MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 2, pp. 231–239, 2003

RESEARCH PAPER

Engineering Tools for Understanding the Hydrodynamics of Dissolution Tests

Joseph Kukura, Paulo E. Arratia, Edit S. Szalai, and Fernando J. Muzzio*

Department of Chemical and Biochemical Engineering,
Rutgers University, Piscataway, New Jersey, USA

ABSTRACT

In this article, three well-established engineering tools are used to examine hydrodynamics in dissolution testing apparatuses. The application of these tools would provide detailed information about the flow, shear, and homogeneity in dissolution tests. Particle image velocimetry successfully measures two-dimensional cross-sections of the velocity field in an experimental device under both laminar and turbulent conditions. The velocity field is also calculated with computational fluid dynamics (CFD), which can rapidly provide data that is difficult or impossible to obtain experimentally. The occurrence of segregated regions within a USP Apparatus II under mild agitation conditions is revealed by CFD simulations and confirmed by laser-induced fluorescence experiments. The results clearly demonstrate that under current operation settings, the USP Apparatus II operates in a regime where the flow is in incipient turbulence, which is a highly time-dependent condition that might explain possible inconsistencies in dissolution results. It is further demonstrated that proposed changes advocating lower speeds or smaller vessels displace the system toward laminar flow conditions characterized by segregation, compromising the robustness of the test and making it vulnerable to variability with respect to sample location.

Key Words: Dissolution; Hydrodynamics; Computational fluid dynamics.

INTRODUCTION

The USP tablet dissolution test is an evaluation tool for the verification of drug release processes and formulation selection in research and development within the pharmaceutical industry. Failed dissolution tests resulted in 14 product recalls (18% of non-manufacturing recalls for oral solid dosages) in 1999,

*Correspondence: Fernando J. Muzzio, Department of Chemical and Biochemical Engineering, Rutgers University, 98 Brett Road, Piscataway, NJ 08854-8058, USA; Fax: (732) 445-6758; E-mail: muzzio@sol.rutgers.edu.

DOI: 10.1081/DDC-120016731
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

and 20 product recalls in 2000 (24% of nonmanufacturing recalls for oral solid dosages) were attributed to dissolution failures.[1,2] Clearly, failure of a dissolution test can have significant financial ramifications for a pharmaceutical company, so it is highly desirable to avoid such failures, especially if a failure is because of flaws in dissolution methods and unrelated to actual product performance. Given the impact of this test, it is surprising that operating conditions and testing devices have been selected by trial and error rather than thorough analysis. An unfortunate consequence of this lack of rigorous methodology is that dissolution testing is prone to unpredictability. It appears likely that, in many cases, the pharmaceutical industry and the regulatory agency may be expending tremendous efforts to overcome ''dissolution problems'' that are caused by the nature of the test itself rather than the quality of the products the tests are meant to evaluate.

As less soluble drugs and controlled release delivery systems become more available, and as Food and Drug Administration requirements on dissolution get correspondingly tighter, the impact of dissolution tests is likely to become even more important. The negative consequences of inconsistency during dissolution are becoming increasingly unacceptable. Continuing to address on a product-specific basis problems that occur more and more frequently will be costly in the near future. The most common equipment for dissolution testing are the USP Apparatus I and USP Apparatus II. These devices produce flow with a rotating basket and paddle stirrer, respectively, and specifications and discussions of their design are well documented.[3] Because the fluid flow within various USP dissolution tests are very different from the environments in which the products will ultimately be exposed (GI environment), the design and operation of dissolution equipment can and should be challenged as these tests continue to demonstrate greater significance. A rational challenge should start with detailed examinations of the fundamental physics of their operation.

