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ABSTRACT

EFFECT OF TABLET COMPRESSION ON THE DISSOLUTION OF ASPIRINTABLETS USING A NOVEL OFF-CENTER PADDLE IMPELLER (OPI) DISSOLUTION TESTING SYSTEM

by
Chuan Sun

In the pharmaceutical industry, dissolution testing is routinely carried out to determine the dissolution rate of oral solid dosage forms. Among several testing devices, the USP Dissolution Apparatus 2 is the device most commonly used. However, despite its widespread use, this apparatus has been shown to produce test failures and to be very sensitive to a number of small geometry changes.

The objective of this study was to determine whether a novel dissolution system termed "OPI" for "off-center paddle impeller" was sensitive enough to determine differences in tablet dissolution profiles caused by different compression pressure during the tablet manufacturing process. The OPI Dissolution System simply consists of a modified Apparatus 2 in which the impeller is placed 8mm off center in the vessel.

In this work, aspirin tablets were manufactured from powder with a manual tablet press using three different compression pressures. The dissolution profiles of these tablets were then obtained in both the OPI system and the standard USP Apparatus 2 system. Tests were conducted by dropping the tablets in the vessels at the beginning of an experiment, and, in separate experiments, by initially immobilizing the tablets on the vessel bottom at nine different locations. This

approach has been used in the past by our group to determine the sensitivity of the dissolution apparatus to minor changes in the geometry of the dissolution system.

All dissolution profiles were found to be affected by the compression pressure. Faster dissolution profiles were obtained at lower compression pressures. When tablets were dropped in the vessel, a comparison of the dissolution profiles obtained in the standard Apparatus 2 system and in the OPI system showed that similarly manufactured tablets produced statistically similar dissolution profiles in both systems, i.e., that the OPI system was just as sensitive as the standard system to variations in the tablet manufacturing process. However, when the tablets were immobilized during the dissolution process, the standard system generated very different dissolution profiles even for tablets manufactured at the same compression pressure. By contrast, the dissolution profiles in the OPI system for tablets manufactured at different pressure but located at different positions were very similar.

It can be concluded that the OPI system is sensitive enough to detect differences in intrinsic tablet dissolution rates (such as those caused, as in this case, by changes in the manufacturing process), while being unaffected by small changes in the system geometry that instead caused the standard system to fail. Therefore, the OPI system appears to be a more reliable dissolution testing apparatus than the current apparatus.

EFFECT OF TABLET COMPRESSION ON THE DISSOLUTION OF ASPIRINTABLETS USING A NOVEL OFF-CENTER PADDLE IMPELLER (OPI) DISSOLUTION TESTING SYSTEM

by
Chuan Sun

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APPROVAL PAGE

EFFECT OF TABLET COMPRESSION ON THE DISSOLUTION OF ASPIRINTABLETS USING A NOVEL OFF-CENTER PADDLE IMPELLER (OPI) DISSOLUTION TESTING SYSTEM

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This thesis is dedicated to my parentsand teachers for their support and encouragement**.**

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CHAPTER 1

INTRODUCTION

Dissolution is a process by which the drug substance in a formulation dissolves into solution. Solid dosage forms such as tablets are the most common used method to administer drugs. Therefore, dissolution testing is widely used in the pharmaceutical industry to determine the dissolution rate of solid dosage forms. The dissolution testing is a critical tool in the process of drug discovery that measuring the stability of the solid dosage product. Also it's an overriding method determining solid dosage drug in-vivo availability. Thus this Dissolution testing is an essential requirement for the development, establishment of in vitro dissolution and in vivo performance (IVIVR), registration and quality control of different dosage forms.

Although the USP lists several different dissolutiontest apparatuses,most dissolution testsare currently conducted with USP DissolutionTest Apparatuses 1 and 2. The USP DissolutionTest Apparatus 2 is the most commonly andwidely used apparatus specified by the USP. The dimensions, characteristics,and operating conditions of USP DissolutionTest Apparatus 2 are detailed by the USP, [1]and all users must conform to these prescriptionswhen conducting dissolution tests.The USP Dissolution Test Apparatus 2comprises a glass vessel and an agitation system.The glass vessel is a cylindrical glass tank with asemispherical bottom, and a working volume of900 mL. The agitation system consists ofa two-blade paddle impeller mounted on a shaftcentrally located in the vessel and profiled to followthe hemispherical portion of the vessel. In theindustrial practice, replicate dissolution tests aretypically conducted in parallel using commerciallyavailable systems containing six or more individualUSP Dissolution Test Apparatus 2 units. These

systemsallow the agitation system(motor and impellers) to be lifted above the rackholding the vessels, as shown in this figure, inorder to prepare the system for the actual test.Each vessel is filled with a prescribed amount of afluid simulating gastric or intestinal fluids, andmaintained at constant temperature of 37℃byeither a water bath or a heating jacket.

The USP Dissolution Test Apparatus 2 hasbeen used in the pharmaceutical industry fordecades, since this test was first officiallyintroduced many years ago.[2] Nevertheless,the hydrodynamics of USP Apparatus 2 vessel hasbeen reported to play a major role in the poor reproducibilityof dissolution testing data and the inconsistencyof dissolution results.[17–19]And despite its widespread use in the industry,dissolution testing remains susceptible to significanterror and test failures. A review of theliterature shows that there have been numerousreports describing high variability of testresults,[3-10] even when the so called ‘‘calibratortablets’’ (i.e., tablets manufactured for the solepurpose of testing the proper operation of thedissolution test equipment) are used.[4,6,9,11,12]Failures linked to dissolution testing resulted inover forty product recalls during the period 2000–2002,representing 16% of non-manufacturing recalls fororal solid dosage forms. Irrespective of theunderlying causes (such as incorrect use of theequipment or deviation of dissolution profile fromthe standard caused by incorrect tablet formulation)failed dissolution tests can result in productrecalls, costly investigations, potential productiondelays, which, in turn, can have a significantlynegative financial impact because standard system isstrongly affectedby even small variations in the geometry of theapparatus.[13-15]

In previous experiments16-18, data have shown that OPI System is very reliable.

Due to the fact that OPI system has faster dissolution rate of the tablet and was respectively independent to the tablets locations on the bottom of the vessel, we can see OPI System is more robust and more effective than the Standard System in the dissolution test. However, whether new system is sensitive enough to detect the slice difference between tablets is worth to discuss.

The main objective of this study was to verify the sensibility of the OPI system regarding tablets compression pressure difference. To do so, twodifferent methodologies were used in this study. Efforts were made to eliminate any other factors that could also affectthe test results in order to analyze solely tablets compression differences andits effect on thedissolution profiles in both Standard system and OPI system.

In addition,as shown in previous study on the USP Dissolution Apparatus 2 (Bai etal., 2007), the exact location of the dissolving tablet introduces significant variations inthe flow and in the shear stress experienced by the tablet, which, in turn, can affect thedissolution process and the dissolution profiles. In order to confirm the reliability of the OPI system, dissolution testswere conducted in USP Dissolution Testing Apparatus 2and in OPI system using tablets with different compression pressure at 9 different locations at the bottom of the USP Apparatus 2dissolution vessel, i.e., with tablets located $10°$ or $20°$ off-center and at different positions. Statistical tools were then used to evaluate and compare theresults of dissolution profiles in standard system and in OPI system.

CHAPTER 2

EXPERIMENTAL APPARATUS, MATERIALS, AND METHOD

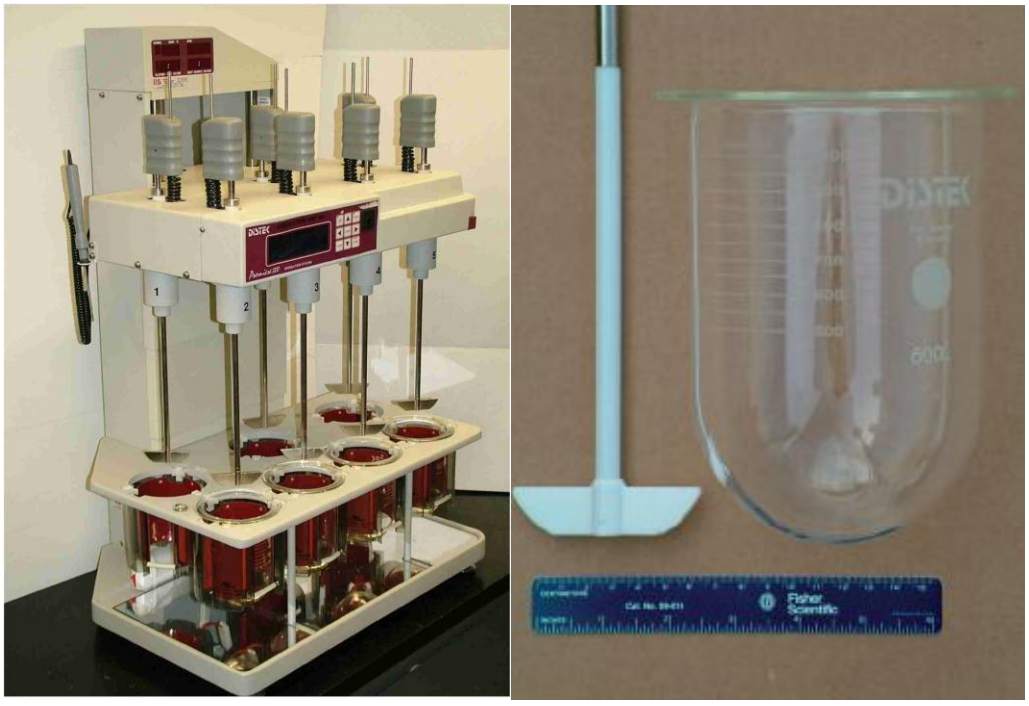
2.1 Dissolution Apparatuses

In this work, two dissolution testing apparatus systems were used. A standard USP Dissolution TestingApparatus 2 (hereafter called the “Standard System”)and a modified system, which, in this work, isreferred to as “OPI system” for “off-center paddle impeller”system.

The Standard System consisted of a Distek 5100bathless dissolution apparatus shown in Figure 2.1(Distek Inc., North Brunswick, New Jersey).Seven dissolution vessels can be operated at a time. EachUSP Apparatus 2 vessel used as the dissolution vesselconsisted of an unbaffled, cylindrical, transparentglass tank with a hemispherical bottom, an internaldiameter, T, of 100.16mm, and an overall capacityof 1L. When the vessel was filled with 500mLof dissolution media, the corresponding liquid height,H, as measured from the bottom of the vessel, was78.6mm.

The impeller consisted of a two-blade paddle impeller connected to the Disteksystem (Distek Inc.) motor with the steel shaft. The exact geometry of each componentofthe impeller was: shaft diameter, 9.53mm; length of thetop edge of the blade, 74.10mm; length of the bottomedge of the blade, 42.00mm; height of the blade, 19.00mm; thickness of the blade, 5.00mm. The distancebetween the lower edge of the impeller bladeand the vessel’s inside bottom was 25mm. These dimensions were obtained bymeasuring themwith a caliper. Figure 3a shows the standardUSP Dissolution Testing Apparatus 2.

The OPI system was a modification of the standard system(Figure 2.2)in which the impeller which wasplaced 8mm off center with respect to the vessel centerline(Figure2.3). To make this change, one of the plastic spring inserts mounted on the metal plate ofthe Distek dissolution equipment (Distek Inc.), which ensuresthat the vessel locates at the centerline (Figure2.4), was removed. After removing this plastic spring insert, the vessel was shifted with respect to the paddle shaft by an exactly 8mm, thusresulting in an off-centered impeller with respect tothe vessel.The clearance from the bottom to the paddle end is 25mm, that is, the same as inthe Standard System. Figure 2.3 shows the OPI dissolutiontesting system.



(a) (b)

Figure 2.1USPdissolution testing System:(a) Distek 5100 bathless dissolution apparatus,(b) USP dissolution testingapparatus 2: paddle impeller andglass vessel.

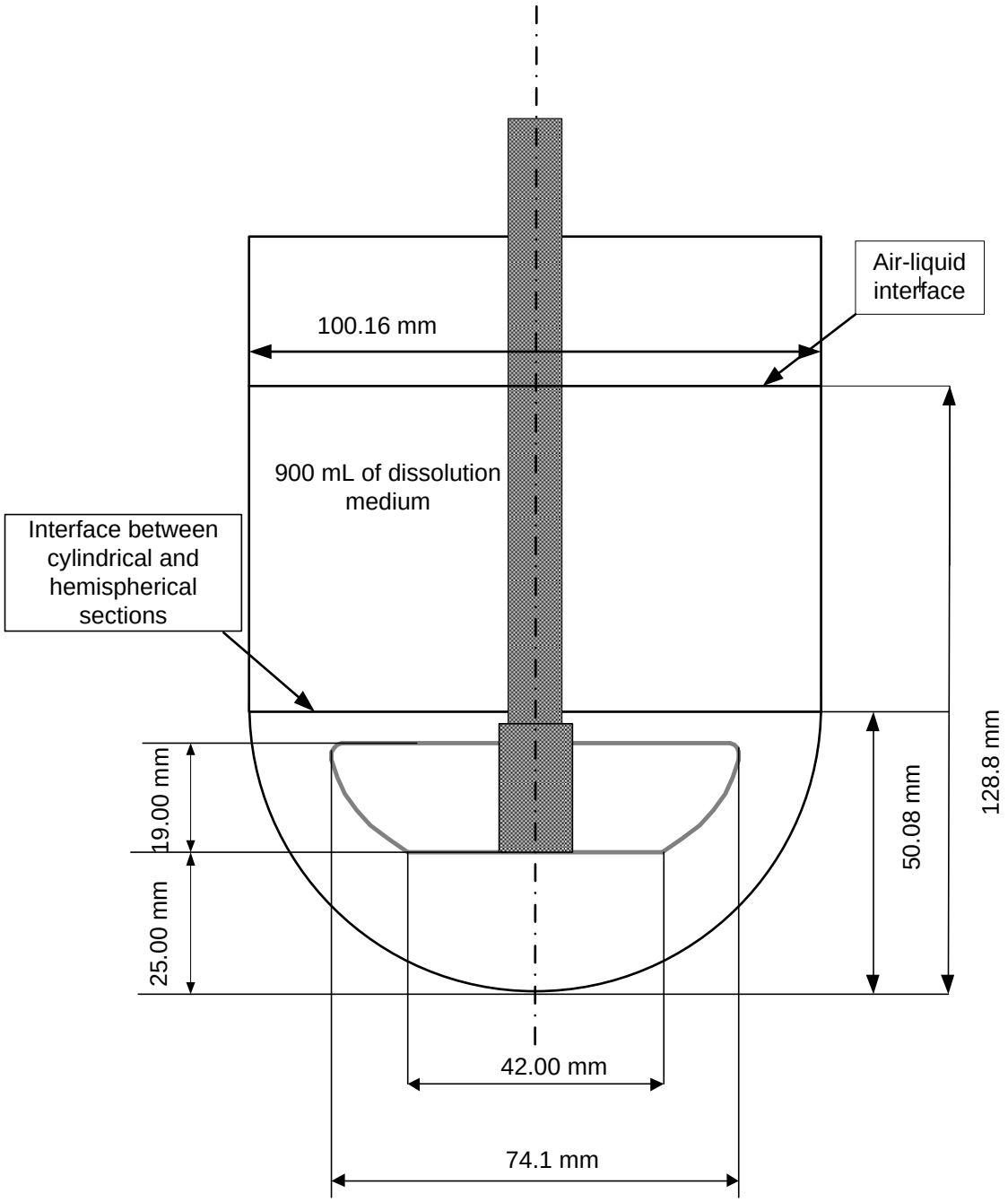


Figure 2.2 Standard USP dissolutiontestingapparatus 2.

