FAILURE MODES OF PEO BASED ABUSE DETERRENT OPIOIDS AND PROMETHAZINE HYDROCHLORIDE TABLETS

by

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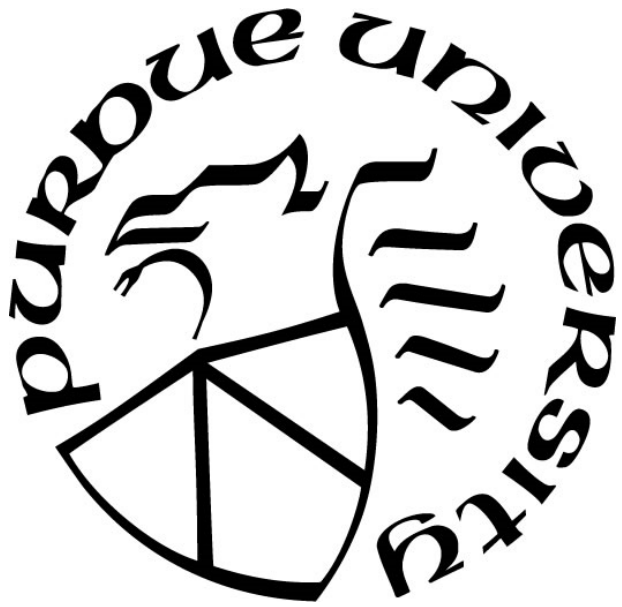

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To my family

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADF:	Abuse Deterrent Formulations
ANN:	Artificial Neural Network
APIs:	Active Pharmaceutical Ingredients
AUC:	Area Under the Curve
CDC:	Centers for Disease Control and Prevention
CDER:	U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research
Cmax:	Maximum free concentration
CPM:	Chlorpheniramine maleate
CSA:	Controlled Substances Act
DC:	Direct Compression
Drug	Evaluation and Research
FDA:	Food and Drug Administration FDA
HME:	Hot Melt Extrusion
HPLC:	High-performance liquid chromatography
ME:	Melt Extrusion
MW:	Molecular Weight
NME:	New Molecular Entity
OROSTM:	Osmotic (Controlled) Release Oral (Delivery) System
PEO:	Polyethylene oxide
PEG:	Polyethylene Glycol
PMH:	Promethazine hydrochloride
PMZ HCL:	Promethazine Hydrochloride

SGF: Simulated Gastric Fluid

Tg: Glass transition temperature

T_{max}: Time to reach C_{max}

T1/2: Terminal elimination half-life

ABSTRACT

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Opioid addiction has become a global epidemic and a national health crisis in recent years. In 2016, approximately 64,000 Americans under 50 years old were killed because of opioid overdoses. The aim of developing an abuse deterrent opioid is to render any form of manipulation that encourages abuse challenging and therefore, non-profitable. With this goal, the Food and Drug Administration (FDA) is extensively supporting research into the development of abuse deterrent technologies and prioritizing their production as a public health necessity. Abuse deterrent approaches include but are not limited to the following: (1) using a physical barrier (e.g., Polyethylene oxide PEO) that basically limit the release of the drugs in the blood or the digestive tract and prevent mechanical alteration of the drugs by crushing, grating, grinding, chewing etc, (2) using chemical barriers that employ gelling agents that prevent the aqueous or organic extraction of the drugs, and (3) combining the drug with an antagonist that blocks the post-abuse euphoria.

PEO is a popular polymer used as a matrix in these complex opioid products. The polymer is responsible for the abuse deterrent properties as well as extended release behavior of opioid drugs. PEO hinders the extraction of Opioid drugs from Abuse Deterrent Formulations (ADF), makes it challenging to be injected, and resists mechanical stress and pulverization when crushed. PEO can be subjected to thermal processing such as thermal curing, compression molding, melt extrusion, and injection molding owing to its thermoplasticity.

Assessment of the impact of using various manufacturing processes to develop ADFs and the effect of using various grades of this polymer is essential to improve upon the next generation of ADFs. There are three main categories of premarket studies: Category 1 – laboratory based (in-vitro manipulations and drug extractions), category 2 – pharmacokinetic and category 3 –clinical. These studies are required by the FDA to demonstrate that a given formulation exhibit abuse deterrent properties before a drug product is released to the market. In vitro laboratory based manipulation and extraction studies which are used to assess AD properties of these products are challenging, but essential for product development and generic abuse deterrent product approvals. It is important to realize that there is a great correlation between the laboratory based in vitro manipulation and extraction studies and the expectations of potential abuse and misuse of opioid drugs. The ability of these studies to mimic the manipulation techniques applied by abusers to defeat the abuse deterrent properties of a given formulation optimizes predictions on post-market abuse and misuse potential of ADFs. These studies should also correlate well with *in-vivo* studies since there is a direct correlation with the concentration (mg/mL in water) and the "high" obtained by an abuser.

This research aimed to conduct laboratory based in vitro manipulation and extraction studies to investigate failure modes of PEO-based prescription opioids and Promethazine Hydrochloride PMZ HCl tablets. It highlighted the formulation components and the manufacturing parameters that might affect the dose dumping of Active Pharmaceutical Ingredients (APIs). Furthermore, this research identified model compounds that can be used as surrogates for Oxycodone and the best experimental setup that can be used to conduct smoking simulation experiments. Moreover, it provided an overview of the societal impacts of the opioid crisis in the state of Indiana.

Investigations of the failure modes of the PEO-based prescription opioids and PMZ HCL tablets showed that physical manipulation techniques via chopping or grinding are much more effective in the destruction of the PEO matrix than thermal manipulation via the application of heat thus promoting the fast release. The factor with the most significant effect on the failure modes of PMZ HCL tablets was the application of physical manipulation, while the one with the lowest impact was the polymer grade. Moreover, producing PEO-based matrix tablets via Direct Compression DC significantly affected dose dumping behavior of the API from the drug products. The production of the PEO-based matrix tablets via DC was found to be favored over the usage of the melt extrusion method and molding techniques. It was clear that DC kept the integrity of the polymer, allowed for slow and controlled release fashion of the API, and rendered the extraction process relatively hard compared to the Hot Melt Extrusion HME and Molding techniques.

Furthermore, the release profile of the investigated PMZ HCL products consisted of various phases of polymer swelling and API release. Thermal manipulations via the application of heat were found to accelerate the dose dumping behavior (90% release) of the APIs from the compressed, extruded, and molded PEO-based matrix formulations similarly. On the other hand, heating was much more effective in the extraction of APIs than chopping or grinding thus promoting the ability to draw a solution containing the API into a syringe for injection relatively easy and facilitate higher % API recovery.

Among the formulation components that might have an impact on the AD properties of the PEO-based drug products are; the choice of the antioxidant, the use of complexing agents, chelating agents, and plasticizers. On the other hand, manufacturing process variables that might have a critical impact on AD properties of the PEO-based drug products include but are not

limited to; processing temperature compared to the melting point of the polymer and time of exposure

PMZ HCl was used as a model drug for Oxycodone in dissolution and extractability studies, while Caffeine and L-Nicotine were used as model drugs in smoking simulation experiments. The combination of the propane torch and Kugelrohr apparatus mimic the real-world scenario for smoking Opioids; however, this experimental setup caused thermal degradation rather than vaporization of some model drugs.

According to the National Center for Health Statistics; a statistically significant increase in drug overdose death rates was reported in 2016 in the state of Indiana among other states. The number of deaths related to opioid pain relievers increased by 3732 folds in 2017 compared to the number of deaths in 2014. Moreover, Males were more affected by the opioid crisis than females. On the other hand, the age group 25-44 years, and white people were the most affected by the opioid crisis in Indiana.

CHAPTER 1. INTRODUCTION

This chapter introduces an overview of the research work, including the statement of the problem, research questions, scope, significance, assumptions, limitations, delimitations, and definitions of key terms.

1.1 Statement of the Problem

Opioid addiction has become a global epidemic and a national health crisis in recent years, with the number of opioid overdose fatalities steadily increasing since the 1990s, as shown in figure 1.1. Therefore, President Trump declared the opioid crisis to be a public health emergency (Davis, 2017). Per The New York Times, "the current opioid epidemic is the deadliest drug crisis in American history." In 2016, approximately 64,000 Americans under 50 years old were killed as a result of opioid overdoses. Deaths rates caused by the current opioid epidemic is higher than that caused by the HIV epidemic at its peak and more than guns and car accidents (Salam, 2017). Per the Centers for Disease Control and Prevention, "In 2015, the amount of opioids prescribed was enough for every American to be medicated around the clock for three weeks". Indiana is among the states that have the highest number of prescription painkillers per 100 people, as shown in the color-coded U.S map displayed in figure 1.2 (Centers for Disease Control and Prevention, 2012).

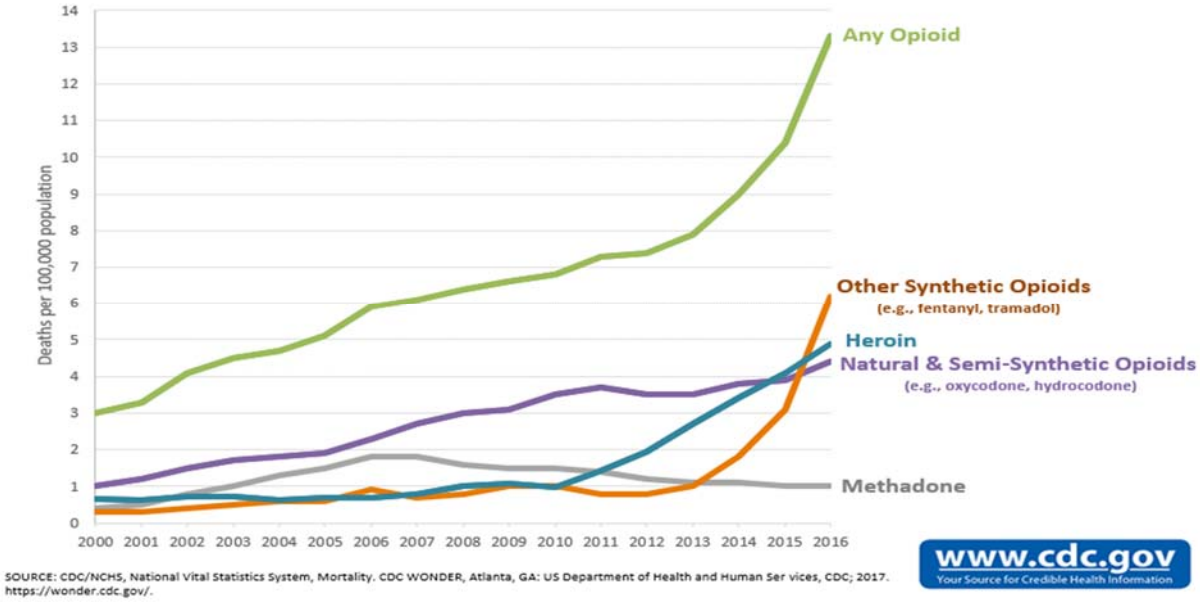


Figure 1.1 Number of overdose deaths caused by opioids per 100,000 populations, 2000-2016 (Centers for Disease Control and Prevention, 2017).

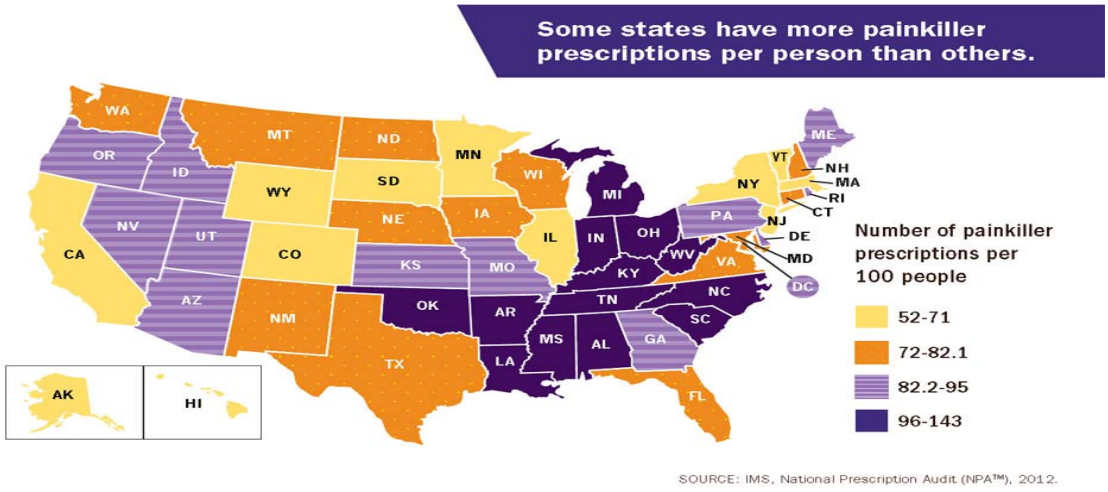


Figure 1.2 Opioid painkiller prescribing infographic (Centers for Disease Control and Prevention, 2012).

The aim of developing an abuse deterrent opioid is to render any form of manipulation that encourages abuse, whether by altering administration routes or their extended release (ER), challenging and therefore non-profitable. With this goal, the FDA is extensively supporting

research into the development of abuse deterrent technologies and prioritizing their production as a public health necessity. Abuse of an opioid drug is defined as its intentional misuse for non-therapeutic or recreational purposes, usually to achieve a psychological 'high.' As the name implies, abuse deterrent properties only deter, i.e., discourage abuse, not prevent it completely. Opioid drugs are abused in myriad ways, e.g., snorting, swallowing, smoking, injecting after they are crushed and/or dissolved. The abuse deterrent drugs should, therefore, target these routes of administration, and with that purpose, their formulations, as well as evaluation, needs to evolve.

Polyethylene oxide (PEO) is a popular polymer used as a matrix in these complex opioid products. The polymer is responsible for the abuse deterrent properties as well as extended release behavior of opioid drugs. PEO hinders the extraction of Opioid drugs from Abuse Deterrent Formulations ADF, makes it challenging to be injected, and resists mechanical stress and pulverization when crushed. Assessment of the impact of using various manufacturing processes to develop ADFs and the effect of using multiple grades of this polymer is essential to improve upon the next generation of abuse deterrent products. Furthermore, in vitro laboratory manipulation and extraction studies which are used to assess abuse deterrence properties of these products are challenging, but essential for product development and generic abuse deterrent product approvals.

1.2 Purpose and Objectives of the Study

I. Investigating the impacts of applying thermal and mechanical manipulations on the release percentage, syringeability, extractability, and smoking ability of several Abuse Deterrent Formulations ADFs.

II. Investigating the impacts of applying thermal and mechanical manipulations on the release percentage, syringeability, and extractability of PMZ HCL from PEO based products.

III. Investigating the impacts of applying different manufacturing processes; (Hot Melt Extrusion HME, Molding, and Direct Compression DC) on the release percentage, syringeability, and extractability of Promethazine Hydrochloride PMZ HCL from Polyethylene Oxide PEO based products.

IV. Investigating the impacts of using PEO with different molecular weights MWt (4M and 7M) on the release percentage, syringeability, and extractability of PMZ HCL from PEO based products.

V. Investigating the impacts of using PEO obtained from different suppliers, Dow Chemicals and Sumitomo Seika manufacturers on the release percentage, syringeability, and extractability of PMZ HCL from PEO based products.

VI. Determine the possible release patterns of PMZ HCL from PEO-based products.

VII. Determine the corresponding quantitative impacts of the critical variables that affect the release percentage, syringeability, and extractability of PMZ HCL.

VIII. Investigating the societal impacts of the opioid crisis on the state of Indiana.

IX. Exploring the formulation differences that might affect the dose dumping of active ingredients.

1.3 Research questions

1. What are the failure modes of ADFs and PEO based PMZ HCL tablets?

2. What are the formulation and manufacturing differences between ADFs that might affect the dose dumping of active ingredients?
3. What are the effects of applying different manufacturing processes (Hot Melt Extrusion HME, Molding, and Direct Compression DC), using PEO with high and low MWt, and using PEO obtained from different suppliers on the failure modes of PMZ HCL from PEO-based products?
4. What are the possible release patterns of PMZ HCL from PEO-based products?
5. What are the corresponding quantitative impacts of the critical variables that affect the release percentage of PEO based PMZ HCL?
6. Which model compounds can be used as surrogates for Oxycodone in smoking simulation testing?
7. What is the best experimental setting that can be used for the smoking simulation of Oxycodone and its surrogate model compounds?
8. What are the societal impacts of the opioid crisis in the state of Indiana?

1.4 Significance

Every year, 100 million people in the U.S. suffer from pain, with 9-12% of these individuals experiencing pain that is considered chronic. Opioid therapy is an essential component of chronic pain management for many patients, but the addictive and euphoric properties of these drugs make them vulnerable to misuse, abuse, addiction, and possible death by overdose. The FDA is responding to prescription opioid abuse by prioritizing abuse-deterrent formulations and overdose treatments.

1.5 Assumptions

- Data regarding the abuse, misuse, and death rate related to prescription opioid are available, accurate, and trustful.
- Equipment that will be used to evaluate the failure modes of ADFs and their surrogate products are accurate, reliable, and calibrated.

1.6 Limitations

This study is limited to the following:

- The conduction of laboratory-based in vitro manipulation and extraction studies that are categorized as category I in the premarket studies to evaluate the failure modes of ADFs and PEO base PMZ HCL tablets.
- The assessment of the impacts of different manufacturing processes, molecular weight, PEO suppliers, and thermal and mechanical manipulations on the release percentage, syringeability, and extractability of Active Pharmaceutical Ingredients APIs from opioids simulated products that contain Polyethylene oxide and Promethazine Hydrochloride.
- The assessment of the impacts of applying thermal and mechanical manipulation techniques on the rerelease percentage, syringeability, and extractability of APIs from ADFs.

1.7 Delimitations

Delimitations of the study include the following:

- Category II of premarket studies that evaluate the pharmacokinetic profile of the ADFs.

- Category III of premarket studies that evaluate the clinical abuse potential the ADFs.
- Non-abuse-deterrent formulations of specific opioids are not considered.
- The assessment of the impacts of formulations differences on the dose dumping of APIs.
- The political climate impacting the crisis.

1.8 Definitions of Key Terms

Abuse is the "*intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.*" (U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2015).

Addiction is a "*primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.*" (Savage et al., 2001)

Polyethylene oxide (PEO), a semi-crystalline homo-polymer of ethylene oxide, is used to prepare the matrix for various pharmaceutical capsules.

Hot Melt Extrusion (HME) is a widely applied technology in the pharmaceutical industry that offers several advantages such as being solvent free and involving fewer processing steps in comparison to other techniques.

1.9 Summary

This chapter has provided an overview of the research study, including the statement of the problem, research questions, significance, objectives, assumptions, limitations, delimitations, and definitions of key terms.

CHAPTER 2. LITERATURE REVIEW

This chapter presents an overview of the relevant literature. It has introduced an overview of the studies that should be conducted to demonstrate that a given formulation exhibit abuse deterrent properties, the well-known abuse deterrent strategies, and the applications of the hot-melt extrusion technology. Furthermore, it provides an overview of the potential Oxycodone surrogate APIs and discusses the impacts of ADFs on opioid usage and the implications of the failure modes of ADFs on public health.

2.1 How do scientists demonstrate that a given formulation has abuse-deterrent properties?

Due to the crowded patent scenario, it is essential to conduct premarket studies to ascertain the abuse-deterrent properties of various formulations. The evaluation standards need to be evolved and adapted continuously to make way for newer drugs and abuse routes. The aim of developing an abuse deterrent opioid is not only to reduce the actual abuse but also any potential abuse. With this goal, the FDA is extensively supporting research into the development of abuse deterrent technologies. There are three primary levels of premarket studies: Category 1 – laboratory-based (in-vitro manipulations and drug extractions); category 2 – pharmacokinetic and category; and 3 –clinical abuse potential studies. A complete study of abuse deterrent technologies ought to include data from all categories.

2.1.1 Category 1. Laboratory Manipulation and Extraction Studies

Category 1 studies are focused on the possible in-vitro manipulative techniques that can breach the abuse deterrent barriers with relative ease. This information is vital for designing the

following category 2 and 3 studies, which further expand on the characteristics and in-vivo performance of the drug. Designing a category 1 study requires the knowledge of a) physicochemical properties of the formulation and b) possible methods of abuse that are readily available to users. Furthermore, these studies should be carried on the final formulation of the drug that will be marketed. In addition to the intentional abuse, the researchers should also focus on the unintentional ways by which users may alter the release rate of the drug. A common occurrence is 'dose dumping,' which refers to drug ingestion with alcohol that may unwittingly lead to rapid drug release.

Drug tests should yield sufficient information regarding its abuse-deterrent barriers as well as the methods of bypassing those barriers. It is also very useful to directly question drug abusers about those methods. There are three common ways by which an opioid drug can be manipulated: 1) disrupting the controlled release of the opioid, 2) altering the drug formulation to instant release via other routes of administration and 3) removing the opioid antagonist, if present in the original formulation. A category 1 study aims to determine the simplest conditions that can manipulate the drug and breach the abuse deterrent features. For instance, if a set of conditions can extract 90% of the drug within 10 minutes, the procedure need not be continued for 20-30 minutes longer. To test the ease of mechanical manipulation, household items like cutlery, grinders, etc. should be tested for their ability to crush and grind the drug. The size of the particles should be measured after physical tampering as this affects the rate of opioid extraction.

Similarly, the impact of extreme temperatures on the physical integrity of the drug should also be assessed. The ease of chemical extraction of an opioid should be tested using common solvents like water, vinegar, alcohol, acetone, and other spirits. It is also essential to examine the effect of pH, temperature, and mechanical agitation on solvent extraction as well as precipitation.

Once it has been established that an opioid can be manipulated, the chemical extractability of the intact drug should be compared with that of the manipulated drug as well as other similar drugs. In case a formulation has more than one opioid, it is essential to determine the solubility and extractability of the different active substances. The conditions for chemical extraction should be tested for 12 hours or till 80% of the opioid has been released. Lastly, a known robust chemical dissolution method should be tested for both the intact and manipulated form of the drug.

To summarize, the in vitro studies usually evaluate one or more of the following:

1. Drug particle size following physical disintegration by melting, crushing, or grinding.
2. The solubility of the opioid and active ingredients in a solvent.
3. The quantity of the extracted opioid using the above methods.
4. The amount of the opioid antagonist released.
5. The remaining amount of the active opioid after in-vitro manipulation.

2.1.2 Category 2. Pharmacokinetic Studies

Category 2 studies compare the pharmacokinetic profile of the manipulated drug with that of the intact drug as well as with the known profiles of other drugs. Pharmacokinetic is preferably evaluated through more than one route of administration and it is important that the test and the control samples are compared via the same routes. In any case, the route(s) of administration should be chosen based on the previous knowledge of similar drugs and their abuse. Besides, the mode of manipulation of the test drug should be such that it results in maximum release and can be determined based on in-vitro data collected in category 1 studies. The most relevant parameters for opioids and general psychoactive drugs regarding their potential are:

• Maximum free concentration (C_{max})

• Time to reach C_{max} (T_{max})

• The area under the curve from AUC0-t (any given time point) to AUC0-∞

• Relevant partial AUC that entails early time points (30 min. – 2 hours) and the expected duration of C_{max}

• Terminal elimination half-life ($T_{1/2}$)

2.1.3 Category 3. Clinical Abuse Potential Studies

Category 3 studies are performed in conjunction with the recommendations of the Controlled Substances Act (CSA) to determine the abuse deterrent potential of new drugs. The ideal study should be double-blind, randomized, placebo- and positive-controlled and preferably conducted on recreational users. Only those subjects should be considered who can distinguish between placebo and drug to improve the efficacy of the drug. This can be achieved by a pre-clinical phase (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), 2015).

2.2 Abuse Deterrent Strategies

Novel abuse deterrent opioids have been at the forefront of the development of safe opioid analgesics, a public health necessity that has prompted the FDA to prioritize their production. The basis of these abuse deterrent opioid formulations is to render any form of manipulation that encourages abuse, whether by altering administration routes or their extended release (ER), challenging and therefore non-profitable. As the name implies, abuse deterrent properties only deter i.e. discourage abuse, not prevent it completely. Abuse of an opioid drug is

defined as its intentional misuse for non-therapeutic or recreational purposes, usually to achieve a psychological 'high.' Opioid drugs are abused in myriad ways, e.g. snorting, swallowing, smoking, injecting after they are crushed and/or dissolved. The abuse deterrent drugs should, therefore, target these routes of administration, and with that purpose, their formulations, as well as evaluation, needs to evolve. Different approaches to develop abuse-deterrent formulations are represented in table 2.1. The basic abuse deterrent strategies are classified as follows:

1. Using a physical/chemical barrier that basically limits the release of the drugs in the blood or digestive tract or renders the drug unamenable to an unintended route. The physical barriers prevent mechanical alteration of the drugs by crushing, grating, grinding, chewing, etc. while the chemical barriers employ gelling agents that prevent the aqueous or organic extraction of the drugs.
2. Combining the drug with an antagonist that is released only when the drug is abused and that either blocks or at-least limits the post-abuse euphoria. The formulation needs to sequester the antagonist in a clinically inactive form that is activated once the drug is manipulated, e.g. crushed or dissolved in an organic solvent.
3. Adding adverse tasting or irritant substances that will be unpalatable to the user if the drug is used at a higher dose. For instance, if a drug tends to be abused nasally, i.e. by snorting, then a mucosal irritant can be added.
4. Making the drug delivery system challenging, e.g. by using subcutaneous implants or slow release capsules/bolus. Such formulations are hard to manipulate for drug abuse.
5. Making molecular alterations can affect the drug's physiological properties. For instance, the drug can be made in an inactive 'pro-drug' form that can only be activated by enzymatic action, different receptor binding profiles or include with a

new molecular entity (NME) which results in slower diffusion into tissues. The chemical barrier of such prodrugs can only be broken inside the body and not ex-vivo, thus making it a robust abuse deterrent. NMEs and prodrugs are subject to the same standards of abuse potential evaluation as detailed in the Controlled Substances Act (CSA).

6. Any Combination of the above strategies
7. Novel strategies that have not been conceptualized yet

Table 2.1 Abuse-deterrent technologies and physical barriers of approved drugs (Maincent & Zhang, 2016)

Product Name	Active Ingredient	Original Manufacturer	Physical Barrier	Manufacturing Process	Year Approved	Platform Technology
OxyContin® extended-release tablets	Oxycodone HCl	Purdue Pharma LP	PEO	Proprietary thermal processing	2010	RESISTEC™
EXALGO® extended-release tablets	Hydromorphone HCl	Mallinckrodt Pharmaceuticals	PEO/Cellulose acetate	Compression and coating	2010	OROS®
OPANA® ER extended-release tablets	Oxymorphone HCl	Endo Pharmaceuticals, Inc.	PEO	Melt extrusion and cold molding	2011	INTAC™
NUCYNTA® ER extended-release tablets	Tapentadol HCl	Janssen Pharmaceutical	PEO	Melt extrusion and cold molding	2011	INTAC™
OXAYDO® immediate-release tablets	Oxycodone HCl	Acura Pharmaceuticals, Inc.	PEO	Direct compression	2011	AVERSION®
ZOHYDRO® ER extended-release capsules	Hydrocodone bitartrate	Zogenix Inc.	PEO	Granulation and coating	2013	BeadTek™
TARGINIQ® ER extended-release tablets	Oxycodone HCl and Naloxone HCl	Purdue Pharma LP	PEO	Proprietary thermal processing	2014	RESISTEC™
HYSINGLA™ ER extended-release tablets	Hydrocodone bitartrate	Purdue Pharma LP	PEO	Proprietary thermal processing	2014	RESISTEC™
XARTEMIS® XR extended-release tablets	Oxycodone HCl and acetaminophen	Mallinckrodt Pharmaceuticals	PEO	Direct compression	2014	Not Available
MORPHABOND™ extended-release tablets	Morphine sulfate pentahydrate	Inspirion Delivery Technologies LLC	Xanthan gum/ HPMC	Compression and film coating	2015	SentryBond™
Xtampza® ER controlled-release capsules	Oxycodone free base	Collegium Pharmaceuticals	Fatty acid/wax	in-situ salt formation and spray congealing	2016	DETERx®

Polyethylene Oxide PEO is a hydrophilic, non-ionic, and high molecular weight (MW) polymer obtained from ethylene oxide following its free-radical polymerization of ethylene oxide (Maximilien, 2009). PEO is similar to polyethylene glycol (PEG) in terms of chemical composition but owing to a higher number of repetitive monomer units, has a greater MW ranging from 100,000 to 7,000,000 (Davidson, 1980) as shown in figure 2.1. It is currently being manufactured on a large scale by the Dow Chemical Company and is available in various grades

depending on viscosity and MW. PEO is miscible in water in any ratio and rapidly hydrates and swells to several times its volume forming a gel. This property has enabled its use in osmotic pumps as a 'push layer' (Bottenberg et al., 1991; Dhawan et al., 2005) and recently as a matrix for opioid tablets. The degree of swelling is directly proportional to its MW, and the highest-grade polymers are known to swell as much as seven times its original volume.

