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ABSTRACT

DISSOLUTION TESTING OF PREDNISONE AND SALICYLIC ACID CALIBRATOR TABLETS AT DIFFERENT TABLET LOCATIONS

by
Anandhavalavan Arulmozhi

Dissolution testing is routinely carried out in the pharmaceutical industry to determine the rate of dissolution of solid dosage forms. This test is one of the several tests that pharmaceutical companies typically conduct on oral dosage formulations (e.g., tablets) to determine compliance. The USP Dissolution Testing Apparatus 2 is the most common of the apparatuses listed in the USP. However, it has been shown previously that the dissolution profile of a tablet undergoing dissolution in the USP Dissolution Apparatus 2 can be affected by the tablet location in the apparatus.

In this work, the dissolution rates of both non-disintegrating tablets (salicylic acid) and disintegrating tablets (Prednisone) were experimentally determined for many different tablet locations, both centered on the vessel bottom and off-center. The location of the tablet was experimentally varied in very small increments in order to determine the exact location where a transition in the dissolution profile occurred. It was found that in a small region (2-4 mm in radius) centered around the vessel centerline just below the impeller the dissolution profiles were similar to those observed with a centered tablet. However, outside this region the dissolution profiles were found to be significantly different, as indicated by the values of the Similarity Factor f_1 and the Difference Factor f_2. These finding are consistent with previous hydrodynamic investigations that showed the existence of a poorly mixed zone below the USP Apparatus 2 impeller. The results of

this work can guide the practitioner on when to accept dissolution testing results based on tablet location.

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by
Anandhavalavan Arulmozhi

A Dissertation
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Pharmaceutical Engineering

Otto H.York Department of Chemical Biological and Pharmaceutical Engineering

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APPROVAL PAGE

DISSOLUTION TESTING OF PREDNISONE AND SALICYLIC ACID CALIBRATOR TABLETS AT DIFFERENT TABLET LOCATIONS

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Dedicated to my parents for their, Love, Support and Encouragement

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Dissolution testing is routinely carried out in the pharmaceutical industry to determine the rate of dissolution of solid dosage forms. In addition to being routinely used by pharmaceutical companies to demonstrate adequate drug release *in vivo* (through *in vivo/in vitro* (IVIVC) correlation), *in vitro* dissolution testing is used to assist with formulation design, process development, and especially the demonstration of batch-to batch reproducibility in production. Dissolution testing is one of the several tests that pharmaceutical companies typically conduct on oral dosage formulations (e.g., tablets) to determine compliance and to release products for distribution and sales.

Although the USP lists several different dissolution test apparatuses (USP, 2008), most dissolution tests are currently conducted with USP Dissolution Test Apparatuses 1 and 2. The USP Dissolution Apparatus 2 is the most commonly and widely used apparatus specified by the USP, and it is the focus of the study presented in this work. The dimensions, characteristics, and operating conditions of USP Dissolution Apparatus 2 are detailed by the USP and all users must conform to these prescriptions when conducting dissolution tests. The USP Dissolution Apparatus 2 comprises a glass vessel and an agitation system. The glass vessel is a cylindrical glass tank with a semispherical bottom, and a working volume of either 500 mL or 900 mL (Figure 1.1). The agitation system consists of a two-blade paddle impeller mounted on a shaft centrally located in the vessel and profiled to follow the hemispherical portion of the vessel.

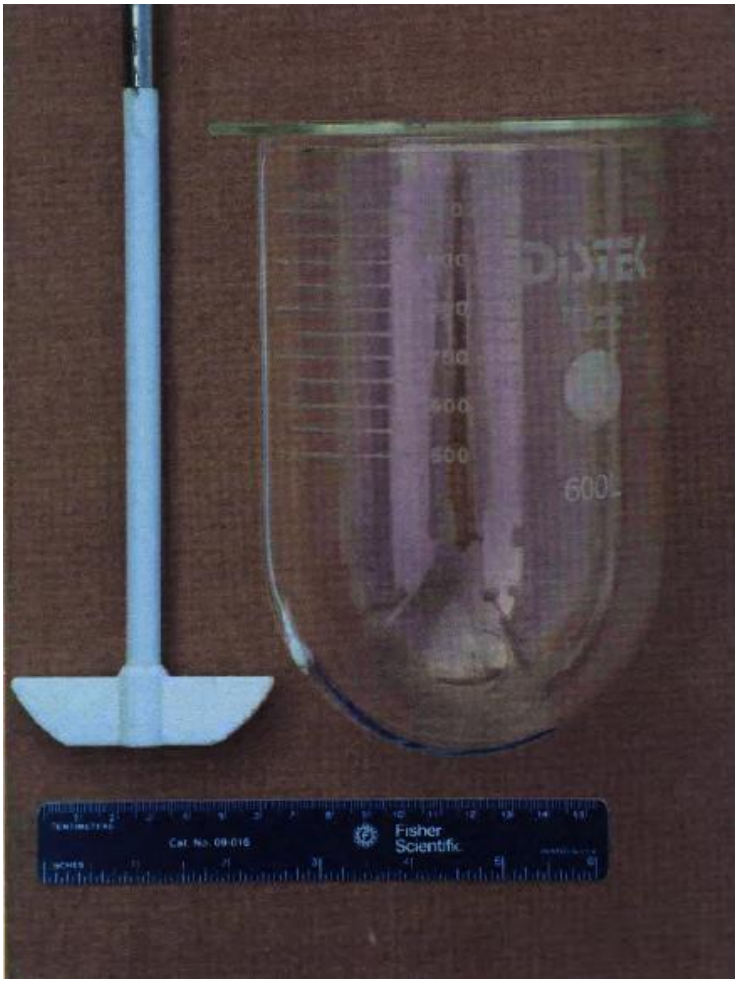


Figure 1.1 USP Dissolution Apparatus 2: paddle impeller and glass vessel.

In the industrial practice, replicate dissolution tests are typically conducted in parallel using commercially available systems containing six or more individual USP Dissolution Apparatus 2 units (Figure 1.2). These systems allow the agitation system (motor and impellers) to be lifted above the rack holding the vessels, as shown in this figure, in order to prepare the system for the actual test. Each vessel is filled with a prescribed amount of a fluid simulating gastric or intestinal fluids, and maintained at constant temperature of 37°C by either a water bath or a heating jacket. The test consists of lowering the agitation system so that the paddles reach their predetermined location

inside the vessels, as required by the USP, starting the agitation so that the paddles rotate at 50 RPM or 100 RPM, adding a single dosage form unit, such as a tablet, to each vessel simultaneously, drawing liquid samples over time from a prescribed location within the vessel, analyzing the drug concentration in each sample, and determining the dissolution profile over time. These profiles must be within a predefined range, and cannot differ significantly from the dissolution profile that the drug manufacturer has initially submitted to the FDA when the drug was approved. Any dissolution profile that is found to be statistically different, according to a predefined criterion (Moore and Flanner, 1996), from the reference profile established for that dosage form implies failure of the test and non-compliance of the production batch being tested. When this occurs, the batch cannot be released for commercialization and it is often disposed of. The cost of such failure is often significant given the typical high value of the product.

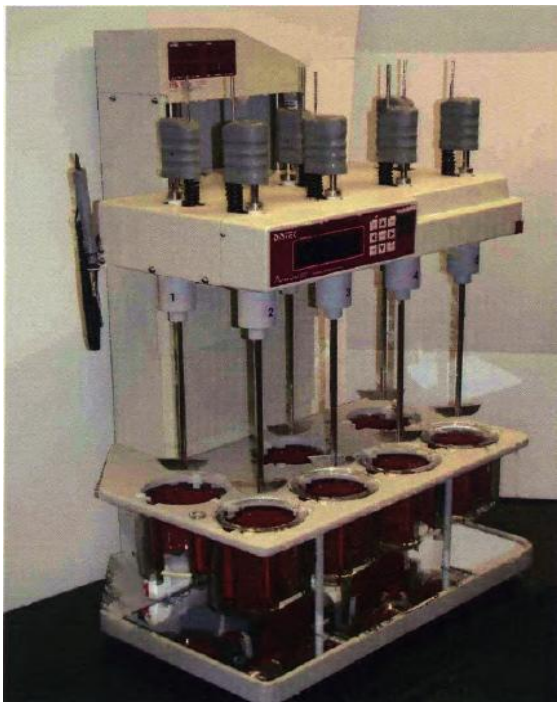


Figure 1.2 USP Dissolution Apparatus 2: typical commercial dissolution

CHAPTER 2

LITERATURE REVIEW

The USP Dissolution Apparatus 2 has been used in the pharmaceutical industry for decades, since this test was first officially introduced almost 30 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. A review of the literature shows testing systems containing seven Apparatus 2 units (Distek 5100 bathless dissolution apparatus). that there have been numerous reports describing high variability of test results (Manger et al. 2003, Moore et al. 1995, Qureshi and McGilveray, 1999, Qureshi and Shabnam, 2001, Costa and Lobo, 2001, Bocanegra et al. 1990, Cox and Furman, 1982, Cox et al. 1983) even when the so called "calibrator tablets" (i.e., tablets manufactured for the sole purpose of testing the proper operation of the dissolution test equipment) are used (Moore et al. 1995, Qureshi and Shabńam, 2001, Cox and Furman, 1982, Kukura et al. 2003, Baxter et al. 2005) 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. Some of the same studies have indicated that the hydrodynamics of the USP dissolution 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 is associated with a complex hydrodynamics resulting in fluid velocities whose directions and intensities are highly dependent on the location within the vessel (Bai and Armenante, 2008). To complicate the issue farther, tablets have often been reported to land at different locations at the bottom of the vessel after they are dropped in the vessel at the beginning of a test, making the dissolution process even more susceptible to hydrodynamic factors. Until recently, limited information has been available on the hydrodynamics of the dissolution apparatus and the effects of operating and geometric variables on the velocity distribution in the system. Such information is critical to advance the fundamental understanding of the dissolution rate process, enhance the reliability of dissolution testing, and eliminate artifacts associated with test methods, especially since dissolution measurements have often been reported to be inconsistent and poorly reproducible. Only a few researchers (Kukura et al. 2004, Baxter et al. 2005, Bai and Armenante, 2008) have conducted dissolution test in which drug tablets were fixed at different locations along the bottom of the USP Dissolution Apparatus 2.

CHAPTER 3

OBJECTIVE OF THIS WORK

The literature review presented in the previous chapter shows that our current knowledge of the dissolution testing systems is still incomplete, and that there is a need for conducting work aimed at understanding the impact of a number of operating variables. In particular, although it is now known that the location of the tablet on the vessel bottom can, in general, affect the dissolution profiles, especially if the location is significantly different from that of a centered tablet, it still remains to be determined whether small changes in tablet location can still affect the results of dissolution test, as it had been hypothesized in the literature (Ge and Armenante, 2008).

Therefore, the overall goal of this research work is to conduct dissolution testing experiments with disintegrating and non-disintegrating calibrator tablets (10-mg Prednisone tablets and 300-mg salicylic acid tablets) in order to determine precisely the effect of tablet location on dissolution profiles, especially when the tablet location is varied in small increments. The achievement of this objective can help the dissolution testing practitioners understand whether it is prudent to discard the results of a dissolution test even before the test is completed, based on the initial position of the tablet after it has been dropped in the vessel and it has reached its resting position at the beginning of a dissolution test.

CHAPTER 4

EXPERIMENTAL APPARATUS, MATERIALS, AND METHOD

4.1 Dissolution Vessel and Agitation System

All dissolution experiments were conducted using a Distek 5100 Bathless Dissolution Apparatus 2 (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*, equal to 100.16 mm and overall capacity of 1 L was used as the dissolution vessel. 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 specified 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. When the vessel was filled with 900 mL of dissolution media, *H* was 128.8 mm. Figure 4.1shows the Dimensions of USP Dissolution Testing Apparatus 2.

