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Solubility Enhancement via Melt Extrusion: Drug-polymer Solubility, Physicochemical Characterization and Quality by Design

Ketaki Patwardhan
University of Mississippi, ketakipatwardhan@gmail.com

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SOLUBILITY ENHANCEMENT VIA MELT EXTRUSION

DRUG-POLYMER SOLUBILITY, PHYSICOCHEMICAL
CHARACTERIZATION AND QUALITY BY DESIGN

A Dissertation Submitted
In The Partial Fulfillment of Requirements For
The Doctoral of Philosophy Degree
in Pharmaceutical Sciences
with an emphasis in Pharmaceutics

by
KETAKI PATWARDHAN

February, 2014
ABSTRACT

Many new drugs developed face oral delivery challenges and absorption due to poor biopharmaceutical properties. Formation of solid dispersions is a very widely applied technique for solubility enhancement of water insoluble drugs. In order to form stable solid dispersions it is important to select appropriate excipients that will maintain the drug in its amorphous form for an extended period of time. Selection of appropriate excipients is critical during the development of stable amorphous solid dispersions. The solubility parameter concept has been explored for theoretically identifying the excipients that will be suitable based on the structure of the active. In this work, the use of solubility parameter has been explored for strategic selection of excipients for a model drug ibuprofen. The predicted miscibility limits are verified with experimentally determined solubility limits. Dissolution experiments have been conducted to demonstrate the advantage of amorphous solid dispersions.

This has been further extended by in depth thermal and chemical characterization of the ibuprofen and Eudragit® E PO system. A phase diagram is predicted based on the understanding of the relationship between temperature, ratio of ibuprofen and the Gibbs free energy. Room temperature miscibility of the two components is demonstrated using microscopic studies. The potential of ionic interactions is investigated using
spectroscopic techniques. Melt extruded formulations are evaluated for the physical state of ibuprofen and stability of the amorphous form.

A complete Quality by Design study was performed for preparation of ibuprofen-Eudragit® E PO extrudates. Risk assessment was performed using the fishbone diagram and Failure Mode Effect Analysis and the factors influencing this melt extrusion process were shortlisted and prioritized. The most critical factors were then assessed in a 30 run experimental design. Torque, Glass Transition temperature, Assay and Dissolution at 30 min were measured as responses and the results were statistically analyzed to predict a design space. Finally, mechanistic evaluation of Ketoconazole and Kollidon® VA 64 solid dispersions was performed using thermal techniques, dissolution, swelling and erosion studied.
DEDICATION

To my family.
ACKNOWLEDGMENTS

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CHAPTER 1

INTRODUCTION
Increasing number of New Drug Entities (NDEs) filed have limited or no water solubility thus requiring specialized formulation techniques to increase the apparent solubility of the drug. It has been reported by several sources that about 40-50% NCEs fail due to their low water solubility or poor ‘drug like’ properties (1-6). Amidon et al proposed the Biopharmaceutical Classification System (BCS) which classifies drugs in four classes based on their aqueous solubility and permeability (7) (Table 1.1). Bergström et al have shown that drugs belonging to Class II can be completely absorbed upon oral administration (8). By using specific solubility enhancing formulation development techniques it is possible to increase the solubility and thus oral absorption of drugs belonging to BCS Class II.

**Table 1.1: Biopharmaceutical Classification System with examples**

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
<td>Caffeine, Metoprolol, Quinidine</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>High</td>
<td>Ibuprofen, Ketoconazole, Carbamazepine</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
<td>Atenolol, Metformin, Tetracycline</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
<td>Ritonavir, Acetazolamide, Oxcarbazepine</td>
</tr>
</tbody>
</table>

**Solid Dispersion Formulation**

Several approaches are available for improving the in vivo performance of poorly water soluble drugs such as amorphous solid dispersions (9), micronization (10), complexation (11), salt formation (12), and prodrugs (13). Preparation of amorphous solid
dispersions is gaining high interest as it can be easily adapted to almost any drug molecule and has a wide range of techniques available for manufacturing. The most common techniques for preparation of solid dispersions are hot melt extrusion (14), spray drying (15), co-grinding (16), co-precipitates (17) and freeze drying (18). Regardless of the method of manufacturing solid dispersions increase the apparent solubility of a drug by stabilizing its most high energy amorphous state. The polymer chains cause physical barrier and prevent (or delay) the crystallization and agglomeration of the drug molecules. A recent review of solid dispersions with 40 Active Pharmaceutical Ingredients (API) shows that 82% of the compounds exhibited increased bioavailability than the reference compound (19).

Solid dispersions are mixtures of two or more ingredients that have the drug dispersed as amorphous, crystalline or solubilized in a matrix of an inert material (20). Solid dispersions can broadly be classified as below

1. Eutectic mixtures: The two components are completely miscible in the liquid state but partially miscible in the solid state;

2. Solid solution: The two components are completely dissolved and form a single phase. The solid solutions are further classified as continuous and discontinuous depending on the range of miscibility of the drug and the carrier materials;

3. Solid dispersions: Either amorphous or crystalline drug particles are dispersed throughout the carrier matrix;

Although a lot of interest has been generated on the subject of solid dispersions there are not many marketed formulations. This can be attributed to some of the known
challenges for formulation development using the solid dispersion approach such as selection of manufacturing technique, reproducibility and scale-up of the manufacturing process, maintaining the amorphous state during shelf life of the formulation and in vitro/in vivo correlation. The carrier material is generally selected based on the chemical structure of the drug and the manufacturing process used for solid dispersion preparation. The carriers commonly selected for melt extrusion formulation development are discussed in further sections.

**Mechanisms of drug release**

The most important advantage of solid dispersion formulation is apparent solubility enhancement of water insoluble drug molecule. Reduction in particle size or changes to the physical properties of the drug molecule are regarded as the main reasons for increased solubility. Corrigan et al. showed correlation between dissolution rate of the drug and dissolution rate of the carrier by separately measuring both (21). In the carrier controlled drug release the dissolution rate of the drug is controlled by the dissolution of the carrier material. The rate of dissolution can be described with the Noyes-Whitney equation.

\[
\frac{dW}{dt} = \frac{DA(C_s-C)}{L}
\]  \hspace{1cm} (1.1)

Where,

\[
\frac{dW}{dt}
\]  is the rate of dissolution, D is the diffusion coefficient, A is the surface area of the solid, \( C_s \) is concentration of solid in the diffusion layer, L is the thickness of diffusion layer.
The dissolution rate of the individual component (drug or carrier) will affect the composition of the diffusion layer which in turn dominates the drug release mechanism. Craig et al. summarize the three scenarios of where the drug dominates dissolving surface, carrier dominates dissolving surface and where both components dissolve in the same proportion(22). The knowledge of the dissolution mechanism will assist in prediction of the performance of a certain formulation. This could govern the selection of carrier materials at early stages of formulation development.

**Solid State Solubility**

During solid dispersion formulation development, often the drug is regarded as a solute and the polymer is considered as a solvent. The knowledge of solid state solubility/miscibility of drug and polymer is imperative for successfully preparing a stable formulation. Several theoretical as well as practical methods have been outlined for prediction of drug-polymer solid state solubility. The theoretical approach for solubility/miscibility determination is based on the solubility parameter approach. Solubility parameter ($\delta$) is defined as the square root of cohesive energy density. References to this concept as early as 1916 are available however the symbol $\delta$ and the current definition was proposed in 1949 by Hildebrand. This concept was refined further by Fedors in 1974(23) exploring the additive properties of solubility parameter showcasing the group contribution theory.

Although this solubility parameter is inclusive of energy contributions from the polar, dispersive and hydrogen bonding effects, this approach was further extended into a 3 dimensional solubility parameters to separately account for energy contributions from
polar, dispersive and hydrogen bonding by Hansen(24). Further refinement of the concept of 3-D solubility parameters was made by Hoy(25) and Hoftyzer-Van Krevelen(26). It is generally considered that materials with close solubility parameter values are likely to have high miscibility. The solubility parameter when used in conjunction with the Flory-Chi parameter gives the ability to determine quantitative values for solid state solubility limits of drug in polymer. Several researchers have demonstrated the use of Flory-Chi parameters for estimation of solid state drug-polymer solubility (27, 28).

The knowledge of the solid state solubility is beneficial for selecting drug loadings to yield stable solid dispersions and to stay below the saturation solubility. This approach reduces the time and resources required for development of formulation as it allows strategic shortlisting of the carrier polymers based on the molecular structure of the drug. Polymeric carriers that have a close structural similarity are likely to form thermodynamically stable molecular dispersions with enhanced apparent solubility of the drug molecule.

**Hot Melt Extrusion (HME)**

Hot Melt Extrusion (HME) has been explored as a tool to manufacture solid dispersions and solid solution for over two decades (14). HME has numerous applications within the pharmaceutical industry ranging from oral drug delivery applications such as solubility enhancement(29), controlled release(30), taste masking(31) and enteric protection(32) to manufacturing of implants for controlled parenteral drug delivery(33). There are mainly two basic types of extruders: single screw extruders and twin screw extruders.
Twin Screw Extruders (TSE) are most commonly used in the pharmaceutical industry and are available in a variety of manufacturing capacities (34). Most of the expertise associated with operation of TSE has been adopted from the plastics industry which has been continuously evolving for over 70 years (14, 35). Since its introduction in the pharmaceutical industry, the TSE have been modified to adapt to the pharmaceutical operation by using pharmaceutically compatible construction material like stainless steel, modified fittings and cleaning components, use of approved lubricants and gear oil as well as additional documentation for GMP qualification.

HME is a thermal process where the drug along with other excipients is intimately mixed in the molten state. This technique has several advantages compared to traditional pharmaceutical compounding techniques. HME is a series of unit operations where feeding, mixing, melting, conveying and cooling takes place in a streamlined continuous operation (36). HME also offers the ability to tailor the final product based on the dosage form and intended application. One of the main advantages of HME is that the need of solvents is completely eliminated. The molten polymer acts as a binder, solubilizer and a vehicle during the manufacturing process. The intense heat and shear during the extrusion process melts and solubilizes the crystalline drug which on cooling gets entrapped in its most high energy amorphous state. Due to the nature of this process it is not suitable for heat sensitive drugs however the formulation can be adjusted to bring down the extrusion temperature.
Figure 1.1: Schematic representation of unit operations involved in a melt extrusion process

Components of HME

An average extruder is composed of a feeder/hoper, single or twin screws, barrel to hold the screws, heating elements, a die and a choice of downstream processing equipment (Figure 1.1). Additionally an extruder may have heat and pressure sensors, liquid/gas injection, additional feeding zones and Process Analytical Technology (PAT) tools for in line monitoring of the process. PAT tools like Near Infrared (NIR) (37) and Raman spectroscopy (38) have been used in conjunction with a TSE for in line quantification of the drug levels as well as monitoring drug-polymer interactions taking place inside the extruder.

Extrusion process can be categorized as either a ram extrusion or screw extrusion. A ram type extruder operates with positive displacement ram that generates high pressure to push the molten material through a die whereas screw extruder has rotating screws positioned inside a stationary barrel. The barrel itself has separate heating zones
designed to control the temperature of individual sections of the barrel. The barrel temperature can impact the physical characteristics of the formulation and is selected based on the thermal and chemical characterization of the ingredients (39).

Most extruder screws have configurable screw elements having either mixing or conveying functions. Depending on the make and the model of the extruder, the conveying elements may have different flight lengths. The mixing elements are designed to generate intense shear and have maximum contribution to the overall torque levels experienced by the machine. Therefore, it is important to ensure that the temperature in the mixing region is sufficient to maintain appropriate viscosity of the extruding material. The direction of the screws can be either co-rotating or counter-rotating. Co-rotating extruders may have an intermeshing, self-wiping design and are most commonly encountered in pharmaceutical industry as they can be run at high speeds while maintaining the product quality. The counter-rotating TSE generate a high amount of shear and works best in cases where intense mixing is desired (35). In process torque generation is dependent on the screw configuration, screw rotational direction and speed, melt viscosity of the material and extrusion temperature.

The geometry of an extruder is defined in terms of its length to diameter ratio and typical extruder L/D ratios are in the range of 20 to 40:1. The length of the extruder along with the screw speed directly affects the residence time. Average residence time in the extruders can vary between 5 sec to 10 min depending on the operating conditions. Scale-up of extrusion process to an extruder with similar geometry is relatively easy (40). Theoretical values of the barrel temperature, screw speed and feed rate can be
calculated based on equations based on specific mechanical energy calculations\(^{(41)}\). Scale-up of pharmaceutical melt extrusion process and its influence on the formulation characteristics have been investigated by Guns et al\(^{(41)}\).

Several choices of downstream processing equipment are available to use with the melt extrusion process. The molten material can either be pushed through a die to yield films, rods or pellets or it can be injection molded into any desired shape. Specially designed melt extrudates have been prepared for transmucosal, buccal, vaginal and transdermal drug delivery. Often, melt extrudates are milled to fine powder mixed with other excipients and either filled into capsules or compressed into tablets for conventional pharmaceutical solid dosage.

**Formulation Development for HME**

**Selection of carrier material**

Along with appropriate processing conditions, selection of excipients is very important to success of a HME formulation and efficiency during manufacturing. Several pharmaceutically compatible carriers are available to use with the melt extrusion process. The main characteristics of a carrier material are: it should be inert, melt at a low temperature, stable over the shelf life of the product, cheap and easily available. Polymers from a wide range of chemical classes are available to select from. The selection of polymers for HME formulation may be based on the chemical structure of the drug as well as intended final application of the product. Low molecular amorphous polymers such as Polyvinyl pyrrolidones (PVP) or polymethacrylates may be selected
for immediate release formulations whereas high molecular weight cellulosic polymers may offer good sustained release. Use of wax as a matrix former for controlled release of diclofenac is reported by Miyagawa et al(42).

Polymethacrylate polymers are synthetically derived polymers based on dimethylamioethyl methacrylate, methacrylic acid and methacrylic acid esters. These polymers have glass transition temperatures ranging from 40 to 140°C depending the grade. Eudragit® E PO (Figure 1.2) is a cationic pcopolymer based on dimethylaminoethyl methacrylate chemistry and is soluble up to a pH 5.0. Eudragit® RS and RL (Figure 1.3) are pH independent polymers based on ethyl acrylate, methyl methacrylate methacrylic acid ester chemistry. Eudragit® L 100-55 (Figure 1.4) is an anionic polymer based on methacrylic acid and ethyl acrylate chemistry with dissolution above pH 5.5. Several applications of polymethacrylate polymers in HME are recorded for immediate release(31), controlled release(30), enteric protection(43) as well as taste masking(44).

