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ABSTRACT

DISSOLUTION OF DISINTEGRATING SOLID DOSAGE FORMS IN A MODIFIED DISSOLUTION TESTING APPARATUS 2

by
Shrutiben Rameshbhai Parekh

Dissolution tests are routinely carried out in the pharmaceutical industry to determine the dissolution rate of solid dosage forms. Dissolution testing serves as a surrogate for drug bioavailability through in vitro–in vivo correlation (IVIVR), and it additionally helps in guiding the development of new formulations and in assessing lot-to-lot consistency, thus ensuring product quality. The United States Pharmacopoeia (USP) Dissolution Testing Apparatus 2 is the device most commonly used for this purpose. Despite its widespread use, dissolution testing using this apparatus remains susceptible to significant error and test failures. There is documented evidence that this apparatus is sensitive to several geometric variables that can affect the release profile of oral dosage forms, including tablet location during the dissolution process.

In this work, the dissolution profiles of disintegrating calibrator tablets containing Prednisone were experimentally determined using two systems, i.e., a Standard USP Dissolution Testing Apparatus 2 (Standard System) and a Modified Standard USP Dissolution Testing Apparatus 2 (Modified System) in which the impeller was located 8 mm off the vessel centerline. The dissolving tablets were located at different off-center positions on the vessel bottom to test the effect of tablet location in these two systems.

Tablet dissolution in the Standard System was found to be strongly dependent on tablet location, as previously reported by this and other research groups. This apparatus appears to generate variable results that may not be associated with the tablets

undergoing testing but with the hydrodynamic characteristics of the apparatus itself and the location of the tablet on the vessel bottom. However, when the same experiments were conducted in the Modified System, the dissolution profiles for the same tablets were found to be nearly completely insensitive to tablet location.

The dissolution process in the Modified System was faster than that in the Standard System because of the improved mixing performance of the Modified System resulting from the non-symmetrical placement of the impeller. However, when the Modified System was operated at 35 rpm, the dissolution profiles for centrally located tablets were found to be very similar to those for the Standard System operating at 50 rpm. Unlike the Standard System however, the dissolution profiles obtained at 35 rpm in the Modified System were found to be insensitive to tablet location.

It can be concluded that the newly proposed Modified System for dissolution testing is a simple and yet robust and valid alternative to the current dissolution testing practice using the Standard USP Dissolution Testing Apparatus.

DISSOLUTION OF DISINTEGRATING SOLID DOSAGE FORMS IN A MODIFIED DISSOLUTION TESTING APPARATUS 2

by
Shrutiben Rameshbhai Parekh

A Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
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Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering

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APPROVAL PAGE

DISSOLUTION OF DISINTEGRATING SOLID DOSAGE FORMS IN A MODIFIED DISSOLUTION TESTING APPARATUS 2

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This thesis is dedicated to my God and my family

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ACKNOWLEDGMENT

This thesis arose in part out of months of research that has been done since I came to Dr. Armenante's group. By that time, I have worked with a great number of people whose contribution in assorted ways to the research and the making of the thesis deserved special mention. It is a pleasure to convey my gratitude to them all in my humble acknowledgment.

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CHAPTER 1

INTRODUCTION

Dissolution testing is widely used in pharmaceutical industry to determine the dissolution rate of solid dosage forms. Dissolution testing is one of the many tests that pharmaceutical companies must conduct on oral solid dosage forms, as required by the Food and Drug Administration (FDA) and specified in the United State Pharmacopoeia (USP). Dissolution testing serves as a surrogate for drug bioavailability through in vitro–in vivo correlation, and it additionally helps in guiding the development of new formulations and in assessing lot-to-lot consistency, thus ensuring product quality. Thus, dissolution testing is an essential requirement for the development and establishment of in vitro dissolution and in vivo performance (IVIVR), as well as for registration and quality control of different dosage forms.

The United States Pharmacopoeia (USP) Dissolution Apparatus 2 is the device most commonly used for this purpose. However, there is documented evidence that this apparatus is sensitive to several variables which affect the drug release profile of dosage forms. A number of studies have been published in literature to determine effects of tablet location, location of impeller, presence of baffles on drug release rate. In particular, previous work of the hydrodynamics of in vitro dissolution testing (Bai and Armenante, 2009) has shown that tablet location can have a significant impact on drug dissolution rate in the USP Dissolution Apparatus 2. Their results show that statistically significant differences exist in the dissolution profiles between centrally located tablets and tablets positioned off-center. This work was conducted in a Standard USP Dissolution Apparatus 2.

Despite recent findings, current dissolution testing practice remains susceptible to significant errors and test results. Therefore, there is a need for the development of a more robust test possibly using a modification of the current USP Dissolution Apparatus 2. Thus, this project is aimed at filling this gap by investigating how the current USP Dissolution Apparatus 2 could be improved to yield a more robust testing device.

To achieve this goal, a modified USP Dissolution Apparatus 2 was designed and assembled and the drug dissolution rates of disintegrating tablets (Prednisone 10mg) were obtained at different tablet locations at the bottom of the vessel. In this Modified (USP) Dissolution Testing Apparatus 2 (Modified System) the impeller is located in an off-center position which produces extensive changes in drug release profile due to change in the velocity profiles and shear rates. Compared to the Standard USP Dissolution Apparatus 2, the modified apparatus produces much more consistent dissolution profiles. Therefore, it is proposed here that this Modified System be used for dissolution testing because of its simplicity and robustness, which could potentially make it a valid alternative to the current dissolution testing practice using the Standard USP Dissolution Testing Apparatus 2.

CHAPTER 2

LITERATURE REVIEW

2.1 Background

Solid dosage forms, such as tablets, are a convenient way of administering drugs to patients. Upon ingestion, tablets disintegrate into smaller fragments in the body compartment where absorption by the body is initiated, typically in the stomach or the upper intestine. These fragments dissolve in the digestive juices and can become absorbed by an epithelial layer such as the lining of the upper intestine. This complex in vivo process is routinely simulated in in vitro dissolution tests mandated by the food and drug administration (FDA) and specified in United States pharmacopoeia (USP).

The USP (United States Pharmacopeia) Dissolution Apparatus 2 has been used in the pharmaceutical industry for decades, since this test was first was first was officially introduced almost 20 years ago (Cohen et al., 1990). Nevertheless, and despite its widespread use in the industry, dissolution testing remains susceptible to significant error and test failures. There have been numerous reports describing high variability of test results even when the calibrated tablets (i.e., tablets manufactured for the sole purpose of testing the proper operation of the dissolution test equipment) are used. The variability in dissolution rates is more pronounced in Apparatus 2 at the commonly used rotation speed of 50 rpm due to radial flow in the cylindrical USP vessel. Failures linked to dissolution testing resulted in 47 product recalls during the period 2000-2002, representing 16% of non-manufacturing recalls for oral solid dosage forms (FDC Reports, 2001, FDC Reports, 2002, FDC Reports, 2003). Irrespective of the underlying causes (such as incorrect use

of the equipment or deviation of dissolution profile from the standard caused by incorrect tablet formulation) failed dissolution tests can result in product recalls, costly investigations, potential production delays, which, in turn, can have a significantly negative financial impact. Therefore, the robustness and ruggedness of the test must be thoroughly evaluated during method development and validation.

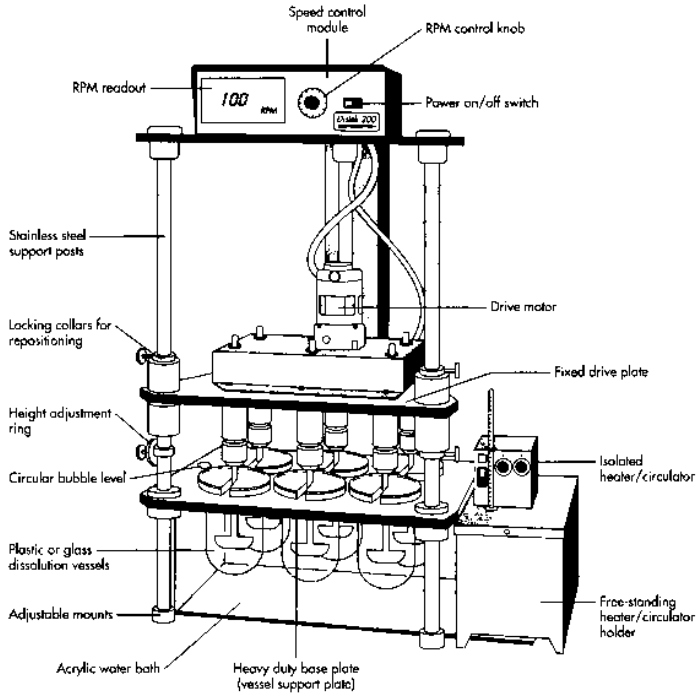


Figure 2.1 USP Dissolution Apparatus 2: typical commercial dissolution testing system containing several Apparatus 2 units.

Some of the same studies have indicated that the hydrodynamics of the USP Apparatus 2 appears to play a major role in the poor reproducibility of dissolution testing data and the inconsistency of dissolution results. This is hardly surprising considering that the USP Dissolution Apparatus 2 is a small, unbaffled vessel with a hemispherical bottom provided with a slowly rotating paddle, in which a tablet (or another dosage form) is dropped. This system can be expected to be associated with a complex hydrodynamics

resulting in fluid velocities whose directions and intensities are highly dependent on the location within the vessel (Bai et al., 2006). A pharmaceutical and analytical department of Novartis Pharmaceutical Corporation had also evaluated hydrodynamics of dissolution in USP Peak ^{TM} and flat bottom vessels using different solubility tablets and resulted in higher dissolution rates for Prednisone calibrator tablets indicating the presence of minimal flow or 'dead zone' at the bottom of the vessel underneath the paddle.

A literature review shows that numerous investigators have conducted hydrodynamic studies. Bocanegra et al. (1990) measured the flow field by Laser Doppler Anemometry, the first experimental measurement of this kind in dissolution vessels. More recently, Kukura et al. (2003) obtained experimental flow patterns using Particle Image Velocimetry (PIV) and Laser-Induced Fluorescence (LIF), and computed the velocity flow field using Computational Fluid Dynamics (CFD). Other researchers also made an effort to determine the flow field inside the USP Apparatus 2 vessel through CFD. Kukura et al. (2004) and Baxter et al. (2005) predicted the flow pattern and shear effects with CFD. Only a few researchers (Kukura et al. 2004, Baxter et al. 2005) have conducted dissolution test in which drug tablets were fixed at different locations along the bottom of the USP Dissolution Apparatus 2. More recently, Bai et al. (2007a, 2007b, 2011) and Bai and Armenante (2008, 2009) have quantified the flow field in the USP Apparatus 2 under typical operating conditions as well as its performance. Despite these advances however, there is very little information in the literature on possible modifications of the existing system in order to improve its performance.

2.2 OBJECTIVES

The overall objective of this research work was to determine how the performance of a standard USP Dissolution Testing Apparatus 2 can be improved by introducing simple modifications to its geometry. This goal was achieved here by assembling a slightly modified USP Dissolution Testing Apparatus 2 in which the impeller was placed off-center by 8 mm, and then by determining the dissolution profiles of disintegrating calibrator tablets of Prednisone in both the Standard USP Dissolution Testing Apparatus 2 and the Modified USP Dissolution Testing Apparatus 2.

More specifically this study had a total of four specific objectives designed to compare the performance of these two systems, as follows:

Objective 1: Determination of the dissolution profiles of Prednisone tablets obtained in the Standard Dissolution USP Testing Apparatus 2 (Standard System) at 50 rpm for three different tablet locations on the vessel bottom (0°, 10° and 20° from the vertical vessel centerline) in order to verify that these profiles are affected by tablet location, as previously reported (Bai and Armenante, 2009);

Objective 2: Determination of the dissolution profiles of Prednisone tablets obtained in the Modified Dissolution USP Testing Apparatus 2 (Modified System) at 50 rpm for nine different nine tablet locations on the vessel bottom (one at 0°, and four each at 10° and 20° from the vertical vessel centerline, because of the non-symmetry of the Modified System).

Objective 3: Determination of the impeller agitation speed in the Modified System resulting in a dissolution profile for a centrally located tablet as close as possible

to that also for a centrally located tablet but in the Standard System rotating at 50 rpm.

Objective 4: Determination of the dissolution profiles of Prednisone tablets obtained in the Modified Dissolution USP Testing Apparatus 2 (Modified System) rotating at the optimum impeller rotation speed for nine different nine tablet locations on the vessel bottom (one at 0°, and four each at 10° and 20° from the vertical vessel centerline, because of the non-symmetry of the Modified System).

Throughout this work, the results were interpreted by potting C/C^* (drug release) against time (min) and by calculating the FDA recommended similarity factor (f_1) and difference factor (f_2) described below.

Table 2.1 lists the cases (i.e., different experiments done on USP Dissolution Testing Apparatus 2) that were studied in this research work.

