IN-VITRO TESTING OF THE INFLUENCE OF ETHANOL ON THE RELEASE RATE OF ORAL EXTENDED-RELEASE SOLID DOSAGE FORMS

by

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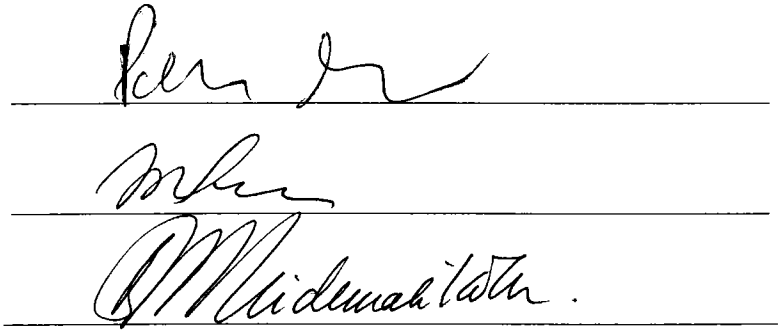

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ABSTRACT OF THE THESIS

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There are many factors that can affect the rate of drug release from an extended-release formulation, such pH of the gastrointestinal tract and dietary intake [1]. However, there is on going concern that alcohol could also greatly affect the release rate of extended-release products. It has recently come to the FDA's attention that some extended-release oral dosage forms are comprised of drugs and/or excipients that exhibit higher solubility in ethanolic solutions than compared to water. Because of this, it can be expected that more rapid drug dissolution may occur when a patient simultaneously consumes alcohol with an extended-release product that is highly soluble in ethanol. This could potentially cause a large dose of the drug to be released at once instead of the slow steady release that was intended, posing a potential health risk to the patient [2].

Currently, there is a strong need to look at the potential of alcohol altering the drug release profile of controlled-release products. A large concern of the FDA is if there are alcohol sensitive extended-release products currently on the market. The goal of this research was to study the affect ethanol has on the release profile of four different types of extended-release formulations. Dissolution testing was conducted on the different dosage forms without ethanol to serve as the control and with various levels of ethanol to determine if the ethanol had an effect on drug release. Dissolution testing was used for the testing because of its ability to provide insight into an oral drug product's characterization and its *in vivo* performance [3]. High performance liquid chromatography was used as the means of analysis to determine such release rates.

The affect of ethanol on the drug release profiles of Palladone® XL Capsules, Detrol® LA Capsules, Cystrin® CR Tablets and Concerta® Tablets has been studied. The drug release profiles for all the formulations were altered by the presence of ethanol in the dissolution media, especially for the Palladone® XL Capsule formulation. The extended-release function of these melt-extrusion pellets was diminished with the smallest amount of ethanol present.

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Section 1 a: Introduction to Extended-Release Dosage Forms

Oral delivery is the most preferred route of drug delivery due to its ease of administration. Of the two most common types, immediate-release and extended-release formulations, the latter is preferred because of the many advantages it holds over the former [4]. Extended-release (ER) formulations, also referred to as sustained-release (SR) or controlled-release (CR) typically contain the entire daily dose of a drug in a single tablet or capsule and are designed to steadily and continuously deliver this drug over an extended period of time [1]. The goal of controlled drug delivery is to better control the magnitude and duration of drug action [5].

The majority of drugs cause side effects or have an action in the body outside of their primary therapeutic function [5], therefore, the lowest dose that has a successful pharmacodynamic effect is strived for. Typically in ER formulations, the entire daily dose of drug is in one dosage form; therefore fewer doses are required per day. In addition, the total administered dose is reduced, while still providing efficient therapeutic effects [4]. Therefore, the major benefits of this continuous delivery is a prolonged duration of efficacy and a reduction in harmful effects of the drug [1].

Since the number of doses required per day is reduced, further benefits include improved patient compliance and a reduction in fluctuations in drug plasma concentration, or reduced highs and lows of drug concentration in the body. Therefore, ER dosage forms minimize toxic side effects that result from high drug plasma

concentrations above the therapeutic window while also improving the effectiveness of the therapeutic agent [6].