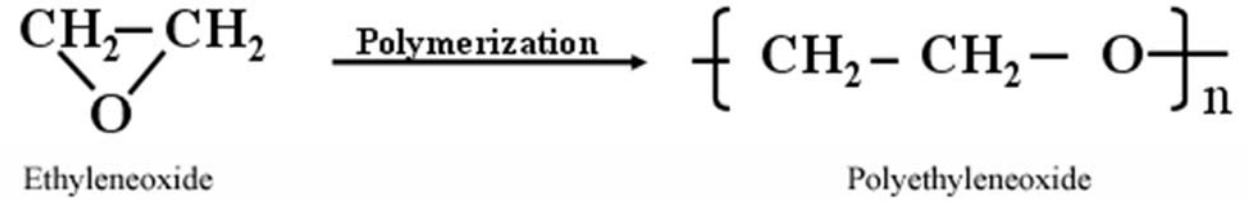


Figure 2.1 PEO structure and synthesis (Ma, Deng, & Chen, 2014).

There are several properties of PEO that make it a suitable matrix for opioid drugs vis-à-vis abuse deterrence. The melting point of PEO ranges from 65-70°C depending on its MW, and due to its semi-crystalline structure, the glass transition temperature (Tg) lies between 50-57°C. The low Tg allows PEO to be ductile rather than brittle under mechanical stress, which in turn prevents it from getting pulverized when crushed. Furthermore, its high viscosity, which depends on its MW, prevents easy extraction of the drug by both physical and chemical means and makes it difficult to be injected (Rahman et al., 2016). The lowest grade PEO available is WSR N-10 that has a MW of 100kDa, and the highest grade is WSR 303 with a MW of 7000kDa; the viscosity of a 5% solution of WSR N-10 is 12-50 mPa and that of a 1% solution of WSR 303 is 7500-10000 mPa at 25°C (The Dow Chemical Company, 2015). The insolubility of PEO in household solvents also prevents drug extraction (Bailey and Kolesky, 1976).

PEO can be subjected to thermal processing such as thermal curing, compression molding, melt extrusion, and injection molding owing to its thermoplasticity. Thermally

processed PEO forms strong matrices which instead of breaking, simply flatten thus preventing physical interference (Crowley et al., 2002; Zhang and McGinity, 1999). However, thermal processing also renders PEO liable to oxidative degradation, resulting in chain shearing and rapid drug release. To improve the thermal and storage stability of PEO, antioxidants such as vitamin E and hydroxytoluene are added during formulation. Opioids can be incorporated in the PEO matrix in two ways: dispersion in the form of crystals or molecular dissolution. For drug formulations, PEO of higher MW is used, which results in stronger matrices and allows a slow, sustained release of the drug. Lastly, PEO is highly compressible with good flow characteristics, which further helps in creating highly viscous matrices.

PEO of high MW grade, with or without PEG, has been used by the pharmaceutical industry to manufacture slow release tablets by the thermal melt extrusion process. The first of its kind was OXAYDO® or OXECTA®, an instant release oxycodone hydrochloride formulation directly compressed into tablets (McGinity and Zhang, 1999; Zhang and McGinity, 1999). There are six main techniques for manufacturing PEO matrices: 1) direct compression, 2) direct compression and thermal curing, 3) melt extrusion and molding, 4) injection molding, 5) compression and coating and 6) rotary granulation and coating. Grünenthal GmbH is the leading the research on using thermal processes in combination with ultrasonic compression techniques to develop PEO matrices of strength higher than 500N (Ashworth et al., 2010; Bartholomaus et al., 2012). Their patented INTACT™ technology uses melt extrusion, blending, cooling, cutting, forming and coating to form the PEO matrices, with the later addition of hypromellose and PEG (Bartholomaeus et al., 2012). The INTACT™ technology has so far being used successfully to manufacture extended-release oxymorphone hydrochloride (OPANA® ER) and tapentadol hydrochloride (NUCYNTA® ER) tablets in which the active drug is molecularly dispersed in the

PEO matrix during extrusion. A detailed analysis of the effect of melt extrusion on the PEO matrix quality was recently published (Baronsky-Probst et al., 2016) which implicated three parameters of the process – feed rate, screw speed, and barrel temperature – on deterring drug abuse.

The combination of thermal compression and curing using high MW PEO (4000kDa) has been developed by Purdue Pharma (McKenna et al., 2014). In the curing step, which is mainly dependent on the process temperature, the PEO particles fuse increasing the physical strength of the matrices forming highly compressed and crush resistant tablets (Rahman et al., 2016) as shown in figure 2.2.

Three abuse-resistant opioid drugs have been designed by Purdue Pharma based on this technique: OXYCONTIN® (oxycodone hydrochloride), TARGINIQ® ER (oxycodone hydrochloride and naloxone hydrochloride) and HYSINGLA® ER (hydrocodone bitartrate). The injection molding technique, wherein a molten polymer is injected into specific casts and molded into the desired shape, has been remodeled by Egalet Ltd. to manufacture drugs in both immediate- and sustained-release formats and is called the Guardian technology.

Figure 2.2 Physical appearance of original OxyContin1 ER tablets (left) and new abuse-deterrent OxyContin1 ER tablets (right) after being struck with a hammer (Dolgin, 2015)

Pharmaceutical injection molding was invented in 1964 by Speiser (El-Egakey et al., 1971) and over the years has been used to create matrices for soy protein, ethyl-cellulose, HPMC and polyethylene (Quinten et al., 2009). The Guardian technology uses tamper resistant hard shell molds of various shapes and with two openings to easily release the tablets. The shells can be further reinforced by strength enhancing materials that are either molded along-with the shell wall or manufactured separately and then combined later (Tygesen et al., 2013). The injection molding systems of Egalet Ltd. is sold under the trade name of Guardian™ and consists of erosion resistant, waterproof shell made of ethyl-cellulose and ceto-stearyl alcohol and a PEO/PEG matrix (Bar-Shalom et al., 2003). After formulation, the mold shells are dissolved in a particular media, which frees the tablets; the shells are not essential at this step because the PEO matrices have high mechanical strength. The release of drugs can be restrained by optimizing the structure and make-up of the tablets (Hemmingsen et al., 2011) as well as the matrix (Andersen et al., 2013; Fischer et al., 2014). In addition, the hard shell protects from physical tampering,

and the high viscosity of the matrix prevents chemical extraction. Multilayered PEO matrices have also been developed by Egalet Ltd. that uses compression along-with molding (Hemmingsen et al., 2014).

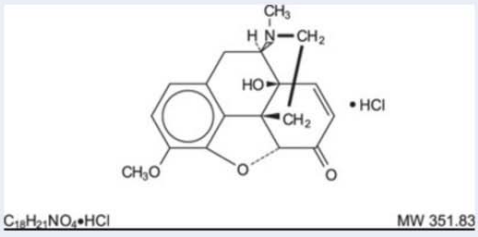
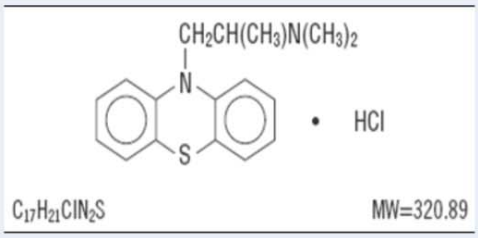
Alkermes Pharma has introduced the BeadTek® technology that combines placebo PEO beads with drug-coated beads that are physically similar and hence indistinguishable. The PEO beads are made by mixing PEO powder (WSR grade) with a binder solution (e.g., isopropyl alcohol and povidone K30 20% w/w in water) and then layering the powder by rotary granulation using either Granurex® or Freund Vector. The drug beads are also synthesized the same way, by replacing PEO with the drug. The ZOHYDRO® ER capsules are made with this principle, and consist of PEO coated, and hydrocodone bitartrate coated beads that release the drug in a sustained manner (Rekhi and Sidwell, 2015).

An osmotic drug delivery system was developed by Alza Pharmaceuticals in 1976 (Theeuwes, 1977), which allowed zero order release of the drug. The Osmotic (Controlled) Release Oral (Delivery) System or OROS™ consists of a capsule made of a semipermeable cellulose acetate membrane enclosing the drug. Since the membrane is permeable to water and not the drug, when suspended in a suitable media, the capsule slowly imbibes water and pushes the drug out of a laser drilled orifice (Siegel and Rathbone, 2012). The polymeric material of OROS™ is made of PEO and ethyl acetate, which allows sustained drug release and is, therefore, abuse deterrent. A 'push-pull' version of OROS™ was used to synthesize EXALGO® ER hydromorphone hydrochloride tablets (Pande et al., 2011). Apart from providing an extended release, the OROS™ capsules are highly tamper resistant. The PEO is the best osmo-polymer for OROS™ due to its viscosity, mechanical strength, and ethanol insolubility.

2.3 Oxycodone and surrogate APIs

Oxycodone is a semi-synthetic, morphine-like opioid alkaloid with analgesic activity and a Full Opioid Agonist. Promethazine hydrochloride has very similar properties to oxycodone as shown in Table 2.2.

Table 2.2 Properties of oxycodone hydrochloride and promethazine hydrochloride

Drug Name	Structure	pKa	Water Solubility at 25°C (mg/mL)	Melting Point (°C)
Oxycodone hydrochloride	 $C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83	8.5	142.9	271
Promethazine hydrochloride	 $C_{17}H_{21}ClN_2S$ MW=320.89	9.1	150.0	230

To simulate oxycodone hydrochloride, a model compound should meet the following criteria: (1) pharmaceutical salt with similar pKa, (2) similar solubility in water, and (3) same melting point. pKa and solubility in water have a significant impact on the extractability during abuse deterrence testing while melting point affects the interaction between drug and polymer during thermal processing.

Promethazine hydrochloride (PMH) was selected as the model compound in this study. As shown in 2.2, PMH and oxycodone hydrochloride have similar pKa, solubility in water and melting point.

The physical properties and the chemical structures of the other potential surrogate APIs that can be smoked; Ibuprofen, Acetanilide, Caffeine, L-icotine, and Nicotine Ditartrate Dihydrate are shown in table 2.3 and table 2.4 respectively.

Table 2.3 Physical Properties of Oxycodone and its potential model APIs for smoking simulation testing.

Property	**Oxycodone**	**Ibuprofen**	**Thymol**	**Acetanilide**	**Caffeine**	**L-Nicotine**	**Nicotine Ditartrate Dihydrate**
Molecular Weight (g/mol)	315.369	206.285	150.22	135.166	194.194	162.236	498.438
Melting Point °C	219	75-77	49.6	114.3	238	_	97-100 ("6019-06-3 cas msds (nicotine ditartrate dihydrate) melting point boiling point density cas chemical properties," n.d.)
Boiling Point °C	501.6	157	232.5	304.0	178	247	_

Table 2.4 Chemical Structures of potential model APIs for smoking simulation testing.

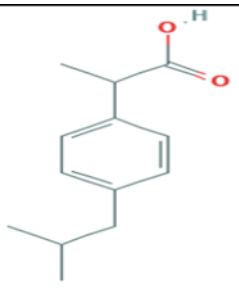
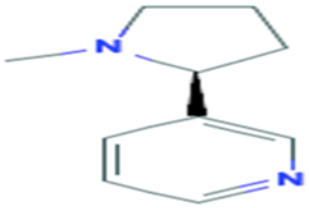
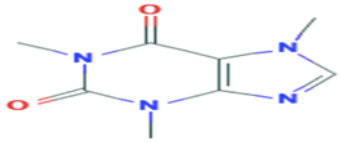
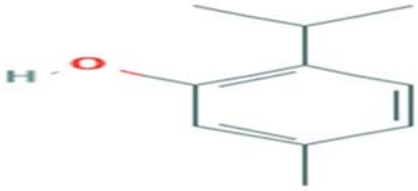
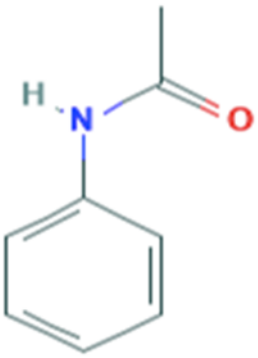
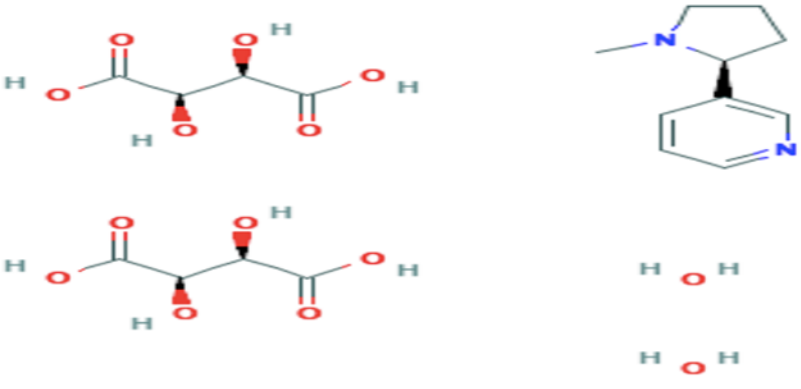
API	**Chemical Structure**
Ibuprofen (Pubchem, n.d.-b)	

Table 2.4 Continued

L-Nicotine (PubChem, n.d.-b).	
Caffeine (PubChem, n.d.-a) .	
Thymol (Pubchem, n.d.-c)	
Acetanilide (Pubchem, n.d.-a)	
Nicotine Bitartrate (PubChem, n.d.-c)	

2.4 Hot Melt Extrusion Technology

Over the past decades, Hot Melt Extrusion HME technology has been widely applied in the pharmaceutical industry as a viable drug delivery option in the drug development process. Applications of HME technique including but not limited to the following aspects; taste masking, solid-state stability enhancement, solubility enhancement, and the development of abuse-deterrent formulations. HME offers several advantages, such as being solvent free and involving fewer processing steps in comparison to other techniques (Maddineni, 2013). The technology puts a lot of thermal, mechanical, and oxidative stress on PEO. High temperatures often cause de-polymerization by either random or terminal scission, leading to the 'unzipping' of the attached substitutes. Mechanical stress occurs due to shearing caused by the rotating screws, while oxidative stress is a result of the atmospheric oxygen. Therefore, the stability of PEO prepared using this method is a legitimate concern which needs to be addressed. Thermal stability of PEO prepared by HME has been studied.

Chlorpheniramine maleate (CPM) tablets using PEO of 1M and 1000kD molecular weight was used to study the impact of the low molecular weight (100kD or PEO 100k), storage temperatures - 40°C, 60°C and 80°C at the relative humidity of 75%, presence of antioxidants – vitamins E, E-succinate and E-TPGS, and ascorbic acid, and screw rotation speed of the instrument – 10, 20, 40 or 60 rpm on the sustained release of the drug (Crowley, Zhang, Koleng, & McGinity, 2002). PEO was de-polymerized starting at 200^{o} C into smaller oligomers. De-polymerization rate was faster at higher storage temperatures. When the storage temperature dropped below the melting point (55^{o}C-80^{o}C) between 40^{o} C- 60^{o} C, only the amorphous and crystalline areas of the polymer were susceptible to oxidative degradation. However, when the tablets were stored at 80^{o} C, both the amorphous and crystalline areas melted and the entire

structure were exposed to oxidative degradation. The molecular weight of PEO was a major determinant of its thermal degradation. The rate of degradation was inversely proportional to its molecular weight; the PEO 100k degraded faster than PEO 600k, which in turn degraded more rapidly than PEO 1M. This is due to the fact that smaller crystals melt at lower temperatures compared to the larger crystals. However, since polymer crystals sizes are highly variable, they exhibit a range of melting points instead of just one melting point.

The molecular weight of PEO crystals depends mainly on the extrusion process, especially if the cooling rate and retention times of the polymer are not standardized. Furthermore, a screw speed of 20 rpm and processing temperature ranging from 70–105^{o} C lead to an 8.2% to 11.3% decrease in PEO molecular weight. Polymer degradation increased with decreasing screw speeds and higher extrusion temperatures. Higher screw speeds lowered the rate of polymer degradation till melt fracture, which only occurred at higher zone temperatures. For example, at the screw speed of 60 rpm, melt fracture was observed at 80°C, 90°C, 110°C, and 120°C. When the speed was increased to 80 rpm, correspondingly higher zone temperatures were required for melt fracture, i.e. 85°C, 100°C, 120°C, and 140°C. Drive overload prevented melt fracture at lower screw speeds. In addition to the processing temperature, the transit time of the polymer through the extruder was also a significant parameter influencing PEO degradation. The drive amperage or resistance against the drive depends on the extent of polymer degradation independent of the processing temperature. Stable polymers have higher melt viscosity, which results in higher resistance against the drive, whereas polymer scission and uncoiling, which precedes de-polymerization lead to a decrease in viscosity which correlates with lower drive amperage. Therefore, just like the screw speed, the drive amperage is a useful indicator of polymer stability until the point of melt fracture.

With an increasing percentage of the lower weight PEO 100K, PEO 1M stability also increased, and the drive amperage correspondingly decreased. PEO 100k did not have any significant effect on the rate at which CPM was released from the tablets.

The degradation of PEO was halted by the addition of Vitamin E (1%) as well as its derivatives Vitamin E succinate (5%) and Vitamin E TPGS (30%). Furthermore, the addition of Vitamin E also lowered the release rate of CPM. This is likely due to its hydrophobic nature, which delayed water intake into the PEO matrix and slowed down the gel hydration.

The thermal stability of PEO mainly dependent on two variables – the molecular weight and the storage temperature. Oxidative degradation occurred in the amorphous region below the melting point, and rapid de-polymerization was seen above the melting point. The temperature of the extrusion process and the screw speed also influenced PEO stability. At higher screw speeds, melt fracture caused most of the degradation and the energy (in amperage) taken up by the motor served as a reliable indicator. In other words, the de-polymerization process was both mechanical and thermal. Also, PEO 100K improved the process but did not have any significant effect on the CPM release rate from the tablets.

Vitamin E and its derivatives significantly stabilized PEO during the extrusion process. The derivatives Vitamin E succinate and Vitamin E TPGS were dispersed in the tablets at the molecular level. On the other hand, ascorbic acid increased PEO degradation, and due to its hydrophilic nature, the release rate of the CPM was enhanced (Crowley et al., 2002).

2.5 The Impact of Abuse Deterrent Formulations on Opioid Usage

A study has been conducted to examine the extent of abuse of novel formulations of OxyContin® and other opioids that contained abuse deterrent barriers. Data was collected from

2566 patients with opioid dependence on a quarterly basis between July 1, 2009, and March 31, 2012. Opioid dependence was defined as per the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and data were collected through anonymous surveys of subjects entering drug rehabilitation programs in and around the USA. All the participants were abusing a prescription opioid, which excluded those that were addicted to non-prescription drugs like heroin from the final analysis. From the cohort, 103 consented to direct interviews, which helped add qualitative data to the survey. Upon introducing the abuse deterrent version of OxyContin, the percentage of those choosing it as the primary drug dropped from 35.6% to 12.8% in 21 months ($P<0.001$). This was accompanied by an increase in the use of other opioids like fentanyl and hydromorphone from 20.1% to 32.3% ($P = 0.005$). Over the entire study period, the usage of OxyContin fell from 47.4% to 30.0% ($P<0.001$). Interestingly, the percentage of heroin abusers doubled over the study duration. Figure 2.3 shows the opioids used to get high by the respondents at least once in the past thirty days from July 1, 2009, through March 31, 2012 (Cicero et al., 2012).

Patients who abused both forms of OxyContin were interviewed and showed a clear preference for the older version. Only 24% of those chose to tamper with the novel OxyContin while the remaining preferred to switch to heroin since it is cheaper and easier to abuse. Therefore, the regular OxyContin users did not cease drug abuse when the abuse deterrent version came to market but changed to a completely different opioid.

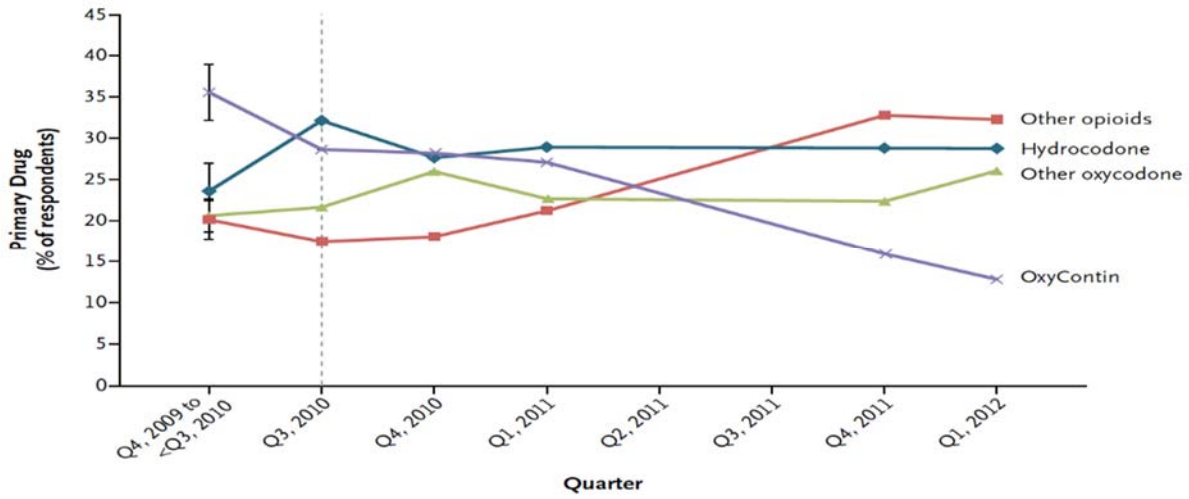


Figure 2.3 Effect of Abuse-Deterrent OxyContin (Cicero et al., 2012)

2.6 The Implications of the Failure Modes of Approved Abuse Deterrent Formulations on Public Health

The FDA recalls various drugs due to the high abuse risk that they pose, using the case of Endo Pharmaceutical's Opana® ER whose side effects outweigh the benefits. In a press release on June 8, 2016, they announced that they had requested Endo Pharmaceutical to voluntarily recall of Opana® ER since it has been linked to the outbreak of Hepatitis C and HIV. If Endo fails to comply, FDA will initiate the forcible recall of this drug. Opana® ER, an extended release version of oxymorphone which was first marketed in 2006, was approved by the FDA in 2012. The new formulation prevented the physical tampering of the capsules for inhalation. However, reports surfaced of continued abuse by drug addicts through intravenous injections, which in turn has increased the risk of HIV and Hepatitis C through needle sharing, and a rare blood disease called thrombotic microangiopathy. Opana® ER abuse was linked to an HIV outbreak in Indiana in 2015, which started when drug addicts discovered that the injectable form of Opana® ER was

far more potent than morphine. After reviewing the post-marketing and acting on the advice of an independent advisory panel, the FDA decided to recall Opana® ER. The US Centers for Disease Control and Prevention reported that Opana® ER users injected themselves several times a day due to the opioid's short half-life, which results in a faster onset of withdrawal symptoms. The addicts melt the gel coating, crush the pills, and dissolve in water to prepare the injectable drug. Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, has reiterated in the press release that Opana® ER has severe unintended consequences which call for its immediate recall for the sake of public health and safety. Endo Pharmaceuticals, which earned a total of $158 million in Opana® ER sales, maintains that the drug is safe and is currently deliberating (Jackson, 2017).

2.7 Summary

This chapter has provided an overview of the review of relevant literature. It has introduced an overview of the studies that should be conducted to demonstrate that a given formulation exhibit abuse deterrent properties, the well-known abuse deterrent strategies, and the applications of the hot-melt extrusion technology. Furthermore, it provides an overview of the potential Oxycodone surrogate APIs and discusses the impacts of ADFs on opioid usage and the implications of the failure modes of ADFs on public health.

CHAPTER 3. RESEARCH METHODOLOGY

This chapter provides the theoretical framework and the research design, the analytical methods, and statistical analysis techniques that are used to investigate the failure modes of the approved drugs and the opioid surrogate products. Furthermore, it provides the data collection procedures, sources of data, and the data analysis techniques that are used to investigate the societal impacts of the opioid crisis in the state of Indiana and the manufacturing and formulation differences between the approved ADFs.

3.1 Theoretical Framework and Research Design

There are three common ways by which an opioid drug can be manipulated: 1) disrupting the controlled release of the opioid, 2) altering the drug formulation to instant release via other routes of administration and 3) removing the opioid antagonist if present in the original formulation. This research aimed to conduct category I laboratory-based in vitro manipulation, and extraction studies to explore the failure modes of FDA approved Abuse Deterrent Formulations and PEO based Promethazine Hydrochloride PMZ HCL tablets as shown in figure 3.1. The goal of our laboratory-based in vitro manipulation and extraction studies was to conduct:

- Mechanical and thermal In-vitro manipulation techniques: to evaluate the ease with which the potentially abuse-deterrent properties of the FDA approved drug products can be defeated or compromised.
- Dissolution experiments: to evaluate the release profile (% release) of each drug product in a standard dissolution environment.
- syringeability studies: to test the impedance of intravenous abuse.

- High-performance liquid chromatography HPLC experiments: to evaluate the percent of Active Pharmaceutical Ingredient (% API recovery) that could be recovered after applying the mechanical and thermal In-vitro manipulation techniques.
- A smoking-simulation technique to determine an experimental setup with low variability results and a model drug for Oxycodone.
- Database exploration to investigate the societal impacts of the opioid crisis in the state of Indiana.
- Database exploration to investigate the manufacturing and formulation's differences between ADFs.

3.2 Failure Modes Investigations

This section of the study aimed to use several analytical methods to determine the impacts of applying mechanical and thermal manipulation techniques on the release percentage, syringeability, and extractability. Furthermore, it aimed to use the same analytical methods to determine the impacts of applying mechanical and thermal manipulation techniques on the release percentage, syrimgeability, and extractability of PEO based PMZ HCL tablets as surrogate products for prescription opioids.

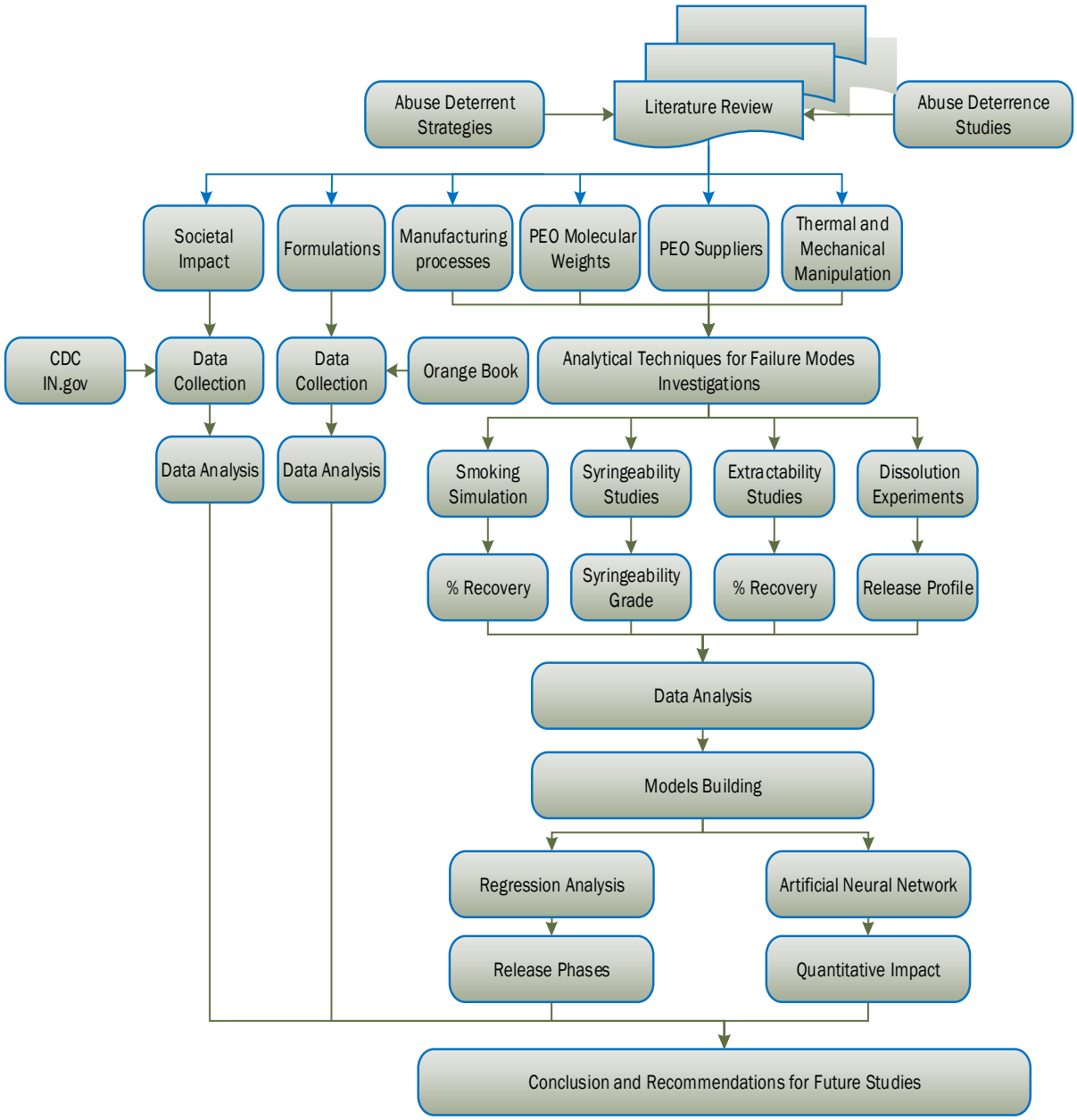


Figure 3.1 Research Methodology

3.2.1 Tampering and physical manipulation

Mechanical and thermal in-vitro manipulation procedures were performed including cutting, chopping, grinding, and heating.