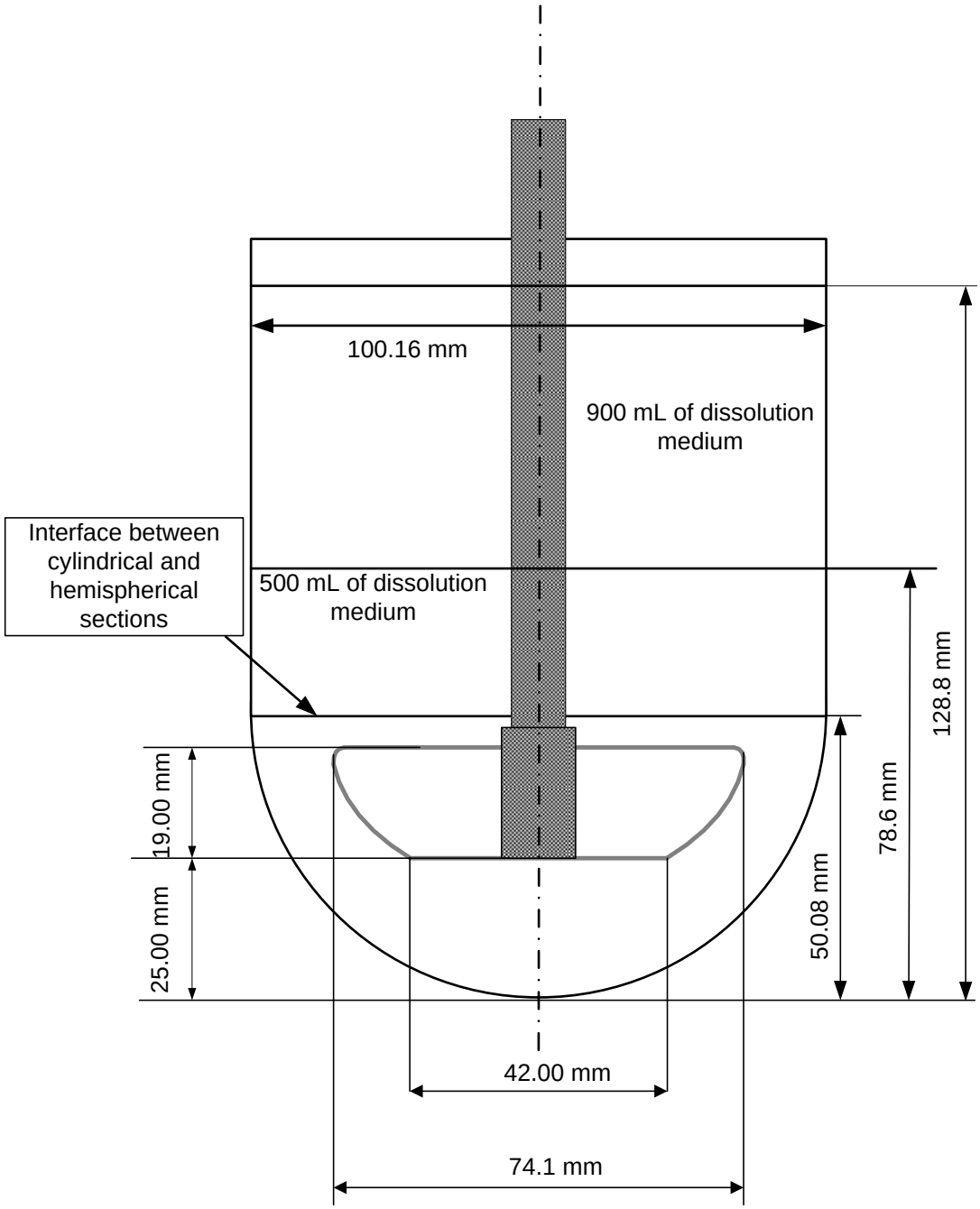


Figure 4.1 Dimensions of USP Dissolution Testing Apparatus 2

4.2 Experimental Materials

Dissolution studies were conducted using both disintegrating and non-disintegrating solid oral dosage forms, i.e., respectively, 10-mg Prednisone calibrator tablets (disintegrating tablets, NCDA #2), kindly provided by Dr. Zongming Gao (Food and Drug Administration (FDA), Division of Pharmaceutical Analysis, Center for Drug Evaluation and Research, St. Louis, MO), and 300-mg salicylic acid calibrator tablets (non-disintegrating tablets; USP Lot Q0D200), purchased from USP, Rockville, MD. The dimensions of the tablets were measured using a caliper. Their diameters were found to be 7.80 mm for Prednisone tablets and 9.52 mm for salicylic acid tablets. Their corresponding thicknesses were 3.76 mm and 4.4 mm, respectively. A commercial acrylic glue was used to fix the tablet at a particular location on the bottom of the dissolution vessel.

The dissolution medium for Prednisone tablets consisted of de-aerated distilled water. The dissolution medium for salicylic acid tablets consisted of a de-aerated 0.05 M monobasic potassium phosphate buffer solution to which an NaOH solution (50% (w/w) concentration) was added to reach a final pH value of 7.4.

All media were de-gassed in the de-gassing apparatus shown in Figure 4.2 following the USP General Test Chapter on DISSOLUTION <711>, based on to the degassing method developed by Moore (Moore, 1996). 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. Stock solutions

were used as needed, i.e., in 500 mL aliquots for the experiments with Prednisone tablets and 900 mL aliquots for the experiments with salicylic acid tablets.

Disposable PVDF 0.45 μm filters were during sampling to remove possible solid particles that could have entered the sample prior to sample analysis as described below.

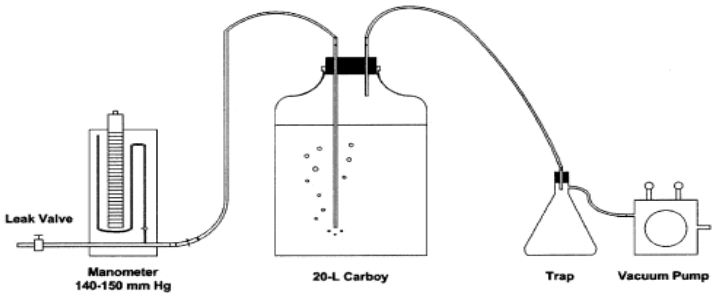


Figure 4.2 Equipment used to de-aerate the dissolution medium.

4.3 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 with a minute amount of glue 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.). In order to test the effect of tablet location during dissolution testing, a tablet was attached at one of eight predefined points on the vessel bottom with a very small bead of commercial glue. The locations of the tablets on the vessel bottom are shown in Figure 4.3. Centered tablets were placed at the center of

the vessel bottom. Off-center tablets were placed so that their center was at one of seven off-center locations on the vessel bottom, 2°, 4°, 6°, 8°, 10°, 15° or 20° away from the vessel vertical centerline. 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). Additional details of the experimental operating conditions are presented in Table 4.1.

Once the tablet and the vessel were setup properly, the de-aerated dissolution medium (500 mL of distilled water for Prednisone or 900 mL of buffer medium for salicylic acid), 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. Agitation was started immediately after the addition of the dissolution medium. The agitation speed was 50 rpm for Prednisone tablets and 100 rpm for salicylic acid tablets, respectively (USP, 2008). The first sample was taken immediately after agitation was started. 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 triplicates for each tablet location (0˚, 2˚, 4˚, 6˚, 8˚, 10˚. 15˚, and 20˚).

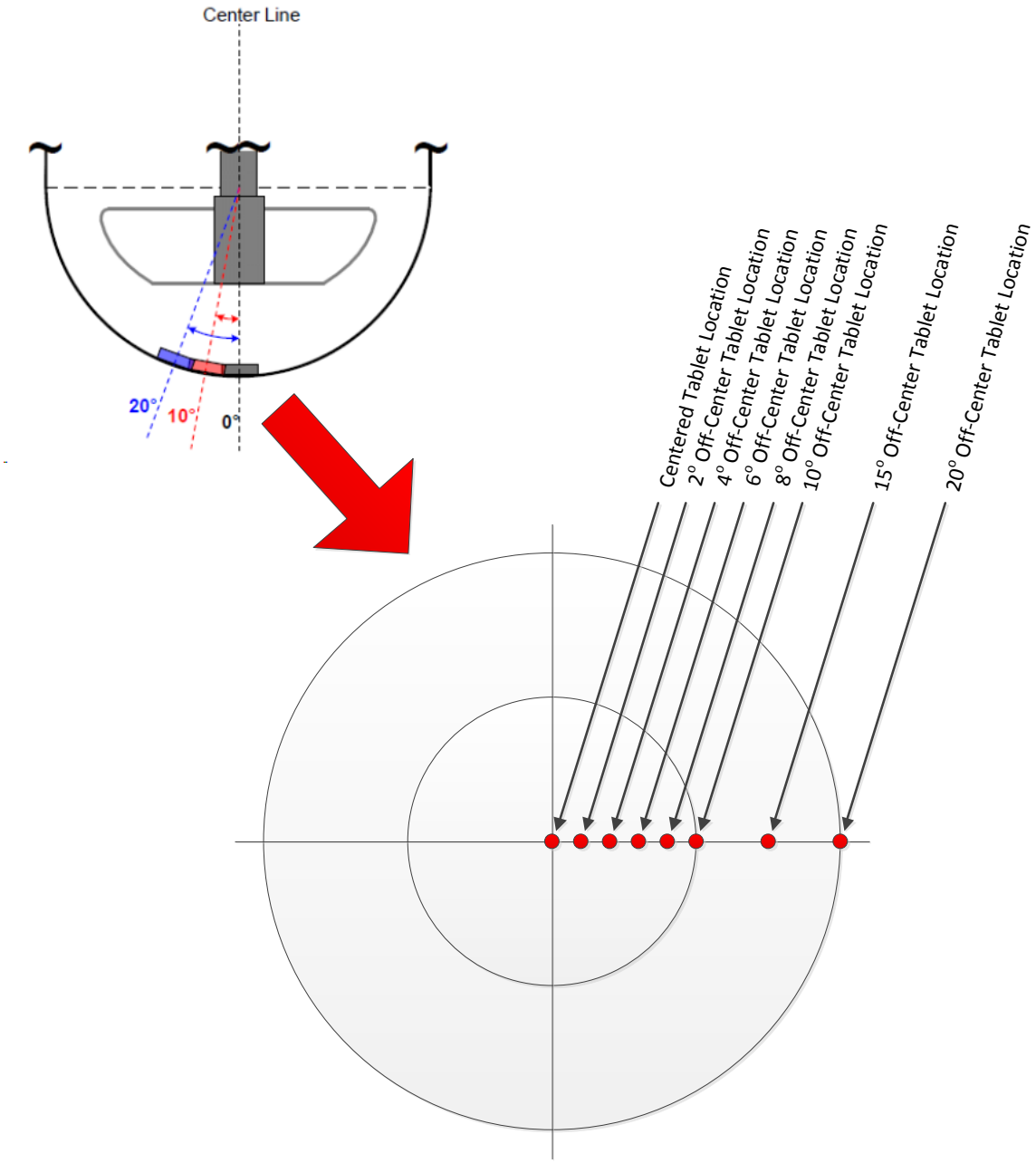


Figure 4.3 Top Panel: side view of the bottom portion of the USP Apparatus 2 showing the different locations of a tablet center during dissolution experiments (only centered, 10°, and 20° tablets are shown); Bottom Panel: top view of a smaller section of the bottom of a USP Apparatus 2 showing the different locations of a tablet during dissolution experiments.

Table 4.1 Operation Conditions for Dissolution Experiments.

Dose	10 mg (Prednisone tablets) 500 mg (Salicylic acid tablets)
Medium	500 mL of de-aerated, distilled water (Prednisone tablets) 900 mL of de-aerated buffer solution
Temperature	37^{o}C
Agitation Speed	50 rpm (Prednisone tablets) 100 rpm (Salicylic acid tablets)
Filter	PVDF 0.45um
UV Wavelength in spectrophotometer)	242 nm (Prednisone tablets) 296 nm (Salicylic Acid tablets)
Standard Tablets	Calibrated tablets
Sampling time	5-minute intervals; 45 minutes total

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 1-cm quartz cells filled with the solution and placed in a UV-visible spectrophotometer (Varian CARY 50 Bio) measuring absorbance at a specified wavelength, i.e., 242 nm for Prednisone and 296 nm for salicylic acid (the approximate wavelengths of maximum absorbance for the respective tablets). Before placing 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 or salicylic acid in the sample.