The therapeutic window is the range between the subtherapeutic level and the toxic level. Below the subtherapeutic window, the concentration of drug in the body is not sufficient enough for therapeutic effects. Above the toxic level, the concentration of drug in the body is too high and has a high potential to cause serious side effects or toxicity [7]. Controlling the concentration of drug in the body and/or controlling the release rate of drugs can be especially important for drugs with a narrow therapeutic window. Examples of drugs that have a narrow therapeutic window include warfarin, phenytoin, carbamadepine and theophylline [8].

Section 1 b: Introduction to Extended-Release Formulations

The active drugs selected for ER products should have good gastrointestinal (GI) permeability and an extended site of absorption [9]. The formulation parameters and its excipients are also important to achieve controlled drug release. Examples of a typical extended-release dosage form are reservoir and matrix tablets. A reservoir system consists of a drug/excipient core coated with a controlling membrane. A matrix tablet is made up of drug/excipient implanted in a matrix. Coating and matrix materials are mainly hydrophobic polymers such as polyethylene, polypropylene and ethylcellulose, or hydrophilic polymers such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, derivatives of polylactoglycolic acid and polymethacrylates [10].

Other formulations options employed in controlled drug delivery are pH-dependent polymers. These are used for targeting drug delivery to the small intestine because they protect the dosage form from releasing the drug in the acidic environment of

the stomach. These enteric polymers, such as cellulose derivatives, have very low solubility in acidic environments because of free carboxylic acid functional groups on the molecule, which stay unionized at low pH. As the dosage form travels through the body, the pH of the environment around it changes. The functional groups begin to ionize which increases its hydrophilicity and solubility. It then begins to the release the drug in the targeted area. They are also employed to protect drugs that are sensitive to acidic conditions of the stomach [11].

All CR tablets have a common goal of restricting free movement of drug into the lumen of the gastrointestinal tract (GIT). They have a barrier zone that restricts this free movement such as a tablet coating or a core matrix that the drug must move through [12].

Section 1 c: Movement in the Body

The movement of drug via the formulation through the GIT determines the length of time the compound will be in contact with its absorption site. The small intestine transit time is fairly constant in the human body and is approximately three hours. Meaning, it takes approximately three hours for a meal or a drug formulation to move from the stomach to the ileo-caecal junction. However, transit through the colon is much longer with time up to 20 hours or more. The drastic differences in dosage form transit time can affect how much drug is absorbed into the system. Further, if a drug is mostly or exclusively absorbed in the upper GIT, the bioavailability of that drug will be affected by factors that change movement in the GIT. For example, the rate of gastric emptying is slowed when food is in the stomach. Since the transit time is increased, an increase in bioavailability may occur because the dosage form will be kept in the absorption window for a longer period of time [13].

Section 1 d: Disadvantages of Extended-Release Dosage Forms

Although there are many benefits of ER dosage forms, there are also a few undesired situations that could occur in the body to cause a disruption to the slow release rate. One situation that is known to affect the constant release rate is a quick release of drug at the early period after ingestion of the dosage form [14]. This quick burst of drug could cause a larger dose to be absorbed than what was intended.

Another strongly undesired situation in controlled drug delivery is when the extended-release mechanism is disrupted. If this occurs, there is a potential for the entire dose of the drug to be released into the body immediately. This could temporarily expose the patient to a much higher drug concentration than desired. This unintended rapid release of either the entire amount or a large portion of the amount of the drug contained in an ER dosage form is commonly referred to as "dose dumping". Dose dumping could pose serious risks to patients either for safety issues, diminished efficacy or both. The severity of these risks is dependent upon the therapeutic indication and the therapeutic index of the drug. Generally, dose dumping occurs due to a compromise in the release-rate controlling mechanism.

It is currently known that factors such as pH of the gastrointestinal tract and dietary intake can influence the drug release from sustained-release formulations [1]. For example, a study involving felodipine ER tablets showed that the release rate was influenced by the length of time required for gastric emptying. The length of time it takes for gastric emptying to occur is affected by fasted or fed states. The plasma concentrations of the drug after intake of the tablet were also strongly dependent upon the

location of the tablet within the gastrointestinal tract [6]. Further studies have also shown the effect of food [6, 15-19] and antacids [1] on the release rate of ER dosage forms.