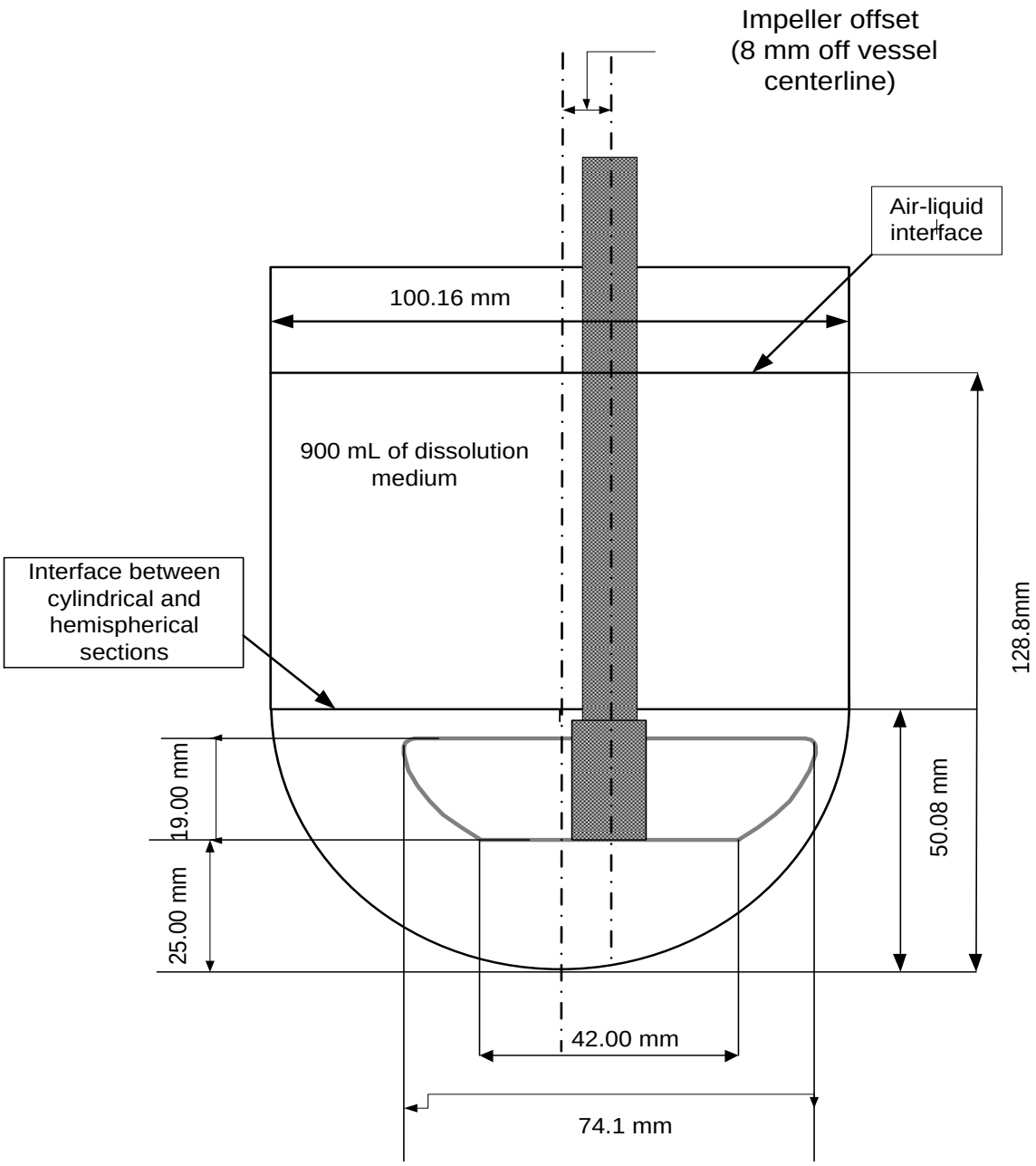


Figure 2.3 OPIdissolutiontestingapparatus 2.

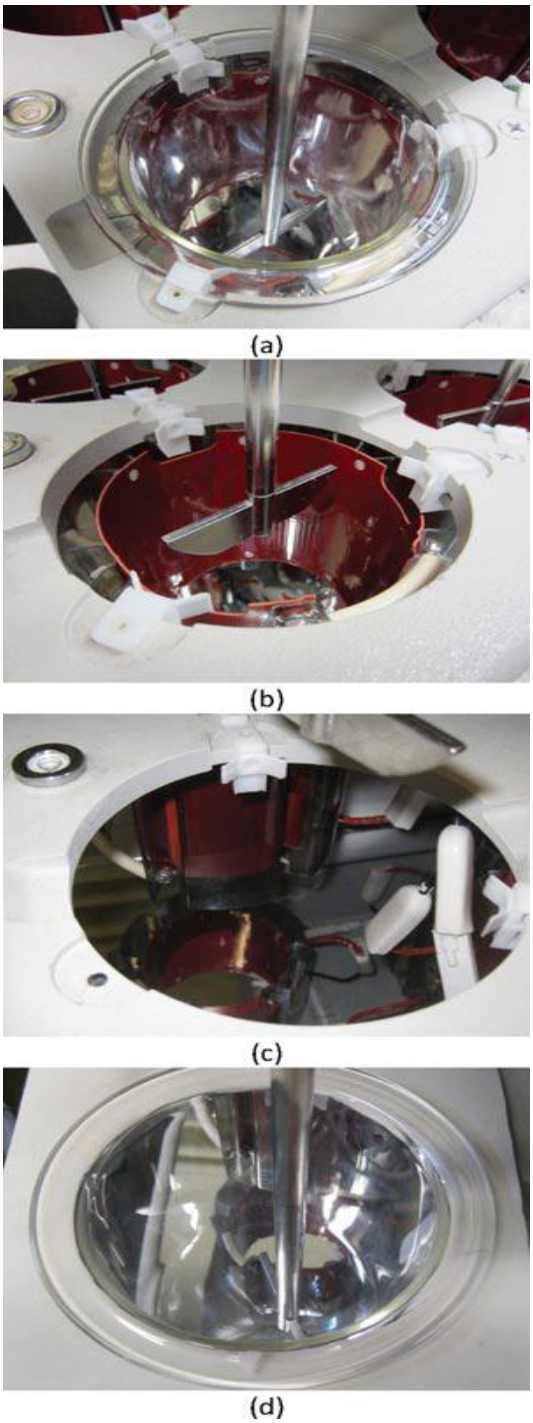


Figure 2.4Modification of the standard system to obtainthe OPI system: (a) vessel in the standard system, (b) plasticspring inserts exposed after removing the vessel in thestandard system, (c) system after one of the plastic springinserts has been removed, and (d) system after the vesselwas repositioned to obtain the OPI system.

2.2 Experimental Materials

Four types of aspirin tablets were tested in this work, i.e., commercial 360mgwhite, round shaped uncoated aspirin tablets (Item Code: NDC:59779-249; Active Ingredient: Aspirin (325 mg); Inactive Ingredient: Starch) with diameter of 11 mm, purchased from CVS Pharmacy, as well as three other types of tablets obtained by grinding and reconstituting tablets using different compression tablets.In order to make these tablets, 100 tablets were well ground to a fine powder using a mortar(Figure 2.6b) and pestle for ten minutes. The resulting powder was apportioned in 360-mg doses (the mass of each was measured with an analytical balance). The average tablet mass was measured to be 360 ± 5 mg. Each dose was then poured in a die and the die was placed in a press (Carver Laboratory Press, Fred S. Carver Inc.; Model C; Figure 2.5). The powder was manually compressed at the desired compression pressure. Three compression pressures were used here i.e., 1000 lb/0.12in^2, (here referred to as "1000 pound"), 2000 lb/0.12in^2 ("2000 pound"), and 3000 lb/0.12in^2 ("3000 pound")(Figure 2.6a), respectively.The compression pressurewas determined with the pressure gauge connected to the press. All the tablets needed in all the experiments were manufactured in one single batch to insure the uniformity of the compressed tablets at each pressure. The resulting tablets consisted of cylindrical disks, 1 cm in diameter and approximately 2-3 mm thick (the actual thickness depended on the compression pressure).

The dissolution medium for the aspirintablets consisted of a0.05 M acetate buffer to which glacial acetic acid wasadded to reach a final pH value of 4.5 ± 0.05. This mediumwas deaerated according to the degassing methoddeveloped by Moore following the USP GeneralTest Chapter on Dissolution. Accordingly, themedium was placed in a

carboy tank, which was thenconnected to a vacuum pump. Vacuum was appliedfor 30min, whereas all other valves in the systemwere closed. This stock solution was used as needed(typically in 500mL aliquots per experiment).

Figure 2.5 Carverlaboratory press model C.

(a) (b)

Figure 2.6(a) From left to right: Commercial tablets, 1000-pound tablets, 2000-pound tablets, 3000-pound tablets; (b)Mortar used for manufacturing powder.

2.3 Experimental Method

Two testing methods were used here to conduct dissolution tests, as follows.

- **Testing Method #1**: the tablet was dropped in the dissolution medium at the beginning of the experiment (USP Method);
- **Testing Method #2**: the tablet was fixed in place at one of nine different tablet positions at the bottom the vessel (i.e., 0°, 10°, 20°) prior to the addition of the dissolution medium as specified below.

When Testing Method #1 was used, a prescribed volume (500 mL) of the appropriately

deaerated dissolution medium, previously preheated at 37◦C, was gently poured into the vessel in order to minimize the introduction of gas. Because of the thermal inertia of the vessel, the resulting temperature of the liquid was 37◦C. This temperature was maintained throughout the dissolution experiment by the system's temperature controller. Then a tablet was dropped in the Standard System vessel and another in the OPI System vessel, agitation was started, and a first set of samples was manually removed as described below. The agitation speed was 50 rpm for the aspirin dissolution tests in Standard System, and 36 rpm in the OPI System, as specified in previous work by this group. This agitation value had been previous identified as the agitation speed at which the OPI system would generate the same dissolution profile as a standard system stirred at 50 rpm when a tablet was located at the central position (as better described below).

The time interval between samples was 5 min for the first 30 min, and every 15 min from 30 min to 60 min. Each experiment lasted 60 min, and a total of 8 samples were taken for each experiment. All experiments were performed in triplicates.

When Testing Method #2 was used, the tablet was glued in place prior to the addition of the dissolution medium at the beginning of the experiment in order to determine the sensitivity of the dissolution system to tablet location during a typical dissolution experiment. Accordingly, a tablet was attached at one of several predefined locations at the vessel's bottom with a very small bead of a commercial acrylic glue prior to each experiment. Three tablet positions were studied in the Standard System, that is, the tablet was centered in the vessel, placed 10o off center, or placed 20^{o} off center (Figure 2.5). 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).

As for the OPI system, nine positions at the vessel's bottom were selected, as shown in Figure 2.6. Position O in this figure represents the center of the vessel bottom. Positions A1–D1 were all 10º off center from the vessel's vertical centerline (Figure 2.6). Positions A1–D1 were all on the same inner circle and were spaced 90 ºapart from each other. Positions A2–D2 were 20º off center from the vessel's vertical centerline (Figure 2.6). The vertical centerline through the impeller intersected the vessel's bottom between Position 1 and Position 3, some 8mm away from the vessel's bottom.

The vessel with the attached tablet was placed in the Distek apparatus, and then the appropriate medium volume (500 mL based on USP dissolution test for aspirin) of deaerated dissolution medium, previously preheated at 37.5◦C, was gently poured into the vessel in order to minimize the introduction of gas and prevent rapid initial dissolution of the tablet. Again, because of the thermal inertia of the vessel, the resulting temperature of the liquid was 37◦C. This temperature was maintained throughout the dissolution experiment by the system's temperature controller. Because of the potential sensitivity of the process to the initial tablet dissolution caused by liquid addition, extreme care was taken to ensure that this procedure was consistent and reproducible and that it did not result in any liquid splashing. The agitation was started immediately after the addition of the dissolution medium. Sampling was conducted with the same time frequency as specified above.

Sampling consisted of removing a 10 mL medium aliquot with a 10-mL syringe connected to a cannula (2 mm internal diameter). The volume of medium removed by sampling was not replaced, in accordance with the USP procedure (USP, 2012). 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, that is, within the sampling zone prescribed by USP. After the sample withdrawal, about 2 mL of the sample was discarded, the cannula was removed, and a polyvinylidene fluoride (PVDF) 0.45-μm filter was mounted on the syringe. The remaining sample volume (about 8 mL) was transferred to a vial until analyzed.

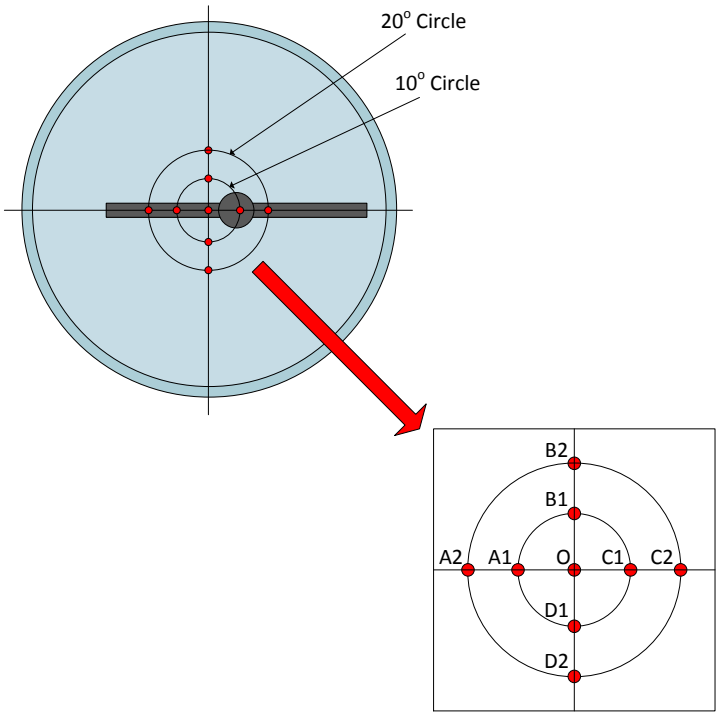
Analysis of samples was carried out using 1-cm quartz cells placed in an ultraviolet (UV)–visible spectrophotometer (Varian Cary 50 Bio, Varian, Inc., Palo Alto, CA) measuring absorbance at specified wavelengths, that is, 265nm for aspirin. Beforeputting the quartz cell into the UV spectrometer, the cell was rinsed three times with the same solution sample.

A calibration curve was obtained bypreparing reference standard solutions of aspirin tablets with known concentrations to obtain solutions of differentknown concentrations. In order to obtain a calibration curve, pure aspirin (A2093 Sigma-Aldrich) was used. The absorbance of these solutionswas obtained in order to generate an absorbanceversus concentration standard curve. The calibrationcurves were linear (R^2=0.9999 for aspirin) in the concentrationranges of interest here.

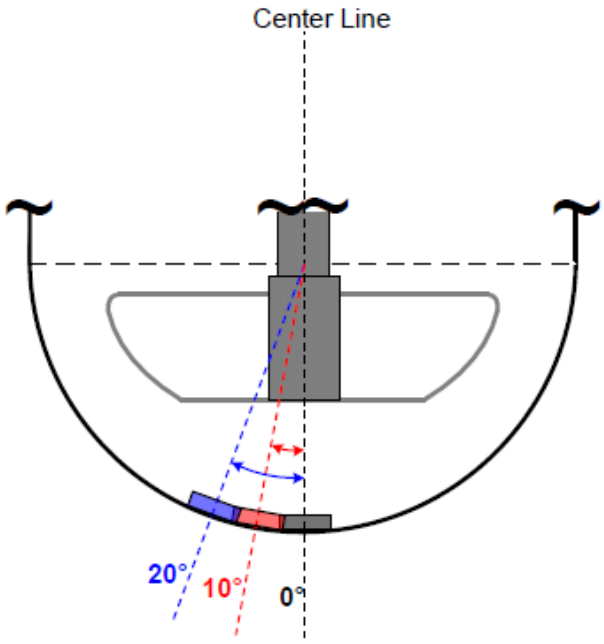
Thecalibration data and calibration curve for aspirinusing the UV spectrophotometer to determine the sample absorbance at the wavelength 265nm are presented in Table 2.2 and Figure 2.6, respectively. These results showed that the calibration curve was linear (R^2=0.9999) in the concentration range of interest here.

Table 2.1 Operating Conditions for Dissolution Experiments

Medium	500 mL, 0.05 M acetate buffer, pH of 4.50 ±0.05
Temperature	37.5^{o}C
Agitation Speed for Standard System	50 rpm
Agitation Speed for OPI System	36 rpm
Filter	PVDF 0.45 m
UV Wavelength (UV Spectroscopy)	265 nm
Standard Tablets	CVS Uncoated Aspirin Tablets
Compressed Tablets	CVS Uncoated Aspirin Tablets obtained at pressure of 1000, 2000, 3000 lb/in^2
Time	5-min interval; 60 min total



(a)



(b)

Figure 2.4 Tablet positions in the OPI system and standard system: (a) top view of the bottom of the dissolution vessel with nine different tablet positions in the OPI system, (b) the front view of the dissolution vessel with three different tablet positions (0 °,10 °, 20 °) in the standard system.

