Evaluation and enhancement of physical stability of amorphous solid dispersions

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EVALUATION AND ENHANCEMENT OF PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSIONS

A Dissertation
presented in the partial fulfillment of requirements
for the degree of Doctoral of Philosophy
in the Department of Pharmaceutics and Drug Delivery
The University of Mississippi

by

XIN FENG

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ABSTRACT

A major concern during formulation development has been to enhance the dissolution rate and bioavailability of poorly water-soluble drugs. Amorphous forms of APIs have attracted considerable attention as amorphous forms tend to exhibit significantly higher levels of supersaturation in aqueous media when compared to the crystalline forms. For drugs which bioavailability is limited by aqueous solubility (biopharmaceutical classification system (BCS) class II drugs), which is a significant number of recently discovered drug candidates, the improved solubility may lead to enhanced bioavailability. Oral absorption of APIs depends on two broad, but crucial, events, namely drug solubilization and gastrointestinal permeation. Amorphous solid dispersions have been widely investigated to increase the gastrointestinal permeability, and the roles played by polymers and other excipients were also studied.

However, even after 40 years of active research there have not been many commercial products have reached the market based on amorphous solid dispersion technology. The primary reason for this is a combination of the stability and scale up issues associated with this approach, which has been reported by several authors. Hot-melt extrusion currently stands as the most promising approach for solving the scale-up issues associated with amorphous solid dispersion systems. Unfortunately, amorphous solid dispersion systems still face the issue that the amorphous form is, in general, thermodynamically unstable relative to its crystalline counterpart(s), and therefore may ultimately result in unacceptable changes in the API’s physical properties. The most common approach of preserving the solubility/bioavailability enhancement imparted by the high-energy amorphous form is to kinetically stabilize the drug
substance in the amorphous state for the duration of the anticipated shelf life. Amorphous solid
dispersions can be stabilized as such if there exists a sufficient energy barrier provided by the
polymer(s) with a high glass transition temperature, or by way of molecular interactions between
the API and polymeric carriers, such as hydrogen bonding. So the study to evaluate and enhance
the physical stability of amorphous solid dispersions is with great importance for the
pharmaceutical industry. This thesis would focus on the evaluation and enhancement of the
physical stability of amorphous solid dispersion.
DEDICATION

This thesis is dedicated to all my family members, especially my parents, Jiancan Feng and Yujie Zhang, and Yixuan Dong for all their support, encouragement and affection all through these years.
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First of all, I would like to express the sincere appreciation to my supervisor, Dr. Michael A. Repka, Chair and Professor in the Department of Pharmaceutics and Drug Delivery, for his continuous guidance, support, and encouragement in the last five years, not only about the pharmaceutical science but the things about being a real scientist.

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CHAPTER 1

INTRODUCTION

A major concern during formulation development has been to enhance the dissolution rate and bioavailability of poorly water-soluble drugs.[1],[2] The amorphous forms of APIs have attracted considerable attention as the amorphous forms tend to exhibit significantly higher levels of supersaturation in aqueous media when compared to the crystalline forms.[3],[4] For drugs which bioavailability is limited by aqueous solubility (biopharmaceutical classification system (BCS) class II drugs), which is a significant number of recently discovered drug candidates, the improved solubility may lead to enhanced bioavailability.[5-7] Oral absorption of APIs depends on two broad, but crucial, events, namely drug solubilization and gastrointestinal permeation.[8] Amorphous solid dispersions have been widely investigated to increase the gastrointestinal permeability, and the roles played by polymers and other excipients were also studied.[9],[10]

However, even after 40 years of active research there have not been many commercial products that have reached the market based on amorphous solid dispersion technology. [11, 12] The primary reason for this is a combination of the stability and scale up issues associated with this approach, which has been reported by several authors.[13-15] Hot-melt extrusion currently stands as the most promising approach for solving the scale up issues associated with amorphous solid dispersion systems.[16] Unfortunately, amorphous solid dispersion systems still face the issue that the amorphous form is, in general, thermodynamically unstable relative to its crystalline counterpart(s), [17], [18] and therefore may ultimately result in unacceptable changes in the API’s physical properties. [19] The most common approach of preserving the
solubility/bioavailability enhancement imparted by the high-energy amorphous form is to kinetically stabilize the drug substance in the amorphous state for the duration of the anticipated shelf life. Amorphous solid dispersions can be stabilized as such if there exists a sufficient energy barrier provided by the polymer(s) with a high glass transition temperature, or by way of molecular interactions between the API and the polymeric carrier, such as hydrogen bonding. So the study to evaluate and enhance the physical stability of the amorphous solid dispersions is with great importance for the pharmaceutical industry.

Solid dispersions were initially defined as a solid formulation system in which one or more active pharmaceutical ingredients (APIs) are dispersed into one inert carrier by Chiou and Riegelman[20]. According to the molecular arrangement of the API inside the carrier matrix and the physical state of polymer carriers, solid dispersion could be further classified into three categories, crystalline solid dispersion, amorphous solid dispersion and amorphous solid solution[1, 21, 22] (Figure 1-1). The carrier, commonly polymers, could be amorphous, semi-crystalline or crystalline, while the API(s) could be either molecularly dispersed into the matrix or dispersed as aggregates. In a crystalline solid dispersion system, multiple phases will exist simultaneously, which can be identified by differential scanning calorimetry (DSC) with a glass transition temperature ($T_g$) corresponding to the carrier and a melting endotherm ($T_m$) representing the crystalline drug. Therefore, a solid crystalline dispersion is also referred to as a solid crystalline suspension[1].

The solubility of a drug substance can be enhanced by the approach of breaking down the size of drug particles into micro or nano region [23]. The amorphous solid dispersion is generated when the drug is converted into an amorphous state and dispersed throughout the carrier matrix by heating or physical energy input; however, they have a tendency to revert to
their more stable, lower energy level crystalline forms from a thermodynamic standpoint. At the same time, a kinetically induced recrystallization will also occur since the amorphous solid dispersion often contains a drug-concentrated region [22, 24]. In a solid solution, which can be defined as a particular subgroup of amorphous solid dispersion, the drug substance is molecularly dispersed into the carrier with only one single glass transition temperature observed in DSC.

![Diagram of drug/polymer solid dispersion structures](image)

Figure 1-1 The three possible structures of a drug/polymer solid dispersion where hexagonal symbols represent drug molecules and curvy lines represent polymer chains. [2]

Basically, fusion-based method and solvent-based method were the two main type of methodologies to manufacture the solid dispersion systems in pharmaceutical field [22, 24, 25]. A solid dispersion can be prepared by a fusion-based method simply by heating the drug-carrier mixture along with other formulation additives to a temperature above their glass transition temperature, melting point or eutectic point, and then followed by cooling at a controlled rate [26-32]. A prerequisite for any material to be processed by this method is thermal stability [24, 25, 33]. Moreover, the miscibility and compatibility between drug and carrier needs to be seriously considered. The high viscosity of a molten carrier can lead to phase separation and result in an
inhomogeneous dispersion which will further threaten the stability of the final products[34]. In terms of a solvent-based method, the hydrophobic drug substances will dissolve with the hydrophilic carriers into their common solvent which will be evaporated [35-47]. Compared to a fusion-based method, this type of technology is often operated at a lower temperature which is more suitable for heat sensitive compounds. However, it is not very straightforward to find a common solvent for the rapidly increasing NCEs and carriers[22]. Moreover, it is always a hurdle to eliminate the solvent residue in the solid dispersions.

Hot melt Extrusion has been used in the manufacturing process for plastics and food since the 1930s [49]. HME has been shown by a number of studies to be useful in the production of pharmaceutical products using pellets, granules, mini-tablets, transmucosal, and transdermal delivery systems and implants. Furthermore, HME is a continuous manufacturing process that does not require drying or discontinuous steps in processing, making it extremely efficient.

There are two types of extrusion, wet and dry, that can be used for extrusion processing. With wet extrusion, the ingredients are mixed with a solvent such as water or alcohol which activates a binder and forms a wet mass, which is extruded through a sieve. Pellets are created by cutting and spheronizing the strands which result from extrusion through a sieve. The ripening action of the excipients during wet extrusion produces a uniform product with a better finish than dry-extruded products [50]. Wet extrusion is also preferable for use with heat-sensitive drugs and excipients because it reduces localized heat build-up. In contrast to wet extrusion, dry extrusion does not use solvents, but rather utilizes a thermoplastic agent which forms a homogenous matrix with the compounds when processed with a hot melt extruder.

Spray drying is a unit operation capable of transforming solutions or suspensions into a solid product. The first use of drying of products from an atomized liquid stream was already
described in a patent from Percy in 1872. Since then, a tremendous development of the spray
drying process with the refinement in the hardware and equipment configuration and improved
understanding of fluid dynamics has made it versatile technique operational in diverse industrial
fields ranging from food and dairy processing, ceramics, paints, fertilizers, detergents and
pharmaceutical industry. In the pharmaceutical field, spray drying is a well utilized unit
operation employed for simple drying operations to particle engineering of bulk active
pharmaceutical ingredients (API) and excipient and pulmonary formulations, granulation,
encapsulation, etc. Besides, it is also used for processing vitamins and biopharmaceutical
products such as peptides and proteins. One of the characteristics of a spray drying process is the
very fast solvent evaporation. This makes it interesting with respect to preparation of amorphous
solid dispersions: using the improved Avrami equation was utilized to evaluate the
recrystallization kinetics for several amorphous solid dispersion systems including fenofibrate
with different grades of hydroxypropylcellulose (Klucel™ LF/EF/ELF); investigating the effects
of polymeric carrier, HME processing and other downstream processing parameters on the
moisture sorption properties of amorphous solid dispersions; studying the impact of commonly
used surfactants and polymers on the stability of amorphous solid dispersion suspensions using a
Nikon polarized microscopy equipped with an automatic stage.
CHAPTER 2
EVALUATION OF THE RECRYSTALLIZATION KINETICS OF HOT MELT EXTRUDED POLYMERIC SOLID DISPERSIONS USING AN IMPROVED AVRAMI EQUATION

2.1 Introduction

Hot-melt extrusion currently stands as the most promising approach for solving the scale up issues associated with amorphous solid dispersion systems.[16] Unfortunately, amorphous solid dispersion systems still face the issue that the amorphous form is, in general, thermodynamically unstable relative to its crystalline counterpart(s), [17], [18] and therefore may ultimately result in unacceptable changes in the API’s physical properties.[19] The most common approach of preserving the solubility/bioavailability enhancement imparted by the high-energy amorphous form is to kinetically stabilize the drug substance in the amorphous state for the duration of the anticipated shelf life. Amorphous solid dispersions can be stabilized as such if there exists a sufficient energy barrier provided by the polymer(s) with a high glass transition temperature, or by way of molecular interactions between the API and the polymeric carrier, such as hydrogen bonding.

The most commonly used methods of evaluating the physical stability of these dispersed systems are short and long term stability tests in accordance to ICH guidance.[51] However, during the research and development process of a new solid dispersion drug product, hundreds of
formulations need to be evaluated, which is neither cost nor time efficient. Fortunately, the recrystallization process of the drug-polymer system can be quantitatively described by kinetics models.\textsuperscript{[52-54]} Among these models, the Avrami model/equation is most frequently used to express and predict the solid-state recrystallization processes.

\[ \alpha(t) = 1 - \exp(-kt^n) \]  

(Equation 1)

Where the \( \alpha(t) \) is relative crystallinity, \( k \) represents the recrystallization rate constant and \( n \) is the Avrami exponent.

