

A Numerical Model of a Drug Particle Dissolving in a Dissolution Test Apparatus

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The dissolving compact, or tablet, is the most widely used method of drug delivery. Dissolution tests are used to ensure consistency during tablet manufacture, to assess the dissolution characteristics of a particular tablet design, to establish in vitro/in vivo correlations, and to predict how the drug will perform in the body. Dissolution tests also form a part of the drug approval process. The United States Pharmacopeia (USP) Type 2 Paddle Dissolution Apparatus, from here on referred to as *the USP apparatus*, is a standard dissolution test device, used by the Food and Drug Administration (FDA) and the pharmaceutical industry. Although the USP apparatus is much used, detailed theoretical descriptions of its characteristics are still not well developed. This work considers one possible end state of a dissolving tablet, i.e. fragmentation into small particles with dissolution continuing from the disintegrated solid masses. A framework for calculating the motion of and mass transfer from a drug particle moving through the USP apparatus is outlined. Calculations demonstrate that small particles move with the USP apparatus flow and that, for small particles below a critical diameter, natural convection and radial diffusion dominate, i.e. forced convection effects can be neglected for small particles.

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1 Introduction

G.I. Taylor’s 1940 paper was the starting point for this research [1]. The technique described in this paper for the treatment of a particle motion in the case of a jet impinging on a flat plate was implemented on computer using step-by-step techniques, similar to those used by Glauert [2]. This work was adapted and extended to the problem of particle motion and mass transfer in the USP apparatus.

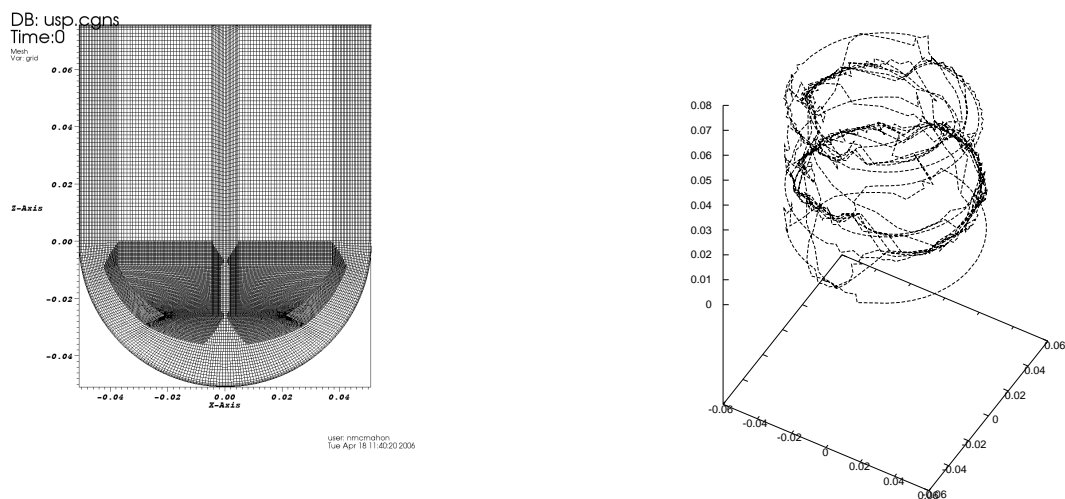


Fig. 1: (Left) A schematic of the USP apparatus; overall height 126 mm and radius 50.8 mm. (Right) A trace of a particle’s path as it moves through the 3D USP apparatus flow field.

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2 Theory and Methods

The simplified equations of motion for a particle moving through a flow-field can be given as:

$$\frac{4}{3}\pi\rho a^3\frac{du_1}{dt} = \frac{1}{2}\pi C_d\rho a^2q(u - u_1) \quad (1)$$

$$\frac{4}{3}\pi\rho a^3\frac{dv_1}{dt} = \frac{1}{2}\pi C_d\rho a^2q(v - v_1) \quad (2)$$

where C_d is the drag coefficient, u and v are the local velocity components of the fluid, u_1 and v_1 are the velocity components of the particle, $2a$ its diameter, ρ its density and ρ the density of the fluid. To calculate the path of a particle moving through the velocity field, the discrete versions of these equations of motion are integrated using a Runge-Kutta method. A generalised particle tracking process is: (1) Calculate the fluid velocities at time t at a finite number of grid points, (2) Search the grid to find the fluid velocities at the position of the particle, (3) Interpolate data from the grid points closest to the particle to determine the fluid velocities at its location, (4) Integrate the equations of motion using these velocities and determine the new particle position, and (5) Analyse and/or visualise the resulting data. For unsteady flows, this process must be completed at each time-step. For steady flows, it is necessary to perform step (1) only once. The pseudo steady-state velocity field within the USP Dissolution apparatus was produced by D'Arcy et al [3] using the commercial CFD code Fluent. LPA and Verlet integration schemes were used to calculate the motion of a particle through the USP velocity field. Mass transfer rates were calculated using empirical correlations [4, 5].

3 Results and Discussion

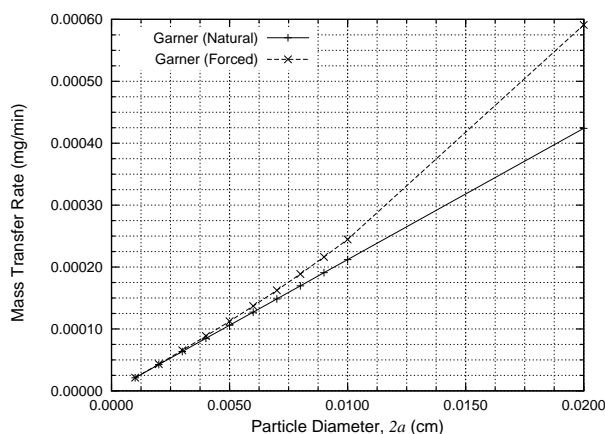


Fig. 2: A graph of mass transfer rates for particles of diameter 200 microns and smaller using only the experimental correlations of Garner [3] together with material properties of 0.1M HCl and Benzoic Acid. Forced convective results were generated using calculated average Reynolds numbers.

Miller reports Harriott's finding that radial diffusion becomes the dominant mode of mass transfer for particles of diameter 205 microns and less in an agitated flow [4–7]. From our numerical study of the average Reynolds number of particles of various sizes moving through the USP apparatus, we estimated that radial diffusion becomes the principal mode of mass transfer for particles of diameter 200 microns and smaller. This is close to Harriott's figure. Mass transfer correlations were used to estimate the mass transfer from particles for the case of free and forced convection as well as for diffusion-only transfer. From Fig. 2 it can be seen that, for small particles of diameter 200 microns and smaller, natural convection dominates as the primary mode of mass transfer while for particles of diameter 100 microns and smaller, radial diffusion dominates.

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