Shear-induced Variability in the United States Pharmacopeia Apparatus 2: Modifications to the Existing System

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ABSTRACT

The hydrodynamics within the United States Pharmacopeia Apparatus 2 have been shown to be highly non-uniform with a potential to yield substantial variability in dissolution rate measurements. Through the use of readily available engineering tools, several geometric modifications to the device were evaluated in this study. Specifically, we examined the influence of impeller clearance, agitator type (radial and axial), and vessel geometry (PEAK vessel) on the fluid flow properties and their relation to measured dissolution rates. Increasing the impeller clearance was observed to exacerbate the heterogeneity in shear and would likely result in greater variability in dissolution measurements. Altering the impeller type was shown to yield changes in the hydrodynamic behavior; however, the overall properties and problems with the test remain the same. Use of the PEAK vessel was observed to reduce shear heterogeneity in the regions where tablets are most likely to visit during testing; however, higher shear rates may result in the inability to discriminate between true differences in dissolution rates.

KEYWORDS: USP II, tablet dissolution, hydrodynamic variability, callibrator tablets, bioavailability

INTRODUCTION

The importance of in vitro dissolution testing has been recognized by pharmaceutical scientists since the early 1930s.¹ The regulatory test was made official in 1970 with the adoption of the United States Pharmacopeia (USP) Apparatus 1 as the official apparatus, followed later by the introduction of the USP Apparatus 2. Since the introduction of the USP Apparatus 2 test, there have been numerous reports of unexplained variability in products that are otherwise shown to be highly uniform.²⁻⁵ The consequences of failed dissolution tests cannot be underestimated. Failures can cause product recalls, costly investigations, and production delays and may even cause a company to lose its first-to-market advantage. From 2000 to 2002 alone there were 47 product recalls

attributed to dissolution failures, representing 16% of non-manufacturing recalls for oral solid dosage forms.⁶⁻⁸ If even a fraction of these failures are the result of test variability rather than product inhomogeneities, there is a substantial motivation to understand and improve the test itself.

Throughout the past 4 decades, there have been numerous studies aimed at evaluating the importance of hydrodynamics in drug dissolution testing. Levy et al⁹ showed that the sensitivity of the dissolution rate of a tablet to small changes in agitation intensity can yield in vitro results contrary to those obtained in vivo. In 1962, Hamlin et al¹⁰ reported that the agitation rate has a strong effect on distinguishing differences in the measured dissolution rates of methylprednisolone forms I and II. They also showed that the diminishing of the thickness of the boundary layer around tablets due to increasing the intensity of agitation led to inability to distinguish between the dissolution rates of the polymorphs.

The influence of the shear rate (or rate of deformation) on the boundary layer thickness is well known in the field of fluid mechanics. In general, the thickness of the boundary layer is inversely proportional to the fluid velocity and rate of strain. The dissolution of a solid dosage form is given by the application of Fick's Law, as shown in Equation 1 below:

$$dM/dt = D h A (C_S - C) \quad (1)$$

Here, M is the mass of drug to be dissolved, A is the surface area exposed to the dissolution medium, D is the dissolution coefficient, C_S is the solubility of drug, C is the drug concentration in the medium, and h is the thickness of the diffusion boundary layer. Consequently, variations in the rate of shear can greatly affect dissolution measurements in the device.

A recent study by Baxter et al¹¹ applied these fluid mechanics principles to conduct a characterization of the hydrodynamics within the USP Apparatus 2. The study revealed that under normal operating conditions, the flow in the USP Apparatus 2 exhibits large fluctuations in the velocity field, strong enough to displace tablets along the vessel bottom. In addition, the authors showed that highly non-uniform shear rates are observed along the vessel bottom, with shear rates at the local maximum 2 to 3 times higher than at the center of the dish. Experiments were then conducted with calibrator tablets and over-the-counter naproxen sodium tablets to show that tablets dissolve 70% to 140% faster, when placed

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at the local maxima relative to those placed at the center. Because technicians have no control over tablet motion, and because tablets are observed to get “stuck” at different positions, at times for a few minutes, sometimes indefinitely, these results demonstrate that in its present form, the USP Apparatus 2 test has significant potential for variability owing to the test itself.