The kinetic description of crystallization processing is composed of two main independent procedures: nucleation and crystal growth. The Avrami equation has been used to model crystallization kinetics for decades; however, one of the primary assumptions inherent in this equation is that the nucleation rate is a constant. Treating the nucleation process as such leads to an over-prediction in the recrystallization rate. This becomes particularly apparent during the later stages of the process. In our previous study,\textsuperscript{[55]} an improved description of the nucleation rate was proposed that is proportional to the amorphous fraction.

\[ J(t) = J_0 (1 - \alpha(t)) \]  

(Equation 2)

Where the \( J(t) \) term is the nucleation rate of sample at time of \( t \), \( J_0 \) is the initial nucleation rate, and \( 1 - \alpha(t) \) is a function of the time of the experiment.

The improved kinetic equation enables enhanced predictability by using the experimental date of formulations under high temperature and high RH conditions to predict the performance of formulations under ambient conditions, which could, in turn, save a great deal of time and expense in terms of the formulation screening.

In this study, the improved Avrami equation was utilized to evaluate the recrystallization kinetics for several amorphous solid dispersion systems including fenofibrate with different
grades of hydroxypropylcellulose (Klucel™ LF/EF/ELF). Fenofibrate is an agonist of the nuclear per-oxisome proliferator-activated receptor α. It reduces the blood triglyceride levels and, to a lesser extent, the total cholesterol and low-density lipoprotein (LDL) cholesterol levels.\[^{56}\]

Fenofibrate is practically insoluble in water which as a result of being a neutral and lipophilic molecule with a log P value of 5.2.\[^{57},^{58}\] Hydroxypropylcellulose (Klucel™ HPC) is a nonionic water-soluble cellulose ether, with a remarkable combination of properties including organic solvent solubility, thermoplasticity, and surface activity.\[^{57}\] Klucel™ HPC has been widely used in solid dispersion formulations to control drug release,\[^{59}\] inhibit drug recrystallization,\[^{60}\] and also serve as a granulation binder.\[^{61}\]

The solid dispersion systems of fenofibrate with different grades of HPC (Klucel™) were compared to investigate the influence of polymer molecular weight on the physical stability of the amorphous systems. Compared to the original Avrami equation, the improved Avrami equation model performance was examined and validated by comparing the predicted values with experimental data. The effects of polymer content, temperature and relative humidity on the recrystallization rate were also investigated by the improved Avrami equation. To the best of our knowledge, this is the first study using this kinetics equation to evaluate the physical stability of amorphous solid dispersions prepared by hot melt extrusion.

**2.2 Materials and methods**

**2.2.1 Materials**

Hydroxypropylcellulose (Klucel™; grades LF/EF/ELF) was kindly donated by ASHLAND Specialty Products (Wayne, NJ, USA) and fenofibrate was purchased from Aurobindo Pharma Ltd. (Hyderabad, India). Reagent grade methanol was purchased from Sigma–Aldrich (St. Louis, MO, USA).
2.2.2 Methods

2.2.2.1 Preparation of amorphous solid dispersions using hot-melt extrusion

Amorphous solid dispersions of fenofibrate and Klucel™ LF/EF/ELF were prepared using hot-melt extrusion technology. The extrusion temperature range was determined by Thermal gravimetric analysis (TGA). The API and polymer were mixed in a V-cone blender (MaxiBlendTM, GlobePharma) at 30 rpm for 20 min and then extruded with a co-rotating twin-screw extruder (Process 11, ThermoFisher Scientific) into uniform rod extrudates at an extrusion temperature range of 120°C to 130°C based on the molecular weight of Klucel™ and a screw speed of 100 rpm. The feed rate was 12 g/min so that the extruder % torque indicator was in a safe range of 40-50%. The extrudates were milled using a comminuting Fitz Mill (Model#L1A, Fitzpatrick Company, IL) at a speed of 3600 rpm using a 0.0232 inch-sieve. Each formulation and its process parameters are shown in Table 2-1.

Table 2-1. Composition of solid dispersions and hot melt extrusion parameters for each formulation.

<table>
<thead>
<tr>
<th>Content of Fenofibrate (%)</th>
<th>Polymer Carrier</th>
<th>Temp. (°C)</th>
<th>Screw Speed (rpm)</th>
<th>Torque (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Content (%)</td>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>80</td>
<td>ELF</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>85</td>
<td>ELF</td>
<td>120</td>
<td>100</td>
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<td>10</td>
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<td>ELF</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>LF</td>
<td>130</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>EF</td>
<td>125</td>
<td>100</td>
</tr>
</tbody>
</table>

2.2.2.2 Thermal gravimetric analysis (TGA)
TGA studies were performed on Perkin Elmer Pyris 1 TGA with the Pyris software. 3-5 mg samples were heated at heating rate of 20°C/min from 20°C to 300°C.

2.2.2.3 Differential scanning calorimetry (DSC)

DSC was utilized to measure the melting enthalpy of the solid dispersions. Samples were weighed (3-5 mg) in an aluminum sample pan and hermetically sealed at each time point using a heating rate of 20°C/min from -40°C to 180°C (Perkin Elmer, Diamond DSC). The nitrogen purge rate was 20 mL/min. An empty pan was used as reference. Measurements were repeated three times. An Indium standard was used for calibration.

2.2.2.4 HPLC-UV Analysis

A Waters HPLC-UV system (Waters Corp, Milford, MA), equipped with a Luna 5μm C18 100Å column (Phenomenex, US), was used at a detection wavelength of 286 nm. The mobile phase consisted of acetonitrile and phosphoric acid in water (pH=2.5) at a ratio of 85:15 (v/v). The flow rate was maintained at 1.0 mL/min. The retention time of fenofibrate was 6 minutes. The injection volume was 20 μL. All of the HPLC data was analyzed using Empower V. software.

2.2.2.5 Evaluation of crystallinity on hot-melt extrudates

The freshly extruded samples were stored in stability chambers with different temperature (±0.1°C) and relative humidity (±1%) conditions, which were predetermined for different formulations (Temperature: 40, 50, 60°C and %RH: 10, 40, 70). Samples were removed from the chambers at each sampling time point and the degree of recrystallization was measured by DSC. The absolute percentage of crystallinity, \( x(t) \), could be determined by the ratio of melting enthalpies from recrystallized fenofibrate over the melting enthalpies of the physical mixture of fenofibrate and polymeric carrier. The relative crystallinity, \( \alpha(t) \), was determined by
the ratios of the melting enthalpies of sample with the final melting enthalpy without any change. The equations\textsuperscript{[62]} are listed below:

\[ x(t) = \frac{\Delta H(t)}{\Delta H(P.M.)} \]  \hspace{1cm} (Equation 3)

Where \( \Delta H(t) \) is the melting enthalpy of the recrystallized solid dispersion sample and the \( \Delta H(P.M.) \) represents the melting enthalpies of physical mixtures of the API and polymers for each formulation.

The relative crystallinity, \( \alpha(t) \), was calculated using the following equation:

\[ \alpha(t) = \frac{\Delta H(t)}{\Delta H_{\infty}} \]  \hspace{1cm} (Equation 4)

Where \( \Delta H_{\infty} \) is the final melting enthalpy of solid dispersion sample for a certain stress condition (this value was constant and did not change during testing), \( \alpha(t) \) varies from 0 to 1.

2.2.2.6 Improved kinetic model

An improved kinetics model was developed in a previous study\textsuperscript{[55]} to quantify the physical stability of each amorphous dispersion system.\textsuperscript{[63]} All the experimental data were fitted into the improved Avrami equation using a multivariate nonlinear regression method to get the optimized parameters (\( k \) values and \( \Delta E_A \)) by MatLab software (version R2011b, MathWorks Inc.).

\[ \alpha(t) = 1 - \frac{1}{1 + k t^n} \]  \hspace{1cm} (Equation 5)

\[ k = k_0 \exp \left( -\frac{\Delta E_A}{RT} \right) \]  \hspace{1cm} (Equation 6)\textsuperscript{[55],[64]}

Where \( n \) represents the dimensionality of crystal growth and \( k \) is the recrystallization rate constant, which can be expressed as Equation 6 where \( k_0 \) describes the pre-exponential factor, \( \Delta E_A \) is activation energy, \( R \) is the universal gas constant and \( T \) is the absolute temperature (in kelvin).
2.3 Results and discussion

2.3.3.1 Preparation of solid dispersions utilizing hot-melt extrusion

All three grades of Klucel™ HPC with fenofibrate showed excellent extrudability under the utilized processing parameters. The TGA figure indicated both API and polymer were stable in the extrusion temperature range (Figure 2-1). Higher molecular weight grades of Klucel™ (LF and EF) required higher extrusion temperatures to decrease the torque on the extruder. Polymers with higher molecular weights usually have a higher glass transition temperature, which requires higher energy input to soften the polymer.\textsuperscript{[65]} Milling of the extrudates was difficult due to the polymer’s high degree of thermoplasticity. Cryomilling, keeping the extrudate in -80°C for several hours before milling, was utilized to resolve this issue.

![Figure 2-1. TGA figure for fenofibrate and Klucel ELF.](image)

Currently, many different polymers are used for hot-melt extrusion processing, and for a certain type of polymer, there might be multiple grades with different molecular weights or different substitution ratios (e.g. PVP, PEG, etc). The improved Avrami equation could be a powerful screening tool to arrive at the most suitable polymer for hot-melt extrusion processing.
The same evaluation process should be applicable to determine the effects of other excipients in a given formulation.

**2.3.3.2 HPLC analysis**

HPLC analysis of the freshly extruded solid dispersions showed no reduction of drug content nor was the appearance of a degradation peak from fenofibrate observed, which indicated that the extrudates were very stable during the processing conditions. All of the extrudates were well within the specifications (85~115%) of content uniformity standards. The results obtained in this study showed that the hot-melt extrusion process with Klucel™ and fenofibrate could have very high homogeneity regardless of the molecular weight of HPC used.

**2.3.3.3 Physical stability of solid dispersions determined by DSC**

The freshly extruded samples were tested by DSC and the absence of melting peaks indicated that the solid dispersion were in the amorphous state as shown in Figure 2-2 (red curve). As the stress test was conducted, the API in the dispersions transformed back into its crystalline phase, which was indicated by the increasing integration values of the melting peaks as shown in Figure 2-2 (purple curve). The peak area on the DSC thermogram is the $\Delta H(t)$, which is the melting enthalpies of the recrystallized solid dispersion sample. The peak area of physical mixture thermogram indicates the $\Delta H(P.M.)$, which represents the melting enthalpies of the physical mixture of the API and polymer. The ratio of these peak areas can be used to evaluate how much amorphous API recrystallized. In the early stage of recrystallization processing, different formulations had significant different $\Delta H(t)$ which indicated different relative crystalinity. This phenomenon might due to the specific recrystallization activation energy of each formulation that caused different nucleation energy barrier for the API molecular. While in
the late stage of recrystallization processing, nucleation rate decreased as the portion of amorphous API decreased, the crystal growth rate turned into the governing factor.\textsuperscript{24}

Figure 2-2. Evaluation of crystallinity using DSC: pure fenofibrate (blue curve), physical mixture of 20\%fenofibrate with Klucel LF (green curve), recrystallized solid dispersion (purple curve), amorphous solid dispersion (red curve).