Table 2.1 Different Operating Conditions of USP 2 Vessel Studied in This Work

Experiments	Agitation Speed (rpm)	Fill Volume (mL)	Impeller location
Dissolution Testing in Standard System	50	500	Standard (i.e., centrally located and 25 mm off the vessel bottom)
Dissolution Testing in Modified System	50	500	Modified (i.e., 8 mm off centrally located and 25 mm off the vessel bottom)
Dissolution Testing in Modified System	30, 33, 34, 35, 36, 37, 40	500	Modified (i.e., 8 mm off centrally located and 25 mm off the vessel bottom)
Dissolution Testing in Modified System	35	500	Modified (i.e., 8 mm off centrally located and 25 mm off the vessel bottom)

CHAPTER 3

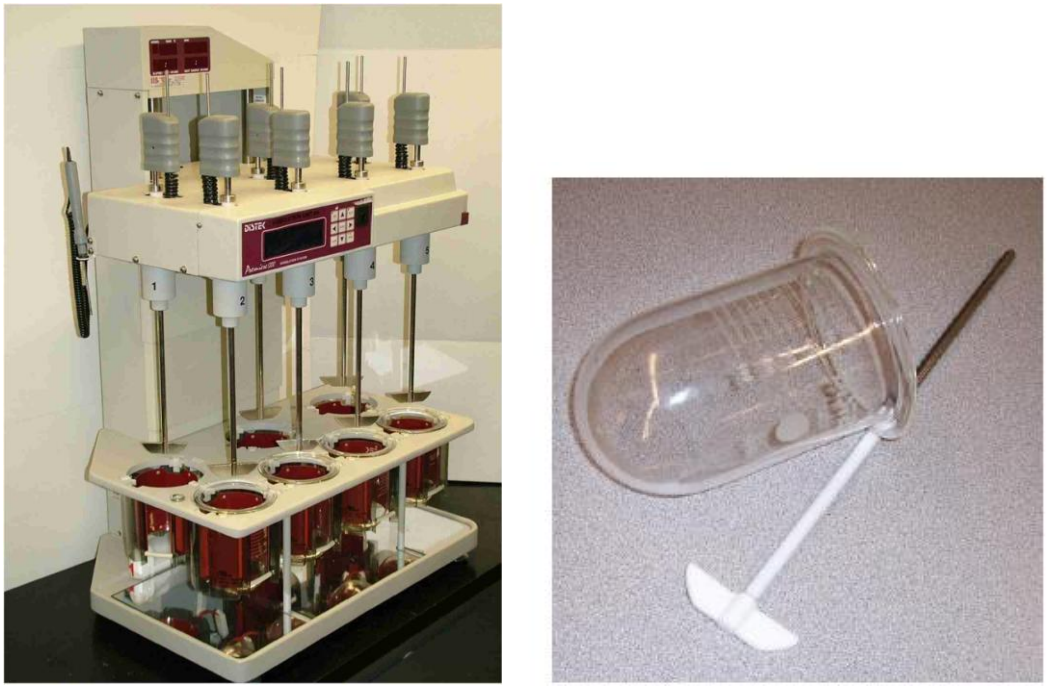
EXPERIMENTAL APPARATUS, MATERIALS, AND METHOD

3.1 Dissolution Vessel and Agitation System

Two USP Dissolution Testing Apparatus 2 systems were used in this work, i.e., a Standard System and a Modified System. The Standard System consisted of a Distek 5100 Bathless Dissolution Apparatus shown in Figure 3.1a. (Distek Inc., North Brunswick, NJ) capable of operating seven dissolution vessels at a time. An Apparatus 2 vessel consisting of an unbaffled, cylindrical, transparent, glass tank with hemispherical bottom, and internal diameter, T, of 100.16 mm and overall capacity of 1 L was used as the dissolution vessel (Figure 3.1b). The agitation system consisted of a standard USP 2 two-blade paddle impeller mounted on a shaft and connected to the motor in the Distek system. The exact geometry of each component of the impeller was obtained by measuring the actual dimensions with a caliper, which were found to be as follows: shaft diameter, 9.53 mm; length of the top edge of the blade, 74.10 mm; length of the bottom edge of the blade, 42.00 mm; height of the blade, 19.00 mm; and thickness of the blade, 5.00 mm. The impeller clearance off the vessel bottom was 25 mm, as mandated by the USP (2008). When the vessel was filled with 500 mL of dissolution media, the corresponding liquid height, H, as measured from the bottom of the vessel, was 78.6 mm. Figure 3.2 shows the Standard USP Dissolution Testing Apparatus 2.

The Modified System was identical to the Standard System except for the location of the impeller, which was placed 8 mm off center with respect to the vessel centerline

(Figure 3.3). This was accomplished by removing, for any given vessel, one of the three retaining spring inserts mounted on the metal plate of the Distek dissolution equipment that are used to keep a vessel centered in each cavity in the plate. This resulted in a sideway shift of the vessel that produced a misalignment of the vessel centerline with respect to the impeller centerline. By inserting a proper spacer, the distance between these centerlines was made to be exactly 8 mm, thus resulting in an off-centered impeller with respect to the vessel. Also for this configuration, the impeller clearance off the vessel bottom was 25 mm, i.e., the same as in the Standard System. Figure 3.3 shows the Modified USP Dissolution Testing Apparatus 2.



(a) (b)

Figure 3.1 (a) Distek 5100 Bathless Dissolution Apparatus (b) USP Dissolution Testing Apparatus 2: Paddle Impeller and Glass Vessel.

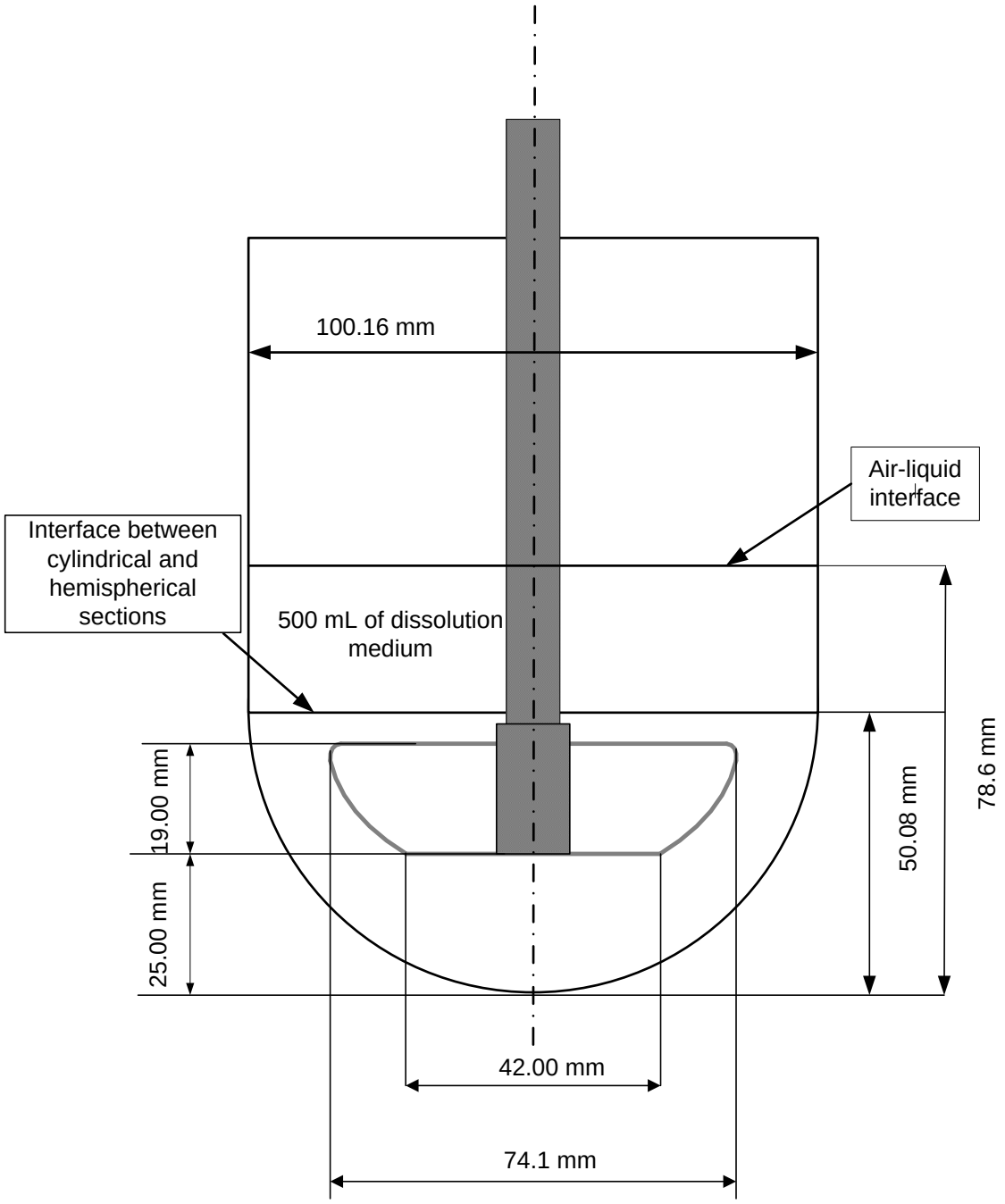


Figure 3.2 Standard USP Dissolution Testing Apparatus 2.

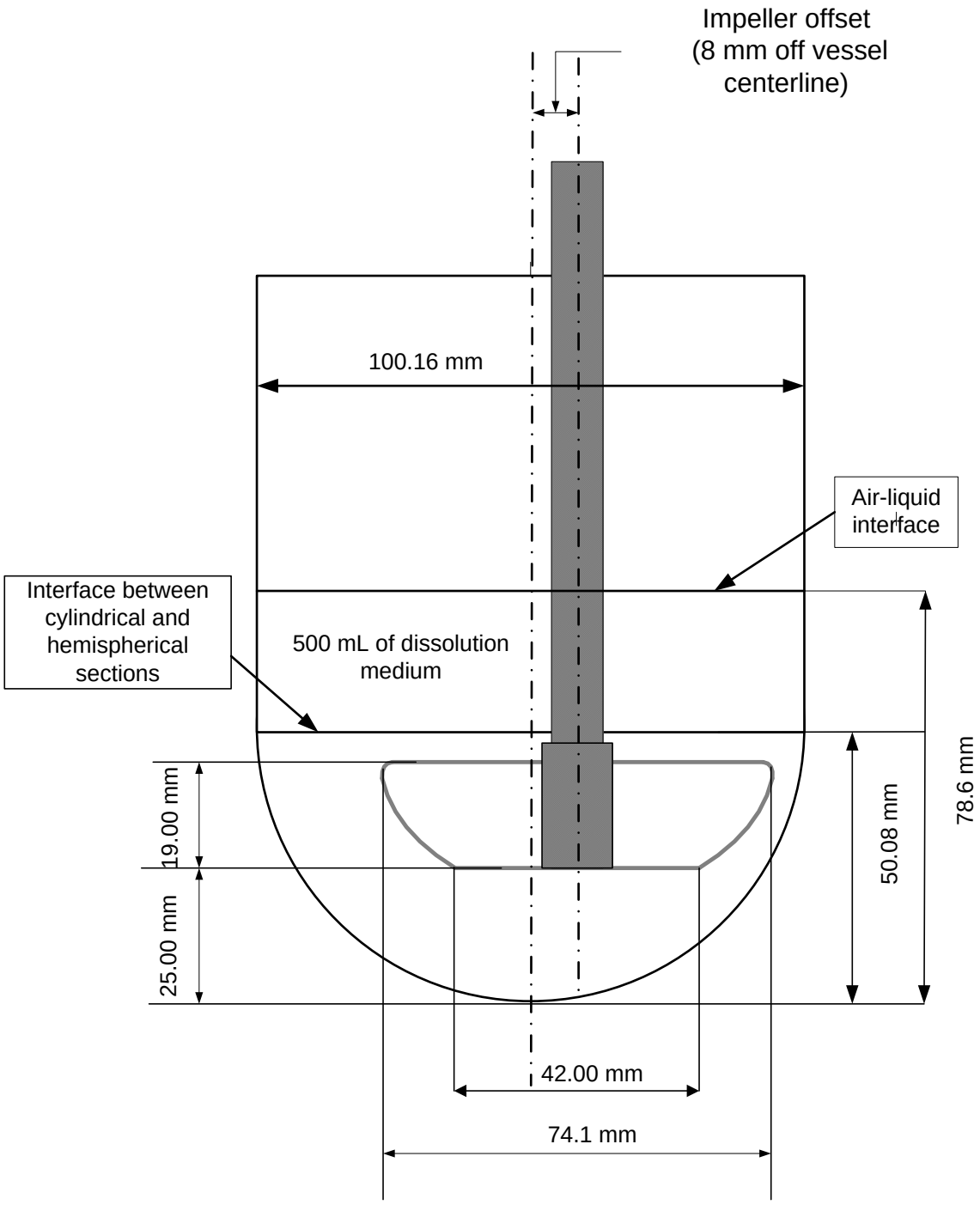


Figure 3.3 Modified USP Dissolution Testing Apparatus 2.