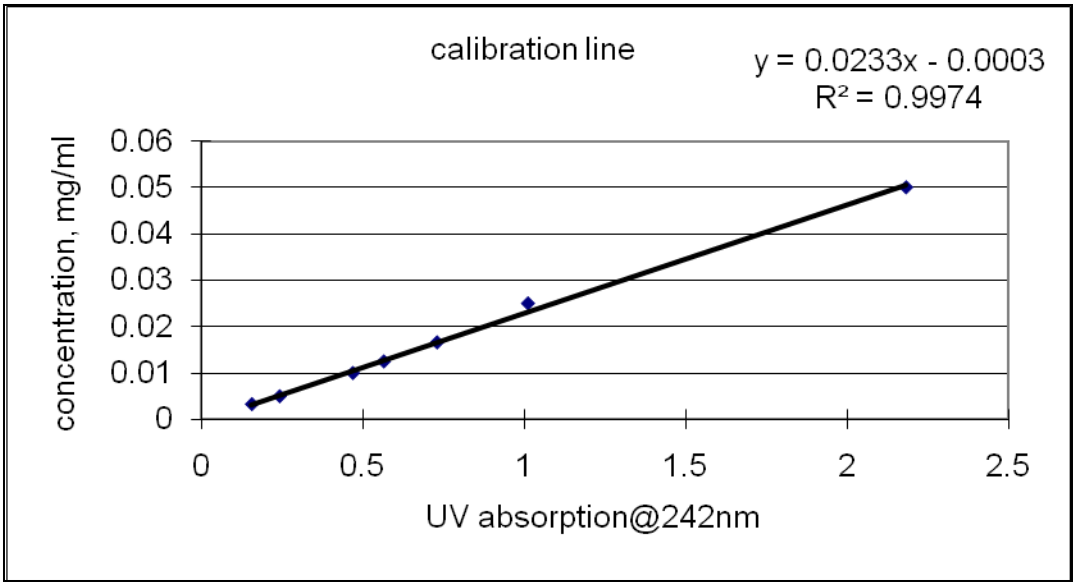
Calibration curves for Prednisone and salicylic acid tablets were obtained. Reference standard solutions of each drug were prepared in the dissolution medium and diluted to obtain solutions of different known concentrations. The absorbance of these solutions was obtained in order to generate absorbance-vs.-concentration standard curves. The calibration curves are presented in Table 4.2 and Figure 4.5. These results show that the calibration curves were always linear (R^2=0.9974 for Prednisone, and R^2=0.9999 for salicylic acid) in the concentration range of interest here.

Table 4.1 Calibration data for Prednisone

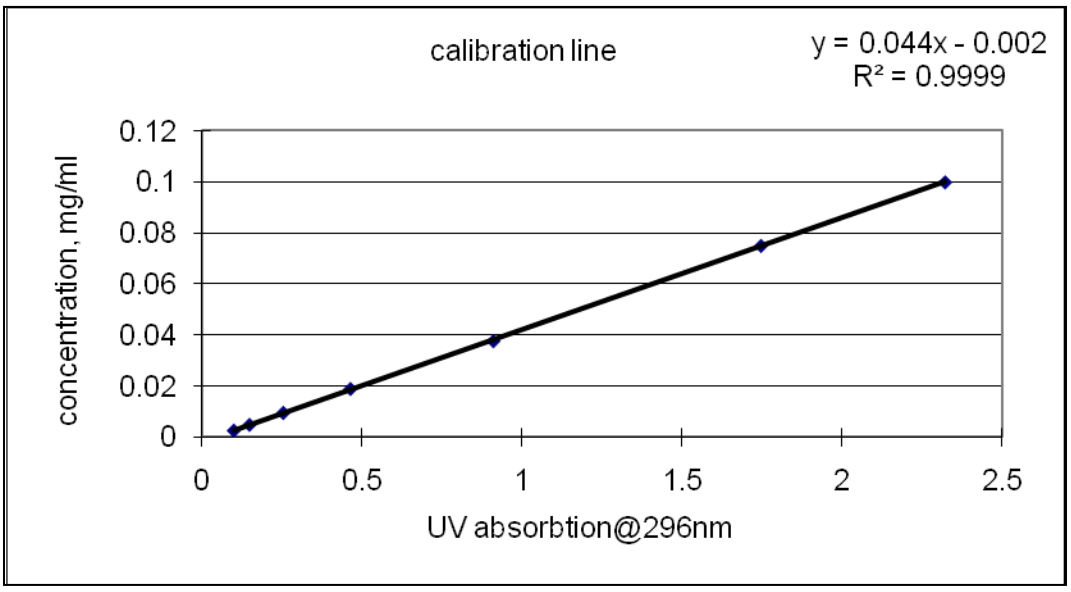
Absorption1	Absorption2	Absorption3	Average Absorption	Concentration (mg/mL)
0.156	0.155	0.155	0.155333333	0.0033
0.241	0.242	0.241	0.241333333	0.005
0.469	0.468	0.467	0.468	0.01
0.564	0.565	0.563	0.564	0.0125
0.73	0.729	0.728	0.729	0.0166
1.012	1.011	1.009	1.010666667	0.025
2.185	2.182	2.181	2.182666667	0.05

Table 4.2 Calibration data for Salicylic Acid

Absorption1	Absorption2	Absorption3	Average Absorption	Concentration (mg/mL)
2.321	2.324	2.32	2.321667	0.1
1.749	1.745	1.746	1.746667	0.075
0.911	0.91	0.912	0.911	0.0375
0.464	0.465	0.464	0.464333	0.0187
0.255	0.254	0.255	0.254667	0.0093
0.149	0.15	0.149	0.149333	0.0046
0.101	0.1	0.1	0.100333	0.0023



(a)



(b)

Figure 4.5 (a) Calibration curve for Prednisone. **(b)** Calibration curve for salicylic acid.

4.4 Data Analysis

The dissolution profiles obtained with tablets at off-center locations in the USP Apparatus 2 were compared to those obtained with the centrally located tablets in the same apparatus in order to determine whether these dissolution curves were statistically similar or different.

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):

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \qquad (4.4.1)$$

$$f_2 = 50 \log_{10}\{[1 + (\frac{1}{n})\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\} \qquad (4.4.2)$$

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 5

RESULTS

5.1 Results for Dissolution of Prednisone Tablets

In this section of the study, the dissolution profiles are presented for Prednisone tablets at eight different tablet locations (0°, 2°, 4°, 6°, 8°, 10°, 15°, and 20°) at the bottom of the dissolution vessel using the Standard USP Dissolution System at an agitation speed of 50 rpm. The results are reported 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 was completely dissolved. Figure 5.1 presents these results. One can see that there is a significant similarity between the dissolution profiles for the tablets located at the 0°, 2° and 4° locations. However, these profiles are very different from those obtained at tablet locations where the angle was equal to, or larger than, 6° off the vertical centerline. 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 were in the required range when the tablets were at the 2° and 4° locations. When the tablet was 6° off center, the f_1 value was out of range, whereas the f_2 value was in-range, although barely above 50. However, for tablets at locations 6° or above, both the f_1 values and the f_2 values were out of the required range to insure statistical similarity, which implies that tablets at or above the 6° locations would fail the dissolution test. These results confirm that the dissolution profiles for the chosen disintegrating solid

dosage form (Prednisone) depend strongly on tablet location in a standard USP Apparatus 2 Dissolution System. These results are in agreement with previously reported work from this and other research groups, although the results presented here show a very high degree of sensitivity of the dissolution profiles to even small deviations of the tablet location from the centered symmetric position. In other terms, even tablet locations only a few degrees (as low as 6°) off center result in dissolution profiles that are statistically different from those for the "regular" center-position tablet. Detailed results are presented in Appendix C.

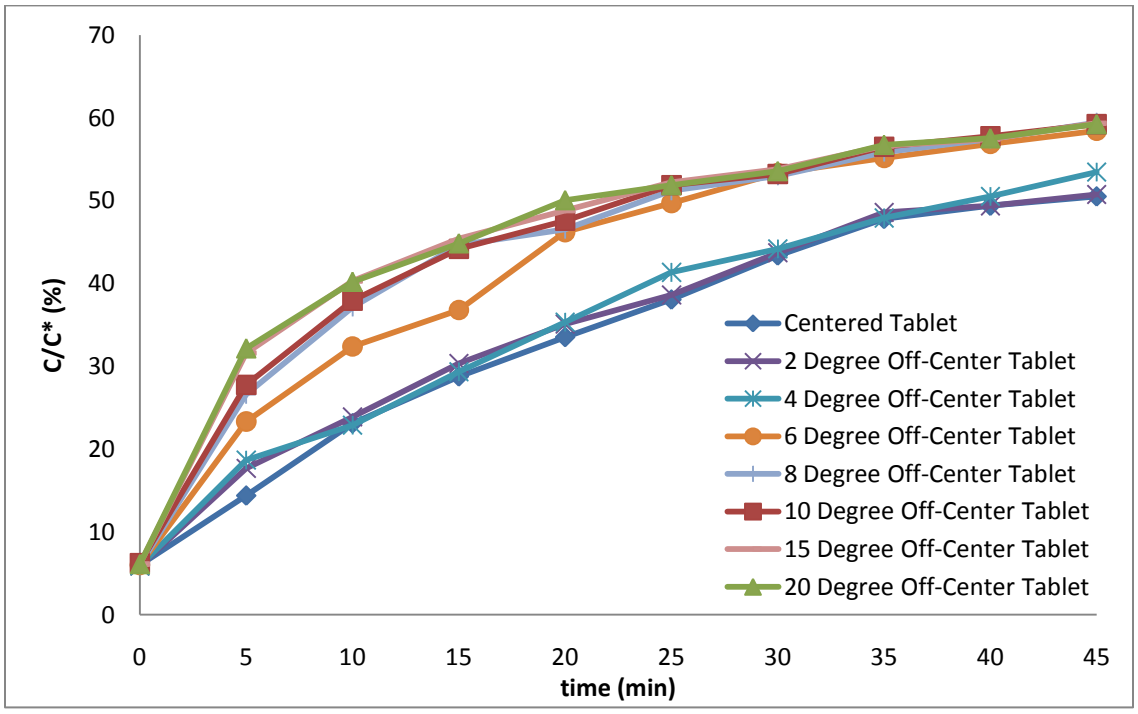


Figure 5.1 Dissolution profiles for Prednisone for eight different tablet positions during dissolution testing experiments.

Table 5.1 f_1 and f_2 values for the dissolution profiles of Prednisone tablets at different off-center locations compared to that for a centered tablet.

Tablet off-center angle	f_1	f_2
2	2.789	88.993
4	4.614	81.779
6	25.344	52.286
8	31.301	47.556
10	32.575	46.714
15	35.468	44.607
20	37.81	44.445

5.2 Results for Dissolution of Salicylic Acid Tablets

In this section of the study, the dissolution profiles are presented for salicylic acid tablets at eight different tablet locations (0°, 2°, 4°, 6°, 8°, 10°, 15°, and 20°) at the bottom of the dissolution vessel using the Standard USP Dissolution System at an agitation speed of 100 rpm. As before, the results are reported in terms of C/C^*, i.e., the ratio of salicylic acid concentration in the dissolving medium, C, at a given time, t, relative to the final concentration, C^*, obtained when the entire 300 mg tablet was completely dissolved. Figure 5.2 presents these results. One can see that there is a significant similarity between the dissolution profiles for the tablets located at the 0° and 2° locations. However, these profiles are very different from those obtained at tablet locations where the angle was equal to, or larger than, 4° off the vertical centerline. 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 5.2. Both f_1 and f_2 were in the required range when the tablet was at the 2° location. However, when the tablets were 4° off center or above, the f_1 values were out of range, although the f_2 values were

(barely) in-range, which still implies that these tablets would fail the dissolution test. These results confirm that the dissolution profiles for the chosen disintegrating solid dosage form (salicylic acid) depend strongly on tablet location in a standard USP Apparatus 2 Dissolution System. These results are in agreement with previously reported work from this and other research groups, although the results presented here show a very high degree of sensitivity of the dissolution profiles to even small deviations of the tablet location from the centered symmetric position. In other terms, even tablet locations only a few degrees (as low as 4°) off center result in dissolution profiles that are statistically different from those for the "regular" center-position tablet. Detailed results are presented in Appendix D.