In particular, the underlying hydrodynamics of dissolution tests is a readily apparent source of potential problems and warrants an in-depth evaluation. Hydrodynamics have been shown to influence dissolution test performance for several decades. For instance, changing the agitation speed altered the measured dissolution rates and affected the ability of the in vitro tests to discriminate in vivo performance in several studies.[4–6] The hydrodynamic influences of geometrical changes, such as the shape of the vessel and placement of sample probes, have also been studied, albeit without thorough hydrodynamic measurements.[7–9] The majority of previous work has focused on correlating operating conditions or configurations to dissolution rates, but did not include a comprehensive analysis of the nature of fluid motion, either under standard conditions or after changes in geometry or operation. For example, Levy suggested operating at ''mild agitation intensity'' to match qualitative observations of mild agitation in the stomach.[10] Visualization studies by Mauger with dye released from a nondisintegrating tablet show that shear patterns can be unstable across the surface of the tablet in a USP Apparatus II.[11] Using velocity measurements at selected fixed locations, Bocanegra et al.[12] observed a secondary flow within the same device (the complete flow field and its mixing properties were not studied in detail). A closer examination is needed to define more precisely when and where these secondary flows occur, because sampling from these regions can produce inconsistent and/or unrepresentative data. The flow field and mixing characteristics of standard dissolution equipment are not well understood, despite available proof from previous work that they strongly influence the data generated from dissolution tests. A thorough understanding of the velocity field in the device, leading to its optimization, can eliminate such problems with test performance because of unfavorable hydrodynamics described previously.

Advanced engineering technologies can be utilized to explore further the hydrodynamics within the dissolution apparatus and develop a better physical understanding of the process. In this article, three such tools—particle image velocimetry (PIV), laser-induced fluorescence (LIF), and computational fluid dynamics (CFD)—are used to observe the hydrodynamics within a standard test apparatus. Several unexpected effects are readily observed, including highly inconsistent flow under standard testing conditions and segregated regions at lower agitator speeds or for smaller vessels.

EXPERIMENTAL AND COMPUTATIONAL METHODS

Particle Image Velocimetry

Particle image velocimetry is used as a tool to investigate flow patterns in many mixing devices. The technology has been applied to several

common flow systems in the chemical and pharmaceutical industries.[13] This quantitative, nonintrusive technique measures a two-dimensional velocity field at a given plane of the mixer. The experimental velocity data directly reveals information about the flow and is also used to validate computational simulations. In the most obvious implementation of PIV in a dissolution apparatus, a laser sheet cuts the stirred tank transversally. A diagram of the experimental setup is shown in Fig. 1. The fluid has been seeded with neutrally buoyant 10-μm silver-coated particles. The spherical particles used in this work were obtained from Potters Industries, Inc. (Valley Forge, PA, USA). These particles follow the same trajectories as the fluid molecules. Particles reflect the laser light, and a digital camera is used to capture images of the illuminated plane. In such images, the particles located in that plane appear as bright points in a dark background. The amount of particles placed in the fluid is optimized to experimental conditions by starting with dilute solutions and taking measurements with increasingly more particles until sufficient resolution is achieved. Two successive snapshots of the illuminated plane are required to calculate the two-dimensional velocity field using a fast-Fourier transform, cross-correlation algorithm. We used a Dantec® PIV system (Dantec Dynamics, Mahwah, NJ) to calculate the velocity fields, which includes a Flow Manager 3.0® software package to perform cross-correlations, averaging, noise filtering, and validation procedures.

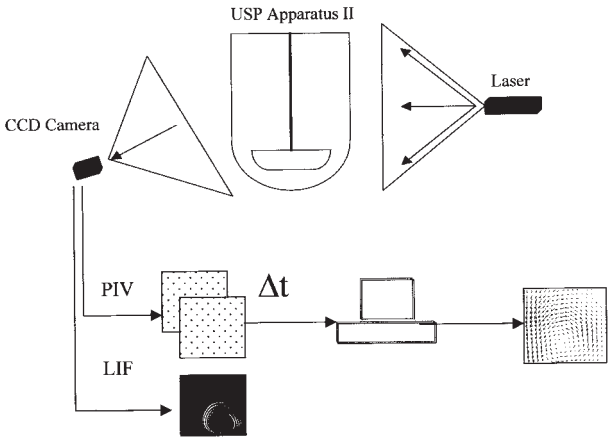

Figure 1. Experimental setup diagram for PIV and LIF experiments.