3.2 Experimental Materials

Dissolution testing experiments were conducted using disintegrating solid oral dosage forms, i.e., Prednisone tablets (NCDA #2), which were kindly donated by Dr. Zongming Gao, Food and Drug Administration (FDA), Division of Pharmaceutical Analysis, Center for Drug Evaluation and Research, St. Louis, MO. Each Prednisone tablet contained 10 mg of Prednisone. A commercial acrylic glue was used to fix the tablet at a particular location on the bottom of the dissolution vessel.

The dissolution medium consisted of de-aerated distilled water. The medium was de-aerated according to the degassing method developed by Moore (Moore, 1996) following the USP General Test Chapter on DISSOLUTION <711> (Figure 3.4). Accordingly, the medium was placed in carboy tank, which was then connected to a vacuum pump. Vacuum was applied for 30 minutes while all other valves in the system were closed. This stock solution was used as needed (typically in 500 mL aliquots per experiment).

A disposable PVDF 0.45 μm filter was used to remove possible solid particles that could have entered the sample prior to sample analysis as described below.

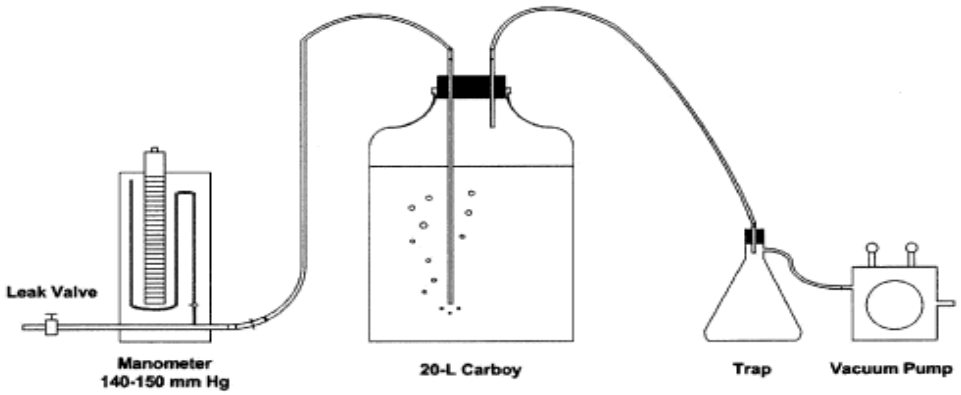


Figure 3.4 Equipment used to de-aerated the dissolution medium.

3.3 Experimental Method

The experimental procedure used in this work was slightly different from that typically used in dissolution testing (USP, 2008) since the tablet was not dropped in the stirred dissolution medium but was glued in place prior to the addition of the dissolution medium and the beginning of the experiment.

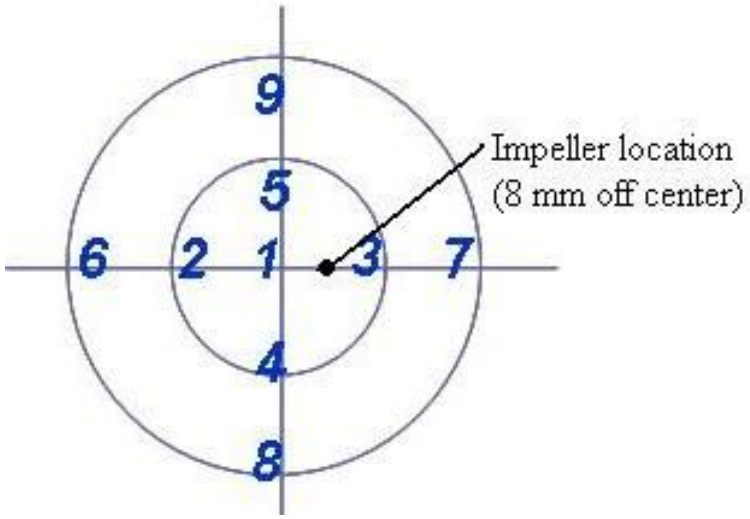
Before each experiment, all key geometrical measurements were checked (impeller clearance, impeller position, etc.). When needed, the dissolution apparatus was modified by shifting the impeller 8 mm off center. In order to test the effect of tablet position during dissolution testing, a tablet was attached at a predefined spot on the vessel bottom with a very small bead of commercial glue. Nine positions on the vessel bottom were selected in the non-symmetrical Modified System, as shown in Figure 3.5 (a). Position 1 in this figure represents the center of the vessel bottom. Positions 2-5 were all 10° off-center from the vessel vertical centerline (Figure 3.5(b)). This angle originated from the center of the sphere comprising the hemispherical vessel bottom, and was measured starting from the vertical centerline to the point of interest, (e.g., the angle

would be zero for the central point below the impeller). Positions 2-5 were all on the same inner circle, and were spaced 90° apart from each other. Positions 6-9 were 20° off-center from the vessel vertical centerline (Figure 3.5(b)). The vertical centerline through the impeller intersected the vessel bottom between Position 1 and Position 3, some bottom 8 mm away from the vessel bottom.

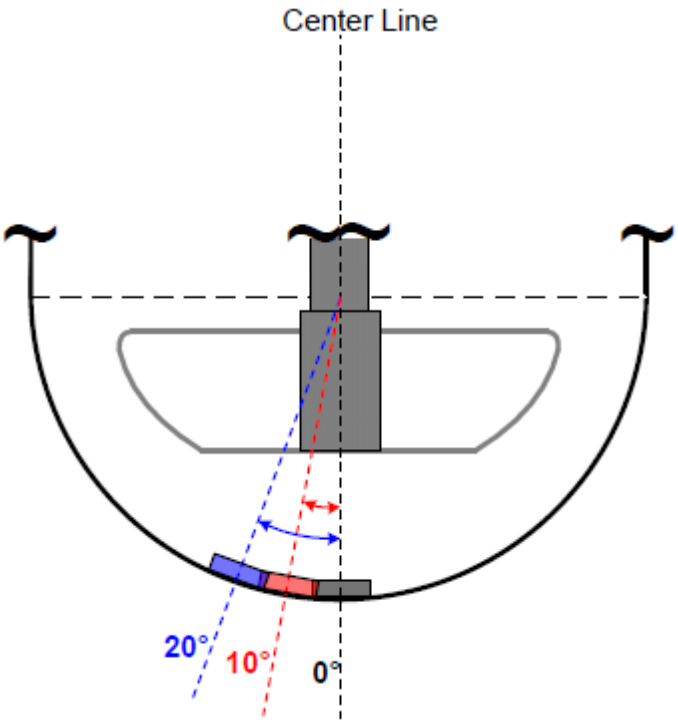
As for the Standard System, only three tablet positions were studied, i.e., Positions 1, 2 and 6, since the vessel centerline and the impeller centerline coincided, implying that the system was symmetrical and that Positions 3-5 were identical to Position 2, and Positions 7-9 were identical to Position 6. Additional details of the operating conditions are presented in Table 3.1.

Table 3.1 Operating Conditions for Dissolution Experiments with Prednisone

Prednisone Tablet	Operating Conditions
Dose	10 mg
Medium	500 ml de-aerated, Distilled water
Temperature	37^{o}C
Agitation Speed	50 rpm
Filter	PVDF 0.45um
UV Wavelength (UV Spectroscopy)	242nm
Standard Tablets	Calibrated Tablets
Time	5-min interval; 45 min total



(a)



(b)

Figure 3.5 (a) Top View of the Bottom of the Dissolution Vessel with Nine different Tablet Positions in Modified System **(b)** The Front View of the Dissolution Vessel with Three different Tablet Positions (0°, 10°, 20°) in Standard System.

Once the tablet and the vessel were setup properly, 500 mL of the de-aerated dissolution medium, previously preheated at 37.5 ^{o}C, was gently poured into the vessel in order to minimize the introduction of gas and prevent the rapid initial dissolution of the tablet. Because of the thermal inertia of the vessel, the resulting temperature of the liquid was 37 ^{o}C. This temperature was maintained throughout the dissolution experiment by the system's temperature controller. The agitation was started immediately after the addition of dissolution medium. The agitation speed was always 50 rpm. The first sample was taken immediately after starting agitation. This data was defined as zero-time point. The time interval between samples was 5 minutes. Each experiment lasted 45 minutes and a total of 10 samples were taken for each experiment. Experiments were performed in six replicates for each tablet location in the Modified System and in triplicates in the Standard System.

Sampling consisted of removing a 10-mL medium aliquot with a 10-mL syringe connected to a cannula (2 mm ID). The volume of medium removed by sampling was not replaced, in accordance to the USP procedure (2008). The sampling point was horizontally located midway between the impeller shaft and the vessel wall, and midway between the top edge of the impeller and the surface of the dissolution medium, i.e., within the sampling zone prescribed by the USP. After sample withdrawal, about 2-mL of the sample were discarded, the cannula was removed, and a PVDF 0.45 μm filter was mounted on the syringe. The remaining sample volume (about 8-mL) was transferred to a vial until analyzed.

Analysis of samples was carried out using and 1-cm quartz cells placed in a UV-visible spectrophotometer (Varian CARY 50 Bio) measuring absorbance at a specified

wavelength, i.e., 242 nm for Prednisone (the approximate wavelength of maximum absorbance). Before putting the quartz cell into the UV spectrometer, the cell was rinsed three times with the same solution sample. Knowing the calibration curve described below, this absorption reading was used to obtain the concentration of dissolved Prednisone in the sample.

A calibration curve for Prednisone was obtained. Reference standard solutions of the drug were prepared in the dissolution medium and diluted to obtain solutions of different known concentrations. The absorbance of these solutions was obtained in order to generate an absorbance-vs.-concentration standard curve. These results are presented in Table 3.2 and Figure 3.6. These results show that the calibration curve was linear (R^2=0.9974) in the concentration range of interest here.

Table 3.2 Calibration data for Prednisone

Absorbance 1	Absorbance 2	Absorbance 3	Average Absorbance (At 242 nm)	Concentration (mg/mL)
0.156	0.155	0.155	0.155333333	0.0033
0.241	0.242	0.241	0.241333333	0.005
0.469	0.468	0.467	0.468	0.01
0.564	0.565	0.563	0.564	0.0125
0.73	0.729	0.728	0.729	0.0166
1.012	1.011	1.009	1.010666667	0.025
2.185	2.182	2.181	2.182666667	0.05

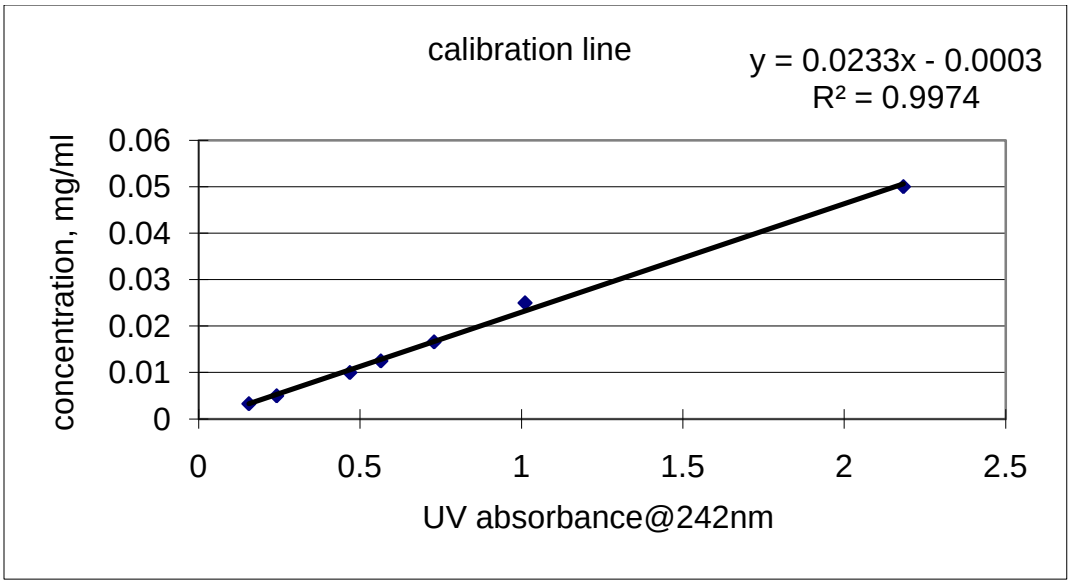


Figure 3.6 Calibration Curve for Prednisone.

