Intrinsic Dissolution Performance Testing of the USP Dissolution Apparatus 2 (Rotating Paddle) Using Modified Salicylic Acid Calibrator Tablets: Proof of Principle

John Mauger[1], John Ballard[2], Robert Brockson[2], Sinjan De[3], Vivian Gray[4], and Dennis Robinson[3]

email correspondence to: jmauger@deans.pharm.utah.edu

Introduction

Knowledge of operating variables for a dissolution apparatus is important to the pharmaceutical scientist interested in product development, quality assurance, and research applications. The dissolution performance of USP Apparatus 1 and 2 is dependent on both convection and diffusion as coupled dissolution mechanisms. The sensitivity and variability of the data may be compromised when either the convection or diffusion mechanism dominates. When convection dominates, there may be a loss of sensitivity. For example, Hamlin et al., (1) demonstrated a loss of sensitivity in distinguishing real differences in dissolution rates due to increasing agitation intensity. When diffusion is the predominant mechanism, the dissolution results are affected by density gradients and may vary considerably (2, 3). USP Apparatus 1 and 2 depend on a balance between these two mechanisms in order to produce sensitive and reproducible data.

Experimental dissolution methods that employ configurations linked with convective-diffusion models, such as the rotating disk or the stationary disk, are useful to understand the relationship between the diffusion and convective mechanisms. The dissolution rates determined from either of these two experimental methods are often termed "intrinsic dissolution rates". Intrinsic dissolution rates have been defined as "the rate of dissolution of a pure pharmaceutical active ingredient when conditions such as surface area, temperature, agitation or stirring speed, pH, and ionic strength of the dissolution medium are kept constant" (4).

This research was motivated by previous studies (2, 3) that suggested the possibility of using modified salicylic acid calibrator tablets supplemented by visualization studies (5) as a method to evaluate the intrinsic dissolution performance of USP Apparatus 2. Intrinsic dissolution performance in this context is the intrinsic dissolution rate due to the inherent convection and diffusion mechanisms that govern dissolution for a given apparatus. The premise for the current study is that these dissolution rates provide a framework for evaluating the dissolution performance of USP Apparatus 2.

Therefore, the goals of this study were to:

1) Demonstrate the usefulness of a simple visual analysis technique.
2) Characterize the variability associated with the dissolution data for USP Apparatus 2.
3) Test the premise that USP Apparatus 2 operates within a convective-diffusion model that explains the relationship between dissolution rate and stirring speed as well as other hydrodynamic and fluid mechanical factors.
4) Demonstrate that the convective-diffusion model reflects an accurate picture of the physicochemical aspects of dissolution within the micro environmental region at the tablet surface.

While prednisone and salicylic acid calibrators have been used since 1978 in connection with apparatus suitability testing, these tests are aimed primarily at demonstrating the influence of perturbations such as vibration (6, 7). This study will focus on the use of modified USP Salicylic Acid Calibrator Tablets as a method to characterize the intrinsic dissolution performance characteristics of USP Apparatus 2 within the framework of a convective-diffusion model that explains the influence of stirring speed, the underlying fluid mechanical factors, and the diffusional and physicochemical parameters.

Intrinsic Dissolution Performance Testing

An intrinsic dissolution test should not only be based on a convective-diffusion model, but also on previous knowledge of the actual fluid flow regime relevant to the apparatus. Previous research reported by Bocagnegra et al. (8) demonstrated the use of laser Doppler anemometry in characterizing the three-dimensional fluid flow components in USP Apparatus 2. Of singular interest is the finding that close to the bottom of the vessel of this apparatus, the tangential component of flow dominates and approximates solid body rotation. This finding implies that the intrinsic dissolution properties of this apparatus may be predictable within the framework of a fluid mechanics-based dissolution model that incorporates and couples the convective and diffusion mechanisms.

