New Applications of Hot Melt Extrusion Techniques for Advancing Oral Drug Delivery

ARUN BUTREDDY

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NEW APPLICATIONS OF HOT MELT EXTRUSION

TECHNIQUES FOR ADVANCING ORAL DRUG DELIVERY

A Dissertation
presented in partial fulfilment of requirements
for the degree of Doctor of Philosophy
in pharmaceutical sciences with emphasis in Pharmaceutics and Drug Delivery
The University of Mississippi

By

ARUN BUTREDDY

August 2022
ABSTRACT

Hot melt extrusion (HME) is a promising technology in the pharmaceutical field, as evidenced by its application in the development of various formulations such as abuse deterrent (AD), amorphous solid dispersions (ASDs), cocrystals etc.

The extended-release (ER) HME pellets of acetaminophen, a model drug, by utilizing high molecular weight polyethylene oxide (PEO) and gelling agents (xanthan gum, guar gum, and gellan gum) were prepared using HME to provide abuse-deterrent properties. The PEO/xanthan gum-based formulation showed higher viscosity, syringe and injection forces, and lower syringeable volume in all manipulation conditions compared to the other formulations, suggesting the AD potential of PEO and xanthan gum pellets against intravenous abuse.

The impact of peroxides in Plasdone™ S630 Ultra and Plasdone™ S630 on the oxidative degradation of quetiapine fumarate hot melt extruded ASDs were investigated. The N-oxide impurity levels in the quetiapine fumarate - Plasdone™ S630 Ultra milled extrudates and tablet formulations were reduced by 2- and 3-folds, respectively, compared to those in quetiapine fumarate - Plasdone™ S630. The reduced oxidative degradation and improved HME processability of Plasdone™ S630 Ultra make it a better choice for oxidation-labile drugs over Plasdone™ S630 copovidone.

The impact of binary and ternary ASDs on the supersaturation kinetics of NIF using the polymers hydroxypropylmethylcellulose acetate succinate (HPMCAS) LG, and HG, Eudragit® RSPO, Eudragit® FS100, Kollidon® VA64 and Plasdone™ K-29/32 was investigated to maintain nifedipine supersaturation over a prolonged period. A synergistic effect emerged for ternary
NIF/HPMCAS-LG/HPMCAS-HG, and NIF/HPMCAS-LG/Eudragit®FS100 systems maintained the supersaturation level with enhanced dissolution performance, demonstrating the potential of polymeric combinations for improved ASD performance.

The pharmaceutical cocrystals were prepared by a solvent-free HME to improve the solubility and dissolution rate. Aripiprazole (ARP) and adipic acid (ADP) were used as a drug and coformer, respectively. Incorporating 5% SOL into the ARP-ADP blend reduced the processing torque and improved processability. FTIR spectra revealed non-covalent interaction between ARP and ADP. The PXRD data exhibited characteristic peaks confirming the formation of new crystalline material with higher dissolution rates compared to the pure ARP, suggesting the suitability of cocrystals in the development of solid dosage forms.
DEDICATION

This dissertation is dedicated to my parents Saroja and Gopal Reddy Butreddy, my sisters Anjali and Ashwini.
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HME</td>
<td>Hot melt extrusion</td>
</tr>
<tr>
<td>ER</td>
<td>Extended release</td>
</tr>
<tr>
<td>PEO</td>
<td>Polyethylene oxide</td>
</tr>
<tr>
<td>AD</td>
<td>Abuse deterrent</td>
</tr>
<tr>
<td>PSR</td>
<td>Particle size reduction</td>
</tr>
<tr>
<td>ADFs</td>
<td>Abuse-deterrent formulations</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate-release</td>
</tr>
<tr>
<td>MW</td>
<td>Molecular weight</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>APAP</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>IPA</td>
<td>Isopropyl alcohol</td>
</tr>
<tr>
<td>DSC</td>
<td>Differential scanning calorimetry</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning electron microscopy</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and drug administration</td>
</tr>
<tr>
<td>Tg</td>
<td>Glass transition temperature</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>cP</td>
<td>Centipoise</td>
</tr>
<tr>
<td>PS630U</td>
<td>Plasdone™ S630 Ultra</td>
</tr>
<tr>
<td>PS630</td>
<td>Plasdone™ S630</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
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<tr>
<td>QF</td>
<td>Quetiapine fumarate</td>
</tr>
<tr>
<td>PM</td>
<td>Physical mixture</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-Performance Liquid Chromatography</td>
</tr>
<tr>
<td>PVDF</td>
<td>Polyvinylidene difluoride</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier Transform Infrared</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>------------</td>
</tr>
<tr>
<td>MCC</td>
<td>Microcrystalline cellulose</td>
</tr>
<tr>
<td>TS</td>
<td>Tensile strength</td>
</tr>
<tr>
<td>Cs</td>
<td>Saturation solubility</td>
</tr>
<tr>
<td>RH</td>
<td>Relative humidity</td>
</tr>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>PVP</td>
<td>Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>Hydroxypropyl methylcellulose acetate succinate</td>
</tr>
<tr>
<td>NIF</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>DLS</td>
<td>Dynamic light scattering</td>
</tr>
<tr>
<td>PXRD</td>
<td>Powder X-ray diffraction</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>T&lt;sub&gt;m&lt;/sub&gt;</td>
<td>Melting point</td>
</tr>
<tr>
<td>SI</td>
<td>Sink index</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum (supersaturation) concentration</td>
</tr>
<tr>
<td>LLPS</td>
<td>Liquid-liquid phase separation</td>
</tr>
<tr>
<td>ADP</td>
<td>Adipic acid</td>
</tr>
<tr>
<td>ARP</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>HR</td>
<td>Hausner ratio</td>
</tr>
<tr>
<td>HSM</td>
<td>Hot-stage microscopy</td>
</tr>
</tbody>
</table>
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Without my advisor, Dr. Michael A. Repka, I might not have been able to complete my Ph.D. His consistent intellectual support, experience, and professional direction aided me in broadening the scope of my research. Throughout my graduate studies, I am grateful for his invaluable advice, insightful comments, encouragement, patience, understanding, and support. I express my sincere gratitude to Dr. Suresh Bandari, Research Scientist in Dr. Repka’s lab for his valuable guidance, support, encouragement and patience throughout my studies.

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# TABLE OF CONTENTS

1. INTRODUCTION ...................................................................................................................... 1

1.1. Introduction to hot melt extrusion (HME) ........................................................................ 1

1.2. Introduction to various formulation strategies .......................................................... 2

1.2.1. Abuse deterrent formulations .................................................................................. 2

1.2.2. Amorphous solid dispersions .................................................................................. 3

1.2.3. Cocrystals .................................................................................................................... 4

1.3. Research objectives ......................................................................................................... 5

1.3.1. Specific Aims ............................................................................................................. 6

2. EXTENDED RELEASE PELLETS PREPARED BY HOT MELT EXTRUSION

TECHNIQUE FOR ABUSE DETERRENT POTENTIAL: CATEGORY-1 IN-VITRO

EVALUATION ......................................................................................................................... 7

2.1. Introduction .................................................................................................................... 7

2.2. Materials and methods ............................................................................................... 11

2.2.1. Materials .................................................................................................................... 11

2.2.2. Solubility determination .......................................................................................... 11

2.2.3. HME process .............................................................................................................. 11

2.2.4. Differential scanning calorimetry (DSC) ............................................................... 12

2.2.5. Physical manipulation and particle size reduction .............................................. 12

2.2.6. Thermal treatment .................................................................................................... 13

2.2.7. Morphological characterization by scanning electron microscopy .................. 13
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.8.</td>
<td>In-vitro drug release studies</td>
<td>13</td>
</tr>
<tr>
<td>2.2.9.</td>
<td>Small volume in-vitro extraction studies</td>
<td>14</td>
</tr>
<tr>
<td>2.2.10.</td>
<td>Syringeability and injectability</td>
<td>15</td>
</tr>
<tr>
<td>2.2.11.</td>
<td>Viscosity analysis</td>
<td>15</td>
</tr>
<tr>
<td>2.3.</td>
<td>Results and discussion</td>
<td>16</td>
</tr>
<tr>
<td>2.3.1.</td>
<td>Solubility</td>
<td>16</td>
</tr>
<tr>
<td>2.3.2.</td>
<td>HME process</td>
<td>17</td>
</tr>
<tr>
<td>2.3.3.</td>
<td>Thermal characterization by DSC</td>
<td>18</td>
</tr>
<tr>
<td>2.3.4.</td>
<td>PSR studies</td>
<td>19</td>
</tr>
<tr>
<td>2.3.5.</td>
<td>SEM imaging</td>
<td>22</td>
</tr>
<tr>
<td>2.3.6.</td>
<td>In-vitro drug release studies</td>
<td>23</td>
</tr>
<tr>
<td>2.3.7.</td>
<td>Small volume extraction and IV injection studies</td>
<td>25</td>
</tr>
<tr>
<td>2.3.8.</td>
<td>Syringeability and injectability</td>
<td>29</td>
</tr>
<tr>
<td>2.3.9.</td>
<td>Viscosity measurement</td>
<td>32</td>
</tr>
<tr>
<td>2.4.</td>
<td>Conclusion</td>
<td>33</td>
</tr>
</tbody>
</table>

3. INFLUENCE OF PLASDONE™ S630 ULTRA—AN IMPROVED COPovidone ON THE PROCESSABILITY AND OXIDATIVE DEGRADATION OF QUETIAPINE FUMARATE AMORPHOUS SOLID DISPERSIONS PREPARED VIA HOT-MELT EXTRUSION TECHNIQUE | 34  |
| 3.1.    | Introduction | 34  |
| 3.2.    | Materials and methods | 37  |
3.2.1. Materials .................................................................................................................................................. 37
3.2.2. Solubility parameter calculation .................................................................................................................. 37
3.2.3. Melt rheology ................................................................................................................................................ 38
3.2.4. HME processing .......................................................................................................................................... 39
3.2.5. Differential scanning calorimetry .................................................................................................................. 40
3.2.6. Fourier transform infrared spectroscopy ....................................................................................................... 40
3.2.7. Tableting and determination of tensile strength ........................................................................................... 40
3.2.8. High performance liquid chromatography .................................................................................................... 41
3.2.9. Dissolution studies ......................................................................................................................................... 42
3.2.10. Stability study ............................................................................................................................................. 42
3.3. Results and Discussion ....................................................................................................................................... 42
3.3.1. Solubility parameter ....................................................................................................................................... 42
3.3.2. Melt rheology ................................................................................................................................................ 44
3.3.3. HME processing .......................................................................................................................................... 47
3.3.4. DSC ............................................................................................................................................................... 49
3.3.5. FTIR ............................................................................................................................................................. 51
3.3.6. Tableting and tensile strength measurement .................................................................................................. 53
3.3.7. Dissolution studies ....................................................................................................................................... 55
3.3.8. Stability study ............................................................................................................................................... 56
3.4. Conclusion ....................................................................................................................................................... 59
4. INTERPLAY OF POLYMERIC COMBINATIONS FOR IMPROVED SUPERSATURATION KINETICS AND DISSOLUTION PERFORMANCE OF HPMCAS BASED AMORPHOUS SOLID DISPERSIONS PREPARED VIA HOT-MELT EXTRUSION TECHNIQUE ........................................................................................................ 61

4.1. Introduction.................................................................................................................. 61

4.2. Materials and methods .............................................................................................. 64

4.2.1. Materials.................................................................................................................. 64

4.2.2. Determination of crystalline and amorphous solubility ........................................ 65

4.2.3. Nucleation induction time measurement.................................................................... 66

4.2.4. DLS ......................................................................................................................... 66

4.2.5. HME processing...................................................................................................... 67

4.2.6. DSC ....................................................................................................................... 67

4.2.7. FTIR ...................................................................................................................... 68

4.2.8. In-vitro non sink dissolution ................................................................................... 68

4.3. Results and discussion .............................................................................................. 69

4.3.1. Polymer carrier selection........................................................................................ 69

4.3.2. Crystalline and Amorphous solubility .................................................................... 71

4.3.3. Nucleation induction time measurement................................................................. 74

4.3.4. DLS ....................................................................................................................... 78

4.3.5. HME processing..................................................................................................... 80

4.3.6. DSC ....................................................................................................................... 81
4.3.7. FTIR .................................................................................................................. 82
4.3.8. Non-sink in vitro dissolution............................................................................. 84
4.4. Conclusion ............................................................................................................. 90
5. POLYMER-ASSISTED ARIPIPRAZOLE-ADIPIC ACID COCRYSTALS
PRODUCED BY HOT MELT EXTRUSION TECHNIQUES........................................... 92
5.1. Introduction .......................................................................................................... 92
5.2. Materials and methods .......................................................................................... 94
5.2.1. Materials .......................................................................................................... 94
5.2.2. Liquid-assisted grinding and HME processing for preparation of cocrystals . 95
5.2.3. DSC analysis..................................................................................................... 95
5.2.4. HSM analysis ................................................................................................... 96
5.2.5. FTIR and chemical imaging analysis ............................................................... 96
5.2.6. PXRD measurement ....................................................................................... 97
5.2.7. SEM analysis ................................................................................................... 97
5.2.8. Solubility and in-vitro dissolution studies....................................................... 97
5.2.9. Drug content analysis ...................................................................................... 98
5.2.10. Flow properties (bulk and tapped density measurement)............................. 98
5.2.11. True density measurement ............................................................................ 99
5.3. Results and discussion.......................................................................................... 99
5.3.1. Cocrystal formation by liquid-assisted grinding ........................................... 99
5.3.2. HME processing ............................................................................................... 100
5.3.2.1. Effect of HME processing parameters on cocrystal formation ............... 101
5.3.2.1.1. Temperature .......................................................................................... 101
5.3.2.1.2. Screw speed .......................................................................................... 102
5.3.3. DSC analysis .................................................................................................. 103
5.3.4. HSM analysis ............................................................................................... 106
5.3.5. FTIR and chemical imaging analysis ............................................................. 107
5.3.6. PXRD analysis ............................................................................................... 109
5.3.7. SEM analysis .................................................................................................. 111
5.3.8. Solubility and in-vitro dissolution studies ..................................................... 112
5.3.9. Flow properties and true density ................................................................. 114
5.4. Conclusion ......................................................................................................... 115
Bibliography ............................................................................................................. 116
VITA ............................................................................................................................ 130
List of Figures

Figure 1.1: Schematic representation of HME technique to produce ADFs. .............................................. 3

Figure 1.2: Schematic representation of the HME process flow in ASD development. .................. 4

Figure 1.3: Schematic representation of HME processed polymer assisted cocrystals. .............. 5

Figure 2.1: Overview of in-vitro AD features. Evaluation of AD performance of ER HME pellets under various manipulation conditions .......................................................... 10

Figure 2.2: Solubility of APAP in various aqueous and alcoholic solvents. All values expressed as mean ± SD (n = 3). ................................................................................................... 17

Figure 2.3: DSC thermograms of A) APAP, B) PEO, C) guar gum, D) xanthan gum, E) gellan gum, and the F) F4, G) F3, H) F2, and I) F1 formulations. .................................................. 19

Figure 2.4: Images of household tools used during physical manipulation attempts (F2 formulation). ........................................................................................................................................ 20

Figure 2.5: Particle size distribution of HME pellets after grinding with a coffee blender for up to 3 min. All values expressed as mean ± SD (n = 3). ................................................................. 21

Figure 2.6: SEM images of A) intact, B) physically manipulated, and C) thermally manipulated pellets of F1 and F2 formulations. ............................................................................. 23

Figure 2.7: Dissolution profiles of intact HME pellets (A, B, C, D) and intact versus physically and thermally manipulated pellets (C and D). All values expressed as mean ± SD (n = 3). ....... 24
Figure 2.8: Small-volume extraction of APAP at A) static, B) agitating conditions and C) mean percentage of APAP extracted from thermally manipulated pellets after incubation in 10 mL water. All values expressed as mean ± SD (n = 3). ................................................................. 27

Figure 2.9: Images of samples of a) F2 and b) F1 formulations after incubation in 10 mL water with agitation for up to 90 min. ........................................................................................................... 29

Figure 2.10: Texture analyzer setup of A) syringeability and B) injectability test. ..................................... 31

Figure 2.11: A) Syringeability and B) injectability profiles of HME pellets using a 3-mL syringe with a 25-gauge needle. C) Mean viscosities of formulations with agitation at RT and thermal manipulation at 90°C for 30 min. All values expressed as mean ± SD (n = 3). ......................... 32

Figure 3.1: A) Oxidation mechanism of quetiapine fumarate (QF) containing a piperazine group with peroxide impurities; B) Potential known oxidative degradation impurities of QF. ............. 36

Figure 3.2: A) Complex viscosity profile as a function of temperature; B) and C) plot of $G'$ and $G''$ versus temperature .................................................................................................................. 46

Figure 3.3: Images of QF copovidone extrudates processed at different barrel temperatures. .... 49

Figure 3.4: A) DSC thermograms of pure QF, PS630, PS630U, PM, and extrudates processed at 140 °C, 150 °C, and 160°C; B) Glass transition temperatures of QF, PS630U, PS630, and the extrudates of QF-PS630 and QF-PS630U. ....................................................................................... 51

Figure 3.5: The FTIR spectra of A) pure QF; B) PS630; C) PS630U; D) PM of QF-PS630; E) PM of QF-PS630U; and F), G) extrudates of QF-PS630 and QF-PS630U respectively. .......... 53

Figure 3.6: Tensile strength of tablets prepared from QF-PS630 and QF-PS630U milled extrudates, pure PS630, PS630U, and MCC ................................................................................................. 54
Figure 3.7: The dissolution profile of QF-PS630U, QF-PS630 and pure QF tablets. .................. 56
Figure 3.8: Oxidative degradation profile of A), B) milled extrudates, and C) tablet formulations. ....................................................................................................................................... 57
Figure 3.9: DSC thermograms of QF-PS630 (A) and QF-PS630U (B) extrudates after 3 months of storage at 40 °C/75% RH. ........................................................................................................................................... 59
Figure 4.1: Chemical structure of drug and polymers used in the ASDs. ........................................ 64
Figure 4.2: Amorphous solubility of NIF in the presence of polymers alone (A) and in combination of polymeric blends (B). .................................................................................................................................. 73
Figure 4.3: Absorbance-time profile of NIF in A) pre-dissolved polymers alone, B) pre-dissolved polymeric combinations. ..................................................................................................................................... 74
Figure 4.4: Visual examination of turbidity for NIF supersaturated solutions in the presence of LG, HG, LG+HG, LG+FS100 and LG+RSPO polymers. ....................................................................................................... 76
Figure 4.5: Mean particle size of NIF upon supersaturation in the presence of polymer alone or in combination. ...................................................................................................................................... 80
Figure 4.6: DSC thermograms of pure NIF and ASD formulations. .................................................. 82
Figure 4.7: FTIR spectra of A) NIF/LG binary ASD, B) NIF/LG+PVP, NIF/LG+VA64 ASD, C) NIF/LG+FS100 and NIF/LG+RSPO ASD. ........................................................................................................... 84
Figure 4.8: In-vitro non sink dissolution profiles of NIF, binary and ternary ASD formulations.88
Figure 5.1: Chemical structures of (A) aripiprazole, (B) adipic acid. ............................................ 94
Figure 5.2: Schematic diagram of screw configuration used in HME. .......................................... 101
Figure 5.3: DSC thermograms of a) pure ARP, b) bulk ADP, c) cocrystals prepared by liquid grinding method, and d) cocrystals processed at 100°C, 50 rpm, e) at 115°C, 25 rpm, f) at 115°C, 50 rpm, g) at 115°C, 75 rpm and h) PM of ARP-ADP.

Figure 5.4: HSM images of a) ARP, b) ARP-ADP cocrystals.

Figure 5.5: FTIR spectra of a) ARP, b) ADP, c) PM of ARP-ADP, and d) ARP-ADP cocrystals at screw speed 25 rpm, e) 50 rpm, and f) 75 rpm.

Figure 5.6: A) Chemical image of ARP-ADP cocrystals with Ge ATR at 1.1 μm spatial resolution, B) FTIR spectra of cocrystals specific to chemical imaging.

Figure 5.7: PXRD diffractograms of a) ARP, b) ADP, c) PM of ARP-ADP and d) ARP-ADP cocrystals at screw speed 25 rpm, e) 50 rpm, and f) 75 rpm.

Figure 5.8: SEM images of A) ARP, B) ADP, and C) ARP-ADP cocrystals.

Figure 5.9: Dissolution profiles of pure ARP, ARP-5% SOL and cocrystals processed at different screw speeds.
List of Tables

Table 2.1: Formulation composition of pellets prepared by HME. ........................................ 17

Table 2.2: Volume recovered (mL) and amount of drug extracted in the recovered volume (mg) after incubation with water at room temperature under static, agitating conditions and after thermal manipulation. (mean ± SD, n = 3). ........................................................................................................ 28

Table 3.1: Summary of the improvements in PlasdoneTM S630 Ultra compared to PlasdoneTM S630. ........................................................................................................................................ 35

Table 3.2: Calculation of the solubility parameter of quetiapine fumarate by using the group contribution method. .................................................................................................................. 43

Table 3.3: Hot-melt extrusion process conditions and measured output parameters of QF-PS630 and QF-PS630U amorphous solid dispersion. .................................................................................. 47

Table 3.4: Composition of excipients used for tableting. .............................................................. 55

Table 4.1: Properties of polymers employed in ASD formulations (Kawakami et al., 2018a; LaFountaine et al., 2015; Lu et al., 2018; Zhang, 2016). ......................................................................................... 70

Table 4.2: Details of formulation composition for binary and ternary ASDs. ............................. 81

Table 4.3: Characterization of dissolution performance of ASD with different polymer combinations. ........................................................................................................................................ 90

Table 5.1: Effect of HME process parameters on the formation of cocrystals. ......................... 103

Table 5.2: Flow properties of pure ARP and cocrystals. ............................................................ 114
CHAPTER-1
1. INTRODUCTION

1.1. Introduction to hot melt extrusion (HME)

The application of HME in the pharmaceutical industry has grown since the late 1990s; successful implementation has been achieved in the development and manufacturing of numerous drug delivery systems such as amorphous solid dispersions (ASDs), abuse deterrent formulations (ADFs), cocrystals, controlled and sustained release drug delivery systems. [1,2]. HME is a proven continuous manufacturing process for the development of ASDs with commercially available marketed formulations [3]. The HME process involves feeding, conveying, mixing, melting, and pressurization of the physical blend within the barrel to produce final dosage form [4,5]. The main components of the extruder are the barrel, feeder, and screw elements [6]. The barrel of the extruder comprises a feeding section, venting, and closed segment configuration [7]. Each section of the barrel can be heated to soften or reduce the viscosity of the polymer. The feeder aids in the transfer of the material to the barrel. The starve feeder with a screw speed independent of feed rate is most commonly used in the HME process. Screw elements (conveying and kneading) help with mixing, transporting, and subsequently pushing the melt through a die. The arrangement of screws facilitates the setup of different screw configurations to achieve either low or high shear. The conveying elements help to push the solid material within the barrel, whereas kneading elements are used for mixing, dispersing, and to apply mechanical shear to the solid material [4,5]. The key mixing mechanisms that occur inside the barrel are distributive and dispersive mixing. Distributive
mixing ensures the homogenous distribution of the active pharmaceutical ingredient (API) throughout the polymer matrix. In contrast, dispersive mixing acts to break down the solid material or any agglomerates to the molecular level owing to the greater shear stress generated by the screw elements present in the mixing zone [8,9]. Typically, a combination of distributive and dispersive mixing is desired to develop the ASDs [6]. Further, in the HME process, thermal and mechanical energies are applied to the physical blend of drug and polymer owing to the presence of the heated barrel and rotating screws. As a result, drug molecules are dissolved in the polymer and or molecularly dispersed within the molten polymer [10].