Over the years there have been many reports in the literature of ad hoc solutions to some of the typical problems encountered in dissolution testing. With better tools and a more complete understanding of the issues, a re-evaluation of some of these solutions can be valuable. For example, PEAK vessels were introduced by Vankel (Cary, NC) several years ago to combat the issue of cone formation,¹² while Collins and Nair¹³ reported that use of PEAK vessels not only eliminates the formation of cones but also results in higher release rates and lower variability. One might wonder if the presence of this inverted cone might sufficiently alter the distribution of shear rates along the vessel bottom, minimizing the exposure of the tablet to shear heterogeneity. In this study, computational fluid dynamics is used to evaluate the influence of minor geometrical modifications to the USP Apparatus 2 on hydrodynamics. Specifically, we examined the influence of agitator height, impeller type (radial and axial), and vessel geometry (PEAK vessel).

MATERIALS AND METHODS

Geometries

Several geometries were considered in this study, all consisting of minor modifications to the standard configuration of the USP Apparatus 2. First, a 1-L spherical bottom vessel, 102 mm in diameter, and a 7.5-cm paddle positioned 50 mm from the bottom of the dish was considered. Next, the conventional USP 1-L vessel with a 3-cm 6-blade Rushton impeller positioned 25 mm from the vessel bottom was examined. In addition, the conventional USP 1-L vessel paired with a 5-cm 3-bladed axial turbine positioned 25 mm from the vessel bottom was studied. Last, a 1-L PEAK vessel, manufactured by Varian Inc Dissolution Systems (Cary, NC) coupled with the standard 7.5-cm paddle was considered. All simulations were performed assuming the vessel contents were composed of an aqueous medium with a density of 1 g/cm³ and a viscosity of 1 cP.

Computational Fluid Dynamics

Computational fluid dynamics (CFD) modeling of the dissolution apparatus was performed using a compilation of several software programs. The 3-dimensional geometry specification and mesh generation were accomplished using ICEM-CFD (ICEM CFD Engineering, Berkeley, CA). An unstructured tetrahedral mesh was used for all the geometries

discussed in this article and consisted of 1.9 million volumetric elements for the standard case, 1.6 million tetrahedral for the adjusted impeller height, 0.5 million elements for the Rushton impeller, 1.8 million for the axial turbine, and 1.6 million tetrahedral for the peak vessel model. The commercially available AcuSolve program (ACUSIM software, Mountain View, CA) was employed to solve the algebraic form of the Reynolds-Averaged Navier Stokes equations at each of the nodes defined by the mesh. This solver used a Galerkin least-squares finite element formulation that provided second order accuracy. The Spalart-Allmaras closure model was implemented for turbulence modeling, and we required all of the weighted residuals of the governing equations to converge to less than 10⁻⁴. Additional technical details regarding the use of this CFD code for investigations of stirred tanks have been described,¹⁴ as well as a detailed discussion of the development and validation of the computational model used for this device.¹¹ Consequently, the details are not discussed in this article.

Particle tracking simulations were accomplished using commercially available software provided by ACUSIM. Subsequent mixing analysis was performed using custom software developed at the Pharmaceutical Engineering Program at Rutgers University.^{15,16}

Tablet Visualization

Tablet visualization experiments are performed using non-disintegrating salicylic acid indicator tablets. The tablets are produced by blending powdered salicylic acid with 3 wt % phenolphthalein (according to the procedure suggested by Mauger et al¹⁷) and compressed in a tablet press. The tablet, 6.5 mm in diameter, was dropped into the dissolution vessel filled with 0.1N sodium hydroxide solution and allowed to settle. The agitator was started at 50 rpm, and the movement of the tablet was recorded.

RESULTS AND DISCUSSION

To serve as a basis for comparison, the results obtained from the analysis of the USP Apparatus 2 standard operating conditions are presented in this report. A detailed discussion of these results can be found elsewhere.¹¹

Impeller Clearance

One of the simplest changes that can be made to the system is the alteration of the agitator clearance. First, we considered the case of setting the paddle height to 50 mm in place of the standard 25-mm height. Figure 1B shows the CFD-generated time-averaged velocity fields for agitation speeds of 50 and 100 rpm. The vectors in the 2 plots were each scaled, using different scaling factors, according to the

Figure 1. Time-averaged velocity fields generated by CFD at agitation speeds of 50 and 100 rpm for (A) the standard USP Apparatus 2 configuration, (B) a paddle height of 50 mm, (C) a Rushton turbine, (D) a pitched blade turbine, and (E) the PEAK vessel.