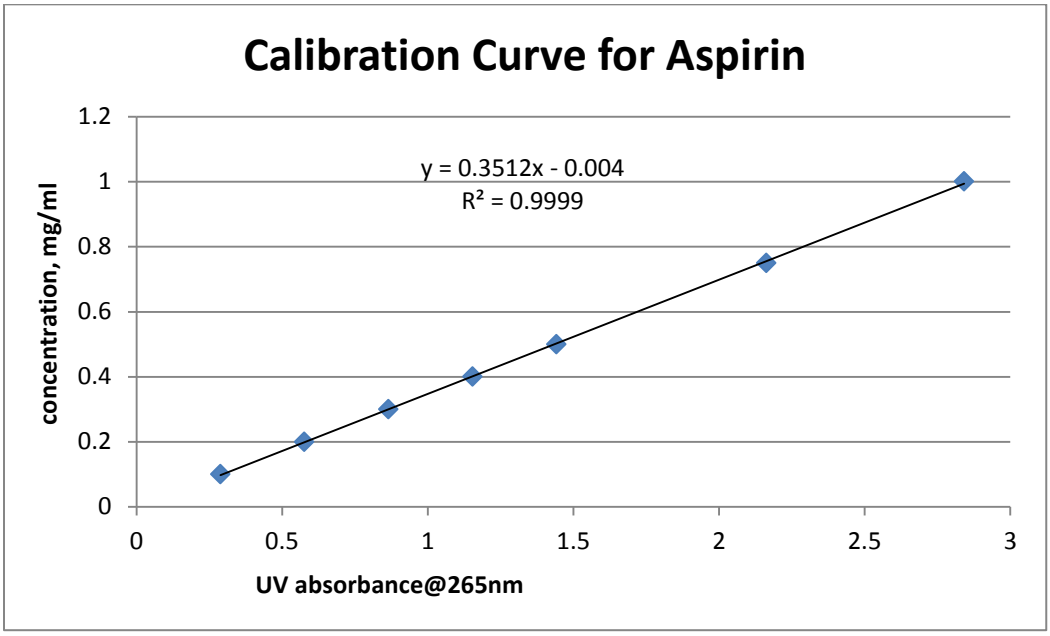


Figure 2.6 Calibrationcurve for aspirin

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Table 2.2 Calibration Data for Aspirin

Absorption 1	Absorption 2	Absorption 3	Average	Concentration(mg/mL)
0	0	0	0	0
0.2885	0.2887	0.2883	0.2885	0.1
0.579	0.576	0.576	0.577	0.2
0.866	0.869	0.86	0.865	0.3
1.151	1.157	1.155	1.154	0.4
1.441	1.443	1.442	1.442	0.5
2.165	2.161	2.163	2.163	0.75
2.844	2.845	2.837	2.842	1

2.4 Data Processing

The dissolution profiles are presented in terms of drug release fraction (m_D/m_T), that is, the mass of released drug in the dissolution medium at any time t out of the total mass of drug initially in the tablet, as a function of time. The absorbance data obtained from the UV spectrophotometer was first converted to aspirin concentration at given time, (C_j, in mg/mL), and then transformed into drug mass release fraction (m_D/m_T) using the following equations, in order to account for the drug mass removed with each sample:

$$\frac{m_D(t_1)}{m_T} = \frac{C_1}{C^*} \qquad for\ j = 1 \tag{2.1}$$

$$\frac{m_D(t_j)}{m_T} = \frac{C_j}{C^*}\left[1-(j-1)\frac{\Delta V}{V}\right] + \frac{\Delta V}{V}\sum_{k=1}^{j-1} C_k \qquad for\ 2 \le j \le n \tag{2.2}$$

where j is an index identifying the number of sampling (j=1, 2, … 8), $m_D(t_j)$ is the mass of released salicylic acid at time t_j, $m_T$is the total mass of salicylic acid initially in the tablet, C_j is the dissolved aspirin concentration in the j^{th} sampling at time t_j, C^* is the concentration of aspirin when the tablet is fully dissolved in 500 mL dissolution medium, ΔV is each sampling volume (10 mL) and V is the initial volume of dissolution medium (500 mL). At the beginning of the experiment(t=t_1=5 minutes) the first sample was taken (j=1) resulting in an initial concentration C_1, and the 8th sample was taken at t_8=60 minutes (j=8).

The dissolution profiles obtained with tablets at each position in the testing system were compared to those from its paired standard system in order to determine whether these dissolution curves were statistically similar or not. Two approaches were used. The first approach was that recommended by the FDA to quantify the

similarity/difference of two dissolution profiles. This approach consists of a model-independent method based on the difference factor (f_1) and similarity factor (f_2):

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \quad (2.3)$$

$$f_2 = 50 \log_{10}\{[1 + (\frac{1}{n})\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\} \quad (2.4)$$

where $R_t$is the reference assay at time t (i.e., the results from the standard system),$T_t$is the test assay at the same time (i.e., the paired results from the testing system), and n is the number of time points. The difference factor(f_1) calculates the percent (%) difference between the two curves at each time point and measures the relative error between two curves. The higher the f_1(which can be in the range of 0 to 100), the higher the average difference between reference and test curves is (Moore and Flanner, 1996). The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum-squared error of differences between the reference and test profiles over all time points (which can be in the range -α to 100). The higher the f_2, the lower the average difference between reference and test curves is (Costa and Lobo, 2001). Public standards have been set by FDA for $f_1$and f_2 factors. Accordingly, statistical similarity between the two curves being compared requires that $0<f_1<15$ or $50<f_2<100$(FDA, 1997).

CHAPTER 3

RESULTS

The drug release profile of aspirin tablets compressed at different pressures used regular dissolution method in the standard USP Dissolution Testing Apparatus 2. Then the drug release profile of aspirin tablets with different pressures used regular dissolution method in the OPI system. The dissolution profile of aspirin tablet with different pressures at three different tablet locations (0°, 10° and 20°) in the Standard USP Dissolution Testing Apparatus 2 (Standard System) were obtained third as per USP method. The forth is the drug release profile of aspirin tablet with different pressures at nine different tablets locations was obtained for the Modified System as per the method described in the previous chapter. The results were interpreted by potting m_D/m_T (%)(drug release) against time (min) and by calculating similarity factor (f_1) and difference factor (f_2).

3.1Results for Dissolution Tests in the Standard USP Dissolution Testing Apparatus by Dropping Tablets into Medium Using Testing Method #1

In the Standard USP Dissolution System, the dissolution profiles for aspirin tablet were obtained by dropping into the dissolution vessel under an agitation speed of 50 rpm. The results are reported here in terms of drug release ratiom_D/m_T(%). Figure 3.1 presents these results.

Based on the USP specifications for the Aspirin tablets used in this work, each individual run should produce a dissolved amount of aspirin no less than 80% (Q) of the labeled amount of C9H8O4 contained in the tablet (360 mg) when sampling at 30

minutes. This is the case here for the centrally located tablet, since the experimentally obtained fractions at 30 minutes were found to be 87.49%, implying that the equipment was suited to conduct dissolution testing with aspirin tablets.

A noticeable difference of dissolution profiles between different tablets compression pressures was found through the figure 3.2. Three curves started at the same mass at the beginning, butthey diverged with time depending on the tablet with different compression pressure.The dissolution curve for the commercial tablet began atm_D/m_T = 0, and then increased fast, reaching m_D/m_T = 68% at10th min. After 10 min, a lowerrelease rate of Commercial tablets was observed.from45min, the release rate of commercial tablets almost kept constant. For tablets with 1000-pound compression pressure, its dissolution profile was extremely similar to the commercial tablets, figure 3.1 showed the tendency of the similarity. According to Table 3.1, $f_1$and f_2 values of the 1000-pound tablets reached 2.97 and 75.90 respectively, indicating the similarity between commercial tablets and 1000-pound tablets. For tablets with compression pressure of 2000 pound and 3000 pound, a significant difference was found in the figure 3.1, especially for the 3000-pound tablets. At t =5min, the dissolution curves were foundto be much lower than the dissolution curve of commercial tablets, only reaching m_D/m_T = 50%. After 5 min, the dissolutionrates increased slightlyrespect to time. At t=60 min, m_D/m_T value of 3000 pound tablets was 10% lower than the m_D/m_T value of commercial tablets. Respectively, the $f_1$and f_2 values of the 2000-pound tablets were 5.65, 65.3, and $f_1$and f_2 values of the 3000-pound tablets were over 10 and lower than 56.Based on the $f_1$and f_2 values listed above (table. 3.1), the difference between the dissolution profiles for aspirin tablets with different compression pressure in the standard system could be easily recognized.

Although $f_1$and f_2 values fortablets with pressure of 2000 pound and 3000 pound were within FDA range, the difference still existed, which verified the existence of the difference produced by different tablets compression pressure.

In addition, f_1 and f_2 values reported in Table 3.1 implied that tablets with the pressure of 1000 pound, 2000 poundand 3000 pound would have different dissolution profiles despite a certain degree of similarity was shown. These results confirm that the dissolution profiles of aspirin tablets depend on the compression pressure.

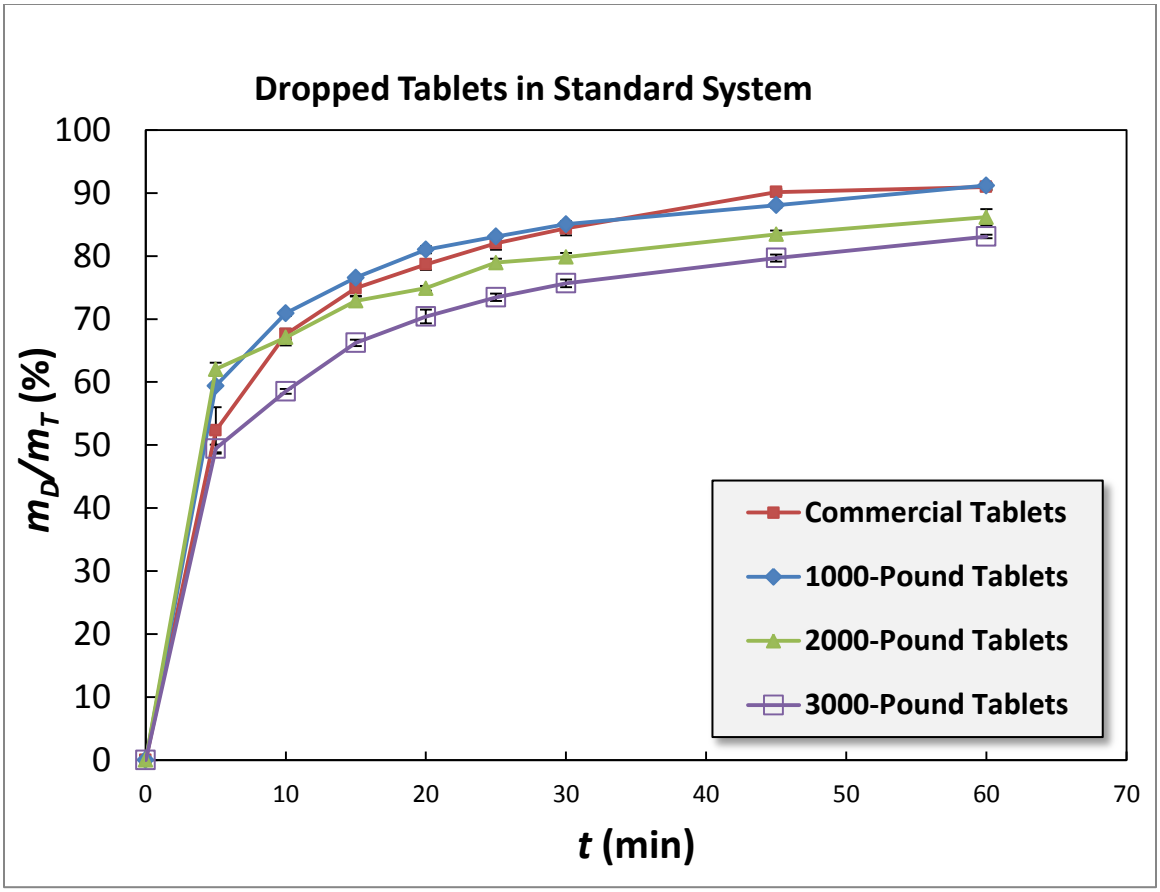


Figure 3.1 Dissolution profiles of aspirin tablets with different pressures in standard system by dropping tablets into medium using testing method #1.

Table 3.1f_1 and f_2 Value of Tablets with Different Pressure in Standard System by Dropping Tablets into Medium Using Testing Method #1.

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Standard Tablets		
Tablets with 1000 pound pressure	2.97	75.70
Tablets with 2000 pound pressure	5.66	65.29
Tablets with 3000 pound pressure	10.39	55.07

3.2Results for Dissolution Testsin the OPI Systemby Dropping Tablets into Medium Using Testing Method #1

The dissolution difference between pressures were tested in standard system by USP method, the similar dissolution profiles in the standard system were found in OPI system, which indicated the sensitivity of the OPI system can be verified.

f_1 and f_2 methods were used to identify the similarity/difference between aspirin tablets with different pressures in OPI system. Meanwhile, f_1 and f_2 methods were used to analyze the dissolution data of tablets with same pressure in two systemsin order to compare the tablets dissolution profiles with same pressure under standard system and OPI system.

A difference between different pressures was also foundin OPI system through the figure 3.2.1. The corresponding f_1 and f_2 values quantifying the similarity/difference of the dissolution profiles with different pressures are presented in the Table 3.2.1. In this case, f_1 was foundto be in the range 2.3–10.0, stating a relatively small differencebetween the release profiles at different compression pressures and the reference release profile(standard tablets); $f_2$values in this part were found to be in therange 55.2–78.8,indicating that the release profiles were statisticallysimilar to the reference release profile, however as previous experiment, f_1 value of tablets with 3000 pound pressure was 10.41, which was much higher than the f_1 of tablets with 1000 pound, that is 2.3, and 2000 pound, that is 4.9. The comparison between standard system and OPI system in each particular tablet pressure were shown in Figure 3.2.2-3.2.5. According to f_1 and f_2 values in table 3.2.2-3.2.5, one fact can be seen that f_1 and f_2 values between experiments

operated under standard system and experiments operated under OPI system were corresponding, indicating that like standard system, OPI system was sensitive enough to detect differences of the tablets.

The comparison between tablets with each compression pressure was conducted in this section. f_1 and f_2 values of tablets with every compression pressure between OPI and standard system were shown Table 3.2.2-3.2.5. Through the Figure 3.2.2-3.2.5, and the Table 3.2.2-3.2.5, curves of tablets dissolution profiles were highly corresponding.

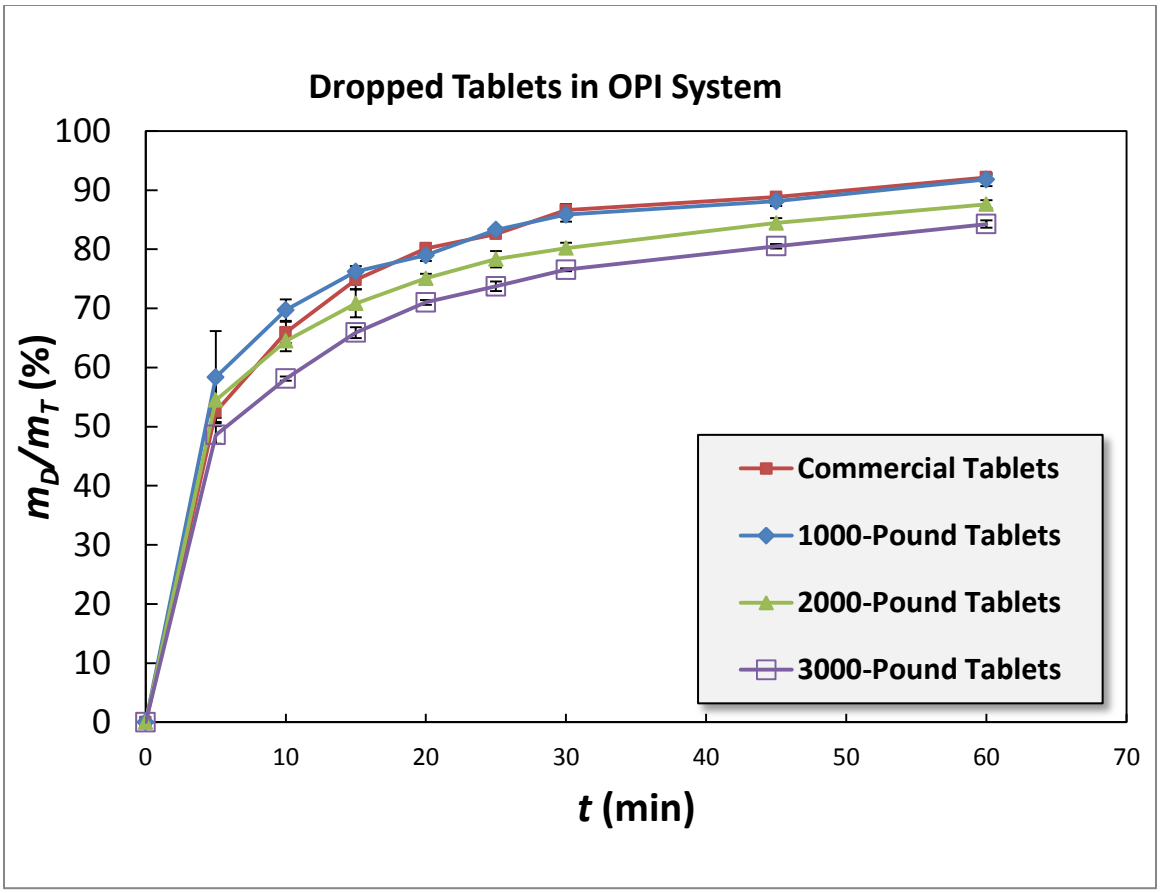


Figure 3.2.1 Dissolution profiles of aspirin tablets with different pressures in OPI system by dropping tablets into medium using testing method #1.

