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Dissolution of different commercial aspirin tablets using a novel off-center paddle impeller (OPI) dissolution testing system

Yang Qu
New Jersey Institute of Technology

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ABSTRACT

DISSOLUTION OF DIFFERENT COMMERCIAL ASPIRIN TABLETS USING A NOVEL OFF-CENTER PADDLE IMPELLER (OPI) DISSOLUTION TESTING SYSTEM

by
Yang Qu

Dissolution testing is routinely conducted in the pharmaceutical industry to provide *in vitro* drug release information for quality control purposes. The most common dissolution testing system for solid dosage forms is the United States Pharmacopeia (USP) Dissolution Testing Apparatus 2. In this work, a modified Apparatus 2, termed "OPI" System for "off-center paddle impeller," in which the impeller is placed 8 mm off center in the vessel is tested to determine its sensitivity to differentiate between the dissolution profiles of differently formulated and manufactured tablets. Dissolution tests are conducted with both the OPI System and the Standard System using three different brands of aspirin at nine different tablet positions. The OPI system produces dissolution profiles that are highly dependent on the different brands of aspirin used, similarly to those generates in the Standard System. However, the dissolution profiles obtained with the OPI apparatus are found to be largely independent of the tablet location at the vessel bottom, whereas those obtained in the Standard System generates statistically different profiles depending on tablet location. It can be concluded that the newly proposed OPI system can effectively eliminate artifacts generated by random settling of the tablet at the vessel bottom, thus making the test more robust, while at the same time being just as sensitive as the Standard System to actual differences in differently manufactured tablets having intrinsically different dissolution profiles.

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by
Yang Qu

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APPROVAL PAGE

DISSOLUTION OF DIFFERENT COMMERCIAL ASPIRIN TABLETS USING A NOVEL OFF-CENTER PADDLE IMPELLER (OPI) DISSOLUTION TESTING SYSTEM

Yang Qu

Dr. Piero M. Armenante, Dissertation Advisor — Date
Distinguished Professor of Chemical Engineering, NJIT

Dr. Laurent Simon, Committee Member — Date
Associate Professor of Chemical Engineering, NJIT

Mr. Gerard Bredael, Committee Member — Date
Associate Principal Scientist, Merck & Co., Inc.

BIOGRAPHICAL SKETCH

Author: Yang Qu

Degree: Master Science

Date: March 2013

Undergraduate and Graduate Education:

- Master of Science in Pharmaceutical Engineering,
  New Jersey Institute of Technology, Newark, NJ, 2013

- Bachelor of Science in Clinical Laboratory Science,
  Tianjin Medical University, Tianjin, P. R. China, 2011

Major: Pharmaceutical Engineering

Presentations and Publications:

- Lin Nong, **Qu Yang**, Zhang Weijia, (2009). "Non-contraceptive Benefits of Oral Contraceptives," Journal of International Reproductive Health/Family Planning, 28(2), 89.
- Shen Lilin, Hou Qingchang, Liu Miaomiao, **Qu Yang**, (2009). "Effects of Compound Policresulen Gel on Trichomonads," Tianjin Pharmacy, 21(6), 1.
- Wang Limei, Wang Huijin, Lin Nong, Zhang Shumin, Wu Hua, Liu Guifeng, Zhao Xun,Qu Yuan, Xu Qingxiang,Rong Lijie, Zhang dongling, **Qu Yang**, (2010). "Clinical effects of luteal phase treatment with mifepristone and misoprostol for fertility regulation on menstrual patterns", Chinese Journal of Family Planning, 18(7), 421.

This thesis is dedicated to my parents 渠源 and 侯左鸣 who have been my constant source of inspiration. They give me the drive and discipline to tackle any task with enthusiasm and determination.

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CHAPTER 1

INTRODUCTION

1.1 Background

The dissolution of a drug substance contained in a solid dosage form is the process by which the drug substance is released from its original formulation into a suitable solution under controlled conditions. Although dissolution appears to be a simple process, developing a suitable dissolution test for the drug content of solid dosage forms is not a trivial task, especially considering that dissolution testing is a critical step in quality control for manufactured final products and it is one of the standard methods for assessing batch-to-batch consistency of solid oral drug delivery systems such as tablets and capsules. Therefore, careful consideration should be given in the selection of equipment to be used for such test and the specifications of the test operating variables.

Currently there are seven dissolution testing apparatuses specified by USP [1]. Different types of drug dosage forms have specific dissolution apparatuses and operation conditions for dissolution testing, such as dissolution medium, medium volume, agitation speed, detecting UV wavelength, and others.

USP Apparatus 1, the rotating basket dissolution apparatus was developed in 1960s. This system consists of a 1 L cylindrical, hemispherical bottom, unbaffled vessel and a meshed basket. This device is appropriate for dosage forms such as capsules, beads and suppositories. The design of the basket can prevent light drugs from floating around during the dissolution tests.

The rotating paddle apparatus, USP Apparatus 2, was developed shortly after Apparatus 1. It consists of a paddle agitator and the same vessel as USP Apparatus 1. This system is helpful for heavier drugs such as tablets, which can rapidly sink when dropped in the dissolution medium. For light drugs, a sinker would be used to help sinking the tablet. USP Apparatus 2 is used for both immediate release and modified release drug delivery systems. In general, three dissolution volumes are used, i.e., 500 mL, 900 mL and 1000 mL. This system is routinely used to test oral dosage tablets and capsules.

In 1995, USP introduced the reciprocating cylinder apparatus as an alternative to the basket and paddle apparatuses for drug release testing. The reciprocating cylinder apparatus has six inner tubes moving vertically. There is a screen at each end, containing the drug delivery system. This apparatus has been successfully used for tablets, capsules and some extended-release dosage. When small testing volumes (200-300 mL) are required, reciprocating cylinder is a good choice.

The flow-through cell was originally developed to simulate gastrointestinal conditions by exposing extended-release and poorly soluble dosage forms to media of varying pH. It was designed for non-disintegrating drugs. This apparatus consists of six cells, which can be of various sizes depending on the drug delivery system. The apparatus has been used for capsules, powders, tablets, implants, and suppositories and has been used with a wide range of media volume.

USP Apparatuses 5 and 6 are employed for testing transdermal patches, and the official vessels are the same as in Apparatuses 1 and 2, i.e., a 1 L unbaffled hemispherical-bottom glass vessel. Apparatuses 5 and 6 were originally introduced as

supplements to USP Apparatus 1 and 2. USP Apparatus 5 is also called paddle over disk. This device is simply a modified version of USP Apparatus 2. The vessel and agitator are the same as in USP Apparatus 2. The only difference is there is the presence of horizontal disk whose purpose of the disk is to act as a sinker to hold the transdermal patch during dissolution tests. USP Apparatus 6 is usually referred to as rotating cylinder. The device uses the same vessel of Apparatus 1 where the basket is replaced with a hollow stainless steel cylinder. The transdermal patch is pasted on the cylinder with the drug release side placed outwards.

Apparatus 7, incorporating a reciprocating holder was originally introduced as a small volume option for small transdermal patches. Currently, Apparatus 7 can accommodate a dissolution environment as low as 5 mL.

The USP Apparatus 2 and the test associated with it are routinely used in the pharmaceutical industry to help formulate solid drug dosage forms, develop quality control specifications for its manufacturing process, provide critical in vitro drug release information for quality control purposes, and especially to assess batch-to-batch consistency of solid oral dosage forms, such as tablets, for both immediate-release and modified-release drug delivery systems. Despite its apparent simplicity, there are a number of issues associated with USP Apparatus 2 and its use. Although most solid oral dosage forms are tested in USP Apparatus 2, it is not uncommon to have a drug recall due to a failed dissolution test. Failed dissolution tests resulted in 47 product recalls in 2000–2002, representing 16% of nonmanufacturing recalls for oral solid dosage forms. A review of the weekly published US Food and Drug Administration (FDA) Enforcement Reports shows that failed dissolution testing routinely account for a significant fraction of

the recalls. Failed dissolution tests can result not only in product recalls, but also in costly investigations and potential production delays, all of them having substantial financial impact to the pharmaceutical industry. These inconsistencies present even greater challenges when trying to implement Quality by Design, which defines the future state of dissolution, its value, method design, and links to the design space. In addition, dissolution testing is sensitive to a number of parameters. The challenges generally are divided into two classes, i.e., variability and bio-relevancy [2]. Variability in dissolution testing is an area that has received a great deal of attention. Many studies demonstrated the source and extent of test variability [3, 4, 5, 6]. Even to this day, dissolution testing remains susceptible to significant error and test failures.

The hydrodynamics of USP Apparatus 2 vessel has been reported to play a major role in the poor reproducibility of dissolution testing data and the inconsistency of dissolution results [7, 8, 9]. Previous studies have pointed out that the hydrodynamics of this apparatus is actually quite complex [10-14] and it is strongly affected by even small variations in the geometry of the apparatus [15-17]. These studies have shown that even when the impeller is exactly centered in an ideal, perfectly cylindrical vessel with a hemispherical bottom, the velocity distribution inside USP Apparatus 2 is highly nonhomogeneous [12, 14-17]. The flow is dominated by a strong tangential component across the entire liquid volume (swirling motion) with weak axial and radial velocities, resulting in a poor top-to bottom recirculation and the possible formation of a loosely aggregated pile of solid tablet fragments (“coning” effect) below the impeller.

In addition, just under the impeller, a central inner core region can be found where both axial and radial velocities are extremely low regardless of the impeller agitation

speed. This is the region where the tablet is often located during a test. Outside this inner core region, the velocities are appreciably higher. As a result, the distribution of shear strain rate along USP Apparatus 2 vessel's bottom is highly non-uniform, and a zone always exists just below the shaft where the strain rate remains very low even when the impeller agitation speed is increased [17-22]. The non-uniformity of the shear and strain rate distributions can have a significant impact on the mass transfer rate and, hence, the dissolution rate of a tablet, depending on where the tablet is located during the dissolution testing [17].

The possibility that a tablet is not always centered during a test is a real one because the tablet is dropped from above the liquid before the test begins and can land anywhere at the vessel bottom. If the tablet finds itself at an off-center location, it may remain there for the rest of the test or a significant portion of it. This is especially the case for capsules and dosage forms with a gelatinous shell. Tablets located outside the inner core region have been shown to dissolve much more rapidly than those located within this zone, resulting in possible test failures because their dissolution curves are statistically different from those obtained with centered tablets [17, 22].

Another source of variability during dissolution testing is associated with small changes in the geometry of the system. For example, small alterations in the vessel geometry resulting in a slightly irregular inner shape of a glass vessel28 can produce very different dissolution profiles that result in test failures [29–30]. Also, placing the paddle just 2mm off center within the vessel (i.e., within the alignment tolerances specified in the USP) results in a flow pattern near the vessel's bottom that is appreciably different from that of a centered impeller [16]. This can be expected to impact the shear stress

experienced by a tablet sitting at the vessel's bottom and hence the dissolution profile. Even slightly tilting the vessel has been shown to change the rate of dissolution significantly [31]. External vibrations have also been shown to introduce significant variability in the dissolution profiles [16-19]. Similarly, even inserting a permanently placed sampling probe rather than sampling intermittently has enough of an impact on the hydrodynamics to result in an increase in the dissolution rate [29].

The reason for this extreme sensitivity of USP Apparatus 2 dissolution test to different types of small geometric changes can be attributed to the fact that USP Apparatus 2 consists of a symmetrical vessel with no baffles. Therefore, any small perturbations in the system's symmetry, such as those mentioned above, can result in a nonsymmetrical flow, especially around the dissolving tablets (which typically finds itself in an extremely weak flow field anyway), and can produce significantly different dissolution profiles as a result.

In the past, two approaches have been used to address such dissolution testing variability issues. The first consisted in developing a modified dissolution testing system. Examples include crescent shaped spindle [28-31] or the PEAK vessel (originally available from Varian, Inc. Palo Alto, CA, and currently available from Agilent Technologies Santa Clara, CA) [18-22]. In general, these systems still try to maintain symmetry and do not alter significantly the overall, strongly tangential flow pattern observed in the standard USP Apparatus 2.

Actually, because of its construction, the support arm of the crescent shaped spindle may unintentionally introduce some asymmetry in the system, which can be one of the reasons for the improved performance of this system. As for the PEAK vessel, its central

peak serves the function of preventing the tablet from being located in the center of the vessel, thus partially avoiding the above-mentioned, poorly agitated zone below the impeller. However, the advantages offered by both systems are limited and neither system has found wide acceptance in the industry.

The second and most common approach that practitioners and equipment vendors have used to minimize test variability is to reduce as much as possible all sources of asymmetry. This has resulted in a number of mechanical calibration tests, test devices, and tools designed to maximize the achievement of a symmetric system and remove imperfections as much as possible. For example, centering gauges, wobble meters, and other devices can be used to check for geometric irregularities and misalignments in the central placement of the impeller in the vessel. Similarly, glass vessels with very precise geometry can be purchased for a premium price [29–30]. For the same reason, sampling cannulas are not typically permanently inserted inside the dissolution vessel, although automation may eventually require the use of permanent sampling systems and this issue may be revisited in the future.

1.2 Objective of This Work

This overview shows that there are still a number of issues currently associated with dissolution testing in USP Apparatus 2, which are directly traceable to the system geometry and the resulting hydrodynamics. Therefore, recently this research group developed a slightly modified variation of USP Apparatus 2, called “OPI” (Off-Center Paddle Impeller) System which retains the key features of Apparatus 2, while reducing its shortcomings. Accordingly, the paddle impeller in USP Apparatus 2 was deliberately moved from its central location and placed in an off-center, asymmetric position as

shown in Figure 1.1 in order to take advantage of the nonsymmetrical but more homogeneous flow that asymmetric impellers generate, especially near the vessel's bottom. It has been shown by this group that this simple modification of the standard USP Apparatus 2 can result in a much more robust dissolution testing system, thus making this test insensitive not only to tablet location, but, most likely, also to other small geometric differences between the test systems [9].

Even though the OPI System can reduce some of the shortcomings of the current Apparatus 2, it is important to determine whether it can also discriminate between different tablets that have different dissolution profiles. Therefore, the objective of the work described here was to test whether the OPI System is sensitive enough to determine differences in tablet dissolution profiles caused by different formulations of the same drug product. This approach was tested here by experimentally by obtaining the dissolution profiles for three different brands of aspirin and statistically comparing these results with the dissolution results obtained in the current Standard System. In this work the dissolution characteristics of both the Standard Apparatus 2 and the OPI System were studied in detail. From this work it can be concluded that the OPI System is just as capable of differentiate the dissolution characteristics of different formulations while, at the same time, eliminating the sensitivity of the current Apparatus 2 system to minor changes in experimental and geometric variables.

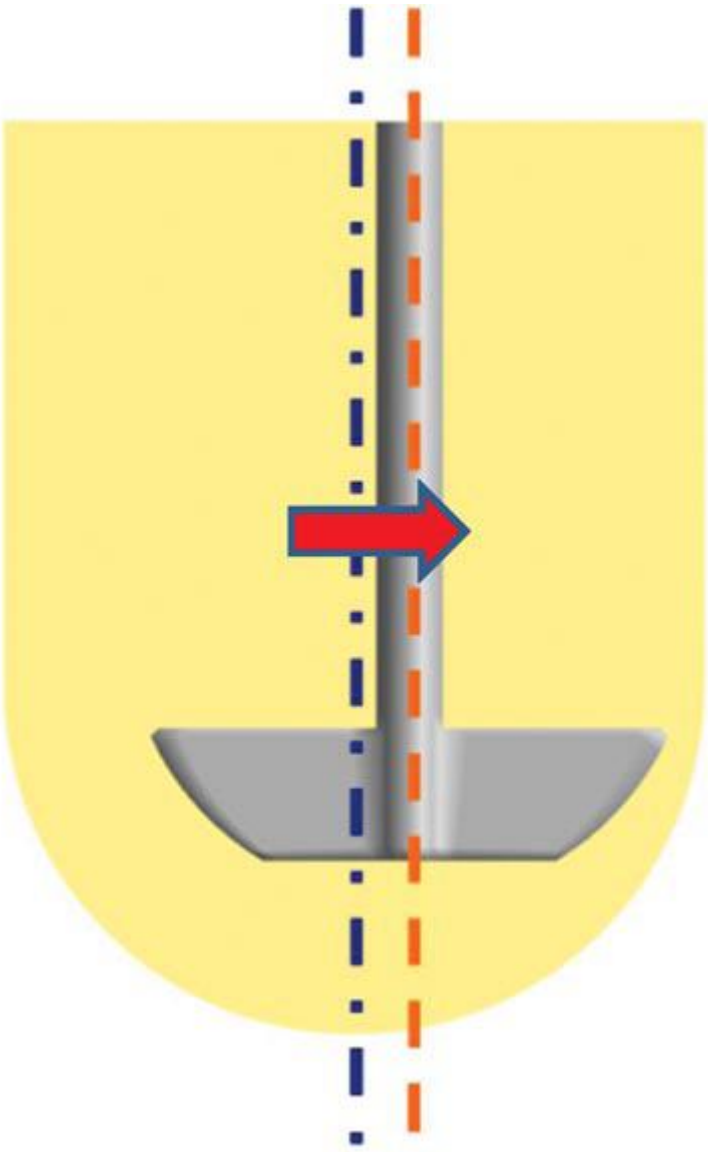


Figure 1.1 Illustration of the basic approach used to design OPI Dissolution Testing System.

