation of local behaviors of the dissolution process. Under this theoretical assumption, the particle suspended in fluid moves passively back and forth at the same frequency as the external flow but with a phase lag. The particle's inertia along with the flow conditions determine the amplitudes of the displacement and velocity of the particle and the phase lag of its motion

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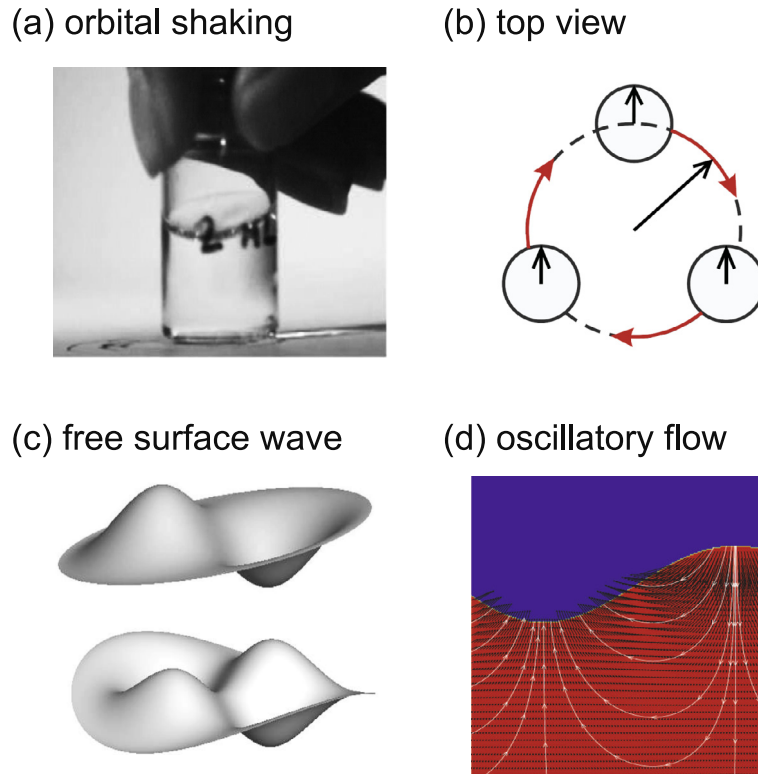


Fig. 1. (a) A typical vial used for protein reconstitution by manual shaking, the vial size is about 1 cm in diameter and 2 cm in height, (b) a top view of the orbital motion while the vial itself does not rotate, (c) the first two eigenmodes of a simplified free surface wave, and (d) the oscillatory flow beneath the wave.

relative to the flow. Intuitively we know that relative motion between the particle and the flow promotes the convective mass transfer and enhances the overall dissolution rate. A quantitative analysis is essential in determining the baseline dissolution efficiency. Early investigations on the correlation of enhanced heat or mass transfer have focused on steady flow under various strength of convective flows [18–25]. Others are on a steady acoustic streaming flow in which the nonlinear inertial effect dominates [26–29]. In this paper we focus on the time dependency of mass transfer characteristics driven by a monochromatic oscillatory flow. The particle size and the relative velocity between the flow and the particle are in the low Reynolds number regime so that the nonlinear inertial effect of the flow is negligible. The transient dissolution of a solid colloidal particle has a much longer time scale than momentum transport so that the coupling of flow dynamics and the particle motion can be resolved analytically based on a quasi-steady approximation of the moving boundary condition. The coupling of mass transfer and long-time dissolution kinetics are numerically computed for various saturation concentration, flow strength, and driving frequency.

2. Theoretical analysis

Fig. 2 illustrates the problem in hand, a spherical colloidal particle (presumably in the colloidal regime and the particle size is less than 1 mm, much smaller than the vial size) is undergoing a single-frequency periodic translational motion driven by an oscillatory external flow. The assumed far field velocity is $Ue^{-i\omega t}\hat{e}_x$, and the particle velocity has an assumed phase lag relative to the flow, $\tilde{U}_pe^{-i\omega t}\hat{e}_x$, where U is a real amplitude and \tilde{U}_p is a complex amplitude that accommodates the phase lag ϕ . The phase lag for the periodic motion is to be found based on the simplified linear momentum equation. The axisymmetric coordinates in radial r

and polar θ directions define the position in the field, and x indicates the axial direction along which the flow and particle oscillate. The periodic flow and passive particle motion are on a relatively short time scale compared to the long time dissolution process. We therefore apply a quasi-steady moving boundary for the dissolution interface to facilitate the analytical solution. The particle size or moving interface is applied to the momentum and mass transfer explicitly from the computed dissolution kinetics.

2.1. Flow dynamics

Assuming that the oscillatory flow is in the Stokes regime (e.g., particle radius less than 1 mm, kinematic viscosity of the aqueous solution about 10^{-6} m²/s, and characteristic flow velocity less than 1 mm/s). The linear viscous flow for a Newtonian fluid is governed by the transient Stokes equation:

$$\rho \frac{\partial \mathbf{v}}{\partial t} \simeq -\nabla p + \eta \nabla^2 \mathbf{v} \quad (1)$$

for a periodic motion within the fluid domain $R(t_L) \leq r \leq \infty$ and $0 \leq \theta < \pi$, where t_L indicates the long time scale, $R(t_L)$ is the particle radius, assumed constant during transient fluid motion, \mathbf{v} is flow velocity, p is pressure, t is time, ρ is fluid density, and η is the dynamic viscosity. Note that we use t to present the short time dynamics and transient diffusion, and t_L to represent a long time dissolution process. The incompressible continuity equation is $\nabla \cdot \mathbf{v} = 0$. In the laboratory coordinate system, the corresponding pressure and velocity boundary conditions can be defined as

$$p \rightarrow p_\infty = \tilde{p}_\infty e^{-i\omega t} + p_0 \quad \text{as } r \rightarrow \infty, \quad (2)$$

$$\mathbf{v} \rightarrow \mathbf{v}_\infty = Ue^{-i\omega t}\hat{e}_x \quad \text{as } r \rightarrow \infty, \quad (3)$$

and

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