3.4 Data Processing

The dissolution profiles obtained with tablets at off-center locations in the Modified System were compared to those obtained with the centrally located tablets in the same Modified System in order to determine whether these dissolution curves were statistically similar or different. Similarly, dissolution profiles obtained with tablets at off-center locations in the Standard System were compared to those obtained with the centrally located tablets in the same Standard System.

The similarity of two dissolution profiles was determined using the FDA-recommended approach consisting of using a model-independent method based on the similarity factor (f_1) and difference factor (f_2) proposed by Moore and Flanner (Moore and Flanner, 1996; Baxter et al. 2005):

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \qquad (3.1)$$

$$f_2 = 50\log_{10}\{[1+(\frac{1}{n})\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\} \quad (3.2)$$

where R_t is the reference assay at time t, T_t is the test assay at the same time, and n is the number of points. The f_1 factor measures the percent error between two curves for all points. The percent error is zero when the test and drug reference profiles are identical, but increases proportionally with the dissimilarity between the two dissolution profiles. The higher the similarity factor f_1 (which can be in the range 0 to 100), the higher the average difference between reference and test curves is. The f_2 factor is a logarithmic transformation of the sum-squared error of differences between the test and the reference products over all time points (which can be in the range -α to 100). If this difference is higher than 100, normalization of the data is required. The higher the difference factor f_2, the lower the average difference between reference and test curves (Costa and Lobo, 2001). Public standards have been set by Food and Drug Administration (FDA) for f_1 and f_2. Accordingly, statistical similarity between the two curves being compared requires that both $0<f_1<15$ and $50<f_2<100$ (FDA, 1997; Baxter et al. 2005).

CHAPTER 4

RESULTS

As discussed above, this study had a total of four objectives to compare the performance of the Standard USP Dissolution Testing Apparatus 2 and the Modified USP Dissolution Testing Apparatus 2. The dissolution profile of Prednisone at three different tablet locations (0°, 10° and 20°) in the Standard USP Dissolution Testing Apparatus 2 (Standard System) were obtained first as per USP method. Then the drug release profile of Prednisone at nine different tablet location positions was obtained for the Modified System as per the method described in the previous chapter. In the third series of experiments the optimum impeller agitation speed in the Modified system was obtained by changing the impeller rotation speed. Finally, in the fourth series of experiments the robustness of the Modified System at an optimum agitation speed was determined. The results were interpreted by potting C/C* (drug release) against time (min) and by calculating similarity factor (f_1) and difference factor (f_2).

4.1 Results for the Standard USP Dissolution Testing Apparatus 2

In this section of the study, the dissolution profiles for Prednisone was obtained at three different tablet location (0°, 10°, 20°) at the bottom of the dissolution vessel using the Standard USP Dissolution System and an agitation speed of 50 rpm. The results are reported here in terms of *C/C**, i.e., the ratio of the Prednisone concentration in the dissolving medium, *C*, at a given time, *t*, relative to the final concentration, *C**, obtained when the entire 10 mg tablet is completely dissolved. Figure 4.1 presents these results.

One can easily see that there is a significant difference between all three dissolution profiles at three different tablet positions. The corresponding f_1 and f_2 values quantifying the similarity/difference of the dissolution profiles with respect to that for the centrally located tablet are presented in the Table 4.1. Both f_1 and f_2 are out of the required range to insure statistical similarity, which implies that tablets at the 10° and 20° locations would fail the dissolution test. These results confirm that the dissolution profiles of the chosen disintegrating solid dosage form (Prednisone) depend strongly on the tablet location in the dissolution vessel for the Standard System. These results are in agreement with previously reported work from this and other research groups. The results obtained in this study are shown in detail in Tables B.1, B.2 and B.3 in Appendix B.

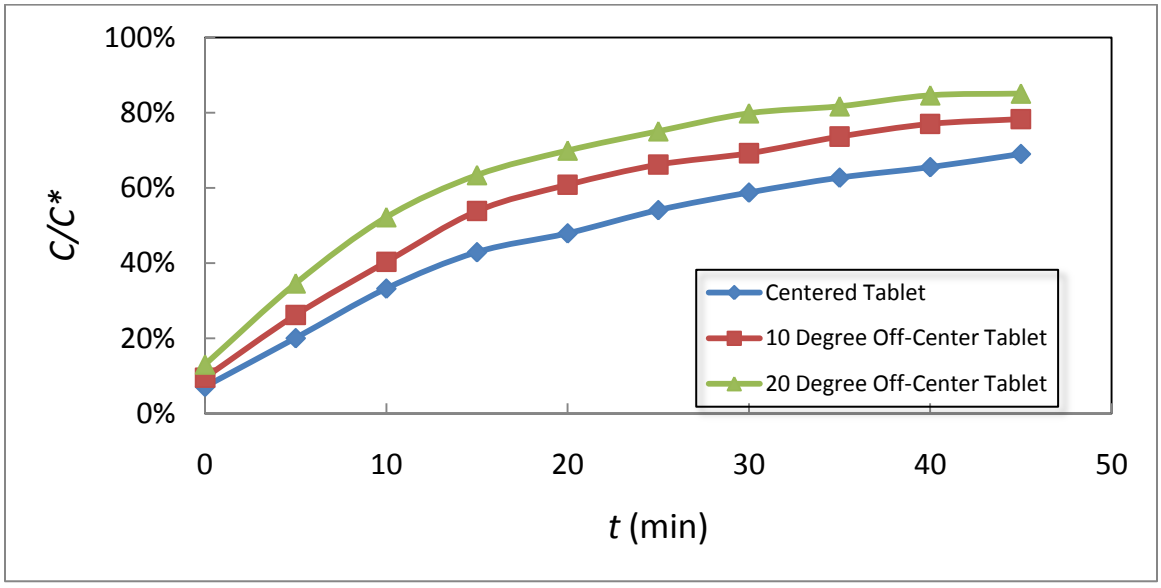


Figure 4.1 Dissolution profiles for Prednisone for three different tablet positions in the Standard System.

Table 4.1 f_1 and f_2 values for Dissolution profiles in the Standard System at 50 rpm (grey areas indicate out-of-range values)

Tablet Location	f_1 (Similarity Factor)	f_2 (Difference factor)
0°		
10°	20.168	50.193
20°	37.951	36.853

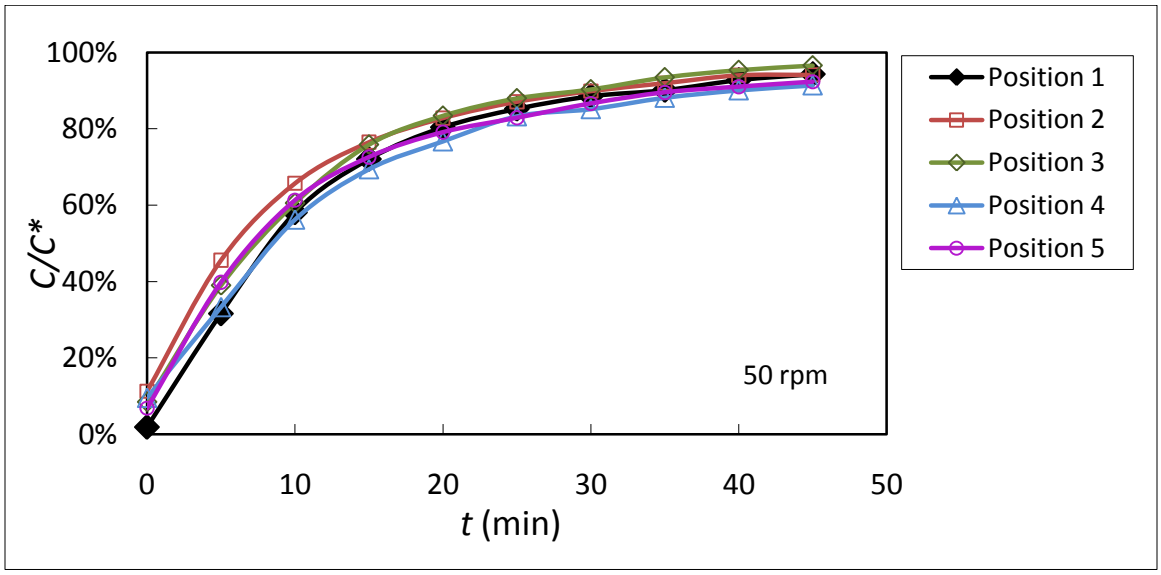
4.2 Results for the Modified USP Dissolution Testing Apparatus 2

In this series of experiments, drug release profiles for Prednisone were obtained by placing the tablets at nine different locations in the Modified USP Dissolution Testing Apparatus 2. The dissolution results for the centrally located tablet and for the tablets 10° off center i.e., at the four locations on the inner circle, are shown in Figure 4.2a. Figure 4.2b shows the corresponding results for the tablets on the outer circle, if for the four tablet locations 20° off center. Figure 4.3 presents the combined results. These figures show the average non-dimensional concentrations (C/C^*) at each time from the six replicate experiments at each location. The standard deviation was typically found to be lower than 1% of the average value of the 6 replicates at any given time, and it was not reported in these figures since it was too small to be adequately displayed in the graphs. This small number indicates that the experiments were highly reproducible. The actual dissolution data (including the standard deviations) are provided in Appendix B (Tables B.4-B.12). In addition, Figures A.1 and A.2 in Appendix A show the specific drug release profiles for Prednisone at the four inner positions (Position 2, 3, 4 and 5), i.e., those on the inner circle (10° away from the center) and the four outer positions

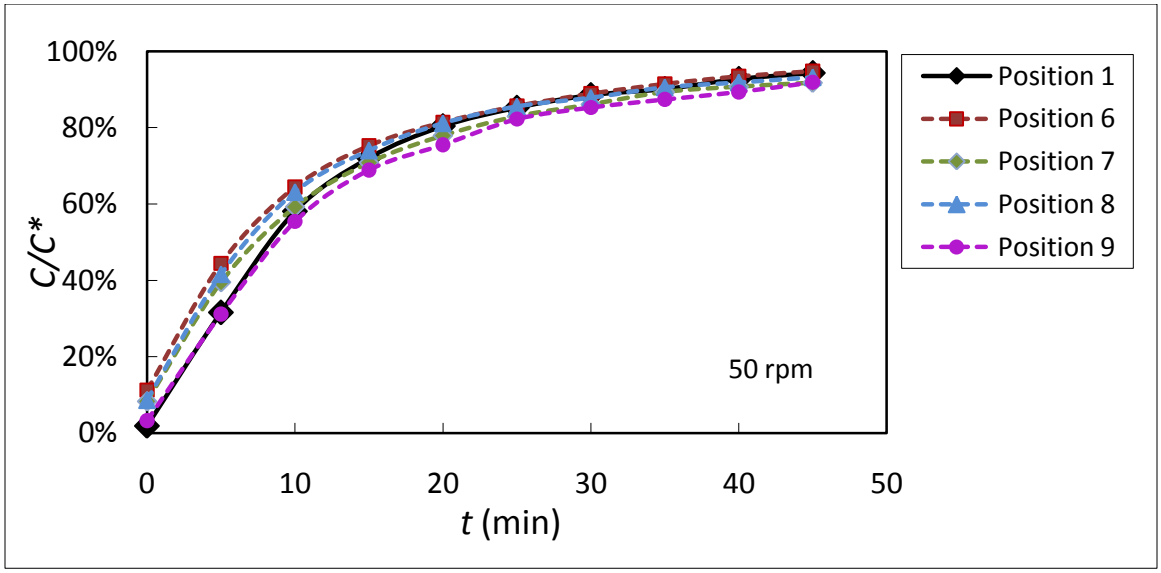
(Positions 6, 7, 8 and 9), i.e., those on the outer circle (20° away from the center), as described in Figure 3.5.

The curves in Figure 4.3 shows that the dissolution profiles for all nine positions are visually overlapping on each other. This implies that there is a significant similarity between all nine dissolutions profiles at nine different positions. To confirm this visual observation, the similarity factors (f_1) and difference factors (f_2) were calculated for each of the experimental dissolution profiles for each off-center tablet with respect to the dissolution profile for the centrally located tablet. The results are reported in Table 4.2. In all cases, the f_1 factor was between 0 to15 and the f_2 factor was between 50 and 100, indicating that the dissolution profiles for the off-center tablets were statistically similar to that for the centrally located tablet, according to the FDA criteria.

From the data in this table, one can see that the tablets on the inner circle produced, on average, dissolution profiles that were slightly less similar to that for the central table than those on the outer circle. In addition, tablet locations that were farther away from the impeller centerline (Positions 2 and 6), resulted in curves with slightly higher values for f_1 and smaller values for f_2, implying slightly reduced similarity between the profiles at these locations and that for the centrally located tablet.



(a)



(b)

Figure 4.2 Dissolution profiles of Prednisone at different positions in the Modified System at 50 rpm: (a) 10° off-center tablets; (b) 20° off-center tablet.