Figure 1.2: Molecular Structure of Eudragit® E PO
Figure 1.3: Structure of Eudragit® RL PO- x:y:z → 1:2:0.2 and Eudragit® RS PO- x:y:z → 1:2:0.1

Figure 1.4: Molecular Structure of Eudragit® L 100-55

Polyethylene oxide (PEO) (Figure 1.5) polymers are semi-crystalline polymers synthesized by heterogeneous catalytic polymerization of ethylene oxide monomers. Depending on the molecular weight the melting temperature may range between 55 to 75°C. Their applications as HME carrier materials have been investigated but additional antioxidants and crystallization inhibitors are needed for stabilization of the formulation(45).
Cellulose based polymers are derived from naturally occurring cellulose in the plant cells. Several types of cellulose based polymers have been investigated for HME formulation development including Hydroxypropyl Cellulose (HPC), Hydroxypropyl Methyl Cellulose (HPMC) (Figure 1.6), Ethyl Cellulose (EC) and Hydroxypropyl Methyl Cellulose Acetate Succinate (HPMCAS). These polymers have been explored as HME carriers for immediate release (46), controlled release (47) and muco-adhesive film (48) formulations.

PVP based polymers are synthetic polymers derived from vinyl pyrolidone and have been utilized as carriers for melt extrusion technology. They have been investigated as carriers for immediate release formulations (17, 49). Kollidon® VA 64 (Figure 1.7) and Soluplus® are some of the commonly used pharmaceutical polymers belonging to this class. Being a relatively new product, applications of Soluplus® for solubility enhancement are still being evaluated and currently it is not a part of any approved product.
Figure 1.7: Molecular structure of Kollidon® VA 64
Table 1.2: Commonly used carriers for HME formulations

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Trade Name</th>
<th>$T_g$ ($^\circ$C)</th>
<th>$T_m$ ($^\circ$C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonio methacrylate copolymer</td>
<td>Eudragit® RS/RL</td>
<td>63 - 68</td>
<td>--</td>
</tr>
<tr>
<td>Poly(dimethylaminoethylmethacrylate-co-methacrylic esters)</td>
<td>Eudragit® E</td>
<td>45 - 48</td>
<td>--</td>
</tr>
<tr>
<td>Poly(methacrylic acid-co-methyl methacrylate) 1:2</td>
<td>Eudragit® S/L</td>
<td>160</td>
<td>--</td>
</tr>
<tr>
<td>Cellulose Acetate Phthalate</td>
<td>--</td>
<td>165</td>
<td>192</td>
</tr>
<tr>
<td>Poly(vinyl pyrrolidone)</td>
<td>Kollidon®</td>
<td>90 - 156</td>
<td>--</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Phthalate</td>
<td>--</td>
<td>137</td>
<td>150</td>
</tr>
<tr>
<td>Polyvinyl pyrrolidone-co-vinyl acetate</td>
<td>Kollidon® VA64</td>
<td>101</td>
<td>--</td>
</tr>
<tr>
<td>Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer</td>
<td>Soluplus®</td>
<td>70</td>
<td>--</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose (HPMC)</td>
<td>Methocel®, Benecel®</td>
<td>160 - 210</td>
<td>--</td>
</tr>
<tr>
<td>HPMC Acetate Succinate</td>
<td>Aqoat-AS®</td>
<td>~ 120</td>
<td>--</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>Ethocel® Aqualon® EC</td>
<td>130 - 133</td>
<td>--</td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose</td>
<td>Klucel®</td>
<td>~130</td>
<td>--</td>
</tr>
<tr>
<td>Polyethylene Glycol</td>
<td>Carbowax®</td>
<td>-17</td>
<td>37 - 63</td>
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<tr>
<td>Polyethylene Oxide</td>
<td>PolyyOx® WSR</td>
<td>-57 - 50</td>
<td>62 - 67</td>
</tr>
<tr>
<td>Carnuba Wax</td>
<td>---</td>
<td>81 - 86</td>
<td>--</td>
</tr>
</tbody>
</table>
**Processing Aids**

As with any pharmaceutical process there may be a need for additional processing aids to increase the efficiency of the HME process. Plasticizers are generally required for high molecular weight, high melt viscosity polymers to bring the processing temperature down. Plasticizers are low molecular weight compounds with low $T_g$ that reduce the overall softening temperature of melt. Depending on the hydrophilic or hydrophobic nature of the plasticizer it may have a positive or negative effect on the drug release rate. Plasticizers also assist in reducing the brittleness of the HME films thereby increasing the strength.

In order for a material to work successfully as a plasticizer, it should be compatible with the drug and the carrier material used and be stable over the shelf life of the product. Citrate esters, fatty acid esters, sebacate esters, phthalate esters, glycol derivatives, mineral oil, castor oil and Vitamin E TPGS derivatives have been explored as plasticizers for HME process. In some instances where the $T_g$ of the drug molecule is low, it can act as a plasticizer. Wu et al. reported the use of ibuprofen as a solid state plasticizer for extrudates prepared with Eudragit® RS PO(50). Formulation stability testing is recommended when working with plasticizers as due to the low molecular weight of the plasticizers there is a likelihood of the molecules leaching out over time thereby compromising the performance of the formulation. Additional processing aids such as anti-oxidants, preservatives, crystallization inhibitors, complexing agents, lubricants, anti-tacking agents may be necessary to cater specific needs of the drug molecule(36).
Analysis of Melt Extrudates

Based on the thermo-mechanical properties of polymers, they are commonly classified as thermoplastics, elastomers and thermosets. Owing to their linear nature, thermoplastics deform and flow when heat is supplied and will retain any shape as they cool. Most polymers selected for pharmaceutical melt extrusion belong to this category. Thermosets and elastomers due to their cross-linked nature retain the shape that they were manufactured for the first time forming a cross linked network. Due to these properties, thermosets and elastomers have limited pharmaceutical melt extrusion applications (26).

Thermoplastic polymers can either be crystalline, amorphous or partially crystalline in nature. The crystallinity is associated with a long range three-dimensional order arising from the arrangement of the macromolecular chains. Amorphous polymers are hard and brittle at temperatures below their glass transition temperatures (T_g) whereas soft and pliable at higher temperatures. The glass transition temperature can be determined by either thermal or thermo-mechanical methods. Partially crystalline polymers like Polyethylene oxide may exhibit both a melting point (T_m) as well as a T_g. Below the glass transition temperature, the movements of the chain segments vibrate around fixed positions. When the temperature increases, the amplitude of the vibrations increases and the rise in tension is translated to the intermolecular interactions. On further increase in the temperature, a fraction of the chain segments acquire enough energy to overcome these interactions. The glass transition temperature is the critical temperature
at which the molecular mobility can be detected. The glass transition temperature also affects the shelf stability of the melt extruded formulation.

Melt extrusion experiments are performed at a temperature above the glass transition temperature of the polymeric carrier to ensure that the dry physical mixtures are sufficiently molten to allow for intimate mixing. Addition of drug, plasticizer and other processing aids may alter the range of the glass transition temperature. The final $T_g$ of a formulation may be a result of additive effects from all the components and their proportions in the final mixture. The well-known fox equation has been demonstrated for prediction of $T_g$ of a mixture based on the $T_g$ of the individual components and their molar ratio in the mixture(51).

$$\frac{1}{T_g} = \frac{w_1}{T_{g,1}} + \frac{w_2}{T_{g,2}}$$ (1.2)

Where, $w_1$ and $w_2$ are weight fractions of components 1 and 2 respectively.

During development of a solid dispersion formulation it is necessary to characterize the physical state of the drug, *in vitro* and *in vivo* performance as well as shelf stability of the prepared formulation. Several analytical techniques have been utilized for characterization of solid dispersion formulations as discussed below.

1. **Differential Scanning Calorimetry (DSC)**

DSC is a thermo-analytical technique which quantifies the amount of heat required to increase the temperature of a sample in comparison to a reference. The sample and
reference both are contained in identical aluminum pans that have the capacity for hermetic sealing. The samples are heated at a constant heating rate and the heat required to maintain constant temperature is recorded. Both high and low heating rates have been utilized for characterization of solid dispersions. The lower heating rates yield accurate melting point temperature measurement whereas the higher heating rates have been demonstrated as a tool to measure the solid state drug-polymer solubility(52, 53). DSC is the most commonly used tool to determine the glass transition temperature of pure polymers as well as polymer mixtures(54). Although widely used for characterization of the physical state of the drug, DSC has several limitations. Conventional DSC falls short when analyzing materials with overlapping melting or transition events. Moreover, DSC cannot detect trace amount of crystalline phase therefore is often used in conjunction with XRPD analysis.

2. X-Ray Powder Diffraction (XRPD)

XRPD is a tool used for detection of crystalline phase in a sample utilizing the relationship between density of the material and absorption of X-rays. During XRPD measurement, the sample is subject to a beam of x-ray. The crystals in the samples diffract the x-ray in a characteristic pattern whereas an amorphous sample does not exhibit a diffraction pattern. XRPD is often utilized in conjunction with DSC to detect trace amount of crystalline phase. XRPD is an important tool during solid dispersion formulation development due to the accuracy of detecting phase change. A main disadvantage of using XRPD for melt extruded formulations is that the physical form of
the formulation is disturbed when milling in to a powder potentially changing the delicate thermodynamic balance.

3. Thermogravimetric analysis (TGA)

Due to the inherent nature of the melt extrusion process, thermal characterization is an important preformulation consideration. TGA analysis measures loss in weight of a preweighed sample as the temperature of the sample chamber is elevated at a constant rate(55). An additional application of TGA is to analyze the volatiles released from a sample upon heating.

4. Fourier Transform Infrared Spectroscopy (FTIR)

All chemicals exhibit characteristic IR spectra which have been used for identification, quantification and analysis of pure materials and mixtures. The FTIR spectra is generated from the chemical structure of a compound through the characteristic absorption bands associated with vibration of atoms in the infrared region. FTIR is often used to detect intermolecular interactions during melt extrusion processing. The shift in the absorption wavelength or appearance/ disappearance of characteristic peaks can allow investigators to identify potential molecular interactions(56).

Quality by Design

Quality by Design (QbD) is an initiative by the Food and Drug Administration (FDA) to harmonize the process for new and generic drug applications. QbD is defined as “A systematic approach to development that begins with predefined objectives and
emphasizes product and process understanding and process control, based on sound science and quality risk management”(57). 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. 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 initially may be thought to be cumbersome, it eventually means less paperwork and resources when a change needs to be introduced in the manufacturing process. It will also reduce overall waste produced during manufacturing as well as allow efficient globalization for companies with manufacturing sites across the world(58),(59).

QbD has been developed with an approach to improve the efficiency of the entire drug manufacturing and filing process. A typical QbD study has the following steps: 1. Establishment of Quality Target Product Profile, 2. Risk Assessment, 3. Screening and Optimization studies, 4. Generation of Design Space and 5. Control Strategy(57). A schematic for process development using implementation of QbD principles is presented in Figure 1.8. Application of QbD concept has been published for several pharmaceutical techniques such as fluid bed granulation(60, 61), spray drying(62, 63),
tablet compression (64, 65), liposomes(66, 67), sterile products(68) and gel manufacturing(69).

**Figure 1.8:** A schematic representation of process development using the QbD approach

**Establishment of Quality Target Product Profile (QTPP)**

The QTPP outlines the specifications of the final product that are essential to be built into the product during the developmental stage. This describes the profile of the product with respect to the physical appearance, assay, dosage strength, container enclosure system, pharmacokinetic characteristics as well as *in vitro* and *in vivo* performance. This profile acts as guidance throughout the product development phase.
Critical Quality Attributes (CQAs)

A CQA is defined as “any physical, chemical, biological or microbiological property that should be within an appropriate range limit or distribution to ensure the desired product quality”(57). CQAs are measurable product attributes that can be derived from the QTPP or prior knowledge of the product. For a solid dosage form like tablets the CQAs can be tablet hardness, friability, disintegration time, assay, dissolution time. A CQA can also be an esthetic attribute of the product such as the physical appearance like color, size and shape of the logo, glossiness and so on. Additional CQAs from the manufacturing process such as curing time, temperature and feed rate may be considered for monitoring during the product development phase.

Risk Assessment

Out of the hundreds of factors potentially affect a pharmaceutical process, it is often difficult to select the most important factors. Risk assessment is a scientific tool for systematically shortlisting and prioritizing the factors that potentially have an impact on the CQAs. While there are several risk assessment tools available to use, the most commonly used techniques include construction of the fishbone (or Ishikawa) diagram and Failure Mode Effect Analysis (FMEA). Ishikawa diagrams were created by Kaoru Ishikawa to show the causes associated with a particular event(70). The causes are separated based on their source and each arm highlights causes associated with that particular source. The commonly addressed sources are people involved with the process, plant environment related factors, methods used for manufacturing, use of
specific machinery and equipment, source and nature of raw materials and analytical methods.

The FMEA analysis is a tool to systematically analyze all the factors that potentially affect the product development. In a FMEA study, all possible factors are listed down as failure modes. The parameters listed in an FMEA study can be related to the process as well formulation. An interdisciplinary team of experts then grades each failure mode based on its occurrence, detectability and severity. Each failure mode is given an average score for each individual category and a product of these scores is further used to generate a Risk Priority Number (RPN). These failure modes are prioritized based on their RPN score and failures with the highest RPN are likely to cause a significant impact on the CQAs of the product. The shortlisted factors are then considered for a DoE based screening and optimization study.

Design Space

The DS is defined as “the multidimensional combination and interaction of input variable and process parameters that have been demonstrated to provide assurance of quality”(57). The parameters shortlisted in the risk assessment stage are further quantitatively analyzed using a DoE study. This also could be an opportunity for investigators to determine the levels of processing aids such plasticizer, glidants, antitacking agent at which optimum performance is achieved. Generally a full factorial or an Response Surface Model (RSM) is then employed to investigate the significance of each parameter in the study. The CQAs such as the dissolution rate, tablet hardness, disintegration time, assay and drug content uniformity are measured as responses.
Data analytical techniques like multi linear regression or partial least squares are then utilized for generating predictive models for measurement of individual responses. The analysis of the DoE study culminates into a DS that describes the relationship between process inputs (CPPs) and the measurable final product attributes (CQAs). A DS may be described in terms of the ranges of material attributes and process parameters or through complex mathematical relationships. A change of manufacturing conditions within the predefined design space does not require additional documentation and filing.