3.2.1.1 Cutting

Cutting the intact tablets into four separate quarters using a tablet cutter to evaluate the dissolution profile of the quarter tablet.

3.2.1.2 Chopping

Chopping the quarter tablets using a razor blade and a petri dish to evaluate the effect of the particle size reduction on the release profile of different drug products.

3.2.1.3 Grinding

Grinding the quarter tablets using a dermal tool to evaluate the effect of the particle size reduction on the release profile of different drug products.

3.2.1.4 Heating

Quarter tablets, chopped, and grounded samples were heated in a conventional toaster oven at 350 F for approximately 3-10 minutes until they turned into golden brown. The time frame was adjusted based on the sample size of both intact and/or physically manipulated tablets. The length of time required for heating a quarter tablet until it turns into a golden-brown color is greater than the length of time needed to turn a chopped and/or a ground quarter tablet into the specified color.

3.2.2 Analytical Methods

Suitable analytical methods were used to investigate the failure modes of ADFs and their surrogate products.

3.2.2.1 Dissolution Experiments

Dissolution experiments for the intact tablets and the manipulated samples of each drug and surrogate products were conducted. Dissolution experiments were performed using a paddle apparatus (USP Apparatus 2) to investigate the release profiles of PEO based ADFs, and PMZ HCL compressed, molded, and extruded tablets. The dissolution apparatus was equipped with a CCD Array UV-Vis Spectrophotometer (S.I. Photonics, Inc. Tucson, Arizona USA) and SI 400 Series Spectrophotometer software. The paddle apparatus used was set up at 37^{o} C and 100 rpm. Dissolution media included 900 ml of DI water or 1000 ml of simulated gastric fluid (SGF).

3.2.2.2 Syrengiability and Extractability Studies

The research also focused on conducting both syringeability and HPLC Tests. Sample preparation included the following steps: (1) Performing thermal and mechanical in-vitro manipulation techniques. (2) Mixing with 4ml of DI water in a 5 or 7 ml glass vial and stirring with a magnetic stirrer for 5 minutes at 300 rpm. (3) Extracting the solution into a 5 ml syringe fitted with a needle through a cotton ball filter. A (1-10) scale was developed based on the ease of the extraction process. Grade 1 represented the easiest way of API extraction and Grade 10 represented the hardest way of the API extraction.

A reverse phase High-Performance Liquid Chromatography (HPLC) based analytical method was applied for the quantification of the various APIs in the FDA approved ADFs and the PMZ HCl in the PEO based compressed, molded, and extruded tablets. The applied HPLC methods were validated according to FDA guidelines for chromatographic methods. An HPLC

(Agilent 1100 Series) equipped with a UV detector, an Agilent 150 mm X 4.6 mm, 3 µm particle size, C18 (2) column, and an isocratic mode of elution with the mobile phase consisting of acetonitrile- 25 mM phosphate buffer (pH 4.0), 50: 50 (v/v) at a flow rate of 1 mL/min. This method was employed to quantify the drug at a wavelength (λmax) of 249 nm based on the peak area with UV detection. The acquired data were processed using Agilent 1100 LC System (DAD) software to quantify PMZ HCl.

The instrument was equipped with a UV detector, an alltima C18, 4.6x 150 mm column, and an isocratic mode of elution with the mobile phase consisting of 25% ACN: 75% Buffer (2 gm/L Na octanesulphonate, 13.3 ml/L glacial AcOH, PH: 3.5) at a flow rate of 1.0 ml/min and injection volume of 20 µl. This method was employed to quantify the drug (Oxycodone Hydrocloride) at 25º C and a wavelength (λmax) of 280 nm based on the peak area with UV detection. The acquired data were processed using Agilent 1100 LC System (DAD) software.

3.2.2.3 Smoking Ability Studies

In vitro smoking studies involve the sublimation of the pure APIs (e.g., either opioid or a surrogate API for opioid) and the intact and manipulated form of the drug product (e.g., either approved prescription opioids or surrogate products). The % API recovered in vapor for the pure form and intact and manipulated drug products was determined to evaluate the smoking ability and the formulation impacts on the smoking ability of the API. The measure used to evaluate the % API recovered in the vapor is the percent of opioid sublimation calculated as (vaporized amount/amount of API in the sample) * 100, where the vaporized amount is the amount of drug available for smoking following heating of the pure API and the product. HPLC analysis was

conducted to calculate the % API recovery in vapor and the overall % API recovery (sum of the % API recovered in vapor collecting flask and the % API residues in the smoking flask).

An HPLC (Agilent 1100 Series) instrument was equipped with a UV detector, an alltima C18, 4.6x 150 mm column, and an isocratic mode of elution with the mobile phase consisting of 25% ACN: 75% Buffer (2 gm/L Na octanesulphonate, 13.3 ml/L glacial AcOH, PH: 3.5) at a flow rate of 1.0 ml/min and injection volume of 20 µl. This method was employed to quantify the drug (Oxycodone Hydrochloride) at 25º C and a wavelength (λmax) of 280 nm based on the peak area with UV detection. The acquired data were processed using Agilent 1100 LC System (DAD) software.

The instrument was equipped with a UV detector, an Agilent C18, 4.6x 250 mm column, and an isocratic mode of elution with a combination of Methanol: H_2O (33: 67 by volume) at a flow rate of 2 ml/min and injection volume of 10 µl. This method was employed to quantify the API (Acetanilide) at 25º C and a wavelength (λmax) of 254 nm based on the peak area with UV detection. The acquired data were processed using Agilent 1100 LC System (DAD) software.

The instrument was equipped with a UV detector, a Hypersil Gold Phenyl (150 mm × 4.6 mm, 3 μm) column. A gradient method was used. Mobile Phase MP A was 0.1% (v/v) triethyl amine in water with pH adjusted to 7.6 ± 0.05 by orthophosphoric acid (85%) and sodium hydroxide solution (1 N). Mobile phases B and C were 0.1% (v/v) triethyl amine in methanol and acetonitrile, respectively. Mobile phase D and diluent were 80% (v/v) methanol in water. The chromatographic conditions were run as following: from time (0-4min), a combination of 60% MP A, 26% MP B, 14% MP C, and 0% MP D was used, from time (4.1-7min), 0% MP A, 0% MP B, 0% MP C, and 100% MP D was used, and from time (7.1-12min), a combination of 60% MP A, 26% MP B, 14% MP C, and 0% MP D was used at a flow rate of

0.8 ml/min and injection volume of 10 μL. This method was employed to quantify the API Nicotine at column oven temperature 25º C, sample cooler temperature 5 º C, and a wavelength (λmax) of 260 nm nm based on the peak area with UV detection. The acquired data were processed using Agilent 1100 LC System (DAD) software (Gholap, Kosmider, & Halquist, 2018).

The instrument was equipped with a UV detector, an Agilent 4.6x 150 mm column; the separation was achieved on a reversed-phase C18 column using a mobile phase composed of water: methanol (50:50) at a flow rate of 1.0 ml/min-1. The detection was carried out on a UV detector at 272 nm to quantify Caffeine (Naveen, Lingaraju, Deepak, Medhini, & Prasad, 2018).

The instrument was equipped with a UV detector, an Agilent 3.9 mm x 150 mm column; the separation was achieved on a reversed-phase C18 column using a mobile phase composed of water preadjusted with phosphoric acid at PH= 2.5 and Acetonitrile ACN. The detection was carried out on a UV detector at 214 nm at 30 deg C to quantify Ibuprofen.

The instrument was equipped with a UV detector, an Agilent C18, 4.6x 250 mm, 5 micron column; the separation was achieved on a reversed-phase C18 column using a mobile phase composed of methanol: Acidic water PH=3.8 (58:42% v/v) at a flow rate of 1.2 ml/min-1. The injection volume was 25 micro L. The detection was carried out on a UV detector at 271 nm to quantify Tapentadol HCl.

A smoking simulator was built to investigate the smoking ability of the various ADFs. The apparatus was equipped with a vacuum and an Argon gas cylinder to create a flow of the vaporized API that condensated on the glass wall of the vacuum adaptor, and the vapor trap that contains 10% concentrated Hydrochloric acid HCl diluted with DI water to rinse both Oxycodone smoking and vapor receiving flasks. Moreover, Kugelrohr distillation apparatus

with/without propane torch was used for smoking simulation purposes of different APIs. The mobile phases used for the HPLC quantification method were used to rinse the smoking and the vapor receiving flasks of each corresponding API.

The potential Oxycodone model APIs were smoked in the pure form to assess their ability to mimic Oxycodone based on the volatility and % API recovery. Furthermore, the reproducibility of the results from different smoking simulators or different experimental setup was assessed to determine the optimum smoking simulation apparatus with a simple experimental setup and reproducible % API recovery.

3.2.3 Variables

The Independent variables include:

1. The manufacturing process of the tested drugs.
2. Molecular weight of the polymer contained in the formulation of interest.
3. Source of the polymer.
4. Application of thermal conditions (heat).
5. Application of mechanical conditions (sample size reduction).

Dependent variables include:

1. The % release of each drug product in Deionized DI water and Simulated Gastric Fluid SGF as the dissolution media.
2. The percent of Active Pharmaceutical Ingredient (% API recovery) that could be recovered after applying the mechanical and thermal In-vitro manipulation techniques and extraction studies.
3. Syringeability (the impedance of intravenous abuse of each drug product).

4. The percent API recovery after applying mechanical and thermal manipulations and smoking simulation studies on ADFs.

3.2.4 Material

Melt Extruded ME tablets of PEO based PMZ HCl were prepared at the University of Texas at Austin. Compressed and Molded tablets of PEO based PMZ HCl were prepared at the University of Maryland. Commercially available solvents, reagents, and pure APIs such as L-Nicotine, Nicotine Ditartrate Dihydrate, Caffeine, Acetanilide, Oxycodone free base, and Oxycodone HCL were also used. PEO was purchased from Dow Chemical or Sumitomo Seika, as shown in table 3.1. The FDA approved products were purchased from the Purdue pharmacy. Approved products are shown in table 3.2. PEO-based Caffeine 40 mg tablets were prepared at Purdue University via Direct Compression.

Table 3.1 The characteristics of the material used to investigate the PEO based PMZ HCL tablets.

Approximate MW of PEO	**Supplier**	**Manufacturing Method**
4M	Sumitomo Seika	Extrusion/Molding
7M	Sumitomo Seika	Extrusion/Molding
4M	Dow Chemicals	Extrusion/Molding
7M	Dow Chemicals	Extrusion/Molding
4M	Sumitomo Seika	Compression/Curing
7M	Sumitomo Seika	Compression/Curing
4M	Dow Chemicals	Compression/Curing
7M	Dow Chemicals	Compression/Curing
4M	Sumitomo Seika	Molding
7M	Sumitomo Seika	Molding
4M	Dow Chemicals	Molding
7M	Dow Chemicals	Molding

Table 3.2 Product name, abuse deterrent strategy, and the manufacturing process of the selected FDA approved drugs.

Product Name	**Abuse Deterrent Strategy**	**Manufacturing Process**
Product X1 extended-release tablets	Physical Barrier (Polyethylene Oxide PEO)	Proprietary thermal processing
Product X2 ER extended-release tablets	Physical Barrier (Polyethylene Oxide PEO)	Melt extrusion and cold molding
Product X3 ER extended-release tablets	Physical Barrier (Polyethylene Oxide PEO)	Melt extrusion and cold molding
Product X4 immediate-release tablets	Physical Barrier (Polyethylene Oxide PEO)	Direct compression
Product X5 ER extended-release capsules	Physical Barrier (Polyethylene Oxide PEO)	Granulation and coating
Product X6 ER extended-release tablets	Physical Barrier (Polyethylene Oxide PEO)	Proprietary thermal processing
Product X7 XR extended-release tablets	Physical Barrier (Polyethylene Oxide PEO)	Direct compression

3.2.5 Data Analysis

Percent release of the Active Pharmaceutical Ingredients APIs and % recovery of APIs using the Area Under the Curve AUC obtained from HPLC results after the extractability and smoking simulation studies were collected. Significance testing using Minitab® 18 was performed.

3.2.6 Models Building

Regression models were built using Minitab® software to determine the release patterns. Then, the Artificial Neural Network (ANN) NeuroShell®software was used to measure the quantitative impacts of each factor on the release percentage of PEO based PMZ HCl tablets.

3.2.6.1 Release Phases Modeling

Building a regression model for PEO based PZ HCl surrogate products using Minitab® 18 to identify possible release phases. For this stage, Minitab statistical software was employed for building the models. The software was mainly used because of its capabilities to apply various functions such as analysis, variance, and correlation in a user-friendly environment.

3.2.6.2 Variables Impact quantification on the Release Percentage and Extractability of the PEO Based PMZ HCl Tablets

Building an Artificial Neural Network (ANN) model for surrogate products using NeuroShell® was performed to identify the criticality and the quantified impact of each variable. The ANN was used because of its capabilities to quantify the significance of every variable on the output. The effect of the manufacturing process, molecular weight, and source of the polymer, and applied thermal and applied mechanical techniques on release percentage were quantified.

3.3 Societal Impacts of the Opioid Crisis in the State of Indiana

Data regarding the number of opioid overdose deaths among Indiana residents by year, drug category, sex, age, race, non-fatal hospitalizations, and non-fatal emergency department visits by county and drug category were collected and analyzed.

3.3.1 Data Collection

According to the National Center for Health Statistics; a statistically significant increase in drug overdose death rates was reported in 2016 in the following states: Connecticut, Delaware, Florida, Illinois, Indiana, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Vermont, Virginia, West Virginia, and Wisconsin. This section of the study was conducted to investigate the societal impacts of the opioid crisis in the state of Indiana. Indiana specific data regarding the number of opioid overdose deaths among Indiana residents by year, drug category, sex, age, and the race were collected.

3.3.2 Data Sources

Data were collected from:

- The official site of the Centers for Disease Control and Prevention (CDC).
- The official site of Indiana state department of health.

3.3.3 Data Analysis

Plots and information graphs were created to compare and communicate the acquired data clearly and efficiently.

3.4 Formulation Differences between Different Abuse deterrent Formulations

Data regarding the manufacturing and formulation differences between the FDA approved ADFs were collected to compare the different products and determine other possible critical variables that might be affecting the dose dumbing behavior of these products.

3.4.1 Data Collection

This part of the study was conducted to investigate the manufacturing and formulation differences between the FDA approved Abuse Deterrent Formulations ADFs. Patent and exclusivity information regarding different drug products was collected.

3.4.2 Data Sources

Data were collected from:

- The official site of the Food and Drug Administration FDA.

3.4.3 Data Analysis

The collected data were used to compare different ADFs based on the manufacturing and formulation differences among these products. Furthermore, data were used to identify other critical variables that might be affecting the dose dumping of APIs.

3.5 Summary

This chapter has presented the different elements of the research methodology. It showed the theoretical framework and the research design, the procedures, analytical methods, and statistical analysis techniques that are used to investigate the failure modes of the approved drugs

and the opioid surrogate products. Furthermore, this chapter showed the data collection procedures, sources of data, and the analysis techniques that are used to investigate the societal impacts of the opioid crisis in the State of Indiana and the manufacturing and formulation differences between the approved ADFs.

CHAPTER 4. RESULTS AND DISCUSSION

This chapter discusses the failure modes of the PEO-based PM HCL tablets, and the investigated FDA approved prescription opioids. It shows the release profiles, release phases, significance testing results, the quantitative impact of the research variables on the release percent, and the syringeability and extractability data of the PEO-based PMZ HCL tablets. This chapter shows the release profiles and the syringeability, and extractability results of the investigated FDA approved prescription opioids. Furthermore, this chapter shows the smoking simulation results of different pure APIs and the societal impacts of the opioid crisis in the state of Indiana.

4.1 Release Profiles

Twelve types of PEO-based PMZ HCL tablets have been investigated. The tablets have two different molecular weights of PEO 4,000,000 and 7,000,000, three different manufacturing methods (extrusion/molding, compression/curing, and molding, and two different suppliers (Dow and Sumitomo Seika). Product X1 was used as a comparator. The Product X1 data is published in US Patent 8501160.

Figures 4.1 to 4.11 and Tables 4.1 to 4.10 show the release profile and the % release of the average of three dissolution runs of the various intact and manipulated tablets along with Product X1 from the literature. All of the tablets have a similar profile.

Table 4.1 The release % of Product X1 ER and extruded and compressed whole tablets comprising PMZ HCl and Sumitomo Seika PEO.

Time (h)	**Whole ME Tablets 4M**	**Whole ME Tablets 7M**	**Whole DC Tablets 4M**	**Whole DC Tablets 7M**	**Whole Tablet M 4M**	**Whole Tablet M 7M**	Product X1
0	0	0	0	0	0	0	0
0.5	21.5	21.4	20.9	23.8	36	30	35.9
1	34.0	35.3	30.6	37.2	50	42	47.1
2	52.7	56.2	46.0	61.9	71	61	60.5
3	66.5	69.2	58.5	73.8	84	75	69.4
4	75.8	76.9	69.0	82.2	92	85	76.2
6	88.6	88.2	83.4	89.2	96	94	86.0
8	94.4	95.4	92.1	91.4	98	98	92.8
10	98.4	97.3	96.3	94.1	97	98	
12	99.4	98.8	97.5	99.2	98	102	100.7
14	100.2	101.4	99.0	100.1	101	102	103.9

Table 4.2 The release % of Product X1 ER and extruded and compressed whole tablets comprising PMZ HCl and DOW PEO.

Time (h)	**Whole ME Tablets 4M**	**Whole ME Tablets 7M**	**Whole DC Tablets 4M**	**Whole DC Tablets 7M**	**Whole Tablet M 4M**	**Whole Tablet M 7M**	**Product X1**
0	0	0	0	0	0.0	0	0
0.5	37.7	45.4	35.3	21.6	14	22	35.9
1	60.4	71.0	53.2	32.7	28	35	47.1
2	87.3	94.1	76.8	50.1	43	57	60.5
3	100.2	105.2	89.7	60.2	55	73	69.4
4	99.8	107.0	101.4	70.0	65	82	76.2
6	102.1	113.4	108.0	81.3	79	95	86.0
8	100.1	104.9	110.4	86.3	88	94	92.8
10	103.3	98.2	104.1	91.9	95	99	
12	97.1	104.1	100.6	98.5	98	102	100.7
14	100.1	96.3	95.7	100.5	100	99	103.9

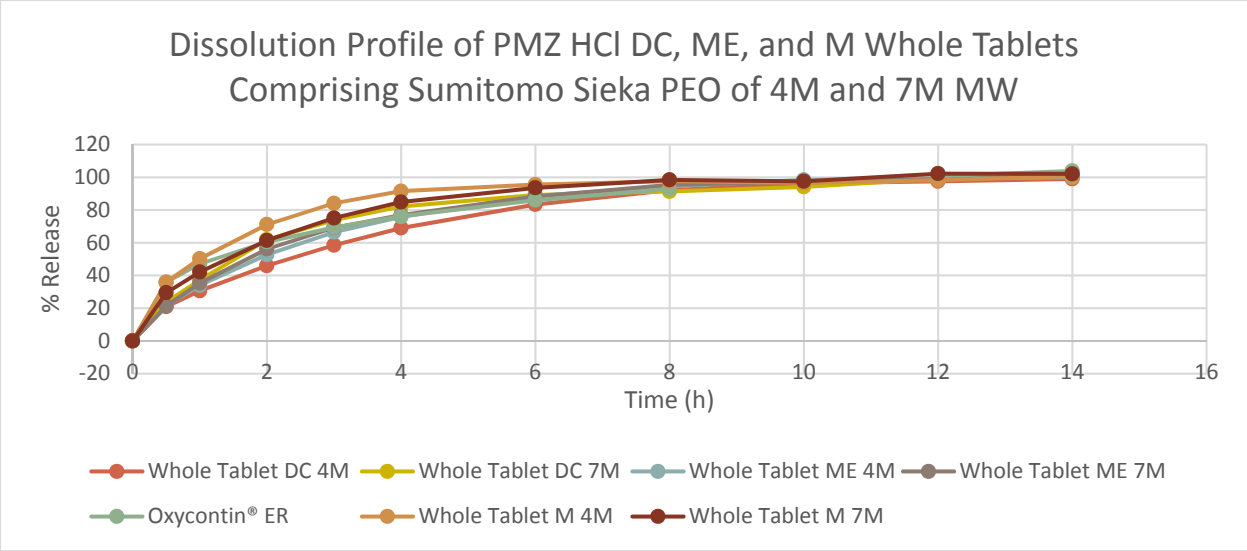


Figure 4.1 Release profile of Product X1 ® ER and PMZ HCl extruded and compressed whole tablets comprising Sumitomo Seika PEO in a standard dissolution test.

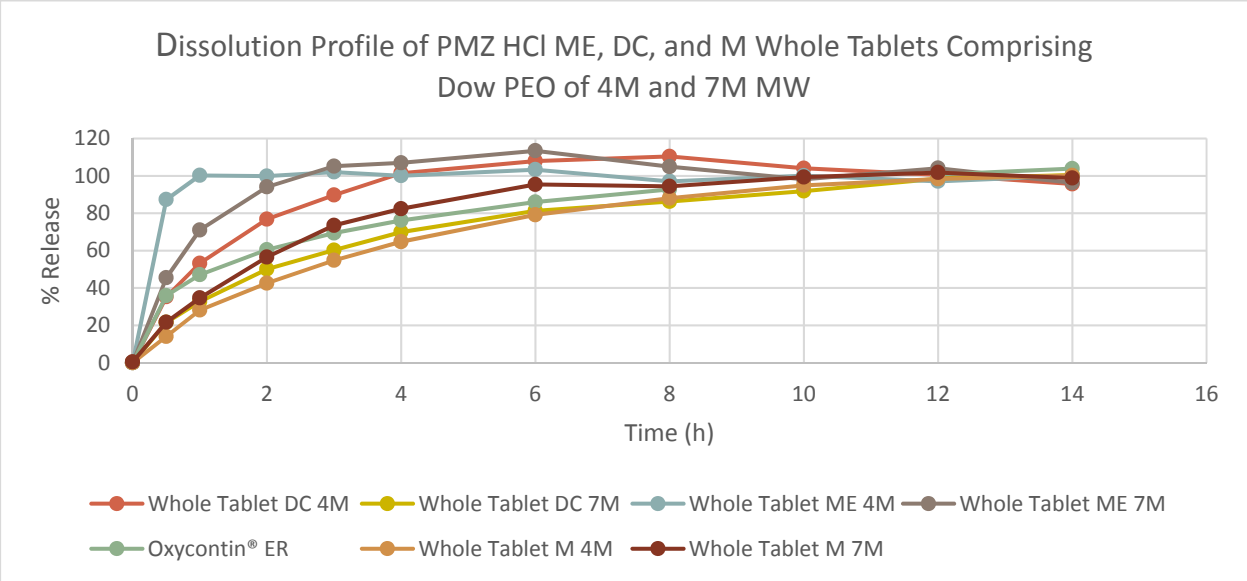


Figure 4.2 Release profile of Product X1 ER and PMZ HCl extruded and compressed whole tablets comprising Dow PEO in a standard dissolution test.

Analysis of the whole tablet data showed that extruded tablets comprising Dow PEO showed more dumbing behavior compared to the extruded tablets comprising Sumitomo Seika PEO at the early time points (0.5, 1, and 2 hours). The release percent at the time point 0.5 h for the extruded tablets comprising Sumitomo Seika of 4,000,000 was 21.5% whereas it was 37.7%

for the extruded tablets comprising Dow,4,000,000 PEO. The release percent at the time point 2 h for the extruded tablets comprising Sumitomo Seika PEO of 4,000,000 was 52.7% whereas it was 87.3% for the extruded tablets comprising Dow PEO. The release percent at the time point 0.5 h for the extruded whole tablets comprising Sumitomo Seika PEO of 7,000,000 was 21.4% whereas it was 45.4% for the extruded tablets comprising Dow, 7,000,000 PEO. The release percent at the time point 2 h was 56.2% for the extruded tablets comprising Sumitomo Seika, 7,000,000 PEO and it was 94.1% for the extruded tablets comprising Dow, 7,000,000 PEO. On the other hand, the analysis showed that different sources of PEO did not show great impact on the release profile of the compressed tablets except that compressed whole tablets of 4,000,000 MW showed the fastest release rate. The release percent at the time point 0.5 h for the compressed whole tablets comprising Sumitomo Seika PEO of 4,000,000 was 20.9% and it was 35.3% for the compressed whole tablets comprising Dow, 4,000,000 PEO. The release percent at the time point 2 h was 46.0% for the compressed tablets comprising Sumitomo Seika, 4,000,000 PEO whereas it was76.8% for the compressed tablets comprising Dow, 4,000,000 PEO. The release percent at the time point 0.5 h for the whole tablets comprising Sumitomo Seika PEO of 7,000,000 was 23.8 %, and it was 21.6% for the compressed whole tablets comprising Dow, 7,000,000 PEO. The release percent at the time point 2 h was 61.9% for the whole tablets comprising Sumitomo Seika, 7,000,000 PEO and it was 50.1% for the compressed whole tablets comprising Dow, 7,000,000 PEO.

The analysis showed that molded tablets comprising Sumitomo PEO of 4M and 7M MW showed more dumping behavior compared to the molded tablets comprising Dow PEO of 4M and 7M. The release percent at the time point 0.5 h for the molded tablets comprising Sumitomo Seika of 4,000,000 was 36.0% whereas it was 14% for the molded tablets comprising

Dow,4,000,000 PEO. The release percent at the time point 2 h for the molded tablets comprising Sumitomo Seika PEO of 4,000,000 was 71.0% whereas it was 43% for the molded tablets comprising Dow PEO. The release percent at the time point 0.5 h for the molded whole tablets comprising Sumitomo Seika PEO of 7,000,000 was 30.0% whereas it was 22.0% for the molded tablets comprising Dow, 7,000,000 PEO. The release percent at the time point 2 h was 61.0% for the molded tablets comprising Sumitomo Seika, 7,000,000 PEO and it was 57.0% for the molded tablets comprising Dow, 7,000,000 PEO respectively.

The manufacturing methods used did not have a large effect on the dissolution profile of the extruded and compressed whole tablets comprising Sumitomo Seika PEO whereas molded tablets comprising Sumitomo PEO of 4M MW showed very fast release compared to the others. At the time point 2 h, the release percent was 52.7 %, 46.0%, and 71.0% for extruded, compressed, molded whole tablets comprising Sumitomo Seika PEO of 4,000,000 MW and 56.2%, 61.9%, 61.0% for the extruded, compressed, and molded whole tablets comprising Sumitomo Seika PEO of 7,000,000 MW respectively.

However, the release profile of the whole tablets comprising Dow,4,000,000, and 7,000,000 PEO showed a variability based on the manufacturing process. Extruded tablets showed a faster dissolution rate compared to compressed and molded tablets at the early time points. At the time point 2 h, the release percent was 87.3%, 76.8%, and 43.0% for extruded, compressed, and molded whole tablets comprising Dow PEO of 4,000,000 MW and 94.1%, 50.1%, and 57.0% for extruded, compressed, and molded whole tablets comprising Dow PEO of 7,000,000 MW respectively.

Importantly, the release profile of oxycodone hydrochloride form Product X1 whole tablets showed faster release profile compared to the whole tablets comprising PMZ HCL and

Sumitomo Seika PEO for the early time points 0.5 hours and 1 hour but then similar to those products at the time points (3, 4, 6, 8h). This result suggested that it was possible to interchange these two APIs and to interchange the manufacturing methods and obtain a similar release profile. On the other hand, the release profile of oxycodone hydrochloride form Product X1 whole tablets showed slower release profile compared to the whole tablets comprising PMZ HCL and Dow PEO except that the compressed and molded whole tablets comprising Dow PEO of 7,000,000 showed slower release at the early time points compared to the extruded tablets.