Table 4.2 f_1 and f_2 values of the dissolution curves for tablets at different off-center locations compared to that for the tablet in the central position (Position 1) for the Modified System at 50 rpm

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Position 1 (centered tablet)		
Position 2 (10° off-center tablet)	5.074	63.050
Position 3 (10° off-center tablet)	4.174	72.520
Position 4 (10° off-center tablet)	3.299	78.517
Position 5 (10° off-center tablet)	3.011	74.353
Position 6 (20° off-center tablet)	3.758	66.326
Position 7 (20° off-center tablet)	3.279	74.640
Position 8 (20° off-center tablet)	3.070	71.002
Position 9 (20° off-center tablet)	3.328	77.225

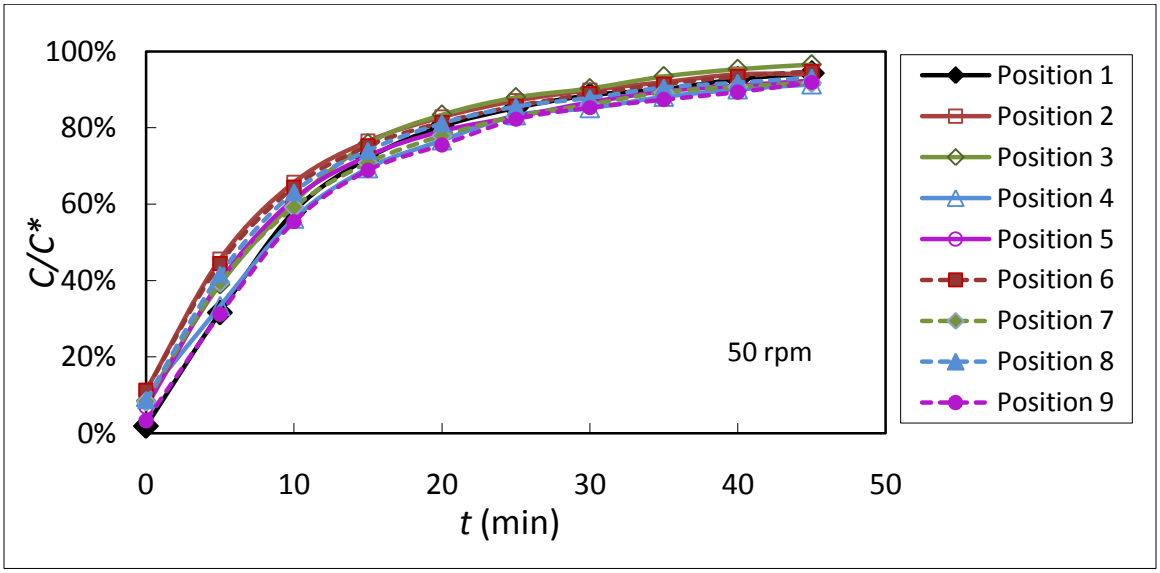


Figure 4.3 Dissolution profiles of Prednisone at nine different positions in the Modified System at 50 rpm.

4.3 Determination of the Optimum Impeller Rotation Speed in the Modified System Resulting in a Dissolution Profile Similar to That in the Standard System for a Centrally Placed Tablet

In this portion of the work, the dissolution profile for a centrally located tablet in the Standard System operating at 50 rpm was compared with the dissolution profiles in the Modified System obtained at different agitation speeds in order to determine for what speed in the latter system the two profiles in the Standard and Modified Systems were similar.

Initial experiments were conducted in both systems at the same agitation speed, i.e., 50 rpm. The results, reported in Figure 4.4, clearly show that dissolution in the Modified System was appreciably faster than in the Standard System. This is to be expected, since the non-symmetrical, off-center location of the impeller produces a "baffling effect" in the vessel similar (but not identical) to that observed in a stirred tank provided with a vertical baffle. Baffles are routinely inserted in mixing vessels to prevent swirling and vortex formation, reduce the tangential component of the fluid velocity while increasing the vertical component, thus improving fluid mixing. Such improved mixing can be observed in Figure 4.4 for the Modified System.

However, the objective of dissolution testing is not to conduct efficient mixing operations, but to simulate dissolution in the gastrointestinal tract. Therefore, an additional objective of this work was to determine for which agitation speed the Modified System behaved similarly to the Standard System, at least for the case of a centrally located tablet. Therefore, additional dissolution experiments were conducted at different agitation speeds in the Modified System in order to mimic the behavior of the Standard System. Figure 4.5 shows the results for experiment that were conducted in the Modified

System at different speeds (i.e., 30 rpm, 33 rpm, 34 rpm, 35 rpm, 36 rpm, 37 rpm and 40 rpm), until the appropriate speed was determined. Table 4.3 gives the f_1 and f_2 values obtained when the profiles in the Modified System were compared with that for the Standard System at 50 rpm. From this table, it can be concluded that the Modified System produces results similar to the Standard System when operated at an agitation speed between 34 and 35 rpm. It was decided to choose 35 rpm as the Modified System's "equivalent agitation speed" for the Standard System operating at 50 rpm. At this speed the Modified System produces dissolution profiles that are statistically similar to those in the Standard System (f_1=2.578; f_2=88.120). Additional details for these experiments are shown in Tables B.13-B.19 in Appendix B.

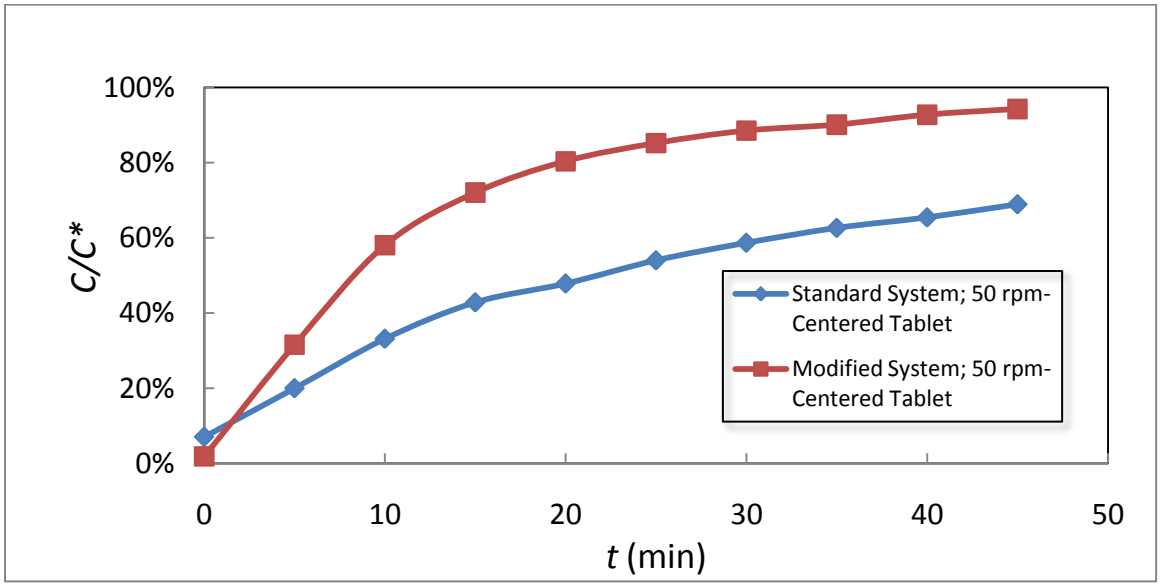


Figure 4.4 Comparison of dissolution profiles for a centrally located tablet in the Modified and Standard Systems at 50 rpm.

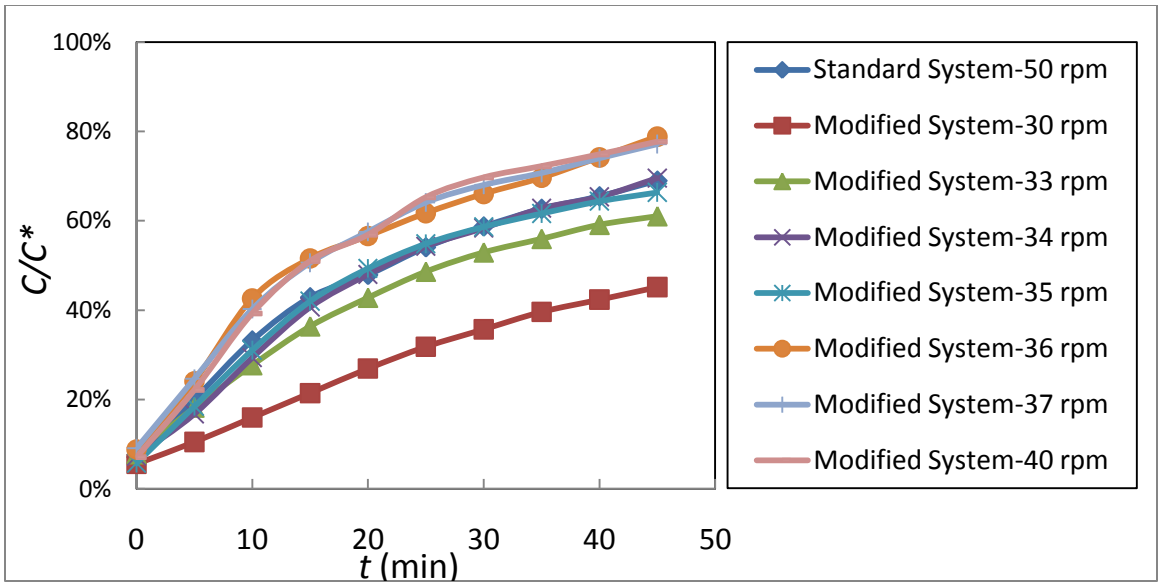


Figure 4.5 Dissolution profiles for a centrally located tablet in the Standard System at 50 rpm and the Modified System at different agitation speeds.

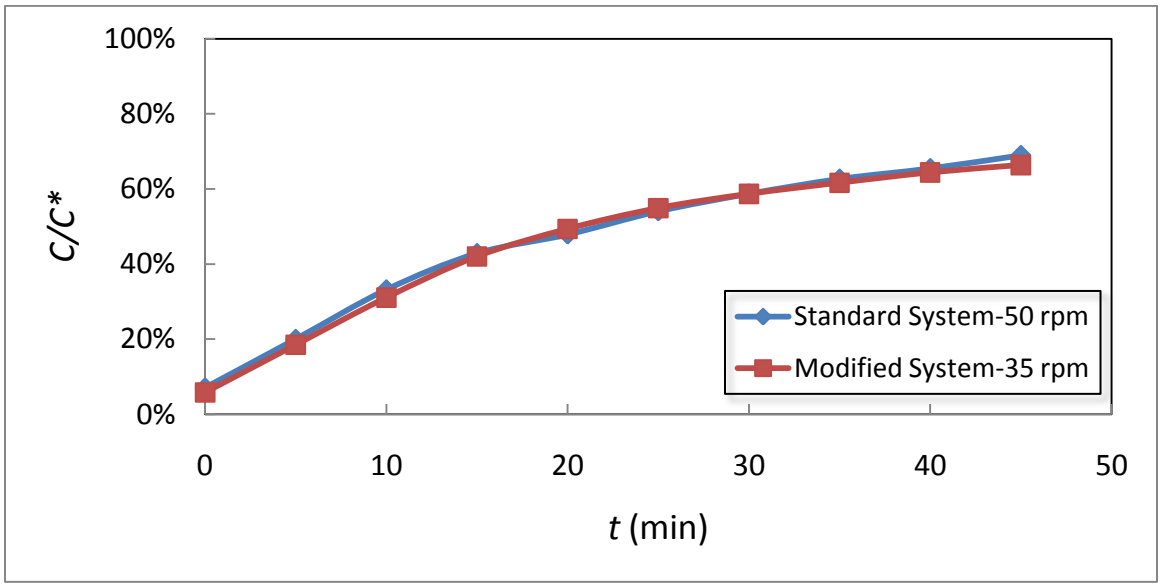


Figure 4.6 Comparison of dissolution profiles for a centrally located tablet in the Standard System at 50 rpm and in the Modified System at 35 rpm.

Table 4.3 f_1 and f_2 values for the dissolution profiles at different agitation speeds in the Modified System with respect to the Standard System operated at 50 rpm

Agitation Speed (rpm)	f_1 (Similarity factor)	f_2 (Difference factor)
30	40.632	35.066
33	11.341	62.128
34	2.386	84.713
35	2.578	88.120
36	15.665	55.613
37	16.093	55.108
40	16.507	53.931

4.4 Dissolution in the Modified System at the Optimum Agitation Speed (35 rpm) for This System

The results from the previous section show that the Modified System at 35 rpm is equivalent to the Standard System at 50 rpm at least for the centrally located tablet. However, it was still unclear whether the Modified System operated at 35 rpm was still robust enough to be insensitive to variation in tablet location, i.e., if it still behaved similarly to what found for the Modified System operated at 50 rpm. Therefore, a new series of experiments was conducted at 35 rpm in the Modified System in which the tablets were placed at each one of the nine locations mentioned previously (Figure 3.5).