[1] Corresponding author, University of Utah, College of Pharmacy, 30 South 2000 East, Rm. 201, Salt Lake City, UT 84112-5820, jmauger@deans.pharm.utah.edu
[2] DuPont Pharmaceuticals, Greenville, DE
[3] College of Pharmacy, 986000 Nebraska Medical Center, Omaha, NE, 68198
[4] V.A. Gray Consulting, Inc., 9 Yorkridge Trail, Hockessin, DE 19707

The fluid mechanical component of dissolution is represented by the dimensionless Reynolds number, which is the ratio of inertial to frictional forces (9) where:

$$1) \quad \textbf{Re} = U\, r/\nu$$

The representative fluid velocity is given by U (cm/sec), ν is the kinematic viscosity of the fluid at a given temperature (cm^2/sec) and r is the dimension of a physical body over which the fluid is flowing, say the radius of a tablet (cm). This relationship shows that the Reynolds number is directly proportional to the fluid velocity and inversely proportional to the kinematic viscosity.

The convective-diffusion component of dissolution is represented by the dimensionless Peclet number (9):

$$2) \quad \textbf{Pe} = U\, r/D$$

where U and r are previously defined and D is the diffusion coefficient (cm^2/sec) of the drug.

For a rotating disk in an unstirred fluid, or a stationary disk in a rotating fluid, the Reynolds and Peclet numbers are modified to include the radius of the disk (r, in cm) and the rotational rate of the disk (ω, in radians/sec):

$$3) \quad \textbf{Re} = r^2\omega/\nu \quad \text{and} \quad \textbf{Pe} = r^2\omega/D$$

For the rotating disk, the dimensionless Reynolds and Peclet numbers are related to the dissolution rate per unit surface area, J, by:

$$4) \quad J = 0.62\, (D/r)\, (\textbf{Re})^{1/2}\, (\textbf{Pe/Re})^{1/3}\, Cs$$

where Cs (g/cm^3) is the saturation solubility at a given temperature. The relationship given by equation 4 is predictive and contains information concerning the convective and diffusional components of the intrinsic dissolution properties. Furthermore, it is based on a fluid mechanics model for a rotating disk in an unstirred fluid (9, pp. 60-71).

Given the findings of Bocanegra et al. (6) the fluid flow at the bottom of the USP Apparatus 2 is approximated by a model for a rotating fluid over a stationary disk. This system has been studied in connection with engineering and pharmaceutical applications (10, 11, and 12). Colton and Smith (10) gave the following relationship for the dissolution rate per unit area when averaged over the surface of the disk,, where:

$$5) \quad \langle J \rangle = 0.77\, (D/r)\, (\textbf{Re})^{1/2}\, \gamma^{1/2}\, (\textbf{Pe/Re})^{1/3}\, Cs.$$

The stationary disk is similar to the rotating disk model since it is predictive and includes both the convective and diffusional components contributing to the dissolution rate. However, there are important differences related to the direction of fluid flow on the dissolution surface. With the rotating disk configuration, fluid flows outward from the center of the disk and the disk is uniformly accessible across the dissolving surface. With the stationary disk configuration, the dissolving surface is not uniformly accessible to dissolution as the fluid sweeps from the leading outer edge to the center of the tablet. According to Colton and Smith (10) approximately 80% of the mass transport occurs in the outer 20% of the tablet area.

With the stationary disk, a plume forms at the center of the tablet as the fluid and dissolved material exits from the tablet surface upward toward the center of the paddle blade. The three-dimensional fluid flow profiles associated with the stationary disk have been described by Schlicting (13).

Another differing characteristic between the rotating and stationary disks is the γ term, which is a dimensionless ratio of the representative fluid velocity at some axial distance below the paddle to the maximum paddle tip velocity. Below the paddle and just above the surface of the dissolution vessel, the fluid velocity is expected to be less than the paddle tip velocity and greater than zero, resulting in a ratio bounded between zero and one. In keeping with this expectation, the data from the study by Bocanegra et al. (8) indicates that for the USP Apparatus 2, this ratio is approximately 0.4 in the vicinity of the dissolving surface below the stirring source.

This experimentally determined value is dependent upon the radial distance from the center of the vessel and approaches zero under two conditions: 1) at the center of the vessel, in keeping with the solid body rotation model where V = ωr and 2) at the surface of the vessel due to frictional forces.

Equations 4 and 5 were tested in the present study as a basis for an intrinsic dissolution performance test in USP Apparatus 2. The test was undertaken using modified USP Salicylic Acid Calibrator Tablets that were coated on the rim and one side with a water impervious shellac, with the uncoated surface facing the paddle. These tablets present a constant surface area for dissolution during the experiment.