Table 4.3 % Release of PMZ HCl 80 mg DC, ME, and M Quarter Tablets Comprising Sumitomo PEO of 4M and 7M MW.

Time	Quarter Tablet DC 4M	Quarter Tablet DC 7M	Quarter Tablet ME 4M	Quarter Tablet ME 7M	Quarter Tablet M 4M	Quarter Tablet M 7M
0	0	0	0	0	0	0
0.5	20	14	21	22	20	22
1	32	33	34	37	32	35
2	52	49	55	60	54	56
3	68	66	72	78	70	73
4	80	78	85	88	81	85
6	95	91	100	97	93	96
8	100	96	100	99	98	99
10	100	100	100	100	100	100

Analysis of the ME, DC, and M PMZ HCL quarter tablets comprising Dow and Sumitomo PEO of 4M and 7M MW showed similar release profiles except that molded tablets comprising Dow PEO of 4M MW showed the slowest release of 9.0% at the early time point 0.5 (h). The release percent at the early time point 0.5 (h) was 20.0%, 21.0%, and 20% for the DC, ME, and M quarter tablets comprising Sumitomo PEO of 4M MW respectively, while it was 14%, 22%, and 22% for the DC, ME, and M quarter tablets comprising Sumitomo PEO of 7M MW. At the same time point, the release percent was 17.8%, 24%, and 9% for the DC, ME, and

M quarter tablets comprising Dow PEO of 4M MW, while it was 24.0%, 21.0% and 20% for the DC, ME, and M quarter tablets comprising Dow PEO of 7M MW.

Table 4.4 % Release of PMZ HCl 80 mg DC, ME, and M Quarter Tablets Comprising DOW PEO of 4M and 7M MW

Time	QuarterTablet DC 4M	Quarter Tablet DC 7M	Quarter Tablet ME 4M	Quarter Tablet ME 7M	Quarter Tablet M 4M	Quarter Tablet M 7M
0	0.0	0	0	0	0	0
0.5	17.8	24	24	21	9	20
1	28.9	40	40	38	28	33
2	46.7	60	61	63	47	54
3	61.8	75	76	84	63	72
4	74.2	82	87	96	76	85
6	89.7	89	98	104	92	99
8	98.4	103	98	106	98	101
10	100.0	101			100	100

Analysis of the ME, DC, and M PMZ HCL quarter heated tablets comprising Dow and Sumitomo PEO of 4M, and 7M MW showed accelerated release profiles compared to the quarter unheated samples of the same tablets. The DC tablets comprising Dow PEO of 4M MW and the M samples comprising Dow PEO of 4M and 7M MW showed very slow release behavior compared to the other samples. At the early time point 0.5 (h), the Release percent was 40.0%, 32.0%, and 44.0% for the DC, ME, and M quarter heated tablets comprising Sumitomo PEO of 4M MW respectively, while it was 41.0%, 43.0%, and 40.0% for the DC, ME, and M quarter tablets comprising Sumitomo PEO of 7M MW. At the same time point, the release percent was 49.0%, 48.0%, and 18.0% for the DC, ME, and M quarter heated tablets comprising Dow PEO of 4M MW, while it was 25.0%, 45.0% and 27% for the DC, ME, and M quarter heated tablets comprising Dow PEO of 7M MW.

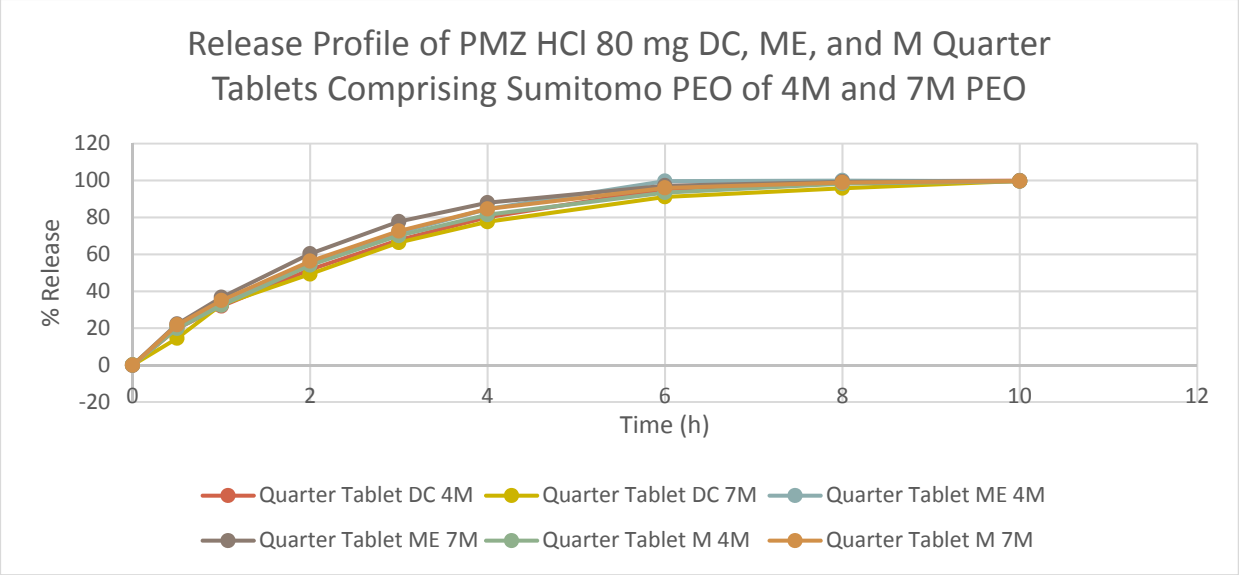


Figure 4.3 Release Profile of PMZ HCl 80 mg DC, ME, and M Quarter Tablets Comprising Sumitomo PEO of 4M and 7M PEO.

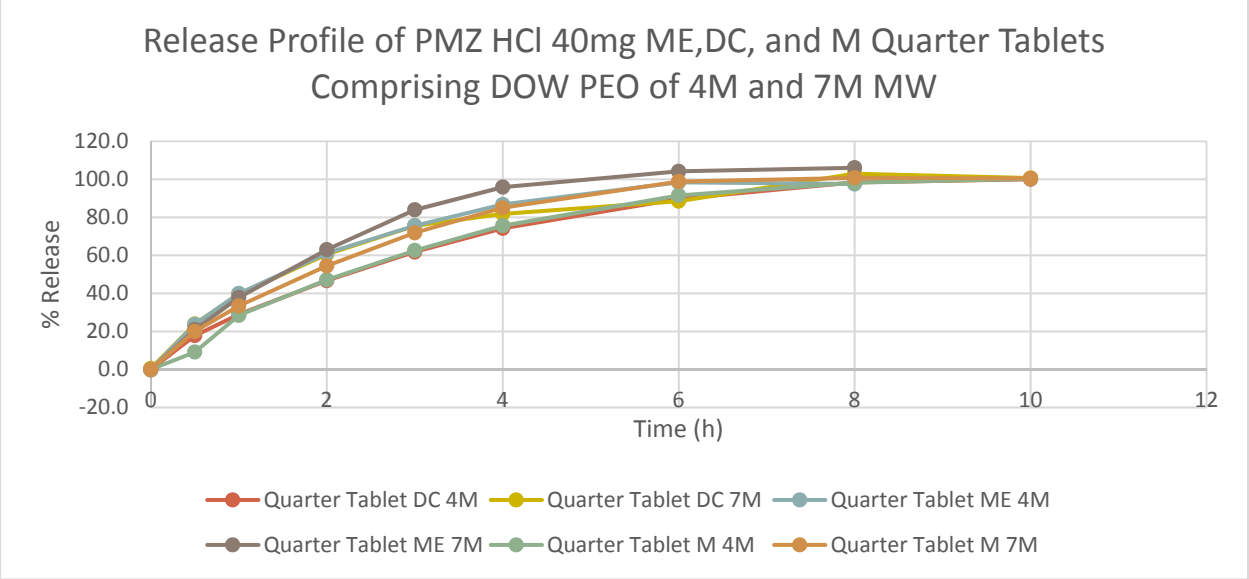


Figure 4.4 Release Profile of PMZ HCl 40mg ME, DC, and M Quarter Tablets Comprising DOW PEO of 4M and 7M MW.

Table 4.5 % Release of PMZ HCl 80 mg DC, ME, and M Quarter Heated Tablets Comprising Sumitomo PEO of 4M and 7M MW

Time	Quarter Heated DC 4M	Quarter Heated DC 7M	Quarter Heated ME 4M	Quarter Heated ME 7M	Q Quarter Heated M 4M	Quarter Heated M 7M
0	0	0	0	0	0	0
0.5	40	41	32	43	44	40
1	66	66	47	69	66	65
2	93	93	71	97	100	93
3	99	96	88	101	100	101
4	100	99	97	101	100	101
6	100	99	100	100	100	100
8	100	98	99	100	100	100
10	100	102	100	100	100	100

Table 4.6 % Release of PMZ HCl 80 mg DC, ME, and M Quarter Heated Tablets Comprising DOW PEO of 4M and 7M MW

Time	Quarter Heated Tablet DC 4M	Quarter Heated Tablet DC 7M	Quarter Heated Tablet ME 4M	Quarter Heated Tablet ME 7M	Quarter Tablet Heated M 4M	Quarter Tablet Heated M 7M
0	0.0	0	0	0	0	0
0.5	49.0	25	48	45	18	27
1	79.8	48	68	66	62	46
2	99.0	84	84	84	95	78
3	99.3	100	94	99	99	98
4	99.9	100	93	101	99	100
6	99.6	100	96	102	99	100
8	99.9	100	100	99	100	100
10		100	96	98	100	100

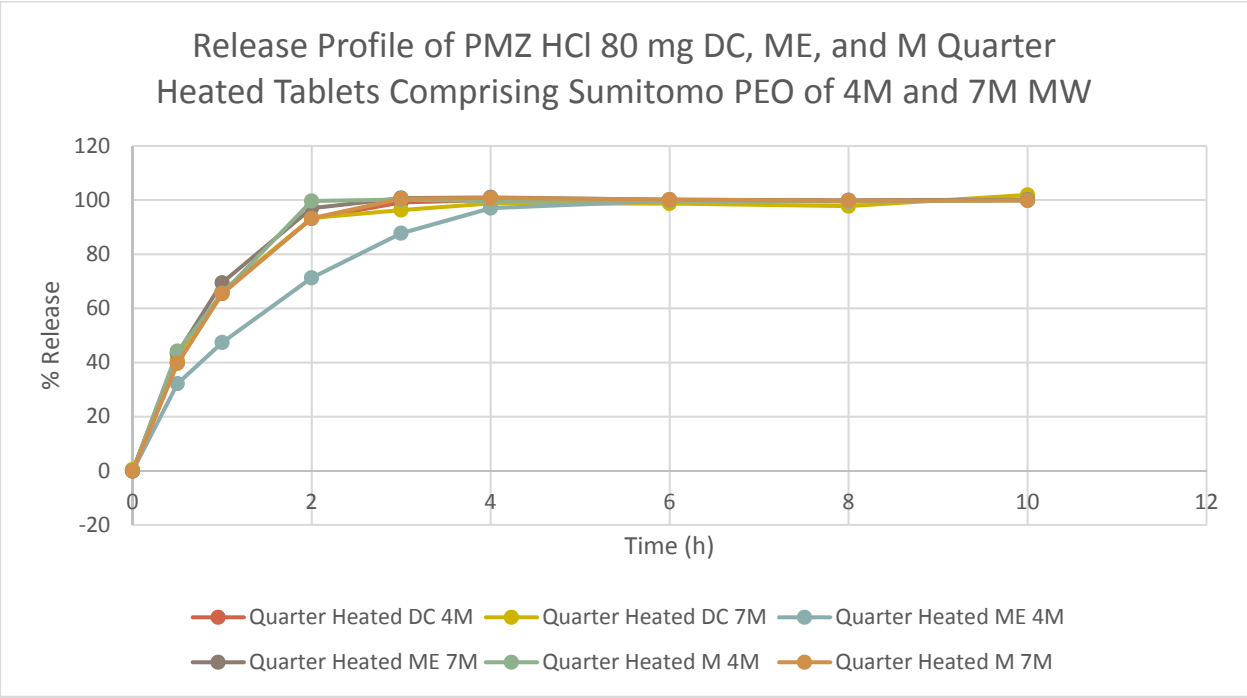


Figure 4.5 Release Profile of PMZ HCl 80 mg DC, ME, and M Quarter Heated Tablets Comprising Sumitomo PEO of 4M and 7M MW.

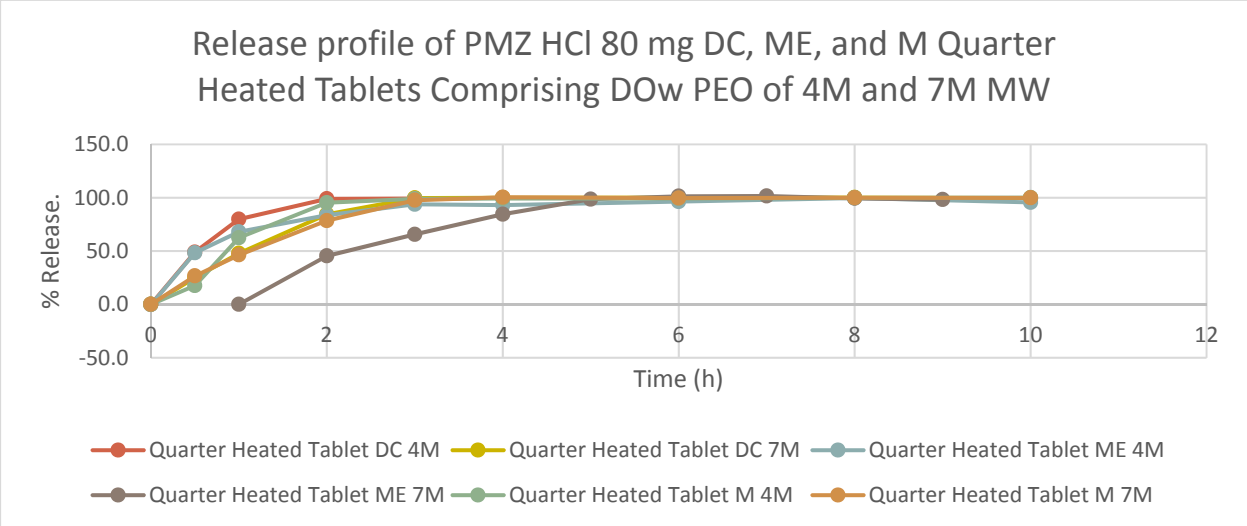


Figure 4.6 Release profile of PMZ HCl 80 mg DC, ME, and M Quarter Heated Tablets Comprising DOw PEO of 4M and 7M MW.

Tables 4.7, 4.8, Figures 4.7, and 4.8 show the release profile of chopped tablets and pieces of Product X1. These data showed that both the chopped tablets and the pieces of Product X1 tablets show a release profile of between 91.6 % and 100 % release at the 3-hour time point. At the 3-hour time point, the chopped/pieces released 90.0 to 100% whereas the whole tablets released 55.0% to 105.2 %. It was clear that reducing the tablet into smaller particles accelerates release. Additionally, the release of PMZ HCL from the manufactured tablets in this study was similar to the release of oxycodone from Product X1.

Figures 4.11 shows graphically how much faster the release of the chopped/pieces of the tablet is compared to the intact tablet. In Figure 4.11 at the 1-hour time point, the chopped/pieces of the tablet had dissolution percentages of 70.0% to 87.6%, whereas the intact tablets had dissolution percentages of 82.0 to 71.0%. At the 2-hour time point, the chopped/pieces of the tablet had dissolution percentages of 85.4 to 102.2% whereas the intact tablet had dissolution percentages of 43.0 to 94.1%.

Table 4.7 The release % of Product X1 ER and extruded and compressed chopped tablets comprising PMZ HCl and Sumitomo Seika PEO.

Time (h)	**Chopped ME Tablets 4M**	**Chopped ME Tablets 7M**	**Chopped DC Tablets 4M**	**Chopped DC Tablets 7M**	**Chopped M 4M**	**Chopped M 7M**	**Product X1**
0	0	0	0	0	0	0	0
0.5	57.5	54.0	50.1	59.9	48	51	61
1	85.0	82.7	71.8	82.8	72	70	73.4
2	98.5	98.7	91.5	95.7	94	90	85.4
3	100.0	99.4	98.4	99.2	99	98	91.6
4	100.0	100.0	101.2	100.3	100	99	95.4

Table 4.8 The release % of Product X1 ER and extruded and compressed chopped tablets comprising PMZ HCl and DOW PEO.

Time (h)	Chopped ME Tablets 4M	Chopped ME Tablets 7M	Chopped DC Tablets 4M	Chopped DC Tablets 7M	Chopped M 4M	Chopped M 7M	Product X1
0	0	0	0	0	0.0	0	0
0.5	63.0	52.2	60.8	57.8	31.2	56	61
1	86.8	80.7	87.6	79.7	75.1	83	73.4
2	97.1	98.5	102.2	95.0	95.5	99	85.4
3	99.2	99.1	-	100.0	99.6	100	91.6
4	98.0	101.0	-	100.6	101.0	101	95.4

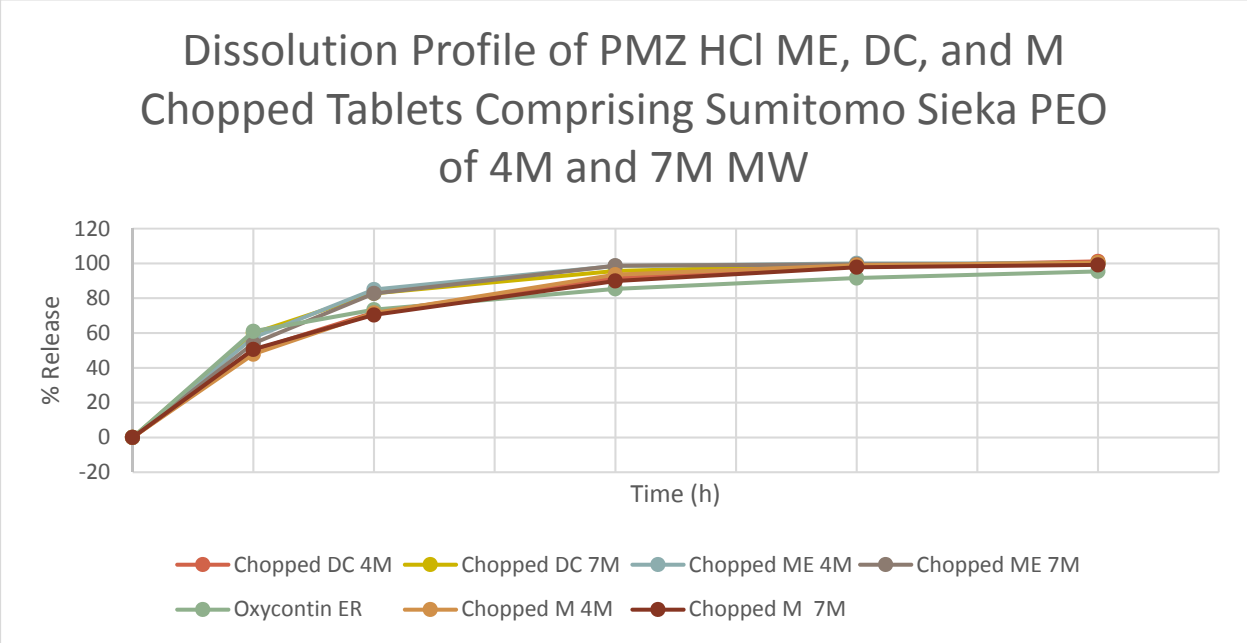


Figure 4.7 Release Profile of Product X1 ER and extruded and compressed chopped tablets Comprising PMZ HCl and Sumitomo Seika PEO.

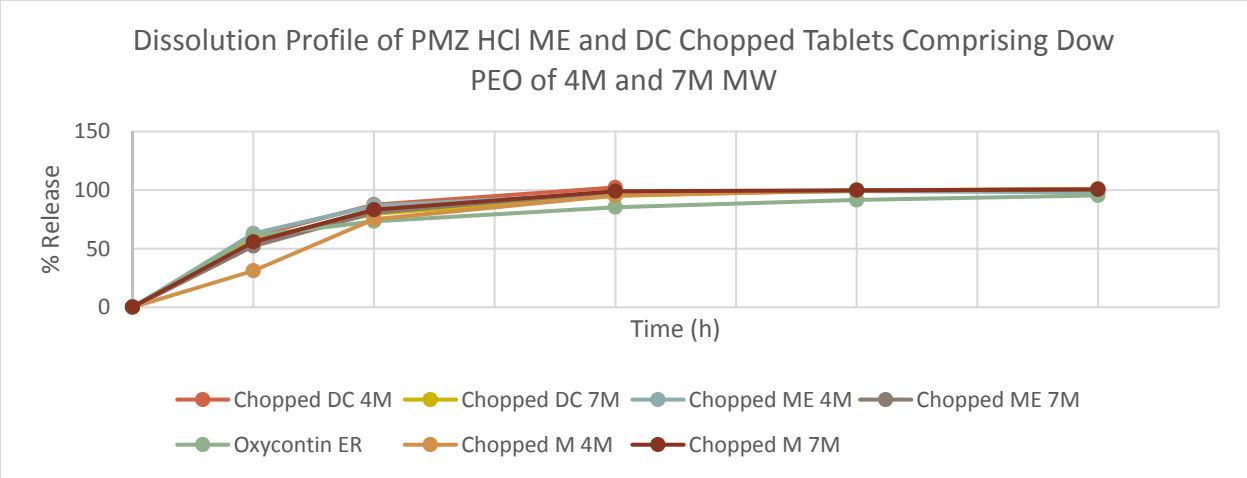


Figure 4.8 Release Profile of Product X1 ER and extruded and compressed chopped tablets Comprising PMZ HCl and Dow PEO.

Table 4.9 and 4.10 show the release % and figure 4.9 and 4.10 show the release profile of chopped heated tablets. Heating accelerated the dose dumping of PMZ HCL from all tablets under study. The release profile was not affected by the manufacturing process used, the MW, and the source of the polymer once the tablets were chopped and heated. At the 0.5-hour time point, the copped heated tablets had dissolution percentage of 42.2% to 90.0 % whereas chopped/pieces of tablets had dissolution percentages of 31.2 % to 63.0%

Table 4.9 The release % of extruded and compressed chopped heated tablets comprising PMZ HCl and Sumitomo Seika PEO.

Time (h)	**Chopped Heated ME Tablets 4M**	**Chopped Heated ME Tablets 7M**	**Chopped Heated DC Tablets 4M**	**Chopped Heated DC Tablets 7M**	**Chopped Heated M 4M**	**Chopped Heated M 7M**
0	0	0	0	0	0	0
0.5	72.3	74.2	76.4	86.7	67	70
1	95.3	98.3	99.3	99.2	93	92
2	100.2	99.8	100.1	100.7	99	99

Table 4.10 The release % of extruded and compressed chopped heated tablets comprising PMZ HCl and DOW PEO.

Time (h)	Chopped Heated ME Tablets 4M	Chopped Heated ME Tablets 7M	Chopped Heated DC Tablets 4M	Chopped Heated DC Tablets 7M	Chopped Heated M 4M	Chopped Heated M 7M
0	0	0	0	0	0.0	0
0.5	63.3	66.8	90.0	86.2	42.2	54
1	92.6	93.8	99.5	98.3	92.3	91
2	100.0	97.1	99.0	99.2	99.7	100
3		100.8	100.0	101.0	100.2	100
4		99.1	100.3	100.3	100.4	100

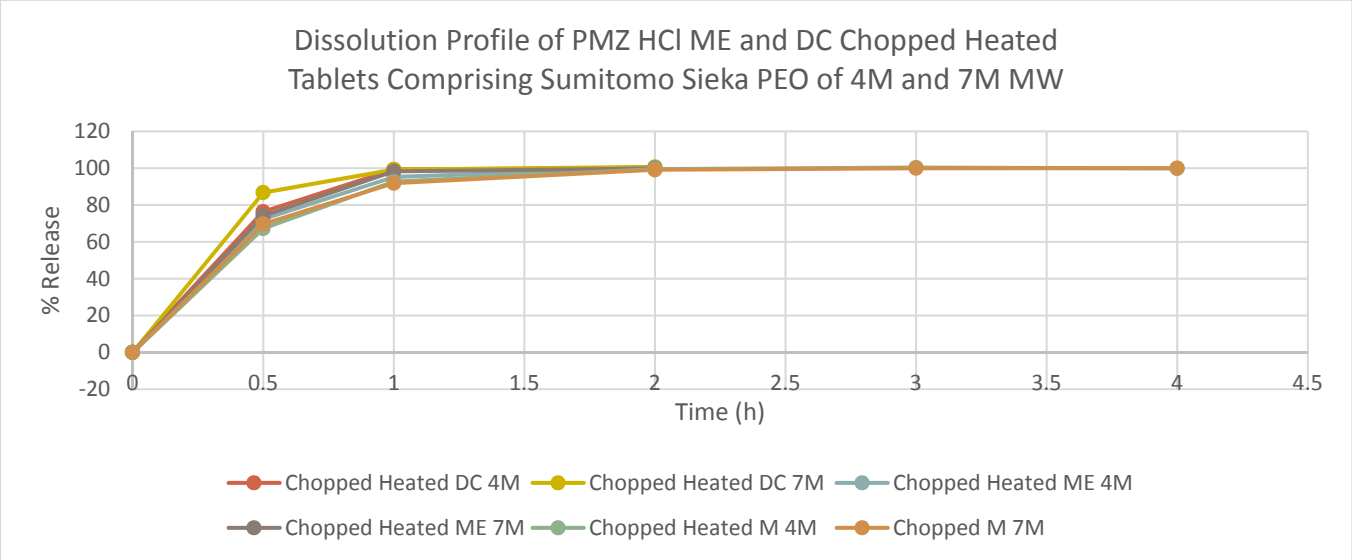


Figure 4.9 Release Profile of ME and DC chopped heated tablets comprising PMZ HCl and Sumitomo Seika PEO of 4M and 7M MW.

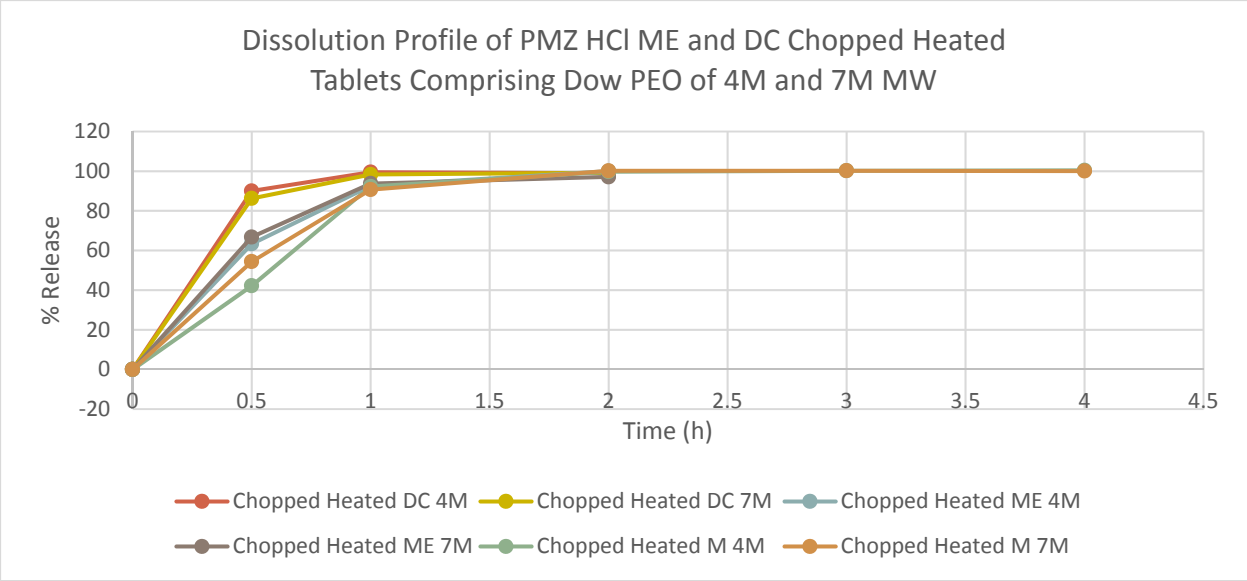


Figure 4.10 Release Profile of ME and DC chopped heated tablets comprising PMZ HCl and Dow PEO of 4M and 7M MW.