Another example of a substance that could affect the release rate of ER dosage forms is ethanol. It is known that ethanol can inhibit gastric motility or gastric emptying. It has been reported that coingestion of felodipine ER tablets with red wine resulted in increased plasma peak levels. This was concluded to be caused by the physiological effect of ethanol decreasing gastric motility [6].

Section 1 e: In-Vitro-In-Vivo Correlation

It is necessary to develop a formulation that is rugged and will not be overly sensitive to any certain environment it may be placed in. It is especially important because of these potentially dangerous situations in which an overdose of drug could occur. A rugged formulation is necessary in order to limit the chances of failure in vivo. Therefore, a key goal in formulation development of a pharmaceutical drug is a well-understood and good predictive in vitro and in vivo model to track the performance of the dosage form. In vitro-In vivo correlations (IVIVC) can be established to correlate in vitro drug release information of various immediate-release and extended-release pharmaceutical formulations to the in vivo drug profiles. The benefits of this correlation are numerous including decreased drug development time, improved quality of the product and a reduced number of human studies during development, because the IVIVC can serve as a surrogate for in vivo bioavailability [20]. Dissolution testing is the tool used to establish IVIVC.

Dissolution testing is a very good way to study the release rate of dosage forms to ensure that the formulation will release the drug steadily in a variety of bodily conditions.

In vitro dissolution data aids in predicting the in vivo performance of solid oral dosage forms. Therefore, in vitro dissolution testing is not only utilized as a method for determining quality of the dosage form, but it can also be used to predict the clinical performance of the product [21].

Section 2: Introduction to Dissolution Testing

Section 2 a: Usefulness of Dissolution Testing

Dissolution has been previously defined as the addition of a substance to a liquid to form a homogeneous solution [22]. Over the past three decades, dissolution testing has become an increasingly useful laboratory technique for the pharmaceutical industry because of its ability to provide insight into an oral drug product's characterization and in vivo performance [3]. By definition, in vitro dissolution testing determines the rate and extent of drug release. Dissolution testing is routinely used to monitor drug products, and it is often used in the development and quality control of drugs and medicinal products [23]. Dissolution testing is major significance for SR formulations due to the complexity of their formulation and the critical need to monitor their controlled release rate.

Drug release from a dosage form and absorption of the drug in the body not only rely on the physiochemical properties of the drug, but are also heavily influenced by the formulation and the physiologic environment of the GIT. Based on the Noyes-Whitney and Nernst-Brunner models, the rate of drug dissolution is determined by the surface area of the dosage form, diffusion coefficient of the drug, the thickness of the diffusion layer, solubility of the drug, volume of dissolution medium and the amount of drug in solution [24].

Section 2 b: History of Dissolution Testing

The concept of dissolution began over 100 years ago in 1897 when physical chemists, Noyes and Whitney, studied the dissolution of two slightly soluble compounds, benzoic acid and lead chloride in water. From this research, they were the first to derive an equation correlating the change in instantaneous concentration with time as a function

of saturation solubility. This was the stepping stone to many great advances in dissolution testing [25].

The idea that a relationship existed between drug dissolution and bioavailability did not occur until the 1950's and for the next 30 years, many dissolution studies gave strong evidence to that link. One of the major factors found to affect the rate of absorption was the product formulation, including the type and brand of excipients used, because they strongly affected the dissolution rate. Due to these findings, bioavailability of products became a huge concern. Therefore, monographs for dissolution requirements of tablets and capsules were introduced in pharmacopeias. Shortly following, Apparatus 1 and Apparatus 2 were adopted as an official test in the United States Pharmacopoeia (USP) and National Formulary (NF) in 1970. Soon after, dissolution testing became a commonly used tool in the pharmaceutical industry [25].

Section 3: Dissolution Testing Conditions

Section 3 a: General Requirements for Dissolution Testing

In the pharmaceutical industry, especially for the quality control unit, the release profiles of ER formulations must strictly adhere to the conditions set by guidance's of the US, Japan and Europe [26]. In the US, the United States Pharmacopeia (USP) provides this direction [27]. In vitro dissolution testing is a requirement in all USP monographs of oral solid dosage forms, at least for formulations in which drug absorption is necessary to achieve a therapeutic effect [24].

