

Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be “used for any purpose other than private study, scholarship, or research.” If a user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of “fair use” that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation

Printing note: If you do not wish to print this page, then select “Pages from: first page # to: last page #” on the print dialog screen

The Van Houten library has removed some of the personal information and all signatures from the approval page and biographical sketches of theses and dissertations in order to protect the identity of NJIT graduates and faculty.

ABSTRACT

COMPARATIVE ANALYSIS OF THE DISSOLUTION PERFORMANCE OF ASPIRIN TABLETS IN THE USP APPARATUS 2 AND IN A MINIVESSEL DISSOLUTION SYSTEM

by

Annmarie C Walker

Dissolution testing is a critical component of quality control procedures in the pharmaceutical industry in order to ensure that the final solid dosage forms have consistent dissolution properties. Dissolution tests are also routinely conducted to evaluate the in-vitro performance of solid dosage forms during pharmaceutical development, to aid in the behavior of formulations, and to optimize drug release from dosage forms.

The use of compendial dissolution test apparatus and techniques, such as the USP 2 (Paddle), to characterize the dissolution performance of oral drug delivery system is an established area of pharmaceutical science. However, this method is not always appropriate, particularly in dissolution tests that involves the use of very small tablets or when there is not enough drug substances available for appropriate test in the USP 2 system, particularly during the early stages of drug development.

Mini vessel systems, i.e., a small-volume dissolution apparatus, require a small drug amount and utilize a small volume of dissolving medium. Therefore, they are an emerging technology in the pharmaceutical industry that can be used to overcome the limitations associated with the USP 2-based dissolution testing method. Mini vessels offer cost effective solutions in the characterization of drug release profiles by utilizing smaller sample sizes and

smaller volumes of media. Despite the industrial relevance of mini vessels only a small number of studies on mini vessel dissolution systems have appeared in the literature.

In this work, a commercially available non-compendial Minivessel Dissolution System and a USP 2 dissolution system were used to conduct dissolution tests using two different dosage forms, both containing aspirin as the Active Pharmaceutical Ingredient (API). Specifically, dissolution tests were conducted in the standard USP 2 with coated 325-mg aspirin caplets and with half doses in the USP 2 and in the Minivessel. Additionally, 81-mg enteric-coated delayed release aspirin tablets were used. Five 81-mg tablets were used in simultaneously used in dissolutions test in the USP 2 using 500 ml of dissolution medium while a single 81-mg dose and 100 ml of medium were used in the Minivessel in order to achieve similarity of surface area of tablets to volume of medium in both systems. Experiments in the USP 2 were conducted at compendial speeds of 50, 75, and 100 rpm. Minivessel experiments were conducted at different agitation speeds, i.e., 50, 75, 100, 125, 150 rpm, as well as at the agitation speeds equal to 86.2, 109.7, and 129.2 rpm since at these agitation speeds the tablet-medium mass transfer coefficients were previously predicted to be similar to those in the USP 2 at 50, 75, and 100 rpm, respectively.

The dissolution curves in the Minivessel and in the USP 2 were compared and it was found that operating the Minivessel as predicted to achieve similar mass transfer coefficients in the USP 2 produced similar dissolution curves in both systems. The comparison was additionally quantified by using the difference factor f_1 and the similarity factor f_2 recommended by the Food and Drug Administration (FDA).

It can be concluded that appropriately operating Minivessel can result in dissolution profiles similar to those obtained in the USP 2. The results of this work could be of

significant importance to dissolution scientists in the pharmaceutical industry and help them operate mini vessels, especially during the early stages of drug development, so as to predict future dissolution profiles of the same drug product during commercialization, when the USP 2 system is routinely used.

**COMPARATIVE ANALYSIS OF THE DISSOLUTION PERFORMANCE OF
ASPIRIN TABLETS IN THE USP APPARATUS 2 AND IN A MINIVESSEL
DISSOLUTION SYSTEM**

by
Annmarie C Walker

**A Thesis
Submitted to the Faculty of New Jersey Institute of Technology
in Partial Fulfilment of the Requirements For the degree of
Master of Science in Pharmaceutical Engineering**

**Otto H York Department of
Chemical, Biological and Pharmaceutical Engineering**

December 2017

Blank Page

APPROVAL PAGE

**COMPARATIVE ANALYSIS OF THE DISSOLUTION PERFORMANCE OF
ASPIRIN TABLETS IN THE USP APPARATUS 2 AND IN A MINIVESSEL
DISSOLUTION SYSTEM**

Annmarie C Walker

Dr. Piero M. Armenante, Thesis Advisor

Date

Distinguished Professor of Chemical Engineering, NJIT

Professor Boris Khusid, Committee Member

Date

Professor of Chemical Engineering, NJIT

Professor Sagnik Basuray, Committee Member

Date

Professor of Chemical Engineering, NJIT

BIOGRAPHICAL SKETCH

Author: Annmarie Cerina Walker
Degree: Master of Science
Date: December 18, 2017

Undergraduate and Graduate Education:

- Master of Science in Pharmaceutical Engineering,
New Jersey Institute of Technology, Newark, NJ, 2017
- Bachelor of Science in Chemical Engineering,
University of Technology, Kingston Jamaica, 2009

Major: Pharmaceutical Engineering

Presentation:

Annmarie C. Walker and Piero M. Armenante “Comparative Analysis of The Dissolution Performance of Aspirin Tablets in the USP 2 Apparatus and in a Minivessel Dissolution System.

The Race is not for the Swift or the Strong, but those Who Can Endure to the End

ACKNOWLEDGEMENT

I must express my gratitude to the following persons who have guide and inspired me throughout the duration of this project. Without their assistance, my effort would have been futile.

Dr Piero M. Armenante, Thesis Advisor, Distinguished Professor of Chemical Engineering, NJIT. Thanks for giving me the opportunity to work with him and providing his exceptional insights during my course of research.

I must express my appreciation to Professor Boris Khusid and Professor Sagnik Basuray for being a part of my thesis committee.

My gratitude to Mr Yogesh Ghandi, and Mr Shawn Yetman is unwavering. Thanks for making the resources within their capacities available to me.

The encouragement of my sister, Imogene and my nephew, Andréa, the ever-present persevering memory of my mother, you are my fortress.

TABLE OF CONTENTS

Chapter		Page
1	INTRODUCTION.....	1
2	BACKGROUND AND OBJECTIVE OF THIS WORK.....	10
3	EXPERIMENTAL APPARATUS, MATERIALS AND METHOD.....	14
	3.1 Experimental Test Apparatuses.....	14
	3.2 Experimental Materials.....	21
	3.3 Experimental Methods.....	23
	3.4 Data Analysis.....	31
4	RESULTS.....	37
	4.1 Results for In-Vitro Dissolution Tests with 325-mg Coated Aspirin Caplet and with Half Caplets.....	37
	4.2 Results for Invitro-Dissolution Test For 81-mg Enteric Coated Aspirin.....	43
5	DISCUSSION.....	61
6	CONCLUSIONS.....	67
	Appendix A.....	70
	Appendix B.....	75
	Appendix C.....	81
	Appendix D.....	85
	REFERENCES.....	91

LIST OF TABLES

Table	Page
2.1 Prediction of Agitation Speeds in Usp2 and Minivessel (Wang et al)	12
3.1 Dimensions of USP Dissolution Apparatus 2, Paddle.....	16
3.2 Dimensions of Minivessel Dissolution System, Paddle.....	20
3.3 Operation Conditions for Dissolution Experiments.....	28
3.4 Calibration Data for 325-mg Aspirin Caplets.....	29
3.5 Calibration Data for 81-mg Aspirin Tablets.....	30
4.1 f_1 and f_2 Values for 325mg Aspirin Caplets in Standard System.....	42
4.2 f_1 and f_2 Values for 325mg Aspirin Caplets in Standard System.....	42
4.3 f_1 and f_2 Values for 81-mg Aspirin Tablets in Standard System.....	56
4.4 f_1 and f_2 Values for 81-mg Aspirin Tablets in Minivessel System.....	57
4.5 f_1 and f_2 Values Comparing Dissolution in Standard System and Minivessel.....	58
4.6 Properties of 81mg Aspirin Tablets and Dissolution System.....	60
4.7 Mass Transfer Coefficient Values for 81mg Aspirin Caplets in Standard System.....	60
4.8 Mass Transfer Coefficient values for 81mg Aspirin Tablets in Minivessel.....	60

LIST OF FIGURES

Figure	Page
2.1 Prediction Model for Equivalent Dissolution Profile in USP2 and Minivessel.....	13
3.1 Dimension of USP2 Dissolution Testing Apparatus -Paddle, Glass.....	16
3.2 Distek Premier -5100 Dissolution System used in this work.....	17
3.3 Minivessel Dissolution Apparatus –(a)Small vessel, Mini-paddle, Lid.....	18
3.3 Minivessel Dissolution Apparatus –(b)Small vessel, Mini-paddle, Mounting plate.....	19
3.4 Dimension of Mini-paddle – Paddle, Glass.....	19
3.5 Distek Premier -2100 Dissolution System for support of Mini-vessel	20
3.6 Plexi-Glass Water Bath attached Cole Palmer Circulating Bath.....	21
3.7 Equipment used to de-aerate the dissolution medium.....	22
3.8 Front Schematic of Dissolution vessel -Tablet and paddle position in Standard USP11.....	24
3.9 Front Schematic of dissolution vessel – Tablet and paddle position in Minivessel.....	26
3.10 Calibration Curve 325mg Aspirin CVS.....	29
3.11 Calibration Curve 81mg Enteric Coated Aspirin.....	30
4.1 Dissolution Profile for 325 mg Coated Aspirin CVS (full dose) in Standard System (100 rpm)	40
4.2 Dissolution Profile for 325mg Coated Aspirin CVS (Half Dose) in Standard System (50, 100rpm)	40
4.3 Dissolution Profile for 325mg Coated Aspirin Tablet in Minivessel System (Higher Speed)	41
4.4 Dissolution Profile for 325mg Coated Aspirin CVS in Standard System.....	41

LIST OF FIGURES

(Continued)

Figures	Page
4.5 Dissolution Profile for 81mg Enteric Coated Aspirin (Single Dose) in Standard System.....	50
4.6 Dissolution Profile for 81 *5mg Enteric Coated Aspirin in Standard System (50,100 rpm)	50
4.7 Dissolution Profile for 81mg Enteric Coated Aspirin in Minivessel System (Lower Speeds)	51
4.8 Dissolution Profile for 81mg Enteric Coated Aspirin in Minivessel System (Higher Speeds)	52
4.9 Dissolution Profile for 81*5 mg Aspirin Tablets in USP2 (50 Rpm), (500ml) compared to Minivessel System (at agitation speeds of 50, 75, 86.3 rpm)	52
4.10 Dissolution Profile for 81*5mg Aspirin Tablets in USP2 (75 rpm, 500ml) compared to Minivessel System (at agitation speeds of 75, 100, 109.7 rpm)	53
4.11 Dissolution Profile for 81*5 mg Aspirin Tablets in USP2 compared to Minivessel System (at agitation speeds of 100, 125, 150 rpm)	53
4.12 Dissolution Profile for 81*5 mg Aspirin Tablets in USP2 compared to Minivessel System (at agitation speeds of 125, 129.2, 150 rpm)	54
4.13 Dissolution Profile for 81*5 mg Aspirin Tablets in USP2 compared to Minivessel System (at agitation speeds of 86.3, 109.7 rpm)	54
4.14 Dissolution Profile for 81*5 mg Aspirin Tablets in USP2 compared to Minivessel System (at agitation speeds of 109.7, 129.2 rpm)	55

CHAPTER 1

INTRODUCTION

Dissolution can be defined in a narrow sense as the process by which a solid substance is incorporated into a solvent to form a solution. However, in a broader sense it is more than a single measurement of solubility rate and can be better described as a physical test to predict the drug release from a dosage form for given area for a precise time.

Dissolution testing of solid dosage forms is a laboratory test process that attempts to replicate *in vitro* the complex *in vivo* process associated with tablet disintegration and dissolution in the gastro-intestinal tract. Additionally, this is a test that pharmaceutical companies typically conduct on oral dosage formulations to determine compliance and to release products for distribution and sales. The United States Pharmacopeia (USP) lists several standardized dissolution testing methods and apparatuses (USP 39-NF 34, 2016). The most widely used of these devices is the USP Dissolution Testing Apparatus 2, typically referred to as USP 2 (Cohen et al., 1990; Cox et al., 1984; Mauger et al., 2003; Moore et al., 1995; Moore and Flanner, 1996; U.S FDA, 1997).

Common dosage forms such as tablets, capsules, suspensions, suppositories, chewable and transdermal, typically contain milligram levels of the Active Pharmaceutical Ingredient (API) and are easily quantified in dissolution medium from 500 mL to 4L depending upon on the dosage form and its respective method. Dissolution rate is also the limiting step for drug absorbed in the systemic circulation for immediate release dosage forms. Dissolution test for these types of drugs are performed using the USP apparatus, namely the basket, paddle, rotating cylinder and flow through cell.

Newer designs for the testing of these dosage forms include the Minivessel apparatus. Dissolution of typical high potency, low dose compounds need a reduction in vessel volume, further accompanied by modification of the apparatus design due to some drawbacks in the official compendial apparatus. This include inability to maintain quantitative levels of analyte during dissolution test.

The use of small volume dissolution apparatus satisfies the need to give reliable correct data, for decision making during early development stages of drugs. They also provide quality control at the time when the formulation reaches scale up and provides assurance of product stability.

The Minivessel is based on the USP paddle set up, but the size is scaled down to exactly 1/3 of the USP and 40% with respect to vessel volume and impeller sizes. The volume used is approximately 250-mL and the working volume is typically 100-mL.

The main advantage of Minivessel are that it requires a small dose of a drug that is used for paddle apparatus, smaller volumes of media used offer various advantages in terms of substance, analytical and material cost savings. This set up is also a promising alternative in the case of high-potency drugs.

Dissolution testing is a requirement for all solid dosage forms, and is used throughout the development life cycle for product release and stability testing. The dissolution test is the most important analytical test for detecting physical changes in an API and in the formulation. Dissolution testing has more and more evolved to establish relationships with in vivo performance or with manufacturing Critical Quality Attributes (CQA) in the scope of Quality by Design (QbD) [1].

At early stages of the drug the development processes in vitro dissolution testing underpins the optimization of drug release from a given formulation. To aid with dosage form optimization the dissolution testing is a standardized method for measuring the rate of drug release from a given dosage form, while at later stages [4,5].

In short, for the development and validation of dissolution test procedure, the foremost requirement is to ascertain that the apparatus and procedure are capable of simulating an in-vivo environment through which the product will pass. At present, the industry standard dissolution testing methodologies are the Pharmacopeial, United States Pharmacopeia Apparatus 1, (basket), and apparatus 2, (paddle) [2,3,4].

The USP Apparatus 2 and its accompanying test are routinely used in the pharmaceutical industry to help formulate solid drug dosage forms, particularly for immediate release (IR) of the solid dosage form, [2,6].

Also during product development, dissolution testing consists of two components. This involves preparation of the test drug product followed by the analysis of the sample collected during dissolution test. The standard dissolution apparatus such as USP 2 is used. Surprisingly these apparatuses do not provide the necessary product medium interaction. This is due to the lack of adequate stirring and mixing within the vessel. This lack of stirring and mixing appears to cause difficulties, stagnation and result in errors in the development of proper dissolution method through variability. Extensive work has been done that provides extensive literature that adequately covers the hydrodynamics of the apparatus 2, [2-9,11].

Sample analysis, are done primarily by chromatographic or spectrophotometric techniques. The two components of the dissolution test, sample preparation and assay are separated by a filtration step. Filters must be validated to prove their efficiency in removing undissolved Active Pharmaceutical Ingredient (API) from the sample and to verify that they do not absorb dissolved API, which affects the integrity of the sample concentration. The first step taken to overcome concentration and sensitivity issues is usually modification of analytical method by taking advantage of a larger path length for spectrometer or larger injection volume for high performance liquid chromatography, (HPLC). When success with these techniques are limited, the focus on the dissolution apparatus where a reduction in media volume may be a more rugged solution becomes relevant. [23].

Only a few of the compendial dissolution and drug release apparatus are designed for low dose compounds and volume requirements less than 100ml presents additional challenges to the traditional paddle and basket apparatus. Rugged dissolution methods should quantify the low levels of analyte accurately and precisely especially in the initial stages of analytical concentration in the presence of reliable and consistent agitation is the primary requirement of any dissolution test but demands extreme precision in low volume conditions to ensure data accuracy [23].

The dissolution apparatus must operate under conditions of controlled temperature, agitation rate and precise hydrodynamics and volume. To maintain precise hydrodynamics the apparatus must maintain an overall physical uniformity and alignment throughout the test. Standard dissolution apparatus may be obtained from manufacturers that produce the equipment according to specification and tolerances outlined in General Test Chapter (711) Dissolution [4].

For low dose concentrations of API, official compendial is seen to be incapable of maintaining quantitative levels of an analyte during dissolution of oral dosage units containing microgram or nanogram levels. [16,17] Accordingly Crail et al stated, "It has been our experience that the apparatus 2 is suitable for the evaluation of the dissolution characteristics in developing a dissolution method for a new propriety tablet containing 200 microgram actives the early dissolution points could not be quantified using the current this assayed method". To increase the drug concentration several options were considered. The first was to use multiple tablets in a single vessel using 500ml to 900ml of media, another option was to use a conversion a 200ml vessel offered by Van Kel Technologies, [17].

Dissolution of typical high potency low dose compounds may require reduction in vessel volume accompanied by an alteration in apparatus design due to limitations in detection and quantification. if a reduction in volume accompanied by an alteration, the apparatus should maintain the same degree of precision and alignment required for any other compendial dissolution apparatus. Small volume apparatus is not desired only for high potency, low dose formulations, but also in cases where specific physiological environment is a requirement Specifically for some biorelevant studies, during drug formulation, dissolution should be ideally conducted in a specific medium, such as an animal gastrointestinal medium with a similar dissolution medium as in the animal physiology, [6,12,17,].

To address the issues in industry, practice the standard (USP2) dissolution method has been modified and a small volume dissolution vessel with a mini paddle has been suggested as an alternative to standard dissolution equipment in early stages development

studies that require large volumes of biorelevant medium. This can be very expensive and there may be limitations of large sample sizes or active drug availability in early stages of drug development [11].

The solubility and dissolution rate of a drug can be linked to bioavailability in many cases. To achieve physiologically relevant results, it is necessary to use well designed test set up. The choice of the most appropriate hydrodynamics is essential for development of a biorelevant dissolution method. The modification of existing system and new apparatus is proposed in specific cases. When tablets contain very small amounts of active ingredient or when extended release tablets are tested in which small amounts are released and may be difficult to detect using conventional methods [12,13, 17,21].

The Minivessel dissolution system consist of a small vessel with typically working volume of 100ml, and a small size impeller in the shape of that used in USP2. However, such Minivessel dissolution apparatus and the associated dissolution method are not yet included in the USP Pharmacopeia although Section (1902) mentions that this mini paddle and Minivessel may have some utility with proper justification, qualification, documentation, and superiority to apparatus 2 standard equipment, and they may be considered for low dosage strength products. During development of the small volume method, it is important to consider that the current small or low volume vessels are non-compendial. The commercially available vessels are well defined, but there are still differences from supplier to supplier [13, 23]. It was demonstrated that differences in the actual compendia apparatuses existed between suppliers even if within the standardized dimensions and that those differences marginally affected the results [23].

In case of small volume vessels there is no currently fixed dimension between suppliers. This means that each investigation should be carry out specifically and that transfer is more complicated than using the classical pharmacopeia one-liter vessel. Small volume USP2 has gained popularity due to the reduced mass of material required, whilst retaining the analytical methodology and discriminating power of the conventional apparatus. Furthermore, the small volume apparatus may be beneficial in the development of biorelevant methods, particularly for pediatric population [11,12]

The dissolution apparatus has been modified to provide for testing in in smaller volumes of dissolution media. With the modification, physical parameters critical to the ruggedness of the dissolution must also be maintained. In the current state, the apparatus possesses individual limitations when attempting to conduct small volume dissolution, [23].

Although the Minivessel is miniaturized version of the conventional apparatus there is still a need to analyses the hydrodynamics, since the miniaturized system do not exactly replicate the conditions of the standard paddle system, nor the conditions in the GI Tract [11].

Developing literature on the Minivessel generally quite limited. This implies some important issues are still to be addressed that includes apparatus calibration, reliability, reproducibility and method validation before the apparatus can be widely accepted. In addition to understand how the dissolution test conducted in Minivessel compare to those obtain in standard USP2, [6,12-13,23]. This requires more important understanding of the dissolution rate and drug release. In the current regulatory environment, our dissolution

methods must be accurate, sensitive and specific and the reproducibility of the test method employed must be established, verified and documented [14].

Despite progress in dissolution testing, little information is available on mini vessel systems in general. More importantly, it is still unclear how dissolution data obtained during product development in such non-compendial mini vessels can be interpreted to predict how the drug product would dissolve in a compendial dissolution testing apparatus such as the USP 2 during commercial manufacturing.

Recently, a study conducted by our research group (Wang et al., 2017) has resulted in computational predictions of the operating conditions under which Minivessel should be operated in order to generate dissolution profiles that are similar to those expected in USP 2 system. However, those predictions were not supported by experimental evidence. Therefore, there is still a need to determine whether the approach proposed by Wang et al. is valid as far as being able to predict the corresponding dissolution profiles in USP 2 systems. More in general, there is the need to compare actual dissolution profiles in the two systems to establish how dissolution profiles in Minivessel compare with those in USP 2 systems. Then, by either experimentation alone, or possibly through experiments conducted according to model predictions, it may be possible to determine how Minivessel tests should be conducted to replicate results in the USP 2. The present work was conducted to partially address this question by using a simple drug product, i.e., aspirin caplets and tablets, and experimentally testing their dissolution characteristics in both the USP 2 and the Minivessel under different operating conditions.

CHAPTER 2

BACKGROUND AND OBJECTIVE OF THIS WORK

Accurate concentration of analyte and consistent agitation are primary requirements for any dissolution test. However, for small volume dissolution, the requirement for extreme precision to ensure data accuracy is also essential. The standardization of the miniaturized equipment is critical for subsequent scale-up to the standard USP 2 and for future acceptance by regulatory agencies if this method is also being used for quality control. However, before Minivessel can acquire wider acceptance the dissolution profiles that they generate must somehow be related to those obtained in the standard USP 2 systems.

The literature review above has shown that the Minivessel is a device often used to provide testing in smaller volume of dissolution medium. Given the geometric differences between the USP 2 and the Minivessel, one can expect that the dissolution profiles obtained in the Minivessel will not necessarily be comparable with those generated in the standard USP 2 setup [23]. It may be still possible to determine the operating conditions in the Minivessel (mainly the agitation speed and the characteristics of the tablet to be used in this apparatus) that can result in dissolution profiles vs. time that are similar or have strong analogy to the dissolution profiles obtained with an actual commercially-ready tablet in a USP 2. This can be achieved by conducting enough experiments in both systems under different operating conditions until dissolution profile similarity is achieved. A better approach is to have some insight into the process that can be used to provide guidance on how to conduct experiments in order to achieve similarity in dissolution profiles, and only then test experimentally the validity of this approach.

Recent work on the hydrodynamics of Minivessel and the USP 2 by our group has resulted in a detailed mapping of the velocity profiles in both systems (Wang et al., 2017). In addition, this knowledge has been used to generate predictions on what hydrodynamic conditions should be maintained in the lower portion of the two systems, i.e., in the region where the dissolving tablet is, in order to achieve similar values of the tablet-medium mass transfer coefficients. According to that work, a non-disintegrating tablet in the USP 2 and in the Minivessel should experience the same mass transfer coefficient k_{prd} if the two systems are operated at the agitation speeds N reported in Table 2.1. [26]

In general, a simple mass balances for the dissolving drug in a dissolution system, results in the following equation for the drug fractional mass released from the tablet (M_D/M_T): as in Equation 2.1 below

$$\frac{M_D}{M_T} = \frac{C V_L}{C^* V_L} = \frac{C}{C^*} = \left[1 - \exp\left(-\int_0^t \frac{k_{prd} A(t')}{V_L} dt'\right) \right]$$

Where M_D is the mass of drug released at any time t , M_T is the total mass of drug initially in the tablet, k_{prd} mass transfer coefficient if the two systems operates at agitation speeds N is the surface area of tablet presented for dissolution, V_L perfectly mixed volume of medium

Table 2.1 Predictions of the agitation speeds in a mini vessel required to achieve the same mass transfer coefficients for a salicylic acid tablet as in a USP 2 system operating at a given agitation speed (50, 75 and 100 rpm). (Wang et al., 2017).

Agitation speed in USP 2 System (rpm)	Agitation speed in Minivessel (rpm) required to achieve the same k_{prd} as in the USP 2
50	86.3
75	109.7
100	129.2

Source: Wang, B., Bredael, G. and Armenante, P. M. (2017) Prediction of the Operating Conditions for Similarity of Dissolution Performance in a Mini Vessel and a USP 2 Dissolution Testing System Using Hydrodynamic Comparison, Intern. J. Pharm., submitted and under review

In order for M_D/M_T to exhibit the same profile as a function of time in both the USP 2 and the Minivessel, the term $(k_{prd} A(t)/V_L)$ must be the same in both systems. Similarity of k_{prd} is predicted to be achieved if the two systems are operated as shown in Table 2.1 and Figure 2.1. For non-disintegrating tablet the initial ratio A/V_L is the same only if the area of the tablet in the Minivessel is appropriately scaled down with the liquid volume with respect that of the tablet in the USP 2. This could be achieved in practice by using a single (small) tablet in the Minivessel and number of tablets in the USP 2 equal to the ratio $V_{L-USP2}/V_{L-Minivessel}$. Therefore, similarity of dissolution profiles in the Minivessel and in the USP 2 is expected if non-disintegrating tablets are tested as just indicated here.

If the tablet is of the disintegrating type, then the tablet should more or less rapidly form small granules once added to the vessel and the granules may or may not reside only in the lower portion of the vessel. Therefore, similarity of dissolution profiles following this approach may not happen. Nevertheless, at least during the initial phases of the dissolution process even these tablets can be expected to generate similar dissolution profiles if the above-mentioned protocol is used.

Consequently, the objective of this work was to study experimentally the dissolution profiles both the USP 2 and the Minivessel aiming at establishing a relationship between them. Aspirin tablets were used for this purpose. Initially, large 325-mg caplets were used in order to establish baselines. Then smaller 81-mg aspirin tablets were tested following Wang et al's (2017) approach, i.e., by stirring at the agitation speeds recommended in Table 2.1 and by using the appropriate different number of tablets in the two systems to compare M_D/M_T profiles that were expected to be similar, although coming from two different systems, and despite the fact that the tablets were of the disintegrating types.