\textbf{2.3.3.4 Assessment of the improved kinetic model}

The recrystallization predictions based on the original Avrami model and the new improved kinetic model is shown in Figure 2-3. The experimental data were fitted into the new modeling equation by a multivariate nonlinear regression method using MatLab software. Initial values of $k = 0.1$ were given to compute the optimized values of model parameters by minimizing the sum of residual squares using a successive linear programming method. Correlation coefficient, $r^2$, for improved Avrami equation is 0.986, while $r^2$ for the Avrami equation is 0.971, which suggests that the improved model provides a better fit than the Avrami equation. However, this is especially true in the late stages of recrystallization (after 50 hours). This is attributed to the changing of the nucleation rate in the improved Avrami equation, which
is decreasing with the decline of amorphous content in the system. The Avrami exponent $n$ describes dimensionality of crystal growth in the solid dispersion, when $n$ equals to 2, 3, 4, indicate, respectively, the rod, plate, spherical geometry for nucleation. For this study and most situations for small molecular API, $n$ equals to 3.

![Figure 2-3](image)

Figure 2-3. Comparison of Avrami equation ($r^2=0.971$) and Improved Avrami equation ($r^2=0.986$) on recrystallization prediction based on relative crystallinity $a(t)$ plotted against time for 15% fenofibrate with 85% Klucel ELF under 60°C /10% RH stability condition.

### 2.3.3.5 The effect of polymeric carrier on amorphous solid dispersions stability

Three different formulations of fenofibrate and Klucel™ ELF were prepared with different drug loadings of 10, 15, and 20%. The experimental data showed a significant decrease in the recrystallization rate ($k$) with an increase in polymer content. With lower drug loading, the density of API in the polymeric matrix is lower, and the change in nucleation, along with the amount of molecules to nucleate in later stages, are both lower. Two formulations of fenofibrate
with Klucel™ LF and EF, respectively, were produced at a fixed drug loading of 10%. For the different grades of HPC (Klucel™ LF/EF/ELF), under the same drug loading and same stress test condition (60°C/10%RH), LF exhibited a better recrystallization inhibitory effect than was observed for EF and ELF (LF>EF>ELF) (Table 2-2).

Table 2-2. Recrystallization prediction results by the improved Avrami equation for fenofibrate amorphous solid dispersion with different grades of Klucel™ HPC under storage condition of 60°C/10%RH.

<table>
<thead>
<tr>
<th>Content of Fenofibrate (%)</th>
<th>Polymer Carrier</th>
<th>( \Delta H_\infty/\Delta H(P.M.) )</th>
<th>Final time (Hours)</th>
<th>( k ) (10^{-6})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Content (%)</td>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>LF</td>
<td>61.1%</td>
<td>~168</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>EF</td>
<td>67.7%</td>
<td>~144</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>ELF</td>
<td>73.3%</td>
<td>~144</td>
</tr>
</tbody>
</table>

Concerning the recrystallization rate constant \( (k) \) values, ELF>EF>LF. These data indicated that under the specified conditions, the API in ELF recrystallized faster than that with EF, or LF. The data also revealed from the ratio between \( \Delta H_\infty \) and \( \Delta H(P.M.) \), that more API was remaining in the amorphous phase in the API/LF system. This difference might due to the difference of molecular weight between these three grades of HPC (Table 2-3). Klucel™ LF is a higher molecular weight polymer compared to EF and ELF. Klucel™ ELF, with the lowest molecular weight, possesses comparatively lower viscosity due to smaller chains, which could not provide the same energy barrier as EL or LF to prevent the recrystallization of the API. The polymer with the higher molecular weight could have a higher T_g [67],[68] which is a commonly accepted indication of physical stability improvement of amorphous solid dispersions.
Table 2-3. Molecular weight of Klucel™ LF/EF/ELF

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Klucel™ LF</th>
<th>Klucel™ EF</th>
<th>Klucel™ ELF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight (Da)</td>
<td>90000</td>
<td>80000</td>
<td>45000</td>
</tr>
</tbody>
</table>

To develop a stable, high quality amorphous solid dispersion system for one API, the best polymeric carrier can be chosen by calculating the solubility parameters,[69] miscibility[70] and molecular interactions.[71] However, final physical and chemical stability assessment of a formulation is confirmed by long-term stability testing according to ICH regulations. The improved Avrami equation could be an accurate tool to evaluate the physical stability of various formulations within an abbreviated interval, thus saving valuable research and development time.

Figure 2-4. Relative crystallinity α(t) plotted against time for formulations with different polymer content (90, 85 and 80% of Klucel ELF) under 60 °C /10% RH stability condition.

2.3.3.6 The effect of temperature on the recrystallization rate constant
The samples were stored in stability chambers with fixed RH and three different temperatures (10% RH and 40, 50, 60°C). The selected storage temperatures were higher than those normally used for pharmaceutical stability testing in order to promote rapid recrystallization within a short time according to the ICH 2AQR guidance for stability testing. Under all of these conditions the characteristic S-shaped curve was noted again, which was observed in “Assessment of the improved kinetic model”, with faster recrystallization at increasing temperatures (Figure 2-5).

Figure 2-5. Relative crystallinity a(t) plotted against time for 10% fenofibrate with 90% Klucel ELF under different temperature conditions (40, 50 and 60 °C /10% RH).

The semi-log plot of $k$ vs $1/T$ reveals that the crystallization rate constant increased exponentially with temperature within the temperature range studied (Figure 2-6). According to

$$k = k_0 \exp \left( -\frac{\Delta E_A}{RT} \right) \text{ (Eq. 4)}$$

the recrystallization activation energy was determined by the slope of the linear regression of the $\ln k$ and $1/T$ since $k_0$ and $R$ are both constant. The formulation
with a greater slope indicates that the system has lower activation energy and could have faster recrystallization rate. Based on the value of the activation energy, the equation allows the prediction of recrystallization kinetics at temperatures outside the experimental range.

Figure 2-6. An Arrhenius plot of recrystallization constant against temperature for 10% fenofibrate with 90% Klucel ELF under different temperature conditions 40, 50 and 60 °C /10%RH.

Some samples stored in high temperature/low RH conditions (60°C/10%RH) deliquesced in the late stages of the experiments. This event is due to the fact that the high temperature could decrease the critical RH for deliquescing by enhancing water uptake rate whereby the samples could reach the equilibrium weight gain more quickly.\textsuperscript{[72]} Consequently, the higher moisture content of the system and increased molecular mobility triggered more recrystallization of API.

2.3.3.7 The effect of relative humidity on the recrystallization rate constant
Initial amorphous solid dispersions samples were stored in the stability chambers with fixed temperature and three different RH (60°C and 10, 40, 70%RH) to determine the influence of humidity on the recrystallization process. Rapid recrystallization rates were observed under high RH (Figure 2-7).

Figure 2-7. Relative crystallinity a(t) plotted against time for 10% fenofibrate with 90% Klucel ELF under different RH conditions (10, 40 and 70%RH/60°C).

Linear regression of the experimental data (Figure 2-8) suggests that k increases linearly rather than exponentially over the range of RH studied, which confirmed Yang’s results for PVP-efavirenz solid dispersion systems. Different polymer-API combinations would have regression equations with different sloped and the slopes could be a quantitative factor to evaluate how sensitive the system is to the RH condition. On the other hand, the Y-intercept of the regression equation could serve as an indicator to quantify the other factors’ contribution to the recrystallization rate under 0% RH, such as polymer and temperature. Moisture potentially
acted as a plasticizer and hence lowered the glass transition temperature of the solid dispersion system, which increased the recrystallization rate constant.\cite{73} The rapid recrystallization might also be due to the increased molecular mobility of APIs in the systems caused by high RH which can increase the molecular rotation and movement subsequently to a lower glass transition temperature of the dispersion system.\cite{74} Since the recrystallization rate constant has a liner relationship with the RH, we can assume that the moisture content of the solid dispersion system, which is determined by the polymer’s hydroscopic nature, is proportional to the recrystallization rate of the API during stability testing. This indicates that characterizing the water uptake ability of the polymer carrier and other excipients is very important when developing a solid dispersion system.

![Graph showing recrystallization rate constant plotted against RH for 10% fenofibrate with 90% Klucel ELF under different RH conditions (10, 40 and 70%RH/60 °C).](image)

Figure 2-8. Recrystallization rate constant plotted against RH for 10% fenofibrate with 90% Klucel ELF under different RH conditions (10, 40 and 70%RH/60 °C).

The deliquescence phenomenon was also observed under high RH conditions. Study of the consequence of deliquescence on amorphous solid dispersion samples and hygroscopicity of
polymer carriers will be helpful in developing solid dispersion system with better physical stability. Surface properties (e.g. surface free energy, surface area, etc.), water uptake ability and mechanisms of the polymer carrier,\textsuperscript{[75]} might be the causes of different recrystallization inhibition abilities for the amorphous solid dispersion system under the same RH conditions, which will be the focus of our future studies.

2.4 Conclusion

The improved Avrami equation demonstrated more accurate evaluation for all of the solid dispersion systems investigated in this study. This is particularly evident for the late stages of the recrystallization process, which provides a novel approach for early stage formulation development of amorphous solid dispersion systems. This can be viewed as both time and cost effective when compared to the conventional ICH stability tests. By resolving the relationships between the recrystallization rate constant, temperature, relative humidity and formulation, an accurate and reliable prediction can be obtained in reference to recrystallization kinetics. The polymers (Klucel\textsuperscript{TM} EF/LF/ELF) inhibited the recrystallization process of the amorphous API and HPC grades with a higher molecular weight exhibited more favorable results. The method utilized in this study would also be useful for screening the most suitable polymeric carrier and other excipients in solid dispersion systems.

2.5 Declaration of interest

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CHAPTER 3

THE EFFECTS OF POLYMER CARRIER, HOT MELT EXTRUSION PROCESS AND DOWNSTREAM PROCESSING PARAMETERS ON THE MOISTURE SORPTION PROPERTIES OF AMORPHOUS SOLID DISPERSIONS

3.1 Introduction

There are many technologies currently used to prepare solid dispersion systems, which include solvent casting, spray drying, and hot melt extrusion [76-78]. It is argued by many, among all of these techniques that hot melt extrusion (HME) [79], or melt extrusion, is the most promising techniques, which include, advantages such as continuous processing, easy to scale up, solvent free fabrication and lower production costs [80-84].

For most of the HME formulations, polymer carriers entail a large proportion of all of the components, which performs the role of recrystallization inhibitor, as well as that of the dissolution controller [85, 86]. However, at the same time, most commonly used polymers in HME processing are hydrophilic polymers or hygroscopic materials. Most amorphous solid dispersion systems containing only the API and polymer carrier, are difficult to be stabilized under the environmental conditions with moisture and temperature near the glass transition temperature (Tg). Moreover, the polymer carriers are hygroscopic in nature and this could aggravate the influence of moisture by lowering the systems Tg, which consequently increases molecular mobility and facilitates the recrystallization of the API.
Evaluation of drug-polymer solubility and miscibility, and the effect of polymer type on the stabilization of amorphous APIs have been reported [86-88]. However, once exposed to moisture, the drug-polymer binary system will alter to a drug-polymer-water ternary system.

