1-1-2021

Abuse deterrent formulation using Hot Melt Extrusion Technology

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“ABUSE DETERRENT FORMULATION USING HOT MELT EXTRUSION TECHNOLOGY”

A thesis

Submitted to the Graduate School at The University of Mississippi

In partial fulfillment of the requirements for the degree of
Master of Science in Pharmaceutical Sciences

By

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August 2021

ABSTRACT

The purpose of the current study was to formulate hot melt extruded (HME) abuse deterrent pellets of acetaminophen(APAP), a model drug with the aid of high molecular weight hydroxypropyl methylcellulose (HPMC 4M) and gelling agents (starch, pectin and carbopol). The formulated HME pellets were assessed for their abuse-deterrence (AD) potential using Category- 1 laboratory in-vitro evaluation standards. The pellets were examined for the particle size reduction (PSR), extraction in small volume, syringeability, thermal manipulation and dissolution for evaluating the resilience of the AD properties. Though, most of the formulation showed complete particle size reduction after grinding, grounded pellets were able to show AD properties. The drug extraction was < 30% in 10 mL of different level of solvents (Level 1- DI water, Level 2- 40% ethanol, Level 3- 100% Ethanol) under static, agitation, and thermal manipulation conditions with an incubation time of 30 min. The grounded pellets formed gel under agitation condition with every level of the solvent. The HPMC 4M/ Low Methoxy pectin formulation showed lowest extraction of drug from grounded pellet using all levels of solvents and using thermal manipulation conditions among all formulations. These studies support the abuse deterrent potential of HPMC 4M and pectin against intravenous abuse.

DEDICATION

I would like to dedicate this thesis to my loving mother (Kalpana Jadhav).

ACKNOWLEDGMENTS

I would sincerely like to thank Dr. Michael A. Repka for letting me join the wonderful research group. I was fortunate to have a supervisor who gave me the freedom to explore my own ideas mingled with his valuable suggestions.

I would like to extend my heartiest thanks to Dr. Suresh Bandari for his constant supervision and guidance. I am grateful to Dr. Eman and Dr. Majumdar for agreeing to be a part of the committee, to evaluate my work and provided me with valuable comments on my research and thesis. I would like to express my gratitude to Dr. Ashpole for her constant guidance, support and care throughout my Master's.

This acknowledgement will be incomplete without acknowledging Ms. Deborah, Ms. Melissa and all other staff at the school of pharmacy.

My sincere thanks to all Ph.D. scholars Ruchi, Priyanka, Sagar, Dinesh, Ahmed for their time to time help. Especially, I would like to thank Arun for being around all the times and helping me out in whichever way possible. It was really great to have a senior and PhD mentor like him.

Finally moving to those without whom the stay in oxford wasn't a very stranger encounter. I would like to thank Ruchi, Sayntan, Pranav, Miguel, Priyanka, Poorva, Satadru, Shambu, Disha and Sushrut.

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LIST OF ABBREVIATIONS

APAP	Acetaminophen
HPMC	Hydroxypropyl methylcellulose
EtOH	Ethanol
DI	Deionized
PSR	Particle Size Reduction
HME	Hot Melt Extrusion
UV/VIS	Ultraviolet/Visible spectroscopic detection
DSC	Differential Scanning Microscopy
RPM	Rotations/revolutions/rate per minute
IV-RT	*in vitro* release testing
API	Active pharmaceutical ingredient

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CHAPTER I: INTRODUCTION

Opioid abuse is an epidemic and is rising at an alarming rate in various regions of the world. The majority of the cases of addiction are evidenced in the US, being the global issue Pharmaceutical industries are trying to combat the threat of drug addiction from opioid formulations. The FDA started different labeling on the formulations and later on the specific guidelines for the development of the Abuse deterrent formulations. The development of Abuse-Deterrent Formulations is the area facing higher challenges and involves technology till now people have tried the different forms of technology-based abused deterrent formulations which are commercialized. The data from the United States (US) Centers for Disease Control and Prevention (CDC) indicate that annual opioid prescribing rates increased from 72.4 to 81.2 prescriptions per 100 persons between 2006 and 2010, were constant between 2010 and 2012, and then decreased by 13.1% to 70.6 per 100 persons from 2012 to 2015. [1] During the same time, the actual dosage of opioids prescribed in the US maxed in 2010 at 782 morphine milligram equivalents (MME) per capita and then declined each year through 2015 to 640 MME per capita. Despite these reductions, the amount of opioids prescribed in 2015 remained more than 3 times higher than the amount prescribed in 1999, when the amount prescribed was 180 MME per capita. The increases in opioids prescribed in the US has resulted in increased prescription opioid-related overdose deaths and diagnoses of opioid-use disorder (addiction) associated with prescription opioids.[2]

The most common form of prescription opioid abuse is ingestion of a larger dose of intact formulation than prescribed.[3] Although, routes of administration that allow for more rapid

delivery of drug to the brain than oral ingestion (e.g. intranasal-snorting and intravenous Injection) result in a faster and more compelling effect and, hence, are related with greater abuse potential.[4]