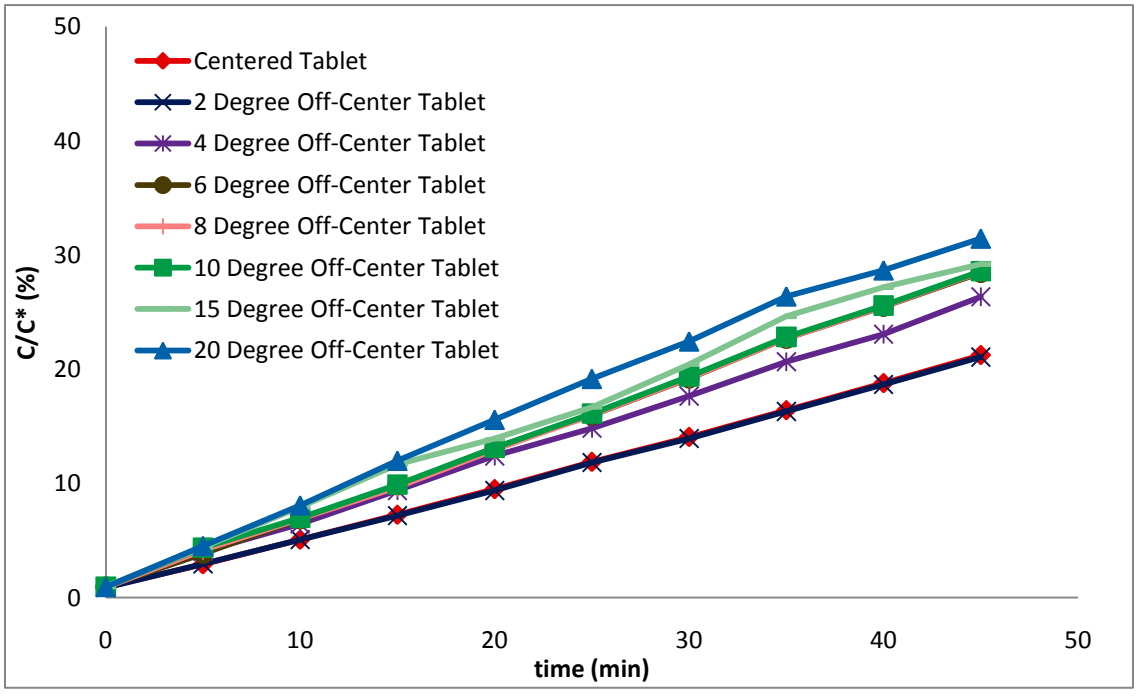


Figure 5.2 Dissolution profiles for salicylic acid for eight different tablet positions during dissolution testing experiments.

Table 5.2 f_1 and f_2 values for the dissolution profiles of salicylic acid tablets at different off-center locations compared to that for a centered tablet.

Tablet off-center angle	f_1	f_2
2	0.71756	99.90817
4	25.92636	73.90919
6	35.83108	66.75391
8	36.00753	66.70632
10	36.23103	66.65084
15	45.77109	62.17712
20	55.46406	58.09357

CHAPTER 6

DISCUSSION

The experimental results presented here clearly demonstrate the importance of tablet location during dissolution testing. The experimental dissolution data for both disintegrating and non-disintegrating tablets indicate that the location of the tablet produces statistically different dissolution testing results. This is in good agreement with the previous results of Bai and Armenante (2009), Bai and Armenante, (2007), and Baxter et al. (2005). The statistical difference between the results obtained here for different tablet locations can be quantified by examining the value of the difference factor, f_1 , which is always outside the range established by FDA for statistical similarity (Table 4.1 and 4.2). The difference factor f_2 calculated for the off-center tablets vs. the centered tablets produces more ambiguous results, since many of the values reported in Table 4.1 and 4.2 for this factor are within the FDA limits (50-100), although always borderline. This apparent conflict between the factors recommended by the FDA is caused by the fact that f_2 is not a very sensitive statistical tool to assess differences among dissolution curves. The contradictory outcome of these two factors has also been reported by other researchers (Bai and Armenante, 2009, Baxter et al. 2005, Costa. and Lobo, 2001), who have pointed out that the conflict between the two methods shows that the similarity factor f_2 may not be very robust for its intended task. While the difference between dissolution curves obtained at different tablet locations may make sense for non-disintegrating, eroding tablets (since the complex hydrodynamics of the Apparatus 2 can be expected to produce different flows around tablets at different locations (Bai and Armenante, 2007; Bai and Armenante, 2009), it is more difficult to justify for

disintegrating tablets, since the tablet fragments, once the tablet disintegrates, move toward the center of the vessel, thus possibly eliminating any further effect of the initial tablet location on the remaining portion of the dissolution process. The explanation for this apparent contradiction comes from a closer examination of Figure 4.1. This figure shows that at t=0 minutes all curves start at the same point, and that the concentration ratio C/C^* at this time is appreciably high (6%). Within 5 minutes, the curves for the off-center tablets diverge from those for the centrally located ones. However, after this time the two sets of curves remain nearly parallel to each other. One can conclude that what happens during the first 5 minutes is critical to promote dissolution and disintegration, and that the reminder of the dissolution process simply adds to that initial basis. In fact, it was visually observed that by t=5 minutes the off-center tablets were nearly completely disintegrated, whereas it took about 8 minutes for the centered tablet to do the same. Apparently, the improved hydrodynamics experienced by off-center tablets results in a more rapid dissolution *and* disintegration of the tablet, generating a higher dissolved concentration of the drug during the initial phase of the dissolution process. Once this initial process is complete and the tablet is fully disintegrated, the dissolution process proceeds at a similar rate irrespective of the initial location of the tablet in the vessel.

The process is different for non-disintegrating tablets. Here, since the tablets remain at their initial location during the whole process, the improved hydrodynamics experienced by off-center tablets results in their faster dissolution rate throughout the entire dissolution test. This can be clearly seen in Figure 4.2, where the gap between the curves keeps growing as times goes by (obviously this cannot go on forever, as predicted by Equation 2.6, since eventually all curves must reach the same C/C^* ratio of 1 if

$C^* < C_S$, where C_S is the saturation concentration). Unlike the disintegrating prednisone tablets, the non-disintegrating salicylic acid tablets are subjected to higher dissolution rates during the entire test, and not only until disintegration occurs. Although a major difference in dissolution performance can be seen between off-center and centered tablets, not all off-center tablet positions are equal. A small off-center tablet displacement of only 4° is already capable of producing significantly and statistically different dissolution results compared to the centered tablet case. One can only speculate on how many dissolution tests routinely fail simply as a result of such small random variations in the tablet resting position after it has been dropped in the vessel. However, greater off-center deviations of the tablet location from the centerline can produce even larger variations in test results. Both Figure 4.1 and Figure 4.2 show that the dissolution curves for tablets above 10° off-center deviate the most from the curves for the centered tablets.

CHAPTER 7

CONCLUSION

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

1. The dissolution performance of both disintegrating Prednisone tablets and non disintegrating salicylic acid tablets in 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 the hydrodynamic characteristics of the apparatus itself and the location of the tablet on the vessel bottom.
2. In most of the cases reported here with calibrator tablets, displacing and keeping the tablet off center often resulted in failing the dissolution test. Test failures occurred with both disintegrating and non-disintegrating tablets even when the tablets were only slightly displaced from the centered tablet location ($\leq 4°$ for Prednisone tablets and $\leq 2°$ for salicylic acid tablets), as indicated by the systematic and statistically significant off-specification values of the similarity factor f_1. In the same experiments, the difference factor f_2 was less sensitive to detect differences in dissolution profiles, and its value was either off-specification or borderline.
3. Non-disintegrating off-center tablets may fail because the flow fields surrounding them are appreciably different from the flow field surrounding a centrally placed tablet throughout the entire dissolution process.

4. Disintegrating off-center tablets may fail because the initial disintegration and dissolution process during the first few minutes of the test is sufficiently different between off-center and centered tablets.
5. These finding are consistent with previous hydrodynamic investigations that showed the existence of a poorly mixed zone below the USP Apparatus 2 impeller (Ge and Armenante, 2007; Ge and Armenante, 2009).
6. The results of this work can guide the practitioner on when to accept or discard dissolution testing results based on tablet location.

APPENDIX A

DISSOLUTION PROFILE OF PREDNISONE TABLETS

Figure A.1 to A.8 show Dissolution of Prednisone Tablet at different locations.

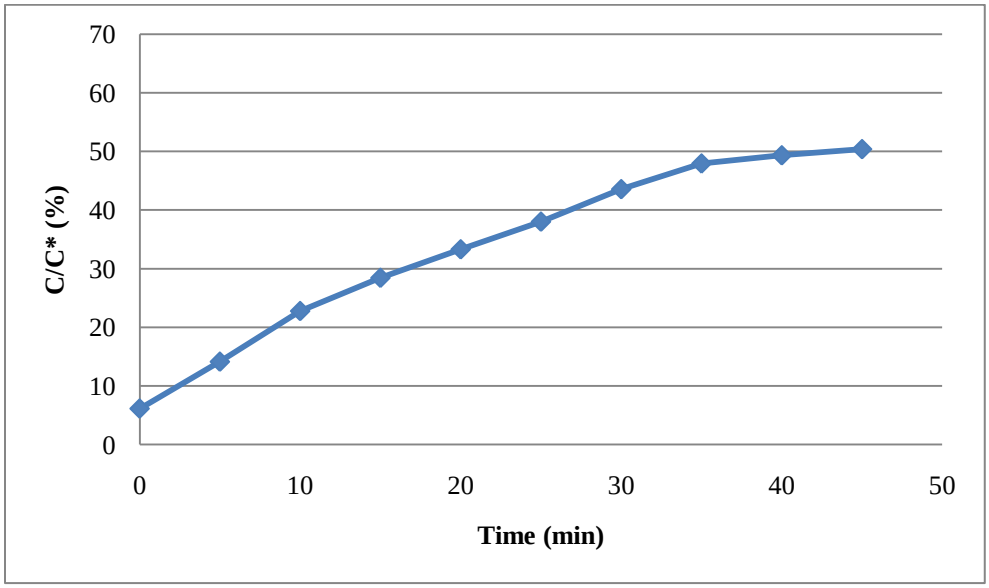


Figure A.1 Dissolution profile of Prednisone tablet at Central location.

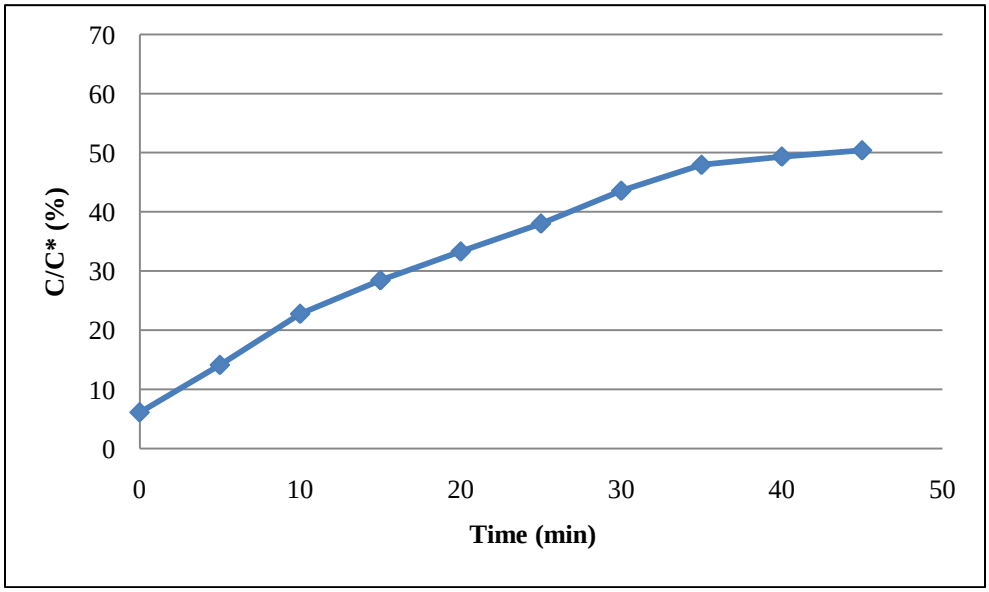


Figure A.2 Dissolution profile of Prednisone tablet at2˚off-center.

