Melt Extrusion and Continuous Manufacturing of Pharmaceutical Materials

by

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Massachusetts Institute of Technology

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1. Abstract

Melt extrusion is an alternative processing technique that operates continuously, reduces the total number of unit operations, allows for incorporation of difficult-to-process drug substances, and has the potential to achieve tablets of better quality and consistency compared to traditional methods. Thus, our goal was to evaluate melt extrusion as a viable processing alternative and expand our scientific knowledge such that we gain predictive capabilities of tablet characteristics, i.e., quality by design. This new knowledge will aid future process design thereby helping to reduce time and costs associated with pharmaceutical solid dosage form production.

The residence time distribution for melt extrusion has been characterized using a single parameter model. When combined with assumed first-order reaction rate kinetics and an Arrhenius reaction rate constant, the model can accurately predict the amount of drug product lost to temperature driven degradation. The model prediction agreed well with experimentally determined fractional conversion.

The physical stability of amorphous Molecule A was characterized using enthalpy of relaxation measurements. Molecular level rearrangements are the source of physical instability for the fragile glass forming Molecule A. The instability can be modified by introducing a second component, which contributes to the overall enthalpy change.

Coating amorphous Molecule A tablets with a polyvinyl alcohol based coating material reduces moisture uptake during storage. The coating material preferentially uptakes water from the atmosphere, restricting moisture from entering the tablet core and causing premature dissolution or degradation.

The dissolution behavior of Molecule A tablets can be tailored with the addition of water soluble materials. Dissolution rate constants for Molecule A tablets have been calculated for different formulations and can be used as a resource when designing new solid dosage forms with desired dissolution characteristics.

A novel 100% Molecule A melt extrusion process has been created, reducing the number of overall unit operations and eliminating troublesome blending inconsistencies. An additional formulation that maintains the crystallinity of Molecule A by processing with polyethylene glycol below Molecule A’s melting temperature is physically and chemically stable and ready for implementation in a continuous production line. The mixing achieved within the extruder for this formulation is sufficient to eliminate a pre-mixing unit operation.

Erin Bell

Thesis Advisor: Professor Charles L. Cooney, Robert T. Haslam (1911) Professor
2. Acknowledgements and Dedication

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<table>
<thead>
<tr>
<th>3. Table of Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abstract:</td>
</tr>
<tr>
<td>2. Acknowledgements and Dedication:</td>
</tr>
<tr>
<td>3. Table of Contents:</td>
</tr>
<tr>
<td>4. Introduction:</td>
</tr>
<tr>
<td>4.1. Traditional Tablet Manufacturing:</td>
</tr>
<tr>
<td>4.1.1. Granulation and Compaction:</td>
</tr>
<tr>
<td>4.1.2. Direct Compaction:</td>
</tr>
<tr>
<td>4.1.3. New Active Pharmaceutical Ingredients:</td>
</tr>
<tr>
<td>4.2. Melt Processing:</td>
</tr>
<tr>
<td>4.2.1. Melt Processing Advantages:</td>
</tr>
<tr>
<td>4.2.2. Melt Processing Disadvantages:</td>
</tr>
<tr>
<td>4.2.3. Pharmaceutical Binders in Melt Processing:</td>
</tr>
<tr>
<td>4.3. Continuous versus Batch Manufacturing:</td>
</tr>
<tr>
<td>4.3.1. Batch Melt Processing:</td>
</tr>
<tr>
<td>4.3.2. Continuous Melt Processing (i.e., Melt-Extrusion):</td>
</tr>
<tr>
<td>4.4. Melt-Extrusion Uses and Advancements:</td>
</tr>
<tr>
<td>4.5. Extrudate Forming:</td>
</tr>
<tr>
<td>4.5.1. Direct Extrudate Cutting:</td>
</tr>
<tr>
<td>4.5.2. Calendaring:</td>
</tr>
<tr>
<td>4.5.3. Injection Molding:</td>
</tr>
<tr>
<td>4.5.3.1. Injection Molding Literature:</td>
</tr>
<tr>
<td>4.5.3.1.1. Full Scale:</td>
</tr>
<tr>
<td>4.5.3.1.2. Small Scale:</td>
</tr>
<tr>
<td>4.5.3.1.3. Co-extrusion:</td>
</tr>
</tbody>
</table>
4.6. Motivation and Aims ................................................................. 20
Bibliography ..................................................................................... 21

5. Materials and Methods ........................................................................ 26
  5.1. Materials .................................................................................... 26
    5.1.1. Active Pharmaceutical Ingredients ........................................... 26
    5.1.2. Excipients ............................................................................. 27
    5.1.3. Coatings ............................................................................... 31
    5.1.4. Tracer Materials .................................................................. 31
  5.2. Processing .................................................................................. 32
    5.2.1. Extrusion and Forming .......................................................... 32
    5.2.2. Coating ................................................................................. 33
  5.3. Analytical Techniques ................................................................... 34
  5.4. Bibliography ................................................................................. 38

  6.1. Introduction ................................................................................. 39
  6.2. Experimental ............................................................................... 40
  6.3. Theory ....................................................................................... 41
    6.3.1. Degradation Kinetics ............................................................. 41
    6.3.2. Residence Time Distribution .................................................. 42
  6.4. Results and Discussion ................................................................. 46
    6.4.1. Degradation Kinetics ............................................................. 46
    6.4.2. Residence Time Distribution .................................................. 48
  6.5. Conclusions ................................................................................ 52
  6.6. Bibliography ................................................................................. 53

7. Physical Stability of Melt Extruded Molecule A ........................................ 55
7.1. Enthalpy of Relaxation ........................................................................................................ 55
  7.1.1. Introduction .................................................................................................................. 55
  7.1.2. Results and Discussion .................................................................................................. 56
  7.1.3. Conclusions .................................................................................................................. 64
7.2. Tuning Enthalpy of Relaxation .......................................................................................... 65
  7.2.1. Conclusions .................................................................................................................. 71
7.3. Water Uptake and Moisture Barrier Coatings ................................................................. 71
  7.3.1. Water Uptake ................................................................................................................ 71
  7.3.2. Moisture Barrier Coatings .......................................................................................... 75
  7.3.3. Conclusions .................................................................................................................. 80
8. Dissolution .......................................................................................................................... 84
  8.1. Introduction ....................................................................................................................... 84
  8.2. Excipient Selection ............................................................................................................. 85
  8.3. Ratio of Excipient to Drug Substance ............................................................................... 88
  8.4. Coating Material ............................................................................................................... 89
  8.5. Conclusions and Implications .......................................................................................... 90
  8.6. Bibliography ..................................................................................................................... 91
9. Continuous Melt Extrusion of Molecule A ........................................................................... 92
  9.1. Introduction ....................................................................................................................... 92
  9.2. Pure Molecule A Extrusion ............................................................................................... 92
  9.3. 50-50 Molecule A-PEG 8000 Extrusion .......................................................................... 96
  9.4. Molding and Extrudate Forming ...................................................................................... 97
  9.5. Conclusions and Implications .......................................................................................... 98
10. Future Work and Recommendations ................................................................................ 100
11. Conclusions ........................................................................................................................ 102
4. Introduction

4.1. Traditional Tablet Manufacturing

In the pharmaceutical industry, two tablet production unit processes dominate. Granulation followed by compaction (with additional unit operations as needed) has been used for over 100 years while direct compaction is a relative newcomer.

4.1.1. Granulation and Compaction

The process that has been used for the manufacture of tablets for decades is still commonly used today [1]. In the most basic scenario, as a first step, the active pharmaceutical ingredient (API) and other tablet components (excipients) are combined with a solvent to form agglomerated particles [2]. This step, called granulation, is often used for several reasons, as listed below [2].