The results presented in Figure 4.7 show that that the dissolution profiles for the Modified system at 35 rpm at all nine positions are visually overlapping on each other. This implies that there is a significant similarity between the dissolutions profiles at all nine different positions, even at 35 rpm. To confirm this observation, the similarity factors (f_1) and difference factors (f_2) were calculated for each of the experimental dissolution profiles for each off-center tablet with respect to the dissolution profile for the centrally located tablet. The results reported in Table 4.4 show that in all cases, the f_1

factor was between 0 and 15 and the f_2 factor was between 50 and 100, indicating that the dissolution profiles for the off-center tablets were statistically similar to that for the centrally located tablet, according to the FDA criteria. Additional details are provided in Tables B.20-B.27 in Appendix B.

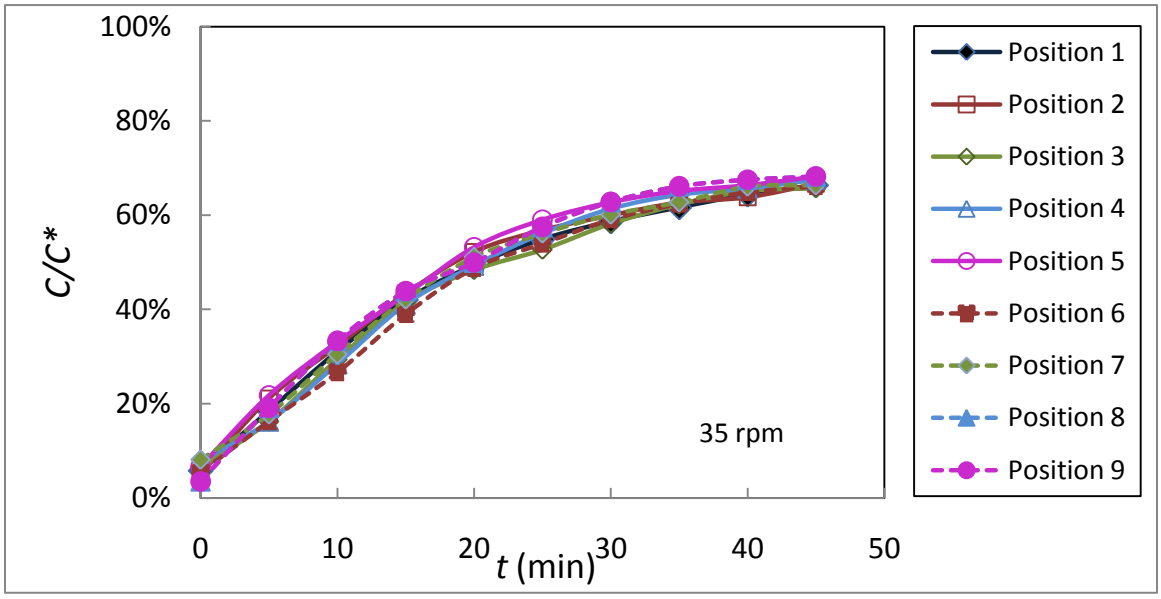


Figure 4.7 Dissolution profile for Prednisone at nine different tablet positions in the Modified System at 35 rpm.

Table 4.4 f_1 and f_2 values of the dissolution curves for tablets at different off-center locations compared to that for the tablet in the central position (Position 1) for the Modified System at 35 rpm

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Position 1 (centered tablet)	2.933	86.388
Position 2 (10° off-center tablet)	2.276	89.727
Position 3 (10° off-center tablet)	3.337	84.481
Position 4 (10° off-center tablet)	5.761	75.669
Position 5 (10° off-center tablet)	2.919	83.456
Position 6 (20° off-center tablet)	2.530	91.600
Position 7 (20° off-center tablet)	4.836	77.859
Position 8 (20° off-center tablet)	5.957	73.253
Position 9 (20° off-center tablet)	3.328	77.225

CHAPTER 5

DISCUSSION

The results of this work confirm that the location of the tablet on the vessel bottom has a significant impact on the dissolution profiles in the Standard USP Apparatus 2, where the impeller is centrally located in the vessel. When the tablet is located in a central position at the bottom of the vessel, the dissolution process at 50 rpm and with 500 mL of dissolving medium is slower than when the tablet is at other locations, such as 10° and 20° from the vertical centerline. This is consistent with the results of other investigators, and with the hydrodynamics of this system. In fact, in the region just below the impeller the flow is in general weak and the dissolution rate slow in comparison with the flow just outside this region, i.e., where the 10° and 20° off-center tablets are located. This is further confirmed by the values of the f_1 and f_2 parameters for these cases.

By contrast, when the Modified USP Dissolution Testing Apparatus 2 is used, the dissolution profiles obtained with tablet at different locations appear to be much more similar to each other and to the dissolution profile for the centrally located tablet. The reason for this can be attributed to the non-symmetric position of the impeller, which is likely to produce a sweeping flow along the vessel bottom, thus avoiding the formation of a nearly stagnant zone near the center of the vessel bottom, as in the Standard System, and making the tablets dissolve at similar rates irrespective of their position. This behavior is again confirmed by the appropriate values for the f_1 and f_2 parameters.

As a result of its non-symmetrical location of the impeller, the Modified System is a better missing device than the Standard System. Therefore, a comparison with the

dissolution profiles with the two systems when the tablet is in the same central location shows that the dissolution process in the former system is faster than that in the latter system at the same agitation speed. Since the operators or dissolution testing laboratories are familiar with the Standard Systems and expect the process to proceed at this slower rate, it was considered necessary here to determine the agitation intensity in the Modified System that produced a dissolution profile similar to the Standard System for the "normal" case in which the tablet is centrally located. This agitation speed was found to be in the range 34-35 rpm, implying that a Modified System operated at this speed produces a dissolution curve very similar to that obtained at 50 rpm with the Standard System.

In order to determine whether operating the Modified System at this speed would still results in dissolution curves insensitive to tablet location, a new series of experiments were conducted with the tablets placed at different locations. The results showed that the Modified System is still insensitive to tablet location as evidenced by the appropriate values of the f_1 and f_2 parameters.

Therefore, it can be concluded that the Modified System when operated at 35 rpm instead of 50 rpm generates not only dissolution rates and dissolution profiles that are similar to those obtained in current systems, but it is additionally much more robust in terms of reproducibility and insensitivities to parameter that can instead significantly affect the results of the Standard System.

Modifying a Standard System is very simple, and a number of ways to do so have been reported in a recent patent disclosure by this group. Therefore, it is expected that

the newly proposed Modified System for dissolution testing could be a valid alternative to the existing approach used in industry to test the release profiles of solid dosage forms.

CHAPTER 6

CONCLUSION

A number of conclusions can be drawn from this work, as follows:

1. The dissolution performance of Prednisone tablets, as disintegrating oral dosage forms, in the Standard Dissolution System where the impeller is placed centrally and symmetrically with respect to the unbaffled hemispherical-bottom vessel of the USP Dissolution Testing Apparatus 2 is strongly dependent on tablet position, as previously reported by this and other research groups. Thus, this apparatus is prone to highly variable results which may not be associated with the tablets undergoing testing but with hydrodynamic characteristics of the apparatus itself and the location of the tablet on the vessel bottom.

   A modification of the USP Dissolution Testing Apparatus 2 in which the impeller was placed off-center by 8 mm was proposed, and a prototype was assembled, and tested in this work. This Modified System generated dissolution profiles for Prednisone tablets that were nearly completely insensitive to tablet location.

2. The dissolution profiles for Prednisone in the Modified System were steeper than in the Standard System because of the improved mixing performance of the Modified System resulting from the non-symmetrical placement of the impeller.

3. When the Modified System was operated at 35 rpm, the dissolution profiles for centrally located tablets were very similar to those for the Standard System at 50 rpm.

4. The dissolution profiles for Prednisone tablets at 35 rpm in the Modified System were found to be insensitive to tablet location.

5. The newly proposed Modified System for dissolution testing could be a simple and valid alternative to the current dissolution testing practice using the Standard USP Dissolution Testing Apparatus 2.

APPENDIX A

FIGURES FOR CHAPTER 4

Appendix A includes figures of Chapter 4. It includes Dissolution profiles of Prednisone in Modified System (Figure A.1-A.2).

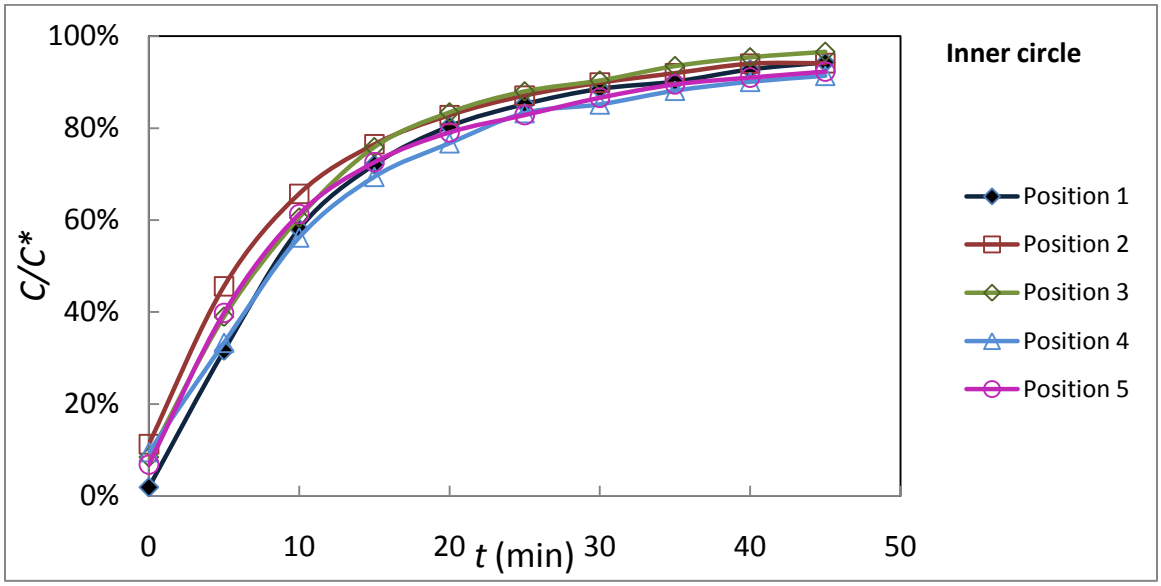


Figure A.1 Dissolution profile of Prednisone in Modified System at different positions (Position 2, 3, 4 and 5).

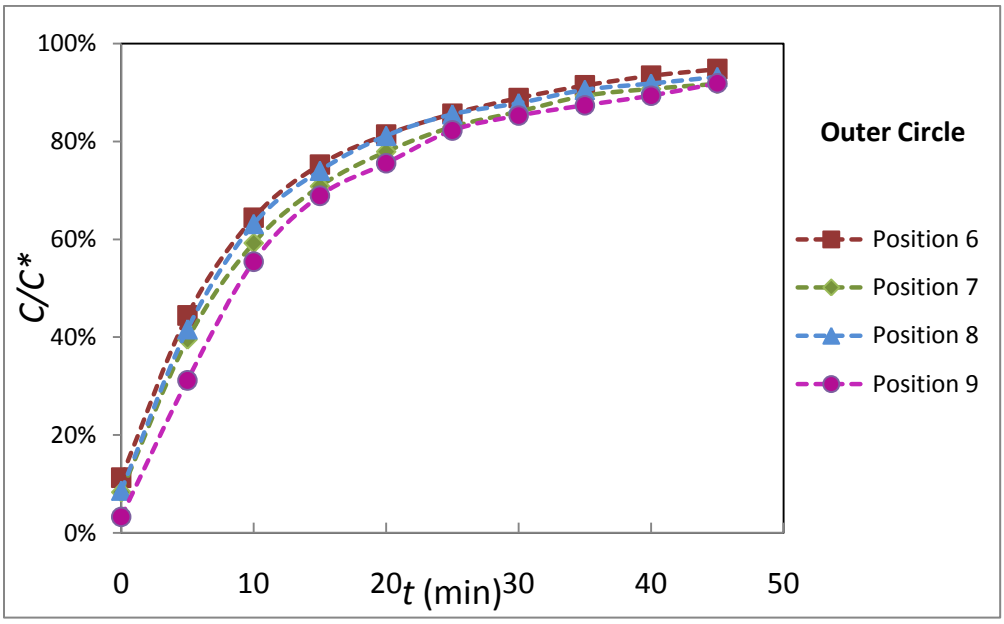


Figure A.2 Dissolution profile of Prednisone in Modified System at different positions (Position 6, 7, 8, 9).

