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

by

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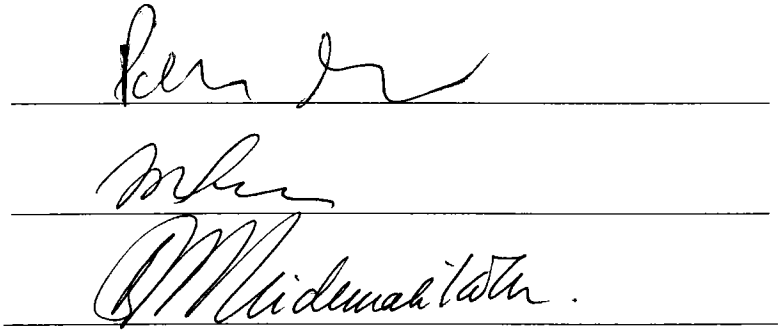

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ABSTRACT OF THE THESIS

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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].

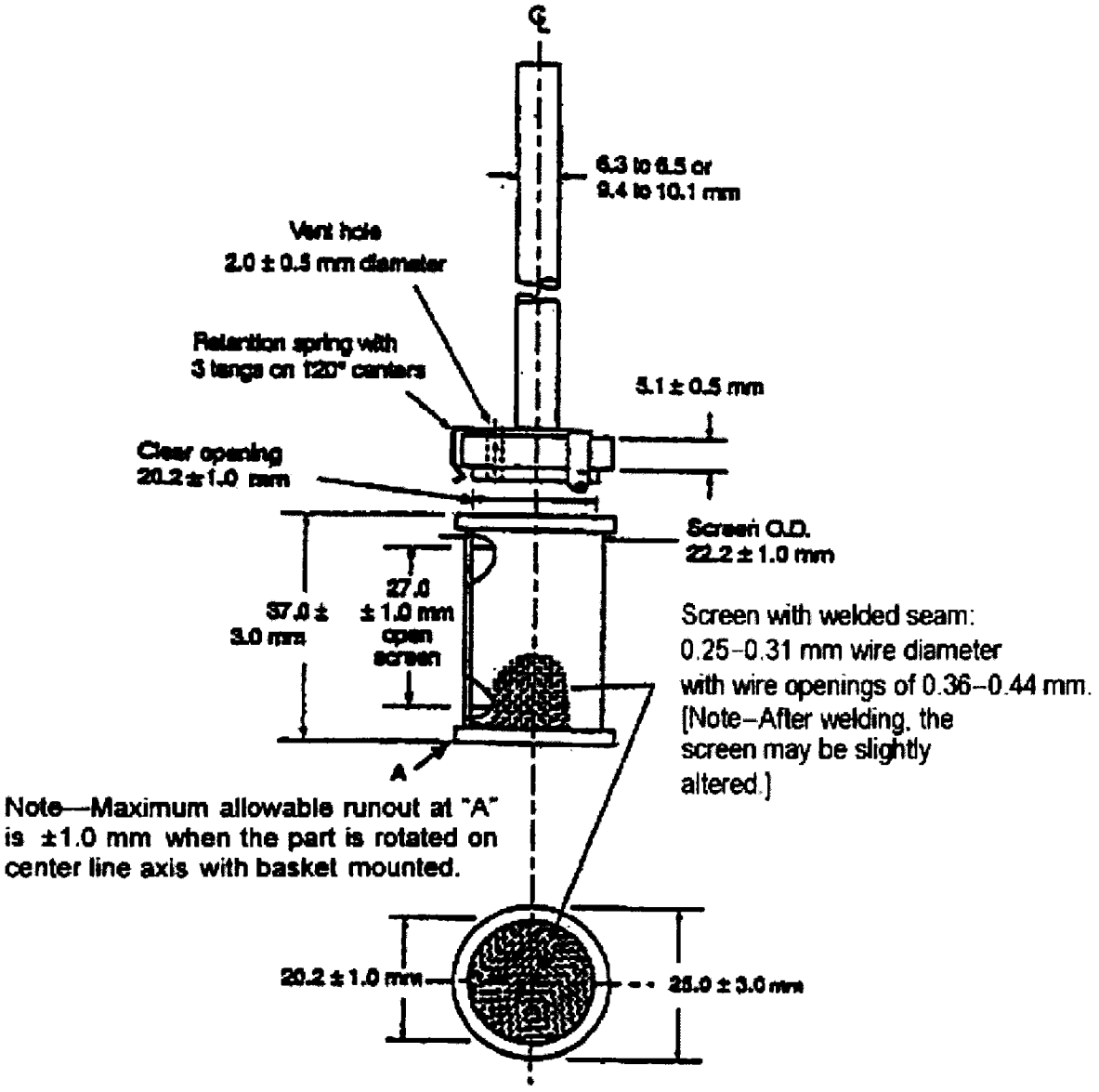
Deaeration is important in dissolution testing because air bubbles in the dissolution vessels can be a potential problem that affects the dissolution rate of the drug. In some cases, the air bubbles act as a barrier to dissolution if they are present on the dosage unit or on the basket mesh. They may 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)

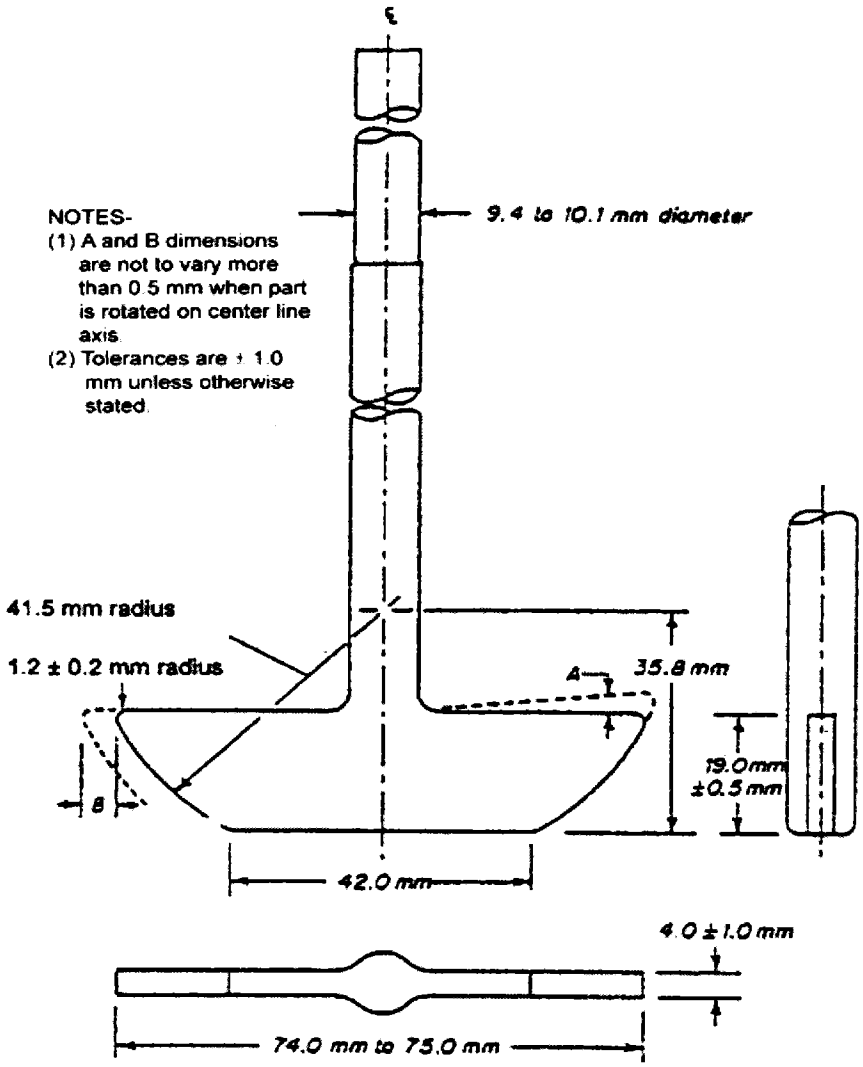
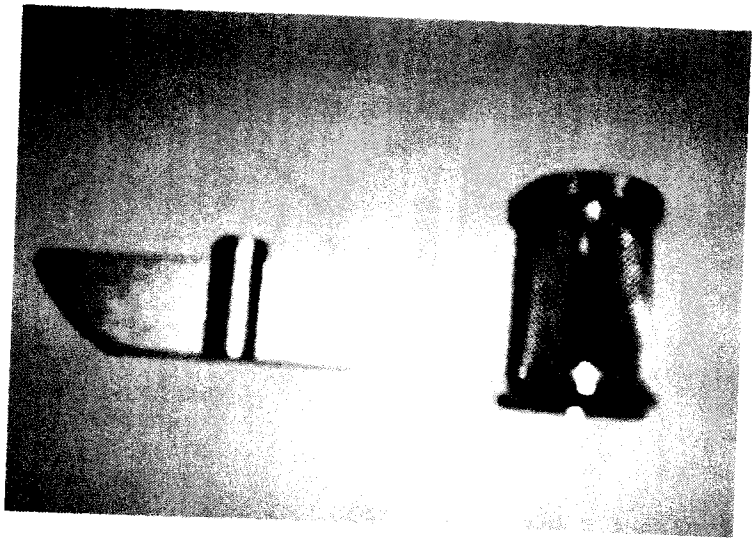


Figure 3: Picture of a typical Dissolution Bath Paddle and Basket



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

lacking due to the timeframe they did this research in and the need for English translation.

Section 6 b: Recent Pharmacokinetics Study on Palladone® XL Capsules

It was not until July 2005 when the potential risk of ethanol on ER dosage forms was found. At this time, the FDA determined that there was a definite severe risk of alcohol induced dose dumping from a hydromorphone modified-release product called Palladone® XL Capsules. This conclusion was partially due to a pharmacokinetic study in healthy subjects, which demonstrated that co-ingestion of the Palladone® XL Capsules with 240 mL (8 ounces) of 40% (80 proof) alcohol caused an average peak hydromorphone concentration of approximately six times greater than when with water. One subject even showed a 16-fold increase when they consumed that amount of alcohol with the drug.

Furthermore, the release rate was also increased by only a small amount of alcohol. The pharmacokinetic study also showed that in some subjects, co-ingested of the drug with only 8 ounces of 4% alcohol showed almost twice the peak plasma hydromorphone concentration than when ingested with water [2]. This study showed that dose dumping occurred with one of the lowest doses, which could lead to serious, or even fatal, adverse events in some patients. An even greater risk exists for the higher strengths of the product [41].

In addition, these dose dumping effects were found to be more pronounced in the fasted state. Luckily, no cases have been reported of injury resulting from alcohol-induced dose dumping from this product. However, due to the alarming results of the pharmacokinetic study, the product was removed from market due to potential fatalities.

Laboratory studies were conducted at the time of licensing for the product that indicated alcohol could accelerate the drug release from these capsules. It was believed that alcohol interacts with the capsule, causing it to break down and release too much drug into the blood at once [42].

Currently, there is a strong need to look at the potential of alcohol altering the drug release profile of other controlled-release products with the potential for dose dumping or retardation of release rate. There is also the possibility that the active drug is much less soluble in alcohol, which could potentially cause a decrease in the bioavailability of the drug or possibly inactivation of the drug [41].

A large concern of the FDA is if there are other alcohol sensitive extended-release products currently on the market. To determine if this is true, an in-vitro approach is preferred. The FDA always strives to minimize health risks to subjects involved in clinical trials and in-vivo pharmacokinetic studies would involve high alcohol loads, to represent the worst-case scenario, as well as a drug product [36]. Several risks exist for the subject, such as high alcohol loads, risk of dose dumping and possible pharmacologic antagonist. If it is an opioid, naltrexone is often administered to block the drugs effect. However, this may not be adequate enough to block all effects of the drug. Also, pharmacologic antagonists may not always be available for cases when other drugs are used [42].

Section 6 c: Recent In-Vitro Alcohol Study

The very first recent study to be published on this subject observed the affect ethanol had on the release rate of aspirin from hypromellose matrices. The in-vitro dissolution and solubility studies indicated that both the mechanism of drug release and

the rate of which the drug released were affected by the presence of ethanol. They believed that the increase in release rate could have been the result of increased drug solubility in the dissolution medium. They also stated that their initial rapid release in the beginning of the tests may be the result of a polymer-alcohol interaction [43].

Section 6 d: Combining Alcohol and Stimulants:

Because of the dangers that exist from the combination of alcohol and pharmaceutical drugs, doctors, pharmacists and labeling on drug products all advise against combining the two. However, several studies have shown that this advice is not always noted and followed. For example, the Center for Substance Abuse Research in the University of Maryland College Park reviewed a few studies of prescription stimulant abuse by college students. They reported that college students often abuse these stimulants, such as methylphenidate, in order to stay awake for longer hours for studying and partying [44].

Hydromorphone has been reported to be a highly abused prescription drug and as addictive as morphine. Pharmacokinetic studies have found that after oral administration of immediate-release and controlled-release formulations, maximum mean plasma concentrations of approximately 18 and 20 ng/mL, respectively. Blood samples taken during several autopsies have shown hydromorphone toxicities with concentrations found between 77 to 2684 ng/mL when hydromorphone was the sole drug detected. Fatal intoxications have also been reported where hydromorphone and ethanol are both detected. Blood alcohol concentrations of 0.160 to 0.090 g/100 mL showed hydromorphone blood concentrations of 110 and 100 ng/mL, respectively [45]. This

could indicate that fatal overdoses could occur at lower drug concentrations when alcohol is present in the system.

Ethanol and hydromorphone alone may cause mild to severe respiratory depression. The dose of each and the tolerance of the person determine the severity of the depression. When the two are co-ingested, the central nervous system detrimental effects can be additive and even fatal [45].

Section 7: Palladone® XL Capsules:

Section 7 a: Formulation Information

Palladone® XL Capsules contain hydromorphone hydrochloride in an extended-release form. It is a multi-particulate melt-extrusion pellet capsule formulation give once daily. Palladone® XL Capsules are an opioid analgesic previously available in 12 mg, 16 mg, 24 mg and 32 mg strengths. The pellet formulation is the same for all capsule strengths. The capsules are filled with identical pellets using different fill weights to achieve different strengths [46].

Hydromorphone, the active drug, is a μ-opioid agonist that has strong analgesic properties depending on the amount dosed. The opioid analgesia category of drugs is very commonly prescribed as a painkiller for cancer-related pain and nonmalignant etiology. It has been used since the 1920s. The benefits it holds over other common painkillers such as morphine and oxycodone is that there is no ceiling effect with hydromorphone hydrochloride and increasing dosage is not as much of a concern [47]. Hydromorphone hydrochloride is qualitatively similar to morphine but approximately 8 times more potent on an equivalent milligram basis when given orally [48].