In order to investigate the moisture induced changes in the solid dispersion, utilizing FTIR spectroscopy in the analysis provides several advantages [89]. Sensitive and non-invasive characterization of drug-polymer interactions can be performed quickly, even with the controlled sample temperature and atmosphere. Moreover, FTIR chemical imaging provides straightforward information of miscibility or mixing of the drug and polymer [90, 91]. However, the effect of moisture on the drug dispersion homogeneity is still limited by using this visualized technology.

Previous research has been conducted to investigate the influence of moisture on the formulations containing hygroscopic polymers [92-94]. However, evidence is still deficient as to how polymer properties, HME processing and downstream processing, affects moisture uptake within the systems. In order to achieve a good commercial solid dispersion product, thoroughly understanding the effect of formulation as well as the preparation technology is paramount. It is well recognized that different processing technologies could impart huge differences on the physical properties of solid dispersions [95-98]. However, research on how preparation techniques and downstream processing affects the solid dispersion is still very limited.

Therefore, the objective of the present study was to investigate the effects of polymeric carrier, HME processing and other downstream processing parameters on the moisture sorption properties of amorphous solid dispersions. Polyethylene glycol (PEG), Hydroxypropyl cellulose (HPC) and Ethyl cellulose (EC) were chosen as polymer carriers and fenofibrate (FF) was used as a model drug. The moisture sorption/desorption isotherms were measured for various
molecular weight (MW) grades of the polymer carrier, physical mixture (PM) of polymer and
drug, and amorphous solid dispersions prepared by HME technology. To the best of the authors’
knowledge, this is the first study compared the moisture uptake ability of melt extruded
amorphous solid dispersion with different hygroscopic nature polymer carriers and different
molecular weight. Also the effects of hot melt extrusion processing and downstream processing
on the moisture sorption ability of solid dispersions were investigated for first time.

3.2 Materials and methods

3.2.1 Materials

Hydroxypropylcellulose (Klucel™ HPC; grades LF/EF/ELF) and Ethylcellulose (Aqualon® EC; grades N7/N14/N22) were kindly donated by ASHLAND Specialty Products (Wayne, NJ, USA). Polyethylene glycol (3350, 4000, and 6000) were purchased from Sigma–Aldrich (St. Louis, MO, USA). And fenofibrate was purchased from Aurobindo Pharma Ltd. (Hyderabad, India). Reagent grade methanol was purchased from Sigma–Aldrich (St. Louis, MO, USA). All the other reagents used in this study were of the analytical grade.

3.2.2 Methods

3.2.2.1 Preparation of amorphous solid dispersions using hot-melt extrusion

Amorphous solid dispersions of fenofibrate and model polymer with various MWs were
prepared using HME technology. Thermal gravimetric analysis (TGA) and differential scanning
 calorimetry (DSC) were utilized to determine the extrusion processing temperature range. The
API and polymer were mixed in a V-cone blender (MaxiBlend™, GlobePharma) at 30 rpm for
10 min and then extruded with a co-rotating twin-screw extruder (Process 11, ThermoFisher Scientific) into uniform rod extrudates, at an extrusion processing temperature range based on
the formulation composition and a screw speed of 100 rpm. The maximum feed rate utilized was
10 g/min, in order to maintain the torque (%) indicator of the extruder within a safe mode range. The extrudates were milled using a comminuting Fitz Mill (Model#L1A, Fitzpatrick Company, IL) at a rotor speed of 3600 rpm.

3.2.2.2 Dynamic vapor sorption (DVS)

The water sorption behavior of API, physical mixture, milled extrudates, and compressed milled extrudates were determined by Intrinsic DVS (Surface measurement systems, London, UK). 20±0.5 mg samples were exposed to the controlled relative humidity profile (0– 90 – 0% in 10% steps) at a constant temperature (25°C), and the weight changes were measured by a CahnD200 ultra-microbalance (±0.01mg mass resolution). The dm/dt mode was used in all the steps, and the limitation was set at 0.001%/min to detect the equilibrium (the instrument would start next step when the samples dm/dt value equal or less than 0.001%/min). At first step, sample was dried at 0%RH, and the equilibrated mass at 0%RH was used as reference mass. The water sorption isotherms were calculated using the equilibrated sample mass from each step [99].

3.2.2.3 Thermal gravimetric analysis (TGA)

TGA studies were performed on Perkin Elmer Pyris 1 TGA with the Pyris™ software (PerkinElmer Life and analytical sciences, CT, USA). 3-5 mg of the sample was weighed and heated from 20 °C to 300 °C under an inert nitrogen atmosphere at a flow rate of 20 °C/min. Percent weight loss was plotted against temperature to determine the weight loss. The TGA sample of fenofibrate was holding at the highest extrusion temperature (145 °C) for 15 min to test the thermal stability.

3.2.2.4 Differential scanning calorimetry (DSC)

DSC (Perkin Elmer, Diamond DSC) was utilized to measure the melting enthalpy of the solid dispersions. Samples were weighed (3-5 mg) in an aluminum sample pan and hermetically
sealed at each time point using a heating rate of 20°C/min from 30°C to 200°C under an inert nitrogen atmosphere at a flow rate was 20 mL/min. An empty pan was used as reference. Measurements were repeated three times. An Indium standard was used for calibration.

3.2.2.5 HPLC-UV Analysis

A Waters HPLC-UV system (Waters Corp, Milford, MA), equipped with a Luna 5μm C18 100Å column (Phenomenex, US), was used to detect fenofibrate at a wavelength of 286 nm. The mobile phase consisted of acetonitrile and phosphoric acid in water (pH=2.5) at a ratio of 85:15 (v/v). The flow rate was maintained at 1.0 mL/min. The injection volume was 20 μL. The observed retention time of fenofibrate was 6 min. The data was acquired and processed using Waters Empower 3 software suite.

3.2.2.6 Scanning electron microscopy (SEM)

SEM was used to study surface morphology of the solid dispersions. Samples were mounted on aluminum stubs held with a carbon adhesive film. Gold was used to coat the Samples by a Hummer® 6.2 sputtering system (Anatech LTD, VA, USA) in a high vacuum evaporator. The surface topography of the sample was analyzed by a scanning electron microscope operating at an accelerating voltage from 1.0 kV to 5.0 kV (JEOL JSM-5600).

3.2.2.7 FTIR and Chemical Imaging

Infrared spectra were collected on an FTIR bench (Agilent Technologies Cary 660) fitted with a MIRacle ATR (Pike Technologies) sampling accessory in the spectral range of 4000-650 cm⁻¹. The bench ATR was equipped with a single bounce diamond coated ZnSe internal reflection element. Chemical images were collected using an infrared microscope (Agilent Technologies Cary 620 IR), which was equipped with a 64 x 64 focal plane array (FPA) detector.
The images were collected with a germanium micro ATR sampling accessory giving a field of view (FOV) of approximately 70 x 70 microns with 1.1µm spatial resolution.

### 3.2.2.8 Statistical Analysis

All statistical analysis was calculated using SPSS v.18.0 (IBM Corp., Armonk, NY, USA). To compare the differences of moisture sorption between solid dispersions with different polymers, one-way ANOVA followed by t-test was used for continuous variables. All significant tests were two-tailed and \( p<0.05 \) was considered significant.

### 3.3 Results and discussion

#### 3.3.1 Preparation of amorphous solid dispersions utilizing hot-melt extrusion

The TGA study results confirmed that all of the polymers and the model drug were stable at the temperature range of 30-200°C, as no degradation peaks were observed (Figure 3-1). The TGA sample of model drug was holding at 145 °C for 15 min, and the weight change was less than 0.5% which indicated the thermal stability of fenofibrate since the holding time was much longer than retention time in the extruder(less than 5 min). All grades of model polymer with the model drug fenofibrate showed excellent extrudability under the utilized processing parameters (Table 3-1). Formulations containing higher MW grades of model polymers required higher extrusion temperatures to decrease the torque on the extruder, and pure polymers without fenofibrate needed even higher temperatures for processing. Polymers with higher MW usually have a higher Tg, which requires higher energy input to soften the polymer [65]. However, fenofibrate with a Tg of -20°C could lower the systems Tg by acting as a plasticizer [100]. The extrudates of HPC were difficult to mill due to the polymers high degree of thermoplasticity. Cryomilling, keeping the extrudate in -80°C for several hours before milling, was utilized to resolve this issue. All physical mixture and milled extrudates were passed through the same
number sieve to ensure the same particle size. From Figure 3-2, DSC data confirmed that all of the extruded formulations with the drug were amorphous solid dispersions (PXRD also corroborated the DSC findings, data not shown). HPLC analysis of the freshly extruded solid dispersions showed no reduction in the drug content nor demonstrated a degradation peak from fenofibrate, which indicated that the extrudates were very stable during the processing conditions. All of the extrudates’ content uniformities were well within the range of 85-115%.

Figure 3-1. Thermal gravimetric analysis results for all polymer carriers and the model drug (polyethylene glycol, ethyl cellulose and hydroxypropylcellulose) did not show any degradation, so the three lines overlapped).
Figure 3-2. Differential scanning calorimetry result for pure model drug and hot melt extruded amorphous solid dispersions. Red line: fenofibrate; blue line: PEG 3350 with 10% fenofibrate; green line: HPC ELF with 10% fenofibrate; orange line: EC N7 with 10% fenofibrate.

Table 3-1. Composition of solid dispersions and hot melt extrusion parameters for each formulation. (For all formulations containing PEG, the last 3 zones temperature were set at 30°C to avoid liquid extrudate.)

<table>
<thead>
<tr>
<th>Polymer Carrier</th>
<th>Drug Content (%</th>
<th>Temp. (°C)</th>
<th>Screw Speed (rpm)</th>
<th>Torque (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Content (%)</td>
<td>Molecular weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPC</td>
<td>LF</td>
<td>95000</td>
<td>10</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>EF</td>
<td>80000</td>
<td>10</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>ELF</td>
<td>40000</td>
<td>10</td>
<td>125</td>
</tr>
<tr>
<td>EC</td>
<td>N7</td>
<td>65000</td>
<td>10</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>N14</td>
<td>120000</td>
<td>10</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>N22</td>
<td>140000</td>
<td>10</td>
<td>145</td>
</tr>
<tr>
<td>PEG</td>
<td>3350</td>
<td>3350</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>4000</td>
<td>4000</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>6000</td>
<td>6000</td>
<td>10</td>
<td>80</td>
</tr>
</tbody>
</table>

3.3.2 Effect of Polymer carrier on the moisture sorption of solid dispersions

For the same model drug, fenofibrate, three different polymers HPC, EC and PEG corresponding to hygroscopic amorphous, hydrophobic amorphous, and hygroscopic semi-
crystalline polymer, respectively, were selected to prepare the solid dispersions for testing (Figure 3-3, 3-4 and 3-5). To clarify the comparisons, all of the important parameters are summarized in Table 3-2.