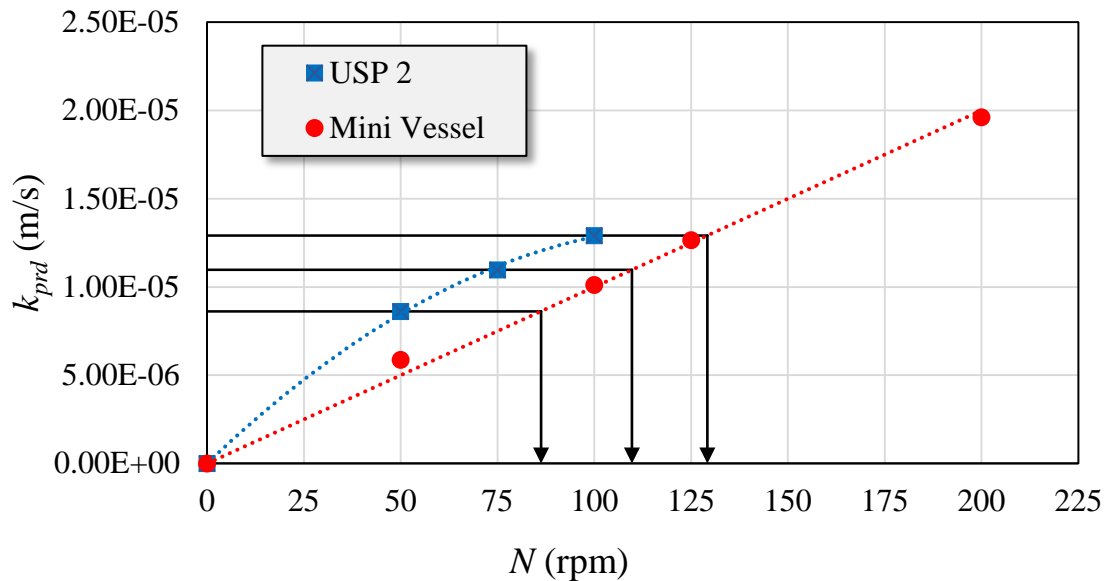


Figure 2.1 Approach proposed by Wang et al. (2017) to predict the agitation speed in a mini vessel resulting in the same mass transfer coefficient as in a USP 2 system operating at a given agitation speed. The arrows point to the agitation speeds that should be used in the mini vessel to obtain tablet-liquid mass transfer coefficients that are the same as those for the USP 2 operating at 50, 75, and 100 rpm (from left to right), respectively.

Source: Wang, B., Bredael, G. and Armenante, P. M. (2017) Prediction of the Operating Conditions for Similarity of Dissolution Performance in a Mini Vessel and a USP 2 Dissolution Testing System Using Hydrodynamic Comparison, Intern. J. Pharm., submitted and under review

CHAPTER 3

EXPERIMENTAL APPARATUS, MATERIALS AND METHOD

In this work two different types of dissolution testing apparatuses were used. They included the Standard USP-Dissolution Testing Apparatus 2, which will be referred to as the Standard System or USP 2, and the Minivessel-Minipaddle dissolution system, referred to as Minivessel.

3.1 Experimental Test Apparatuses

3.1.1 Standard Dissolution Vessel and Agitation System (USP 2)

The Standard USP 2 system consisted of a Distek 5100 bathless dissolution system (Distek Inc., North Brunswick NJ), capable of using seven unbaffled cylindrical glass dissolution vessels. Each vessel had an internal diameter, T equivalent to 100.16 mm and an overall capacity of 1 Liter, and a hemispherical bottom (Figures 3.1 and 3.2).

The agitation system consisted of a standard two-blade paddle impeller mounted on a shaft which was connected to a motor in the Distek system. Actual measurements were taken to determine the geometry of each component of the impeller using a caliper. The dimensions were as follows: shaft diameter was 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 inside bottom was 25 mm, as specified in the USP (Table 3.1; Figure 3.1).

When 900 mL of dissolution media were added to the USP 2 vessel, the liquid height, H, measured from the bottom of the vessel, was 128.8 mm, and it was 82 mm when the vessel was filled with 500 ml of media.

Table 3.1 Dimensions of impeller used in Standard USP 2 Dissolution System

Component	Dimension (mm)
Shaft Diameter	9.53
Length of Top Edge of Blade	74.10
Bottom Edge of Blade	42.00
Height of Blade	19.00
Thickness of Blade	5.00

Source: Armenante P. M, Wang: Experimental and Computational Determination of the Hydrodynamics of the Minivessel Dissolution Testing System

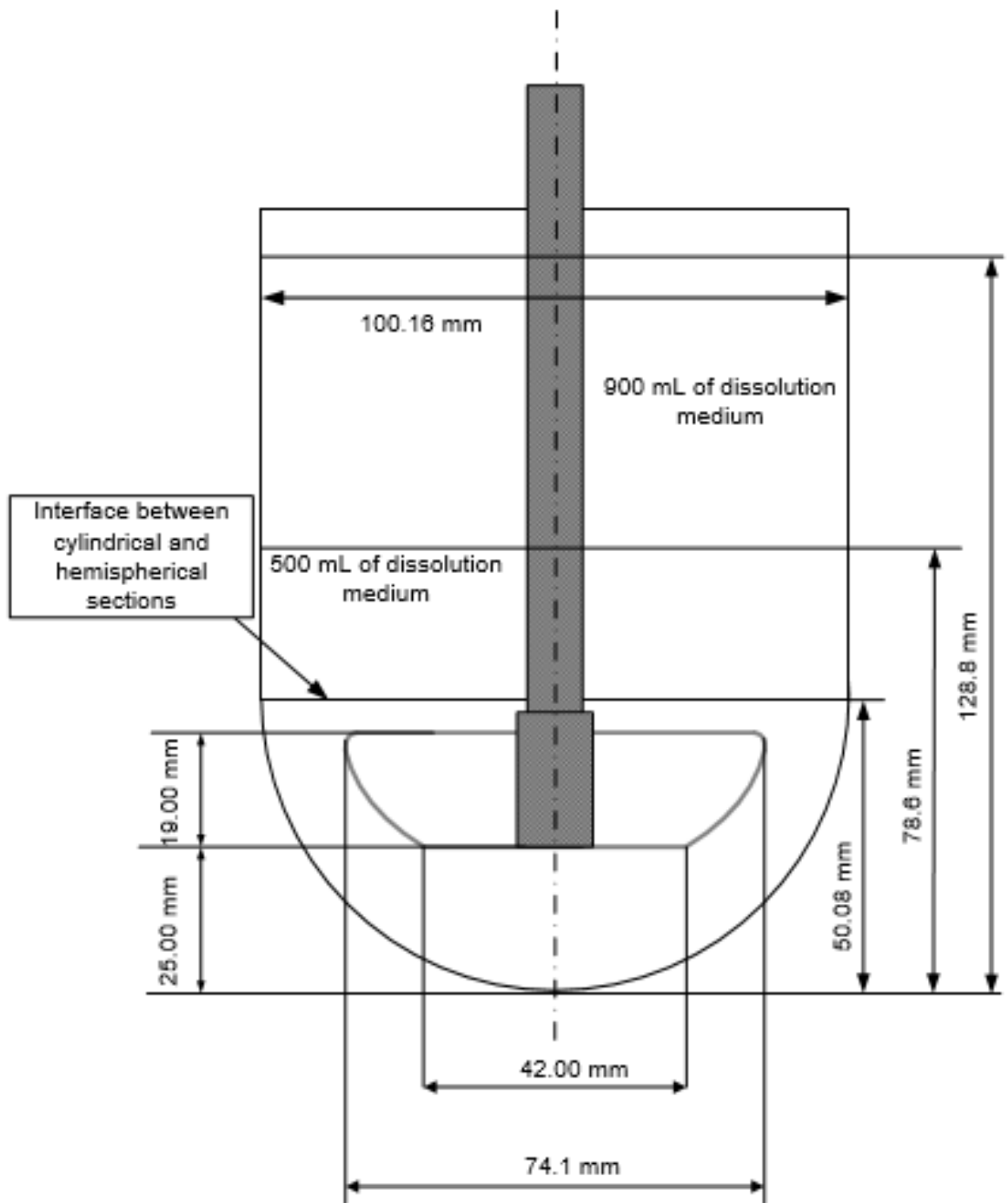


Figure 3.1 Dimensions of USP 2 dissolution testing apparatus.

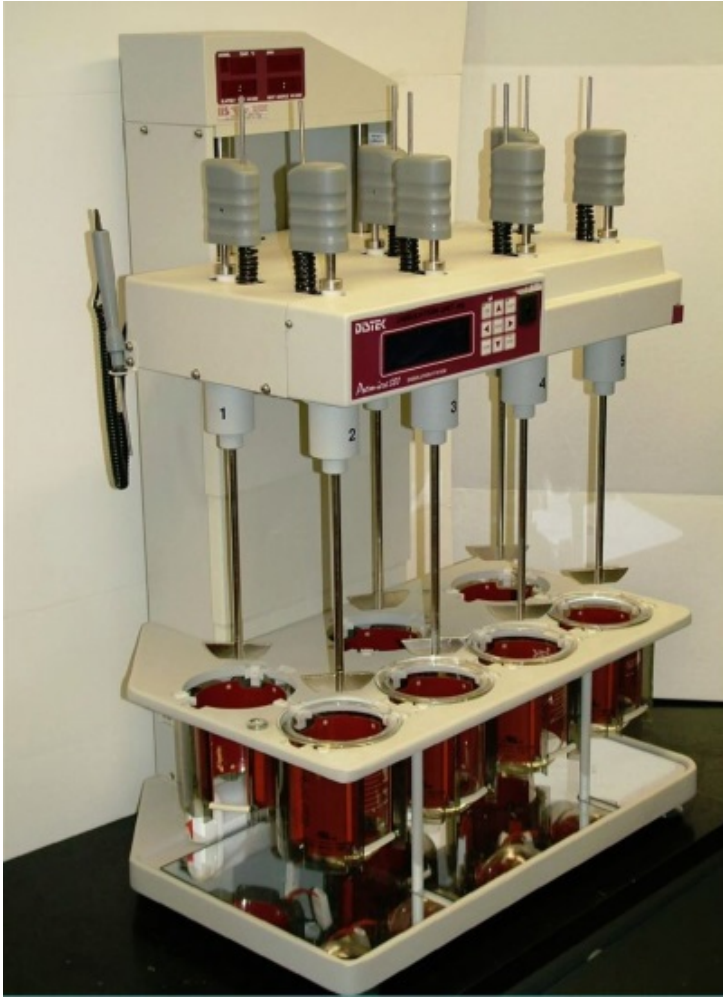


Figure 3.2 Distek Premier 5100 dissolution system used in this work.

3.1.2 Minivessel System

The Minivessel apparatus was one of the most common commercially available minivessel systems. It consisted of a small cylindrical glass vessel with a hemispherical bottom and a working volume of 100 ml, provided with a mini paddle placed centrally in the vessel (Figure 3.3). The exact dimensions of the minivessel system under investigation are given in Table 3.2 and Figure 3.4. These dimensions were obtained by direct measurement of the minivessel provided by Merck Company, Rahway, New Jersey (courtesy of Gerald

Bredael) [6]. Since the temperature in Minivessel could not be appropriately maintained with the Distek Premier 5100, a different system was used, i.e., the Distek 2100B Dissolution System. This system is similar to the Distek 5100 but is provided with a Plexiglas bath in which the Minivessel was immersed in order to keep the temperature in the Minivessel constant. The temperature in this system was maintained at the desired value by recirculating water from a thermostatic external recirculation apparatus (Digital Polystat Temperature Controller, Cole-Palmer Circulating System), as shown in Figure 3.5 and 3.6.

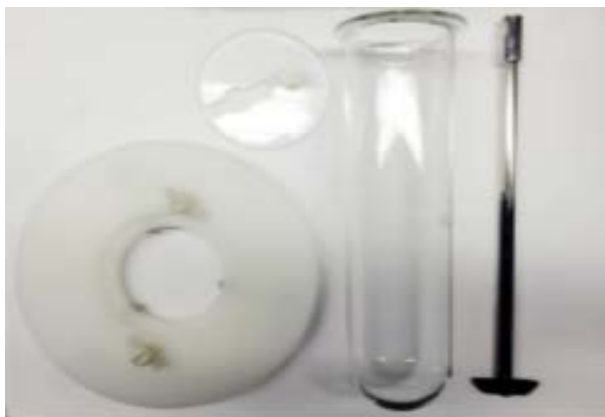


Figure 3.3 (a) Minivessel dissolution apparatus including small volume vessel, minipaddle impeller, small lid, --



Figure 3.3 (b) mounting plate to adapt minivessel to standard opening for USP2 vessel in typical dissolutin testing system.

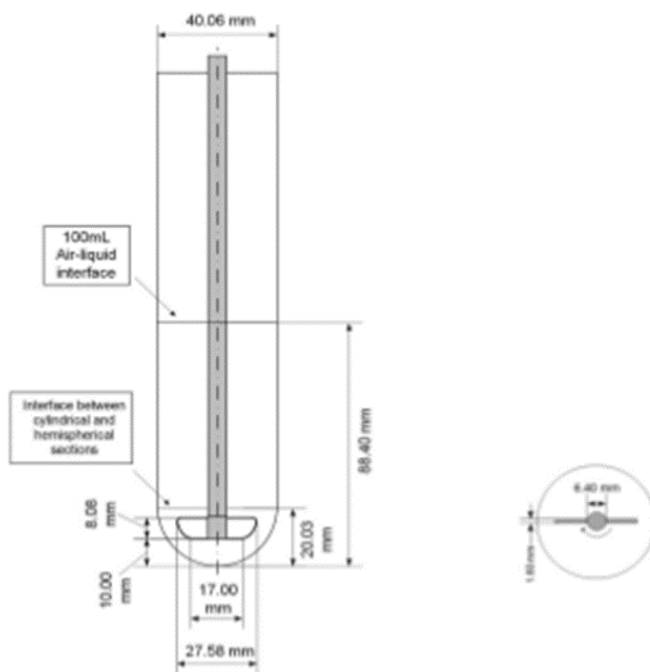


Figure 3.4 Dimensions of Minivessel used in work.

Table 3 2 Dimensions of Mini Paddle

	Dimension (mm)
Shaft Diameter	6.40
Length of Top Edge of Impeller Blade	27.58
Length of Bottom Edge Impeller Blade	17.00
Length of Impeller Blade	8.08
Thickness of Impeller Blade	1.60

Source: Armenante P. M, Wang: Experimental and Computational Determination of the Hydrodynamics of the Minivessel Dissolution Testing System



Figure 3.5. Distek 2100B Dissolution System used in this work to support the Minivessel.

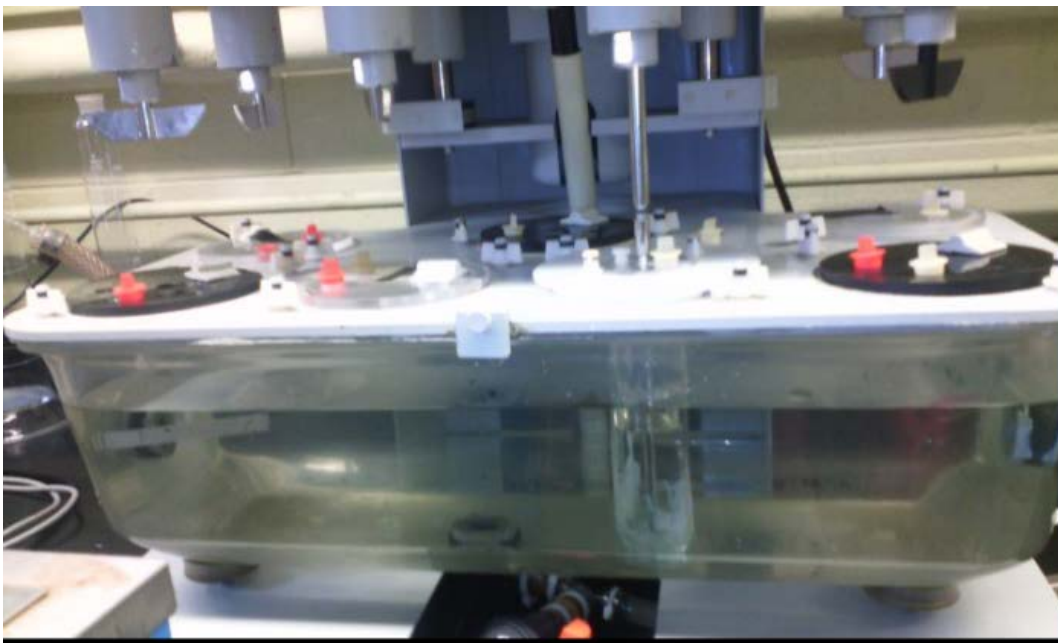


Figure 3.6 Plexiglas water bath used in this work attached to Cole Palmer Circulating System (not shown).

3.2 Experimental Materials

Dissolution studies were conducted using 325-mg enteric-coated aspirin caplets (CVS Pharmacy) and 81-mg, round, enteric-coated aspirin tablets (Bayer Enteric Coated Aspirin) as the dissolving tablets. The dimensions of the tablets were measured using a caliper. The width, length, and thickness of the 325-mg caplet were found to be 4.1 mm, 9.3 mm, and 4.0 mm, respectively. The round 81-mg tablet had a 6.5-mm diameter and a 3.0-mm thickness.

The dissolution medium for the 325-mg aspirin caplets consisted of a 0.05 M acetate buffer solution prepared by mixing 14.95 gram of sodium acetate trihydrate and 8.3 ml of glacial acetic acid with distilled water to obtain to 1-Liter solution with a pH of 4.5 +/- 0.05, as describes in the USP (32). The dissolution medium for 81-mg aspirin tablet consisted of a solution of 0.1N hydrochloric acid and 0.20 M tribasic sodium phosphate,

which was adjusted when necessary with 2 N sodium hydroxide to a pH of 6.8+/-0.05, as specified in the USP (32).

All media were degassed in the degassing apparatus shown in Figure 3.7 following the USP General test chapter on DISSOLUTION <711> based on the degassing method developed by Moore and Flanner, (1966) (2). The medium was placed in the Carboy tank which was then connected to a vacuum pump for 30 minutes, while all other valves in the system were closed. This stock solution was used in 100ml, 500ml and 900ml aliquots, as required by the experiments. Stock solutions were used as needed, i.e. 500 ml and 900ml in experiments with the USP 2 system and 100 ml in the experiments using the Minivessel dissolution testing apparatus.

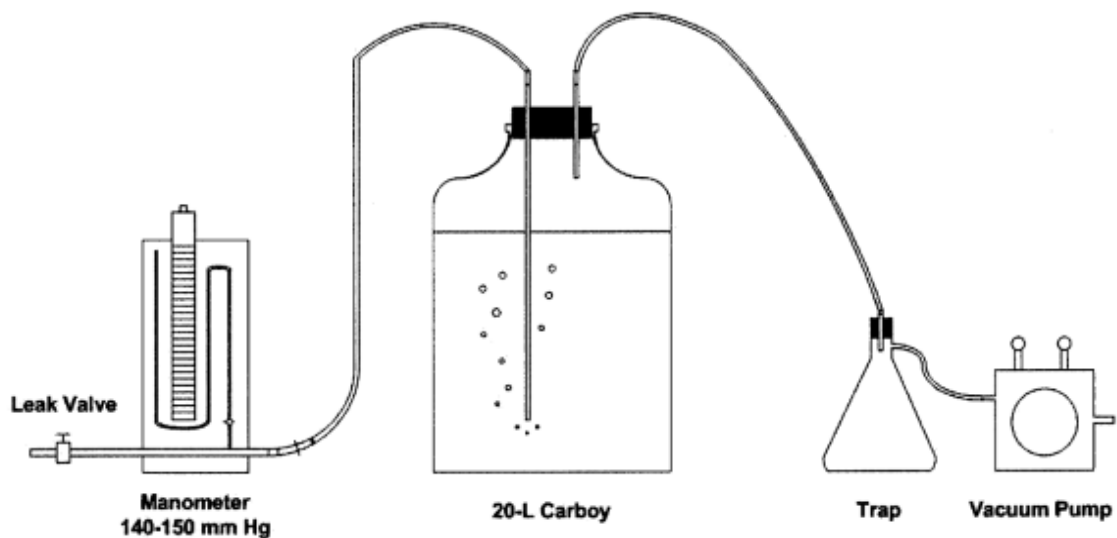


Figure 3.7 Equipment set-up used in the de-aeration process for dissolution medium.

3.3 Experimental Methods

Two testing methods were used to conduct the dissolution tests. A summary of the Operating Conditions for Dissolution Experiments is reported in Table 3.3. All experiments with both methods systems were conducted in nine replicates to determine reproducibility.

3.3.1 Method 1-USP 2

This experimental method was utilized with the USP 2. Although the Distek 5100 unit is equipped with seven standards stations, each one capable of receiving individual one-liter vessels, here only one vessel was used each time. Dissolution studies were conducted with a 325-mg full dose of aspirin as well as with approximately half dose (after splitting a tablet in two). Additionally, tests were similarly run using 81-mg aspirin tablet, with 5 such tablets at the same time (i.e., 405 mg).

Method 1 consisted of placing the vessel in the Distek 5100 dissolution unit, lowering the paddle impeller in the vessel, measuring key geometrical parameters (impeller clearance, impeller position), and adding the proper volume of medium. The previously de-aerated medium was gently poured into the vessel to minimize the introduction of air. The dissolution medium temperature was raised to 37 ± 0.05 degree centigrade and the system was allowed to equilibrate at this temperature prior to starting the experiments. The thermal inertia of the vessel caused the resulting temperature of the liquid to be 37 degrees centigrade. This medium was kept at 37 degrees centigrade throughout the dissolution experiment by the Distek 5100 temperature controller.

When the whole 325 mg tablet was used the volume of medium was 900 ml. When half caplet was used, 500-ml of medium was added. In addition, experiments were conducted in the USP 2 using 81-mg tablet, 5x81-mg tablets were used at once. In each experiment the tablet or the tablets (when using 5 at once) were dropped into the 500 ml of the medium in standard system vessels according to the USP (USP2008). Agitation speed was started as soon as the tablet(s) reached the bottom of the vessel. In all USP 2 experiments the agitation speed was kept constant, at either 50, 75 or 100 rpm, depending on the experiment.

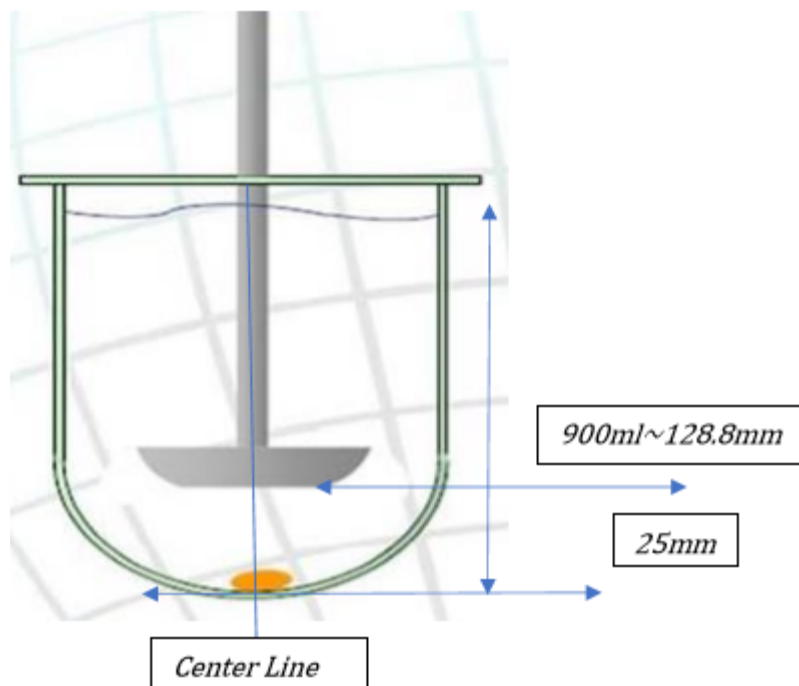


Figure 3.8 Schematic of the USP 2 dissolution vessel showing tablet position.

3.3.2 Method 2-Minivessels

Mini paddle experiments were run with half dose of the 325-mg aspirin that was used in the standard paddle apparatus. Single doses of 81 mg aspirin were used in the second set of tests. Experiments were run at stirring speeds of 50 rpm, 75rpm, 100rpm, 125 rpm and 150 rpm.

This method was used with the minivessel. The minivessel was mounted in the commercial Distek 2100 B Dissolution Testing System, using a round mounting plate with a central opening to accommodate the minivessel inside the round opening where the one-liter vessel is typically placed during a dissolution test (Figure 3.9). The mini impeller was similarly assembled on the same system by unscrewing the large apparatus 2 paddle and replacing it with the entire minipaddle impeller shaft instead. The off-bottom impeller clearance used in this work, measured from the bottom of the paddle to the bottom of the vessel was 10 mm, which, when appropriately scaled, is very close to that of the standard USP 2 system. This is the clearance commonly used in industry.

In order to maintain the dissolution temperature of the medium constant at 37 \pm 0.5 degree centigrade, water was circulated the water bath in the Distek 2100 B system using the external Cole Palmer Circulating Bath (Figure 3.6)

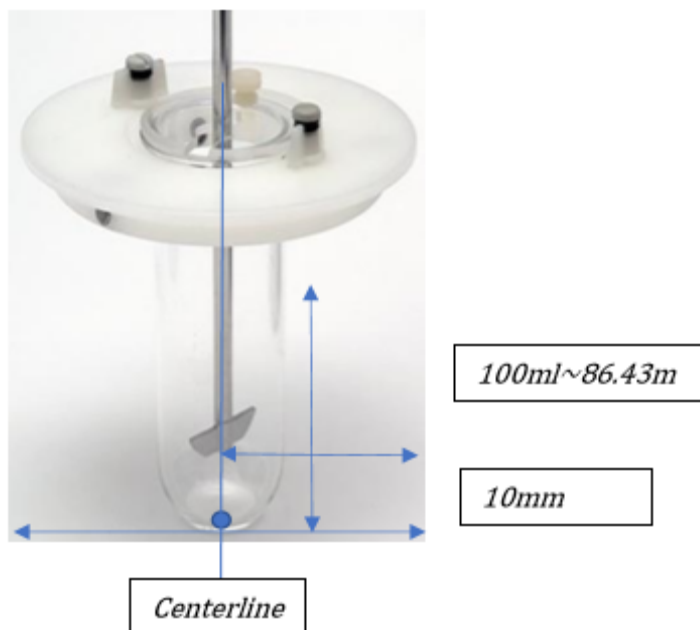


Figure 3.9 Schematic of Minivessel system showing tablet position.

The tablet was dropped into medium after the temperature of 37 degree centigrade was verified using a hand-held thermometer. When the tablet had reached the bottom of the vessel the agitation was started at the prescribed impeller speed. Experiments in the minivessel were conducted at 50, 75, 100, 125, 150 rpm, as well as at 86.3, 109.7, and 129.2 rpm (in order to verify the appropriateness of a previously developed dissolution model).

3.3.3. Sample Collection and Analysis

In both methods, the first sample was taken right after the agitation had started (defined as the zero-time). Each experiment lasted 45 minutes. The samples were taken manually, at five-minute intervals during the 45-minute period. Samples were taken with a 10-ml syringe (HSW) connected to a 2mm cannula. The volume of each sample was 10 ml for

the USP 2 experiments and 2.5 ml for the minivessel experiments. The volume of medium removed was not replaced in accordance to USP 2 procedure [2, 7,8,9].