Hydromorphone is a fine, white crystalline powder and is a semi-synthetic congener of morphine. It is freely soluble in water but only moderately soluble in alcohol [49]. Hydromorphone has a short elimination half-life of 1 to 4 hours for parenteral and immediate-release dosage forms. Therefore the extended-release formulation was advantageous due to its reduction in maximum and minimum plasma concentrations [48]. Purdue Pharma received FDA approval for Palladone® XL Capsules in 2004, but it was later pulled off the market due to it potentially fatal interaction with alcohol [2].

The capsules are based on a controlled-release melt extrusion technology. The pellets containing the active ingredient, hydromorphone hydrochloride and co-melted excipients, release the active ingredient at a slow rate over 24 hours. The inactive ingredients of the pellets consist of ammonio methacrylate copolymer type B, ethylcellulose and stearyl alcohol. The inactive ingredients of the capsule include FD&C blue #2 (for 24 mg strength capsule only), gelatin, red iron oxide (12 mg an 16 mg strengths capsule only), synthetic black iron oxide and titanium dioxide [46].

Section 7 b: Melt Extrusion Technology

Melt extrusion allows the dispersion of drugs in a given matrix to form a true solution or a solid molecular dispersion. The process of extrusion changes a raw material into a product of uniform shape and density. This is achieved by forcing the material through the die under controlled conditions. Two distinct parts that make up an extruder are: a conveying system to move the material and a die system that molds the material into the desired shape. The main advantage of this technology is that solid dispersions of drugs with poor solubility generally have remarkably higher bioavailability [50].

Several studies conducted on the release rate of diffusion controlled ER dosage forms have shown that the drug release rate from hot-melt extrusion (HME) preparations are slower than the drug release rate from traditional ER formulations. This is most likely due to the lower porosity and higher tortuosity, or cross-linking, of the HME formulations [51].

The most popular application of melt extrusion in the pharmaceutical industry is to formulate pellets or granules of consistent size, shape, and density. Palladone® XL Capsules utilized pellets prepared by melt extrusion. The first step to prepare such pellets

is to mix dry powders, drug and excipients using conventional blenders. A liquid phase is then added and further mixing occurs to ensure homogeneity. The wet powder mass is extruded through cylindrical dies or perforated screens with circular holes which forms cylindrical extrudates. Typically, the holes are between 0.5-2.0 mm in diameter. The thermoplastic material leaving the extruder is shaped on-line. For pellets, a rotating knife that cuts the product into spaghetti-like extruded strands is typically used for shaping [50].

In pellet formulations, the two main factors that contribute to and stabilize the molecular dispersions are intermolecular interactions between the drug and the carrier and the viscosity of the carrier. The melt extrusion technology can be utilized for drug delivery due to the availability of a large variety of pharmaceutically approved carrier systems. Examples of these carrier systems include propylvinyl pyrrolidone (PVP) or its co-polymers such as poly(ethylene-co-vinylacetate), polyethylene glycol (PEG), cellulose-ethers and acrylates. Oral pharmaceutical products utilizing the melt extrusion technology have been approved in the USA, European and Asian countries [50].

It has been defined previously that dosage forms classified as solid dispersion typically means that the drug is dispersed in a biologically inert matrix at solid-state prepared by either melting, solvent or a combination of melting and solvent. This approach can increase the bioavailability of the drug. The exact dispersion of the drug in the matrix and therefore the exact release mechanism it employs is not completely understood. The two main theories of drug release from solid dispersions include carrier-controlled release, which means the properties of the drug have no effect on release. This is also dependent upon whether the polymer is soluble or not. The other theory is that the

properties of the drug dictate release and not the polymer itself. The solubility of the drug in concentrated solutions of the carrier seems to be the predominant factor [52].

Section 7 c: Excipient Information

Ammonio methacrylate copolymer is a commonly used excipient in pharmaceutical formulations. It is commonly used as a coating agent, tablet binder and polymer membrane for pellet and tablet dosage forms [53]. Ammonio methacrylate copolymer is soluble to freely soluble in alcohol. Its copolymer type B used in this formulation dissolves only partially in alcohol [49].

Ethylcellulose (EC) is a hydrophobic polymer commonly used in pharmaceutical dosage forms because of its non-toxic, stable and compressible nature. These properties have made them popular in extended-release formulations such as film coated tablets, microspheres, microcapsules and matrix tablets for soluble and poorly soluble drug [51]. Ethylcellulose is also commonly used as a coating agent and tablet binder. Ethylcellulose is freely soluble in alcohol [49].

When an EC polymer matrix is prepared using hot-melt extrusion, the drug release from the porous, hydrophobic polymer matrices begins when the active drug makes contact with the release medium that surrounds it. When this occurs, the drug dissolves and diffuses through the pores. When formulating with hot-melt extrusion, controlling the geometry and structure of the pore network is necessary [51].

Section 8: Detrol® LA Capsules:

Section 8 a: Formulation Information

Detrol® LA Capsules contain tolterodine tartrate in an extended-release drug formulation used to treat overactive bladders. The extended-release formulation was developed to deliver tolterodine over a period of 24 hours [13]. This formulation, manufactured by Pharmacia and Upjohn Company, is a once-a-day capsule available in 2 mg and 4 mg dosage strengths. The recommended dose is 4 mg taken once daily.

The active moiety in Detrol® LA Capsules is, tolterodine [54]. The chemical name of tolterodine tartrate is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. It is a white, crystalline powder with a 12 mg/mL solubility in water. It is also slightly soluble in ethanol [49].

Tolterodine is a competitive, muscarinic receptor antagonist and was the first antimuscarinic agent specifically developed for the treatment of overactive bladder [55]. Antimuscarinic agents, such as tolterodine or oxybutynin, are the primary pharmacologic treatment for overactive bladder [56].

This muscarinic receptor antagonists prevent the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle and gland cells. Tolterodine is used due to is antispasmodic effect it has on the bladder. It functions by reducing the activity of the detrusor muscle. This particular muscle is mainly mediated by cholinergic muscarinic receptors [54].

The main components of this capsule formulation consist of a sugar spheres with a sealcoat polymer layer, a drug layer of tolterodine tartrate and hydroxypropyl methylcellulose, followed by a prolonged-release polymer layer also containing

hydroxypropyl methylcellulose and then an overcoat layer also containing hydroxypropyl methylcellulose . The shell of the formulation is a hard gelatin capsule.

The inactive ingredients include sucrose, starch, hydroxypropyl methylcellulose 2910, ethylcellulose, ammonium hydroxide, medium chain triglycerides, oleic acid, gelatin and FD&C Blue #2. Both capsule strengths are imprinted with a pharmaceutical grade printing ink which contains shellac glaze, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone [54].

According to Patent 6630162 filed by Pharmacia AB filed November 9, 2000 for an extended-release pellet formulation for tolterodine tartrate, the capsules were prepared with a four-layer coating. Beginning with a starch-containing sugar sphere of approximately 0.8 mm in diameter. The first "sealcoat" layer consists of Surelease®, which is an aqueous film-coating layer used for a more consistent core surface. It is comprised of ethylcellulose plasticized with fractionate coconut oil and is manufactured by Colorcon, Inc, USA. The second layer is a 5:1 ratio of active drug and HPMC and its main purpose is for the supply of the drug. The third layer is a mixture of Surelease®. and HPMC in a 6:1 ratio. The first and third layers are used as the main source for controlled drug delivery. A final coat of HPMC is then added, comprising only 1% w/w, to decrease tackiness of beads so they can be cured and encapsulated [57].

Section 8 b: Excipient Information

Hydroxypropyl methylcellulose (HPMC) is a semisynthetic cellulose ether derivative. These hydrophilic polymers are one of the most popular cellulose ether polymers in extended-release formulations due to the several advantages they carry [58]. HPMC is used in controlled drug delivery because it is non-toxic, not dependent upon pH

and is able to hold a wide range of drugs, have high drug loading capacities and are ideal for formulation because they are easily compressed [59]. In addition, it's popularity in hydrophilic matrices is partly due to the reliable slow and steady drug release rate it provides [60].

ER hydrophilic matrices are comprised of the drug dispersed in a compressed water-swellable polymer matrix [61]. HPMC is water soluble; therefore the water is permitted to enter the polymer matrix. When this hydration occurs, the polymer chains uncross and are removed from the matrix. The disentanglement of the chains from the polymer matrix occurs in two different steps. The first step is depends on the speed the fluid penetrates the matrix. This step therefore involves the disentanglement of individual molecules at the surface. The point at which this disentanglement occurs is termed the critical polymer concentration, or polymer disentanglement concentration or $C_{p,\,dis.}$ The critical polymer concentration is determined by the properties of the polymer as well as solvent. The next step transports the molecules from the surface across and aqueous diffusion layer to the bulk solution [62].

Drug release from HPMC matrices is commonly explained as following two different means: drug diffusion through the swollen gel layer and drug release by matrix erosion of the swollen gel layer. However, overall the drug release is mainly determined by diffusion. Erosion is significant for low molecular weight polymers, but for other systems its contribution to release rate is minimal. In addition, release rate studies from published data indicate that release from such HPMC matrices is determined by the viscosity grade of the material [62]. The rate of swelling and erosion of HPMC-based ER tablets in aqueous media determine the release profile of the dosage form. Unfortunately,

they are affected by a variety of factors such as physiochemical properties of the polymer and drug, formulation parameters and composition, and the testing medium surrounding it [63].

Surelease® is an aqueous ethylcellulose (EC) dispersion. As described previously, EC is a water-insoluble polymer and is advantageous in film-coating because of its ability to form flexible but robust coatings. Parameters that influence the drug release rate from EC-coated pellets have been studied extensively previously. These studies reported drug solubility, coating equipment, process of coating and core characteristics have affected the release rates.

Of these influences, the drug's aqueous solubility is the most important factor for coated-pellets when the drug is released by the movement of dissolved drug via diffusion either through the film-coating itself or through water-filled pores formed within the coating. In general, poorly water-soluble drug compounds release slower than water-soluble compounds. The solubility of the drug in water is also very important because it affects the osmotic pressure inside the pellets when surrounded by dissolution medium. The difference in the osmotic pressure between the pellets and the dissolution medium strongly affects the drug release from the pellets [64].

Section 9: Cystrin® CR Tablets:

Section 9 a: Formulation Information

Cystrin® CR Tablets contain oxybutynin chloride in an extended-release formulation given once daily. Oxybutynin is a muscarinic receptor antagonist used for the treatment of overactive bladder [65]. In particular, Oxybutynin inhibits muscarinic acetylcholine receptors. It has one chiral centre and exists in both an R- and S-conformation. Oxybutynin is extensively metabolized in the liver, therefore, after oral absorption it goes through a apparent first-pass metabolism [66]. Oxybutynin chloride is a white, crystalline power that is freely soluble in water and in alcohol [49].

Cystrin® CR Tablets are available in 3 mg, 5mg and 10 mg dosage strengths. This particular formulation is not approved for use in the United States. Penwest along with its collaborator, Leiras, received marketing in Finland in October 1997. Penwest has successfully delivered brand and generic drugs on the market with its patented controlled release drug delivery technology, TIMERx® [67], such as Slofedinipe® XL [12]. The advantages of this drug delivery system include, easy manufacturing and a wide range of drug classes can be used with it. Soluble, insoluble drugs as well as drugs with a narrow therapeutic window can all be formulated in this drug delivery system [67].

Cystrin® CR was the first marketed product that used the TIMERx® drug delivery technology. This unique technology utilizes two heterodisperse polysaccharides, xanthan (X) and locust bean gum (LBG), that self-assemble into a complex three-dimensional structure. The interactions between the two polysaccharides can be altered to permit them to become entwined, more or less entangled or dissolved with time depending on physiological conditions. The Londen-van der Waals, hydrogen and/or ionic bonds

between X and LBG are the chemical factors that influence their response in entanglement [12].

Section 9 b: Excipient Information

Polysaccharides are biopolymers that occur naturally. They are biodegradable, bioadhesive, nontoxic, biocompatible, widely available and inexpensive. Because of these advantageous features, they are commonly used in food, biomedical and cosmetic products [68]. X and LBG are both safe and naturally occurring vegetable materials [12].

Xanthan, a heteropolysaccharide is water-soluble and forms a viscous solution when exposed to water. This thickening is a result of reversible dimerization of the X molecules. When in solution, one X molecule will associate with a second X molecule via hydrogen bonding which will result in a helical structure. The thickening is due to the dispersion of the X helices through the solution, which inhibits water molecules to move freely. The separate X-helices do not bind to other X-helices, therefore it can only form a viscous solution, not a true gel when used alone. Therefore, X is normally not used alone in CR formulations because it does not produce a true gel on its own, which is a weakness in these types of formulations [12].

Locust bean gum is a long-chain polysaccharide that is more complex than X in terms of it physiochemical properties. The LBG molecule has two regions, hairy and smooth regions, which alternate along the mannose polymer backbone. The hairy regions are comprised of successions of galactose molecules that are attached to and stick out from the backbone. These galactose residues are attached to approximately every fourth mannose unit during biosynthesis. The smooth regions are the regions without these galactose residue attachments. In an aqueous environment, two LBG molecules can

become hydrogen bonded at their smooth regions. Since each molecule has several smooth regions, several different LBG molecules become entangled by hydrogen bonding, forming a three-dimensional interlocking network. Unfortunately, this gel structure can only form when the aqueous environment is greater than 60°C. Therefore, LBG is useless in CR tablets when used alone [12] since the body temperature is approximately 37°C.

Combining two or more polysaccharides have complex but highly advantageous properties that depend on the total polymer concentration as well as the proportions of each type of polymer, temperature and solvent medium characteristics. The sensitivities to these conditions is due to the effect they have on the self and hetero interactions between the polymer molecules [68].

Therefore, to achieve optimum formulations, many industrial products use more than one polysaccharide because in many cases the combination enhances their properties. For example, combining a gelling polymer with a non-gelling polymer improves their performance due to the interaction of different chain polymers. The most highly used combinations of polymers, especially by the food industry, are those involving xanthan gum and the plant galactomannans, like locust bean gum. When used together they form a firm, thermoreversible gel with synergistic effects [68].