Tables 4-11, 4-12, and 4-13 show the time required for 90% release of the drug. In our data analysis, this 90% release time appears to be one of the best gauges of dose dumping. In effect, the 90% release time is the time required for 90% of the dose to be dumped into a dissolution vessel containing 900 mL of water with paddle stirring at 100 rpm.

The data showed that the ME comprising Dow PEO of 4M and 7 M MW tablets have the fastest release profile of any intact tablet. Further, the ¼ tablet chopped and heated showed a 90% release time of 30-66 min for all 12 types of tablets. Interestingly, this processing appears to render the release times of all 12 tablets identical. The ¼ tablet ground, manufactured by any method and containing either 4,000,000 MW or 7,000,000 MW PEO from either Dow or Sumitomo, showed very fast release, dumping 90% of its contents in between 5 and 29 min. It should be noted that the release of a whole tablet ground would be expected to be the same as a ¼ tablet ground since the pieces formed would be the same. That is the grinding process produces particles of the same size; rather, it starts with a whole tablet or a ¼ tablet. By far the

fastest release was seen for the tablet ground and heated. All 12 tablets released 90% of the drug within 5-11.7 min.

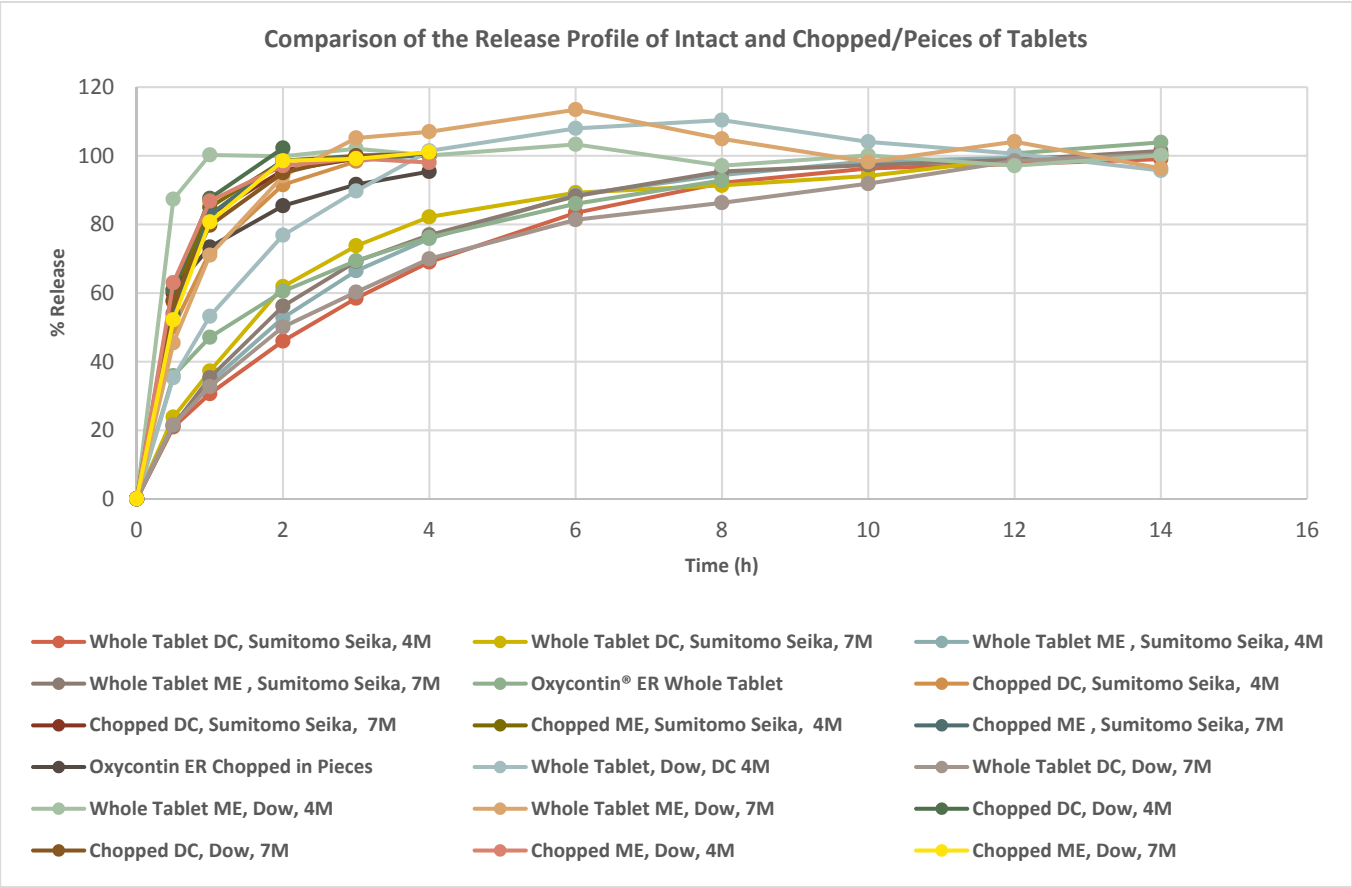


Figure 4.11 Comparison of release profiles of chopped/pieces of tablets to intact tablets.

4.1.1 Time Required to Reach the 90% Release

This study also showed that the behavior of promethazine hydrochloride tablets was similar to those of oxycodone tablets and that significant differences between these tablets are not apparent.

Table 4.11 Effect of heat and chopping on 90% release of Dow and Sumitomo PEO based PMZ HCl compressed tablets.

Sample Information	**Manipulation Parameters**	**Compression and Curing, Dow PEO, 4,000,000**		**Compression and Curing, Dow PEO, 7,000,000**		**Compression and Curing, Sumitomo Seika PEO, 4,000,000**		**Compression and Curing, Sumitomo Seika PEO, 7,000,000**	
		Avg	Stdev	Avg	Stdev	Avg	Stdev	Avg	Stdev
Whole Tablet	None	3.1 (h)	1.0	7.7 (h)	3.9	8.2 (h)	0.9	6.8 (h)	4.8
¼ Tablet	None	6.0(h)	0.5	5.7(h)	0.7	5.1(h)	0.6	5.4(h)	1.8
¼ Tablet	Heated (5min,350 ^{o}F)	1.3(h)	0.1	2.3(h)	0.0	1.9(h)	0.4	1.9(h)	0.1
¼ Tablet	Chopped	1.3 (h)	0.3	1.5 (h)	0.0	2.2 (h)	0.7	1.4 (h)	0.8
¼ Tablet	Chopped Heated (5min,350 ^{o}F)	0.5 (h)	0.0	0.6 (h)	0.1	0.8 (h)	0.0	0.6 (h)	0.1
¼ Tablet	Grounded	5.0 (min)	0.0	5.0 (min)	0.0	8.3 (min)	5.8	5.0 (min)	0.0
¼ Tablet	Grounded Heated (3min,350 ^{o}F)	5.0 (min)	0.0	5.0 (min)	0.0	5.0 (min)	0.0	6.7 (min)	2.9

4.1.2 Release Phases

Regression models for the ME, DC, and M PMZ HCl 80mg tablets comprising DOW and Sumitomo PEO of 4M and 7M MW were built using Minitab® 18 software to determine the release patterns of the quarter samples. The developed regression models showed that the destruction of the polymer matrix that causes the API release in the standard dissolution medium follows multi patterns. The release profile of each drug product consisted of various phases that can be used to predict the dissolution behavior of the PEO-based PMZ HCL matrix formulations, as shown in table 4.14.

Table 4.12 Effect of heat and chopping on 90% release of Dow and Sumitomo PEO based PMZ HCl extruded tablets.

Sample Information	**Manipulation Parameters**	**Extrusion and Molding, Dow PEO, 4,000,000**		**Extrusion and Molding Dow PEO, 7,000,000**		**Extrusion and Molding Sumitomo Seika PEO, 4,000,000**		**Extrusion and Molding Sumitomo Seika PEO, 7,000,000**	
		Avg	**Stdev**	**Avg**	**Stdev**	**Avg**	**Stdv**	**Avg**	**Stdev**
Whole Tablet	None	2.0 (h)	0.7	2.0(h)	0.4	6.0(h)	1.6	5.8(h)	2.0
¼ Tablet	None	2.4(h)	2.7	3.6(h)	0.8	4.6(h)	0.1	4.3(h)	1.3
¼ Tablet	Heated (5min,350 ^{o}F)	2.8(h)	1.0	2.0(h)	1.1	3.3(h)	0.3	1.8(h)	0.3
¼ Tablet	Chopped	1.1(h)	0.1	1.3(h)	0.1	1.2(h)	0.1	1.1(h)	0.5
¼ Tablet	Chopped Heated (5min,350 ^{o}F)	0.9(h)	0.1	0.8(h)	0.1	0.9(h)	0.1	0.8(h)	0.0
¼ Tablet	Grounded	20.0(min)	0.0	13.3(min)	5.8	11.7(min)	7.6	23.3(min)	16.1
¼ Tablet	Grounded Heated (3min,350 ^{o}F)	5.0 (min)	0.0	5.0 (min)	0.0	5.0 (min)	0.0	11.7 (min)	5.8

Table 4.13 Effect of heat and chopping on 90% release of Dow and Sumitomo PEO based PMZ HCl molded tablets.

Sample Information	**Manipulation Parameters**	**Molding, Dow PEO, 4,000,000**		**Molding Dow PEO, 7,000,000**		**Molding Sumitomo Seika PEO, 4,000,000**		**Molding Sumitomo Seika PEO, 7,000,000**	
		Avg	Stdev	Avg	Stdev	Avg	Stdv	Avg	Stdev
Whole Tablet	None	8.2(h)	2.1	5.5(h)	1.4	3.8 (h)	0.5	4.8(h)	1.3
¼ Tablet	None	5.3(h)	0.3	4.6(h)	0.4	5.1 (h)	1.4	4.8(h)	0.4
¼ Tablet	Heated (5min,350 oF)	1.7(h)	0.1	2.6(h)	0.3	1.6 (h)	0.3	1.9(h)	0.4
¼ Tablet	Chopped	1.6(h)	0.1	1.3(h)	0.2	1.8 (h)	0.4	2.1(h)	0.6
¼ Tablet	Chopped Heated (5min,350 oF)	0.9(h)	0.5	1.1(h)	0.1	1.0 (h)	0.4	1.0(h)	0.4
¼ Tablet	Grounded	6.7(min)	2.9	29.0(min)	13.9	8.3 (min)	5.8	10.0(min)	5.0
¼ Tablet	Grounded Heated (3min,350 oF)	5.0(min)	0.0	6.0(min)	2.2	6.7 (min)	2.9	5.0(min)	0.0

Table 4.14 Release patterns of the quarter samples of the ME, DC, and M PMZ HCl 80mg tablets comprising DOW and Sumitomo PEO of 4M and 7M MW.

Polymer	Manufa-cturing	Phases	Interval Hours	Model	Std error	R-Sq	R-sq adjst.	R-sq Pred.
Sumitomo (4M)	**Molded**	**Phase 1**	0.25 – 2.75	% Release = 9.713 + 21.508 Time	1.49	99.37	99.3	98.86
		Phase 2	3.00 – 4.25	% Release = 38.38 + 10.764 Time	0.496	99.23	99.04	97.51
		Phase 3	4.75 – 6.50	% Release = 66.038 + 4.558 Time	0.261	99.26	99.13	98.48
		Phase 4	6.75 – 7.25	% Release = 72.13 + 3.463 Time	0.085	99.52	99.04	93.52
DOW (4M)		**Phase 1**	0.25 – 2.75	% Release = 7.56 + 19.474 Time	1.671	99.04	98.94	98.27
		Phase 2	3.0 – 5.0	% Release = 29.70 + 11.277 Time	0.653	99.38	99.29	98.76
		Phase 3	5.25 – 5.75	% Release = 46.26 + 7.733 Time	0.098	99.87	99.75	98.28
		Phase 4	6.0 – 6.50	% Release = 60.79 + 5.107 Time	0.166	99.16	98.32	88.68
Sumitomo (7M)		**Phase 1**	0.25 – 2.50	% Release = 11.00 + 22.514 Time	1.743	99.08	98.96	98.21
		Phase 2	2.75 – 4.25	% Release = 37.04 + 11.887 Time	0.627	99.21	99.05	97.94
		Phase 3	4.50 – 5.25	% Release = 61.10 + 6.169 Time	0.193	99.38	99.07	96.58
DOW (7M)		**Phase 1**	0.25 – 3.00	% Release = 10.16 + 21.725 Time	1.88	99.03	98.93	98.29
		Phase 2	3.25 – 4.75	% Release = 42.18 + 10.546 Time	0.565	99.19	99.02	97.82
Sumitomo (4M)	**Compressed**	**Phase 1**	0.50 – 3.00	% Release = 12.54 + 19.070 Time	1.34	99.36	99.29	98.85
		Phase 2	3.25 – 5.25	% Release = 40.31 + 9.814 Time	0.646	99.20	99.08	98.35
DOW (4M)		**Phase 1**	0.50 – 4.00	% Release = 12.46 + 16.318 Time	1.77	99.13	99.06	98.70
		Phase 2	4.25 – 6.00	% Release = 47.62 + 7.226 Time	0.597	98.46	98.21	97.54
Sumitomo (7M)		**Phase 1**	0.50 – 2.50	% Release = 10.20 + 16.311 Time	0.927	99.40	99.32	98.75
		Phase 2	2.75 – 6.50	% Release = 31.31 + 8.536 Time	1.021	99.07	99.00	98.64
		Phase 3	6.75 – 9.25	% Release = 56.774 + 4.467 Time	0.318	99.34	99.27	98.89
DOW (7M)		**Phase 1**	0.50 – 2.50	% Release = 13.30 + 22.722 Time	1.820	99.01	98.89	98.35
Sumitomo (4M)	**Extruded**	**Phase 1**	0.25 – 3.00	% Release = 11.15 + 21.426 Time	1.817	99.07	98.96	98.32
		Phase 2	3.25 – 5.00	% Release = 40.93 + 10.859 Time	0.607	99.29	99.17	98.45
DOW (4M)		**Phase 1**	0.25 – 1.50	% Release = 9.33 + 28.63 Time	1.44	99.08	98.85	97.87
Sumitomo (7M)		**Phase 1**	0.25 – 2.75	% Release = 11.21 + 23.960 Time	2.103	99.00	98.89	98.20
		Phase 2	3.00 – 4.00	% Release = 47.16 + 10.312 Time	0.454	99.08	98.77	96.16
		Phase 3	4.25 – 6.00	% Release = 72.353 + 4.166 Time	0.208	99.43	99.34	98.79
DOW (7M)		**Phase 1**	0.25 – 1.75	% Release = 4.84 + 31.31 Time	1.845	99.02	98.82	97.29
		Phase 2	2.00 – 3.50	% Release = 26.57 + 18.661 Time	0.99	99.20	99.04	98.35

*Time in hours

4.1.3 Results of the Significance Testing

Results of the two samples T-Test showed that, at 95% confidence level, there was no significant difference between the chopped and the chopped heated samples of the PMZ HCl 80 mg molded tablets comprising DOW and Sumitomo PEO of 4M MW. The P-Values were 0.305, and 0.826 for the chopped and chopped heated samples, respectively. Data showed that obtaining the PEO from both suppliers has no statistically significant impact on the dose dumping behavior (time required to reach the 90% release) of the PEO based PMZ HCL tablets in the standard dissolution medium (900 ml DI water). The average time required to reach the 90% release and the standard deviation are shown in table 4.15.

Results of the two samples T-Test showed that, at 95% confidence level, there was no statistically significant difference between the chopped and the chopped heated samples of the PMZ HCl 80 mg molded tablets comprising Sumitomo PEO of the two polymer grades. The P-values were 0.595 and 1.000 for the chopped and the chopped heated samples respectively. The data showed that using PEO of the two polymer grades 4M and 7M PEO has no statistically significant impact on the dose dumping behavior (time required to reach the 90% release) of PEO-based PMZ HCL tablets in the standard dissolution medium (900 ml DI water). The average time required to reach the 90% release and the standard deviation are shown in table 4.15.

Results of the two samples T-Test showed that, at 95% confidence level, there was no significant difference between the chopped samples of the PMZ HCl 80 mg molded and compressed tablets comprising Sumitomo PEO of 4M MW (the P-Value was 0.059). Data showed that using the two manufacturing processes; molding and Direct Compression has no statistically significant impact on the dose dumping behavior (time required to reach the 90% release) of the PEO-based PMZ HCL tablets in a standard dissolution medium (900ml DI water). The average time required to reach the 90% release and the standard deviation are shown in table 4.15.

Results of the two samples T-Test showed that, at 95% confidence level, there was a significant difference between the chopped samples of the PMZ HCl 80 mg molded and melt extruded tablets comprising Sumitomo PEO of 4M MW the P-Value was 0.033. The average of the time required for the molded samples to dump 90% of the AI was 1.9 (h), and the Stdev was 0.5, while the average of the time required for the melt extruded samples to dump 90% of the AI was 1.2(h), and the Stdev was 0.2.

Producing PMZ HCl tablets via molding had a statistically significant impact on the dose dumping (90% Release) of the chopped samples of PMZ HCl 80 mg tablets comprising PEO of 4M MW at 95% confidence level. This manufacturing process applies less processing heat and was favored over the melt extrusion method. However, results of the two samples T-Test showed that, at 95% confidence level, there was no significant difference between the chopped heated samples of the PMZ HCl 80 mg molded and melt extruded tablets comprising Sumitomo PEO of 4M MW. The average time required to reach the 90% release, the standard deviation, and the P-Value are shown in table 4.15. Data showed the efficiency of heat application in the destruction of the polymer backbone and the fast release of the API from the PEO-based PMZ HCL tablets regardless of the manufacturing process.

Moreover, results of the two samples T-Test showed that, at 95% confidence level, there was a significant difference between the chopped samples of the PMZ HCl 80 mg compressed and melt extruded tablets comprising Sumitomo PEO of 4M MW, while there was no significant difference between the chopped heated samples. Heating accelerateed the dose dumping (90% Release of the compressed and extruded chopped PMZ Hcl samples. Table 4.15 shows the P values of the two samples T-Test for the previous samples.

Table 4.15 Results of the two samples T-Test.

Samples	# of Samples	Mean	StDev	P Value
Molded PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 4M MW	5	1.850	0.487	*0.305
Molded PMZ HCl 80mg ¼ tablet chopped, DOW PEO of 4M MW	3	1.583	0.144	
Molded PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 4M MW	5	1.850	0.487	*0.595
Molded PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 7M MW	6	2.042	0.660	
Molded PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 4M MW	5	1.850	0.487	*0.059
Compressed PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 4M MW	3	2.417	0.144	
Molded PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 4M MW	5	1.850	0.487	0.033
Melt Extruded PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 4M MW	6	1.167	0.204	
Compressed PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 4M MW	3	2.417	0.144	0.000
Melt Extruded PMZ HCl 80mg ¼ tablet chopped, Sumitomo PEO of 4M MW	3	1.167	0.144	
Molded PMZ HCl 80mg ¼ tablet chopped heated, Sumitomo PEO of 4M MW	4	1.000	0.354	*0.826
Molded PMZ HCl 80mg ¼ tablet chopped heated, DOW PEO of 4M MW	3	0.917	0.520	
Molded PMZ HCl 80mg ¼ tablet chopped heated, Sumitomo PEO of 4M MW	4	1.000	0.354	*1.000
Molded PMZ HCl 80mg ¼ tablet chopped heated, DOW PEO of 7M MW	4	1.000	0.354	

Table 4.15 Continued

Molded PMZ HCl 80mg ¼ tablet chopped heated, Sumitomo PEO of 4M MW	4	1.000	0.354	
Compressed PMZ HCl 80mg ¼ tablet, chopped heated, Sumitomo PEO of 4M MW	3	0.667	0.144	*0.163
Molded PMZ HCl 80mg ¼ tablet chopped heated, Sumitomo PEO of 4M MW	4	1.000	0.354	
Melt Extruded PMZ HCl 80mg ¼ tablet chopped heated, Sumitomo PEO of 4M MW	6	0.958	0.102	*0.833
Compressed PMZ HCl 80mg ¼ tablet chopped heated, Sumitomo PEO of 4M MW	3	0.583	0.289	*0.161
Melt Extruded PMZ HCl 80mg ¼ tablet chopped heated, Sumitomo PEO of 4M MW	6	0.958	0.102	

4.1.4 Quantitative impact of the research variables on the release percent of PEO based PMZ HCL tablets

NeuroShell© (Ward Systems Group, 1995) was used to perform the ANN analysis and obtain a rank with the level of importance of each factor in predicting the values for the variable of interest (Release Percentage). The predictors (independent variables) were Physical Manipulation, Manufacturing Process, Thermal Manipulation, Supplier, and Polymer Grade. The importance weight of each variable has been calculated as following:

1- The data sets have been prepared as MS Excel spreadsheet and have been uploaded;
2- The inputs and outputs have been defined. All variables are Inputs except the % Release is an output;
3- Set test extraction percentage. The percent of 20% of the data sets was excluded to be used for testing the developed model;

4- Backpropagation network architecture has been selected as three hidden slabs with different activation functions. The architecture is five neurons in a scale of [-1,1], 0.1 learning rate, 0.1 momentum, and 0.3 initial weights; and

5- The training criteria have been set as follows:

- Random pattern selection
- Momentum weight update
- Minimum average error 20000 epochs
- Error condition for missing values

The results showed, as shown in table 4.16, that the greatest effect of Physical Manipulation and the lowest impact of polymer Grade, which were relatively compatible with the results obtained in the Significance Analysis. To test the sensitivity of the ANN, coefficient of determination (R squared) test has been selected. The model showed 0.87 R^2 value, which is satisfactory for the purpose of finding the importance of variables.

Table 4.16 Importance of Variables Affecting the Release Percentage

Variables	**Importance**
Physical Manipulation	25.50 %
Manufacturing Process	22.90 %
Thermal Manipulation	21.30 %
Supplier	16.90 %
Polymer Grade	13.40 %

4.2 Syringeability and Extractability Data

Syringeability test results showed that it was relatively easy to draw a solution containing DC, ME, and/or M PMZ HCl tablets into a syringe for injection if the samples used are either cut

into pieces, chopped, and/or heated. Once the samples were grounded, the difficulty of drawing into a syringe was significantly increased, as shown in tables 4-17 to 4-21.

Table 4.17 Syringeability and % API recovery from PEO based PMZ HCL quarter samples.

Polymer Inf.	**Manufacturing Process**	**# of Tests**	**AV. Syringeability**	**StDev**	**AV. % API Recovery**	**StDev**
Sumitomo, 4M	DC	3	2	0.6	0.7	0.1
Sumitomo, 7M		3	2.0	1.0	0.7	0.1
Dow, 4M		3	1.3	0.6	12.4	1.6
Dow, 7M		3	2.7	1.2	8.8	1.0
Sumitomo, 4M	ME	3	2.0	0.0	8.6	1.4
Sumitomo, 7M		3	1.0	0.0	0.5	0.1
Dow, 4M		3	1.7	0.6	6.7	0.4
Dow, 7M		3	1.3	0.6	6.5	0.8
Sumitomo, 4M	M	3	1.3	0.6	10.4	1.1
Sumitomo, 7M		3	1.3	0.3	7.7	0.5
Dow, 4M		3	1.0	0.0	10.3	1.1
Dow, 7M		3	1.7	0.6	7.4	1.3

Table 4.18 Syringeability and % API recovery from PEO based PMZ HCL quarter heated samples.

Polymer Inf.	**Manufacturing Process**	**# of Tests**	**AV. Syringeability**	**StDev**	**AV. % API Recovery**	**StDev**
Sumitomo, 4M	DC	3	1	0	0.7	0.1
Sumitomo, 7M		3	1.0	0.0	0.7	0.0
Dow, 4M		3	1.0	0.0	12.0	2.7
Dow, 7M		3	1.0	0.0	10.7	0.7
Sumitomo, 4M	ME	3	1.0	0.0	11.0	2.7
Sumitomo, 7M		3	1.0	0.0	5.4	4.1
Dow, 4M		3	1.0	0.0	10.6	1.2
Dow, 7M		3	1.0	0.0	9.2	1.2
Sumitomo, 4M	M	3	1.0	0.0	15.1	5.8
Sumitomo, 7M		3	1.0	0.0	9.5	0.1
Dow, 4M		3	1.0	0.0	13.3	2.0
Dow, 7M		3	1.0	0.0	10.7	1.0

Table 4.19 Syringeability and % API recovery from PEO based PMZ HCL quarter chopped samples.

Polymer Inf.	**Manufacturing Process**	**# of Tests**	**AV. Syringeability**	**StDev**	**AV. % API Recovery**	**StDev**
Sumitomo, 4M	DC	3	4.3	0.6	1.5	0.2
Sumitomo, 7M		3	1.7	0.6	1.2	0.3
Dow, 4M		3	2.0	0.0	21.9	2.6
Dow, 7M		3	5.0	1.0	12.7	2.6
Sumitomo, 4M	ME	3	1.0	0.0	18.9	5.3
Sumitomo, 7M		3	2.7	0.6	143.1	13.2
Dow, 4M		3	3.3	0.6	19.5	7.4
Dow, 7M		3	2.3	0.6	18.3	5.9
Sumitomo, 4M	M	3	2.0	0.0	33.1	6.3
Sumitomo, 7M		3	1.8	0.3	13.6	4.1
Dow, 4M		3	4.3	1.2	14.4	1.2
Dow, 7M		3	2.7	0.6	15.6	2.4

Table 4.20 Syringeability and % API recovery from PEO based PMZ HCL quarter Chopped heated samples.

Polymer Inf.	**Manufacturing Process**	**# of Tests**	**AV. Syringeability**	**StDev**	**AV. % API Recovery**	**StDev**
Sumitomo, 4M	DC	3	1.7	0.6	1.3	0.1
Sumitomo, 7M		3	1.0	0.0	1.2	0.1
Dow, 4M		3	1.3	0.6	37.8	2.2
Dow, 7M		3	1.3	0.6	23.3	4.1
Sumitomo, 4M	ME	3	1.0	0.0	20.4	6.0
Sumitomo, 7M		3	1.3	0.6	138.4	14.1
Dow, 4M		3	1.0	0.0	17.5	2.6
Dow, 7M		3	1.0	0.0	18.1	5.5
Sumitomo, 4M	M	3	1.0	0.0	26.7	3.6
Sumitomo, 7M		3	1.0	0.0	15.4	2.4
Dow, 4M		3	1.0	0.0	22.8	4.7
Dow, 7M		3	1.0	0.0	18.7	1.8

Table 4.21 Syringeability and % API recovery from PEO based PMZ HCL quarter grounded samples.

Polymer Inf.	**Manufacturing Process**	**# of Tests**	**AV. Syringeability**	**StDev**	**AV. % API Recovery**	**StDev**
Sumitomo, 4M	DC	2	6	0	2	0
Sumitomo, 7M		3	2.7	1.2	2.0	1.3
Dow, 4M		3	6.0	1.7	17.9	16.0
Dow, 7M		3	4.0	0.0	26.7	7.8
Sumitomo, 4M	ME	3	2.3	0.6	2.6	3.3
Sumitomo, 7M		3	3.0	0.0	48.1	25.6
Dow, 4M		3	3.3	0.6	31.7	4.6
Dow, 7M		3	5.5	1.3	41.1	10.8
Sumitomo, 4M	M	3	3.3	0.6	67.0	9.3
Sumitomo, 7M		3	3.0	0.0	44.9	39.9
Dow, 4M		3	5.0	1.0	19.8	16.9
Dow, 7M		3	4.0	1.0	48.6	19.7

Table 4.22 Syringeability and % API recovery from PEO based PMZ HCL quarter grounded heated samples.

Polymer Inf.	**Manufacturing Process**	**# of Tests**	**AV. Syringeability**	**StDev**	**AV. % API Recovery**	**StDev**
Sumitomo, 4M	DC	3	2.7	0.6	2.6	0.2
Sumitomo, 7M		3	1.3	0.6	2.6	0.5
Dow, 4M		3	1.0	0.0	66.3	11.9
Dow, 7M		3	1.0	0.0	62.1	6.3
Sumitomo, 4M	ME	3	1.0	0.0	6.0	0.2
Sumitomo, 7M		3	3.3	0.6	70.1	10.2
Dow, 4M		3	1.0	0.0	84.9	13.7
Dow, 7M		3	1.3	0.6	79.2	5.0
Sumitomo, 4M	M	3	1.0	0.0	72.8	7.9
Sumitomo, 7M		3	1.0	0.0	95.4	2.5
Dow, 4M		3	1.3	0.6	87.9	5.7
Dow, 7M		3	1.0	0.0	89.6	8.4

4.2.1 Differences between the Polymer Grade

Results of the two sample T-Test of the % API recovered from Molded PMZ HCl 80 mg tablets comprising Sumitomo PEO of 4M and 7M MW showed no statistically significant difference between the two polymer grades for all sample forms at 95% confidence level. The P-Values were 0.606, 0.138, 0.202, 0.195, 0.881, and 0.943 for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped and heated, quarter tablet grounded, and quarter tablet grounded and heated respectively.