The sampling location (where the tip of the cannula was) was midway between the impeller shaft and the vessel wall, horizontally, and midway between the top edge of the impeller and the surface of the dissolution medium vertically. This is within the sampling zone prescribed by USP. A total of ten samples were taken in each experiment.

The samples collected during the experiments with the 325-mg caplets were filtered through a Whatman filter paper #2 to remove possible solid particles that could enter the sample prior to analysis. The samples collected during all experiments with the 81-mg tablets were filtered with an in-line disposable Polypropylene 0.45 μm filters (Whatman Puradisc 25 PP) mounted at the end of the cannula, and later with an in-line 10 μm polypropylene filter (Distek) mounted in a small Teflon housing in the cannula.

For all samples collected in the USP 2 experiments, the first 2 ml of the 10-ml sample were discarded, and the remaining 8 ml were filtered and transferred to a vial until analyzed. The samples collected in the Minivessel experiments were filtered and used as such.

Sample analysis to determine the aspirin concentration in the sample was carried out using a 1-cm quartz cell placed in an ultraviolet (UV) visible spectrophotometer (Cole-Palmer S2100+ Series). The absorbance of the drawn samples was measured at the specified wavelength of 265-nm for aspirin. The quartz cell was rinsed twice with the same solutions, and cleaned before it was placed in the spectrophotometer.

Table 3.3 Operating Conditions for the Dissolution Experiments

Dose	325mg (CVS Coated Aspirin) 81mg (Bayer Enteric Coated Aspirin)
Medium	500ml, 900 ml De-Aerated Acetate Buffer 500ml, De-Aerate (0.1NHCL+Tribasic Phosphate Buffer.) 100ml De-Aerated Sodium Acetate Buffer 100ml De-Aerated (0.1NHCL +Tribasic Phosphate Buffer)
Temperature	37 Degrees Centigrade
Agitation Speed	USP2 - 50 rpm, 75rpm,100 rpm Mini vessel 50 rpm, 75 rpm 100 rpm,125 rpm 150 rpm, and also 86.3, 109.7, and 129.2 rpm
Filter	Polypropylene 0.45 μ m filters (Whatman Puradisc 25 PP) Whatman Filter Paper #2 10 μ m propylene filter (Distek)
Ultraviolet Wavelength	265nm
Sampling Time	5minute interval; Total 45minutes

Calibration curves were generated from reference standard aspirin solutions (using the appropriate medium for each) for the 325-mg coated caplets and 81-mg enteric coated tablets, and diluting them with the appropriate aspirin dissolution medium to obtain solutions of known concentrations. The absorbance of solutions of known aspirin concentrations was obtained to generate absorbance vs. concentration standard curves, as reported in Table 3.4 and Table 3.5. The calibration curves were found to be linear in concentration ranges of interest here ($R^2=1$ and $R^2=0.999$, respectively). The aspirin

concentration in a given sample was obtained by entering the absorbance value in the appropriate calibration curve.

Table 3.4 Calibration Data for 325mg Aspirin Caplets

Concentration (mg/ml)	Absorbance 1(nm)	Absorbance 2(nm)	Average Absorbance(nm)
0.146	0.499	0.451	0.450
0.286	0.861	0.854	0.858
0.429	1.288	1.289	1.289
0.572	1.706	1.710	1.708
0.715	2.130	2.126	2.128
0.858	2.548	2.542	2.545
1.00	2.968	2.965	2.967

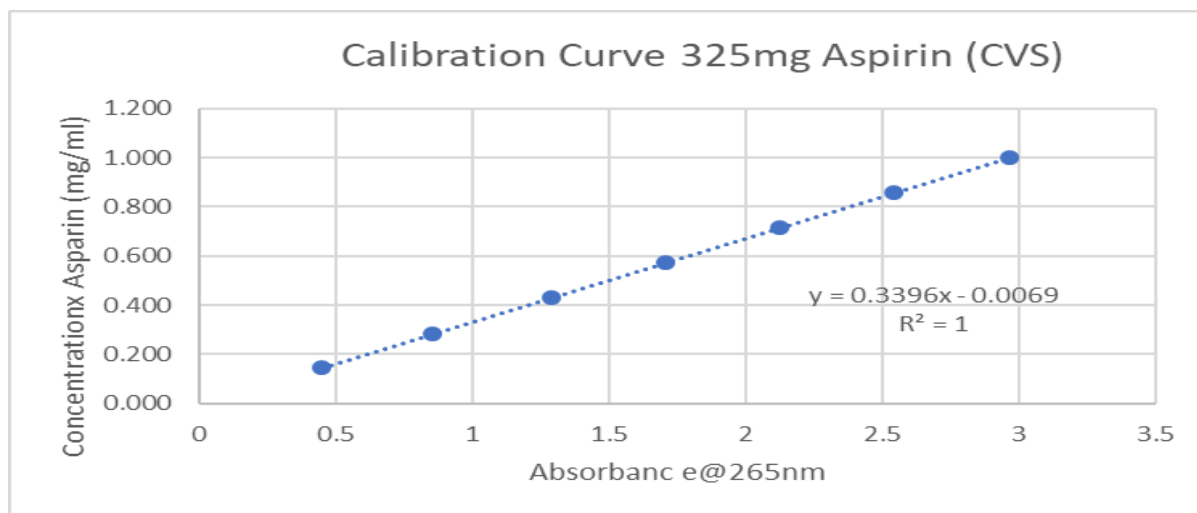


Figure 3.10 Calibration Curve for 325mg Aspirin tablets. (CVS).

Table 3.5 Calibration Data 8 mg Aspirin Tablets

Concentration (mg/ml)	Absorbance1 (nm)	Absorbance 2(nm)	Average Absorbance (nm)
0.0081	0.089	0.088	0.089
0.0162	0.116	0.117	0.117
0.0243	0.139	0.138	0.139
0.0324	0.166	0.166	0.166
0.0495	0.192	0.192	0.192
0.0486	0.214	0.215	0.215
0.0567	0.236	0.235	0.236
0.0648	0.265	0.264	0.265

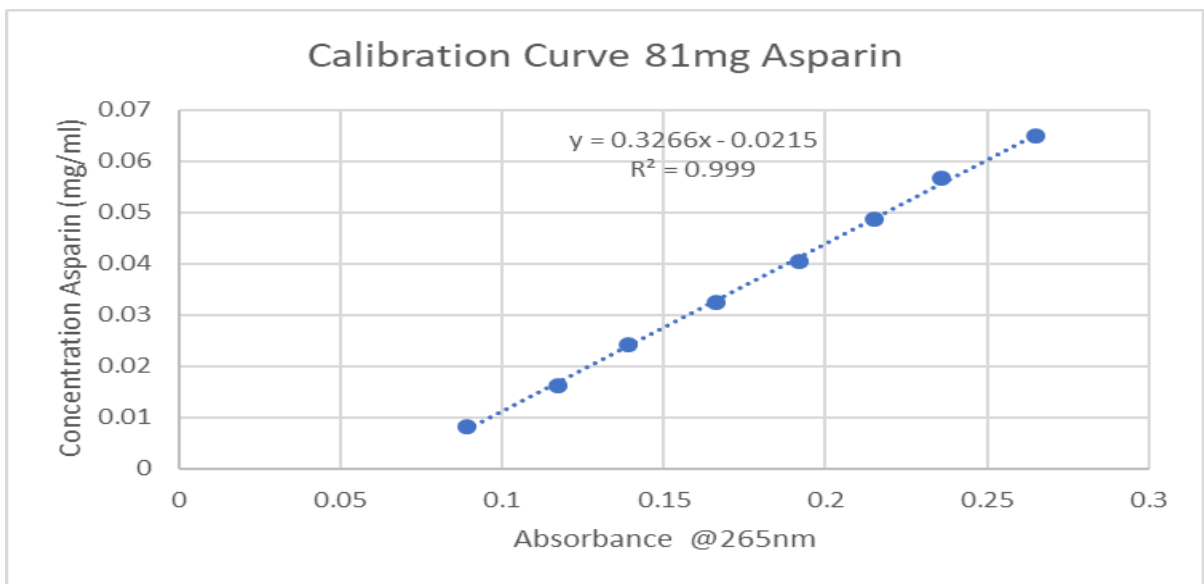


Figure 3.11 Calibration Curve for 81-mg Aspirin Tablets.

3.4 Data Analysis

3.4.1 Calculation of the Fractional Drug Mass Released During Dissolution from Experimental Data

The drug concentrations were used to calculate the total mass of drug released in the medium during the experiments. In this work, the dissolution profile is represented as a cumulative percentage of the amount of drug released at each sampling time. The amounts of drug released at each time are presented in terms of drug release fraction, M_D/M_T , i.e., the mass of released drug in the dissolution medium at any time t divided by the total mass of the drug initially in the tablet.

The absorbance data were obtained from the spectrophotometric analysis. Then the method described below utilizes the concentration of aspirin in the dissolution medium at any given time (C_j in mg/mL), and then transforms it into fraction of drug mass released from the tablet (M_D/M_T) using the equations 3.1 and 3.2 to account for the drug mass removed with each sample, [18].

$$\frac{m_D(t_1)}{m_T} = \frac{C_1}{C^*} \quad \text{for } j=1 \quad (3.1)$$

$$\frac{m_D(t_j)}{m_T} = \frac{C_j}{C^*} \left[1 - (j-1) \frac{\Delta V}{V} \right] + \frac{\Delta V}{V} \sum_{k=1}^{j-1} C_k \quad \text{for } 2 \leq j \leq n \quad (3.2)$$

where j is an index identifying the sample number ($j=1, 2, \dots, 10$); $m_D(t_j)$ is the mass of released salicylic acid at time t_j ; m_T is the total mass of the salicylic acid initially in the

tablet; C_j is the dissolved aspirin concentration in the j^{th} sample; C^* is the concentration of the aspirin when the tablet is fully dissolved in a specific dissolution volume (500ml or 900ml for the USP2 and 100ml in the minivessel). ΔV is the sampling volume (10ml or 2.5 ml), V is the initial volume of dissolution, (500ml,900 ml, or 100ml). At the beginning of the experiment when ($t=t_1=0$) minutes, the first sample was taken immediately at ($j=1$) resulting in a concentration C_1 .

The dissolution profiles obtained from dissolving the tablet in the standard dissolution apparatus and the minivessel setup were compared to determine whether these dissolution curves were statistically similar or not. A model-independent approach that produces a single value from a dissolution profile providing direct comparison of the dissolution data was employed. Consequently, the results do not depend on the choice of specific parameters for fitting data, but on the chosen sampling time t_i , ($i=1$ n) in the calculation. Model independent approaches include ratio tests and fit factors, [5,9,10].

The fit factor approach is that recommended by the FDA to quantify the similarity/difference of the two dissolution profiles. This approach includes a difference factor f_1 and a similarity factor f_2 . The difference factor f_1 calculates the percentage difference between the two curves at each point and measures the percentage error between them over all time points, which is given by equation 3.3.

$$f_1 = \frac{\sum_{i=1}^n |R_i - T_i|}{\sum_{i=1}^n R_i} \times 100 \quad (3.3)$$

where R_i is the reference assay time t and T_i is the test assay at the same time, and n is the number of points respectively at each sample point, j . The higher f_1 (which can be in the

range of 0 to 100), the higher the average difference between the reference and test curve is [9,10].

The similarity factor f_2 (9,10) is a logarithmic reciprocal square root transformation of the sum of squared errors of differences between the test and product dissolution profiles over all time points and is a measurement of the similarity between the two test methods by comparing the drug release profile as shown in equation 3.4.

$$f_2 = 50 \log_{10} \left\{ \left[1 + \left(\frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right)^{0.5} \times 100 \right] \right\} \quad (3.4)$$

where n is the number of sampling points, Σ is the summation of all time points and R_t and T_t are the cumulative percentage dissolved at each of the selected time point of the reference and test product respectively. When two profiles are identical $f_2 = 100$, and with an average difference of 10 percent at all measured time the result is a f_2 value of 50.

The higher the f_2 value (which can be in the range - ∞ to 100), the lower the average difference between the reference and the test curve is, [5]. Public Standards have been set by the Food and Drug Administration, (FDA) for f_1 and f_2 factors. Accordingly, statistical similarity between the two curves being compared requires that $0 < f_1 < 15$, and $50 < f_2 < 100$ [4-5,9].

In general, comparison of dissolution profile is intended to compare the results of different batches of product to ensure batch-to-batch conformity, product quality after scaling up or post approval changes (SUPAC) or company release rates for different strength of products for biowaiver purposes. However, the principle can be applied any

time a profile comparison is needed [12,15]. During the last decade f_2 calculation has been a recommended method in several FDA Guidance [12,14-15].

3.4.2 Determination of the Tablet-Medium Mass transfer Coefficient from Experimental Dissolution Data

For a dissolution process in which a non-disintegrating tablet slowly erodes as a result of dissolution, it is possible to extract the tablet-liquid mass transfer coefficient from the experimental dissolution data. This is achievable by rearranging, and integrating the basic mass transfer equation. The dissolution of chemical species from the surfaces of a tablet into the adjacent fluid such as dissolution medium can be expressed as [24]:

$$dC/dt = kA/V_L(C_s - C) \quad (3.5)$$

where C is the drug concentration in the dissolution medium, C_s is the solubility concentration of the drug, k is the mass transfer coefficient, A is the tablet surface area exposed to the dissolution medium, and V_L is the liquid volume, and is liquid bulk is assumed to be well mixed. The primary objective is to determine the mass transfer coefficient k using the experimental data:

$$k = V_L/A(C_s - C) dC/dt \quad (3.6)$$

As time progresses and the tablet erodes, the surface area is reduced. The tablet under investigation has a defined height-to-diameter ratio β . Even though it is circular as it erodes it can be assumed that it will maintain this height to diameter ratio during the dissolution process. This assumption is considered as reasonable if the mass transfer coefficient is similar on all exposed sides. Then A can be calculated by knowing the ratio

$$\beta = h_t/d_t \quad (3.7)$$

where h_t and d_t are the height and diameter respectively of the tablet. For the case of the 81mg aspirin h_t and d_t were 3mm and 6.5mm, respectively, giving a β value of 0.462. If only the top and side surface of the are exposed to the dissolution medium, the interfacial area available for mass transfer can be expressed as

$$A = \frac{\pi d_T^2 (1+4\beta)}{4} \quad (3.8)$$

From a mass balance for the drug disappearing from the tablet and appearing in the dissolution medium it must be at any time that:

$$C = \frac{\rho_T (V_{TO} - V_T)}{V_L} + C_0 \quad (3.9)$$

Where ρ_T , V_{TO} and V_T are, respectively, the density, initial volume and volume at time t of the tablet, and C_0 is the initial concentration of the drug in the dissolution medium (which is zero in this work). The volume of the tablet is given by:

$$V_T = h_T \frac{\pi d_T^2}{4} = \beta \frac{\pi d_T^3}{4} \quad (3.10)$$

When this equation is substituted in equation 7, one can obtain the tablet diameter as the tablet dissolves and C increases:

$$d_T = \left[d_{TO}^3 - \frac{4(C-C_0)V_L}{\pi\beta\rho_T} \right]^{1/3} \quad (3.11)$$

Substituting this equation into equation 6 gives an expression for A as a function of C :

$$A(C) = \frac{\pi \left[d_{TO}^3 - \frac{4(C-C_0)V_L}{\pi\beta\rho_T} \right]^{2/3} (1+4\beta)}{4\pi\beta\rho_T} \quad (3.12)$$

An estimation of the mass transfer coefficient k , assumed to be independent of time and varying tablet volume, can be obtained by substituting this expression for A in equation 4 and integrating it. The result is:

$$k = \frac{1}{tV_L} \int_{C_0}^{C_t} \pi \left[d_{T0}^3 - \frac{4(C - C_0)V_L}{\pi \beta \rho_T} \right]^{2/3} \left(\frac{1 + 4\beta}{4} \right) \left(\frac{1}{C_s - C} \right) dC \quad (3.13)$$

where C_t is the drug concentration in the dissolution medium at time t . Since experimental data of C_c versus t are available this equation can be used to calculate k by numerical integration, for the case of 81mg aspirin since these tablets were not broken.

CHAPTER 4.

RESULTS

4.1 Results for In-Vitro Dissolution Tests with 325-mg Coated Aspirin Caplet and with Half Caplets

The results for the dissolution tests conducted using Method #1 (USP2 or Standard Dissolution System) and Method # 2 (Minivessel Dissolution System) when both the 325-mg tablet were used are presented in this section. To check whether the drug release rate for the test formulation was influenced by different stirring speeds, dissolution profiles were generated using both the USP 2 and the minivessel dissolution systems.

The dissolution profiles for the 325-mg full dose aspirin caplets are presented in figure 4.1 for the USP. Figures 4.2 also demonstrate the dissolution profile for the half dose 325mg aspirin at the agitations speeds of 75 and 100rpm both at an operating volume of 500 ml and 4.3 for the Minivessel for the case in which only half caplet was used. The results are presented in terms of (M_D/M_T) , the ratio of the mass of drugs in solution at any time relative to the total initial amount of drug in the tablet, obtained with the 325mg caplet in both the USP 2 in case and with half caplet for the minivessel case. These figures show how the dissolution profiles vary with agitation speed. In the standard system, all curves began at the same initial mass ratio ($M_D/M_T = 0$) but then independently diverged with time, displaying an increasing release rate with time, as one would expect.

The dissolution profile for full dose 325mg tablet in Figure 4.1 showed 3 different drug release steps. The initial step occurred between 0-5 minutes, where the largest amount.

of drug was release, approximately 80%. Between 5 and 15 minutes another 20% was released, the system approached saturation thereafter and plateaued.

Examination Figure 4.2. with the curves for the half dose, 50 rpm curve showed that the drug release at 5 minutes was $M_D/M_T=48\%$. There was a gradual increase in the amount of drug released up to the 35-minute mark. The curve then plateaued at $M_D/M_T=97\%$ for the final 15 minutes. The curve for the half dose 100- rpm showed the most significant release rate: at 5 minutes $M_D/M_T=90\%$ and the amount of drug released increased to $M_D/M_T=115\%$ at 10 minutes and then fluctuated for the next 20 minutes and then settled to $M_D/M_T=110\%$ This value was indicative of 4.066 standard deviation from the average weight used in analysis.

The release rates at the agitation speeds remained distinct throughout the dissolution process. In addition, the f_1 and f_2 values quantifying the significant difference or similarity/between the dissolution curves can be seen in Table 4. 1.. In this table the baseline was the 100 rpm value. Clearly, visual observation showed that the profiles exhibit different release rate, higher agitation rate guaranteed higher release, and consistent results were obtainable with half dose in this regime.

The dissolution profiles for the 325mg aspirin using half caplet in the minivessel are presented in Figure 4. 3.. There is a significant similarity between the dissolution profile for the tablet dissolved at 100 rpm, 125 rpm, and 150 rpm. These curves are however different from those representing dissolution obtained at the lower agitation speeds of 50 rpm and 75 rpm, which remained distinct and separate throughout the dissolution process. As before, all five curves began at $M_D/M_T=0$, but diverged with time. At 5 minutes the dissolved fraction for the three upper impeller speeds increased nearly simultaneously to

$M_D/M_T = 45\%$ and then at 10 minutes they had an identical value ($M_D/M_T = 62\%$). Then the curves coalesced, plateaued and stay at that value from 10 to 45 minutes since the solution had then reached saturation, given the large amount of drug and the small liquid volume.

The release rates of the 50 rpm, and 75 rpm were much slower, and at 5 minutes they were at $M_D/M_T = 10\%$, and $M_D/M_T = 20\%$, respectively. These curves stayed distinct and separate throughout the dissolution process and plateaued at 30 minutes at values of $M_D/M_T = 45\%$ and $M_D/M_T = 55\%$ respectively.

For each agitation speed, the corresponding f_1 and f_2 values of replicated experiment, shown in Table 4.3., quantified the similarity/difference and showed good agreement ($f_2 > 50$, and $f_1 < 15$ as per FDA recommendations [5,10]).

Figure 4.4. compares the dissolution profile from both systems. Clearly, there is no similarity seen among the curves in both systems. This demonstrates the unsuitability of minivessel to replicate the drug release process for dosage forms that are routinely used in the USP 2 and are not of low dosage. Saturation was approached as early as 15 minutes in the minivessel operating at the higher agitation speeds, and corresponded to an M_D/M_T ratio of about 60%.

No coning was seen in the minivessel or the standard system for the full dose and half dose 325 mg aspirin at any agitation speed. The experiment results were always within 1% as quantified by the average coefficient of variation for each experiment.

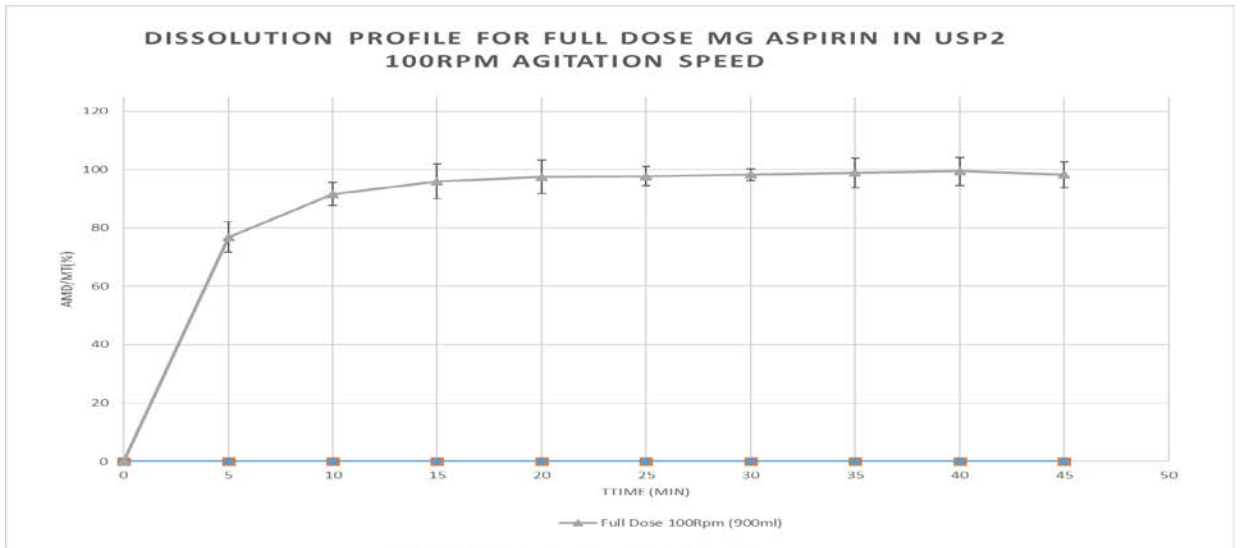


Figure 4.1 Dissolution profiles for Full Dose 325mg Aspirin at a agitation speeds of 100rpm USP 2 ($V_L=900$ ml).

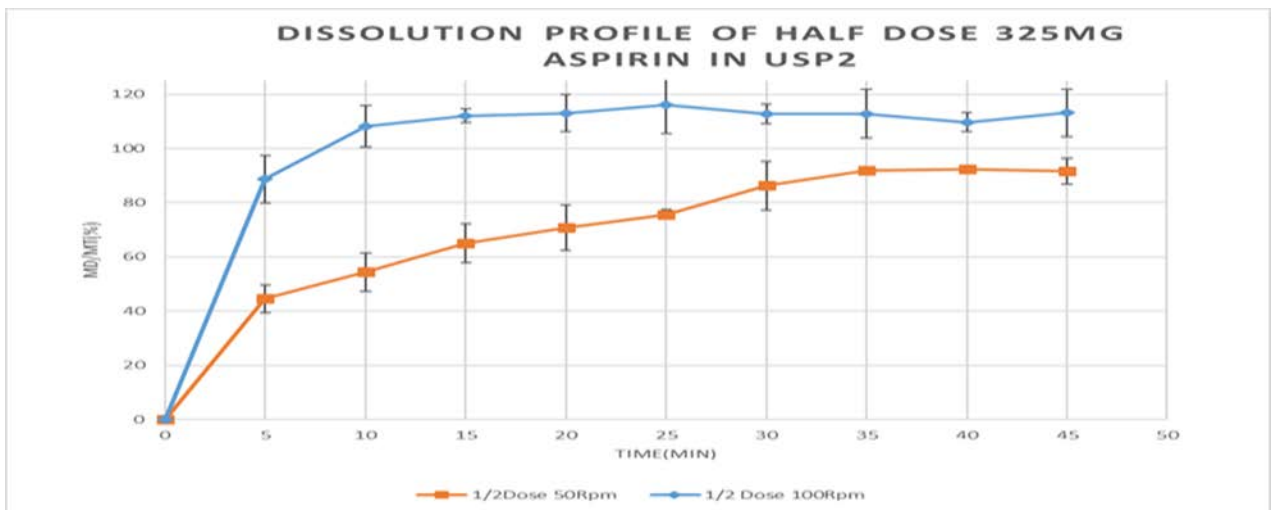


Figure 4.2 Dissolution profiles for Half Dose 325mg Aspirin at two agitation speeds USP 2 ($V_L=500$ ml).

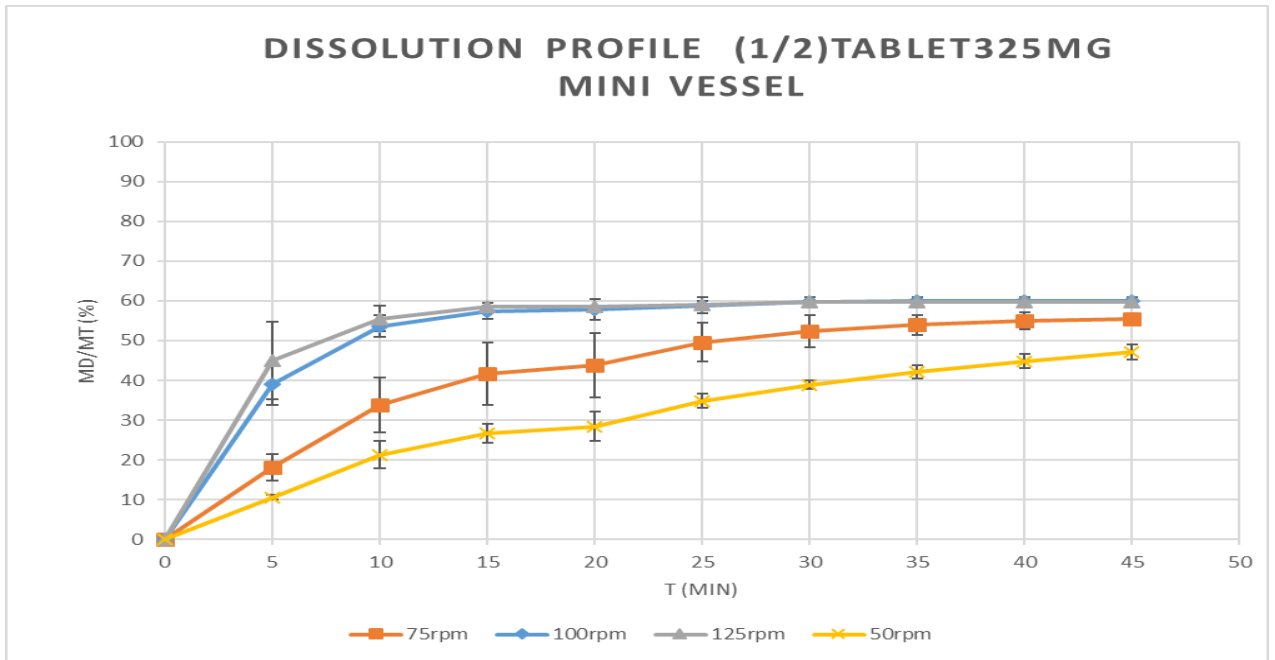


Figure 4.3 Dissolution profiles for 325mg Aspirin Half Dose at mixing speeds, (50- rpm, 75 rpm, 100 rpm, 125 rpm) in minivessel ($V_L=100\text{ml}$).