Experimental
Materials— Tablets for the visualization studies were prepared by blending a known weight of salicylic acid, Sigma Chemicals Lot #70K002451, with 3% by weight of phenolphthalein, Sigma Chemicals Lot #30K1353. Previous studies showed that this concentration of phenolphthalein was sufficient to give a clear visualization of the dissolution process at the surface of the tablet without flooding the bulk solution with color. Three hundred milligrams of this

Intrinsic Dissolution Performance Testing … *continued*

blend was compressed into a tablet using 0.5 metric tons of pressure for 30 seconds with a Carver press. These tablets were used for the visualization studies after inspection for chipping and surface imperfections. The diameter and thickness of these tablets approximated USP calibrator tablets.

USP Salicylic Acid Calibrator Tablets, Lot N, 300 mg, were coated on one side and around the rim with water impervious shellac that contained as the primary ingredient toslyamide epoxy resin. These tablets were used in the intrinsic dissolution study.

Visualization Studies – Visualization studies were performed using commercially available dissolution equipment, (VanKel), USP Apparatus 1 and 2. The visualization studies were performed under conditions of no agitation and at 25, 50, and 100 rpm in 900 ml of sodium hydroxide solution of known concentration at 37°C. Salicylic acid tablets containing phenolphthalein were placed in the vessels containing sodium hydroxide solution and the dissolution process was visualized by observing the color at the surface of the tablet as dissolution of the salicylic acid and phenolthalein blend occurred in the alkaline solution. Photographs were then taken between 1 and 10 minutes after placing the tablet in the dissolution medium.

Dissolution Studies - Dissolution studies were performed on commercially available dissolution equipment, (VanKel), USP Apparatus 2. Test conditions were consistent with USP <711> Apparatus System Suitability requirements. The intrinsic dissolution studies were performed using the USP Calibrator Tablet procedure, with 900 mL of 0.05 M phosphate buffer (pH 7.4) as the medium. The sampling times were 5, 10, 15, 20, 25, and 30 minutes at 50 and 100 rpm. All sampling was performed using the fiber optic automated system of CTechnology instruments. The solutions were read at 296 nm using the Cary 50 spectrophotometer. Care was taken to locate the tablet, active face up and coated surface down, at the center of the vessel. Independent studies were undertaken to confirm that salicylic acid did not leak through the epoxy resin and that the resin did not interfere with the assay results.

Results and Discussion

1. Visualization Studies

Visualization studies were undertaken as the first step in affirming the fluid flow patterns demonstrated previously using laser Doppler anemometry (8). The photograph from the first study is shown in Figure 1 to demonstrate the principle.

This experiment was undertaken with the active side of the salicylic acid tablet down in 0.05 N sodium hydroxide solution in USP Apparatus 1 using unstirred conditions. The more dense dissolved material is easily visualized as it
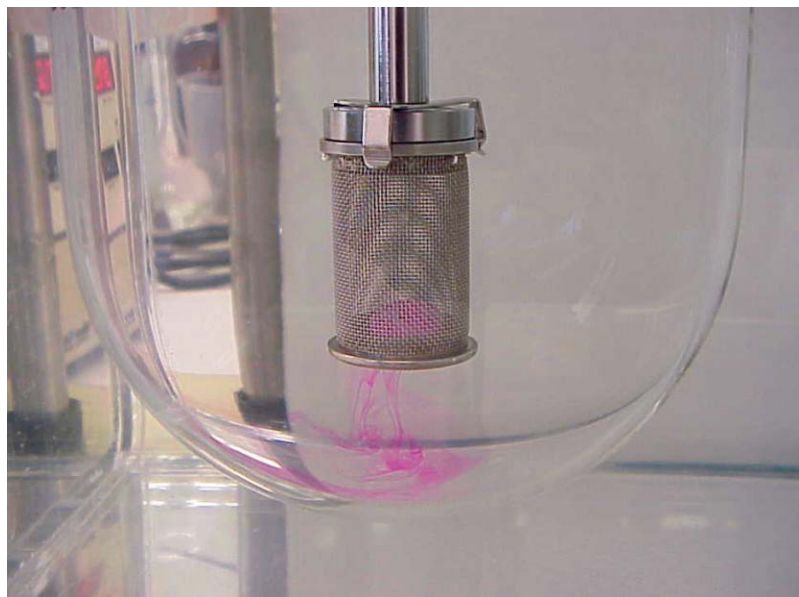