TIMERx® uses a combination of LBG and X because when they are both in solution, the rigid helices of X are incorporated in the true gel structure of LBG molecules. This induces an increase in viscosity than when either is used alone. This is because the X helices form molecular rigid poles within the LGB matrix, which results in a stronger three-dimensional gel. Other critical advantages of the combination are that

the swelling will occur at ambient temperatures, which is necessary for CR formulations and it is not pH dependent. Lastly, a true gel is formed and not just a viscolysed solution such as in hydrogels produced by HPMC other cellulose matrices [12].

Section 9 c: Drug Release from TIMERx® Formulations

In this formulation type, the drug can move out of the gel into the dissolution medium when a pore or molecular "valve" is open, but is not permitted to leave the matrix when this pore or "valve" is closed. This formulation would have several pores open or closed at one time because they are formed due to the interlocking of the polymers. The pores would be open when the intermolecular bonding between X and LBG is either at a maximum or at a minimum.

Therefore, the pores in TIMERx® gels are controlled by the degree of cross-linking at a given time. For example, when the polymer chains have a low degree of cross-linking, it is believed to cause the pores to open. This is because the drug has straightforward channels to be released from. As the cross-linking increases, the pores become more torturous and constricted, causing the "valves" to close. Therefore, formulations employing this technology can achieve their desired release rate by manipulating the interaction rate of the polymers [12].

The swelling, erosion and solvent front penetration properties of mini-matrices of xanthan gum and locust bean gum. In general, xanthan gum showed the greatest swelling index but a moderate erosion rate. Locust bean gum displays a high erosion rate but a low swelling index [69]. The solubility of these polymers in ethanol is unknown.

Section 10: Concerta® Tablets

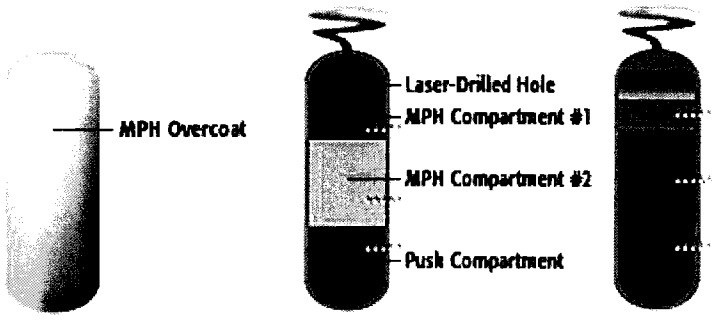
Section 10 a: Formulation Information

Concerta® Tablets contain methylphenidate hydrochloride in an ER formulation used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Concerta® Tablets are a once a day formulation available in 18, 27, 36 or 54 dosage strengths are designed to have a 12-hour duration of effect [70]. Methylphenidate, a central nervous system (CNS) stimulant is the most commonly prescribed drug for ADHD [71]. It is believed that ADHD could result from a lack of dopamine due to induced levels of the dopamine transporter [72]. CNS stimulants are the only pharmacologic agents approved by the Federal Drug Administration (FDA) for this disorder. Although the mode of therapeutic action remains unknown, methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space [71].

Chemically, methylphenidate HCl is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. In this racemic mixture, comprised of the d- and l-isomers, the d-isomer is more pharmacologically active than the l-isomer. Methylphenidate HCl USP is a white, odorless crystalline powder. It is freely soluble in water and in methanol, and is soluble in alcohol [70].

This osmotic pump formulation utilizes osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, is comprised of several components. It entails an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The illustration below depicts the compartments of the formulation [73].

Figure 4: Figure of the Concerta® Tablet Formulation



Morning
The MPH overcoat provides immediate release of 22% of the dose within 1 hour.

1 hour later
The push compartment expands, releasing MPH from MPH compartment #1 for the rest of the morning.

Afternoon
The push compartment continues to expand, releasing MPH from MPH compartment #2 during the afternoon.

This extended delivery results in efficacy through 12 hours.

The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. A precision-laser drilled orifice is made on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate.

Eventually, water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The controlled release membrane component controls the drug delivery rate by controlling the rate at which water enters the tablet core. Additionally, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of Concerta® Tablets. The biologically inert components of the tablet remain intact when in the gastrointestinal tract and are eliminated in the stool as a tablet shell along with insoluble core components.

Concerta® Tablets contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide and triacetin [70].

STUDY DESIGN

Section 11: Study Design

Section 11 a: Purpose of the Study

The purpose of this study was to determine the effect of alcohol on the drug release profile of four different ER formulations. In vitro drug release studies were conducted on Palladone® XL Capsules, Detrol® LA Capsules, Cystrin® CR Tablets and Concerta® Tablets in designated media with varying amounts of ethanol. The release rate of each formulation in a control medium was compared to its respective release rate in ethanolic medium to detect any release rate changes due to the presence of alcohol.

Dissolution and HPLC conditions used were either taken from the USP Monographs or were based on a previously validated analytical method. In cases where USP Monographs were used, dissolution and HPLC analysis conditions were only listed for the immediate-release dosage form. Therefore, these previously defined conditions were also used for the ER dosage forms with minor adjustments such as time points for the release profile, HPLC columns and flow rates to obtain more suitable test methods.

The alcohol levels chosen were mentioned by the FDA due to their association with commonly consumed alcoholic beverages. These levels were 40%, the concentration of hard liquor, 10% and 20%, the concentration of wine or a mixed drink, 5%, the concentration of a European beer and 0%, normal medium to serve as control [1]. The highest level represents the worst-case scenario. Additionally, the highest dosage form available was tested for each formulation to also represent worst-case scenario. Each control and each ethanolic media were tested as a six-unit dissolution test for more

accurate results. All profiles shown are the average of the six-unit dissolutions with the error bars of ± the standard deviation.

Section 11 b: Equation Used to Calculate Drug Release

The equation used to calculate the percent of drug released per time point is a validated calculation in the Millenium®[32] Software. This general equation is shown below:

$$\%\ \text{Drug Released} = \frac{\text{Area of std}}{\text{Area of Sample}} \times \frac{\text{Weight Std (mg)} \times \text{Std Dilution} \times \text{Std Purity} \times \text{Volume of Media}}{\text{Volumetric Flask} \qquad\qquad \text{Label Claim}}$$

The basis of the calculation compares the area of each dissolution sample to the area of the standard peak. The standard used in these analyses were at a known concentration, which is entered into the software before calculation. The amount of sample withdrawn per time point is also entered into the software before calculation as well, so that the volume that is used in the calculation at each time point is normalized for the volume removed from previous sampling points. For example, if 5.0 mL is removed per time point, the software will subtract 5.0 mL from the total volume of media for each sequential time point. .

Section 11 c: Release Rate Comparison Calculation

In order to determine if there was a statistical difference in drug release rates between the control and the ethanolic media, drug release results with alcohol were compared to the drug release results without alcohol (control) by performing f_2 statistical tests on the data as per the current USP. The similarity factor, f_2, is used as a measure for assessing the similarity of two dissolution profiles. This method, which was originally proposed by Moore and Flanner, uses mathematical indices to define the similarity factor.

The factor is derived from the Minkowski mean-squared difference. Due to the usefulness of this calculation, it became recommended for dissolution profile comparisons in the Food and Drug Administration's Guidance for Industry.

In order to accurately use this calculation to compare two dissolution profiles, the dissolution measurements for both profiles should be generated under the same test conditions and the same dissolution time points [74]. In this study, all testing conditions for each formulation were the same, except for the various ethanol concentrations in the media. All time points for the same formulation were the same for accurate comparisons.

The calculation is as follows:

$$f2 = 50 \text{ LOG } \{[1+1/n \text{ Sn } (Rt - Tt)2] -0.5 \text{ x } 100.$$

In this calculation, a 90% confidence interval is assumed due to slight variations in the samples. Since a 90% confidence interval is used, the corresponding f_2 limit to show if two dissolution profiles are statistically similar is 50. A value over 50 indicates that the profiles are statistically similar and a value less than 50 indicates that the profiles are statistically different. The details of this calculation have been extensively described by Shah et al [74].

Section 12: Experimental Design for Palladone® XL Capsules:

Section 12 a: Instrumentation

All dissolution testing was performed on Distek Dissolution Systems with Distek Automated Fraction Collectors (Distek, Inc. North Brunswick, New Jersey Model Number: 2230). All HPLC testing was done on a Waters Separations Module (Waters, Milford, Massachusetts Model Number: 2695), using a Waters Dual Wavelength Absorbance Detector (Waters, Milford, Massachusetts Model Number: 2487). All data was collected and calculated by Millenium®32 Software (Waters, Milford, Massachusetts Version Number: 3.2).

Section 12 b: Materials

Palladone® XL Capsules were obtained from Purdue Pharma L.P. (Stamford, CT). Hydromorphone hydrochloride standard was obtained from the USP (Rockville, MD). Ethyl alcohol, absolute 200 proof with 99.5% ACS purity obtained from Acros (Morris Plains, NJ) was used for ethanolic dissolution medium. All other materials such as sodium dodecyl sulfate, glacial acetic acid and acetonitrile were of analytical grade or above.

Section 12 c: Dissolution Conditions

Hydromorphone hydrochloride release from the 32 mg capsules was performed in a USP II dissolution bath (Distek, Inc. North Brunswick, New Jersey Model Number: 2230). Each capsule (n = 6 for each medium) was placed in a stainless steel coil and immersed in a dissolution vessel containing the dissolution medium. The dissolution vessels were pre-equilibrated in a water bath controlled at 37°C ± 0.5°C. 500 mL of dissolution medium was continuously agitated by rotating the paddles in the dissolution

vessel at 50 rpm. An aliquot of dissolution solution was withdrawn at the end of every hour for the first 12 hours and then at the end of every 2-hour interval for the next 12 hours. No dissolution media was replaced. The calculation for percent release accounted for the loss of media for every time point. The amount of hydromorphone hydrochloride released per time point was measured by HPLC using a validate assay described below.

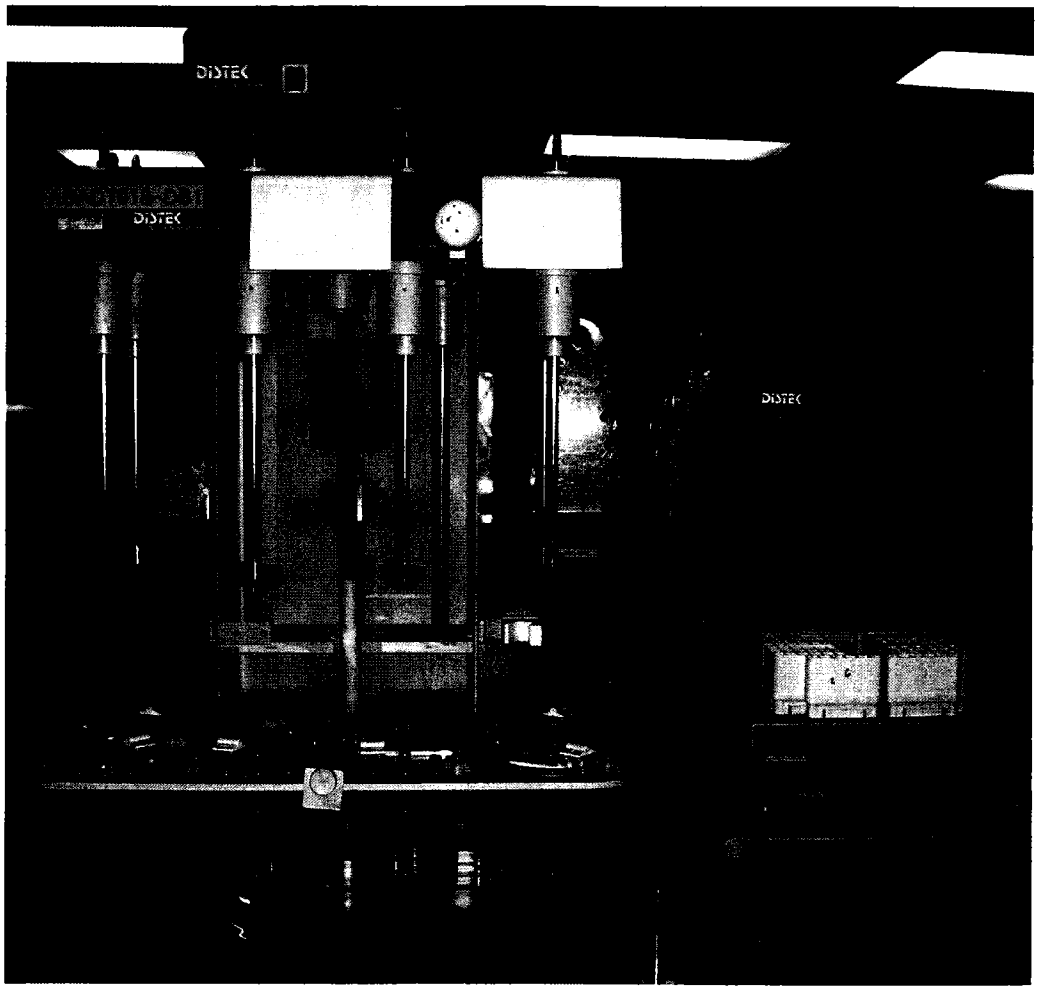
Experimental Media:

The following media were used:

- Milli-Q Water
- Milli-Q Water with 5% ethanol
- Milli-Q Water with 10% ethanol
- Milli-Q Water with 20% ethanol

All media was degassed with a helium sparge and was measured out using a Class A 500 mL-volumetric flask for accuracy. To prepare the ethanolic media, the corresponding amount of water was replaced with the absolute 200 proof ethanol. For example, to prepare 500 mL of water with 5% ethanol, 25 mL of ethanol was mixed with 475 mL of water.