Figure 3-3. Dynamic vapour sorption measurements of EC N14–FF amorphous solid dispersions prepared by hot melt extrusion (n = 1): (a) change in mass plot and (b) isotherm plot.
Figure 3-4. Dynamic vapour sorption measurements of HPC EF–FF amorphous solid dispersions prepared by hot melt extrusion ($n = 1$): (a) change in mass plot and (b) isotherm plot.
Figure 3-5. Dynamic vapour sorption measurements of PEG 4000–FF amorphous solid dispersions prepared by hot melt extrusion ($n = 1$): (a) change in mass plot and (b) isotherm plot.

At the 90% RH condition, the pure drug fenofibrate only had a weight change of 0.125%. This would indicate that even at high RH conditions the API absorbs very little water from the moist air. According to the isotherm hysteresis, after desorption processing, the weight change approached 0%, which would suggest that the API had very low ability to hold the moisture.
In the case of the hydrophobic polymer carrier, the EC-FF solid dispersion system showed similar water uptake properties as the pure drug. The low water solubility nature of EC makes it a perfect polymer candidate for sustained and controlled release formulations[92]. Although, EC is considered as water insoluble, the polymer still can sorb some moisture by the mechanism of hydrogen bonding, which was led due to the polarity difference between the oxygen atom and the ethyl group in the ethoxy group [101].

However, the controlled release formulation is only a small part of all drug products. To achieve other dissolution profiles or release mechanisms, water soluble polymer carriers are applicable to be incorporated into a formulation. Indeed, even for the same dissolution type, different dosage forms might require other polymer with special physicochemical properties, such as HPC and PEG for HME extruded films [83, 102].

The hygroscopic characteristic of polymers depend on its structure, hence the water uptake ability for both PEG and HPC polymers depends on either oxygen atoms or hydroxyl – OH groups, which may contribute greatly to the high water solubility by forming hydrogen bonding with water [103].

Both PEG and HPC exhibited high moisture sorption properties, however due to their hygroscopic nature, these two polymers had significantly different sorption isotherm curves. HPC begins water uptake from the environment at low RH conditions, and with the increase in the RH there was an increase in the % weight change. Conversely, PEG did not take up much moisture until the RH exceeded a specific point. This phenomenon was caused by the hydrophilic nature of the polymer and due to the commencement of deliquescence [104]. For both amorphous and semi-crystalline polymers with a hygroscopic nature, after the exposure to high moisture environment, the physical properties are altered by the sorbed moisture, coupled
with the visible change such as caking and finally transforming into a semi-liquid state. Previous studies have shown that for semi-crystalline polymers like PEG, the phenomenon of deliquescence would happen once the atmospheric RH exceeds a critical relative humidity $\text{RH}_0$ [105, 106].

3.3.3 Effect of Polymer Molecular Weight on the moisture sorption of solid dispersions

For all of the polymers (EC, PEG and HPC) used in this study, three different grades of various MW were used in the ASD formulations to investigate how MW affects the moisture sorption properties of the solid dispersion systems. Statistical analysis showed that maximum weight changing % for the HPC group and PEG group demonstrated significant differences ($p<0.05$), whereas no significant difference was observed for EC group ($p>0.05$). ASD containing different grades of EC revealed very low maximum weight changes % and no significant difference in between N7/N14/N22 was observed, which is most likely due to the hydrophobic nature of the polymer (Table 3-2).
Table 3-2. Important parameters summarized from vapor sorption isotherms of amorphous solid dispersion samples. (Mean ± SD, n=3)

<table>
<thead>
<tr>
<th>Polymer Carrier</th>
<th>Maximum Weight Changing (%)</th>
<th>Weight Changing at 60%RH (%)</th>
<th>Hysteresis at 0% RH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>Molecular Weight</td>
<td>22.81±0.19</td>
<td>8.21±0.23</td>
</tr>
<tr>
<td>EF</td>
<td>80000</td>
<td>20.81±0.17</td>
<td>8.96±0.21</td>
</tr>
<tr>
<td>LF</td>
<td>95000</td>
<td>19.23±0.17</td>
<td>6.29±0.17</td>
</tr>
<tr>
<td>EC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N7</td>
<td>65000</td>
<td>3.42±0.04</td>
<td>1.70±0.07</td>
</tr>
<tr>
<td>N14</td>
<td>120000</td>
<td>3.15±0.08</td>
<td>1.49±0.05</td>
</tr>
<tr>
<td>N22</td>
<td>140000</td>
<td>3.10±0.04</td>
<td>1.45±0.03</td>
</tr>
<tr>
<td>PEG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3350</td>
<td>3350</td>
<td>29.30±0.14</td>
<td>0.49±0.10</td>
</tr>
<tr>
<td>4000</td>
<td>4000</td>
<td>25.20±0.44</td>
<td>0.44±0.03</td>
</tr>
<tr>
<td>6000</td>
<td>6000</td>
<td>23.26±0.27</td>
<td>0.39±0.03</td>
</tr>
</tbody>
</table>

HPC LF exhibited a lesser amount of water sorption as compared to the other grades of HPC with lower MW (LF<EF<ELF). PEG also demonstrated similar MW related sorption properties. However besides these findings, key changes were observed. Each MW of PEG displayed an abrupt increase in weight change when the step RH arrived at one certain point. As stated earlier, this should be the critical RH₀ for the semi-crystalline polymer. When the vapor pressure was lower than the critical vapor pressure of the saturated aqueous solution of the PEG, a very small amount of water could be captured by the polymer via surface hydrogen bonding;
when it surpassed the RH₀, the phase transformation would commence, directing the sample into a semi-solid state. Since at this stage, the aqueous solution is thermodynamically more stable than the semi-crystalline phase, the dissolution of the solid dispersion and water sorption continued until this ternary system arrived at a thermodynamic equilibrium state. As the critical RH was concentrated in the range of 70-90%, the DVS method for PEG was changed by 5% in each step in this range and the critical RH increased as the MW of PEG in the solid dispersion increased. Since the deliquescence process was temperature and RH dependent, the weight change may increase significantly if the formulation is stored at high RH for a longer period of time.

Although this deliquescence and critical RH had been investigated for several small molecules, there are very limited studies for crystalline polymers reported in the literature. Generally speaking, a higher MW polymer always possesses longer polymer chains, which may decrease the mixing entropy of the polymer and water, hence lowering the aqueous solubility of the polymer. At the same time, lower MW polymers tend to be more hydrophilic due to the higher relative fraction of hydroxyl groups. The effect of MW could be limited if increasing MW could not change the fraction of hydrophilic groups.

At the same time, the all the polymer used in this study, the polymer with higher MW exhibit higher viscosity. Once the moisture saturated the surface of the solid dispersion sample, polymer-water mixture would form with different viscosity. And the polymer with higher MW and viscosity would slow the late stage of moisture absorption comparing with the same kind of polymer with lower MW. With the higher viscosity, longer equilibrium time might be needed since the molecular mobility and phase transaction would be slower. This higher viscosity caused
by higher MW might be another factor caused the less hygroscopic of the solid dispersion samples with higher MW polymer carrier.

### 3.3.4 FTIR Analysis and Chemical Imaging

Compared with DVS data, FTIR spectrums provided more detailed information of the solid dispersion systems at the molecular level. Figure 3-6 illustrates a detailed perspective of how the peak positions and intensity vary with HPC molecular weight after exposure to 90% RH for 24 hours.

![FTIR spectrum of HPC fenofibrate solid dispersion after storing at 25°C/90%RH for 12 h. Blue line: HPC ELF with 10% fenofibrate; black line: HPC EF with 10% fenofibrate; red line: HPC LF with 10% fenofibrate; and purple line: HPC ELF with 10% fenofibrate before exposed to RH.](image)

FTIR imaging (Figure 3-7) indicated that the API was homogeneously dispersed within the freshly prepared amorphous solid dispersion, however the homogeneity was changed after storage at the high RH condition (25 °C/90% RH). With regard to API homogeneity as illustrated in the chemical images, considering the relatively small field of view (70 x 70 microns) and the marked intensity of absorbance resulting from fenofibrate’s characteristic and spectrally resolved carbonyl centered at 1723cm⁻¹, the API is homogenously dispersed in the fresh
extrudates (Figure 3-7A; time point 0). The additional accumulation of adsorbed water, resulting from continued exposure to the relative humidity, produced areas of migrated fenofibrate. In the chemical images (Figures 3-7 A-D), this is graphically illustrated by the growing intensities of both fenofibrate pockets, represented by the colour orange and red, and the voids where it is increasingly missing, represented by the colour blue.

As stated previously, the polymers’ hygroscopic nature attributed to sorption of moisture. This may result in many implications such as accelerating degradation by providing a reactant or reaction medium, and also negatively affecting the physical stability of the ASD by increasing molecular mobility and promoting recrystallization \([107-109]\). As the molecular mobility increases and the miscibility decreases driven by moisture, the drug-rich and polymer-rich amorphous domains could be potentially formed, prior to complete phase separation and drug recrystallization \([110]\). The uneven distribution of yellow color peaks, as shown in Figure 3-7, could be evidence of amorphous-amorphous phase separation.

![Figure 3-7. FTIR chemical imaging of HPC LF amorphous solid dispersions after storing at 25°C/60% RH for (a) 0, (b) 2, (c) 3 and (d) 4 weeks.](image)

**3.3.5 Influence of Hot Melt Extrusion processing**
Polymer carriers, APIs, and other additives normally comprised the solid dispersion systems. All of these components and their respective interactions determine the characteristics of the system. However even for the same formulation, if prepared by different technologies, the physicochemical properties could be changed significantly. The moisture sorption of polymer and polymeric solid dispersions have been documented in some studies, Konno found that the polymer in solid dispersion system could increase the moisture content of the system comparing to that of the pure amorphous drug part [111]. Rumondor stated that solid dispersion with different polymer carrier could go under phase separation at different RH conditions mainly effected by the molecular interaction between API and polymer carrier [112]. To date, no study has reported how processing such as HME affects the water sorption/desorption of amorphous polymeric solid dispersion systems.

The kinetics of water uptake for each physical mixture (P.M.) and corresponding milled HME extrudates were measured at 25 °C by DVS and all of the important parameters are summarized in Table 3-3.

Table 3-3 Important parameters summarized from vapor sorption isotherms and physical properties of amorphous solid dispersions (HME) and physical mixture (P.M.). (Mean ± SD, n=3)

<table>
<thead>
<tr>
<th>Drug Content</th>
<th>Maximum Weight Changing (%)</th>
<th>Density (g/cm³)</th>
<th>Surface area (m²/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC ELF</td>
<td>HME 22.81±0.19</td>
<td>0.43±0.03</td>
<td>0.358±0.02</td>
</tr>
<tr>
<td></td>
<td>P.M. 24.2±0.17</td>
<td>0.38±0.01</td>
<td>0.441±0.02</td>
</tr>
<tr>
<td>EC N7</td>
<td>HME 3.42±0.04</td>
<td>0.33±0.01</td>
<td>0.298±0.03</td>
</tr>
<tr>
<td></td>
<td>P.M. 3.53±0.06</td>
<td>0.31±0.03</td>
<td>0.301±0.04</td>
</tr>
<tr>
<td>PEG 3350</td>
<td>HME 29.30±0.14</td>
<td>1.17±0.04</td>
<td>1.162±0.13</td>
</tr>
<tr>
<td></td>
<td>P.M. 29.98±0.07</td>
<td>1.06±0.03</td>
<td>1.217±0.08</td>
</tr>
</tbody>
</table>
The comparison of the sorption isotherms of the physical mixture and milled HME extrudates demonstrated that HME processing could significantly change the maximum moisture sorption of the samples with HPC-FF, EC-FF and PEG-FF ($p<0.05$). The maximum weight changing % difference was not that much between EC-FF HME and PM. The moisture sorption ability of the EC-FF PM system was already very low (approximately 3%) that the effect of HME processing was limited.