1.2. Introduction to various formulation strategies

1.2.1. Abuse deterrent formulations

The misuse, abuse, and illicit use of prescription opioid analgesics is a global public health concern. However, there are many viable therapeutic options for the treatment of patients with chronic pain. Both intact and manipulated opioid drug products are abused by various routes such as oral, nasal, and injection which may lead to overdose, drug addiction, and even death. To combat the abuse of these medications, regulatory agencies and pharmaceutical companies are switching their interest towards developing Abuse deterrent formulations (ADFs), with the intent to deter the abuse of opioid products to a maximum extent. These ADFs have the potential to deter or reduce product manipulation, such as crushing, chewing, or solvent extraction for different routes of abuse such as oral, inhalation, smoking, and injection. However, these formulations cannot prevent the multiple ingestions of intact Abuse deterrent (AD) drug products. There are several manufacturing strategies implemented in an attempt to develop ADFs. An example includes matrix tablets of high molecular weight polymers such as polyethylene oxide. The scalable and continuous manufacturing techniques, such as hot melt extrusion (HME), is increasingly accepted by
pharmaceutical companies to advance the development and manufacturing of ADFs. The application of the HME technique in the development of ADFs may overcome the challenges of opioid analgesic formulation development and provide improved protection against misuse and abuse, while also ensuring access to safe and effective use in patients with chronic pain. [1].

Figure 1.1: Schematic representation of HME technique to produce ADFs.

1.2.2. Amorphous solid dispersions

ASDs have been reported as the most effective strategy to enhance the solubility, dissolution rate and consequently, the oral bioavailability of poorly water-soluble drugs [11]. ASDs enable the oral delivery of drugs with poor aqueous solubility because the increased apparent solubility in ASDs leads to a concomitant increase in apparent permeability [12,13]. The APIs in the ASDs exist in higher energy state, which results in increased kinetic solubility and a greater dissolution rate than for the crystalline API [10]. ASDs are a single-phase system that contain drug molecules dispersed or dissolved in one or more polymeric carriers. The addition of polymeric carriers offers several
advantages, such as long-term storage stability and better dissolution properties, compared with pure amorphous drugs [14]. Different methods to improve the dissolution and stability of ASDs include drug-polymer interactions, the maintenance of supersaturating conditions by delaying recrystallization, and adjustment of the water uptake properties of hydrophilic polymeric carriers during dissolution. The ASDs manufactured via HME have garnered increased attention owing to the clinical and commercial success of numerous products available in the market [15,16]. The ASD formation depends on the degree of miscibility and solubility of the drug in the polymeric carrier, and molecular level interaction between the drug and polymer [9].

Figure 1.2: Schematic representation of the HME process flow in ASD development.

1.2.3. Cocrystals
Solid state property improvements hold a great potential for overcoming the low aqueous solubility and bioavailability issues of poorly soluble active pharmaceutical ingredients (APIs). Multicomponent solid forms (cocrystals) of poorly soluble drugs have gained increasing interest in the alteration of physicochemical property of APIs [17,18]. The development of cocrystals is one most effective strategy, used in the pharmaceutical industry for enhancement of dissolution rate[19]. Different solvent free and solid state techniques to prepare cocrystals and salts includes ball milling and HME. HME technique utilizes the combination of both melting and mixing of drug molecule and coformer via the use of temperature and shear [20]. In recent years, co-processing of API and coformer in the presence of polymer is investigated as a matrix or polymer assisted cocrystallization technique to enable the feasibility of extrusion process and to improve the processability, and throughput during the extrusion. However, the amount of polymer required for matrix assisted cocrystalization need a careful investigation to avoid the formation of multicomponent or ternary amorphous matrices [21,22].

Figure 1.3: Schematic representation of HME processed polymer assisted cocrystals.

1.3. Research objectives
The main objective of this work is to investigate the abuse deterrent potential of HME processed pellets and design various formulation strategies using hot melt extrusion technique to address the solubility and dissolution issues of poorly soluble drugs. The aim of the first project was to develop abuse deterrent formulations to tackle the misuse, abuse, manipulation issues of prescription opioid analgesics. The scope of second and third project was to improve the performance of amorphous solid dispersions by decreasing the oxidative degradation and increasing the solubility and dissolution rate. The objective of fourth research work was solid state property improvements of poorly soluble drugs for improved solubility and dissolution performance.

1.3.1. Specific Aims

1. Extended release pellets prepared by hot melt extrusion technique for abuse deterrent potential: Category-1 in-vitro evaluation

2. Influence of Plasdone™ S630 Ultra—an improved copovidone on the processability and oxidative degradation of quetiapine fumarate amorphous solid dispersions prepared via hot-melt extrusion technique

3. Interplay of polymeric combinations for improved supersaturation kinetics and dissolution performance of HPMCAS based amorphous solid dispersions prepared via hot-melt extrusion technique

4. Polymer assisted Aripiprazole–Adipic Acid cocrystals produced by hot melt extrusion techniques for improved dissolution rate
CHAPTER-2

2. EXTENDED RELEASE PELLETS PREPARED BY HOT MELT EXTRUSION TECHNIQUE FOR ABUSE DETERRENT POTENTIAL: CATEGORY-1 IN-VITRO EVALUATION

2.1. Introduction

Millions of people in the United States (US) experience chronic pain. Non-opioid (non-steroidal anti-inflammatory) and opioid drugs are used to alleviate pain. However, owing to the different mechanisms of action of opioid analgesic drugs, some patients find better pain relief with these drugs than from the non-opioid therapies; thus, opioid therapies are more effective for symptomatic relief of chronic pain [23,24].

The rise in abuse of prescription opioid drugs in the US has attracted the attention of regulatory authorities, guiding focus on the design and development of robust abuse-deterrent formulations (ADFs). Depending on the route of administration chosen for abuse, the frequent nonmedical use of opioids leads to drug addiction, overdose, and sometimes death [25]. Different ways in which prescription opioid drugs can be abused are ingestion (chewing), inhalation (snorting and smoking), injection (parenteral route of administration) by mechanical manipulation (crushing or grinding) [26]. To combat prescription opioid drug abuse, abuse-deterrent (AD) products are designed to resist or make it difficult to manipulate by various formulation approaches, such as physical/chemical barriers, agonist/antagonist combinations, aversion agent inclusion, new molecular entities, and prodrugs [27]. Physical and chemical barriers are the most effective approaches to prevent or reduce abuse. The physical barrier approach is to make the formulation
resistant to crushing, whereas a chemical barrier approach is to prevent or reduce the extraction of drug using common household solvents [28]. Currently, commercially available opioid formulations with AD label claims are based on either physical/chemical barrier or antagonist/agonist combination approaches to impede the drug abuse [26].

Extended-release (ER) opioid formulations are more desirable for potential opioid abusers owing to the higher amounts of active ingredient compared with immediate-release (IR) formulations. To achieve rapid onset of the euphoric or psychoactive effects, opioid abusers manipulate the ER opioids to bypass the ER profile, rendering it into an IR form, to seek a rapid rise in opioid blood level. Several novel ADFs have been introduced to reduce the abuse of ER opioid formulations and reduce their attractiveness to abusers [29,30]. The FDA guidance document describes three categories of premarket studies recommended for the development of a new AD products, namely: Category 1-laboratory-based in vitro manipulation or chemical extraction; Category 2-pharmacokinetic; and Category 3- clinical abuse potential studies [31].

The FDA-approved opioid products with ADF labeling utilize polyethylene oxide (PEO), a commonly used excipient for abuse deterrence. PEO is a nonionic, water-soluble, and thermoplastic homo-polymer with a molecular weight (MW) of 100,000 to 8,000,000 Da and a melting temperature range of 65°C–70°C [32]. The PEO-based matrix formulations are prepared using HME technology because of its low melting temperature and thermoplastic nature[33,34]. Hot-melt extrusion (HME) has become popular in the manufacture of ADFs. The INTAC® drug delivery platform, developed by Grünenthal GmbH, uses HME with high MW PEO to make a tamper-resistant formulation, which is less prone to abuse [35]. Owing to hydration and swelling in aqueous solvents, the higher molecular weight PEOs are used to produce highly viscous, gel-like solutions that deter abuse by injection. The major drawback with PEO is its susceptibility to
thermal auto oxidative degradation, which leads to reduction in polymer molecular weight and lower viscosity of solutions [36,37]. Abusers have been known to manipulate formulations using an oven, microwave, or other heating devices, resulting in reduced viscosity of the PEO solutions, which facilitates syringeability and injectability and nullifies the intravenous (IV) AD properties of ER opioid ADF.

Owing to the restrictions and controls on access to opioid analgesics, Acetaminophen (APAP) was selected as a model drug in this study because of its high aqueous and alcoholic solubility. Given the high solubility of APAP in ethanol, it will start to dissolve or extract in alcoholic media, resulting in dose dumping and consequently nullifying the AD characteristics of the formulation. Therefore, to exhibit AD properties, an ideal formulation should withstand the influence of alcohol and remain intact under all tested manipulation conditions. PEO with MW of 7,000,000 Da was utilized in the formulation of ER pellets of APAP. The high MW and crush resistance properties of PEO have led to its use in several commercialized ADFs [38]. The aqueous solutions of PEO are known to exhibit lower viscosity owing to temperature-dependent oxidative degradation [37]; however, this confers susceptibility to abuse by the IV route. Hence, the addition of gelling agents (xanthan gum, guar gum, and gellan gum) was investigated with the PEO matrix to impart IV AD properties. Xanthan gum is a polysaccharide produced predominantly by Xanthomonas campestris [39]. Gellan gum is a polysaccharide gum produced by culture of the microbe Sphingomonas elodea as a fermentation product. Guar gum is a polysaccharide of galactose and mannose, obtained from the endosperms of Cyamopsis tetragonoloba [40]. All these gelling agents are insoluble in alcohol, and show hydration and swelling behavior in non-alcoholic and alcoholic media.
The novelty of the current work was to investigate the effect of PEO, and PEO with different gelling agents, namely xanthan gum, guar gum, and gellan gum, on the AD properties of multiple-unit ER pellets manufactured by using HME technology. Further, we aimed to investigate the effect of gelling agents on the IV AD performance and to examine an effective manipulation tool for particle size reduction (PSR). The ER pellets manufactured were evaluated for in-vitro laboratory AD characteristics. The overall evaluation of ER HME pellets under various manipulation conditions have been represented in Figure 2.1.

Figure 2.1: Overview of in-vitro AD features. Evaluation of AD performance of ER HME pellets under various manipulation conditions
2.2. Materials and methods

2.2.1. Materials

APAP selected as a model drug, was obtained from Spectrum Chemicals (New Brunswick, NJ, USA). Polyox™ WSR-303 with a MW of 7,000,000 Da was obtained from Colorcon (West Point, PA, USA). The gelling agents xanthan gum, guar gum, and gellan gum were obtained from CP Kleo (Atlanta, GA, USA), Aqua Solutions (Deer Park, TX, USA), and MP Biomedicals (Santa Ana, CA, USA), respectively. Hydrochloric acid, sodium hydroxide, and isopropyl alcohol (IPA) were purchased from Fisher Scientific (Fair Lawn, NJ, USA). Ethanol was purchased from Decon Labs (Glennie Circle, PA, USA). All other chemicals used were analytical grade and were used as received.

2.2.2. Solubility determination

The solubility of APAP was determined in water, 0.1 N NaOH, 0.1 N HCl, and 0.1 N HCl containing 20% and 40% v/v of ethanol, and in organic solvents such as 96% ethanol and isopropyl alcohol (IPA). Excess APAP was added to a 20 mL scintillation vial, containing 10 mL of each of the aqueous and non-aqueous solvents, and was vortexed and agitated at 25°C for 48 h. After 48 h, the samples were centrifuged for 5 min at 13000 rpm to separate the undissolved drug. The supernatant solutions were suitably diluted, and the concentration of the dissolved drug was measured at a wavelength of 244 nm by using a UV-Vis spectrophotometer (Genesys 190, Thermo Scientific, NJ, USA). The test was performed in triplicate.

2.2.3. HME process

Powder mixtures of APAP with PEO, and APAP/PEO with each gelling agents (i.e., xanthan, guar gum, and gellan gum) were sieved through a USP #30 (600 μm) mesh and blended by using a
Maxiblend™ V-shell blender (Globe Pharma, New Brunswick, NJ, USA) at 25 rpm for 10 min to obtain a homogeneous blend. The physical mixture was gravimetrically fed into a co-rotating twin-screw extruder (16 mm Prism EuroLab; Thermo Fisher Scientific, Waltham, MA, USA) with a length-to-diameter ratio (L/D) of 40/1. The powder blend was extruded at a temperature of 110°C using a 3 mm circular die. The screw design utilized was composed of three mixing zones along with conveying zones. The screw speed and feed rate of the extruder were set at 100 rpm and 5 gm/min, respectively. The extrudate strands obtained were cooled at ambient temperature and then pelletized into 3 mm pellets by using a bench-top pelletizer (Thermo Fisher Scientific, Waltham, MA, USA). The pellets were filled into 000 size hard gelatin capsules.

2.2.4. Differential scanning calorimetry (DSC)

The thermal properties of the drug substance, excipients, and the HME pellets were characterized by using a DSC (Discovery DSC25, TA Instruments, New Castle, DE, USA). Accurately weighed 5–8 mg of samples were sealed in the aluminum pans and equilibrated for 1 min at 25°C followed by heating from 25°C to 200°C at a ramp rate of 10°C/min, with ultra-pure nitrogen as the purge gas at a flow rate of 50 mL/min. An empty aluminum pan was used as a reference.

2.2.5. Physical manipulation and particle size reduction

The purpose of reducing particle size of an ADF is to determine the potential of the drug product to be amenable to abuse by the intranasal route (snorting). Physical manipulation studies were performed using destructive methods, including manual (hammer or pestle and mortar) and mechanical (coffee blender) tests. These are common household items used for tampering with prescription opioid medications. For PSR, the intact pellets were hit by a hammer with ten repeated strokes [41]. Approximately 5 g of each formulation was weighed, and placed in a motor or coffee blender, and ground for 3 min using a pestle and 1–3 min in the coffee blender. Particle size
distribution was determined after each physical manipulation technique by passing the obtained particles through a USP # 25 (500 μm) mesh, and the fraction retained on the sieve was recorded.

2.2.6. Thermal treatment

Thermal treatment was performed by heating the intact pellets in an oven (Precision, Econotherm, OH, USA) at 90°C for 30 min. After the thermal exposure, the pellets were analyzed by performing in-vitro dissolution studies.

2.2.7. Morphological characterization by scanning electron microscopy

The surface morphology of intact, physically manipulated (crushed by hammer), and thermally manipulated (oven at 90°C for 30 min) pellets was determined by using scanning electron microscopy (SEM, JSM-5610LV, JOEL, Peabody, MA, USA) with an accelerating voltage of 5 kV. The pellets were placed on the SEM stubs and adhered by using double-sided adhesive tape. Prior to imaging, the samples were sputter-coated with platinum using a Hummer 6.2 Sputter Coater (Ladd Research Industries, Williston, VT, USA) under an argon atmosphere.

2.2.8. In-vitro drug release studies

The in-vitro dissolution behavior of the intact, physically and thermally manipulated pellets were examined by using an USP type- II Apparatus (Hanson SR8-plus™; Hanson Research, Chatsworth, CA, USA) in 900 mL of 0.1 N HCl (pH 1.2, non-alcoholic) dissolution medium maintained at 37°C±0.5°C with paddle speed of 50 rpm. For each formulation, 500 mg of the pellets (equivalent to 100 mg of APAP) was transferred into the dissolution vessel. Approximately 3 mL of sample was collected at 0.5, 1, 2, 4, 6, 8 h and filtered through a 10-μm filter. The drug released was analyzed at 244 nm by using a UV spectrophotometer. All dissolution studies were performed in triplicate (n = 3). For the alcohol dose dumping studies, dissolution testing was
conducted in 900 mL 0.1 N HCl with 40% v/v ethanol (alcoholic dissolution medium, equivalent to hard liquor) over a period of 8 h. The drug release profiles of intact formulations in alcoholic and non-alcoholic media and the manipulated formulations in non-alcoholic media were compared by using the $f_2$ similarity factor [42].

$$f_2 = 50 \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{0.5} \times 100 \right\}$$  \hspace{1cm} (1)

where $n$ represents the number of dissolution time points considered and $R_t$ and $T_t$ are the percentage of the drug dissolved in the reference (0.1 N HCl) and test (0.1 N HCl with 40% ethanol) formulations at time point $t$. The dissolution profiles were considered similar when the $f_2$ value was in the range of 50–100, and the formulation was considered non-alcohol resistant when the $f_2$ value was below 50.

2.2.9. Small volume in-vitro extraction studies

Intact formulations were tested for in-vitro extraction studies by using different levels of solvents, as recommended by FDA to evaluate drug extraction from ADF [27]. The different levels of solvents employed for extraction studies were water (level-1); 40% ethanol (level-2); and 96% ethanol, IPA, 0.1 N HCl, and 0.1 N NaOH (level-3). Accurately weighed intact pellets (500 mg) equivalent to 100 mg APAP were placed into scintillation vials containing 10 mL of different solvents. The vials were vortexed for 15 s and then kept under static or agitation (1000 rpm) conditions by using a bench mixer (Benchmark Scientific, USA) for 30 min at room temperature (RT). After 30 min, the samples were withdrawn into a previously weighed vial by using a 10-mL syringe, and the volume withdrawn was calculated from the density of the solvents. The extracted samples were appropriately diluted and analyzed at 244 nm by using a UV spectrophotometer to quantify the extraction of the drug in various solvents.
Extraction studies of intact pellets were also performed in 10 mL water using an oven and a microwave (Sharp Electronics Corporation, NJ, USA) as thermal manipulation tools. Briefly, 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–95°C) and microwave (1500 W) for 30 min and 15 s, respectively. The extraction of drug and the volume withdrawn was similar to the process utilized for static and agitated samples.

2.2.10. Syringeability and injectability

Syringeability and injectability tests are key testing parameters for a drug product that is abused intravenously. Each 500 mg of intact pellet formulation was placed into scintillation vials containing 10 mL water, and the vials were kept under static and agitating conditions (1000 rpm) at RT for 30 min and in the oven at 90°C–95°C for 30 min for thermal manipulation. The texture analyzer (TA-XT2i, Texture Technologies, Hamilton, MA, USA) was equipped with a syringe setup (TA-270N, TA272B) and employed to evaluate the syringeability (pulling) and injectability (pushing) force exerted by each formulation. A 25-gauge needle (Becton Dickinson) equipped with a 3-mL syringe was used during the measurements. The test parameters utilized were: measurement mode compression or distance; pre-test speed of 1.0 mm/s; post-test speed of 20.0 mm/s; an automatic trigger force at 15.0 g, and the syringe plunger was set to move a distance of 30 mm each time during pushing and pulling. The target distance and compression mode were used to record the syringeability and injectability force, respectively. The data were collected and analyzed by exponent software version 6.1.5.0 (Stable Micro Systems, Godalming, UK).

2.2.11. Viscosity analysis

Viscosity of formulations was measured after manipulation of intact pellets in various conditions (i.e., agitation at 1000 rpm at RT, and at 90°C in the oven for up to 30 min). After 30 min, the
viscosity of the aqueous extracts was measured by using a Brookfield cone-and-plate rheometer (LVDV-II+ Pro Viscometer, Middleboro, USA). A test sample of 0.5 mL was placed onto the middle of the plate and then equilibrated for 2 min. The measurements were performed with spindle number 40 at 6 rpm, a cone radius of 1.2 cm, at 25.0°C±0.3°C.

2.3. Results and discussion

2.3.1. Solubility

The solubility of APAP in alcoholic and non-alcoholic media could affect the in-vitro extraction and dissolution rate. The solubility data for APAP in various solvents are presented in Figure. 2.2, and results indicated that APAP showed high solubility in all the tested solvents. The solubility was significantly increased with a gradual increase in ethanol concentration, and was very high in 96% ethanol and IPA. In alcoholic media, the solubility of APAP was approximately 6 and 12-fold higher in 40% and 96% ethanol, respectively, compared with the non-alcoholic media, i.e., water. The saturation solubility in aqueous solvents varied from 13.11 ± 0.57 to 30.34 ± 1.18 mg/mL, with the highest solubility in 0.1 N NaOH, followed by that in 0.1 N HCl and water.
**Figure 2.2:** Solubility of APAP in various aqueous and alcoholic solvents. All values expressed as mean ± SD (n = 3).

### 2.3.2. HME process

The extrusion trials were performed using PEO at 80% w/w and APAP at 20% w/w. Similarly, the polymeric blends of PEO at 50% w/w were examined with three gelling agents (xanthan gum, guar gum, and gellan gum) each at 30% w/w and APAP at 20% w/w at a temperature of 110°C, screw speed of 100 rpm, and a feed rate of 5 g/min. The drug load was maintained at 20% w/w for all formulations. The process temperature (110°C) was selected on the basis of the glass transition temperature (69°C) of Polyox™ WSR 303. At this temperature, APAP and gelling agents are non-molten and are molecularly dispersed in the PEO matrix to obtain homogeneous extrudates. The obtained extrudates of PEO and the blends of PEO 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 provided in Table 2.1.