The epidemic has been a long-time root, and there are no magic bullets that will quickly restore a more balanced use of opioids in clinical practice. During the past decade, the FDA has conducted various initiatives in an effort to enhance the risk-benefit proportion of opioids, including strengthening warnings on the drug label, enlarging patient and prescriber educational campaigns, "upscheduling" hydrocodone so that patients were no longer able to refill a prescription automatically but instead required a new prescription from a prescriber, and issuing guidance for the pharmaceutical industry regarding the development of abuse-deterrent formulations of opioid products.[5] The FDA guidance document depicts three categories of premarket studies advised for the development of a new AD product, namely: Category 1-laboratory-based in vitro manipulation or chemical extraction; Category 2-pharmacokinetic; and Category 3- clinical abuse potential studies.[6] Hot-melt extrusion (HME) has become famous in the manufacture of ADFs. The INTAC® drug delivery platform, formulated by Grünenthal GmbH, uses hot melt extrusion with high molecular weight Poly-Ethelene-Oxide (PEO) to make an abuse deterrent/ tamper-resistant formulation, which is less susceptible to abuse.[7] Higher molecular weight PEOs forms highly viscous, gel like solution because of the properties- hydration and swelling in aqueous solution, which does not allow deter abuse by injection. A significant disadvantage with PEO is its vulnerability to thermal auto oxidative degradation.[8] The degradation cause decrease in polymer molecular weight and hence lower viscosity of the solution. To avoid this we decided to use HPMC 4M which is also a high molecular weight polymer and which is stable at a

higher temperature. [9] As for category 1 laboratory evaluation as suggested by the FDA, extract APAP in alcoholic media. This causes dose dumping and accordingly overriding the abuse-deterrent properties of the formulation.[10] The optimum formulation should not deter its properties even under the impact of the alcohol and other manipulation circumstances. To enhance the properties of the formulation further, other viscosity-enhancing agents were used. Pectin with low methoxy and high methoxy grade was used. [11] Starch and carbopol were other viscosity enhancing agents which were used along with HPMC 4M. The aim of the current study was to evaluate the effect of HPMC 4M and HPMC 4M with different viscosity enhancing agents: pectin, starch, and carbopol on the abuse-deterrent properties of hot melt-extruded pellets. For investigation, category 1 laboratory-based manipulation methods were used.

CHAPTER II: METHODOLOGY

Materials

Chemicals

Affinisol™ HPMC HME 4M, Acetaminophen, GENU® pectin type LM-104 AS-FS (LM pectin), GENU® pectin type D slow set-Z (HM pectin), Starch, Carbopol, HPLC grade Ethanol and Deionized (DI) water were used for analysis.

11 mm Twin screw extruder (ThermoFisher Scientific), (Discovery DSC25, TA Instruments), a UV–Vis spectrophotometer (Genesys 190, Thermo Scientific), bench mixer (Benchmark Scientific), MaxiblendTM V-shell blender (Globe Pharma), coffee blender.

Equipment and auxiliaries

11 mm Twin screw extruder (ThermoFisher Scientific), (Discovery DSC25, TA Instruments), a UV–Vis spectrophotometer (Genesys 190, Thermo Scientific), bench mixer (Benchmark Scientific), MaxiblendTM V-shell blender (Globe Pharma), coffee blender.

Methods

Formulation Composition

Batch of 70g was prepared for each of the formulation. The principal component HPMC 4M were combined with other viscosity enhancing polymers. Formulation 5 used only 20% of carbopol as it was producing high percentage (more than 70%) of torque during the HME process. Using 20% carbopol desired torque percent were achieved.

Table 1. Formulation Composition of pellets prepared using HME technology.

	F1	**F2**	**F3**	**F4**	**F5**
Acetaminophen	20%	20%	20%	20%	20%
HPMC 4M	80%	50%	50%	50%	60%
LM Pectin		30%			
Starch			30%		
HM Pectin				30%	
Carbopol					20%

Hot-melt extrusion process (continuous manufacturing process)

Active pharmaceutical ingredient (APAP) and all other excipient were passed through were sieved through a USP #30 (600 μm) mesh. After that according to formulation composition components were weighed and then mixed in 6’’×9’’ self-sealing polyethene bag thoroughly.

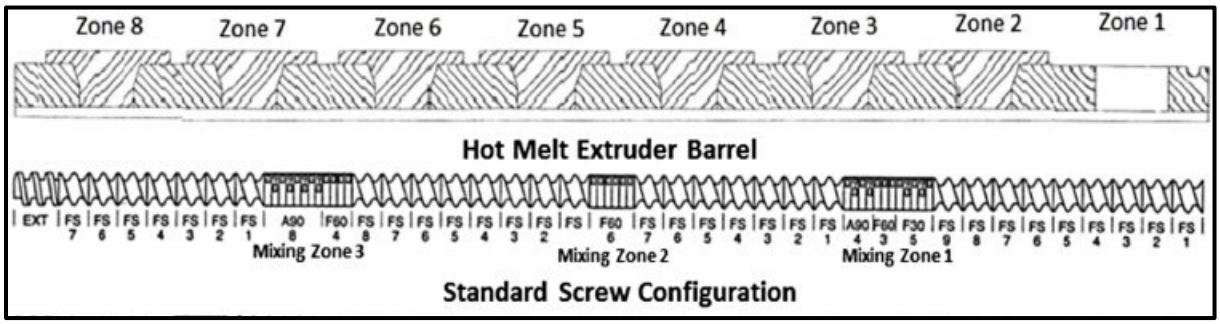

Figure 1. Standard screw design for manufacturing of the abuse deterrent formulation.

The mixture then blended by using a MaxiblendTM V-shell blender for 10 minutes. The rotation speed for the blender was 25 RPM. The homogeneous blend was fed to the rotating twin screw 11mm hot melt extruder. Different temperature and screw speed conditions were used for different formulations. The screw configuration used was a standard screw configuration. It had three mixing zone together with conveying zones. The filaments obtained were allowed to cool down to the room temperature, after that filaments were cut down into 3mm pellets using the pelletizer. Pellets then were stored into self-sealing polyethene bags.

Table 2. Processing parameters maintained for the manufacturing of abuse deterrent formulation by Hot melt extrusion.