Figure 5: Picture of a 2230 Distek Dissolution Bath with Automated Fraction Collector

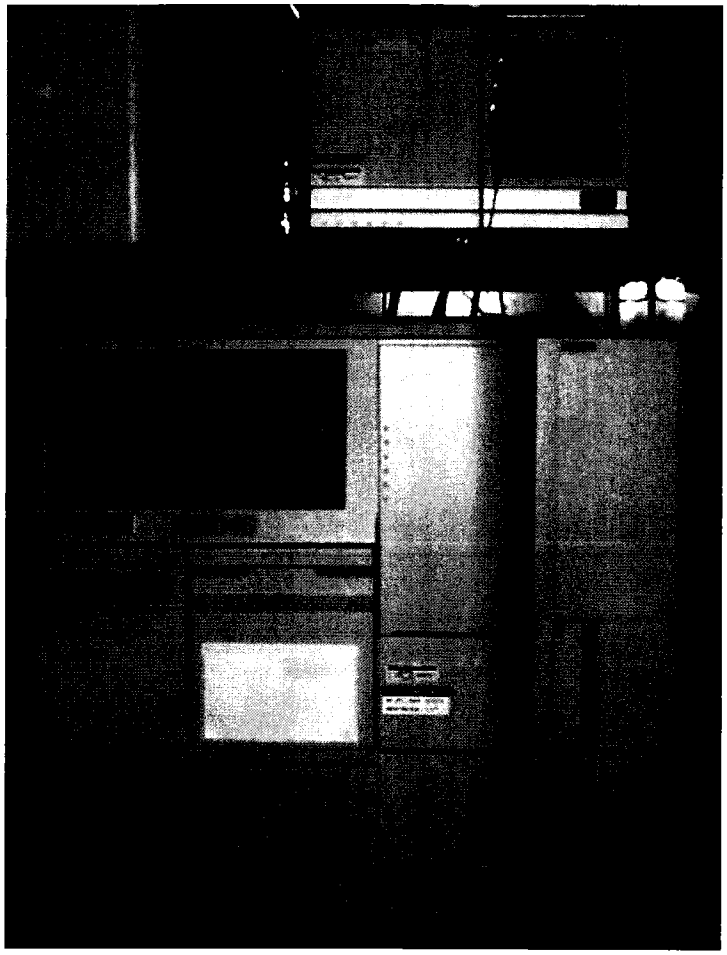


Section 12 d: HPLC Conditions

50 µL aliquots of the in vitro samples were analyzed by HPLC (Separations Module : Waters, Milford, Massachusetts Model Number: 2695, Dual Wavelength Absorbance Detector: Waters, Milford, Massachusetts Model Number: 2487) using a mobile phase of sodium dodecyl sulfate buffer with glacial acetic acid (66%) and acetonitrile (34%). A Symmetry C18 column (4.6mm x 50mm, 3.5µm, Waters Corporation, Ireland) was used for the analysis of hydromorphone hydrochloride at a flow rate of 1.5 mL/min. The column was maintained at 35°C. UV detection was

conducted at 280 nm. Data was collected and processed with Millenium Data Acquisition software (Waters, Milford, Massachusetts Version: 3.2).

Figure 6: Picture of a Waters 2695 Separations Module with a 2487 Dual Wavelength Absorbance Detector



Section 12 e: Dissolution Results for Palladone® XL Capsules

Table 1: Percent of hydromorphone hydrochloride released per time point for each medium.

Control

Time points (h)	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24
Vessel 1	13	21	27	33	38	42	46	50	54	58	61	64	69	74	78	82	85	87
Vessel 2	12	20	27	32	37	42	46	50	53	57	60	63	68	73	76	80	85	86
Vessel 3	13	21	28	33	38	43	47	52	56	59	62	65	71	75	79	83	85	88
Vessel 4	13	21	28	33	38	43	47	52	55	59	63	65	71	75	79	83	84	88
Vessel 5	13	22	29	34	40	44	49	53	57	60	63	67	72	77	81	85	88	90
Vessel 6	13	21	27	33	38	43	47	51	54	58	61	64	69	74	78	81	85	87
Mean	**13**	**21**	**28**	**33**	**38**	**43**	**47**	**51**	**55**	**59**	**62**	**65**	**70**	**75**	**79**	**82**	**85**	**88**
%RSD	**3**	**3**	**3**	**2**	**3**	**2**	**2**	**2**	**3**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Std Dev	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**1**	**2**	**2**	**1**	**1**

5% EtOH

Time points (h)	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24
Vessel 1	26	42	53	62	70	77	82	86	90	93	95	97	100	101	102	102	101	101
Vessel 2	28	44	57	67	75	82	88	92	96	99	102	104	107	108	108	108	108	107
Vessel 3	27	44	57	66	74	81	87	92	95	98	101	102	105	106	106	106	106	105
Vessel 4	27	43	55	65	72	79	85	89	93	96	98	100	103	104	104	104	103	103
Vessel 5	27	43	55	65	72	79	84	88	92	95	97	99	102	103	103	103	102	102
Vessel 6	27	43	55	65	73	79	85	89	93	96	98	100	103	104	104	104	103	103
Mean	**27**	**43**	**55**	**65**	**73**	**80**	**85**	**89**	**93**	**96**	**99**	**100**	**103**	**104**	**105**	**105**	**104**	**104**
%RSD	**2**	**2**	**3**	**3**	**2**	**2**	**3**	**3**	**2**	**2**	**3**	**2**	**2**	**2**	**2**	**2**	**3**	**2**
Std Dev	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**3**	**2**	**2**	**2**	**2**	**2**	**3**	**2**

Table 1: Percent of hydromorphone hydrochloride released per time point for each medium, contd.

10% EtOH

Time points (h)	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24
Vessel 1	62	90	103	107	108	109	108	109	107	107	107	107	107	107	108	107	106	105
Vessel 2	63	92	105	109	110	111	110	110	109	109	109	109	109	108	109	109	108	107
Vessel 3	62	89	102	106	108	108	108	108	106	107	107	106	107	107	107	107	107	108
Vessel 4	63	91	104	107	109	109	109	109	107	107	107	107	107	108	107	107	107	107
Vessel 5	61	89	102	110	107	107	107	107	106	106	106	99	106	106	105	105	105	107
Vessel 6	65	93	106	110	111	111	111	111	109	109	110	100	110	109	109	109	109	109
Mean	**63**	**91**	**104**	**108**	**109**	**109**	**109**	**109**	**107**	**108**	**108**	**105**	**108**	**108**	**108**	**107**	**107**	**107**
%RSD	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**4**	**1**	**1**	**1**	**1**	**1**	**1**
Std Dev	**1**	**2**	**2**	**2**	**1**	**2**	**1**	**1**	**1**	**1**	**2**	**4**	**2**	**2**	**1**	**2**	**1**	**1**

20% EtOH

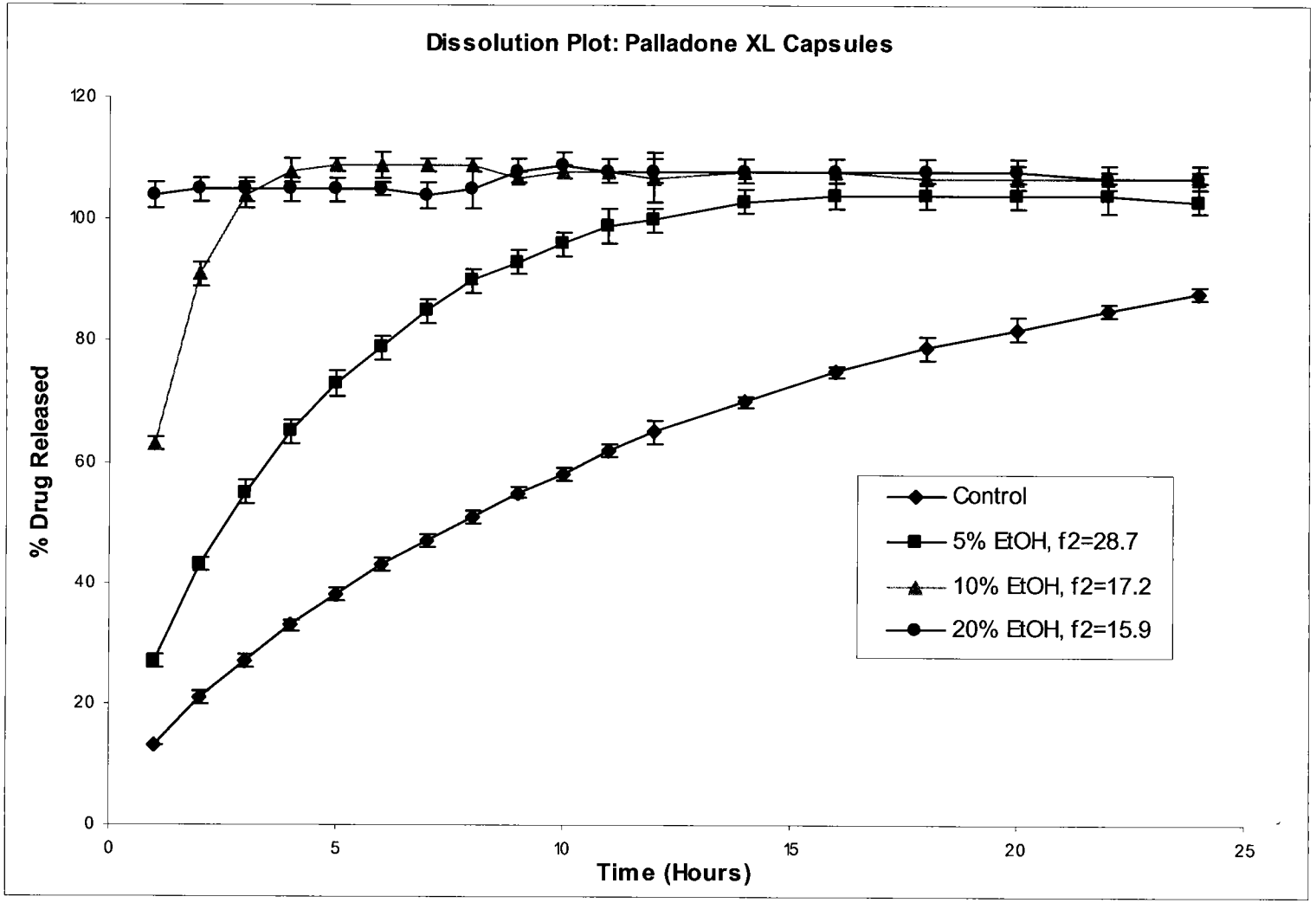
Time points (h)	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24
Vessel 1	101	102	104	103	105	104	103	103	104	107	108	107	107	107	107	107	106	106
Vessel 2	105	105	108	106	107	106	107	109	108	111	111	111	110	111	111	111	110	110
Vessel 3	102	103	103	102	102	104	102	102	106	106	106	106	106	105	105	106	105	104
Vessel 4	105	107	106	106	107	106	106	107	110	110	109	109	109	109	109	108	108	108
Vessel 5	104	106	105	106	108	107	106	108	110	110	110	110	110	110	110	109	109	109
Vessel 6	104	106	104	106	103	104	103	103	108	107	107	107	107	107	107	106	106	106
Mean	**104**	**105**	**105**	**105**	**105**	**105**	**105**	**105**	**108**	**109**	**109**	**108**	**108**	**108**	**108**	**108**	**107**	**107**
%RSD	**2**	**2**	**2**	**2**	**2**	**1**	**2**	**3**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Std Dev	**2**	**2**	**2**	**2**	**2**	**1**	**2**	**3**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**

Table 2: Average and standard deviation of hydromorphone hydrochloride released for each medium (n=6 for each medium)

Release Profiles for Palladone® XL Capsules

	% Drug Dissolved Per Time Period							
Time points (hours)	Control	SD	5% EtOH	SD	10% EtOH	SD	20% EtOH	SD
1	13	0	27	1	63	1	104	2
2	21	1	43	1	91	2	105	2
3	27	1	55	2	104	2	105	2
4	33	1	65	2	108	2	105	2
5	38	1	73	2	109	1	105	2
6	43	1	79	2	109	2	105	1
7	47	1	85	2	109	1	104	2
8	51	1	90	2	109	1	105	3
9	55	1	93	2	107	1	108	2
10	58	1	96	2	108	1	109	2
11	62	1	99	3	108	2	108	2
12	65	2	100	2	107	4	108	2
14	70	1	103	2	108	2	108	2
16	75	1	104	2	108	2	108	2
18	79	2	104	2	107	1	108	2
20	82	2	104	2	107	2	108	2
22	85	1	104	3	107	1	107	2
24	88	1	103	2	107	1	107	2

Graph 1: Dissolution Plot for Palladone® XL Capsules



Note: The plot shows the average value for each time point ± standard deviation.

Section 12 f: Discussion

The control release profile shows the expected slow, steady release of the active drug over the course of 24 hours. The entire amount of drug did not release in 24 hours, but it can be assumed by studying the profile that it would completely release in 30 hours. Additionally, the alcohol studies were performed to look for any signs of dose dumping with ethanol present; therefore the complete release profile is not necessary.

The results clearly show that the drug release rate increased drastically with an increase in alcohol. Obvious dose dumping occurs in less than one hour for the drug in 20% ethanolic medium, therefore the 40% ethanol test was not necessary. Each result was calculated against a known concentration of hydromorphone hydrochloride reference standard. The results for 20% and 40% ethanolic medium are above 100% for the amount of drug released. This high result is most likely due to slight evaporation from the test tubes due to the high alcohol content as well as the long run time.

As shown in Graph 1, the f_2 value even at 5% ethanol was 28.7, which indicates a very significant difference between the control and the 5% ethanol release profiles. Clearly, dose dumping occurs when even the slightest amount of alcohol is present. A possible reason for such a vulnerability to alcohol is due to the solid dispersion melt-extrusion pellet formulation. In this type of formulation, the drug and excipients are evenly dispersed in the pellet. The pellet is designed to evenly erode in order to release the drug over an extended period of time.

The excipients in this formulation are ammonio methacrylate copolymer type B, ethylcellulose and stearyl alcohol [46]. The ammonio methacrylate copolymer type B is commonly used as a coating agent, tablet binder and polymer membrane. Ethylcellulose

is also commonly used as a coating agent and tablet binder. Ammonio methacrylate copolymer is soluble to freely soluble in alcohol. Its copolymer type B used in this formulation dissolves only partially in alcohol. However, ethylcellulose is freely soluble in alcohol [49]. Therefore, it these two inactive excipients are used as the binders to maintain the controlled release function, even the slightest presence of alcohol could diminish the solid dispersion pellet formation and cause immediate dose dumping.

In addition, according to the previously mentioned study on drug release from melt-extrusion formulations, the two main theories include carrier-controlled release, which is also dependent upon whether the polymer is soluble or not. The properties of the drug have no effect on release in this theory. The other theory is that the properties of the drug dictate release and not the polymer itself. The solubility of the drug in concentrated solutions of the carrier seems to be the predominant factor [52].

The active drug in this formulation is only moderately soluble in alcohol [48]. Therefore, because the drug release rate drastically increases in ethanol, it is likely that the release rate is dependent upon the carrier-system and not on the drug itself. This further supports the theory that the dose dumping occurs due to the increased ethanol solubility of the main excipients holding together the pellets.

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Section 13: Detrol® LA Capsules:

Section 13 a: Instrumentation

All dissolution testing was performed on Distek Dissolution Systems with Distek Automated Fraction Collectors (Distek, Inc. North Brunswick, New Jersey Model Number: 2230). All HPLC testing was done on a Waters Separations Module (Waters, Milford, Massachusetts Model Number: 2695), using a Waters Dual Wavelength Absorbance Detector (Waters, Milford, Massachusetts Model Number: 2487). All data was collected and calculated by Millenium®32 Software (Waters, Milford, Massachusetts Version Number: 3.2).