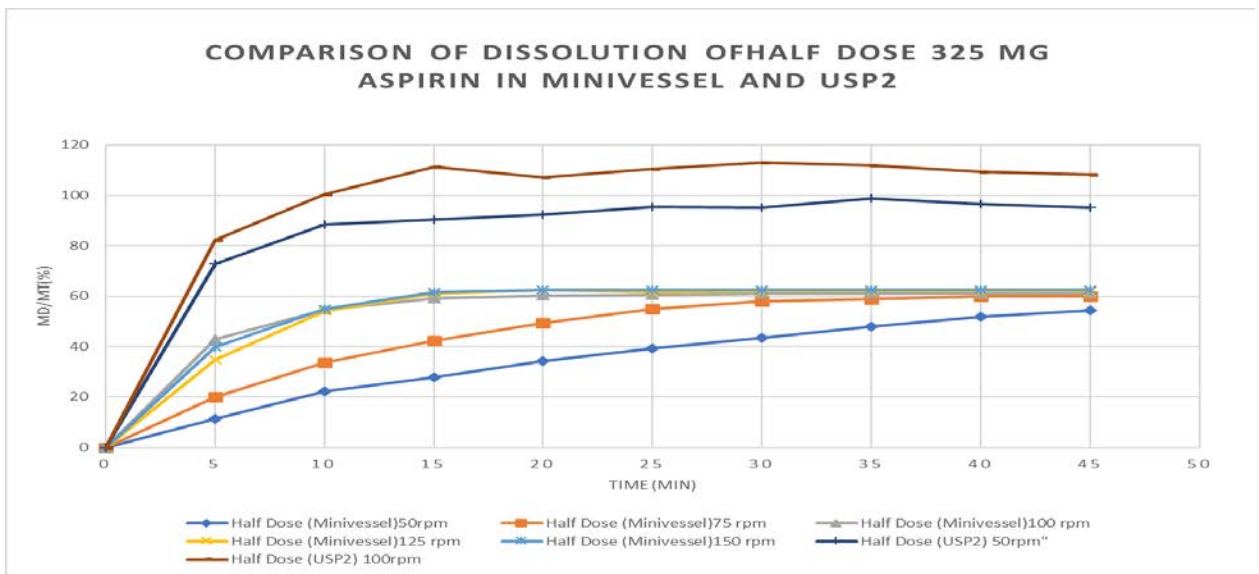


Figure 4.4 Dissolution profiles for Half Dose 325 mg Aspirin in USP 2 ($V_L=500\text{ml}$) and Minivessel Apparatus ($V_L. =100\text{ml}$).

Table 4.1 f_1 and f_2 values for dissolution profiles of 325mg Aspirin Caplet-Half Dose in the USP 2 at different mixing speeds

Rotational Speed (rpm)	Dosage	Run Number	Difference Factor f_1	Similarity Factor f_2
50	Half Dose	1	-	-
		2	7.583	61.279
		3	9.247	55.519
100	Half Dose	1	-	-
		2	3.125	74.608
		3	8.1239	53.563
100	Full Dose	1	-	-
		2	3.125	74.608
		3	8.1239	53.563

Table 4.2 f_1 and f_2 values for dissolution profiles of 325mg Aspirin Caplet-Half Dose in minivessel system at different agitation speeds. The 100-rpm was used as the baseline value

Impeller Speed (rpm)	Dosage	Run Number	Difference Factor f_1	Similarity Factor f_2
50	Half Dose	1	-	-
		2	8.181	67.910
		3	13.910	78.460
75	Half Dose	1	-	-
		2	1.5426	90.961
		3	6.5187	75.962
100	Half Dose	1	-	-
		2	2.5887	82.052
		3	4.4011	75.962
125	Half Dose	1	-	-
		2	3.834	74.910
		3	6.1468	65.292
150	Half Dose	1	-	-
		2	1.6052	84.432
		3	2.701	85.618

4.2 Results for Invitro-Dissolution Test For 81-mg Enteric Coated Aspirin

The Results for the Dissolution Test conducted with the 81-mg tablets using Method #1, (Standard Dissolution System) and Method # 2 (Minivessel Dissolution System) are presented in this section. To check whether the drug release rate for the test formulation was influenced by different stirring speeds, dissolution profiles were generated with the standard system and the minivessel dissolution system. The dissolution profiles of aspirin tablet are presented in Figures 4.5 and 4.6. for the USP 2 and FiguresS 4.7 and 4.8 for the Minivessel. A comparison of the dissolution rates in both systems are shown in Figures 4.9 to 4.14. The results are presented in terms of (M_D/M_T), the ratio of the amount of drugs in solution at a generic time relative to the total initial amount of drug in the tablet, obtained when the 81-mg tablet is completely dissolved. These figures show that the dissolution profiles vary with different mixing speeds.

4.2.1 Dissolution Results for the USP 2 Using a Single 81-mg Aspirin Tablet and 5 Doses of the 81-mg Aspirin Tablets

The dissolution curves in Figure 4.5 describes the dissolution profiles with a single 81-mg aspirin tablet at an agitation speed of 100 rpm, operating at a volume of 500-ml (as specified in the USP). while Figure 4.6. shows the dissolution profiles with 5x81-mg aspirin tablets at 50 rpm, 75 rpm and 100 rpm, also operating at volume of 500ml.

The 100rpm single dose profile showed three distinct stages of drug release a 80 % dissolution release was observed during the initial step at 20 minutes,during the second stage $M_D/M_T=25%$,more of the drug was dissolved to produce adissolution of 105% where

the curve plateaued .This curve showed the most vigorous dissolution rate but the least reproducible results.

The curves in Figure 4.6. show similar values up to 5 minutes, but then diverge thereafter ..They differed in both shape and profile , requiring different times to plateau.All curves in Figure 4.6. showed distinct stages in their release rate. During the first 5 minutes the 5-dose, 100- rpm standard curve showed a release amount of $M_D/M_T=10\%$. The greatest percentage of the drug dissolved in the shortest time was at 100 rpm, with 5 doses ($M_D/M_T=50\%$) and it occurred between 5 and 10 minutes to reach 60% dissolution; 19% more drug dissolved at $t=15$ minutes to reaching $M_D/M_T=79\%$. At 20 minutes the dissolution rate was $M_D/M_T=85\%$ the curve then plateaued at 94% at 45 minutes.The 75-rpm, 5-dose profile showed the highest amount of drug release between 5and 10 minutes and between 10 and 15 minutes .Dissolution during these two steps were $M_D/M_T=27\%$ and $M_D/M_T=23\%$ respectively. The drug released progressively increased to 80% at 30 minutes then the curve increased slightly ,remained constant at 35, and 40 minutes and increased slightly at 45 minutes.

As for the 5-dose 50-rpm dissolution curve, at 5 minutes the dissolution amount was $M_D/M_T=5\%$ and increased gradually up to $M_D/M_T=70\%$ at 45 minutes. This release rate did not comply with the dissolution specification stated in the USP that after 45 minutes $M_D/M_T=85\%$ of the drug should be released ,the other profiles suggested a greater compliance [3,4].

The standard deviations among replicate curves were low with a maximum value ranging from a maximum of 2.73 to a minimum of 0.93. The results for the f_2 values in Table 4.2.0 show that the curves at any given agitation speed are reproducible. Coning

was observed during the dissolution of the 5-dose, 50-rpm tablets, and the 5-dose 75-rpm tablets, but was not observed at 100 rpm.

4.2.2 Dissolution Results for the Minivessel Using a Single 81-mg Aspirin

Tablet

Figures 4.7 and 4.8 show the averaged dissolution profile for a single 81-mg aspirin in the minivessel at different agitation speeds. Figures 4.9. to 4.14. compare the dissolution profiles of 81mg aspirin in both the standard USP2 and the Minivessel. Examination of Figures 4.7 and 4.8. showed that the initial dissolution started at $M_D/M_T=0$ for all curves and became increasingly distinct as they reached the 5 minute mark. Here they diverged with time depending on the agitation speed. The curves describing the dissolution at 125 rpm and 150 rpm remained close and became undistinguishable at 25 minutes. The 100 rpm curve showed a similar profile but a slower dissolution rate.

The 50 rpm and 75 rpm curves converged up to $t=10$ minutes where the amount was identical at $M_D/M_T=30\%$. The curves then diverged into two separate profiles with slightly similar shape but different drug release rate. The curves showed a consistent 10% difference between them as they gradually progressed up to 30 minutes when they plateaued at 55% and 65% respectively.

The curves for the 125 rpm and 150 rpm agitation speeds showed three stages in their release rate. The greatest percentage of drug dissolved occurred in the second step between 5 and 10 minutes at agitation speeds of 125 rpm and 150 rpm. Approximately 55%, and 60% of the drug were dissolved in 5 minutes, respectively. The 150-rpm profile

showed that between 10 and 15 minutes 15% more of the drug dissolved, bringing the total percentage of drug dissolved at this time to around 80% and remaining at this value for the next 5 minutes up to the 20 minute mark. There was a further increase by approximately 18% to reach 98%, where the curve plateaued. At 125-rpm agitation speed the curve reached the 80% drug release at 30 minutes, fluctuated below this value at 35 minutes but re-emerged at this 80% value at 40 to 45 minutes. Table 4.3 shows consistent similarity between replicated experiments at each speed.

Figure 4.9. shows the profiles for the USP 2 system with 500ml at 50 rpm using five doses of 81mg aspirin tablets and the results for the minivessel at agitation speeds of 50 rpm and 75 rpm and the predicted speed of 86.3 rpm. The profiles at both impeller speeds of 75 rpm, and 50 rpm in the minivessel showed a somewhat similar profile to the 50 rpm 5-dose in the USP 2. However, the 86.3 rpm profile with minivessel showed a greater similarity to the 5-dose 50 rpm profile in the USP 2, as also evidenced by the f_1 and f_2 values in Table 4.4.. Coning was observed in the minivessel at 50 rpm and at both 50 rpm and 75 rpm in the standard system.

Figure 4.10. shows that the profile for the 5-dose, 75-rpm, 500-ml in the USP 2 were similar to those at agitation speeds of 100 rpm and 109.7 rpm in the minivessel system, but not similar at 75 rpm in the minivessel. This was particularly evident in the early stages of dissolution between 0 and 25 minutes. Coning was observed at 75 rpm in the USP 2.

Figure 4.11. demonstrated the ability of the minivessel operating at 125 rpm, 150 rpm to produce a drug release profile similar to the 5-dose 100-rpm, 500-ml in the USP 2. The 125 rpm curve however showed an even closer relationship. The 100 rpm curve, from

the minivessels was also observed to generated a similar profile to the 125rpm curve, but with a lower drug release than in the other curves.

Figure 4.12. presents the profiles for the 5-dose, 100-rpm case in the standard system and the profile produce in the minivessel system operating at athe motion speeds of 125 rpm,129.2 rpm,and 150 rpm. The profiles are all very similar.

Figure 4.13 and 4.14. show a comparison between the dissolution profiles for 5-dose 81-mg aspirin tablets in the USP 2 at different standard agitations speeds (50, 75, and 100 rpm) and the corresponding profiles for a single-dose 81-mg aspirin tablet in the minivessel at the agitation speeds that were predicted by Wang et al. (2017) to generate similar mass transfer coefficients (86.3, 109.7 and 129.2 rpm, respectively). The profiles appear to be similar, which implies that the Wang et al. approach to operated the two systems, based on a similarity of the the A/V_L ratio and k values between the USP 2 and the minivessel, appears to be correct. This is further confirmed by the results shown in Table 4.5. indicating that the f_1 and f_2 values comparing the USP 2 profiles with the minivessel profiles at the prescribed agitation speeds are almost alwasys the most appropriate values for profile similarities. This appears to be so even although the predictions by Wang et al. were obtained for a non-disintegrating tablet.

The calculated f_2 values in Table 4.5 are in good agreement with these observations. Drug release profile with $f_2 > 50$ were obtained at all stirring rates in the minivessel. However, a higher f_2 value was obtained for 129.2 rpm which is closest to that of the 100-rpm 5 dose in the standard system. The average standard deviation was observed to be consistent with the f_2 values ran Similarly, the f_2 values showed a consistent relationship between the predicted value of 86.3rpm in the minivessel and the 50rpm 5 dose

in the standard system. There was however a slight deviation with the predicted value of 109.7 rpm in the minivessel and the 75 rpm 5-dose curve obtained in the standard system as the 100rpm in the minivessel resulted in a closer visual relationship as well as a higher f_2 correlated value.

4.2.3 Experimental Determination of the Tablet-Medium Mass Transfer Coefficient from Dissolution Data for 81-mg Aspirin Tablets

The average experimental dissolution data, from 0 to 45 minutes, the properties of 81 mg aspirin tablet and the dissolution system were used as an input in equation 3.13 to obtain the average tablet-medium dissolution mass transfer coefficients k , through numerical integration of equation 3.13

Studying comparatively the dissolution process of 81-mg aspirin at different motion speeds in both the standard USP2 paddle dissolution system and the minivessel system it is observed from Table 4.2.3 and 4.2.4 that the mass transfer coefficient intensified as the stirring rate increase and seem to be impacted by the power volume relationship of the vessel. This result is supported by earlier works [9].

The mass transfer coefficient values in the standard system increased with increasing agitation speeds as well as the surface available. These values were one order of magnitude smaller than that derived in the minivessel system except for the 50 rpm. It was observed that as the agitation speed increased there was a consistent difference in the mass transfer coefficient values which increased correspondingly with agitation speed. The mass transfer coefficient in the minivessel were for the respective agitation speeds of 50

rpm,75 rpm,86.3 rpm,100 rpm,109.7 rpm,125 rpm ,129.2 rpm and 150 rpm and is shown in Table 4.2.4 .

The correspondingly percentge difference for these speeds when compared to the standard 100rpm 5 dose in the standard system.It is shown to be proportionate in the folowing order 80%,83%,84%,86%, 86.8%, 86.9%, 87.3% and 87.4% larger than the mass transfer coefficient for the 5-dose 100-rpm in the standard system.

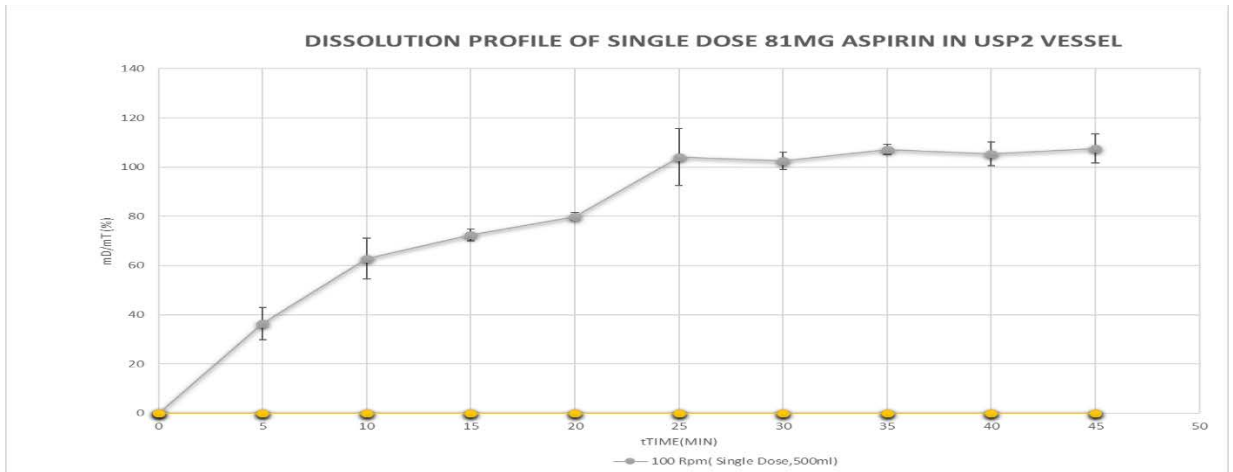


Figure 4.5 Dissolution profiles for single-dose 81-mg aspirin tablet at 100 rpm impeller speed ($V_L=500\text{ml}$) in the USP 2.

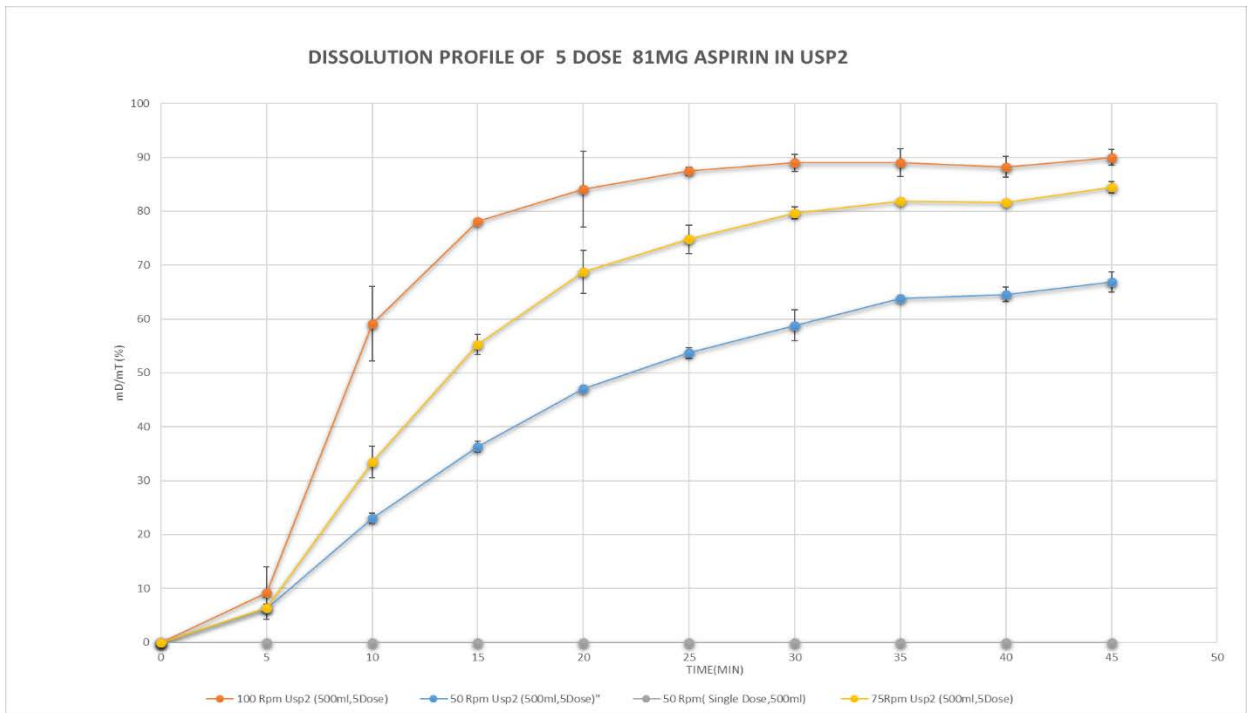


Figure 4.6. Dissolution profiles for 5-dose 81-mg aspirin tablets at two different impeller speeds in the USP 2 ($V_L=500\text{ ml}$ in all cases).

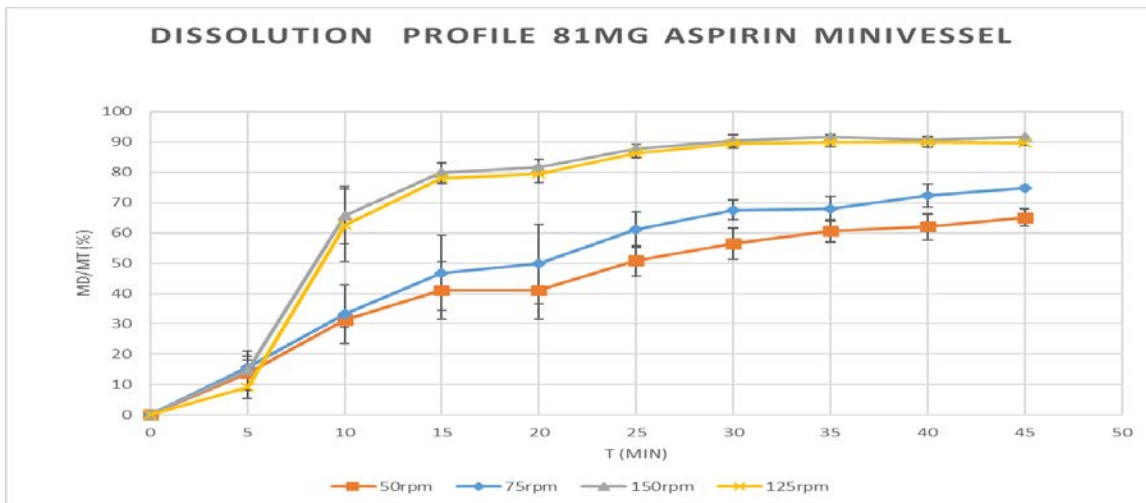


Figure 4.7 Dissolution profiles for single-dose 81-mg aspirin at different agitation speeds, (50 rpm, 75 rpm, 100 rpm, 125 rpm) in Minivessel apparatus ($V_L=100\text{ml}$).

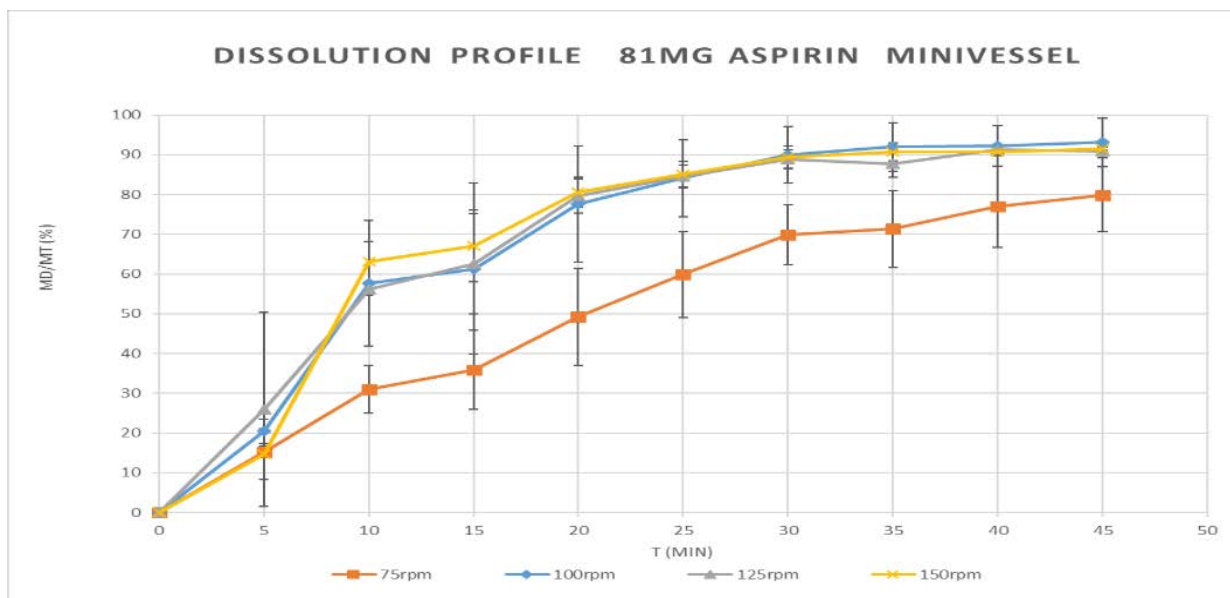


Figure 4.8 Dissolution profiles for single-dose 81-mg Aspirin at different agitation speeds, (75 rpm, 100 rpm, 125 rpm, 150 rpm) in Minivessel apparatus ($V_L=100\text{ml}$).

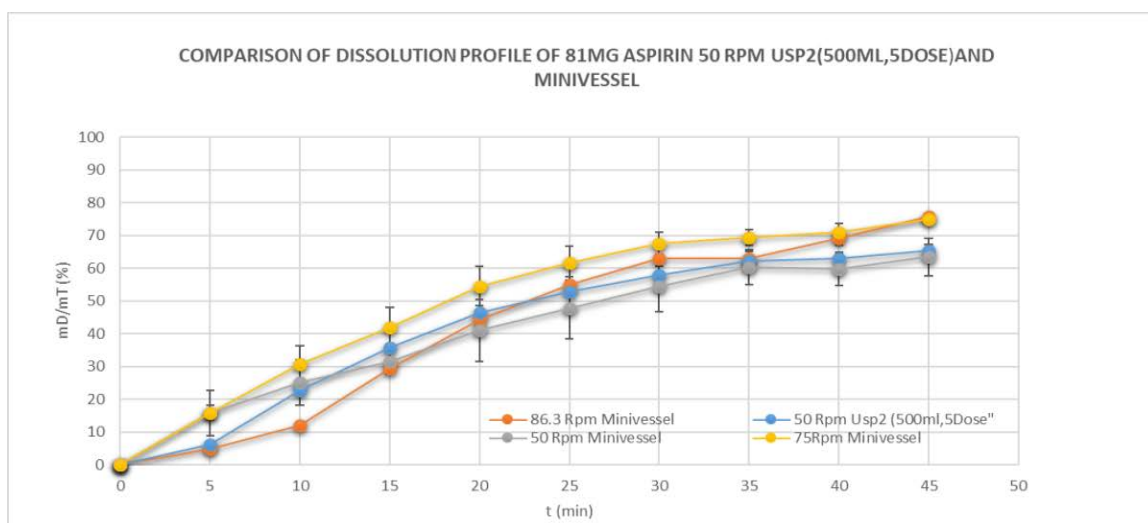


Figure 4.9 Dissolution profiles for 5-dose 81-mg aspirin tablets in the USP 2 at 50 rpm and for a single-dose 81-mg aspirin tablet in the Minivessel ($V_L=100\text{ml}$) at agitation speeds of 50, 75, 86.3rpm).