4.2.2 Differences Between the Suppliers

Results of the two sample T-Test of the % API recovered from compressed PMZ HCl 80 mg tablets comprising Sumitomo and Dow PEO of 4M MW showed that, at 95% confidence level, there was a statistically significant difference between the two suppliers for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped and heated, and quarter tablet grounded and heated as shown in table 4.23. The P-values were 0.006, 0.018, 0.005, 0.001, and 0.011 for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped heated, and quarter tablet grounded heated samples respectively. The analysis showed that the % API recovered from the compressed PMZ HCl 80 mg tablets comprising Dow PEO of 4M MW was significantly higher than the % API recovered from the compressed PMZ HCl 80 mg tablets Comprising Sumitomo PEO of the same grade. However, results of the two sample T-Test of the % API recovered from compressed PMZ HCl 80 mg tablets comprising Sumitomo and Dow PEO of 4M MW showed that, at 95% confidence level, there was no statistically significant difference between the two suppliers for the quarter tablet grounded samples, the P- value was 0.102 as shown in table 4.23.

Table 4.23 Results Two sample T-Test between the % API recovered from the Compressed PMZ HCl 80 mg tablets comprising Dow and Sumitomo PEO of 4M MW.

Manufacturing Process	Sample Info.	Manipulation	Supplier	Mean	StDev	P value
Compression	¼ tablet	None	Sumitomo	0.678	0.138	0.006
			Dow	12.44	1.55	
	¼ tablet	heated	Sumitomo	0.693	0.137	0.018
			Dow	12.04	2.70	
		chopping	Sumitomo	1.497	0.211	0.005
			Dow	21.89	2.58	
		Chopping, heating	Sumitomo	1.3168	0.0541	0.001
			Dow	37.80	2.20	
		Grounded	Sumitomo	2.117	0.130	*0.102
			Dow	26.82	5.62	
		Grounded heated	Sumitomo	2.583	0.172	0.011
			Dow	66.3	11.9	
			Dow			

Results of the two sample T-Test of the % API recovered from ME PMZ HCl 80 mg tablets comprising Sumitomo and Dow PEO of 4M MW showed that, at 95% confidence level, there was a statistically significant difference between the two suppliers for the quarter tablet grounded and the quarter tablet grounded and heated as shown in the table. The P-Values were 0.003, 0.010 for the quarter tablet grounded and the quarter tablet grounded and heated samples, respectively. The analysis shows that the % API recovered from the ME PMZ HCl 80 mg tablets Comprising Dow PEO of 4M MW was significantly higher than the % API recovered from the ME PMZ HCl 80 mg tablets Comprising Sumitomo PEO of the same polymer grade. However, results of the two sample T-Test showed that, at 95% confidence level, there was no statistically significant difference between the two suppliers for the quarter tablet, quarter tablet heated, quarter tablet chopped, and quarter tablet chopped and heated samples as shown in Table 4.24. The P-Values were 0.159, 0.860, 0.915, and 0.524 for the quarter tablet, quarter tablet heated, quarter tablet chopped, and quarter tablet chopped, heated samples respectively.

Table 4.24 Results Two sample T-Test between the % API recovered from the ME PMZ HCl 80 mg tablets comprising Dow and Sumitomo PEO of 4M MW.

Manufacturing Process	Sample Info.	Manipulation	Supplier	Mean	StDev	P value
Melt Extrusion	¼ tablet	None	Sumitomo	8.57	1.39	*0.159
			Dow	6.715	0.427	
	¼ tablet	heated	Sumitomo	10.96	2.69	0.860
			Dow	18.93	5.29	
		chopping	Sumitomo	19.54	7.44	*0.915
			Dow	21.89	2.58	
		Chopping, heating	Sumitomo	20.42	5.96	*0.524
			Dow	17.54	2.58	
		Grounded	Sumitomo	2.64	3.33	0.003
			Dow	31.70	4.59	
		Grounded heated	Sumitomo	6.028	0.211	0.010
			Dow	84.9	13.7	

Results of the two sample T-Test of the % API recovered from molded PMZ HCl 80 mg tablets comprising Sumitomo and Dow PEO of 4M MW showed that, at 95% confidence level, there was a statistically significant difference between the two suppliers for the quarter tablet chopped and the quarter tablet grounded samples as shown in the table. The P-Values were 0.037 and 0.024 for the quarter tablet chopped and the quarter tablet grounded samples, respectively. The analysis showed that the % API recovered from the molded PMZ HCl 80 mg tablets Comprising Sumitomo PEO of 4M MW was significantly greater than the % API recovered from tablets Comprising DOW PEO of the same polymer grade as shown in table 4-25. However, results of the two sample T-Test showed that, at 95% confidence level, there was no statistically significant difference between the two suppliers for the quarter tablet, quarter tablet heated, quarter tablet chopped, heated, and the quarter tablet grounded heated samples as shown in the table. The P-Values were 0.939, 0.664, 0.330, and 0.074 for the quarter tablet, quarter tablet heated, quarter tablet chopped, heated, and the quarter tablet grounded heated samples respectively.

Table 4.25 Results Two sample T-Test between the % API recovered from the Molded PMZ HCl 80 mg tablets comprising Dow and Sumitomo PEO of 4M MW.

Manufacturing Process	Sample Info.	Manipulation	Supplier	Mean	StDev	P value
Molding	¼ tablet	None	Sumitomo	10.35	1.06	*0.939
			Dow	10.28	1.11	
	¼ tablet	heated	Sumitomo	15.07	5.79	*0.664
			Dow	13.29	2.00	
		chopping	Sumitomo	33.06	6.30	0.037
			Dow	14.39	1.16	
		Chopping, heating	Sumitomo	26.74	3.59	*0.330
			Dow	22.78	4.70	
		Grounded	Sumitomo	66.98	9.34	0.024
			Dow	19.8	16.9	
		Grounded heated	Sumitomo	72.79	7.88	*0.074
			Dow	87.94	5.72	
			Dow			

4.2.3 Differences between the Manufacturing processes

Results of the Two Sample T-Test showed that, at 95% confidence level, there was a statistically significant difference between the % API recovered from the ME and DC PMZ HCl 80 mg tablets comprising Sumitomo PEO of 4 M MW. The P-Values were 0.01, 0.022, 0.029, 0.031, and 0.000 for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped and heated, and quarter tablet grounded and heated samples respectively. The Analysis showed that the % API Recovered from the ME samples was significantly higher than the % API Recovered from the DC samples. However, the analysis showed that there was no statistically significant difference between the grounded samples; the P-Value was 0.813, as shown in table 4.26.

Table 4.26 Results of the Two sample T-Test between the % API recovered from the ME and DC PMZ HCl 80 mg tablets comprising Sumitomo PEO of 4M MW.

Sample Info.	Manipulation	Manufacturing Process	Mean	StDev	P value
¼ tablet	None	ME	8.57	1.39	0.010
		DC	0.678	0.138	
¼ tablet	heated	ME	10.96	2.69	0.022
		DC	0.693	0.137	
	chopping	ME	18.93	5.29	0.029
		DC	1.497	0.211	
	Chopping, heating	ME	20.42	5.96	0.031
		DC	1.3168	0.0541	
	Grounded	ME	2.64	3.33	*0.813
		DC	2.117	0.130	
	Grounded heated	ME	6.028	0.211	0.000
		DC	2.583	0.172	

Results of the two samples T-Test showed that, at 95% confidence level, there was a statistically significant difference between the intact and manipulated samples of the molded and DC tablets comprising Sumitomo PEO of 4MMW. The P-values were 0.004, 0.05, 0.013, 0.007, 0.007, 0.004 for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped and heated, and quarter tablet grounded and heated samples respectively. The % API recovered from the prespecified samples of the ME product was higher than that was recovered from the same samples for the DC product are shown in table 4.27.

Table 4.27 Results of the Two sample T-Test between the % API recovered from the M and DC PMZ HCl 80 mg tablets comprising Sumitomo PEO of 4M MW.

Sample Info.	Manipulation	Manufacturing Process	Mean	StDev	P value
¼ tablet	None	M	10.35	1.06	0.004
		DC	0.678	0.138	
¼ tablet	heated	M	15.07	5.79	0.050
		DC	0.693	0.137	
	chopping	M	33.06	6.30	0.013
		DC	1.497	0.211	
	Chopping, heating	M	26.74	3.59	0.007
		DC	1.3168	0.0541	
	Grounded	M	66.98	9.34	0.007
		DC	2.117	0.130	
	Grounded heated	M	72.79	7.88	0.004
		DC	2.583	0.172	

Results of the two samples T-Test showed that, at 95% confidence level, there was no significant difference between the Molded and ME PEO-based PMZ HCL tablets comprising Sumitomo PEO of 4M MW in the form of a quarter tablet, quarter tablet heated, quarter tablet chopped, and the quarter tablet chopped and heated samples. The P-Values were 0.176, 0.381, 0.059, and 0.213 for the quarter tablet, quarter tablet heated, quarter tablet chopped, and the quarter tablet chopped and heated samples respectively. However, the analysis showed that, at 95% confidence level, there was a significant difference between the Molded and ME PEO-based PMZ HCL tablets comprising Sumitomo PEO of 4M MW in the form of quarter tablet grounded and quarter tablet grounded and heated samples. The P-Values were 0.008 and 0.005 for the quarter tablet grounded and quarter tablet grounded and heated samples, respectively. The % API recovered from later samples of the molded product was greater than that was recovered from the same samples of the ME product as shown in table 4.28.

Table 4.28 Results of the Two sample T-Test between the % API recovered from the M and DC PMZ HCl 80 mg tablets comprising Sumitomo PEO of 4M MW.

Sample Info.	Manipulation	Manufacturing Process	Mean	StDev	P value
¼ tablet	None	M	10.35	1.06	*0.176
		ME	8.57	1.39	
¼ tablet	heated	M	15.07	5.79	*0.381
		ME	10.96	2.69	
	chopping	M	33.06	6.30	0.059
		ME	18.93	5.29	
	Chopping, heating	M	26.74	3.59	*0.213
		ME	20.42	5.96	
	Grounded	M	66.98	9.34	0.008
		ME	2.64	3.33	
	Grounded heated	M	72.79	7.88	0.005
		ME	6.028	0.211	

4.3 Release Profiles of the prescription opioids

4.3.1 Release Profiles

The dose dumping behavior (time required to reach the 90% release) of the PEO-based prescription opioids showed that physical manipulation via chopping or grinding was much more effective in the destruction of the PEO matrix than thermal manipulation via the application of heat thus promoting the fast release. The time that was required to reach the 90% release of the quarter heated samples of Product X1, Product X7, Product X3, Product X5, and Product X6 was 1.5 (h), 4.75 (h), 2.25 (h), 1(h), and 4.25(h) respectively, while it ranged from 5-30 min for the same products. Figures 4.12 to 4.19 show the dissolution profiles of the previously identified FDA approved drug products.

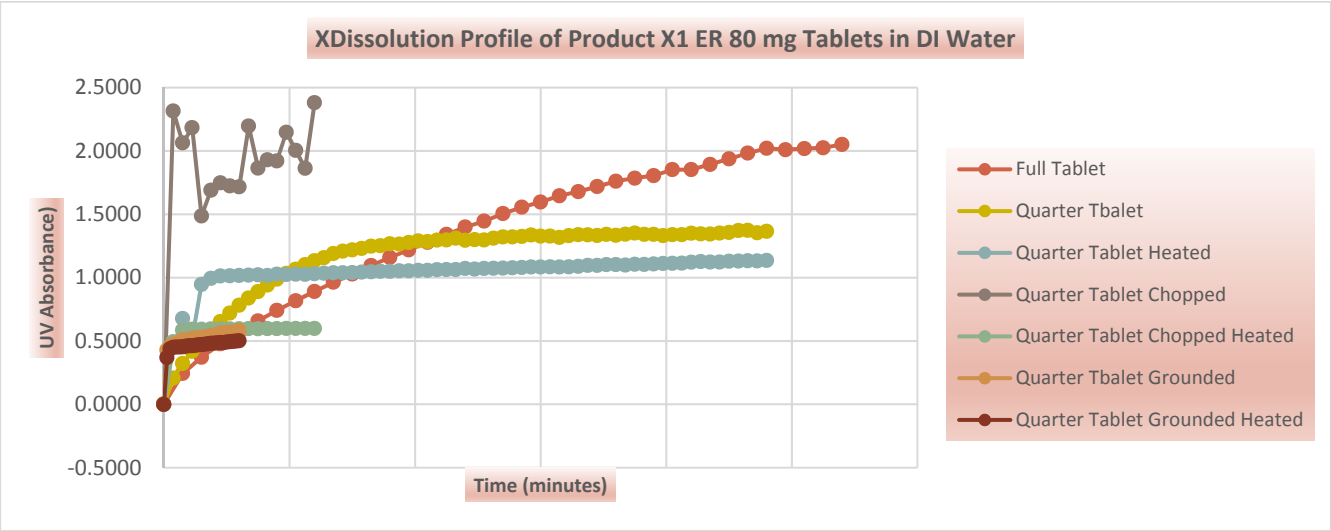


Figure 4.12 The dissolution profile of Product X1 ER 80 mg tablets in 900ml of DI water.

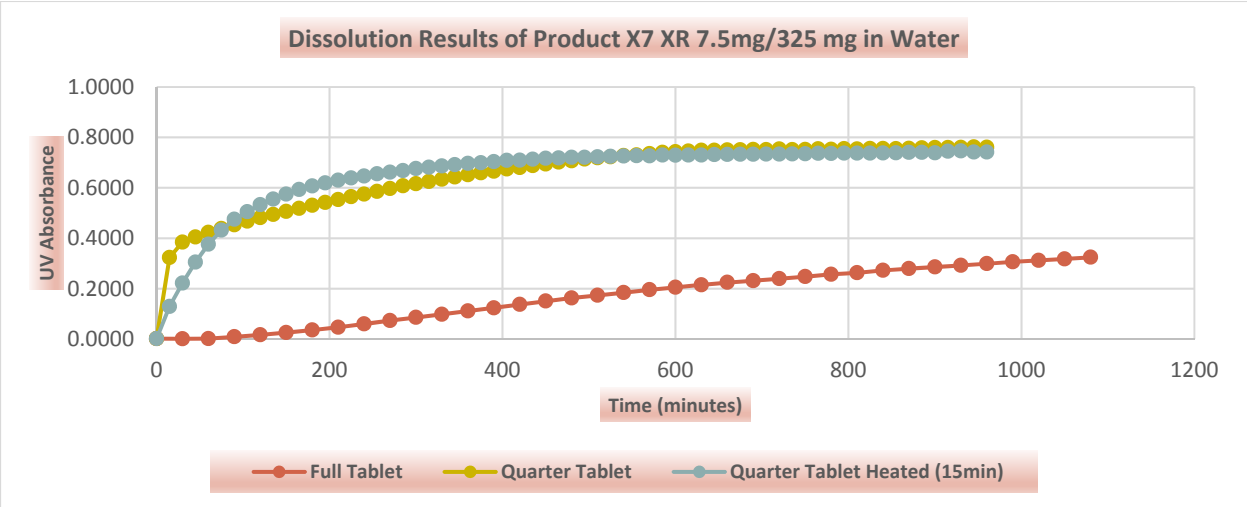


Figure 4.13 The dissolution profile of Product X7 XR 7.5 mg/325 mg tablets in 900 ml of DI water.

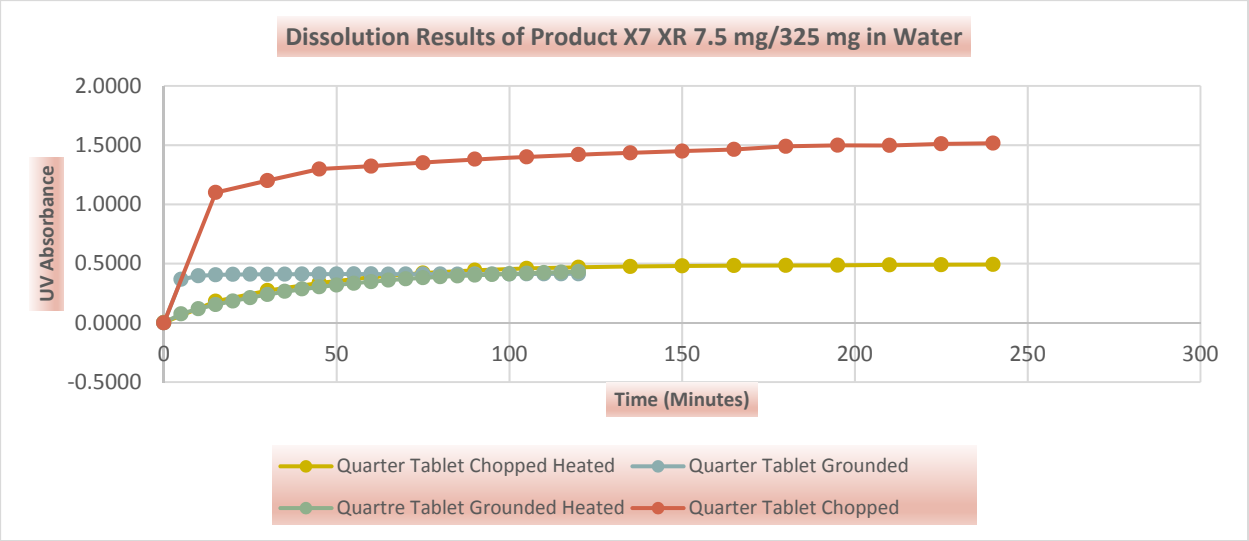


Figure 4.14 The dissolution profile of Product X7 XR 7.5 mg/325 mg tablets in 900 ml of DI water.

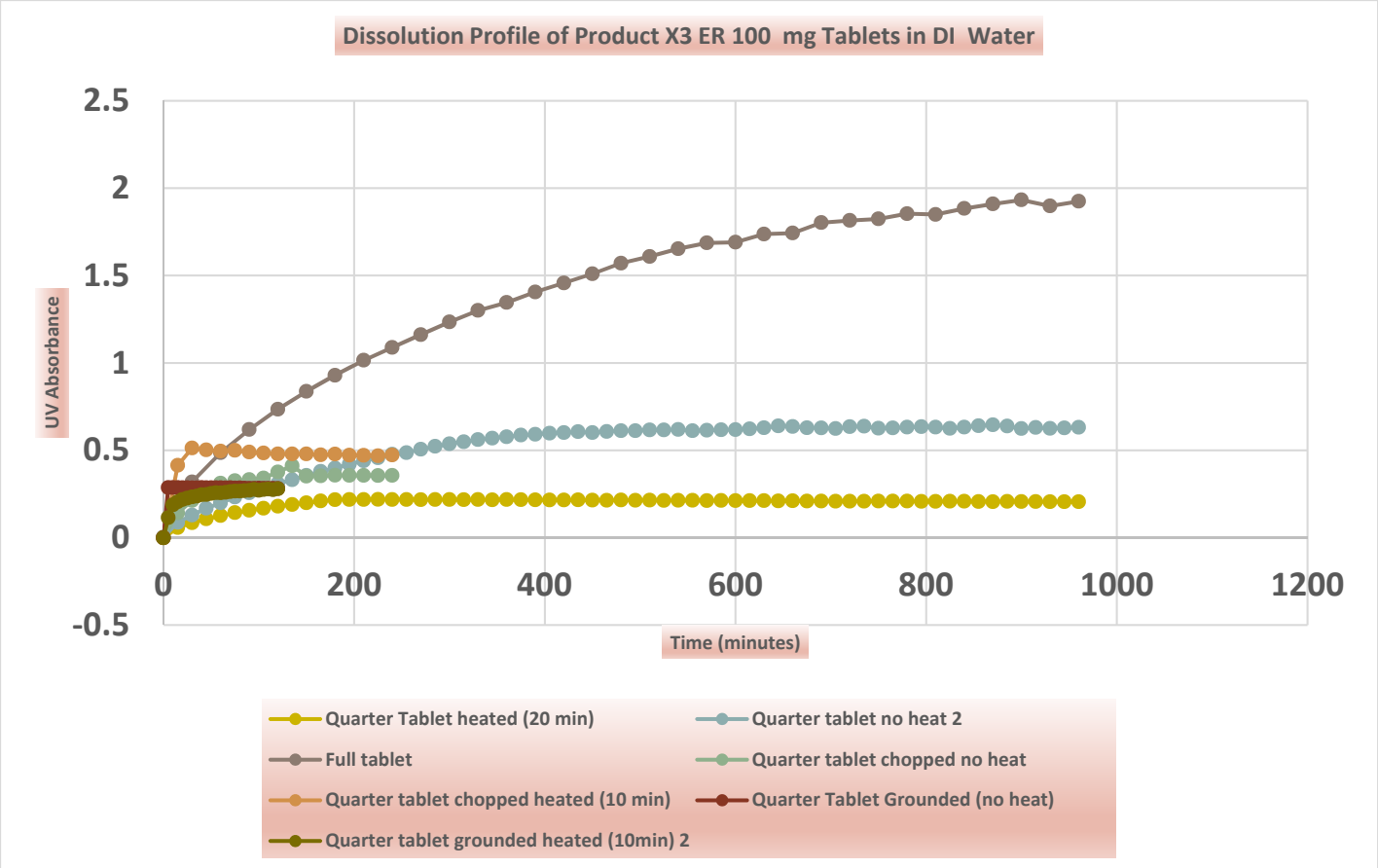


Figure 4.15 The dissolution profile of Product X3 ER 100 mg tablets in 900ml of DI water.

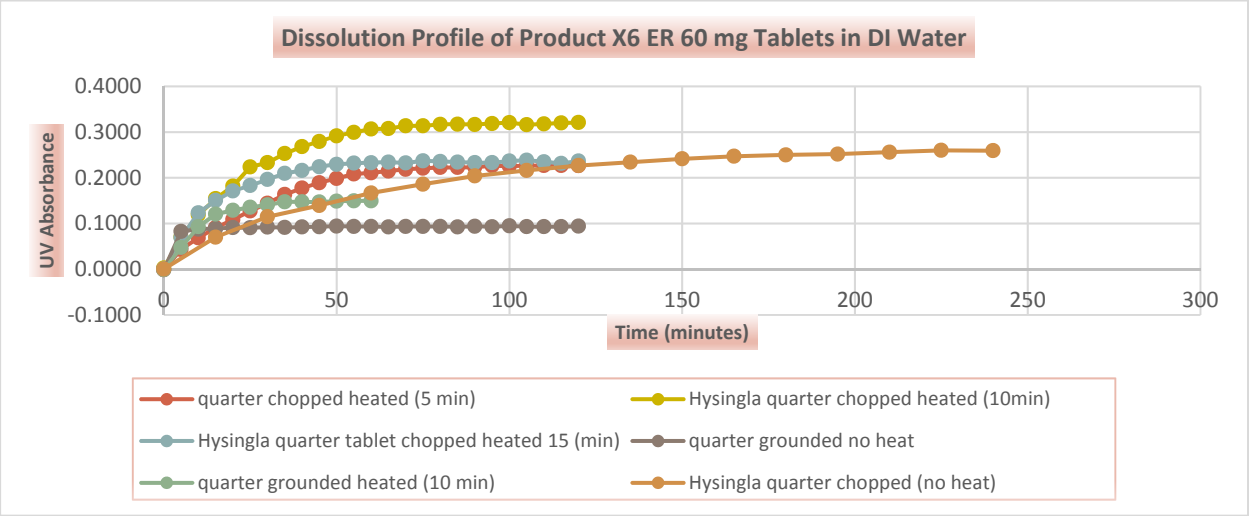


Figure 4.16 The dissolution profile of Product X6 ER 60 mg tablets in 900 ml of DI Water.

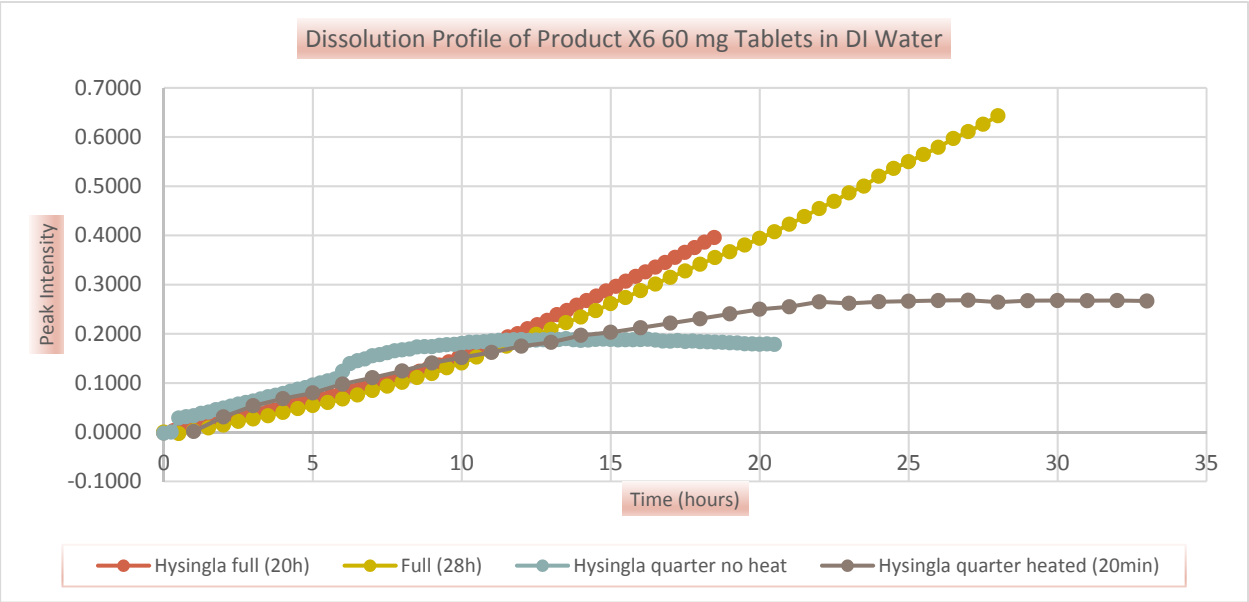


Figure 4.17 The dissolution profile of Product X6 ER 60 mg tablets in 900 ml of DI Water.

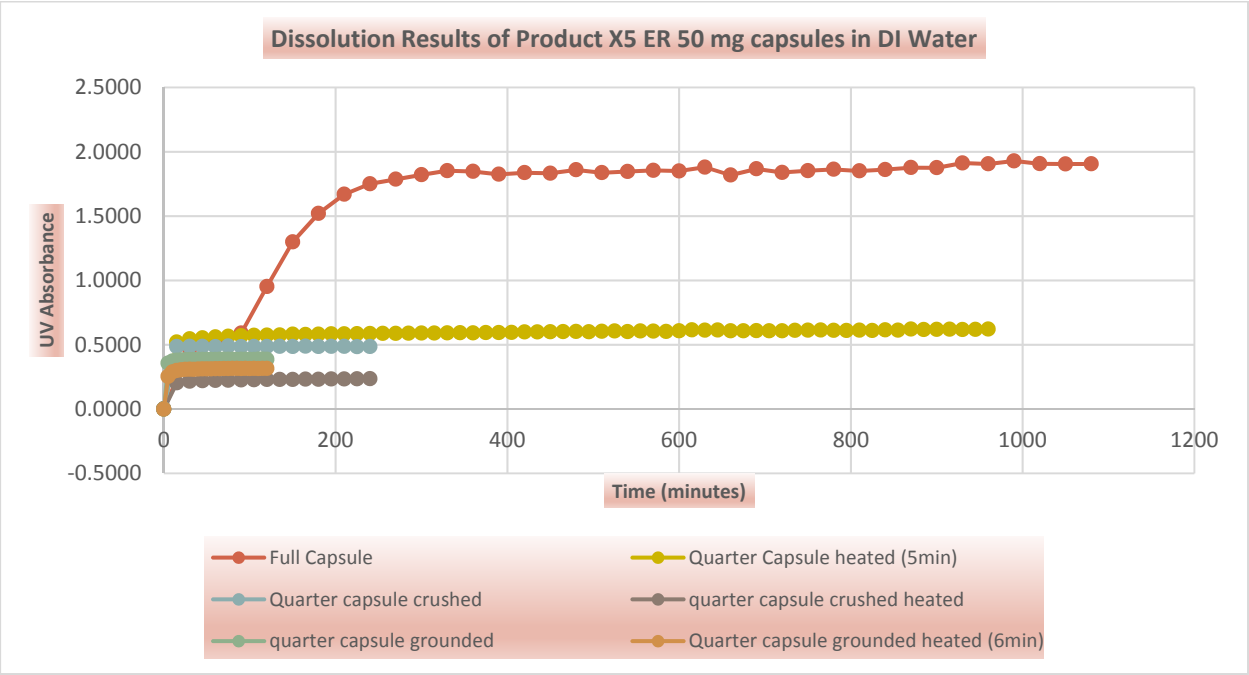


Figure 4.18 The dissolution profile of Product X5 ER 50 mg capsules in 900ml of DI water.