The maximum weight change was always attained at the highest RH, or so called water activity, which was the most important indicator for the potential sorption of moisture by the formulation. The entire sorption isotherm was a process in which the moisture mixed with the solid dispersion by physical adsorption, chemisorption and multilayer condensation was attained. When comparing the isotherms curves of all of the HPC-FF containing samples, an interesting phenomenon was observed. The physical mixture and HME formulations exhibited identical sorption behavior at an early stage, and the differences in weight change for all formulations were observed in the later stages (RH$>$60%). The properties of water absorbed in the later stages should be similar to those of the free water that was held in the large capillaries or voids. According to the relatively short desorption equilibrium time, the later stage water was loosely bonded to the solid dispersion surface, which indicates that the vaporization enthalpy should be almost the same as the pure water. From this point of view, the authors hypothesized that HME processing may change the volume of the crevices and the space of the large capillaries. To confirm this hypothesis, both physical mixture and HME formulations were characterized by SEM, density meter and surface area measurement (Figure 3-8). The physical mixture sample had rough surface and lots crevices were observed. And the HME sample exhibited smooth surface and dense structure.
Figure 3-8. Scanning electron microscopic images for the physical mixture and milled hot melt extrudates: (a and b) physical mixture of HPC ELF with 10% fenofibrate; (c and d) milled HME solid dispersion of the same formulation.

During the HME processing, the physical mixture was soften and melted under high temperature and high shear rate. All materials were reshaped by two key steps, first forcing through small round shape die and second milling into small size particles. By pushing the formulations through the die, density of the material could be increased, and no more small cavities could exist in the solid dispersion particles. And the high condensation polymer could have chains with less flexibility and less space to rotate which could lead to lower moisture uptake. The milling processing could only affect the surface of the solid dispersion particles, not the inside. Comparing with the raw material, milled extrudate tend to have smoother surface. The physical absorption of moisture could be lowered by the less surface area. At same time, the PM samples with higher surface area would provide more hydrogen bonding sites, so that more water could be uptake by chemisorption. As in the melt extruded solid dispersion, fenofibrate was
dispersed in the polymer matrix on molecular lever, the molecular interaction like hydrogen bonding between API and polymer could reduce the available hydrogen bonding sites for water which would lead to a slower moisture uptake, less weight change and less hygroscopicity of the system [113].

3.3.6 Effect of different Compression Force

The hot melt extruded solid dispersion can be shaped into many different final dosage forms, such as pellets, films, and suppositories. However, the tablet is still the most popular dosage forms on the market, which means that a few additional downstream processing steps might be needed for the extrudates. In the downstream processing, compression force utilized in the tableting step might have a significant effect on the moisture sorption ability of the tablet. In order to eliminate the effects from other excipients, only milled extrudates were used to compact tablets(200mg) by different compression force (5, 10, 15, 20, 25 kN) using 8mm round flat tooling set with manual compaction machine. The HPC-LF-FF ASD system was chosen as a model system and the water content of the samples were measured under 25°C/90% RH for 48 hours (n=3) (Figure 3-9).
Figure 3-9 Water content (weight changing) plot of tablets containing HPC LF–FF amorphous solid dispersions with different compression force under 25°C/90% RH for 48 h (mean ± standard deviation, n = 3).

The statistical analysis showed the significant differences between 5, 10, 15 and 20 kN force groups (p<0.05). However, the statistical analysis between the 20 and 25 kN groups did not indicate a significant difference (p=0.43). Higher compression force can decrease the moisture sorption of the ASD tablet, but this effect arrived at a plateau after 15 kN (samples with 20 and 25 kN compression force did not show any significant difference). Also, high compression force (20 and 25 kN) exhibited a sticking issue during the compression process and previous studies have shown that higher compression force might induce the immiscibility of drug and polymer by weakening and/or disruption of intermolecular hydrogen bonding [114].

The porosity of the compacts was measured to explain the effect of compression force. From low to high compression force groups, the compacts porosities were: 13.6±3.7%, 9.2±2.1%, 7.2±1.3%, 6.3±0.9% and 6.5±1.7% (n=3), respectively. The porosity was decreased as the compression force increased. As the porosity decreasing, the surface to absorb the moisture would also decrease which could slow the water uptake process. At same time, less surface area could lead to less hydrogen bonding sites which could lower the hygroscopicity of the samples with higher compression force.

3.4 Conclusion

In this study, HPC-FF, EC-FF and PEG-FF amorphous solid dispersion systems were successfully prepared by HME technology. This is the first time that the moisture sorption abilities of amorphous solid dispersions prepared by hot melt extrusion technology with different
polymeric carriers has been reported. Also, this study investigated the moisture sorption from both the formulation as well as processing approaches, which are very limited as reported in previous literature. The nature of the polymer, molecular weight of the polymer, HME process and downstream processing parameters were found to have a significant effect on the moisture sorption ability of the amorphous solid dispersion systems. As moisture plays an important role in the physical and chemical stability of the solid dispersion, it becomes imperative to understand the effect of both formulation and processing parameters that influence the moisture sorption properties of the solid dispersions. The data, and hence knowledge, attained within this study would be extremely valuable for future commercialization of drug products containing solid dispersions.

3.5 Acknowledgement

This project was partially supported by Grant Number P20GM104932 from the National Institute of General Medical Sciences (NIGMS), a component of NIH. The authors also thank Dr. Vijayasankar Raman, National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, for his valuable assistance with the SEM imaging studies.
CHAPTER 4
SCREENING OF AQUEOUS SUSPENSION STABILIZER FOR SPRAY DRIED AMORPHOUS SOLID DISPERSION

4.1 Introduction

Several technologies now are widely used to prepare amorphous solid dispersions, which include confined impinging jet method, hot melt extrusion and spray drying, etc. Among these methods, spray drying has its own advantages. Spray drying is capable of generating ASDs directly from solutions by fast drug/polymer solidification from rapid removal of organic solvent in the solutions by single step with a high efficiency. However, comparing with technology like hot melt extrusion, the yield rate for traditional spray drying is still very low. This will be an issue when the batch size is small and the amount of compound is limited. This makes it impractical for utilizing spray drying to formulate the water poorly soluble APIs during the drug discovery and early research stages.

The Buchi B-90 nano spray dryer equipped with nozzles with different sizes vibrating meshes (4-7 µm) to control the spray droplets, also the advanced electrostatic particle collector to collect the spray dried particles. This model of spray dryer is able to produce ADSs with very small amount of spray volumes and keeps the particle size consistent. Li et al., reported using this process to archive nanoparticles with high yield (70-90%) using 4 µm nozzle cap mesh.

However the ASD particles produced by spray drying always have a small particle size which might cause some issues for the downstream processing and dosing to animals during the
toxicology studies. For the animal studies, spray dried particles can be formulated into mini-
tablets, mini-capsules and suspensions. Even with the small size, mini-tablets and mini-capsules
are difficult to dose to animals like rats and beagle dogs. The suspension of spray dried particles
turned into the first choice of dosage forms for the animal study, but the physical stability of the
ASDs could play a vital role to affect the drug release and bioavailability.

In toxicology studies, spray dried particles are usually formulated as suspensions and
dosed to animals by oral gavage. When ASD containing pH-dependent polymers are used, the
suspension can be maintained by adjusting the pH of the aqueous medium to acidic conditions in
which the ASD is largely insoluble, so that minimum about of the drug could release before
dosing to the animals. At same time, the ASD with enteric polymers should not undergo
recrystallization before dosing and during present in the stomach. Also, though the spray dried
particles might have consistent particle size distribution, after formulated into suspensions,
aggregation and flocculation could hinder the dissolution and bioavailability of the ASDs.

Currently, formulations of ASD suspension is still mainly depends on empirical methods
like high throughput screening to screen for a viable suspension formulation for a given solid
dispersion system. Suspension formulations are further complicated by the presence of other
stabilizers adding into the liquid medium to achieve a stable and functional suspension.
Surfactants are often used to improve the wettability of the solid dispersion particles and
maintain the rheological properties of the properties of the suspension. Polymers can be used to
increase the viscosity of the liquid medium and keeping the particles suspended.

In this project, we systematically studied the impact of commonly used surfactants and
polymers on the stability of ASD suspensions using a Nikon polarized microscopy equipped with
an automatic stage. Also, different combinations of polymer carrier and model drugs were used
in the study to investigate the general rules choosing the appropriate stabilizer for the aqueous suspension of ASD which can prevent the particle aggregation, ASD recrystallization and drug releasing during storage.

![Figure 4-1. Schematic of suspension preparation and PLM characterization of the samples.](image)

### 4.2 Materials and methods

#### 4.2.1 Materials

HPMC-AS LF was purchased from Shin-Etsu (Shin-Etsu Chemical Co., Ltd Japan). Polyvinyl Acetate Phthalate (PVAP) was purchased from Colorcon (Harleysville, PA, USA). Indomethacin and Ketoconazole were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemical reagents used in the study were of ACS and high grade purity.

#### 4.2.2 Methods

##### 4.2.2.1 Spray drying
All powders in the study were prepared via spray drying using the B-90 (BÜCHI Labortechnik AG, Flawil, Switzerland). A 1% w/v solution of polymer carrier in acetone was prepared by dissolving polymer in acetone and stirring overnight. The model drug was dissolving into the polymer solution to make polymer:drug ratio to 2:1 (drug loading 33.3% w/w). All solutions were centrifuged at 3000 rpm for 15 min, and the supernatant was used for spray drying to minimize the nozzle blockage. For the spray-drying process, the flow rate was set as 2, a 7 µm mesh nozzle cap was used, and 100% of the feeding solution was sprayed. Air flow rate was 115L/min and inlet temperature were set as 75°C. The dried powder was collected from the particle collecting chamber using a scraper and dried in a vacuum chamber for 24 hours, then stored in refrigerator for further characterization.

4.2.2.2 Preparation of suspension

The 5 mg of spray dried particles were accurately weighted into a 10 ml glass vial and 4 ml aqueous solution was added into the vial. The aqueous solution with different stabilizer candidates with predetermined concentrations was prepared and stirring overnight. The vial was vortex 5 seconds and sonication for 10 seconds, then vortex 5 seconds again. All the suspensions were keep still and stored at room temperature for 4 hours, then repeated the suspension processing. The 40 µl re-suspended suspension was transferred into one well of the 96-well plate for further investigation. Maximum 96 samples can be tested at one time.