CHAPTER 2

EXPERIMENTAL APPARATUSES, MATERIALS, AND METHODS

2.1 Dissolution Tests

2.1.1 Dissolution Apparatus

Two dissolution testing apparatus systems were used in this work, that is, a standard USP Dissolution Testing Apparatus 2 (hereafter called the "Standard System") and a modified system, which, in this work, is referred to as "OPI system" for "off-center paddle impeller" system. The Standard System consisted of a Distek 5100 bathless dissolution apparatus shown in Figure 2.1 (Distek Inc., North Brunswick, New Jersey), capable of operating seven dissolution vessels at a time. Each USP Apparatus 2 vessel used as the dissolution vessel consisted of an unbaffled, cylindrical, transparent glass tank with a hemispherical bottom. The internal diameter, T, is 100.16 mm and the overall capacity is 1L. The agitation system includes a standard USP Apparatus 2 two-blade paddle impeller mounted on a shaft and connected to the motor in the Distek system (Distek Inc.). The exact geometry of each component of the impeller was obtained by measuring the actual dimensions with a caliper: 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; thickness of the blade, 5.00 mm. The distance between the lower edge of the impeller blade and the vessel's inside bottom was 25mm, as specified in the USP. After the vessel was filled with 900 ml of dissolution media, the liquid height, H, which is measured from the bottom of the vessel, was 128.8 mm, whereas it was 78.2 mm when filled with 500 mL of the medium. Figure 2.2a shows the standard USP Dissolution

Testing Apparatus 2.

The OPI system was similar to the Standard System except for the location of the impeller, which was placed 8 mm off center with respect to the vessel centerline (Figure 2.2a). This was accomplished by removing one of the three retaining plastic spring inserts which mounted on the metal plate of the Distek dissolution equipment to keep a vessel centered in each cavity in the plate (Figure 2.3). This resulted in an off-center alignment of the vessel centerline with respect to the impeller centerline. The distance between these centerlines was made to be exactly 8 mm by inserting a proper spacer, thus resulting in an off-centered impeller with respect to the vessel. The distance between the lower edge of the impeller blade and the vessel's inside bottom in the OPI system was 25 mm, that is, the same as in the Standard System. Figure 2.2b shows the OPI dissolution testing system.

Figure 2.1 Distek Premiere 5100 dissolution system used in this work.

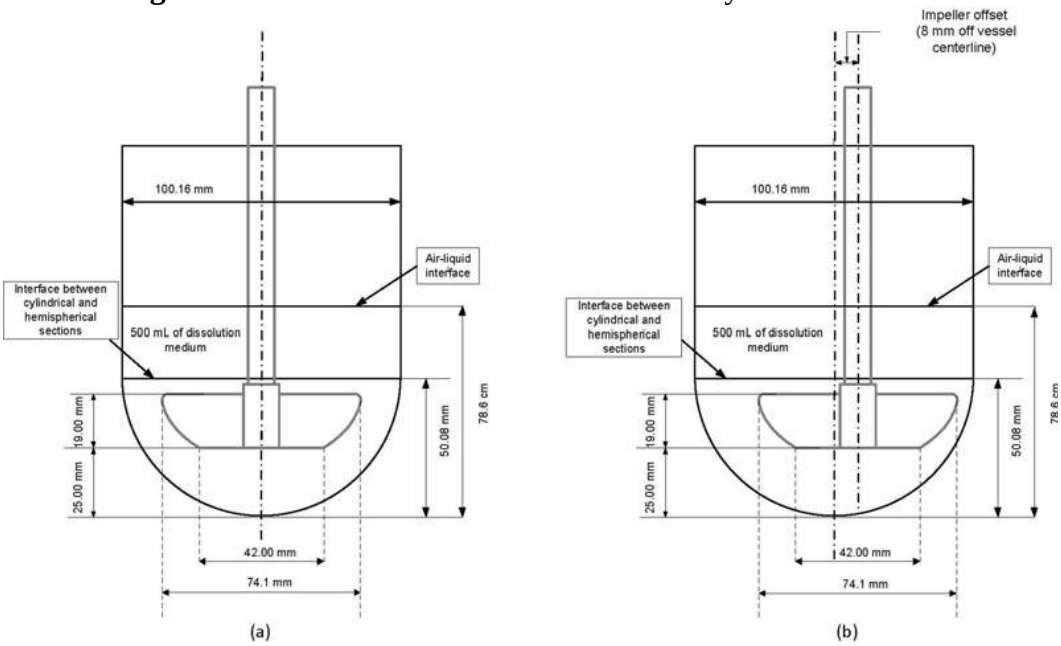


Figure 2.2 (a) Schematic of the standard USP Dissolution Testing Apparatus 2 and (b) schematic of OPI dissolution testing apparatus. Air-liquid interface refers to the 500-mL liquid volume.

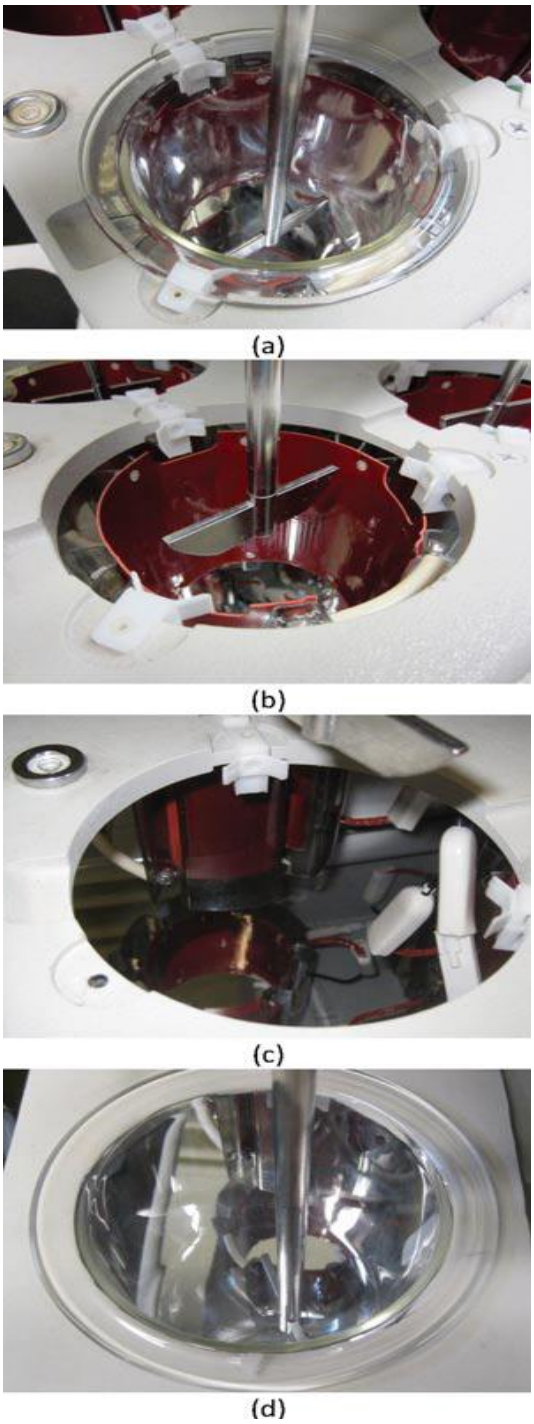


Figure 2.3 Modification of the Standard System to obtain the OPI system: (a) vessel in the Standard System, (b) plastic spring inserts exposed after removing the vessel in the Standard System, (c) system after one of the plastic spring inserts has been removed, and (d) system after the vessel was repositioned to obtain the OPI system.

2.1.2 Materials

Dissolution studies were carried out with three commercial types of aspirin tablets, that is:

- 325 mg uncoated Aspirin tablets, CVS Pharmacy
- 325 mg coated Aspirin tablets, BAYER
- 325 mg coated Aspirin tablets, CVS Pharmacy

Information about each tablet formulation is given below.

325 mg Uncoated Aspirin Tablets, CVS Pharmacy

UNCOATED ASPIRIN
aspirin tablet

Product Information			
Product Type	HUMAN OTC DRUG	Item Code (Source)	NDC:59779-249
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
ASPIRIN (ASPIRIN)	ASPIRIN	325 mg

Inactive Ingredients	
Ingredient Name	Strength
STARCH, CORN	

Product Characteristics			
Color	WHITE	Score	no score
Shape	ROUND	Size	11mm
Flavor		Imprint Code	44;249
Contains			

Packaging		
#	Item Code	Package Description
1	NDC:59779-249-16	1000 in 1 BOTTLE, PLASTIC

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC MONOGRAPH NOT FINAL	part343	08/04/1993	

325 mg Coated Aspirin tablets, BAYER

BAYER ADVANCED ASPIRIN REGULAR STRENGTH
aspirin tablet

Product Information			
Product Type	HUMAN OTC DRUG	NDC Product Code (Source)	0280-2605
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Aspirin (Aspirin)	Aspirin	325 mg

Inactive Ingredients

Ingredient Name	Strength
Carnauba Wax	5.00 mg
Silicon Dioxide	8.50 mg
Hypromelloses	16.00 mg
Sodium carbonate	25.00 mg
Zinc stearate	4.61 mg

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	24mm
Flavor		Imprint Code	
Contains			

Packaging

#	NDC	Package Description	Multilevel Packaging
1	0280-2605-01	876000 TABLET In 1 DRUM	None

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC MONOGRAPH FINAL	part343	12/01/2010	

325 mg Coated Aspirin tablets, CVS pharmacy

Product Information

Product Type	HUMAN OTC DRUG	Item Code (Source)	NDC:59779-416
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ASPIRIN (ASPIRIN)	ASPIRIN	325 mg

Inactive Ingredients

Ingredient Name	Strength
DIBASIC CALCIUM PHOSPHATE DIHYDRATE	
TRIACETIN	
HYPROMELLOSES	
TALC	
STARCH, CORN	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	14mm
Flavor		Imprint Code	Aspirin;L
Contains			

Packaging

#	Item Code	Package Description
1	NDC:59779-416-78	1 BOTTLE (BOTTLE) in 1 CARTON
1		100 TABLET (TABLET) in 1 BOTTLE
2	NDC:59779-416-87	1 BOTTLE (BOTTLE) in 1 CARTON
2		300 TABLET (TABLET) in 1 BOTTLE
3	NDC:59779-416-90	500 TABLET (TABLET) in 1 BOTTLE

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

The dissolution medium for aspirin was prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 ml of glacial acetic acid with water to obtain 1000 mL of solution having a pH of 4.50 ± 0.05. The temperature of the dissolution medium was raised to 37±0.5 °C; 500ml prior to its use in the experiments.

2.1.3 Experimental Method

The medium was de-aerated before using, according to the method developed by Moore (1996) following the USP requirement [1] (Figure 2.4). Accordingly, the medium was placed in carboy tank, which was then connected to a vacuum pump. Vacuum was applied for 30 minutes while all other valves in the system were closed. This stock solution was used as needed (typically in 500 mL aliquots per test).

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 37.5°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.

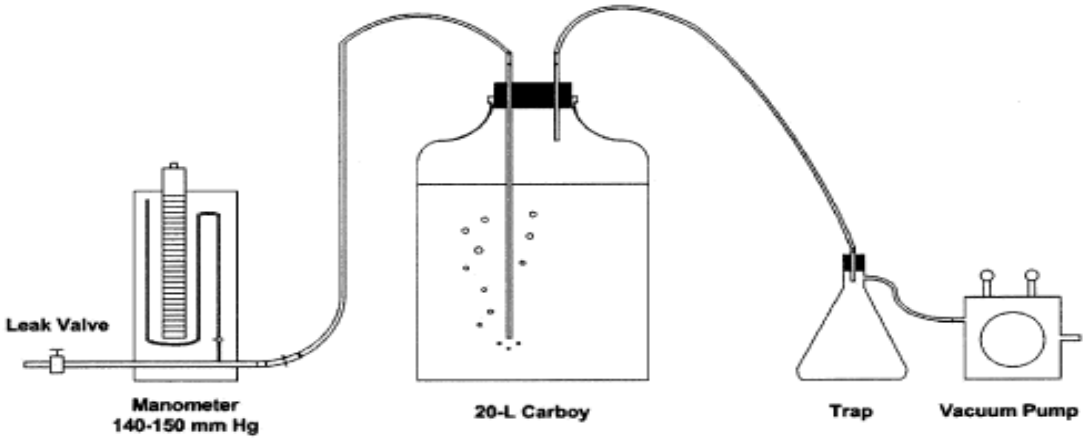


Figure 2.4 Setup of de-aeration process for dissolution medium.

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 10^{o} 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's 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 90º apart 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. Before putting the quartz cell into the UV spectrometer, the cell was rinsed three times with the same solution sample.

Calibration curves were obtained separately by preparing reference standard solutions of each aspirin formulation and by diluting them with aspirin dissolution medium 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 data and calibration curves for the CVS uncoated aspirin, Bayer coated aspirin, and CVS coated aspirin, are reported in Tables 2.1, 2.2, 2.3 and in Figures 2.7, 2.8, 2.9, respectively. The calibration curves were linear in the concentration ranges of

interest here (R^2=0.9999 for the CVS uncoated aspirin, R^2=0.9998 for Bayer coated aspirin, and R^2=0.9992 for CVS coated aspirin).

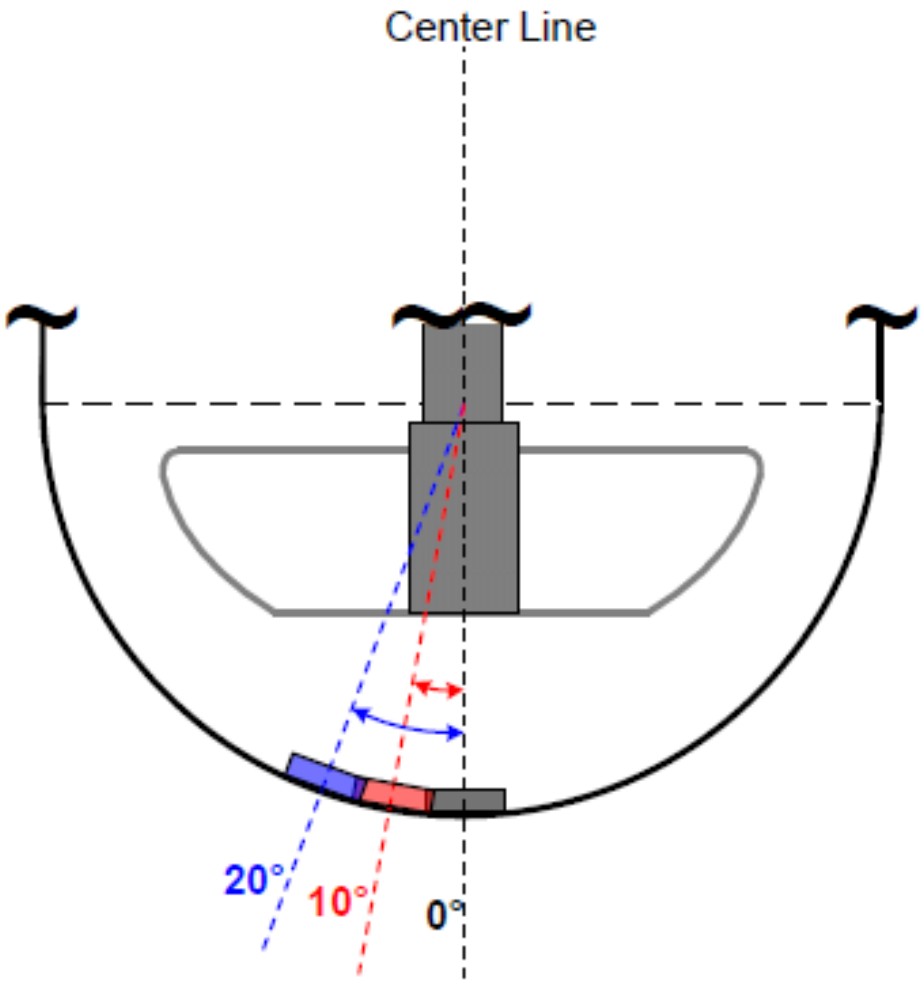


Figure 2.5 Front schematic of the dissolution vessel with three different tablet positions (0◦, 10◦, and 20◦) in the Standard System.