- Increase content uniformity
- Increase particle density
- Aid in powder flow
- Reduce dust generation
- Improve appearance

The granulated mixture is then formed into tablets by applying force using a tablet press [3]. This step is called compaction. These two unit operations, while conceptually straightforward, involve complex kinetics and depend heavily on component properties, both of which are topics of concern and current research. Thus, an iterative design approach is often required. Additional processing steps, including drying, blending, size reduction, etc., are often added to the granulation-compaction processing scheme as needed [3]. Any additional steps quickly add complexity to an already complex process. Overall, granulation-compaction is expensive and time intensive.

4.1.2. Direct Compaction

A more recent technology is direct compaction. In this case, the granulation step is by-passed and the powder is compacted directly [4]. This process cuts out variability introduced by granulation, decreases labor and equipment costs, decreases production time, and decreases energy requirements. Direct compaction requires specific excipients, sometimes called filler-binders. Common filler-binders include spray-dried lactose, microcrystalline cellulose, and Pharmatose DCL 40. In the 1990’s about 50% of tablets were produced by direct compaction.

While direct compaction has made great strides when compared to the granulation-compaction process, there are several important drawbacks to consider [4]:

- The number of filler-binders to choose from is limited [1]
- Filler-binders are not compatible with all APIs [1]
A large API to excipient ratio using an API with poor compactability and poor flow properties cannot be processed because direct compaction is based on filler-binder properties [4].

4.1.3. New Active Pharmaceutical Ingredients

In the pharmaceutical industry, high throughput screening methods are used for drug discovery. Increasingly, drug molecules are high in molecular weight, vastly functionalized, and hydrophobic [5, 6]. All of these characteristics are counteractive to the current processing techniques. A compatible and safe solvent is required for granulation and a well-matched filler-binder is required for direct compaction. It is estimated that approximately 60% of new drugs in the coming years will not be compatible with the traditional tablet manufacturing methods [7]. Also, high-load tablets (large API to excipient ratio) are becoming more commonly used, where a high drug load is typically 50 wt% or greater [8]. Therefore, a new method of processing must be actively investigated.

4.2. Melt Processing

A new processing method has stirred up the interest of many pharmaceutical companies: melt processing. While new to the pharmaceutical industry, melt processing is common to the plastics and food industries where polymers are prevalent e.g., polystyrene [9] and starch [10]. In these two industries, products of size and properties similar to what is desired during tablet production are created, leading to a natural interest [1]. The incorporation of melt-processing in the area of tablet processing, however, has been slow.

In general, the API and excipient(s) are added to a vessel and heated above the glass transition temperature ($T_g$) or melting temperature ($T_m$) of the mixture to create a melt. The melted material helps create a solid dispersion of API in the thermoplastic medium (i.e., the API dissolves in the molten carrier) [11], a molecular dispersion of API in the molten carrier (API is dispersed as discrete particles in the carrier), or a combination of a solid solution and molecular dispersion. If the API is poorly soluble, a solid solution and/or molecular dispersion increases bioavailability of the drug [12]. It is also possible that the API transforms from a crystalline form to an amorphous form. The amorphous state is less stable and higher in energy than the crystalline form leading to a better release when introduced to the patient. However, the amorphous state may be problematic because the higher energy state may lead to unwanted phase changes when the final tablet is transported or stored.

4.2.1. Melt Processing Advantages

There are various advantages of melt processing with regards to the process and the final product.

1. Melt processing is solvent free. Solvent removal alleviates important safety concerns associated with organic solvents and allows processing of water-sensitive APIs [1, 13].
2. Processing is achieved with a minimal number of unit operations.
3. The API is distributed evenly in the excipient matrix which aids the appropriate delivery in the patient.
4. The tablet size is often reduced because a higher drug load is obtainable [12].
5. Melt processing avoids problems associated with polymorphic changes during processing [12].
6. Patient gastrointestinal irritation can be reduced [14].

4.2.2. Melt Processing Disadvantages

While melt processing simplifies processing and evenly distributes the API, there are disadvantages. Melt processing requires elevated temperatures and in some excipients and APIs, a high temperature will cause thermal degradation and scorching. Thus, only thermally stable materials may be used. In addition, for instant release, the excipients need to be water soluble/degradable in order to effectively deliver the API to the patient once the tablet has been ingested. Finding materials that are soluble, thermally stable, and compatible with a specific API can be difficult [1].

4.2.3. Pharmaceutical Binders in Melt Processing

Pioneering work by Doelker [15] showed that thermoplastic materials can be used to create pharmaceutical tablets. However, the thermoplastic materials used to make these tablets were sparingly soluble, restricting drug bioavailability [16]. Luckily, many excipients commonly used as pharmaceutical binders work well in melt processing. They are thermally stable, provide a good matrix for the API, and are soluble. A number of binders are readily available including cellulose derivatives, methacrylates, polyethylene glycols [17, 18], and polyvinylpyrrolidones [1].

4.3. Continuous versus Batch Manufacturing

Melt processing may be operated in batch mode or continuously. Batch operation has and continues to be prevalent in the pharmaceutical industry, but a movement towards continuous processing has gained interest.

4.3.1. Batch Melt Processing

To create a melt in batch mode, the powder mixture of API and excipient(s) is added to a vessel. The powder is mixed while the temperature is increased to create the melt. Problems are often encountered with unequal heat distribution within the material allowing some of the product to encounter high temperatures for a long period of time and some of the product to experience temperatures too low to create a melt. Batch thermal processes are also difficult to scale as a consequence of the surface area to volume ratio. Thus, high temperature is required for a long period of time to melt all of the powder, creating a product with nonuniformities [1].

4.3.2. Continuous Melt Processing (i.e., Melt-Extrusion)

If operated continuously, melt processing can be achieved in a screw-type extruder (melt-extrusion). The continuous operation is desirable for several reasons. An extruder temperature can be controlled at several points along the shaft of the screw ensuring that the product has a uniform “temperature history.” Scaling may be done by extension of time and without altering the surface area to volume ratio of the reactive zone. Also, because of the extruder design, the
time required to create the desired melt is significantly lower than with batch operation [1]. Economically, the capital costs, operation costs, and energy costs are all lower than the costs for a batch operation of similar scale [19].

A screw extruder may have one or several screws, but commonly contain one (single screw) or two screws (twin screw). A single screw extruder acts similarly to a drag-flow pump. Material is transported to the end of the barrel by action of the screw and the friction at the barrel wall. It is possible for material to stick to the screw and/or adhere to the barrel wall, increasing the residence time of the material and its exposure to high temperature. Single screw extruders also have little mixing capability, but are cheaper and easier to model than twin-screw extruders.

Twin screw extruders may be co-rotating or counter-rotating. Counter-rotating screws impart a large pressure and shear on the material being processed, sometimes forcing the screws to push outwards towards the barrel walls. Co-rotating screws are self-wiping and do not cause the screws to push outwards and thus are used most frequently in pharmaceutical applications. Twin screw extruders impart distributive and dispersive mixing on the material and due to the self-wiping action of the screws, material is unlikely to remain in the barrel for extended periods of time. An obstacle with twin screw extrusion is modeling the large number or variables and non-Newtonian flow inside the barrel. Co-rotating twin screw extruders, for the reasons outlined here, dominate pharmaceutical extrusions.

Melt-extrusion is specifically the “process of converting a thermoplastic raw material into a product of uniform shape and density by forcing it through a die” [20]. This process is usually considered in two parts. Initially, a conveying system transports the powder (API and excipient(s)) and promotes a degree of distributive mixing, followed by the die system which imparts the required shape [10, 11].