**Table 2.1: Formulation composition of pellets prepared by HME.**

<table>
<thead>
<tr>
<th>Component</th>
<th>Composition (wt %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>20.0</td>
</tr>
<tr>
<td>PEO</td>
<td>80.0</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>-</td>
</tr>
<tr>
<td>Guar gum</td>
<td>-</td>
</tr>
<tr>
<td>Gellan gum</td>
<td>-</td>
</tr>
</tbody>
</table>
2.3.3. Thermal characterization by DSC

DSC thermograms of pure APAP, PEO, gelling agents, and HME pellets are shown in Figure 2.3. APAP and PEO showed endothermic melting peaks at 170.2°C [43] and 69.85°C [23], respectively, due to the crystalline and semi-crystalline nature of APAP and PEO. For xanthan gum, guar gum, and gellan gum, no thermal events were recorded between 25°C and 200°C, and a broad endothermic event observed at approximately 110°C, which may have been due to evaporation of moisture content [43]. A thermogram of HME pellets did not show the melting peak of APAP, indicating that the drug substance was molecularly dispersed in the matrix of PEO-gelling agents. The decrease in the melting point of PEO in the thermograms of HME pellets was due to the change in crystallinity of the PEO matrix polymer upon thermal treatment and the molecular dispersion of the drug in the crystalline polymer matrix. This decrease in the degree of melting point depends on the MW and duration of the thermal treatment. These findings were in accordance with the previous literature [23,44].
Figure 2.3: DSC thermograms of A) APAP, B) PEO, C) guar gum, D) xanthan gum, E) gellan gum, and the F) F4, G) F3, H) F2, and I) F1 formulations.

2.3.4. PSR studies

Manipulation refers to any process used to alter or destroy the integrity of the intact pellets. PSR of ADF is a common practice to increase the drug release, turn an ER formulation into IR, and to prepare a formulation amenable to abuse by the nasal or IV routes. The feasibility of PSR was evaluated by using a hammer, pestle and mortar, and coffee blender (Figure. 2.4). Of these, the coffee blender was identified as an effective tool for PSR.
Figure 2.4: Images of household tools used during physical manipulation attempts (F2 formulation).

Particle sizes greater than 500 microns are difficult to abuse by snorting/insufflation and also lower the absorption through the nasal mucosa [35,45]. Hence, particles of <500 μm were set as the limit to determine the resistance to nasal abuse. PSR using hammer and a pestle and mortar resulted in deformation and minor fractures of the intact pellets, showing that these tools were not able to reduce the particles below 500 μm. PSR achieved by using a coffee blender (< 500 μm) is shown in Figure. 2.5. Approximately < 2% of particles of manipulated pellets were smaller than 500 μm for the PEO-based formulation (F1). In contrast, other formulations resulted in approximately 25% of particles smaller than 500 μm. Owing to the high percentage of PEO (80%) in the F1
formulation, the pellets were hard to reduce to particle sizes below 500 μm, and this was attributable to the crush resistance potential of high MW PEO polymers. There was no significant difference (p > 0.05) between the particle size distribution of pellets manufactured with the three gelling agents.

Figure 2.5: Particle size distribution of HME pellets after grinding with a coffee blender for up to 3 min. All values expressed as mean ± SD (n = 3).

The decrease in PSR, with an increase in PEO percentage, can be explained by the high MW and thermoplastic nature of PEO, which imparts elastic deformation and crush resistance properties to the HME pellets. Thus, the deformation properties of plain PEO-based pellets showed a decrease in the potential for PSR. In contrast, the increase in PSR was significant (p < 0.05) for all formulations containing gelling agents, which was attributable to the relatively smaller percentage of PEO, and may increase the susceptibility to PSR because of the evolution of minor fractures during physical manipulation. These results suggested that a formulation containing a high percentage of PEO was not suitable for snorting, and it was observed that formulations containing
gelling agents could potentially be snorted following physical manipulation using a coffee blender. However, the particles smaller than 500 μm was less than 25% this may be equivalent to immediate dose of API in the formulation. Further, this may vary with different API’s with abuse deterrent potential.

2.3.5. SEM imaging

SEM images of intact and manipulated pellet formulations are presented in Figure 2.6. The surface of intact pellets of formulation (F1) was rough with a few cracks. The surface of physically manipulated F1 pellets showed minimal changes, with a few fragments on the surface, whereas thermally manipulated pellets showed surface cracks and fissures. These changes were the result of polymer melting and fusion due to manipulation above the melting point of PEO. The surface of the intact F2 formulation was smooth with few cracks, whereas the physically manipulated pellets showed a large number of cracks and crevices, indicating that the F2 formulation was susceptible to PSR compared with F1. The surface characteristics of the thermally manipulated F2 formulation showed more cracks and fissures than those of F1. This was probably due to presence of xanthan gum, which clearly interferes with the fusion/bridge formation of PEO and the difference in density of pellets after thermal curing. The F1 formulation contains a large amount of PEO (80%); upon cooling, the PEO matrix shrinks, leaving behind deep cracks on the surface [37,46]. However, in the F2 formulation, the PEO content was 50%, and the xanthan gum in the formulation could interfere with the fusion and densification of PEO polymer matrix, resulting in an increased number and depth of cracks. These observed microstructural changes in the F2 formulation may be due to the less dense packed structure of xanthan gum in thermally manipulated pellets. In the case of F1 formulation, these microstructural changes are less significant because of densification in the heat-cured PEO matrix.
Figure 2.6: SEM images of A) intact, B) physically manipulated, and C) thermally manipulated pellets of F1 and F2 formulations.

2.3.6. In-vitro drug release studies

In-vitro dissolution testing of intact pellets was performed in 0.1 N HCl, and 0.1 N HCl with 40% v/v ethanol for up to 8 h. The dissolution studies in 0.1 N HCl with 40% ethanol were performed to assess the dose dumping potential of HME pellets when co-ingested with alcohol. The percentage of drug release over a period of 8 h is shown in Figure 2.7A–7D. All the formulations have shown more than 90% drug release in both non-alcoholic and alcoholic media over the 8 h interval. The ER profile of the pellet formulations is due to the high MW and viscosity of the PEO matrix polymer. The mechanism of drug release from the pellets is mainly through the erosion of the polymer matrix and diffusion of the dissolved drug through a gel layer formed on the outer surface of the pellets [34]. The gelling agents did not have a major impact on the ER characteristics owing to their rapid hydration and faster dissolution when in contact with aqueous media.
Dissolution profile of F2, F3, and F4 formulations was not significantly (p > 0.05) different because of the similar wettability of the pellets in 0.1 N HCl and 0.1 N HCl with 40% ethanol. This indicates that the drug release was completely dependent on the PEO concentration. The dissolution rate of the intact pellets in nonalcoholic medium (0.1 N HCl) was similar to that in alcoholic medium (0.1 N HCl with 40%) indicated by an F2 value of >50, suggesting that the HME pellet formulations withstood the alcohol-induced dose dumping. This robust dissolution profile in 0.1 N HCl with 40% alcoholic medium was due to the insolubility of PEO and gelling agents.

Figure 4 Dissolution profiles of intact HME pellets (A, B, C, D) and intact versus physically and thermally manipulated pellets (C and D). All values expressed as mean ± SD (n = 3).

The dissolution testing of physically and thermally manipulated pellets was performed in 0.1 N HCl. The percentage of in-vitro drug release of manipulated pellets compared to intact pellets is shown in Figure 2.7E and 7F. Physically manipulated pellets demonstrated a relatively higher dissolution profile from those observed with the intact pellets owing to the deformation and fracture of manipulated pellets. There was no significant difference (p > 0.05) in the drug release
for thermally manipulated pellets versus intact pellets owing to the hardening, densification, and increased crushing strength of the PEO matrix after thermal treatment [37]. The dissolution profile of physically and thermally manipulated pellets in nonalcoholic medium (0.1 N HCl) was similar (F2 < 50) to that of intact pellets. These results demonstrated that HME pellets maintained their ER profile, even after physical and thermal manipulation.

2.3.7. Small volume extraction and IV injection studies

After the oral route, the most common route of abuse for ER opioid products is the IV route. To determine the feasibility of preparing HME pellets as a solution for IV abuse, in vitro extraction studies were conducted by using a small volume of potentially injectable solvents, as recommended by the FDA. Because of common availability, water, and water with 40% alcohol are the preferred first-line household solvents for small-volume extraction studies. The data from extraction studies performed on different levels of solvents are shown in Figure. 2.8A and 8B. For intact pellets, the mean percentage of the drug extracted after 30 min in water and 40% alcohol was in the range of 1.39% ± 0.44 to 6.22% ± 0.33, and 1.92% ± 0.49 to 4.20% ± 0.35, respectively, under static conditions compared with the 13.68% ± 0.22 to 29.75% ± 0.31 and 9.62% ± 0.50 to 13.91% ± 0.31 respectively for water and 40% alcohol under agitation. There was a significant difference (p < 0.05) in the drug extraction profile in water and 96% ethanol for the F2 formulation compared with the F1 formulation under agitating and static conditions. However, this difference was relatively less in 40% ethanol under both static and agitating conditions. This was attributable to the higher viscosity and more rapid gel formation with xanthan gum when hydrated in small volumes of alcoholic and non-alcoholic media. Drug extraction studies were also conducted in level 3 solvents (reflective of different polarity and pH) to assess the ability of these solvents for preparation of drug solutions intended for IV abuse. As per the FDA draft guidance for industry
on evaluation of abuse-deterrent properties of generic oral opioid products, formulations are considered without abuse deterrent properties if they are above the threshold of ≥50% drug extracted at 30 min at various temperatures and agitation conditions [27]. The percentage of drug extracted was in the range of 8.0% ± 0.51% to 15.6% ± 0.19%, and 3.2% ± 0.38% to 16.5% ± 0.28% for 96% ethanol and IPA, respectively, in static conditions. Similarly, under agitated conditions, drug extraction in 96% ethanol and IPA was in the range of 34.33% ± 0.18 to 48.45± 0.22%, and 18.44% ± 0.41 to 31.22% ± 0.18%, respectively. The higher drug extraction in IPA and 96% ethanol was due to higher drug solubility, and the drug was extracted by the capillary action of solvents through the pores of HME pellets [47]. The percentage drug extraction in 0.1 N HCl (pH 1.2) was < 7.3% and < 22.32% for static and agitating conditions, respectively. The drug extraction in 0.1 N NaOH (pH 11.5) was < 11.31% and < 33.78% under static and agitating conditions, respectively. The higher drug extraction in 0.1 N NaOH was related to the high solubility of the drug at alkaline pH compared with the solubility at acidic pH values. The lower drug extraction of the F2 formulation in water and 40% ethanol can be explained by solubility and the gelling phenomenon of xanthan gum, as it forms a rapid gelling matrix in the water and 40% alcohol compared with other formulations.
Figure 2.8: Small-volume extraction of APAP at A) static, B) agitating conditions and C) mean percentage of APAP extracted from thermally manipulated pellets after incubation in 10 mL water. All values expressed as mean ± SD (n = 3).

Another extraction study was performed to evaluate the effect of thermal manipulation on the extraction profile of intact pellets in 10 mL water by incubating the pellets in the oven (90 °C) or microwave (1500 W) for 30 min and 15 s, respectively. All the formulations showed < 35% drug extraction (Figure. 2.8 C) following both types of thermal manipulation. The drug extraction profile of F2 formulations was 15.62% and 5.43% less, respectively, for oven and microwave conditions compared with the F1 formulation. The presence of xanthan gum in the F2 formulation significantly reduced (p < 0.05) the drug extraction under both manipulation conditions compared with other formulations (F3 and F4).

The volume withdrawn from each formulation after 30 min of extraction was recorded for intact formulations under static, agitating, and thermal manipulation conditions (Table 2.2). The volume
withdrawn from the F2 formulation was 7.0 ± 0.19, 5.8 ± 0.41, and 6.1 ± 0.59 mL under static, agitating, and thermal manipulation conditions, respectively. In contrast, the volume withdrawn for other formulations was > 8 mL under static and agitating conditions. Thermally manipulated formulations result in a relatively lower volume available for withdrawal compared with static and agitating conditions. The low drug extraction i.e., below the threshold level (≤50%) may be due to the relatively lower temperature (90-95°C) applied during thermal manipulation. Further, extraction potential of APAP may vary depending on the thermal treatment conditions such as temperature and time. The lower withdrawable volume from the F2 formulation when manipulated suggested AD properties that may deter IV abuse.

**Table 2.2: Volume recovered (mL) and amount of drug extracted in the recovered volume (mg) after incubation with water at room temperature under static, agitating conditions and after thermal manipulation. (mean ± SD, n = 3).**

<table>
<thead>
<tr>
<th>Manipulation condition</th>
<th>Volume recovered (out of 10 mL) and amount of drug extracted (mg) in the recovered volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td><strong>Static</strong></td>
<td></td>
</tr>
<tr>
<td>Volume recovered (mL)</td>
<td>8.7 ± 0.15</td>
</tr>
<tr>
<td>Amount of drug extracted (mg)</td>
<td>5.41 ± 0.33</td>
</tr>
<tr>
<td><strong>Agitation</strong></td>
<td></td>
</tr>
<tr>
<td>Volume recovered (mL)</td>
<td>8.4 ± 0.29</td>
</tr>
<tr>
<td>Amount of drug extracted (mg)</td>
<td>24.99 ± 0.32</td>
</tr>
<tr>
<td><strong>Thermal (oven)</strong></td>
<td></td>
</tr>
<tr>
<td>Volume recovered (mL)</td>
<td>8.6 ± 0.49</td>
</tr>
<tr>
<td>Amount of drug extracted (mg)</td>
<td>28.58 ± 1.62</td>
</tr>
</tbody>
</table>

The F2 formulation continued to exhibit gelling properties for up to 90 min. At the end of 90 min, the formulation became a gel with no further volume remaining for withdrawal, whereas the F1
formulation showed the gelling property at the bottom of the vial, with < 8 mL remaining for withdrawal (Figure 2.9).

![Images of samples of a) F2 and b) F1 formulations after incubation in 10 mL water with agitation for up to 90 min.](image)

**Figure 2.9:** Images of samples of a) F2 and b) F1 formulations after incubation in 10 mL water with agitation for up to 90 min.

### 2.3.8. Syringeability and injectability

Syringeability and injectability studies were conducted to assess the AD potential of HME pellets by the IV route. The term syringeability refers to the force or pressure required to withdraw the dissolved drug or extract from a vial through hypodermic needle prior to the injection, whereas injectability refers to the amount of force or pressure required during injection [48]. These tests are key performance attributes of any ADF intended to provide resistance to drug abuse by the IV route. A texture analyzer equipped with syringeability and injectability accessories (Figure. 2.10) was used to measure the syringeability and injectability of pellet formulation using water as a control. The syringeability and injectability results of the intact and thermally manipulated formulations are shown in Figure. 2.11A and 2.11B. The pulling and pushing forces (N) of water were 1.74 and 2.59, respectively. The syringeability forces of static, agitating, and thermally
manipulated pellets varied from $3.1 \pm 0.3$ to $4.5 \pm 0.5$, $4.2 \pm 0.2$ to $5.5 \pm 0.3$, and $3.2 \pm 0.3$ to $9.2 \pm 0.8$, respectively. Similarly, the injectability force was observed to be from $2.4 \pm 0.4$ to $10.8 \pm 0.4$, $3.5 \pm 0.2$ to $16.1 \pm 0.3$ and $2.5 \pm 0.4$ to $9.1 \pm 0.7$, respectively for static, agitated, and thermally manipulated pellets. The decrease in resistance to syringe (pulling) and injection (pushing) for the PEO formulation (F1) after thermal manipulation may be due to a reduction in solution viscosity, degradation, and a shortened polymer chain end-to-end distance of PEO after thermal treatment [32]. Thus, reduced pulling and pushing forces could be attributed to ease of syringeability and injectability, which led to compromising the IV abuse deterrent potential. Similar observations were reported by [23], and they reported a significant reduction in the syringeability and injectability of thermally cured formulations prepared with Polyox™ WSR 301 and 303 when compared with the uncured formulations. Of all the studied formulations, higher pulling and pushing forces, i.e., greater resistance to syringeability and, injectability was observed for the PEO-xanthan gum pellets (F2). This could be attributable to the rapid hydration and swelling behavior of xanthan gum pellets, which form a highly viscous solution under intact and manipulated conditions. The low syringeability and injectability of xanthan gum based formulation (F2) demonstrated greater IV abuse deterrent potential because of characteristics of both difficulty of withdrawal (syringeability) of an extracted solution and their subsequent passage (injectability) via a 25-gauge needle.
Figure 2.10: Texture analyzer setup of A) syringeability and B) injectability test.
Figure 2.11: A) Syringeability and B) injectability profiles of HME pellets using a 3-mL syringe with a 25-gauge needle. C) Mean viscosities of formulations with agitation at RT and thermal manipulation at 90°C for 30 min. All values expressed as mean ± SD (n = 3).

2.3.9. Viscosity measurement

The viscosity of extracted solutions provides a determination of effectiveness of formulation deterrent for parenteral abuse. The viscosity of extracted solutions prepared from intact and manipulated formulations is shown in Figure. 2.11C. Among all the formulations, the PEO-xanthan gum pellets (F2) produced highly viscous solutions under agitation and thermal manipulation. The viscosities of all the formulations in increasing order were as follows: F2 > F3 > F4 > F1. The higher viscosity of the F2 formulation could be attributed to the rapid hydration and swelling characteristics of xanthan gum, which forms a gel in a small volume of water. Moreover, xanthan gum has been widely used as a thickener in pharmaceutical products, and a low concentration of xanthan gum can produce highly viscous solutions with shear-thinning properties [49]. The aqueous extracts of thermally manipulated F1 formulation have lower viscosity (9.33 ± 0.90 cp) compared with extracts of intact F1 and other formulations in both agitation and thermal manipulation conditions. Thus, the reduction in solution viscosity of the F1 formulation, after thermal manipulation, was due to random chain scission of the PEO structure into smaller fragments at high temperature. Joshi et al., 2018 reported the effect of temperature and concentration of PEO on the solution viscosity [32]. The reduction in solution viscosity was observed as the temperature increased up to 110°C and a further increase in temperature from 110°C to 150°C resulted in a sharp drop in solution viscosity. Compared with F1, the other formulations containing gelling agents have shown higher viscosities and can also produce a gel-like consistency in small-volume aqueous solutions. These results suggested that the F2
formulation is difficult to be drawn into a syringe and deter abuse by the parenteral route (IV) of administration.

2.4. Conclusion

Extensive laboratory-based category-1 in-vitro AD studies performed by using various manipulation methods revealed the AD characteristics of the formulation. Results demonstrated that ER pellets manufactured by the HME process provide resistance to PSR, which creates a barrier for oral and nasal routes of abuse. The in-vitro dissolution study revealed that ER properties were maintained even after the thermal and physical manipulation of pellets, indicating that dissolution was not affected by the manipulation method. The PEO/xanthan gum formulation (F2) exhibited superior viscosity and gelling properties, making it difficult to extract in different levels of solvents and thus making IV abuse less desirable. The syringeability, injectability, and viscosity measurements showed that intact and thermally manipulated xanthan gum-based formulations possessed high viscosity and gelling properties when prepared as IV solutions. Furthermore, the intact and manipulated PEO formulation showed decreased solution viscosity, syringe and injection forces when compared with other formulations, suggesting that PEO alone may not be the excipient of choice to deter the IV abuse of formulations. Thus, a combination of PEO with xanthan gum makes the formulation difficult to abuse via injection route, thus diminishing the feasibility of IV abuse. Therefore, the pellets manufactured by the HME process using PEO and gelling agents improves the AD properties of the formulation by preventing the IV abuse. However, controlled substances as model drugs should be evaluated for AD properties when prepared using the HME process.
CHAPTER-3

3. INFLUENCE OF PLASDONE™ S630 ULTRA—AN IMPROVED COPOVIDONE ON THE PROCESSABILITY AND OXIDATIVE DEGRADATION OF QUETIAPINE FUMARATE AMORPHOUS SOLID DISPERSIONS PREPARED VIA HOT-MELT EXTRUSION TECHNIQUE

3.1. Introduction

Trace levels of reactive impurities such as peroxides have been found in many pharmaceutical excipients, including povidones, copovidones, polyethylene glycol, and polysorbates. The presence of peroxide impurities leads to the degradation of drug products containing oxygen-sensitive active pharmaceutical ingredients (APIs), resulting in decreased product performance, loss in potency, and formation of toxic degradation impurities [50]. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use entails that the characterization and biological safety evaluation of degradation impurities are needed if the impurity profile is above the threshold levels based on daily dose [51]. Several approaches have been investigated for reducing the generation of peroxides from excipients, including chemical modification of the cross linker; use of enzymes and metals; and supercritical fluid extraction [50,52,53]. However, these approaches can limit the usage of excipients in a drug product because of the requirement of additional methods or additives for reducing peroxide concentration. Therefore, novel excipients such as Plasdone™ S630 Ultra (PS630U) copovidone, in which the initial peroxide levels as well as subsequent peroxide generation during storage can be controlled, were investigated as a choice of excipient for drug product stabilization against oxidative
degradation. The molecular weight, particle size and distribution, flowability, and peroxide stability of the new PS630U copovidone were improved compared to those of regular Plasdone™ S630 (PS630) copovidone (Table 3.1).

Table 3.1: Summary of the improvements in Plasdone™ S630 Ultra compared to Plasdone™ S630.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Plasdone™ S630 Ultra</th>
<th>Plasdone™ S630</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder flowability flow function</td>
<td>&gt; 9</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Molecular weight, polydispersity</td>
<td>14,000–18,000</td>
<td>&gt;20,000</td>
</tr>
<tr>
<td></td>
<td>3.3–3.6</td>
<td>&gt; 3.8</td>
</tr>
<tr>
<td>Peroxide stability</td>
<td>&lt; 100 ppm</td>
<td>&gt; 300 ppm</td>
</tr>
<tr>
<td>Particle size and distribution</td>
<td>Less fine and narrow</td>
<td>More fine and broad</td>
</tr>
</tbody>
</table>

Copovidone is a synthetic random copolymer consisting of N-vinyl-2-pyrrolidone and vinyl acetate in 60:40 ratios. Copovidones have low glass transition temperature (Tg; 108–110°C) and are less hygroscopic [54]. Plasdone-grade copovidones are commonly used as a matrix polymer for amorphous solid dispersion (ASD) formulations to enhance the solubility and bioavailability of poorly soluble drugs [55]. However, the use of copovidones in ASDs is associated with stability concerns because of the presence of trace amounts of peroxides, which may accumulate upon storage and cause the degradation of APIs that are sensitive to oxygen. Copovidones may induce oxidative degradation via the following mechanisms: radical-initiated oxidation (autoxidation) and peroxide-mediated oxidation [56]. Drug substances that are sensitive to oxidation, especially APIs with piperazine and tertiary amine functional groups, are highly susceptible to interaction with copovidones via different mechanisms such as N-oxide formation (Figure 3.1A) [57]. As per
United States Pharmacopeia USP-35, the initial limit of peroxides in copovidones should not be more than 400 ppm (NMT 0.04%). Although the initial peroxide levels are within the limit, controlling the generation and growth of peroxides upon stability is necessary for drug product stabilization [58].

![Oxidation mechanism of quetiapine fumarate (QF) containing a piperazine group with peroxide impurities; B) Potential known oxidative degradation impurities of QF.](image)

Figure 5 A) Oxidation mechanism of quetiapine fumarate (QF) containing a piperazine group with peroxide impurities; B) Potential known oxidative degradation impurities of QF.