APENDIX B

TABLES FOR CHAPTER 4

This appendix includes all tables of Chapter 4. Dissolution profiles of Prednisone in both Standard (Tables B.1-B.3) and in Modified (Tables B.4-B.12) Systems are represented in detail in this appendix. Dissolution profiles of prednisone in Modified system at 0° position at different impeller rotation speed (Tables B.13-B.19) are presented in this appendix. It also includes the Dissolution profile of prednisone in Modified system at 35 rpm at different positions (Tables B.20-B.27).

Table B.1 Dissolution profile of Prednisone in Standard System at 0° Position

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**
0	0.074	0.0233	-0.0003	0.0014242	0.07121	0.000577
5	0.185	0.0233	-0.0003	0.0040105	0.200525	0.001
10	0.298	0.0233	-0.0003	0.0066434	0.33217	0.001155
15	0.381	0.0233	-0.0003	0.0085773	0.428865	0.000577
20	0.424	0.0233	-0.0003	0.0095792	0.47896	0.001
25	0.477	0.0233	-0.0003	0.0108141	0.540705	0.000577
30	0.517	0.0233	-0.0003	0.0117461	0.587305	0.000577
35	0.551	0.0233	-0.0003	0.0125383	0.626915	0.000577
40	0.575	0.0233	-0.0003	0.0130975	0.654875	0.001
45	0.605	0.0233	-0.0003	0.0137965	0.689825	0.000577

Table B.2 Dissolution profile of Prednisone in Standard System at 10° Position

Time (min)	Average Absorption	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.095	0.0233	-0.0003	0.0019135	0.0956	0.0005774	20.16	50.19
5	0.238	0.0233	-0.0003	0.0052454	0.2622	0.0005774		
10	0.359	0.0233	-0.0003	0.0080647	0.4032	0.0005774		
15	0.475	0.0233	-0.0003	0.0107675	0.5383	0.0005774		
20	0.535	0.0233	-0.0003	0.0121655	0.6082	0.0005774		
25	0.581	0.0233	-0.0003	0.0132373	0.6618	0.0005774		
30	0.607	0.0233	-0.0003	0.0138431	0.6921	0.0005774		
35	0.645	0.0233	-0.0003	0.0147285	0.7364	0.0005774		
40	0.674	0.0233	-0.0003	0.0154042	0.7702	0.0005774		
45	0.685	0.0233	-0.0003	0.0156605	0.7830	0.0005774		

Table B.3 Dissolution profile of Prednisone in Standard System at 20° Position

Time (Min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.125	0.0233	-0.0003	0.0026125	0.13062	0.0005774	37.95	36.85
5	0.31	0.0233	-0.0003	0.006923	0.34615	0.0057735		
10	0.461	0.0233	-0.0003	0.0104413	0.52206	0.0005774		
5	0.557	0.0233	-0.0003	0.0126781	0.63390	0.0005774		
20	0.613	0.0233	-0.0003	0.0139829	0.69914	0.0005774		
25	0.657	0.0233	-0.0003	0.0150081	0.75040	0.0051962		
30	0.698	0.0233	-0.0003	0.0159634	0.79817	0.0005774		
35	0.714	0.0233	-0.0003	0.0163362	0.81681	0.0005774		
40	0.739	0.0233	-0.0003	0.0169187	0.84593	0.0005774		
45	0.743	0.0233	-0.0003	0.0170119	0.85059	0.0005774		

Table B.4 Dissolution profile of Prednisone in Modified System at Position 1 (Central)

Time (Min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**
0	0.029	0.0233	-0.0003	0.00037958	0.0189	.00009512
5	0.284	0.0233	-0.0003	0.006323	0.3160	0.00018935
10	0.511	0.0233	-0.0003	0.011615	0.5807	0.000190244
15	0.631	0.0233	-0.0003	0.014410	0.7205	0.000366559
20	0.702	0.0233	-0.0003	0.016076	0.8038	0.000120321
25	0.744	0.0233	-0.0003	0.017040	0.8520	0.000141089
30	0.772	0.0233	-0.0003	0.017704	0.8852	0.000120321
35	0.786	0.0233	-0.0003	0.018020	0.9010	0.000104201
40	0.808	0.0233	-0.0003	0.01854	0.9274	0.000475609
45	0.822193	0.0233	-0.0003	0.018857	0.9428	0.0010914

Table B.5 Dissolution profile of Prednisone in Modified System at Position 2

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.109	0.0233	-0.0003	0.00225	0.11256	0.000337649	5.07	63.04
5	0.404	0.0233	-0.0003	0.00912	0.45608	0.00440035		
10	0.577	0.0233	-0.0003	0.01314	0.65732	0.003295461		
15	0.672	0.0233	-0.0003	0.01529	0.76496	0.00539455		
20	0.723	0.0233	-0.0003	0.01656	0.82818	0.002342104		
25	0.760	0.0233	-0.0003	0.01741	0.87098	0.001020068		
30	0.784	0.0233	-0.0003	0.01797	0.89894	0.001189023		
35	0.802	0.0233	-0.0003	0.01839	0.91971	0.001221862		
40	0.820	0.0233	-0.0003	0.01880	0.9403	0.001605842		
45	0.821	0.0233	-0.0003	0.01882	0.94360	0.013433752		

Table B.6 Dissolution profile of Prednisone in Modified System at Position 3

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.0855	0.0233	-0.0003	0.00169	0.08460	0.000141089	4.17	72.52
5	0.347567	0.0233	-0.0003	0.00779	0.38991	0.0000951		
10	0.5276	0.0233	-0.0003	0.0119	0.59964	0.053162615		
15	0.664	0.0233	-0.0003	0.01517	0.75856	0.001591693		
20	0.7289	0.0233	-0.0003	0.01668	0.83416	0.00070448		
25	0.7681	0.0233	-0.0003	0.01759	0.87983	0.001424448		
30	0.788267	0.0233	-0.0003	0.01806	0.90373	0.000975869		
35	0.8153	0.0233	-0.0003	0.01869	0.93482	0.001001268		
40	0.83225	0.0233	-0.0003	0.01907	0.95459	0.00104396		
45	0.84172	0.0233	-0.0003	0.01931	0.96559	0.000622667		

Table B.7 Dissolution profile of Prednisone in Modified System at Position 4

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.095	0.0233	-0.0003	0.00191583	0.097386	0.004377931	3.29	78.51
5	0.299	0.0233	-0.0003	0.0066667	0.33253	0.011311104		
10	0.495	0.0233	-0.0003	0.011249033	0.56245	0.003944977		
15	0.608	0.0233	-0.0003	0.013885817	0.69429	0.005592202		
20	0.671	0.0233	-0.0003	0.01534595	0.76729	0.007408673		
25	0.727	0.0233	-0.0003	0.016658517	0.83292	0.003691721		
30	0.744	0.0233	-0.0003	0.0170352	0.85176	0.00399625		
35	0.769	0.0233	-0.0003	0.01762935	0.8798	0.003617445		
40	0.786	0.0233	-0.0003	0.018017683	0.90088	0.004064999		
45	0.797	0.0233	-0.0003	0.018277867	0.91383	0.00282177		

Table B.8 Dissolution profile of Prednisone in Modified System at Position 5

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.071	0.0233	-0.0003	0.001406	0.07031	0.003213092	3.01	74.35
5	0.356	0.0233	-0.0003	0.00800	0.40030	0.003234772		
10	0.539	0.0233	-0.0003	0.01226	0.61333	0.000586756		
15	0.636	0.0233	-0.0003	0.01451	0.7264	0.000695122		
20	0.691	0.0233	-0.0003	0.01590	0.79510	0.004700839		
25	0.724	0.0233	-0.0003	0.01659	0.82967	0.002588031		
30	0.756	0.0233	-0.0003	0.01736	0.86838	0.004648141		
35	0.782	0.0233	-0.0003	0.01792	0.89613	0.00110132		
40	0.796	0.0233	-0.0003	0.01824	0.91246	0.003194452		
45	0.806	0.0233	-0.0003	0.01850	0.9251	0.002512099		

Table B.9 Dissolution profile of Prednisone in Modified System at Position 6

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.108	0.0233	-0.0003	0.00225	0.11156	0.001054952	3.75	66.32
5	0.395	0.0233	-0.0003	0.0089	0.44614	0.002489577		
10	0.566	0.0233	-0.0003	0.012748	0.6374	0.007477812		
15	0.652	0.0233	-0.0003	0.01490	0.74535	0.029953568		
20	0.714	0.0233	-0.0003	0.01635	0.81758	0.004522041		
25	0.747	0.0233	-0.0003	0.01711	0.8556	0.002290838		
30	0.776	0.0233	-0.0003	0.01778	0.88905	0.002210944		
35	0.798	0.0233	-0.0003	0.01830	0.91544	0.000951219		
40	0.815	0.0233	-0.0003	0.01870	0.93505	0.000974709		
45	0.827	0.0233	-0.0003	0.01894	0.94923	0.00175396		

Table B.10 Dissolution profile of Prednisone in Modified System at Position 7

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.082	0.0233	-0.0003	0.001658753	0.0829	0.00265729	3.13	74.80
5	0.352	0.0233	-0.0003	0.007902377	0.3951	0.001433786		
10	0.521	0.0233	-0.0003	0.01184396	0.5921	0.001061152		
15	0.621	0.0233	-0.0003	0.014165417	0.7082	0.002802223		
20	0.681	0.0233	-0.0003	0.015582057	0.7791	0.00057743		
25	0.725	0.0233	-0.0003	0.016593277	0.8296	0.000731882		
30	0.753	0.0233	-0.0003	0.01725927	0.8609	0.003456472		
35	0.783	0.0233	-0.0003	0.017955457	0.8932	0.003456472		
40	0.794	0.0233	-0.0003	0.018228163	0.9074	0.004949491		
45	0.801	0.0233	-0.0003	0.018366873	0.9175	0.004457806		

Table B.11 Dissolution profile of Prednisone in Modified System at Position 8

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.087	0.0233	-0.0003	0.00174651	0.08732	0.001714834	3.07	71.00
5	0.370	0.0233	-0.0003	0.0083353	0.41676	0.00121257		
10	0.555	0.0233	-0.0003	0.012639	0.63196	0.002017839		
15	0.648	0.0233	-0.0003	0.0148111	0.74056	0.000672613		
20	0.711	0.0233	-0.0003	0.0162815	0.81407	0.007434428		
25	0.747	0.0233	-0.0003	0.0171128	0.85564	0.000672613		
30	0.766	0.0233	-0.0003	0.0175478	0.87739	0.004035678		
35	0.791	0.0233	-0.0003	0.0181357	0.90678	0.000641632		
40	0.804	0.0233	-0.0003	0.01834487	0.9224	0.000672613		
45	0.815	0.0233	-0.0003	0.0186972	0.93486	0.001165		

Table B.12 Dissolution profile of Prednisone in Modified System at Position 9

Time (Min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	C/C* (%)	Standard Deviation	*f1*	*f2*
0	0.04417	0.0233	-0.0003	0.000729083	0.0364	0.004798707	3.32	77.22
5	0.2878	0.0233	-0.0003	0.0064057	0.32028	0.020559263		
10	0.50018	0.0233	-0.0003	0.01135427	0.56771	0.024343808		
15	0.61352	0.0233	-0.0003	0.0139949	0.69974	0.025359609		
20	0.6632	0.0233	-0.0003	0.0151541	0.75770	0.003732851		
25	0.7205	0.0233	-0.0003	0.016481825	0.82409	0.002839112		
30	0.74238	0.0233	-0.0003	0.016997532	0.84987	0.00487489		
35	0.76472	0.0233	-0.0003	0.017517898	0.87589	0.004135613		
40	0.77982	0.0233	-0.0003	0.017869728	0.89348	0.001189023		
45	0.80187	0.0233	-0.0003	0.0183834	0.91917	0.000610561		

Table B.13 Dissolution profile of Prednisone in Modified System at 0° **(At 30rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.061	0.0233	-0.0003	0.0011213	0.05606	0.002828	40.63	35.06
5	0.103	0.0233	-0.0003	0.0020999	0.10499	0.005657		
10	0.150	0.0233	-0.0003	0.003195	0.15975	0.002828		
15	0.197	0.0233	-0.0003	0.0042901	0.21450	0.001414		
20	0.244	0.0233	-0.0003	0.0053852	0.26926	0.004243		
25	0.286	0.0233	-0.0003	0.0063638	0.31819	0.009899		
30	0.319	0.0233	-0.0003	0.00714435	0.35721	0.013435		
35	0.353	0.0233	-0.0003	0.0079249	0.39624	0.014142		
40	0.376	0.0233	-0.0003	0.00847245	0.42362	0.016263		
45	0.400	0.0233	-0.0003	0.00903165	0.45158	0.014849		