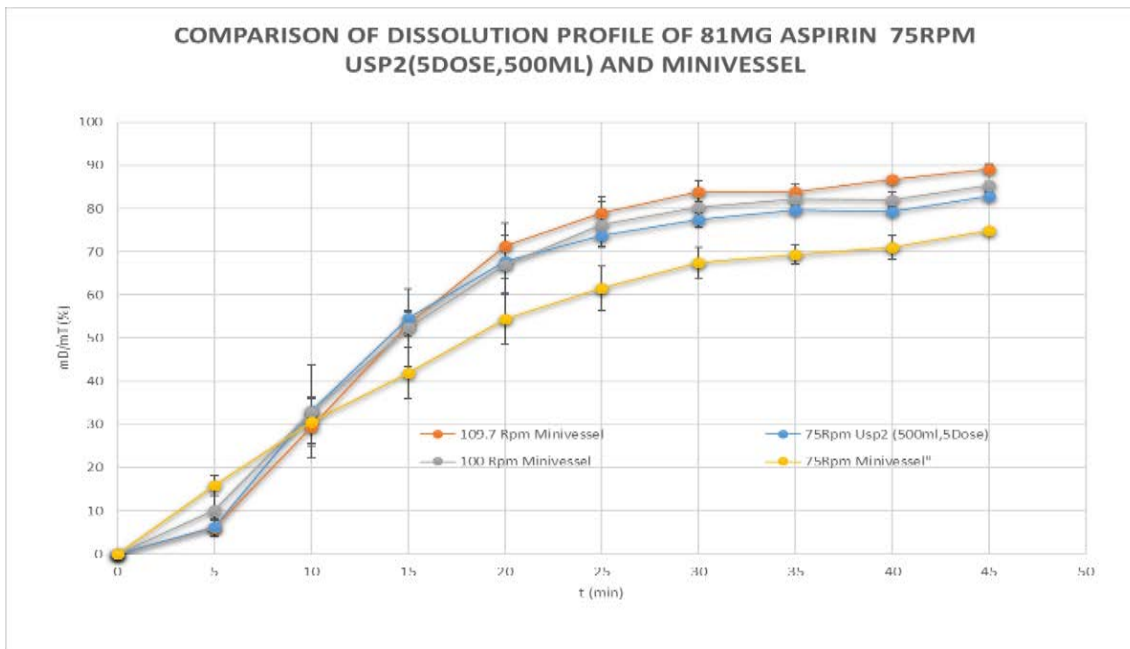


Figure 4.10 Dissolution profiles for 5-dose 81-mg aspirin tablets in the USP 2 at 75 rpm ($V_L=500\text{ml}$) and for a single-dose 81-mg aspirin tablet in the Minivessel ($V_L=100\text{ml}$) agitation speeds (75,100,109.7Rpm).

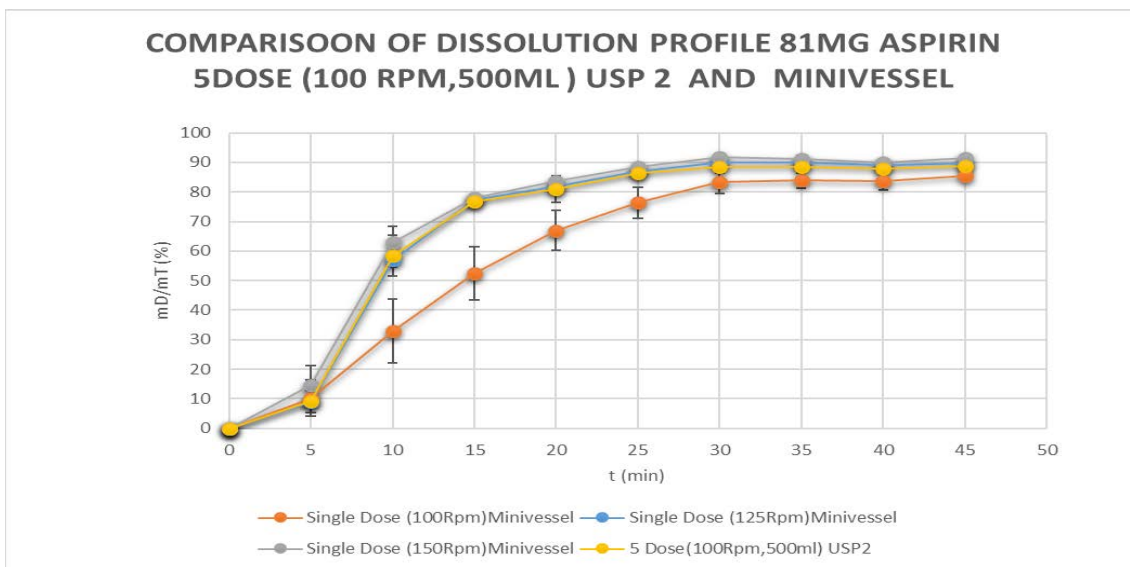


Figure 4.11 Dissolution profiles for 5-dose 81-mg aspirin tablets in the USP 2 at 100 rpm ($V_L=500\text{ml}$) and for a single-dose 81-mg aspirin tablet in the Minivessel ($V_L=100\text{ml}$) at agitation speeds(100,125,150Rpm).

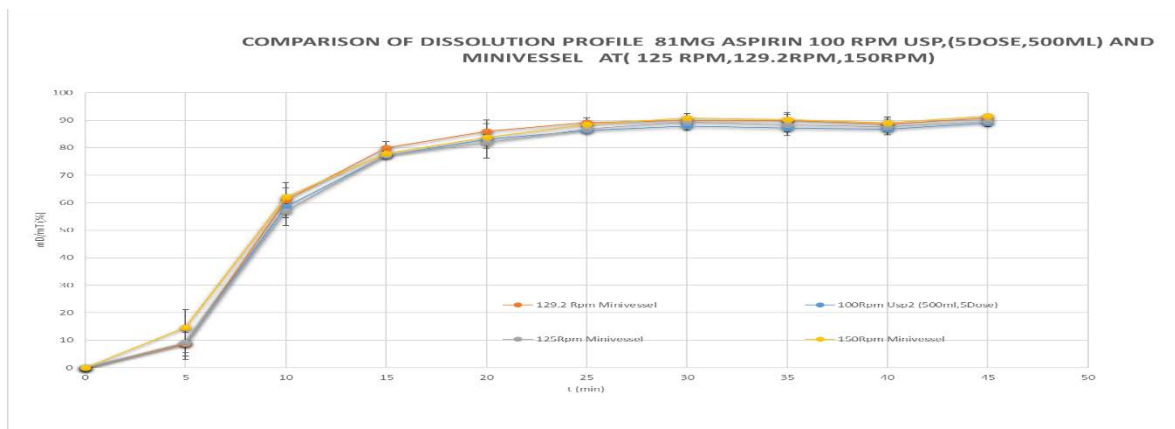


Figure 4.12 Dissolution profiles for 5-dose 81-mg aspirin tablets in the USP 2 ($V_L=500\text{ml}$) at 100 rpm and for a single-dose 81-mg aspirin tablet in the Minivessel at different agitation speeds. (125,129.2,150 Rpm).

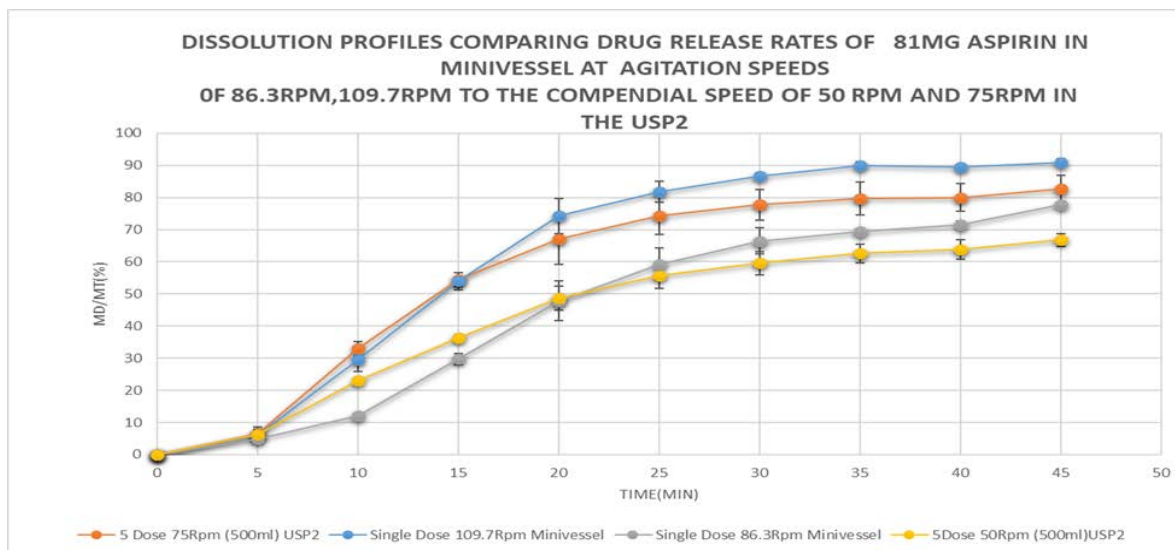


Figure 4.13 Dissolution profiles for 5-dose 81-mg aspirin tablets in the USP 2 at different standard agitations speeds (50 and 75 rpm), $V_L=500\text{ml}$ and for a single-dose 81-mg aspirin tablet in the Minivessel at the corresponding predicted agitation speeds (109.7 rpm and 86.3 rpm) ($V_L=100\text{ml}$) for mass transfer coefficient similarity

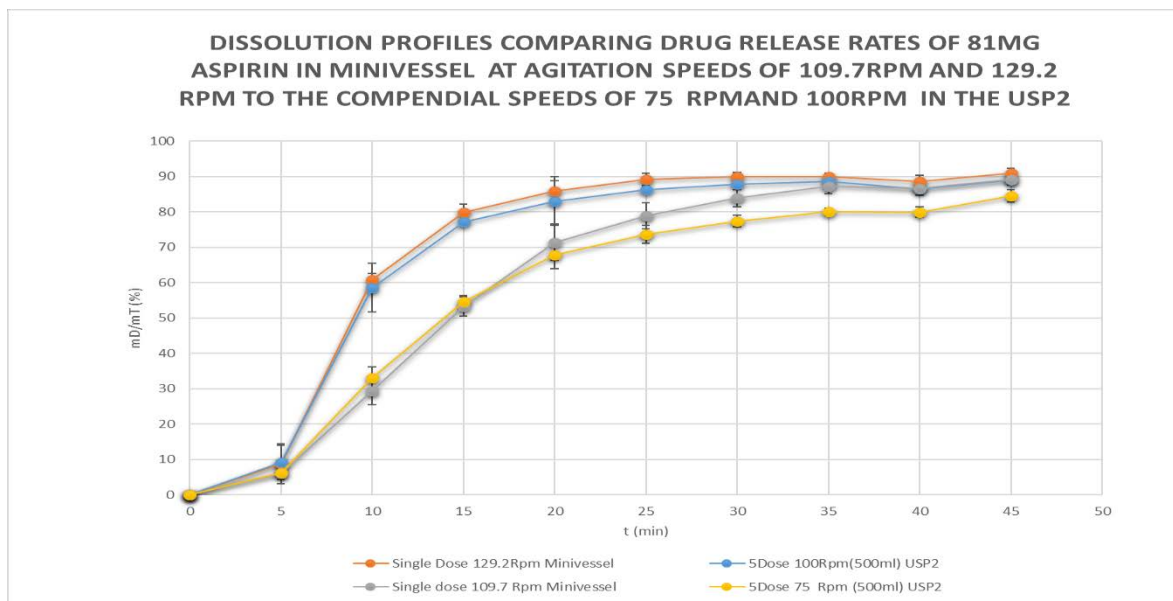


Figure 4.14 Dissolution profiles for 5-dose 81-mg aspirin tablets in the USP 2 at different standard agitations speeds (75, and 100 rpm), $V_L=500\text{ml}$ and for a single-dose 81-mg aspirin tablet in the Minivessel at the corresponding predicted agitation speeds (86.3 and 109.7rpm) $V_L=100\text{ml}$ for mass transfer coefficient similarity.

Table 4.3 f_1 and f_2 values for dissolution profiles of 81 mg Aspirin Tablet in Standard System USP2 at different agitation speeds

Impeller Speed (rpm)	Dosage	Run Number	Difference Factor, f_1	Similarity Factor, f_2	Average Difference Factor (f_1)	Average Similarity Factor (f_2)
50	Single	1	-	-		
	Single	2	6.03132	59.2135		
	Single	3	10.119	51.6933	4.64281	65.8195
50	5 Doses	1	-	-		
	5 Doses	2	5.6545	74.8906		
	5 Doses	3	8.9853	66.3745	5.5753	76.2044
75	5 Doses	1	-	-		
	5 Doses	2	2.9353	3.2933		
	5 Doses	3	77.488	79.813	2.3893	84.26
100	5 Doses	1	-	-		
	5 Doses	2	2.3646	82.775	1.9346	82.826
	5 Doses	3	2.7035	80.064		

Table 4.4 f₁ and f₂ values for dissolution profiles of 81 mg Aspirin Tablet in Minivessel Dissolution System at different impeller speeds

Impeller Speed (rpm)	Dosage	Run Number	Difference Factor f ₁	Similarity Factor f ₂	Average Difference Factor (f ₁)	Average Similarity factor (f ₂)
50	Single	1	-	-		
	Single	2	7.6578	68.2967		
	Single	3	6.0502	72.0413	6.0502	72.638
75	Single	1	-	-		
	Single	2	5.2741	71.686		
	Single	3	4.9439	73.4827	2.4903	72.4846
83.6	Single	1	-	-		
	Single	2	7.3945	69.8169	2.90488	86.839
	Single	3	2.2486	89.8026		
100	Single	1	-	-		
	Single	2	7.6598	68.2967		
	Single	3	5.9756	72.0413	3.25399	73.4969
109.7	Single	1	-	-		
	Single	2	4.1473	73.557		
	Single	3	4.9660	73.211	1.4948	91.0094
125	Single	1	-	-		
	Single	2	2.7432	77.4877		
	Single	3	3.4548	84.6141	1.95807	84.6141
129.2	Single	1	-	-		
	Single	2	4.4182	65.2391		
	Single	3	2.8170	70.9521	2.2555	75.4969
150	Single	1	-	-		
	Single	2	3.9649	72.6918		
	Single	3	4.5565	68.8592	2.3877	81.3763
	Single					

Table 4.5 Comparison of f1 and f2 values for dissolution profiles of 5-dose 81-mg Aspirin Tablet in USP 2 and single-dose 81-mg aspirin tablet in the Minivessel at different agitation speeds

Impeller Speed (rpm)	Vessel	Vessel Volume	Dosage of 81-mg aspirin tablets	Difference Factor f ₁	Similarity Factor f ₂	Average Standard Deviation (Compendial Profiles)
50 rpm	USP 2	500ml	5 Doses	5.5733	76.2044	
50 rpm	Minivessel	100ml	Single Dose	16.05	52.86	3.41
75 rpm	Minivessel	100ml	Single dose	18.18	52.36	5.96
86.3 rpm	Minivessel	100ml	Single Dose	12.39	59.96	1.06
75 rpm	USP 2	500ml	5 Doses	2.3893	76.2044	
75 rpm	Minivessel	100 ml	Single Dose	20.67	43.35	3.410
100 rpm	Minivessel	100ml	Single Dose	5.508	71.65	1.760
109.7 rpm	Minivessel	100ml	Single Dose	7.126	64.86	2.320
100 rpm	USP 2	500ml	5 Doses	1.9346	82.826	
100 rpm	Minivessel	100ml	Single Dose	16.0631	44.7086	2.6108
125	Minivessel	100ml	Single Dose	2.3937	81.0636	2.042
129.2	Minivessel	100ml	Single Dose	2.6849	81.9899	1.534
150	Minivessel	100ml	Single Dose	2.2652	80.5464	2.082

Table 4.6 Properties of 81mg Enteric Coated Aspirin and Dissolution System

Properties	
C_s	3.14 kg/m ³
ρ_T	1350 kg/m ³
V_L (Minivessel)	1*10 ⁻⁴
V_L (USP2)	500*10 ⁻⁴ m ³ /9.00*10 ⁻⁴ m ³
d_{TO} 5Dose	0.035m
d_{TO} Single Dose	6.5*10 ⁻³ m
B	0.462

Table 4. 7 Mass Transfer Coefficients for 81mg Aspirin at different Mixing Speeds Calculated from Experimental Dissolution in standard System

Impeller Speed (rpm)	Dosage	Mass Transfer Coefficient from Experimental Dissolution data k_{exp} (ms ⁻¹)
50	Single Dose	1.20*10 ⁻³
50	5Dose	1.56*10 ⁻³
75	5Dose	1.60*10 ⁻³
100(500ml)	5Dose	1.70*10 ⁻³

Table 4. 8 Mass Transfer Coefficients for 81mg Aspirin at different Mixing Speeds Calculated from Experimental Dissolution in Minivessel System

Impeller Speed rpm	Dosage	Mass Transfer Coefficient from Experimental Dissolution Data k_{exp} (ms ⁻¹)
50	Single Dose	8.77*10 ⁻³
75	Single Dose	1.02*10 ⁻²
86.3	Single Dose	1.10*10 ⁻²
100	Single Dose	1.23*10 ⁻²
109.7	Single Dose	1.29*10 ⁻²
125	Single Dose	1.30*10 ⁻²
129.2	Single Dose	1.34*10 ⁻²
150	Single Dose	1.35*10 ⁻²

CHAPTER 5

DISCUSSION

An overall comparison between results from the Standard USP 2 paddle dissolution system and the non-compendial Minivessel dissolution apparatus shows that, in general, there is an apparent agreement between the experimental results and the predictions obtained with the Model Independent Approach of Fit Factors recommended by the FDA guidelines for the industry, for the comparison of dissolution profiles, [5,9]

The dissolution profile from the predicted speeds of 50, 75, 100 rpm, running with 5dose in the standard system and the 86.3,109.9, and 129.2 rpm running at single dose for 81mg enteric coated aspirin was alternately selected as the reference profiles in this study.

The aim of these series of test was to establish the relationship between the reference one-liter vessel and the small vessel assembly, comprising a small vessel and a minipaddle.

The experimental dissolution data for the 81mg aspirin rather than the 325-mg aspirin indicated that using Minivessel with a higher impeller speed as determined by the fit factor and equations was more insightful to deduce an accurate result. These results appear to give a very decisive similarity dissolution rate for the 81mg aspirin single dose with the 100- rpm, 5dose according to the USP2 monograph to that of a single unit at 125 rpm and 129.2 rpm in the Minivessel. The 129.2 rpm showed a slightly higher f_2 value This is in good agreement with the earlier results [17] .

The alternate speeds of 50 rpm and 75rpm in the standard system, produced profiles which were comparable to those derived in the Minivessel at 86.3, and 109.7rpm in the Minivessel. There similarity was not as distinctive as those obtained at the higher speeds.

It was expected that placing multiple dosages in one single vessel would form a cone of in- soluble excipients on the bottom of the vessel, that would further decrease the rate of dissolution. this did not occur at the 100 rpm motion speed, 5 dose or single dose, but at the 50 rpm 5dose, and 75 rpm 5 dose run. This agrees with unprecedent work in literature [17].

Coning effect during drug release would result in a decrease in the dissolution rate, and concentration of these products, such coning effects are confined to formulations with high amounts of insoluble excipients such as disintegrating tablets which form a disintegrated mass at the bottom of the vessel. Coning effect at low speed had the highest impact on drug release.

The statistical similarity obtained in this work for the different motion speeds in both the standard systems and the Minivessel system respectively can be quantified by examining the values of the similarity/difference factors f_1 , and f_2 in tables 4.1- 4.2 for the 325mg, and tables 4.3 and 4.4 for the Minivessel. Table 4.5. compares the profiles in both systems

In both vessels all the agitation speeds produced results which were within the range set up for FDA, similarity. When the profiles of the motion speeds in the Minivessel systems, and the standard system was compared it was seen that a consistent similarity

existed among the profiles of the higher motion speeds and the 5 doses 100 rpm 500ml, with 129.2 rpm in the Minivessel exhibiting the highest similarity value.

The higher impeller speeds resulted in a better dispersion of the disintegrated particles and therefore a more significant dissolution profile [12].

The 75-rpm motion speed in the Minivessel showed values that were out of range with the stipulated FDA f_2 , and f_1 values when compared to the 75 rpm curve in the standard system. The 109.7 rpm motion speed in the Minivessel system, however presented f_2 , and f_1 values that made the profile produced claimed similarity to that of 75 rpm in the standard system. At the lower speed regimes, both 50 rpm, and 75 rpm motion speeds in the Produced at 50 rpm in the standard system. Even though the f_2 values were in range the f_1 values were out of range, the 86.3 rpm however presented values that made the profile produced similar.

The similarity factor f_2 is found to be more sensitive in finding dis-similarity between dissolution curves than the difference factor f_1 . The values of the fit factors are dependent on the number of sampling time points chosen [5].

According to the FDA guidelines, f_1 values up to 15 and f_2 values greater than 50 should ensure equivalence of dissolution curves, showing an average difference of no more than 10% at the sample time points. Based on these guidelines the 125 rpm, and 129.2rpm, and 150 rpm curves in the Minivessel and the 5dose 100 rpm curve for the 81m aspirin tablets show dissolution curve equivalence [10,18].

When using both the standard dissolution system, and the Minivessel system at an identical agitation speed, the small volume vessel showed a lower percentage drug

dissolution than the one-liter system for all the chosen impeller speeds for both the 325-mg aspirin and the 81mg aspirin.

When a comparison of the dissolution rate of the half caplet ,325mg aspirin and that of the 81-mg aspirin in the Minivessel was done, it was seen that a higher drug release was achieved for the single unit 81mg aspirin than the half caplet of the 325mg aspirin. Saturation for the half caplet 325 mg aspirin was reached as early as 15 minutes for the agitation speeds of 100 rpm,125 rpm and 150 rpm, and 25 minutes for the lower speeds of 50 rpm and 75 rpm. These trends can be seen in Figures 4.2, 4.3, and 4.4 for the 325-mg aspirin and figure 4.7 ,4.8. for the 81mg aspirin where saturation sets in at 35 minutes.

This outcome could be attributed to the size and shape of the dosage forms that also impact drug release. This shows that the Minivessel should preferably be used for powders, multi-particulate dosage forms and small tablets where the paddle apparatus would be the usual method of choice [13].

These investigations clearly showed that using small vessel setup, at equivalent or higher speeds are necessary to obtain similar dissolution rate in the standard USP 2 one-liter vessel. When compared to the one-liter vessel, a speed factor of 1.29 have been seen to be a suitable prediction in the case of 81mg aspirin.

The variation of the total mass transfer coefficient was studied experimentally for the 81mg aspirin. These studies were made in the same conditions with those presented for earlier determination of dissolution curve equivalence. The difference in the curve and the saturation concentration C^* represents the concentration variation which is used to

calculate the total mass transfer coefficient over 45 minutes with respect to each dissolution speeds.

The properties of the dissolution system, tablet properties and the values of these coefficients are presented in Tables 4.6, 4.7, and 4.8. respectively.

It is seen that there is a gradual increase of the mass transfer coefficient during the dissolution process in both dissolution systems as the motion speed increased. This is consistent with the decrease in the tablet dimension which leads to change of the limit layer thickness as well as the existence of a solvent diffusion process in the granules.

Comparing the values of the total mass transfer coefficient k at dissolution it is seen that an intensification of the hydrodynamic conditions by increasing the stirring rate have a favorable effect over the dissolution process. This resulted an increase in the k value. It is noticeable that as the motion speed increased, the mass transfer coefficient increased, however there was marked difference in values of the Minivessel dissolution system from that in one-liter standard system.

It is noticeably that at the higher motion speed of 100 rpm, 109.2 rpm 125 rpm, 129.2 rpm and 150 rpm in the Minivessel there exist a proportionate percentage difference between the mass transfer coefficient of the 5 dose 81mg aspirin in the standard system at 100- rpm. This disparity between the values in both system could be attributed to the geometric di-similarity between the Minivessel and the standard system, in terms of the ratio of the height of the fluid to tank diameter and the position of the impeller relative to bottom of the vessels impeller diameter ratios, [7].

Since the rate of dissolution of solids into liquids is a function of the power to volume ratio put into the fluid this will increase with scale-up. The standard USP2 system however operates in regime where the flow is incipient- turbulent and time dependent, the smaller vessel on the other hand displaces the dissolution system towards a laminar flow regime [22].

The derivation of identical mass transfer coefficient at the predicted agitation speed by the former group was not obtained. This could be due to the utilization of a disintegrating tablet instead of a non- disintegrating tablet, that will ultimately explode into thousands of small particles of which a definite surface area is impractical to determine. It was however evident that a proportionate ratio of agitation speed, surface area and volume will produce equivalent dissolution profiles in both systems. The results from both system was also able to prove that the concentration, or the change in the mass with time compared to the initial mass was proportional to the mass transfer coefficient.

CHAPTER 6.

CONCLUSIONS

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

1. Operating the USP 2 system and the Minivessel with the same dosage form in both systems is not an effective method to achieve similarity of dissolution profiles even if the two systems are operated at different agitation speeds.
2. A more appropriate approach consists in operating the two systems with different amounts of drug so as to achieve similarity in both systems as far as ratio of tablet mass to liquid dissolution media and ratio of tablet surface area available for dissolution to liquid dissolution media are concerned. Under these conditions, the dissolution curves in the two systems appear to be somewhat similar if the agitation speeds in the two systems is on the same order of magnitude.
3. An even more effective approach to achieve dissolution profile similarity between the USP 2 and the Minivessel consists in operating the two systems so as to not only maintain the two above-mentioned ratios identical in the two systems but also to operate the USP 2 and the Minivessel at the agitation speeds predicted in a recent study by this group (Wang et al., 2017), i.e., at 50, 75, and 100 rpm in the USP 2 and at the corresponding speed of 86.2, 109.7, and 129.2 rpm in the Minivessel, respectively.
4. Experimental dissolution curves obtained in the two systems under these operating conditions appear to be very similar, as also quantitatively shown using the

difference factor f_1 and the similarity factor f_2 recommended by the Food and Drug Administration (FDA) to test the statistical similarity of two dissolution profiles.

5. These results of this work were obtained with disintegrating tablets used for the rapid release of the drug substance, although the original work of Wang et al., 2017 was based on the use of non-disintegrating slowly eroding tablets. However, the results of this work indicate that their proposed approach appears to have a more general validity.
6. This work was based on the use of tablets containing a specific drug product, namely aspirin. Since the rationale for the use of the proposed method to obtain similarity of dissolution profiles in the two systems does not rely on the use of specific parameters related to the drug product, it can be expected that the results of this work are of more general validity.

In summary, it can be concluded that appropriately operating Minivessel can result in dissolution profiles similar to those obtained in the USP 2.

The results of this work could be of significant importance to dissolution scientists in the pharmaceutical industry and help them operate Minivessel, especially during the early stages of drug development, so as to predict future dissolution profiles of the same drug product during commercialization, when the USP 2 system is routinely used.