Control Strategy

After the initial processing ranges have been established and proven to yield the desired values of CQAs, a control strategy is designed to ensure that the product quality will be maintained. During development of control strategy, sources of variation are identified and their effect on the final product attributes are outlined. Control strategy may be designed to monitor the specifications of the incoming materials, unit operations during manufacturing, as well as real time testing. A control strategy can employ in line monitoring tools to monitor product attributes during manufacturing. This will facilitate in addressing potential failures before they occur.
CHAPTER 2

OBJECTIVES
1. To evaluate application of solubility parameter theory for excipient selection for HME formulation development
   a. To theoretically predict the solubility parameters of ibuprofen and each of the carrier polymer selected based on the group contribution theory and the molecular structure.
   b. To measure the experimental solubility ranges using film casting and melt extrusion
   c. To demonstrate advantage of amorphous solid dispersions in vitro by performing dissolution experiments
2. Thermal and chemical characterization of Ibuprofen-Eudragit® E PO solid dispersions prepared by HME
   a. Prediction of phase diagram based on the Flory-Chi theory outlining the temperature – composition relationship
   b. Evaluate and investigate molecular interactions using spectroscopic techniques
   c. Study the stability of the prepared melt extrudates at room temperature
3. Application of Quality by Design (QbD) approach for product development using HME
   a. Perform qualitative risk assessment by plotting the Fishbone diagram and Failure Mode Effect Analysis
   b. Perform quantitative risk assessment using a Placket-Burman experimental screening design
c. Analysis of the critical factors in a complete experimental design

d. Prediction of the design space based on the analysis of the response values

4. **Evaluation of drug release mechanism of Ketoconazole – Kollidon® VA 64 melt extrudates**

   a. Preparation and analysis of melt extrudates

   b. Investigate the swelling and erosion behavior of the prepared extrudates

   c. Determine the drug release mechanism based on *in vitro* dissolution studies
CHAPTER 3
POLYMER SCREENING APPROACHES FOR FORMULATION DEVELOPMENT
USING MELT EXTRUSION
**Introduction**

Solubility enhancement with the aid of solid dispersion formation has continued to be a topic of interest within the pharmaceutical industry and academia (18, 71). To become bioavailable, a drug should be soluble in gastrointestinal fluids and also be permeable through the cell membranes in the intestine. Solid dispersions offer the ability to freeze the drug molecule in its highly soluble amorphous form thus increasing the solubility and most likely the bioavailability of the drug (72).

Pharmaceutical Hot Melt Extrusion (HME) is a thermal technique that involves mixing of the drug and polymeric excipients at temperatures above the Glass Transition ($T_g$) of the polymer thereby solubilizing the drug in the polymer(72). HME has gained significant momentum in recent years within the pharmaceutical industry for manufacturing solid solutions with enhanced solubility addressing the bioavailability issues of increasing number (~70%) of BCS II and IVNDAs (New Drug Applications) in the current R&D pipelines(3).

Solid solutions are formed when there is significant structural similarity between the polymer and the drug. The drug-polymer miscibility has been estimated using theoretical (23, 73-76) approaches where the cohesive energy densities corresponding each individual functional group in a molecule is accounted towards calculation of the total solubility parameter of the molecule. Extending this method, researchers have determined individual energy contribution from the polar, dispersive and hydrogen bonding forces (26). Such computationally calculated 3-D solubility parameters and their application in developing stable solid solution formation has been evaluated (76, 77).
Experimental approaches for solubility determination include melting point depression (27, 28), annealing(78), diffusion based(79), determination of drug-monomer solubility(80) and inverse gas chromatography(81). Knowledge of the drug-polymer miscibility values facilitates in selecting appropriate functional excipients to achieve the desired in vivo release profile. Depending on the choice of the excipients a wide range of dissolution profiles for immediate release as well as modified release can be accomplished using HME (39, 73, 82).

Traditionally a more time consuming, trial and error based method is employed in which several excipients are screened in the laboratory. Efforts to expedite this process using automated robotic systems have been evaluated(82-84). These techniques demand specialized equipment, high amount of drug and therefore may not be always practical.

Solubility prediction methods can be used as screening tools to shortlist the chemically most compatible polymeric carriers for a given drug component and thereby reduce the number of experimental trials. To increase chances of solubility enhancement using solid solution formation, it is important that the drug is maintained in its high energy amorphous form(18). Solid solution can be formed by ensuring that the concentration of the drug is below the saturation solubility ($C_S$) of the drug in given polymer. For this reason, it is important to know the solubility of the drug in the polymeric carrier in consideration.

The objective of the present study was to evaluate the application of solubility parameters for selection of excipients for solid dispersion formulation development using melt extrusion. 3-D solubility parameter values for Ibuprofen and each polymer
selected for this study is predicted using Hoftyzer/Van Krevelen method that accounts for polar, dispersive and hydrogen bonding forces separately (26). Recently, after comparing theoretical and experimental solubility parameters, researchers have concluded that these conventional solubility parameter techniques are more accurate for common polymers (85). The difference in the solubility parameter gives an indication of miscibility of the two components. These ranges are then verified experimentally using film casting and melt extrusion experiments. A fourth type of force ie ionic interactions are studied separately experimentally in chapter 4. Ibuprofen a weakly acidic, non-steroidal anti-inflammatory drug categorized as BCS class II having a melting point ($T_m$) in the range of 75 to 77°C is used as a model drug for solubility determination. Eight pharmaceutical grade polymers with distinct chemistry were selected for the screening studies.

**Materials**

Ibuprofen (Albemarle, USA; BCS Class II) was used as model drug in this study. Polymers EUDRAGIT® E PO, EUDRAGIT® L 100-55, EUDRAGIT® RL PO and EUDRAGIT® RS PO were obtained from Evonik Pharma Polymers (Evonik Corporation Piscataway, NJ, USA), HPMCAS-LF was obtained from Shin Etsu (Tokyo, Japan), Kollidon® VA 64 and Soluplus® were obtained from BASF specialty chemicals (Ludwigshafen, Germany). HPMC E5 was obtained from Dow Chemical (Midland, Michigan, USA). All polymers were used as received. Ibuprofen was sieved with a USP #35 screen to remove agglomerates. USP grade 190 proof ethanol purchased from Fisher Scientific was used as a solvent for film casting.
Methods

Solubility Parameter Calculation

The solubility parameter ($\delta$) is a measure of cohesive energy density ($E_{coh}$) per unit volume of a material. The $E_{coh}$ represents the total attractive forces within a condensed state of the material and can be defined as the amount of energy needed to separate the atoms/molecules to a distance where no interactions occur. Solubility parameters for ibuprofen and all polymers were calculated using the group contribution method outlined by Fedors which was later expanded by Hoftyzer-Krevelen (23, 26). The solubility parameters for polymers were calculated in two steps 1- calculation of solubility parameters of individual monomers and 2- calculation of solubility parameter of polymers based on proportional average of the monomers components.

3D solubility parameters were originally defined by Hansen where the energy contribution from dispersion, polar and hydrogen bonding are separately calculated based on the molecular structure(24). Hansen defines the total solubility parameter as

$$E_{coh} = E_d + E_p + E_h \quad (3.1)$$

$$\delta^2_t = \delta^2_d + \delta^2_p + \delta^2_h \quad (3.2)$$

Where, subscript d stands for dispersive forces, p stands for polar forces and h stands for hydrogen bonding energy from self-association of the molecule. Contributions associated with dispersive, polar and hydrogen bonding forces were individually calculated using the following equations.
\[ \delta_d = \frac{\sum F_{di}}{V} \]  (3.3)

\[ \delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} \]  (3.4)

\[ \delta_h = \frac{\sqrt{\sum F_{hi}}}{V} \]  (3.5)

Based on the theory that ‘like dissolves like’, it is generally considered that materials with closely related solubility parameters are miscible. A drug is considered miscible in a polymer if the difference in their solubility parameter is less than 7 (\(\delta_d - \delta_p < 7\)) (73, 86).

**Film Casting**

Accurately weighed drug-polymer mixtures with the desired drug load (Total wt: 1.00 gm) were dissolved in 30 mL ethanol using a magnetic stir station and allowed to equilibrate for 24 hrs. The resultant clear solution was transferred in a glass petri-dish and allowed to dry in a fume hood and tested for absence of solvent using a loss on drying apparatus. The prepared films were stored in air tight clear storage bags until further testing.
Melt Extrusion

Binary mixtures of Ibuprofen with each polymer were prepared by weighing individual components and blending using a Turbula T2F shaker mixer (Glen Mills Inc. Clifton, NJ) for 10 min to ensure homogenous mixing. The mixtures were extruded using a 16mm co-rotating twin screw extruder (Leistritz Corporation, Allendale, NJ) complete with a bottom plunger feeding assembly and a 4mm round die. The four heating zones for this extruder equipment were set to 70, 140, 140, 140 °C however due to the plasticizing
effect of Ibuprofen(87) temperatures needed to be lowered for high drug load formulations. Extrusion screw rotation speed (150 rpm) and the feed rate (5cc/min) were maintained constant for all the batches. The extruded material was allowed to cool on a conveyor belt (Dorner, Hartland, WI) supplied with a jet of cool air and stored in airtight containers in a dark cabinet until further processing. All samples were milled using IKA A11 basic analysis mill and sieved through a USP #35 mesh screen. A small portion of the extrudate was flattened between two glass slides for microscopic analysis. The screws were pulled out and the barrel was cleaned after each set of formulations.

All samples were milled using IKA A11 basic analysis mill and sieved through a 35 mesh screen. Any material that did not pass through 60 mesh screen was transferred back in IKA A11 to be milled and sieved again. This process was repeated until all material passed through 60 mesh screen. The material that did not go through the sieve was stored separately and used for further analysis. The fines were eliminated by sieving through a screen with mesh number 200.

**Differential Scanning Calorimetry**

Differential scanning calorimetric analysis was performed on the milled extruded samples using a Pyris 6 DSC (PerkinElmer, Waltham, MI). 8 – 10 mg of the milled extrudate was weighed, crimped in an aluminum pan. The samples were heated to 100°C at 20°C/min, cooled to 0°C and heated to 120°C at 20°/min under nitrogen purge of 20 ml/min.. The first heating eliminated the thermal history and moisture whereas the second heating facilitated in the determination of T_g. Samples with increasing ratio of
ibuprofen were analyzed and the ratio at which crystalline phase of ibuprofen could be detected was noted.

**Microscopy**

Optical analysis were performed on the film casted and extruded samples using an Olympus BX51 microscope (Center Valley, PA) coupled with polarized filters to evaluate the drug’s physical state. A drug-polymer film is placed between two glass slides and observed with transmission mode under polarized light. The samples were stored at room temperature (25±2.5°C) and examined for recrystallized drug crystals periodically up to 1 year.

**Dissolution Testing**

The milled sample (equivalent to 200mg of ibuprofen) was filled in a size 00 clear capsule. Dissolution on the filled capsules was performed (n=3) using USP apparatus 2 with a Varian VK 750 D dissolution equipment, at 37°C and with a stir speed of 50 rpm in two media pH 1.2 and pH 6.8 separately. Dissolution samples were withdrawn using a Varian auto sampler connected to a spectrophotometer. A control sample, where 200mg of pure drug was placed in a size00 clear capsule was used for comparison. The dissolution profiles obtained for ibuprofen samples were compared to that of marketed Ibuprofen soft gelatin capsules and IR tablets both with a dose of 200mg.
Results and Discussion

Solubility Parameter Calculation

The use of solubility parameters as tools to predict compatibility between drug/polymer systems have been demonstrated for many pharmaceutical systems (23, 73, 86, 88). The most common method used for calculation of solubility parameters is by using the group contribution theory developed by Hildebrand (89). This approach was further extended to separately calculate the contributions from hydrogen bonding, polar and dispersive forces (24, 26). In this study, structure of model drug ibuprofen was defragmented into individual functional groups in order to determine the Hildebrand Solubility Parameter including the individual contributions corresponding to hydrogen bonding, polar and dispersive forces using the Hoftyzer-Van Krevelen method (26). Figure 3.2 shows defragmentation of the molecular structure of Ibuprofen and the groups that were used for solubility parameter calculation by group contribution method. Cohesive energies associated with each group were added to calculate the total cohesive energy $E_{coh}$ for the entire molecule. The solubility parameter was then calculated based on the equation 3.2. Similar method was applied to calculate the solubility parameters of monomers. The solubility parameter of the polymer $\delta_{poly}$ was then calculated by taking proportional average of individual monomers.

The cohesive energy is the summation of all the molecular interactions including dispersive, polar, hydrogen bonding as well as the ionic interactions. Compounds with similar cohesive energies are likely to be miscible with each other. If the difference in solubility parameters of the drug and that of the polymer is less than 7 ($\delta_p - \delta_d$) then the
two are generally considered to be miscible (86). Several researchers have explored use of solubility parameters approach to determine drug/polymer miscibility and solubility (53, 73, 74, 78). The calculated solubility parameter and miscibility estimations in terms of difference in solubility parameter for ibuprofen and each polymer considered in this study is given in Table 3.1. The lower values of \( \delta_p - \delta_d \) indicate higher miscibility. In the case of ibuprofen, the higher miscibility is expected for Eudragit® E PO, Eudragit® L 100-55, Eudragit® RS PO, Eudragit® RL PO, Kollidon® VA 64 and Soluplus® whereas borderline miscibility is expected in polymers HMPCAS-LF and HPMC.

Bagley et al observed the similarities between \( \delta_d \) and \( \delta_p \) and derived the following expression (90)

\[
\delta_v = \sqrt{\delta_d^2 + \delta_p^2} \tag{3.6}
\]

A plot of \( \delta_v \) and \( \delta_h \) can outline the compatible solvents for a certain drug molecule based on the chemical structure of the drug and the polymers. Such a diagram for ibuprofen and the polymers considered in this study is shown in Figure 3.3. The circle represents an approximate delimited region of solubility for ibuprofen. It can be seen that the predictions based on the difference in solubility parameter are further confirmed using the \( \delta_v - \delta_h \) plot. These estimations are further verified using experimental techniques.
Figure 3.2: Molecular Defragmentation of Ibuprofen Structure

Table 3.1 Difference in solubility parameter of the drug and polymer

| Drug                | Solubility Parameter (δ) | |δ-δd| |
|---------------------|--------------------------|---|---|
| Ibuprofen           | 18.98                    | NA|
| Eudragit® E PO      | 21.40                    | 2.42|
| Eudragit® L 100-55  | 19.77                    | 0.79|
| Eudragit® RS PO     | 21.61                    | 2.63|
| Eudragit® RL PO     | 21.53                    | 2.55|
| Kollidon® VA 64     | 26.12                    | 7.14|
| Soluplus®           | 22.97                    | 3.99|
| HPMC                | 37.51                    | 18.53|
| HPMCAS-LF           | 36.23                    | 17.25|
Experimental Solubility

To further test the reliability of this predicted miscibility approach, the ranges of solubility were determined experimentally using ethanol casting and melt extrusion using various drug loads. Spray drying and melt extrusion are two commonly used techniques for manufacturing of solid dispersions. Due to the solvent interactions involved, results obtained from ethanol casting are likely to be comparable to solid dispersion manufacturing techniques like spray drying where the effects of solvents need to be taken into consideration. Melt extrusion experiments were conducted for each polymeric excipient with varying ibuprofen concentrations. The extrudates were analyzed using DSC and microscopy to identify recrystallization. Table 3.2 compares the predicted and the experimental solubilities of ibuprofen in select pharmaceutical polymers.