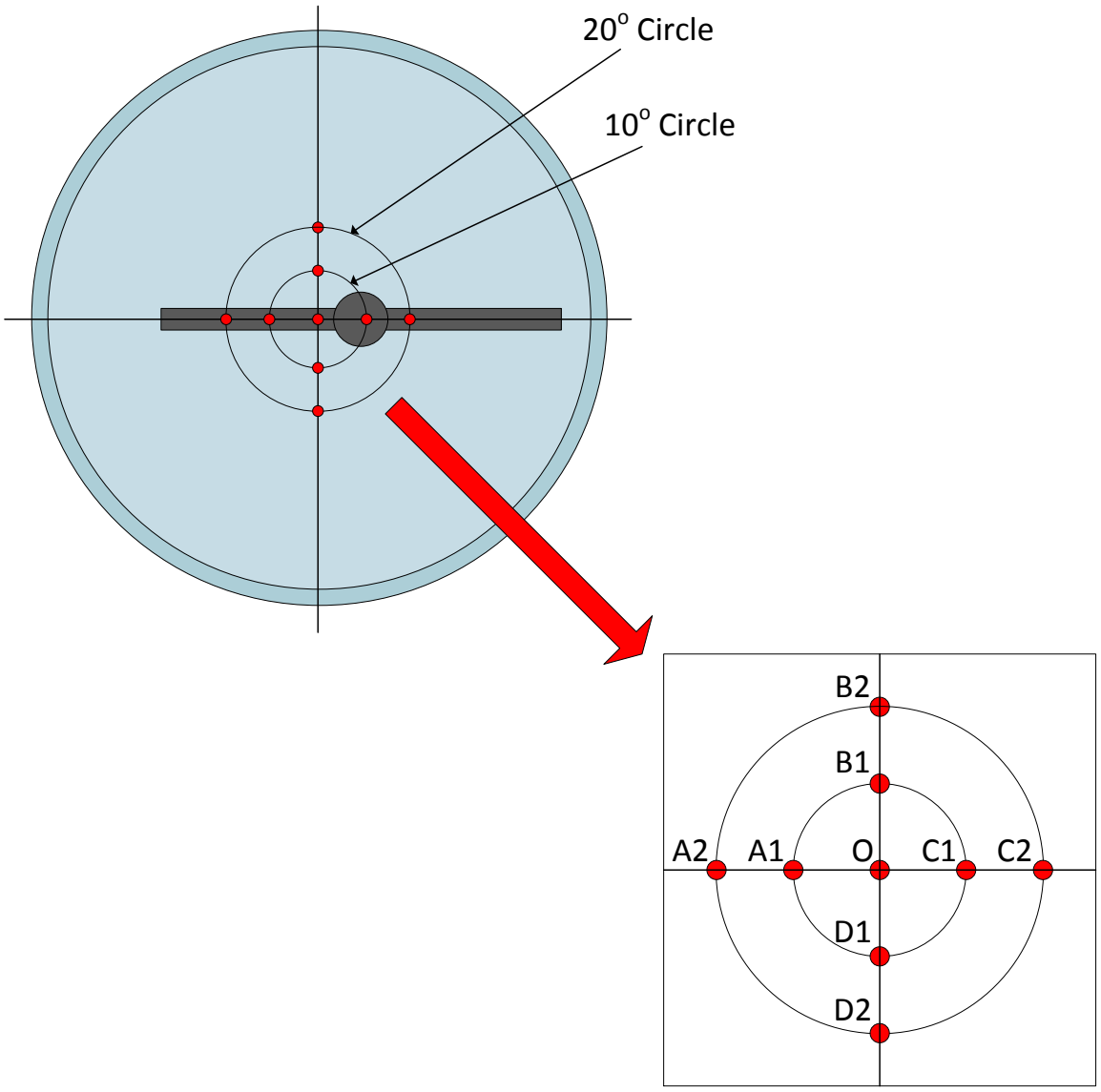


Figure 2.6 Expanded view of the bottom of the dissolution vessel, with letters identifying the nine different tablet positions.

Table 2.1 Calibration Data for CVS Uncoated Aspirin Tablets

Concentration (mg/ml)	Absorbance 1	Absorbance 2	Average Absorbance
0.131	0.398	0.396	0.397
0.177	0.534	0.538	0.536
0.208	0.625	0.631	0.628
0.246	0.735	0.741	0.738
0.301	0.896	0.891	0.894
0.306	0.912	0.895	0.904
0.329	0.978	0.971	0.975

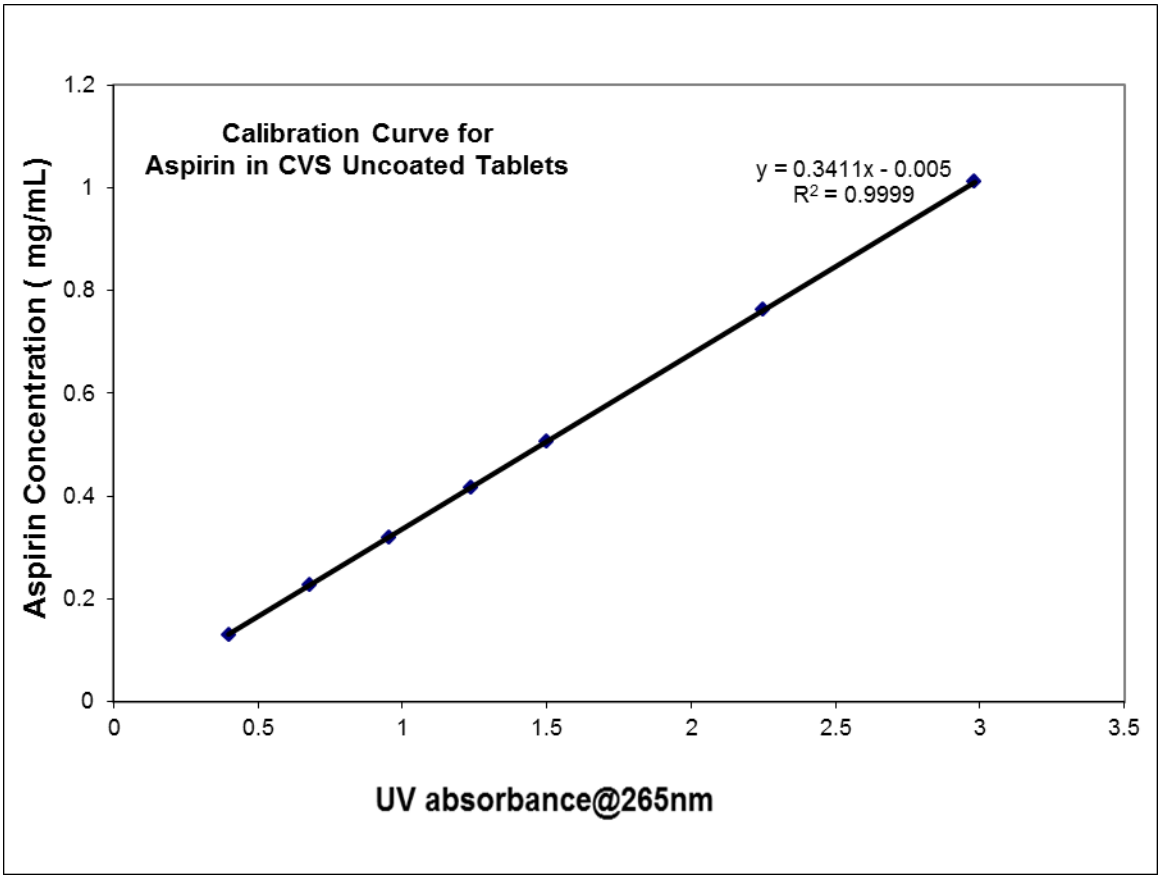


Figure 2.7 Calibration curve and regression for CVS uncoated aspirin tablets.

Table 2.2 Calibration Data for BAYER Coated Aspirin Tablets

Concentration (mg/ml)	Absorbance 1	Absorbance 2	Average Absorbance
0.115	0.389	0.392	0.391
0.199	0.657	0.651	0.654
0.273	0.893	0.899	0.896
0.377	1.224	1.229	0.1.227
0.460	1.489	1.481	1.485
0.695	2.235	2.231	2.233
0.900	2.891	2.897	2.894

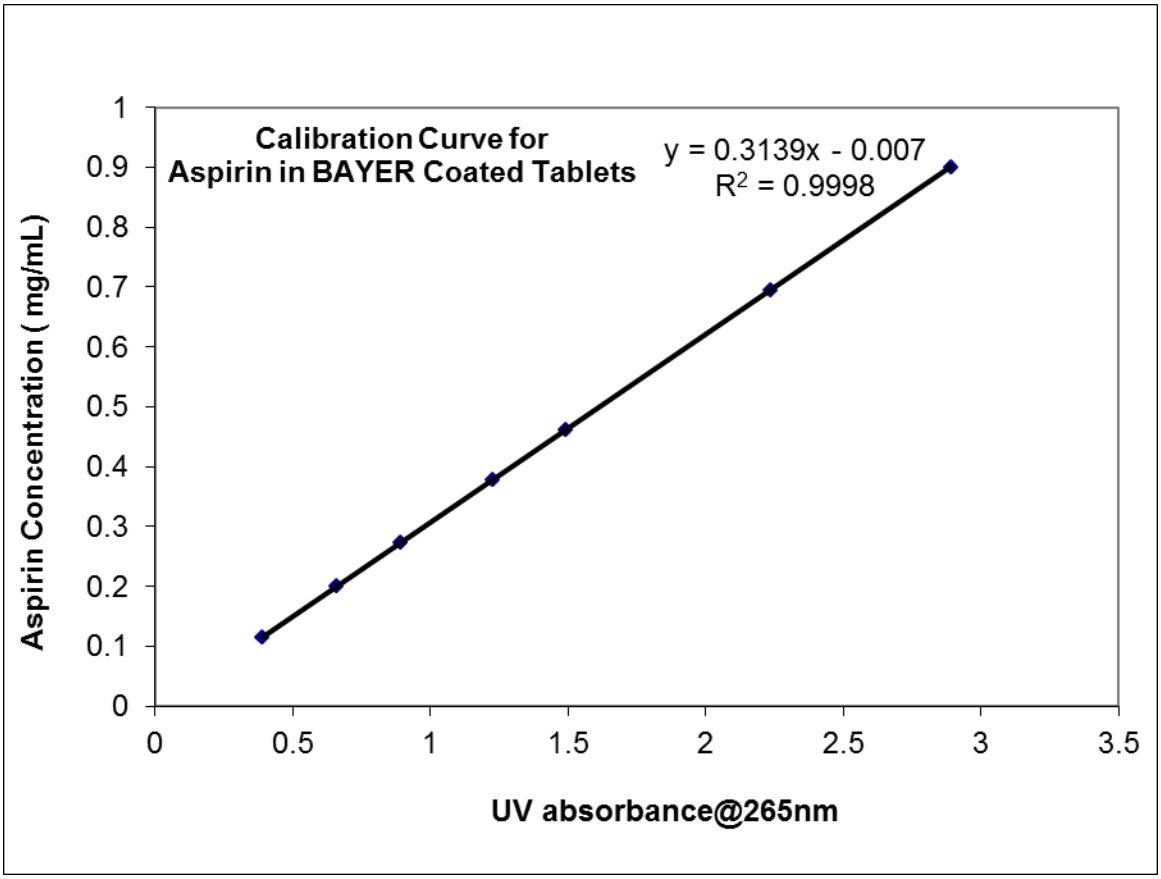


Figure 2.8 Calibration curve and regression for BAYER coated aspirin tablets.

Table 2.3 Calibration Data for CVS Coated Aspirin Tablets

Concentration (mg/ml)	Absorbance 1	Absorbance 2	Average Absorbance
0.127	0.391	0.392	0.391
0.255	0.768	0.761	0.765
0.324	0.973	0.975	0.974
0.450	1.342	1.349	1.345
0.526	1.567	1.561	1.564
0.770	2.287	2.281	2.284
0.865	2.567	2.561	2.564

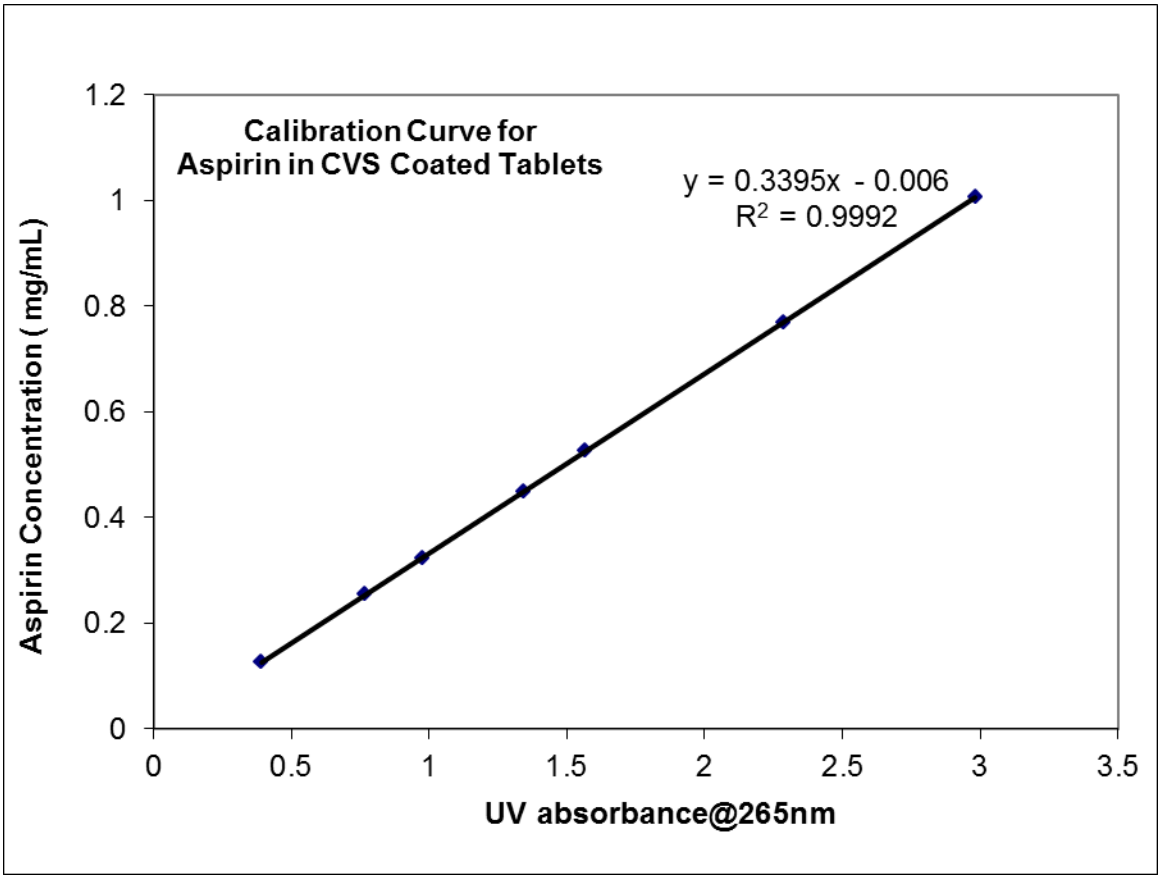


Figure 2.9 Calibration curve and regression for CVS coated aspirin tablets.

2.1.4 Data Analysis

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, … 10), $m_D(t_j)$ 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=0 minutes) the first sample was taken immediately (j=1) resulting in an initial concentration C_1, and the 18th 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) [32]:

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

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

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 AND DISCUSSION

3.1 Results

3.1.1 Results for Dissolution Tests Conducted Using Testing Method #1 (Tablet Dropped in Dissolution Medium)

The dissolution profiles for three different brands of aspirin tablets are presented in Figure 3.1 for the Standard System and in Figure 3.2 for the OPI System. The results are reported in terms of m_D/m_T, that is, the ratio of the amount of drug in solution at any time t, relative to total initial amount of drug in the tablet, obtained when the entire 325mg tablet is completely dissolved. The reproducibility of the experimental results was always within 1%, as quantified by the value of the average coefficient of variation for each experiment, which was always about or below 1% in all cases, irrespective of the system used.

In the standard system, three curves started at the same initial mass, but they diverged with time depending on the tablet brand. The dissolution curve for the CVS coated aspirin tablet began at $m_D/m_T = 0$, and then increased somewhat linearly, reaching $m_D/m_T = 58\%$ over the next 15 min. From 15min to 25min, CVS coated aspirin was released at a lower release rate. In the last 35min, the release rate of CVS coated aspirin almost kept constant. For CVS uncoated and BAYER coated aspirin tablets, during the initial 15min, the dissolution curves showed that a faster dissolution process (m_D/m_T =68%, m_D/m_T =63%) was taking place as compared with CVS coated aspirin tablet ($m_D/m_T = 58\%$). From t = 15min to t = 20 min, the dissolution curves were found to be

parallel to the curves obtained for CVS coated aspirin tablet. From t = 25 min to t = 30 min, the dissolution rates decreased slightly and showed the same dissolution rates as the CVS coated aspirin tablet in the last 30 min. In general, the main difference between the dissolution curves occurred during the initial 15 min time period. In addition, the difference between the dissolution profiles for three brands of aspirin tablets in the standard system could be easily recognized. The f_1 and f_2 values, quantifying the significance of similarity/difference of dissolution profiles of BAYER coated aspirin and CVS coated aspirin with respect to the dissolution profile for CVS uncoated aspirin in the standard system at 50 rpm, were found all within the required FDA range except for the f_2 value of CVS coated aspirin tablet. Although f_1 and f_2 values of BAYER coated aspirin tablet with respect to CVS uncoated aspirin tablet is within FDA range, the difference still existed but not large enough to out of FDA range. The f_2 value of CVS coated aspirin tablet with respect to CVS uncoated aspirin tablet is 49.1, which is out of FDA range. Obviously, the difference is significant.

The dissolution profiles for three bands of aspirin tablets studied here in the OPI system are presented in Figure 3.2. The dissolution profiles are almost as similar to those in the standard system. The f_1 and f_2 values for the dissolution profiles of BAYER coated aspirin and CVS coated aspirin with respect to the dissolution profile for CVS uncoated aspirin in the OPI System at 36 rpm are presented in Table 3.2. Based on the values presented in Table 3.2, the difference of dissolution profiles between three brands of aspirin tablets is clearly showed.

In addition, the dissolution profiles for CVS uncoated aspirin tablets, BAYER coated aspirin tablets and CVS coated aspirin tablets were obtained using both OPI system and the standard system. The results of each brand of aspirin tablet from these two systems are

reported here in terms of drug release ratio m_D/m_T over time, and presented in Figure 3.3, 3.4, 3.5. The values of the f_1 and f_2 values were calculated and are presented in Table 3.3, 3.4, 3.5.

The similarity between the dissolution profiles for the OPI system and the standard system could be easily recognized from Figure 3.3, 3.4, 3.5. On the other hand, the f_1 and f_2 values, quantifying the significance of similarity/difference of the dissolution profile of the OPI system with respect to the corresponding standard system, were found all within the required FDA range. The f_1 and f, values presented in Table3.3, 3.4, 3.5 were in the FDA range ($0<f1<15$, $50<f2<100$). Therefore, it shows the dissolution profiles were similar.