During the conveying system step, a mixture of API and excipient(s) is added to a single or twin screw extruder via a hopper. The temperature of the powder in the extruder is increased to approximately 30 - 50°C above the T_g of the mixture [21, 22] such that the solid powder becomes a melt. Up to 80% of the heat requirement is generated by friction as the material is sheared in the extruder and this facilitates uniform heating of the material. The remaining heat is supplied by electric or liquid heaters on the extruder shaft [11]. A simplified single-screw extruder diagram is presented in Figure 1.

In the die system step the newly acquired melt is forced through a die to create a desired shape. Following extrusion, the extrudate is processed into a tablet shape directly or further processed using traditional techniques such as tablet compaction. Extrudate forming will be discussed in a subsequent section.
4.4. Melt-Extrusion Uses and Advancements

At the present, melt-extrusion research is focused primarily in three areas in the pharmaceutical tablet industry: increasing the bioavailability of poorly soluble APIs, processing APIs that are difficult to compact, and modifying drug release [24]. The literature is extensive with a particularly dense patent literature. A short summary of sources categorized by excipient material is presented in Table 1 for reference. Many other excipients have been used for melt extrusion, but those presented here are most commonly used.

Table 1: Literature sources for popular melt-extrusion excipients. Note, this list is not exhaustive.

<table>
<thead>
<tr>
<th>Excipient Material</th>
<th>Literature Source</th>
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</thead>
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<tr>
<td>Cellulose Derivatives</td>
<td>[25-30]</td>
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<tr>
<td>Eudragit® *(RS/RL, E, 4135F, S)</td>
<td>[31-39]</td>
</tr>
<tr>
<td>Polyethylene Glycols</td>
<td>[40-44]</td>
</tr>
<tr>
<td>Polyvinylpyrrolidones</td>
<td>[21, 45]</td>
</tr>
<tr>
<td>Sugar Alcohol</td>
<td>[46-48]</td>
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Four commercial solid dosage forms have been produced thus far using melt-extrusion [20]. They are summarized in Table 2. Although these are the only drugs that have been introduced to the market, pharmaceutical companies are actively working on the introduction of many other melt-extruded drug products.

Table 2: Drugs produced by melt-extrusion.

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Targeted Illness</th>
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<tbody>
<tr>
<td>Troglitazone (Rezulin)*</td>
<td>Park-Davis</td>
<td>Type II Diabetes</td>
</tr>
<tr>
<td>Verapamil (Isoptin)</td>
<td>Abbott</td>
<td>Irregular Heartbeat</td>
</tr>
<tr>
<td>Fast Acting Ibuprofen</td>
<td>Abbott</td>
<td>Pain</td>
</tr>
<tr>
<td>Kaletra</td>
<td>Abbott (Soligis)</td>
<td>HIV (Protease Inhibitor)</td>
</tr>
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* Taken off the market due to liver toxicity
4.5. Extrudate Forming

Extrusion has proven advantages for the pharmaceutical industry. Blending steps involving complicated inter- and intra-particle interactions can be eliminated, organic solvents can be removed, the number of processing steps and production time can be reduced, solid solutions and/or molecular dispersions can be formed, content uniformity can be improved, and a consistent and reliable product can be produced. With all of these advantages it seems that hot melt extrusion is a desirable processing choice for heat-stable drug substances. There is, however, a major drawback that faces extrusion enthusiasts. How can extrudate be formed into tablets? Following traditional methods, extrudate can be ground or milled into a powder and subsequently pressed into tablets or filled into capsules [11, 49, 50]. These techniques may allow for a solid solution and/or molecular dispersion gained during hot melt extrusion to increase the bioavailability of a poorly soluble drug, but a powder handling step(s) is added. From a production standpoint, the benefits of extrusion have been reduced because eliminating powder handling is a benefit of hot melt extrusion and a manufacturing goal. Nonetheless, this technique is used because it utilizes well known and available methods and allows poorly soluble drug substances to be delivered.

Other methods used to further process extrudate include melt pelletization and sheet formation [51]. These techniques do not introduce powder handling steps post-extrusion, but do require subsequent processing. Melt pelletization produces pellets with diameter ranging from approximately 400 μm to 3 mm [51]. Pellets are then further processed or filled into capsules. Sheets are commonly formed in the plastics industry, but have yet to find an application in solid dosage forms. Current applications include packaging and transdermal patches. Opportunities exist for an innovative solid dosage platform, but have yet to be invented.

The extrudate processing steps described thus far do not allow for the direct formation of an oral solid dosage form. Three techniques, including direct cutting, calendaring, and injection molding, will be presented for direct production of such dosage forms. These techniques have been developed and/or researched in some capacity in the pharmaceutical industry and academia. However, the application of these techniques has been limited.

4.5.1. Direct Extrudate Cutting

Conceptually, the simplest way to form tablets from extrudate is to cut the extrudate using a blade or blades. Zettler et al. [52] of BASF patented a process for shaping melt extrudate with blades. The shape is achieved using two steps. (1) The extrudate is broken into cylindrical pieces and fed towards a rounding tool, and (2) rounding of edges and corners is carried out to give an oblong shape. A diagram summarizing this process is presented in Figure 2. Guillotine or shear cutters can be used to cut extrudate, but are relatively slow (15 – 20 cuts/min). The relative slowness of the blade can cause momentary stoppage of the extrudate and lead to product deformation or fracturing [51]. Rotary knife cutters can make cuts up to 350 times per minute. Product deformation is usually reduced with this technique, but rubbing of the blade at the extruder die can cause scratches or wear. Tearing of the extrudate or metal particulate generation may occur [51]. An advantage of direct extrudate cutting is low to zero waste.
generation. This feature is important when working with expensive pharmaceutical materials that cannot be easily recycled due to high temperature sensitivities and strict regulations.

**Figure 2:** Cutting procedure for producing oblong tablets from melt extrudate [52]. Extrudate exits the extruder on the left and is cut to size using the blade that moves up and down as indicated with the arrow. A sensor downstream from the blade senses when the extrudate has reached the predefined length. The oblong tablet shape is created using a rounding tool shown on the right.

### 4.5.2. Calendaring

Calendaring of pharmaceutical melt extrudate is a highly patented area of interest. BASF has several patents, now owned by Soliqs – the drug delivery division of Abbot Labs, [53-55] describing the calendaring process for pharmaceutical extrudate. Figure 3 demonstrates the calendaring process. Molding rolls which counter-rotate have surface depressions on their surfaces for receiving and molding the melt. This process has been used with formulations dominated by polyvinylpyrrolidone and likely a host of other polymeric excipients. An inherent problem associated with calendaring is the loss of material between the depressions during forming. This in-between area can be reduced, but not eliminated. Ideally material which did not enter the mold depressions could be collected and recycled by adding to the extruder entrance, but the heat sensitivity of most drug substances contraindicates repeated heating and cooling. A photograph of the calendaring process is presented in Figure 4.
4.5.3. Injection Molding

Injection molding is used extensively in the plastics industry. A mold can be created to fit just about any application desired: everything from outdoor chairs to cell phone bodies and everything in between. While there are many intricacies, the basic principles remain the same.

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Figure 5: Injection molding machine [57].