In the present study, quetiapine fumarate (QF), an oxidation-labile, atypical antipsychotic agent was used as a model drug substance to determine the potential of PS630U and PS630 in the prevention of oxidative degradation when processed via hot-melt extrusion (HME). Quetiapine sulfoxide, quetiapine N-oxide derivative, and hydroxy quetiapine are the three oxidative
degradation impurities of QF [59]. Previous studies have indicated that N-oxide derivative is one of the major oxidative impurities of QF [60]. Hence, in this study, the levels of quetiapine N-oxide (Quetiapine EP Impurity H) were measured as an oxidative impurity. The degradation pathway and structures of the oxidative impurities are shown in Figure 3.1B. This study aimed to investigate the potential of novel PS630U and comparing it with that of PS630 in reducing the formation of oxidative impurities in tablets and milled extrudate formulations and evaluate the influence of the two copovidone grades on HME processability and QF ASD stability.

3.2. Materials and methods

3.2.1. Materials

Two types of copovidone grades PS630 and PS630U were supplied by Ashland, Inc. (Lexington, KY, USA). QF was obtained from RIA International LLC (East Hanover, NJ, USA). Avicel PH® 101 (microcrystalline cellulose) and Ac-Di-Sol® (croscarmellose sodium) were gift samples from FMC Biopolymer (Walnut Street, PA, USA); magnesium stearate and Aerosil® 200 (colloidal silica) were purchased from Alfa Aesar (Ward Hill, MA, USA). All other chemicals used were of analytical reagent grade.

3.2.2. Solubility parameter calculation

The miscibility of QF with Plasdone-grade copovidones was determined using the Hansen solubility parameters (δ) of the compounds by using group contributions from the chemical structures. The solubility parameter is a measure of the dispersion forces (δd), polarity forces (δp), and forces associated with hydrogen bonds (δh). The solubility parameter values were calculated using Van Krevelen and Hoftyzer group contribution method by using the following equations: [61]
\[ \delta^2 = \delta^2_d + \delta^2_p + \delta^2_h \]

\[ \delta_d = \frac{\sum F_{di}}{V} \]

\[ \delta_p = \frac{(\sum F^2_{pi})}{V} \]

\[ \delta_h = \frac{\sum E_{hi}}{V} \]

where \( \delta^2 \) is the total solubility parameter; \( \delta_d, \delta_p, \) and \( \delta_h \) are the parameters associated with dispersive forces, polar forces, and hydrogen bonding, respectively; and \( F_{di}, F_{pi}, \) and \( E_{hi} \) are the molar attraction constants due to dispersion, polar component, and hydrogen bonding energy, respectively. \( V \) is the molar volume. \( \delta^2 \) is commonly used to identify miscible drug–polymer combinations, and a system with similar \( \delta^2 \) is expected to be miscible [62].

### 3.2.3. Melt rheology

The rheological properties of pure PS630, PS630U polymers, and binary physical mixture (PM) of QF-PS630 and QF-PS630U at a weight ratio of 30:70 were studied using an AR-G2 controlled-stress rotational rheometer (TA Instruments, New Castle, DE). A parallel plate geometry with plate diameter of 25 mm and gap distance of 1 mm was used. Disk specimens (slugs) of pure polymer and PM of QF–polymer was prepared by compressing approximately 1 g of each PM sample in a die by using a carver laboratory press. Dynamic temperature sweep was conducted across a temperature range of 130 to 180°C with a heating/cooling rate of 5°C/min to determine the effect of temperature on complex viscosity. Other experimental conditions used for dynamic temperature sweep were fixed strain of 0.2%, which was within the linear viscoelastic region to minimize microstructure destruction, and fixed angular frequency of 6.2 rad/s. The measurement
temperature used for the study (130°C to 180°C) was above the Tg and below the degradation temperature of the polymer. Viscoelastic properties such as $G'$ (elastic modulus), $G''$ (viscous modulus), and $\eta^*$ (complex viscosity) were recorded as a function of temperature.

3.2.4. HME processing

A binary PM of QF with PS630 and PS630U at a weight ratio of 30:70 was passed through a USP #25 mesh sieve, and the PM was mixed in a V-shell blender (Maxiblend, GlobePharma, NJ, USA) for 10 min at 20 rpm. HME was performed using a 16 mm Prism Euro Lab co-rotating twin-screw extruder (Thermo Fisher Scientific, Waltham, MA) consisting of 10 barrel zones. The PM was fed into the extruder by using a volumetric feeder (Brabender Technologies, Germany). The screw configuration consisted of 3 mixing zones. The kneading elements in the mixing zones were set at 90°, 60°, and 30° angle (mixing zone-1); 60° angle (mixing zone-2); and 90° and 60° angle (mixing zone-3) to facilitate adequate mechanical shear and allow dissolution of QF in the molten polymer. The extrusion process was performed at a screw speed of 100 rpm and feed rate of 10 g min$^{-1}$. The barrel temperature for extrusion processing was identified on the basis of melt rheology analysis. During extrusion, the temperature of zone 1 was set at 50°C; for zones 2–9, temperatures were varied in the range of 140–160°C, and the temperature for zone 10 (near die region) was set at 140°C. The extrusion process parameters such as die pressure and torque values were monitored throughout the extrusion run. The obtained extrudates were cooled to ambient temperature and then milled using a laboratory-scale FitzMill (model L1A; Fitzpatrick, Perth Amboy, NJ, USA) by passing them through a 0.0200 inch (equal to 500 microns) mesh screen by using an amplitude of 20 Hz at a speed of 1200 rpm. Milled extrudates were stored in an aluminum pouch until further processing.
3.2.5. Differential scanning calorimetry

Thermal analysis of QF, PS630, PS630U, and PM of QF-polymer and extruded samples was performed using Discovery differential scanning calorimetry (DSC) 25 (TA Instruments, New Castle, DE, USA), integrated with an RCS90 cooling device. In brief, approximately 5 mg of sample was weighed and placed in an aluminum pan, and then crimped with the lid on. The samples were equilibrated at 25°C for 1 min under nitrogen gas, followed by heating at 10°C per minute to 200°C under a nitrogen purge of 50 mL min\(^{-1}\). The Tg of the API, polymer, and milled extrudates was measured using the heat-cool-heat cycle, where the samples were heated to 200°C at 10°C min\(^{-1}\) and then cooled to -20°C at a rate of 10°C min\(^{-1}\), followed by heating to 125°C at 2°C min\(^{-1}\). The thermograms were analyzed for Tg and melting temperature, to determine whether the crystalline drug had completely converted to the amorphous form after extrusion.

3.2.6. Fourier transform infrared spectroscopy

The Fourier transform infrared (FTIR) spectra of the drug, polymers, PM, and extrudate formulations were obtained using an Agilent Cary 660 FTIR Spectrometer (Agilent Technologies, Santa Clara, CA, USA). A small amount of the sample was placed on the surface of a diamond crystal and pressed with a MIRacle high-pressure clamp. The spectra were recorded in the absorption mode from 600 to 4000 cm\(^{-1}\) wavenumber range with 16 samples/background scan and a resolution of 4 cm\(^{-1}\).

3.2.7. Tableting and determination of tensile strength

Tablet formulations were developed using milled extrudates of QF-PS630, QF-S630U, and extra-granular excipients such as fillers, superdisintegrants, lubricants, and glidants. The milled extrudates, microcrystalline cellulose (Avicel pH 101), and croscarmellose sodium (Ac-Di-Sol)
were mixed in the V-shell blender for 10 min at 25 rpm. Next, colloidal silica and magnesium stearate were added and mixed in the V-shell blender for 3 min at 25 rpm. The final blend equivalent to 50 mg quetiapine base was compressed into a tablet (380 ± 10 mg) on a Piccola 10 station tablet compression machine equipped with a force feeder by using a 10 mm round concave tablet punching set at a compression force of 4.0 KN and turret speed of 12 rpm. Similarly, pure microcrystalline cellulose (MCC) and Plasdone™ copovidone tablets were also compressed. After compression, the tablets were characterized for weight, hardness, thickness, and diameter to determine the tensile strength (TS). The TS of the convex-faced tablets was calculated using the following formula: [63,64]

\[
\sigma_x = \frac{10F}{\pi D^2} \left[ \frac{2.84H}{D} - \frac{0.126H}{W} + \frac{3.15W}{D} + 0.01 \right]^{-1}
\]

where \(\sigma_x\) is the tensile strength, \(F\) is the breaking force, \(D\) is the tablet diameter, \(H\) is the tablet thickness, and \(W\) is the central cylinder thickness/tablet wall height.

### 3.2.8. High performance liquid chromatography

The oxidative impurity analysis of the samples was evaluated using high-performance liquid chromatography (HPLC; Waters Corp., Milford, MA, USA), where mobile phase (A) comprised 0.1% trifluoroacetic acid in DI water (v/v), and mobile phase (B) comprised methanol and acetonitrile at a ratio of 80:20 (v/v). The analytical column used was Xbridge C18, 3.5 μm, and 100 × 4.6 mm, which was operated at 30°C with a flow rate of 0.5 mL min⁻¹ and UV detection at 220 nm. The injection volume and run time were 15 μL and 60 min, respectively. For impurity analysis, sample solutions were prepared using the following procedure: The extrudates and tablet formulations equivalent to 20 mg of QF were accurately weighed into a 100 mL volumetric flask. Next, 75 mL of diluent (water: acetonitrile at 50:50 (v/v)) was added, and the resultant mixture was sonicated for 5 min, cooled to room temperature, diluted to final volume with the diluent, and
then filtered. The filtered solution at a concentration of 206 µg mL\(^{-1}\) was transferred to an HPLC vial for analysis.

### 3.2.9. Dissolution studies

The *in vitro* drug release studies of pure QF tablet and extrudate tablet formulations were performed at a dose equivalent to 50 mg quetiapine base (57.5 mg QF) in 900 mL of 0.05M phosphate buffer by using USP apparatus type I (SR8-plus\(^{TM}\); Hanson), maintained at 37 ± 0.5°C with a speed of 100 rpm for 60 min (n = 3). Sample aliquots were collected at different time intervals by filtering through a 0.45 µm pore size PVDF membrane filter (Durapore\(^{®}\); Millipore Sigma, MA, USA) and analyzed for the amount of drug released by using HPLC.

### 3.2.10. Stability study

Stability studies were conducted by placing milled extrudates and tablet formulations in high-density polyethylene bottles. The bottles were stored at 25°C/60% RH and 40°C/75% RH stability conditions. The milled extrudates were collected at 1 and 3 months (25°C/60% RH and 40°C/75% RH), and tablet formulations were collected at 1, 2, 3, and 6 months (40°C/75% RH) storage period. At each time point, samples were analyzed for the presence of oxidative impurities. The extrudate samples at 3-month 40°C/75% RH condition were analyzed using DSC to detect any recrystallization of QF in the ASD formulations.

### 3.3. Results and Discussion

#### 3.3.1. Solubility parameter

The calculation of the Hansen solubility parameters for QF and copovidones depends on the intermolecular interactions, various types of cohesive and repulsive forces, and molecular volume of each component [65]. Depending on the functional groups present in the chemical structure of
QF, the calculated solubility parameter (\(\delta\)) for QF was 22.82 MPa\(^{1/2}\); the details are shown in Table 3.2. The solubility parameter value for PS630 (26.40 MPa\(^{1/2}\)) used in this study was obtained from the literature [65]. The functional groups present in both PS630U and PS630 copovidones are similar; hence, the solubility parameter values for both copovidone grades are comparable. Similar solubility parameter values of QF and Plasdone\textsuperscript{TM} copovidones indicate miscibility. The difference in solubility parameters between the drug and polymer reflects the intermolecular interactions and miscibility of the drug within the polymer. A \(\Delta\delta\) of < 7 MPa\(^{1/2}\) indicates miscibility, because of the balance between the energy of mixing from intermolecular and intramolecular interactions [66]. In contrast, \(\Delta\delta\) of > 10 MPa\(^{1/2}\) indicates immiscibility [67] and might result in phase separation and/or recrystallization owing to the less prevalent intermolecular interactions. The difference in \(\delta\) between QF and PS630 was found to be < 4 MPa\(^{1/2}\), suggesting the miscibility of QF within the polymer matrix. In this study, QF and Plasdone\textsuperscript{TM} copovidones (PS630 and PS630U) had hydrogen bonding molar attraction constant values of 8.3 MPa\(^{1/2}\) and 11.86 MPa\(^{1/2}\), respectively. Because of their high molar attraction constant, intermolecular hydrogen bonding may play a main role in drug–polymer interactions [68].

Table 3.2 Calculation of the solubility parameter of quetiapine fumarate by using the group contribution method.

<table>
<thead>
<tr>
<th>Functional group</th>
<th>No. of groups</th>
<th>(F_{di})</th>
<th>(F_{pi}^2)</th>
<th>(E_{hi})</th>
<th>(V_m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylene (ACH)</td>
<td>4</td>
<td>4692</td>
<td>254.8</td>
<td>161.6</td>
<td>209.6</td>
</tr>
<tr>
<td>-S-</td>
<td>2</td>
<td>1631.8</td>
<td>392</td>
<td>595</td>
<td>24</td>
</tr>
<tr>
<td>-N=</td>
<td>2</td>
<td>760</td>
<td>200</td>
<td>500</td>
<td>10</td>
</tr>
</tbody>
</table>
\[
\begin{array}{cccccc}
-N< & 4 & 120 & 600 & 3000 & 36 \\
=C< & 2 & 113.4 & 0 & 0 & 10 \\
\text{Ring5-} & 4 & 571.2 & 0 & 0 & 64 \\
-\text{CH2-} & 16 & 3753.6 & 0 & 0 & 257.6 \\
-O- & 2 & 153 & 2450 & 202 & 7.6 \\
-\text{OH} & 2 & 153 & 2450 & 12120 & 20 \\
-\text{COOH} & 2 & 1122 & 1666 & 29290 & 57 \\
-\text{CH=} & 2 & 510 & 0 & 0 & 27 \\
\hline
\Sigma & 13353 & 8012.8 & 45868.6 & 630.8 \\
\end{array}
\]

\[\delta_d = 21.68 \quad \delta_p = 0.14 \quad \delta_h = 8.53\]

\[\delta_t \text{ QF} = 22.82 \text{ Mpa}^{1/2}\]

3.3.2. Melt rheology

In general, the rheological behavior can be measured as a function of temperature, time, frequency, and stress or strain amplitude. In this study, the melt rheology for pure PS630, pure PS630U, and PM of QF with both grades of copovidones was characterized by measuring the viscoelastic properties—\(\eta^*\), \(G'\), and \(G''\)—as a function of temperature at constant strain and shear rate. Rheological analysis was performed in the linear viscoelastic region, where \(\eta^*\), \(G'\), and \(G''\) were measured by varying the stress or strain up to 100% while maintaining the temperature and frequency constant. Measuring the temperature-dependent melt viscosity is useful for predicting the HME process temperature. During temperature sweep, other parameters such as frequency and strain were held constant. The \(\eta^*\), \(G'\), and \(G''\) values of pure PS630, pure PS630U, and QF with PS630 and PS630U as a function of temperature are shown in Figure 3.2. The \(\eta^*\) refers to the resistance of the polymer or PM to flow. \(G'\) is a measure of deformation, i.e., energy
stored/recovered, and is related to molten polymer swelling. The loss of the rigid structure because of the applied temperature is referred to as $G''$, and it is a measure of energy lost or dissipated. The magnitude of crossover of $G'$ and $G''$ indicates the temperature at which the behavior of a material changes from elastic to viscous [69–71]. The plot of $G'$ and $G''$ as a function of temperature showed that these factors decrease as the temperature increases, and their curves intersect or reach close to each other at temperatures above 160°C and 180°C (Figure 3.2B and 3.2C), respectively, for PM and pure Plasdone™ copovidones, suggesting a transition from a glassy to rubbery state [71]. The complex viscosity profiles of QF-PS630 and QF-PS630U PMs in the measured temperature range were less than those of pure PS630 and PS630U (Figure 3.2A), indicating the plasticizing effect of QF. The extent of plasticizing may vary depending on the functional groups such as hydrogen bond donors and acceptors present in the API [72]. Previous studies suggested that a complex viscosity between 10,000 and 1000 Pa s should be ideal for optimal extrusion [73]. This range was established on the basis of the following considerations: (i) the polymer should be sufficiently less viscous to allow the dissolution of the drug; (ii) the plasticity of the polymer must be maintained so that the material can be extruded through the barrel and does not settle on the bottom of the barrel, thereby avoiding degradation; and (iii) extrudate strands need to exit from the die for successful extrusion [70].
The η* values for pure PS630 and PS630U were approximately 10,000 Pa s at temperatures above 160°C (Figure 3.2A) and decreased gradually with increasing temperature, and those of 30% QF with PS630 and PS630U was approximately 10,000 Pa s at above 135°C. Thus, the decreases in the complex viscosity of the PM below the melting temperature of QF suggested that the PM can be extruded well below the melting temperature of QF (174°C) owing to an increase in the separation of the copovidone polymer chains because of the plasticizing effect of QF and miscibility of QF in the polymer. These effects of QF may be attributed to the reduced complex viscosity of the PM compared to that of pure PS630 and PS630U [74]. The η* of PM decreased further when the temperature was increased to above 160°C, suggesting that QF might be completely miscible or might have dissolved into the polymer matrix.

Similarly, G’ and G” for the PM decreased as the temperature increased (Figures 3.2B, 3.2C); this magnitude of drop in G’ and G” indicates a drop in elasticity and subsequent drop in
complex viscosity. The plot of $G'$ and $G''$ as a function of temperature provides information regarding the amount of energy dissipated or lost in a sample. The higher value of $G''$ than that of $G'$ explains the viscoelastic or liquid state behavior of the sample as the temperature increases [70,71]. The $G'' > G'$ in pure PS630, pure PS630U, and PM of QF-PS630 and QF-PS630U can be explained by the viscoelastic nature of the pure polymers and PM samples. These results suggest the plasticizing effect of QF, and the complex viscosity of PM samples was in the range of 10,000 to 1000 Pa s at a temperature range of 135–160°C. These observations aid in the selection of the extrusion processing temperature that does not generate high torque.

### 3.3.3. HME processing

The melt viscosity results revealed that the lowest possible extrusion temperature for PM of QF copovidones was 135°C. In the case of pure PS630 and PS630U, extrusion was not possible at 140°C or below by using any screw configuration and feed rate because the torque exceeded the upper limit of the extruder [55]. However, PM at 30% drug load extruded successfully at 140°C with a processing torque value well below the instrument limit. This is because QF acted as a plasticizer for PS630 and PS630U, as confirmed by the melt rheology observations. The QF-PS630 PM (30:70) was extruded at 140, 150, and 160°C (Zones 2–9) at a feed rate of 10 g min$^{-1}$ and screw speed of 100 rpm (Table 3.3). The copovidones were compared using the process conditions optimized with QF-PS630 PM extrusion for the extrusion of QF-PS630U PM.

**Table 3.3 Hot-melt extrusion process conditions and measured output parameters of QF-PS630 and QF-PS630U amorphous solid dispersion.**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Extrusion process temperature</th>
<th>Process conditions</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zones (°C)</td>
<td>Feed rate (g/min)</td>
<td>Screw speed (rpm)</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>2</td>
<td>3-9</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>QF-PS630</td>
<td>50</td>
<td>150</td>
</tr>
<tr>
<td>50</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>QF-PS630U</td>
<td>50</td>
<td>160</td>
</tr>
</tbody>
</table>

The PS630 extrudates prepared at 140°C and 150°C appeared to be opaque with a rough surface, which could be attributed to the incomplete dissolution of crystalline QF. With increasing barrel temperature, torque decreased in the temperature range of 140–160°C (Table 3.3), which reveals the shear-thinning behavior of the two Plasdones™ copovidone grades [75]. At 160°C, extrudates prepared with PS630 were brittle, transparent, and yellowish; for PS630U-containing formulations, extrudates were brittle, clear, and light yellowish, which could be attributed to the homogenous mixing. Crystalline QF dissolved into both copovidone grades. Furthermore, the yellowness decreased for PS630U extrudates, suggesting an improved performance and greater HME processability compared to those of the extrudates of PS630. The enhanced HME processability of PS630U could be attributed to the improvements in molecular weight, particle size distribution, and flowability compared to those of regular PS630. Traditionally, yellowness index analysis measures the sensitivity of a formulation to degradation and provides valuable information regarding the efficiency of the polymeric stabilizer. The greater the tendency of extrudates to turn yellow, the more is the sensitivity to degradation [76].
images of PS630 and PS630U extrudates processed at different temperatures are shown in Figure 3.3. During the extrusion, the processing torque and die melt pressure were in the range of 35–40% and 13–14 PSI, respectively, for formulations with both copovidone grades, suggesting that the selected process parameters were adequate and did not show excessive pressure generation inside the extruder. In the case of extrudates processed at 160°C, air bubbles were formed on the extrudates after the exit from the die. However, when the temperatures of zone 10 and die were decreased to 140°C, extrudates with little or no signs of air bubbles were produced.

![Images of QFcopovidone extrudates processed at different barrel temperatures.](image)

**Figure 3.3:** Images of QF copovidone extrudates processed at different barrel temperatures.

3.3.4. DSC

The thermal characteristics of QF, pure copovidones, and milled extrudates are shown in Figure 3.4. The DSC thermogram of pure QF showed a sharp endothermic peak at 174°C (Figure 3.4A) attributed to the melting of the crystalline drug [77]. The DSC thermogram of PM exhibited pronounced peak broadening and shifting of the QF melting point to a lower temperature value, which could be attributed to the gradual dissolution and/or miscibility of the drug into the polymer [78]. The extrudates of QF-PS630 prepared at a barrel temperature of 140 °C and 150°C showed
residual amount of crystalline QF, as evidenced by the small endothermic peak around 168°C (Figure 3.4A). In contrast, extrudates prepared at 160°C showed no distinct endothermic peak of QF, indicating the complete transformation of crystalline QF into an amorphous form, suggesting the successful formation of ASDs via HME processing. The heat-cool-heat cycle showed a Tg of 47°C, 108.7°C, and 110.6°C, respectively, for QF, PS630, and PS630U (Figure 2.4B). The DSC analysis of the milled extrudates revealed the presence of a single Tg at 77.5°C and 79.8°C, respectively, for PS630 and PS630U extrudates, signifying the molecular-level miscibility of QF in the polymer. For an ASD, a distinctive single Tg has been considered as an indication of molecular-level dispersion or dissolution of a drug in the polymeric system, which is critical for the physical stability of ASDs against crystallization [79]. For both copovidone grades, the Tg of the formulation did not vary considerably and showed an identical single Tg, confirming the similarity in homogeneous and molecular-level mixing of the drug and polymer.
Figure 3.4: A) DSC thermograms of pure QF, PS630, PS630U, PM, and extrudates processed at 140 °C, 150 °C, and 160°C; B) Glass transition temperatures of QF, PS630U, PS630, and the extrudates of QF-PS630 and QF-PS630U.