Laser-Induced Fluorescence

Laser-induced fluorescence is a nonintrusive, visual technique that reveals the time evolution of a mixing process. Figure 1 contains a diagram of the experimental setup. Fluorescent dye is injected in a mixing system and illuminated with a planar laser so that mixing patterns and a concentration field created by the flow can be captured. The buoyancy of the dye must be properly matched to the density of the fluid to reveal the flow structures. Illumination is used to reveal mixing patterns at specific two-dimensional planes within the vessel. Images of the illuminated plane are captured using a CCD camera. The advection of the dye tracer reveals well-mixed and poorly mixed regions in the mixer. Convection carries dye rapidly to regions where mixing is good, while segregated regions of the mixer remain dark for a long time because diffusion is the primary mechanism to bring dye into poorly mixed zones (unless it is intentionally injected there). In addition to observing how the dye distributes, which is mostly qualitative, the intensity of the emitted light can be correlated to the dye concentration in each region of the mixer to quantify homogeneity.[14,15] For the images reported in this work, a 32 mJ YAG laser (New Wave Research, Sunnyvale, CA) was used to generate the laser sheet with a wavelength of 532 nm. Rhodamine B (manufactured by Exciton, Inc., Dayton, Ohio, USA) was used as the fluorescent dye. The flow field was imaged using a DANTEC 80C42 Double Image 700 CCD camera (Dantec Dynamics) with a 552-nm filter on the camera lens. The FLOWMAP software package (Dantec Dynamics) was used for data acquisition and laser/camera synchronization.

Computational Fluid Dynamics

Computational fluid dynamics is a tool that can provide fast and accurate models for fluid flow and give useful insight to mixing processes. A CFD system involves four basic steps: 1) creating a model of the geometry of interest; 2) discretizing the geometry into a mesh; 3) solving the mass, momentum, and energy balance equations for the velocity and pressure field at specific points called nodes defined by the mesh; and 4) utilizing the discrete velocity and pressure data from the solver to characterize mixing and particle motion. Experimentation is necessary to validate CFD models before

simulations can be trusted for design and optimization purposes, but a validated computational model can be a relatively fast and cost efficient means of evaluating design changes. The simulations we present here utilized the ORCA CFD package (Dantec Dynamics), and custom software developed at Rutgers University (Piscataway, NJ) for further data processing and mixing analysis. Our model of a standard USP Apparatus II uses an unstructured tetrahedral mesh with 1.8 million volumetric elements. Acusolve solves the incompressible Reynolds-Averaged Navier Stokes equations based on a Galerkin least-squares, finite-element formulation. This iterative method provides fourth-order accuracy with respect to spatial discretization and second-order accuracy with respect to time.

VELOCITY FIELD ANALYSIS: EXPERIMENTAL AND COMPUTATIONAL

Flow behavior in stirred vessels is usually characterized by the dimensionless Reynolds number (Re), $\mathrm{Re} = \rho N D^2/\mu$, where ρ is the fluid density, N is the rotational speed of the agitator, D is the diameter of the agitator, and μ is fluid viscosity. The behavior of the flow field in a stirred tank during isothermal operation is only a function of the Reynolds number for a given geometrical shape, provided there is not a significant vortex. Dimensionless groups like the Reynolds number are useful because multiple conditions, agitator speeds, and vessel sizes can be captured with a small number of experiments. The Reynolds number is typically correlated to the nature of a flow. Steady, laminar flows are produced from low Reynolds numbers. Time-dependent turbulent flows result from operating at high Reynolds numbers.

Figures 2 and 3 show velocity fields measured by PIV experiments at two different agitator speeds for both a laminar and a turbulent flow in a USP Apparatus II. Each figure contains two velocity field measurements taken at small time intervals at a vertical plane slightly off-set from the center of the tank. The figures correspond to two different flow regimes: a laminar flow in Fig. 2 ($\mathrm{Re} = 100$) and a turbulent flow ($\mathrm{Re} = 5{,}000$) in Fig. 3, bracketing a broad range of operating conditions. Figure 2 depicts a laminar, symmetric steady flow, so only half of the tank is shown in each image (the center of the vessel is on the left half of the images with the wall on the right half). The velocity field clearly gives the direction of the flow: fluid is ejected radially toward the tank walls and is reinjected through the