A hopper feeds material into a heated barrel containing one or two rotating screws. The material is heated by the shearing action of the screw(s) and heat supplied from the outer wall of the barrel. As material is conveyed towards the end of the screw, it is mixed thoroughly and collects in a small reservoir at the end of the barrel in front of the screw. Material continually collects in the reservoir and the collected mass forces the screw(s) to move back towards the hopper end of the barrel. Once the screw has moved a defined distance, the screw(s) act as a piston, forcing the collected material into the mold at the end of the barrel. The distance the screw moves...
determines the appropriate amount of material that will be injected into the mold. Meanwhile, the clamp has moved into place, holding tight against the front of the mold. The injected material is allowed to cool in the mold before the clamp retracts and allows the newly molded product to drop from the mold into a collection bin. If required, pins are placed at the back of the mold to help the molded part exit the mold.

**Figure 7: Details of a tablet-shaped mold.**

Material loss during injection molding originates from the design of the mold. A mold created for the production of tablets is shown in Figure 7. Molten extrudate enters via the sprue as shown at the top of the figure. It then flows through the runner (two shown) and enters the mold cavity. As the tablet cools and solidifies, material in the sprue and the runners will also solidify. This extra material is considered waste and can be recycled if the material can withstand several iterations of heating and cooling as mentioned earlier, but this is difficult to validate in the case of pharmaceutical materials. The volume of the sprue and the runner can be minimized, but not entirely eliminated. The point at which the runner meets the mold cavity is called a gate. A small amount of material will protrude from the molded tablet at the gate, i.e., a gate mark. All injection molded parts will have a gate mark, but strategic placing of the gate can all but eliminate the imperfection.

In addition to potential material loss via the runner and sprue, a traditional injection molding machine utilizes one single screw that acts to push material into the mold. A single screw extruder has the ability to provide some mixing if needed, but a twin-screw extruder is usually required to obtain acceptable content uniformity to a multi-component formulation. Alternative machine configurations are required, with two examples presented here. A twin-screw extruder can be used in conjunction with a series of molds on a turntable as shown in Figure 8. Molten extrudate exits the twin-screw extruder and falls to the waiting mold below. Once the mold has been filled, the turntable rotates and the next mold is filled in a similar fashion. A heating source may be added to ensure that the molten material entering the mold does not prematurely solidify before the mold has been completely filled. This process is particularly suited for the production of parts requiring long cooling or heating times. Likewise, this process is suited for extrudates with low viscosities in the molten state.
Another molding configuration separates the injection unit (i.e., the extruder) from the piston. In this case, a twin-screw extruder melts and mixes the formulation and feeds the molten material into a heated piston. The piston then doses the material into a clamped mold, similar to a traditional injection molding mold. This process is advantageous for formulations that require high plasticization because the screws always rotate. This system also has the potential to produce very small and intricate parts because the piston device can be used with a small plunger. The separate piston injection molding technique is presented schematically in Figure 9.

There are a number of other molding techniques used in the polymer industry, but those presented here are believed to be of importance for the application to pharmaceutical materials. For additional alternatives to injection molding, the book by Avery is a good resource [58].

### 4.5.3.1. Injection Molding Literature

Injection molding literature relating to pharmaceutical technology is limited and largely based on final tablet properties rather than the forming technology itself. The literature can be broken into categories according to the molding equipment used.

#### 4.5.3.1.1. Full Scale

Cuff and Raouf [59] explored the injection molding potential of 14 drug substances with polyethylene glycol (PEG) molecular weight 8000 as the carrier. The authors posed three
questions: can we make acceptable tablets, can injection molding be applied to pharmaceuticals, and what drug substances can be processed? Drug substances were categorized by the way in which they interacted with the carrier: dispersed in PEG as discrete crystalline particles, dissolved in PEG to form a solid solution, or partially soluble in PEG. Drug substances that were sparingly soluble in PEG (<0.4%) and were chemically stable were considered good candidates because the presence of a solid solution was deemed detrimental to processability and stability. A 50-ton injection molding machine was used to produce tablets. Of the 14 drug substances, 10 were selected as good candidates and successfully injection molded. The tablets produced met dissolution, hardness, and size uniformity requirements. This study demonstrated that a pharmaceutical formulation can be injection molded successfully on a full scale injection molding machine. It should be noted, however, that an additional extrusion step was required to form uniform granules before being processed via a single-screw injection molder.

Vaz et al. developed a soy protein tablet matrix using a DEMAG D25 NC IV injection molding machine [60]. The researchers found that the dissolution of soy protein injection molded tablets was different at neutral and slightly acidic conditions and that crosslinking during extruding and molding can change dissolution behavior. The injection molding machine was used to produce tablets of industrial scale and allowed the results to be more widely interpreted. Their conclusions included: ease of tablet production using this technique, suitability for a large number of pharmaceutical materials, applicability to different drug substances, and acceptable biodegradability.

4.5.3.1.2. Small Scale

A group from Ghent University in Belgium has published several literature articles in which an injection molding technique is used for producing ethyl cellulose (EC) tablets containing model drugs (e.g., metoprolol tartrate) [61-64]. A swellable release modifier was added to the formulations to aid dissolution of the tablets. The group used a Haake Mini-lab II Microcompounder from Thermo Electron to extrude the material and produced tablets using a complementary Haake Mini-jet System to mold tablets. The research focused on the influence of EC grade, extruder operating temperature, screw design, production rate, and composition of the tablets on the dissolution and stability behavior of the tablets. The researchers concluded that the dissolution behavior could be controlled by changing one or more of the input variables listed. However, the other main conclusion was that injection molding of tablets is a viable processing technique. This conclusion is unfounded given the equipment used to produce tablets. The Haake Mini-lab and Mini-jet are lab scale equipment. The Mini-jet in particular is a non-continuous process in which molten material exiting the extruder is added to the mold inlet and pressure is applied to mimic an injection molding process. While tablets were made under pressure at elevated temperatures required for molding, these findings do not address the practicality of actually implementing an injection molding process.

4.5.3.1.3. Co-extrusion

A Danish based company called Egalet has successfully produced sustained release tablets using a molding technology. The process creates two distinct areas within the tablet: an outer layer
consisting of a slowly eroding material and a tablet core containing the drug substance. Figure 10 describes the process. In this process, the outer layer does not cover the ends of the tablet core, allowing for dissolution to occur at those points. The advantage of this strategy is that the dissolution surface area is constant as dissolution occurs.

Figure 10: A step-by-step diagram of Egalet technology [65]. (1) the mold is empty with molten coating material ready to enter from the top and molten tablet core material ready to enter from the right, (2) tablet coating material is injected after a piston moves in from the left, occupying the space that will be occupied by the tablet core, (3) the piston retreats and tablet core material is injected into the mold, (4), the piston is moved forward and ejects the hardened and cooled tablet, (5) the final tablet.

Vaz et al. [66] have reported a similar process that is used for the creation of double-layer tablets. Material A and material B are injected into the mold using two separate extruders. Material A is injected first and moves to the front of the barrel containing material B. The two materials are simultaneously injected into the mold. Material A moves to the outside of mold, attracted to the cold walls followed by material B which further forces material A to the outer edges of the mold. Material B then cools and forms the tablet core. This technique as well as the process developed by Egalet opens the possibility of combining an extrudate forming step with a coating step at full scale.

Figure 11: Co-extrusion process by Vaz et al. [66]. From left to right, materials A and B are extruded simultaneously, material A is injected into the barrel of material B, materials A and B are injected into the mold, with material A forming the outer layer and material B forming the tablet core.