In general, although the three brands of aspirin tablets were tested in a different system, OPI system, the release profiles were similar to the profile for the three bands of aspirin tablets in standard system, indicating that the OPI system has same sensitivity to different tablet formulations with standard one.

Table 3.1 f_1 and f_2 Values for the Dissolution Profiles of BAYER Coated Aspirin and CVS Coated Aspirin with Respect to the Dissolution Profile for CVS Uncoated Aspirin in the Standard System at 50 rpm

Tablet	Difference Factor f_1	Similarity Factor f_2
CVS uncoated	-	-
BAYER coated	4.49	72.64
CVS coated	14.38	49.10

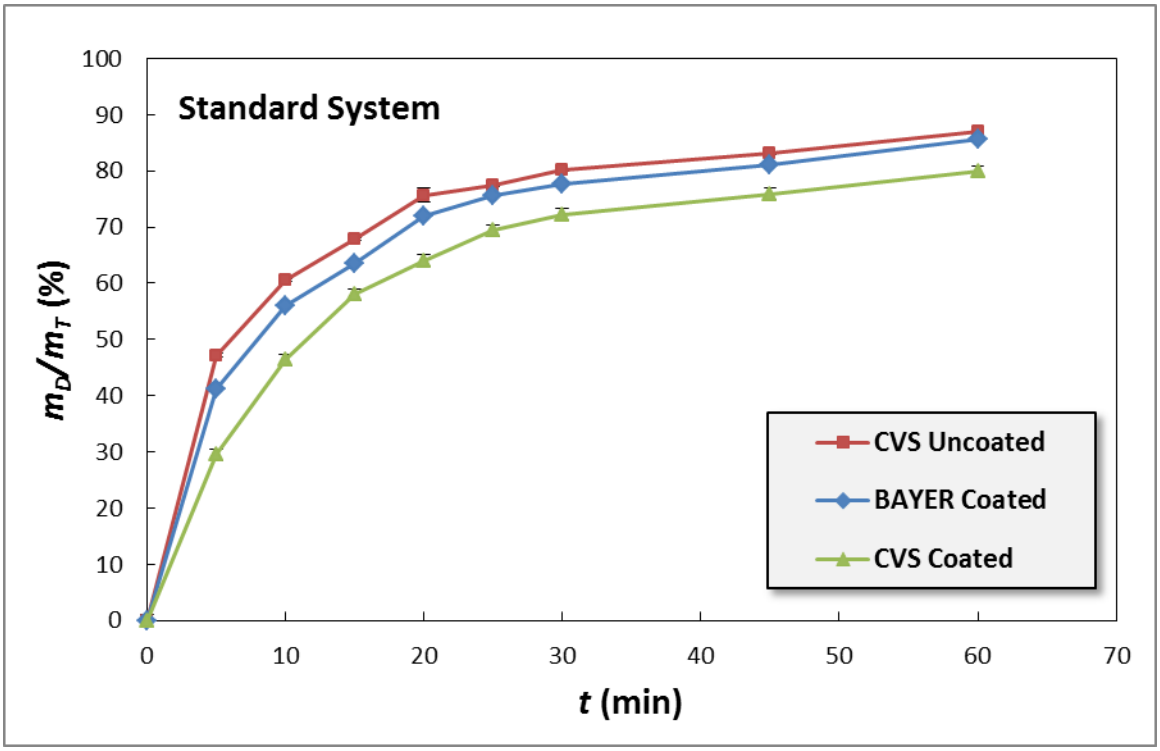


Figure 3.1 Results for Tablets Dropped in the Standard USP Apparatus 2.

Table 3.2 f_1 and f_2 Values for the Dissolution Profiles of BAYER Coated Aspirin and CVS Coated Aspirin with Respect to the Dissolution Profile for CVS Uncoated Aspirin in the OPI System at 36 rpm

Tablet	Difference Factor f_1	Similarity Factor f_2
CVS uncoated	-	-
BAYER coated	3.41	74.53
CVS coated	12.65	49.81

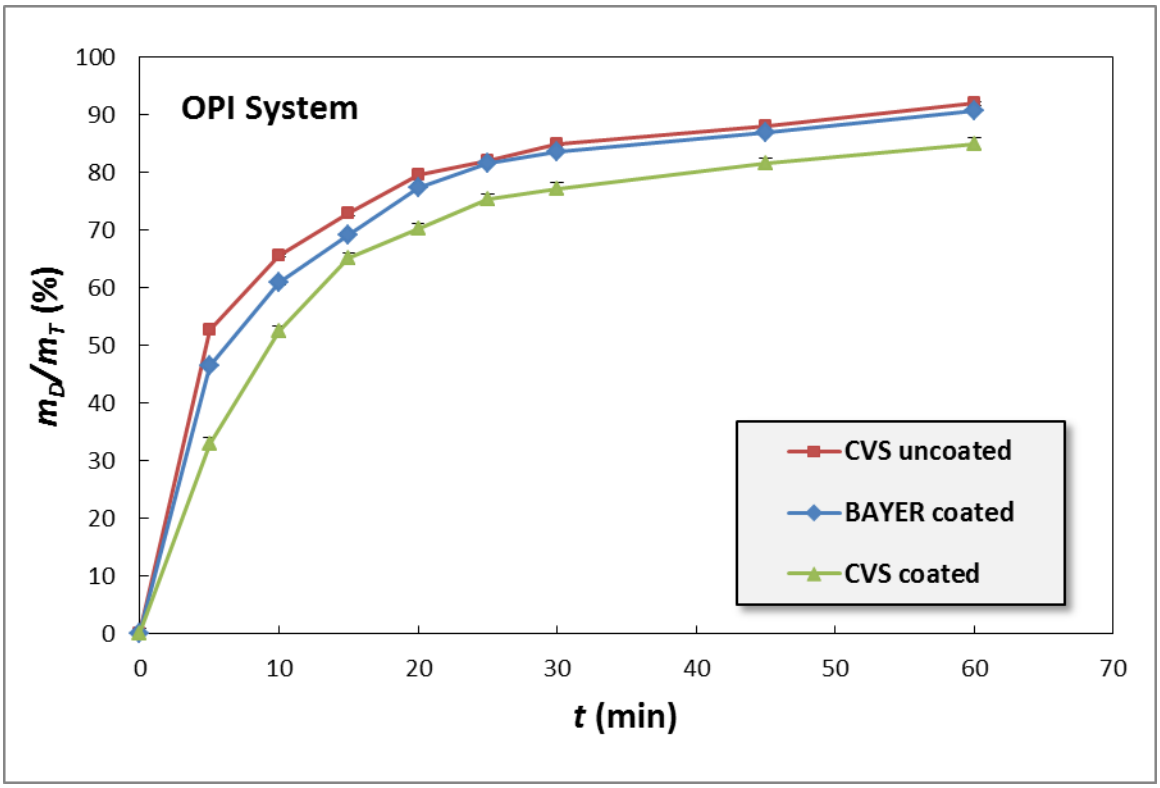


Figure 3.2 Results for Tablets dropped in the OPI System.

Table 3.3 f_1 and f_2 Values for the Dissolution Profiles of CVS Aspirin Uncoated in OPI system with Respect to the Dissolution Profile for CVS uncoated Aspirin Tablets in the Standard System

System	Difference Factor f_1	Similarity Factor f_2
Standard	-	-
OPI	6.75	66.25

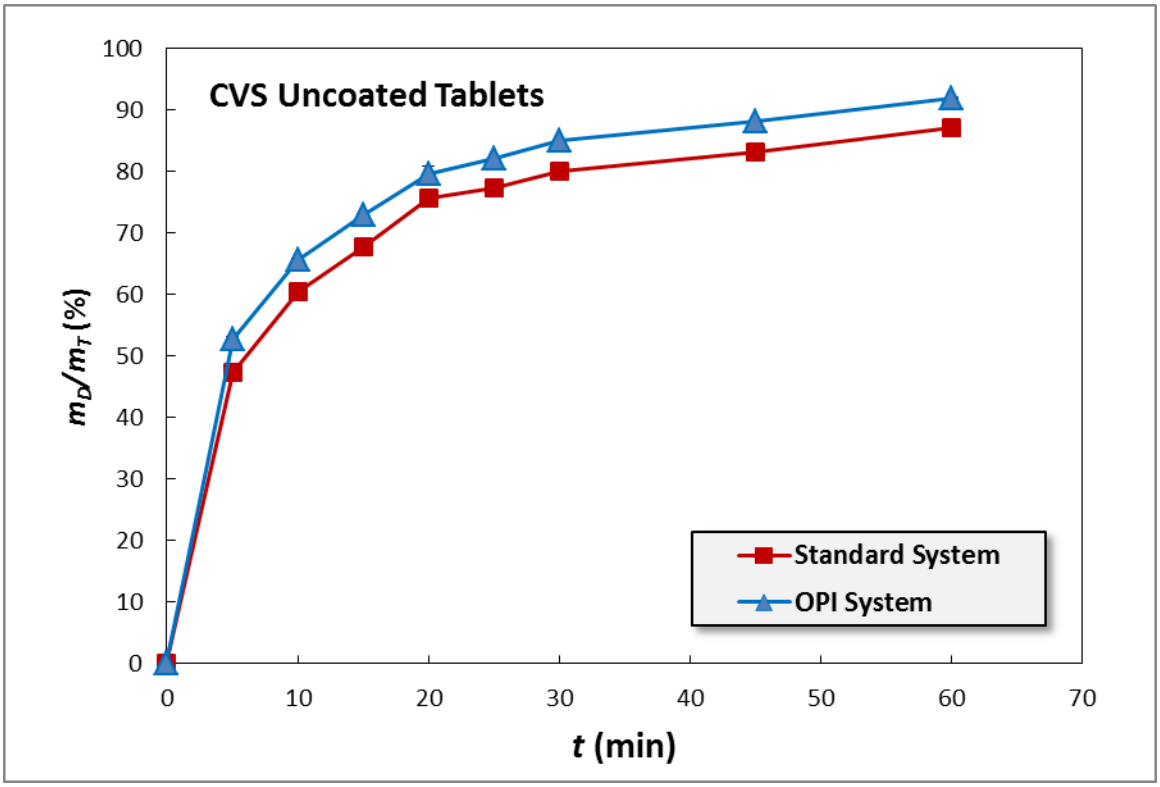


Figure 3.3 Results for CVS uncoated aspirin tablet in the Standard and OPI system.

Table 3.4 f_1 and f_2 Values for the Dissolution Profiles of BAYER Coated Aspirin in OPI system with Respect to the Dissolution Profile for BAYER Coated Aspirin in the Standard System

System	Difference Factor f_1	Similarity Factor f_2
Standard	-	-
OPI	7.96	63.82

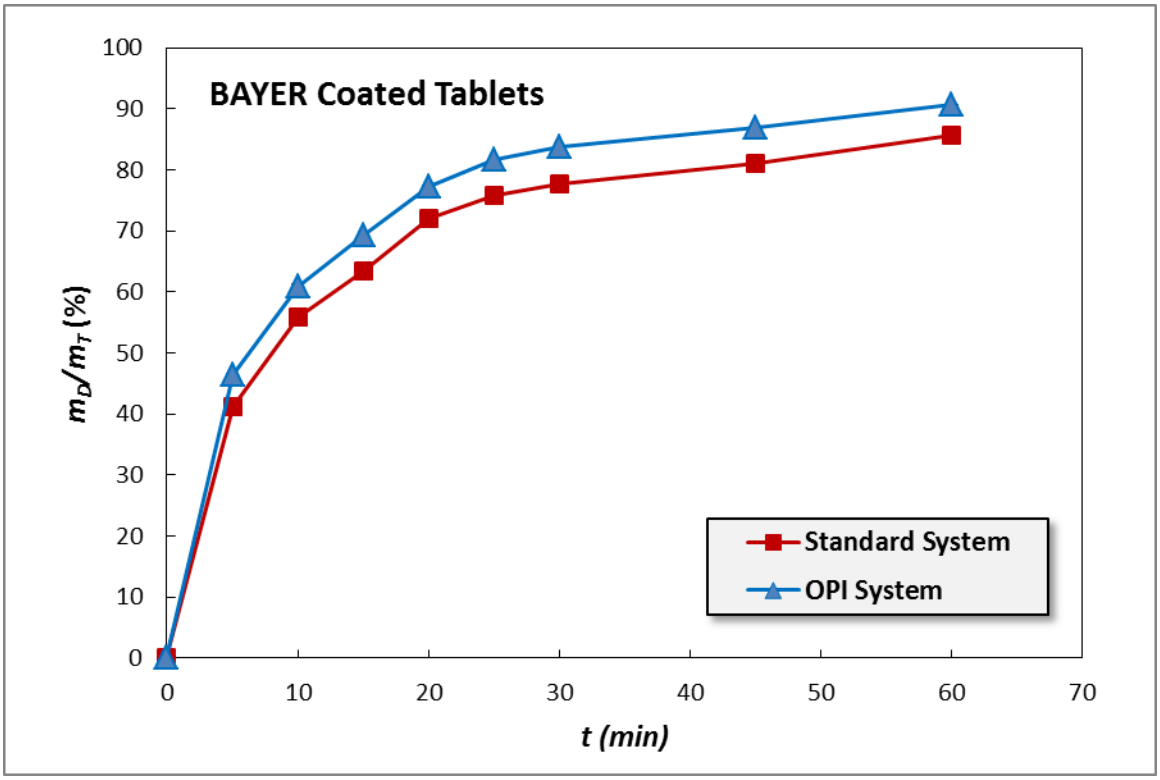


Figure 3.4 Results for BAYER coated aspirin tablet in the Standard and OPI system.

Table 3.5 f_1 and f_2 Values for the Dissolution Profiles of CVS Coated Aspirin in OPI system with Respect to the Dissolution Profile for CVS Coated Aspirin in the Standard System

System	Difference Factor f_1	Similarity Factor f_2
Standard	-	-
OPI	8.91	63.46

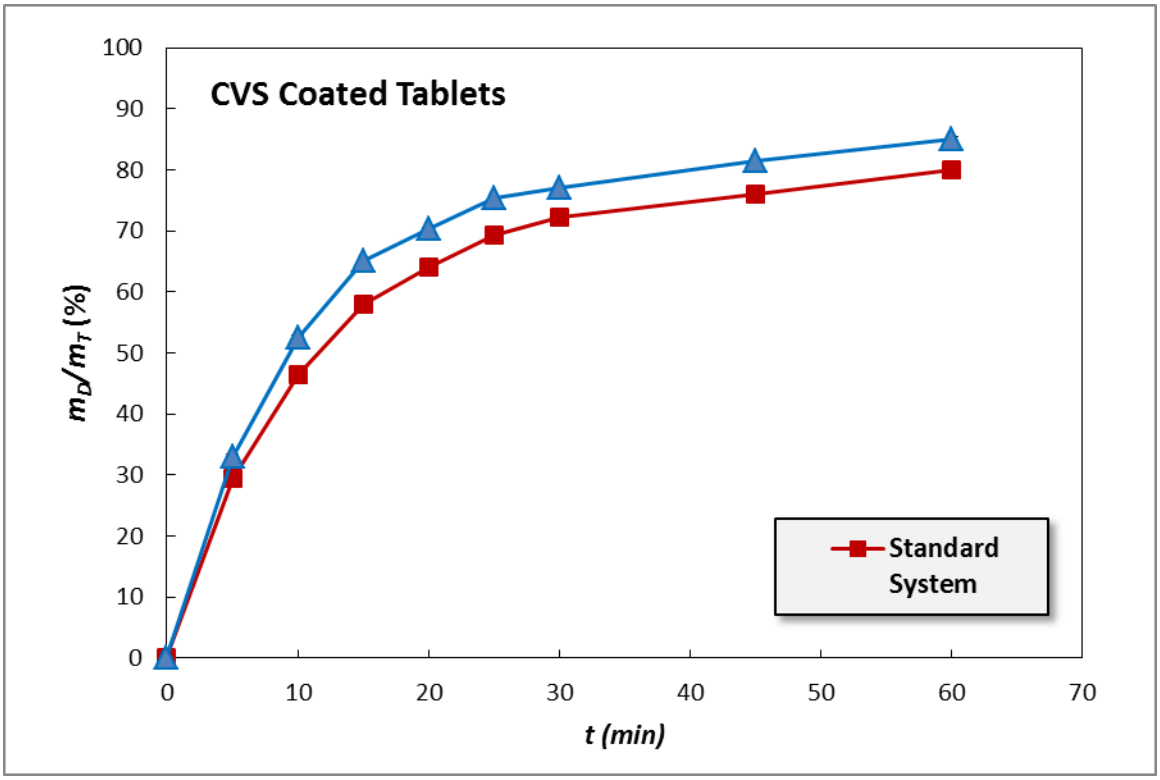


Figure 3.5 Results for CVS coated aspirin tablet in the Standard and OPI system.

3.1.2 Results for Dissolution Tests Conducted with CVS Uncoated Aspirin Tablets Using Testing Method #2 (Tablet Fixed in Place at Different Tablet Positions)

The dissolution profiles for 325 mg CVS uncoated aspirin tablets are presented in Figure 3.6 for the Standard System and in Figure 3.7(a) and 3.7(b) for the OPI system. The results are reported in terms of m_D/m_T, that is, the ratio of the aspirin mass in the dissolving medium, m_D, at a given time, t, relative to the final mass, m_T, obtained when the entire 325 mg tablet is completely dissolved. The reproducibility of the experimental results was always within 1%, as quantified by the value of the average coefficient of variation for each experiment, which was always about or below 1% in all cases, irrespective of the system used.