As defined under General Chapter <1092> The Dissolution Procedure: Development and Validation in the USP, performing a dissolution test requires a dissolution apparatus, test medium and test conditions that provide a method that is not only discriminating, but is also rugged and reproducible enough for day-to-day use. A discriminating procedure implies that it is capable of distinguishing between significant changes in composition and/or in a manufacturing process, that might be expected to affect in vivo performance [27].

Satisfying sink conditions is one of the main goals in dissolution testing [28]. Sink conditions is the three times the volume of medium that is needed in order to form a saturated solution of drug substance. In most cases, when sink conditions are met, changes in the properties of the dosage form will be shown in the dissolution results [27]. The advantages of using a dissolution test method that meets sink conditions is that it is much easier to understand the drug release mechanism when sink conditions are met. In addition, it is believed that the drug release will take place under sink conditions in vivo, meaning the dissolved amount of drug will be absorbed into the blood circulation system

quickly [28]. And a goal of dissolution testing is to mimic the in vivo scenario as much as possible.

During the development of a new pharmaceutical product, there is a strong need for an in vitro tool that gives insight into the in vivo performance of the drug. Dissolution testing is the most common tool used in the pharmaceutical industry for this purpose. It is performed from formulation development to quality control when the drug is on the market. In formulation development, information of the dissolution properties of the drug and the excipients is important. The dissolution data generated is also used by clinical scientists to establish IVIVC between drug release and drug absorption [29].

Section 3 b: Dissolution Medium

Typically, a volume of between 500 mL and 1000 mL of dissolution medium is used when testing with Apparatus 1 or Apparatus 2 [27]. The dissolution medium should be chosen based on the physical and chemical data of the drug substance, or active drug, and the dosage unit. The solubility and solution state stability of the active drug as a function of pH should be considered. The type of dosage unit such as immediate release (IR) or ER, must be known because this will directly affect the disintegration of the dosage form and the dissolution of the drug. This is because that all formulations vary in release mechanisms, hardness, friability and excipients [27].

The composition of the dissolution medium should simulate what would be found in vivo and should maintain sink conditions for the drug to aid in establishing the IVIVC [30]. Dissolution testing should be evaluated in the physiologic pH range of 1.2 to 6.8 for an IR oral formulation and in the pH range of 1.2 to 7.5 for ER oral formulations. Examples of commonly used media for dissolution include water, dilute hydrochloric

acid, buffers in the physiologic pH range of 1.2 to 7.5 and simulated gastric or intestinal fluid, with or without enzymes. The pH of the dissolution medium has less of an impact on the release rate of most nonionizable and poorly water-soluble drugs. However, adding surfactants to the medium can substantially increase drug solubility [28]. Surfactants, such as polysorbace 80, sodium lauryl sulfate and bile salts, can also be added to dissolution media to enhance the drug solubility [27].

Controlling the pH of the medium is important, especially for ionisable drugs since the pH of the environment is a strong influencing factor on the solubility and dissolution of these drugs. Therefore, commonly used dissolution media include hydrochloric acid, acetate, citrate, phosphate or Tris in the pH range of 1-7.6. In current practice, the buffer capacity of the media varies greatly even though evidence does exist that the buffer capacity can have a strong impact on the dissolution rate from formulated products [30].