Other literature related to pharmaceutical injection molding is summarized in Table 3.
Table 3: Additional pharmaceutical injection molding literature.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule Production</td>
<td>Eith et al. [67]</td>
</tr>
<tr>
<td>Coated Dosage Form</td>
<td>Sowden et al. [68]</td>
</tr>
<tr>
<td>Membrane Production</td>
<td>Dong et al. [69]</td>
</tr>
<tr>
<td>Formulation Development</td>
<td>Speiser [70], Goertz et al. [71], Snipes et al. [72, 73]</td>
</tr>
</tbody>
</table>

4.6. Motivation and Aims

Published work and patents in the pharmaceutical melt extrusion literature largely focus on “simulated polymer processing” [20] or the delivery of poorly soluble drug substances [74]. These development-based endeavors have quickly brought several melt extruded products to the market with more in the pipeline. However, very little is understood scientifically in terms of operating parameters, chemical interaction between components, and the stability of the amorphous form. In this study I aim to study the application of hot melt extrusion to pharmaceutical materials.

This work fits nicely into the current initiative supported by the FDA: Quality by Design (QbD). QbD is a scientific, risk-based, and holistic approach to pharmaceutical development which includes a full understanding of how product attributes and processing relate to product performance [75, 76]. Thus, I believe that the results of this thesis can be immediately applied to the pharmaceutical industry.

The specific aims of this thesis work are summarized below.

- Temperature sensitivity
  - Characterize and model a pharmaceutical melt extrusion process using residence time distribution methods and estimation of kinetic parameters associated with the creation of a degradation product

- Physical stability
  - Demonstrate amorphous stability control with the use of a two-component solid solution and characterization of the long-term stability of an amorphous state with respect to physical ageing
  - Characterize of the effect of a polyvinyl acetate coating on the water uptake of a drug product

- Engineer dissolution behavior
  - Explore “tuning” extruded tablets to achieve varied dissolution profiles using excipients

- Implement hot melt extrusion and forming to continuous manufacturing
Bibliography


5. Materials and Methods

5.1. Materials

Materials in the pharmaceutical industry are classified into two categories: active pharmaceutical ingredients (APIs) and excipients. An API provides the desired therapeutic effect and an excipient is any other material present in a formulation. Formulations typically contain one to ten excipients, which serve to modify tablet physical properties (e.g., disintegration, binding) and/or aid processing (e.g., lubricate tablet compaction).

5.1.1. Active Pharmaceutical Ingredients

*Molecule A*

Molecule A, donated by Novartis AG (Basel, Switzerland) is the API investigated in this work. It is a small molecule API used for the treatment of hypertension. It is a poorly flowing white powder and is easily compacted at low compression forces. Molecule A is observed in two primary crystalline forms (Form A and Form B) as well as an amorphous form. In this study, Molecule A form A and the amorphous form were investigated.

Molecule A has a melting temperature range of 95 - 100°C and a glass transition temperature range of 55 - 58°C as determined by differential scanning calorimetry. These relatively low temperatures make the crystalline and amorphous forms readily accessible at experimentally obtainable temperatures. The crystalline and/or amorphous physical form can be formulated in combination with numerous excipients with varying melting temperature ranges. If used in combination with a low melting temperature excipient (e.g., polyethylene glycol, melting temperature of 65°C), the crystalline or the amorphous form of Molecule A may be experimentally obtained. The amorphous form is obtained by melting the Molecule A / polyethylene glycol mixture above the melting temperature of Molecule A. The crystalline form of Molecule A can be maintained by heating the mixture to above the melting temperature of polyethylene glycol and below the melting temperature of Molecule A.

Molecule A can likewise be used in combination with a high melting / softening temperature excipient (e.g., polyvinylpyrrolidone, glass transition temperature of 165°C). The possible scenarios are presented in Figure 12.
Figure 12: The unique properties of Molecule A allow for the investigation of many excipient – physical form combinations. (Note: crystalline includes semi-crystalline)

The unique thermal properties of Molecule A may at first seem to limit the applicability of this study, but in fact, the properties and readily accessible physical forms open windows of operation not usually encountered with a typical high melting temperature API (e.g., caffeine).

5.1.2. Excipients

Polyethylene Glycol

Polyethylene glycol (PEG) was purchased from Sigma Aldrich (St. Louis, MO). It is a water soluble polymer commonly used in the pharmaceutical industry as an ointment base, plasticizer, lubricant, etc. [1]. Recently it has gained popularity for melt extrusion applications because of its low melting temperature and plasticizing properties [2]. It is available in a number of different molecular weights (MW) ranging from the liquid 400 MW to the solid 20,000 MW. PEG is a hydrogen bond acceptor, allowing for interaction of PEG with other materials via hydrogen bonding. The chemical structure of PEG is presented in Figure 13.

![Chemical structure of PEG](image)

Figure 13: Polyethylene glycol where n is the number of repeating units.

This work focused on PEG 8,000 MW. Above a MW of 4,000, PEG is not hygroscopic and at 8,000 MW has sufficient binding affinity to act as a primary matrix for an API. The melting temperature range for PEG 8,000 is 60 - 63°C. The DSC data are presented in Figure 14.
Figure 14: Experimentally determined DSC pattern of polyethylene glycol 8,000 MW (Measured with TA Instruments DSC Q2000, 10 K/min)

PEG is highly crystalline and displays characteristic peaks when analyzed by X-ray diffraction (Figure 15).

Figure 15: Experimentally determined X-ray diffraction pattern of polyethylene glycol 8,000 MW (Measured with Pananalytical X’Pert Pro, step size 0.02°, 5 – 40° 2θ).

*Polyvinylpyrrolidone*

Polyvinylpyrrolidone (PVP or povidone) was purchased from Sigma Aldrich (St. Louis, MO). It is a water soluble amorphous polymer. PVP has been used extensively in the pharmaceutical industry for binding and disintegration purposes during wet granulation and/or tablet compaction operations [1]. PVP is classified by a “K” value which indicates the viscosity of PVP relative to
water. Common K-values include K19, K30, and K90. The K-value can also be used as a rough estimate of the molecular weight with K19 corresponding to approximately 10,000 and K90 corresponding to approximately 360,000. The chemical structure is given in Figure 16.

Figure 16: Polyvinylpyrrolidone where \( n \) is the number or repeating units.

PVP has also been used extensively during melt extrusion of pharmaceutical materials [3-5]. The design space surrounding PVP melt extrusion has been heavily patented because of two desirable attributes. First, its glass transition temperature of approximately 165°C is significantly higher than room temperature, reducing the probability of premature softening. Second, PVP is a hydrogen bond acceptor and readily interacts favorably with many APIs, reducing instability and creating molecular interactions. This second attribute is highly desirable because of the strong desire in the pharmaceutical industry to deliver highly insoluble APIs.

There are, however, major drawbacks to using PVP during melt extrusion. The glass transition temperature dictates that the operation temperature must be at least 165°C to obtain a suitable flow within the extruder. This temperature requirement means that the API must be thermally stable at this temperature range. The viscosity of PVP is also higher than other pharmaceutically accepted polymers, requiring the use of a plasticizer during production. For example, when PVP K30 is added to Molecule A at 10 wt%, the viscosity is orders of magnitude larger than if PEG 8000 were added at 10 wt% (Figure 17). A plasticizer, such as sorbitol, can act to lower the overall glass transition temperature of the formulation, but can be a cause for concern due to a shortened shelf life [2]. In addition, incorporating a plasticizer, usually in low weight percentages, can be difficult to meter during continuous manufacturing.

Figure 17: Viscosity versus shear rate for Molecule A and PVP K30 or PEG 8000 melt extrudates. Molecule A is present at 90 wt% and PVP or PEG at 10 wt%. Also note shear thinning behavior for the PVP formulation.
Hydroxypropyl Cellulose

Hydroxypropyl cellulose (HPC) was purchased from Sigma Aldrich (St. Louis, MO). It is a water soluble, amorphous polymer used as a binder and/or disintegrant for traditional pharmaceutical manufacturing techniques [1]. HPC is a white powder with an average molecular weight of 80,000 and a glass transition temperature of approximately 120°C. The chemical structure of HPC is presented in Figure 18.