The dissolution curve for tablets fixed in the central position in the Standard System began at $m_D/m_T = 0$. After addition of the medium to the vessel containing the fixed tablet, the dissolution profile increased linearly, reaching $m_D/m_T = 34\%$ over the next 10 min. From 10min to 30min, CVS uncoated aspirin was released at a lower release rate. The last 30min, the dissolution rate is pretty low, the mass ratio is 64% when t=60min. For the 10° and 20° off-center tablets, the dissolution curves started at the same m_D/m_T as those at reference center position. During the initial 5min, the dissolution curves showed that a faster dissolution process ($m_D/m_T = 45\%$ for 10° off-center tablets, $m_D/m_{T=}$ 51% for 20° off-center tablets) was taking place as compared with the reference position. From t =5min to t = 30 min, it showed that two faster dissolution curves were found to be more slant to the curves obtained at the reference position. From t = 30 min to t = 60 min, the dissolution rates decreased slightly and showed the same dissolution rates as the reference position. In general, the main difference between the dissolution curves

occurred the initial 5min. The corresponding f_1 and f_2 values of the dissolution profiles at off-center tablet locations with respect to that for the central position tablets are presented in the Table 3.6. Both f_1 and f_2 were found to be outside the required range to insure statistical similarity, implying that the tablets at the 10° and 20° locations would fail the dissolution test. In this case, even f_2 was found to be outside the 50–100 range, which means that a significant difference between the dissolution profiles between the dissolution profiles for the centrally located tablets and those in the off-center position existed in the Standard System. These results confirmed that the dissolution profiles of the chosen CVS uncoated aspirin tablet depended strongly on the tablet location in the dissolution vessel for the Standard System. These results are in agreement with previously reported work [7] [17].

The curves for CVS uncoated aspirin tablets at nine different tablet locations studied here in the OPI system are presented in Figure 3.7a for the tablets on the inner 10º circle and in Figure 3.7b for the tablets on the outer 20º circle. In general, although the tablets were located at very different locations, the release profiles were similar to each other and to the profile for the centrally located tablets, indicating that OPI system is strongly independently on tablet position. In the first 10 min, the plot shows that the dissolution rate was typically very fast (m_D/m_T = 61%). From t = 10 min to t = 30 min, the dissolution rate went to a transition period. The release rate was smooth when compared with the initial 10 min. The relative mass ratio changed from 61% to 88% gradually. In the last 30 min, the release rate was lower and the relative mass ratio varied from 88% to 95%. The fastest release rate of CVS uncoated aspirin tablets occurred in the first 10min.

In the OPI system, a quantitative comparison of each profile with the corresponding profile for the central position tablets in the same system could be obtained using f_1 and f_2, presented in Table 3.7. f_1 and f_2 was found to be in the range 1.7–4.6, indicating a very small difference between the release profiles at different tablet location and the reference release profile for tablets in the central position. The f_2 values were found to be in the range 71.1-88.1, which are all within the FDA range, indicating that the release curves were statistically similar to the reference release profile. Both f_1 and f_2 ensured the similarity of all release profiles in the OPI system. Thus, it can be concluded that the OPI system generated release data that were very consistent and reproducible.

Table 3.6 f_1 and f_2 Values for the Dissolution Profiles of CVS Uncoated Aspirin at Different Tablet Location with Respect to the Dissolution Profile for a Centrally Located Tablet in the Standard System at 50 rpm

Tablet Location	Difference Factor f_1	Similarity Factor f_2
0° (Centered tablet)	-	-
10° Off-Center tablet	56.95	31.21
20° Off-Center tablet	67.78	27.38

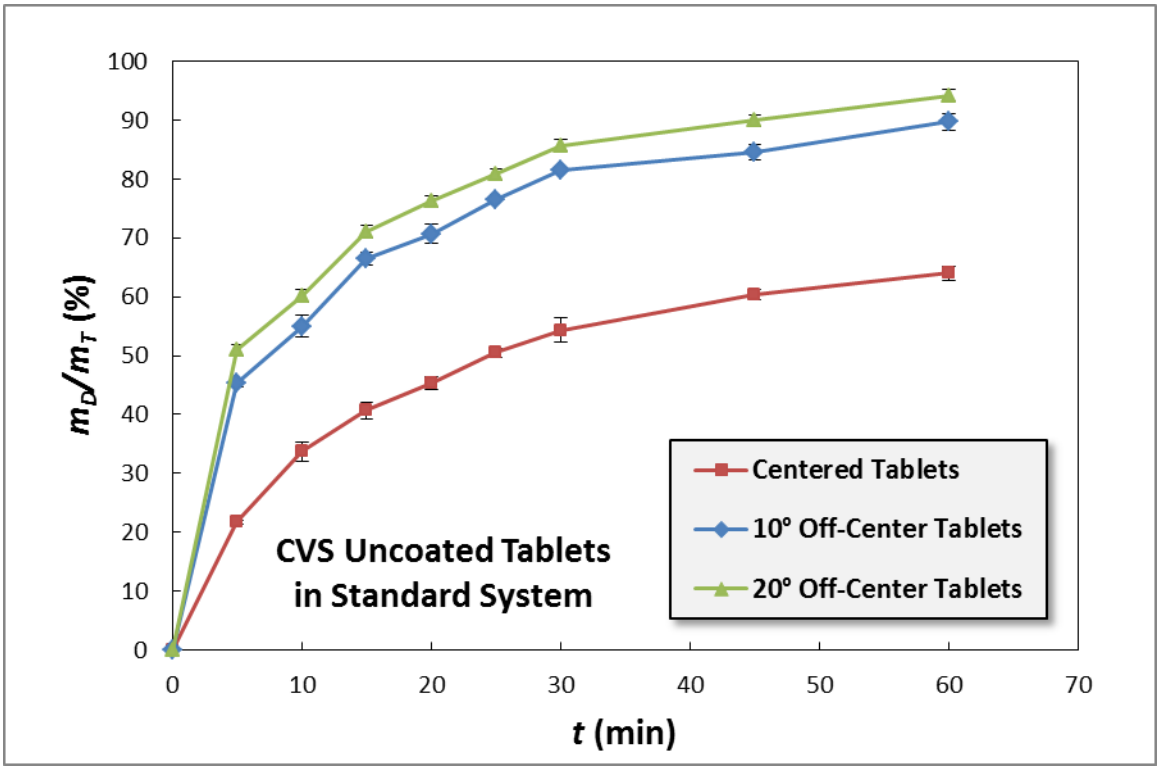
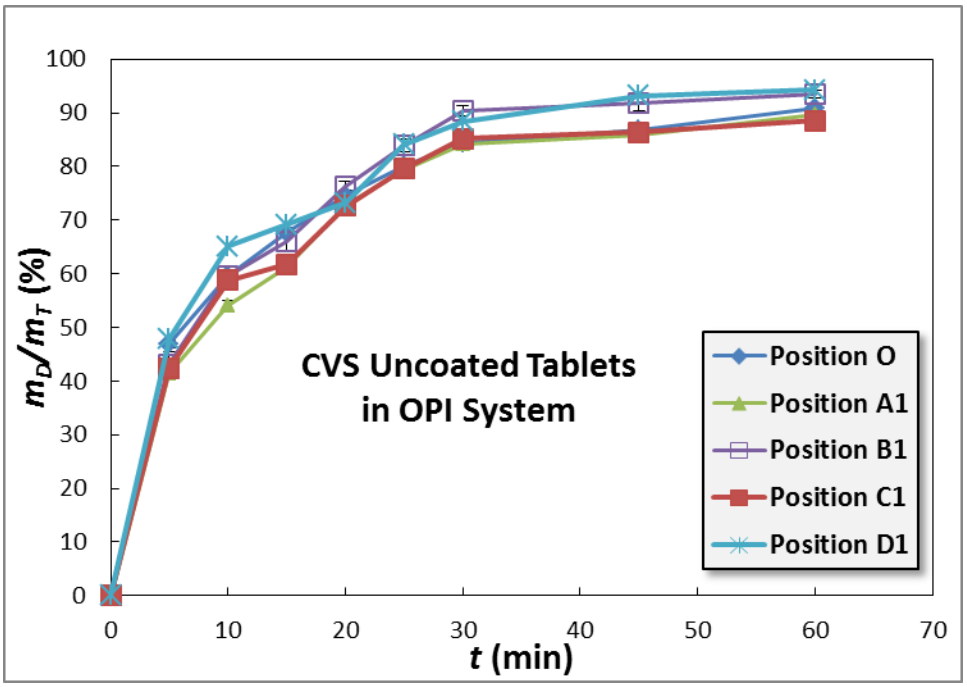


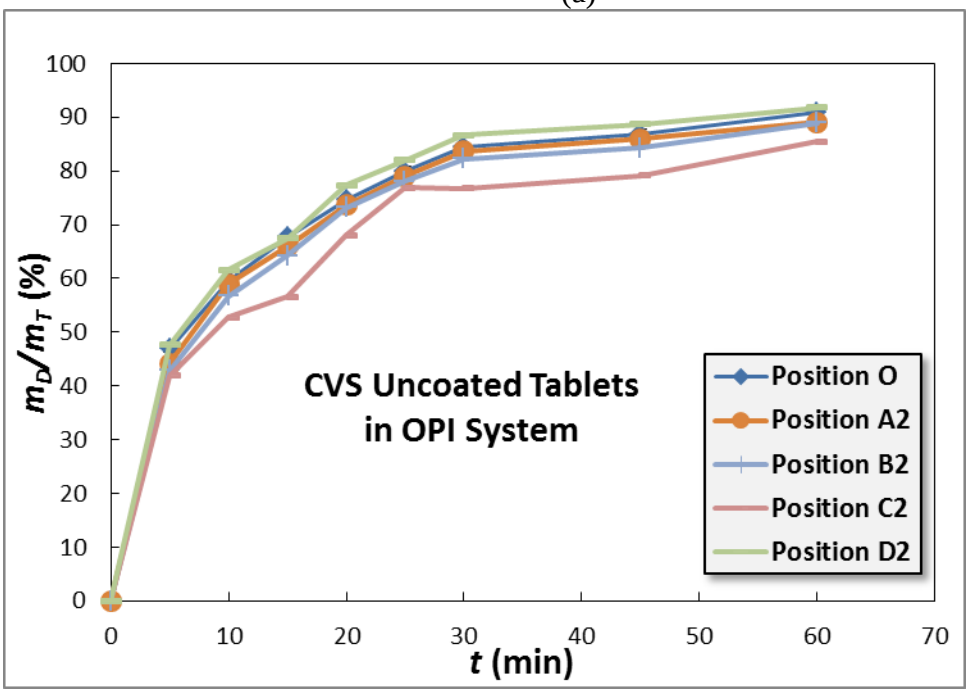
Figure 3.6 Dissolution test results for CVS uncoated aspirin tablets in the Standard System.

Table 3.7 f_1 and f_2 Values for the Dissolution Profiles of CVS Uncoated Aspirin at Different Tablet Locations with Respect to the Dissolution Profile for a Centrally Located Tablet in the OPI System at 36 rpm

Tablet Location	Difference Factor f_1	Similarity Factor f_2
PositionO (centered tablet)		
Position A1 (10° off-center tablet)	3.9	71.6
Position B1 (10° off-center tablet)	2.9	76.7
Position C1 (10° off-center tablet)	4.2	72.5
Position D1 (10° off-center tablet)	4.6	71.1
Position A2 (20° off-center tablet)	1.8	88.1
Position B2 (20° off-center tablet)	1.7	85.9
Position C2 (20° off-center tablet)	3.6	77.7
Position D2 (20° off-center tablet)	2.1	85.7



(a)



(b)

Figure 3.7 Dissolution test results for CVS Uncoated Aspirin tablets in the OPI system: (a) results for tablets in the inner 10° circle and (b) results for tablets in the outer 20° circle.

3.1.3 Results for Dissolution Tests Conducted with BAYER Coated Aspirin Tablets Using Testing Method #2 (Tablet Fixed in Place at Different Tablet Positions)

Dissolution profiles at different tablet locations were also obtained for 325 mg BAYER coated aspirin tablets. The results are presented in Figure 3.8 for the Standard System and in Figure 3.9 for the OPI system. The reproducibility of the experimental results was always within 1%, as quantified by the value of the average coefficient of variation for each experiment, which was always about or below 1% in all cases.

The dissolution profiles diverged with time depending on the tablet location even though they started at the same initial mass ratio. The greater the distance from the central location, the higher the dissolution rate. The f_1 and f_2 values for the BAYER coated tablets in the Standard System are reported in Table 3.8. Both f_1 and f_2 were found to be outside the required range to insure statistical similarity, implying that the tablets at the 10° and 20° locations would fail the dissolution test. In this case, even f_2 was found to be outside the 50–100 range, which means that a significant difference between the dissolution profiles between the curve for the centrally located tablets and those in the off-center position existed in the Standard System. These results confirm that the dissolution profiles for the selected BAYER coated aspirin tablets strongly depended on the tablet location in the dissolution vessel for the Standard System. These results are in agreement with previously reported work [8].

Figure 3.9 presents the dissolution curves obtained in the OPI system. Although the tablets were located at nine different locations, the release profiles almost overlapped, indicating that the initial position of the tablet did not affect the dissolution results. A comparison of the release profiles obtained in the OPI system at different tablet locations

with the corresponding profile for the centrally located tablets in the same system could be made using the f1 and f2 factors reported in Table 3.9, which shows that f_1 was in the range 1.3–4.4 and f_2 in the range 74.2–90.0. These results indicate that the release profiles for BAYER coated tablets were also statistically similar to the corresponding reference release profile. Therefore, it can be concluded that the OPI system generated release data that were more consistent and not strongly dependent on the tablet location.

Table 3.8 f_1 and f_2 Values for the Dissolution Profiles of BAYER Coated Aspirin at Different Tablet Location with Respect to the Dissolution Profile for a Centrally Located Tablet in the Standard System at 50 rpm

Tablet Location	Difference Factor f_1	Similarity Factor f_2
0° (Centered tablet)	-	-
10° Off-Center tablet	56.8	31.6
20° Off-Center tablet	72.2	26.4

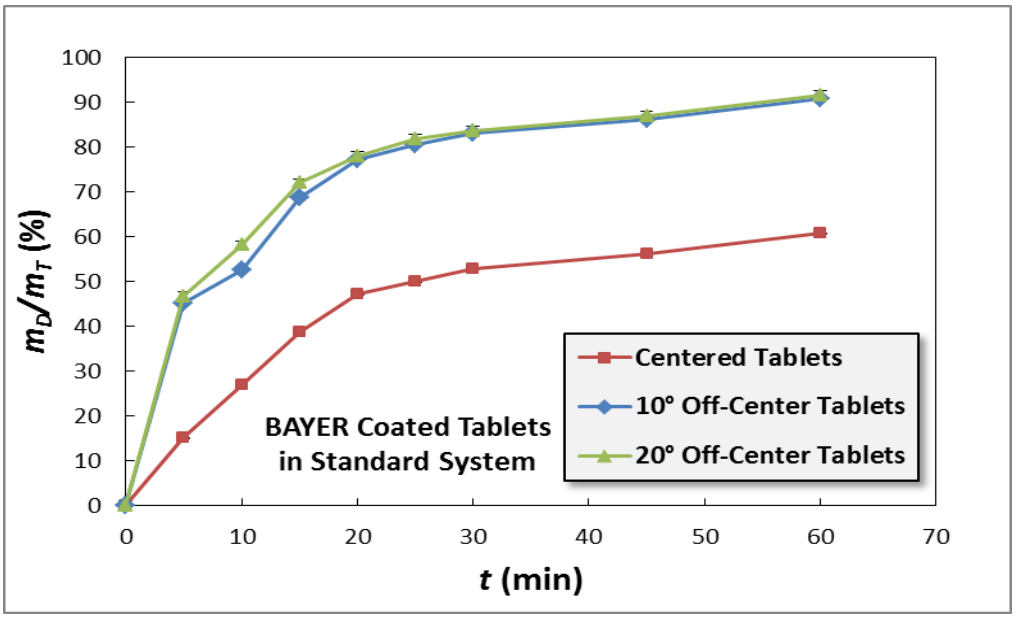
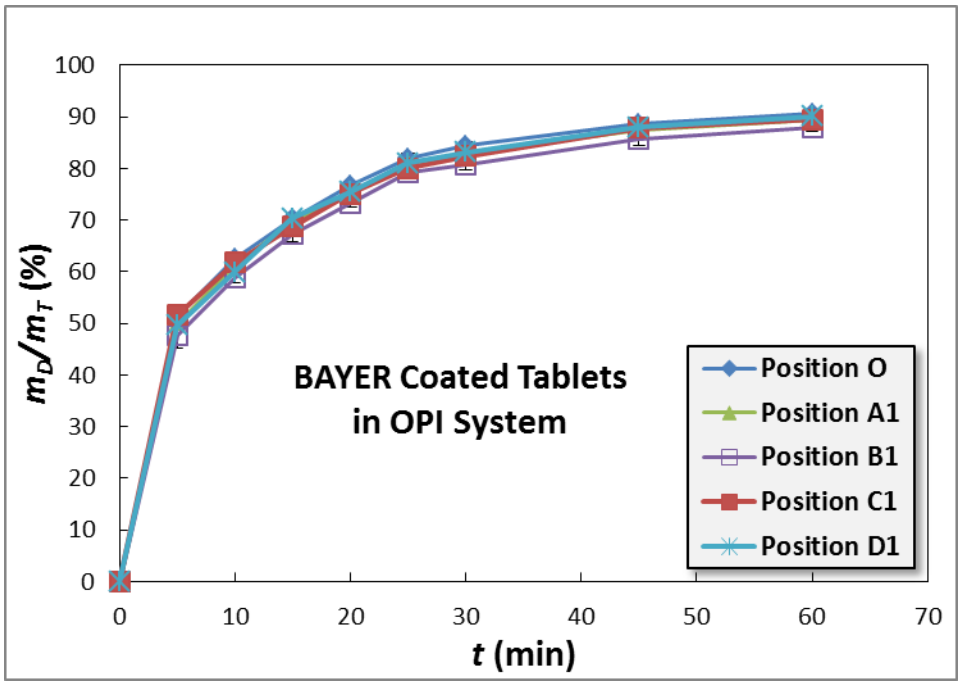