Extrudate Analysis

DSC studies were conducted for characterization of the physical state of the drug. The change in the enthalpy due to melting of the crystalline drug results in a characteristic melting event in the DSC thermogram. In absence of a crystalline drug no such event was observed. Samples with increasing ibuprofen loading were screened and compared with a thermogram of a blank polymer sample. The concentration at which a melting event could be seen was regarded as the saturation solubility of the drug in the polymer solvent. DSC scans for melt extrudates of ibuprofen with each polymer are presented in Figure 3.12. The saturation solubility values obtained from the DSC studies were further confirmed with microscopic examination of the films.
Figure 3.3: $\delta v - \delta h$ diagram showing solubility of Ibuprofen in selected polymers

Figure 3.4: DSC thermograms of Ibuprofen- Eudragit® E PO melt extrudates
Figure 3.5: DSC thermograms of Ibuprofen- Eudragit® L 100-55 melt extrudates

Figure 3.6: DSC thermograms of Ibuprofen- Eudragit® RS PO melt extrudates
Figure 3.7: DSC thermograms of Ibuprofen- Eudragit® RL PO melt extrudates

Figure 3.8: DSC thermograms of Ibuprofen- HPMCAS-LF melt extrudates
Figure 3.9: DSC thermograms of Ibuprofen- HPMC melt extrudates

Figure 3.10: DSC thermograms of Ibuprofen- Soluplus® melt extrudates
Figure 3.11: DSC thermograms of Ibuprofen- Kollidon® VA 64 melt extrudates

Polarized light is reflected by crystals present in the study sample thus making detection of crystals easy. The optical microscopic analysis performed on the samples allowed detection of recrystallization in the solid solutions prepared by film casting and HME. Microscopic analysis was performed to verify the results of the DSC scanning. In certain instances when the percent crystallinity is low, the DSC thermograms may not detect enthalpy associated with crystallization. An amorphous solid solution appears black under polarized light (Figure 3.12) and the crystals appear luminescent making them easy to identify (Figure 3.12 (b)). From the DSC and microscopic results, a range of the solubility/miscibility of drug in each of the polymeric matrix was obtained. These experimental solubility ranges for all the samples is given in Table 3.2 in comparison to the predicted miscibility ranges based on difference in the calculated solubility parameter.
Figure 3.12: Ibuprofen -Eudragit® E PO melt extrudate under polarized light (a) 55% ibuprofen (b) 70% ibuprofen

Table 3.2: Comparison between predicted and experimental solubility values

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Predicted miscibility</th>
<th>Film Casting</th>
<th>HME</th>
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<tbody>
<tr>
<td>Eudragit® E PO</td>
<td>High</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Eudragit® L100-55</td>
<td>High</td>
<td>7.5</td>
<td>35</td>
</tr>
<tr>
<td>Eudragit® RL PO</td>
<td>High</td>
<td>27.5</td>
<td>25</td>
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<td>Eudragit® RS PO</td>
<td>High</td>
<td>27.5</td>
<td>25</td>
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<tr>
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<td>Low</td>
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<td>25</td>
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<td>55</td>
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<tr>
<td>Soluplus®</td>
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</table>

Evaluation of Solid Dispersions prepared by HME

The prepared melt extrudates were evaluated for solubility enhancement using in vitro dissolution apparatus. For each polymer, formulations with ibuprofen concentration
below the maximum solubility were selected for dissolution testing therefore the drug was in the amorphous form in all the formulations. Being a weak acid, Ibuprofen shows pH dependent solubility. Practically no drug release was observed in the pH 1.2 media except for the Eudragit® E PO formulation, where the release 3 folds higher when compared to the pure ibuprofen as well as the standard ibuprofen tablet and soft gel formulation (Figure 3.13). This increase in dissolution can be attributed to the formation of ionic interactions between the anionic drug and the cationic polymer and is further investigated in chapter 4 of this document. It has been reported by Jamali et al. that increase in the dissolution at the gastric pH overall increases the drug absorption across the gastro-intestinal tract(91). As soon as the pH of the media is switched to 6.8 the ibuprofen control releases 90% within the first 60 minutes (Figure 3.14). At this pH, the influence of the properties of the carrier polymer on the release profile is evident. Release from the melt extruded formulations appears to be slower due to the fact that additional time is required for polymer dissolution and matrix erosion.
Figure 3.13: *In vitro* dissolution of prepared ibuprofen melt extrudates with individual polymers at a concentration below the maximum solubility in pH 1.2
Figure 3.14: *In vitro* dissolution of prepared ibuprofen melt extrudates with individual polymers at a concentration below the maximum solubility in pH 6.8

Conclusion

In summary, this study compares the predicted miscibility ranges based on the molecular structure with the actual experimental values obtained from the film casting and HME experiments. Theoretical solubility prediction has several limitations due to the fact that it does not consider the steric and isomeric hindrances as well as interactions introduced due to the processing factors like heat, torque or solvent related interactions.
In spite of these limitations, this method provides a reasonable alternative to expensive and time consuming experimental screening and provides a starting point for short listing of suitable excipients. The predicted values were in accordance with the experimentally determined ranges of solubility. The solubility parameter concept does not account for ionic interactions between the drug and the polymer that may explain the discrepancy in experimental and predicted solubility levels for ionic polymers like Eudragit® E PO. The solubility of drug in polymer ranking order is supported with experimental data.

Solubility parameters can aid in selection and shortlisting of excipients for a HME formulation and can generate miscibility profiles for an API with commonly available pharmaceutical polymers if the chemical structures are known. In this study, the use of solubility parameter concept in selection of excipients for a model drug ibuprofen was demonstrated. Such methods will reduce the time and resources required during the initial stages of product development. This approach for polymer screening is intended to serve as a starting point for experimental trials followed by further in depth analysis and may also serve as a guide in selection of specific functional excipients for enteric, sustained and modified release applications. Knowledge of solid state solubility will facilitate in determining percent drug loading while design and development of solid dispersion formulation for solubility enhancement.
CHAPTER 4

THERMAL AND CHEMICAL CHARACTERIZATION OF SOLID DISPERSIONS
PREPARED WITH EUDRAGIT® E PO AND IBUPROFEN
Introduction

Solubility enhancement of poorly water soluble BCS Class II and IV drugs has been one of the most important challenges as about 40-70% of new drug molecules are poorly water soluble (3). Solid dispersions offer the ability to freeze a drug molecule in its most high energy amorphous form increasing the apparent solubility (18, 46, 71, 92). Methods for manufacturing solid dispersions include freeze drying, spray drying, solvent film casting, self-emulsifying lipid formulations and hot melt extrusion (HME). Formation of a solid facilitates stabilization of the API in its high energy amorphous state for an extended period of time. A lot of focus is given to characterization of physical form of the drug in solid dispersions. In some instances however, amorphization of the drug may not be the sole contributing factor for solubility enhancement. Systems containing ionic complex of a drug with an excipient offer the ability to further increase the apparent solubility of a poorly water soluble drug (93, 94).

Solubility of a drug in a polymer is usually very low therefore it is difficult to meet the conventional dose requirements with solid dispersion formulations. For this reason, most solid dispersions potentially are developed as supersaturated systems. In some cases additional stabilizers and solubilizers are necessary to assist in solubility enhancement. Selection of the appropriate polymeric excipient is critical to have the highest concentration of drug solubilized. Strong drug-polymer interactions are favorable due to their ability to produce stable, higher drug load solid dispersions. Strategic selection of excipients to form ionic interactions offers the ability increase the apparent solubility of the drug. In the previous chapter polymers of varying chemistries
were investigated for compatibility with the model drug ibuprofen. In this chapter further thermal and chemical characterization of binary solid dispersions prepared using Ibuprofen and Eudragit® E PO is performed.

For formulation optimization using HME, it is essential to understand the important physicochemical properties such as the Glass Transition ($T_g$), melt viscosity, solid-state saturation solubility and interactions between the drug and the excipients incorporated. A phase diagram describing the effect of temperature and the ratio of ibuprofen on the physical state of the drug is investigated in this study. Since maintaining stable amorphous state of the drug via solid dispersion formulation is critical for solubility enhancement knowledge of the phase diagram will provide vital information required for developing stable solid dispersions.

For an immediate release formulation, increased solubility of a drug in the gastric pH is advantageous as the dissolution process starts as soon as the drug is orally administered. This also ensures that the drug is in the solubilized form and ready for absorption on entering the intestine (91). Eudragit® E PO is a good solvent for many classes of drug molecules mainly anionic and neutral drug. Due to the low $T_g$ of this polymer processing using solid dispersion manufacturing techniques like HME and spray drying can get challenging when working with a drug molecule with a low $T_g$. For this reason, thorough understanding of thermal and chemical properties of this excipient is essential in order to determine experimental conditions within which stable processing can be achieved. In detail study on the effect of processing parameters on quality of the final product is presented in chapter 5.
In the present study, thermal and chemical characterization of ibuprofen and Eudragit® E PO binary mixtures have been performed using thermal and spectroscopic methods. Eudragit® E PO, is an amorphous polymer with a $T_g$ at about 45°C is insoluble in aqueous systems above pH 5.5 making it an excellent carrier for taste masking bitter drugs. Ibuprofen a low melting (75-77°C), anionic drug is selected as a model drug as model drug. Ionic interactions between Eudragit® E PO and acidic drugs have been investigated by solubility measurement and FTIR spectroscopy.

**Materials**

Ibuprofen was generously donated by Albermarle. Eudragit® EPO was obtained from Evonik (Piscataway, NJ). Chloroacetic acid, acetonitrile and ammonium hydroxide were purchased from fisher Scientific (Pittsburgh, PA)

**Methods**

**Phase Diagram**

Phase diagram was calculated based on the melting point depression method and the Flory-Huggins theory(95). According to the Flory-Huggins theory, a temperature composition phase diagram can be constructed for a given drug-polymer system if the Flory chi parameter is known for a given temperature range. Melting point depression method has been used previously to predict the value of $\chi$ by Marsac et al based on the equation 4.1.

$$\frac{1}{T_m} - \frac{1}{T_m^0} = -\frac{R}{\Delta H} \left[ \ln \phi + \left( 1 - \frac{1}{m} \right) (1 - \phi) + \chi(1 - \phi)^2 \right]$$

(4.1)
Where $T_m$ is the melting point of the drug polymer mixture, $T_m^0$ is the melting point of the pure drug, $\phi$ is the volume fraction of the drug, $m$ is a constant derived from the ratio of the volume of a polymer to that of the drug molecule and $\chi$ is the Flory- Huggins interaction parameter (27, 53). It was recently noted that the Flory-Huggins interaction parameter is temperature dependent (96, 97). A relationship between $\chi$ and temperature can be expressed based on the equation 4.2.

$$\chi = A + \frac{B}{T}$$  \hspace{1cm} (4.2)

Where $A$ is a constant from non-combinatorial entropic contribution to $\chi$ and $B/T$ is a constant coming from the enthalpic contribution (98).

The free energy of mixing can be written in terms of the Flory-Huggins parameter as shown in equation 4.3

$$\Delta G = RT \left[ \phi \ln \phi + \frac{1-\phi}{m} \ln(1 - \phi) + \chi \phi(1 - \phi) \right]$$  \hspace{1cm} (4.3)

The crystalline phase boundary is calculated using predicted values of $T_m$ based on the equations 4.1 and 4.2. In order to calculate the spinoidal curve for phase separation, $T_s$ is calculated from the second derivative of equation 4.3 equated to zero as shown in equation 4.4.

$$\frac{1}{\phi} + \frac{1}{m(1-\phi)} - 2\chi = 0$$  \hspace{1cm} (4.4)
Melt Extrusion

Powder blends of Ibuprofen with Eudragit® E PO were prepared by mixing accurately weighed powder components using a Turbula T2F shaker mixer (Glen Mills Inc. Clifton, NJ) for 10 min. Melt extrusion was performed in 40 gm batch sizes using a co-rotating twin screw extruder (Leistritz Nano 16, American Leistritz Corporation, Somerville, NJ). Screw rotation speed (150 rpm) and feed rate (5cc/min) using the bottom plunger feeder was maintained constant for the entire set of experiment. Due to the plasticizing effect of ibuprofen, extrusion temperature was adjusted based on the $T_g$ of the mixture and ranged from 80 to 140°C. The resulting extrudates were stored at room temperature in air tight containers until further analysis.

Thermal Analysis

Differential Scanning Calorimetric (DSC) analysis was performed on the drug polymer solid dispersions using a Pyris 6 DSC (PerkinElmer, Waltham, MI). 8 – 10 mg of the milled extrudate was weighed, crimped in an aluminum pan and subjected to a heat-cool-heat cycle.

**Measurement of glass transition:** Samples were heated from 0 to 100°C at the rate of 10°C/min, cooled to -50°C at 40°C/min and reheated up to 120°C at heating rate of 10°C/min under nitrogen purge of 20 ml/min. The first heating eliminated the deviations caused from the thermal history and moisture whereas the second heating facilitated in the determination of $T_g$. DSC scans for the pure ibuprofen and Eudragit® E PO was measured as controls.
Melting point depression measurement: Binary mixtures of ibuprofen and Eudragit® E PO containing 65, 70, 75, 80, 85, 90 and 95% ibuprofen were dissolved in 5mL ethanol and stirred until a homogenous solution is obtained. This solution was poured into a petri dish (35mm) and allowed to dry for 3 days under a hood. The resulting films were analyzed in a DSC first by cooling to -50°C, heating from -50°C to 40°C at 10°C/min followed by heating from 40°C to 90°C at 1°C/min to measure the melting point. The melting point was calculated at the falling edge of the melting endotherm.

Optical Microscopy

Optical analysis were performed on the extruded samples using an Olympus BX51 microscope (Center Valley, PA) coupled with polarized filters to evaluate the drug's physical state. A 1:1 physical mixture of ibuprofen and Eudragit® E PO was observed under a microscope for 12 days. The melt extruded samples were examined for recrystallized ibuprofen periodically over a span of 1 year.

XRPD

X-ray diffraction (XRD) was investigated using D4 Endeavor (Bruker Corporation, Billerica, MA, USA). XRPD measurements assisted in physically determining the presence of crystalline phase. This analysis verified the results of the DSC measurements as well as phase diagram prediction.
FTIR

The ATR-FTIR was used to identify the ionic interactions between the drug and the polymer. The IR spectra of the samples were collected by placing the samples in powder or film form on a single-reflection diamond ATR (Attenuated Total Reflectance) accessory. 32 scans were obtained for each sample at the resolution of 2 cm\(^{-1}\).