APPENDIX A

Table A.1 Dissolution Profile for Half Dose 325 mg Aspirin in Minivessel (50 rpm)

Time Min	Avg. Abs (1)	Avg Abs (2)	Avg Abs (3)	Avg Conc. (mg/ml) 1	Avg Conc. (mg/ml) 2	Avg Conc. (mg/ml) 3	Avg C/C* (%) 1	Avg C/C* (%) 2	Avg C/C* (%) 3	Avg Std. Dev. C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.5613	0.5106	0.554	0.1837	0.1665	0.1812	11.3203	10.260	11.166	0.0043
10	1.0883	0.970	0.9033	0.3626	0.3225	0.2998	22.3473	19.871	18.476	0.0141
15	1.3543	1.280	1.2436	0.4530	0.4277	0.4154	27.9132	26.357	25.597	0.0086
20	1.6596	1.486	1.604	0.5567	0.4977	0.5378	34.3020	30.668	33.137	0.0135
25	1.901	1.7576	1.780	0.6386	0.5900	0.5978	39.3517	36.352	36.833	0.0122
30	2.0926	1.9946	1.998	0.7037	0.6704	0.6717	43.3622	41.311	41.388	0.0089
35	2.308	2.146	2.179	0.7768	0.7218	0.7332	47.8679	44.478	45.175	0.0135
40	2.4923	2.314	2.328	0.8394	0.7790	0.7836	51.7249	48.000	48.286	0.0159
45	2.6113	2.410	2.5233	0.8799	0.8117	0.8500	54.2149	50.016	52.376	0.0145

Table A.2 Dissolution Profile for Half Dose 325 mg Aspirin in Minivessel (75 rpm)

Time Min	Avg. Abs (1)	Avg Abs (2)	Avg Abs (3)	Avg Conc. (mg/ml) 1	Avg Conc. (mg/ml) 2	Avg Conc. (mg/ml) 3	Avg C/C* (%) 1	Avg C/C* (%) 2	Avg C/C* (%) 3	Avg Std. Dev. C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.98366	1.03766	0.724	0.324497	0.34269	0.237016	19.993	21.114	14.6035	0.0264
10	1.644	1.74966	1.3975	0.546964	0.582563	0.463918	33.700	35.894	28.583	0.0276
15	2.0536	2.135	1.7635	0.68498	0.712382	0.587223	42.205	43.892	36.1813	0.0305
20	2.395	2.55833	1.98	0.799976	0.855003	0.660162	42.289	52.680	40.6754	0.0458
25	2.6953	2.73033	2.333	0.889029	0.912949	0.779088	54.776	56.2507	48.0029	0.0333
30	2.81266	2.84033	2.49	0.940687	0.9008	0.831981	57.959	58.534	51.2619	0.0310
35	2.84833	2.893	2.683	0.952704	0.967752	0.897003	58.7001	59.627	55.2619	0.0173
40	2.913	2.92033	2.767	0.97449	0.97696	0.925302	60.425	60.1947	57.0118	0.0138
45	2.913	2.927667	2.854	0.97449	0.979431	0.954613	60.042	60.346	58.8178	0.0061

Table A.3 Dissolution Profile for Half Dose 325 mg Aspirin in Minivessel (100 rpm)

Time Min	Avg. Abs (1)	Avg Abs (2)	Avg Abs (3)	Avg Conc. (mg/ml) 1	Avg Conc. (mg/ml) 2	Avg Conc. (mg/ml) 3	Avg C/C* (%) 1	Avg C/C* (%) 2	Avg C/C* (%) 3	Avg Std. Dev. C/C*
0	0	0	0	0	0	0	0	0	0	0
5	2.0743	2.0346	1.646	0.6975	0.6840	0.5523	42.9786	42.1486	34.0300	0.0379
10	2.633	2.6073	2.524	0.8872	0.8785	0.8503	54.6683	54.1312	52.3945	0.0089
15	2.8476	2.8393	2.765	0.9601	0.9573	0.9322	59.1600	58.9856	57.4372	0.0072
20	2.906	2.887	2.881	0.9799	0.9735	0.9714	60.3806	59.9830	59.8575	0.0020
25	2.9276	2.945	2.921	0.9873	0.9932	0.9851	60.8339	61.1966	60.7014	0.0019
30	2.944	2.9603	2.951	0.9928	0.9984	0.9953	61.1757	61.5175	61.329	0.0011
35	2.944	2.9676	2.967	0.9982	1.0009	1.0008	61.1757	61.6709	61.663	0.0021
40	2.944	2.9756	2.984	0.9928	1.0036	1.0064	61.1757	61.8383	62.0127	0.0033
45	2.944	2.993	2.992	0.9928	1.0095	1.0094	61.1757	62.2020	62.1940	0.0045

Table A.4 Dissolution Profile for Half Dose 325 mg Aspirin in Minivessel (125 rpm)

Time Min	Avg. Abs (1)	Avg Abs (2)	Avg Abs (3)	Avg Conc. (mg/ml) 1	Avg Conc. (mg/ml) 2	Avg Conc. (mg/ml) 3	Avg C/C* (%) 1	Avg C/C* (%) 2	Avg C/C* (%) 3	Avg Std. Dev. C/C*
0	0	0	0	0	0	0	0	0	0	0.0752
5	1.683	2.4166	2.5673	0.5646	0.8138	0.8649	34.7903	50.1417	53.2942	0.0199
10	2.604	2.7626	2.8736	0.8774	0.9311	0.9689	54.0615	57.3814	59.7040	0.0045
15	2.9326	2.8736	2.9133	0.9890	0.9689	0.9824	60.9386	59.7040	60.5340	0.0085
20	3.010	2.9033	2.9356	1.0153	0.9780	0.9900	62.5567	60.2620	61.0013	0.0057
25	3.010	2.937	2.9593	1.0153	0.9905	0.9980	62.5567	61.0292	61.4965	0.0042
30	3.010	2.952	2.9756	1.0153	0.9955	1.0036	62.5567	61.343	61.8383	0.0041
35	3.010	2.952	2.984	1.0153	0.9955	1.0064	62.5567	61.343	62.0127	0.0041
40	3.010	2.952	2.984	1.0153	0.9955	1.0064	62.5567	61.343	62.0127	0.0041
45	3.010	2.952	2.984	1.0153	0.9955	1.0064	62.5567	61.343	62.0127	0.0041

Table A.5 Dissolution Profile for Half Dose 325 mg Aspirin in Minivessel (150 rpm)

Time Min	Avg. Abs (1)	Avg Abs (2)	Avg Abs (3)	Avg Conc. (mg/ml) 1	Avg Conc. (mg/ml) 2	Avg Conc. (mg/ml) 3	Avg C/C* (%) 1	Avg C/C* (%) 2	Avg C/C* (%) 3	Avg Std. Dev. C/C*
0	0	0	0	0	0	0	0	0	0	0.0924
5	1.7353	1.919	2.821	0.5824	0.6447	0.9511	35.8853	39.7284	58.6020	0.0438
10	2.3063	2.6416	2.9133	0.7763	0.8902	0.9824	47.8331	54.8457	60.5340	0.0086
15	2.855	2.9593	2.9356	0.9626	0.9980	0.9900	59.3135	61.4966	61.0013	0.0035
20	2.983	3.010	2.9593	1.0068	1.0153	0.9980	62.0336	62.5567	61.496	0.0023
25	3.010	3.010	2.9833	1.0153	1.0153	1.0065	62.5567	62.5567	62.0196	0.0023
30	3.010	3.010	2.9833	1.0153	1.0153	1.0065	62.5567	62.5567	62.0196	0.0023
35	3.010	3.010	2.9833	1.0153	1.0153	1.0065	62.5567	62.5567	62.0196	0.0023
40	3.010	3.010	2.9833	1.0153	1.0153	1.0065	62.5567	62.5567	62.0196	0.0023
45	3.010	3.010	2.9833	1.0153	1.0153	1.0065	62.5567	62.5567	62.0196	0.0023

Table A.6 Dissolution Profile for Half Dose 325 mg Aspirin in USP 2 (50 rpm)

Time Min	Avg. Abs (1)	Avg Abs (2)	Avg Abs (3)	Avg Conc. (mg/ml) 1	Avg Conc. (mg/ml) 2	Avg Conc. (mg/ml) 3	Avg C/C* (%) 1	Avg C/C* (%) 2	Avg C/C* (%) 3	Avg Std. Dev. C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.4890	0.4410	0.3900	0.1597	0.1433	0.1264	50.2089	45.0829	39.7433	0.1214
10	0.5656	0.5770	0.4557	0.1857	0.1895	0.1483	58.6067	59.6067	46.6492	0.1509
15	0.6987	0.6500	0.5637	0.2309	0.2143	0.1850	72.5997	67.4025	58.1827	0.1788
20	0.7523	0.7280	0.6017	0.2491	0.2408	0.1979	78.3309	75.7323	62.2408	0.1969
25	0.7417	0.7590	0.7270	0.2455	0.2514	0.2405	77.1918	79.0429	75.6255	0.1998
30	0.9494	0.7807	0.7990	0.3160	0.2587	0.2469	99.3726	81.3567	83.3146	0.2305
35	0.9053	0.7870	0.8927	0.3011	0.2609	0.2968	94.6701	82.0330	93.3175	0.2256
40	0.9317	0.9103	0.9000	0.3099	0.3027	0.2992	97.4824	95.2042	94.1006	0.2463
45	0.9343	0.8483	0.9300	0.3109	0.2817	0.3094	97.7672	88.5830	97.3040	0.2380

Table A.7. Dissolution Profile for Half Dose 325 mg Aspirin in USP 2 (100 rpm)

Time Min	Avg. Abs (1)	Avg Abs (2)	Avg Abs (3)	Avg Conc. (mg/ml) 1	Avg Conc. (mg/ml) 2	Avg Conc. (mg/ml) 3	Avg C/C* (%) 1	Avg C/C* (%) 2	Avg C/C* (%) 3	Avg Std. Dev. C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.5387	0.6123	0.5093	0.1760	0.2010	0.11601	87.1442	99.5298	82.2126	0.0660
10	0.6957	0.701	0.6183	0.2293	0.2316	0.2030	113.5388	114.4354	100.5376	0.0598
15	0.694	0.7113	0.6830	0.2287	0.2347	0.2250	113.246	116.1726	111.4093	0.0170
20	0.7413	0.7083	0.6577	0.2449	0.2337	0.2164	121.2162	115.6683	107.1502	0.0501
25	0.795	0.6903	0.6777	0.2631	0.2275	0.2230	130.2386	112.6421	112.992	0.0832
30	0.72	0.7000	0.6920	0.2376	0.2308	0.2281	17.6297	114.2673	111.8016	0.0179
35	0.766	0.7097	0.6853	0.2532	0.2341	0.2258	125.3631	115.8925	109.3358	0.0511
40	0.713	0.6643	0.6707	0.2352	0.2187	0.2208	116.4529	108.2719	109.3358	0.0339
45	0.766	0.6790	0.6637	0.2532	0.2237	0.2184	125.3631	110.7368	108.1590	0.0707

Table A.8 Dissolution Profile for Full Dose 325 mg Aspirin in USP 2 (100 rpm)

Time Min	Avg. Abs (1)	Avg Abs (2)	Avg Abs (3)	Avg Conc. (mg/ml) 1	Avg Conc. (mg/ml) 2	Avg Conc. (mg/ml) 3	Avg C/C* (%) 1	Avg C/C* (%) 2	Avg C/C* (%) 3	Avg Std. Dev. C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.9643	1.0324	0.9063	0.3205	0.3443	0.3009	77.436	83.1786	72.678	0.0350
10	1.1593	1.196	1.0996	0.3868	0.3992	0.3665	94.432	96.440	88.537	0.0284
15	1.2373	1.2617	1.121	0.4133	0.4215	0.3737	99.850	101.826	90.287	0.0468
20	1.2593	1.2727	1.1453	0.4208	0.4252	0.3820	101.635	102.728	92.283	0.0439
25	1.250	1.2533	1.1836	0.4176	0.4187	0.3950	100.869	101.142	95.428	0.0247
30	1.2533	1.3306	1.1793	0.4194	0.4449	0.3936	101.307	107.486	95.072	0.0414
35	1.2203	1.2583	1.225	0.4075	0.4204	0.4091	98.436	101.553	98.819	0.0130
40	1.2537	1.3167	1.196	0.4188	0.4402	0.3992	101.170	106.338	96.44	0.0334
45	1.235	1.2903	1.1807	0.4125	0.4313	0.3940	99.639	104.178	95.182	0.0300

APPENDIX B

Table B.1 Dissolution Profile Single Dose 81mg Aspirin Minivessel (50 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.2693	0.5497	0.426	0.0648	0.1580	0.1176	8.011	19.509	14.522	0.0400
10	0.564	0.7483	0.868	0.1483	0.2229	0.2619	18.312	27.519	32.344	0.0516
15	0.9273	0.961	0.8953	0.2445	0.2924	0.2709	30.187	36.094	33.446	0.0203
20	1.2043	1.414	1.042	0.3457	0.4403	0.3188	42.686	54.359	39.360	0.0592
25	1.3986	1.5596	1.3183	0.4404	0.4879	0.4091	54.379	60.232	50.502	0.0346
30	1.5863	1.7373	1.4813	0.4799	0.5459	0.4623	59.285	67.396	57.074	0.0410
35	1.683	1.761	1.5873	0.5613	0.5536	0.4969	69.298	68.351	61.348	0.0332
40	1.7983	1.857	1.6217	0.5612	0.5849	0.5081	69.278	72,222	62.732	0.0356
45	1.825	1.903	1.767	0.5961	0.6000	0.5556	73.593	74.076	68.593	0.0232

Table B.2 Dissolution Profile Single Dose 81 mg Aspirin Minivessel (75 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.4070	0.5323	0.462	0.1114	0.1523	0.1293	13.756	18.809	15.973	0.0175
10	0.8470	1.007	0.7163	0.2551	0.3073	0.2124	31.497	37.984	26.228	0.0403
15	1.2640	1.233	0.9776	0.3913	0.3811	0.2978	48.311	47.061	36.766	0.0485
20	1.5430	1.6363	1.3306	0.4824	0.5129	0.4130	59.560	63.324	50.999	0.0454
25	1.7320	1.8186	1.5586	0.5441	0.5724	0.4875	67.181	70.676	60.192	0.0388
30	1.9523	1.9023	1.787	0.6161	0.5998	0.5621	76.065	74.049	69.399	0.0251
35	1.8937	1.993	1.781	0.5969	0.6294	0.5601	73.700	77.705	69.157	0.0290
40	2.1013	2.0593	1.9166	0.6647	0.6510	0.6044	82.073	80.380	74.627	0.0293
45	2.0950	2.1033	2.1266	0.6627	0.6654	0.6730	81.818	82.154	83.094	0.0044

Table B.3 Dissolution Profile Single Dose 81 mg Aspirin Minivessel (86.3 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.1743	0.190	0.1956	0.0354	0.04044	0.0424	4.3749	4.9932	5.2351	0.0523
10	0.375	0.395	0.358	0.1009	0.1075	0.0954	12.4660	13.2725	11.7806	0.1178
15	0.8823	0.845	0.794	0.2667	0.2544	0.2378	32.9222	31.4169	29.3605	0.2936
20	1.2976	1.281	1.1803	0.4023	0.3968	0.3639	49.6688	48.9667	44.9379	0.4493
25	1.589	1.539	1.5467	0.4974	0.4810	0.4836	61.4157	59.3862	59.7088	0.5970
30	1.8107	1.808	1.7593	0.5698	0.5691	0.5530	70.3535	70.2594	68.2837	0.6828
35	1.916	1.982	1.944	0.6042	0.6257	0.6134	74.6006	77.2484	75.7297	0.7572
40	2.054	1.960	2.077	0.6493	0.6186	0.6568	80.1649	76.3748	81.0923	0.8109
45	2.1627	2.198	2.204	0.6848	0.6963	0.6983	84.5465	85.9712	86.2131	0.8621

Table B.4 Dissolution Profile Single Dose 81mg Aspirin Minivessel (100 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.2987	0.1843	0.496	0.0760	0.0387	0.1405	9.3882	4.7782	17.3449	0.0309
10	0.986	0.613	1.1593	0.3005	0.1787	0.3571	37.1021	22.0624	44.0911	0.0637
15	1.4193	1.2243	1.683	0.4421	0.3783	0.5281	54.5746	46.7120	65.2059	0.0310
20	1.805	1.6963	2.026	0.5680	0.5325	0.6402	70.1251	65.7435	79.036	0.0233
25	2.0637	2.0113	2.249	0.6525	0.6354	0.7130	80.5548	78.4446	88.0276	0.0364
30	2.2033	2.1533	2.310	0.6981	0.6817	0.7329	86.1862	84.1702	90.0757	0.0528
35	2.2527	2.3373	2.399	0.71422	0.7418	0.7620	88.1754	91.5893	94.0757	0.0608
40	2.3037	2.3613	2.3737	0.7309	0.7497	0.7537	90.2318	92.5569	93.0542	0.0712
45	2.3633	2.3927	2.37	0.7513	0.7599	0.7541	92.7586	93.8204	93.0946	0.0795

Table 5.B Dissolution Profile Single Dose 81 mg Aspirin Minivessel (109.7 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.2727	0.192	0.1977	0.0675	0.0412	0.0430	8.33	5.087	5.315	0.0112
10	0.9437	0.7913	0.7533	0.2867	0.2369	0.2245	35.39	27.72	27.720	0.0248
15	1.4957	1.523	1.3897	0.4669	0.4759	0.4327	57.65	53.38	53.378	0.0173
20	2.1217	1.9357	1.8507	0.6714	0.6107	0.5829	82.89	71.96	71.966	0.0331
25	2.2947	2.1203	2.1333	0.7279	0.6710	0.6751	89.86	83.35	83.350	0.0253
30	2.3807	2.2547	2.346	0.7560	0.7148	0.7448	93.34	91.95	91.952	0.0157
35	2.475	2.3687	2.435	0.7868	0.7521	0.7737	97.14	95.53	95.527	0.0125
40	2.4883	2.4733	2.497	0.7912	0.7862	0.7939	97.68	98.01	98.013	0.0027
45	2.4373	2.5333	2.491	0.7745	0.8058	0.7921	95.62	97.78	97.785	0.0109

Table 6.B Dissolution Profile Single Dose 81mg Aspirin Minivessel (125 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.3753	0.1945	0.3183	0.1019	0.0420	0.0824	12.4794	5.1881	10.1811	0.0272
10	1.5446	1.615	1.484	0.4829	0.5059	0.4631	59.6281	62.4641	57.1820	0.0180
15	2.105	2.109	2.0683	0.6659	0.6672	0.6540	82.2213	82.3826	80.7429	0.0069
20	2.2706	2.167	2.2136	0.7201	0.6862	0.7014	88.9012	84.7212	86.6029	0.0143
25	2.3576	2.3675	2.3583	0.7485	0.7517	0.7487	92.4091	92.8056	92.4360	0.0017
30	2.471	2.402	2.4243	0.7855	0.7529	0.7702	96.9788	94.1966	95.0971	0.0103
35	2.482	2.407	2.4713	0.7891	0.7646	0.7856	97.4223	94.3983	96.9922	0.0124
40	2.483	2.39	2.4846	0.7894	0.7590	0.7899	97.4626	93.7128	97.5298	0.0168
45	2.437	2.225	2.4546	0.7744	0.7706	0.7801	95.6079	95.1442	96.3202	0.0041

Table 7.B Dissolution Profile Single Dose 81mg Aspirin Minivessel (129.2 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.4523	0.2013	0.2077	0.1236	0.0442	0.04632	15.584	5.4636	5.7190	0.0359
10	1.693	1.6497	1.6073	0.5314	0.5173	0.5034	65.6091	63.8619	62.1549	0.0093
15	2.190	2.0913	2.1993	0.6937	0.6615	0.6968	85.6486	81.6703	86.0250	0.0149
20	2.333	2.2503	2.3987	0.7404	0.7134	0.7619	91.4145	88.0813	94.0622	0.0149
25	2.4277	2.3663	2.4553	0.7713	0.7513	0.7804	95.2316	92.7585	96.3471	0.0167
30	2.4467	2.4083	2.4687	0.7776	0.7651	0.7947	95.9977	94.4521	96.8848	0.0109
35	2.4643	2.4187	2.4343	0.7833	0.7684	0.7736	96.7100	94.8687	95.5004	0.0071
40	2.5017	2.421	2.494	0.7955	0.7692	0.7930	98.2153	94.9628	97.9062	0.0054
45	2.4837	2.4293	2.496	0.7897	0.7719	0.7937	97.4896	95.2988	97.9869	0.011

Table 8.B Dissolution Profile Single Dose 81mg Aspirin Minivessel (150 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.279	0.6073	0.430	0.0696	0.1768	0.11893	8.595	21.8339	14.6837	0.0453
10	1.7226	1.8253	1.5623	0.5411	0.5746	0.48875	66.8053	70.9449	60.3405	0.0379
15	2.0876	2.0966	2.127	0.6603	0.6632	0.67317	81.5524	81.8853	83.1084	0.0062
20	2.2973	2.248	2.2413	0.7288	0.7126	0.71051	89.9764	87.9872	87.7184	0.0094
25	2.4086	2.3826	2.3976	0.7651	0.7566	0.76157	94.4655	93.4171	94.0219	0.0036
30	2.519	2.415	2.4193	0.8012	0.7672	0.76865	98.9142	94.7208	94.8955	0.0182
35	2.5066	2.4926	2.4616	0.7971	0.7926	0.78248	98.4169	97.8524	96.6025	0.0068
40	2.4723	2.420	2.485	0.7859	0.7688	0.79010	97.0326	94.9224	97.5433	0.0105
45	2.4943	2.4667	2.502	0.7931	0.7841	0.79565	97.9196	96.8041	98.2297	0.0056

Table 9.B Dissolution Profile Single Dose 81mg Aspirin USP2 (50 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.2206	0.2436	0.2857	0.0506	0.0580	0.0717	31.2159	35.8528	44.3202	0.0479
10	0.3650	0.4357	0.3580	0.0977	0.1208	0.0954	60.3142	74.5609	58.9029	0.0665
15	0.4240	0.4450	0.4420	0.1169	0.1238	0.1228	72.2089	76.4426	75.8378	0.0175
20	0.4820	0.4833	0.4670	0.1359	0.1363	0.1310	83.9019	84.1707	80.8779	0.0140
25	0.5383	0.6417	0.6520	0.1543	0.1880	0.1914	95.2591	116.0916	118.1748	0.0972
30	0.6277	0.5860	0.5927	0.1834	0.1699	0.1721	113.2691	104.8689	106.2129	0.0343
35	0.6220	0.6590	0.6117	0.1816	0.1937	0.1783	112.1267	119.586	110.0434	0.0377
40	0.6036	0.6543	0.6376	0.1756	0.1922	0.1868	108.4306	118.6452	115.2851	0.0379
45	0.6590	0.6440	0.5897	0.1937	0.1883	0.1711	119.586	116.562	105.6081	0.0554

Table 10.B Dissolution Profile 5 Dose 81 mg Aspirin USP 2 (50 rpm)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.2303	0.2017	0.2417	0.0537	0.0443	0.0663	5.7428	6.6329	5.4771	0.0061
10	0.6790	0.6547	0.6317	0.2002	0.1944	0.2472	18.4802	24.7236	23.9957	0.0068
15	1.0270	1.0180	0.9083	0.3139	0.3109	0.3876	29.8677	38.7553	38.3924	0.0075
20	1.2880	1.3163	1.2833	0.3992	0.4084	0.4928	39.7637	49.2791	50.4215	0.0054
25	1.500	1.9047	1.4517	0.4684	0.4654	0.5783	45.2614	57.8272	57.4508	0.0078
30	1.6757	1.6663	1.5327	0.5258	0.5227	0.6491	47.9069	64.9102	64.5339	0.0248
35	1.7677	1.7033	1.6427	0.5548	0.5436	0.6849	51.4994	68.4988	67.1144	0.0188
40	1.8743	1.7987	1.7130	0.5907	0.5659	0.7292	53.7966	72.9206	69.8697	0.0221
45	1.9203	1.8447	1.8180	0.6057	0.5809	0.7477	57.2259	74.7754	71.7245	0.0159

Table 11.B Dissolution Profile 5 Dose 81 mg Aspirin USP 2(75 rpm,100ml)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.2207	0.178	0.2947	0.0506	0.0365	0.0747	6.2431	4.5094	9.2269	0.0191
10	0.885	0.881	1.014	0.2675	0.2663	0.3097	33.0297	32.8819	38.2311	0.02166
15	1.4267	1.550	1.5037	0.4529	0.4848	0.4695	55.9186	59.8567	57.975	0.0076
20	1.8523	1.977	1.7647	0.5834	0.6243	0.5549	72.0335	77.0737	68.4988	0.0347
25	2.0253	2.108	1.9645	0.6399	0.6670	0.6202	79.0009	82.3557	76.5629	0.02346
30	2.136	2.188	2.0987	0.6761	0.6931	0.6639	83.4713	85.568	81.9659	0.01459
35	2.234	2.240	2.187	0.7081	0.7107	0.6928	87.4227	87.6781	85.5277	0.0087
40	2.2673	2.280	2.242	0.7190	0.7231	0.7107	88.7667	89.2775	87.7453	0.0062
45	2.3343	2.323	2.279	0.7409	0.7371	0.7229	91.4683	91.0113	89.2506	0.0071

Table 12.B Dissolution Profile 5 Dose 81 mg Aspirin USP 2(100 rpm,500ml)

Time Min	Avg. Abs (1)	Avg. Abs (2)	Avg Abs (3)	Avg Conc (mg/ml) (1)	Avg. Conc. (mg/ml) (2)	Avg Cons. (mg/ml) (3)	C/C* (%) (1)	C/C* (%) (2)	C/C* (%) (3)	Avg Std. Dev C/C*
0	0	0	0	0	0	0	0	0	0	0
5	0.410	0.3196	0.1633	0.1124	0.0829	0.0318	13.88	10.23	3.93	0.0096
10	1.7237	1.6537	1.389	0.5414	0.5186	0.4321	66.845	64.02	53.351	0.0291
15	2.047	2.026	1.8577	0.64071	0.6402	0.5852	79.882	79.03	72.248	0.3818
20	2.2603	2.2627	2.059	0.7167	0.7175	0.6509	88.48	88.57	80.366	0.5395
25	2.3217	2.3593	2.346	0.7367	0.7491	0.7447	90.95	92.47	91.938	0.5963
30	2.3333	2.421	2.405	0.7405	0.7691	0.7639	91.42	94.96	94.317	0.7124
35	2.3453	2.446	2.4317	0.7444	0.7773	0.7726	91.91	95.97	95.392	0.7338
40	2.353	2.4483	2.444	0.7469	0.7781	0.7767	92.22	96.06	95.890	0.7425
45	2.371	2.4533	2.4237	0.7529	0.7797	0.7707	92.96	96.22	95.070	0.7473

APPENDIX C

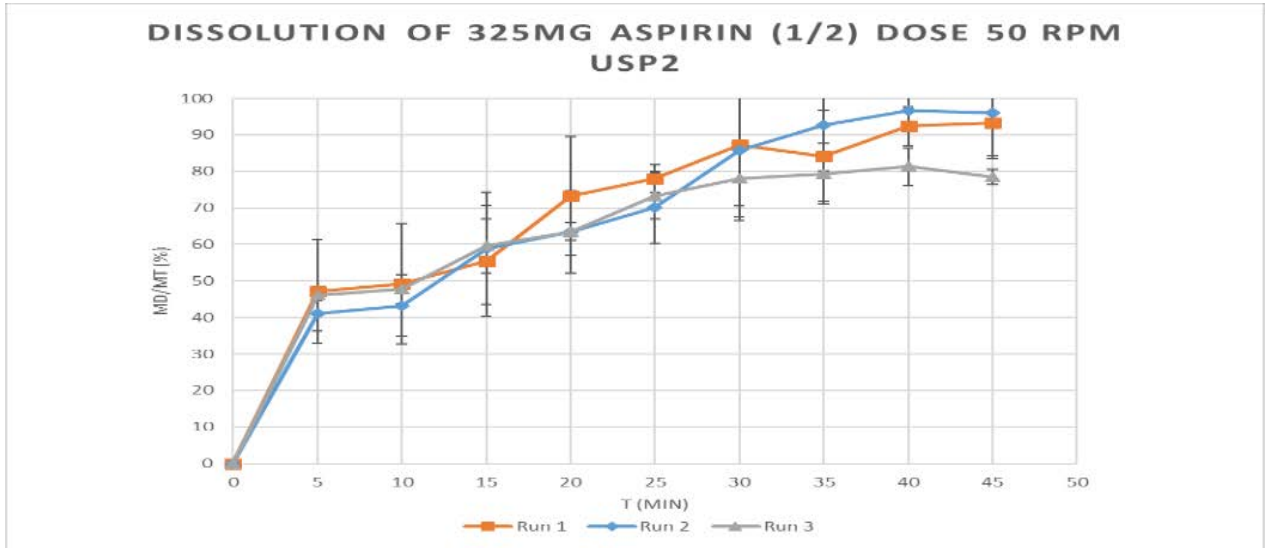
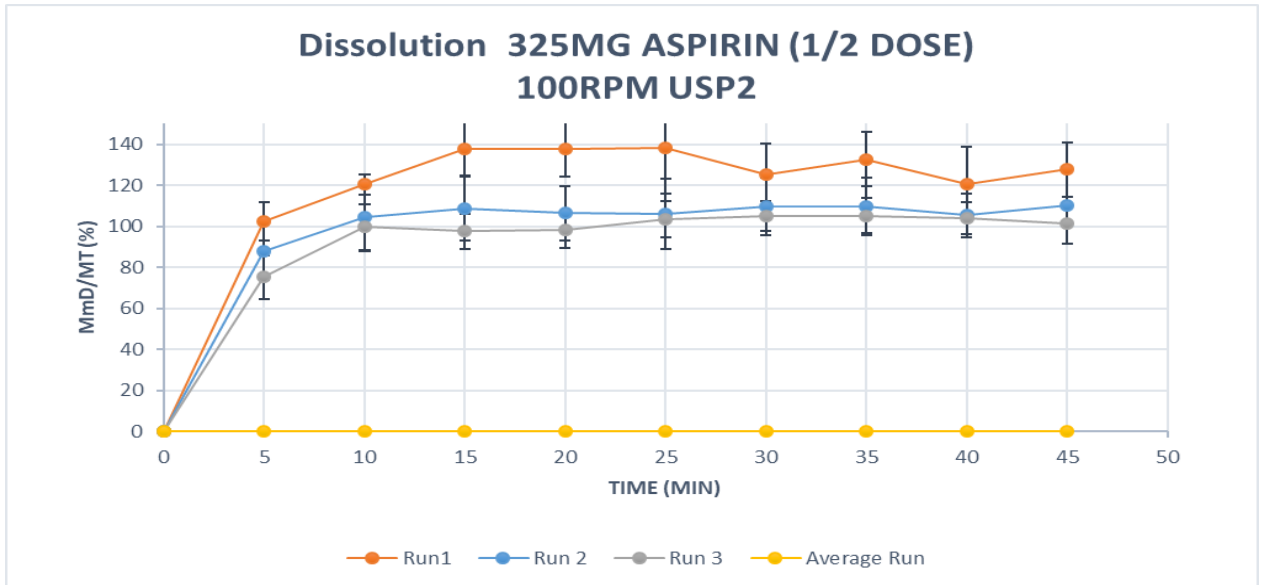


Figure 1.C Dissolution Profile Half Dose 325mg Aspirin USP2(50 rpm).