3.3.5. FTIR

The FTIR spectra were used to characterize and understand the possible hydrogen bonding and drug–polymer interactions of the QF-PS630 and QF-PS630U ASDs. The FTIR spectra of pure QF, pure PS630, pure PS630U, PM, and extruded formulations are shown in Figure 3.5. The FTIR spectra of QF showed characteristic bands of C=O at 1599 cm⁻¹ and the O–H stretching vibrations at 3,250–3,500 cm⁻¹. The characteristic peaks at 2887 and 2945 cm⁻¹ corresponded to the –C–H
stretching vibrations. The peaks at 3100 cm\(^{-1}\) were attributed to aromatic =C–H stretching from the thiazepine ring. The peaks at 1260 and 1305 cm\(^{-1}\) corresponded to C–O–C asymmetrical stretching and C–N stretching, respectively [80]. The Plasdone\(^{TM}\) copovidones showed characteristic bands of C=O stretch of vinyl acetate and amide carbonyl at 1731 and 1670 cm\(^{-1}\), respectively. The PM spectra showed frequency bands corresponding to individual components, suggesting the absence of interaction between the drug and polymer in the PM sample [65]. In the FTIR spectrum of milled extrudates, the characteristic C=O stretch of the amide carbonyl shifted from 1670 cm\(^{-1}\) to 1656 (QF-PS630U) and 1661 cm\(^{-1}\) (QF-PS630), and a new peak was observed at 1598 cm\(^{-1}\), indicating intermolecular hydrogen bonding between the drug and polymer. Hydrogen bonding between QF and Plasdone\(^{TM}\) copovidones can disrupt the polymer chain arrangement, which results in the plasticization effect of QF [74].

The literature states that the vinyl acetate C=O carbonyl group of copovidones is a weak hydrogen bond acceptor, and the hydrogen-bond-donating functional groups in drug molecules are likely involved in intermolecular interactions and restrict crystallization. Furthermore, the strong intermolecular interactions between the drug and polymer might account for the improved ability of the polymers to inhibit nucleation and crystallization [81,82]. In addition, the reduced intensities of the characteristic bands of QF in the formulation might be attributed to the molecular-level distribution of QF in the copovidone polymers.
3.3.6. Tableting and tensile strength measurement

From the downstream processing perspective, a substantial amount of extragranular excipients was required to improve the flowability, compressibility, and disintegration properties of the milled extrudates. Initially, milled extrudates at a level of 60–70% with 40–30% of extragranular excipients were evaluated for their compression feasibility. The tableting blend at these levels of milled extrudates exhibited poor compression characteristics, which could be attributed to the denser, less internal voids; brittleness of the extruded filaments; and lower porosity of the tablet blend. During compression, the force required to compress a tablet blend containing 60% and 70% level of milled extrudates was 15 and 20 kN, respectively. Furthermore, decreasing the milled extrudate level to 50% and increasing the MCC level to 40% resulted in a decrease in compression force to 4.2 kN, suggesting increased porosity of the tablet blend by increasing the MCC level. The high intraparticle porosity and greater surface area characteristics of MCC could promote the

Figure 3.5: The FTIR spectra of A) pure QF; B) PS630; C) PS630U; D) PM of QF-PS630; E) PM of QF-PS630U; and F), G) extrudates of QF-PS630 and QF-PS630U respectively.
Tableting of the milled extrudates [83]. Tabletability is described as the magnitude of a powder blend to produce tablets of specific tensile strength under the influence of compression force [84]. The compressed tablets were characterized for breaking force (KP), diameter (mm), and thickness (mm) in order to calculate the tensile strength. The tensile strength of the milled extrudates, pure PS630, PS630U, and MCC, is shown in Figure 3.6, and the composition of the tablets selected for tensile strength measurement is provided in Table 3.4.

![Tensile strength of tablets prepared from QF-PS630 and QF-PS630U milled extrudates, pure PS630, PS630U, and MCC.](image)

**Figure 3.6:** Tensile strength of tablets prepared from QF-PS630 and QF-PS630U milled extrudates, pure PS630, PS630U, and MCC.

The tablets of pure MCC and copovidones (PS630, PS630U) exhibited high TS, which could be attributed to the inter-particulate bonding or inherent adhesion properties of the material within a tablet under the applied compression force [85,86]. In contrast, a tableting blend containing milled extrudates showed lower TS owing to the increase in particle density and loss of voids caused by heat and shear stress during HME [87]. This suggests that melt extrusion reduces the ability of milled extrudates to form strong bonds during compression. These observations were in accordance with those of previous studies. Iyer et al. [88] evaluated the impact of HME on the TS
of tablets containing milled extrudates of copovidone and compared it with that of unprocessed or pure copovidone tablets. The results indicated that the TS of copovidone tablets decreased upon HME compared to that of the tablets of pure copovidone owing to the brittle nature of the extrudates formed upon melt extrusion, suggesting the densification and poor bonding properties of milled extrudates.

**Table 3.4: Composition of excipients used for tableting.**

<table>
<thead>
<tr>
<th>Material</th>
<th>Amount (% w/w)</th>
<th>mg/Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milled extrudates of PS360/PS630U</td>
<td>50.5</td>
<td>191.85*</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>40.5</td>
<td>153.95</td>
</tr>
<tr>
<td>Crosscarmellose sodium</td>
<td>8.0</td>
<td>30.40</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Colloidal silica</td>
<td>0.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Dose equivalent to 50 mg quetiapine base

**3.3.7. Dissolution studies**

The drug release of pure QF tablets and QF-PS630 and QF-PS630U tablet formulations was performed in 0.05M phosphate buffer as a dissolution medium (Figure 3.7). The pure QF and tablet formulations with both grade copovidones showed 100% drug release within 15 min. This rapid dissolution rate could be attributed to the high solubility of QF in the dissolution medium. During the initial time points, the dissolution rate was relatively slow for tablet formulations, which can be described by polymer hydration and formation of a gel layer on the surface of the tablets [89]. QF exhibits a pH-dependent solubility profile with a high solubility in the pH range of 1.2–6.8. The reported solubility was found to be >9.2 mg mL⁻¹ in 50 mM phosphate buffer [90]. Because of the high solubility in the studied dissolution media, no limitations of supersaturation and
precipitation phenomenon of QF were observed during the dissolution study, and copovidone grades had no significant influence on the dissolution rate.

The saturation solubility (Cs) to the dose (Cd) ratio of QF in the dissolution media was notable. The calculated Cs and Cd of QF in phosphate buffer were found to be 9.2 and 0.064 mg mL$^{-1}$, respectively. These results indicated that the dissolution rate may not be a rate-limiting step for QF.

![Dissolution Profile](image)

**Figure 3.7:** The dissolution profile of QF-PS630U, QF-PS630 and pure QF tablets.

### 3.3.8. Stability study

The milled extrudates and tablet formulations of QF-PS630 and QF-PS630U subjected to long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions were analyzed to determine the oxidative degradation profile. The oxidative impurities of the milled extrudates and tablet formulations of QF-PS630 and QF-PS630U during the stability study are shown in Figure 3.8.

The PS630U milled extrudates had the lowest percent oxidative impurity with 0.19% and 0.42% at 3 months of 25°C/60% RH (Figure 3.8A) and 40°C/75% RH (Figure 3.8B) conditions, respectively. In contrast, the extrudates of PS630 showed relatively high percentage of oxidative
impurities (0.42% and 0.95%, respectively) at 25°C/60% RH and 40°C/75% RH stability conditions, respectively.

Figure 3.8: Oxidative degradation profile of A), B) milled extrudates, and C) tablet formulations.

For QF-PS630 tablet formulations (Figure 3.8C), the 6-month stability at 40°C/75% RH condition showed an oxidative impurity of 0.39%. In contrast, tablets prepared with QF-PS630U showed 0.13% oxidative impurity, which is 3-fold less than that of tablets developed with regular PS630-grade copovidone. The increase in oxidative impurity at accelerated stability conditions (40°C/75% RH) suggests the temperature-dependent oxidative degradation of QF in the ASD formulations. For PS630U formulations, the lower levels of oxidative impurities could be attributed to the low initial level of peroxides present in PS630U and the generation of reactive impurities during storage, as revealed by stability studies compared to regular PS630-grade copovidone formulations. Peroxides are reactive impurities present in various copovidone-grade
polymers that can directly react with the piperazine moiety of QF, initiate radical chain reactions, and induce the formation of oxidative degradation impurities [91].

Milled extrudates of both PS630 and PS630U showed variable oxidative degradation profiles with 2.2- and 2.4-fold less oxidative impurities in PS630U than in PS630 at 25°C/60% RH and 40°C/75% RH conditions, respectively. The oxidative impurity levels clearly increased for both the milled extrudates and tablet formulations. In addition, the initial level of oxidative impurities for QF-PS630 milled extrudates was found to be 0.15%. In the case of QF-PS630U milled extrudates, no oxidative impurities (below the limit of detection) were present, suggesting the existence of very low levels of peroxides in PS630U-grade copovidones.

Furthermore, the mechanism responsible for the oxidative degradation of QF could be either free radical chain mechanism or direct tertiary amine oxidation due to peroxide impurities present in the Plasdone™ copovidone polymers [58,92]. Peroxides can be either organoperoxides (ROOR) or hydroperoxides (ROOH). The free radical chain mechanism for peroxide generation involves the cleavage of the bonds, followed by the addition of oxygen next to a hetero atom, which leads to the formation of peroxy free radicals [50].

While designing new formulations comprising oxygen-sensitive APIs, considering the initial peroxide levels and potential growth of reactive impurities of copovidones upon stability is necessary. The oxidative impurity data suggested that PS630U had better stability and prevented peroxide-induced oxidative degradation under stability conditions compared to regular PS630-grade copovidones.

The physical stability was evaluated by characterizing the extrudate formulations by using DSC after storage for 3 months under 40°C/75% RH stability condition. The melting thermograms of the stability samples are shown in Figure 3.9.
DSC thermograms of stability samples showed that QF with PS630 and PS630U remained amorphous in the formulations with both copovidone grades and the slight endothermic peak observed at a temperature of approximately 100°C could be attributed to the evaporation of moisture during DSC analysis. The DSC results of the stability samples confirmed the homogeneity, and no phase separation of the amorphous drug was noted, as evidenced by the absence of the melting peak of QF, suggesting that HME formulations were physically stable during the stability study.

3.4. Conclusion

The impact of peroxide levels of PS630 and PS630U on oxidative degradation was successfully studied using the HME technique. Melt viscosity results provided insights into the selection of the HME processing temperature of both copovidone grades and exhibited similar complex viscosity profiles as a function of temperature. The extrudates of PS630U were transparent and light yellow in color, and PS630 extrudates appeared as dark yellow. These observations could be attributed to the superior HME processability of PS630U compared to that of regular PS630 copovidone.
Thermal characterization and tabletability of both PS630U and PS630 formulations showed comparable Tg and TS profiles, respectively, indicating similar physicochemical characteristics between PS630 and PS630U copovidones. The stability study of the milled extrudates and tablet formulations confirmed that QF is highly sensitive to trace amounts of peroxides in copovidones, which caused the oxidation of QF to generate N-oxide impurities. The low initial peroxide levels, reduced growth, and peroxide generation in PS630U, as evidenced by low oxidative impurities after 6M stability studies, suggested that PS630U is relatively stable and showed less peroxide generation at ambient and accelerated stability conditions compared to regular PS630. Furthermore, the outcome from this study revealed the applicability of the novel Plasdone™ 630 Ultra for improved drug product stability against oxidative degradation in ASDs developed using the HME technique.
CHAPTER-4

4. INTERPLAY OF POLYMERIC COMBINATIONS FOR IMPROVED SUPERSATURATION KINETICS AND DISSOLUTION PERFORMANCE OF HPMCAS BASED AMORPHOUS SOLID DISPERSIONS PREPARED VIA HOT-MELT EXTRUSION TECHNIQUE

4.1. Introduction

Over the past few years, there has been increasing understanding that simply enhancing the solubility or dissolution rate of poorly soluble active pharmaceutical ingredient (API) is often insufficient to obtain a desired bioavailability. Therefore, a delivery system that promote supersaturation has gained increased interest [93]. Amorphous solid dispersions (ASDs), where a poorly soluble drug is molecularly dispersed or suspended into a polymeric matrix typically as an amorphous state has been studied as a most effective formulation approach which can provide supersaturation [94]. When amorphous supersaturated drugs dispersed in aqueous or aqueous buffer solutions, it shows a drug concentration higher than its crystalline solubility. However, crystallization or precipitation of drug molecules in a supersaturated solution changes the drug concentration by revert back to its intrinsic or crystalline solubility [95].

To exploit supersaturation, the generation and maintenance of supersaturated state of drug is needed to improve or sustain absorption of poorly soluble drugs. Once supersaturation has been achieved, the drug molecules have a tendency to crystalize or precipitate, this may be controlled by kinetic or thermodynamic way. For sufficient absorption, the supersaturated state of drug has to be maintained for prolonged period of time, this may require polymeric carriers or other
excipients such as surfactants to delay or inhibit the precipitation and interfere with the nucleation, crystal growth of drug molecules [96,97].

Depending on the nature of the polymer being dissolved in the dissolution medium, the dissolved polymer can retard the extent of decline in drug concentration by increasing the drug solubility (thermodynamically), thereby decreasing the degree of supersaturation, which could be the driving force for crystallization [98,99]. At this stage, rapid desupersaturation can be avoided by reducing the degree of supersaturation to well below the critical supersaturation, thereby suppresses the rate of precipitation. Further, intermolecular interactions such as hydrogen bonding and hydrophobic interactions between the drug and polymer can affect the kinetics of precipitation by inhibiting the nucleation and crystal growth of supersaturated drug [100,101]. In the past extensive research have been shown that hydrophilic polymers namely polyvinylpyrrolidone K-29/32 (PVP), polyvinylpyrrolidone-vinyl acetate (PVPVA64) and the hydrophobic hydroxypropylmethylcellulose acetate succinate (HPMCAS) and methacrylate copolymers i.e., Eudragit® RSPO and Eudragit® FS100 play a key role as a precipitation inhibitors by maintaining the drug supersaturation levels in a solution [94,102].

In general, it is assumed that hydrophobicity between drug and polymer promote stabilization of supersaturated drug by extending the supersaturation i.e., inhibition of precipitation for a sufficient duration. However, when formulating as ASD, in many cases the hydrophobic polymers exhibit a slower dissolution rate compared to that of ASD made with hydrophilic polymers [103,104]. On the contrary, the ASD consist of hydrophilic polymer and hydrophobic drug can exhibit a fast dissolution rate, but the ability to maintain supersaturation level upon dissolution of the ASD is limited. Therefore, the combination of two different polymers in ternary ASD formulation could be beneficial in achieving supersaturation maintenance with optimal dissolution rate compared to
the respective binary ASDs [105,106]. The dissolution rate and precipitation inhibition potential of ternary solid dispersion depends on the characteristics of each polymer.

Previously, few studies have been reported the impact of HPMCAS grades (LG, MG, HG) on the supersaturation kinetics and dissolution profile of spray dried itraconazole and hot-melt extruded nifedipine (NIF) ASD formulations. The findings of their study revealed that HG grade had greater precipitation inhibition effect on supersaturated drug in a solution, while the LG grade had shown faster dissolution rate compared to other two grades [107–109]. To best of our knowledge, no studies have been reported on polymer blends containing LG grade with other polymers to overcome the drawback of rapid nucleation induction or desupersaturation potential of the LG grade without compromising its ability to promote faster dissolution rate.

The aim of the current study was to investigate the potential of hydrophilic polymers (PVP, PVPVA64) and hydrophobic polymers (HPMCAS HG, Eudragit® FS100, Eudragit® RSPO) in combination with HPMCAS LG to stabilize the supersaturated state of NIF in a solution. The chemical structures of respective polymers and the model drug NIF are presented in Figure 4.1.

We aimed to assess the potential of polymeric combinations that can quickly dissolve ASD formulation with a delay in nucleation (strong precipitation inhibition effect). In order to find a suitable polymeric combination, the amorphous solubility of NIF in the presence and absence of polymer was determined by generating a supersaturated solution of NIF. The generated supersaturated solution was examined for nucleation induction and characterized using dynamic light scattering (DLS) to understand the precipitation inhibition potential of polymer alone or in combination. The dissolution behavior of ASDs was tested by performing non sink dissolution study and the dissolution parameters (Cmax and AUC) were calculated to assess the ASD
performance. Further, the physical properties of the ASD formulations were determined using Fourier-transformed infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC).

Figure 4.1: Chemical structure of drug and polymers used in the ASDs.

4.2. Materials and methods

4.2.1. Materials

HPMCAS LG, HPMCAS HG (Aquasolve™), PVP K-29/32 (Plasdone™) were obtained as gift samples from Ashland, Inc. (DE, USA), Poly (1-vinylpyrrolidone-co-vinyl acetate) (Kollidon VA64) was donated by BASF corporation (New Jersey, USA) and Poly (ethyl acrylate-co-methylmethacrylate-co-trimethylammonioethyl methacrylate chloride) (Eudragit® RSPO), methyl acrylate-methyl methacrylate-methacrylic acid terpolimer (Eudragit® FS100) were received as a
4.2.2. Determination of crystalline and amorphous solubility

The crystalline solubility of NIF in phosphate buffer pH 6.8 was determined by adding excess drug to the media and then subjected to agitation at 500 rpm, 37°C for 48 hrs. Aliquot was withdrawn after 48 hrs and centrifuged to separate the undissolved drug. The supernatant was analyzed by measuring the UV absorption spectrum at 340 nm.

The amorphous solubility of NIF was determined by performing liquid-liquid phase separation experiments using an ultra-centrifugation method. A supersaturated solution stock of NIF in dimethyl sulfoxide (DMSO) at a concentration of 20mg/mL was prepared. The final concentration of DMSO solution in the buffer medium was kept at \( \leq 2\% \) in order to minimize the influence of the DMSO on drug solubility [110]. From the stock solution, 200\( \mu \)L was added to 20mL of pH 6.8 phosphate buffer media, in which 7 mg of polymer (LG, HG, PVP, VA64, FS 100 and RSPO) or polymeric combination (LG+HG, LG+PVP, LG+VA64, LG+FS100, LG+ RSPO) had previously been dissolved (suspended in the case of HG, FS 100 and RSPO) at 37°C and the media was stirred at 500 rpm. The amount of pre-dissolved polymer was equivalent to the amount of polymer in the ASDs used during dissolution study [111]. The experiments were also performed without polymer to determine the amorphous solubility of pure NIF. After addition of NIF stock to the pre-dissolved polymer solutions, samples were stirred for 30 minutes at 37°C, then withdrawn and centrifuged at 13000 rpm for 25 minutes to separate the two liquid like phases [112]. The supernatant was analyzed using a UV spectrophotometer.
4.2.3. **Nucleation induction time measurement**

The effectiveness of the polymer alone or in combination on crystallization inhibition from the supersaturated solution was evaluated by measuring the nucleation induction time. The induction time for nucleation is defined as the time required for the appearance of the small crystals with a detectable size in a supersaturated solution. The precipitation induction time of polymers alone or in combination was determined by monitoring the changes in absorbance using modified plate reader detection technique [113]. Two hundred microliters of 20 mg/mL NIF stock solution was pipetted into 20 mL of pH 6.8 phosphate buffer containing 0.35 mg/mL pre-dissolved polymer. The solution was equilibrated at 37°C and stirred at 500 rpm. Then, 200µl of supersaturated solutions were withdrawn, transferred into a 96-well polypropylene plate at every 3-minutes time interval in first 30 min, then after every 5 min until 120 min. The change in UV absorption spectra of samples were measured at 340 nm using plate reader (Bio-Tek, Winooski, VT, USA). Absorbance as a function of time was measured for 2 h and plotted. Induction time was determined as the time at which sharp decrease or shift in the baseline of the UV absorbance spectrum or the concentration of the supersaturated solution had decreased by 2.5% [114]. It should be noted that precipitation or crystallization was the only contributor to the decreased absorbance. The study was performed for supersaturated NIF solution in the presence of polymer alone or in combination.

4.2.4. **DLS**

The particle size of NIF precipitates with or without presence of polymers in a supersaturated solution was investigated to screen the precipitation inhibitor for NIF. The supersaturated solution obtained in the nucleation induction study was analyzed to determine any sub-visible aggregates. Supersaturated samples were obtained at 0 and 120 min and filtered through 2µ filter before the
measurements. The mean particle size (z-average) of precipitates in a supersaturated solution was measured using Malvern Zetasizer Nano ZS90 (Malvern Instruments, Worcestershire, UK) at 25°C. Scattered light intensity was collected at 90° and refractive index was set at 1.33.

4.2.5. HME processing

The physical mixtures of NIF, polymeric blends were sieved through a #25 mesh ASTM and blended in a V-shell blender (Maxiblend; GlobePharma, New Jersey, USA) at 20 rpm for 15 min. The drug-polymer binary and ternary powder mixture at 30% drug load was extruded using a pharma 11 co-rotating twin screw extruder (Thermo Fisher scientific, Waltham, MA, USA). A screw configuration consisted of three mixing zones at a feed rate of 2.5 g/min, screw speed of 50 RPM and temperature range of 160 -170°C was employed for extrusion processing. The feeding zone was kept 50°C while the zones 2-8 were maintained at the same temperature. The output parameters such as die pressure and torque values were recorded. The resulting extrudates were milled using a laboratory grinder, milled extrudates passed using a #30 ASTM mesh and stored in HDPE container at room temperature till further use.

4.2.6. DSC

DSC analysis was performed for NIF and extrudates to determine the melting point (Tm) and glass transition temperatures. DSC studies were carried out via heat-cool-heat cycle using Discovery DSC 25 (TA Instruments DSC, New Castle, DE, USA). Approximately weighed 5-10 mg samples were sealed in aluminum pan. In the first heating cycle, samples were heated to 200°C at a ramp rate of 10°C/min, then cooled to -10°C followed by a heating to 120°C to identify the Tm and Tg.
4.2.7. FTIR

FTIR studies were performed to study the drug-polymer interaction. The analysis was performed using Agilent Cary 660 FTIR Spectrometer (Agilent Technologies, Santa Clara, CA, USA) and the spectrum was collected in 1000–3800 cm\(^{-1}\) range with 4 cm\(^{-1}\) resolution and a scans of 16. The FTIR bench was equipped with an ATR (Pike Technologies, Madison, WI, USA), which was arranged with a single-bounce, diamond-coated ZnSe internal reflection element.