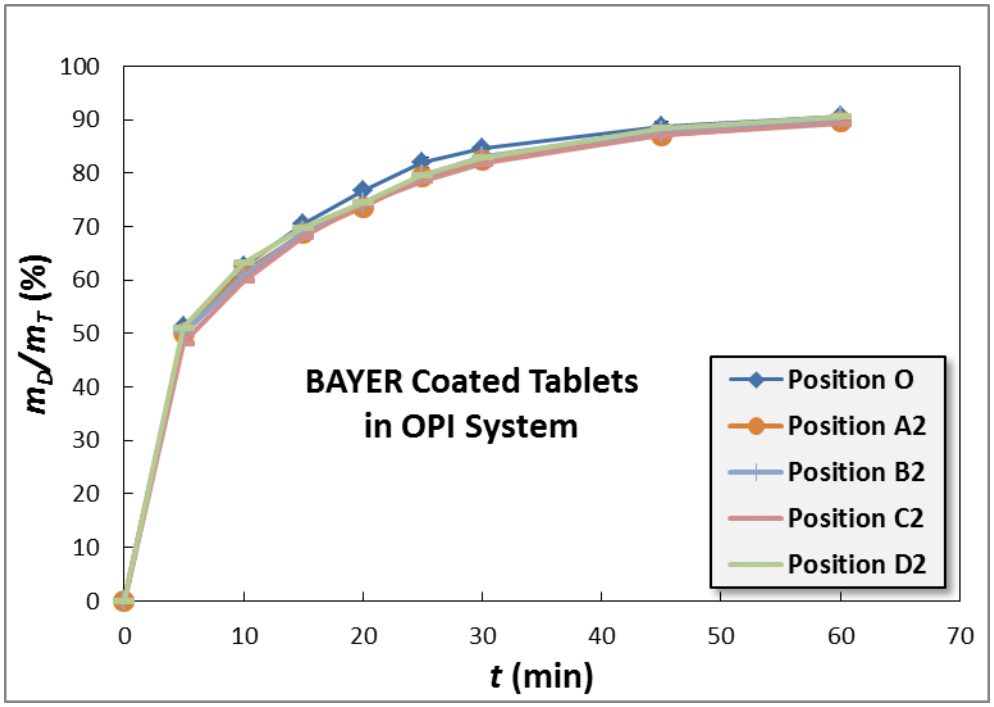
Figure 3.8 Dissolution test results for BAYER Coated Aspirin Tablets in the Standard System.

Table 3.9 f_1 and f_2 Values for the Dissolution Profiles of BAYER Coated Aspirin at Different Tablet Locations with Respect to the Dissolution Profile for a Centrally Located Tablet in the OPI System at 36 rpm

Tablet Location	Difference Factor f_1	Similarity Factor f_2
PositionO (centered tablet)		
Position A1 (10° off-center tablet)	1.8	89.4
Position B1 (10° off-center tablet)	4.4	74.2
Position C1 (10° off-center tablet)	1.8	88.4
Position D1 (10° off-center tablet)	1.6	89.0
Position A2 (20° off-center tablet)	2.4	83.8
Position B2 (20° off-center tablet)	2.0	86.6
Position C2 (20° off-center tablet)	3.4	78.9
Position D2 (20° off-center tablet)	1.3	90.0



(a)



(b)

Figure 3.9 Dissolution Test Results for BAYER Coated Aspirin in the OPI system: (a) results for tablets in the inner 10° circle and (b) results for tablets in the outer 20° circle.

3.1.4 Results for Dissolution Tests Conducted with CVS Coated Aspirin Tablets Using Testing Method #2 (Tablet Fixed in Place at Different Tablet Positions)

The dissolution profiles for 325mg CVS coated aspirin tablets are presented in Figure 3.10 for the Standard System and in Figure 3.11 for the OPI system. The results are reported in terms of m_D/m_T, that is, the ratio of the amount of drug in solution at any time t, relative to total initial amount of drug in the tablet, obtained when the entire 325mg tablet is completely dissolved. The reproducibility of the experimental results was always within 1%, as quantified by the value of the average coefficient of variation for each experiment, which was always about or below 1% in all cases, irrespective of the system used.

In the standard system, three curves started at the same initial mass ratio, but they diverged with time depending on the tablet location. The greater the distance from the central location, the higher the dissolution rate. The dissolution profile for the central tablet began at $m_D/m_T = 0$, and then increased linearly, reaching $m_D/m_T = 55\%$ over the next 20 min. During the following 25min, the dissolution rate decreased slightly and the mass ratio at 45min is 63%. In the last 15min, aspirin tablet was released at a little higher release rate. The mass ratio at t = 60 min was $m_D/m_T = 69\%$. For the 10◦ and 20° off-center tablets, the dissolution curves started at the same m_D/m_T as those at reference 0° position. During the initial 20min, the dissolution curves showed that a faster dissolution process ($m_D/m_T = 80\%$ for 10° off-center tablets, m_D/m_T =84% for 20° off-center tablets) was taking place as compared with the reference position ($m_D/m_T = 55\%$). From t = 20min to t = 45 min, the dissolution curves were found to be parallel to the curves obtained at the reference position. From t = 45 min to t = 60 min, the dissolution rates of

10° off-center tablets increased slightly and showed the same dissolution rates as the reference position in the last 15 min, but the dissolution rate of 20° off-center tablets keep constant. In general, the main difference between the dissolution curves occurred during the initial 20min time period. The f_1 and f_2 values for the CVS coated tablets in the Standard System are reported in Table 3.10. Although f2 was within the 50–100 range, the f1 values were found to be out of the required range to insure statistical similarity, implying that tablets at the 10° and 20° locations would fail the dissolution test. As already pointed out above, the f_2 value for the dissolution profiles of CVS coated aspirin at 10° off-center tablet location in the Standard System at 50 rpm was often found to be in the prescribed range ($50< f_2 <100$), even when the dissolution profiles were appreciably dissimilar. Therefore, it is not surprising that in Table 3.11 the values of the f1 factor were found to be outside the permissible range, whereas those for the f_2 factor were not. Furthermore, Table 3.11 shows that the f2 values, although in range in this case, were close to the lower limit of the range (50). These results confirm that the dissolution profiles for the selected CVS coated aspirin solid dosage form depended strongly on the tablet location in the dissolution vessel for the Standard System. These results are in agreement with previously reported work [7].

The dissolution profiles obtained in the OPI system presents in Figure 3.11. Although the tablets were located at nine different locations, the release profiles almost superimposed, indicating that the initial position of the tablet did not affect the dissolution results. A comparison of the dissolution profiles obtained in the OPI system at different tablet locations with the corresponding profile for the centrally located tablets in the same system could be made using the f_1 and f_2 factors reported in Table 3.11, which

shows that f_1 was in the range 0.6–2.0 and f_2 in the range 86.7–97.8. These results indicate that the dissolution profiles for CVS coated aspirin tablets at off-center position were also statistically similar to the corresponding reference release profile. Therefore, it can be concluded that the OPI system generated release data that were more consistent and not strongly dependent on the tablet location.

Table 3.10 f_1 and f_2 Values for the Dissolution Profiles of CVS Coated Aspirin at Different Tablet Location with Respect to the Dissolution Profile for a Centrally Located Tablet in the Standard System at 50 rpm

Tablet Location	Difference Factor f_1	Similarity Factor f_2
0° (Centered tablet)	-	-
10° Off-Center tablet	49.4	60.8
20° Off-Center tablet	31.6	27.1

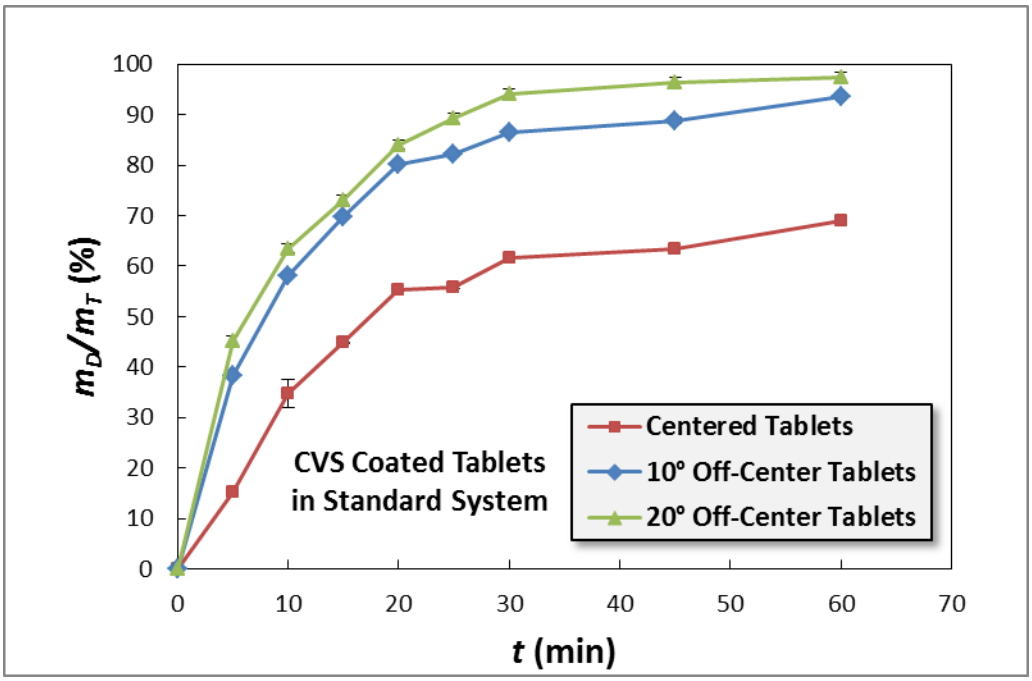
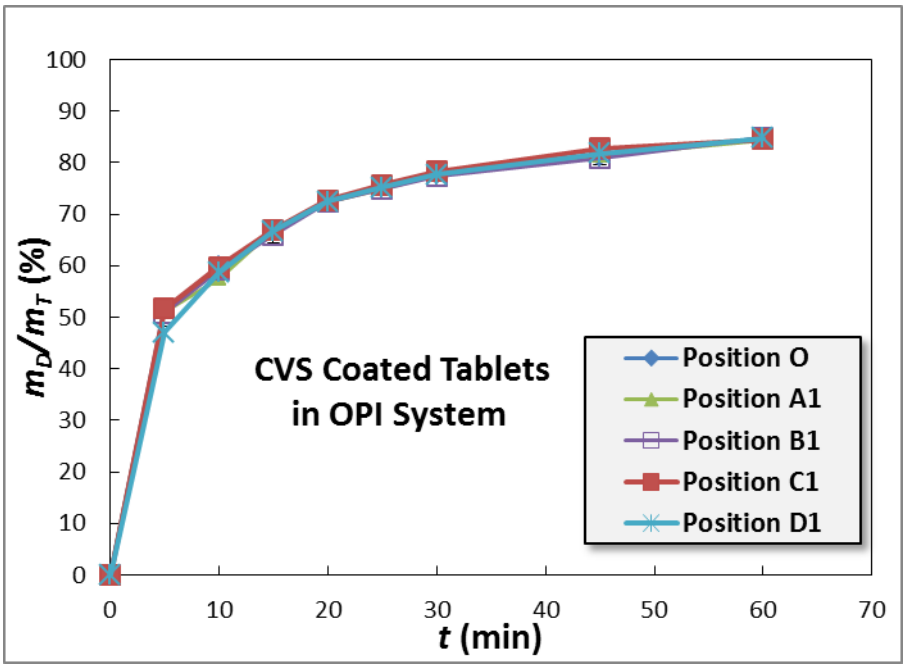


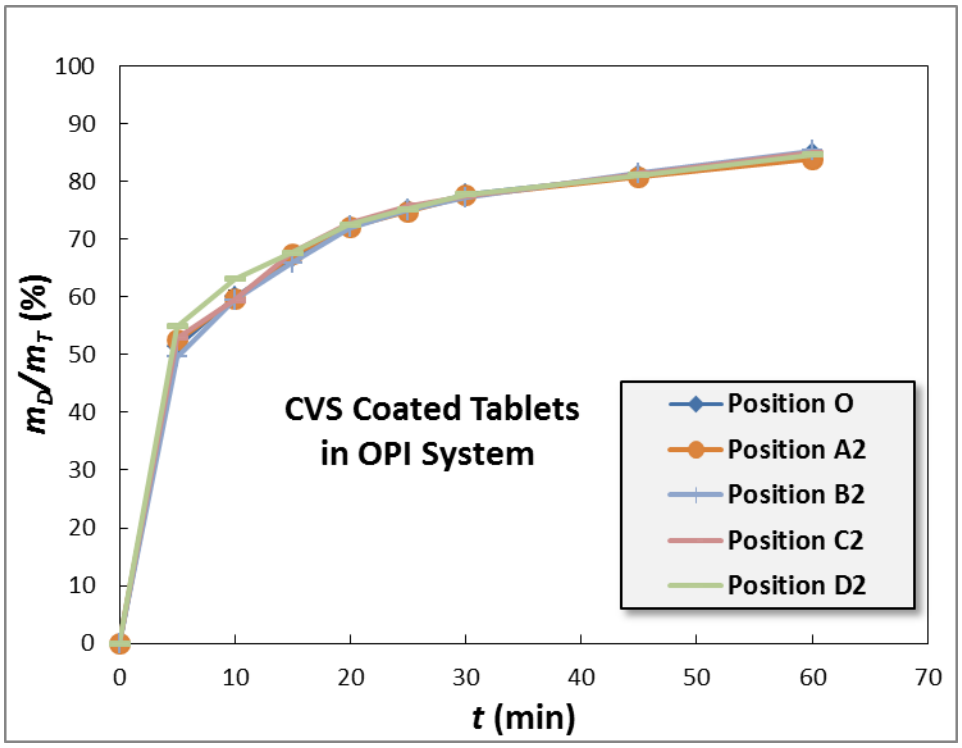
Figure 3.10 Dissolution Test Results for CVS Coated Aspirin Tablets in the Standard System.

Table 3.11 f_1 and f_2 Values for the Dissolution Profiles of CVS Coated Aspirin at Different Tablet Locations with Respect to the Dissolution Profile for a Centrally Located Tablet in the OPI System at 36 rpm

Tablet Location	Difference Factor f_1	Similarity Factor f_2
PositionO (centered tablet)		
Position A1 (10° off-center tablet)	0.8	93.4
Position B1 (10° off-center tablet)	0.6	97.8
Position C1 (10° off-center tablet)	0.7	96.2
Position D1 (10° off-center tablet)	1.2	86.7
Position A2 (20° off-center tablet)	0.8	96.9
Position B2 (20° off-center tablet)	0.9	95.1
Position C2 (20° off-center tablet)	2.0	91.0
Position D2 (20° off-center tablet)	1.9	90.4



(a)



(b)

Figure 3.11 Dissolution Test Results for CVS Coated Aspirin in the OPI system: (a) results for tablets in the inner 10° circle and (b) results for tablets in the outer 20° circle.

3.2 Discussion

The results of this work confirm that the dissolution rate for three different bands of aspirin tablets in standard system is strongly affected by the position of the tablet, as also described in previous work [7] [8]. In addition, this work also shows that a small and simple modification of the standard USP Apparatus 2 can obviate to this problem and result in a much more robust dissolution testing system, thus making this test insensitive to tablet location. In addition, the OPI system appears to have has same sensitivity to different tablet formulations as the standard apparatus based on the results of this work,

The reason for this improvement was accomplished by removing the symmetry, obtained by positioning the impeller off center with respect to the vessel centerline, the OPI system. In the Standard System, the symmetric position of the impeller generates a poorly mixed region just below the impeller, precisely where the tablet is usually located [7] [8] [9]. The hydrodynamics in this region of the vessel is such that a centrally located tablet experiences only a weak flow around it during dissolution, resulting in low shear rates and mass transfer coefficients [8]. However, whenever the tablet is off-center located, as it often happens during actual dissolution tests due to the erratic path of the tablet trajectory as it is dropped in the vessel, the hydrodynamic regime around the tablet is different, even though the tablet is only slightly displaced from the central location. This point was clearly shown by previous work utilizing both experimental methods such as Particle Image Velocimetry (PIV) and Laser Doppler Velocimetry (LDV)) and computational approaches such as Computational Fluid Dynamics (CFD)) [7] [8] [9]. The poorly mixing zone under the impeller persists even when the impeller speed is increased from 50 to 75 rpm and even 100 rpm [9]. In addition, a symmetrical agitation system

lacking baffles, such as the Standard USP Apparatus 2 System, produces a highly tangential flow with very limited velocity components in the vertical and radial directions [7] [9], thus promoting "coning" effects, as often observed during dissolution testing. By contrast, in a "fully baffled" mixing system (i.e., a system typically provided with vertical baffles near the wall), the axial velocities, especially near the vessel's bottom, are overall higher and the poorly mixed zone below the impeller is largely removed. In other words, baffled mixing systems are "better mixers" than the corresponding unbaffled systems, resulting in better solid suspension, shorter blend times, increased turbulence, and other improved mixing effects [30][31].