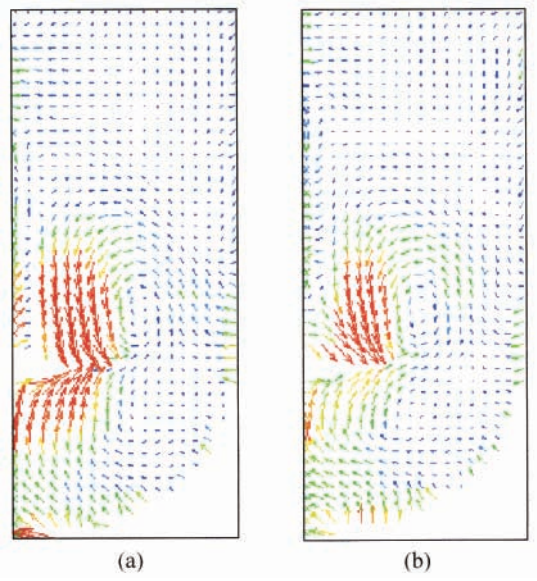

Figure 2. Two instantaneous laminar velocity fields measured using PIV at $\mathrm{Re} = 100$, revealing the steady nature of the flow. Velocity vectors are colored according to velocity magnitude, ranging from 0 mm/s (blue) to 6.9 mm/s (red). Only half of the cross-section is shown in each image, with the shaft on the left and wall on the right. (*See color insert at end of issue.*)

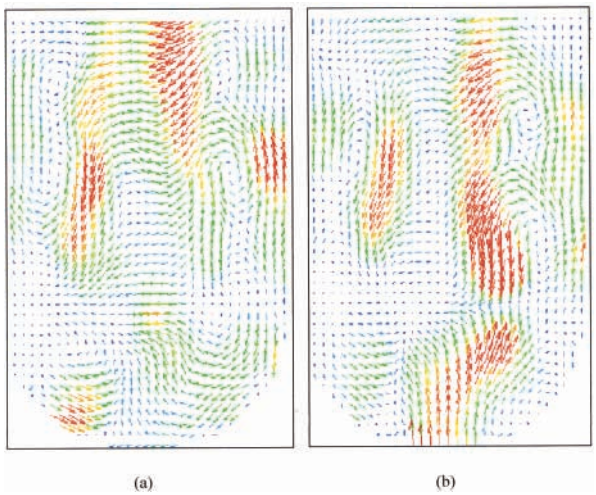

Figure 3. Two instantaneous turbulent velocity fields measured using PIV at $\mathrm{Re} = 5{,}000$, revealing the unsteady and nonsymmetric nature of the flow. Velocity vectors are colored according to velocity magnitude, ranging from 0 mm/s (blue) to 17.4 mm/s (red). (*See color insert at end of issue.*)

shaft, revealing the existence of recirculation zones. We can readily see recirculation zones above and below the impellers, suggesting the presence of dead zones. In addition, a tangential line of vectors is observed at the impeller midplane, which in turn indicates poor communication between the upper and lower halves of the vessel. Potential mixing problems from segregation are evident at these conditions corresponding to a test using slow agitation, a small vessel, and/or viscous fluid.

The turbulent flow field at the higher Reynolds number is presented in Fig. 3. Note that these two pictures (taken a few seconds apart) are significantly different and not symmetric, unlike the steady flow captured in Fig. 2. Turbulent flows are intrinsically time-dependent and experience a continuous reorientation of the flow streamlines, which in turn can yield good mixing. However, not all turbulent motion is equivalent if the goal is testing reproducibility and consistent mixing performance. Fully developed turbulence is steady in a time-averaged sense despite rapid small-scale fluctuations. Transitional turbulence, which is precisely what is obtained under standard testing conditions for the USP Apparatus II, can have significantly large fluctuations that do not allow consistent performance in time. An important feature of turbulent flows is the presence of eddies of different length scales, which can aid the mixing process. These large eddies have large variations in velocity and are thought to contain the bulk of the kinetic energy in the system. Interactions of these large eddies with slower moving streams produce smaller eddies of higher frequency. Even though the random, unsteady nature of the turbulent velocity field is desirable from a micromixing standpoint, the large-scale fluctuations in the flow can be detrimental to macromixing and uniformity within the system. The images in Fig. 3 show large eddies and unstable flow patterns that change significantly in the small time interval. These large flow fluctuations in the velocity field may be highly undesirable for testing consistency. The macroscale unstable regions (eddies) are of the same size scale as the solid tablets, which means that large portions of the disintegrating material can be caught in the flow and distributed through the dissolution device. The uncontrolled, heterogeneous release of solids creates a potential for inconsistent test results from hydrodynamic conditions. Flow phenomena such as this could even pick up small tablets and displace them to various regions of the vessel, causing further variability.