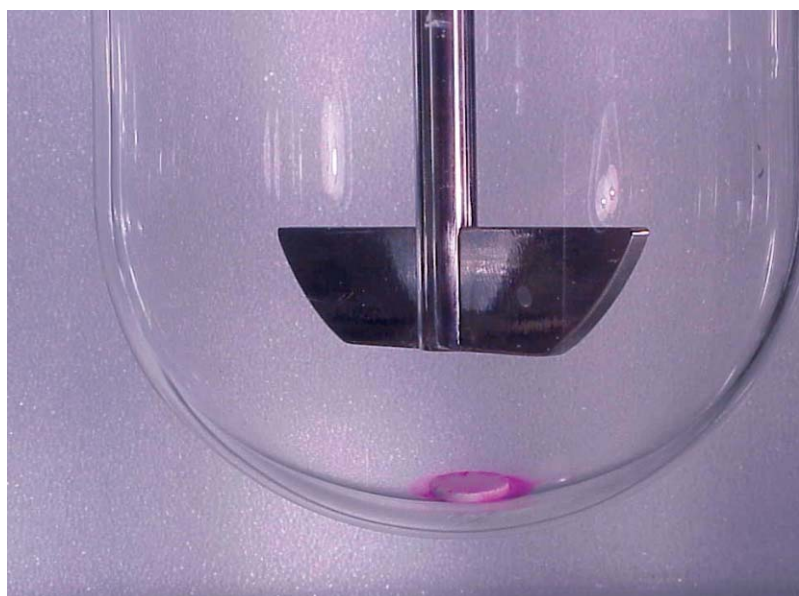Figure 1. Basket apparatus, no stirring

Figure 2. Paddle apparatus, no stirring

falls to the bottom of the vessel, with movement created by the density gradients.

The next photograph in Figure 2 shows the results from a visualization experiment where the active side of the tablet is facing up in 0.05 N sodium hydroxide solution in USP Apparatus 2 under unstirred conditions. This photograph shows that the dissolving material collects under and around the sides of the tablet due to the difference in density between dissolved material and the bulk medium.