Table 3.2.1f_1 and f_2 Value of Tablets with Different Pressure by Dropping Tablets into Medium Using Testing Method #1.

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Standard Tablets		
Tablets with 1000 pound pressure	2.29	78.78
Tablets with 2000 pound pressure	4.96	69.05
Tablets with 3000 pound pressure	10.02	55.28

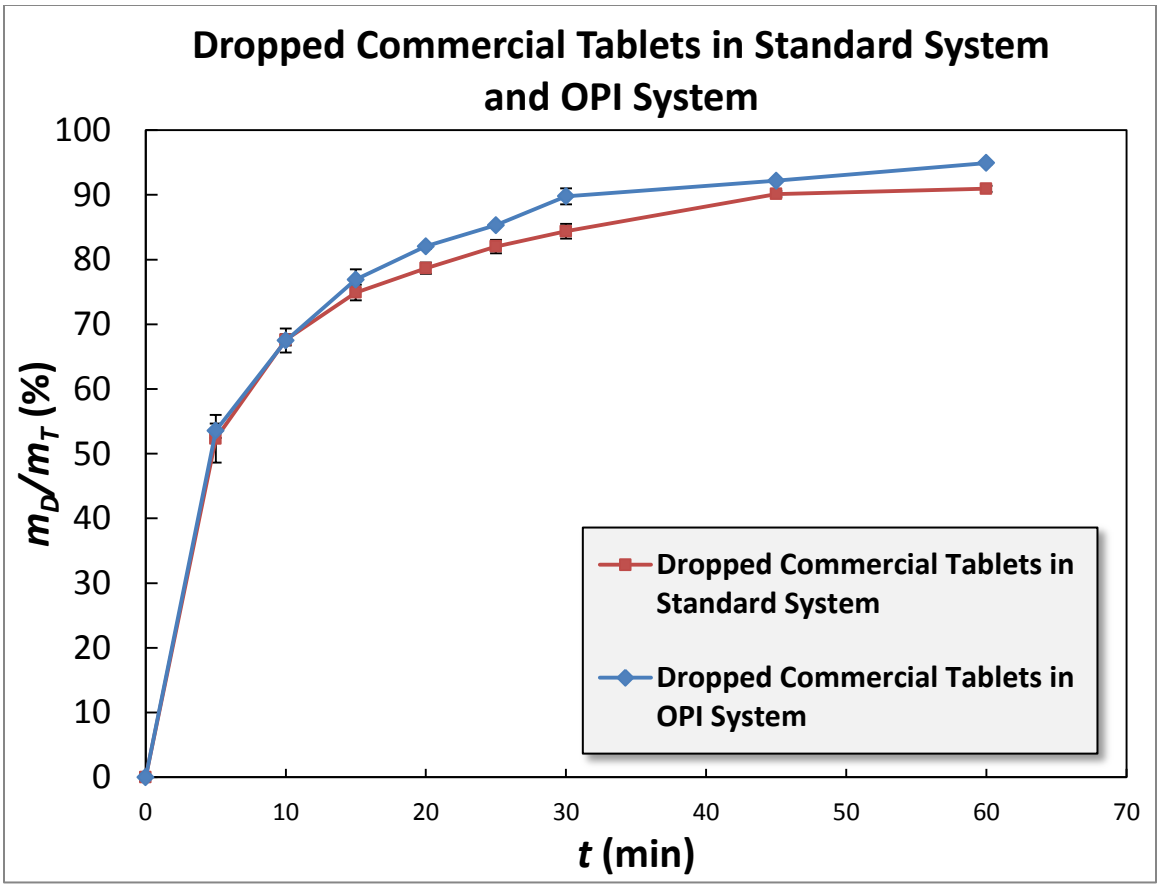


Figure 3.2.2 Comparison of dissolution profiles of aspirin commercial tablets in standard system and OPI system by dropping tablets into medium using testing method #1.

Table 3.2.2 f_1 and f_2 Values of Aspirin Commercial Tablets In OPI System by Dropping Tablets into Medium Using Testing Method #1.

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Dropped commercial tablets in standard system		
Dropped commercial tablets in OPI system	3.46	75.48

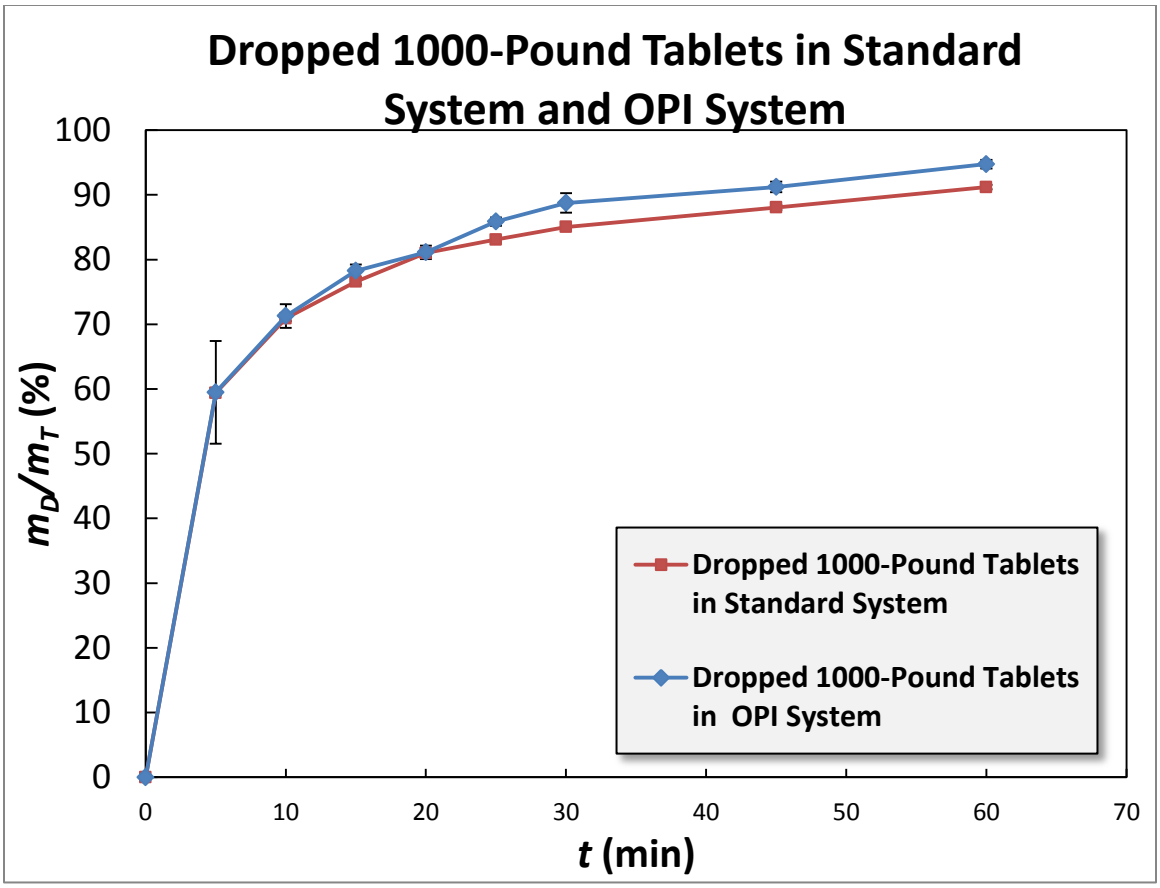


Figure 3.2.3 Comparison of dissolution profiles of aspirin 1000-pound tablets in standard system and OPI system by dropping tablets into medium using testing method #1.

Table 3.2.3f_1 and f_2 Values of Aspirin 1000-Pound Tablets In OPI System by Dropping Tablets into Medium Using Testing Method #1.

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Dropped 1000-pound tablets in standard system		
Dropped 1000-pound tablets in OPI system	2.44	80.12

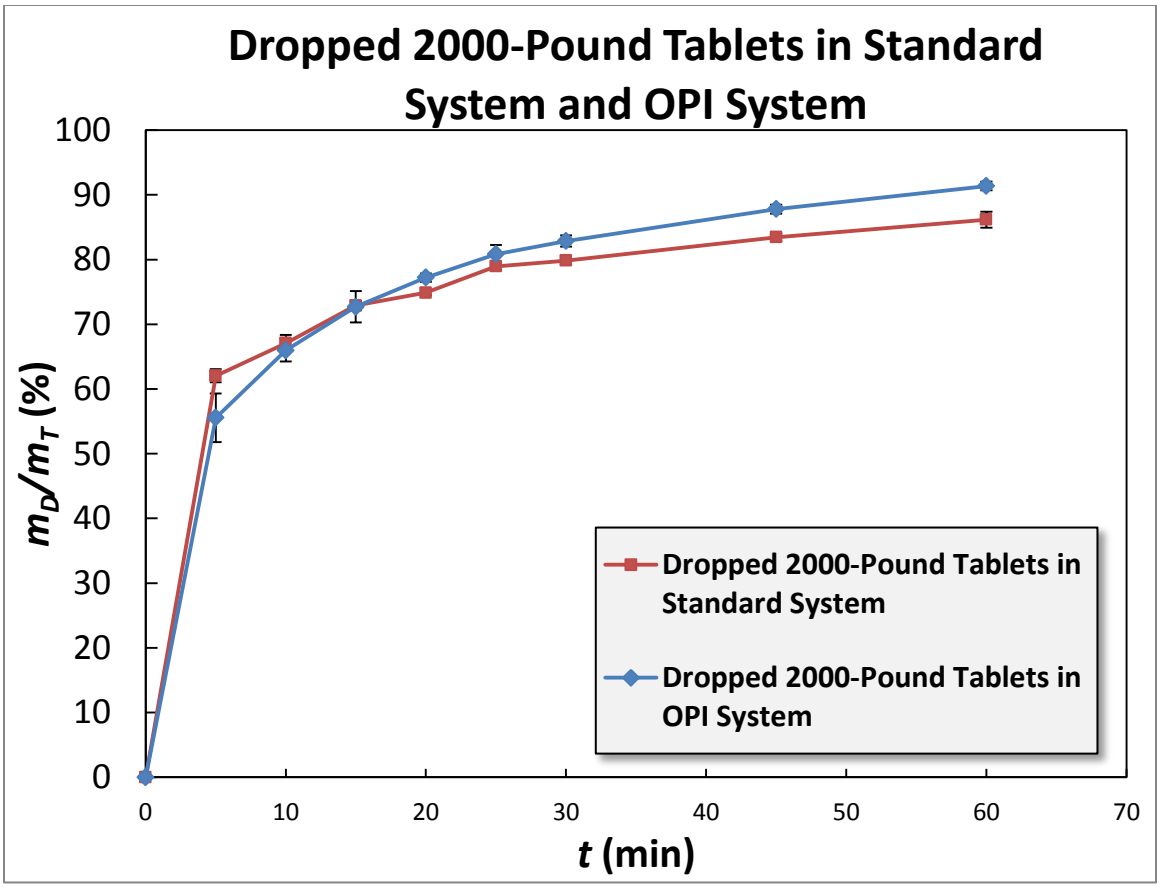


Figure 3.2.4 Comparison of dissolution profiles of aspirin 2000-pound tablets in standard system and OPI system by dropping tablets into medium using testing method #1.

Table 3.2.4f_1 and f_2 Values of Aspirin 2000-Pound Tablets In OPI System by Dropping Tablets into Medium Using Testing Method #1.

Tablet Location	**f_1 (Similarity factor)**	**f_2 (Difference factor)**
Dropped 2000-pound tablets in standard system		
Dropped 2000-pound tablets in OPI system	4.06	72.17

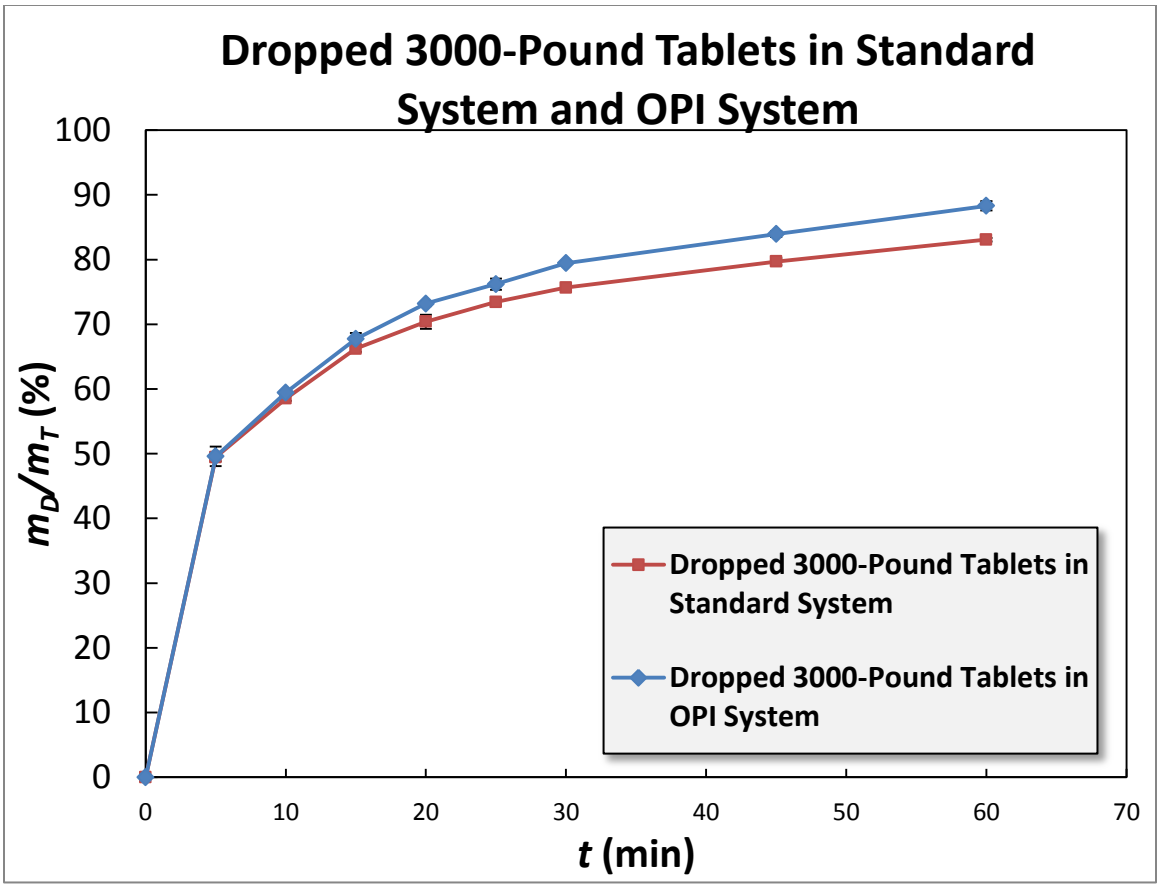


Figure 3.2.5 Comparison of dissolution profiles of aspirin 3000-pound tablets in standard system and OPI system by dropping tablets into medium using testing method #1.

Table 3.2.5f_1 and f_2 Values of Aspirin 3000-Pound Tablets In OPI System by Dropping Tablets into Medium Using Testing Method #1.

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Dropped 3000-pound tablets in standard system		
Dropped 3000-pound tablets in OPI system	3.84	75.33

3.3Results for Tablets at Three Positions in the Standard USP Dissolution

TestingApparatus 2 Using Testing Method #2

There are various factors that affect the drug release profile in USP Dissolution Apparatus 2. A number of studies related to the location of tablet and impeller, presence of baffles, geometric effects of the vessel, and even vibration effects ondrug dissolution rate have been carried on.The position may vary from time to time when the tablet reaches the vessel bottom. Therefore, tablet location has a major effect, and that statistically significant differences exist in the dissolution profiles between centrally located tablets and tablets positioned off-centered.

In the Standard USP Dissolution System, the dissolution profiles for aspirin tablet was obtained at three different tablet locations (0°, 10°, 20°) on the bottom of the dissolution vessel under an agitation speed of 50 rpm. Figure 3.4.1-3.4.4 presentthese results.

There was a significant difference between all three dissolution profiles at three different tablet positions.As the data showed in figure 3.3.1, the fact was foundthe greater the distance from the central location,the higher the dissolution rate. In the figure 3.3.1, the dissolution curve of tablets in central position was similar to the dissolution curve for tablets dropped into the medium using method #1. With the increasing of the deviation of the distance to the centerline, the dissolution rate of the tablets increased obviously. 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 3.4.1. Even thoughf_1 and f_2 are in the required range to insure statistical similarity, f_1 of tablets at 20° locations is much higher than the value of tablets at 10°locations, which imply that the dissolution profile difference exists. These results confirm that the dissolution profiles of the aspirin tablets 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.