Solubility Measurement

Increasing amount of Eudragit® E PO was added to super saturated solutions of ibuprofen in 10 mL 0.1N HCl and allowed to equilibrate overnight. Resulting solutions were filtered and the supernatant solution was analyzed using a HPLC system equipped with a photodiode array detector at 254nm (Waters Corporation, Milford, MA) along with a C\(_{18}\) column (Waters Xbridge, 3.5 micron, 4.6x 150 mm). A mobile phase consisting of 1% chloroacetic acid buffer solution adjusted to pH 3.0 with ammonium hydroxide and acetonitrile in the ratio 20:80 was used at a flow rate of 0.8 mL/min. All the standards and assay samples were prepared in acetonitrile. To test the effect of change in pH on the saturation solubility of ibuprofen supersaturated solutions of ibuprofen were prepared using pH 4.5 and 6.8 buffer solutions. pH values for all the solubility samples along with 300mg and 500mg Eudragit® E PO dissolved in 10 mL 0.1N HCl as controls were recorded.
Results and Discussion

1. Thermal Characterization: Phase Diagram

The DSC thermograms measured for various ratios of ibuprofen and Eudragit® E PO are shown in Figure 4.1. The solvent casting may increase the amount of amorphous drug due to the presence of polymer chains resulting in melting point depression. This also provides an evidence of intimate mixing between the drug and the polymer. The crystalline ibuprofen shows a sharp melting peak at 78.08°C and this further decreases as the concentration of Eudragit® E PO in the system increase. The melting point depression data was used to calculate the Flory Chi parameter for the ibuprofen – Eudragit® E PO system based on equation 4.1. Table 4.1 shows the values of the physical properties that were used in calculation of the constant m.

Table 4.1: Molecular Weight and Density of Ibuprofen and Eudragit® E PO

<table>
<thead>
<tr>
<th></th>
<th>Molecular Weight</th>
<th>Density (gm/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>206.28</td>
<td>1.03</td>
</tr>
<tr>
<td>Eudragit EPO</td>
<td>47000</td>
<td>0.811</td>
</tr>
</tbody>
</table>
Figure 4.1: DSC thermograms of Ibuprofen and solvent casted solid dispersions of Ibuprofen and Eudragit® E PO obtained at a scanning rate of 1°C/min.

Figure 4.2: Flory-Huggins interaction plot based on equation 4.1.
A Flory-Huggins interaction plot based on the equation 4.1 is shown in Figure 4.2. The slope of the straight line is the value of the Flory Chi interaction parameter and for the current study the calculated Chi is -1.52. Negative Chi values are associated with higher degrees of miscibility therefore the components are predicted to have high compatibility resulting in stable solid dispersions. Measurements of Flory Chi parameter based on the melting point depression data has been performed for similar pharmaceutical systems (27, 28).

**Figure 4.3:** A plot showing the relationship between the interaction parameter and temperature.
The melting point data can be used to extrapolate the value of Chi at different temperatures using equation 4.1. There exists an inverse relationship between Flory Chi and Temperature as shown in equation 4.2. The predicted interaction parameter values are plotted against $1/T$ to get an equation of the straight line based on equation 4.2, $\chi = \frac{5794}{T} - 18.61$. The values of A and B are further used to predict the phase boundaries.

![Figure 4.4: A plot showing Gibbs free energy changes with respect to temperature for Ibuprofen-Eudragit® E PO system](image)

The phase diagram predictions are based on the Gibbs Free energy calculated using the equation 4.3. Phase separation is dependent on the difference of the Gibbs free energy between the mixed and unmixed states which is also referred to as $\Delta G_{\text{mix}}(74)$. A
plot of $\Delta G/RT$ against the ratio of ibuprofen is presented in Figure 4.4. It can be seen that at temperatures above 25°C the $\Delta G$ is negative across all ratios of ibuprofen indicating that at this temperature the system is miscible at all concentrations. At 20°C the $\Delta G$ starts getting positive at an ibuprofen concentration of 75%w/w whereas at 10°C the $\Delta G$ starts becoming positive at a concentration of 25%w/w. Overall, miscibility reduces as the temperature drops.

The relationship between the Gibbs free energy, temperature and volume fraction of the drug can be used to calculate the temperature at which phase change occurs for each volume fraction of the drug. The spinoidal curve is calculated by equating the second derivative of the Gibbs free energy to zero as presented in equation 4.4. This is the boundary that outlines the miscibility limits of the two systems where the drug is present in a metastable state. In this region, the system may be sensitive to fluctuations in the levels of temperature or composition and may cause nucleation and recrystallization with larger fluctuations. The predicted melting points outline the region between crystalline and amorphous ibuprofen.

$T_g$ for the mixtures were measured experimentally using DSC measurements. The first heating eliminated prior thermal history of the material as well as the moisture present in the sample whereas the second heating cycle allowed determination of $T_g$. For samples in which ibuprofen exists in two phases (crystalline and amorphous), a melting event around 70°C can be detected in the first heating cycle. A change in the $T_g$ can be witnessed in the DSC thermograms as seen in Figure 4.5.
Figure 4.5: $T_g$ determination for binary mixtures of Ibuprofen and Eudragit® E PO

Figure 4.6: Predicted phase diagram for Ibuprofen and Eudragit® E PO system
A phase diagram is a graphical representation of phase boundaries in relation to the temperature and composition. A predicted phase diagram for ibuprofen – Eudragit® E PO system is presented in Figure 4.6. Based on the phase diagram, it can be seen that the mixture of two components exists in a miscible state at room temperature.

**Room temperature Miscibility Study**

To further explore the fact that that the $T_g$ of high ibuprofen containing (<50%) samples is well below the room temperature (Figure 4.7) a miscibility study was conducted. A 1:1 mixture of powder Eudragit® E PO and Ibuprofen was observed under an optical microscope (100X) for a period of 12 days. Particles of Eudragit® E PO coated the ibuprofen crystals as seen on day 1 due to their significantly lower particle size and strong adhesive forces. The strong interactions between the two components slowly start dissolution process and the size of the ibuprofen crystal appears to be reduced as the days progress as seen in Figure 4.7 (a – h). Towards the end of 12 days the distinct shape of ibuprofen crystal disappeared indicating that the ibuprofen was most likely converted to its amorphous form due to solubilization in the polymer solvent. This is further confirmed by observation of crystals under polarized light. The outlines for ibuprofen crystals are clearly visible on day 5 whereas the day 10 image shows no reflectance under polarized light indicating absence of crystals as seen in Figure 4.5.
Figure 4.7: Room Temperature Miscibility

(a) Day 1:  
(b) Day 2

(c) Day 5  
(d) Day 6

(e) Day 7  
(f) Day 8
2. Chemical Characterization

The mutual miscibility of ibuprofen and Eudragit® E PO can be attributed to their chemical structure. Chemical characterization was carried out to test for presence of intermolecular interactions.

**FTIR**

The room temperature miscibility study visibly shows the solubilization process between the two components. FTIR scans on the melt extruded samples further verify the formation of molecular interactions. The FTIR spectra show a broad peak at 1567cm$^{-1}$
(absent in the physical mixture) which may be associated with the bending N-H bond vibrations. This could be an indication of interaction between the carboxylic acid group of the ibuprofen molecule and the dimethylaminoethyl group of the EUDRAGIT® E PO. Schematic representation of complex formation is presented in Figure 4.8.

Figure 4.8: FTIR spectra of Ibuprofen-EUDRAGIT® E PO samples (---) Ibuprofen, (—), Eudragit® E PO, (—) Physical Mixture, and (−−) Melt Extrudates with 50% Ibuprofen
The XRD scans are essential to determine the physical state of the drug. In this study XRD analysis was performed to verify the results obtained from DSC. It can be seen in Figure 4.10 that the crystalline ibuprofen shows distinctive peaks at 6, 16.5, 18, 20 and 22.5 degrees owing to the specific arrangement of the atoms. Melt extrudates with 30, 50 and 70% ibuprofen have been analyzed to detect the presence of crystalline phase. Crystalline phase could not be detected in the extrudates with 30 and 50% ibuprofen. However, the melt extruded formulation with 70% ibuprofen shows the same characteristic peaks as that of the pure ibuprofen indicating presence of crystalline
phase. These findings further support the results of the thermal and microscopic assessment.

**Figure 4.10:** XRPD scans of Ibuprofen and Eudragit® E PO melt extrudates

**Increase in apparent solubility**

Ibuprofen has a pH dependent solubility with a pKa=4.85 and is poorly soluble at acidic gastric pH. For an immediate release formulation it is advantageous if the drug dissolution process is triggered as soon as the formulation is administered orally so that the drug is ready to be absorbed upon entering the intestine(91, 99). Solubility studies have shown that the saturation solubility of ibuprofen at pH 1.2 increases with increase
in the concentration of the cationic polymer (Figure 4.11). This increase could be due to the molecular interactions between the carboxylic group of ibuprofen and dimethylaminoethyl group of the EUDRAGIT® E PO. This was further tested by measuring the change in pH of the solubility measurement samples with the addition of the cationic polymer. The pH of the saturated solution of ibuprofen with the maximum concentration of (500mg in 10 ml) of Eudragit® E PO tested was 4.5 whereas that of a control sample with same amount of Eudragit® E PO was about 6.6. The saturation solubilities obtained at pH 4.5 and 6.8 were 0.17 and 2.19 mg/mL respectively. This suggests that the increase in solubility was not due to increase in the pH level.

![Saturation solubility of Ibuprofen Vs Eudragit® E PO amount](image)

**Figure 4.11** Saturation solubility of Ibuprofen Vs Eudragit® E PO amount
Figure 4.12 Saturation solubility of Ibuprofen

Figure 4.13: Melt Extruded samples (70% Ibuprofen loading) at (a) 30 days (b) 365 days

**Stability**

Melt extruded samples stored at room temperature were observed under polarized light for a period of one year. Samples with 40 and 55% ibuprofen show no signs of recrystallization and were stable at room temperature over the study period. Ibuprofen
begins to recrystallize from the melt extruded samples with 70% within a week of manufacturing. Figure 4.13 shows microscopic pictures of ibuprofen crystals as seen under a polarized light microscope captured at 30 and 365 days. The nucleation process started in a week after manufacturing and the crystals were observed to grow in size with aging.

Conclusion

In this study, solid solutions of ibuprofen and Eudragit® E PO are characterized using thermal and microscopic tools. Room temperature miscibility studies provide visible evidence of strong affinity between the two components. The strong mutual affinity is an additive effect attributed to two components viz. the presence of ionic groups together with low \( T_g \) of the mixture. Solid solutions prepared by melt extrusion with ibuprofen loading 40 and 55% are physically stable at the end of 365 days whereas formulations with a drug loading of 70% tend to recrystallize. Stable solid dispersions with high drug loading can be achieved by selecting excipients with favorable functional groups. The saturation solubility of ibuprofen in acidic media increased up to 12 fold which could be attributed to formation of ionic interactions. This is translated in \textit{in vitro} dissolution studies where the ibuprofen release is increased 3 fold as seen in Chapter 3 of this document on page 29. This is advantageous for immediate release formulations since the dissolution process starts as soon as the drug is orally administered.
CHAPTER 5
A QUALITY BY DESIGN (QBD) STUDY ON PREPARATION OF SOLID DISPERSIONS USING MELT EXTRUSION PROCESS
Introduction

Over the past two decades Hot Melt Extrusion (HME) has steadily gained interest in the pharmaceutical industry owing to the versatile nature of this process(14). Depending on the type and combination of excipient selected, HME offers the ability to develop formulations with wide applications ranging from immediate release(29), taste masking(31), controlled release(30), enteric release(32), pulsatile release as well as sterile biological inserts(33). However, solubility enhancement via formation of amorphous solid dispersions (SD) remains to be the most widely explored application for HME as 40 to 70 % of New Chemical Entities (NCEs) are poorly water soluble(3). During SD formation, the drug molecule is entrapped in its most soluble high-energy amorphous form by entrapment within the polymeric matrix(71).

HME offers the ability to combine several individual unit steps such as feeding, melt-mixing along with numerous downstream processing options like pelletization, granules, milled particles, films and custom shapes using injection molding in a continuous sequential manner. In spite of the high interest and extensive research only a handful of products available on the market are prepared using this technology. This could be due to (i) perceived high startup costs (ii) challenges involved in selection of appropriate excipients and subsequent prediction of long term stability, as well as (iii) insufficient understanding of the critical formulation and process parameters and their implications on scale up.

Quality by Design (QbD) is strategic product development approach initiated by the Food and Drug Administration (FDA) that considers both, formulation and process
related factors that affect the quality attributes of the final product(57). 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. 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 initially could be cumbersome it will eventually mean less paperwork and resources when a change needs to be introduced in the manufacturing process. It will also reduce overall waste produced during manufacturing as well as allow efficient globalization for companies with manufacturing sites across the world(58),(59).

The current QbD methodology involves four major stages: 1. Establishing Quality Target Product Profiles (QTPP) and Critical Quality Attributes (CQAs); 2. Risk Assessment; 3. DoE-based screening and hence establishing a Design Space (DS); and 4. Control Strategy and continuous improvement(57). This pharmaceutical QbD approach has been applied to various manufacturing processes such as tablet compression,(59) accelerated stability testing,(100) solubility enhancement and dissolution,(101) liposomes,(66) spray drying,(62, 63) fluid bed granulation(60) and gel manufacturing(69). However this current study focuses on application of QbD
framework to a pharmaceutical melt extrusion process, which to date has not been reported.

This present body of work is a case study for developing taste masked granules of ibuprofen using Eudragit® E PO using a step-by-step QbD approach. Eudragit® E PO is a cationic polymer that is insoluble in water above pH 5.5. This property makes it an excellent excipient for taste masking of bitter drugs as it is insoluble at the normal pH of human saliva, which ranges from 6.5 to 7.4. Ibuprofen is a non-steroidal anti-inflammatory agent belonging to BCS (Biological Classification System) Class II (poorly soluble and highly permeable)(102). It is an anionic drug with pH dependent solubility and readily ionizes at the pH of human saliva (6.5 to 7.4) making it an excellent model drug to test the taste masking efficiency of a formulation.

A thorough risk analysis study using both qualitative and quantitative methods for preparation of granules using melt extrusion was performed. Fishbone diagram and Failure Mode Effect Analysis (FMEA) were the tools used for qualitative risk analysis. For further quantitative investigation a 6 factor 2 level Plackett-Burman screening design was formulated to examine the main effects. In order to study potential interactions four factors within the Plackett-Burman study were selected for an expanded Response Surface Design (RSD). Utilizing these data, a DS for preparation of granules using melt extrusion was developed. The steps involved in this QbD study are summarized in Figure 5.1.
Figure 5.1 QbD steps applied to the melt extrusion process

Materials

Ibuprofen was generously donated by Albemarle Corporation (Orangeburg, South Carolina). Eudragit® E PO was obtained from Evonik Corporation (Piscataway, NJ). PVP 25 was purchased from Sigma-Aldrich (St. Louis, MO). HPLC grade acetonitrile, chloroacetic acid, ammonium hydroxide, potassium phosphate and sodium hydroxide were purchased from VWR chemical supplies (Radnor, PA).
Methods:

Risk Assessment (RA)

Risk assessment facilitates strategic short listing and ranking of select significant parameters from hundreds of potentially critical parameters. The RA study began with devising and enlisting all of the factors that contribute to the quality of the final product in the form of a cause and effect or an Ishikawa diagram.(70) Based on the parameters highlighted by the Ishikawa diagram, a table for Failure Mode Effect Analysis (FMEA) was developed outlining all of the process steps from powder blending to extrusion. A team of 5 multidisciplinary experts graded each failure mode on a scale of 1 to 5 with regards to the severity (S), occurrence (O) and detectability (D) of that particular event. Finally a product of all three values (S*O*D) was computed to yield the Risk Priority Number (RPN).