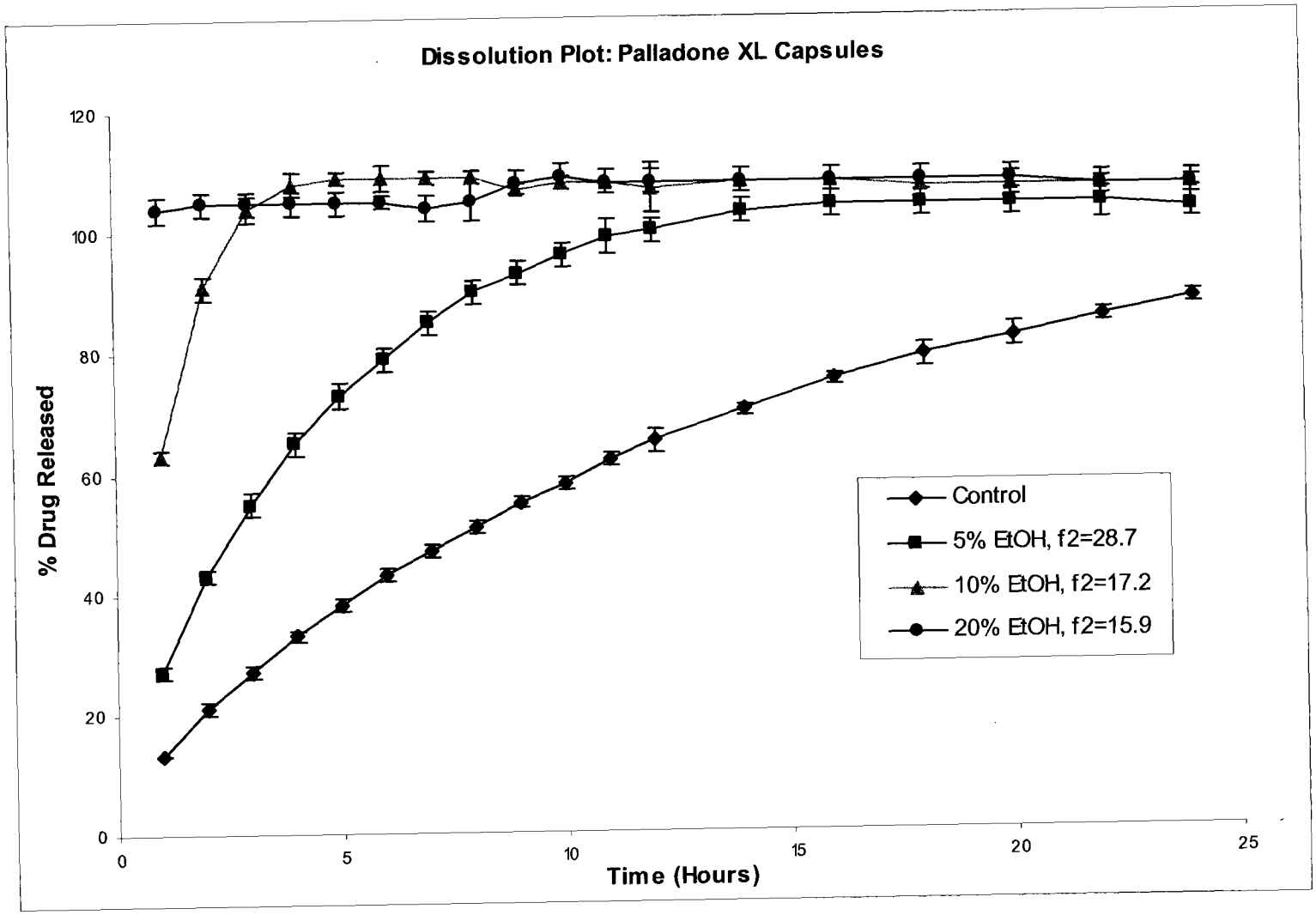
Section 13 b: Materials

Detrol® LA Capsules were obtained from Pharmacia (Kalamazoo, MI. USA). Tolterodine tartrate standard was obtained from Poligono Industrial de Celra. Ethyl alcohol, absolute 200 proof with 99.5% ACS purity obtained from Acros (Morris Plains, NJ) was used for ethanolic dissolution medium. All other materials such as phosphoric acid, sodium phosphate dibasic, potassium phosphate dibasic, hydrochloric acid, acetonitrile, methanol and glacial acetic acid were of analytical grade or above.

Section 13 c: Dissolution Conditions

Tolterodine release from the 4 mg ER capsules was performed in a USP I dissolution bath (Distek, Inc. North Brunswick, New Jersey Model Number: 2230). Each capsule (n = 6 for each medium) was immersed in a dissolution vessel containing the dissolution medium. The dissolution vessels were pre-equilibrated in a water bath controlled at 37°C ± 0.5°C. 900 mL of dissolution medium was continuously agitated by rotating the baskets in the dissolution vessel at 100 rpm. An aliquot of dissolution

Graph 1: Dissolution Plot for Palladone® XL Capsules



Note: The plot shows the average value for each time point ± standard deviation.

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solution was withdrawn at the end of every hour for the following time points: 1, 2, 3, 5, 7, 9, 15 and 20 hours. No dissolution media was replaced. The calculation for percent release accounted for the loss of media for every time point. The amount of tolterodine released was measured by HPLC using a validated assay described below.

Experimental Media:

The following media were used:

- 0.05M K_2HPO_4 (pH 6.8)
- 0.05M K_2HPO_4 (pH 6.8) with 5% ethanol
- 0.05M K_2HPO_4 (pH 6.8) with 10% ethanol
- 0.05M K_2HPO_4 (pH 6.8) with 20% ethanol
- 0.05M K_2HPO_4 (pH 6.8) with 40% ethanol

All media was degassed with helium sparge and measured out using a Class A 900 mL-volumetric flask for accuracy. To prepare the ethanolic media, the corresponding amount of water was replaced with the absolute 200 proof ethanol.

Section 13 d: HPLC Conditions

50 µL aliquots of the in vitro samples were analyzed by HPLC (Separations Module : Waters, Milford, Massachusetts Model Number: 2695, Dual Wavelength Absorbance Detector: Waters, Milford, Massachusetts Model Number: 2487) using a mobile phase of sodium phosphate dibasic buffer adjusted to a final pH of 7.0 with concentrated phosphoric acid (50%), acetonitrile (30%) and methanol (20%). A Luna C18 analytical column with dimensions of 4.6 mm x 150 mm and 5.0 µm particle size (Phenomenex, Torrance, CA, USA) was used for the analysis of tolterodine at a flow rate of 1.2 mL/min. The column was maintained at 40°C. UV detection was conducted at

220 nm. Data was collected and processed with Millenium Data Acquisition software (Waters, Milford, Massachusetts Version Number: 3.2).

Section 13 e: Dissolution Results for Detrol® LA Capsules

Table 3: Percent of tolterodine tartrate released per time point for each medium.

Control

Time points (h)	1	2	3	5	7	9	15	20
Vessel 1	16	47	69	87	91	93	96	97
Vessel 2	17	48	70	87	91	93	96	97
Vessel 3	18	46	70	87	91	93	96	95
Vessel 4	19	48	75	91	93	97	100	100
Vessel 5	18	51	72	91	95	97	100	101
Vessel 6	16	46	67	85	90	91	95	95
Mean	**17**	**48**	**71**	**88**	**92**	**94**	**97**	**98**
%RSD	**7**	**4**	**4**	**3**	**2**	**3**	**2**	**3**
Std Dev	**1**	**2**	**3**	**2**	**2**	**2**	**2**	**3**

5% Ethanol

Time points (h)	1	2	3	5	7	9	15	20
Vessel 1	12	23	38	71	93	99	101	102
Vessel 2	11	21	34.0	66	88	96	100	99
Vessel 3	11	21	35.0	67	90	98	100	100
Vessel 4	11	22	36.0	68	90	96	100	100
Vessel 5	11	21	34.0	70	90	97	100	102
Vessel 6	10	20	34.0	67	88	94	96	99
Mean	**11**	**21**	**35**	**68**	**90**	**97**	**100**	**100**
%RSD	**6**	**5**	**5**	**3**	**2**	**2**	**2**	**1**
Std Dev	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**1**

Table 3: Percent of tolterodine tartrate released per time point for each medium, contd.

10% Ethanol

Time points (h)	1	2	3	5	7	9	15	20
Vessel 1	10	18	28	64	93	100	102	101
Vessel 2	9	17	27	62	91	100	101	100
Vessel 3	10	18	28	63	93	101	104	102
Vessel 4	10	20	31	65	91	97	101	100
Vessel 5	10	20	30	64	90	99	100	101
Vessel 6	9	19	30	65	92	101	102	103
Mean	**10**	**19**	**29**	**64**	**92**	**100**	**102**	**101**
%RSD	**5**	**6**	**5**	**2**	**1**	**2**	**1**	**1**
Std Dev	**1**	**1**	**2**	**1**	**1**	**2**	**1**	**1**

20% Ethanol

Time points (h)	1	2	3	5	7	9	15	20
Vessel 1	12	26	50	86	99	101	102	101
Vessel 2	12	25	49	87	99	101	102	102
Vessel 3	13	26	52	92	100	102	102	102
Vessel 4	15	35	64	97	103	104	102	104
Vessel 5	15	32	59	95	103	103	101	101
Vessel 6	16	34	63	99	106	106	105	105
Mean	**14**	**30**	**56**	**93**	**102**	**103**	**102**	**103**
%RSD	**12**	**15**	**12**	**6**	**3**	**2**	**1**	**2**
Std Dev	**2**	**5**	**7**	**5**	**3**	**2**	**1**	**2**

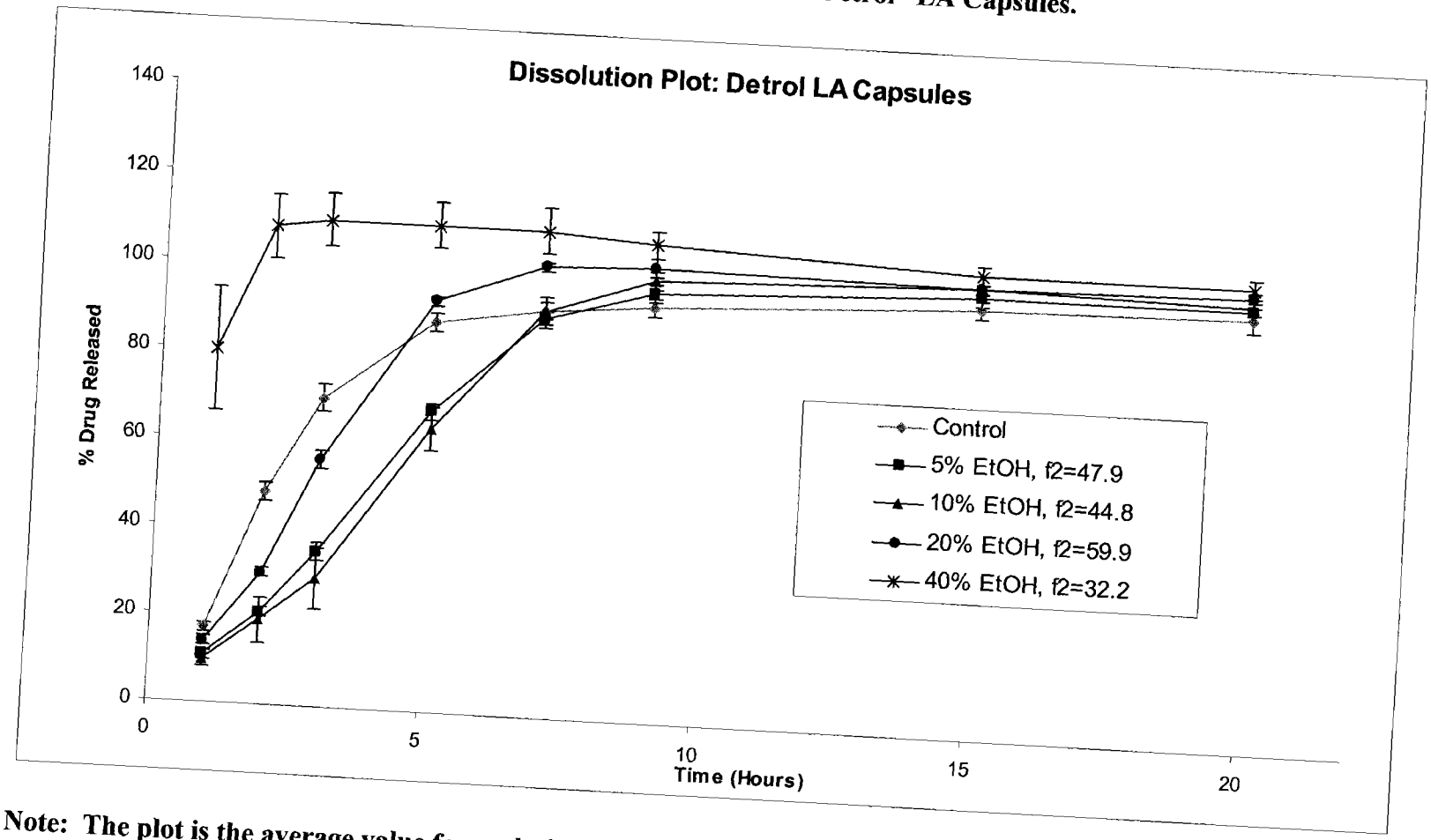
Table 3: Percent of tolterodine tartrate released per time point for each medium, contd.

	40% Ethanol							
Time points (h)	1	2	3	5	7	9	15	20
Vessel 1	91	111	113	111	112	108	103	103
Vessel 2	94	116	117	116	118	112	107	107
Vessel 3	92	114	115	113	114	110	105	104
Vessel 4	69	106	109	105	109	108	107	107
Vessel 5	67	101	105	104	106	105	105	105
Vessel 6	67	100	103	109	103	103	102	102
Mean	**80**	**108**	**110**	**110**	**110**	**108**	**105**	**105**
%RSD	**17**	**6**	**5**	**4**	**5**	**3**	**2**	**2**
Std Dev	**14**	**7**	**6**	**5**	**5**	**3**	**2**	**2**

Table 4: Average and standard deviation of the percent of tolterodine tartrate released for each medium (n=6 for each medium).