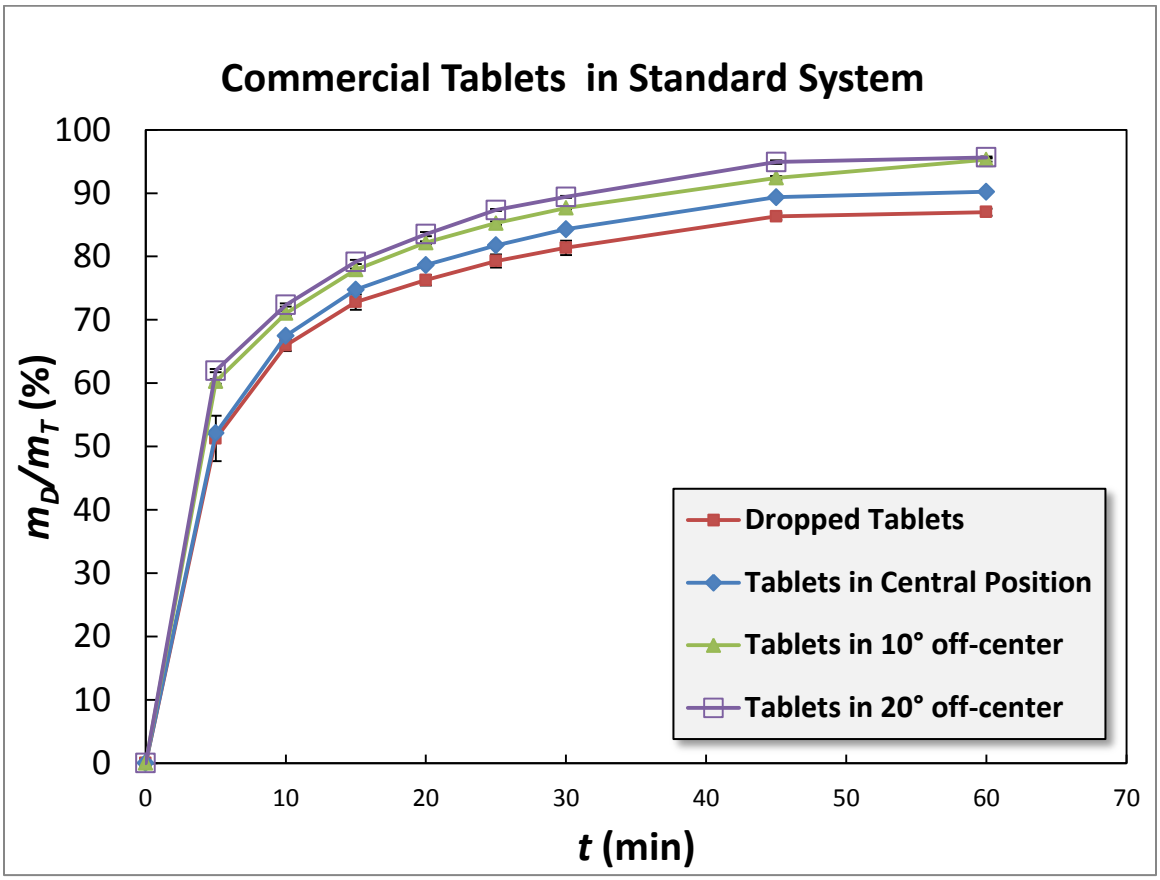


Figure 3.3.1 Dissolution profiles of commercial tablets at 3 positions in standard system

Table 3.3.1f_1 and f_2 Value of Commercial Tablets at 3 Positions in Standard System

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Tablets using official method		
Tablets at center	3.06	80.20
Tablets at 10 °off-center	8.63	59.99
Tablets at20 °off-center	10.67	55.64

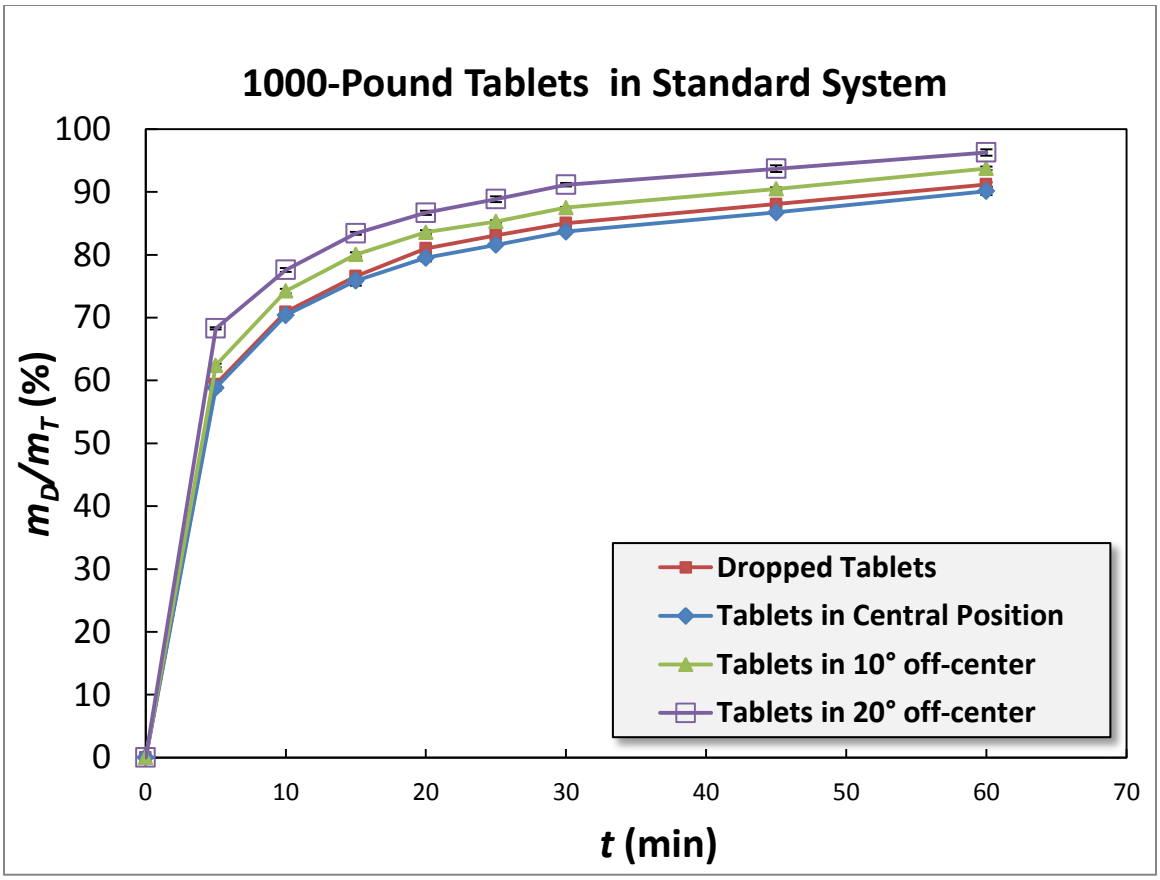


Figure 3.3.2 Dissolution profiles of 1000-pound tablets at 3 positions in standard system

Table 3.3.2 f_1 and f_2 Value of 1000-Pound Tablets at 3 positions in Standard System

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Tablets using official method		
Tablets at center	1.35	91.68
Tablets at 10 °off-center	3.46	77.57
Tablets at20 °off-center	7.97	60.59

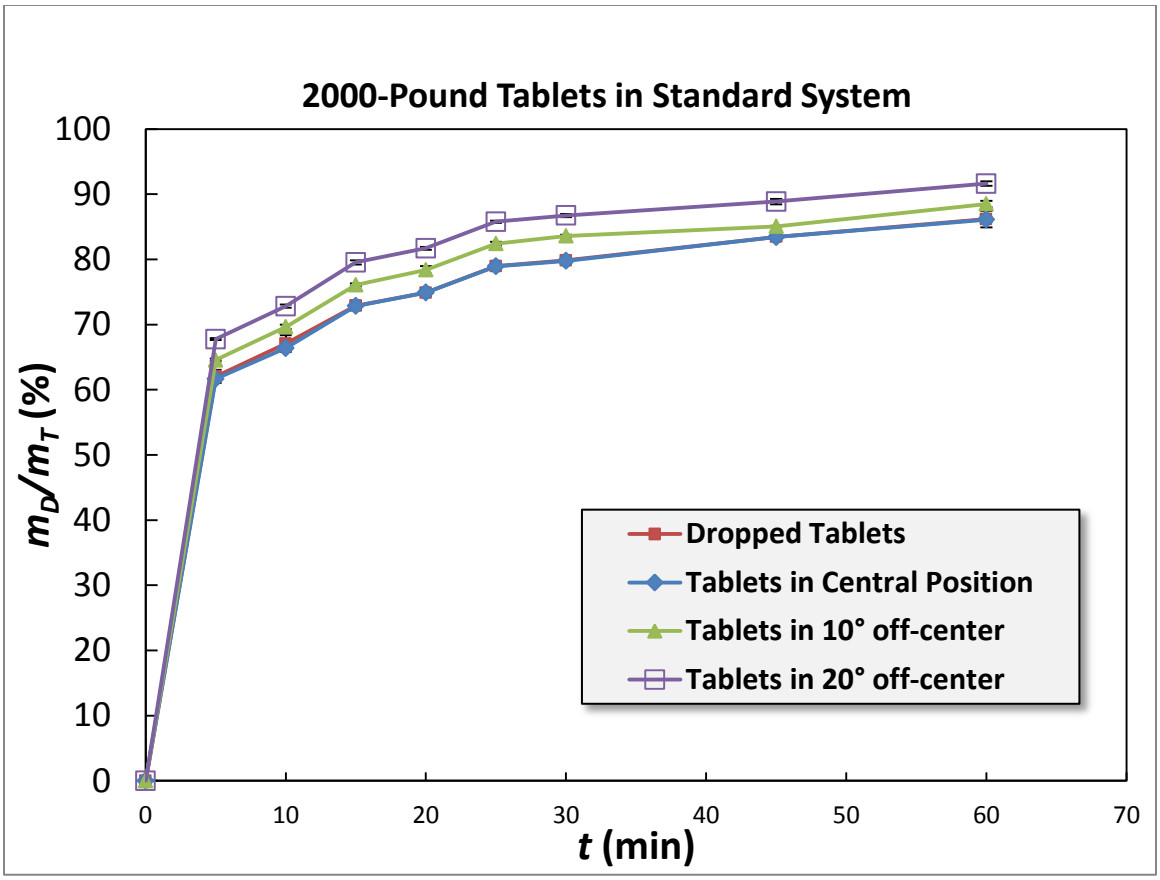


Figure 3.3.3 Dissolution profiles of 2000-pound tablets at 3 positions in standard system

Table 3.3.3 f_1 and f_2 Value of 2000-Pound Tablets at 3 positions in Standard System

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Tablets using official method		
Tablets at center	0.22	99.25
Tablets at 10 °off-center	3.80	76.44
Tablets at20 °off-center	8.18	61.27

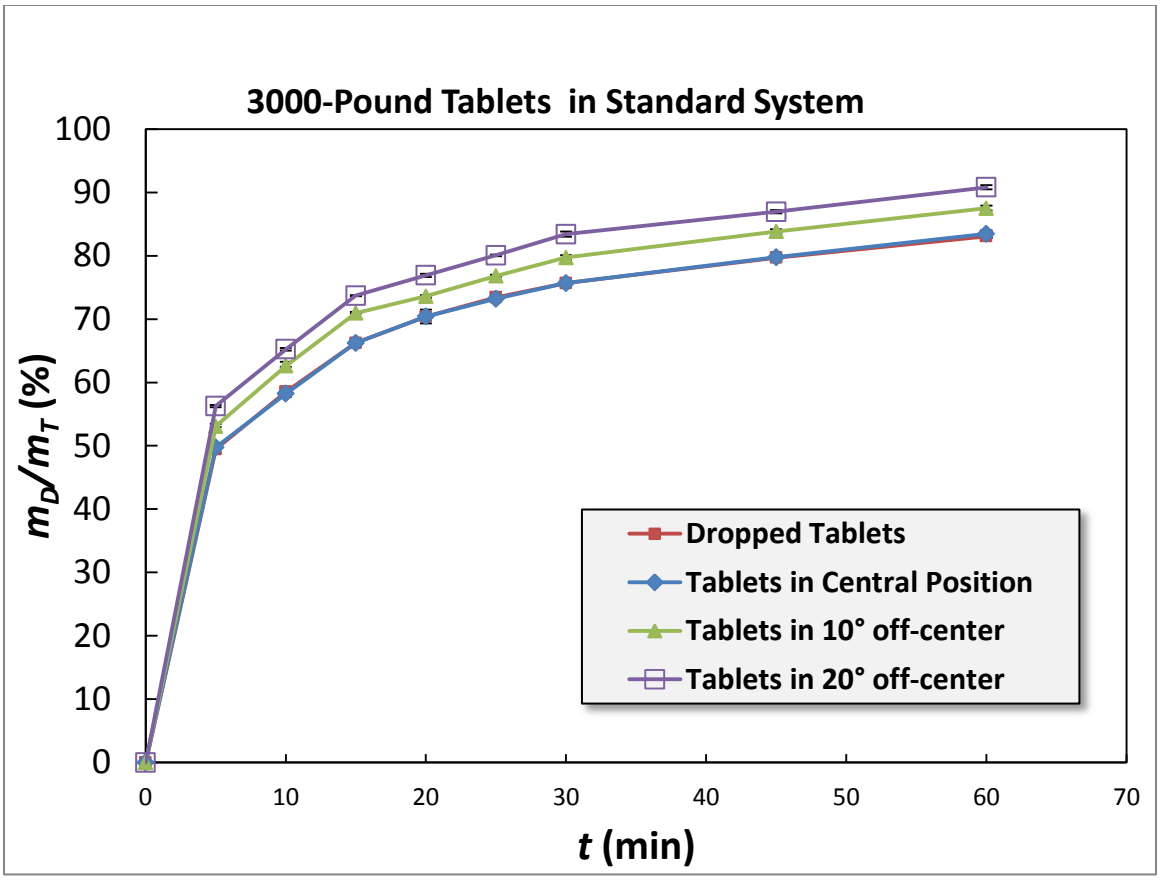


Figure 3.3.4 Dissolution profiles of 3000-pound tablets at 3 positions in standard system

Table 3.3.4 f_1 and f_2 Value of 3000-Pound Tablets at 3 positions in Standard System

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Tablets using official method		
Tablets at center	0.24	99.55
Tablets at 10 °off-center	5.69	70.50
Tablets at20 °off-center	10.22	58.41

3.4Results for the Tablets at Nine Positions in OPI System Using Testing Method #2

In all dissolution tests with the modified system, the aspirin tablets remained at their initial location for the entire duration of the experiment. Since the tablets did not

disintegrate, the dissolution process was driven by erosion. In order to compare the profiles of off-center tablets with centrally located tablets, the similarity values f_1 and difference values f_2 were used. Table 3.4.1-3.4.4 shows the f_1 and f_2 valuesof off-center dissolution profiles comparing with the dissolution profile of the centrally located tablets.

In all cases, when compared to the dissolution profiles in OPI system by dropping in this case,f_1 values were in the range 2-4, much lower than the upper limit required by FDA for similarity (15), and f_2 values were in the range and more than 75, within the FDA range 50-100. Thus, all values were within the acceptance level. Indicating off-center dissolution profiles were statistically similar to the baseline profile obtained from centrally located tablets in the modified USP Dissolution Apparatus 2 and the OPI system can avoid the interferes from tablets initial location.. As shown in Figure below, one can easily see the OPI system is robust enough.