4.2.2.3 Polarized Light Microscopy

The Nikon Ti Eclipse PLM was utilized as a new platform to characterize the particle size, particle size distribution and physical status of solid dispersion in this study. The background was adjusted to blue for the particle size characterization, while red background was used for the recrystallization detection. The stage holding a 96-well plate was programmed to
move from one well to another, and in every single well area, 3 pictures would be taken at 3 random spots. In every picture, a binary system was created by the software using a binary threshold point so that the particles could be separated from the background. All the particle diameter, area would be noted and generated a particle size or area distribution.

4.2.2.4 Powder X-ray diffraction (PXRD)

Crystallinity of spray-dried powders was tested using a benchtop X-ray diffractometer (Rigaku Corp.) to obtain diffraction patterns. The diffractometer was able to generate Cu-ka radiation with current of 10 mA and voltage of 30 kV. A scan rate of 0.5/min with steps of 2θ from 5 to 40 was used for all the scans performed.

4.2.2.5 Modulated differential scanning calorimetry (mDSC)

The suspension was kept still for 4 hours and then transferred into a centrifuge tube filter (0.22 µm cellulose acetate film) to centrifuge for 15 min under 15k rpm. The separated particles was dried in the 40 °C vacuum oven for 12 hours for mDSC test. mDSC was conducted by weighing approximately 2-4 mg of spray dried powder, pre-dried powder, polymer, compound, or polymer/compound physical mixture in a standard DSC pan. The samples were heated at a rate of 2 C/min from 4 C to 200 C at a modulating oscillatory frequency of 0.83 C/80 s in a differential scanning calorimeter (TA Instruments, U.S.). The thermograms were recorded and glass transition temperatures (Tg) were analyzed using Universal Analysis software (TA Instruments).

4.3 Results and Discussion

4.3.1 Surfactant group
Figure 4-2. Polarized light microscopy images of re-suspended HPMCAS-INDO suspension with surfactant stabilizer with different concentrations for characterization of recrystallization.

In the surfactant group, taurocholic acid sodium (TAS), sodium dodecyl sulfate (SDS), Pluronic® F-127 and polysorbate 80 (TWEEN 80) were tested as suspension stabilizer for the suspension of spray dried particles of HPMCAS-INDO, at 0.1, 0.2 and 0.5% w/v concentrations respectively. From figure 4-1, all samples in surfactant 0.1 and 0.2% groups showed needle shape crystalline particles or birefringence particles.

However, for the samples with 0.5% of all these surfactant stabilizers, no needle shape crystalline particles or birefringence particles were observed. The in suspension with 0.5% SDS, all particles dissolved into the aqueous medium, and the suspension turned into clear solution. This is due to the increasing pH values caused by higher concentration of SDS increased the solubility of HPMCAS and also solubilized the drug.
4.3.2 Cellulosic group

In the polymer stabilizer groups, hydroxypropyl methylcellulose (HPMC E5), methylcellulose (MC), hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (Kollidon PVP-K30), vinylpyrrolidone-vinyl acetate copolymer (Kollidon VA64), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) were tested as suspension stabilizer for the suspension of spray dried particles of HPMCAS-INDO, at 0.1, 0.5 and 1% w/v concentrations respectively. All samples in the polymer stabilizer groups did not show any needle shape crystalline indicating that all candidates had strong recrystallization inhibition effect for the ASD suspension. However, from the DSC thermograms, the samples with HPC showed small melting peak which is an evidence of recrystallization. Comparing with other polymer candidates, HPC has less hydrophobic function groups which means level of molecular interaction with the hydrophobic drug could be lower. Though the drug did not release and recrystallization did not happen in the solution, the phase separation and recrystallization could still happen.

4.3.3 Particle size characterization

The stabilizer candidates could inhibit recrystallization in the suspension for 4 hours were chosen for further investigation of preventing aggregation of the particles. The % of particle with size (area) larger than 100 µm² was calculated and compared within all stabilizer and concentrations (ANOVA applied to test the significant difference followed by a two tailed student’s T test, p=0.05). From figure 4-5, TAS showed best ability to prevent the particles aggregation. The 0.1% MC inhibit the aggregation to less than 5%, but as the concentration increasing, more particles grouped up forming large agglomeration. The 1% MC solution has higher viscosity which could hinder the dispersion of the particles in the suspension.
4.3.4 Other ASDs systems

For the other model drug ketoconazole, there were no needle shape crystalline particles or birefringence particles observed under the polarized light microscopy, even when DSC data indicated the existing of recrystallization. This Nikon Ti PLM platform might not be suitable to characterize all the recrystallization in the ASD suspension, but still could be used to investigate the particles aggregation.

4.4 Conclusion

The Nikon Ti PLM equipped with automatic stage is a powerful tool to characterize the particle size of the ASD suspensions, and can also serve as a screening tool for the suspension stabilizers.

Taurocholic acid sodium(TAS), hydroxypropyl methylcellulose (HPMC E5), methylcellulose (MC), polyvinylpyrrolidone (Kollidon PVP-K30), vinylpyrrolidone-vinyl acetate copolymer (Kollidon VA64), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) can be used as recrystallization inhibitor for the ASD suspensions even at low concentration (0.1%). But at 1% concentration, MC accelerated the aggregation which might affect the dissolution and bioavailability of the suspensions. For the surfactant candidates, due to the increased pH values and increased solubility for drug, surfactant might not be proper stabilizer to be used in ASD suspensions.
Figure 4-3. DSC thermograms for HPMCAS-INDO dried particle from the suspension with different concentrations of SDS.

Figure 4-4. DSC thermograms for HPMCAS-INDO dried particle from the suspension with different concentrations of F-127.
Figure 4-5. DSC thermograms for HPMCAS-INDO dried particle from the suspension with different concentrations of TW80.

Figure 4-6. DSC thermograms for HPMCAS-INDO dried particle from the suspension with different concentrations of TAS.
Figure 4-7. DSC thermograms for HPMCAS-INDO dried particle from the suspension with 1% polymer stabilizers.

Figure 4-8. Polarized light microscopy images of re-suspended HPMCAS-INDO suspension with cellulosic polymer stabilizers with different concentrations for characterization of particle size.
Figure 4-9. Polarized light microscopy images of re-suspended HPMCAS-INDO suspension with vinyl polymer stabilizers and TAS with different concentrations for characterization of particle size.

Figure 4-10. PLM images of the HPMCAS-INDO spray dried particles in 0.1% HPMC suspension medium (left) and binary system (right).
Figure 4-11. Drug released after 24 hours storage of the suspension with different surfactant stabilizer, DI water and pH=3 HCl suspension medium.

Figure 4-12. pH values of suspension medium with surfactant stabilizers with different concentrations.
Figure 4-13. Drug released after 24 hours storage of the suspension with different polymer stabilizers.

Figure 4-14. pH values of suspension medium with polymer stabilizers with different concentrations.
Figure 4-15. Statistical analysis results for aggregation inhibition ability of stabilizer candidates.

Figure 4-16. Polarized light microscopy images of re-suspended HPMCAS-KETO suspension with different stabilizers with different concentrations.
Figure 4-17. Polarized light microscopy images of re-suspended EUDRAGIT-INDO suspension with different stabilizers.

Figure 4-18. Polarized light microscopy images of re-suspended PVAP-INDO suspension with different stabilizers.
CHAPTER 5

A DESIGN OF EXPERIMENT APPROACH FOR THE INFLUENCE OF PROCESSING PARAMETERS ON MELT-EXTRUDED SOLID DISPERSIONS

5.1 Introduction

Quality by Design (QbD) is a concept first outlined by quality expert Joseph M. Juran in publications, most notably Juran on Quality by Design. Designing for quality and innovation is one of the three universal processes of the Juran Trilogy, in which Juran describes what is required to achieve breakthroughs in new products, services, and processes. Juran believed that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned.

While Quality by Design principles have been used to advance product and process quality in industry, and particularly the automotive industry, they have also been adopted by the U.S. Food and Drug Administration (FDA) for the discovery, development, and manufacture of drugs.
Pharmaceutical QbD requires a thorough understanding of the product and the process, along with the knowledge of the relationship between the critical quality attributes (CQAs) and the clinical performance of the product. With the concept of QbD, a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight can be achieved.

The effect of individual process parameters on the final product’s CQAs is studied with the help of statistical design of experiments (DoE) through which an operational design space (DS) is established. As a result of this, a range of variability is defined for each variable under which the CQAs remain within the pre-established limits. Thus, a controlled DS is generated for the process. Although adapting QbD methodology could be cumbersome initially, it will eventually increase the robustness and quality of the product. It will also reduce overall waste produced during manufacturing, as well as allow efficient globalization for companies with manufacturing sites across the world.

In the QbD system, Design of Experiment (DoE) is most important part since the traditional changing of one factor at a time is not an efficient and economic strategy. The
traditional experimental plan does not give any information about the position of the optimum and can, at its best, lead only to a local optimum of the system and is based on large number of experiments and often relies merely on the experience of the analyst. The one-at-a-time optimization also ignores interactions between factors and calls for unnecessarily numerous runs. With rapidly rising costs of experiments, it is very important that the development and optimization of any experimental plan is done with as few experiments and with as low costs as possible.

The present study was a Design of Experiment approach, or partial QbD (quality by design) approach to understand the effect of processing parameters on immediate release melt-extruded solid dispersions. The DoE approach was applied to melt extrusion and processing with Soluplus® for solubility enhancement using fenofibrate as a poorly soluble API.

5.2 Material and methods

5.2.1 Materials

Soluplus, a hydrophilic graft copolymer of polyvinyl caprolactam–polyvinyl acetate–polyethylene was kindly donated by BASF Corporation (Florham Park, NJ). Fenofibrate was purchased from Letco Medical (Decatur, AL). Avicel PH-102 (microcrystalline cellulose, USP/NF) was donated by FMC Biopolymer (Philadelphia, PA). Magnesium stearate, USP/NF was purchased from Spectrum Chemicals Corporation (Gardena, CA). All other materials utilized in the study were of ACS grade or higher and purchased from Fisher Scientific (Pittsburg, PA). Dissolution enhancing additives utilized in this study were milled with a Fitzpatrick L1A Fitzmill (Fitzpatrick, Elmhurst, IL). Powder passing through a 0.149 mm sieve and retained on a 0.074 mm sieve were used in tablet formulation studies.

5.2.2 Methods
5.2.2.1 Design of Experiment

A Box-Behnken design at three factors (feeding rate, screw speed, temperature) with three levels was prepared by Design Expert® (version 8.06, Stat-Ease Inc.) for quantitative risk evaluation, optimization the processing parameters and identify the design space. The milling efficiency and percentage of drug released at 30 min were chosen as response values. The central point run was repeated 5 times, resulting in a totally 17 runs for one design. The same design method was also applied to milling processing and tablet compression for the optimization of the processing parameters and defines the design space.

5.2.2.2 Hot melt extrusion

Amorphous solid dispersions of fenofibrate and Soluplus was prepared utilizing HME technology. Thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC) were utilized to determine the extrusion processing temperature range, and the actual extrusion parameters were given by the DOE software. The API and polymer were mixed in a V-cone blender (MaxiBlendTM, GlobePharma) at 20 rpm for 5 min and then extruded with a co-rotating twin-screw extruder (Process 11, ThermoFisher Scientific) into uniform rod extrudates.