Experimental Design

Plackett-Burman design has been shown to be efficient for studying the main effects between the critical factors with minimum experimental runs(103). Based on the risk assessment results, the shortlisted factors were further analyzed using a Plackett-Burman screening design consisting of 6 factors studied at two levels along with 2 center points resulting in a total of 14 extrusion experiments. The high and low level values of these factors were based on available literature (31, 104) and prior extrusion experience with Eudragit® E PO (data not shown).
Based on the results of the Plackett-Burman Design, four factors (Level of Drug: X1, Extrusion temperature: X3, Level of processing aid: X6 and level of Eudragit® E PO: X7) which had the highest impact on the CQAs, were selected for a custom designed Response Surface Design (RSM) with 16 additional runs. The RSM design allowed investigation of potential interactions between the independent variables. A list of the factors studied (independent variables) along with their levels and the measured responses (dependent variables) is presented in Table 5.1. The level of each study variable in the experimental design can be seen in Table 5.2.

**Statistical Analysis**

Plackett-Burman design, augmentation of design to a RSM and all statistical calculations were performed using JMP® Version 9 (SAS Institute Inc, Cary, NC, USA) and Modde 10.0 (Design of Experiment software by Umetrix). Responses were analyzed using analysis of variance (ANOVA) and Partial Least Square (PLS).
Table 5.1: Experimental domain in Plackett-Burman Design

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Level</th>
<th>High Level</th>
</tr>
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<tbody>
<tr>
<td>X1 Level of Drug (%w/w)</td>
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<td>70</td>
</tr>
<tr>
<td>X2 Screw Speed (rpm)</td>
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<td>150</td>
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<tr>
<td>X3 Extrusion temperature (°C)</td>
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<td>140</td>
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<tr>
<td>X4 Feed Rate (cc/min)</td>
<td>4</td>
<td>6</td>
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<tr>
<td>X5 Premixing</td>
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<td>10</td>
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<td>X6 Processing Aid (%w/w)</td>
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<td>X7 Level of Eudragit® E PO</td>
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<td>70</td>
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<td>Y1 Torque</td>
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<td>Y3 Assay (%w/w)</td>
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<td>Y4 Drug Released in 0.5 hr</td>
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<tr>
<td>Y5 Phase Change</td>
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<td></td>
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</tbody>
</table>
Table 5.2: Experimental Design (PB-1 to PB-14: Plackett-Burman design, O-15 to O-30: Optimization design)

<table>
<thead>
<tr>
<th>Batch</th>
<th>Ibuprofen (%w/w)</th>
<th>Screw Speed (rpm)</th>
<th>Extrusion Temperature (°C)</th>
<th>Feed Rate (cc/min)</th>
<th>Mixing</th>
<th>Processing Aid (%w/w)</th>
<th>Eudragit® E PO (%w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB-1</td>
<td>0.3</td>
<td>75</td>
<td>100</td>
<td>6</td>
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</tr>
<tr>
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<td>120</td>
<td>4</td>
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<tr>
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</tr>
<tr>
<td>PB-4</td>
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<td>100</td>
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</tr>
<tr>
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</tr>
<tr>
<td>PB-6</td>
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<td>120</td>
<td>6</td>
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<td>0.1</td>
<td>0.6</td>
</tr>
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<td>PB-7</td>
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<td>100</td>
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<td>0.1</td>
<td>0.4</td>
</tr>
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<td>PB-8</td>
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<td>100</td>
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<td>0</td>
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<td>0.1</td>
<td>0.4</td>
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<td>PB-10</td>
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<tr>
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<td>PB-13</td>
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<td>5</td>
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<td>0.05</td>
<td>0.55</td>
</tr>
<tr>
<td>PB14</td>
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<td>110</td>
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<td>0.05</td>
<td>0.55</td>
</tr>
<tr>
<td>O-15</td>
<td>0.3</td>
<td>112.5</td>
<td>80</td>
<td>5</td>
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<td>0</td>
<td>0.7</td>
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<tr>
<td>O-16</td>
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<td>140</td>
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</tr>
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<td>O-17</td>
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</tr>
<tr>
<td>O-18</td>
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<td>110</td>
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<td>0.1</td>
</tr>
<tr>
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<td>140</td>
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<td>140</td>
<td>5</td>
<td>0</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table Continued from previous page
Melt Extrusion

Dry powder ingredients were sieved through a USP# 35 sieve to remove agglomerates and accurately weighed in a plastic bottle. The powder blends were subjected to either mixing for 10 min in a Turbula T2F shaker mixer (Glen Mills Inc. Clifton, NJ) or hand mixed. The blends were then extruded using a 16 mm co-rotating twin screw extruder (Leistritz Corporation, Allendale, NJ) equipped with a bottom feeding assembly and fitted with a 4mm round die. The heating zone closest to the feeding zone was maintained at 70°C throughout the course of this study whereas heating zones 2, 3 and 4 were maintained at a temperature stated in the study design. The screw speed (rpm), feed rate (cc/min) and the concentration of anti-tacking agent were set up according to the study design as shown in Table 5.2. The prepared extrudates were stored in airtight containers until further processing.

<table>
<thead>
<tr>
<th>O-21</th>
<th>0.7</th>
<th>112.5</th>
<th>80</th>
<th>5</th>
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<th>0.1</th>
<th>0.2</th>
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</thead>
<tbody>
<tr>
<td>O-22</td>
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<td>110</td>
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<td>0</td>
<td>0.3</td>
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<tr>
<td>O-23</td>
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<td>110</td>
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</tr>
<tr>
<td>O-24</td>
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<td>110</td>
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<td>0</td>
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<tr>
<td>O-25</td>
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<td>0.1</td>
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<tr>
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<td>110</td>
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<tr>
<td>O-27</td>
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<td>110</td>
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<tr>
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<tr>
<td>O-29</td>
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<td>5</td>
<td>0</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>O-30</td>
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<td>75</td>
<td>110</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Extrudate Characterization

Ibuprofen Content

All melt extruded samples were assayed for ibuprofen content using an Agilent 1100 series HPLC system (Agilent Technologies Inc, Santa Clara, CA, USA) attached to a variable wavelength detector at 254 nm along with a C\textsubscript{18} column (Phenomenex Luna 5µ). A mobile phase consisting of 1% chloroacetic acid buffer solution adjusted to pH 3.0 with ammonium hydroxide and acetonitrile in the ratio 20:80 was used at a flow rate of 0.8 mL/min. All of the standards and assay samples were prepared in methanol.

Dissolution

Milled extrudate samples equivalent to 200mg of ibuprofen was filled in a size 00 clear gelatin capsule. Dissolution on the filled capsules was performed (n=3) using USP apparatus 2 with a Varian VK 750 D dissolution apparatus at 37ºC at a paddle speed of 50 rpm in biphasic media consisting of pH 1.2 for the initial 60 min. This method was followed by utilizing pH 6.8 (simulation of GI tract conditions) until complete ibuprofen release was attained. Dissolution samples were filtered and analyzed using the above-described HPLC method. A control sample, where 200mg of pure drug was placed in a size 00 clear capsule was used for comparison.

Measurement of T\textsubscript{g}

Differential scanning calorimetric analysis was performed on the milled samples using a Pyris 6 DSC (PerkinElmer, Waltham, MI). 8–10 mg of the milled extrudate was weighed,
crimped in an aluminum pan and subjected to a heat-cool-heat cycle. The first heating eliminated the thermal history and moisture whereas the second heating facilitated in the determination of \( T_g \). Samples were heated from -30 to 120°C at the rate of 20°C/min, cooled to -30 °C at 40°C/min and reheated to 120°C at 20°C/min under nitrogen purge of 20 mL/min. The \( T_g \) was calculated from the resulting thermograms using the Pyris 6 software.

**Results and Discussion**

The document Q8 published by the International Conference on Harmonization (ICH) illustrates and defines the steps involved in a pharmaceutical QbD process(57). The steps followed in this study are outlined in

The first step for a Quality by Design study is to establish a vision for the end product by defining the Quality Target Product Profile (QTPP) for the final product. (57, 58) QTPP is a grouping of several chemical, physical, biological, microbiological or esthetic attributes of the product that are essential to ensure the quality and performance of the drug product. Table 5.3 lists the established QTPP for the melt extrudates manufactured in this study, which include the ibuprofen content, in vitro dissolution and physical appearance. These parameters provided as a starting point for establishing the ranges of CQAs that serve as a guide throughout the product development phase. The focus in this QbD study was to understand the relationship between the experimental parameters and formulation composition (independent variables) with the quality attributes (responses) that are involved in the melt extrusion process.
Table 5.3: Quality Target Product Profile

<table>
<thead>
<tr>
<th>Product attribute</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>&gt; 95% w/w</td>
</tr>
<tr>
<td>Dissolution at pH 1.2</td>
<td>&gt; 60% ibuprofen released in 60 minutes</td>
</tr>
<tr>
<td>Dissolution at pH 6.8</td>
<td>100% of ibuprofen released within 30 minutes</td>
</tr>
<tr>
<td>Physical appearance</td>
<td>Clear, non-tacky</td>
</tr>
</tbody>
</table>

**Risk Assessment**

From amongst hundreds of factors that potentially affect the melt extrusion product development, narrowing down to a few most critical parameters for experimental evaluation can be very challenging. A systematic risk assessment study not only outlines several factors affecting the process but also prioritizes them based on the severity of their impact on the product. In this work, a two-stage risk assessment study is conducted to strategically narrow down the most influential parameters. In the first step a cause and effect (or Ishikawa diagram) has been utilized to outline a multitude of factors contributing from categories such as machine, manpower, materials, methods,
measurement and environment (70). The Ishikawa diagram outlining several formulation and process parameters affecting the melt extrusion process is illustrated in Figure 5.2.

All of the resulting factors were then treated as failure modes in a FMEA table, which lists the severity, occurrence and predictability for each factor and prioritizes all of the risks in the form of a risk priority number (RPN). FMEA is a risk assessment tool that focuses on minimizing the potential failures before they occur and assists in developing a step by step approach to reduce the future risk of failure by making appropriate changes to the process (105). Table 5.4 lists several failure modes with respect to the current study along with their effects, causes and controls. These failure modes were graded on a scale of 1 to 5 by five experts in this field of study. The final impact of a failure mode is decided based on its RPN score calculated as an average score from all five evaluations. Drug degradation, melt viscosity, tackiness, flow characteristics and drug recrystallization were the failure modes that received the highest RPN scores. These are process and formulation variables that can be tested within a specified range. These attributes were translated into measurable responses quantified as % Ibuprofen content, $T_g$ of the extrudate, in process torque and % ibuprofen released at 30 min. Extrudates were examined under a microscope to detect crystallization and qualitative phase change.
Figure 5.2: Ishikawa diagram for preparation of extruded particles
Table 5.4: Failure Mode Effect Analysis for Melt Extrusion Process

<table>
<thead>
<tr>
<th>Process step</th>
<th>Failure Mode</th>
<th>Failure effects</th>
<th>Causes of failure mode</th>
<th>Controls</th>
<th>S</th>
<th>O</th>
<th>D</th>
<th>RPN</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Drug polymer ratio</td>
<td>Compromised dissolution</td>
<td>Supersaturation</td>
<td>Optimization of drug-polymer ratio</td>
<td>5</td>
<td>3.3</td>
<td>1.3</td>
<td>23.3</td>
<td>Optimization of drug-polymer ratio</td>
</tr>
<tr>
<td></td>
<td>Phase Change</td>
<td>Recrystallization</td>
<td>Supersaturation</td>
<td>Optimization of drug-polymer ratio</td>
<td>4.6</td>
<td>3</td>
<td>1.6</td>
<td>23</td>
<td>Optimization of drug-polymer ratio</td>
</tr>
<tr>
<td></td>
<td>Chemical Interactions</td>
<td>Tackniess</td>
<td>Lowering of Tg</td>
<td>Lower drug loading, revise formulation</td>
<td>4.3</td>
<td>3</td>
<td>1.3</td>
<td>16</td>
<td>Lower drug loading, revise formulation</td>
</tr>
<tr>
<td>Blending</td>
<td>Content uniformity</td>
<td>Uneven distribution of drug in the drug-polymer mixture</td>
<td>Inappropriate blending time</td>
<td>NIR/HPLC</td>
<td>2</td>
<td>3</td>
<td>3.8</td>
<td>28.3</td>
<td>Optimize blending conditions</td>
</tr>
<tr>
<td></td>
<td>Flow Characteristics</td>
<td>Improper flow, feeder jam</td>
<td>Inadequate understanding of particle properties</td>
<td>Particle Size, Angle of Repose, bulk density, tap density, Addition of glidant</td>
<td>3.8</td>
<td>3</td>
<td>4.8</td>
<td>53.3</td>
<td>Optimize glidant concentration and feed rate</td>
</tr>
<tr>
<td>Feeding</td>
<td>Liquid Injection</td>
<td>Non-uniform feeding</td>
<td>Pump malfunction</td>
<td>Flow rate optimization</td>
<td>5</td>
<td>1.5</td>
<td>3.5</td>
<td>25</td>
<td>Calibrate pump, operate within calibrated range</td>
</tr>
<tr>
<td></td>
<td>Feeder Jam</td>
<td>Inefficient feeder functioning, Bridging or Arching</td>
<td>Poor flowing material</td>
<td>Feeder speed and conveying screw optimization</td>
<td>3.8</td>
<td>2</td>
<td>3.5</td>
<td>33</td>
<td>Add glidant, change feeder screws</td>
</tr>
<tr>
<td>Extrusion</td>
<td>Drug Degradation</td>
<td>Polymer Degradation</td>
<td>High melt viscosity</td>
<td>Low melt viscosity</td>
<td>Extrudate Content Uniformity</td>
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<tr>
<td>----------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
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<td>-----------------------------</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug content loss due to degradation, low assay content</td>
<td>Discoloration/charring, drug content loss due to impurities</td>
<td>Extruder shutdown due to overtorque</td>
<td>Material is very liquid, too sticky for conveyor belt cooling</td>
<td>Uneven mixing of drug in the extrusion batch</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Too high temperature, Drug/Polymer interactions</td>
<td>Too high temperature, Drug/Polymer interactions, Too high shear forces</td>
<td>Temperature lower than necessary, low plasticizer</td>
<td>High extrusion temperature</td>
<td>Screw configuration, Length of the cylinder</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>lower extrusion temperature and monitor color change</td>
<td>lower extrusion temperature and monitor color change</td>
<td>Monitor torque and viscosity values</td>
<td>Lower extrusion temperature</td>
<td>PAT tools (NIR/RAMAN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 3 4.3 62.5 Reduce extrusion temperature</td>
<td>5 3 2.3 33.8 Reduce extrusion temperature</td>
<td>4.8 3 4.3 60.5 Increase temperature/Lower screw speed, increase plasticizer concentration</td>
<td>Decrease temperature/Decrease plasticizer concentration</td>
<td>4.3 3 3.3 41.5 Revise screw design</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process</td>
<td>Issue Description</td>
<td>Causes</td>
<td>Methods</td>
<td>PAT Tools</td>
<td>Adjustments</td>
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<td></td>
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<td>-------------------</td>
<td>-------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystallization of API</td>
<td>Dissolution characteristics, visual appearance, Physical Stability, Cooling Rate</td>
<td>High drug load, extrusion temperature, residence time, polymer</td>
<td>Physical Stability, PAT tools (RAMAN)</td>
<td>4.3 3.5 3 36.5</td>
<td>Revise formulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High back pressure</td>
<td>Blocking of the die, instrument shutdown</td>
<td>die diameter, die temperature</td>
<td>PAT tools: (Pressure sensor)</td>
<td>3.3 1.8 4.3 24</td>
<td>Reduce screw speed, increase die diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooling/Conveying</td>
<td>Uneven diameter of extrudate</td>
<td>Feeder speed, conveyor belt speed</td>
<td>Belt speed</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milling</td>
<td>Uneven thickness, a strand that is not continuous</td>
<td>Blade speed, sieve number</td>
<td>Optimize speed and sieve size</td>
<td>1.5 3.3 3.8 20.5</td>
<td>Optimize speed and sieve size</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Storage conditions</td>
<td>Tackiness</td>
<td>Gravules stick to each other during storage forming lumps</td>
<td>Low glass transition temperature of the drug</td>
<td>Store at a lower temperature, add anti-tacking agent</td>
<td>3.8 3 4.5 52.3</td>
<td>Increase concentration of antitackling agent, Monitor storage conditions, Store in a refrigeration</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Recrystallization</td>
<td>Recrystallization affecting the drug dissolution</td>
<td>Moisture and storage temperature</td>
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<td>5 3.5 3.5 60</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Statistical Design and Analysis