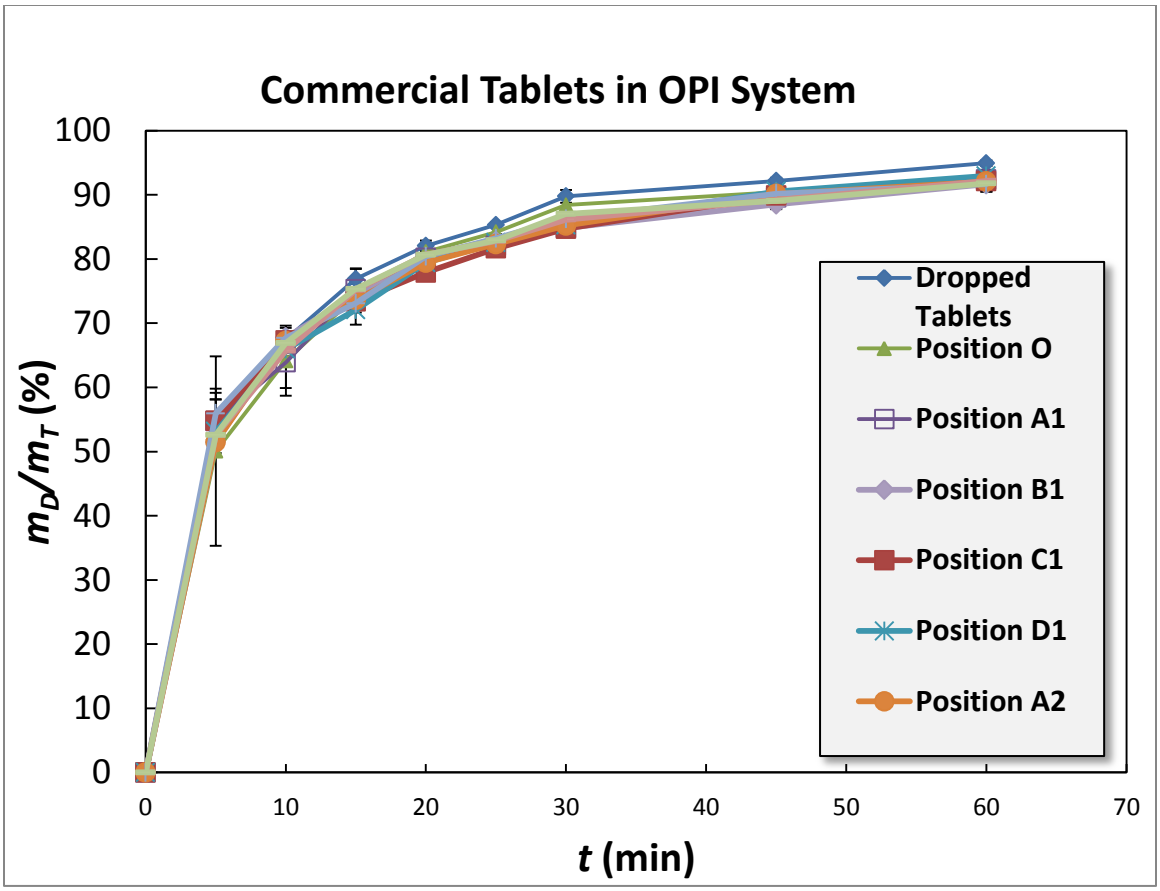


Figure 3.4.1 Dissolution profiles of commercial tablets at 9 positions in OPI system

Table 3.4.1 f_1 and f_2 Value of Commercial Tabletsat 9 Positions in OPI System

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Dropped tablets		
Tablets at position O	2.64	81.03
Tablets atposition A1	3.36	76.63
Tablets atposition B1	3.41	76.04
Tablets atposition C1	3.56	74.71
Tablets atposition D1	3.16	76.85
Tablets atposition A2	3.23	77.21
Tablets atposition B2	2.95	78.81
Tablets atposition C2	2.76	80.57
Tablets atposition D2	2.48	81.87

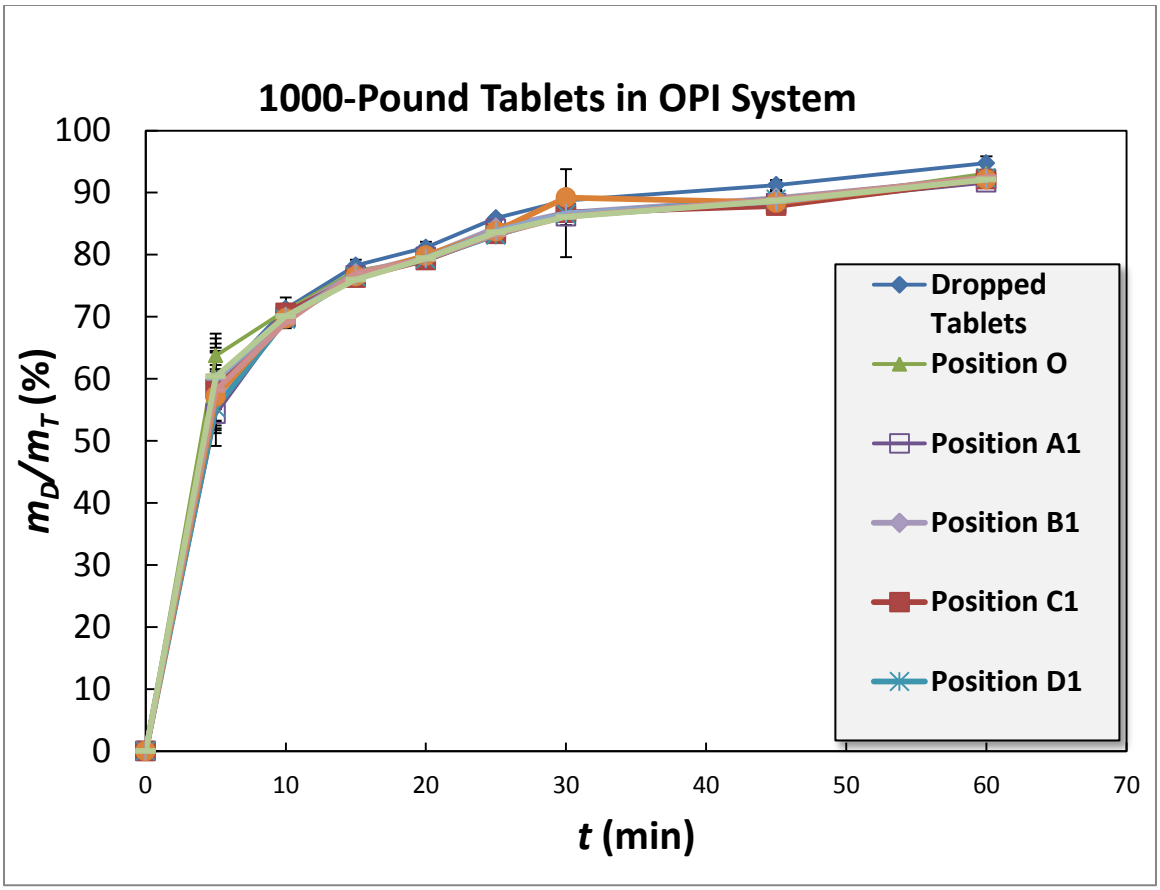


Figure 3.4.2 Dissolution profiles of 1000-pound tablets at 9 positions in OPI system

Table 3.4.2f_1 and f_2 Value of 1000-Pound Tablets at 9 Positionsin OPI System

Tablet Location	**f_1 (Similarity factor)**	**f_2 (Difference factor)**
Dropped tablets		
Tablets at position O	2.59	80.24
Tablets atposition A1	3.07	77.72
Tablets atposition B1	1.83	86.84
Tablets atposition C1	2.50	82.02
Tablets atposition D1	2.95	79.52
Tablets atposition A2	2.29	83.59
Tablets atposition B2	2.20	84.24
Tablets atposition C2	2.51	82.69
Tablets atposition D2	2.49	82.49

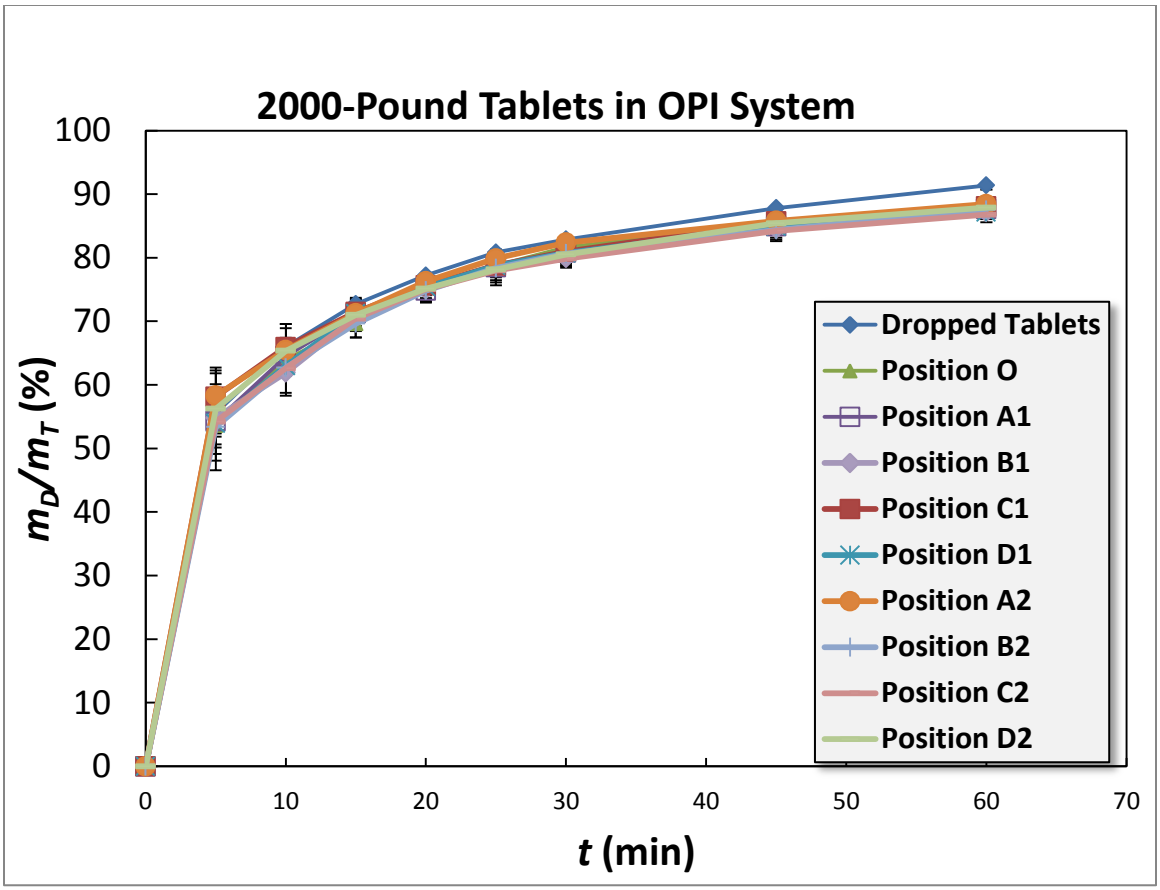


Figure 3.4.3 Dissolution profiles of 2000-pound tablets at 9 positions in OPI system

Table 3.4.3f_1 and f_2 Value of 2000-Pound Tablets at 9 Positionsin OPI System

Tablet Location	f_1 (Similarity factor)	f_2 (Difference factor)
Dropped tablets		
Tablets at position O	2.94	80.65
Tablets atposition A1	2.87	80.84
Tablets atposition B1	3.55	76.61
Tablets atposition C1	2.42	83.02
Tablets atposition D1	3.13	79.24
Tablets atposition A2	1.97	85.64
Tablets atposition B2	3.73	76.63
Tablets atposition C2	3.78	75.82
Tablets atposition D2	2.62	81.79

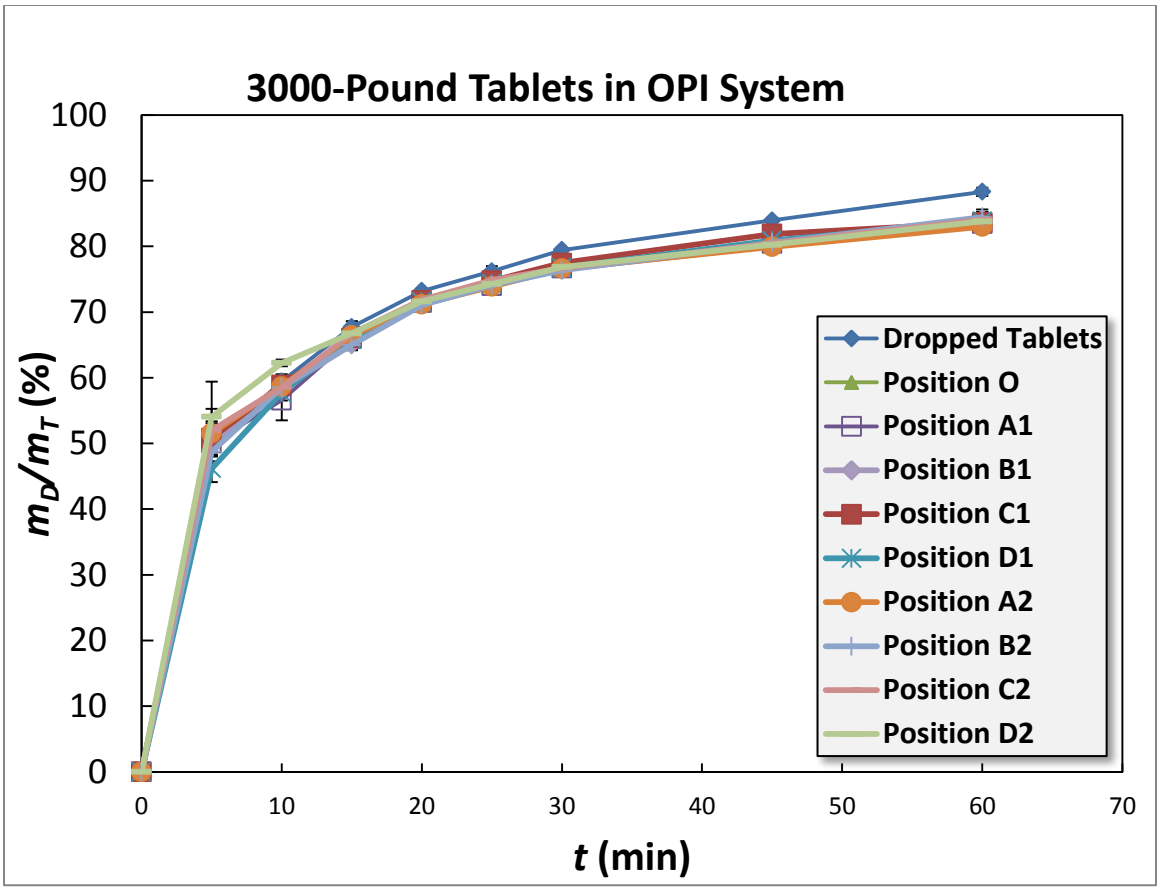


Figure 3.4.4 Dissolution profiles of 3000-pound tablets at 9 positions in OPI system

Table 3.4.4f_1 and f_2 Value of 3000-Pound Tablets at 9 Positionsin OPI System

Tablet Location	**f_1 (Similarity factor)**	**f_2 (Difference factor)**
Dropped tablets		
Tablets at position O	3.03	79.43
Tablets atposition A1	3.51	77.36
Tablets atposition B1	3.27	78.29
Tablets atposition C1	2.61	81.83
Tablets atposition D1	3.58	77.76
Tablets atposition A2	3.55	76.71
Tablets atposition B2	3.31	78.85
Tablets atposition C2	3.03	79.72
Tablets atposition D2	3.91	75.65

CHAPTER 4

DISCUSSION

In previous work[16-18], OPI system was found more robust than the standard USP method. In order to determine OPI is also sensitive enough to detect the difference as USP standard method does under the change of experimental condition, further experiments were conducted. Due to the fact that tablets with different pressures might have different dissolution profile, the pressure difference was selected as the variable in the test. According to USP specification, USP method in Apparatus 2 was used firstly to see whether the difference of dissolution profiles exists under different aspirin tablets with different pressures. Results showed that tablets with different pressures had different dissolution curves. If the similar results concluded by OPI system, the sensibility of the OPI system can be verified.

A difference between different pressures was found in both systems through the figure. $f_1$values was foundto be in the range 2.0–11.0 and $f_2$values in this part were found to be in therange 55.0–79.0 in both systems. f_1 values of tablets with 1000 pound, 2000 pound and 3000 pound in standard system were 2.9, 5.7 10.4 respectively, meanwhile, in Table 3.2.1,$f_1$values of tablets dissolution profiles in OPI system using testing method#1 were 2.3, 4.9 and 10.0; on the other hand, $f_2$values of both systems were corresponding as well. $f_1$and $f_2$values of tablets with specific pressure were shown in the Table 3.2.2-3.2.5, indicating in OPI system, dissolution profiles of tablets with different pressures were extremely similar, that is, just like standard system; OPI system was sensitive enough to detect differences of the tablets.

In the following experiments, significant difference in dissolution performance

can be seen between off-center and centered tablets in the Standard System. A small tablet off-center displacement of only 10 ° is already capable of producing significantly and statistically different dissolution results, with f_1 value of 8.63, more than $f_1$value of central tablets, 3.05 when compared to the curves of dropped tablets as reference curve. When the displacement reaches 20 ° off-center, f_1 value turns to be 10.67, indicating that greater deviation of the tablet location from the centerline can produce larger deviation in dissolution profiles.

Distance effect did not exist in the OPISystem. Greater deviations of the tablet location from the centerline hadsimilar results as the central location tablets in the dissolution profiles, which is different to the Standard System. As shown in Table 3.4.1-3.4.4. That is,all the deviations are within the acceptable range guided by FDA. Thus, tablet locations in the bottom of the vessel are not that important in the OPI System. In typical dissolution tests, the OPI testing apparatus is robust enough to produce similar dissolution profiles even the tablet is freely dropped into the testing vessel at 50 rpm agitation speed.