It is well known from the fluid mixing literature that placing an impeller in an asymmetric position in an unbaffled vessel results in a "partial baffling" effect in which the hydrodynamics of the system resembles, to a partial but significant extent, that of a baffled system [33]. If baffles cannot be introduced in a mixing system for whatever reason, impellers are often placed off center in stirred tanks. An additional advantage of asymmetric placement of the impeller is that the flow that the impeller generates sweeps the vessel bottom, and especially the central region at the bottom of the vessel, thus significantly removing the poorly mixed zone below the impeller. Due to the misalignment between the impeller axis and the vessel's lowest point in the center, this can be expected to be true especially for vessels with a hemispherical bottom. In order to eliminate the poorly mixing zone below the impeller, the OPI system proposed here takes advantage of this effect. Therefore, the location of the tablet at the vessel's bottom is no longer as critical a factor as it is in the Standard System as far as dissolution is concerned because the flow near the vessel's bottom can be expected to be significantly more

uniform than in the Standard System. In other terms, the center of the vessel's bottom is no longer a "special" location with poor mixing characteristics.

This analysis and a review of previous literature on partially baffled systems show that off-center impellers are more effective mixers than the same impellers in corresponding unbaffled mixers. Therefore, due to the improved hydrodynamics near the vessel's bottom, one should expect that the dissolution rates in the OPI system will be faster, resulting in higher flows sweeping the vessel's bottom, including the center vessel location, and higher mass transfer rates. The dissolution profiles obtained in the OPI system show that the dissolution process is faster than that for centrally located tablets in the symmetrical Standard System (Figure 3.6 vs. Figure 3.7 for CVS uncoated aspirin, Figure 3.8 vs. Figure 3.9 for BAYER coated aspirin and Figure 3.10 vs. Figure 3.11 for CVS coated aspirin). More efficient mixing is not necessarily the point of dissolution testing. Although the dissolution profiles obtained with the OPI system show that dissolution process is still slow enough to be observed with the proposed apparatus, it is obvious that if an even slower dissolution process is desired, the agitation speed in the OPI system should be reduced in order to obtain dissolution profiles that resemble those currently obtained with the Standard System, at least when the tablet is centrally located (it should be remarked that the dissolution process is appreciably faster even in the Standard System when the tablet is off center, as shown in Figure 3.6, 3.8 and 3.10).

Another disadvantage of the central placement of the impeller in USP Apparatus 2 is that this system can be expected to be extremely sensitive to any small factors that may introduce slight asymmetries in the otherwise symmetric flow in the USP Apparatus 2 vessel. A review of the literature shows that small imperfections in the geometry of the

vessel (such as those introduced during the fabrication of the glass vessel), small variations in the off-center placement of the impeller (even though within the USP specifications), deviations from the verticality of the vessel placement, the introduction of permanent sampling devices (acting as small baffles), and others have an effect on the rate of dissolution and the outcome of the dissolution test, including possible failure of the test [6][7][24]. For this reason, equipment manufacturers typically go to a significant extent to minimize these potentially test-altering effects by trying to remove the imperfections in the vessels (better cylindrically shaped vessels can be purchased for a higher price) or by providing the user with calibration tools such as centering gauges, wobble meters, precision levels, and other devices to check for geometric irregularities and misalignments [24].

In order to avoid contact between the rotating impeller blade and the vessel wall, the horizontal distance between the shaft centerline and vessel centerline has to be larger than 0mm, but smaller than about 13mm if the impeller is to be placed off center. In this work, the off-center position of the impeller with respect to the impeller centerline was set at 8mm. This distance was selected so that the impeller would be appreciably off center while avoiding the blade passing too close to the vessel wall. Although no other off-center impeller positions were tested in this work, one can postulate that any significant, but not excessive, off-center distance of the impeller from the vessel centerline would produce results similar to those obtained here. What is critical in the proposed novel design is the departure from the current symmetrical design of the dissolution apparatus rather than the exact extent of the off-center impeller placement.

Switching to the USP dissolution system now, one can similarly postulate that the

critical aspect of the design proposed here is the significant departure from the central impeller location rather than the actual extent of such departure.

In order to address the poorly mixing issue in the USP Apparatus 2, the OPI system was developed by positioning the impeller off center with respect to the vessel centerline. As a result, the OPI system is less sensitive to the tablet position. The dissolution profiles for different aspirin tablet formulations are different in the standard system, as one would expect (Figure 3.1, Table 3.1). In the OPI system, the release curves of different aspirin tablet formulations are also different from each other (Figure 3.2, Table 3.2). Based on Figure 3.3, 3.4, 3.5, the release profiles of each aspirin tablet formulation in the two systems are very similar, indicating that the OPI system has same sensitivity to different tablet formulations as the standard system.

Finally, any newly proposed apparatus needs to be evaluated not only for the advantages that it offers, but also in terms of how easily (or not) the new technology can be implemented in the industrial practice. In fact, the pharmaceutical industry already makes extensive use of the standard USP Dissolution Testing Apparatus 2 and it has made significant investments in terms of both equipment and personnel training. Therefore, it will be difficult to justify a radical departure for the current, well-established practice. This is even more so in a highly regulated industry such as the pharmaceutical industry, where both the regulator agency (FDA) and the repository of current practice (USP) have codified the use of the Standard System and are used to it despite its well documented shortcomings.

For this reason, the OPI system proposed here is based on a very simple and potentially readily implementable modification of the current apparatus. In our laboratory,

using a commercially available dissolution testing apparatus, switching from the Standard System to the OPI system required only minutes, as described above. Clearly, the same ad hoc modifications that we used here to test the concept would not be acceptable in the industrial practice as such because mechanical calibration based on the USP/FDA requirements would be needed (the development of a procedure to validate the OPI system was clearly outside the scope of this work, although it could be easily generated). However, there could be a number of readily implementable and easy-to-validate modifications that could be made to existing commercial apparatuses (both new and old), which would enable the operator to switch very rapidly from the Standard System to the OPI system. A recently filed patent by this group describes a number of such approaches. For example, in many commercial apparatuses, including the one used in this work, each dissolution vessel is inserted in the circular hole in the supporting metal plate where it is secured and centered by plastic spring inserts (Figure 2.3). Therefore, each hole is larger than the outer diameter of the dissolution vessel. It would be easy to remove these inserts and replace them with a circular plastic ring insert fitting inside the hole.

In summary, the proposed OPI system is capable of discriminating between different tablet formulations while, at the same time, being less sensitive to small geometric variations, such as tablet location, which instead have a significant impact on the dissolution profiles obtained in the standard system. The OPI system is expected to require very low capital investment for its commercial implementation and minimal retraining of personnel, while providing a much more robust test that is insensitive to tablet location and, most likely, to other small geometric imperfections in the equipment and to small operator-dependent variations in the test procedure.

CHAPTER 4

CONCLUSIONS

Dissolution tests conducted using three different brands of aspirin tablets in a novel OPI Dissolution Testing Apparatus, in which the impeller was placed 8mm off center, resulted in dissolution curves for the same type of tablets that were statistically similar (using both f_1 and f_2) irrespective of where the tablets were located at the vessel's bottom. By contrast, similar tests conducted using the standard USP Dissolution Testing Apparatus 2 resulted in dissolution curves that were not statistically similar.

On the other hand, the release profiles of three different brands of aspirin tablet in OPI system were similar to those in the standard system, indicating that the OPI apparatus is just as sensitive as the standard system to actual differences in differently manufactured tablets having intrinsically different dissolution profiles.

These results can be attributed to the different flow patterns associated with the Standard System and the OPI system. In the standard system, a small but poorly mixing zone exists below the impeller (where the tablet usually resides), resulting in slow dissolution rates. However, when the tablet finds itself outside this zone, due to the erratic path of the tablet trajectory after it is dropped in the vessel, a common occurrence during dissolution testing the hydrodynamic regime around the tablet is very different, resulting in higher dissolution rates. By contrast, the flow pattern near the tank's bottom for the case in which the impeller is placed off center can be expected to be stronger and more uniform, especially at the center of the vessel's bottom, thus resulting in more rapid dissolution and dissolution curves that are nearly independent of the initial tablet location as found here.

The OPI system is a very simple modification of the current dissolution testing USP Apparatus 2 system. A number of inexpensive and easily achievable modifications to the Standard System can be resulting in off-center placement of the impeller within the USP Apparatus 2 vessel. Such OPI system can be operated identical to the current system, thus making the transition to the OPI system very simple from the operator's standpoint.

APPENDIX A

FIGURES OF DISSOLUTION TESTING RESULTS

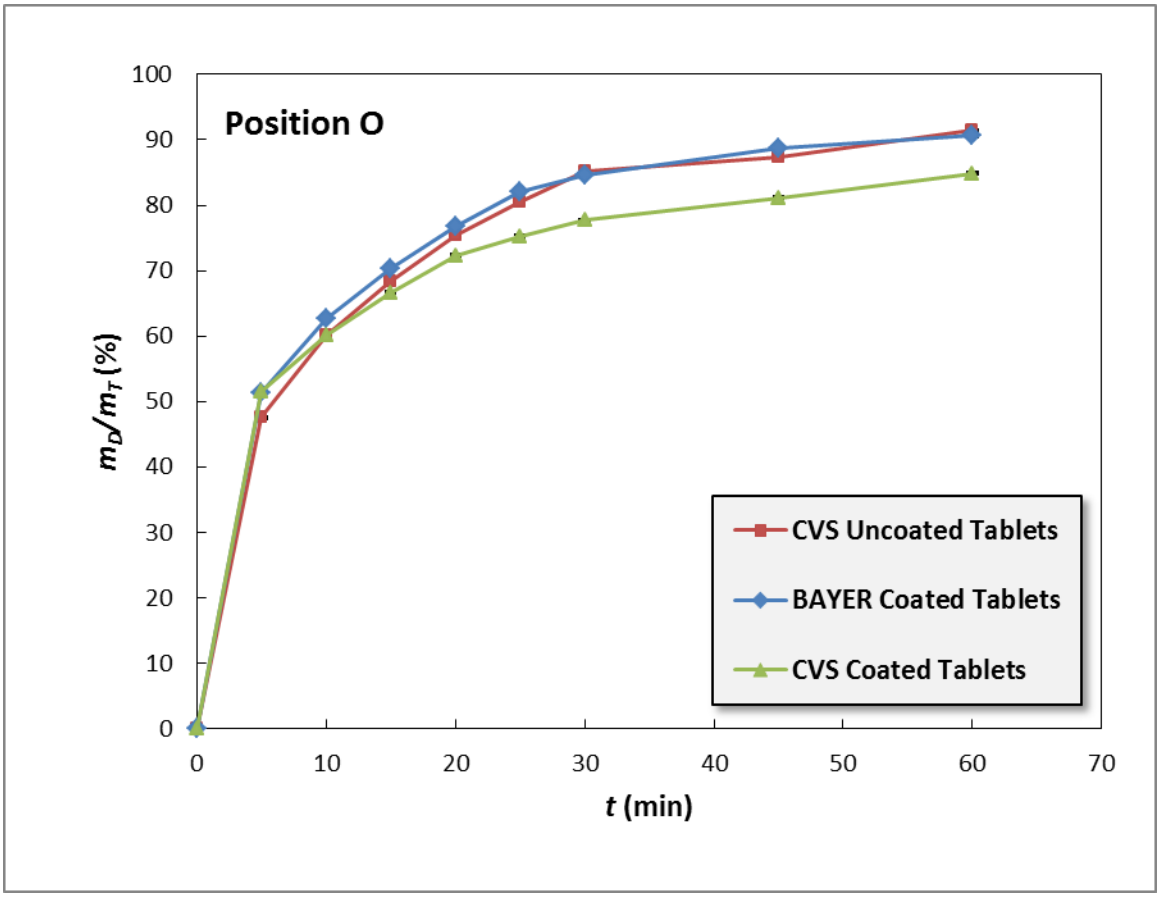


Figure B.1 Dissolution profiles with Position O tablets in OPI System.

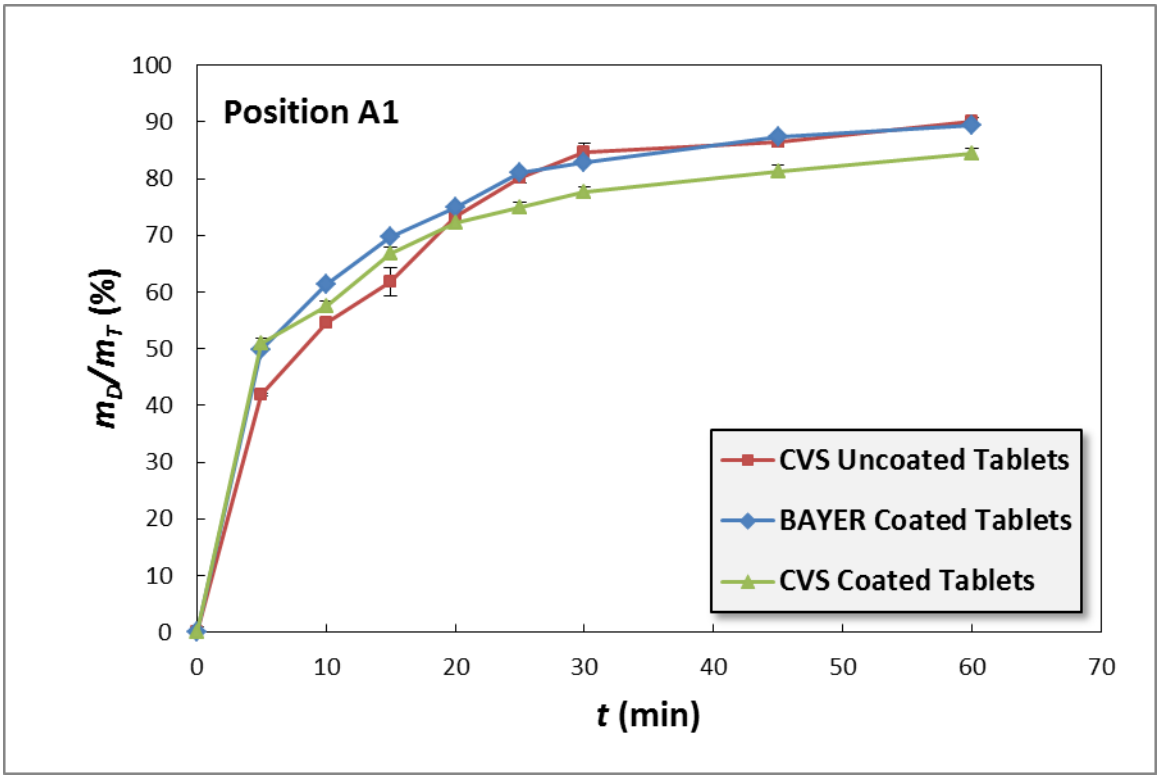


Figure B.2 Dissolution profiles with Position A1 tablets in OPI System.

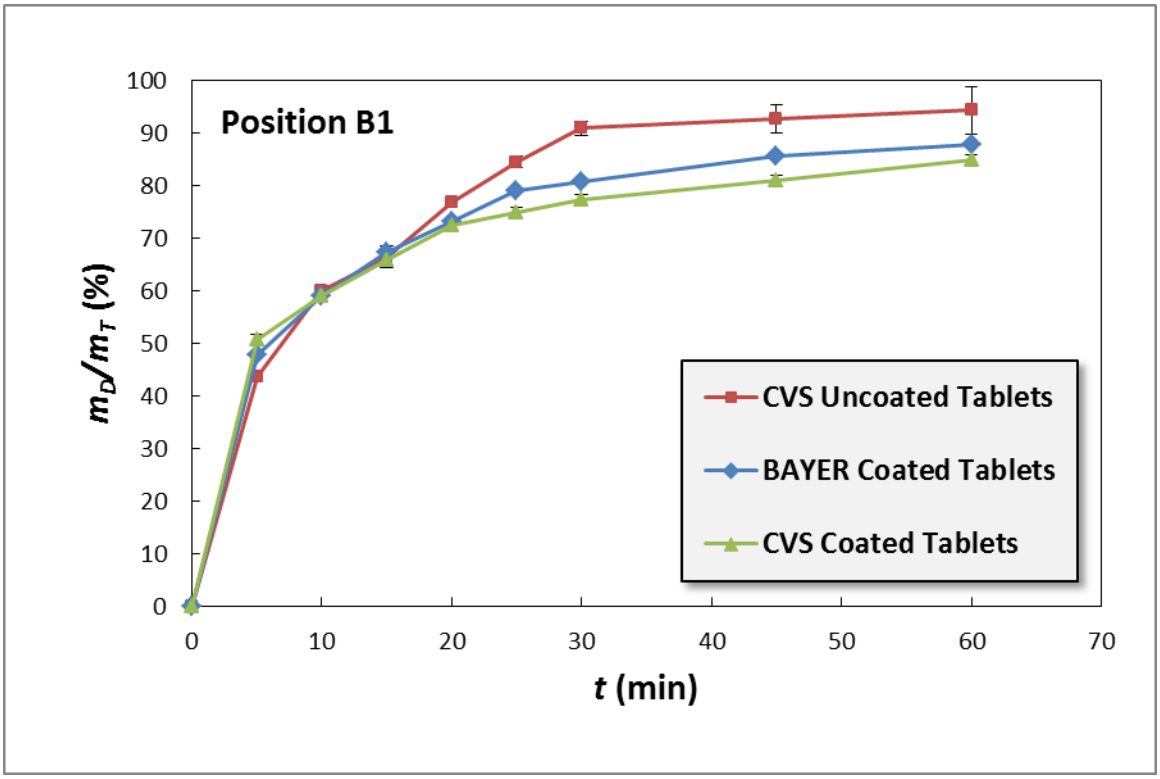


Figure B.3 Dissolution profiles with Position B1 tablets in OPI System.