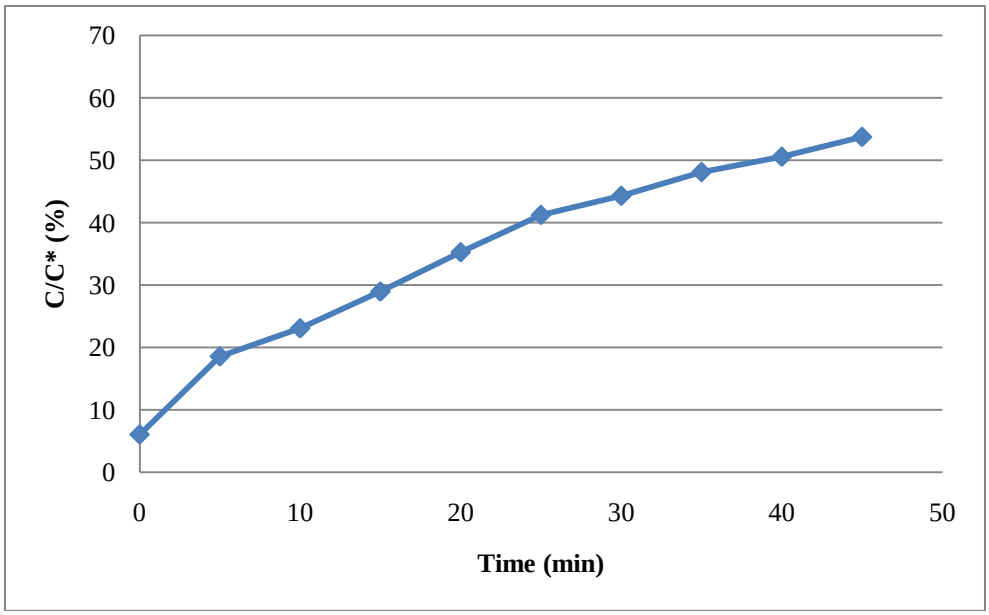


Figure A.3 Dissolution profile of Prednisone tablet at 4˚ off-center.

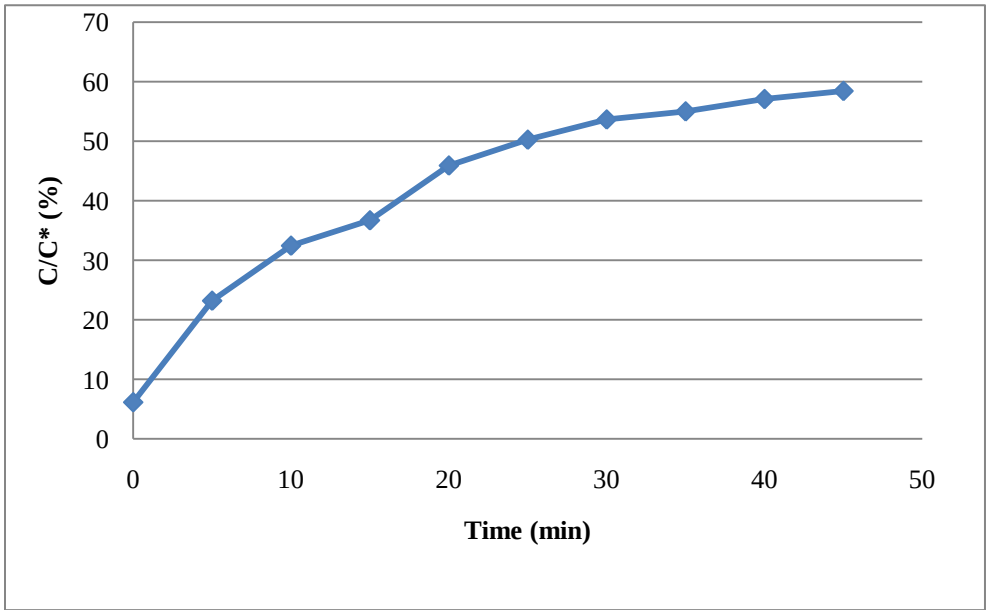


Figure A.4 Dissolution profile of Prednisone tablet at 6˚ off-center.

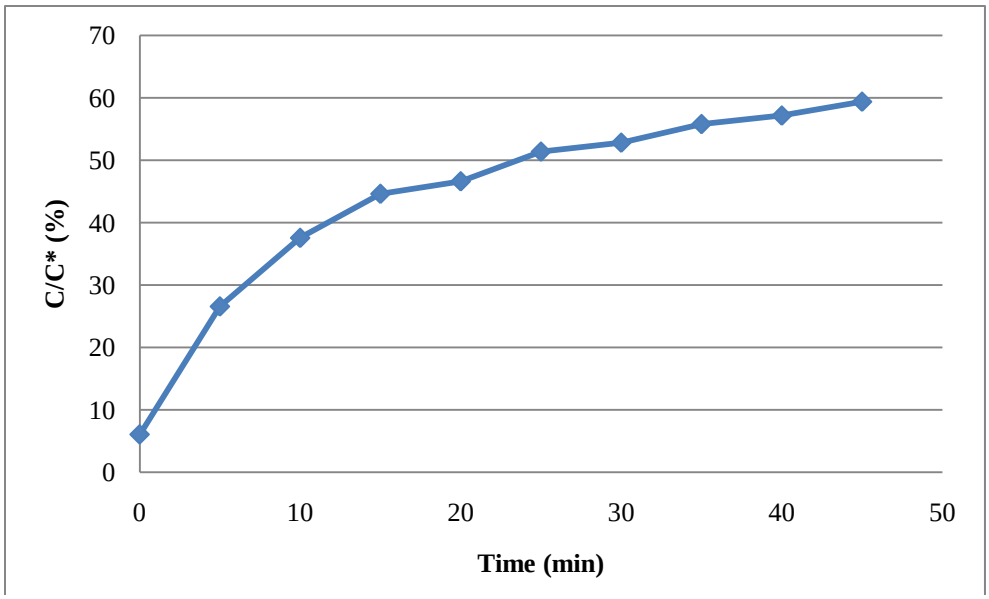


Figure A.5 Dissolution profile of Prednisone tablet at 8˚ off-center.

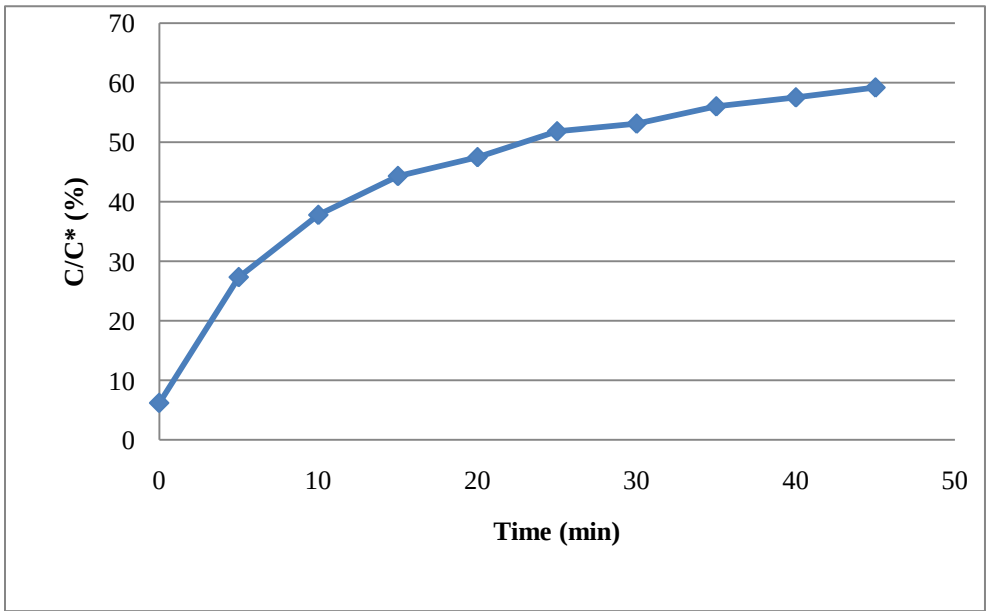


Figure A.6 Dissolution profile of Prednisone tablet at 10˚ off-center.

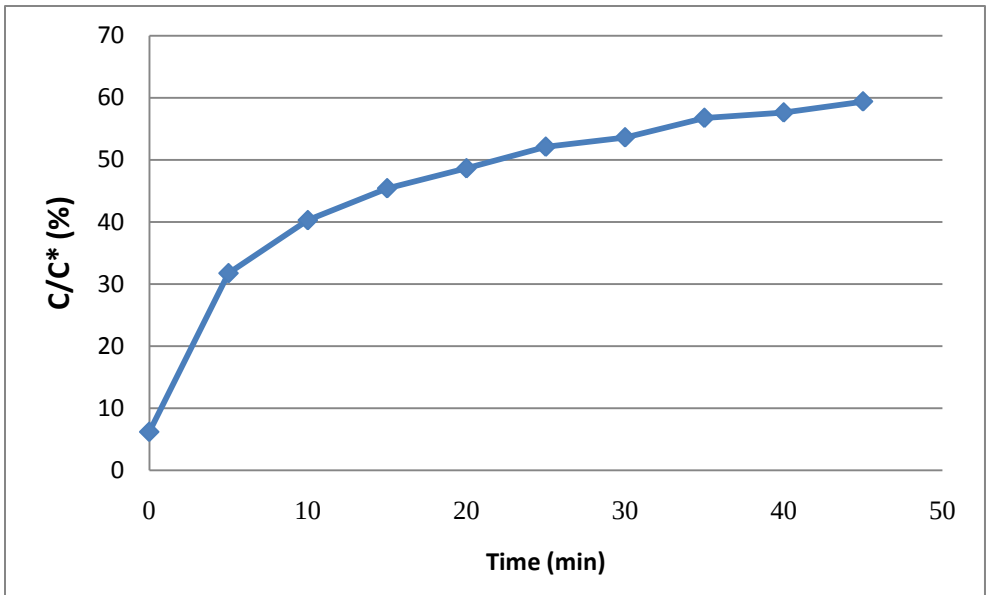


Figure A.7 Dissolution profile of Prednisone tablet at 15˚ off-center.

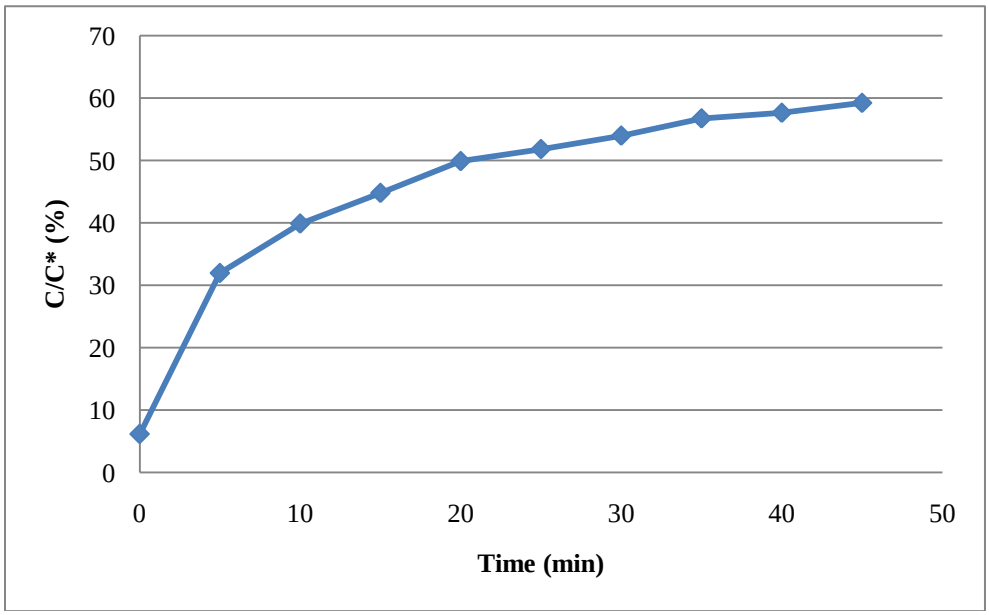


Figure A.8 Dissolution profile of Prednisone tablet at 20˚ off-center.