Table 5.5 shows the response values for all the experiments. The results of the screening study showed that the most critical factors were the X1 (ibuprofen content %w/w) and X6 (concentration of processing aid %w/w). These factors along with one additional factor X3 (extrusion temperature °C) were selected for an optimization study using a RSM design. The levels of drug loading and extrusion temperature were broadened to increase the resolution of the design in the optimization study as shown in Table 5.2. The optimization study design enabled identification of interactions within the factors. The results of the RSM design were analyzed using analysis of variance and the effects of each factor are discussed separately.
Table 5.5: Response values for the extruded batches

<table>
<thead>
<tr>
<th>Batch</th>
<th>Torque (Gm): Y1</th>
<th>Glass Transition (°C): Y2</th>
<th>Assay (%w/w): Y3</th>
<th>Dissolution at 30 min (%w/w): Y4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB-1</td>
<td>1681.04</td>
<td>22</td>
<td>95.17</td>
<td>71.77</td>
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<td>1581.79</td>
<td>16.95</td>
<td>97.54</td>
<td>72.78</td>
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<tr>
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<td>1374</td>
<td>14.28</td>
<td>92.32</td>
<td>72.87</td>
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<tr>
<td>PB-4</td>
<td>1341.03</td>
<td>22.16</td>
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<td>73.76</td>
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<tr>
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<td>1066.72</td>
<td>15.46</td>
<td>95.44</td>
<td>72.77</td>
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<tr>
<td>PB-6</td>
<td>1285.77</td>
<td>22.35</td>
<td>99.03</td>
<td>71.83</td>
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<td>70.37</td>
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<td>94.03</td>
<td>73.2</td>
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<tr>
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<td>8.44</td>
<td>98.87</td>
<td>69.98</td>
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<td>2012.14</td>
<td>15.87</td>
<td>96.17</td>
<td>73.42</td>
</tr>
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</table>

**Effect of Ibuprofen Loading (X1)**

Unlike traditional solid dosage forms such as tablets and capsules, which mostly involve physical mixing and dry processing, melt extrusion is a process where the drug molecule is in intimate contact with the excipients and contributes significantly to the physico-chemical characteristics of the formulation. For this reason, strategies required in formulation development using melt extrusion are unique to a given active ingredient. Level of ibuprofen has a significant effect on three of the responses studied namely, torque, $T_g$ and dissolution.

Ibuprofen is a low melting compound with a glass transition temperature below room temperature (-45°C).

(106) Since ibuprofen exists in its amorphous form within the melt...
extrudates, the overall $T_g$ of the extruded samples is significantly reduced. The $T_g$ lowering effect was found to be a function of ibuprofen concentration in the formulation. It has been previously proven that ibuprofen has a plasticizing effect during melt processing.(87) As seen in Figure 5.3, ibuprofen content has a negative effect on the in-process torque indicating that the two variables share an inverse relationship. This makes processing at lower temperatures possible thus preventing the possibility of adversely affecting the process due to excess torque generation. The $T_g$ lowering effect of ibuprofen can be seen in Figure 5.4 where the lowering of $T_g$ with increased ibuprofen concentration is evident.

Eudragit® E PO is a cationic polymer that has been previously shown to form ionic interactions with ionic drugs(94). Ibuprofen is an anionic drug that readily forms ionic interactions with the cationic polymer Eudragit® E PO thus improving Ibuprofen's solubility in pH 1.2 media. Solubility enhancement also occurs when the API is maintained in its amorphous state. There is a significant increase in ibuprofen dissolution in comparison to pure ibuprofen in the control sample as seen in Figure 5.6. However batches that contain 70% ibuprofen failed the dissolution tests at pH 1.2 due to a phase change of ibuprofen from amorphous to crystalline. All samples released 100% of ibuprofen within 30 minutes of pH change, however the formulations in which the drug was present in the amorphous form dissolved faster when pH was changed as the drug was molecularly dispersed in the media. In summary, ibuprofen loading was a critical parameter having a significant impact on the torque, $T_g$ as well as the dissolution behavior.
Screw Speed(X2) and Feed Rate(X4)

Screw speed and feed rate are interdependent parameters in a melt extrusion process and both can directly influence the torque generation. When extrusion is carried out at higher screw speeds with lower feed rates there is not enough material to fill the screws resulting in a starve fed state. In this type of feeding the material overall spends more time in the screws resulting in intensive mixing of the components. Flood feeding takes place when the feed rate overcompensates the rate at which material is conveyed by the screws resulting in excess material in the barrel. A flood fed state also has the risk of higher torque values (34).

In the current study, the screw speed shows a positive effect on the torque values whereas the feed rate did not significantly affect the processing at the levels investigated in this study design. This can be seen in a Pareto plot for the in process torque values (Figure 5.3). It is also interesting to see a relationship pattern between the T_g values of the formulation with the in process torque encountered during manufacturing.

Extrusion temperature (X3)

The extrusion temperatures used in this study design appear to be within the degradation limits of the model drug ibuprofen. Although the material can be processed as low as 80°C, extrusion temperature of 100°C was found to be most suitable for all of the formulations. At temperatures lower than 100°C, the melt exhibits a higher viscosity and torque making processing more difficult. Also, it is essential that the drug and the
carrier polymer both are in a completely molten state in order to ensure homogenous mixing within the extruder barrel. At extrusion temperatures of 140°C, formulations containing higher ibuprofen loading became very fluid thus making it difficult to contain. Therefore lower extrusion temperatures in the range of 100°C were found to be optimum for smooth operation of the extrusion process. Temperature did not have a significant impact (p=0.05) on any CQAs studied in this design. However, higher extrusion temperatures did have a negative impact on the assay values as seen in Figure 5.5.

**Premixing (X5)**

Besides the prior mixing of the physical mixtures, sufficient mixing takes place inside the extruder barrel due to the shear from the rotating screws. Out of the four total heating zones, mixing elements were positioned between third and fourth zone for this study. This ensured that the material is molten when it reaches the mixing zone. Although mixing of drug and polymer before feeding to the melt extruder is necessary to avoid uneven drug distribution, the method of premixing does not appear to be the most critical parameter affecting the content uniformity. The factor for type of mixing (X5) was eliminated in the optimization design since based on the screening design it was shown to not have direct effect from the type of mixing on the CQAs.

**Processing Aid(X6)**

Due to the low T_g of ibuprofen, batches with a higher ratio of ibuprofen make the melt very fluid, sticky and difficult to handle during processing. Two strategies were
employed to solve this problem viz. addition of processing aid and extrusion at lower
temperatures. PVP 25 was tested as an anti-tacking agent and incorporated within the
study design at 0 and 20%w/w for low and high levels. To test the anti-tacking effect $T_g$
was measured for the extruded formulations using a DSC. Although the addition of
processing aid has a positive effect ($p=0.0407$) on the $T_g$ of formulations (Figure 5.4),
this effect does not appear to tackiness of the formulation at higher drug loading
indicating that PVP 25 did not serve as an efficient anti-tacking agent. Moreover, PVP
25 failed to dissolve completely in formulations containing lower ibuprofen
conzentations making the extruded matrix visibly opaque. Physical examination further
supported the DSC results and it was observed that addition of processing aid was not
sufficient to reduce the stickiness of the melt extrudates.

![Torque Graph](image)

**Figure 5.3:** Sorted parameter estimates showing effect of individual variables on the in
process torque
Figure 5.4: Sorted parameter estimates showing the effect of individual variables on the glass transition (Y2)

Figure 5.5: Sorted parameter estimates showing the effect of individual variables on the Assay
**Figure 5.6:** Sorted parameter estimates showing the effect of individual variables on the% ibuprofen dissolved at 30 min

**Figure 5.7:** *In vitro* release from ibuprofen extrudates
Development of Design Space

A design space describes the relationship between the independent (X) variables and the dependent (Y) variables graphically (57) and outlines the ranges of input variables within which the CQAs remain unaffected, thus maintaining consistent quality. A proposed design space for the current study is presented in Figure 5.8. In order to achieve and maintain the CQAs within the limits that are defined in the QTPP, the ideal drug loading in the range of 35 to 50% w/w and an extrusion temperature ranging between 90 to 125°C is recommended.

In summary, this QbD study assisted in understanding the relationship between the experimental factors and their impact on the quality attributes of the melt extrudates with minimum experimental runs. It was observed that changes to the formulation such as the concentration of the drug and processing aid have the maximum impact on the CQAs. Although changes to the process variables like screw speed, feed rate, type of mixing and extrusion temperature directly affect the processability, they did not significantly affect the CQAs in this study. Experimental limits for formulation and process parameters in order for optimum processing have thus been outlined in this study.
Conclusions

QbD is a step-by-step approach to understand the impact of process variables on the quality attributes of the final product and to decide operational experimental limits within which the product quality is maintained within the specifications. This study demonstrates a qualitative and quantitative risk assessment on factors influencing the pharmaceutical melt extrusion process with help of a model drug, ibuprofen.

Figure 5.8: Design space for preparation of granules using Melt Extrusion
Several formulation and process related factors affecting the quality of melt-extrudates were evaluated via a systematic risk assessment study. Out of numerous potentially critical parameters, 6 parameters were systematically shortlisted for an experimental screening study. Extrusion temperature, screw speed, drug load and level of processing aid were identified as critical parameters and their impact on critical quality attributes were measured in a Plackett Burman study design.

This design was further expanded to a RSM design to study potential interactions between the three critical variables (X1: drug loading, X3: Extrusion temperature and X6: amount of processing aid). Further, the effect of these parameters on the Ibuprofen content, T_g, in process torque and in vitro ibuprofen dissolution was analyzed using multiple linear regression and analysis of variance. The lowering of glass transition with the increase in the Ibuprofen content is evident from the data analysis. The addition of PVP 25 as an anti-tacking agent did not significantly increase the T_g of the mixture. The prepared extrudates were in line with the QTPP limits. The batches with lower levels of ibuprofen exhibited optimal physical attributes whereas the batches with higher drug load were slightly tacky due to lowered T_g values.

A design space plot outlining the ideal operating conditions within which the CQAs remain unchanged is presented. An average drug loading temperature of 100°C and drug loading levels between 30 and 50%w/w ibuprofen is recommended as optimum processing conditions to achieve the QTPP.
CHAPTER 6

EVALUATION OF DRUG RELEASE MECHANISM FROM SOLID DISPERSIONS OF KETOCONAZOLE
Introduction

Solid dispersion technology has been gaining interest as a solubility enhancement tool for several decades (20). The main mechanism for solubility enhancement via solid dispersion formulation is the physical entrapment of drug molecules to maintain the drug in its high energy amorphous state. Solid solution can be formed when a drug is molecularly dispersed (or solubilized) in the polymer matrix. Depending on the type of solid dispersion and the nature of the drug and the carrier materials used, the mechanism of the drug release can be different.

In spite of the intensive research on formulation development of solid dispersions not a lot is known about the mechanism of drug release from solid dispersions (39). Several theories have been proposed on modeling the drug release from matrix type formulations (22, 107). There are generally two types of release mechanisms (carrier controlled or drug controlled) observed in carrier based matrix formulations. In carrier controlled drug release the dissolution of the drug is independent of the properties of the drug molecule. However, at high drug loads there is a shift and the drug dominates the rate of dissolution.

Kollidon® VA 64 is a highly water soluble copolymer prepared from 6 parts of N-vinylpyrrolidone and 4 parts of Vinyl Acetate. The solubility parameter value for Kollidon® VA 64 is 21.1 which means it is likely to be miscible with a broad range of drug molecules with solubility parameters between 14.1 to 28.1. Lower hygroscopicity of the Kollidon® VA 64 is an advantage in developing dosage forms for water sensitive
drug molecules. It is primarily used as a hydrophilic matrix former and helps in solubilization of poorly water soluble API. Ketoconazole (KTZ) is a synthetic imidazole based antifungal drug primarily used to treat fungal infections of the skin, scalp and nails. It is a BCS class 2 compound with low aqueous solubility and is generally administered via the topical or oral route (108).

In this study, the drug release mechanism from melt extruded Kollidon® VA 64 and ketoconazole matrices is investigated. Physical mixtures of the drug and polymer were extruded using a Hot Melt Extruder (ThermoScientific, HAAKE Minilab II) at 140°C and 60 rpm screw speed. Swelling, erosion, *in vitro* release (pH 7.4 phosphate buffer and 0.1N HCl) and mechanical properties of the prepared extrudates were studied. The dissolution profiles were fitted using available dissolution models to determine the dominant mechanism for drug release. Solid state miscibility value of KTZ in Kollidon® VA 64 was measured using a hyper DSC method as described by Gramaglia et al. to identify the solubility limits (52).