According to previous work, the reason for this improvement resides in the deliberateremoval of the symmetry, obtained by positioningthe impeller off center with respect to thevessel, as proposed here for the OPI system. In theStandard System, the symmetric position of the impellergenerates a poorly mixed region just belowthe impeller,precisely where the tablet is usuallylocated

In sum, the results of this work confirm that dissolution of aspirin tablets issignificantly affected by the exact location of the dissolvingtablet, as also described in previous work.However, and more importantly, this work additionallyshows that OPI

system can obviate to this problem and resultin amuchmore robust dissolution testing system. On the other hand, a good sensibility to the difference of the tablets showed in the work, indicating the OPI system is sensitive enough to analyze the tablets while it has a strong independence to the effect factors such as the deviation of the tablet location from the centerline.In addition, the OPI system is expectedto require very low capital investment for its commercialimplementation and minimal retraining ofpersonnel, while providing a much more robust testthat is insensitive to tablet location and, most likely,to other small geometric imperfections in the equipmentand to small operator-dependent variations inthe test procedure.

CHAPTER 5

CONCLUSIONS

The following conclusions can be drawn from this work:

1. Dissolution tests conducted using aspirin tablets with different compression pressures in the standard USPDissolution Testing Apparatus2 resulted in dissolution curves that werenot statistically similar(using both f_1 and f_2) respectiveof the tablets pressures, indicating that tablets pressure in this particular case is one of the variables, which causes the different dissolution profiles and can be detected in the standard USPDissolution Testing Apparatus2.

2. By contrast, similar tests conducted usingthe standard USPDissolution Testing Apparatus2 resulted in dissolution curves that werealso statistically similar just as the former case. Additionally, f_1 and f_2 of each curve was corresponding, stating that the OPI system was sensitive enough to detect the slice difference between tablets as standard USPDissolution Testing Apparatus2 did.

3. In this work the dissolution performance of aspirin tablets with different pressures 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

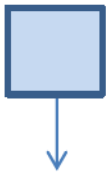
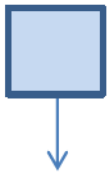
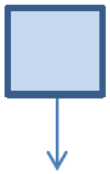
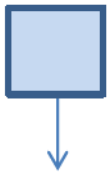
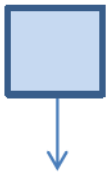
testing but with hydrodynamic characteristics of the apparatus itself and the location of the tablet on the vessel bottom.

4. OPI system 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 OPI system generated dissolution profiles for aspirin tablets that were nearly completely insensitive to tablet location. And when compared to the results in OPI system by dropping the tablets, similarity of the results can be easily seen, which states OPI system is not only sensitive enough to detect the slice experimental condition differences, but also much more robust than the Standard Dissolution System.

Appendix A

DERVIATION OF EQUATION 2.1

In this appendix, Equation 2.1 in Section 2.4 was derived based on the mass balance inthe dissolution system.

	Initial System	t_o=0	t_1	t_2	t_i	t_n
Volume before taking sample		V	V- V	V-2 V	V-i V	V-n V
		 V	 V	 V	 V	 V
Remaining volume after taking sample		V- V	V-2 V	V-3 V	V-(i+1) V	V-(n+1) V

Thedrug release ratio needed to be determined:

$$\frac{mass\ of\ drug\ in\ solution\ at\ t}{initial\ mass\ of\ drug\ in\ tablet} = \frac{m_{Dissolved}(t)}{m_{Tablet}} = \frac{m_D(t)}{m_T}$$

i.e., the amount of drug in solution at any time t out of the total initial amount ofdrug in the tablet.

The initial volume of solution (medium) is V, and each sample has a volumeequal to ΔV. Also, the mass of drug initially in the tablet is:

$$m_T = C^* \cdot V \quad \text{i.e.,} \quad C^* = \frac{m_T}{V}$$

In general, at any time t just after taking a sample, the **mass balance** for the drugremoved from the tablet (and transferred to the solution) gives:

$$\begin{pmatrix}\text{mass of drug}\\ \text{removed from tablet}\end{pmatrix} = \begin{pmatrix}\text{mass of drug}\\ \text{left in solution after}\\ \text{sample is taken}\end{pmatrix} + \begin{pmatrix}\text{mass of drug}\\ \text{in current sample}\end{pmatrix} + \begin{pmatrix}\text{mass of drug in all}\\ \text{previous samples}\end{pmatrix}$$

In our system, the tablet was dropped in the medium at t=t_o, the agitation wasimmediately started, and a sample was taken (at t=t_1=5 min).:

$$\frac{m_D(t_o)}{m_T} = \frac{C_0(V-\Delta V)+C_0\Delta V+0}{C^*V} = \frac{C_0V}{C^*V} = \frac{C_0}{C^*}$$

For t=t_1 (corresponding to a sample concentration C=C_1) the mass balance gives:

$$\frac{m_D(t_1)}{m_T} = \frac{C_1(V-2\Delta V)+C_1\Delta V+C_0\Delta V}{C^*V} = \frac{C_1(V-\Delta V)+C_0\Delta V}{C^*V}$$

For t=t_2 (corresponding to a sample concentration C=C_2):

$$\frac{m_D(t_2)}{m_T} = \frac{C_2(V-3\Delta V)+C_2\Delta V+(C_0+C_1)\Delta V}{C^*V} = \frac{C_2(V-2\Delta V)+(C_0+C_1)\Delta V}{C^*V}$$

For t=t_i(corresponding to a sample concentration C=C_i):

$$\frac{m_D(t_1)}{m_T} = \frac{C_i\left(V-(i+1)\Delta V\right)+C_i\Delta V+\left(C_0+C_1+\ldots+C_{i-1}\right)\Delta V}{C^*V}$$
$$= \frac{C_i\left(V-i\Delta V\right)+\left(C_0+C_1+\ldots+C_{i-1}\right)\Delta V}{C^*V}$$

For $t=t_n$(corresponding to a sample concentration $C=C_n$):

$$\frac{m_D(t_n)}{m_T} = \frac{C_n\left(V-(n+1)\Delta V\right)+C_n\Delta V+\left(C_0+C_1+\ldots+C_i+\ldots C_{n-1}\right)\Delta V}{C^*V}$$
$$= \frac{C_n\left(V-n\Delta V\right)+\left(C_0+C_1+\ldots+C_i+\ldots+C_{n-1}\right)\Delta V}{C^*V}$$

Hence, for $t=t_n$(corresponding to a sample concentration $C=C_n$):

$$\frac{m_D(t_n)}{m_T} = \frac{C_n\left(V-n\Delta V\right)}{C^*V}+\sum_{i=0}^{n-1}\frac{C_i\Delta V}{C^*V}$$

and finally:

$$\frac{m_D(t_n)}{m_T} = \begin{pmatrix}\text{fraction of drug dissolved at } t_n,\\ \text{i.e., immediately after nth}\\ \text{sample was taken}\end{pmatrix} = \frac{C_n}{C^*}\left(1-\frac{n\Delta V}{V}\right)+\frac{\Delta V}{V}\sum_{i=0}^{n-1}\frac{C_i}{C^*}$$

Remark: in this study first sample was taken at $t=t_1=5$ min. Thismeans that the 9_h sample corresponds to n=9, i.e.,n= 1, 2, 3, 4, 5, 6, 7 and 8(9 samples taken every 5 minutes, starting at time $t=t_1=5$min, and ending at time $t_8=60$ minutes).

Appendix B

DISSOLUTION OF TABLETS WITH DIFFERENT COMPRESSION PRESSURES AT EACH POSITION OF NINE POSITIONS IN OPI SYSTEM

In this appendix, dissolution profiles of aspirin tablets in are plotted as concentration ratio m_D/m_T (%) vs. time in Figure B.1 to B.9.

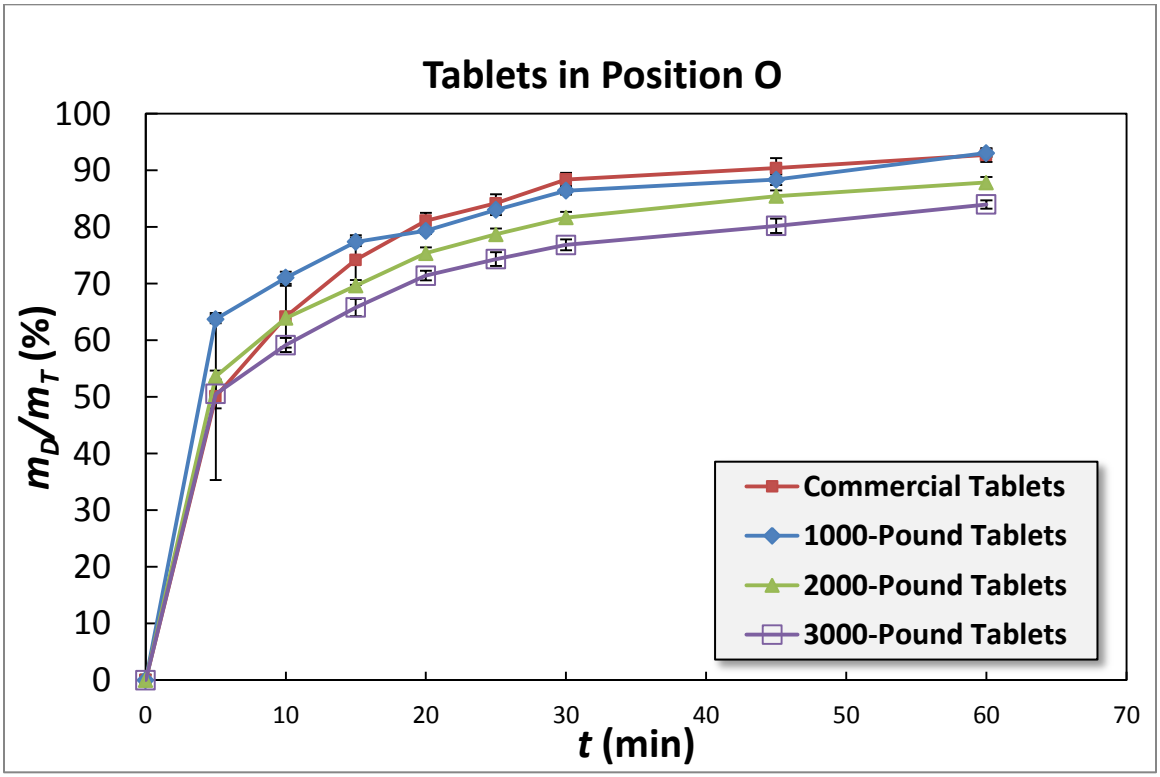


Figure B.1 Dissolution profiles of tablets with different pressures at position Oin OPI system.

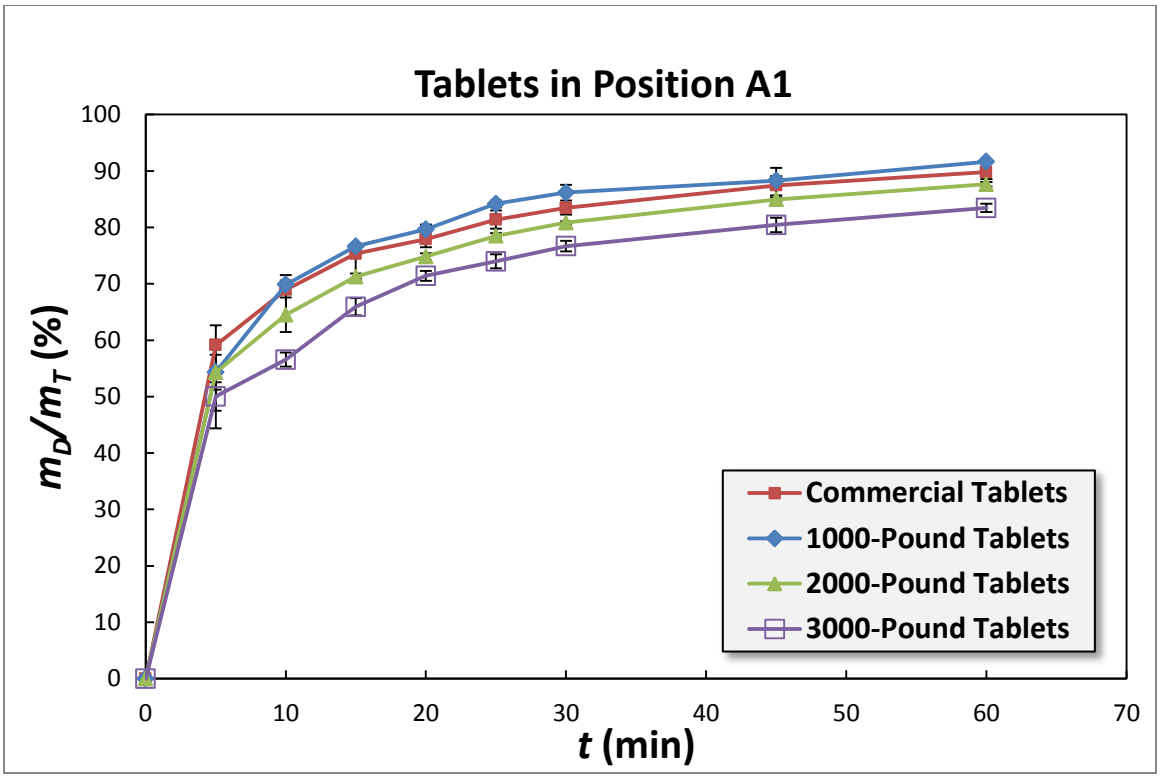


Figure B.2 Dissolution profiles of tablets with different pressures at position A1 in OPI system.

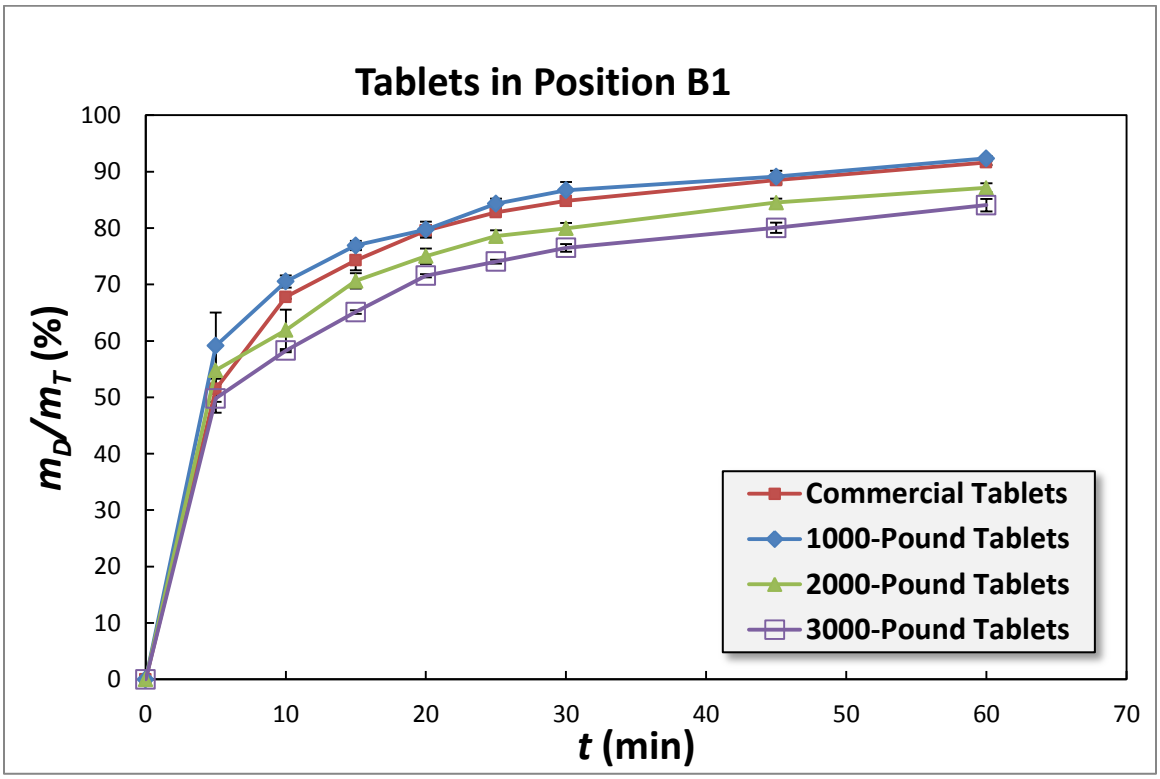


Figure B.3 Dissolution profiles of tablets with different pressures at position B1 in OPI system.