Intrinsic Dissolution Performance Testing ... *continued*

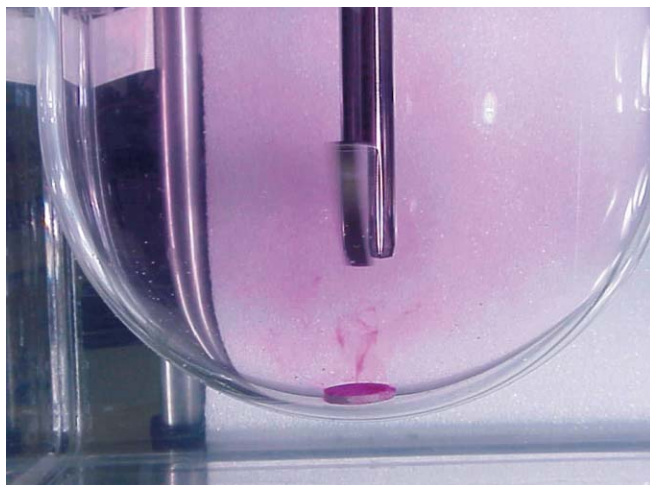*Figure 3. Paddle apparatus at 25 rpm*

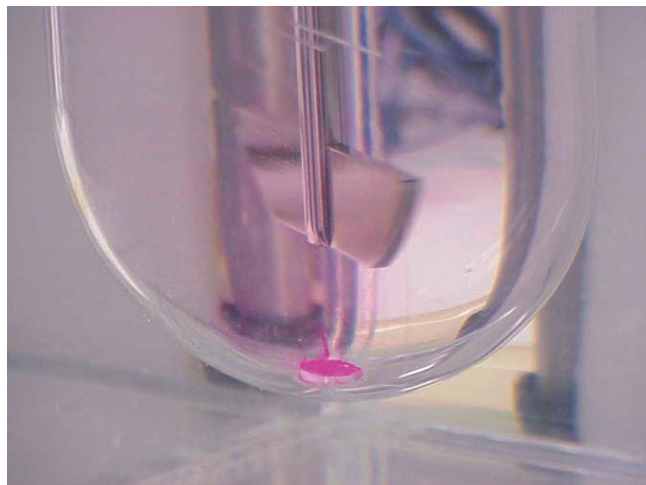*Figure 4. Paddle Apparatus at 50 rpm*

Figure 5. Paddle apparatus at 100 rpm

This visualization experiment underscores the importance of density gradients. While it is expected that the more dense dissolved material will be swept into the bulk solution by fluid flow when the paddle speed is either 50 or 100 RPM, this premise is open to question. In fact, other studies (2,3) designed to test this question have demonstrated that density gradients under the tablet affect the coefficient of variation at both 50 and 100 RPM using Apparatus 2. These findings imply that the outcomes from the USP <711> Apparatus Suitability test using salicylic acid calibrator tablets may be affected by density gradients' influence on the variability of the data.

The next photograph in Figure 3 was taken with the active side up in 0.025 N sodium hydroxide using USP Apparatus 2 at 25 RPM.

Since stirring by the paddle creates fluid flow approximating solid body rotation at the bottom of the vessel, the rotating fluid turns and sweeps inward across the tablet surface near the bottom of the vessel. As the rotating fluid encounters the outer edge of the tablet surface it slows due to friction and then travels radially inward toward the center of the tablet. Then the fluid carrying the dissolved material spirals upward toward the center of the paddle. This photograph clearly shows the plume exiting upward toward the center of the paddle. There is visual evidence of imperfect mixing of the more dense dissolved solution with the bulk solution at this stirring speed.

For comparative purposes, the same experiment was run at 50 and 100 RPM. The resulting photographs from these experiments are shown in Figures 4 and 5 (Figure 4 is at 50 RPM and Figure 5 is at 100 RPM).

At 50 RPM the plume is well formed, and mixing with the bulk solution seems to be uniform. Although the shear pattern at the tablet surface is not evident in this photo-
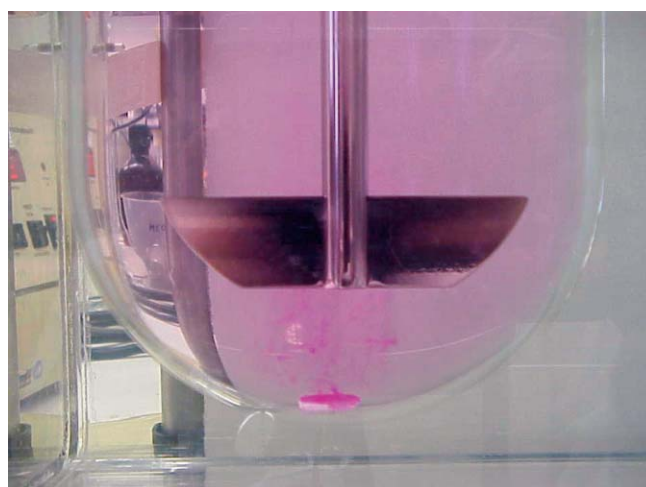
graph, the color at the tablet surface is indicative of the underlying physicochemical process related to dissolution. The physicochemical factors that play a role in the microenvironment at the tablet surface include the solubility of the dissolving material, the pKa of the dissolving material, the buffer capacity of the dissolution medium, and the pKa of the buffer relative to the pKa of the dissolving material.

While this idealized visualization experiment shows the dissolution from one surface facing the paddle, it is important to note that the dissolution process will be different for the rim and the bottom surfaces. This point was emphasized by Freebern (2) as well as Healy et al. (14) who demonstrated the effect of different surfaces on the dissolution rate of benzoic acid compacts.