Formulation No.	Temperature (degree Celsius)	Torque (%)	Speed (RPM)
F1	160	28-30	50
F2	130	22-24	50
F3	160	20-22	50
F4	130	30-32	50
F5	140	55-58	50

Differential scanning calorimetry (DSC)

Differential scanning calorimetry demonstrates different endothermic and exothermic activities happening in the sample with an elevation in temperature. DSC can predict the Tm (Melting point of crystalline substances), Tg (Glass transition of amorphous polymers), and degradation. 4 to 8 mg of samples were weighed and then sealed in the aluminum pans. After placing the pans in DSC instrument, they were allowed to equilibrate at 25 °C. Then it was heated from 25 °C to 200 °C at a ramp rate of 10 °C/min. Ultra-pure nitrogen as the purge gas was used at a flow rate of 50 mL per min. A vacant aluminum pan was used as a reference.

Particle size reduction

The 3mm pellets were mechanically manipulated using a household coffee grinder. A coffee grinder is a common household used for tampering with prescription opioid medications. A 5g sample of each formulation was ground with the coffee blender for 3min. Samples were passed through the sieve with the USP mesh size #40 (425µm) after 1min, 2min, and 3min of grinding. The evaluation was performed in triplicate. The mass of particles maintained on each sieve was recorded, and the percentage of particles retained on each sieve was calculated.

Drug-Extraction Studies

FDA recommends in-vitro evaluation studies of intact as well as manipulated formulation using different levels of solvents. Different levels of solvents are Level 1, Level 2, and Level 3. Deionized water was used as Level 1 solvent, 40% ethanol as level 2 solvent, and 100% ethanol as level 3 solvent were used. Intact / Manipulated Pellets weighed (500 mg) equivalent to 100 mg Acetaminophen were placed into scintillation vials containing 10 mL of different solvents. The vials were vortexed for 15 seconds and then kept under agitation

(1000 rpm) or static condition for 30 minutes at room temperature (RT). After 30 min, the samples were withdrawn into a vial by using a 10mL syringe. Volume extractable was measured. Samples were centrifuged at 10000 rpm for 30 minutes and carefully diluted further. The samples were analyzed at 243 nm by using a UV spectrophotometer to quantify the extraction of the drug in various solvents.

For the study of drug extraction at elevated temperature, 500 mg pellets from each formulation were transferred into scintillation vials containing 10 mL water, and the vials were placed in an oven (90 °C) for 30 minutes. The extraction of the drug and the volume withdrawn was similar to the process used for static and agitated samples.

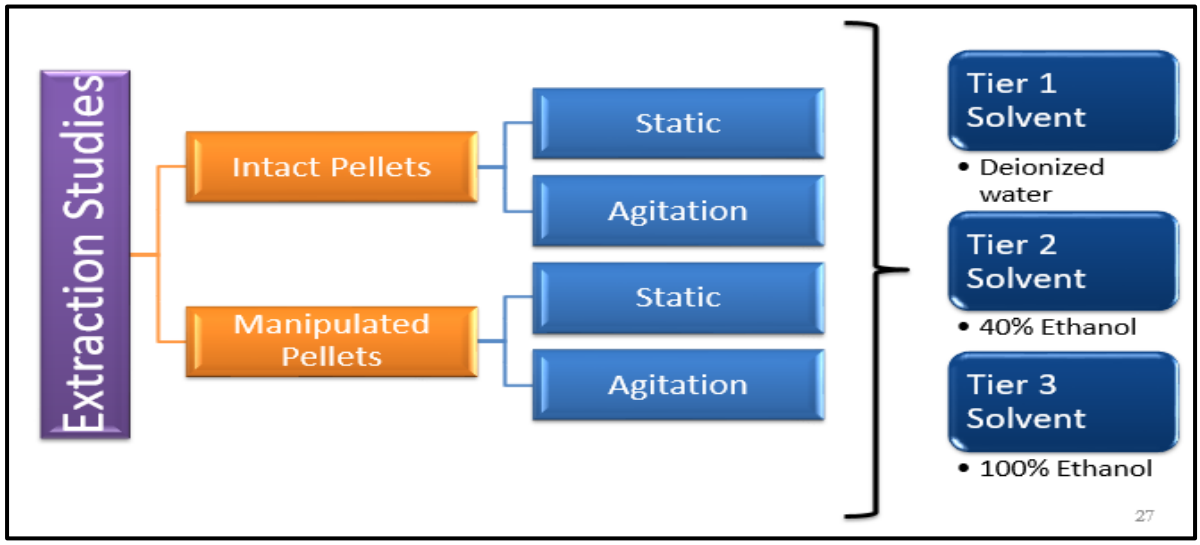

Figure 2. Extraction studies of intact as well as manipulated formulation.

In-Vitro Drug analysis

The in-vitro dissolution behavior of the intact / manipulated pellets was examined by using USP Dissolution Apparatus 1 – Basket (37 °C ± 0.5°C) in 900 ml of Distilled water with the basket rotation speed of 50 rpm. For each formulation, 500 mg of the pellets (equivalent to 100 mg of Acetaminophen) were transferred into the basket and then into the dissolution vessel. Approximately 3 mL of sample was collected at 0.25, 0.5, 0.45, 1, 2, 4, 6, 8 hours and filtered through a 10-µm filter. Samples were centrifuged at 10000 rpm for 30 minutes and carefully diluted further. The drug released was analyzed at 243 nm by using a UV spectrophotometer. All dissolution studies were carried out in triplicate (n = 3).