+Figure 2.C Dissolution Profile Half Dose 325mg Aspirin USP2 (100 rpm).

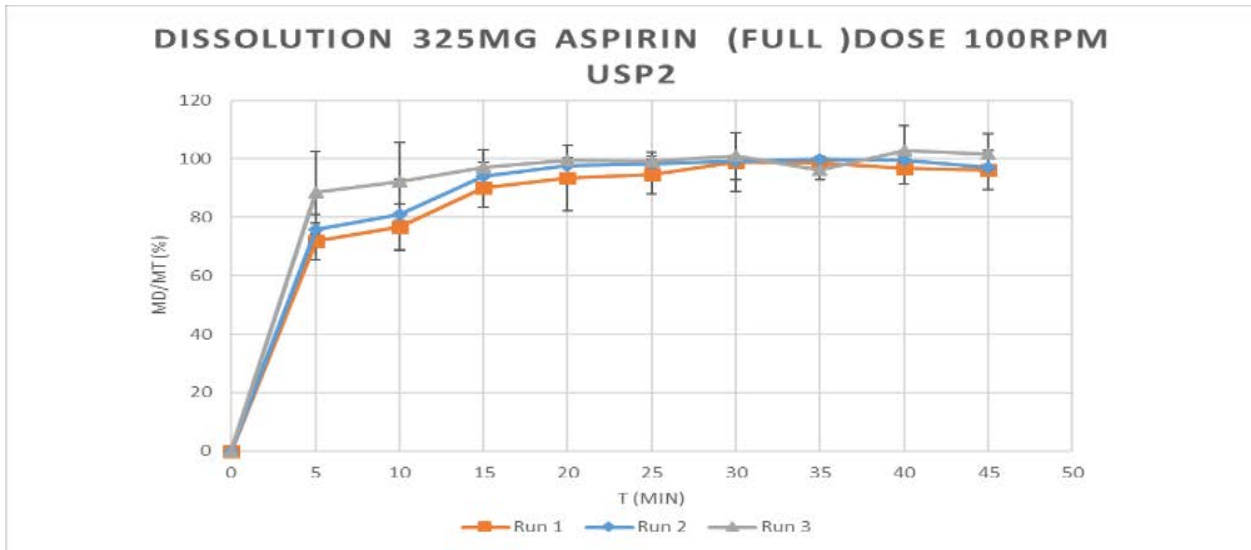


Figure 3.C Dissolution Profile Full Dose 325mg Aspirin USP2 (100 rpm).

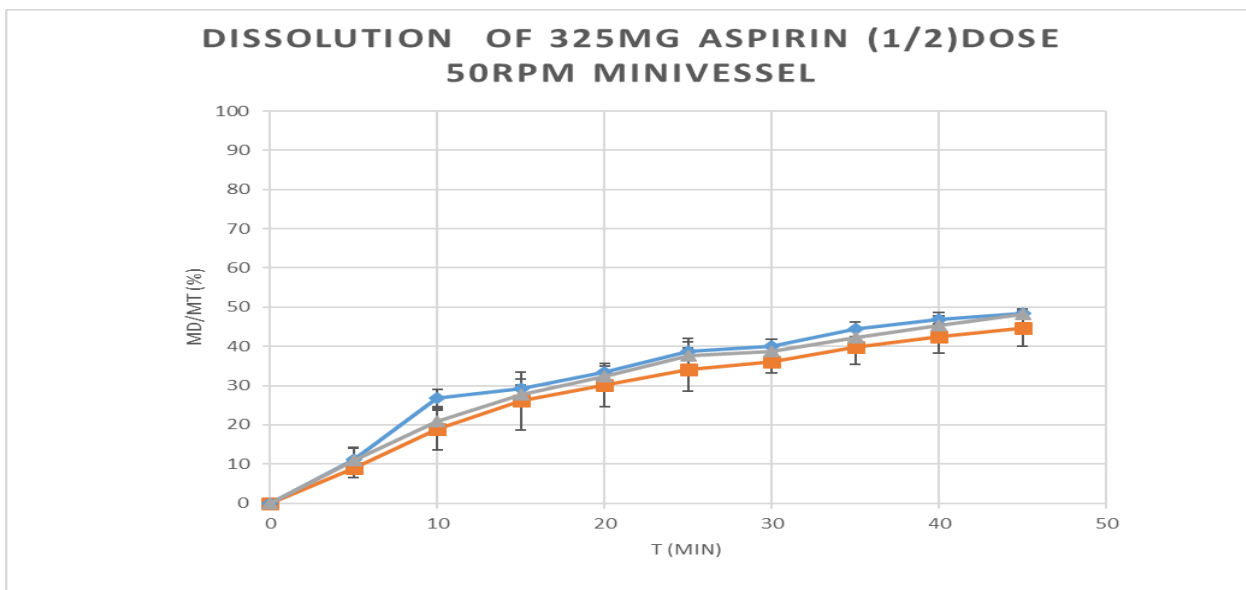


Figure 4.C Dissolution Profile Half Dose 325mg Aspirin Minivessel (50 rpm).

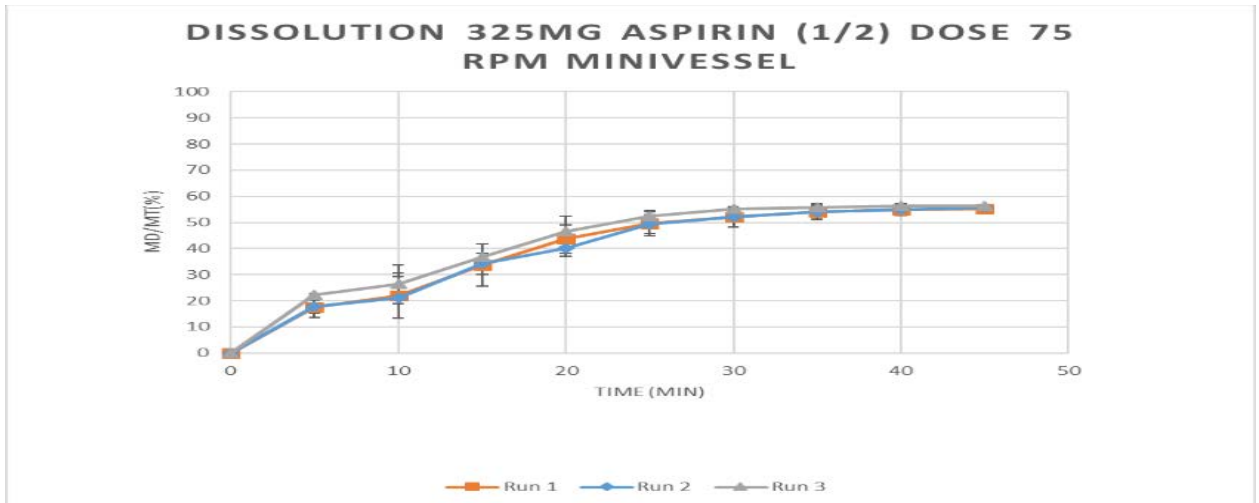


Figure 5.C Dissolution Profile Half Dose 325mg Aspirin Minivessel (75 rpm).

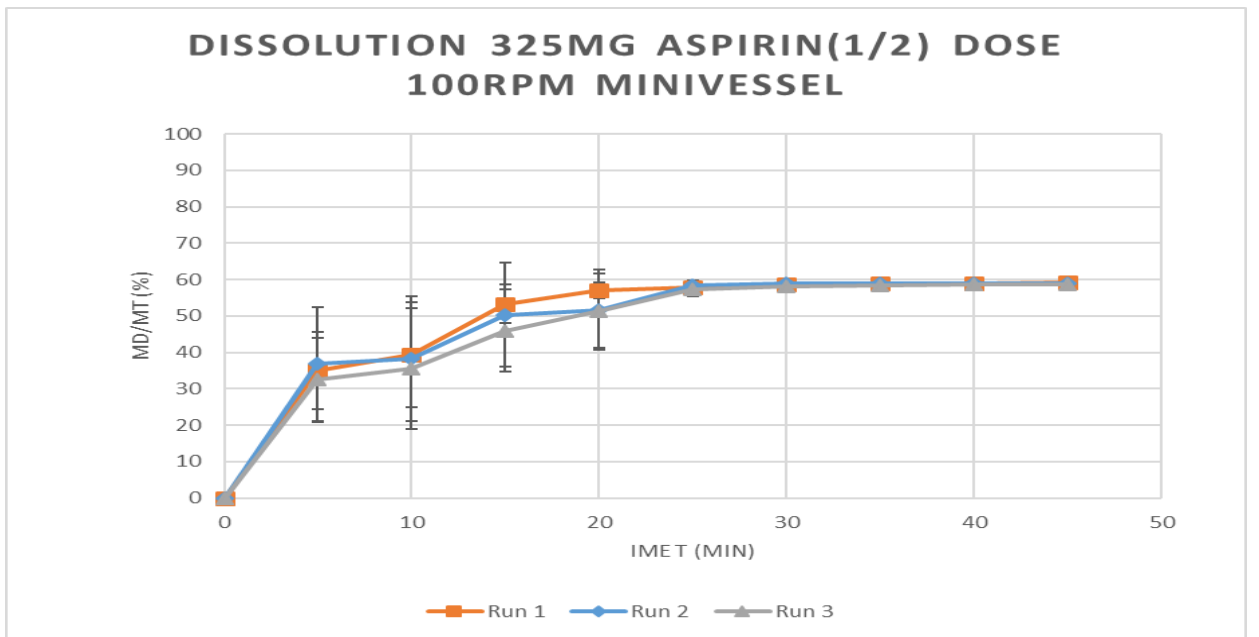


Figure 6.C Dissolution Profile Half Dose 325mg Aspirin Minivessel (100 rpm).

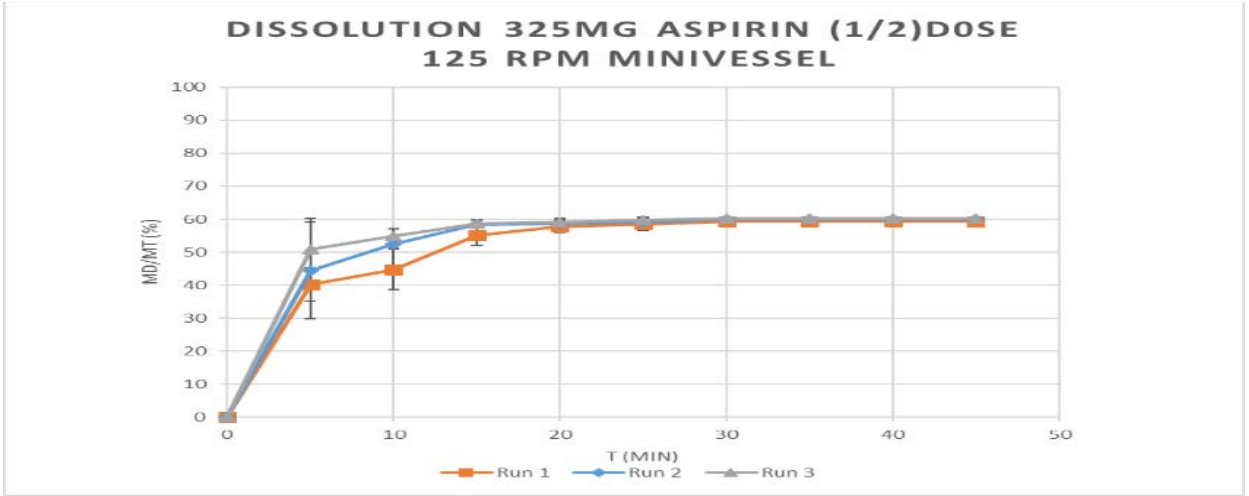


Figure 7C. Dissolution Profile Half Dose 325mg Aspirin Minivessel (125 rpm).

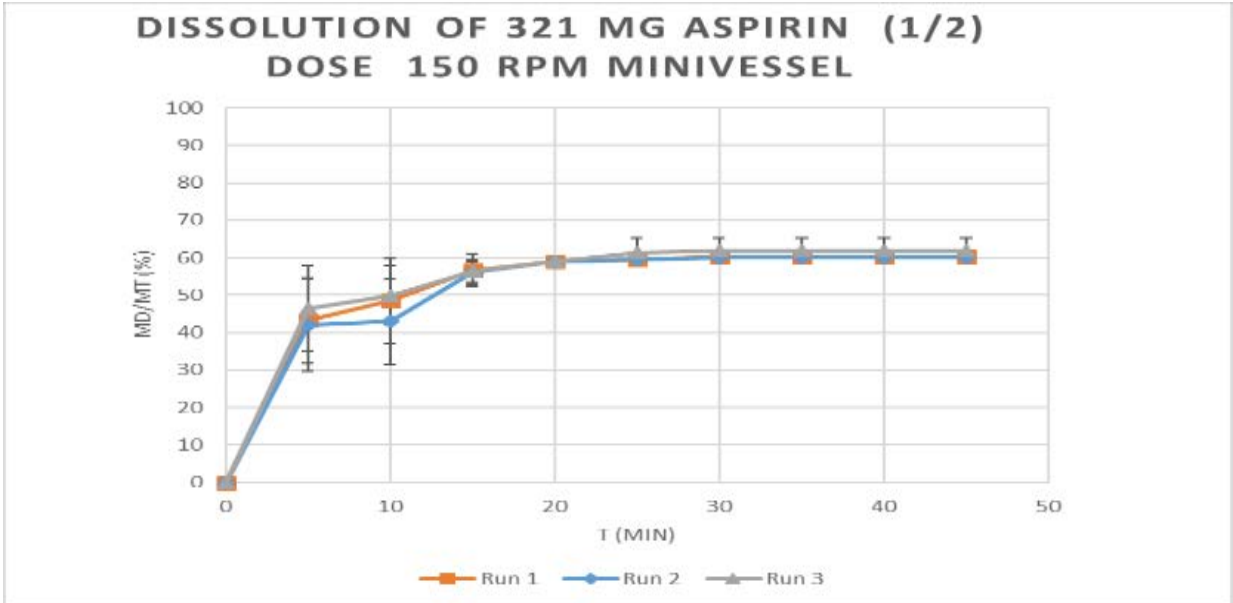


Figure 8C. Dissolution profile Half Dose 325mg Aspirin Minivessel (150 rpm).

APPENDIX D

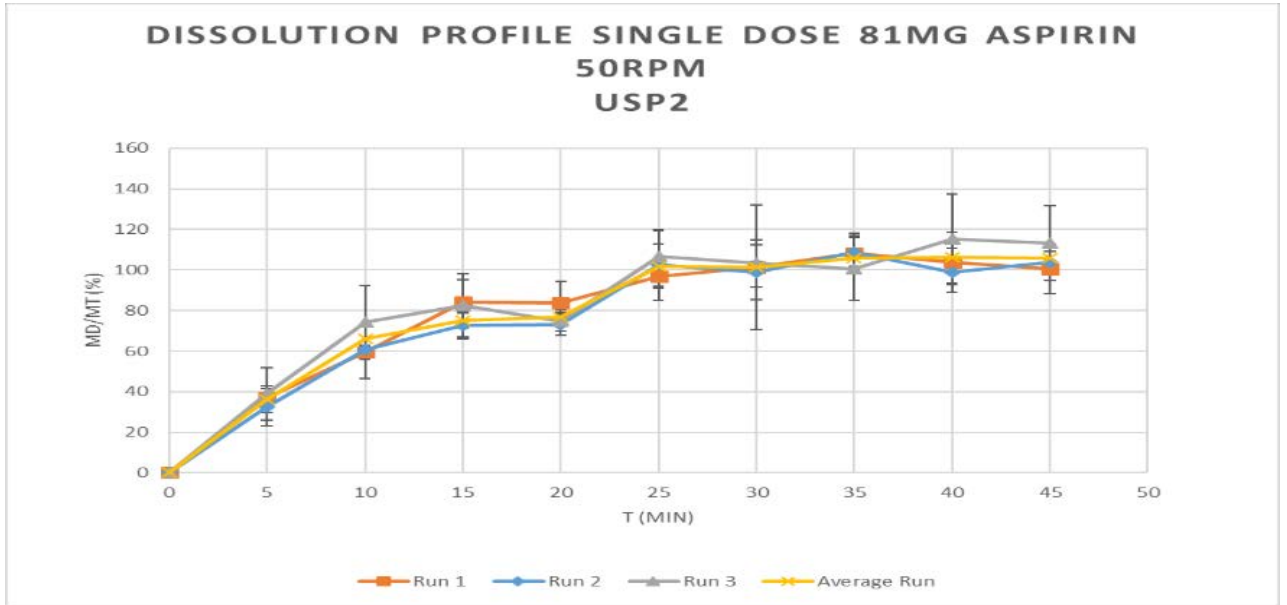


Figure 1.D Dissolution Profile Single Dose 81mg Aspirin USP2 (50 rpm, 500 rpm).

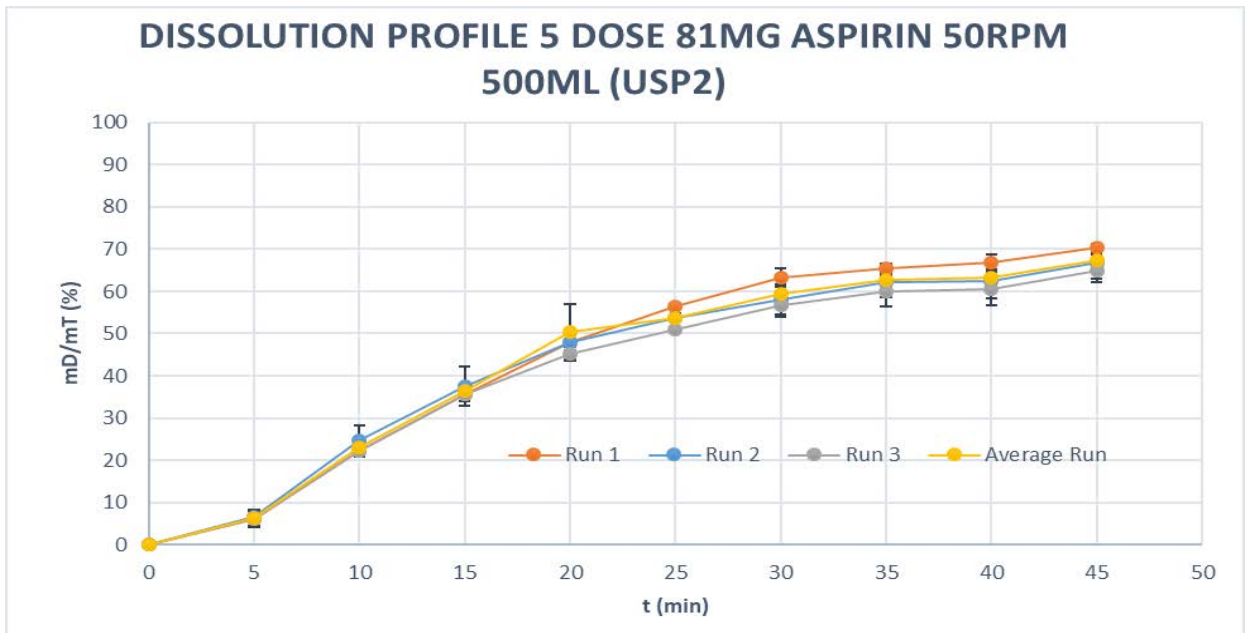


Figure 2.D Dissolution Profile 5Dose 81mg Aspirin USP2 (50 rpm ,500ml).

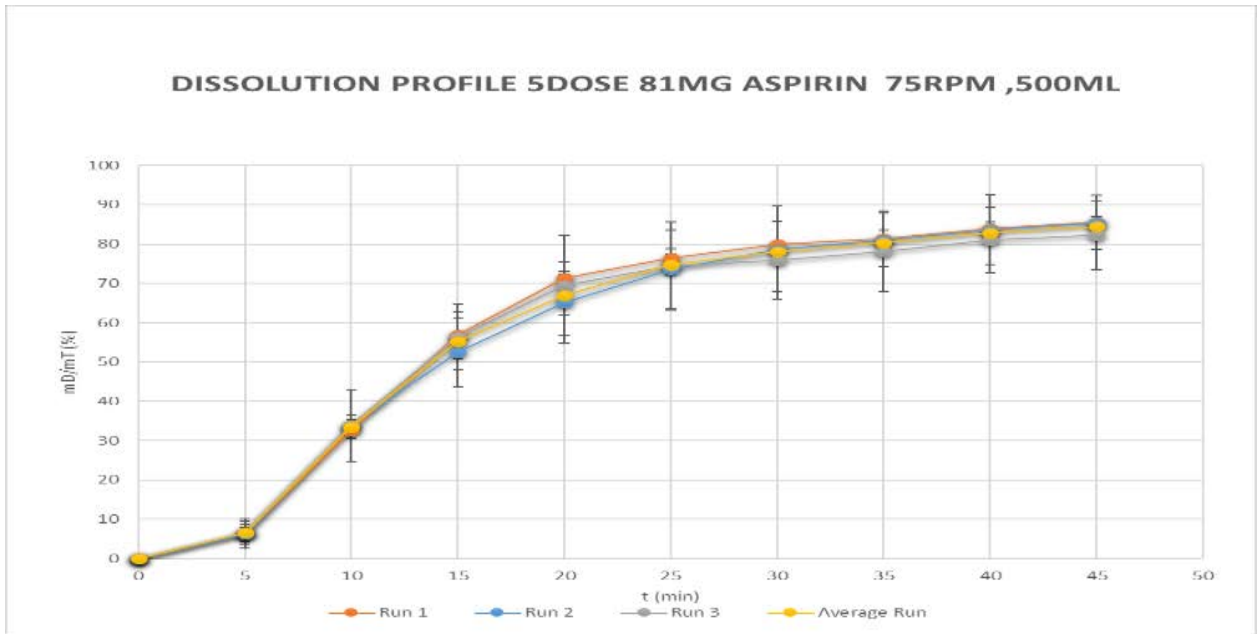


Figure 3.D Dissolution Profile 5 Dose 81mg Aspirin usp2 (75 rpm, 500ml).

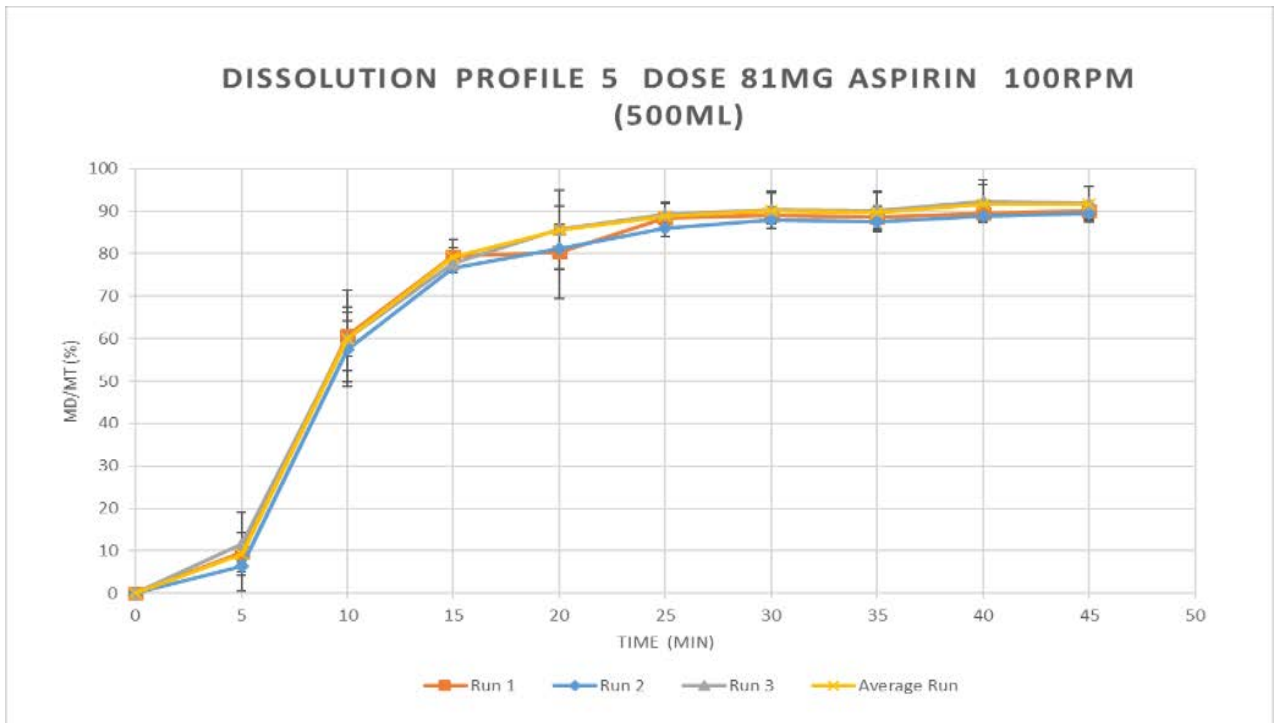


Figure 4.D Dissolution Profile 5 Dose 81mg Aspirin USP2. (100 rpm, 500ml).