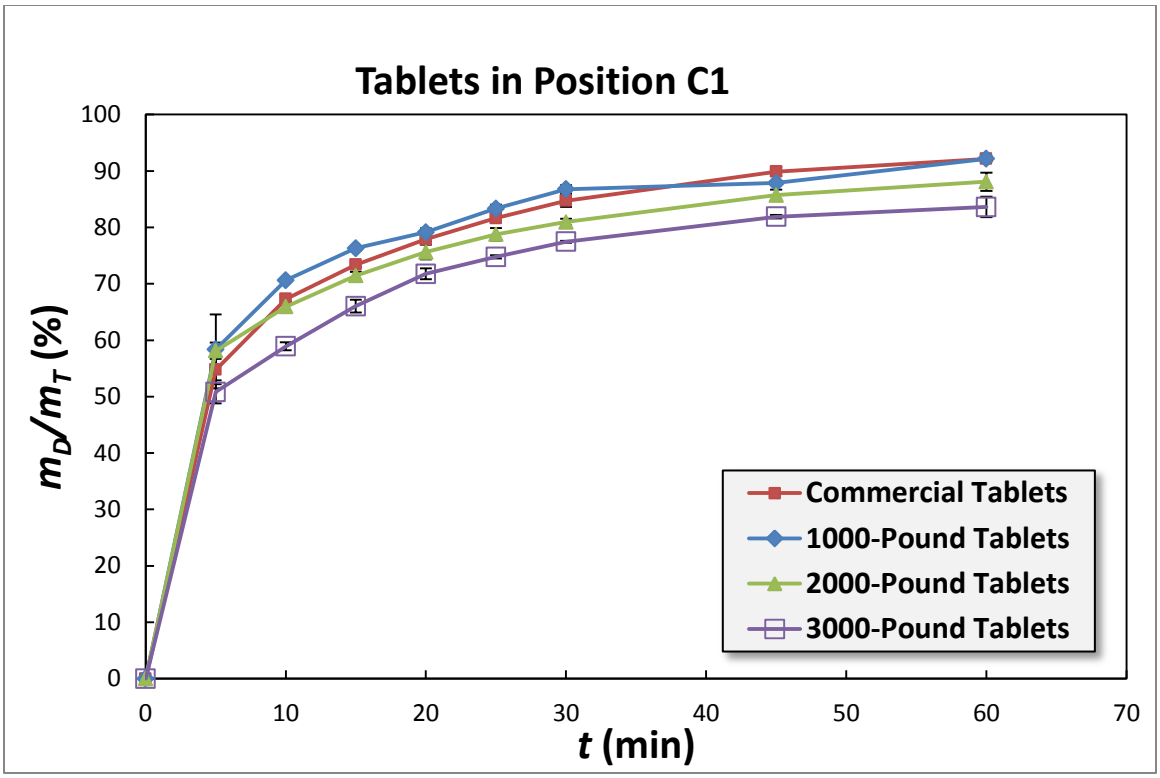


Figure B.4 Dissolution profiles of tablets with different pressures at position C1 in OPI system.

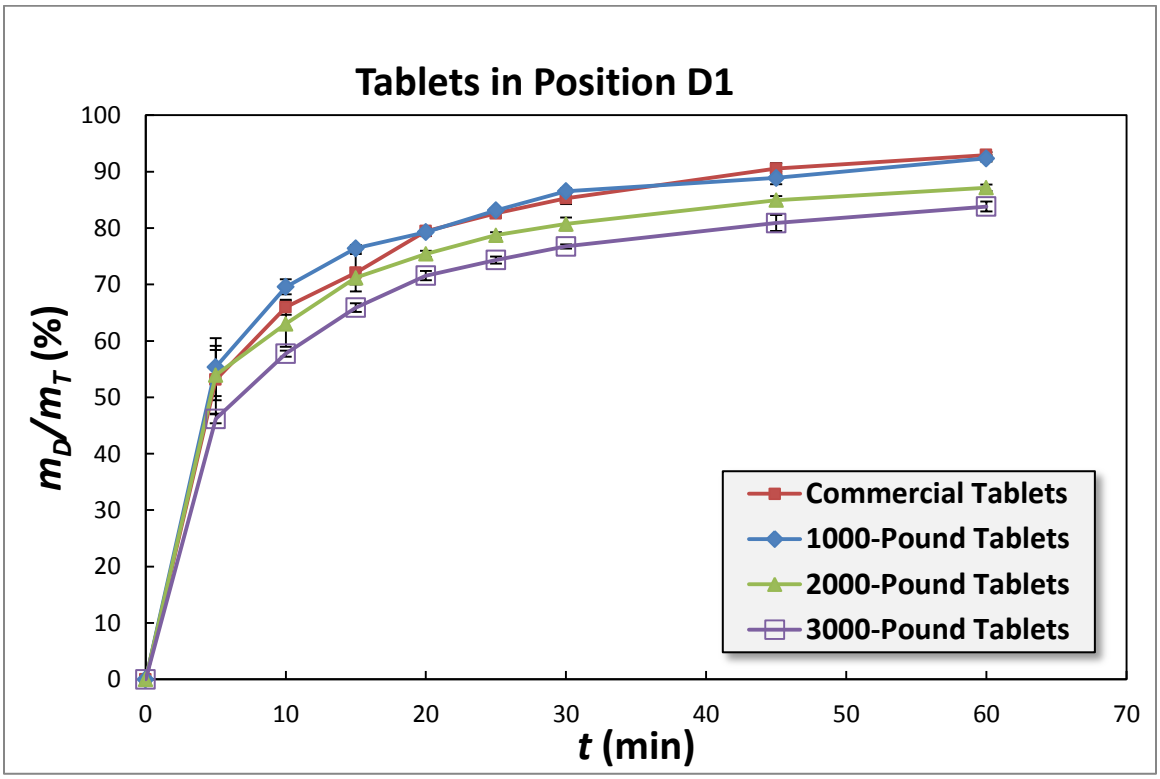


Figure B.5 Dissolution profiles of tablets with different pressures at position D1 in OPI system.

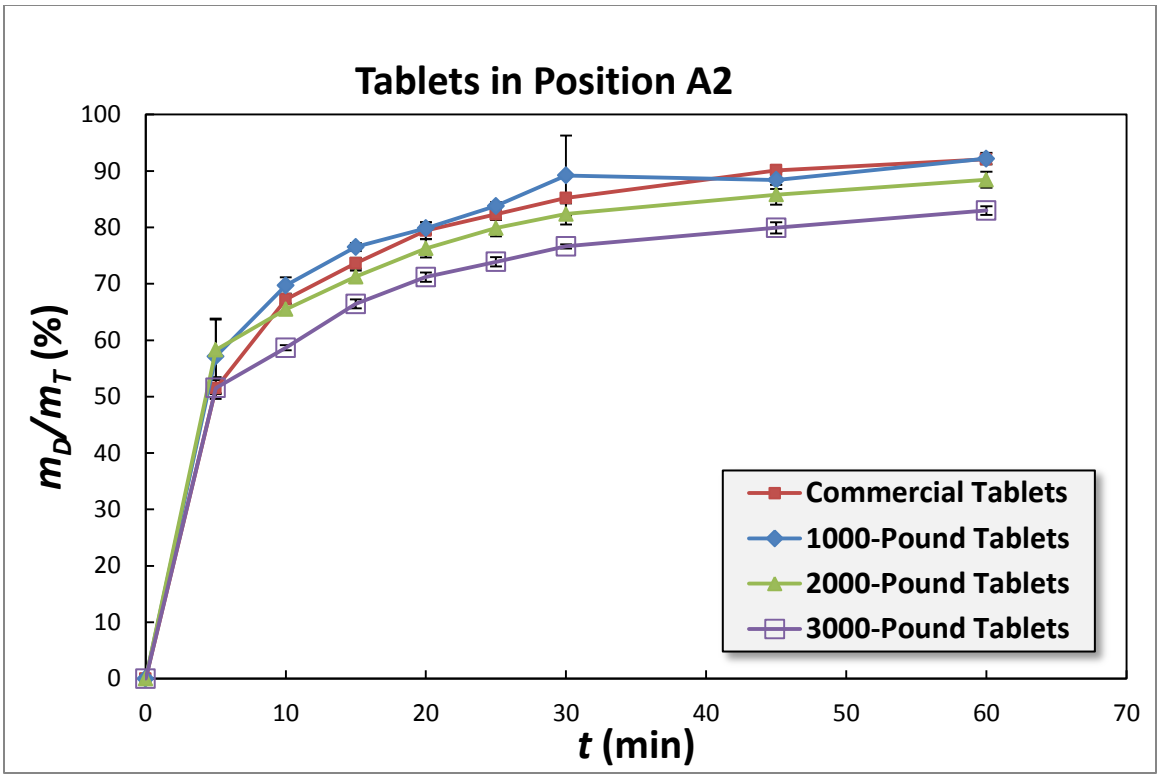


Figure B.6 Dissolution profiles of tablets with different pressures at position A2 in OPI system.

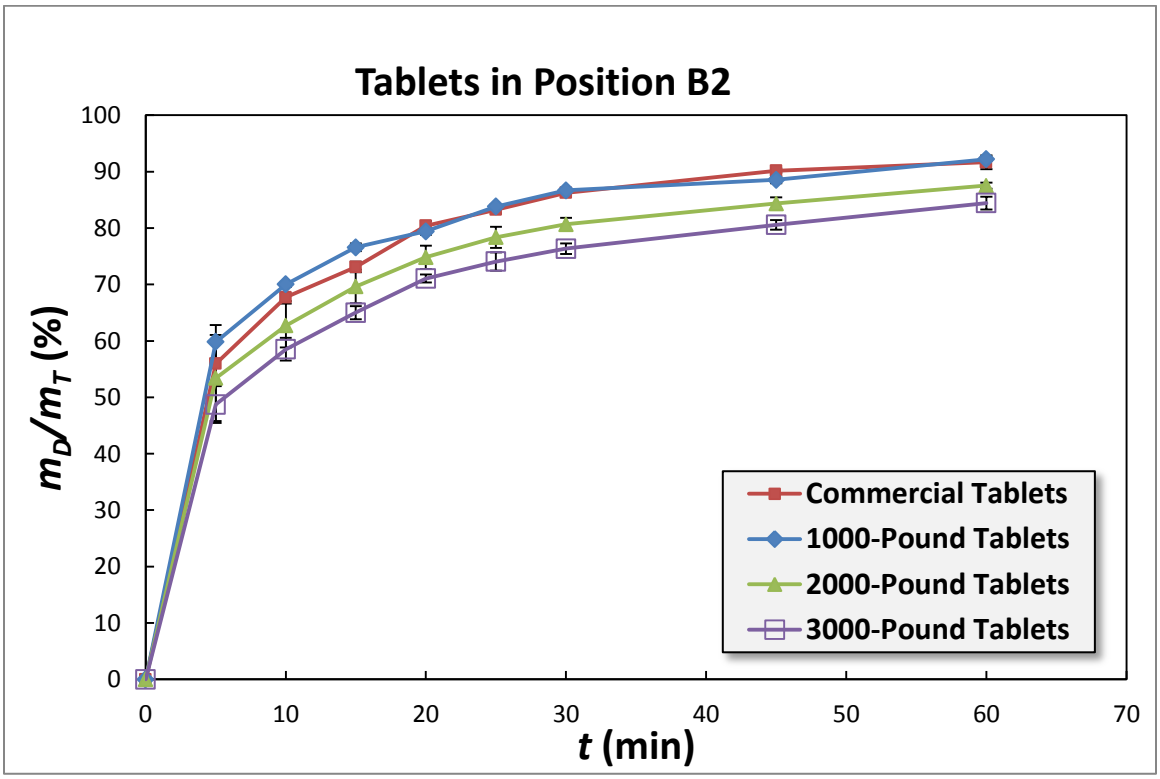


Figure B.7 Dissolution profiles of tablets with different pressures at position B2 in OPI system.

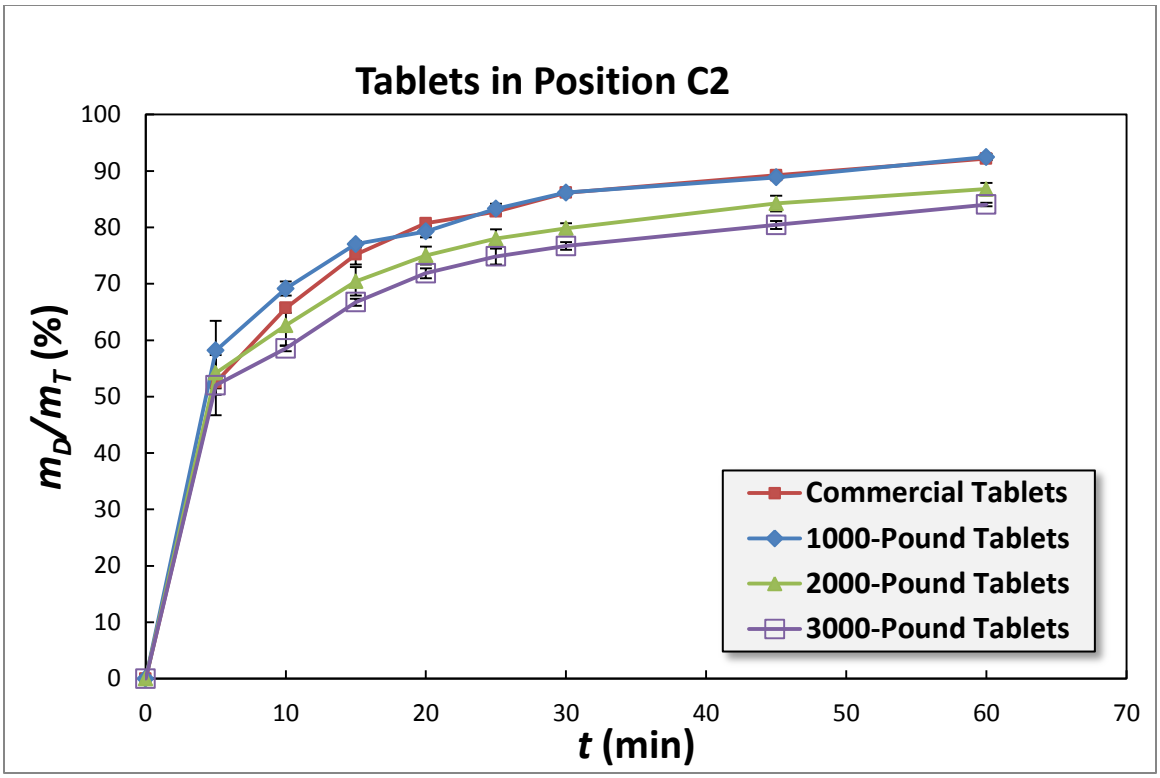


Figure B.8 Dissolution profiles of tablets with different pressures at position C2 in OPI system.

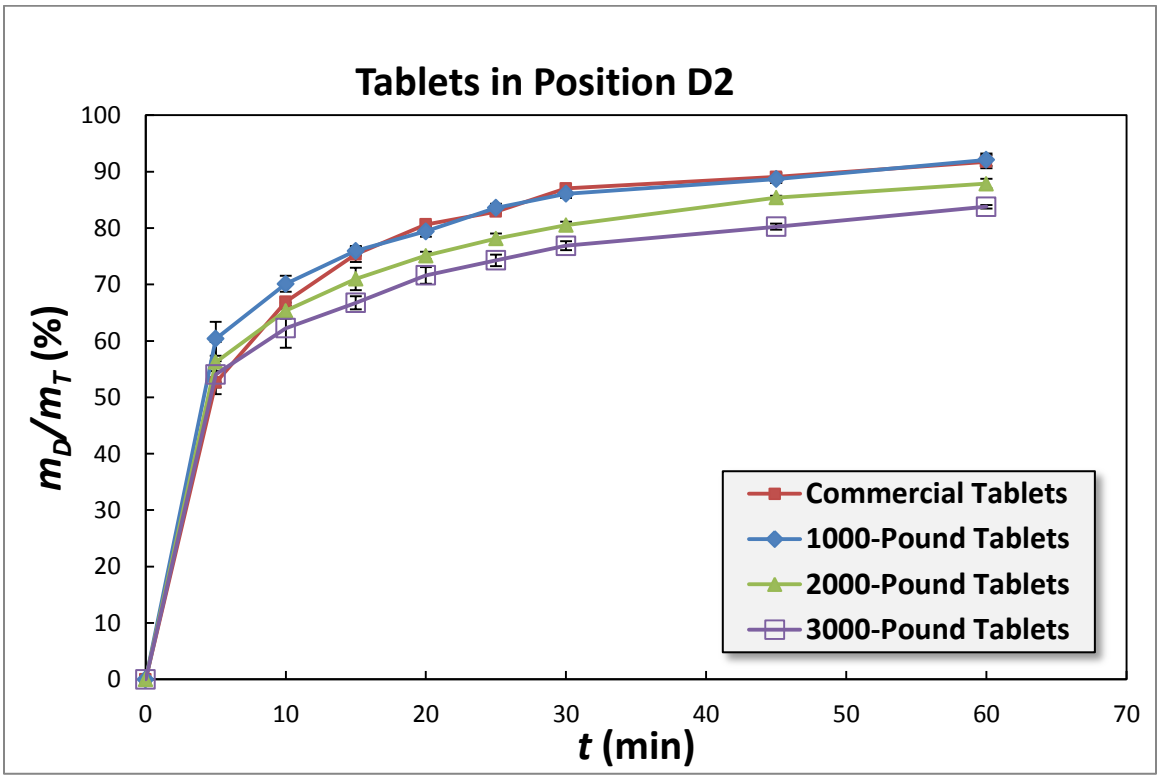


Figure B.9 Dissolution profiles of tablets with different pressures at position D2 in OPI system.

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