CHAPTER III: RESULTS AND DISCUSSION

Hot melt extrusion

The extrusion trials were performed using HPMC at 80% w/w and APAP at 20% w/w. Similarly, the polymeric blends of HPMC at 50% w/w (60% w/w for Blend with carbopol) were examined with four viscosity enhancing agents (LM pectin, starch, HM pectin) each at 30% w/w (20% for the carbopol blend) and APAP at 20% w/w at a screw speed of 50 rpm. The drug load was maintained at 20% w/w for all formulations. The process temperature (130 °C- 160°C) was selected on the basis of the glass transition temperature of Affinisol™ HPMC HME 4M. At this temperature, APAP and gelling agents are non-molten and are molecularly dispersed in the HPMC matrix to obtain homogeneous extrudates. The obtained extrudates of HPMC and the blends of HPMC with individual gelling agents were cut into 3 mm pellets and were evaluated for their potential for abuse via the oral, nasal, and IV routes. The formulation composition is presented in table 1.

Thermal analysis by DSC

The DSC thermograms of pure APAP, HPMC, viscosity enhancing agents, and HME pellets are shown in Fig. 3. For HPMC, LM pectin, starch, HM pectin, and carbopol, no thermal events were recorded between 25 °C and 200 °C. A sharp peak at 170°C was observed for APAP which shows the melting point of acetaminophen. A thermogram of HME pellets did not display the melting peak of Acetaminophen, signifying that the drug substance was molecularly dispersed in the matrix of HPMC-viscosity enhancing agents.

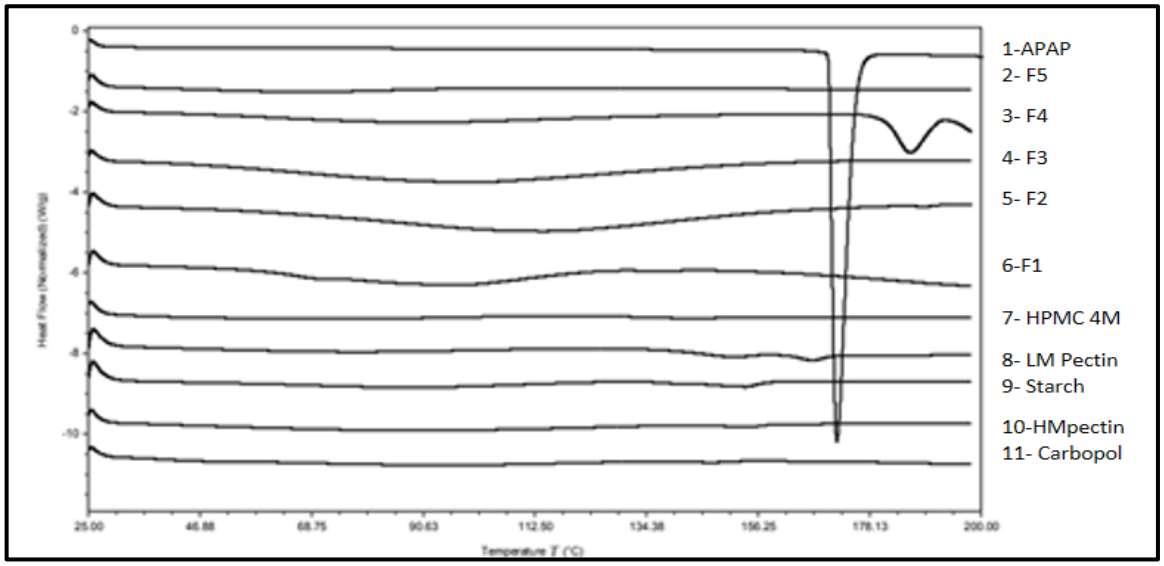

Figure 3. DSC thermograms of formulations, pure excipients and pure drug.

Particle size reduction studies

Manipulation indicates the process in which the integrity of the intact pellets is either altered or destroyed. Particle size reduction of the intact formulation is a usual practice to increase the drug release, to change an extended-release formulation to an immediate release formulation, and also to use the powdered formulation for abusing it via nasal or IV routes. Particle sizes > 425 µm are tough to snort and also give less absorption across the nasal epithelium. For these reasons, the particle sizes of <425 µm were fixed as boundary to evaluate the resistance to nasal abuse. For, F1 and F3 the particle size less than 425 µm were < 58% and <64% respectively after three minutes of grinding. Other formulations (F2, F4, and F5) formed a fine powder having size < 425 µm after 3minutes of grinding in a coffee blender. To ensure the release of the drug from these powdered formulations, release studies were done.

Table 3. Particle size reduction of the formulations using coffee blender.

	Percent of weight of particles having size less than 425 µm		
	1 min of Grinding	**2 min of Grinding**	**3 min of grinding**
F1	27.7	47.8	57.8
F2	90.8	97.4	98.5
F3	27.6	50.4	63.6
F4	82.1	98.6	99.4
F5	93.8	99.4	100.0

Figure 4. F3 after grinding in the coffee Blender for 3 minutes.

Drug-Extraction Studies

After the oral route, the most frequent route of abuse for opioid products is the IV route. To determine the solubility of the formulations and ease with which it can be used for IV abuse, in vitro extraction studies were performed by using a small volume of commonly used injectable solvents recommended by FDA. Commonly available household solvents used for the study were water, 40% ethanol and 100% ethanol. The study performed were both for intact and manipulated formulation at room temperature as well as at elevated temperature of 90 °C. The volume of solvent extractable after 30 minutes of the study from intact pellets were between 8mL to 9.5 mL for both static and agitation condition. The amount of the drug in the extractable volume were calculated. It is mentioned in the fig. 6.