magnitude of their vectors. Vectors in red corresponded to the highest magnitudes, and those in dark blue corresponded to the lowest. The overall flow patterns for the 2 agitation speeds looked similar, although their magnitudes are in fact different. Similar to the velocity fields for the standard paddle height of 25 mm shown in Figure 1A, it was observed that fluid was ejected radially from the impeller and was directed in one of 2 ways. Either the fluid flowed up the wall toward the top surface and then back down the impeller shaft, forming a recirculation zone above the impeller, or the material was directed down to the dish center and was pulled up through the center of the dish back to the paddle, forming a second recirculation zone below the impeller. The figures also show that the lower recirculation zone was larger at the 50-mm height than in the case of the 25-mm height, and a low-velocity mixing region was observed in the region directly beneath the paddle. While this low-velocity region was present at the standard height, it encompassed only a small volume beneath the paddle in comparison to the 50-mm height. Even at this small volume, this low-velocity region could create issues during dissolution testing including the formation of a cone of material for dense, disintegrating tablets. It is likely that these issues would be magnified as this low-flow region increased in size.

The distribution of shear rates can also provide valuable information regarding the impact that hydrodynamics can have on the measured dissolution rate. Figure 2B shows the distribution of the shear forces within the fluid for the 2

agitation speeds. The plots looked similar to those observed at the standard paddle height (Figure 2A); however, a large region of low shear was observed beneath the paddle at the 50-mm height. The highest shear rates were observed in the region surrounding the paddle, while the lowest shear was observed between the wall and the agitator shaft. Evaluation of the shear rates along the dish of the vessel was particularly useful as this represented the region in which the tablet would spend most of the time during testing. Figure 3B contains contour plots of the shear rate distribution along the dish for the 2 agitation speeds, as viewed from the bottom of the vessel. Similar to the standard condition, a circular low-shear region was observed in the bottom center of the device for both agitation speeds. Outside of this small region, the shear rate increased dramatically.

Agitator Type

There are hundreds of impeller types that exist in industry. Determination of the most effective impeller is based on the process requirements and physical properties of the system of interest. Two of the most typical classes of impellers used in transitional and turbulent mixing include axial flow and radial flow impellers. Axial flow impellers are used to promote a downward velocity profile. In general, they are characterized by low shear and high axial dispersion. Radial impellers, on the other hand, discharge fluid radially outward to the vessel walls. They provide higher shear and turbulence levels with less pumping in comparison with axial turbines.

Figure 2. Distribution of shear rates within the fluid at agitation speeds of 50 and 100 rpm for (A) the standard USP Apparatus 2 configuration, (B) a paddle height of 50 mm, (C) a Rushton turbine, (D) a pitched blade turbine, and (E) the PEAK vessel.

Here we examined the impact of substituting the standard paddle, a radial impeller, with a Rushton turbine, a 6-bladed disk style radial flow impeller. Figure 1C presents the time-averaged velocity fields generated by CFD for the Rushton turbine at agitation speeds of 50 and 100 rpm. The overall circulation patterns were the same for the 2 agitation speeds. Fluid is drawn into the impeller from both the top and bottom and was then discharged radially to the tank wall. At the wall, the fluid was directed down to the tank bottom and up to the fluid surface, forming 2 recirculating regions above

and below the agitator. The distribution of shear within the fluid is shown in Figure 2C. At both speeds, the lower region or dish of the vessel was exposed to high shear while the upper region, occupying the majority of the tank, experienced very low shear rates. In addition, the magnitudes of the shear rates produced in this configuration were considerably lower than those observed with the standard paddle. The same was true for the shear distribution along the wall of the dish shown in Figure 3C. Here the distribution of the shear rates appeared comparable with the distribution with

Figure 3. Distribution of shear rates along the wall of the vessel bottom (viewed from the bottom) at agitation speeds of 50 and 100 rpm for (A) the standard USP Apparatus 2 configuration, (B) a paddle height of 50 mm, (C) a Rushton turbine, and (D) a pitched blade turbine.

the standard paddle at the 50-mm height; however, the magnitudes were one-third the size.