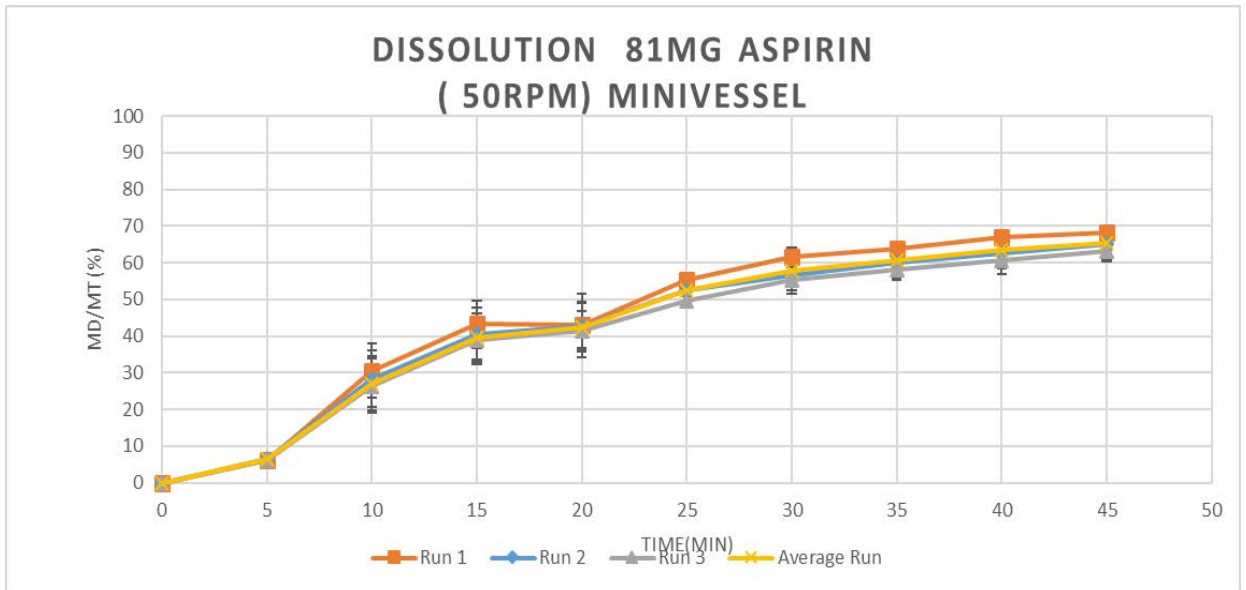


Figure 5.D Dissolution Profile Single Dose 81mg Aspirin Minivessel. (50 rpm).

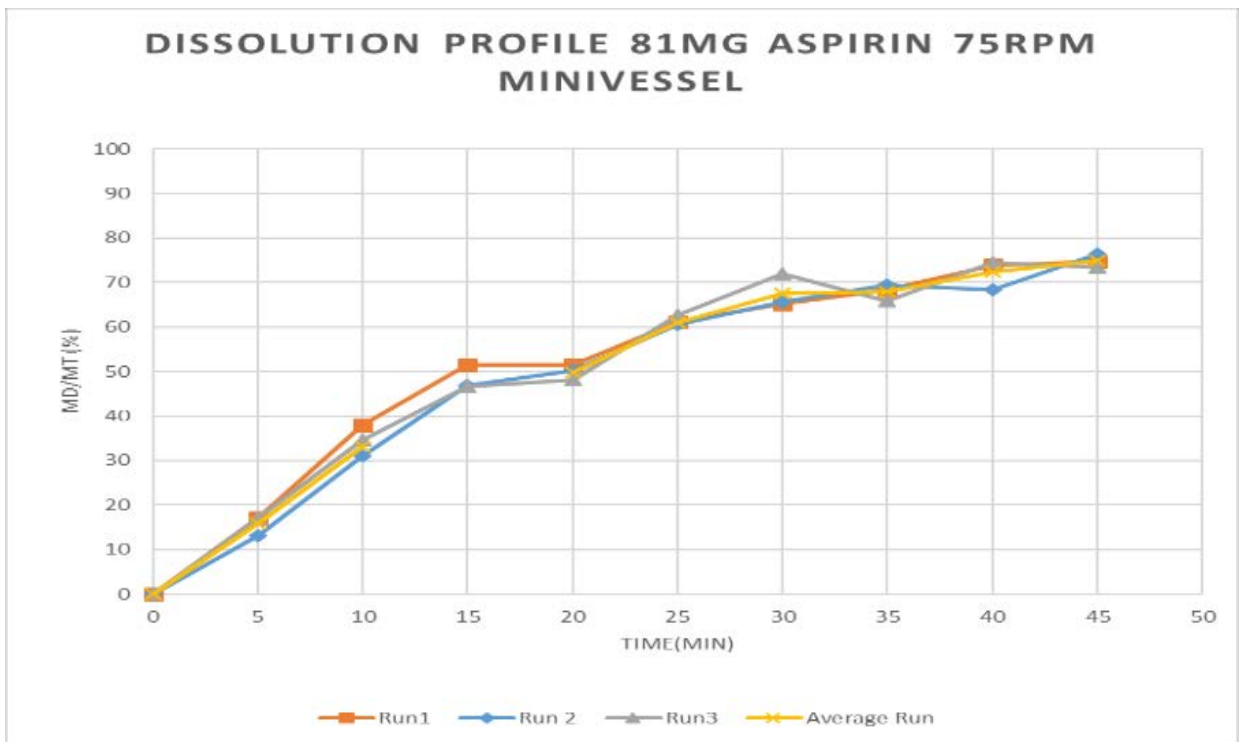


Figure 6.D Dissolution Profile Single Dose 81mg Aspirin Minivessel. (75 rpm).

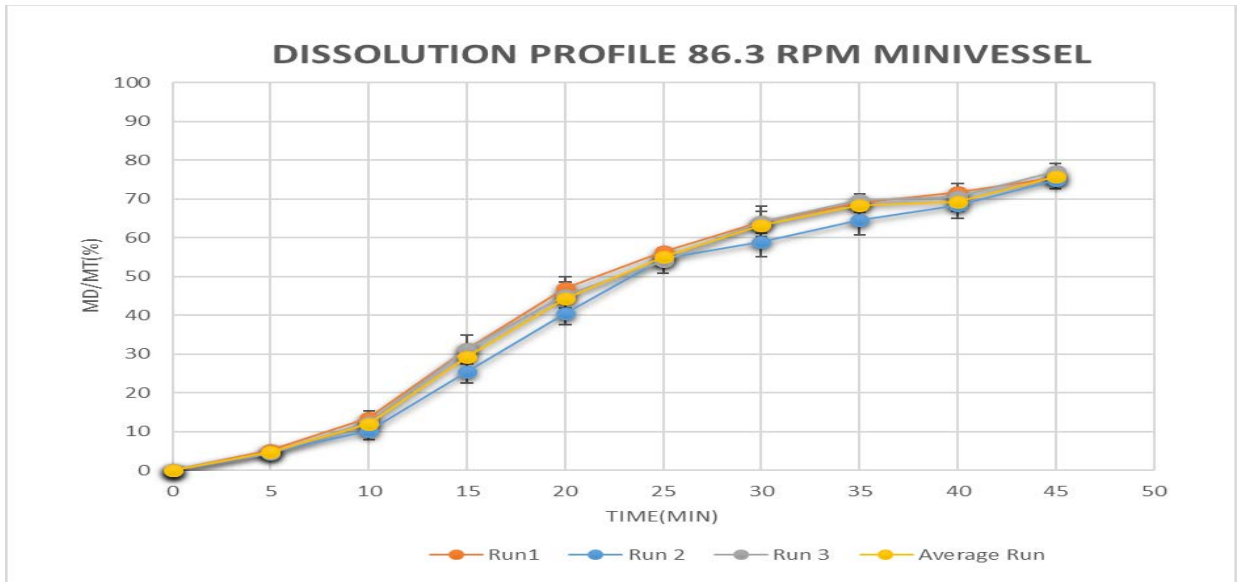


Figure 7.D Dissolution Profile Single Dose 81mg Aspirin Minivessel. (86.3 rpm).

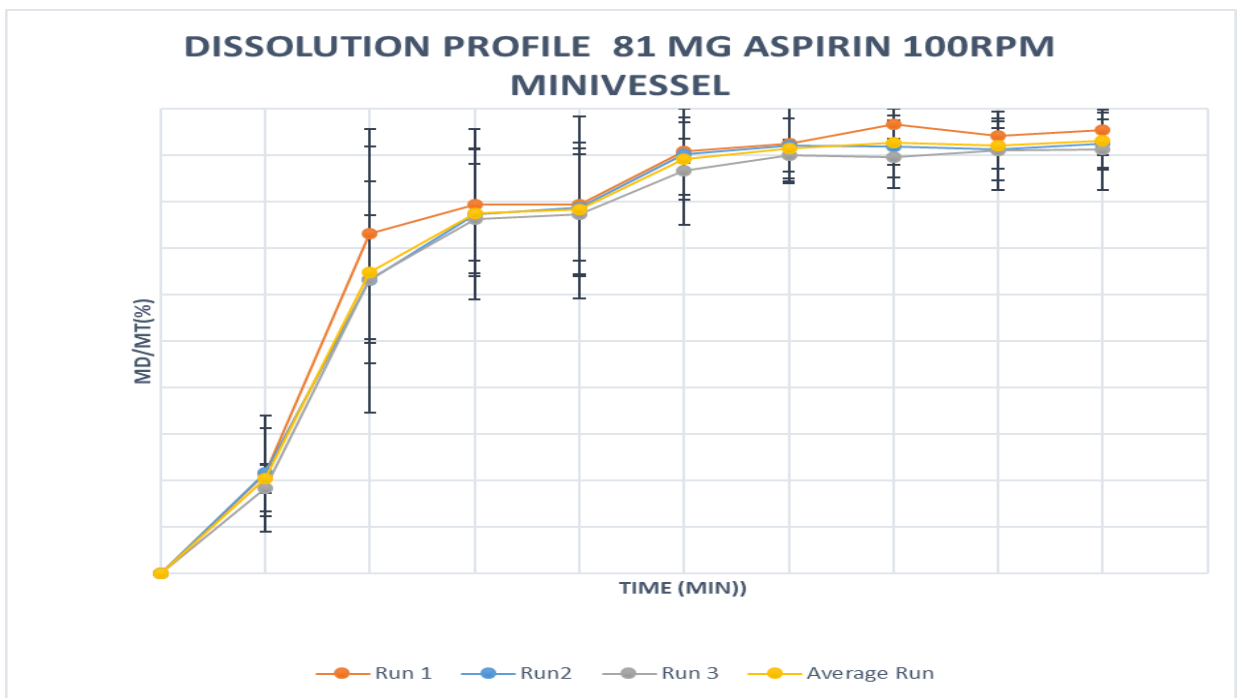


Figure 8.D Dissolution Profile Single Dose 81mg Aspirin Minivessel. (100 rpm).

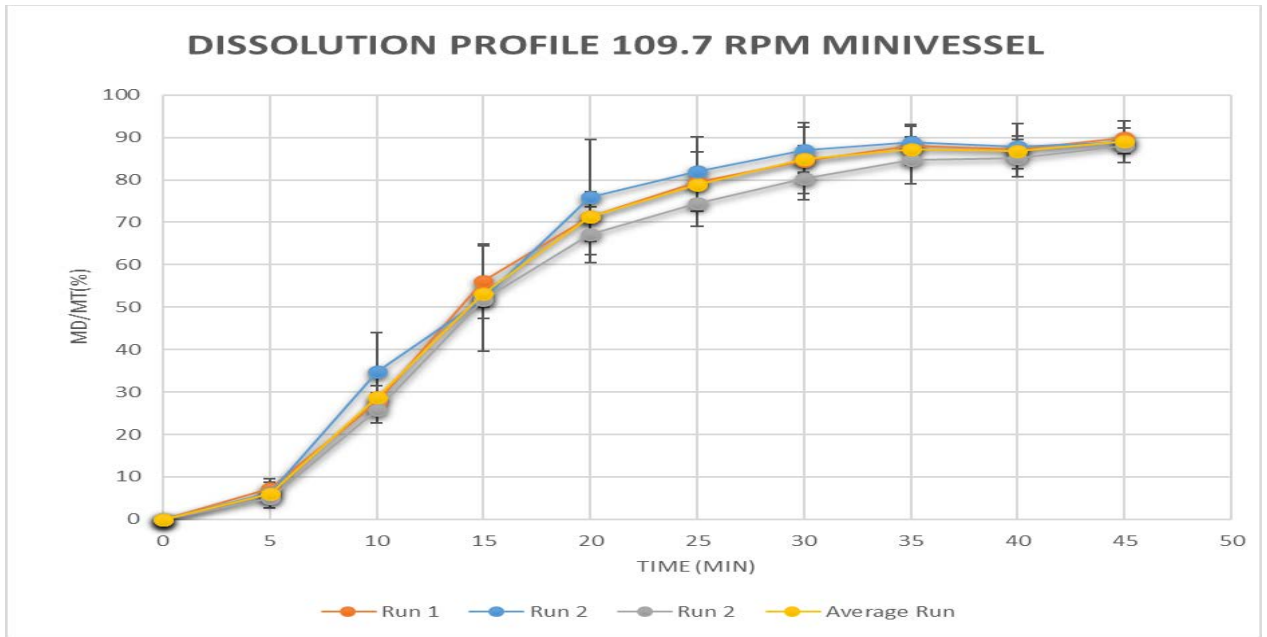


Figure 9.D Dissolution Profile Single Dose 81mg Aspirin Minivessel. (109.7Rpm).

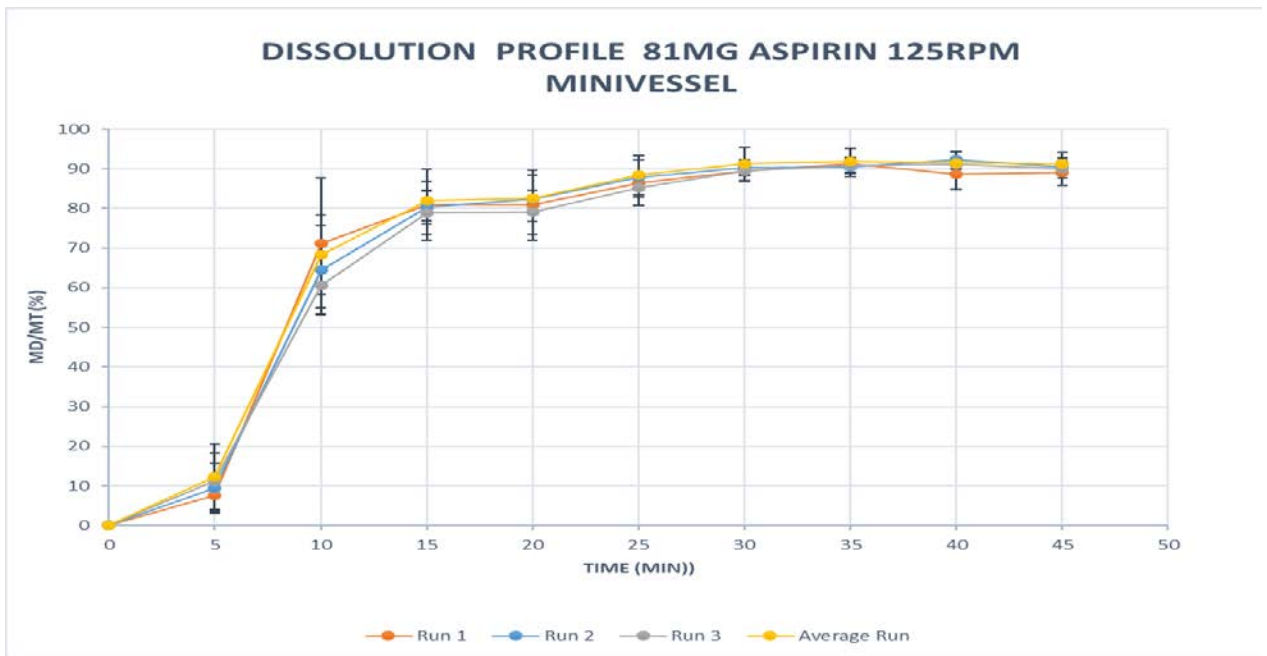


Figure 10. Dissolution Profile Single Dose 81mg Aspirin Minivessel. (125 rpm)

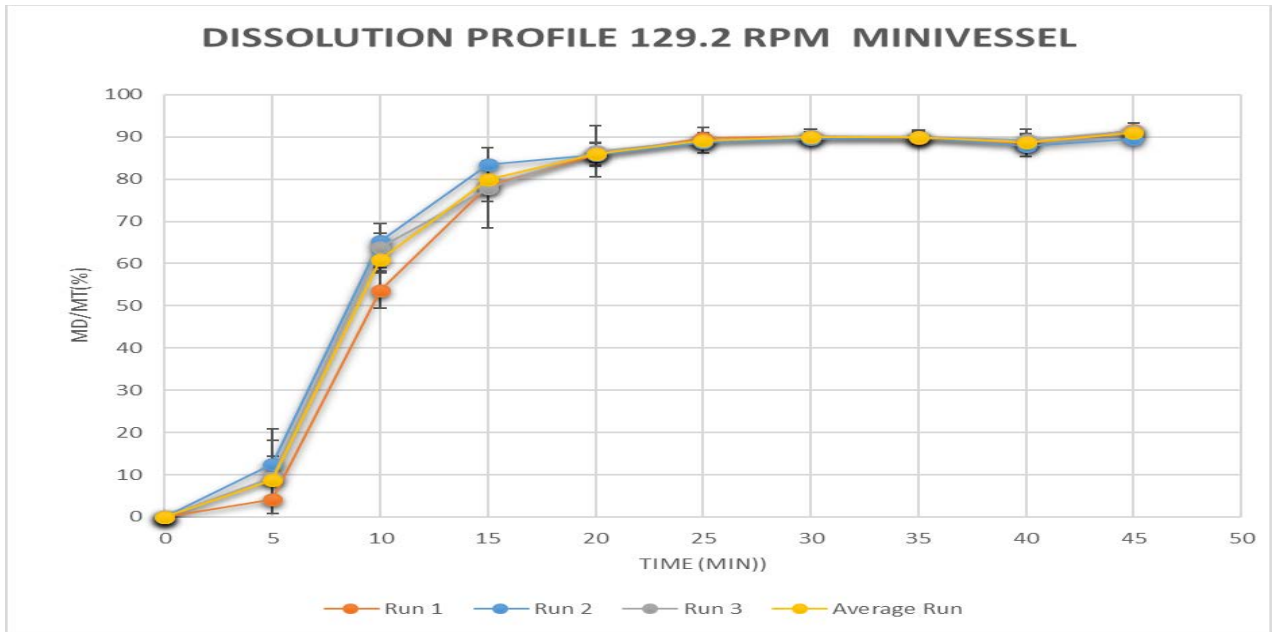


Figure 11.D Dissolution Profile Single Dose 81mg Aspirin Minivessel. (129.2 rpm)

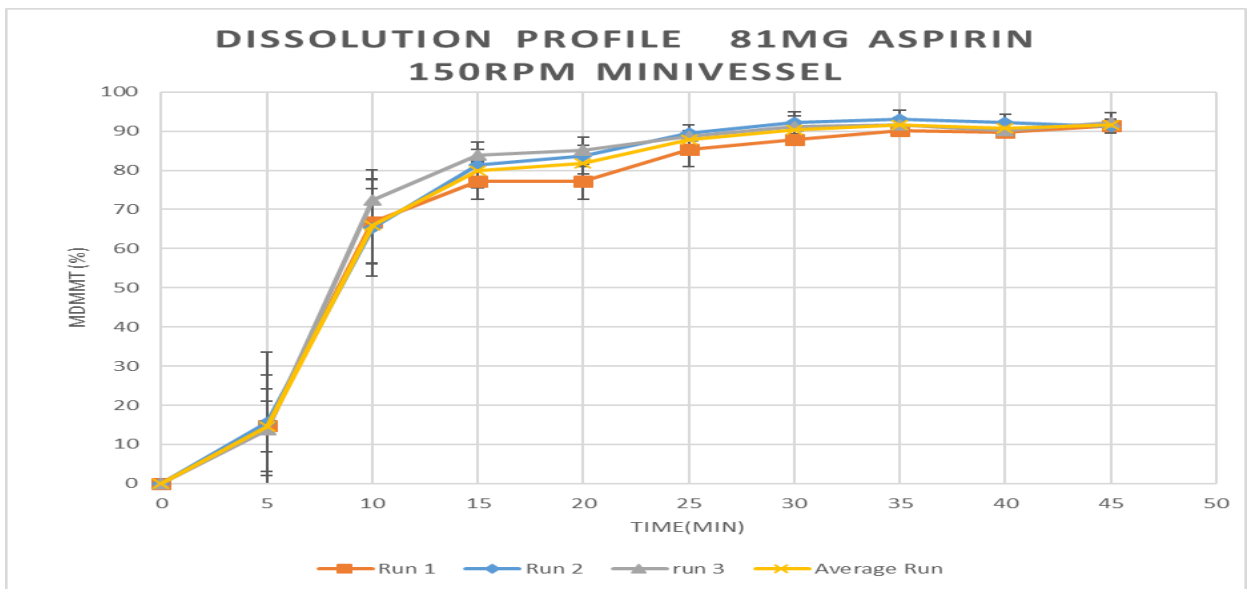


Figure 12.D Dissolution Profile Single Dose 81mg Aspirin Minivessel. (150 rpm)

REFERENCES

- [1] International Committee of Harmonization of technical requirements for Registration of Pharmaceuticals for human use; Harmonized Tripartite Guideline Q8Pharmaceutical development, Proceedings of International Conference on Harmonization Geneva Switzerland November 18, 2004.
- [2] FDA Guidance For industry- Immediate Release Solid Oral Dosage Form, Scale Up and Post Approval Changes.
- [3] European Pharmacopeia 2.9.3 Dissolution for Oral Solid Dosage forms, The Council of Europe (European Directorate for Quality Medicine and Health Care), Strasburg France 2009.
- [4] Dissolution <711>In the United States Pharmacopeia and National Formulary USO 31-NF26; The United States Pharmacopeial Convention, Inc: Rockville MD, 2008 (26) Baxter et al
- [5] Costa P; Sousa Lobo J M Modelling and Comparison of Dissolution Profiles Eurj.PharmSci 2001,13(2)123-133
- [6] Armenante P. M, Wang: Experimental and Computational Determination of the Hydrodynamics of the Minivessel Dissolution Testing System [8].
- [7] Armenante P.M, Bia GE (2008): Velocity Distribution and Shear Rate Variability resulting from change in the Impeller Location in USP Dissolution Testing Apparatus .
- [8] Armenante, P. M., Bai, G. (2009): Hydrodynamic, Mass Transfer, and Dissolution Effects Induced by Tablet Location During Dissolution Testing.
- [9] Baxter et al: Understanding the impact of media Viscosity on Dissolution of Highly Water-Soluble Drugs with USP Dissolution Apparatus using Optical Induce Fluorescence (PLIF) Method.
- [10] Moore J, W Flanner, H, H Mathematical Comparison of Dissolution Profiles. Pharm Tech 1996,20(6)889-896 .
- [11] Chemistry Manufacturing and Controls, in-vitro Dissolution Testing and in-vivo Bioequivalence Documentation US Food and Drug Center for Drug Evaluation and Research, Washington DCUSA ,1995; available on line.
- [12] Klien S, V Shah: The Minipaddle Apparatus a Useful Tool in Early Development Stage. Experiences with Immediate Release Dosage Forms, Dissolution Technol 200613.
- [13] Crist G.B.Trends in Small Volume Dissolution Apparatus for Low Dose Compounds Dissolution Technology ,2009;16.1.
- [14] Testing and release for distribution. Current Good Manufacturing Practice for Finished Pharmaceuticals Code of Federal Regulations Title 21 Vol 4 Part 211.165, (e) ,2008.

- [15] Scale -Up and Post Approval Changes for Modified Release Solid Oral Dosage Forms; Guidance for Industry, US Department of Health and Human Services, Food and Drugs Administration Center for Drug Evaluation and Research (CDER).US Government Printing Office: Washington, DC,1997.
- [16] Mehta M FDA Expectations, Consortium of Drug Eluting Stents. Office of Pharmaceutical Science, Food and Drug Administration Center for Drug Evaluation and Research(CDER)March25,2003.
- [17] Crail Debbie, Tunis Adam: Is the Use of a 200ml Vessel Suitable for Dissolution of low Dose Drug Product .
- [18] Khan Fawzia et al: Comparison of Invitro Dissolution Test for Commercially Available Aspirin Tablet.
- [19] Tamas A, R RMaragine R, Minea R: Experimental Determination of Mass Transfer Coefficient in Dissolution Process
- [20] Koral Emil and George Torosan: Dissolution Behavior of Commercial Enteric Coated Aspirin Tablet.
- [21] Scheubel, Emmanuelle, Lindenberg Marc: Small Volume Dissolution Testing as a Powerful Method During Pharmaceutical Testing
- [22] Kukupa J et al: Engineering Tools for Understanding the Hydrodynamics of Dissolution Test
- [23] Practical solutions Varian's Small Volume dissolution systems,[www.varianinc.com/small volume](http://www.varianinc.com/small-volume)
- [24] Noyes A, Whitney W. R: The Rate of Solid Solution Substances in their Own Solution -J.AM. ChemSociety.1897,19.930-934
- [25] USP Salicylic Acid Tablets
<http://www.org/pdf/EN/refstd=/SATablet/lotQ0d200pdf/>accessed July2017
- [26] Wang, B., Bredael, G. and Armenante, P. M. (2017) Prediction of the Operating Conditions for Similarity of Dissolution Performance in a Mini Vessel and a USP 2 Dissolution Testing System Using Hydrodynamic Comparison, Intern. J. Pharm., submitted and under review.