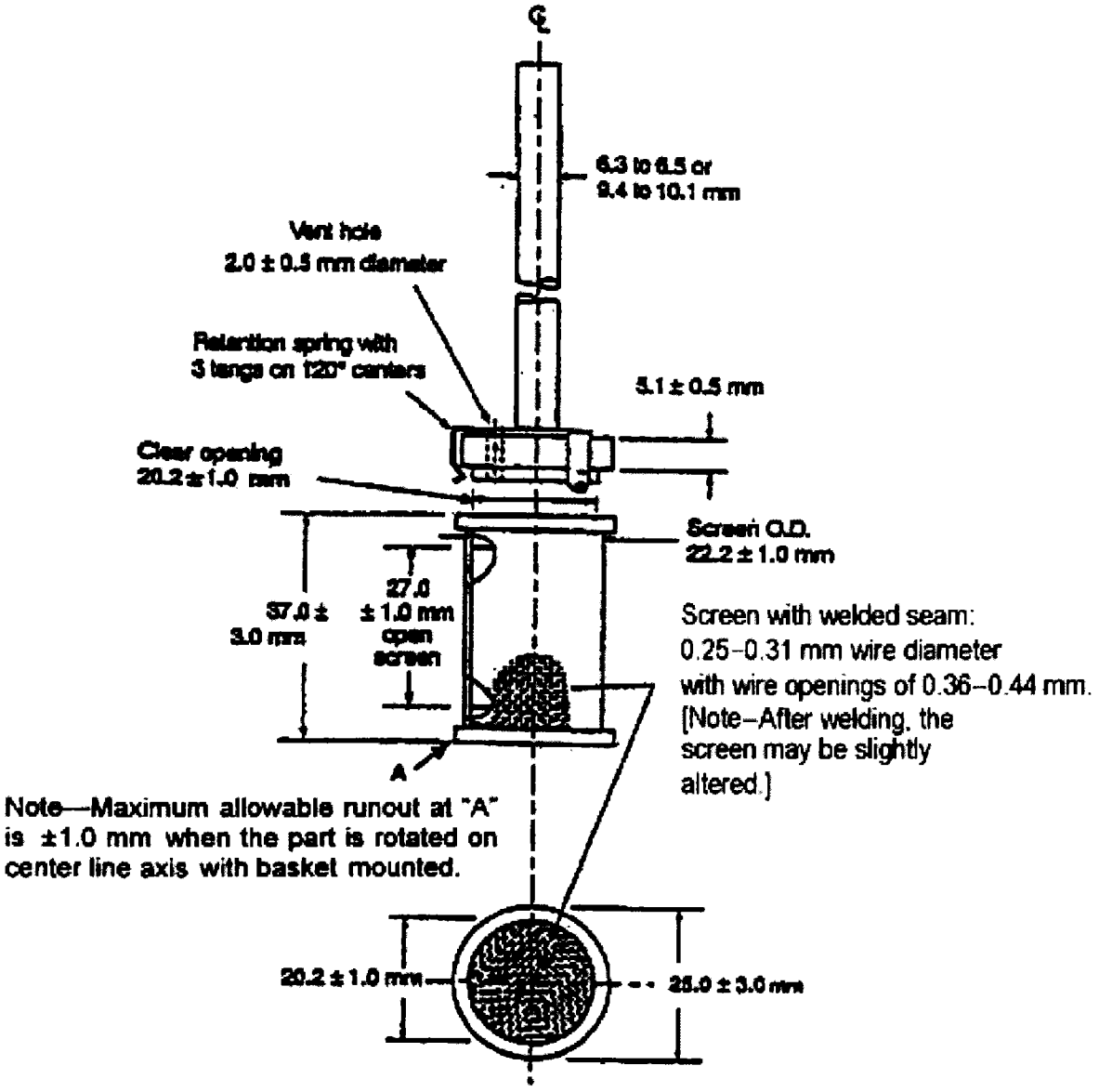
Deaeration is important in dissolution testing because air bubbles in the dissolution vessels can be a potential problem that affects the dissolution rate of the drug. In some cases, the air bubbles act as a barrier to dissolution if they are present on the dosage unit or on the basket mesh. They may also decrease the available surface area of the dosage unit, which could potentially decrease the dissolution rate. The dissolution rate may potentially be increased if bubbles exist on the dosage unit because the buoyancy is increased. Deaeration is commonly achieved by heating the medium, filtering the medium, drawing the medium under a vacuum for a short period of time or utilizing a helium sparge [27].

Section 3 c: Dissolution Baths

The formulation design determines which apparatus should be used. Apparatus 1 (baskets) or Apparatus 2 (paddles) is typically used for solid oral dosage forms [27]. The following diagrams were obtained from the USP : 711 [31]. Both Apparatuses consist of a motor, a metallic drive shaft and a vessel made from glass or any other inert, transparent material. Vessels may be covered to prevent media evaporation. The vessel are heated and maintained at the constant 37 ± 0.5°C by being surrounded by either a water bath or a heating jacket. Cylindrical vessels with a hemispherical bottom are required. Sizes vary depending on the amount of media. The metallic shaft must be no more than 2 mm at any point from the vertical axis of the vessel. It is also necessary for the shaft to rotate smoothly without wobbling. The speed of agitation is monitored and controlled with a speed-regulating device.