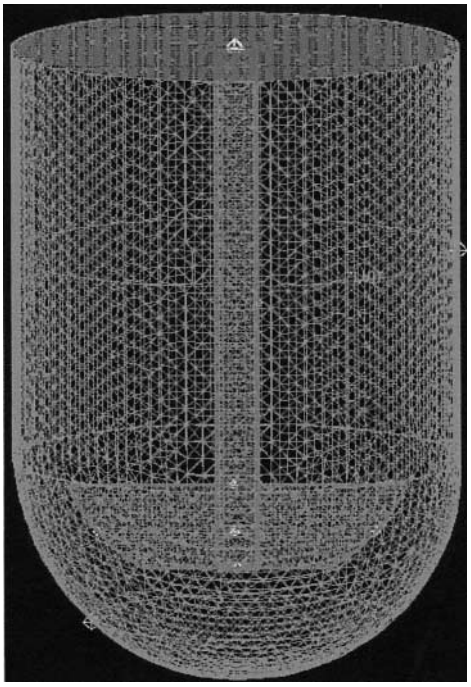

Figure 4. Surface mesh of the USP Apparatus II model used for CFD calculations.

In addition to the experimental velocity fields described, CFD was used to simulate the velocity field throughout a USP Apparatus II vessel. Figure 4 depicts the surface mesh of the model used for the simulations. Although it cannot be seen in the figure, a small cylindrical tablet was included at the bottom of the device and kept in a fixed position throughout the simulations. The velocity field for a Reynolds number of 150 is presented in Fig. 5. The velocity vectors both in the plane of the agitator and in a plane perpendicular to the agitator are shown. Both images correspond to planes that pass through the center of the agitator shaft. The velocity profiles are similar to those in Fig. 2 and do not reveal new information relative to the experimental data by themselves, but the full simulated velocity field can be utilized in a variety of ways to promote understanding the hydrodynamics in the device.

HOMOGENEITY: COMPUTATIONAL AND EXPERIMENTAL

Characterization of the velocity field alone is not sufficient for a thorough hydrodynamic evaluation; an analysis of mixing performance is also required

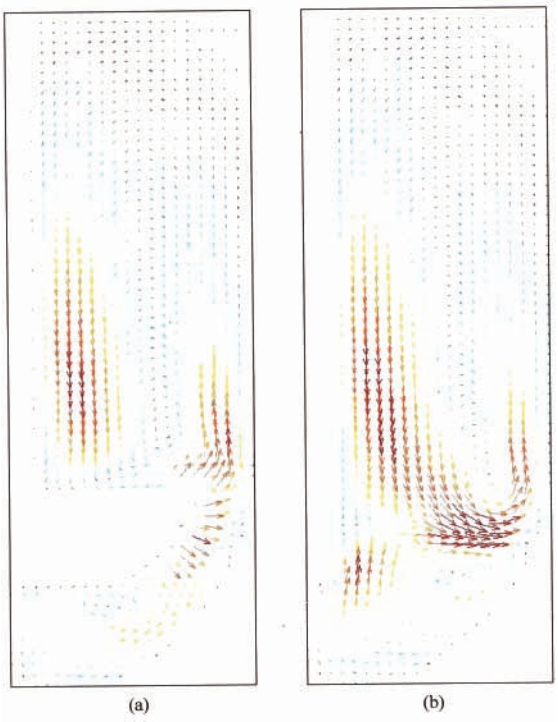

Figure 5. Velocity simulations from CFD at Re = 150 in the plane of the paddle (a) and in the plane perpendicular to the paddle (b). (*See color insert at end of issue.*)

to describe tablet dissolution. Velocity fields only indicate long-term recirculation zones in the flow and possible isolated dead zones, which is not adequate to describe short-time mixing in the dynamic system. Short-term heterogeneities, which can be a primary source of inconsistent behavior, are only revealed by the mixing properties of the flow. Flow visualization experiments and simulations facilitate analysis of mixing phenomena. Carefully conducted dye advection experiments unveil flow patterns and coherent structures that serve as the starting point to analyze fluid mixing. Dye advection experiments use a neutrally buoyant dye such that the tracer moves with the mean velocity of the flow, and simulations can track particles that follow the flow in that manner. A description of the mixing process is then assessed by examining the location of tracers as a function of space and time.