APPENDIX B

DISSOLUTION PROFILE OF SALICYLIC ACID TABLETS

Figure B.1 to B.8 show Dissolution of Salicylic Acid Tablet at different locations.

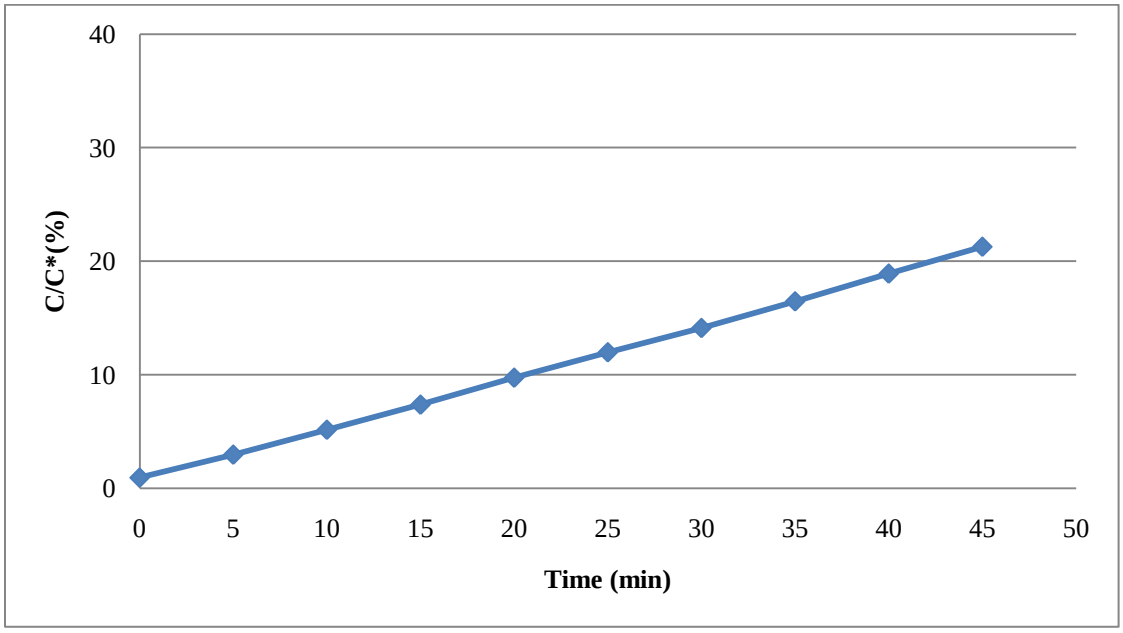


Figure B.1 Dissolution profile of Salicylic Acid tablet at Central location.

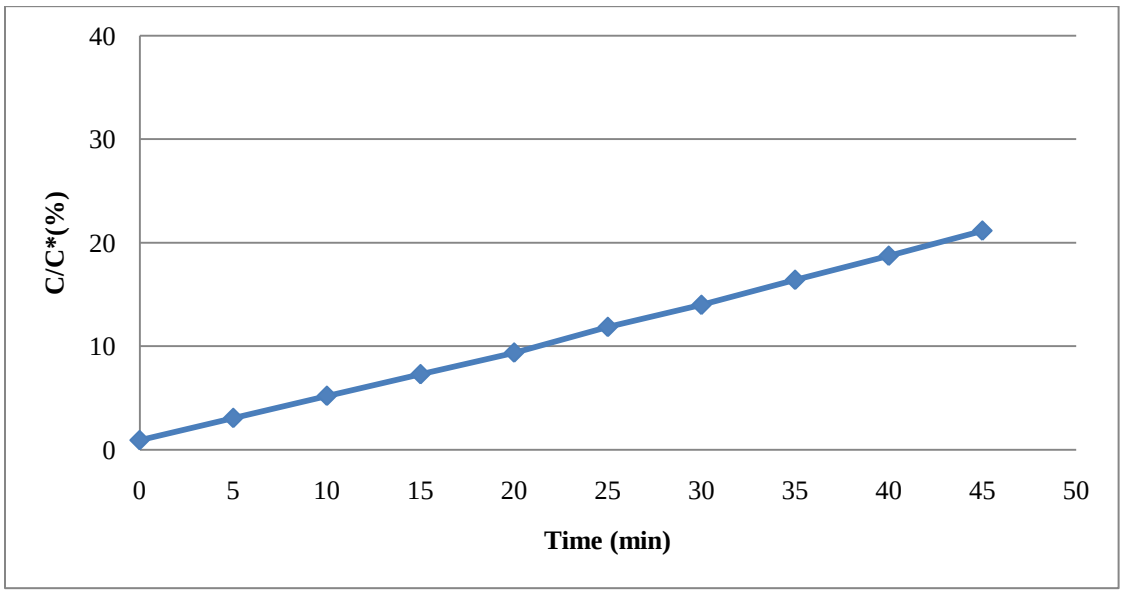


Figure B.2 Dissolution profile of Salicylic Acid tablet at 2˚ off-center.

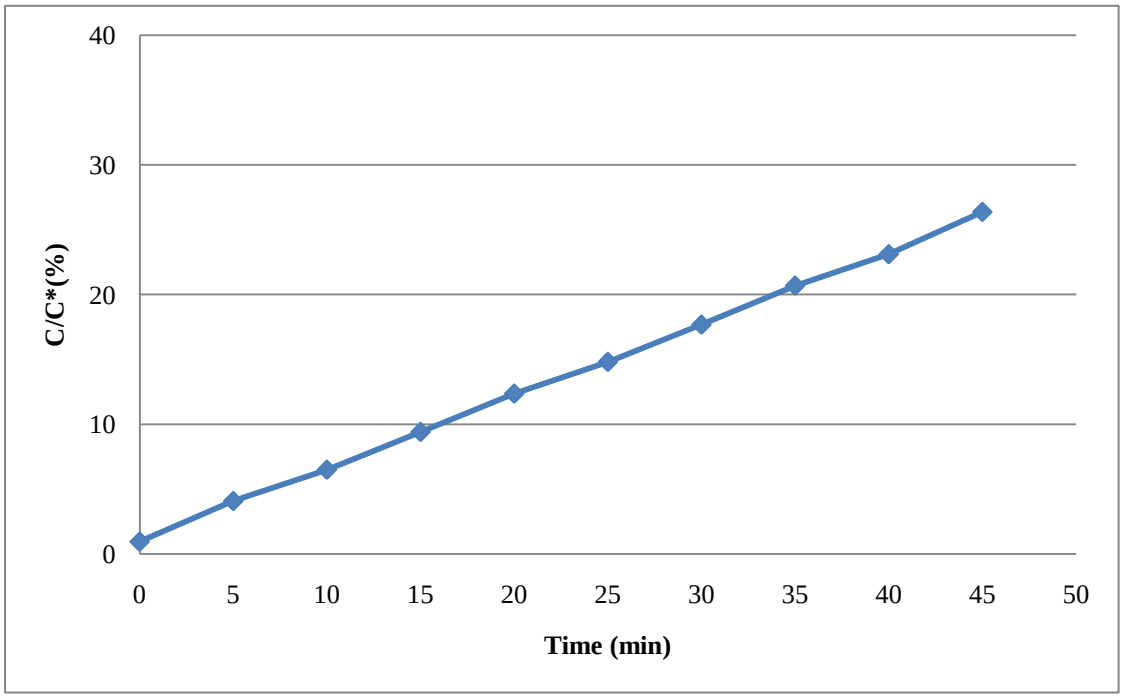


Figure B.3 Dissolution profile of Salicylic Acid tablet at 4˚ off-center.

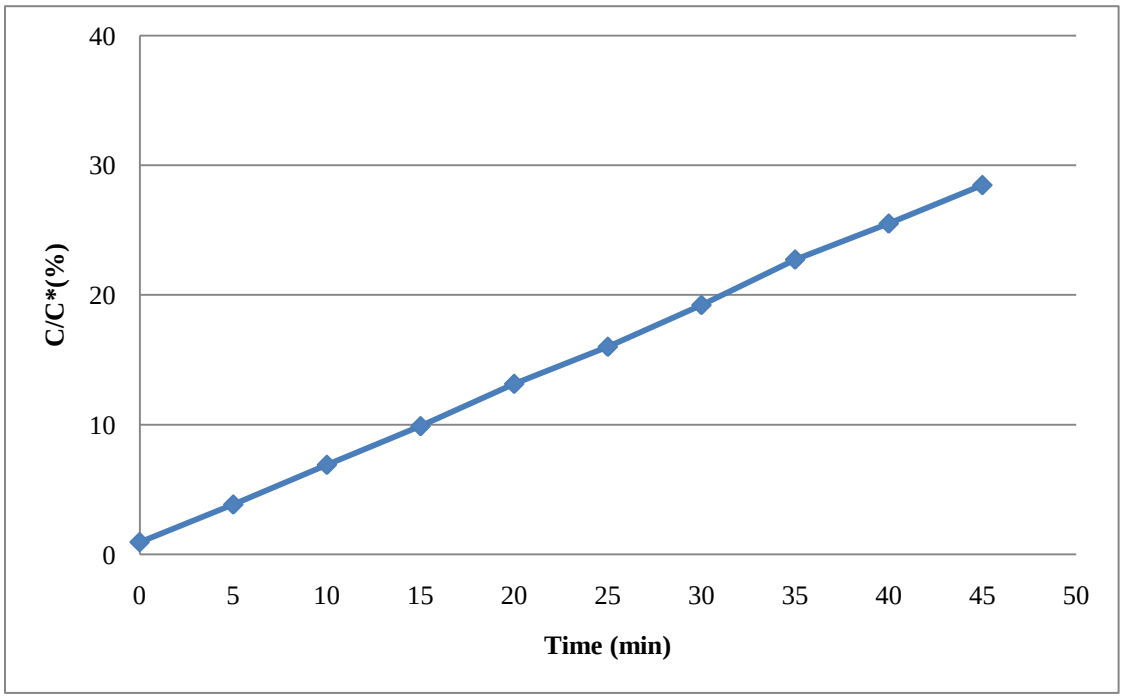


Figure B.4 Dissolution profile of Salicylic Acid tablet at 6˚ off-center.

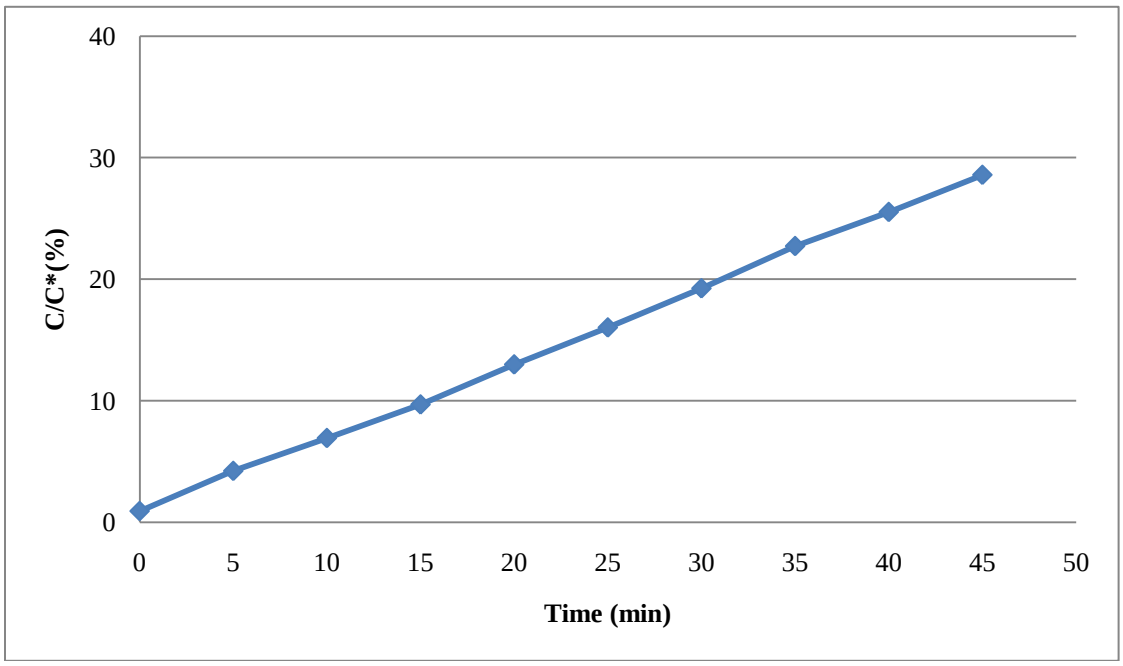


Figure B.5 Dissolution profile of Salicylic Acid tablet at 8˚ off-center.