4.2.8. In-vitro non sink dissolution

In order to evaluate the performance of ASDs and to allow the buildup of supersaturation, nucleation and crystallization events to proceed, a non-sink dissolution was performed. Sink index (SI) was used for supersaturated ASD samples to characterize the degree of departure from sink condition. SI is defined as \(SI = \frac{CsV}{Dose}\), where \(Cs\) is the crystalline drug solubility, \(V\) is the volume of dissolution medium, and \(Dose\) is the total amount of drug in the ASD [115]. In general, a large SI indicates the dissolution medium that is close to the sink condition. As per USP, perfect sink conditions achieved when SI is larger than 3 [99]. During dissolution study, the total amount of NIF in the ASDs was maintained at 135 mg which is corresponding to 150 \(\mu\)g/mL if completely dissolved in 900 mL of dissolution medium. As will be discussed later, the crystalline or equilibrium solubility of NIF in the pH 6.8 phosphate buffer was determined to be 10.4 ± 3.1 \(\mu\)g/mL. Thus, the corresponding SI values for in vitro dissolution was determined to be 0.09, approximately 13 times of the solubility of crystalline NIF.

Dissolution experiments for binary NIF/LG, NIF/HG and ternary NIF/LG+PVP, NIF/LG+FS100, NIF/LG+RSPO, NIF/LG+VA64 ASDs were performed on USP-II dissolution apparatus (SR8-plus™, Hanson) using 900 mL of pH 6.8 phosphate buffer maintained at 37±0.5°C and paddle speed of 50 rpm. At predetermined time interval, 2 mL aliquot was withdrawn using 2 \(\mu\)m filter
and replaced with a fresh dissolution medium. The drug concentration in the supernatant was determined by measuring the UV absorbance at 340 nm. The dissolution performance of the ASD is evaluated on the basis of parameters such as maximum supersaturation concentration ($C_{\text{max}}$), extent of supersaturation (area under the curve, AUC).

4.3. Results and discussion

4.3.1. Polymer carrier selection

NIF with a melting point of 173 °C was selected as a model drug in the present study. It is a poorly soluble drug with medium crystallization tendency and it belongs to class II of crystallization tendency classification [116]. The hydrophilic polymers selected were PVP K-29/32, PVPVA64, has a Tg of 164 °C and 107 °C respectively, these polymers have the potential to inhibit drug crystallization in the solid state as well as in aqueous solution owing to different number of hydrogen bond acceptors and donor that can form hydrogen bond with drug molecules and maintain the supersaturation by both solubilization and crystallization inhibition effect [94]. The HPMCAS grade polymers LG, HG have the Tg of 119°C-122°C, and dissolve at pH ≥ 5.5 (LG) and > 6.8 (HG) [108]. The hydrophobicity of HG grade can retard drug precipitation and stabilizes supersaturated drug, whereas, the hydrophilic nature of LG grade provides rapid and higher supersaturation level, but fails to maintain it for longer period in the aqueous buffer media. The rank order of HPMCAS grades for dissolution performance i.e., faster dissolution rate was LG > HG. For precipitation inhibition or retardation, the HPMCAS grade performance was HG > LG [107,117]. The methacrylic copolymer Eudragit® FS100 has a glass transition temperature of about 50°C and it is soluble only above pH 7 owing to free carboxylic acid moiety on the polymer chain [118]. Eudragit® RSPO is an ammonio methacrylate copolymer with a Tg of 64°C and it is insoluble at physiological pH. These methacrylate copolymers (Eudragit® FS100 and Eudragit®
RSPO) could be utilized to control the drug release in ASDs. The properties of polymers employed in the preparation of ASD are presented in Table 4.1. Studies have been reported that combining insoluble RSPO with soluble PVPVA delayed nucleation and maintained drug in a supersaturation solution for sufficient duration through a diffusion based drug release mechanism [119].

In this study, it was expected that combining LG with other polymers such as HG, FS100, RSPO, PVP and VA64 provides advantage of avoiding rapid drug precipitation or decline in high initial concentration and promote required supersaturation with delay in precipitation. It was hypothesized that change of interaction mode (interpolymer interactions) in the polymer blends could be beneficial for achieving a high initial drug supersaturation and extending the supersaturation level for longer period. The impact of binary and ternary polymer blends on the ASD performance was evaluated using area under the curve (AUC) values as a measure of non-sink dissolution performance.

**Table 4.1: Properties of polymers employed in ASD formulations.**

<table>
<thead>
<tr>
<th>Properties</th>
<th>HPMCAS LG</th>
<th>HPMCAS HG</th>
<th>Eudragit FS100</th>
<th>Eudragit RSPO</th>
<th>PVP K-29/32</th>
<th>Kollidon VA64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass transition temperature, Tg (°C)</td>
<td>119</td>
<td>122 °C</td>
<td>50</td>
<td>64</td>
<td>164</td>
<td>107 °C</td>
</tr>
<tr>
<td>Weight average molecular weight (g/mol)</td>
<td>114,700</td>
<td>75,100</td>
<td>280,000</td>
<td>32,000</td>
<td>58,000</td>
<td>45,000–70,000</td>
</tr>
<tr>
<td>Degradation temperature (°C)</td>
<td>&gt;180</td>
<td>&gt;180</td>
<td>&gt; 300</td>
<td>170</td>
<td>&gt;180</td>
<td>270</td>
</tr>
</tbody>
</table>
4.3.2. Crystalline and Amorphous solubility

The aqueous solubility of crystalline NIF at 37°C, pH 6.8 phosphate buffer was determined to be 10.4±3.1 µg/mL and the amorphous solubility of NIF in the absence of polymer is estimated to be 11.4±0.6 µg/mL. The amorphous solubility was minimal and precipitation was maximum for NIF with no pre-dissolved polymer. The amorphous to crystalline solubility ratio of NIF in the absence of polymer was found to be 1.1, and in the presence of polymer was determined to be 7.4 (LG), 16.2, 14.3 (HG, LG+HG), 1.8, 7.0 (FS100, LG+FS100), 1.1, 6.4 (RSPO, LG+RSPO), 1.7, 7.2 (PVP, LG+PVP) and 3.1, 4.0 (VA64, LG+VA64). From a drug delivery perspective, the amorphous to crystalline solubility ratio provides indication on how greatly the bioavailability might be improved for amorphous form of drugs [93]. These observations suggesting that formulating NIF with HPMCAS polymer might improve the solubility limited bioavailability.

The amorphous solubility represents the maximum achievable supersaturation, described as the free drug concentration achieved in solution of interest after reaching the equilibrium between the solution phase and the amorphous material [93]. Exceeding of the amorphous solubility resulted in liquid-liquid phase separation (LLPS) and leads to the formation of discrete drug rich phase. This drug rich phase can be partitioned from the aqueous solution phase by ultracentrifugation and the free drug concentration available in the supernatant represents the amorphous solubility [112].

Figure 4.2 shows the amorphous solubility results of NIF in polymeric solution alone or in combination of polymeric blends. The amorphous solubility of NIF varied according to the polymer, the highest concentration was obtained with HG grade followed by LG grade, while the lowest concentration was attained by the RSPO. The order of increasing amorphous solubility of polymers followed as HG > LG > VA64 > FS100 > PVP > RSPO. It is apparent that for the solution of NIF with pre-dissolved LG and HG, the LLPS concentration was determined to be 77.62±0.5
and 169±12.1µg/mL respectively. The increased amorphous solubility of NIF in the presence of HPMCAS grade polymers indicating the change in thermodynamic activity of drug-rich phase [120]. Also, the increased of LLPS concentration of NIF in the presence of HPMCAS grade polymers implying that these polymers were greatly incorporated into the drug rich phase and adsorbed at the drug-rich phase interface. Thereby, maintained supersaturation and prevent crystallization of NIF when compared to the other polymers [121–123].

The LLPS concentration of NIF with pre-dissolved RSPO, FS100, VA64 and PVP was found to be between 11.63–32.68 µg/mL respectively, indicating the formation of drug rich phase occur at somewhat lower concentrations with these polymers. The ability of HPMCAS to inhibit the crystal nucleation and growth, and the strong hydrophobic interactions between the drug – polymer within the supersaturated system may lead to stabilization of the LLPS system and resulted in maximum amorphous solubility [107]. The addition of polymers (FS100, RSPO, PVP and VA64) not greatly increases the amorphous solubility of NIF, suggesting the precipitation behaviour or phase separation to crystalline state from the supersaturated solutions.

For polymeric blends, LG+HG and LG+ FS100 has showed the highest amorphous solubility, suggesting that these polymer combinations maintained the supersaturation concentration by retarding the NIF precipitation. However, the amorphous solubility of NIF in the presence of pre-dissolved LG+HG and LG+FS 100 blend was lower than the amorphous solubility of HG and LG grades alone, which could be due to the less amount of HG and LG grades in the solution phase studied. The rank order of polymer combination on amorphous solubility of NIF was LG+HG> LG+FS100 > LG+PVP > LG+RSPO > LG+VA64. The potential of HG grade to inhibit crystallization tendency and promote retardation of NIF precipitation from supersaturated
solutions has been previously reported for drugs such as itraconazole, carbamazepine and phenytoin [107,111,124].

The HG grade alone and in combination with LG grade provide highest amorphous solubility due to stabilization of supersaturated NIF via strong hydrophobic interactions. Although drug-polymer interactions and supersaturated solution stabilization by HG grade was superior than the LG grade, the dissolution performance by HG grade was less compared to LG grade due to less polymer-aqueous state interaction, will be discussed in later section. The findings of the study suggest that LG+HG and LG+FS100 ternary ASDs could be advantageous for achieving and maintaining high NIF supersaturation and play an important role for enhancing overall dissolution performance and absorption of ASDs.

Figure 4.2: Amorphous solubility of NIF in the presence of polymers alone (A) and in combination of polymeric blends (B).
4.3.3. **Nucleation induction time measurement**

The crystallization tendency of NIF from the supersaturated solution can be inferred from the nucleation induction time. At the beginning of the experiment, the supersaturated NIF solution in the presence of polymer was clear and no particulates or turbidity was present in solution. When the nuclei began to form, the turbidity of the solution commenced and began to increase as the nuclei grow into detectable macroscopic crystals. The induction time was determined by plotting absorbance versus time and the point where sharp decrease in absorbance or change in concentration by 2.5% was taken as the induction time. The absorbance-time curve of NIF with and without polymer or polymeric combination was shown in Figure 4.3.

![Absorbance-time profile of NIF](image)

**Figure 4.3: Absorbance-time profile of NIF in A) pre-dissolved polymers alone, B) pre-dissolved polymeric combinations.**

The absorbance profile of the supersaturated solutions was monitored for 2 h, time-cut off 2 h was set based on the crystallization tendency of reported ASDs [125]. Ilevbare et al., [126] studied effect of polymers on the nucleation induction of celecoxib, efavirenz and ritonavir. The drugs celecoxib and efavirenz nucleated within 5 min, while ritonavir nucleation reported at 2h. By utilizing plate reader technique, it is possible to measure the nucleation induction time. In our study, we were collected samples at every three minutes’ time interval to quantitatively distinguish the precipitation or nucleation induction behavior of NIF in the presence of polymer or polymer
combinations. Since we know it is not possible to directly measure the accurate nucleation induction time because of the manual sampling at predetermined time interval. We opted this simple technique to distinguish the impact of polymers or polymer combinations on NIF precipitation. In the absence of polymer, the absorbance of NIF decreased rapidly and crystallization or precipitation commenced within 3 minutes. The solution became turbid with the formation of macroscopic crystals. Nucleation induction time was extended to 120 min (HG) and 15 min in the presence of VA64 and LG polymers. Whereas, in the case of PVP, RSPO and FS100, nucleation induction was commenced within 6 min (PVP) and 3 min (RSPO and FS 100).

As shown in Figure 4.4, no increase in turbidity was observed for NIF in the presence of HG and LG+HG grade polymer at 120 min, demonstrating the delay in nucleation induction or inhibition of precipitation. The inhibitory efficiency by HG grade can be explained by thermodynamic or kinetic properties [102,120]: by thermodynamic way the polymer can change the solubility of the system and makes the solution less prone to precipitation. By kinetic way, the nucleation and crystal growth was reduced in the presence of polymer by adsorbing on the crystal faces and also polymers can reduce the activity coefficient. Both thermodynamic and kinetic way of precipitation inhibition can results in enhanced supersaturation concentration with greater colloidal stability and stronger crystallization inhibition [127]. The order of nucleation inhibition property of polymer is HG>LG>VA64>PVP>FS100>RSPO.
Figure 4.4: Visual examination of turbidity for NIF supersaturated solutions in the presence of LG, HG, LG+HG, LG+FS100 and LG+RSPO polymers.

It is noteworthy that nucleation induction time was prolonged with HG, RSPO and FS100 in the presence of LG compared to the other polymers. No substantial nucleation or crystal growth was commenced and the initial supersaturation level was maintained for 120, 50 and 40 min respectively for polymeric blend of LG+HG, LG+RSPO and LG+FS100, indicating the most effective inhibitors compared to other polymeric combinations. Furthermore, combination of LG grade with hydrophilic polymers (PVP or VA64) had no major impact on the induction time indicating the interaction of hydrophilic polymers with NIF was not strong enough to have an effect on nucleation retardation indicating the less effectiveness of LG+PVP and LG+VA64 combination on delaying the nucleation induction time [116]. From Figure 4.3, the order of stabilizing supersaturation concentration of NIF in the presence of polymeric combination followed as: LG+HG, LG+RSPO, LG+FS100, LG+VA64, LG+PVP. The hydrophilic polymers have moderately effective at delaying induction time, combining LG grade with hydrophobic HG,
RSPO and FS100 polymers have been identified as the most effective in extending nucleation induction time.

Summarizing, strong affinity of the hydrophobic polymers for the drug molecules, relative to the solvent in the solution lead to interaction of the polymer molecules with the solute. In the case of hydrophilic polymers, it would be expected to have a greater affinity of polymer segments to water molecules [126,128]. It is apparent that polymer ability to inhibit crystal nucleation is depending on the properties of the drug and polymer hydrophobicity and drug-polymer-water interaction. The polymer with hydrophobicity similar to that of the drug molecule maximizes the nonspecific interaction between drug and polymer, thereby act as an effective nucleation inhibitor [126]. The observations of this study demonstrate that hydrophobic HG, FS100 and RSPO polymers in combination with LG grade were effective crystallization inhibitors, demonstrating that the hydrophobic properties of the polymer play an important role in retardation of nucleation induction time.

For nucleation to begin, the drug molecules should overcome the strong interactions (drug-polymer) to diffuse and form nucleus. Therefore, the extension of nucleation induction time by the HG, FS100 and RSPO polymers in the presence of LG grade polymer can be explained by stronger interaction and higher binding energy with NIF [120]. Further, the time required for nucleation to take place is depending on the strength of the drug-polymer interactions. The low binding energy and less effective interactions of NIF with hydrophilic polymers (PVP and VA64) in the presence of LG lead to no major effect on the nucleation inhibition or extension. The adsorption of hydrophobic polymer segments (LG+HG, LG+RSPO and LG+FS100) on to the crystal surface and the drug-polymer interaction by the hydrophobic polymer combination might be the reason behind the retardation in nucleation induction and subsequent growth of the NIF crystals
The overall results imply that using the combination of two hydrophobic polymers in the ternary system suggesting the synergistic potential of the polymer combination on drug-polymer interaction and subsequent precipitation inhibition or retardation.

4.3.4. DLS

In order to evaluate the impact of polymer or polymer combination on polymer-mediated drug supersaturation, DLS analysis was performed on NIF supersaturated solution with and without polymers. The particle size of drug-rich droplets in the supersaturated solution obtained from nucleation induction study was characterized for sub-visible drug–polymer aggregates. Figure 4.5 show the particle size of the resulting drug-rich droplets upon induced supersaturation. The pre-dissolved HPMCAS polymeric solutions without NIF have shown initial particle size of 145.5 nm and 201.3 nm respectively for LG and HG grade, while pre-dissolved PVP, VA64, FS100, RSPO and the combination of these polymers with LG grade have shown particle size ranges from 91.2 nm to 1059 nm. The larger particle size observed with RSPO and FS100 polymer solution could be due to less solubility of these polymers and formation of polymer rich aggregates in the pH 6.8 buffer media. In the absence of polymer, the droplet size of NIF observed was 2120.1 nm suggesting the formation of larger size drug rich particles due to nucleation and crystal growth of NIF. The particle size of NIF evolved to larger size in the presence of all pre-dissolved polymers except HG and LG+HG, which is most likely results from the crystallization or precipitation of NIF.

Supersaturated solution may be separated into dispersed/drug rich or concentrated phase, ranges from nanometers to micrometers depending on stabilization of interface by the polymeric carrier. In the case of PVP, VA64, FS100, RSPO and combination of these polymers with LG grade, the larger or increase in particle size of drug rich phase likely to be formed from the supersaturated
solution could be attributed by weak precipitation inhibition or stabilization effect by the polymeric excipient [131].

The pre-dissolved HG and LG+HG do not increase in particle size of NIF in a supersaturated solution (149.4 nm, 154.5 nm respectively for HG, LG+HG), indicating the stabilization of HG grade polymer on drug-rich nanoparticles, effectively slow down the coarsening of drug rich droplets [132]. The comparable size of drug rich nanoparticles in HG, LG+HG system demonstrate the potential of HG grade polymer in preventing crystallization of NIF out of a supersaturated solution. The interactions between the NIF and acetyl moiety of HG leading to formation of sub 200nm nanoparticles with less aggregation of drug molecules. Further, the poor affinity of HG grade towards aqueous buffer could be the driving force for strong drug-polymer interaction and inhibit the growth kinetics of the nanoparticles [133]. The particle size of NIF in the presence of LG is relatively less compared to other polymers alone or in combination (except for HG and LG+HG combination). This is due to electrostatic repulsion owing to the negative charges on the succinate groups of LG grade, which minimizes the formation of large aggregates and stabilizes the drug-polymer colloids [122]. These observations are in accordance with the previous findings. In a study, Huang W et al [134] studied impact of HPMCAS on aggregation inhibition of phenytoin. The results indicate that delay in occurrence of the nucleation and reduction of aggregation was observed owing to strong intermolecular interaction between drug-polymer.
4.3.5. HME processing

It was reported in the literature that pure HPMCAS grade polymers (LG and HG) were extrudable in the temperature range of 160-200°C. At temperature >180°C the change in physicochemical properties were observed with the HPMCAS grade extrudates owing to the release of free acetic and succinic acid at higher temperature [135]. Based on the previous literature reports, 170°C was selected as the processing temperature for extrusion of all binary and ternary powder mixture except NIF/LG+RSPO [108]. Considering the degradation temperature of RSPO (170°C), the extrusion temperature was maintained at 160°C. During extrusion, the processing torque was observed in the range of 30-40% for both binary and ternary NIF powder mixture, indicating the feasibility and easy of extrusion process. The mixing zones in the screw configuration arranged with the kneading elements to make angles of 30°, 60° and 90° (mixing zone-1), 60° (mixing zone-2), 60° and 90° (mixing zone-3) in order to provide both dispersive and distributive mixing action.
A feed rate of 2.5g/min and screw speed of 50 RPM was set considering the process torque values of the extrudates that are processed at 160-170°C. The details of formulation composition for binary and ternary ASDs were presented in Table 4.2.

Table 4.2: Details of formulation composition for binary and ternary ASDs.

<table>
<thead>
<tr>
<th>Formulation ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>HPMCAS LG</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMCAS HG</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>HPMCAS LG + HPMCAS HG</td>
<td>-</td>
<td>-</td>
<td>50+20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMCAS LG + Eudragit® FS 100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50+20</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMCAS LG + Eudragit® RSPO</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50+20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMCAS LG + PVP K29/32</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50+20</td>
<td></td>
</tr>
<tr>
<td>HPMCAS LG + Kollidon® VA64</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50+20</td>
</tr>
</tbody>
</table>

*All the amounts are expressed as % w/w.*

4.3.6. DSC

The pure drug and ASD formulations were characterized by DSC for crystallinity (Figure 4.6). NIF exhibited a sharp endothermic peak at 173°C, confirming the melting point and crystalline nature. The NIF in the binary and ternary extrudates showed absence of melting endotherm indicating the drug possibly dispersed molecularly in the polymer, leading to formation of ASD. [136].
Figure 4.6: DSC thermograms of pure NIF and ASD formulations.

4.3.7. FTIR

The polymers used in the present study possess different functional groups and their ability to interact with the model drug may vary. Therefore, FTIR analysis was used to investigate the potential drug-polymer interactions in the ASDs. The FTIR spectra of pure drug, polymers and ASD samples were presented in Figure 4.7. NIF possesses an absorption bands at 3331 and 2952 cm\(^{-1}\) corresponding to amine and \(-\text{OH}\) stretching respectively. The peaks at 1667 and 1647 cm\(^{-1}\) are due to \(-\text{C}=\text{O}\) and \(-\text{C}^{\equiv}\text{C}\) stretching respectively [136]. The peak at 1530 cm\(^{-1}\) in NIF and NIF-HPMCAS ASD due to the N–O symmetric stretch. The peak at 1720-1730 cm\(^{-1}\) corresponding to \(-\text{C}=\text{O}\) stretching of HPMCAS, FS100 and RSPO [137]. In the case of PVP and VA64, the amide carbonyl \(-\text{C}=\text{O}\) stretching appeared at 1660 cm\(^{-1}\) and an additional \(-\text{C}=\text{O}\) stretch of vinyl acetate was observed at 1731 cm\(^{-1}\) for VA64 [65].

In the ASD samples, the \(-\text{C}=\text{O}\) stretching peaks were broadened and shifted to 1727 and 1693 cm\(^{-1}\) as a doublet peak indicating the interaction between drug and polymer. The peak broadening observed with NIF in ASDs reflecting the amorphization of NIF and disordered nature of the
obtained solid dispersion [138]. However, more pronounced peak broadening was observed in the case of NIF-HPMCAS binary ASDs. Further, the peak position and shift was similar between both LG and HG grade polymer and their respective ASDs samples, hence the FTIR spectra of LG grade ASDs samples were presented in Figure 4.7. Normally, a peak shift or peak broadening of C=O stretching group of drug molecule in solid dispersion attributed to the intermolecular interaction between drug and polymer [139].

The amorphization of NIF resulted in reduced strength of hydrogen bonds between NIF molecules, although the weak hydrogen bond was still present between amorphous NIF molecules [140]. The NH stretching of NIF in the solid dispersions disappeared or decreased in the intensity might be due to rupture of intermolecular hydrogen bond between the amine and –OH functional groups or molecular distribution of NIF in the polymeric matrix [108,141]. The slight shift in the peak positions with peak broadening and reduction in the intensities observed in the ASD samples indicating the intermolecular interaction between drug and polymer, which could have occurred during HME process. From the FTIR spectra, the drug-polymer interactions in the ternary solid dispersions suggest that higher propensity of interaction between NIF and HPMCAS grade polymer than the other polymers owing to its high proportion in the ternary polymeric blend.
4.3.8. Non-sink in vitro dissolution

Figure 4.8 shows the dissolution profiles of NIF ASDs compared with that of crystalline drug. The dissolution study results show the presence of stable supersaturation maintenance, unstable precipitation and drug crystalline state.