![Figure 18: Hydroxypropyl cellulose, where R = H or CH₂CH(OH)CH₃.](image)

HPC is a hydrogen bond donor and acceptor, but does not create molecular dispersions as readily as PVP. For this reason, HPC is not encountered frequently in the melt extrusion literature.

Eudragit E100

Eudragit was donated by Degussa Corporation (Parsippany, NJ). Eudragit is the trade name for a large collection of poly(meth)acrylates used in the pharmaceutical industry for primarily coating and extended release applications. Eudragit E100 is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It is soluble at acidic pH values below 5.0 and swellable and permeable at higher pH. Eudragit E100 has a molecular weight of approximately 47,000 and a glass transition temperature of 48°C. A low glass transition temperature makes Eudragit E100 a good candidate for the processing of APIs which are not heat stable at higher temperatures.

![Figure 19: Eudragit E100.](image)

Eudragit E100 is a hydrogen bond acceptor, allowing for interaction with APIs and the potential to form molecular dispersions or solid solutions. The structure of Eudragit E100 is presented in Figure 19.
5.1.3. Coatings

*Opadry AMB*

Opadry AMB was donated by Colorcon (West Point, PA). It is a commercially available tablet coating product. The coating material is a solid mixture that is suspended in water or organic solvent just before use. The components of Opadry AMB are summarized in Table 4 (note that the exact composition is proprietary).

**Table 4: Components in powder Opadry AMB as received by Colorcon.**

<table>
<thead>
<tr>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinyl Alcohol</td>
</tr>
<tr>
<td>Lecithin</td>
</tr>
<tr>
<td>Titanium Dioxide</td>
</tr>
<tr>
<td>Talc</td>
</tr>
<tr>
<td>Colorant</td>
</tr>
</tbody>
</table>

Opadry AMB was formulated to be used specifically as a moisture barrier coating for water sensitive APIs in humid climates. The coating acts to protect the tablet core from moisture with the uptake of water by polyvinyl alcohol (PVA) and the subsequent preferential hydrogen bonding of that moisture. This mechanism assumes that moisture present in the atmosphere will bond more strongly to the PVA than the materials inside the tablet core.

5.1.4. Tracer Materials

*Carmine*

The tracer material, carmine, was obtained from Sigma-Aldrich (St. Louis, MO) and was used to determine extruder residence time distributions. Carmine is a bright red material that is easy to detect with the naked eye and can also be detected using UV-vis spectroscopy at a wavelength of 526 nm.

![Opadry AMB suspended in DI water (20 wt% solids).](image)
5.2. Processing

5.2.1. Extrusion and Forming

A Leistritz (Somerville, NJ) Nano16 co-rotating 16 mm twin screw extruder was used for all extrusion runs. The extruder has four temperature controlled zones along the barrel (Figure 21). Powder was fed to the extruder via a DP-4 gravimetric disc feeder (Schenck Accurate, Whitewater, WI). The screw speed was maintained at 160 RPM and the die was cylindrical in shape with a 6 mm diameter opening.

![Leistritz Nano16 twin screw extruder.](image)

During an extrusion run, the temperature at all zones, the temperature of the extrudate at the outlet, the pressure at the outlet, the powder feed rate, the torque required, and the screw speed were recorded in real time.

The extrudate was collected and formed into tablets using either a manual or an automatic forming technique. When producing tablets manually, extrudate was collected by hand and forced into a tablet-shaped aluminum mold (cylindrical with a diameter of 9 mm and a height of 4 mm), fabricated by the MIT Machine Shop, as shown in Figure 22. The tablets were allowed to cool to room temperature under ambient conditions and then ejected from the mold. This hand molding technique was intended to be a proxy for an automated injection molding process.

![Aluminum tablet mold.](image)

The automatic molding apparatus was a retrofitted tablet-shaped mold installed at the extruder die outlet. The mold was filled by pressure buildup created by the continuous operation of the extruder. Once a high pressure was produced at the die exit, the mold automatically advanced to the next cavity position. The molding device is shown in Figure 23.
Figure 23: "Strip" molding device retrofitted to the extruder die outlet. From top to bottom: the interfacing joint between the die and mold, 1 mm gates, and the front and back of the tablet sized molds.

The molding device was fabricated from stainless steel by colleagues in the mechanical engineering department at MIT. The tablet shaped molds were comprised of two pieces: a front and back of identical shape. Extrudate exited the extruder die and passed through an interfacing piece designed to securely hold the molds in place. The extrudate was then passed through a 1 mm gate into the mold cavity. After filling the mold, the “strip” of cavities advanced and the neighboring cavity was filled. Once all cavities were filled with extrudate, the tablets were ejected by separating the front and the back of the mold.

5.2.2. Coating

Tablet coating was conducted using a Glatt GMPC mini-coater with a 0.8 L pan (Glatt Air Techniques, Inc., Ramsey, NJ). The pan-style coater was filled with approximately 350 g of tablets and rotated at 15 RPM. The total mass of tablets for each trial (tablets of interest) was on the order of 10 – 20 g with the remainder of the tablet bed made of convex-bisect placebos of similar size and shape supplied by Novartis AG (Basel, Switzerland). Opadry AMB coating was sprayed onto the agitated tablet bed at 6 mL/min, with a process airflow rate of 25 Nm³/hr, atomized air flow of 1.2 bar, and a patterning air pressure of 1.6 bar. Tablets were sampled from the rotating pan every 15 minutes to monitor the coating weight gain until the desired weight gain was achieved.

Solid Opadry AMB coating solution was mixed with de-ionized water for 60 minutes to create a 20% solids solution. During the coating application process, the solution was continually mixed to maintain the stability of the suspension.
5.3. Analytical Techniques

Numerous analytical techniques were utilized in this work. The details of each are described below.

*Differential Scanning Calorimeter (DSC)*

DSC was used to detect the presence of crystalline and or amorphous regions within a sample. Powder samples (3 – 7 mg in weight) were sealed in aluminum pans and analyzed under a dry nitrogen purge using a TA Instruments Q2000 (New Castle, DE). Unless otherwise noted, a heating rate of 10 K/min was used. Glass transition temperatures, melting temperatures, and heat capacities were identified graphically using the software supplied by TA Instruments.

*X-ray Diffraction (XRD)*

A Pananalytical X’pert Pro scanning x-ray powder diffractometer (Almelo, The Netherlands) with radiation generated by a copper Kα filter at 45 kV and 40 mA was used to detect the presence of amorphous or crystalline sample regions. Samples were scanned from 5 – 40° 2θ with a 1° anti-scatter slit and 4 radian soller slit. The step size unless otherwise noted was 0.02°.