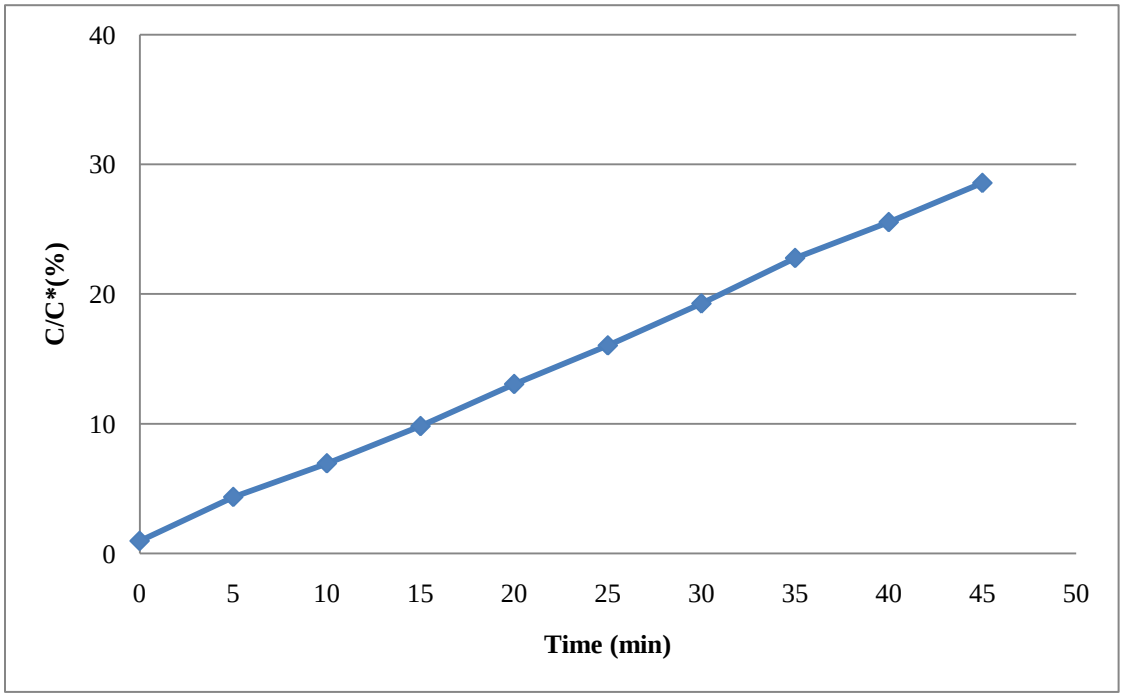


Figure B.6 Dissolution profile of Salicylic Acid tablet at 10˚ off-center.

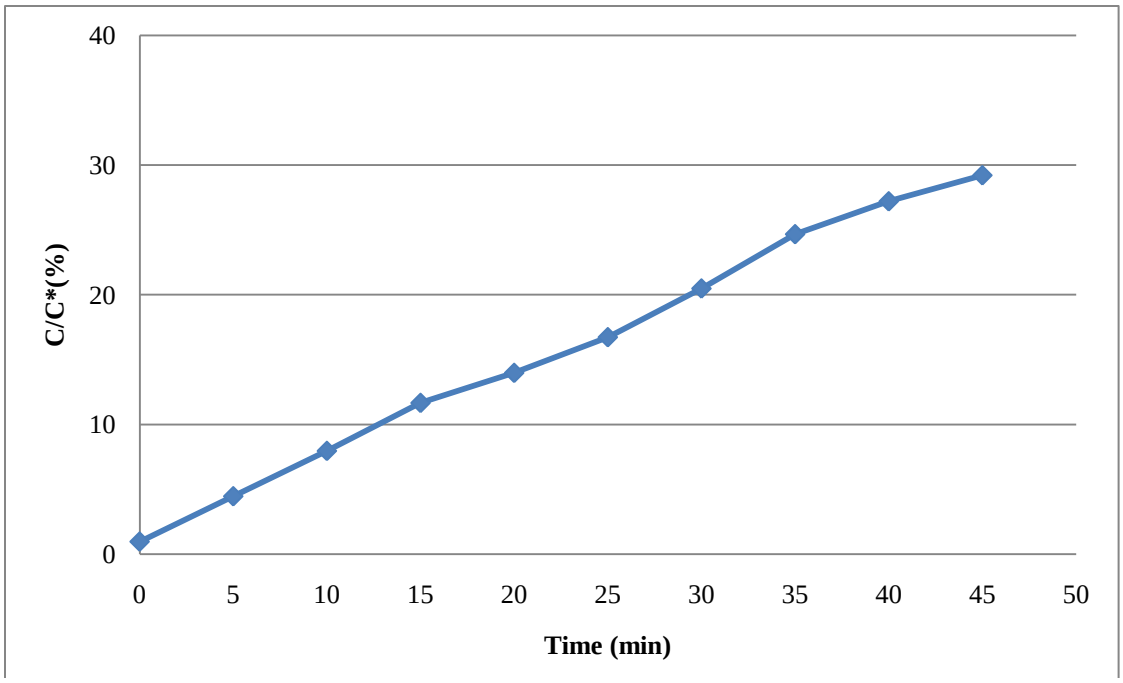


Figure B.7 Dissolution profile of Salicylic Acid tablet at 15˚ off-center.

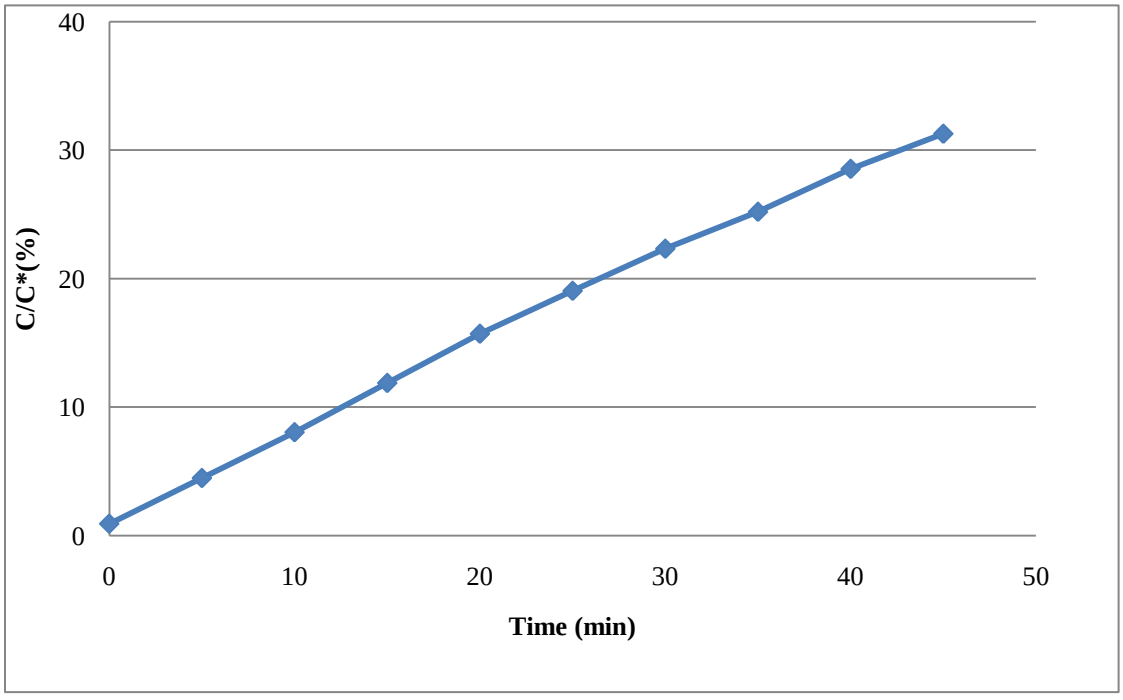


Figure B.8 Dissolution profile of Salicylic Acid tablet at 20˚ off-center.

APPENDIX C

This appendix includes all tables of Dissolution Profiles of Prednisone Tablet at different tablet locations in detail.

Table C.1 Dissolution Profile of Prednisone at Central Location

Time (min)	Average Absorption	Slope	Intercept	C (mg/mL)	C/C*	C/C* Standard Deviation	C/C* (%)
0	0.053	0.023	-0.00035	0.0012	0.0600	0.0011	6.0023
5	0.127	0.023	-0.00035	0.0029	0.1438	0.0036	14.3828
10	0.204	0.023	-0.00035	0.0046	0.2310	0.0034	23.1030
15	0.254	0.023	-0.00035	0.0058	0.2877	0.0049	28.7655
20	0.296	0.023	-0.00035	0.0067	0.3352	0.0060	33.5220
25	0.336	0.023	-0.00035	0.0076	0.3805	0.0051	38.0520
30	0.383	0.023	-0.00035	0.0087	0.4337	0.0043	43.3748
35	0.422	0.023	-0.00035	0.0096	0.4779	0.0047	47.7915
40	0.436	0.023	-0.00035	0.0099	0.4938	0.0040	49.3770
45	0.446	0.023	-0.00035	0.0101	0.5051	0.0041	50.5095

Table C.2 Dissolution Profile of Prednisone at 2° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.052	0.023	-0.00035	0.0012	0.0589	0.0013	5.8890	2.7893	88.993
5	0.156	0.023	-0.00035	0.0035	0.1767	0.0083	17.667		
10	0.211	0.023	-0.00035	0.0048	0.2390	0.0060	23.895		
15	0.268	0.023	-0.00035	0.0061	0.3035	0.0094	30.351		
20	0.31	0.023	-0.00035	0.0070	0.3511	0.0029	35.107		
25	0.341	0.023	-0.00035	0.0077	0.3862	0.0043	38.618		
30	0.386	0.023	-0.00035	0.0087	0.4371	0.0024	43.714		
35	0.429	0.023	-0.00035	0.0097	0.4858	0.0017	48.584		
40	0.436	0.023	-0.00035	0.0099	0.4938	0.0017	49.377		
45	0.448	0.023	-0.00035	0.0101	0.5074	0.0024	50.736		

Table C.3 Dissolution Profile of Prednisone at 4° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.052	0.023	-0.00035	0.0012	0.0589	0.0017	5.8890	4.6143	81.7799
5	0.165	0.023	-0.00035	0.0037	0.1869	0.0011	18.6863		
10	0.202	0.023	-0.00035	0.0046	0.2288	0.0017	22.8765		
15	0.259	0.023	-0.00035	0.0059	0.2933	0.0035	29.3318		
20	0.312	0.023	-0.00035	0.0071	0.3533	0.0013	35.3340		
25	0.365	0.023	-0.00035	0.0083	0.4134	0.0020	41.3363		
30	0.39	0.023	-0.00035	0.0088	0.4417	0.0020	44.1675		
35	0.423	0.023	-0.00035	0.0096	0.4790	0.0017	47.9048		
40	0.446	0.023	-0.00035	0.0101	0.5051	0.0017	50.5095		
45	0.472	0.023	-0.00035	0.0107	0.5345	0.0024	53.4540		

Table C.4 Dissolution Profile of Prednisone at 6° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.053	0.023	-0.00035	0.0012	0.0600	0.0017	6.0023	25.3444	52.2864
5	0.206	0.023	-0.00035	0.0047	0.2333	0.0030	23.3295		
10	0.286	0.023	-0.00035	0.0065	0.3239	0.0024	32.3895		
15	0.325	0.023	-0.00035	0.0074	0.3681	0.0024	36.8063		
20	0.408	0.023	-0.00035	0.0092	0.4621	0.0036	46.2060		
25	0.439	0.023	-0.00035	0.0099	0.4972	0.0057	49.7168		
30	0.471	0.023	-0.00035	0.0107	0.5334	0.0041	53.3408		
35	0.487	0.023	-0.00035	0.0110	0.5515	0.0041	55.1528		
40	0.502	0.023	-0.00035	0.0114	0.5685	0.0036	56.8515		
45	0.516	0.023	-0.00035	0.0117	0.5844	0.0029	58.4370		