5.2.2.4 Statistical analysis

The results obtained are expressed as a mean ± standard deviation calculated using Microsoft Excel (Redmond, WA, USA) software. Statistical analysis was performed using SPSS version 15.0 for windows (SPSS, Inc, Chicago, IL, USA). One-way ANOVA followed by the Tukey multiple comparisons were used to compare the results. A p value of less than 0.05 was considered as statistically significant.

5.2.2.5 Thermal gravimetric analysis (TGA)
TGA studies were performed on Perkin Elmer Pyris 1 TGA with the Pyris™ software (PerkinElmer Life and analytical sciences, CT, USA). 3-5 mg of the sample was weighed and heated from 20 °C to 300 °C under an inert nitrogen atmosphere at a flow rate of 20 °C/min. Percent weight loss was plotted against temperature to determine the weight loss. The TGA sample of fenofibrate was holding at the highest extrusion temperature (145 °C) for 15 min to test the thermal stability.

### 5.2.2.6 Differential scanning calorimetry (DSC)

DSC (Perkin Elmer, Diamond DSC) was utilized to measure the melting enthalpy of the solid dispersions. Samples were weighed (3-5 mg) in an aluminum sample pan and hermetically sealed at each time point using a heating rate of 20°C/min from 30°C to 200°C under an inert nitrogen atmosphere at a flow rate was 20 mL/min. An empty pan was used as reference. Measurements were repeated three times. An Indium standard was used for calibration.

### 5.2.2.7 HPLC-UV Analysis

A Waters HPLC-UV system (Waters Corp, Milford, MA), equipped with a Luna 5um C_{18} 100Å column (Phenomenex, US), was used to detect fenofibrate at a wavelength of 286 nm. The mobile phase consisted of acetonitrile and phosphoric acid in water (pH=2.5) at a ratio of 85:15 (v/v). The flow rate was maintained at 1.0 mL/min. The injection volume was 20 μL. The observed retention time of fenofibrate was 6 min. The data was acquired and processed using Waters Empower 3 software suite.

### 5.2.2.8 Scanning electron microscopy (SEM)

SEM was used to study surface morphology of the solid dispersions. Samples were mounted on aluminum stubs held with a carbon adhesive film. Gold was used to coat the Samples by a Hummer® 6.2 sputtering system (Anatech LTD, VA, USA) in a high vacuum
evaporator. The surface topography of the sample was analyzed by a scanning electron microscope operating at an accelerating voltage from 1.0 kV to 5.0 kV (JEOL JSM-5600).

5.3 Results and Discussion

During the hot melt extrusion processing, achieving the amorphous solid dispersion is the primary target. To convert the crystalline drug into amorphous state, the extrusion temperature should be near or higher than the melt temperature of the drug. If using temperature lower than the melting point of the drug, the screw configuration and screw speed need to be optimized to generate enough shear for the high energy input for the drug. At same time, low extrusion temperature might cause failure of the processing due to high torque. If the extrusion temperature is close to or lower than the glass transition temperature of the binary formulation, the high viscosity could lead to high torque. However, if both high temperature and high shear are applied to the formulation, degradation could happen which would increase the impurities in the extrudate. Even the formulation is thermostable, too high extrusion could also result in liquidize extrudate or sticky formulations which is difficult to handle for the downstream processing.

5.3.1 The Design of Experiment method

In this study, a Box-Behnken design was utilized to qualitatively and quantitatively evaluate the effect of different critical quality attributes on the product quality attributes. The Box-Behnken design is an independent quadratic design, not like other design methods, for example: fractional factorial design or central composite design, in that it does not contain any embedded factorial or fractional factorial design. The treatment combinations are at the midpoints of edges of the process space and at the center when using the Box-Behnken design. These designs are rotatable (or near rotatable) and require 3 levels of each factor. The designs have limited capability for orthogonal blocking compared to the central composite designs.
Table 5-1. Intermediate Product Quality Profile.

<table>
<thead>
<tr>
<th>Product Attribute</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content uniformity (CU)</td>
<td>Conforms to USP&lt;905&gt; Uniformity of Dosage Units</td>
</tr>
<tr>
<td>Percentage of crystalline API</td>
<td>0% (100% amorphous)</td>
</tr>
<tr>
<td>Degradation product</td>
<td>Total impurities: NMT 1.0%</td>
</tr>
</tbody>
</table>

Figure 5-2. Experimental layout by Box-Behnken Design.
Table 5-2. Target Product Quality Profile.

<table>
<thead>
<tr>
<th>Product Attribute</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content uniformity (CU)</td>
<td>Conforms to USP&lt;905&gt; Uniformity of Dosage Units</td>
</tr>
<tr>
<td>Dissolution behavior</td>
<td>NLT 80% of label amount released at 30 min</td>
</tr>
<tr>
<td>Degradation product</td>
<td>Total impurities: NMT 1.0%</td>
</tr>
</tbody>
</table>

The milled solid dispersion particles serving as an intermediate product for the target product should meet the target profile, like total impurities no more than 1%, immediate drug release, content uniformity (Table 5-1). In the R1: disso ANOVA table, values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, C, BC are significant model terms which means feed rate, temperature, screw speed and interaction between temperature and screw speed are significant. However, the p value for screw speed was very close to 0.05 which means the impact of this factor is statistically significant but not huge. The 3D response surface also indicated that temperature was more significant.

Table 5-3. ANOVA for response surface quadratic model for response value 1.
5.3.2 The effect of HME processing parameters on the dissolution rate

The temperature showed more significant effect on the 30 min’s dissolution when the feed rate is high comparing with the low feed rate runs. And the feed rate exhibited more significant effect on the 30 min’s dissolution when temperature is low. This is because that when feed rate is low, even low temperature can provide enough energy input to completely melt the API and polymer carrier, so that the drug is easier to be dispersed homogenously into the whole polymeric matrix. The evenly dispersed system can avoid the existing of drug rich zones in the solid dispersion which could avoid the amorphous drug recrystallization during the dissolution.

Table 5-4. ANOVA for response surface quadratic model for response value 2.
Figure 5-3. The 3D response surface of feed rate and temperature for response value R1.

Figure 5-4. The 3D response surface of feed rate and screw speed for response value R1.
Figure 5-5. The 3D response surface of temperature and screw speed for response value R1.

Figure 5-6. The 2D design space of temperature and feed rate with screw speed at 100 rpm for response value R1.
5.3.3 The effect of HME processing parameters on the milling efficiency

In this study, the melt-extruded solid dispersion was an intermediate product and the assuming final dosage form was tablet. So the extrudate should be milled and sieved, then blend with other excipients for tablet compression. To maximum the productivity, milling efficiency (ME=weight of sample passed milling sieve/input weight×100%) became a factor with great importance. In the R2: ME ANOVA table, feed rate and temperature showed significant effect on the response value. Low feeding rate and high temperature could result in high ME.

The temperature showed more significant effect on the milling efficiency when the feed rate is high comparing with the low feed rate runs. And the feed rate exhibited more significant effect on the milling efficiency. But overall speaking, the low feed rate could increase the milling efficiency of the melt extrudate. When materials extruded through the small size rod die, pressure was built up mainly depend on how much material fed and pushed forward along the screws. The higher the feed rate is, the higher pressure would be build up inside the concave of the die. This could result in the melt extruded solid dispersion with higher density, or higher physical strength.

Figure 5-7. The 3D response surface of feed rate and temperature for response value R2.
Figure 5-8. The 3D response surface of feed rate and screw speed for response value R2.

Figure 5-9. The 3D response surface of temperature and screw speed for response value R2.
Figure 5-10. The 2D design space of temperature and feed rate with screw speed at 100 rpm for response value R2.
CHAPTER 6
SUMMARY AND CONCLUSIONS

6.1 Summary

Over the last few decades, hot-melt extrusion (HME) has been well adapted into the pharmaceutical industry to enhance the solubility and bioavailability of poorly water soluble compounds by producing amorphous solid dispersions. It is critical to evaluate and enhance the physical stability of the amorphous solid dispersion during commercializing the drug product with hot melt extrusion technology. Additionally, processing parameters also play an important role in the formulation development utilizing HME.

In Chapter 2, The improved Avrami equation demonstrated more accurate evaluation for all of the solid dispersion systems investigated in this study. This is particularly evident for the late stages of the recrystallization process, which provides a novel approach for early stage formulation development of amorphous solid dispersion systems. This can be viewed as both time and cost effective when compared to the conventional ICH stability tests. By resolving the relationships between the recrystallization rate constant, temperature, relative humidity and formulation, an accurate and reliable prediction can be obtained in reference to recrystallization kinetics. The polymers (Klucel™ EF/LF/ELF) inhibited the recrystallization process of the amorphous API and HPC grades with a higher molecular weight exhibited more favorable results. The method utilized in this study would also be useful for screening the most suitable polymeric carrier and other excipients in solid dispersion systems.
In Chapter 3, HPC-FF, EC-FF and PEG-FF amorphous solid dispersion systems were successfully prepared by HME technology. This is the first time that the moisture sorption abilities of amorphous solid dispersions prepared by hot melt extrusion technology with different polymeric carriers has been reported. Also, this study investigated the moisture sorption from both the formulation as well as processing approaches, which are very limited as reported in previous literature. The nature of the polymer, molecular weight of the polymer, HME process and downstream processing parameters were found to have a significant effect on the moisture sorption ability of the amorphous solid dispersion systems.

In Chapter 4, The Nikon Ti PLM equipped with automatic stage is a powerful tool to characterize the particle size of the ASD suspensions, and can also serve as a screening tool for the suspension stabilizers. Taurocholic acid sodium(TAS), hydroxypropyl methylcellulose (HPMC E5), methylcellulose (MC), polyvinylpyrrolidone (Kollidon PVP-K30), vinylpyrrolidone-vinyl acetate copolymer (Kollidon VA64), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) can be used as recrystallization inhibitor for the ASD suspensions even at low concentration (0.1%). But at 1% concentration, MC accelerated the aggregation which might affect the dissolution and bioavailability of the suspensions. For the surfactant candidates, due to the increased pH values and increased solubility for drug, surfactant might not be proper stabilizer to be used in ASD suspensions.

In Chapter 5, a Design of Experiment approach, or partial QbD (quality by design) approach to understand the effect of processing parameters on immediate release melt-extruded solid dispersions. The DoE approach was applied to melt extrusion and processing with Soluplus® for solubility enhancement using fenofibrate as a poorly soluble API. The feed rate
and temperature were found to have more significant effect on the milling efficiency and dissolution at 30 min.

6.2 Future Prospective

- Investigate the possibility of including a correction factor of RH into the improved Avrami equation, so that the equation can be used to determine the recrystallization rate constant for a certain condition (both RH and temperature).

- Employ Quality by Design and Risk Assessment to have a systematical understanding of the quality of the hot melt extruded solid dispersion product.

- Use the polarized microscopy system to do the high throughput solid dispersion formulation screening.
BIBLIOGRAPHY


VITA

Xin Feng, son of Mr. Jiancan Feng and Mrs. Yujie Zhang, was born on April 5th, 1987 in Zhengzhou, Henan, China. He received his high school diploma from Zhengzhou No. 1 High School (Zhengzhou, Henan, China). In 2010, he received his Bachelor’s degree in Pharmaceutical Science from Sun Yat-sen University (Guangzhou, Guangdong, China).

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