Table B.14 Dissolution profile of Prednisone in Modified System at 0° **(At 33rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.079	0.0233	-0.0003	0.00155235	0.077	0.000707	11.34	62.12
5	0.169	0.0233	-0.0003	0.0036377	0.181	0.012728		
10	0.250	0.0233	-0.0003	0.00553665	0.276	0.000707		
15	0.325	0.0233	-0.0003	0.0072725	0.363	0		
20	0.380	0.0233	-0.0003	0.008554	0.427	0		
25	0.430	0.0233	-0.0003	0.009719	0.485	0		
30	0.467	0.0233	-0.0003	0.0105811	0.529	0		
35	0.493	0.0233	-0.0003	0.0111869	0.559	0		
40	0.520	0.0233	-0.0003	0.011816	0.590	0		
45	0.5365	0.0233	-0.0003	0.01220045	0.610	0.000707		

Table B.15 Dissolution profile of Prednisone in Modified System at 0° **(At 34rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.076	0.0233	-0.0003	0.0014708	0.0735	0	2.38	84.71
5	0.157	0.0233	-0.0003	0.0033581	0.1679	0		
10	0.265	0.0233	-0.0003	0.0058745	0.2937	0		
15	0.362	0.0233	-0.0003	0.0081346	0.4067	0		
20	0.425	0.0233	-0.0003	0.0096025	0.4801	0		
25	0.479	0.0233	-0.0003	0.0108607	0.5430	0		
30	0.514	0.0233	-0.0003	0.0116762	0.5838	0		
35	0.552	0.0233	-0.0003	0.0125616	0.6280	0		
40	0.574	0.0233	-0.0003	0.0130742	0.6537	0		
45	0.610	0.0233	-0.0003	0.013913	0.6956	0		

Table B.16 Dissolution profile of Prednisone in Modified System at 0° **(At 35rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	*f1*	*f2*
0	0.062	0.0233	-0.0003	0.0011563	0.05781	0.00495	2.57	88.12
5	0.171	0.0233	-0.0003	0.003696	0.18479	0.014849		
10	0.279	0.0233	-0.0003	0.0062124	0.31061	0.009192		
15	0.373	0.0233	-0.0003	0.0084026	0.42012	0.007778		
20	0.436	0.0233	-0.0003	0.0098705	0.49352	0.013435		
25	0.484	0.0233	-0.0003	0.0109772	0.54886	0.005657		
30	0.516	0.0233	-0.0003	0.0117345	0.58672	0.006364		
35	0.542	0.0233	-0.0003	0.0123286	0.61643	0.001414		
40	0.565	0.0233	-0.0003	0.0128762	0.64380	0.009192		
45	0.582	0.0233	-0.0003	0.0132723	0.66361	0.014849		

Table B.17 Dissolution profile of Prednisone in Modified System at 0° **(At 36rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.088	0.0233	-0.0003	0.001762	0.088	0.000707	15.66	55.61
5	0.219	0.0233	-0.0003	0.004814	0.240	0.000707		
10	0.378	0.0233	-0.0003	0.008519	0.425	0.000707		
15	0.455	0.0233	-0.0003	0.010313	0.515	0.000707		
20	0.498	0.0233	-0.0003	0.011315	0.565	0.000707		
25	0.542	0.0233	-0.0003	0.012340	0.617	0.000707		
30	0.579	0.0233	-0.0003	0.013202	0.660	0.000707		
35	0.610	0.0233	-0.0003	0.013924	0.696	0.000707		
40	0.649	0.0233	-0.0003	0.014833	0.741	0.000707		
45	0.689	0.0233	-0.0003	0.015765	0.788	0.000707		

Table B.18 Dissolution profile of Prednisone in Modified System at 0° **(At 37rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.083	0.0233	-0.00013	0.00181555	0.090	0.003536	16.09	55.10
5	0.217	0.0233	-0.00013	0.0049261	0.246	0.011314		
10	0.351	0.0233	-0.00013	0.0080483	0.402	0.022627		
15	0.440	0.0233	-0.00013	0.010122	0.506	0.009899		
20	0.499	0.0233	-0.00013	0.01150835	0.574	0.003536		
25	0.556	0.0233	-0.00013	0.0128248	0.641	0.008485		
30	0.589	0.0233	-0.00013	0.01360535	0.680	0.007778		
35	0.612	0.0233	-0.00013	0.01414125	0.707	0.00495		
40	0.641	0.0233	-0.00013	0.0148053	0.740	0.009899		
45	0.668	0.0233	-0.00013	0.0154344	0.771	0.001414		

Figure B.19 Dissolution profile of Prednisone in Modified System at 0° **(At 40rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.074	0.0233	-0.0003	0.0014242	0.071	0	16.50	53.93
5	0.203	0.0233	-0.0003	0.0044299	0.221	3.4E-17		
10	0.350	0.0233	-0.0003	0.007855	0.392	6.8E-17		
15	0.450	0.0233	-0.0003	0.010200533	0.510	0.000577		
20	0.501	0.0233	-0.0003	0.0113733	0.568	0		
25	0.573	0.0233	-0.0003	0.0130509	0.652	0		
30	0.611	0.0233	-0.0003	0.0139363	0.696	0		
35	0.632	0.0233	-0.0003	0.014441133	0.722	0.000577		
40	0.655	0.0233	-0.0003	0.014969267	0.748	0.000577		
45	0.679	0.0233	-0.0003	0.015536233	0.776	0.000577		

Table B.20 Dissolution profile of Prednisone in Modified System at Position 2 **(35 rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.055	0.0233	-0.0003	0.00099315	0.04965	0.02192	2.93	86.38
5	0.194	0.0233	-0.0003	0.0042202	0.21101	0.007071		
10	0.269	0.0233	-0.0003	0.00644535	0.3222	0.000707		
15	0.385	0.0233	-0.0003	0.0086705	0.4335	0.007071		
20	0.461	0.0233	-0.0003	0.0104413	0.5220	0.015556		
25	0.500	0.0233	-0.0003	0.01136165	0.56808	0.000707		
30	0.527	0.0233	-0.0003	0.01199075	0.59953	0.000707		
35	0.551	0.0233	-0.0003	0.0125383	0.62691	0.002828		
40	0.560	0.0233	-0.0003	0.01275965	0.63798	0.000707		
45	0.585	0.0233	-0.0003	0.0133305	0.666525	0.005657		

Table B. 21 Dissolution profile of Prednisone in Modified System at Position 3 **(35 rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.068	0.0233	-0.0003	0.0012844	0.06422	0.001414	2.27	89.72
5	0.152	0.0233	-0.0003	0.0036377	0.16208	0.016971		
10	0.265	0.0233	-0.0003	0.0058745	0.29372	0.007071		
15	0.369	0.0233	-0.0003	0.00830236	0.41511	0.00396		
20	0.428	0.0233	-0.0003	0.00987045	0.48362	0.001414		
25	0.465	0.0233	-0.0003	0.0105345	0.52672	0.007071		
30	0.512	0.0233	-0.0003	0.01164125	0.58206	0.003536		
35	0.547	0.0233	-0.0003	0.01296935	0.62283	0.030406		
40	0.572	0.0233	-0.0003	0.0130276	0.65138	0.001414		
45	0.577	0.0233	-0.0003	0.0131441	0.65720	0.001414		

Table B. 22 Dissolution profile of Prednisone in Modified System at Position 4 **(35 rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.079	0.0233	-0.0003	0.0015407	0.0770	0.001414214	3.33	84.48
5	0.152	0.0233	-0.0003	0.0032416	0.1620	0.009899495		
10	0.257	0.0233	-0.0003	0.0056881	0.2844	0.004242641		
15	0.365	0.0233	-0.0003	0.00821615	0.4108	0.007778175		
20	0.436	0.0233	-0.0003	0.0098588	0.4929	0.005656854		
25	0.494	0.0233	-0.0003	0.01122185	0.5610	0.006363961		
30	0.539	0.0233	-0.0003	0.01227035	0.6135	0.000707107		
35	0.565	0.0233	-0.0003	0.0128645	0.6432	0.007071068		
40	0.574	0.0233	-0.0003	0.01308585	0.6542	0.00212132		
45	0.592	0.0233	-0.0003	0.01350525	0.6752	0.004949747		

Table B.23 Dissolution profile of Prednisone in Modified System at Position 5 **(35 rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.070	0.0233	-0.0003	0.001332165	0.0666	0.0000705	5.76	75.66
5	0.199	0.0233	-0.0003	0.00434835	0.2174	0.000707107		
10	0.297	0.0233	-0.0003	0.0066201	0.3310	0.002828427		
15	0.382	0.0233	-0.0003	0.00861225	0.4306	0.003535534		
20	0.469	0.0233	-0.0003	0.01063935	0.5319	0.0417193		
25	0.519	0.0233	-0.0003	0.01180435	0.5902	0.000707107		
30	0.551	0.0233	-0.0003	0.01254995	0.6274	0.010606602		
35	0.572	0.0233	-0.0003	0.0130276	0.6513	0.002828427		
40	0.582	0.0233	-0.0003	0.01327225	0.6636	0.00212132		
45	0.598	0.0233	-0.0003	0.01364505	0.6825	0.000707107		

Table B.24 Dissolution profile of Prednisone in Modified System at Position 6 **(35 rpm)**

Time (min)	Average Absorbacne	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.059	0.0233	-0.0003	0.00108635	0.054	0.000707107	2.91	83.45
5	0.152	0.0233	-0.0003	0.00325325	0.162	0.053033009		
10	0.241	0.0233	-0.0003	0.00532695	0.266	0.064346717		
15	0.347	0.0233	-0.0003	0.00779675	0.389	0.003535534		
20	0.431	0.0233	-0.0003	0.00975395	0.487	0.000707107		
25	0.512	0.0233	-0.0003	0.0107908	0.539	0.050911688		
30	0.520	0.0233	-0.0003	0.015	0.590	0		
35	0.548	0.0233	-0.0003	0.01248005	0.624	0.000707107		
40	0.569	0.0233	-0.0003	0.01296935	0.648	0.013435029		
45	0.580	0.0233	-0.0003	0.013322565	0.661	0.000707107		

Table B.25 Dissolution profile of Prednisone in Modified System at Position 7 **(35 rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/ml)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.082	0.0233	-0.0003	0.00162225	0.0811	0.00212132	2.53	9.60
5	0.165	0.0233	-0.0003	0.0035445	0.1772	0.035355339		
10	0.274	0.0233	-0.0003	0.00609585	0.3047	0.030405592		
15	0.374	0.0233	-0.0003	0.00842585	0.4212	0.02192031		
20	0.451	0.0233	-0.0003	0.01021995	0.5109	0.00212132		
25	0.494	0.0233	-0.0003	0.01122185	0.5610	0.006363961		
30	0.529	0.0233	-0.0003	0.0120257	0.6012	0.002828427		
35	0.551	0.0233	-0.0003	0.01254995	0.6274	0.004949747		
40	0.580	0.0233	-0.0003	0.013214	0.6607	0.001414214		
45	0.582	0.0233	-0.0003	0.01327225	0.6636	0.010606602		

Table B.26 Dissolution Profile of Prednisone in Modified System at Position 8 **(35 rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.041	0.0233	-0.0003	0.0006553	0.032765	0.002828427	4.83	77.85
5	0.177	0.0233	-0.0003	0.0038241	0.191205	0.002828427		
10	0.299	0.0233	-0.0003	0.0066667	0.333335	0		
15	0.389	0.0233	-0.0003	0.00877535	0.438767	0.000707107		
20	0.441	0.0233	-0.0003	0.00998695	0.499347	0.000707107		
25	0.506	0.0233	-0.0003	0.01150145	0.575072	0.00212132		
30	0.552	0.0233	-0.0003	0.0125616	0.62808	0.002828427		
35	0.580	0.0233	-0.0003	0.01322565	0.661282	0.000707107		
40	0.592	0.0233	-0.0003	0.01350525	0.67526	0.003535534		
45	0.598	0.0233	-0.0003	0.01364505	0.682252	0.000707107		

Table B.27 Dissolution profile of Prednisone in Modified System at Position 9 **(35 rpm)**

Time (min)	Average Absorbance	Slope	Intercept (mg/mL)	Concentration (mg/mL)	*C/C**	Standard Deviation *C/C**	f_1	f_2
0	0.079	0.0233	-0.0003	0.001562835	0.078141	7.07107E-05	5.95	73.25
5	0.199	0.0233	-0.0003	0.00434835	0.217417	0.000707107		
10	0.288	0.0233	-0.0003	0.0064104	0.32052	0.001414214		
15	0.377	0.0233	-0.0003	0.0084841	0.424205	0.002828427		
20	0.461	0.0233	-0.0003	0.0104413	0.522065	0		
25	0.533	0.0233	-0.0003	0.01213055	0.606527	0.00212132		
30	0.560	0.0233	-0.0003	0.01275965	0.637982	0.003535534		
35	0.578	0.0233	-0.0003	0.0131674	0.65837	0		
40	0.592	0.0233	-0.0003	0.0134936	0.67468	0.001414214		
45	0.590	0.0233	-0.0003	0.01345865	0.672932	0.004949747		

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