At a higher stirring speed of 100 RPM the upward lift of the dissolved material into the bulk solution is evident and
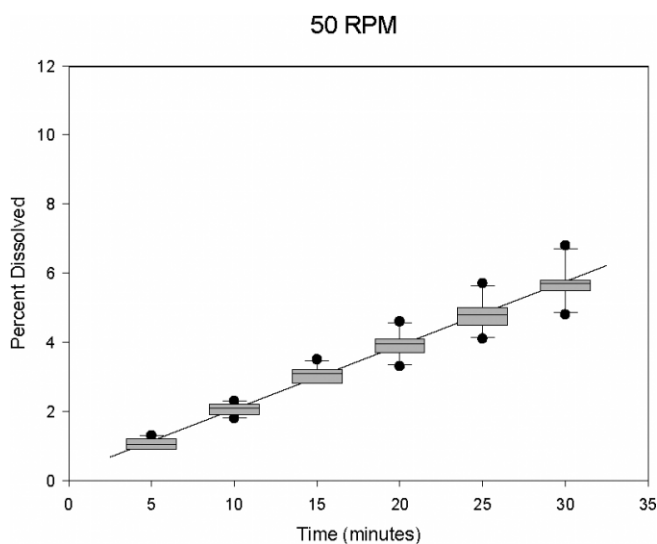
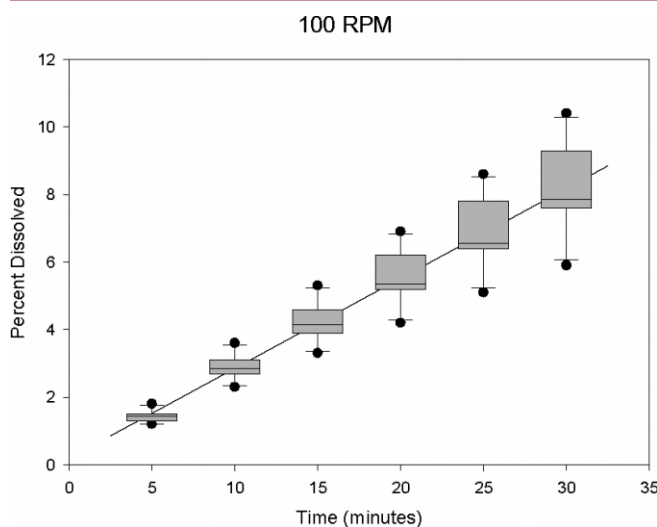Figure 6. Box Plot of paddle apparatus at 50 rpm

Figure 7. Box plot of paddle apparatus at 100 rpm

the plume becomes more diffuse. Other visualization experiments (5) have shown that at even higher agitation rates, the color at the dissolving surface becomes absent or unevenly dispersed across the tablet surface as the dissolved material is lifted from the surface at a faster rate. In this case the convection component of the dissolution mechanism outweighs the diffusional component, and it is anticipated that the sensitivity of the test would be compromised.

In summary, these visualization experiments are simple to perform and provide qualitative information about the underlying fluid flow patterns as well as evidence about the influence of stirring speed on density gradients and mixing of the dissolved material with the bulk solution.

They also reflect the underlying physicochemical process at the tablet surface that controls dissolution.

2. Characterizing the Variability Associated With the Intrinsic Dissolution Rates

The data from the dissolution experiments using USP Apparatus 2 and coated USP Salicylic Acid Tablets, with the active surface facing up toward the paddle, are shown in the following box-whisker plots (15) as Figures 6 and 7 where percent dissolved is plotted versus time under stirring conditions of 50 and 100 RPM. The median for six replicates at each time point is represented by the horizontal line.

The percent dissolved is a linear function of time for these data at both 50 and 100 RPM.

The variability of the data is indicated by the box length. At 50 RPM, the box lengths are approximately the same length over time while at 100 RPM the box lengths tend to increase with increasing time. This finding suggests that the variability may be time dependent at the higher stirring speed.

The plots also show the upper and lower whisker lengths, which represent the largest and smallest values in each data set, respectively. The whisker length appears to increase with time at both 50 and 100 RPM, suggesting that the range of data may be correlated to time. At 50 RPM the whiskers are reasonably symmetric with respect to the median at each time point while at 100 RPM the whiskers are increasingly asymmetric with increasing time. At 100 RPM, the median drifts away from the center of the box as time increases.

In summary, the box-whisker plot analysis has demonstrated that 1) at 100 RPM the values are increasingly asymmetric with increasing time, 2) the box length appears to increase with time, particularly at 100 RPM, and 3) the whisker length appears to increase with increasing time at both 50 and 100 RPM. Since apparatus suitability testing is usually linked with one pre-selected time point for the USP Salicylic Acid Calibrator Tablet, this finding suggests that the apparent time dependence of the variability may be a factor in selecting the time point associated with the acceptance range for suitability testing.

Given the small sample size of this study, additional studies are needed to determine the within-laboratory variability associated with the intrinsic dissolution rates. Within-lab variability will provide a basis on which to more rigorously evaluate the apparent time-dependent variability and will also allow a comparison of the level of difference in variability between 50 and 100 RPM.