Apparatus 1, shown below consists of a cylindrical stainless steel mesh basket. When the basket is connected to the rotating shaft, the distance between the end of the basket and the inside bottom of the vessel should be measured and maintained at 25 ± 2 mm. The dosage form is placed inside a clean dry basket before the test is begun.

Figure 1: Figure of Apparatus 1 (Basket)



Apparatus 2 is identical to Apparatus 1 except a paddle replaces the mesh basket. All other requirements are the same, including the 25 ± 2 mm distance between the bottom of the paddle and the inside bottom of the vessel. The dosage unit is carefully dropped into the vessel immediately before the test is begun. The paddle rotation is then begun [31].

Generally, dissolution rate is effected not only by the tablet surface area that is exposed to the testing medium but also the shape, diameter and size of the paddles used [32]. Therefore, the parameters and specifications of the paddles are tightly controlled to have consistent and accurate test conditions.

Figure 2: Figure of Apparatus 2 (Paddle)

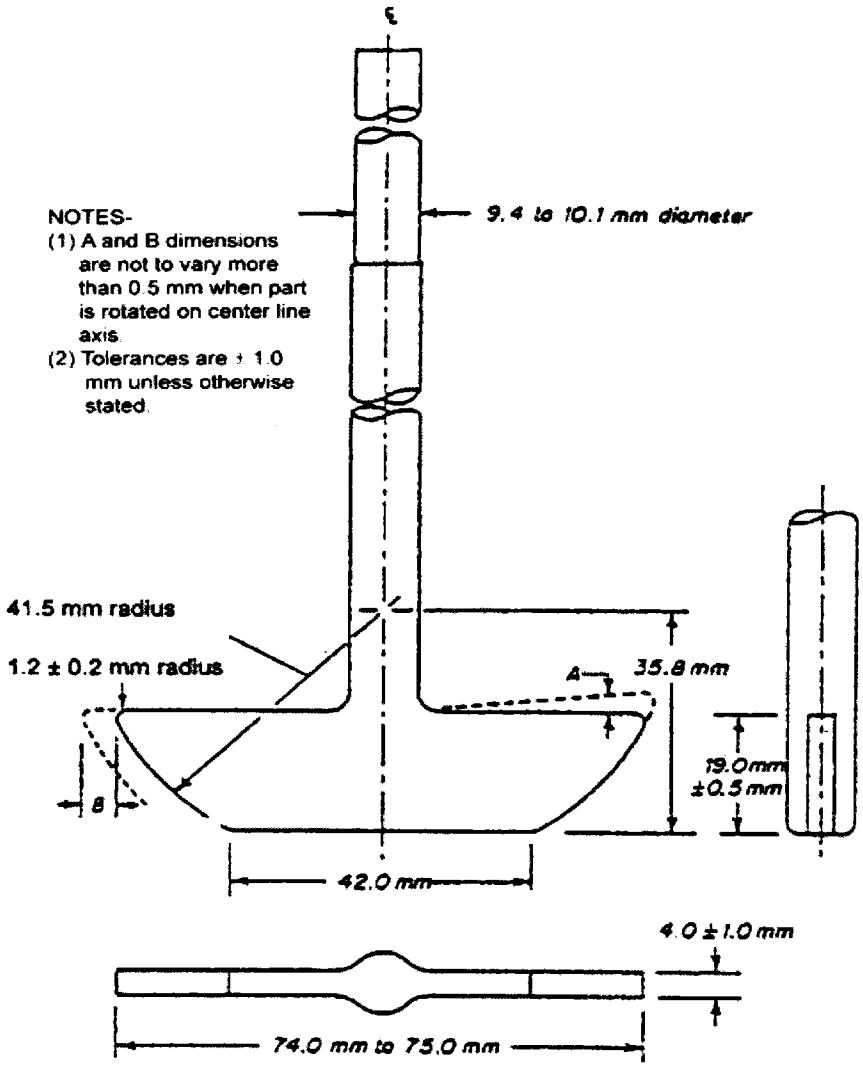
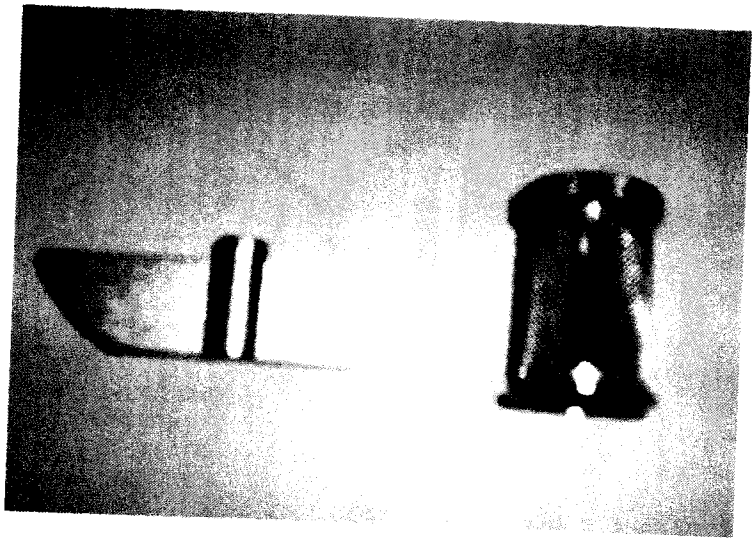