As shown in Figure 4.8, at the initial stage, all the formulations dissolved quickly and showed considerable improvement in dissolution rate compared to pure NIF. However, the supersaturation level and the maximum concentration of all the formulations were not maintained, and part of dissolved system converted to the crystalline state in a time dependent manner. The solid dispersion with made with HPMCAS-LG had the fastest dissolution rate and supersaturation concentration, but the concentration decreased drastically. This high degree of supersaturation compared to other formulations is due to high succinoyl substitution (hydrophilic group) present...
in LG polymer, which play a major role in increasing solubility of poorly soluble drugs. In contrast, HPMCAS-HG based ASD showed much slower dissolution rate, which avoids the rise in supersaturation build up while sustaining the drug release for 6 h. The more hydrophobic acetyl substitution in HG grade promote slow drug release and delay in drug precipitation owing to strong hydrophobic interactions between the drug and polymer. Moreover, this greater hydrophobicity of the HG grade polymer lowers the dissolution performance of the ASD due to decrease in initial polymer interaction with the aqueous buffer medium [107].

For achieving the maximum supersaturation level in the spring and parachute model, the spring component require polymer aided drug release, which includes a polymer-aqueous buffer media interaction. In the case of NIF/LG ASD, the favorable interaction between the polymer-aqueous buffer media leads to more rapid supersaturation (spring effect). This polymer dissolution by polymer-aqueous buffer media interaction will allow for subsequent precipitation (parachute effect). In contrast, in NIF/HG ASD, the greater hydrophobicity reduced the polymer interaction with the aqueous buffer media, resulted in overall slow drug release from ASD [107]. These observations are in accordance with the previously reported studies [117]. Further, it has been previously reported that difference in dissolution rate between LG and HG grades are due to variation in acetyl (hydrophobic) and succinoyl (hydrophilic) substitution. The LG grade possess lowest acetyl and highest succinoyl substitution, whereas, HG grade having highest acetyl and the lowest succinoyl substitution.

The mechanism of increasing dissolution rate and supersaturation concentration by the HPMCAS grade polymers can be explained by: amphiphilic nature of HPMCAS, in which the polymer hydrophobic region provide site for drug association, whereas the hydrophilic region enables the formation of stable nanosized colloidal structure in the aqueous media [142].
The spring-parachute effect by the combination of LG grade with other polymers (HG, FS100, RSPO, PVP, VA64) was studied aiming to provide greater and rapid supersaturation and promote retardation of NIF precipitation. The dissolution performance in terms of relative area under the curve (\(\text{AUC}_{\text{ASD}}/\text{AUC}_{\text{drug}}\)) and supersaturated concentration ratios (\(C_{360}/C_{\max}\)) are calculated and provided in Table 4.2. Cmax refers to maximum supersaturation concentration achieved by the ASD before start of decrease in concentration. AUC describes the extent of supersaturation over the course of dissolution study, which takes into consideration of time and concentration profile of the supersaturated system. The \(\text{AUC}_{\text{ASD}}/\text{AUC}_{\text{drug}}\) is defined as the dissolution curve AUC of the ASD formulations over the AUC of crystalline NIF. While \(C_{360}/C_{\max}\) represent the calculated drug concentration at the end (360 min) of dissolution studies divided by maximum achieved concentration during the test [110,143]. The maximum value of \(\text{AUC}_{\text{ASD}}/\text{AUC}_{\text{drug}}\) ratio can be rated as improved dissolution performance of ASD and retardation of NIF precipitation.

The supersaturation concentration of NIF was not significantly improved by the coexistence of the PVP, VA64, FS100 or RSPO in the presence of LG, suggesting that enhancement in dissolution of NIF mainly depends on the solubilization of drug by the LG polymer. Therefore, LG polymer play a major role in achieving maximum drug concentration and formation of NIF supersaturated solution. The supersaturated solution concentration of approximately 66.1 µg/mL at 30 min was attained by NIF/LG ASD, then after declined gradually to 21.8 µg/mL at 360 min due to the crystallization of NIF. It should be noted that ASD made with LG+HG combination provides a maximum supersaturation concentration of 72.8 µg/mL at 60 min and could maintain NIF concentration at steady state for extended period of time (90 min) followed by gradual decrease to a concentration of 38.1 µg/mL at 360 min. The superior precipitation inhibition or supersaturation
maintenance effect associated with HG grade in the presence of LG grade could possibly explained by the generation of nanosized drug–polymer aggregates, providing a reservoir where the drug is being continuously dissolve and the nanosized amorphous drug–polymer aggregates stabilized through electrostatic repulsion, thereby maintain the supersaturated free-drug concentration [122,143].

The NIF/LG+FS100 ASD achieved maximum NIF concentration of 54.3 µg/mL at 120 min, then the concentration dropped gradually to 37.9 µg/mL at 360 min. In contrast, NIF/LG+RSPO showed a less supersaturation level compared to that of other polymer combinations (except LG+PVP, LG+VA64) with a maximum concentration of 47.1 µg/mL at 30 min following by a desupersaturation concentration of 32.5 µg/mL at 360 min. Schver, et al., [99] evaluated supersaturation of RSPO based ASDs using indomethacin and posaconazole as a model drugs. Study results show that slow rate of drug supersaturation build-up and shorter the sustained supersaturation was observed. Furthermore, the electrostatic drug-polymer interactions resulted in partitioning of indomethacin between the RSPO and the dissolution medium, leading to sustained level or lower degree of supersaturation generation from ASDs.

The superior inhibitory effect associated with LG+FS100 combination can be explained by non-specific interactions (hydrophobic/Van der Waals/intermolecular interaction), this may lead to delay in decreasing the supersaturation level. Ohyagi et al [95] studied the effect of polymer blends hypromellose (HPMC) and methacrylic acid copolymer (Eudragit S® and Eudragit® L) on the dissolution rate and supersaturation level of griseofulvin spray dried dispersion. The results show that ASD made with ternary HPMC/Eudragit® combination provided higher supersaturation level of griseofulvin and improved the dissolution rate, suggesting the interpolymer interactions
(intermolecular interaction) in the polymeric blend could provide a synergetic role for improving the ASD dissolution performance.

Figure 4.8: In-vitro non sink dissolution profiles of NIF, binary and ternary ASD formulations.

The decline in NIF supersaturation level was quite fast in the case of NIF/LG, NIF/LG+PVP and NIF/LG+VA64, suggesting the weak inhibitory effect on NIF crystallization compared with that of HG and FS100 in the presence of LG. The NIF/LG+HG and NIF/LG+FS100 delayed the decrease in NIF concentration and maintained the supersaturation level for prolonged time. This sustained dissolution profiles while achieving higher supersaturation generation and delay in revert back to crystalline drug state suggesting the strong inhibitory effect exerted by the HG and FS100 polymers on NIF crystallization in the presence of LG grade polymer.

The $AUC_{(ASD)}/AUC_{(drug)}$ calculation was performed on the basis 360 min dissolution studies. A slow dissolution was observed with NIF/HG binary ASD without any precipitation during the time scale of dissolution studies, which resulted in lower $AUC_{(ASD)}/AUC_{(drug)}$ ratio.
A significant increase in $\text{AUC}_{(\text{ASD})}/\text{AUC}_{(\text{drug})}$ ratio was observed for LG+HG ASD compared to other formulations. LG+HG ASD showed Cmax of 72.82 $\mu$g/mL and maintained supersaturation for 60 min while ASD of LG+FS100, LG+RSPO showed Cmax of 54.36, 47.02 $\mu$g/mL and maintained supersaturation for 120 and 30 min respectively. A low Cmax, C360 was observed for LG+VA64, LG+PVP dispersions, however, these dispersions showed a very fast dissolution rate and achieve Cmax within 10 min. The magnitude of greater Cmax ratio and $\text{AUC}_{(\text{ASD})}/\text{AUC}_{(\text{drug})}$ ratio designate the enhanced dissolution performance of ASD. The higher C360/Cmax ratio reflects less degree of crystallization or degree of precipitation. However, the C360/Cmax ratio depends on the extent of both supersaturation and desupersaturation concentration attained by the ASD formulations. From the Table 4.3, it can be concluded that ternary solid dispersions comprising of LG+HG and LG+FS100 were able to maintain supersaturation level of NIF for pronged period and did not support complete conversion of supersaturated NIF into its equilibrium solubility level. The maximum supersaturation concentration of drug is greatly influenced by its initial dissolution rate from the ASD and the polymer inhibitory effect on drug precipitation from the supersaturated solution [144,145]. The blending of HG grade polymer with LG grade, can form strong interaction effect with NIF, which can be an advantage for improving the dissolution rate and further maintaining supersaturation level by exerting inhibitory effect on NIF crystalization. Further, increase in $\text{AUC}_{(\text{ASD})}/\text{AUC}_{(\text{drug})}$ ratio for LG+HG combination indicate that these polymers interact differently, modulate the supersaturation kinetics and further enhancing the dissolution performance. The observations from the dissolution study conclude that combining a high solubilizing and fast dissolving polymer (LG) with HG (LG+HG) and FS100 (LG+FS100) can show inhibitory effect on the drug crystallization, which could be a practical strategy for enabling enhanced supersaturation maintenance from ternary ASDs.
Table 4.3: Characterization of dissolution performance of ASD with different polymer combinations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$C_{\text{max}}$ ($\mu$g/mL)</th>
<th>$T_{\text{max}}$ (min)</th>
<th>$C_{\text{max}}$ ratio</th>
<th>$C_{360}$ ($\mu$g/mL)</th>
<th>$C_{360}/C_{\text{max}}$</th>
<th>$\text{AUC}<em>{(\text{ASD})}/\text{AUC}</em>{(\text{drug})}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIF</td>
<td>2.61</td>
<td>-</td>
<td>-</td>
<td>2.61</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NIF/LG</td>
<td>65.14</td>
<td>30</td>
<td>24.91</td>
<td>21.86</td>
<td>0.335</td>
<td>34.92</td>
</tr>
<tr>
<td>NIF/HG</td>
<td>55.16</td>
<td>360</td>
<td>21.09</td>
<td>55.16</td>
<td>1</td>
<td>36.1</td>
</tr>
<tr>
<td>NIF/LG+HG</td>
<td>72.82</td>
<td>60</td>
<td>27.84</td>
<td>38.02</td>
<td>0.52</td>
<td>56.24</td>
</tr>
<tr>
<td>NIF/LG+RSPO</td>
<td>47.02</td>
<td>30</td>
<td>17.98</td>
<td>32.52</td>
<td>0.70</td>
<td>37.89</td>
</tr>
<tr>
<td>NIF/LG+FS100</td>
<td>54.36</td>
<td>120</td>
<td>20.78</td>
<td>37.90</td>
<td>0.70</td>
<td>48.53</td>
</tr>
<tr>
<td>NIF/LG+PVP</td>
<td>44.16</td>
<td>10</td>
<td>16.88</td>
<td>14.81</td>
<td>0.33</td>
<td>23.33</td>
</tr>
<tr>
<td>NIF/LG+VA64</td>
<td>43.81</td>
<td>10</td>
<td>16.75</td>
<td>13.9</td>
<td>0.31</td>
<td>19.98</td>
</tr>
</tbody>
</table>

4.4. Conclusion

In the present study, we have investigated the potential combination of LG with various polymers to attain and maintain supersaturation over time. The in-vitro supersaturation studies revealed the potential of HPMCAS grade (LG and HG) polymers in achieving and maintaining high drug supersaturation. All ASD formulations manufactured via HME were amorphous and showed drug release well above crystalline solubility of NIF. The release of NIF from the dispersion of LG alone was rapid, revert back quickly to the drug crystalline solubility, which is attributed to less
precipitation inhibition potential of LG. In contrast, dispersions of HG grade alone show quite slow and incomplete release could be due to strong drug-polymer interaction and poor interaction of HG with aqueous buffer media. Among all ternary drug-polymer combinations, NIF/LG+HG system presents a promising way of modulating the drug release and inhibiting the precipitation of the drug in a supersaturated solution. Besides, improved dissolution performance of NIF/LG+HG, the DLS analysis of NIF in the presence of LG+HG showed formation of nanoparticulate species with no further increase in particle size over the period of 120 min, suggesting the precipitation inhibition potential of this combination. Our results suggest that combining LG and HG polymers can overcome the desupersaturation drawback of LG and poor interaction potential of HG with aqueous buffer media. Thus the system based on the combination of LG and HG could be promising for enhancing the ASD performance owing to both high supersaturation concentration and retardation of precipitation that are most beneficial for enhancing the in-vivo absorption. Nonetheless, FTIR study confirmed the drug-polymer interaction, analytical tools such as solid state NMR should be used to differentiate and quantify the interaction of NIF with LG+HG polymeric combination.
CHAPTER-5

5. POLYMER-ASSISTED ARIPIPRAZOLE-ADIPIC ACID COCRYSTALS PRODUCED BY HOT MELT EXTRUSION TECHNIQUES

5.1. Introduction

Approximately 90% of new chemical entities in the pipeline and 40% of the marketed drugs are reported to have poor aqueous solubility. Therefore, formulation approaches to enhance the solubility and dissolution rate of poorly soluble drugs play a crucial role in improving the oral bioavailability. Different formulation strategies such as amorphous solid dispersions, cocrystals, complexation, nanonization and lipid-based drug delivery systems have been explored to improve the dissolution rate and bioavailability of poorly soluble drugs. Among these strategies, cocrystals is one of the effective approach to modify the physicochemical properties of APIs such as solubility, physical stability and mechanical properties without altering the physiological or chemical action of the drug substances. Pharmaceutical cocrystals are crystalline materials comprised of an active pharmaceutical ingredient (API) and a coformer, bound together by noncovalent interactions such as hydrogen bonds, van der Waals forces, or π-bonds. Traditional methods have been used in the synthesis of pharmaceutical cocrystals including solution, slurry crystallization and liquid or milling assisted grinding. However, these techniques have been extensively used in the screening of cocrystals. Utilization of these techniques is time-consuming, difficult to scale up, and most of them require organic solvents, which may leave residual solvent impurities in the cocrystals. In the recent years, the
advanced techniques such as ultrasonication, supercritical fluid, microfluidic anti-solvent, thermal ink-jet printing and hot melt extrusion techniques have been employed for cocrystals synthesis.[160–164] Despite the advancement of these techniques, a further understanding and optimization of the process is needed for successful scale-up.

Hot melt extrusion (HME) is a one-step, continuous, scalable, and industrially feasible process to develop cocrystals.[165][166] Recently, use of HME as a continuous process to develop and manufacture cocrystals has gained interest in the field of pharmaceutical research.[149][167] High throughput, low residence time, lack of organic solvents, and a combination of intense mixing and controlled temperature make the HME process more efficient in producing cocrystals than other traditional technologies.

Aripiprazole (ARP, Figure 5.1) is an atypical antipsychotic agent used to treat schizophrenia. It is a weakly basic drug with a pKa of 7.6 and a melting point of 139°C.[168] ARP is a class II drug according to the biopharmaceutics classification system, with an aqueous solubility of 0.007 mg/mL.[169] Thus, solubility and dissolution are rate-limiting steps in the absorption and bioavailability of ARP. The coformer, adipic acid (ADP), is a dicarboxylic acid derivative with a melting point of 155°C.[170] ADP has been used as a coformer with isoniazid[171] and pyrazinamide.[170]. The preparation of ARP cocrystals with phenolic coformers (namely resorcinol, catechol, hydroquinone, pyrogallol, and phloroglucinol) using slow evaporation and solid-state grinding methods has been reported. In previous reports, authors have mainly focused on establishing a melting point correlation between ARP and cocrystals with phenolic coformers.[172] Cho et al.[173] investigated the formation of ARP cocrystals with catechol, resorcinol, phloroglucinol, and orcinol. They reported that ARP cocrystals prepared using neat and
liquid-assisted grinding methods showed an improved dissolution profile compared with pure ARP.

Figure 5.1: Chemical structures of (A) aripiprazole, (B) adipic acid.

The novelty of the current investigation lays in the exploration of the feasibility of producing ARP cocrystals by HME using ADP as a coformer, to investigate the effect of Soluplus® (SOL) on cocrystal formation, and to study the effects of temperature and screw speed on ARP-ADP cocrystal formation. The ARP-ADP cocrystals produced by HME were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), hot-stage microscopy (HSM), scanning electron microscopy (SEM), fourier transform infrared spectroscopy (FTIR), in vitro dissolution studies, and their feasibility to formulate solid dosage forms.

5.2. Materials and methods

5.2.1. Materials

Aripiprazole was obtained from Nexconn Pharmatechs, Ltd. (Tseung Kwan O, Hong Kong), adipic acid was purchased from Spectrum Quality Products, Inc. (Gardena, California, USA), and
Soluplus® was generously supplied by BASF Corp. (Florham Park, New Jersey, USA). All other chemicals used were of analytical reagent grade and were used without further purification.

5.2.2. Liquid-assisted grinding and HME processing for preparation of cocrystals

Physical mixtures (PMs) of ARP and ADP at a 1:1 molar ratio were blended with 100 µL of acetonitrile and manually ground by mortar and pestle for 20 min. The obtained sample was analyzed by DSC to determine the formation of cocrystals.

HME processing was conducted using a co-rotating twin screw 11-mm extruder (Process 11, Thermo Fisher Scientific, Waltham, Massachusetts, USA) with a length-to-diameter ratio of 40:1. An equimolar ratio of plain ARP and ADP with 5% SOL was passed through a US #30 mesh screen and mixed at 25 rpm for 10 min using a Maxiblend™ blender (GlobePharma, New Brunswick, New Jersey, USA).

Physical mixtures were fed into the extruder at a rate of 0.4 g/min using a volumetric feeder at different extruder barrel temperatures (100°C, 115°C, and 125°C) and at screw speeds of 25, 50, and 75 rpm, and torque was monitored continuously during extrusion. The screw configurations used in the extrusion process are shown in Figure 2. After processing, the extrudates were milled in a mortar and passed through a US #25 mesh sieve with a 700-µm aperture, and subsequently stored in a tightly closed glass vial in a vacuum desiccator at room temperature until further analysis.

5.2.3. DSC analysis

The formation of cocrystals was determined by DSC analysis. DSC thermograms of pure components and extrudates were recorded using a Discovery 25 differential scanning calorimeter (TA Instruments, Newcastle, Delaware, USA) equipped with a RCS90 refrigerator cooling system. Samples of approximately 6 to 8 mg were sealed in an aluminum pan, and an empty aluminum
pan was used as a reference. To ensure an inert atmosphere during measurements, samples were equilibrated for 1 min at 25°C and then heated to 200°C at a heating rate of 10°C/min under a nitrogen purge of 50 mL/min.

5.2.4. HSM analysis

HSM analysis was conducted with a Cary 620 IR optical microscope (Agilent, Santa Clara, California, USA) equipped with an electronically controlled hot stage (T95 LinkPad and FTIR 600, Linkam, Epsom, Tadworth, UK). The ARP and cocrystal samples were mounted on glass slips, placed on the hot-stage furnace, and heated to 180°C at a rate of 10°C/min. Changes in sample morphology during heating were recorded as images using Linkam software.

5.2.5. FTIR and chemical imaging analysis

FTIR spectra of pure ARP, ADP, and ARP-ADP cocrystals were obtained with a Cary 660 FTIR Spectrometer (Agilent Technologies, Santa Clara, California, USA) equipped with a MIRacle ATR (Pike Technologies, Madison, Wisconsin, USA) fitted with a single-bounce, diamond-coated ZnSe internal reflection element. A small sample was placed on the crystal surface and pressed using the built-in pressure tower to obtain uniform solid–crystal contact. The spectra were recorded in absorbance mode in the range of 600 to 4000 cm⁻¹ with 16 scans and 4 cm⁻¹ resolutions. An infrared microscope (Agilent Technologies, Santa Clara, California, USA) equipped with a 64 × 64 focal plane array detector and germanium micro ATR sampling accessory was used to collect the chemical images. Images were recorded at a field of view of approximately 70 × 70 µm and a spatial resolution of 1.1 µm.
5.2.6. PXRD measurement

PXRD was performed to confirm the formation of cocrystals. The diffractograms of pure ARP, ADP, and ARP-ADP cocrystals were recorded at room temperature using the Rigaku X-ray system (D/MAX-2500PC, Rigaku Corp., Tokyo, Japan) using Cu rays ($\lambda = 1.54056 \text{ Å}$) with a voltage of 40 kV and a current of 40 mA, over a 2θ scanning range of 2° to 50°, with a step width of 0.02°/S and a scan speed of 2°/min.

5.2.7. SEM analysis

Shape and surface morphology of the ARP, ADP, and ARP-ADP cocrystals were determined by SEM analysis. The samples were mounted on aluminum stubs using carbon adhesive film, gold-coated with a Hummer® 6.2 sputtering system (Anatech Ltd., Battlecreek, Michigan, USA), and placed in a high-vacuum evaporator to increase the conductivity of the samples. The samples were examined at acceleration potentials of 1.0 to 5.0 kV (JEOL JSM-5600; JEOL, Inc.; Peabody, Massachusetts, USA).

5.2.8. Solubility and in-vitro dissolution studies

Solubility studies of ARP and cocrystals were performed by Higuchi and Connors (shake flask) method. Excess amount of the ARP and its cocrystals were added to a vial containing 5mL of DI water and agitated at 500 rpm, 25°C for 48 h using bench mark shaker (Benchmark Scientific Inc, New Jersey, USA). The samples were subsequently centrifuged for 5 min at 13000 rpm to separate the undissolved drug. The supernatant was diluted suitably, and the absorbance was measured at a wavelength of 254 nm by an UV-Vis spectrophotometer (GENESYS™ 180, Thermo Fisher Scientific, Waltham, Massachusetts, USA).

Dissolution studies of pure ARP, ARP-5%SOL and ARP-ADP cocrystals were conducted in 900 mL of DI water using USP apparatus type II (SR8-plus™, Hanson, Chatsworth, California, USA).
The temperature of the media was maintained at 37 ± 0.5°C with a paddle speed of 50 rpm for 2 h. Pure ARP, ARP-5%SOL and cocrystal formulations equivalent to 30 mg of ARP were weighed and poured into a hard gelatin capsule (size 0) and placed in dissolution media. Three-milliliter samples were collected at 15, 30, 45, 60, 90, and 120 min and replaced with 3 mL of fresh medium maintained at 37 ± 0.5°C. The samples were filtered through a 10-μm filter (Quality Lab Accessories LLC, Pennsylvania, USA) and diluted suitably. The ARP content was estimated against blank dissolution medium by UV spectrophotometry at an absorbance of 254 nm.