Next we evaluated the effect of substituting the standard paddle with a pitched blade turbine, designed to promote a vertical flow pattern with lower shear characteristics. The velocity fields for the axial impeller configuration agitated at 50 and 100 rpm are shown in Figure 1D. From these plots, it was observed that a predominantly axial velocity component resulted as fluid was drawn in from above the impeller and was forced down to the bottom of the tank. The distribution of shear rates within the fluid for the axial system is shown in Figure 2D. High shear was observed in the regions surrounding the agitator and shaft, while low shear rates encompass the areas between the vessel wall and impeller shaft. The shear distribution along the wall of the dish, shown in Figure 3D, appeared comparable with the distribution with the standard paddle at the 50-mm height; however, the magnitudes were approximately one half the size.

Vessel Geometry

The low-velocity region in the bottom center of the USP Apparatus 2 standard setup often results in the formation of a cone of material, particularly in dosage forms with dense excipients. Beckett et al¹² reported that much of the variability in dissolution testing with the USP Apparatus 2 is attributable to this cone formation. To remedy this issue, the PEAK vessel was developed by VanKel Industries Inc. The PEAK vessel has an inverted cone molded into the bottom, designed to eliminate the potential for cone formation. Comparative experiments with the PEAK and hemispherical vessels showed better reproducibility and accelerated dissolution rates with the modified vessel shape.^{12,13} A thorough hydrodynamic evaluation of this system would be valuable to determine if the issues identified in the standard configuration are remedied through the use of the modified vessel.

Figure 1E shows the velocity fields generated using a CFD model of the PEAK vessel coupled with a standard 7.5-cm paddle at agitation speeds of 50 and 100 rpm. The overall circulation patterns appeared nearly identical to those in Figure 1A. Similarly, the shear distribution within the fluid shown in Figure 2E showed little difference from the standard configuration. However, significant differences were observed when evaluating the shear rates along the wall of the dish. Figures 4A and C show the distribution of shear rates along the wall of the dish at agitation speeds of 50 and 100 rpm, respectively. The low-shear circular region in the center of the dish, typically observed under the standard test conditions, was now replaced by the inverted cone, which was depicted as the void circular region in the figures. At both speeds, a ring of high shear rates surrounded the inverted cone. Outside of the high-shear ring, a low-shear

Figure 4. Distribution of shear rates along the wall (A) of the vessel bottom (viewed from the bottom) at an agitation speed of 50 rpm, (B) of the inverted cone (side and bottom view) at an agitation speed of 50 rpm, (C) of the vessel bottom (viewed from the bottom) at an agitation speed of 100 rpm, and (D) of the inverted cone (side and bottom view) at an agitation speed of 100 rpm.

ring was observed; however, it is unlikely that a tablet would be exposed to these conditions since the curvature of the dish is quite high.

A visualization experiment is performed in the PEAK vessel to determine the type of tablet movement and the regions where the tablet might go to during testing. Images captured during the visualization experiment are shown in Figure 5. During most of the test, the tablet rotates around the inverted cone in the direction of the impeller rotation as shown in Figures 5A and B. However, occasionally the tablet shifted to its side and leaned against the inverted cone while rotating in a circular fashion, as can be seen in Figure 5C. Consequently, the shear rates along the surface of the inverted cone can affect the measured dissolution rates, particularly if the rates differ significantly from the high shear ring surrounding the cone.

The distributions of shear along the wall of the inverted cone for agitation speeds of 50 and 100 rpm are shown in Figures 4B and D, respectively. Most of the cone consisted of high shear rate, of similar magnitude to the high shear ring surrounding the cone. Low shear was observed at the top of the cone, a region in which a tablet would not likely be exposed. Low shear was also observed in the region where the cone met the vessel wall. This finding was likely an artifact of the computational model since the geometry specification of the model contained a sharp angle at this point, which did not exist in the real vessel. A plot of the shear rate (averaged in the azimuthal direction) versus distance from the bottom center of the dish is shown in Figure 6. The sharp decrease in the shear rate observed at

Figure 5. Images captured from a visualization experiment in the PEAK vessel at 50 rpm.

~0.02 m for both agitation speeds was believed to be an artifact of the computational model. Even if this area was encompassed by low-shear as depicted in the plot, the region was too small to affect the dissolution rate significantly. It is also important to note that the tablet will not likely be exposed to the low shear areas shown at the early part of the plot since they represent the top surface of the inverted cone.