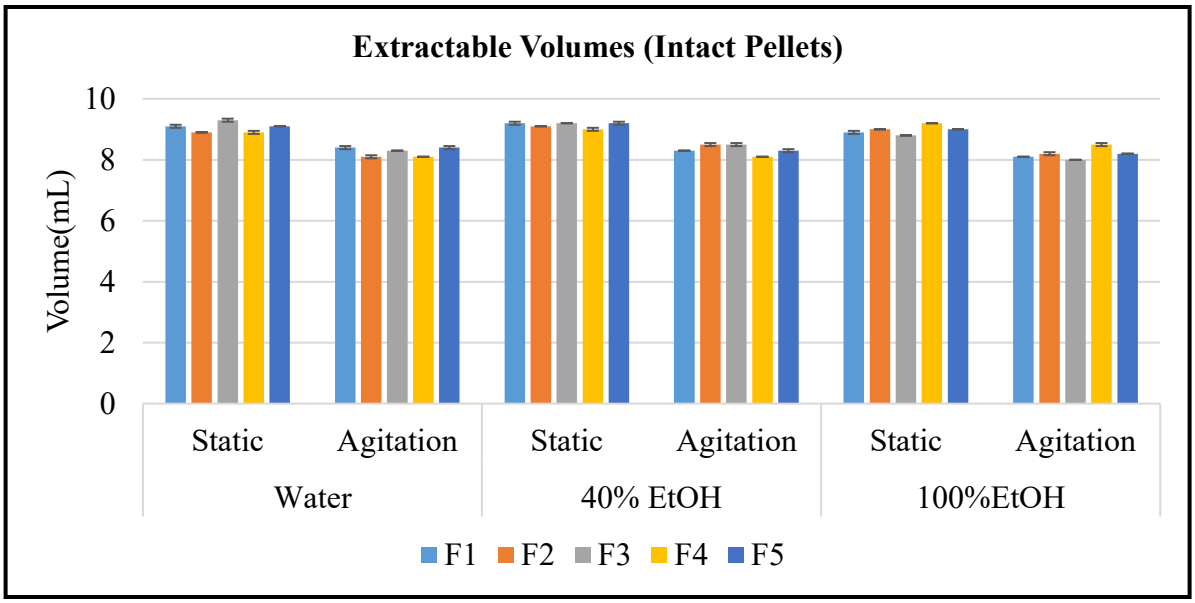

Figure 5.Extractable volume of solvents at static condition for intact pellets.

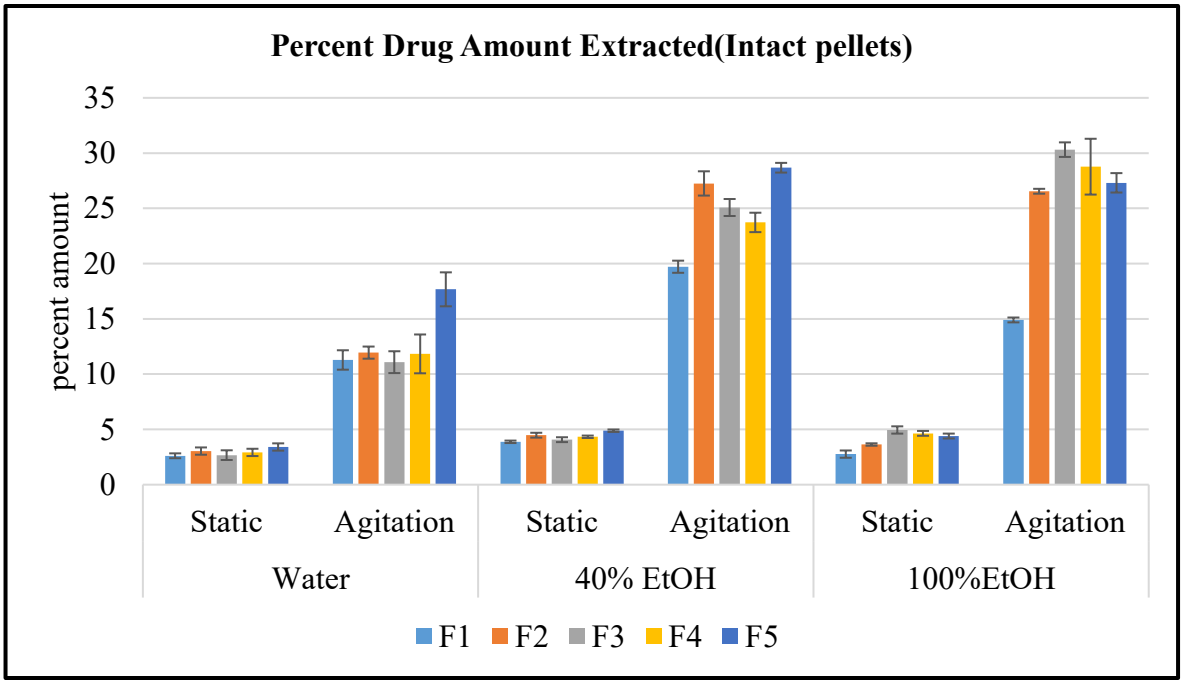

Figure 6.Extracted Percent Amount of API in small volume of different solvents from intact pellets at static and agitation conditions.

The amount of drug extracted from different solvents at static condition were less than 5% for all the solvents and for the agitation conditions it is less than 15% for water as a solvent except for formulation 5 it is more than 15%, less than 30% for 40% ethanol as well as 100% ethanol as a solvent. F1 has consistently shown less than 20% of drug release in all category of solvents.

Results for manipulated pellets are shown in fig. 7 and fig. 8.