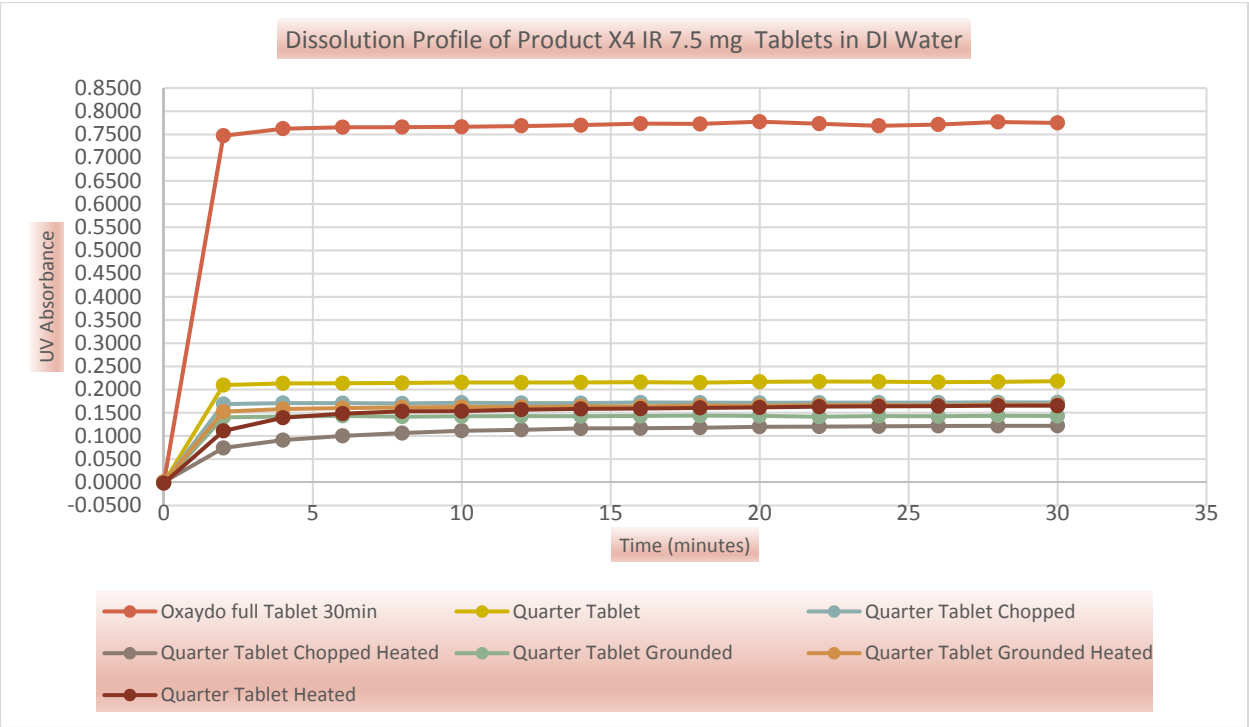


Figure 4.19 The dissolution profile of Product X4 IR 7.5 mg tablets in 900 ml of DI water.

Overall, these data showed that chopping or grinding was much more effective in the destruction of the PEO matrix than heating thus promoting fast release as shown in figures 4.12 to 4.19 and table 4.29. On the other hand, data also shows that the failure modes of these prescription opioids include size reduction and heating. Further, heating was found to render the release of the chopped and ground samples of Product X7 XR tablets slower than the release of the non-heated chopped and grounded samples.

Table 4.29 90% release of Product X1, Product X7, Product X3, Product X5, Product X6, and Product X4.

Sample Information	Manipulation Parameters	Product X1	Product X7	Product X3	Product X5	Product X6	Product X4
Whole Tablet	None	13 (h)	_	10.5 (h)	3(h)	_	2 min
¼ Tablet	None	4.75h	7 (h)	5.75 (h)	_	7.5(h)	2 min
¼ Tablet	Heated (golden brown,350 °F)	1.5 (h)	4.75 (h)	2.25 (h)	1(h)	4.25(h)	6 min
¼ Tablet	Chopped	-	1.15 h	75 (min)	15 (min)	120(min)	2 min
¼ Tablet	Chopped Heated (5min,350 °F)	_	1.5 h	15 (min)	30 (min)	50 min	8 min
¼ Tablet	Chopped Heated (10 min,350 °F)	15 (min)	_	_	_	50 (min)	_
¼ Tablet	Chopped Heated (15min,350 °F)		_	_	_	35(min)	_
¼ Tablet	Grounded	30 min	5 min	5 (min)	5(min)	5 (min)	2 min
¼ Tablet	Grounded Heated (3min,350 °F)	10 (min)	1.15 h	_	10 (min)		2 min
¼ Tablet	Grounded Heated (10 min,350 °F)	_		40 (min)		20 (min)	_

4.3.2 Syringeability and Extractability of the prescription opioids

Syringeability and extractability data showed that heating was much more effective in the extraction of APIs than chopping or grinding thus promoting the ability to draw a solution

containing the API into a syringe for injection relatively easy and facilitate higher % API recovery from PEO-based prescription opioids. The % API recovered from the quarter tablet grounded and heated samples of Product X3 ER 100 mg tablets, Product X1 ER 80 mg tablets, Product X7 XR 7.5 mg/325 mg tablets, Product X6 ER 60 mg tablets, and Product X5 ER 50 mg capsules ranged from 25-79%, while it ranged from 3-32% for the quarter tablet ground unheated samples of the same products. On the other hand, the syringeability grade for the quarter tablet grounded and heated samples of Product X3 ER 100 mg tablets, Product X1 ER 80 mg tablets, Product X7 XR 7.5 mg/325 mg tablets, Product X6 ER 60 mg tablets, and Product X5 ER 50 mg capsules ranged from 2-7, while it ranged from 7-9 for the quarter tablet ground unheated samples of the same products. Data showed that heating was much more effective in the extraction of opioids than chopping or grinding, thus promoting higher % API recovery, as shown in tables 4.30 to 4.36.

Table 4.30 Results of syringeability and extractability testing of Product X3 ER 100 mg tablets.

Sample	Treatment	DI water (ml)	Syringeability (1-10)	% Solution Recovery	% API Recovery
Product X3 Quarter Tablet	_	4	3	90	19
Product X3 Quarter Tablet	Chopping	4	3	75	28
Product X3 Quarter Tablet	Grinding	4	9	10	6
Product X3 Quarter Tablet	Heating for 20 minutes at 350 F	4	3	90	33
Product X3 Quarter Tablet	Chopping and heating for 10 minutes at 350 F	4	3	85	41
Product X3 Quarter Tablet	Grinding and heating for 10 minutes at 350 F	4	5	50	25

Table 4.31 Results of syringeability and extractability testing of Product X1 ER 80 mg tablets.

Sample	Treatment	DI water (ml)	Syringeability (1-10)	% Solution Recovery	% API Recovery
Product X1 Quarter Tablet	_	4 ml	3 out of 10	65	12
Product X1 Quarter Tablet	Chopping	4 ml	8 out of 10	45	49
Product X1 Quarter Tablet	Grinding	4 ml	9 out of 10	32.5	23
Product X1 Quarter Tablet	Heating for 20 minutes at 350 F	4 ml	1 out of 10	100	61
Product X1 Quarter Tablet	Chopping and heating for 10 minutes at 350 F	4 ml	1 out of 10	100	106
Product X1 Quarter Tablet	Grinding and heating for 10 minutes at 350 F	4 ml	2 out of 10	100	50

Table 4.32 Results of syringeability and extractability testing of Product X7 XR 7.5 mg/325 mg tablets.

Sample	**Treatment**	**DI water (ml)**	**Syringeability**	**% Solution Recovery**	**% API Recovery**
Product X7 Quarter Tablet	_	4	3	87.5	11
Product X7 Quarter Tablet	Chopping	4	5	50	8
Product X7 Quarter Tablet	Grinding	4	8	20	3
Product X7 Quarter Tablet	Heating for 20 minutes at 350 F	4	3	85	13
Product X7 Quarter Tablet	Chopping and heating for 10 minutes at 350 F	4	7	60	15
Product X7 Quarter Tablet	Grinding and heating for 10 minutes at 350 F	4	7	60	29

Table 4.33 Results of syringeability and extractability testing of Product X6 ER 60 mg tablets.

Sample	Treatment	DI water (ml)	Syringeability (1-10)	% Solution Recovery	% API Recovery
Product X6 Quarter Tablet	_	4	5	77.5	1
Product X6 Quarter Tablet	Chopping	4	8	25	6
Product X6 Quarter Tablet	Grinding	4	9	10	3
Product X6 Quarter Tablet	Heating for 20 minutes at 350 F	4	1	90	28
Product X6 Quarter Tablet	Chopping and heating for 10 minutes at 350 F	4	4	90	53
Product X6 Quarter Tablet	Grinding and heating for 10 minutes at 350 F	4	3	90	55

Syringeability and extractability testing showed that the average % API recovered from the chopped and the chopped heated samples of Product X1 tablets are approximately one-fold higher than the % API recovered from Product X7 samples as shown in table 4.35. The ease of extraction of the API from Product X1 tablets compared to Product X7 tablets might be attributed to formulation and manufacturing differences that are shown in table 4.37 and table 4.39, respectively.

Table 4.34 Results of syringeability and extractability testing of Product X5 ER 50 mg capsules.

Sample	**Treatment**	**DI water (ml)**	**Syringeability (1-10)**	**% Solution Recovery**	**% API Recovery**
Product X5 Quarter Capsule	_	4	8	20	2
Product X5 Quarter Capsule	Crushing	4	8	20	3
Product X5 Quarter Capsule	Grinding	4	8	20	9
Product X5 Quarter Capsule	Heating for 5 minutes at 350 F	4	3	95	23
Product X5 Quarter Capsule	Crushing and heating for 5 minutes at 350 F	4	6	60	65
Product X5 Quarter Capsule	Grinding and heating for 5 minutes at 350 F	4	5	60	70

Table 4.35 Results of syringeability and extractability testing of Product X2 ER 20 mg tablets.

Sample	Treatment	DI water (ml)	Syringeability (1-10)	% Solution Recovery	% API Recovery
Product X2 Half Tablet	_	4	4	65	12
Product X2 Half Tablet	Chopping	4	8	37.5	8
Product X2 Half Tablet	Grinding	4	7	50	32
Product X2 Half Tablet	Heating for 20 minutes at 350 F	4	1	95	25
Product X2 Half Tablet	Chopping and heating for 10 minutes at 350 F	4	5	60	19
Product X2 Half Tablet	Grinding and heating for 10 minutes at 350 F	4	2	95	79

Table 4.36 Results of syringeability and extractability testing of Product X4 IR 7.5 mg tablets.

Sample	Treatment	DI water (ml)	Syringeability (1-10)	% Solution Recovery	% API Recovery
Product X4 Quarter Tablet	_	4 ml	8	30	12
Product X4 Quarter Tablet	Chopping	4 ml	9	20	9
Product X4 Quarter Tablet	Grinding	4 ml	9	20	8
Product X4 Quarter Tablet	Heating for 20 minutes at 350 F	4 ml	1	95	43
Product X4 Quarter Tablet	Chopping and heating for 10 minutes at 350 F	4 ml	1	87.5	48
Product X4 Quarter Tablet	Grinding and heating for 10 minutes at 350 F	4 ml	1	87.5	30

High molecular weight poly Polyethylene oxide presents in an amount ranging from about 35 -50 wt % of the Product X7 extended release portion, while it presents in an amount ranging from 50-99.99 wt % in Product X1 ER tablets (United States Patent No. US8372432B2, 2013; United States Patent No. US6488963B1, 2002). The amount of the high grade PEO should be enough to form a polymeric matrix that retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles. Furthermore, it depends on the desired drug release rate, the polymer molecular weight, and the formulation composition. The choice of the antioxidant was believed to has an impact on the stabilization of the polymer. Antioxidants, pH-adjusting agents, and chelating agents provide chemical protection. Any oxidative species contained in the environment may react with the

chemically protective excipients before they can reach the polymer and the API (United States Patent No. US8372432B2, 2013).

Table 4.37 Extractability results of Product X7 XR 7.5 mg/325 mg and Product X1 ER 80 mg tablets.

Sample	Treatment	Number of Tests	Water Volume (ml)	Average volume recovery (ml)	SD Volume Recovery (ml)	Average % API Extracted	SD API Extracted
Product X1 Quarter Tablet	Chopping and heating for 10 min. at 350 F	3	4	4	0	125.3	0.6
Product X1 quarter Tablet	Chopping, heating for 10 min. at 350 F, hot water extraction	3	4	4	0	124	5.3
Product X7 Quarter Tablet	Chopping and heating for 10 min. at 350 F	3	4	3.6	0	45.7	4.2
Product X7 Quarter Tablet	Chopping, heating for 10 min. at 350 F, hot water extraction	3	4	2.7	0.31	40.3	10.4

An enhanced ADF of Product X1 was investigated by Kashiv Pharma LLC. The new formulation contains a complexing agent (e.g., colloidal silicon dioxide or colloidal silica Syloid 224FP), a plasticizer (e.g., Triethyl citrate), another type of antioxidants (Vitamin E), and a mixture of low and high MWt PEO. It was claimed that complexing agents form a complex with the API by trapping it into its pores and prevent release upon tampering and plasticizers confer higher crush resistance and cause tissue irritation. The test tablets were manufactured by the combination of HME and compression/curing methods. The first formulation component contains API, antioxidant (Vitamin E), and PEO and was subjected to HME followed by milling. The first component of the test tablets has a PEO with an average MWt of less than 1M, and the

second component has an average MWt of at least 1M. The second component contains only PEO and antioxidant ((Vitamin E) and was not subjected to HME; however, it was subjected to compression and curing to avoid polymer degradation. The curing temp was at least as high as the MP of the PEO of the least MW (65-100 deg C) for 11-24h.

Syringeability and extractability results of Product X1 RLD and test product showed that without heat pretreatment, the amount of oxycodone recovered from the test tablets was higher than the amount recovered from Product X1 RLD. However, after heat pretreatment, the amount extracted from Product X1 RLD was significantly higher than the test tablets, as shown in figure 4.21(Siddhartha. B et al., 2015).

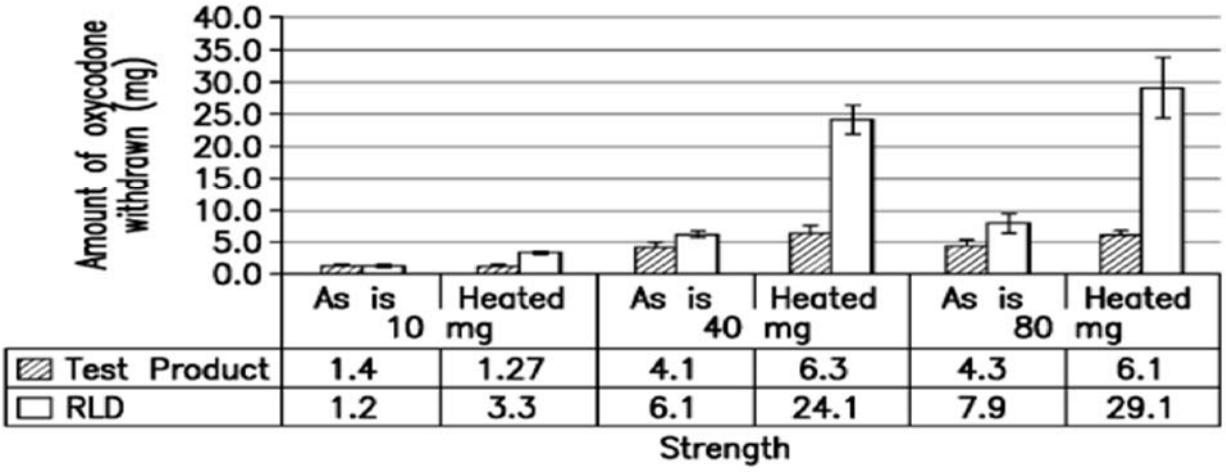


Figure 4.20 Syringeability results of Product X1 RLD and test product (Siddhartha. B et al., 2015).

Table 4.38 Formulation differences between Product X1 and Product X7.

Drug Product	**Additive**	**Function**
Product X7	The citric acid anhydrous powder	Antioxidant and a stabilizer
	Microcrystalline cellulose	Dispersant, semisynthetic gum, viscosity-increasing agent (United States Patent No. US8075872B2, 2011)
	Croscarmellose sodium	water swellable polymer
	Polyvinyl alcohol	
	Colloidal silicon dioxide	
	Talc	Lubricant
	Edentate disodium	A chelating agent, tend to form complexes with a trace amount of heavy metal ions inactivating their catalytic activity in the oxidation of medicaments
	Pregelatinized starch	Disintegrant and binder
Product X1	Butylated hydroxytoluene (BHT)	antioxidant
	Hypromellose (HPMC)	facilitate the manufacturing process of PEO
	Yellow iron oxide	

4.4 Smoking simulation apparatus and Oxycodone model compounds

The experimental setup that was used for the smoking of PEO-based Ibuprofen 40 mg tablets and the PEO-based extruded PMZ HCL 80 mg tablets was equipped with a vacuum and a nitrogen cylinder to create a flow of the vaporized Active Ingredient APIs that condensate on the glass wall of the vacuum adaptor and the vapor trap that contains 10% concentrated Hydrochloric acid HCl diluted with DI water that was also used to rinse both Oxycodone smoking and vapor receiving flasks. Smoking conditions, % API recovered in vapor, and the %

overall recovery are shown in table 4.40 and 4.41 for Ibuprophen 40 mg tablets and PMZ HCL tablets, respectively. The data showed that neither Ibuprophen nor PMZ HCL could be used as model drugs for Oxycodone due to the lack of volatility of both APIs as represented by the 0.0 % API recovered in vapor from the PEO-based Ibuprophen 40 mg and the PEO-based PMZ HCL 80 mg tablets.

Table 4.39 Manufacturing differences between Product X1 and Product X7

Product X7	**Product X1**
1. The CR layer was prepared using a high-shear wet granulator to produce a higher density and lower porosity granules, granulation fluids in the presence of pregelatinized starch, citric acid, microcrystalline cellulose, and EDTA disodium salt flowed by dehydration and drying. 2. Oxycodone HCl-protected granules were granulated by mixing of Oxycodone HCl, antioxidants, pH-adjusting agent, and a chelating agent in a manner such that the amount of oxycodone HCl exposed on the surface of the granule was substantially reduced 3. The granulated mixture was blended with high grade PEO, which represent the exterior regions of the granules in the sustained release layer. The high density and low porosity of the exterior regions resist the penetration by degradative compounds from outside the granule and protect the granules from degradation (United States Patent No. US8980319B2, 2015).	1. It was prepared by melt-extrusion or melt-granulation techniques. 2. Melt Extrusion process includes blending, heating, extruding, cooling the extrudate strands, cutting into multi-particulates, dividing into unit doses. 3. High processing temperature, pressure, and/or torque are required (United States Patent No. US9522919B2, 2016).

Table 4.40 % API recovery from the smoking simulation of PEO-based Ibuprofen 40 mg tablets.

Sample Info.	**Treatment**	**Smoking Time (min)**	**% API recovered in vapor**
Ibuprofen 40 mg 1/4 tablet	–	30	0.0
Ibuprofen 40 mg 1/4 tablet	chopping	37	0.0
Ibuprofen 40 mg 1/4 tablet	Grinding	30	0.0
Ibuprofen 40 mg 1/4 tablet	Chopping	30	0.0
Ibuprofen 40 mg 1/4 tablet	_	15	0.0
Pure Ibuprofen	–	16	0.0

Table 4.41 % API recovery from the smoking simulation of PEO-based extruded PMZ HCl 80 mg tablets.

Sample Info.	Treatment	Smoking Time (min)	Temperature (deg. C)	% API recovered in vapor
Extruded PMZ Hcl (40 mg) & 7M, Dow PEO 1/4 tablet	Chopping	30	240°	0.0
Extruded, PMZ Hcl (40 mg) & 7M, Dow PEO 1/4 tablet	Chopping	45	240°	0.0
Extruded PMZ Hcl (40 mg) & 7M, Dow PEO 1/4 tablet	Grinding	30	240°	0.0
Extruded PMZ Hcl (40 mg) & 7M, Dow PEO 1/4 tablet	_	15	240°	0.0
Pure PMZ Hcl	_	15	240°	0.0

Product X7 tablets were smoked as quarter un-manipulated samples and quarter samples manipulated into chopped pieces and ground powder, as shown in table 4.42. The API was not detected in the vapor receiving flask as represented by the 0.0% API recovered in vapor. Product X1 tablets were smoked as quarter un-manipulated samples and quarter samples manipulated into chopped pieces and ground powder, as shown in table 4.43. The samples did not melt during the smoking time but instead, turn into black and burned material lump that was soaked in 10 % concentrated HCl acid solution to be dissolved and quantified by HPLC. Smoking Product X1 samples for one hour at 203 deg C resulted in the decomposition of the API rather than volatilization in the vapor receiving flask. The % API recovered in the vapor and the

overall % API recovery from the quarter tablet, quarter tablet chopped, and quarter tablet ground of Product X1 smoked for one hour was 17.4%, 19.9%, and 6.2 % respectively, while 0.0% of the API was recovered in the smoking flask. The data showed that Oxycodone HCL can be smoked from Product X1 tablets not from Product X7 due to manufacturing and/or formulation differences between both products. On the other hand, the maximum % API recovery was 23.8% and was obtained from Product X1 quarter tablet chopped and smoked for 45 min at 203 deg C.

Table 4.42 % API recovery from the smoking simulation of Product X7 tablets.

Sample Info.	**Treatment**	**Smoking Time (min)**	**% API recovered in vapor**
Product X7 (APAP; oxycodone Hcl, 325mg;7.5mg) 1/4 tablet	–	30	0.0
Product X7 (APAP; oxycodone Hcl, 325mg;7.5mg) 1/4 tablet	–	45	0.0
Product X7 (APAP; oxycodone Hcl, 325mg;7.5mg) 1/4 tablet	Chopping	30	0.0
Product X7 (APAP; oxycodone Hcl, 325mg;7.5mg) 1/4 tablet	Chopping	45	0.0
Product X7 (APAP; oxycodone Hcl, 325mg;7.5mg) 1/4 tablet	Grinding	30	0.0
Product X7 (APAP; oxycodone Hcl, 325mg;7.5mg) 1/4 tablet	Grinding	45	0.0

Table 4.43 % API recovery from the smoking simulation of Product X1 tablets.

Sample Information	Average temp. deg C	Smoking Time (min.)	% API Recovered in vapor	Overall % API recovery
Product X1 1/4 tablet	203.3	30	14.0	30.4
Product X1 1/4 Grounded	203.3	30	15.0	15.0
Product X1 1/4 tablet	203.3	45	15.6	26.8
Product X1 1/4 Chopped	203.3	45	23.8	29.8
Product X1 1/4 Grounded	203.3	45	18.3	22.8
Product X1 1/4	203.3	60	17.4	17.4
Product X1 1/4 chopped	203.3	60	19.9	19.9
Product X1 1/4 Grounded	203.3	60	6.2	6.2

The smoking simulation apparatus was used to smoke pure Oxycodone HCL and Oxycodone free base APIs. The smoking conditions and results are shown in tables 4.41. The % API recovered form Oxycodone HCl was significantly lower than the % API recovered from Oxycodone free base. The average overall % recovery from Oxycodone free base was 40.6% while it was 16.2 % for Oxycodone HCl. The data showed that it was easier to smoke Oxycodone free base compared to its HCl salt form. Moreover, the standard deviation for both % API recovered in vapor and the overall % recovery from Oxycodone free base was 13.4 and 30.5 respectively, which indicated that the used smoking simulation apparatus was not producing reproducible results as sown in table 4.44.

Table 4.44 % API recovery from Oxycodone free base and Oxycodone HCl.

Sample Information	# of tests	Smoking Time (min)	Temperature Range	Av %API recovered in vapor	SD	Av Overall % Recovery	SD
Oxycodone free base	13	8-15	203.3	19.8	13.4	40.6	30.5
Oxycodone HCl	3	15	203.3	7.4	3.9	16.2	10.7

Kugelrohr distillation apparatus was used for the smoking of pure Acetanilide. The smoking conditions and results are shown in table 4.45. The temperature used for smoking Acetanilide using a Kugelrohr distillation apparatus was ranging from 175 to 250 deg C, and the smoking time was ranging from 20-30 min. An experimental setup contained a propane torch, vapor receiving flask and an ice bath was used to smoke pure Oxycodone free base and pure Acetanilide APIs. The % API recovered in vapor from Oxycodone free base increased from 8.1% to 33.7% after substituting the oven of the Kugelrohr distillation apparatus with the propane torch, however, the % overall recovery dropped from 94.8% to 56.6% as shown in table 4.46. The data showed that using the propane torch was accompanied with very high variability in the results and lack of reproducibility as the standard deviation for the overall % recovery from Oxycodone free base was 29.0. Furthermore, the very low 37% of the overall % recovery from Acetanilide compared to 94.8% of the overall % recovery from Oxycodone showed that the former was not a perfect model drug for the later API.

Table 4.45 Smoking simulation conditions and the % API recovered in vapor after smoking of pure Acetanilide and pure Oxycodone free base.

Sample Info.	# of tests	Apparatus used	% API Recovered in Vapor	SD	Av Overall % Recovery	SD
Pure Acetanilide	3	Kugelrohr distillation apparatus	19.1	10.2	37.0	11.8
Oxycodone free base	1	Kugelrohr distillation apparatus	8.1	_	94.8	_
Oxycodone free base	2	Propane torch, vapor receiving flask, ice bath	33.7	12.2	56.6	29.0

Pure Caffeine was smoked using two different experimental sittings; the Kugelrohr distillation apparatus and the propane torch, as shown in table 4.46. Kugelrohr distillation apparatus was used for 30 min at 250 deg C. The % API recovered in vapor from Caffeine smoked using Kugelrohr distillation apparatus was 5.4 % compared to 32.1 % using the propane torch. The data showed that using Kugelrohr apparatus was not suitable for smoking caffeine due to the very low % API recovered in vapor. Furthermore, data indicated that Caffeine can be used as a model drug for Oxycodone in smoking simulation experiments due to the high overall % recovery of 85.8 %.

Table 4.46 Smoking simulation conditions and the % API recovered in vapor after smoking of pure Caffeine.

Sample Info.	# of tests	Apparatus used	% API Recovered in Vapor	SD	Av Overall % Recovery	SD
Pure Caffeine	3	Propane torch, vapor receiving flask, ice bath apparatus	32.1	7.2	85.8	9.9
Pure Caffeine	1	Kugelrohr distillation apparatus	5.4	-	43.7	-

A Kugelrohr distillation apparatus equipped with three vapor receiving flasks and an ice bath was used for the smoking of pure L-Nicotine and Nicotine Ditartrate Dihydrate. The smoking conditions and % API recovery are shown in table 4.47. A large amount of the salt form of Nicotine was completely decomposed while smoking and 0.0% was recovered in the vapor receiving flask. Data showed that the % API recovered in the vapor and the overall recovery from L-Nicotine increased as the smoking time increased. The % API recovered in vapor from L-Nicotine was 24%, 53%, and 99% for the samples smoked for 3.3 min, 4.1 min, and > 10 min respectively. Moreover, the overall % recovery was 77%, 73%, and 99% for L-Nicotine smoked for 3.3 min, 4.1 min, and > 10 min respectively. The data showed that L-Nicotine can be used as a model compound for Oxycodone in smoking simulation experiments.

Table 4.47 Smoking conditions and % API recovered from the smoking simulation of L-Nicotine.

Sample	Smoking time (min)	Temperature deg C	% Recovery in vapor	% residue in smoking flask	Overall Recovery
Nicotine Base	4.1	250	53	21	73
Nicotine Base	3.3	250	24	53	77
Nicotine Base	>10	250	99	0	99

4.5 Societal Impacts of the Opioid Crisis in the state of Indiana

The number of opioid overdose deaths is increasing steadily since 1999 in the state of Indiana. Example of opioid pain relievers includes but are not limited to Oxycodone, Hydrocodone, Methadone, fentanyl/fentanyl analogs (prescription and illicit), and tramadol. Total drug overdoses include opioids, heroin, unspecified narcotics, cocaine, benzodiazepines, psychostimulants, and unspecified drugs. The number of deaths related to opioid pain relievers was 25 cases in 1999, while it was 933 in 2017 as shown in figure 4.21. The number of deaths related to opioid pain relievers represent 79% and 50% of the number of deaths related to all opioid and the number of deaths related to total drug overdoses in 2017 respectively.