	% Drug Dissolved Per Time Period									
Time Points (h)	Control	SD	5% EtOH	SD	10% EtOH	SD	20% EtOH	SD	40% EtOH	SD
1	17	1	11	1	10	1	14	2	80	14
2	48	2	21	1	19	1	30	5	108	7
3	70	3	35	2	29	2	56	7	110	6
5	88	2	68	2	64	1	93	5	110	5
7	92	2	90	2	92	1	102	3	110	5
9	94	2	97	2	100	2	103	2	108	3
15	97	2	100	2	102	1	102	1	105	2
20	98	3	100	1	101	1	103	2	105	2

Graph 2: Dissolution Plot for Detrol® LA Capsules.



Note: The plot is the average value for each time point ± standard deviation.

Section 13 f: Discussion:

When this formulation was initially tested, only three-unit dissolution profiles were performed. Since most publications perform six-unit dissolutions in order to generate more accurate and reliable data and because ethanol is so volatile, a second set of three-unit dissolution profiles were performed to confirm the first set of data. When the initial sets were generated, the pH of the different ethanolic media was adjusted to the final pH of 6.8 in order to satisfy the method requirements. However, when performing the second set, the final pH of the ethanolic medium was not adjusted. This was because it was later recognized that in the body, the alcohol would be added to the stomach and may not equilibrate to the exact pH of the stomach before having an effect on the release rate. When comparing the profiles of the two sets of data, the results were very similar, showing that there was essentially no impact of pH on the release profile.

The 40% ethanolic medium results however are slightly different between the two sets of data. This is due to the fact that the first set generated was collected into HPLC vials, which were left uncovered overnight. When the second sets were collected, they were collected into test tubes and were also left uncovered overnight. Since the volume in the HPLC vial was only 1.3 mL and the volume collected in the test tubes was 8 mL, the amount that evaporates from the vial caused the sample to concentrate more than from the test tubes. However, when the similarity calculation is performed on the two sets separately, the first set has a f_2 value of 29.2 and the second set has a f_2 value of 35.5. This clearly show that both sets are statistically different that the control and dose dumping does occur in the 40% ethanolic medium.

The Detrol® LA Capsule formulation appears to have a high tolerance to ethanol up to the 40% ethanol concentration. The formulation appears to dissolve slower than the control during approximately the first ten hours of the dissolution testing in the 5% and 10% ethanolic medium. The 20% ethanolic medium has the closest release rate to the control sample. These results are atypical to what was expected. For this particular set of drug testing, two different sets of 3-unit dissolution testing were performed and the results of the two sets were combined. For the two sets, different preparations of buffer and mobile phase were prepared and they were conducted during separate weeks. The relative standard deviation and standard deviation are extremely low, showing the results are reliable, therefore retesting was not performed.

The presence of ethanol may possibly retard the release rate up until the 40% ethanol level is reached. Possibly at this level, the concentration of alcohol is too high and dose dumping does occur. The f_2 values of the 5% and 10% ethanolic media are only slightly lower than 50, with values of 47.9 and 44.8, respectively. The 20% ethanolic medium is not statistically different from the control with a similarity factor of 59.9. The only level that is clearly different is the 40% ethanolic medium with an f_2 value of 32.2. Since the 40% ethanolic solution is an extreme worst-case scenario, it appears that the formulation used to make Detrol® LA Capsules is successful in the resistance to dose dumping.

Further formulation investigations are needed in order to properly understand the reaction to ethanol. The main excipient used for coating is Hypromellose 2910®. This is a fibrous or granular powder commonly used as a coating agent, tablet binder, suspending and/or viscosity increasing agent. It is found to swell in water and then produce a

colloidal mixture. Furthermore, it is insoluble in dehydrated alcohol. Another excipient used in the Detrol® LA Capsule formulation is ethylcellulose, mentioned previously as a coating agent and tablet binder. However, ethylcellulose is freely soluble in alcohol [49]. The difference in solubility of the two main excipients used to layer the drug tolterodine tartrate could be a possible reason for such varying drug release rates.

The formulation was defeated with the highest amount of alcohol and was retarded with the lowest two amounts of alcohol. One possibility for such results is the change in the swelling and erosion properties of HPMC in ethanol versus water. Previous studies have shown that the rate of polymer hydration and therefore swelling is dependent upon the viscosity grade of the polymer. The degree of methoxy, the hydrophobic portion, and hydroxypropoxyl, the hydrophilic portion, substitutions strongly effect the movement of water, ultimately effecting drug release [59].

When this polymer is exposed to water or biological fluids, the liquid hydrates the dry polymer. It then swells, forming a gel diffusion layer. This layer therefore serves as the controlled drug release mechanism because the drug has to diffuse out of the matrix. As the formulation, ER pellets in this case, are further exposed to fluid, the polymer chains become increasingly hydrated creating a more dilute gel. This continues until the critical polymer concentration is met, which is the point when the polymer chains disentangle and breakaway from the gelled matrix. At this point dissolution and diffusion of drug into the receptor medium occurs. When this occurs, the polymer erodes.

For HPMC, diffusion is the release mechanism for soluble drugs and erosion is the release mechanism for poorly soluble drugs [75]. Since tolterodine tartrate is soluble in water, diffusion is the main source of drug delivery. Meaning the water moving into

the matrix will slowly dissolve the drug and move it through the gel layer and into the bulk medium. Therefore changes in swelling behavior is most likely a main factor contributing to the perplexing drug release profiles of Detrol® LA Capsules in ethanolic media.

Recently, a study conducted by Navarro-Lupion, Bustamante and Escalera, examined the swelling of HPMC in various solvents with a wide range of polarities. The swelling experiments were performed in triplicate by taking the weight of HPMC tablets as a function of time. The initial weight of the tablets were taken before immersing them in individual previously weighed vials containing 20-mL of the solvents. The vials were shaken at 90 rpm and kept at 25°C. At the designated time points, the excess solvent was decanted and the vials were weighed again. The weight of the swollen tablets at each time point was calculated by difference. Once the weight of the tablet did no increase, equilibrium swelling existed.

The results obtained showed ethanol has an equilibrium swelling of 6.084 and an initial swelling rate of 175.893 while water has and equilibrium swelling of 30.468 and initial swelling rate of 1.007 [31]. These results indicate that the HPMC Tablets could absorb less ethanol than water but swelled much faster in ethanol. This could possibly explain the dose dumping at the 40% ethanol level since the high amount of ethanol could cause very fast swelling, releasing the drug very quickly.

Finally, another possible reason for the varying results is the solubility of the active drug, tolterodine, in ethanol. As stated previously, the most important factor that affects drug release from ethylcellulose-coated-pellets is it's aqueous solubility when the dissolved drug releases from the matrix via diffusion either through the film-coating itself

or through water-filled pores formed within the coating. Tolterodine is highly soluble in water bug is only slightly soluble in ethanol. Even though the swelling of the polymer may increase with every increase in ethanol, the 5% and 10% ethanolic media may not cause high enough swelling to allow the drug to be dumped out at once, as in the 40% ethanol medium. Therefore, it is possible that the swelling increased Since the drug's solubility is less in ethanol, less drug would be able to dissolve and diffuse out, causing a slower drug release rate at the beginning levels of ethanol. The controlled-release mechanism is defeated in very high alcohol levels, dumping the drug out much faster regardless of it solubility.

Section 14: Cystrin® CR Tablets:

Section 14 a: Instrumentation

All dissolution testing was performed on Distek Dissolution Systems with Distek Automated Fraction Collectors (Distek, Inc. North Brunswick, New Jersey Model Number: 2230) . All HPLC testing was done on a Waters Separations Module (Waters, Milford, Massachusetts Model Number: 2695), using a Waters Dual Wavelength Absorbance Detector (Waters, Milford, Massachusetts Model Number: 2487). All data was collected and calculated by Millenium®32 Software (Waters, Milford, Massachusetts Version Number: 3.2).

Section 14 b: Materials

Cystrin® CR Tablets were manufactured and obtained from Sanofi-Synthelabo (New York, NY). Oxybutynin Chloride standard was obtained from the USP (Rockville, MD). Ethyl alcohol, absolute 200 proof with 99.5% ACS purity obtained from Acros (Morris Plains, NJ) was used for ethanolic dissolution media. All other materials such as triethylamine, methanol and phosphoric acid were of analytical grade or above.

Section 14 c: Dissolution Conditions

Oxybutynin chloride release from the 10 mg Cystrin® CR Tablets was performed in a USP II dissolution bath (Distek, Inc. North Brunswick, New Jersey Model Number: 2230). The USPNF Official Monograph of Oxybutynin Chloride Tablets was used as the basis for the dissolution testing and HPLC analysis. Each tablet (n = 6 for each medium) was immersed in a dissolution vessel containing the dissolution medium. The dissolution vessels were pre-equilibrated in a water bath controlled at 37°C ± 0.5°C. 900 mL of dissolution medium was continuously agitated by rotating the paddles in the dissolution

vessel at 25 rpm. An aliquot of dissolution solution was withdrawn at the first and second hour of the test and then every two hours after that, up to 16 hours. No dissolution media was replaced. The calculation for percent release accounted for the loss of media for every time point. The amount of oxybutynin chloride released was determined using HPLC using a validated assay described below.

Experimental Media:

The following media were used:

- Milli-Q Water
- Milli-Q Water with 5% ethanol
- Milli-Q Water with 10% ethanol
- Milli-Q Water with 20% ethanol
- Milli-Q Water with 40% ethanol

All media were degassed with helium sparge and measured out using a Class A 900 mL-volumetric flask for accuracy. To prepare the ethanolic media, the corresponding amount of water was replaced with the absolute 200 proof ethanol.

Section 14 d: HPLC Conditions

20 μL aliquots of the in vitro samples were analyzed by HPLC (Separations Module: Milford, Massachusetts Model Number: 2695, Dual Wavelength Absorbance Detector: Waters, Milford, Massachusetts Model Number: 2487 using a mobile phase of 0.9 mL of triethylamine to a mixture of water and methanol (3200:800). The mobile phase was then adjusted to a pH of 3.50 using phosphoric acid. A Waters Spherisorb S5 CN RP analytical column with dimensions of 4.6mm x 150mm (Waters, USA) was used at a flow rate of 1.75 mL/min. The column was maintained at 40°C. UV detection was

conducted at 203nm. Data was collected and processed with Millenium®32 Data Acquisition Software (Waters, Milford, Massachusetts Version Number: 3.2).

Section 14 e: Dissolution Results for Cystrin® CR Tablets

Table 5: Percent of oxybutynin hydrochloride released per time point for each medium

Control

Time points (h)	1	2	4	6	8	10	12	14	16
Vessel 1	11	22	37	49	58	66	73	77	81
Vessel 2	16	28	42	54	63	69	76	79	85
Vessel 3	8	19	32	44	54	60	66	70	74
Vessel 4	8	18	34	45	56	64	69	74	78
Vessel 5	10	21	34	46	56	64	70	74	76
Vessel 6	18	28	42	53	62	70	76	79	82
Mean	**12**	**23**	**37**	**49**	**58**	**66**	**72**	**76**	**79**
%RSD	**36**	**19**	**12**	**9**	**6**	**6**	**6**	**6**	**5**
Std Dev	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**

5% Ethanol

Time points (h)	1	2	4	6	8	10	12	14	16
Vessel 1	10	16	29	40	47	53	60	64	67
Vessel 2	15	22	33	44	51	57	61	67	69
Vessel 3	9	15	27	38	47	52	58	63	65
Vessel 4	12	21	32	42	52	59	63	67	69
Vessel 5	8	16	26	36	45	53	60	62	66
Vessel 6	15	24	34	43	51	59	64	66	71
Mean	**12**	**19**	**30**	**41**	**49**	**56**	**61**	**65**	**68**
%RSD	**27**	**20**	**11**	**8**	**6**	**6**	**4**	**3**	**3**
Std Dev	**3**	**4**	**3**	**3**	**3**	**3**	**2**	**2**	**2**

Table 5: Percent of oxybutynin hydrochloride released per time point for each medium, contd.

10% Ethanol

Time points (h)	1	2	4	6	8	10	12	14	16
Vessel 1	9	16	27	35	44	51	57	62	63
Vessel 2	9	16	27	36	43	50	55	58	62
Vessel 3	8	14	25	34	41	49	53	57	60
Vessel 4	8	14	24	34	41	48	54	56	64
Vessel 5	7	18	28	38	46	54	58	62	61
Vessel 6	11	13	23	32	41	48	53	56	59
Mean	**9**	**15**	**26**	**35**	**43**	**50**	**55**	**59**	**62**
%RSD	**16**	**12**	**8**	**6**	**5**	**5**	**4**	**5**	**3**
Std Dev	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**3**	**2**

20% Ethanol

Time points (h)	1	2	4	6	8	10	12	14	16
Vessel 1	6	10	18	24	29	35	39	44	47
Vessel 2	9	12	20	27	32	38	43	47	49
Vessel 3	10	14	21	26	33	38	43	47	50
Vessel 4	7	12	19	24	30	37	40	45	50
Vessel 5	9	12	22	27	34	39	44	47	51
Vessel 6	6	13	19	24	30	35	40	43	47
Mean	**8**	**12**	**20**	**25**	**31**	**37**	**42**	**46**	**49**
%RSD	**2**	**11**	**7**	**6**	**6**	**5**	**5**	**4**	**3**
Std Dev	**2**	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**