5.2.9. Drug content analysis

Cocrystals equivalent to 30 mg of ARP were weighed and dissolved in methanol, sonicated for 30 min, and centrifuged. The supernatant was collected, filtered, and diluted suitably, and the ARP content in the cocrystals was analyzed using a UV-visible spectrophotometer.

5.2.10. Flow properties (bulk and tapped density measurement)

Three grams each of pure ARP and cocrystal formulations were placed in a 10-mL graduated cylinder, and the volume was recorded. The cylinder was tapped on a flat surface from a height of approximately 2 cm, and the powder volume was measured after 100 taps. The process was repeated until the difference between two consecutive volume readings was less than 2.0%.[174] The bulk and tapped densities were calculated from the weight, bulk and tapped volumes of respective pure ARP and cocrystal formulations. Each measurement was performed in triplicate. The Carr's index (CI) and Hausner ratio (HR) of ARP and the ARP-ADP cocrystals were calculated using equations (1) and (2).

\[
CI = \frac{\rho_{\text{tap}} - \rho_{\text{bulk}}}{\rho_{\text{bulk}}} \times 100 \quad (1)
\]
\[ HR = \frac{\rho_{\text{tap}}}{\rho_{\text{bulk}}} \]  

where \( \rho_{\text{tap}} \) indicates the tap density and \( \rho_{\text{bulk}} \) is the bulk density.

5.2.11. True density measurement

The true densities of pure ARP and ARP-ADP cocrystals were determined using a helium pycnometer (AccuPyc II 1340, Micromeritics, Norcross, Georgia, USA). An accurately weighed pure ARP, cocrystals (1-2g) was placed into an empty sample cup. The sample volume was calculated by measuring the pressure in the sample chamber filled with high purity helium gas, and the measurements were repeated for ten cycles.

5.3. Results and discussion

5.3.1. Cocrystal formation by liquid-assisted grinding

DSC analysis of ARP and ADP cocrystals prepared by liquid-assisted grinding showed a single endothermic melting peak at 128°C. The presence of a distinct single endothermic peak suggests interaction between ARP and ADP components and the formation of ARP-ADP cocrystals. The formation of cocrystals by liquid-assisted grinding indicates the feasibility of cocrystallization with the selected components. This preliminary cocrystals formation with the liquid assisted grinding method suggested the selection of HME process temperature. The barrel temperature in the HME process is a primary experimental parameter that can affect the cocrystal formation. Based on the observations from the literature, it was reported that the extrusion process was successful and better quality cocrystals were formed when the extrusion temperature was set close to that of the cocrystals formation temperature.[149,175,176] The optimal process temperature together with mechanical shear provided by HME is critical for cocrystal formation. In this study, the extrusion temperature was selected in the range of 100-125°C based on the cocrystals
formation at 128°C in the liquid assisted grinding method. Selection of temperature range less than the melting temperature of cocrystals, would facilitate the cocrystalization during the extrusion process.

5.3.2. HME processing

Initial extrusion trials were conducted using the Thermo Fisher standard screw configuration, which consists of three mixing zones (Figure 5.2). The first mixing zone contained 12 kneading elements with angles of 30°, 60°, and 90°; the second mixing zone contained 6 kneading elements with an angle of 60°; and the third mixing zone consisted of 8 kneading elements with angles of 60° followed by 90°. Extrusion at 115°C of a plain ARP-ADP PM without a polymer resulted in processing torque exceeding the instrument maximum limit. After the initial extrusion trials, a modified screw configuration (without the third mixing zone and all screws replaced with the conveying elements) was utilized. However, extrusion with the modified screw configuration could not facilitate the processing of plain cocrystal components due to high processing torque values. To facilitate the extrusion with the standard screw configuration, 5% SOL was incorporated into the ARP-ADP blend, which enabled the HME process to complete with processing torque values within the instrument’s normal limit. Therefore, processing of a PM with an equimolar ratio of ARP and ADP was feasible in the presence of 5% SOL which indicated its applicability in producing pharmaceutical cocrystals. The presence of SOL, which is a low glass transition temperature polymeric carrier, improves processability and facilitates the interaction between ARP and ADP to form cocrystals during extrusion. These results indicate the selection of an appropriate polymer with the desired thermal properties to develop pharmaceutical cocrystals. They are in accordance with previous reports using SOL as a polymeric excipient for cocrystals of theophylline and ibuprofen with nicotinamide by the HME process. Further, effects of screw speed
and temperature profile on the formation of cocrystals were reported in Table 5.1, while other HME parameters, such as feed rate (0.4 g/min) and standard screw configuration, were held constant.

![Diagram of screw configuration used in HME](image)

Figure 5.2: Schematic diagram of screw configuration used in HME.

5.3.2.1. Effect of HME processing parameters on cocrystal formation

5.3.2.1.1. Temperature

The temperature of the barrel during extrusion is very important, as it can impact the residence time of components in the extruder and the formation of cocrystals. Extrusion at low temperature increases the processing torque and reduces the mass transfer and contact of cocrystal components, which results in incomplete cocrystallization. In order to obtain good quality cocrystals in the HME process, the processing temperature should be below the melting point of the cocrystals.[22] Daurio et al.[176] studied the effect of extruder barrel temperature on the formation of AMG 519-sorbic acid cocrystals. The results indicate complete conversion of cocrystals when the barrel temperature was less than the melting points of the individual components. The findings also conclude that an increase in the barrel temperature close to the cocrystal formation temperature led to efficient cocrystallization. Therefore, in the present study extrusion was carried out at 100°C,
115°C, and 125°C. At 100°C, the formation of cocrystals was incomplete, indicating that the components were unreacted and the mass transfer between components could not take place. Extrusion at 125°C resulted in the melting of the physical blend within the barrel. However, at 115°C and in the presence of SOL, uniform mixing of ARP and ADP was observed. In order to facilitate contact and mass transfer between ARP and ADP, the processing temperature was set to 115°C.

### 5.3.2.1.2. Screw speed

Screw speed is directly related to the residence time and flow of the blend within the barrel, which impacts the formation of cocrystals. To examine the effect of screw speed on cocrystal formation, the temperature was kept constant at 115°C while the screw speed was varied between 25 and 75 rpm at intervals of 25 rpm. No change in the melting point of the cocrystals was observed in DSC thermograms at different screw speeds, which confirmed that cocrystal formation was complete at all screw speeds studied and indicated that each screw speed provided sufficient residence time in the barrel for components to form cocrystals. Thus, no impact from screw speed on cocrystal formation was observed, which is in line with a similar observation reported by Karimi-Jafari et al[178], studied the effect of screw speeds on the cocristallization. In another study, Daurio et al[175] investigated the effect of screw speed on the residence time and conversion of caffeine-oxalic acid cocrystals. The results indicate that though cocrystal formation was observed at all screw speeds, cocrystals processed at higher screw speed showed the presence of residual caffeine, indicating incomplete cocrystal conversion.

From the DSC results, it was observed that cocrystal formation was complete regardless of the selected screw speeds. Thus, the processing of ARP-ADP cocrystals was optimal with 5% SOL in standard screw configuration at a temperature of 115°C and a screw speed of 50 rpm, and the
extrudates with these process parameters were evaluated by solid state characterization and in vitro dissolution studies.

**Table 5.1: Effect of HME process parameters on the formation of cocrystals.**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Temperature (°C)</th>
<th>Screw speed (rpm)</th>
<th>Processing torque (%)</th>
<th>Formation of Cocrystals</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100</td>
<td>50</td>
<td>30-35</td>
<td>X</td>
</tr>
<tr>
<td>F2</td>
<td>115</td>
<td>25</td>
<td></td>
<td>✓</td>
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<tr>
<td>F3</td>
<td>115</td>
<td>50</td>
<td>11-16</td>
<td>✓</td>
</tr>
<tr>
<td>F4</td>
<td>115</td>
<td>75</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>F5</td>
<td>125</td>
<td>50</td>
<td>&lt;10 (Melting of physical blend)</td>
<td>X</td>
</tr>
</tbody>
</table>

5.3.3. **DSC analysis**

DSC studies were carried out to determine the thermal behavior of ARP, ADP, PM of ARP-ADP and the cocrystals. The thermograms of pure ARP, ADP, PM and the cocrystals are shown in Figure 5.3. Pure ARP exhibited an endothermic peak at 139°C due to its melting behavior[169][172] and ADP showed an endothermic peak at 155°C, indicating the crystalline nature of the cocrystal components. From the DSC thermogram of PM, it was observed that the PM of ARP and ADP forms a eutectic i.e., melting at a lower temperature than that of the two cocrystal components. This could be attributed to the suppression of ARP melting point in the presence of ADP. Similar observations were reported for itraconazole–succinic acid cocrystals, where the PM has shown melting endotherm at 151°C, which is less than the melting temperature
of itraconazole (169°C) and succinic acid (191°C).[179] The PM of ARP and ADP produces two endothermic peaks in the DSC thermogram (Figure 3 H). The first endothermic peak corresponding to the eutectics and the second endothermic peak corresponding to cocrystal melting temperature. The melting temperature of ARP and ADP in the PM was close to the cocrystal melting temperature, which led to the overlapping of thermal effects. These type of thermal effects overlap noticed while analyzing the PM with melting temperature difference between cocrystal components less than 50°C.[180] Cocrystals processed by HME at 100°C showed a blunt endothermic peak at 128°C, suggesting unreacted components of the cocrystals and the cocrystals processed at 115°C showed a sharp endothermic peak at 128°C, suggesting the complete formation of cocrystals. Furthermore, DSC thermograms of cocrystals processed at 115°C, with varied screw speeds of 25, 50, and 75 rpm, showed a sharp endothermic peak at 128°C, confirming the formation of cocrystals without effects from the screw speed. The formation of cocrystals in the extruder is due to the eutectic behavior between cocrystal components.[153] The processing temperature above the eutectic melting temperature is likely to be responsible for efficient cocrystalization in the extruder. From the previous literature, it was evident that cocrystals can be formed from the eutectic melt.[153] The possible mechanisms responsible for mechano-chemical reaction between cocrystal components are the existence of an intermediate phase which can be either eutectic/vapor/ amorphous state.[176]

The melting point depression or enhancement of cocrystals depends on the cocrystallization method. As reported by Schultheiss et al,[17] 59% of cocrystal systems exhibited a melting point between those of drug and the coformer, 39% had a melting point lower than either the drug or the coformer, 4% had similar melting points as the drug or coformer, and 6% had a melting point higher than those of the drug and coformer. The cocrystal formulations exhibited lower heat of
fusion or enthalpy (76.2 and 74.3 J/g respectively for liquid-assisted grinding and HME cocrystals) than the pure ARP (91.3 J/g) and ADP (140.6 J/g). The lower enthalpy value of the cocrystals could be attributed to increased interaction and miscibility between ARP and ADP, which might have led to reduced intensity in the endothermic peaks of cocrystals compared to the pure ARP and ADP. These observations were in accordance with the previous reports[181].

![DSC thermograms](image)

**Figure 5.3:** DSC thermograms of a) pure ARP, b) bulk ADP, c) cocrystals prepared by liquid grinding method, and d) cocrystals processed at 100°C, 50 rpm, e) at 115°C, 25 rpm, f) at 115°C, 50 rpm, g) at 115°C, 75 rpm and h) PM of ARP-ADP.
5.3.4. HSM analysis

HSM studies were conducted to examine the thermal transitions and melting of ARP and cocrystals at different rates of heating.[149] HSM images of pure ARP and cocrystals are shown in Figure 5.4. DSC thermograms supported the HSM findings. No thermal event was observed until melting temperatures of 139°C and 128°C for ARP and cocrystals, respectively. The cocrystals appeared as crystalline material at room temperature, and undissolved cocrystals were observed at temperatures below 128°C. During the progression of thermal events, cocrystals began to dissolve at 128°C, and complete melting was observed above 130°C. Similar results were observed for pure ARP, as shown in the HSM images, and complete melting was observed above 140°C. These findings suggest that ARP and ADP interacted with each other during thermal processing.

Figure 5.4: HSM images of a) ARP, b) ARP-ADP cocrystals.
5.3.5. FTIR and chemical imaging analysis

Figure 5.5 illustrates the FTIR spectra of ARP, ADP, PM of ARP-ADP and the corresponding cocrystals. ARP showed characteristic bands of C=O stretching vibrations at 1673 cm\(^{-1}\) and N-H bending vibrations appeared at 1627 cm\(^{-1}\). Aromatic ring C=C–C stretching vibrations located at 1594 cm\(^{-1}\), aliphatic C–H stretching vibrations arises at 2945 cm\(^{-1}\), and C-H bending vibration appears at 1444 and 1375 cm\(^{-1}\).[150,182,183] The FTIR spectra of ADP showed C=O stretching vibrations at 1681 cm\(^{-1}\) and O-H stretching bands at 2950 cm\(^{-1}\).[184,185] The PM of ARP-ADP shows frequency bands specific to the individual components with the change in intensity of the peaks compared to the individual starting components. The FTIR spectra of cocrystals showed the ARP characteristic bands corresponding to the C=O stretching vibration shifted from 1673 to 1679 cm\(^{-1}\). Also, the ARP characteristic bands 1444 and 1376 cm\(^{-1}\) shifted in the cocrystal spectrum to 1451 and 1387 cm\(^{-1}\), respectively. In the same way, a decrease in O-H stretching frequencies of the adipic acid from 2950 cm\(^{-1}\) to 2938 cm\(^{-1}\) was observed in the cocrystals. The shift in the C=O stretching of ARP and O-H stretching band of ADP in the cocrystals attributed to the formation of a hydrogen bond between the cocrystal components.[184] Moreover, for the cocrystals, a new peak appeared at 1720 cm\(^{-1}\).
Nanubolu et al.[172] investigated the cocrystals of ARP with mutihydroxy benzene coformers. They reported that characteristic amide C=O peak in the ARP shifted in the cocrystals from 1679 cm\(^{-1}\) to 1673, 1662, 1653, 1652 and 1652 cm\(^{-1}\) respectively for cocrystals prepared with catechol, hydroquinone, resorcinol, pyrogallol and phloroglucinol coformers. These shifts in the frequency are attributed to the participation of the carbonyl group (C=O) in the hydrogen bonding with the mutihydroxy benzene coformers. Further, their findings also state that larger C=O shifts are indicative of stronger hydrogen bonding in the cocrystals.

In the ARP-ADP cocrystals, a shift in the frequencies of the functional groups compared to that of ARP and ADP indicate the presence of hydrogen bond formation between ARP and ADP. These findings in the FTIR spectra could be due to the noncovalent interaction between cocrystal
components and results in the formation of cocrystals. There was no change in the band position or intensity of cocrystals processed at different screw speeds.

Figure 5.6 shows chemical imaging of ARP-ADP cocrystals. Analysis was performed to determine the distribution of cocrystals and identify the cocrystals from their components. Attenuated total reflectance (ATR), which is direct contact with the sample surface, was used to investigate the distribution of cocrystals at different positions of the extrudates. As shown by the bench top FTIR spectrum, chemical imaging of cocrystals also exhibited peaks at 1720 cm\(^{-1}\) and 1679 cm\(^{-1}\). The obtained wavenumber position was uniform throughout the different positions of the captured image, indicating the uniform distribution of cocrystals in the obtained extrudate powder. These findings were in accordance with the previous literature.[186]

![Figure 5.6: A) Chemical image of ARP-ADP cocrystals with Ge ATR at 1.1 μm spatial resolution, B) FTIR spectra of cocrystals specific to chemical imaging.](image)

5.3.6. PXRD analysis

The powder X-ray diffraction patterns of ARP, ADP, PM and the cocrystals at different screw speeds are shown in Figure 5.7. The ARP diffractogram shows reflections at 2θ values of 16.46°, 19.36°, 20.22°, 21.82°, and 24.68°[183][187]; the diffractogram of ADP showed diffraction peaks at 2θ values of 13.14°, 21.6°, 26.18°, 31.32°, and 42.16°[185] and these diffraction peaks are attributed to the crystalline nature of the starting components. The diffractogram of PM showed
reflections corresponding to the individual components of ARP, ADP with no change in the position of 2θ values. The cocrystals showed characteristic peaks at 2θ values of 17.32°, 18.46°, 22.3°, and 25.12°, which were not present in either ARP or ADP and were attributed to interactions between the two components resulting in new crystalline material. PXRD is a signature and reliable technique in the characterization and differentiation of cocrystals and eutectics from their parent components.[188] Unlike eutectics where a diffraction pattern represents the combination of individual parent components, cocrystals are characterized by the presence of distinct peaks due to formation of new crystalline material. Hence, the presence of distinct peaks in the PXRD pattern of ARP-ADP cocrystals rules out the formation of eutectics.[189] Diffraction peaks of cocrystals processed at different screw speeds showed no difference in the intensity and 2θ values, indicates the formation of cocrystals was complete. These results were in line with the previous literature. Studies from Daurio et al.[175] concludes that the extent of cocrystal conversion moderately depends on the screw speed of the extruder and significantly depends on the barrel temperature in the extruder.
Figure 5.7: PXRD diffractograms of a) ARP, b) ADP, c) PM of ARP-ADP and d) ARP-ADP cocrystals at screw speed 25 rpm, e) 50 rpm, and f) 75 rpm.

5.3.7. SEM analysis

The SEM images (Figure 5.8) of ARP show broken, irregularly shaped crystals, and those of ADP show smooth surface crystals. The cocrystals were found to be clustered with smooth surfaces, indicating that the cocrystals processed by HME were packed together, which could be attributed to efficient mixing within the barrel. These differences in the size and shape of cocrystals indicate molecular interaction between cocrystal components. Thus, the morphology of the cocrystals was entirely different from those of ARP and ADP, which indicated the formation of new crystalline material. The morphology of newly formed cocrystals could influence physicochemical and mechanochemical parameters, such as solubility, dissolution, flowability, and compressibility characteristics, which could be advantageous to the development of pharmaceutical solid dosage forms.
5.3.8. Solubility and in-vitro dissolution studies

The solubility of ARP and cocrystals was found to be 2.8 ± 0.93, 22.6 ± 1.9 µg/mL respectively. Cocrystals improved the solubility by 8.1-fold compared to pure ARP. In-vitro dissolution studies were conducted to determine the performance of HME-processed cocrystals compared with pure ARP and ARP with 5% SOL. ARP showed solubility that varied inversely with pH;[150] hence, a higher pH dissolution medium has better dissolution rate discrimination compared with a lower pH medium.[165] Therefore, in vitro drug release of cocrystals was performed in deionized (DI) water as a discriminating dissolution medium and compared with pure ARP and ARP with 5% SOL.[173] As shown in Figure 5.9, the dissolution rate of pure ARP and ARP-5% SOL was 2.10 and 2.95 µg/mL respectively at 2 h time interval. In contrast, cocrystals showed a dissolution rate
of 14.80 µg/mL at the end of 2 h. The maximum concentration of ARP from the cocrystals was 14.80 µg/mL, which is approximately 7.0 and 5.1-fold greater than that of pure ARP and ARP-5% SOL respectively. The dissolution profile of ARP with 5% SOL resulted in increased dissolution rate (1.4 fold) compared to the pure ARP. The presence of SOL plays an important role in accelerating the dissolution rate of cocrystals due to its hydrophilic and solubilizing nature.[190] There is no significant difference in the dissolution profiles of cocrystals processed at different screw speeds. This faster dissolution rate of cocrystals may be attributed to intermolecular interaction between ARP and ADP in the formation of cocrystals. The drug content of the cocrystal formulations was in the range of 95.5% to 98.5%, which is within acceptable limits.

Figure 5.9: Dissolution profiles of pure ARP, ARP-5% SOL and cocrystals processed at different screw speeds.
5.3.9. Flow properties and true density

Different flow parameters, such as bulk density, tapped density, CI, and HR, were determined to assess the flowability of pure ARP and the cocrystals. The results of these determinations are presented in Table 5.2. The CI and HR of pure ARP were found to be 41 ± 5.02 and 1.69 ± 0.19, respectively. The CI and HR of the cocrystals were 24 ± 2.02 and 1.31 ± 0.17, respectively. A CI >38 and HR >1.60 are indicative of very, very poor flow characteristics, whereas a CI between 21 and 25 and HR between 1.26 and 1.34 is considered passable flow.[191] These results suggest that the HME-processed cocrystals have better flow properties compared with pure ARP. This improved flow may be due to the relatively good flow properties of ADP and SOL in the cocrystals. The true densities of ARP and the cocrystals were 1.318 ± 0.0009 g/cm³ and 1.391 ± 0.0003 g/cm³, respectively. The true density values show that the cocrystals are relatively denser than pure ARP. An increase in particle density and a loss of voids can occur during hot melt extrusion due to heat and shear stress.[87] Also, increase in density and improved flow properties of cocrystals could be due to the densification of material when processed by HME. This variation in the true density values of ARP and the cocrystals suggests that the cocrystals are more compressible than the pure ARP.

Table 5.2: Flow properties of pure ARP and cocrystals.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pure ARP</th>
<th>Cocrystals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density (g/cm³)</td>
<td>0.302 ± 0.017</td>
<td>0.46 ± 0.023</td>
</tr>
<tr>
<td>Tapped density (g/cm³)</td>
<td>0.511 ± 0.051</td>
<td>0.766 ± 0.068</td>
</tr>
<tr>
<td>Carr's index (%)</td>
<td>41 ± 5.02</td>
<td>24 ± 2.02</td>
</tr>
<tr>
<td>Hausner ratio</td>
<td>1.69 ± 0.19</td>
<td>1.31 ± 0.17</td>
</tr>
<tr>
<td>True density (g/cm³)</td>
<td>1.318 ± 0.0009</td>
<td>1.391 ± 0.0003</td>
</tr>
</tbody>
</table>
5.4. Conclusion

In the present work, HME was successfully employed to produce ARP-ADP cocrystals. The low Tg matrix polymer (SOL) played an important role in the extrusion by facilitating the processability of the ARP-ADP PM. The extrusion temperature was observed to be a critical parameter influencing the formation of cocrystals. Further, cocrystal formation was verified by DSC, FTIR, PXRD studies, and the FTIR results confirmed non-covalent interaction between ARP and ADP. Cocrystals produced by HME technique improved the dissolution rate (7-fold) compared with the pure ARP. *In-vitro* solubility and dissolution advantages of cocrystals need to be confirmed by performing the *in-vivo* studies. The HME process utilized for cocrystals production can be scaled up by volumetric scale-up approach with stability studies in the future. Thus, a scalable and industrially feasible continuous HME manufacturing process may be an alternative to conventional methods for the production of pharmaceutical cocrystals.


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Born in Jangaon, a district of Telangana, India. I completed my elementary, middle, high school, and undergraduate studies at Jangaon before moving to Warangal, Telangana, for my master's degree. After finishing my master's degree, I worked in a variety of organizations in Hyderabad, India, where my research interest got even stronger, prompting me to pursue a research career in the United States. Following that, I began my Ph.D. studies in pharmaceutical sciences at The University of Mississippi as a graduate research assistant.

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