**Figure 6.1:** Structure of Kollidon® VA 64
Figure 6.2: Structure of Ketoconazole (Melting point: 146°C)

Table 6.1: Properties of Kollidon® VA 64

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass Transition ($T_g$)</td>
<td>106.2°C</td>
</tr>
<tr>
<td>Degradation Temperature ($T_{deg}$)</td>
<td>290°C</td>
</tr>
<tr>
<td>Extrusion Temperature Range</td>
<td>90-140°C</td>
</tr>
</tbody>
</table>

Materials

Ketoconazole was purchased from Spectrum Chemicals, New Brunswick, NJ, USA. Kollidon® VA 64 was generously donated by BASF Corporation, Tarrytown, NY, USA.

HPLC grade solvents and buffers were purchased from Spectrum Chemicals, New Brunswick, NJ

Methods

Differential Scanning Calorimetry

Premixed drug-polymer physical mixtures were weighed (5-7 mg) and hermetically sealed into an aluminum sample pan. For determination of solid state solubility, previously weight and mixed binary mixtures were subjected to two heating cycles.
(Perkin Elmer, Diamond DSC). Cycle 1 involved heating at 20°C/min up to 130°C to allow the dissolution and saturation of the drug molecules in the polymer matrix. After cooling, the sample pan was heated rapidly to 280°C at 400°C/min (cycle 2). The sudden heating prevents equilibration and dissolution of crystalline drug into melted polymer thus measuring the enthalpy associated with the crystalline phase in the sample.

**Melt Extrusion**

Physical mixtures of the drug and polymer at three drug loading (20%, 30% and 40% w/w) were prepared by mixing accurately weight drug and polymer in a mortar and pestle for 10 min. The mixtures were extruded using a Hot Melt Extruder (ThermoScientific, HAAKE Minilab II) at a barrel temperature of 140°C and a screw speed of 60 rpm. Material was fed manually using a plunger mechanism. The molten drug polymer mixtures were extruded using a slit die and cut into equal sized pieces for further evaluation. The prepared extrudates were stored in air tight containers until further use. Assay was performed on the melt extruded samples by dissolving the extrudate in methanol and analysis using HPLC.

**HPLC Method**

Dissolution and assay samples were analyzed using a chromatographic system which consisted of a Waters 600 pump and a dual wavelength Waters 2487 UV detector together with a waters Symmetry C\textsubscript{18} column, 5 mm particle size (Waters, Milford, MA, U.S.A). The mobile phase consisted of 50% acetonitrile and 50% of 25 mM Potassium
dihydrogen phosphate buffer (pH adjusted to 4.5 with o-phosphoric acid) with a flow rate of 1 ml/min. Injection volume of 20 µl was used for both, the standard and the samples. The analysis was performed at 225nm.

**In Vitro Dissolution**

Dissolution behavior of the prepared extrudates was evaluated at pH1.2 and pH 7.4 for all prepared extrudates (n=3). The dissolution conditions were set up as indicated in Table 6.2. Samples were analyzed using the above mentioned HPLC method.

<table>
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<tr>
<th><strong>Parameter</strong></th>
<th><strong>Value</strong></th>
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<tr>
<td>Medium</td>
<td>pH 7.4 Phosphate Buffer, 0.1 N HCL</td>
</tr>
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<td>Apparatus</td>
<td>USP Method 5 (Paddle over disc)</td>
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<tr>
<td>Volume</td>
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<tr>
<td>Sampling Time</td>
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<td>Analytical Method</td>
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<td>Paddle Speed</td>
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<td>Temperature</td>
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**Swelling and Erosion**

Swelling and Erosion studies were performed in deionized water maintained at 37°C with a constant stirring at 100rpm. Samples were pre weighed (W₀), placed on a backing membrane and then attached to USP apparatus 5 (Figure 6.3) The rate of dissolution medium uptake was measured using the equilibrium weight method(109) and the erosion studies were performed based on the loss of dry weight method. A
A fresh sample was used for each time point. The films were subjected to the media with rotating paddles for the specified period of time then removed and weighed ($W_1$) after blotting excess solvent for swelling measurements. For measurement of erosion, the samples were further dried in oven (60°C) until a constant weight was obtained.

The percent swelling and erosion were calculated using the following formula

\[
\% \text{ Swelling} = 100 \times \left(\frac{W_1 - W_0}{W_0}\right) \tag{6.1}
\]

\[
\% \text{ Erosion} = 100 \times \left(\frac{W_0 - W_2}{W_0}\right) \tag{6.2}
\]

Where,

$W_0$ = Original weight of patch,

$W_1$ = Weight of patch after media uptake

$W_2$ = Weight of desiccated patch (stored for 24hrs at 60°C)

Figure 6.3: Schematic of USP Apparatus 5 used for swelling and erosion studies
Puncture Test

Puncture test was performed using a Texture Analyzer (Texture Technologies TA XT Plus with a test speed of 2mm/sec attached with a TA-8 probe. The compression force required for breaking a piece of extrudate was measured and the puncture strength was calculated based on the following formula

\[
Puncture \text{ Strength} = \frac{F}{A} \tag{6.3}
\]

Where,

F=Load required to puncture the film

A=Cross Sectional Area

Results and Discussion

Dissolution of Melt Extrudates

Melt extrudates of Kollidon® VA 64 with 20%, 30% and 40% ketoconazole were evaluated for drug content (Figure 6.4). All prepared extrudates have more than 95%w/w of ketoconazole and have a clear glassy appearance. The drug dissolution from solid dispersions may be described based on the Noyce-Whitney equation (Page 4)(22). The rate of dissolution of drug is controlled by either the solubility of the drug or the solubility of carrier in the testing media.
The pH dependent solubility of KTZ has been documented in the literature and it has been reported that KTZ rapidly precipitated out of the solution as the pH of the medium exceeded 5.5 (110). In this study, it was observed that the rate of dissolution of KTZ is faster at pH 1.2 where <80%w/w drug is released within in the first 15 minutes. The drug ratio has a direct relationship with the dissolution rate where the formulations containing 40% KTZ loading appears to show the fastest drug release. The drug release slowed in pH 7.4 with almost all the drug released in 45 minutes and the effect of drug ratio appears to have reversed when compared to acidic pH.
Figure 6.5: \textit{In vitro} dissolution of KTZ from HME Kollidon® VA 64 matrices in pH 1.2

Figure 6.6: \textit{In vitro} dissolution of KTZ from HME Kollidon® VA 64 matrices in pH 7.4
Swelling and erosion studies were performed to determine the dominant mechanism of drug release from the KTZ solid dispersions. According to Noyce-Whitney theory, the composition of the diffusion layer governs the mechanism of drug release. Since Kollidon® VA 64 is a highly water soluble polymer there appears to be very minimal swelling as seen in Figure 6.7. In fact, the loss in weight of the matrix is evident even during the swelling studies. Further, as seen in Figure 6.8, almost 80% of the matrix is dissolved (or eroded) in the first 10 minutes. The high erosion rate can be attributed to the fact that the primary release mechanism is carrier based and the high water solubility of the carrier polymer is responsible for fast matrix erosion.

![Figure 6.7: Swelling behavior of Ketoconazole melt extrudates](image)

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115
Figure 6.8: Swelling behavior of Ketoconazole melt extrudates

Table 6.3: Dissolution data modeling

<table>
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<th>Formulation</th>
<th>First Order</th>
<th>Korsemeyer-Peppas</th>
</tr>
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<tr>
<td>20% KTZ, pH 7.4</td>
<td>0.9865</td>
<td>0.8662</td>
</tr>
<tr>
<td>30% KTZ, pH 7.4</td>
<td>0.9966</td>
<td>0.8916</td>
</tr>
<tr>
<td>40% KTZ, pH 7.4</td>
<td>0.9687</td>
<td>0.8960</td>
</tr>
<tr>
<td>20% KTZ, 0.1NHCl</td>
<td>0.9406</td>
<td>0.9365</td>
</tr>
<tr>
<td>30% KTZ, 0.1NHCl</td>
<td>0.8619</td>
<td>0.9272</td>
</tr>
<tr>
<td>40% KTZ, 0.1N HCl</td>
<td>0.9749</td>
<td>0.8733</td>
</tr>
</tbody>
</table>

Drug release from solid dispersions may overall be classified in two mechanisms. The immediate release formulations generally follow an erosion based release pattern and
controlled release formulations exhibit predominantly diffusion based release from swelling of the carrier polymer. Since Higuchi first published the modeling of sustained drug release, several mathematical models are available to model dissolution data(111). In the current study, dissolution data was fitted into two mathematical models: First order and Korsemeyer-Peppas. As seen in Table 6.3, the first order model appears to be a better fit for the KTZ solid dispersions.

**Puncture Test**

The physical strength of the extrudate can have an impact on the drug release characteristics where slower drug release may be observed from tough, highly compact matrices. In the current study the mechanical strength of the solid dispersion matrix was evaluated using puncture test. A sample graph of the puncture test measurement is shown in Figure 6.9. The drug loading appears to have a direct effect on the mechanical strength of the prepared matrix. The force required to puncture a slab of prepared solid dispersions increased as the drug loading increased. The erosion pattern of these matrices also follows a similar trend as seen in Figure 6.8.
Figure 6.9: Puncture Test Graph (Force (Kg) Vs Time (Sec))

Table 6.4: Puncture Strength of Ketoconazole melt extrudates

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Puncture Strength (dyne/cm²) (X 10⁸)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Kollidon® VA 64</td>
<td>0.74 ±0.19</td>
</tr>
<tr>
<td>20% KTZ</td>
<td>1.07 ±0.46</td>
</tr>
<tr>
<td>30% KTZ</td>
<td>1.05 ±0.53</td>
</tr>
<tr>
<td>40% KTZ</td>
<td>1.1 ±0.11</td>
</tr>
</tbody>
</table>
**Solubility Determination using Rapid DSC**

Enthalpy is a function of crystallinity in a system and is directly proportional to the amount of crystalline drug present. A rapid DSC measures the enthalpy associated with the crystalline phase present in the sample without allowing any time for sample equilibration. This prevents additional drug being solubilized in the molten polymer during the DSC analysis. In this study, the highest concentration of drug that yields a zero enthalpy value is determined\(^\text{(112)}\). The predicted solid state solubility of KTZ in Kollidon\(^\text{®} \) VA 64 is 9.42\%w/w as calculated by the Hyper-DSC method (Figure 6.10). No melting event was observed for extrudate samples well above this limit. This can be attributed to the limitations of Hyper DSC as a method for solid state solubility determination. Although this method is fast and easy the solubility value may be underestimated. Another point to note is that the due to high molecular weight of the polymer chains the molecular movements in solid dispersion are very slow and can take days to achieve equilibrium.
Figure 6.10: Rapid-DSC thermograms (heating cycle 2) and respective enthalpy values of KTZ-Kollidon® VA 64 systems

Figure 6.11: Linearity plot of Enthalpy Vs Concentration of for Kollidon® VA 64-Ketoconazole systems
Conclusions

Whenever new formulations are being developed it is important to understand how they will behave in vivo. Understanding the type of release mechanism will facilitate in vivo prediction based on in vitro results. Melt extruded solid dispersions were successfully prepared and evaluated. Post extrusion drug content was more than 95% in all three formulations tested. Release of ibuprofen from the solid dispersions prepared with Kollidon® VA 64 was dependent on the physical state of the drug, solubility of polymer and the ratio of drug in the matrix. Increase in drug loading increased the physical strength of the extrudates. Swelling and Erosion studies revealed that matrix erosion is the dominant mechanism of matrix disintegration. Thus, the primary mechanism of drug release is postulated to be carrier controlled and the enhanced dissolution is attributed to the high water solubility of the carrier polymer. The dissolution data was fitted into available mathematical models.
CHAPTER 7

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CHAPTER 8

APPENDIX: RESIDENCE TIME DETERMINATION
Residence Time Determination

Melt extrusion is a thermal process in which the components are subjected to high amount of heat, pressure and agitation. It is important that the material in contact with these extreme conditions for the least amount of time possible to minimize the possibility of degradation. In order to achieve this, adequate knowledge about the process parameters is necessary. Residence time analysis enables the investigators to determine the exact amount of time the API will be exposed to the extreme conditions inside the extruder. Using this information, the investigator can make the necessary modifications to the process to achieve minimum degradation.

Residence time analysis is also beneficial when running small sized batches one after the other which is often necessary when handling small amount of API. In such situations, the investigator will know exactly at which point the sample collection should begin. This residence time analysis served as a guide for sample collection for melt extrusion batches prepared in this study.

Method

Residence time measurement studies on the Leistritz Nano 16 twin screw extruder were performed to determine the time spent by the drug inside the extruder barrel. Residence time measurements were performed using demo system of Ibuprofen and Eudragit® E PO at a screw speed of 150 rpm. Talc was fed in the beginning of the batch and acted as a marker. The time required for the first trace of talc to appear was noted. Samples collected at 2 minute intervals were analyzed for ibuprofen content by UV spectroscopy.
20-40 mg sample was dissolved in 10 ml of methanol and the resulting solution was analyzed at 266nm.

Results

Figure 8.1 shows the distribution of ibuprofen as a function of time at which it exits the die. The results of this study indicate that it requires 8 minutes for the drug concentration to reach 80%. Analysis of the placebo batch that was run following the drug loaded batch revealed that the placebo batch continues to carry the drug molecules trapped inside the extruder barrel. It takes three individual placebo batches in order to bring the drug concentration below the detection limits.

![Drug Distribution during melt extrusion](image)

**Figure 8.1: Drug distribution during melt extrusion (n=3)**
Conclusion

Residence time of the contents inside the extruder was determined and the distribution of the drug inside the extruder barrel was analyzed. Such measurements provide valuable information about the movement of material inside the extruder. This information can also help reduce drug loss from the processing.
VITA

Ketaki Patwardhan was born on 23rd September 1986 to Mrs Bhagyada Patwardhan and Dr. Bhushan Patwardhan. She completed her Bachelor of Pharmacy from Poona College of Pharmacy in Pune, India in 2008. She then joined the Department of Pharmaceutics at the University of Mississippi in August 2008 to pursue higher education. Ms. Patwardhan’s main area of focus has been to understand various aspects of solid dispersion formulation development specifically with the Hot Melt Extrusion process. During her PhD, she has completed over two years of internship at Evonik Corporation in Piscataway, NJ where she conducted research in an industrial setting.

During her time at University of Mississippi, she has been involved in the activities of University of Mississippi’s American Association of Pharmaceutical Scientists’ Student Chapter serving as a treasurer. She also was participated in the Graduate Student Council activities by serving as the Director of Technology. She is also a member of the honor society Rho-Chi. Additionally, Ms Patwardhan received a NIH Predoctoral Fellowship sponsored by the Center of Biomedical Research and Excellence from the University of Mississippi.