Table C.5 Dissolution Profile of Prednisone at 8° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.053	0.023	-0.00035	0.0012	0.0600	0.0007	6.0023	31.3017	47.5564
5	0.235	0.023	-0.00035	0.0053	0.2661	0.0017	26.6138		
10	0.328	0.023	-0.00035	0.0074	0.3715	0.0046	37.1460		
15	0.394	0.023	-0.00035	0.0089	0.4462	0.0034	44.6205		
20	0.411	0.023	-0.00035	0.0093	0.4655	0.0007	46.5458		
25	0.452	0.023	-0.00035	0.0102	0.5119	0.0024	51.1890		
30	0.468	0.023	-0.00035	0.0106	0.5300	0.0033	53.0010		
35	0.493	0.023	-0.00035	0.0112	0.5583	0.0017	55.8323		
40	0.507	0.023	-0.00035	0.0115	0.5742	0.0036	57.4178		
45	0.525	0.023	-0.00035	0.0119	0.5946	0.0035	59.4563		

Table C.6 Dissolution Profile of Prednisone at 10° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.055	0.023	-0.00035	0.0012	0.0623	0.0007	6.2288	32.5758	46.7143
5	0.245	0.023	-0.00035	0.0055	0.2775	0.0036	27.7463		
10	0.335	0.023	-0.00035	0.0076	0.3794	0.0036	37.9388		
15	0.39	0.023	-0.00035	0.0088	0.4417	0.0047	44.1675		
20	0.42	0.023	-0.00035	0.0095	0.4757	0.0035	47.5650		
25	0.458	0.023	-0.00035	0.0104	0.5187	0.0017	51.8685		
30	0.47	0.023	-0.00035	0.0106	0.5323	0.0020	53.2275		
35	0.499	0.023	-0.00035	0.0113	0.5651	0.0051	56.5118		
40	0.51	0.023	-0.00035	0.0116	0.5776	0.0023	57.7575		
45	0.523	0.023	-0.00035	0.0118	0.5923	0.0007	59.2298		

Table C.7 Dissolution Profile of Prednisone at 15° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.054	0.023	-0.00035	0.0012	0.0612	0.0011	6.1155	35.4683	44.6077
5	0.279	0.023	-0.00035	0.0063	0.3160	0.0036	31.5968		
10	0.356	0.023	-0.00035	0.0081	0.4032	0.0040	40.3170		
15	0.401	0.023	-0.00035	0.0091	0.4541	0.0045	45.4133		
20	0.431	0.023	-0.00035	0.0098	0.4881	0.0024	48.8108		
25	0.461	0.023	-0.00035	0.0104	0.5221	0.0011	52.2083		
30	0.475	0.023	-0.00035	0.0108	0.5379	0.0017	53.7938		
35	0.5	0.023	-0.00035	0.0113	0.5663	0.0011	56.6250		
40	0.507	0.023	-0.00035	0.0115	0.5742	0.0017	57.4178		
45	0.524	0.023	-0.00035	0.0119	0.5934	0.0017	59.3430		

Table C.8 Dissolution Profile of Prednisone at 20° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.054	0.023	-0.00035	0.0012	0.0612	0.0007	6.1155	37.8104	44.4455
5	0.284	0.023	-0.00035	0.0064	0.3216	0.0023	32.1630		
10	0.355	0.023	-0.00035	0.0080	0.4020	0.0034	40.2038		
15	0.396	0.023	-0.00035	0.0090	0.4485	0.0035	44.8470		
20	0.442	0.023	-0.00035	0.0100	0.5006	0.0017	50.0565		
25	0.458	0.023	-0.00035	0.0104	0.5187	0.0013	51.8685		
30	0.473	0.023	-0.00035	0.0107	0.5357	0.0035	53.5673		
35	0.501	0.023	-0.00035	0.0113	0.5674	0.0017	56.7383		
40	0.508	0.023	-0.00035	0.0115	0.5753	0.0013	57.5310		
45	0.523	0.023	-0.00035	0.0118	0.5923	0.0007	59.2298		

APPENDIX D

TABLES FOR DISSOLUTION PROFILES OF SALICYLIC ACID.

This appendix includes all tables of Dissolution Profiles of Salicylic Acid Tablet at different tablet locations in detail.

Table D.1 Dissolution Profile of Salicylic Acid at Central Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)
0	0.075	0.044	-0.002	0.0032	0.0095	7.3E-05	0.945
5	0.232	0.044	-0.002	0.0097	0.0292	0.00112	2.923
10	0.403	0.044	-0.002	0.0169	0.0508	0.00065	5.078
15	0.576	0.044	-0.002	0.0242	0.0726	0.00091	7.258
20	0.754	0.044	-0.002	0.0317	0.0950	0.00207	9.500
25	0.943	0.044	-0.002	0.0396	0.1188	0.00084	11.882
30	1.116	0.044	-0.002	0.0469	0.1406	0.00045	14.062
35	1.302	0.044	-0.002	0.0547	0.1641	0.00050	16.405
40	1.49	0.044	-0.002	0.0626	0.1877	0.00120	18.774
45	1.685	0.044	-0.002	0.0708	0.2123	0.00032	21.231

Table D.2 Dissolution Profile of Salicylic Acid at 2° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.071	0.044	-0.002	0.0030	0.0089	0.00026	0.895	0.7176	99.9082
5	0.234	0.044	-0.002	0.0098	0.0295	0.00095	2.948		
10	0.404	0.044	-0.002	0.0170	0.0509	0.00093	5.090		
15	0.57	0.044	-0.002	0.0239	0.0718	0.00095	7.182		
20	0.745	0.044	-0.002	0.0313	0.0939	0.00052	9.387		
25	0.939	0.044	-0.002	0.0394	0.1183	0.00041	11.831		
30	1.106	0.044	-0.002	0.0465	0.1394	0.00044	13.936		
35	1.294	0.044	-0.002	0.0543	0.1630	0.00088	16.304		
40	1.482	0.044	-0.002	0.0622	0.1867	0.00044	18.673		
45	1.672	0.044	-0.002	0.0702	0.2107	0.00069	21.067		

Table D.3 Dissolution Profile of Salicylic Acid at 4° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.076	0.044	-0.002	0.0032	0.0096	0.00015	0.958	25.9264	73.9092
5	0.322	0.044	-0.002	0.0135	0.0406	0.00025	4.057		
10	0.513	0.044	-0.002	0.0215	0.0646	0.00032	6.464		
15	0.745	0.044	-0.002	0.0313	0.0939	0.00019	9.387		
20	0.985	0.044	-0.002	0.0414	0.1241	0.00050	12.411		
25	1.177	0.044	-0.002	0.0494	0.1483	0.00033	14.830		
30	1.401	0.044	-0.002	0.0588	0.1765	0.00033	17.653		
35	1.64	0.044	-0.002	0.0689	0.2066	0.00019	20.664		
40	1.831	0.044	-0.002	0.0769	0.2307	0.00033	23.071		
45	2.091	0.044	-0.002	0.0878	0.2635	0.00026	26.347		

Table D.4 Dissolution Profile of Salicylic Acid at 6° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.076	0.044	-0.002	0.0032	0.0096	0.00013	0.958	35.8311	66.7539
5	0.305	0.044	-0.002	0.0128	0.0384	0.00038	3.843		
10	0.546	0.044	-0.002	0.0229	0.0688	0.00048	6.880		
15	0.781	0.044	-0.002	0.0328	0.0984	0.00038	9.841		
20	1.042	0.044	-0.002	0.0438	0.1313	0.00029	13.129		
25	1.268	0.044	-0.002	0.0533	0.1598	0.00026	15.977		
30	1.524	0.044	-0.002	0.0640	0.1920	0.00019	19.202		
35	1.801	0.044	-0.002	0.0756	0.2269	0.00045	22.693		
40	2.022	0.044	-0.002	0.0849	0.2548	0.00025	25.477		
45	2.258	0.044	-0.002	0.0948	0.2845	0.00026	28.451		

Table D.5 Dissolution Profile of Salicylic Acid at 8° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.072	0.044	-0.002	0.0030	0.0091	0.00015	0.907	36.0075	66.7063
5	0.331	0.044	-0.002	0.0139	0.0417	0.00048	4.171		
10	0.547	0.044	-0.002	0.0230	0.0689	0.00033	6.892		
15	0.769	0.044	-0.002	0.0323	0.0969	0.00013	9.689		
20	1.028	0.044	-0.002	0.0432	0.1295	0.00026	12.953		
25	1.271	0.044	-0.002	0.0534	0.1601	0.00038	16.015		
30	1.526	0.044	-0.002	0.0641	0.1923	0.00013	19.228		
35	1.801	0.044	-0.002	0.0756	0.2269	0.00033	22.693		
40	2.024	0.044	-0.002	0.0850	0.2550	0.00041	25.502		
45	2.265	0.044	-0.002	0.0951	0.2854	0.00038	28.539		

Table D.6 Dissolution Profile of Salicylic Acid at 10° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.075	0.044	-0.002	0.0032	0.0095	0.00007	0.945	36.2310	66.6508
5	0.341	0.044	-0.002	0.0143	0.0430	0.00044	4.297		
10	0.548	0.044	-0.002	0.0230	0.0690	0.00048	6.905		
15	0.774	0.044	-0.002	0.0325	0.0975	0.00084	9.752		
20	1.032	0.044	-0.002	0.0433	0.1300	0.00067	13.003		
25	1.267	0.044	-0.002	0.0532	0.1596	0.00086	15.964		
30	1.526	0.044	-0.002	0.0641	0.1923	0.00100	19.228		
35	1.804	0.044	-0.002	0.0758	0.2273	0.00051	22.730		
40	2.024	0.044	-0.002	0.0850	0.2550	0.00038	25.502		
45	2.265	0.044	-0.002	0.0951	0.2854	0.00026	28.539		

Table D.7 Dissolution Profile of Salicylic Acid at 15° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.078	0.044	-0.002	0.0033	0.0098	0.00013	0.983	45.7711	62.1771
5	0.351	0.044	-0.002	0.0147	0.0442	0.00038	4.423		
10	0.63	0.044	-0.002	0.0265	0.0794	0.00025	7.938		
15	0.925	0.044	-0.002	0.0389	0.1166	0.00015	11.655		
20	1.106	0.044	-0.002	0.0465	0.1394	0.00038	13.936		
25	1.325	0.044	-0.002	0.0557	0.1670	0.00032	16.695		
30	1.623	0.044	-0.002	0.0682	0.2045	0.00032	20.450		
35	1.956	0.044	-0.002	0.0822	0.2465	0.00025	24.646		
40	2.158	0.044	-0.002	0.0906	0.2719	0.00033	27.191		
45	2.318	0.044	-0.002	0.0974	0.2921	0.00032	29.207		

Table D.8 Dissolution Profile of Salicylic Acid at 20° off-center Position

Time min	Average Absorption	Slope	Intercept	C mg/mL	C/C*	C/C* Standard Deviation	C/C* (%)	f_1	f_2
0	0.074	0.044	-0.002	0.0031	0.0093	0.00013	0.932	55.4641	58.0936
5	0.356	0.044	-0.002	0.0150	0.0449	0.00133	4.486		
10	0.639	0.044	-0.002	0.0268	0.0805	0.00122	8.051		
15	0.943	0.044	-0.002	0.0396	0.1188	0.00079	11.882		
20	1.247	0.044	-0.002	0.0524	0.1571	0.00081	15.712		
25	1.512	0.044	-0.002	0.0635	0.1905	0.00079	19.051		
30	1.772	0.044	-0.002	0.0744	0.2233	0.00084	22.327		
35	2	0.044	-0.002	0.0840	0.2520	0.00596	25.200		
40	2.265	0.044	-0.002	0.0951	0.2854	0.00063	28.539		
45	2.482	0.044	-0.002	0.1042	0.3127	0.00088	31.273		

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