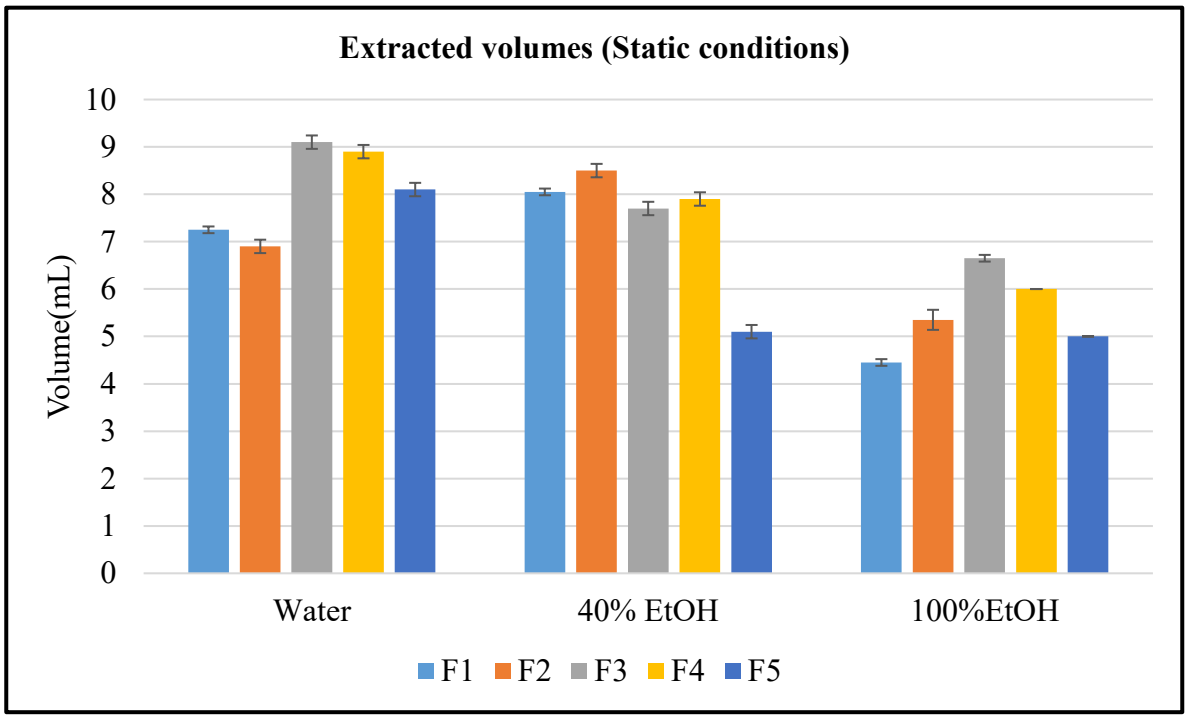

Figure 7. Extractable volume of solvents at static condition for manipulated pellets.

The volume extractable of different solvents is comparatively low for the 100% ethanol. The volume extractable for water and 40% ethanol as a solvent is between 6mL to 9mL, whereas for 100% ethanol as a solvent volume extractable is between 4mL to 7mL. The amount of drug in extractable volumes for manipulated pellets is shown in the fig. 8 for static conditions.

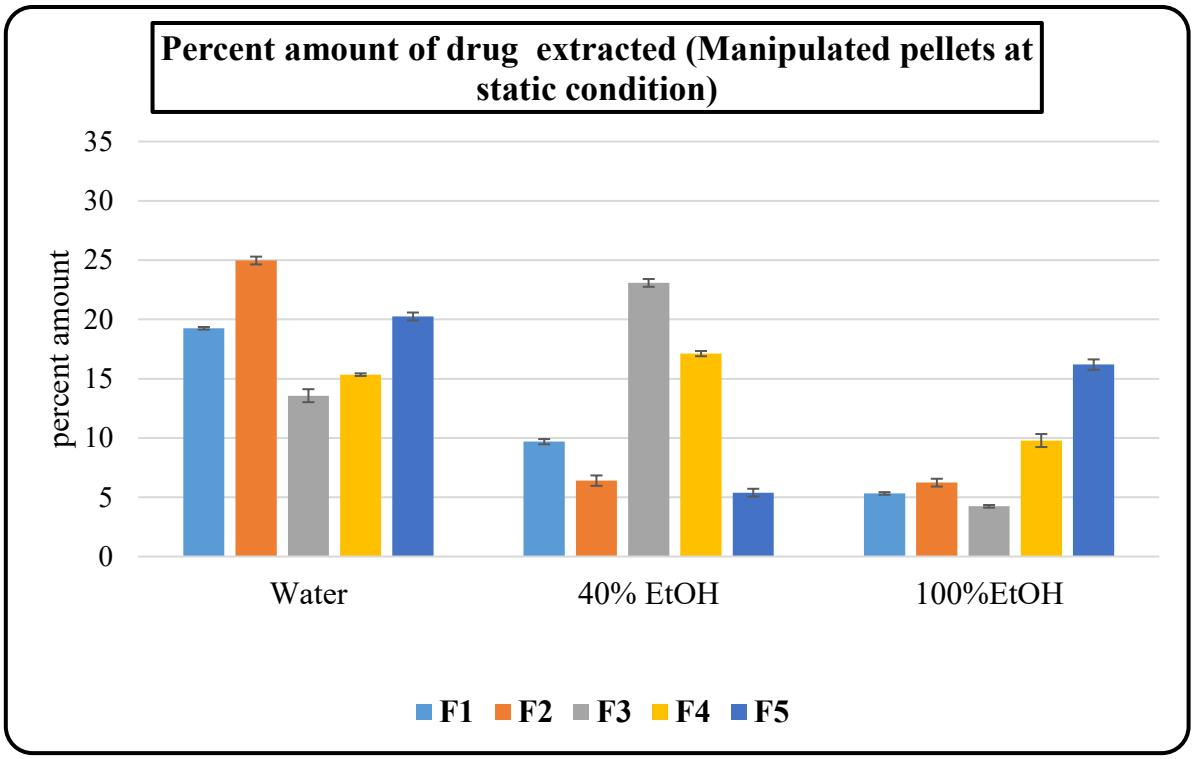

Figure 8. Extracted Percent Amount of API in small volume of different solvents from manipulated pellets at static conditions

The percent amount of drug extracted from manipulated pellets is less than 25% for water as a solvent. For 40% ethanol as solvent F1, F2 and F5 showed really low drug release of less than 10%. F3 and F4 showed drug release of 23% and 17% respectively. Every formulation except F5 showed drug release less than 10% for 100% ethanol as a solvent. F5 showed 16% of drug release. The manipulated pellets formed a viscous gel which was not feasible to collect using a syringe under the agitation conditions.