*High Pressure Liquid Chromatography (HPLC)*

An Agilent HPLC (Santa Clara, CA) equipped with a UV-vis absorbance detector was used to measure the concentration of heat-treated samples. Approximately 40 mg of sample was dissolved in 10 mL of HPLC grade solvent (3:1 water:acetonitrile) and sonicated for 30 minutes. Mobile phase A contained 80 vol% ion pair reagent and 20 vol% HPLC grade acetonitrile, where the ion pair reagent was prepared by dissolving 5.65 g of hexanesulfonic acid sodium salt monohydrate and 2.75 g of sodium dihydrogen phosphate monohydrate in 1 L of HPLC grade water with the pH adjusted to 2.3 using 85% phosphoric acid. Mobile phase B contained 20 vol% ion pair reagent and 80 vol% HPLC grade acetonitrile. The cumulative mobile phase flow rate was 0.8 mL/min according to ratios presented in Table 5. The column, a YMC-Pack ODS-A 3 µm (150 mm length, internal diameter 4.6 mm), was maintained at 30°C and the absorbance was measured at 280 nm.
Table 5: Chromatographic conditions for HPLC mobile phase flow rates.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile Phase A (vol %)</th>
<th>Mobile Phase B (vol %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>

**Thermal Gravimetric Analysis (TGA)**

The mass of a sample was monitored as a function of time and temperature with a micro-balance incorporated into a TA Instruments thermal gravimetric analysis machine (model Q5000IR). The temperature was increased to near or above the decomposition temperature of the sample under consideration. The heating rate was 20 K/min unless otherwise noted.

**Dynamic Vapor Sorption (DVS)**

The absorption of water as a function of relative humidity, temperature, and time was monitored using a TA Instruments dynamic vapor sorption machine (model Q5000SA). A sample of approximately 10 mg was carefully weighed and placed in sample pan. The sample was exposed to designated temperatures and relative humidities according to a programmed method and the mass of the sample was followed using an incorporated micro-balance.

**Solid-State Nuclear Magnetic Resonance (SSNMR)**

Experiments were performed on a custom-built spectrometer operating at 500 MHz $^1$H Larmor frequency (courtesy of D. Ruben, Francis Bitter Magnet Lab, MIT, Cambridge, MA), equipped with a 4 mm triple-resonance Varian-Chemagnetics probe (Varian Inc., Palo Alto, CA). The sample was cooled with a stream of dry air maintained at a temperature of 8°C, while the sample spinning speed at the magic angle (54.7°) was set to 10 kHz. For all experiments, the $^1$H, $^{13}$C, and $^{15}$N channel tuning and matching were optimized.

$^1$D CP/MAS (cross polarization / magic angle spinning) experiments were recorded using a CP contact time of 2 msec and 100 kHz TPPM $^1$H decoupling during acquisition [6]. The relaxation delay was 10 sec. $T_1$ was measured using an inversion recovery scheme employing 100 kHz $^1$H pulses. The relaxation time was varied from 0 to 9000 msec for the $T_1$ experiments and peak intensity was measured for strong drug and polymer peaks after background correction for each time point. The data were fit to the exponential function

$$\text{Intensity} = \exp\left(\frac{-\text{relaxation time}}{T_1}\right)$$

using Origin 8.5 data analysis software.
Dissolution

Dissolution testing was used to determine the amount of time required for a dosage form to dissolve into a specified medium. The aim of this test is to understand how the dosage form will behave once ingested. In some cases dissolution data can be correlated with bioavailability and patient blood concentration levels, but more often dissolution is used to determine the general dissolution behavior under certain conditions and cannot be correlated to \textit{in vivo} data. For this study, dissolution was used to determine if a tablet met instant release specifications and was used as a proxy for bioavailability. If \textit{in vivo} data are desired, a traditional bioavailability study with human subjects is recommended.

All dissolution testing was carried out using a Varian VK7010 (Santa Clara, CA) equipped with a Cassini 10-channel fiber optic sampling system (C Technologies Inc., Bridgewater, NJ) in combination with a Cary 50 UV detection system (Agilent, Santa Clara, CA). Tablets were dissolved in 500 mL of degassed 0.01 M HCl maintained at 37°C. Each tablet was placed in a rotating basket and submersed in the medium according to the US Pharmacopeia (USP) method II. The concentration of API in the vessel was measured using UV detection at 279 nm via a fiber optic probe every one minute for approximately 60 minutes total. The concentration of API in solution was found using Beer's law and standard solutions. These conditions were followed for all dissolution tests unless otherwise specified.

![Schematic of the dissolution apparatus with a fiber optic sampling system and UV detection.](image)

\textit{Hardness}

Tablets were tested for hardness i.e., crush strength, using a Dr. Schleuniger Pharmatron Model 6D tablet tester (Manchester, NH). A tablet is placed between two plates. One plate is stationary while the other moves until the tablet is fractured as show in Figure 26. The force required to break the tablet is recorded and used to interpret the cohesive bonding strength of the tablet. The bonding forces should be sufficiently high such that the tablet can withstand shipping and handling, but not high enough to impede the desired dissolution behavior. The desired hardness for the cylindrical shaped tablets studied here (9 mm diameter and 4 mm height) is between 70 N and 200 N.
Figure 26: Schematic of a hardness tester. The plate on the right moves laterally while the plate on the left is stationary.

*UV-vis*

The UV-vis absorbance of carmine, a tracer material described above, was measured using a Cary 50 Bio (Agilent, Santa Clara, CA) at a wavelength of 526 nm. Extrudate samples were weighed and dissolved in 5 mL of deionized water. The absorbance was measured using 1.5 mL of solution in disposable cuvettes. Beer’s law was used to calculate carmine concentration.

*Accelerated Stability Testing*

Accelerated stability testing is used to predict long-term shelf life in a shorter experimental time frame. The conditions used were 40°C at 75% relative humidity and 25°C at 60% relative humidity. These conditions were maintained in individual test chambers from ESPEC (Hudsonville, MI) (model LHU-113). Samples were placed in induction sealed plastic bottles with a plug-style desiccant. Each bottle contained at least 24 tablets and was placed in the test chamber within one day of tablet production. Bottles were removed from the test chamber after 1.5 months and 3.0 months. Once removed from the chamber, bottles were not returned. Instead, a number of sealed bottles were placed in the chamber initially such that the bottles were undisturbed until the designated sampling time.
5.4. Bibliography


6. Residence Time Distribution and Temperature Sensitive Degradation of a Pharmaceutical Material during Hot Melt Extrusion

6.1. Introduction

Hot melt extrusion has gained a significant amount of attention from the pharmaceutical industry during the last 15 years. The applications are varied and numerous, including oral, transdermal, transmucosal, and transungal drug delivery [1]. The advantages of implementing this technique include, but are not limited to increased homogeneity, reduced number of unit operations, solvent free operation [2, 3], and the opportunity to achieve higher drug loads [4]. However, there are limits to the number of materials that may be processed with this technique. These limits stem from temperature sensitivity and physical instability of the often-created amorphous [5, 6]. A number of previous studies have focused on the stabilization of the amorphous form, but little work has been done to understand the effect of high temperature on active pharmaceutical ingredients (APIs).

The pharmaceutical hot melt extrusion literature has estimated average residence times between 1.5 – 4.0 minutes for a single screw extruder [7], with shorter estimates for twin screw extruders [8]. These estimates have received little scientific inquiry in pharmaceutical applications even though the residence time distribution is a strong contributing factor for temperature-driven API degradation [9]. To properly characterize residence times within an extruder, a formal residence time distribution (RTD) must be determined.

The concept of an RTD has been used in the polymer processing and food industries for decades. The RTD is of great interest for modeling experimental data [10], qualitative estimation of goodness of mixing [11], and scale-up. A distribution of residence times of a material inside an extruder can be experimentally determined using a stimulus-response technique [12]. The distribution of residence times can also be used to predict the extent of reaction at a given operating temperature [11]. In the plastics industry, reactive extrusion allows polymers to be directly modified in the molten state [13] and in the food industry, extrusion cooking (chemical transformation) is commonplace [14]. The degradation reaction during extrusion of an API can be studied in a similar fashion.