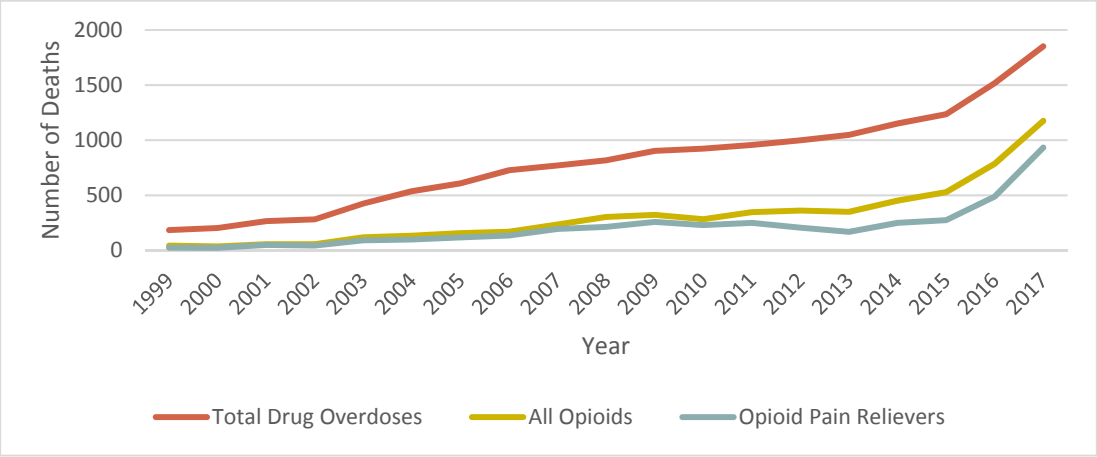


Figure 4.21 Drug overdose deaths in the state of Indiana.

The number of male deaths related to opioid pain relievers was 153 in 2014, while it was 610 cases in 2017. It increased by 399 folds, as shown in figure 4.22. The number of female deaths related to opioid pain relievers was 97 in 2014, while it was 323 in 2017 as shown in figure 4.21. The number of female deaths related to opioid pain relievers represents 53%, 51 %, 54 % and of the number of male deaths related to opioid pain relievers, the number of male deaths related to all opioids, and the number of male deaths related to total drug overdoses in 2017 respectively.

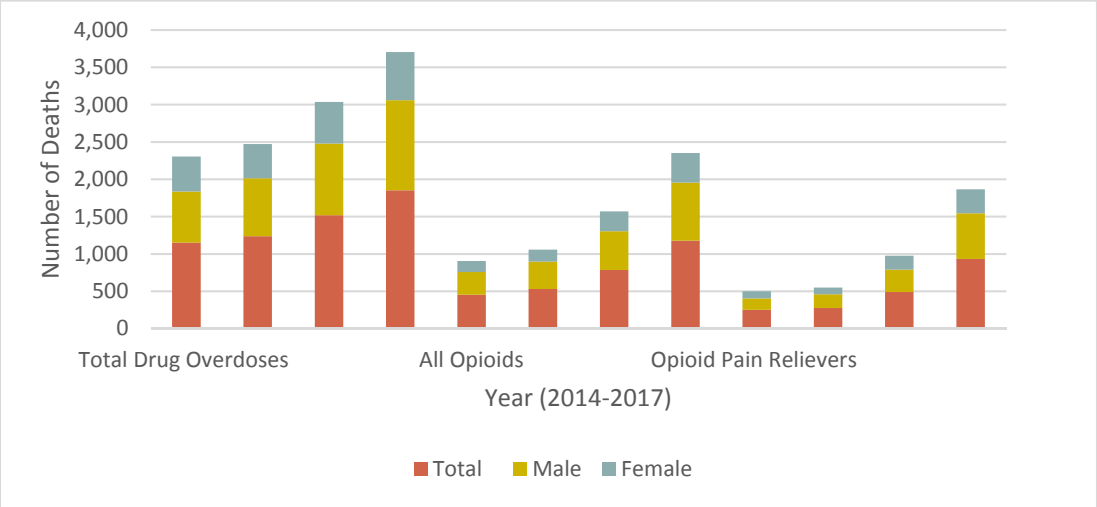


Figure 4.22 Drug overdose deaths by sex in the state of Indiana.

The age group 25-44 years was the most affected by the opioid crisis in the state of Indiana. In 2014, the number of deaths related to opioid pain relievers in the age group 25-44 years was 49% while it was 56% in 2017. The number of deaths related to opioid pain relievers dropped from 24% to 20% and from 11% to 9% for the age groups 45-54 and 15-24 in the years 2014 and 2017 respectively while it was 12 % in 2014 and 2017 for the age group 55-64 years, as shown in figure 4.23.

In 2014, the number of deaths related to all opioids in the age group 25-44 years was 52% while it was 57% in 2017. The number of deaths related to opioid pain relievers dropped from 22% to 19% and from 12% to 9% for the age groups 45-54 and 15-24 in the years 2014 and 2017 respectively while it was 11 % in 2014 and 2017 for the age group 55-64 years, as shown in figure 4.23.

In 2014, the number of deaths related to total drug overdoses in the age group 25-44 years was 45% while it was 53 % in 2017. The number of deaths related to opioid pain relievers dropped from 27% to 22%, 15% to 13 %, and increased from 9 % to 12 % for the age groups 45-54, 55-64, and 15-24 in the years 2014 and 2017 respectively.

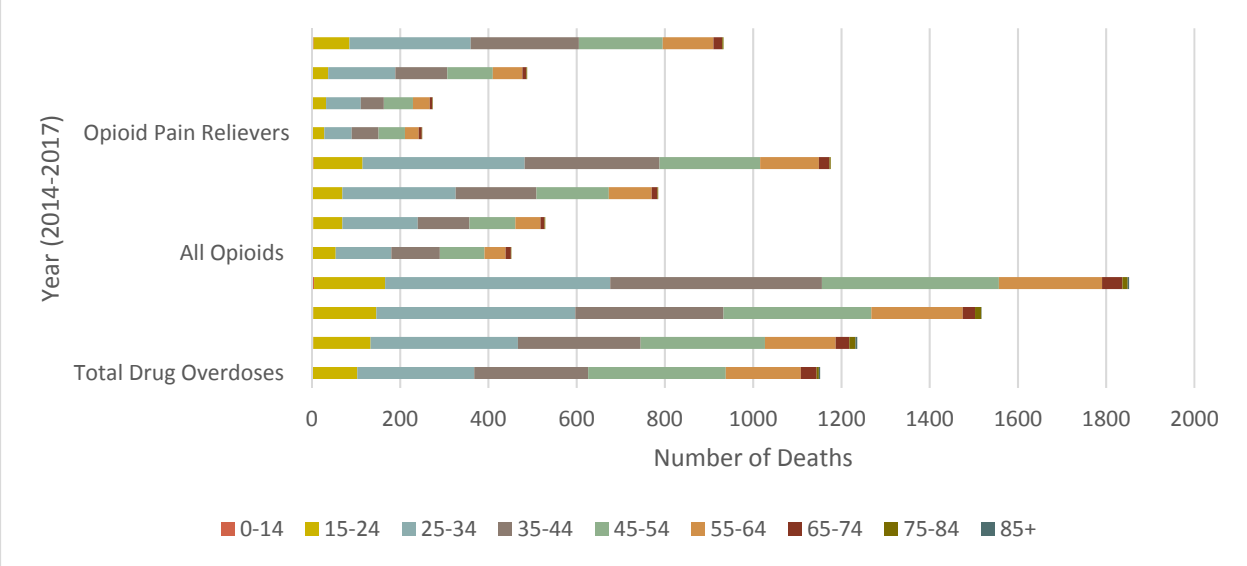


Figure 4.23 Drug overdose deaths by age group in the state of Indiana.

In 2014, 95% of the overdose deaths related to opioid pain relievers was for white people, while the percentage was 5 for black and others from an unknown race. In 2017, the % of deaths from white people dropped to 87%, while it was increased to 13% for black people. The percent

of the overdose deaths related to all opioids dropped from 94% to 88% for white people, while it increased from 6% to 12% for black people and others from the unknown race in 2014 and 2017 respectively. Moreover, the percent of the overdose deaths related to total drug overdoses dropped from 94% to 87% for white people, while it increased from 6% to 13% for black people and others from the unknown race in 2014 and 2017 respectively as shown in figure 4.24.

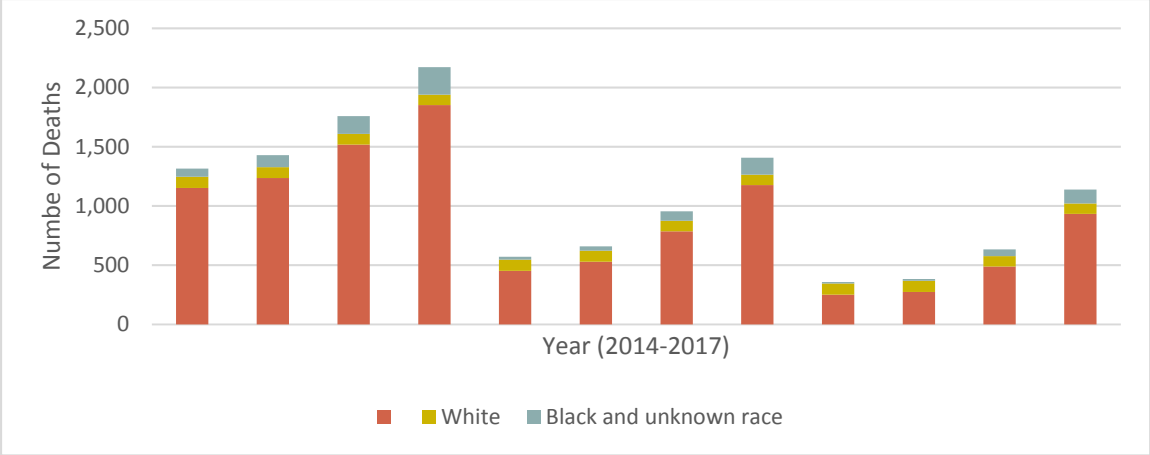


Figure 4.24 Drug overdose deaths per race in the state of Indiana.

4.6 Summary

This chapter has provided an overview of the failure modes of the PEO-based PM HCL tablets, and the investigated FDA approved prescription opioids. It shows the release profiles, release phases, significance testing results, the quantitative impact of the research variables on the release percent, and the syringeability and extractability data of the PEO-based PMZ HCL tablets. This chapter shows the release profiles and the syringeability, and extractability results of the investigated FDA approved prescription opioids. Furthermore, this chapter shows the smoking simulation results of different pure APIs and the societal impacts of the opioid crisis in the state of Indiana.

CHAPTER 5. CONCLUSION AND RECOMMENDATIONS FOR FUTURE STUDIES

Investigations of the dose dumping behavior (time required to reach the 90% release) of the PEO-based prescription opioids showed that physical manipulation via chopping or grinding was much more effective in the destruction of the PEO matrix than thermal manipulation via the application of heat thus promoting the fast release. The time that was required to reach the 90% release of the quarter heated samples of Product X1, Product X7, Product X3, Product X5, and Product X6 was 1.5 (h), 4.75 (h), 2.25 (h), 1(h), and 4.25(h) respectively, while it ranged from 5-30 min for the ground samples of the same products. Moreover, the time that was required to reach the 90% release of the quarter heated samples of the DC PMZ HCL tablets comprising Dow PEO of 4M MW, Dow PEO of 7M MW, Sumitomo PEO of 4M MW, and Sumitomo PEO of 7M MW was 1.3(h), 2.3(h), 1.9(h), and 1.9(h) respectively, while it ranged from 5-6.7 min for the grounded samples of the same products. The time that was required to reach the 90% release of the quarter heated samples of the ME PMZ HCL tablets comprising Dow PEO of 4M MW, Dow PEO of 7M MW, Sumitomo PEO of 4M MW, and Sumitomo PEO of 7M MW was 2.8(h), 2.0(h), 3.3(h), and 1.8(h) respectively, while it ranged from 11.7-20 min for the grounded samples of the same products. Furthermore, the time that was required to reach the 90% release of the quarter heated samples of the molded PMZ HCL tablets comprising Dow PEO of 4M MW, Dow PEO of 7M MW, Sumitomo PEO of 4M MW, and Sumitomo PEO of 7M MW was 1.7(h), 2.6(h), 1.6 (h), 1.9(h) respectively, while it ranged from 6-6.7 min for the quarter tablet grounded samples of the same products. The data showed that there are clear and comparable

failure modes of the prescription opioids and the investigated PEO-based PMZ HCl tablets. Under certain conditions, all studied tablets dose dump in a very short time.

ANN analysis showed that the level of importance of the investigated factors in the dose dumping behavior of the PEO-based PMZ HCl tablets is 25.50%, 22.90%, 21.30%, 16.90%, and 13.40% for the physical manipulation, manufacturing process, thermal manipulation, supplier, and polymer grade respectively. The results showed the highest effect of the physical manipulation and the lowest impact of the polymer grade in the destruction of the PEO matrix and the promotion of the fast release (based on the values for the variable of interest (release percentage) which were relatively compatible with the results obtained in the significance analysis.

The developed regression models showed that the destruction of the polymer matrix that causes the API release in the standard dissolution medium followed multi patterns. The release profile of each drug product consisted of various phases that can be used to predict the dissolution behavior of the PEO-based PMZ HCL matrix formulations.

Syringeability and extractability data showed that heating was much more effective in the extraction of APIs than chopping or grinding thus promoting the ability to draw a solution containing the API into a syringe for injection relatively easy and facilitate higher % API recovery. The % API recovered from the quarter tablet grounded and heated samples of Product X3 ER 100 mg tablets, Product X1 ER 80 mg tablets, Product X7 XR 7.5 mg/325 mg tablets, Product X6 ER 60 mg tablets, and Product X5 ER 50 mg capsules ranged from 25-79%, while it ranged from 3-32% for the quarter tablet ground unheated samples of the same products. The % API recovered from the quarter tablet ground heated samples of the molded PMZ HCL tablets comprising Dow PEO of 4M MW, Dow PEO of 7M MW, Sumitomo PEO of 4M MW, and

Sumitomo PEO of 7M MW ranged from 72.8%-95.4%, while it ranged from 19.8-67.0% for the quarter tablet ground unheated samples of the same products. On the other hand, the syringeability grade for the quarter tablet grounded and heated samples of Product X3 ER 100 mg tablets, Product X1 ER 80 mg tablets, Product X7 XR 7.5 mg/325 mg tablets, Product X6 ER 60 mg tablets, and Product X5 ER 50 mg capsules ranged from 2-7, while it ranged from 7-9 for the quarter tablet ground unheated samples of the same products. The syringeability grade for the quarter tablet grounded and heated samples of molded PMZ HCL tablets comprising Dow PEO of 4M MW, Dow PEO of 7M MW, Sumitomo PEO of 4M MW, and Sumitomo PEO of 7M MW was approximately 1, while it ranged from 3-5 for the quarter tablet grounded unheated samples of the same products.

Incorporation of PEO obtained from Dow chemical or Sumitomo Seika in the production of PEO-based ADFs had no statistically significant impact on the dose dumping behavior (time required to reach the 90% release of the API) in a standard dissolution medium (900ml DI water) at 95% confidence level. Results of the two samples T-Test showed that at 95% confidence level there was no significant difference between the chopped and the chopped heated samples of the PMZ HCl 80 mg molded tablets comprising DOW and Sumitomo PEO of 4M MW. The P-Values were 0.305 and 0.826 for the chopped and chopped heated samples, respectively. On the other hand, the analysis showed that the impact of obtaining the polymer from the both suppliers on the ease with which APIs can be extracted (% API recovery) form PEO-based matrix formulations in a small amount of DI water (4ml) was depending on the manufacturing process. Results of the two samples T-Test showed that the % API recovered from the compressed PMZ HCl 80 mg tablets comprising Dow PEO of 4M MW was significantly higher than the % API recovered from the compressed PMZ HCl 80 mg tablets Comprising Sumitomo PEO with the

same polymer grade. The P-values were 0.006, 0.018, 0.005, 0.001, and 0.011 for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped heated, and quarter tablet grounded heated samples respectively. However, results of the two sample T-Test of the % API recovered from compressed PMZ HCl 80 mg tablets comprising Sumitomo and Dow PEO of 4M MW showed that at 95% confidence level there was no statistically significant difference between the two suppliers for the quarter tablet grounded samples, the P- value was 0.102. Data shows that using Sumitomo Seika PEO significantly lowered the extractability of the API from the DC PEO-based PMZ HCL tablets and was favored in abuse deterrence over using Dow PEO.

Moreover, the analysis showed that the % API recovered from the ME PMZ HCl 80 mg tablets Comprising Dow PEO of 4M MW was significantly higher than the % API recovered from the ME PMZ HCl 80 mg tablets Comprising Sumitomo PEO of the same polymer grade. The P-Values were 0.003, 0.010 for the quarter tablet grounded and the quarter tablet grounded and heated samples, respectively. However, results of the two sample T-Test showed that at 95% confidence level there was no statistically significant difference between the two suppliers for the quarter tablet, quarter tablet heated, quarter tablet chopped, and quarter tablet chopped, heated samples. The P-Values were 0.159, 0.860, 0.915, and 0.524 for the quarter tablet, quarter tablet heated, quarter tablet chopped, and quarter tablet chopped, heated samples respectively. Data showed that using Sumitomo Seika PEO significantly lowered the extractability of the API from the ME PEO-based PMZ HCL tablets and was favored over using Dow PEO.

The analysis showed that the % API recovered from the molded PMZ HCl 80 mg tablets comprising Sumitomo PEO of 4M MW was significantly higher than the % API recovered from tablets comprising Dow PEO with the same polymer grade. The P-Values were 0.037 and 0.024 for the quarter tablet chopped and the quarter tablet grounded samples, respectively. However,

results of the two sample T-Test showed that at 95% confidence level there was no statistically significant difference between the two suppliers for the quarter tablet, quarter tablet heated, quarter tablet chopped, heated, and the quarter tablet grounded heated samples. The P-Values were 0.939, 0.664, 0.330, and 0.074 for the quarter tablet, quarter tablet heated, quarter tablet chopped, heated, and the quarter tablet grounded heated samples respectively. Data showed that using Dow PEO significantly lowered the extractability of the API from the molded PEO-based PMZ HCL tablets and was favored to deter abuse over using Sumitomo Seika PEO.

The usage of PEO with a short or a long chain in the production of PEO-based matrix formulations had no statistically significant impact on the dose dumping behavior and the % API recovery during extraction attempts. Results of the two samples T-Test showed that at 95% confidence level, there was no significant difference between the chopped and the chopped heated samples of the PMZ HCl 80 mg molded tablets comprising Sumitomo PEO of the two polymer grades, the P-Values were 0.595 and 1.000 for the chopped and the chopped heated samples respectively. Moreover, analysis of the extractability data and the results of the two sample T-Test of the % API recovered from Molded PMZ HCl 80 mg tablets comprising Sumitomo PEO of 4M and 7M MW showed no statistically significant difference between the two polymer grades for all sample forms. The P-Values were 0.606, 0.138, 0.202, 0.195, 0.881, and 0.943 for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped and heated, quarter tablet grounded, and quarter tablet grounded and heated respectively.

The production of PEO-based ADFs via molding had no statistically significant impact on the dose dumping behavior (time required to reach the 90% release of the API) of PEO-based matrix formulations in a standard dissolution medium (900ml DI water) compared to the DC

method. Results of the two samples T-Test showed that at 95% confidence level there was no significant difference between the chopped and the chopped heated samples of the PMZ HCl 80 mg molded and compressed tablets comprising Sumitomo PEO of 4M MW, the P-Values were 0.059 and 0.163 for the chopped and chopped heated samples respectively. However, DC significantly lowered the % API that was recovered from PEO-based matrix formulations and rendered extractability attempts relatively hard compared to the molding technique. Results of the two samples T-Test showed that at 95% confidence level there was a statistically significant difference between the intact and manipulated samples of the molded and DC tablets comprising Sumitomo PEO of 4MMW. The P-values were 0.004, 0.05, 0.013, 0.007, 0.007, 0.004 for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped and heated, and quarter tablet grounded and heated samples respectively.

On the other hand, producing PEO-based matrix formulations via molding significantly lowered the dose dumping (90% release) of PMZ HCl 80 mg tablets. Results of the two samples T-Test showed that at 95% confidence level there was a significant difference between the chopped samples of the PMZ HCl 80 mg molded and melt extruded tablets comprising Sumitomo PEO of 4M MW, the P-Value was 0.033. The average of the time required for the molded samples to dump 90% of the AI was 1.9 (h), and the SD was 0.5, while the average of the time required for the melt extruded samples to dump 90% of the AI was 1.2 (h), and the Stdev was 0.2. However, the results of the two samples T-Test showed that at 95% confidence level there was no significant difference between the Molded and ME PEO-based PMZ HCL tablets comprising Sumitomo PEO of 4M MW in the form of a quarter tablet, quarter tablet heated, quarter tablet chopped, and the quarter tablet chopped and heated samples. The P-Values were 0.176, 0.381, 0.059, and 0.213 for the quarter tablet, quarter tablet heated, quarter tablet

chopped, and the quarter tablet chopped and heated samples respectively. While, the % API recovered from the quarter tablet grounded and the quarter tablet grounded, and heated samples of the molded product were greater than that was recovered from the same samples of the ME product. The P-Values were 0.008 and 0.005 for the quarter tablet grounded and quarter tablet grounded and heated samples, respectively.

Data showed that the production of the PEO-based matrix formulations via Direct Compression significantly lowered the dose dumping behavior and render APIs relatively harder to be extracted and injected compared to the ME method. The results of the two samples T-Test showed that at 95% confidence level there was a significant difference between the chopped samples of the PMZ HCl 80 mg compressed and melt extruded tablets comprising Sumitomo PEO of 4M MW, the P-Value was 0.000. The average of the time required for the compressed samples to dump 90% of the AI was 2.4(h), and the Stdev was 0.144, while the average of the time required for the melt extruded samples to dump 90% of the AI was 1.2(h), and the Stdev was 0.144. Furthermore, the analysis showed that the % API recovered from the ME samples was significantly greater than the % API recovered from the DC samples. The P-Values were 0.01, 0.022, 0.029, 0.031, and 0.000 for the quarter tablet, quarter tablet heated, quarter tablet chopped, quarter tablet chopped and heated, and quarter tablet grounded and heated samples respectively. However, the analysis showed that at 95% confidence level there was no statistically significant difference between the grounded samples; the P-Value was 0.813.

Heating was found to efficiently impact the dose dumping behavior of the PEO-based matrix tablets. Results of the two samples T-Test showed that at 95% confidence level there was no significant difference between the chopped heated samples of the PMZ HCl 80 mg molded and melt extruded tablets comprising Sumitomo PEO of 4M MW, the P-Value was 0.833.

Heating accelerated the dose dumping (90% release) of the molded and extruded chopped PMZ Hcl samples. Furthermore, results of the two samples T-Test showed that at 95% confidence level there was no significant difference between the chopped heated samples of the PMZ HCl 80 mg compressed and melt extruded tablets comprising Sumitomo PEO of 4M MW, the P-Value was 0.161.

Data showed that the extraction of the API from Product X1 tablets was relatively easy compared to Product X7 tablets, which was attributed to formulation and manufacturing differences between both products. Formulation components that were believed to have an impact on the AD properties of the PEO-based drug products include but are not limited to: the choice of the antioxidant, the use of complexing agents, chelating agents, and plasticizers. On the other hand, manufacturing process variables that were believed to have a critical impact on AD properties of the PEO-based drug products include but are not limited to; processing temperature compared to the melting point of the polymer and time of exposure. Data showed that avoiding harsh manufacturing conditions during the production of PEO-based ADFs was favored to deter abuse avoid the oxidative degradation of the polymer.

Smoking simulation results showed that it was easier to smoke Oxycodone free base compared to its HCl salt form. The % API recovered form Oxycodone HCl was significantly lower than the % API recovered from Oxycodone free base. The average overall % recovery from Oxycodone free base was 40.6% while it was 16.2 % for Oxycodone HCl. Moreover, it was feasible to vaporize and recover Oxycodone HCL from Product X1 tablets not from Product X7 tablets due to manufacturing and/or formulation differences between both products. The maximum % API recovered in vapor from Product X1 tablets was 23.8% and was obtained from

the quarter tablet chopped and smoked for 45 min at 203 deg C using the smoking simulation apparatus.

The data showed that neither Ibuprophen nor PMZ HCL were perfect model drugs for Oxycodone in the smoking simulation testing due to the lack of vaporization and a high degree of the decomposition of both APIs. 0.0 % API was recovered in vapor from the PEO-based Ibuprophen 40 mg and the PEO-based PMZ HCL 80 mg tablets. Furthermore, the very low 37% of the overall % recovery from the pure Acetanilide compared to 94.8% of the overall % recovery from Oxycodone free base indicated that former was not a perfect model drug for the later API.

Data recommended that Caffeine and L-Nicotine can be used as a model drug for Oxycodone in smoking simulation experiments due to the high overall % recovery of both APIs. Furthermore, data showed that using a Kugelrohr apparatus was not suitable for smoking caffeine due to the very low % API recovered in vapor. However, the apparatus was suitable for the smoking simulation of L-Nicotine because the % API recovered in the vapor, and the overall recovery from L-Nicotine predictably increased as the smoking time increase.

To summarize the research conclusion; failure modes of the prescription opioids included physical and thermal manipulations. Size reduction via chopping and grinding caused dose dumping of the APIs from prescription opioids in a shorter time compared to the application of heat. However, heating was much more effective in the extraction of APIs than chopping or grinding thus promoting the ability to draw a solution containing the API into a syringe for injection relatively easy and facilitate higher % API recovery. Similarly, failure modes of PEO-based PMZ HCl tablets included physical manipulations, production via molding and ME, and thermal manipulations. Dose dumping of PEO-based PMZ HCl tablets was highly impacted by

applying physical manipulation compared to the usage of different polymer grade or obtained from different suppliers.

Moreover, producing PEO-based ADFs via DC had a statistically significant impact on the dose dumping behavior (time required to reach the 90% release of the API) in a standard dissolution medium (900ml DI water). Data showed that the production of the PEO-based ADFs via DC was more effective to deter abuse compared the usage of the melt extrusion method and molding techniques. It was clear that DC kept the integrity of the polymer, allowed for slow and controlled release fashion of the API, and rendered the extraction process relatively hard compared to the ME and Molding techniques. However, thermal manipulations via the application of heat were found to accelerate the dose dumping behavior (90% release) of the APIs from the compressed, extruded, and molded PEO-based matrix formulations similarly.

Formulation components that might have an impact on the AD properties of the PEO-based drug products include but are not limited to the choice of the antioxidant, the use of complexing agents, chelating agents, and plasticizers. On the other hand, manufacturing process variables that might have a critical impact on AD properties of the PEO-based drug products include but are not limited to; processing temperature compared to the melting point of the polymer and time of exposure

PMZ HCl was as a model drug for Oxycodone in dissolution and extractability studies, while Caffeine and L-Nicotine were used as model drugs in smoking simulation experiments. The combination of the propane torch and Kugelrohr apparatus mimic the real-world scenario for smoking Opioids. However, this experimental setup caused thermal degradation rather than vaporization of some model drugs.

According to the National Center for Health Statistics; a statistically significant increase in drug overdose death rates was reported in 2016 in the state of Indiana among other states. The investigations on the societal impacts of the opioid crisis in the state of Indiana shows that the number of deaths related to opioid pain relievers increased by 3732 folds in 2017 compared to the number of deaths in 2014. In 2017, the number of deaths related to opioid pain relievers represented 79% and 50% of the number of deaths associated with all opioid and the number of deaths related to total drug overdoses, respectively. Moreover, Males were more affected by the opioid crisis than females. In 2017, the number of female deaths related to opioid pain relievers represented 53%, 51 %, and 54 % of the number of male deaths related to opioid pain relievers, the number of male deaths related to all opioids, and the number of male deaths compared to total drug overdoses respectively. On the other hand, the age group of 25-44 years was the most affected by the opioid crisis in the state of Indiana. In 2014, the number of deaths related to opioid pain relievers in the age group 25-44 years was 49% while it was 56% in 2017. Furthermore, white people were more affected by the opioid crisis as 95% of the overdose deaths related to opioid pain relievers was for white people compared to 5 % for black people and others from the unknown race, In 2014. However, in 2017, the % of deaths from white people dropped to 87%, while it was increased to 13% for black people.

Recommendations for future studies include: (1) investigations of the ability of the polymer to prevent sublimation of the identified model compounds from PEO-based matrix tablets is very crucial to assess the ability of the newly developed ADFs to deter abuse via smoking; and (2) conducting smoking simulation experiments for PEO-based matrix products using different model compounds with different chemical structures is crucial to assess the ability of the PEO to prevent sublimation of the APIs.

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