The computational velocity field corresponding to Fig. 5 was used for simulations that tracked particles in the USP Apparatus II. The particles were initially placed in a line that spanned a height above and below the paddle in the plane perpendicular to the paddle to reveal flow structures above and

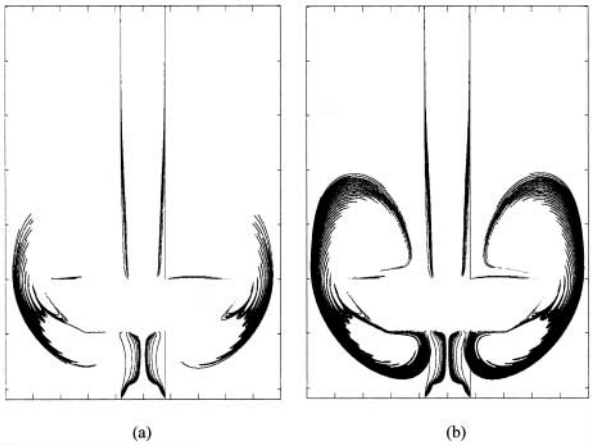

Figure 6. Computational mixing patterns after 10 revolutions (a) and 20 revolutions (b).

below the agitator. Whenever a particle moves through the cross-section parallel with the agitator blade at the center of the vessel, we plot its position in the plane. Plotting the particle positions reveals the mixing structure in the tank, as seen in Fig. 6. The two plots (Fig. 6, a and b), correspond to different times, showing the time evolution of the process. After 10 impeller revolutions, the dye is ejected from the impeller toward the vessel wall. A complex, layered mixing pattern near the paddle is revealed after some time. The folds at the tip of the impeller are created by the flow as the blade passes the plane. After 20 revolutions, more details of the mixing pattern appear. The fluid wraps around the impeller toward the shaft and outlines the slow mixing regions above and below the blade. Note that none of the dye actually gets into the top region of the vessel unless it was originally injected there. The heterogeneous pattern persists for long times. This behavior has a significant influence on the most suitable location and method for obtaining concentration samples from the tank. Identifying slow mixing or segregated areas of a tank is an especially useful function of CFD. Destroying these regions often requires more effort than simply increasing agitation rate or changing the type of impeller.[16]

Laser-induced fluorescence experiments visualize flow patterns in a manner analogous to the simulation results in Fig. 6. Figure 7 shows the image from an LIF experiment conducted in a standard USP Apparatus II. The dye was initially injected at the bottom of the vessel, as if released

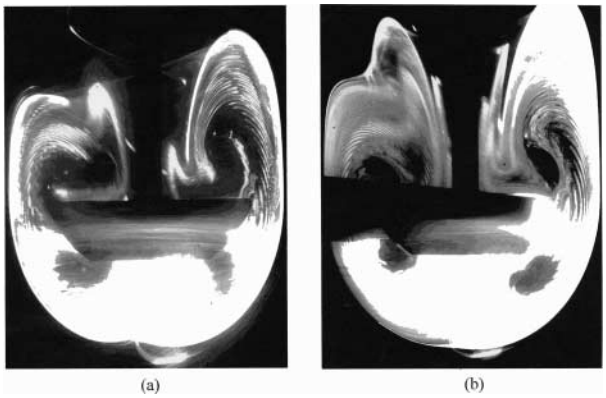

Figure 7. LIF images revealing segregation patterns at Re = 150.

from a tablet located there. Approximately 5 mL of a solution with 200 μg/mL of Rhodamine B was carefully added via a syringe before starting the paddle. After starting agitation, the laser plane was projected through the center of the tank when the paddle was in the plane. The experiment in Fig. 7 was performed with a Reynolds number of 150, which corresponds to laminar flow behavior. Under such flow conditions, the flow produced by most conventional impellers is mainly radial. This type of flow can establish an effective boundary near the impeller midplane and create segregated regions above and below the impeller. The images show that dye is indeed failing to penetrate regions above and below the impeller and that mixing in the device is far from uniform.

