

Study Highlights Flawed Dissolution Testing Procedure

New research work at Rutgers University (Piscataway, NJ) may dramatically impact established industry practices and standards for dissolution testing. A group (Joseph Kukura, Jennifer Baxter) led by Fernando Muzzio, PhD, Director, New Jersey Particle Processing Research Center of the Department of Chemical and Biochemical Engineering, has presented data indicating that differences in hydrodynamic effects corresponding to the relative position of test tablets in test vessels are a likely cause for the high variability often observed in dissolution testing using USP Apparatus II.

The results indicate that tablets or tablet fragments which might move during the dissolution test would likely experience high variations in shear forces and, therefore, produce dramatically different dissolution rates. Says Muzzio, "such variations would likely contribute to intrinsically high variability and non-reproducibility of the test for dosage forms where dissolution is mass-transfer limited."

Using a computational model to simulate the flow field, the Rutgers team measured shear forces as a function of tablet position within the USP II vessel. Shear forces control the thickness of the boundary layer available for mass transport and, as observed by Muzzio, "mass transport is the ultimate bottleneck controlling how quickly a drug leaves a unit dose and enters the surrounding medium, i.e. the dissolution rate." As shown in Figure 1, the center of the test vessel, where a tablet is most likely to remain during the dissolution test, experiences very low shear, while regions further away from center see increasingly higher levels.

The researchers also conducted dissolution experiments in which the position of test tablets was carefully con-

trolled. Prednisone calibrator tablets (USP Lot LO0C056) were evaluated at two locations, the dish center and a position 2 cm from center. Results showed dissolution rates at the off-centered position to be more than twice as rapid as those at the center position (see Figure 2).

The implications of the Rutgers experiments are far from inconsequential in an industry where tighter and tighter regulatory requirements are being imposed on testing processes, validation, and documentation. As noted by Muzzio, FDA requires industry to conduct dissolution testing on every batch of product produced. "And, when you have a situation where a test tablet can dissolve up to twice as fast, just based on a 1-2 cm variation in placement, this raises significant issues." In fact, there are cases where inconsistent dissolution test results have triggered in-depth product re-evaluations or even complete reformulations.

Although USP can't yet comment on the specifics of the Rutgers findings, Eric Sheinin, PhD, USP VP of Standards and Information Development, says there are a number of established procedures within USP for addressing these issues.

Sheinin says information would likely be first presented to the USP's Expert Committee on Biopharmaceuticals. An article might then follow in *Pharmaceutical Forum* to stimulate industry-wide discussion and/or formal

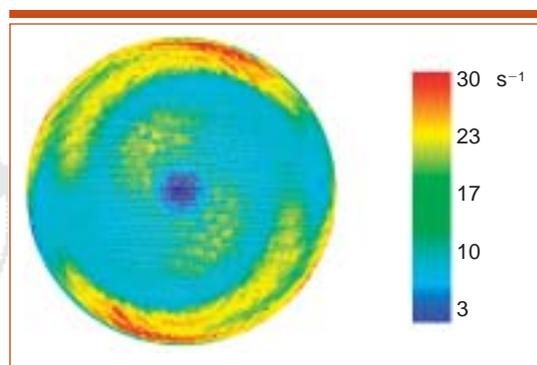


Figure 1 shows shear stress along the walls of the dissolution device at a condition corresponding to agitating an aqueous media at 50 rpm. Regions of high shear are depicted in red, while regions of low shear are shown in dark blue. The computational model was validated through comparison with noninvasive, experimental techniques including particle image velocimetry to verify the two-dimensional flow field, and laser induced fluorescence to compare the evolution of mixing patterns and species transport.

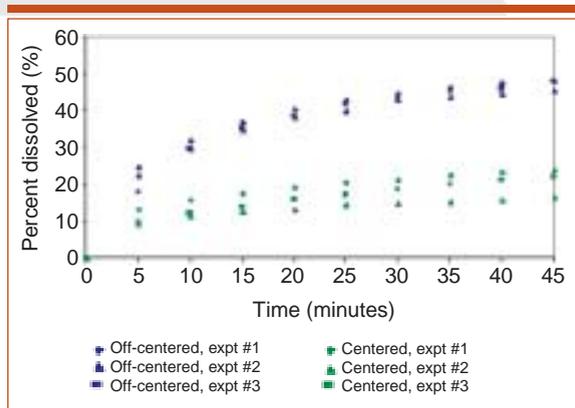


Figure 2 shows the dramatically different dissolution rates measured at different tablet positions. To establish sufficient repeatability, the tests were repeated three times for each tablet position. While some experimental error was observed between runs at each tablet location, the measured dissolution rate variation is apparent and cannot be attributed to error.

comment, and potentially a revision to the *USP-NF*. According to Muzzio preliminary meetings have already been held with USP to discuss possible collaborative efforts. The first formal step in the process, however, would be to submit a "request for revision." A guideline is available electronically on the USP web site (www.usp.org).

A possible complication in the process is that USP is currently in the

midst of harmonizing the dissolution chapter of the US formulary with both the European and Japanese pharmacopeia. The Pharmacopeial Discussion Group, made up of members from all three pharmacopeias, has agreed that once a general chapter has been harmonized, no individual pharmacopeia would unilaterally make changes. The current plan calls for a harmonized document to be approved by early next year.

Meanwhile the Rutgers team is planning follow-up research to characterize the unit dose forms likely to be most vulnerable to this kind of test variability. "We want to first isolate unit dose problems from test problems," says Muzzio. "After that, we'll try to introduce modifications to existing tests as well as help develop new test methodologies that won't have these problems."

John Haystead