Figure 9. Manipulated formulations showing viscous gel which was not syringeable.

Drug extraction at elevated temperature was done for only deionized water as a solvent because ethanol can evaporate at elevated temperature. The results for intact and manipulated pellets are mentioned in the fig. 10 and fig. 11 respectively.

	Volume Extractable in mL
F1	8.0
F2	7.8
F3	8.0
F4	7.3
F5	7.7

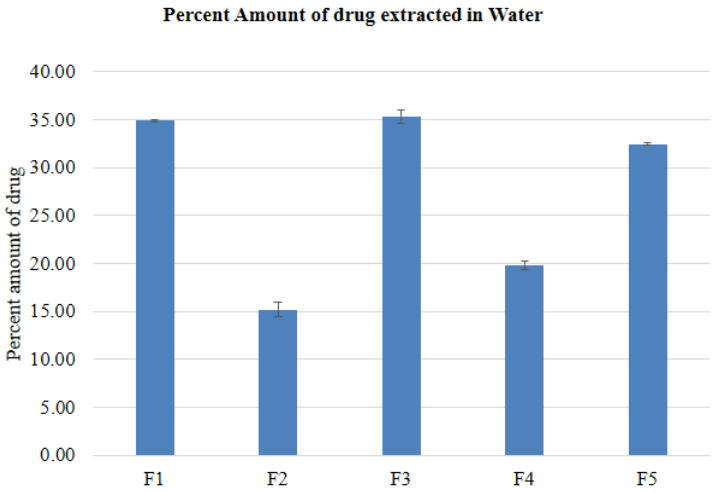

Figure 10. Extractable volume of deionized water and percent amount of drug in deionized water at elevated temperature condition for intact pellets

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F2 and F4 showed lowest drug percent release less than 20% in water at elevated temperature. Whereas other formulation showed drug release more than 30% and less than 35%. The same thing were observed for manipulated formulations extraction study at higher temperature. F2 showed lowest percent drug release of 8.3% followed by F4 showing drug percent release of 14.3%.

	Volume Extractable in mL
F1	7.6
F2	5.25
F3	7.8
F4	5.65
F5	7.8

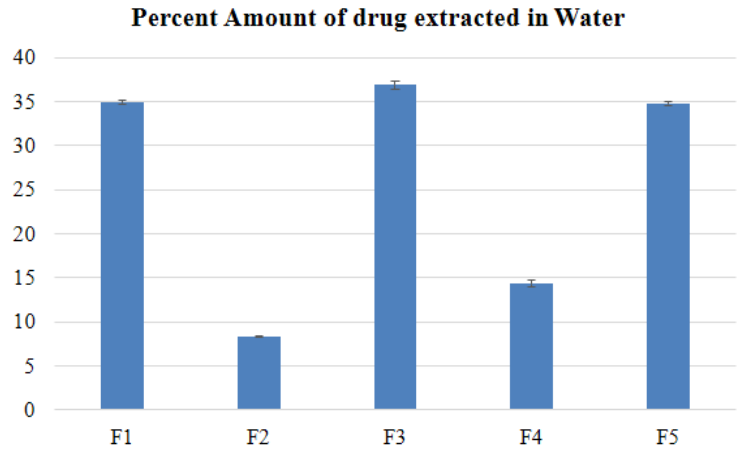

Figure 11. Extractable volume of deionized water and percent amount of drug in deionized water at elevated temperature condition for manipulated pellets.

In vitro drug release

The in-vitro drug release testing were done for both intact and manipulated pellets. The media for dissolution was distilled water. The USP I dissolution apparatus (basket) were choose to keep the pellets together. The graph of percent drug release vs time for intact pellets and manipulated pellets are shown in fig.12 and fig.13 respectively. F2, F4 and F5 showed 100% drug release in 8 hours. F1 and F3 took more than 8 hours for complete drug release.