Figure 3: Picture of a typical Dissolution Bath Paddle and Basket



Section 3 d: Agitation

For immediate-release capsules or tablet dosage forms, Apparatus 1 at 100 rpm or Apparatus 2 at around 50 to 75 rpm are the most common. The range of rpm that is recommended is between 25 and 150, in order to maintain constant hydrodynamics and limit turbulence. Overall, the rotation speed should be adjusted to give a profile that a best represents the in vivo performance while maintaining accuracy and consistency.

Section 3 e: Dissolution Time Points

In most cases, the length of a dissolution test for immediate-release dosage forms is between 30 to 60 minutes. The solubility and characteristics of the drug can determine if a single time-point is sufficient or a profile should be conducted. Immediate-release formulations using highly soluble and highly permeable drugs listed in the Biopharmaceutics Classification System need only one time point if the drug product can be shown to release 85% or more of the active drug in 15 minutes. The Biopharmaceutics Classification System is referred to in various FDA Guidances [27].

This system looks at the key parameters controlling the rate and extent of oral drug absorption, which are solubility and permeability [33].

Most immediate-release dosage forms do not meet the single-time point criteria, so a profile must be performed. The number of time points in the profile should be adequate enough to show the ascending and plateau of the dissolution curve. The most common time points used for immediate-release dosage forms are 15, 20, 30, 45 and 60 minutes.

For an extended-release dosage form, several time points are commonly used but the minimum requirement is at least three. A sampling time within the first two hours of testing is used to show no dose dumping should occur. The intermediate time point indicates the in vitro release profile and the last time point shows if the complete amount of drug was released [27].

Section 4: Dissolution Calculations:

Section 4a: Kinetics of Drug Release in Dissolution Testing

The rate of drug release from pharmaceutical dosage forms is mainly controlled by diffusion. Furthermore, the release kinetics from these dosage forms strongly depends on the size as well as the shape of the device. The geometry, size and surface area can be adjusted in order to obtain a desirable drug release profile [34].

Factors that affect the kinetics of drug dissolution have been summarized in a calculation based on the Nernst-Brunner and Levich modifications to the Noyes-Whitney model. The equation, which indicates the change in the amount of drug already in solution (X_d) with respect to time, is shown below:

$$\frac{dX_d}{dt} = \frac{A * D}{\delta} * (Cs - Xd/V)$$

Where A is the surface area of the solid drug, D is the diffusion coefficient of the drug, δ is the diffusion boundary layer thickness adjacent to the dissolving surface, C_s is the saturation solubility of the active drug under luminal conditions and V is the volume of the dissolution medium. Most of these factors are influenced by the conditions in the gastrointestinal tract and by the physiochemical properties of the drugs. These conditions include the composition, volume and hydrodynamics of the contents in the lumen following the intake of the dosage form. Therefore, in order for the dissolution testing to accurately show dissolution limitations to absorption these factors must adequately represent physiological conditions.

In vivo, the permeability of the compound through the gut wall is a controlling factor in drug absorption. Therefore, sink conditions are strived for in dissolution testing to best mimic this control factor. Again, sink conditions means less than 20% of the

saturation concentration. Sink conditions are strongly desired in dissolution testing because they can show the fastest possible dissolution rate [29].