The dark areas in Fig. 7 are segregated regions where dye does not enter by the convective mixing of the paddle. The edges of the segregation zones have a distinct folding pattern that is also captured in the computer simulation shown in Fig. 6. Also note that the segregated areas in Fig. 6 have comparable sizes and shapes to the regions found experimentally with LIF. Correspondence of the mixing patterns found in the computational and experimental system indicate that the fundamental mechanisms of fluid motion and mixing are being captured in the simulations. Segregated regions, like those observed in Figs. 6 and 7, have also been found in other stirred vessels and are not unique to this geometry or these flow conditions.[17,18] Their sizes, shapes, and locations in a flow are nonintuitive and cannot be inferred from simple correlations. More importantly, small changes in the impeller speed or vessel geometry can induce a transition from one

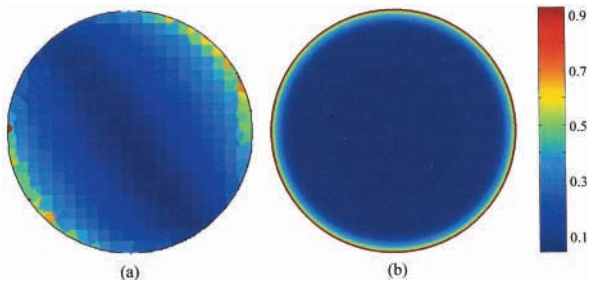

Figure 8. The computationally predicted instantaneous (a) and time-averaged (b) rate of strain distributions on the top surface of a tablet at the bottom of a USP Apparatus II. (*See color insert at end of issue*.)

condition to another. Mixing in complex flows, such as the dissolution test, cannot be predicted a priori. Careful evaluation of the apparatus is needed for the selection of hydrodynamic conditions and sample locations.

UTILIZATION OF CFD DATA

After validating a CFD model with the experimental tools described herein (LIF and PIV), computational data can be gathered faster than experimental measurements. Moreover, some relevant properties are not easily accessible by nonintrusive experimental methods, but can be readily obtained via computations. We present an example using our simulation to measure the strain that is exerted on a tablet surface at the bottom of a USP Apparatus II tank for the conditions corresponding to Figs. 6 and 7. Figure 8 shows the rate of strain exerted on the top surface of a disk-shaped tablet at the bottom of the dissolution apparatus (viewed from above). Both an instantaneous measurement (Fig. 8a) and the time-averaged value (Fig. 8b) are presented. For both figures, regions of low strain are shown in blue and high strain are presented in red on the same color scale. The instantaneous data in Fig. 8a indicates that the force is not uniformly applied, and only small areas of the dosage form experience the maximum shear at any given time.

The time-averaged data in Fig. 8b shows that a very narrow region at the outside of the tablet experiences the highest strain. Mass transfer from the tablet is likely to be controlled by diffusion through a thin laminar layer around the surface. The higher strain (and consequently shear) at the

outside of the tablet will create a thinner layer at the edge than the boundary layer above the center of the tablet. Hence diffusion occurs faster at the outer edge (through the thinner boundary layer near the rim). As the outer edge of a tablet disintegrates and dissolves faster, the center of the tablet is expected to dissolve more slowly because of the nonuniform conditions. This phenomenon may not be well correlated to in vivo tablet dissolution, because the hydrodynamics within the body are not likely to distribute stress in this manner across the surface of the tablet. Although this CFD model needs to be carefully validated and further developed before being used to implement design and procedural changes, the potential value of this information is clearly evident.

CONCLUSIONS

Relying on case-by-case analysis and choosing operating conditions without detailed knowledge of the fluid motion that result from these choices have made dissolution tests vulnerable to inconsistent performance. Unpredictable flow and inconsistent mixing are not so much side effects, but inevitable consequences of this approach. Specifically, agitation speeds as low as 50 rpm in the USP Apparatus II have been proposed as a discriminating in vitro test condition.[4] An engineering analysis of these conditions quickly reveals that the flow is unstable and in a transitional regime between steady laminar flow and full turbulence. Obtaining reproducible data from an inherently unstable environment can be difficult, if not impossible. The process is bound to show inconsistent performance. Further analysis of the hydrodynamic environment and mixing characteristics will allow a rational selection of testing equipment and operating conditions.