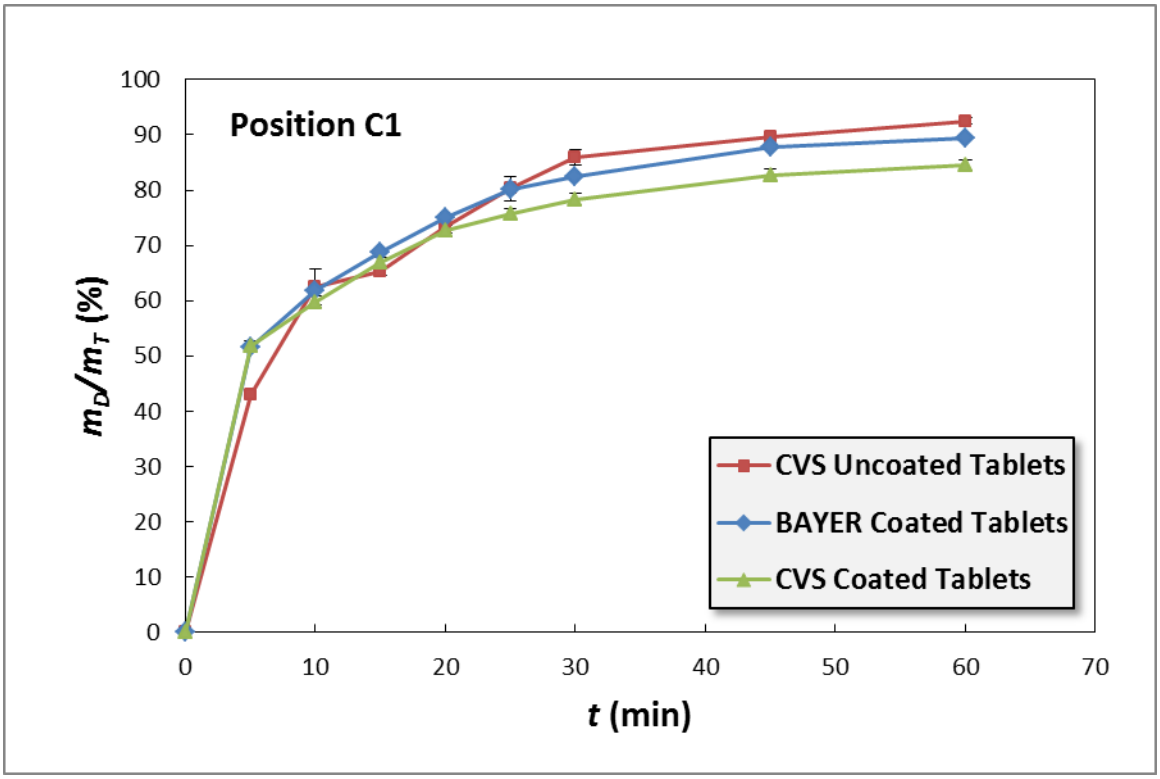


Figure B.4 Dissolution profiles with Position C1 tablets in OPI System.

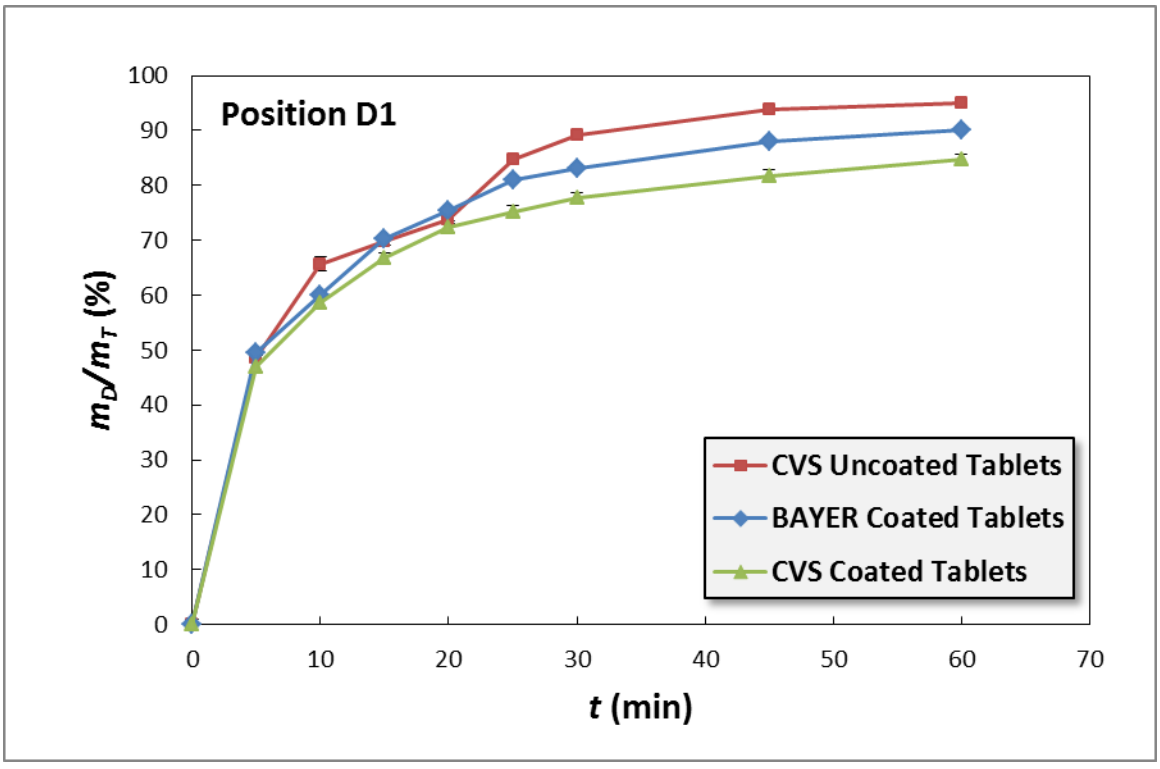


Figure B.5 Dissolution profiles with Position D1 tablets in OPI System.

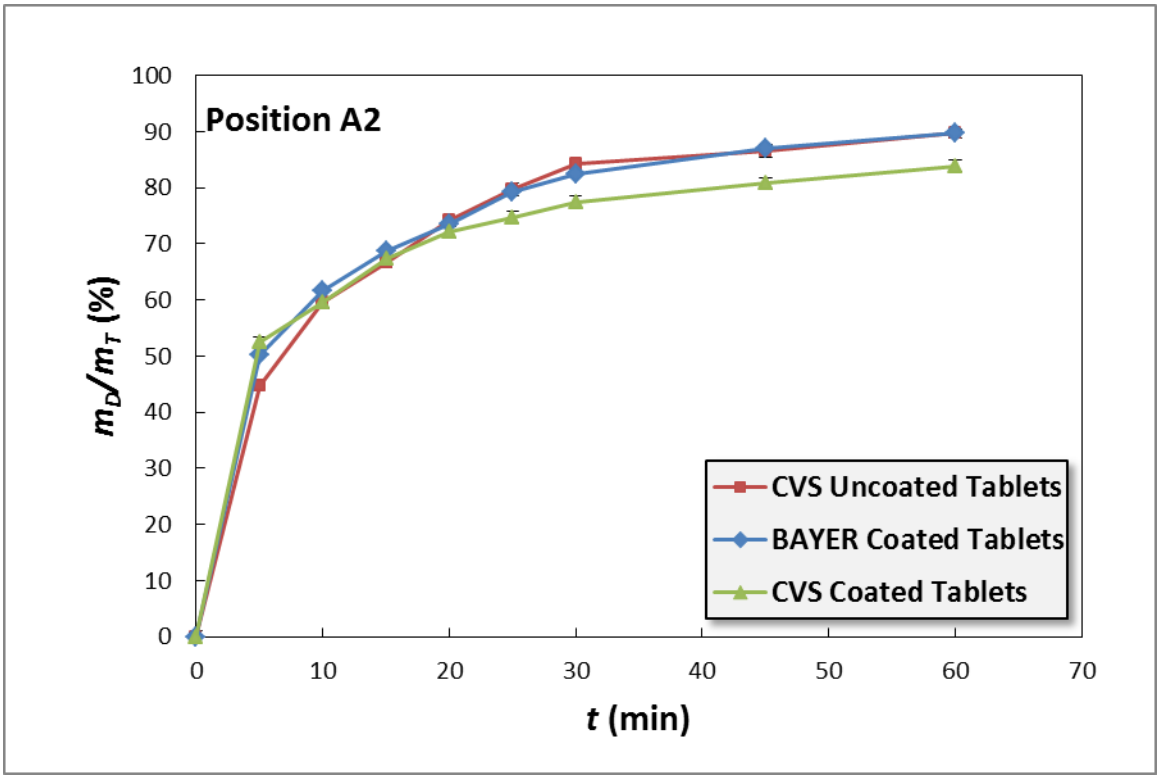


Figure B.6 Dissolution profiles with Position A2 tablets in OPI System.

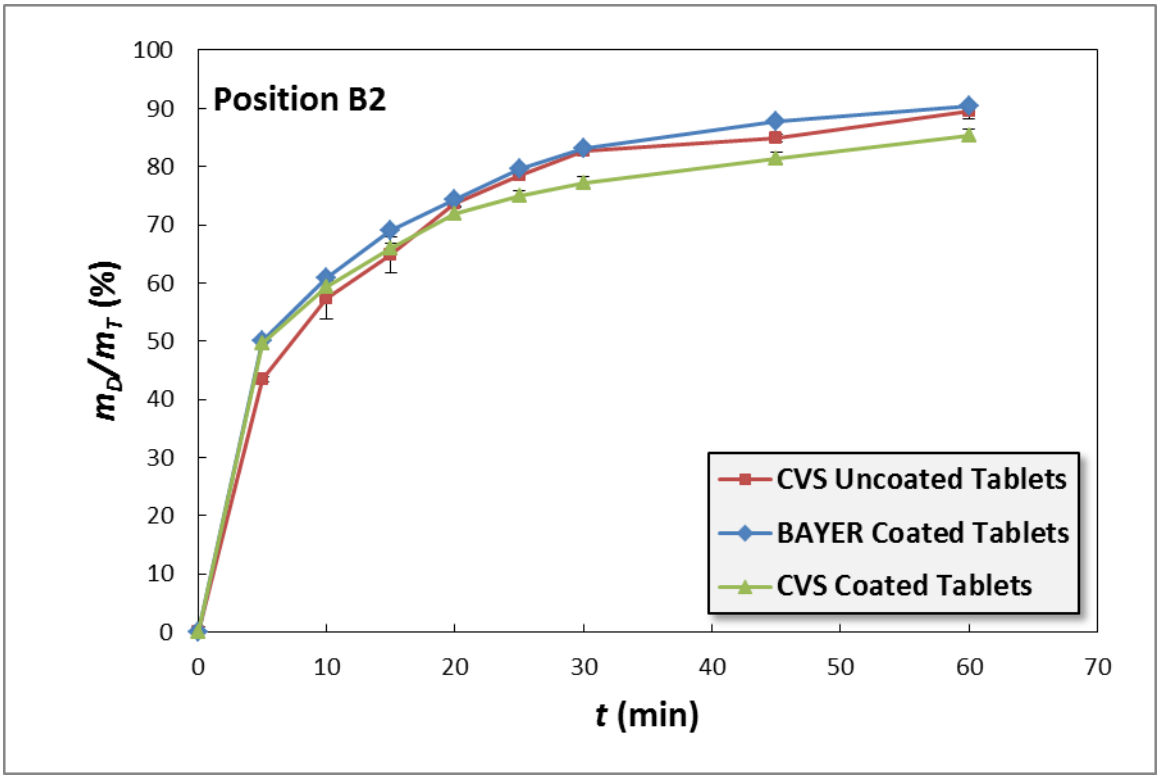


Figure B.7 Dissolution profiles with Position B2 tablets in OPI System.

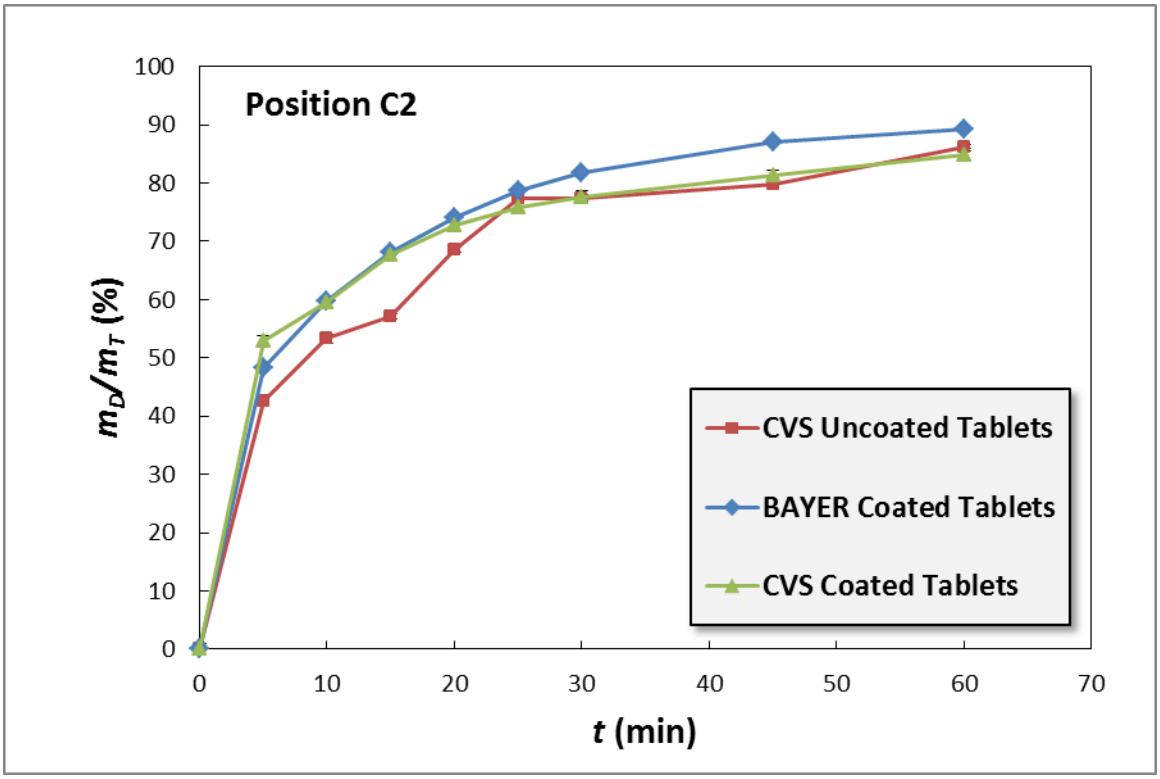


Figure B.8 Dissolution profiles with Position C2 tablets in OPI System.

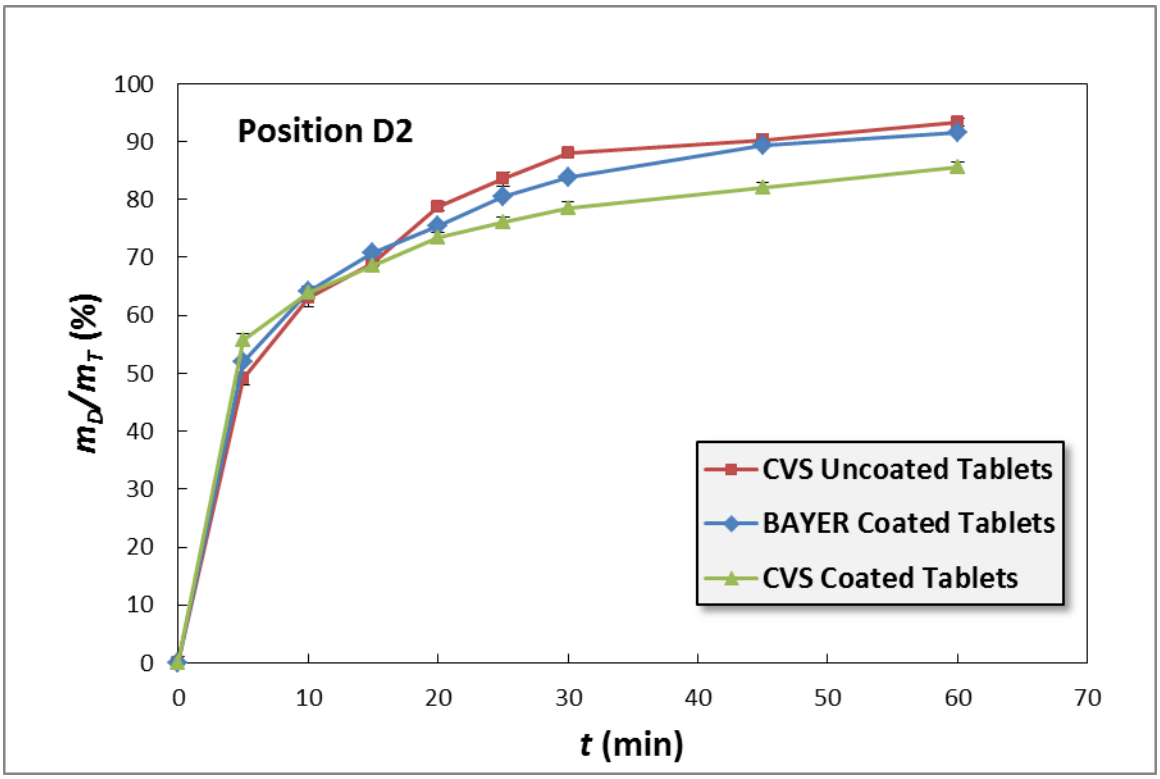


Figure B.9 Dissolution profiles with Position D2 tablets in OPI System.

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