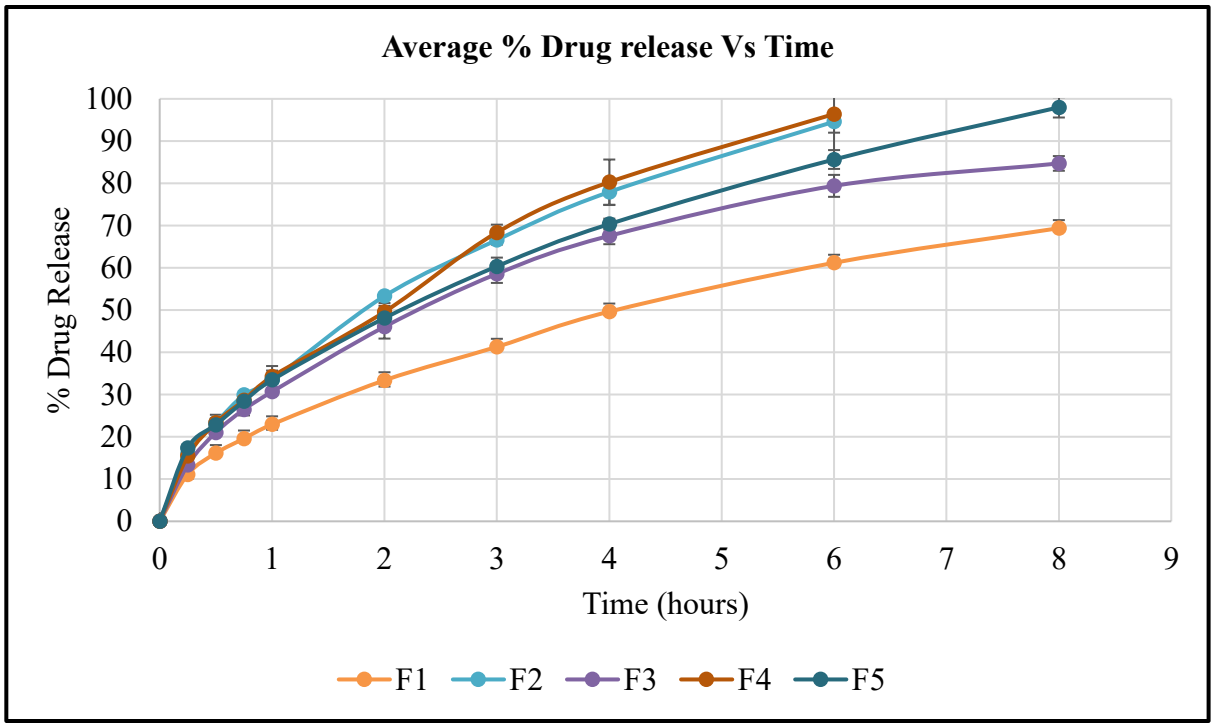

Figure 12. In-Vitro drug release of the intact pellets

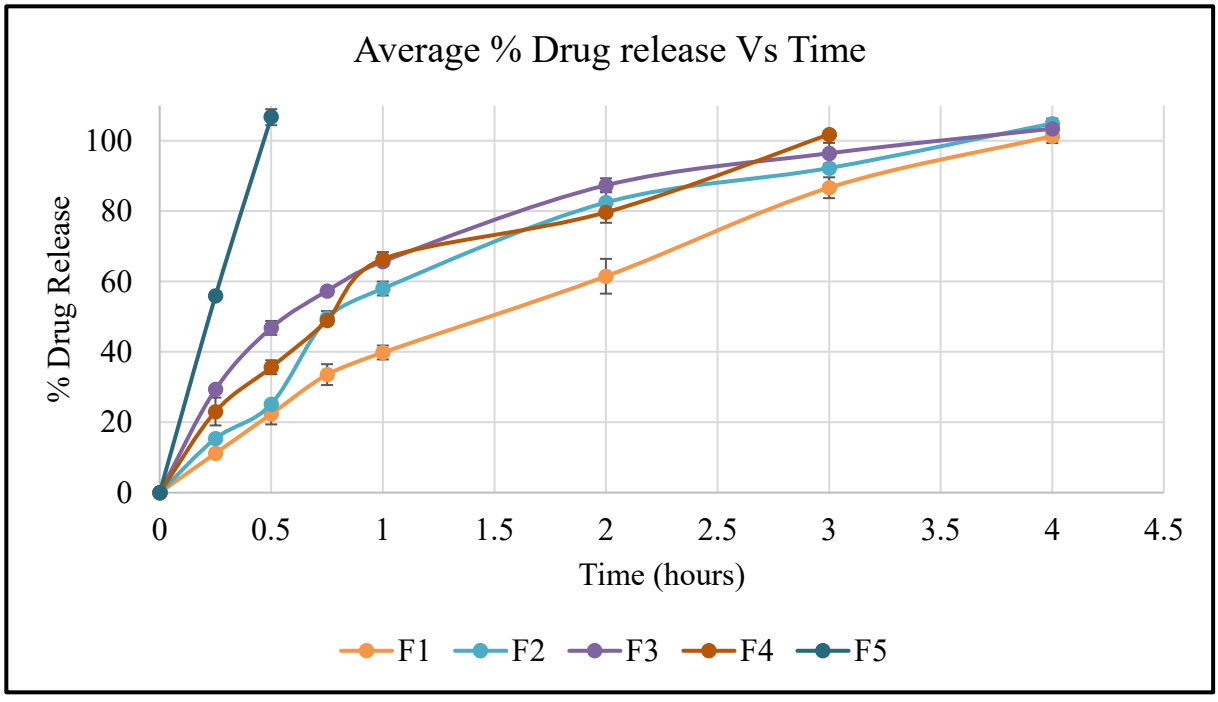

Figure 13. In-Vitro drug release of the manipulated pellets

CHAPTER IV: CONCLUSION

Broad laboratory-based category-1 in-vitro abuse deterrent studies carried out by using various manipulation methods demonstrated the abuse deterrent properties of the formulation. The particle size reduction studies shows that coffee blender is the best way to manipulate pellets. The formulation of HPMC 4M and HPMC 4M with the starch showed minimum particle size reduction among all formulations. As most of the formulation were prone to physical manipulation, drug release and extraction studies were performed on both intact as well as manipulated formulations. The drug extraction studies in the small volume indicates that every formulation gives drug release less than 30% as an intact pellet and less than 25% as a manipulated pellet. At elevated temperature F2 and F4 showed drug % release less than 20% for intact pellets and less than 15% for manipulated pellets. The F2 and F4 contained HPMC and pectin. Pectin shows property of forming gel with the help of water at higher temperature. [12] The swelling of the formulation 2 and formulation 4 under elevated temperature condition might be the reason behind the lower percent drug release compared to other formulations. All formulation formed gel with all three level of solvents at room temperature under agitation conditions. The reason behind this is the high molecular weight of HPMC and effect of the other viscosity agents. This shows that the physical manipulation of pellets does not effect on drug extraction in small volume. Hence given formulations shows abuse deterrent properties against the IV abuse.

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VITA

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