3. Evaluation of the Intrinsic Dissolution Rates Within the Framework of a Convective Diffusion Model

All dissolution data were generated from the modified USP Salicylic Acid Calibrator Tablet, with one face and the

Intrinsic Dissolution Performance Testing … *continued*
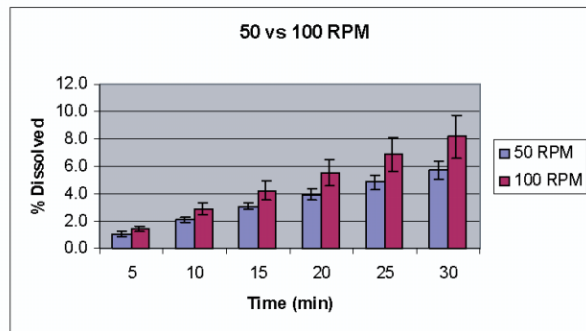
%Dissolved Versus Time Data

Figure 8. Aggregate data, percent dissolved

rim coated with water impervious shellac. The surface area was constant during the experiment and tablet surfaces did not show excess wear patterns at the completion of the run. The aggregate data for each set of six tablets are shown in Figure 8.

The percent dissolved data were transformed to amount dissolved and the data from six tablets at each time period were pooled and analyzed using least squares analysis, which provided an estimate of the slope and the standard error of the slope. These slopes represent the intrinsic dissolution rates, which were then normalized to amount dissolved per unit time per unit area. These results are given in Table I.

Other relevant physical chemical data for salicylic acid and related fluid mechanical data needed to test equations 4 and 5 are given in Table II.

The data in Table II were used with in conjunction with equations 4 and 5 to independently calculate the intrinsic dissolution rates at 50 and 100 RPM from the rotating disk and stationary disk models. Table III compares calculated intrinsic dissolution rates with the experimental rates.

The calculated values using the rotating disk model, equation 4, are considerably greater than the experimental values at both 50 and 100 RPM. In contrast there is good agreement between the experimental and calculated values for the stationary disk at both 50 and 100 RPM, with $\gamma = 0.40$. Therefore, we conclude that the experimentally determined intrinsic dissolution rates are in reasonable agreement with equation 5, the stationary disk model.

These findings imply that the experimental intrinsic dissolution rates are in agreement between 50 and 100 RPM when they are related to the stirring rate by:

$$6) \quad \langle J \rangle \propto (\mathbf{Re}\gamma)^{1/2}.$$

Therefore, within these commonly used stirring ranges, intrinsic dissolution results follow from one underlying

equation that relates the intrinsic dissolution rate to the stirring speed and the Reynolds number.

This analysis has shown that USP Apparatus 2 operates within a convective-diffusion model within specified stirring speed ranges. This finding leads to the idea that intrinsic dissolution testing may have potential as an apparatus suitability test to detect perturbations in the hydrodynamic conditions that affect the intrinsic dissolution rate.

4. Reflecting an Accurate Picture of the Microenvironment at the Dissolving Tablet Surface

The commonly used Nernst model and convective-diffusion models such as equations 4 and 5 both relate the dissolution rate per unit surface area to the saturation solubility of the pure drug (Cs) as follows:

$$7) \quad \langle J \rangle \propto Cs.$$

Other studies have shown that the solubility term is dependent upon the micro environmental pH, which, in turn, is coupled with the buffering capacity of a saturated solution of the drug (17). In fact, the micro environmental pH is dependent upon several factors including the pKa of the buffer, the pKa of the drug, the pH and buffer capacity of the buffer system, and the saturation solubility of the drug (17). Therefore, the bulk pH of the buffer is often an inaccurate approximation of the pH at the dissolving surface.

The importance of this point has been emphasized by Rohrs (18) in a discussion of dissolution methods for poorly soluble compounds. In the case of salicylic acid, the micro environmental pH near the dissolving surface was approximated by determining the pH of a saturated solution of salicylic acid in 0.05 M pH 7.4 buffer.