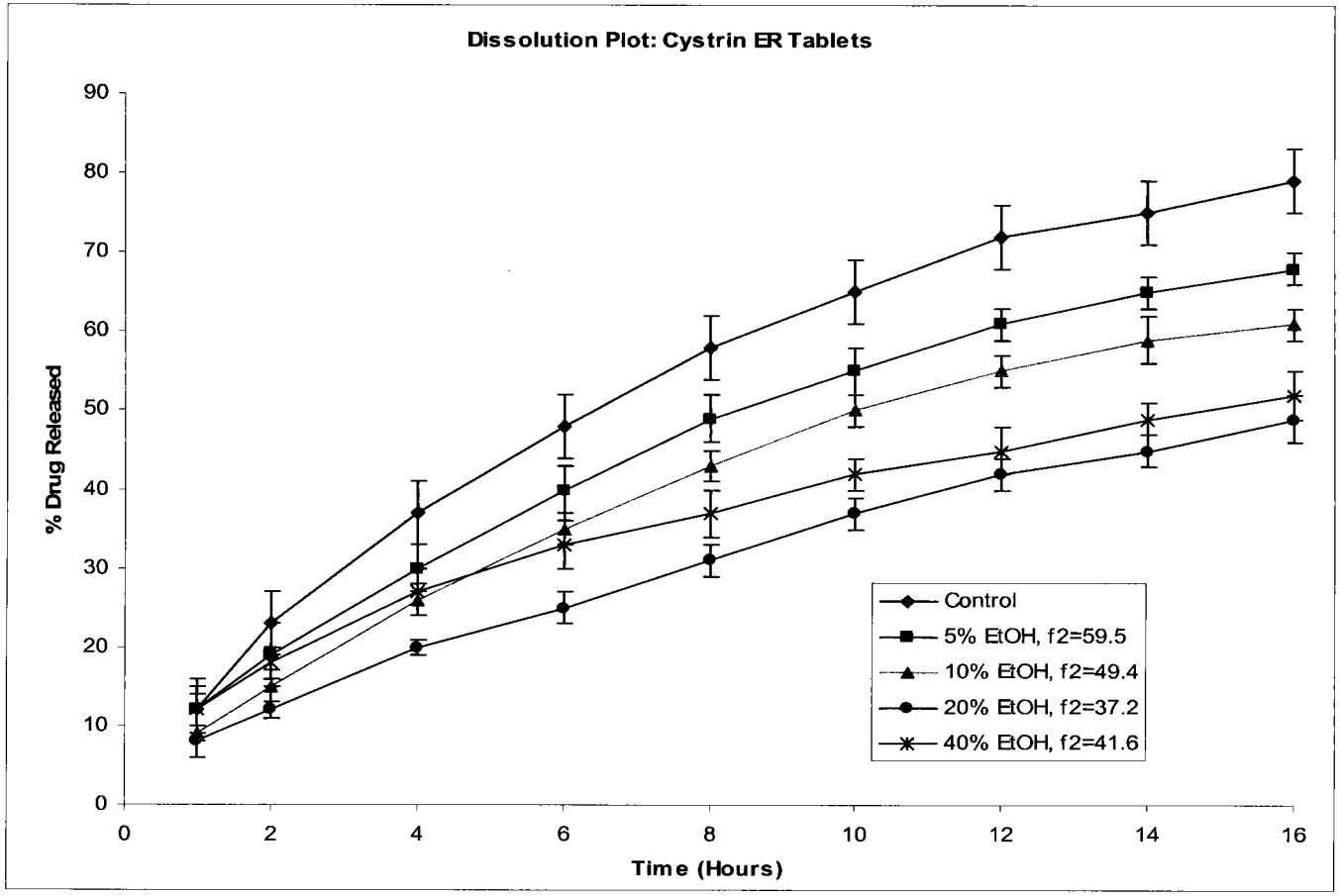
Table 5: Percent of oxybutynin hydrochloride released per time point for each medium, contd.

Time points (h)	40% Ethanol								
	1	2	4	6	8	10	12	14	16
Vessel 1	11	17	25	32	35	39	42	47	50
Vessel 2	14	21	31	37	41	45	49	52	57
Vessel 3	10	15	24	30	34	40	42	46	50
Vessel 4	13	18	26	32	37	42	45	49	53
Vessel 5	11	17	26	32	37	41	46	49	52
Vessel 6	14	19	29	35	40	43	48	51	53
Mean	**12**	**18**	**27**	**33**	**37**	**42**	**45**	**49**	**53**
%RSD	**14**	**11**	**10**	**8**	**7**	**5**	**7**	**5**	**5**
Std Dev	**2**	**2**	**3**	**3**	**3**	**2**	**3**	**2**	**3**

Table 6: Average and standard deviation of oxybutynin hydrochloride released for each medium (n=6 for each medium)

Time points (hours)	% Drug Dissolved Per Time Period									
	Control	SD	5% EtOH	SD	10% EtOH	SD	20% EtOH	SD	40% EtOH	SD
1	12	4	12	3	9	1	8	2	12	2
2	23	4	19	4	15	2	12	1	18	2
4	37	4	30	3	26	2	20	1	27	3
6	48	4	40	3	35	2	25	2	33	3
8	58	4	49	3	43	2	31	2	37	3
10	65	4	55	3	50	2	37	2	42	2
12	72	4	61	2	55	2	42	2	45	3
14	75	4	65	2	59	3	45	2	49	2
16	79	4	68	2	61	2	49	3	52	3

Graph 3: Dissolution Plot for Cystrin® CR Tablets.



Note: The plot shows the average value for each time point ± standard deviation.

Section 14 f: Discussion

The control release profile shows the expected slow, steady release of the active drug over the course of 16 hours. The entire amount of drug did not release in 16 hours, but it can be assumed by studying the profile that it would be completely released by 24 hours. Additionally, the alcohol studies were performed to look for any signs of dose dumping with ethanol present or any alterations in the drug release profile as is. Therefore the complete release profile is not necessary.

The results clearly indicate that the rate of drug release decreases with an increase in alcohol. The percent of drug released at 16 hours decreased from 79% in the control medium to 68% in 5% ethanolic medium, 61% in 10% ethanolic medium, 49% in 20% ethanolic medium and 52% in ethanolic medium. The f2 values were 59.5, 49.4, 37.2 and 41.6 for the 5%, 10%, 20% and 40% ethanolic media, respectively.

The percent of drug released in the 40% ethanol medium is slightly higher than in the 20% ethanolic medium, which does not follow the trend of a decrease in release with every increase in ethanol concentrations. This is most likely due to a small amount of evaporation due to the higher alcohol content in the 40% ethanolic medium. Further more, when the dissolution profiles of the 20% ethanolic medium are compared to the 40% ethanolic medium using the similarity factor calculation, the f2 correlation value is 69.1. This indicates that there is no statistical difference between the two profiles. This further supports the data that the release rate decreases with increasing levels of ethanol.

Oxybutynin chloride is freely soluble in water and alcohol [49], therefore the retardation of the release rate may be due to an interaction between an excipient and ethanol. As described previously, the TIMERx® CR technology combines LBG and X to

form a true gel in solution. This is possible because the rigid helices of X are incorporated in the true gel structure of LBG molecules, increasing the viscosity. The X helices form molecular rigid poles within the LGB matrix, which results in a stronger three-dimensional gel. The interlinking of these polymer chains is what controls drug diffusion out of the matrix [12].

A possible reason for the decrease in the release rate of oxybutynin chloride with increasing levels of ethanol in the medium is that the alcohol decreases the degree of swelling, therefore limiting the three-dimensional gel matrix. Since the swelling is decreased, the release rate of the drug would decrease with every increase in ethanol.

Section 15: Concerta® Tablets

Section 15 a: Instrumentation

All dissolution testing was performed on Distek Dissolution Systems with Distek Automated Fraction Collectors (Distek, Inc. North Brunswick, New Jersey Model Number: 2230) . All HPLC testing was done on a Waters Separations Module (Waters, Milford, Massachusetts Model Number: 2695), using a Waters Dual Wavelength Absorbance Detector (Waters, Milford, Massachusetts Model Number: 2487). All data was collected and calculated by Millenium®32 Software (Waters, Milford, Massachusetts Version Number: 3.2).

Section 15 b: Materials

Concerta® Tablets were obtained from McNeil Consumer and Specialty Pharmaceutical, (Fort Washington, PA). This product is a Class II DEA Substance. Methylphenidate Hydrochloride standard was obtained from the USP (Rockville, MD). Ethyl alcohol, absolute 200 proof with 99.5% ACS purity obtained from Acros (Morris Plains, NJ) was used for ethanolic dissolution media. All other materials such as sodium phosphate monobasic, 1-heptanesulfonic acid sodium salt, acetonitrile, phosphoric acid and hydrochloric acid were of analytical grade or above.

Section 15 c: Dissolution Conditions

Methylphenidate Hydrochloride release from the 54 mg Concerta® Tablets was performed in a USP I dissolution bath (Distek, Inc. North Brunswick, New Jersey Model Number: 4300). A previously validated analytical dissolution method with HPLC analysis was used for the basis of this testing. Each tablet (n = 6 for each medium) was immersed in a dissolution vessel containing the dissolution medium. The dissolution

vessels were pre-equilibrated in a water bath controlled at 37°C ± 0.5°C. 900 mL of dissolution medium was continuously agitated by rotating the paddles in the dissolution vessel at 50 rpm. An aliquot of dissolution solution was withdrawn at 15, 30, 45, 60 minutes due to the immediate-release portion of the tablet. After the first hour, aliquots were drawn every hour for 13 hours. No dissolution media was replaced. The calculation for percent release accounted for the loss of media for every time point. The amount of methylphenidate hydrochloride released was determined using HPLC for the analysis using a validated assay described below.

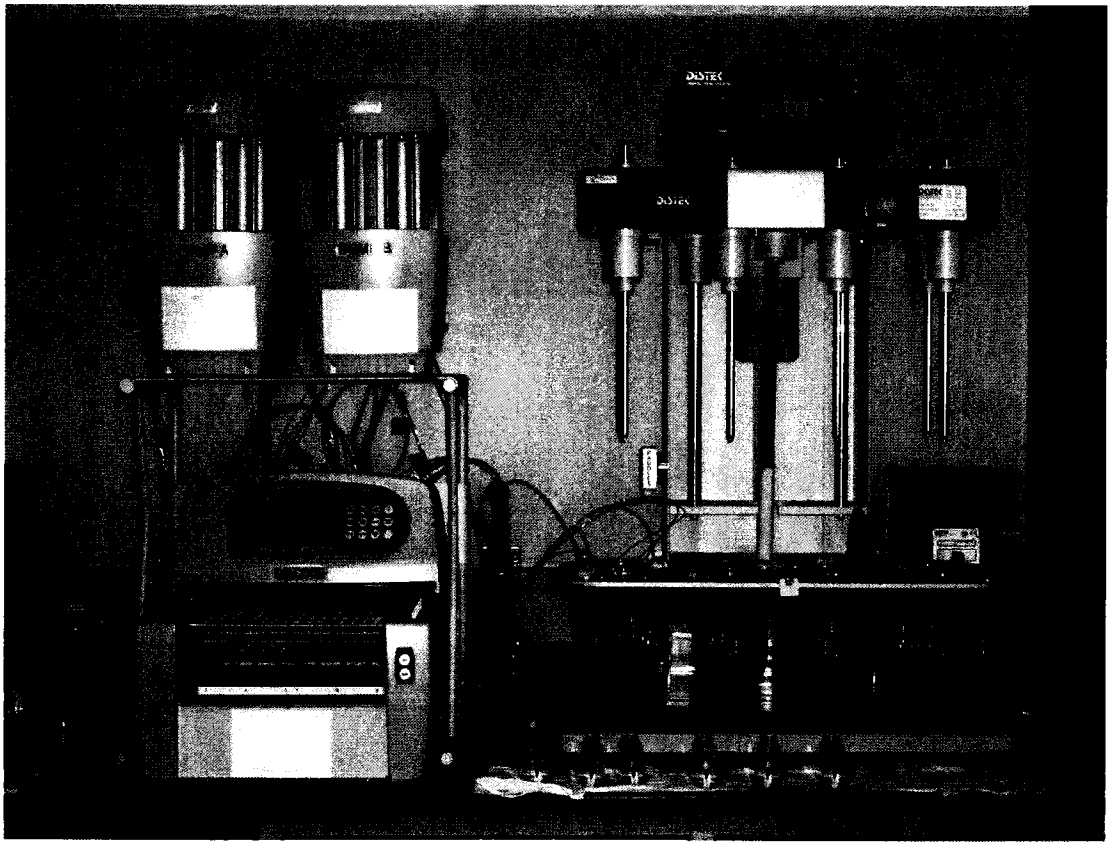
Experimental Media:

The following media were used:

- 0.1 N HCl
- 0.1 N HCl with 5% ethanol
- 0.1 N HCl with 10% ethanol
- 0.1 N HCl with 20% ethanol
- 0.1 N HCl with 40% ethanol

All media was degassed with helium sparge and measured out using a Class A 900 mL-volumetric flask for accuracy. To prepare the ethanolic media, the corresponding amount of water was replaced with the absolute 200 proof ethanol.

Figure 7: Picture of a 4300 Distek Dissolution Bath with an Automated Fraction Collector



Section 15 d: HPLC Conditions

25 µL aliquots of the in vitro samples were analyzed by reverse-phase HPLC (Separations Module: Waters, Milford, Massachusetts Model Number: 2695, Dual Wavelength Absorbance Detector: Waters, Milford, Massachusetts Model Number: 2487) using a mobile phase of 0.01M 1-Heptanesulfonic Acid Sodium Salt/0.025M NaH_2PO_4 adjusted to a final pH of 3.0 with phosphoric acid and acetonitrile in a ratio of 75:25 (v/v). A Phenomenex Prodigy ODS-2 C_{18} analytical column with dimensions of 4.6 mm x 50 mm and a particle size of 5 µm; (Phenomenex, Torrance, CA, USA) was used for the analysis at a flow rate of 1.0 mL/min. The column was maintained at ambient temperature while the auto sampler was maintained at 15°C. UV detection was

conducted at 210nm. Data was collected and processed with Millenium Data Acquisition software (Waters, Milford, Massachusetts Version Number: 3.2).

Section 15 e: Dissolution Results for Concerta® Tablets:

Table 7: Percent of methylphenidate hydrochloride released per time point for each medium

Control

Time points (min)	15	30	45	60	120	180	240	300	360	420	480	540	600	660	720	780
Vessel 1	23	23	23	23	27	34	45	56	68	78	90	100	102	102	102	102
Vessel 2	24	24	25	25	28	36	47	59	70	82	93	101	102	103	103	103
Vessel 3	22	23	22	22	26	33	44	57	69	81	95	99	101	101	101	102
Vessel 4	23	23	23	23	27	34	44	56	68	79	89	98	99	99	100	100
Vessel 5	20	21	21	21	25	34	45	57	73	87	97	99	100	100	100	100
Vessel 6	23	24	24	24	29	38	51	65	77	89	100	102	102	102	102	103
Mean	**23**	**23**	**23**	**23**	**27**	**35**	**46**	**58**	**71**	**83**	**94**	**100**	**101**	**101**	**101**	**102**
%RSD	**6**	**5**	**6**	**6**	**5**	**5**	**6**	**6**	**5**	**5**	**5**	**2**	**1**	**2**	**1**	**1**
Std Dev	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**3**	**4**	**4**	**4**	**1**	**1**	**1**	**1**	**1**

5% Ethanol

Time points (min)	15	30	45	60	120	180	240	300	360	420	480	540	600	660	720	780
Vessel 1	22	22	23	23	26	34	44	57	69	81	92	97	98	99	99	100
Vessel 2	22	22	23	23	26	35	47	62	74	86	98	100	101	102	99	100
Vessel 3	21	21	22	22	26	34	47	61	75	90	99	100	103	103	103	103
Vessel 4	21	21	22	22	26	36	48	60	74	85	96	97	99	99	98	101
Vessel 5	19	20	20	20	24	32	43	55	67	78	90	92	93	93	93	94
Vessel 6	22	23	23	23	27	36	49	60	74	87	98	99	100	100	100	100
Mean	**21**	**22**	**22**	**22**	**26**	**35**	**46**	**59**	**72**	**85**	**96**	**98**	**99**	**99**	**99**	**100**
%RSD	**5**	**5**	**5**	**5**	**4**	**4**	**5**	**5**	**5**	**5**	**4**	**3**	**3**	**4**	**3**	**3**
Std Dev	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**3**	**3**	**4**	**3**	**3**

Table 7: Percent of methylphenidate hydrochloride released per time point for each medium, contd.