Section 5: High Performance Liquid Chromatography

High performance liquid chromatography (HPLC) is the most widely used instrument in the pharmaceutical industry. This is mainly because HPLC testing merely requires the analyte be soluble in the mobile phase. This is ideal in the pharmaceutical industry since the majority of the compounds are highly polar, water-soluble molecules. This is because the human body maintains mainly a polar, water-based system. Therefore, analyzing the drug compound using a HPLC system with a polar mobile phase such as water, acetonitrile and/or methanol is very successful.

Reversed-phase HPLC is by far the most popular application of HPLC since it can be used to analyze polar, semipolar and even nonpolar analytes. Reversed-phase HPLC was used in this research. Reversed-phase differs from normal phase in that it uses a nonpolar stationary phase in the analytical column, such as C18, with a polar mobile phase. The packing in the analytical HPLC columns typically have chemically bonded groups, such as hydrophobic molecules, on the silica surface to aid in compound separation in the sample(s).

The mobile phase in reversed-phase HPLC is typically buffered to aid in controlling the elution order of the solutes because many of them have acid or base functional groups. Typically, the pH of the buffer is around 2 units from the pK so the solute's ionization is fixed and not likely to change. Isocratic elution, which uses constant solvent composition throughout the chromatographic analysis [35], was used in this research.

Section 6: Effect of Alcohol on Extended-Release Dosage Forms

Section 6 a: Previous Studies Conducted

A newly identified substance that could possibly compromise the release rate of ER products is alcohol. It has recently come to the FDA's attention that some ER oral dosage forms are comprised of drugs and/or excipients that exhibit higher solubility in ethanolic solutions than compared to water. Due to this fact, it can be expected that more rapid drug dissolution may occur when a patient simultaneously consumes alcohol with an ER product that is highly soluble in ethanol [36].

This serious issue has not been previously studied in the pharmaceutical science literature or by regulatory agencies. This is largely due to the previous belief that concomitant use of alcohol and sustained-release drugs would be clinically insignificant in terms of dissolution release rate. Additionally, a 20-year old in-vivo study on such effects of ethanol on this dosage form reported no increase in dissolution rate [2].

More specifically, this in vivo study investigated the influence of alcohol on the pharmacokinetics of a diazepam controlled-release formulation. At the time of the study, alcohol reportedly had an impact on the pharmacokinetics as well as the pharmacodynamics of benzodiazepines, with most cases reported for diazepam. Three other studies had also been conducted in the same time period looking at the effects of alcohol also on a CR diazepam formulation.

The pharmacokinetic study conducted to study the influence of alcohol on the pharmacokinetics of diazepam controlled-release capsules involved twelve healthy volunteers in an open-label, three-way crossover study. Each subject was given a 15-mg diazepam controlled-release capsule concomitantly either with 120 mL of water and

another 120 mL of water 2 hours later; or concomitantly with 120 mL of a 50:50 mixture of commercially available vodka and water followed by 120 mL of water 2 hours later; or concomitantly with 120 mL of water followed by another 120 mL of the 50:50 vodka: water mixture 2 hours later. The researchers found that the mean diazepam plasma concentrations at each time point were not different between the three treatments. Therefore indicating the release properties and the pharmacokinetics of the dosage form were not altered with the presence of alcohol [37].

The results from this in vivo pharmacokinetic study further contributed to the lack of research on this topic over the last few decades, even though the number of drugs and the types of release-rate controlling mechanisms has increased drastically [2].

The three other pharmacokinetic studies conducted at the same time period all obtained different results for each study, with outcomes ranging from elevated plasma concentrations with alcohol present, to delayed absorption of the active, to no effect. Wills et al. believed it was due to the fact that all three pharmacokinetic studies varied in their experimental design. In each study the alcohol levels, the drug and alcohol dosing times and the numbers of subjects were all different [37].

In the mid-1970's through 1980, a few studies were also conducted in Germany to determine the effect of ethanol on the in vitro dissolution rate of microencapsulated acetylsalicylic acid [38], the effect of ethanol on the in vivo drug release from microencapsulated acetylsalicylic acid [39] as well as the effect of ethanol on the in vitro and in vivo drug release from acetylsalicylic acid sustained release tablets [40]. It appeared that they too obtained mixed results; however, details of these studies are