The LIF, PIV, and CFD technologies have been shown to be suitable for promoting an improved understanding of hydrodynamics in the dissolution apparatus. Work is actively being performed to apply these techniques to a wide set of operating conditions and geometries. Important tasks that are being completed include refinement of the PIV method, exploration of releasing a fluorescent dye from a nondisintegrating dosage form for LIF measurements, and thorough validation of the CFD models with experimental data. Subsequent work will permit a critical evaluation of the suitability of dissolution test parameters and equipment configuration from the perspective of the hydrodynamics of the flow field. Systematic application of these and other rigorous tools will lead, in the long term, to the development of a test that is both reliable and physiologically relevant.

ACKNOWLEDGMENTS

Funding for this work was provided by Wyeth and Schering-Plough Corporation. Joseph Kukura is funded by the Doctoral Study Program of Merck Research Laboratories.

REFERENCES

1. The Gold Sheet. FDC Reports **2000**, *34* (2), 1–15.
2. The Gold Sheet. FDC Reports **2001**, *35* (3), 1–19.
3. Abdou, H. Factors relating to the dissolution apparatus. In *Dissolution Bioavailability and Bioequivalence*; Mack Publishing Co: Easton, PA, 1989; 115–143.
4. Abrahamsson, B.; Roos, K.; Sjogren, J. Investigation of prandial effects on hydrophilic matrix tablets. Drug Dev. Ind. Pharm. **1999**, *25* (6), 765–771.
5. Cartensen, J.; Lai, T.Y.; Prasad, V.K. USP dissolution IV: comparison of methods. J. Pharm. Sci. **1978**, *67* (9), 1303–1307.
6. Hamlin, W.E.; Nelson, E.; Ballard, B.E.; Wagner, J.G. Loss of sensitivity in distinguishing real differences in dissolution rates due to increasing intensity of agitation. J. Pharm. Sci. **1962**, *51* (5), 432–435.
7. Wells, C. Effect of sampling probe size on dissolution of tableted drug samples. J. Pharm. Sci. **1981**, *70* (2), 232–233.
8. Underwood, F.; Cadwallder, D. Effects of various hydrodynamic conditions on dissolution rate determinations. J. Pharm. Sci. **1976**, *65* (5), 697–700.
9. Durig, T.; Fassihi, R. Evaluation of floating and sticking extended release delivery systems: an unconventional dissolution test. J. of Controlled Release: Official journal of the Controlled Release society **2000**, *67* (1), 37–44.
10. Levy, G. Effect of certain table formulation factors on dissolution rate of the active ingredient I. J. Pharm. Sci. **1963**, *52* (11), 1039–1046.

11. Mauger, J.W. Physiochemical and mechanical factors related to dissolution testing. Dissolution Technologies **1996**, *3* (1), 7–19.
12. Bocanegra, L.M.; Morris, G.J.; Jurewicz, J.T.; Mauger, J.W. Fluid and particle laser doppler velocity measurements and mass transfer predictions for USP paddle method dissolution apparatus. Drug Dev. Ind. Pharm. **1990**, *16* (9), 1441–1462.
13. Adrian, R.J. Particle imaging techniques for experimental fluid mechanics. Ann. Rev. of Fluid Mech. **1991**, *23*, 261–304.
14. Arcoumanis, C.; McGuirk, J.J.; Palma, J. On the use of fluorescent dyes for concentration measurements in water flows. Exp. in Fluids. **1990**, *10*, 177–183.
15. Unger, D.; Muzzio, F.J. Laser-induced fluorescence technique for the quantification of mixing in impinging jets. AIChE J. **1999**, *45* (12), 2477–2485.
16. Lamberto, D.; Muzzio, F.J.; Swanson, P.D.; Tonkovich, A.L. Using time-dependent RPM to enhance mixing in stirred vessels. Chem. Eng. Sci. **1996**, *51* (5), 733–741.
17. Lamberto, D.; Alvarez, M.M.; Muzzio, F.J. Experimental and computational investigation of the laminar flow structure in a stirred tank. Chem. Eng. Sci. **1999**, *54* (7), 919–942.
18. Zalc, J.; Alvarez, M.M.; Arik, B.E.; Muzzio, F.J. Extensive validation of computed laminar flow in a stirred tank with three rushton turbines. AIChE J **2001**, *47* (10), 2144–2154.