10% Ethanol

Time points (min)	15	30	45	60	120	180	240	300	360	420	480	540	600	660	720	780
Vessel 1	22	23	24	24	28	39	53	68	82	97	100	100	101	101	101	101
Vessel 2	19	19	19	20	25	36	51	66	82	95	97	97	98	98	98	98
Vessel 3	19	20	20	20	25	34	47	61	75	88	95	96	97	97	97	97
Vessel 4	21	22	22	22	26	36	50	64	78	94	97	97	98	98	98	98
Vessel 5	20	21	21	21	25	35	49	64	79	95	101	102	102	102	103	103
Vessel 6	20	20	20	20	23	33	47	64	78	94	97	98	99	99	99	99
Mean	**20**	**21**	**21**	**21**	**25**	**36**	**50**	**65**	**79**	**94**	**98**	**98**	**99**	**99**	**99**	**99**
%RSD	**6**	**7**	**9**	**8**	**6**	**6**	**5**	**4**	**3**	**3**	**2**	**2**	**2**	**2**	**2**	**2**
Std Dev	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**3**	**3**	**2**	**2**	**2**	**2**	**2**	**2**

20% Ethanol

Time points (min)	15	30	45	60	120	180	240	300	360	420	480	540	600	660	720	780
Vessel 1	19	21	21	22	29	43	61	76	93	98	98	98	99	100	101	101
Vessel 2	21	24	24	25	32	47	68	84	102	105	102	103	103	102	103	106
Vessel 3	20	21	21	21	28	39	55	72	88	103	103	101	99	99	100	103
Vessel 4	22	23	23	24	31	46	65	81	101	104	105	103	102	103	104	103
Vessel 5	18	20	20	20	23	35	51	70	87	96	98	96	95	96	97	97
Vessel 6	24	28	28	28	34	48	63	79	99	103	103	106	103	105	104	104
Mean	**21**	**23**	**23**	**23**	**30**	**43**	**61**	**77**	**95**	**102**	**102**	**101**	**100**	**101**	**102**	**102**
%RSD	**11**	**13**	**13**	**13**	**13**	**12**	**11**	**7**	**7**	**4**	**3**	**4**	**3**	**3**	**3**	**3**
Std Dev	**2**	**3**	**3**	**3**	**4**	**5**	**6**	**5**	**7**	**4**	**3**	**4**	**3**	**3**	**3**	**3**

Table 7: Percent of methylphenidate hydrochloride released per time point for each medium, contd.

40% Ethanol

Time points (min)	15	30	45	60	120	180	240	300	360	420	480	540	600	660	720	780
Vessel 1	20	22	23	25	34	49	68	95	102	103	103	103	104	104	104	104
Vessel 2	22	24	25	27	41	59	78	101	103	104	105	105	106	106	107	106
Vessel 3	22	25	26	27	41	58	76	99	103	105	105	106	106	106	106	106
Vessel 4	19	22	23	24	35	51	69	88	101	103	103	104	104	104	105	105
Vessel 5	21	24	25	27	42	63	85	102	104	104	105	105	106	106	106	107
Vessel 6	21	25	26	28	41	60	81	104	107	108	109	109	110	110	110	110
Mean	**21**	**24**	**25**	**26**	**39**	**57**	**76**	**98**	**103**	**105**	**105**	**105**	**106**	**106**	**106**	**106**
%RSD	**5.6**	**5.8**	**5.5**	**5.7**	**9.0**	**9.6**	**8.8**	**6.0**	**2.0**	**1.8**	**2.1**	**2.0**	**2.1**	**2.1**	**1.9**	**1.9**
Std Dev	**1**	**1**	**1**	**2**	**4**	**5**	**7**	**6**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**

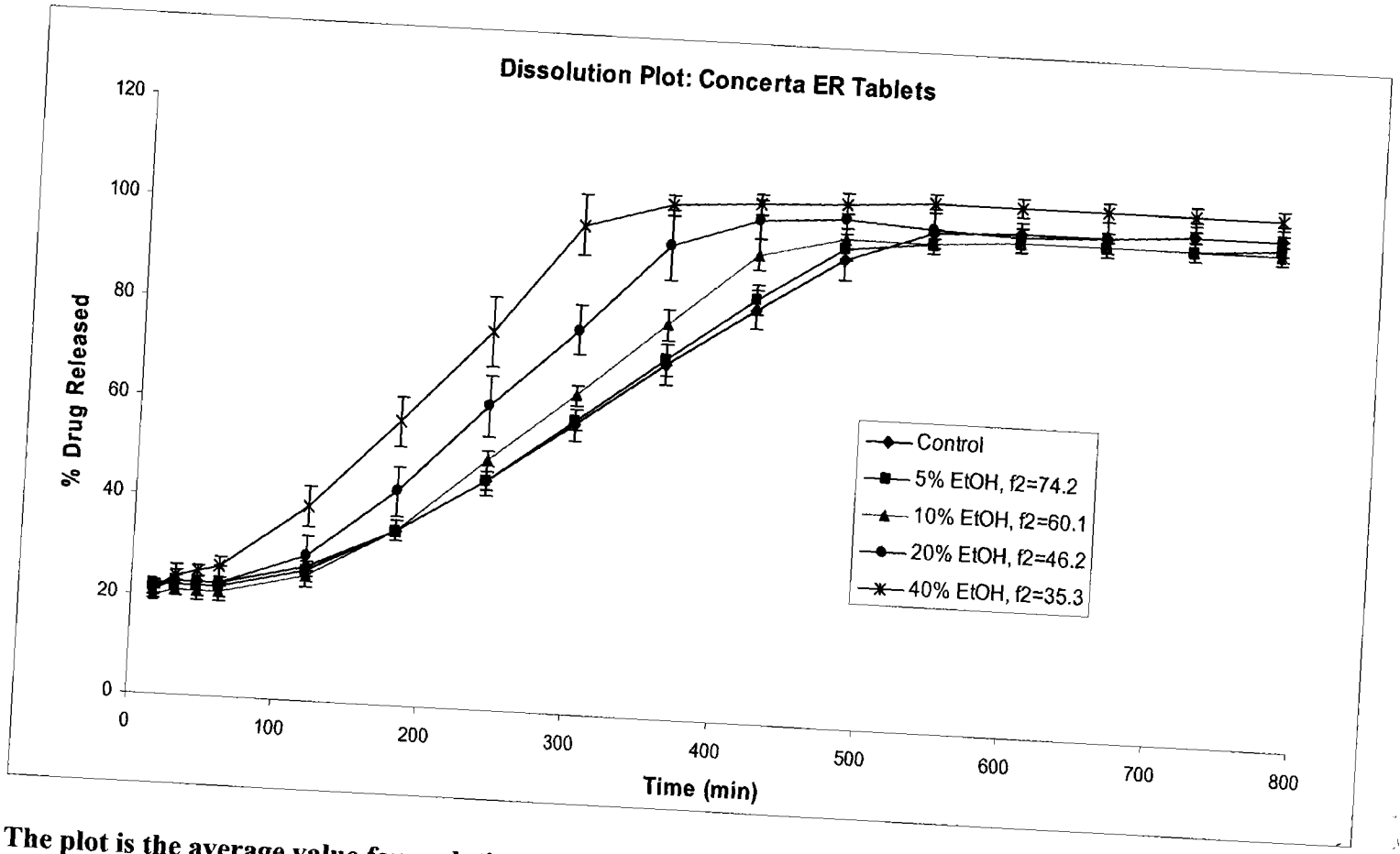
Table 8: Average and standard deviation of methylphenidate hydrochloride released for each medium (n=6 for each medium)

Release Profiles for Concerta ER Tablets

% Drug Dissolved Per Time Period

Time points (minutes)	Control	SD	5% EtOH	SD	10% EtOH	SD	20% EtOH	SD	40% EtOH	SD
15	22	1	22	1	20	1	21	2	21	1
30	23	1	22	1	21	1	23	3	24	1
45	23	1	22	2	21	2	23	3	25	1
60	23	1	22	2	21	2	23	3	26	2
120	27	1	26	2	25	2	29	4	39	4
180	35	2	35	2	35	2	43	5	57	5
240	46	3	46	2	50	2	61	6	76	7
300	58	3	59	2	64	2	77	5	98	6
360	71	4	72	3	79	3	95	7	103	2
420	83	4	85	3	94	3	101	4	104	2
480	94	4	96	2	98	2	102	3	105	2
540	100	1	98	2	98	2	101	4	106	2
600	101	1	99	2	99	2	100	3	106	2
660	101	1	99	2	99	2	101	3	106	2
720	102	1	99	2	99	2	102	3	106	2
780	102	1	100	2	99	2	102	3	106	2

Graph 4: Dissolution Plot for Concerta® Tablets



The plot is the average value for each time point ± standard deviation.

Section 15 f: Discussion

This formulation does appear to be affected by the presence of alcohol. Every increase in ethanol shows an increase in release rate. However, the Concerta® Tablets appear to have a high tolerance to ethanol up to the 20% concentration. The only similarity factors that show statistical differences from the control are 46.2 and 35.3 at the 20% and 40% ethanol concentrations, respectively. The time it takes for the full amount of drug to release for the control samples is approximately 600 minutes (10 hours) versus 300 minutes (5 hours) for the 40% ethanolic medium. The full amount of drug in the tablet releases in half the time in the 40% ethanolic medium than compared to the control medium. This indicates an obvious effect of alcohol on the release mechanism of the osmotic pump formulation.

The effect of alcohol at all on this formulation is surprising since the controlled release design is osmotic pressure. The semi-permeable membrane used in osmotic pump formulations allows water to enter into the table at a controlled rate. The pressure exerted from water entering into the drug compartment forces the drug to be released from the orifice at a controlled rate.

The increase in release rate that occurred with the Concerta® Tablets may be due to the difference in densities of water and ethanol. The density of water is approximately 1.00 while the density of ethyl alcohol is 0.79 [76]. Since the density of ethyl alcohol is lower than the density of water, perhaps either a larger volume of fluid (water and ethanol) is allowed to enter into the capsule with every increase in ethanol or the fluid is permitted into the capsule at a faster rate with every increase in ethanol. This increase in volume or rate could force the active drug out faster.

CONCLUSIONS

Section 16: Conclusions

Section 16 a: Future Research

The affect of ethanol on the drug release profiles for 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. These dissolution methods are assumed to be reliable in predicting what could potentially happen in vivo when the patient simultaneously consumes a pharmaceutical drug listed above and alcohol.

This work is only the very beginning of the investigations that should be conducted on the influence of alcohol on the release rate of extended-release dosage forms. Only four different formulations were studied out of the numerous ER formulations available on the market. Therefore, more in vitro testing should be conducted on other various types of ER formulations to better understand which formulations are sensitive and which are rugged enough to withstand the presence of ethanol.

The type of testing conducted in this research represents the worst-case scenario not only with the high alcohol levels but also with the highest dosage strength available. In addition, the ethanol was added at the beginning of the dissolution test and the concentration remained steady throughout the test. This also represents the worst-case scenario because the dosage form was continuously exposed to the ethanol throughout the test.

If alcohol and a prescription drug are going to be combined, it is more likely that a patient will ingest the drug first and will consume an alcoholic beverage later in the day or evening. Therefore, an in vitro approach that may represent a more realistic scenario would be to begin the dissolution test in the designated control medium and then switch the dosage form into an ethanolic medium one to several hours later. When the dosage form is switched to the new medium, the ER drug release mechanism would have already started to release the drug. Therefore, when it is placed in the ethanolic medium, the dosage form will most likely be more vulnerable and would most likely cause an increase in drug release.

Section 16 b: Extended-Release Formulation Design

In addition, the solubility of all polymers and excipients utilized in controlled-release formulations in ethanol should be known and well documented. Formulations that are comprised of an active drug and/or excipients more soluble in ethanol than in an aqueous environment could be at a high risk of dose dumping. Therefore, if a polymer used in a formulation either exhibits higher solubility in ethanol or it's physiochemical properties or swelling is altered by ethanol, possibly a second layer of ethanol-resistant polymer can be employed and/or other excipients that will resist the increased release rate when in the presence of ethanol.

Since the FDA will most likely expect this type of in vitro testing in the future to demonstrate that the dosage form is not ethanol sensitive, a rugged drug release mechanism in future ER formulations must be developed. Using polymers that have the same solubility and the same swelling properties in water and ethanol are desirable. This information is lacking in the literature. Future research could include testing the

solubility of commonly used polymers in ER formulations so that formulators would have this information available to them to aid them in developing rugged formulations.

Section 16 c: Patient Warnings

Although warning labels on the inserts in pharmaceutical drug packaging normally warn the patient on the dangers of combining alcohol and prescription drugs, this advice is not always noticed and read. This could be due to the fact that patients unfamiliar with pharmaceutical formulations may not know to read these inserts on potential interactions and side effects. And even if the patient reads the insert, the warnings are not always heeded. Therefore, doctors and pharmacists need to educate their patients and customers on the high dosage content as well as the release mechanisms of extended-release formulations. They should also ensure the patient is fully aware of the high risk and dangers of dose dumping when the release mechanisms are compromised. Doctors and pharmacists should be held responsible to make it clear to the patient that alcohol could compromise the ER mechanism of the prescription drug if subjected to ethanol.

If there is a chance a formulation is sensitive to ethanol, the dangers of possible dose dumping should be listed on every applicable drug label. This is necessary for the patient's safety. It is very possible that a highly ethanol-sensitive formulation may have high benefits of the drug that outweigh the risks of a patient mixing alcohol with the drug. In this case, having the drug available to the patient may be more important. In these situations, a black box warning may be necessary. In addition, Dr. Doctor letters may be important to draw special attention to this risk.

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