Comparison of Modifications

Figure 7A shows a plot of the average shear rate versus distance along the bottom of the vessel for each of the configurations agitated at 50 rpm. Significantly higher shear rates were observed with the 50-mm impeller height, magnifying the problems encountered under standard operating conditions. Alternatively, lower shear rates were observed with both the Rushton and Axial turbines; however, the impeller diameters were considerably smaller, consequently the Reynolds numbers are not equivalent to those conditions with the 7.5-cm paddle. Higher shear rates were observed with the PEAK vessel, but no sharp increases were observed in the regions where a dosage form would likely visit during testing. Hamlin et al.¹⁰ found that differences in the dissolution rates of methylprednisolone forms I and II could only be distinguished at low agitation speeds but not at higher speeds. Since the shear rates are considerably higher in the PEAK™ vessel than in the standard configuration, the

ability of the test to discriminate tablet changes might be questioned.

A plot of the average shear rate versus distance along the bottom of the vessel for each of the configurations agitated at 100 rpm is shown in Figure 7B. At the higher agitation speeds the same trends were observed as those at 50 rpm. At the 50-mm paddle height, the shear rates were higher in the off-centered position and lower at the center of the dish as compared with the standard configuration. Consequently, the problems were still magnified using the alternate height. Lower shear rates were once again observed with the 2 alternate impeller type; however, the Reynolds numbers were not equivalent. The PEAK vessel was observed to offer the same advantages at 100 rpm as those observed at 50 rpm.

Figure 8A and b compare the 5 configurations at equivalent Reynolds numbers, specifically $Re = 4688$ and $Re = 9375$. While the standard configuration, alternate impeller height,

Figure 6. Average rate of shear along the wall as a function of distance.

Figure 7. Average rate of shear along the wall as a function of distance for the standard USP Apparatus 2 configuration, a paddle height of 50 mm, a Rushton turbine, a pitched blade turbine, and the PEAK vessel at (A) 50 rpm and (B) 100 rpm.

Figure 8. Average rate of shear along the wall as a function of distance for the standard USP Apparatus 2 configuration, a paddle height of 50 mm, a Rushton turbine, a pitched blade turbine, and the PEAK vessel at (A) $Re = 4688$ and (B) $Re = 9375$.

and PEAK vessel comparisons were unchanged, this new comparison was important in the consideration of the Rushton and pitched-blade turbines. At both Reynolds numbers, the alternate impeller types resulted in comparable shear profiles to the 50-mm height. Consequently, the new impellers offered no advantages to the current USP configuration.

CONCLUSION

Several geometrical modifications were examined with respect to their effects on the hydrodynamics related to dissolution testing. Impeller height, specifically operating the agitator at a height of 50 mm versus the standard 25 mm, magnified the problems associated with shear heterogeneity. A 4- to 5-fold increase in the shear rate was observed between the center of the dish and a distance 20 mm from the center, 2 times larger than the increase observed with the standard conditions. Altering the impeller type changes the hydrodynamics; however, the overall properties and problems with the test were still the same. The use of a Rushton impeller introduced lower rates of shear in the upper region of the vessel; however, the steep increases in shear rate in the lower dish were magnified as compared with the standard configuration for equivalent Reynolds numbers. The axial impeller also showed no advantages over the standard configuration with a paddle. In fact, mixing with the pitched-blade turbine resulted in more severe heterogeneity in shear for equivalent Reynolds numbers. The vessel shape also produced a dra-

matic effect on the shear environment that a dosage form would be exposed to during testing. Instead of a low-shear region surrounded by high shear, a dosage form in the PEAK vessel would only be exposed to high shear. While the heterogeneity was minimized, the high shear rates might result in the inability to discriminate between true differences in the dissolution rates. Experiments should be conducted to determine if subtle differences can be distinguished using this apparatus. Alternatively, lower agitation speeds can be used to achieve relatively homogeneous low shear rates.

In conclusion, minor geometrical modifications to the USP Apparatus 2 can have dramatic effects on the hydrodynamics and subsequently the measured dissolution rates. Any changes to the USP Apparatus 2 should be thoroughly characterized before implementation. The tools used in this study can be easily and straightforwardly applied to extend the knowledge base and select changes based on predictive models, rather than retrospective analysis of trial-and-error experiments.

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