The experimentally determined value under these conditions was 3.2, which is in reasonable agreement with the previously determined value of 3.4 (16). The saturation solubility in pH 7.4 buffer is 0.073 M (16). This value, converted to g/cm^3, was then used in equation 5 to generate the calculated value for the stationary disk model. We conclude that the stationary disk model reflects an accurate picture of the micro environment at the tablet surface where rate controlling interactions occur between the buffer species and the dissolving salicylic acid. This finding has practical implications when selecting buffer species, buffer concentration, and buffer pH for the dissolution medium. More-

Table I – Intrinsic Dissolution Rates Determined under Compendial Conditions at pH 7.4 and at 50 and 100 RPM Paddle Speeds

Paddle Speed (RPM)	Intrinsic Dissolution Rate (g/sec)	Standard Error of the Intrinsic Dissolution Rate	Intrinsic Dissolution Rate Per Unit Surface Area (g/sec/cm²)
50	9.06E-06	±4.02E-07	1.25E-05
100	1.33E-05	±8.74E-07	1.84E-05

Table II - Relevant Physical Chemical Data for Salicylic Acid and Salicylic Acid Calibrator Tablets, Lot N, with Relevant Fluid Mechanical Data

Saturation Solubility of Salicylic Acid in Water at 37 degrees C[1]	1.87E-02M, 2.58 mg/mL
Saturation Solubility of Salicylic Acid in pH 7.4 Phosphate Buffer at 37 degrees C[1]	7.30E-02M, 10.07 mg/mL
Final pH of a Saturated Solution of Salicylic Acid in 0.05M Phosphate Buffer at 37 degrees C	3.2
Diffusion Coefficient for Salicylic Acid[2]	1.132E-05 cm^2/sec
Salicylic Acid Calibrator Tablet Weight	300 mg.
Surface Area of Salicylic Acid Calibrator Tablet	0.7238 cm^2
Kinematic Viscosity of Water at 37 degrees C[3]	0.00699 cm^2/sec
50 RPM; 100 RPM	5.235 radians per sec.; 10.47 radians per sec.
Reynolds Number	1.73E02 at 50 RPM; 3.45E02 at 100 RPM
Peclet Number	1.07E05 at 50 RPM; 2.13E05 at 100 RPM
ν/D	617
Dimensionless stirring speed factor, γ[4]	0.4

[1] Reference 16
[2] M. Gibaldi, S. Feldman, and N. Weiner, Chem. Pharm. Bull. 18, 715-723 (1970).
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[4] Reference 8.

Table III - Comparison of Experimental Dissolution Rates (g/sec/cm^2) with Rates Calculated Using the Rotating Disk and Stationary Disk Models

Stirring Speed (RPM)	Experimental Dissolution Rate per Unit Surface Area	Rotating Disk Dissolution Rate per Unit Surface Area (equation 4)	Stationary Disk Dissolution Rate per Unit Surface Area (equation 5)
50	1.25E-05, n=6	1.65E-05	1.29E-05, $\gamma = 0.40$
100	1.84E-05, n=6	2.33E-05	1.83E-05, $\gamma = 0.40$

over, these findings support the principle that the micro environmental pH rather than the bulk pH controls the dissolution rate process for the salicylic acid calibrator tablet.

Summary

Visualization experiments coupled with intrinsic dissolution rates studies have demonstrated that this methodology is useful in characterizing the performance of USP Apparatus 2 within the framework of a convective-diffusion model. The experimentally determined dissolution rates were found to be in good agreement with those calculated independently from the stationary disk model at both 50 and 100 RPM. This model accounts for convective effects and provides an accurate picture of the physicochemical interactions occurring in the microenvironment at the tablet surface. The model also demonstrates a quantitative relationship between the expected dissolution rate and stirring speed. Furthermore, through box-whisker plot analysis, the data demonstrate that the variability of the dis-

solution data tends to increase with increasing time during the dissolution process and that the relative magnitude of data dispersion is consistently higher at 100 RPM than at 50 RPM.

These findings provide a basis to further develop and refine apparatus suitability test requirements using chemical calibrators. One can envision an acceptance range that is based not only on the statistical analysis of an experimental data set, but also on an interval that is based on the difference between the experimental value and the calculated value from the stationary disk model.

In addition, it may be of value to evaluate calibrator data for relationships between variability and time when selecting the time point for suitability testing. Finally, it would be worthwhile in future studies to determine the cut-off limits where the level of agitation begins to confound the ability to detect hydrodynamic and fluid mechanical perturbations.

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