A RTD model can be developed to further understand flow of material in an extruder and can be compared with experimental results. Several single or multi-parameter models have been developed for flow within a single screw extruder including an axial dispersion model and the Wolf-Resnick model [15]. Others have used a series of continuously stirred tank reactors (CSTRs) [16]. Pinto and Tadmor [11] developed a more sophisticated model based on the velocity profile of material through an extruder, which outperformed a series combination of a CSTR and plug flow reactor (PFR) used by Wolf and Resnick [17]. A model utilizing a PFR in series with a CSTR with dead volume has been proposed for rice flour during single screw extrusion cooking [14] and a series of CSTRs with dead volume has been used to model the extrusion of Eudragit E100 with supercritical CO\textsubscript{2} used as a foaming agent [18]. Poulesquen and Vergnes developed a model for a twin screw extruder by fitting a specific reactor to each
geometrical section of the extruder [19]. Single parameter models will be used as a basis for this study due to their relative simplicity and proven modeling ability.

The RTD is of great interest for the possible prediction of extent of degradation in extrusion of temperature-sensitive materials [11]. Changes in extruded materials are typically temperature and time dependent. The results of an RTD study can be coupled with kinetic reaction estimates to predict what fraction of the extruded material will undergo degradation. Reaction kinetics of a degradation reaction can be estimated by performing an experiment in which time and temperature are varied and the corresponding amount of material lost to degradation is followed. The reaction rate constant and activation energy can be calculated by assuming a reaction order and that the reaction rate constant follows an Arrhenius form [10, 12, 20].

This study investigated the temperature driven degradation of an API during hot melt extrusion by characterizing the residence time distribution and reaction kinetics. Several models were also used to predict the extent of degradation a priori.

6.2. Experimental

Materials

The drug substance, Molecule A, was manufactured by Novartis Pharmaceuticals Corporation (Basel, Switzerland). The structure of Molecule A is given in Figure 28. Molecule A is a semi-crystalline drug substance with a melting temperature of 95 – 100°C and a glass transition temperature of 55 – 58°C. The tracer material, carmine, was obtained from Sigma-Aldrich (St. Louis, MO).

Preparation of Temperature Degraded Samples for Kinetic Parameter Estimation

A Thermo Scientific Precision Vacuum Oven (Marietta, OH) was used to expose Molecule A to predetermined temperatures for intervals of 5, 10, 15, and 20 minutes under atmospheric pressure. Approximately one gram of Molecule A was spread onto an aluminum weigh boat and placed into the pre-heated oven. The samples were removed at the designated times and allowed to equilibrate to room temperature under ambient conditions. The amounts of Molecule A and degradation products were determined using high pressure liquid chromatography.

High Pressure Liquid Chromatography (HPLC)

An Agilent HPLC (Santa Clara, CA) equipped with a UV-vis absorbance detector was used to measure the concentration of heat-treated samples. Approximately 40 mg of sample was dissolved in 10 mL of HPLC grade solvent (3:1 water:acetonitrile) and sonicated for 30 minutes. Mobile phase A contained 80 vol% ion pair reagent and 20 vol% HPLC grade acetonitrile, where the ion pair reagent was prepared by dissolving 5.65 g of hexanesulfonic acid sodium salt monohydrate and 2.75 g of sodium dihydrogen phosphate monohydrate in 1 L of HPLC grade water with the pH adjusted to 2.3 using 85% phosphoric acid. Mobile phase B contained 20 vol% ion pair reagent and 80 vol% HPLC grade acetonitrile. The cumulative mobile phase flow rate was 0.8 mL/min according to ratios presented in
Table 6. The column, a YMC-Pack ODS-A 3 μm (150 mm length, internal diameter 4.6 mm), was maintained at 30°C and the absorbance was measured at 280 nm.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile Phase A (vol %)</th>
<th>Mobile Phase B (vol %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>

Extrusion

A Leistritz Nano 16 twin screw, co-rotating extruder with 25:1 L/D ratio was used for all extrusions (American Leistritz Extruder Corporation, Somerville, NJ). The extruder is sectioned into four separate zones, each of which can be set to a desired temperature. The first section of the extruder was set to 50°C, the second section to 70°C, the third section to 95°C, and the die exit to 95°C. These particular temperatures were chosen based on the physical properties of Molecule A as described in Chapter 9. Temperatures were maintained using a water circulating heat exchanger. The screw speed was 160 RPM. Molecule A was fed to the extruder using a Schenck Accurate DP-4 gravimetric feeder (Whitewater, WI) at a rate of 100 g/hr. Once the system reached steady state according to pressure and temperature readings, approximately 10 mg of carmine powder was quickly added to the extruder inlet as a pulse input. Extrudate was collected from a cylindrical 6 mm diameter die and allowed to cool to room temperature under ambient conditions.

UV-vis

The UV-vis absorbance was measured using a Cary 50 Bio (Agilent, Santa Clara, CA) at a wavelength of 526 nm. Extrudate samples were weighed and dissolved in 5 mL of deionized water. The absorbance was measured using 1.5 mL of solution in disposable cuvettes. Beer’s law was used to calculate carmine concentration.

6.3. Theory

6.3.1. Degradation Kinetics

A first order degradation reaction of the following type

\[ A \rightarrow B + C \]  

(1)

can be characterized using the rate expression

\[ \text{rate} = -k C_A \]  

(2)
where $k$ is the reaction rate constant, $C_A$ is the concentration of reactant $A$, and $j$ is the reaction order. The reaction order will be assumed first order, a typical assumption for this type of degradation reaction.

$$\text{rate} = \frac{dC_A}{dt} = -kC_A$$

This rate expression can be integrated with integration limits of the initial concentration of species $A$, $C_{A,0}$, to the concentration of species $A$ at any time $t$ ($C_A$).

$$\ln(C_A) = -kt + \ln(C_{A,0})$$

If the natural log of $C_A$ is plotted against time at a given temperature, an estimate for the first order rate constant can be determined. This goodness of the linear fit from this graphical method will also indicate the validity of the first order reaction assumption.

We further assume that the reaction rate constant can be expressed in terms of the activation energy ($E$), frequency factor ($A$), and temperature in a classical Arrhenius form

$$k = A \exp\left(-\frac{E}{RT}\right)$$

where $R$ is the gas constant. This equation can be rearranged to allow for a graphical determination of the activation energy and frequency factor

$$\ln(k) = -\frac{E}{R(1/T)} + \ln(A).$$

### 6.3.2. Residence Time Distribution

Different material elements will take different lengths of time to flow through an extruder. To determine how long these different elements will remain in the system, a residence time distribution (RTD) was generated utilizing an inert pulse stimulus of carmine.

The residence distribution function, $E(t)$, quantitatively describes how much time different material elements have spent in the extruder[20]. $E(t)$ is defined as follows

$$E(t) = \frac{C(t)}{\int_{0}^{\infty} C(t) \, dt}$$

where $C(t)$ is the concentration of carmine at time $t$. The mean residence time ($\tau$) is equal to the first moment of $E(t)$.

$$\tau = \int_{0}^{\infty} tE(t) \, dt$$

The variance of the distribution ($\sigma^2$) is the second moment of $E(t)$ and is defined as

$$\sigma^2 = \int_{0}^{\infty} (t - \tau)^2 E(t) \, dt$$
The magnitude of $\sigma^2$ is an indication of the distribution spread. The residence time distribution curve can be non-dimensionalized to aid comparison between data sets and scale-up. A new quantity is defined

$$\theta = \frac{t}{\tau} \quad (10)$$

such that $E(t)$ can be expressed in a dimensionless form

$$E(\theta) = \tau E(t) \quad (11)$$

The fraction of extrudate that has been in the extruder for less than time $t$ is represented using the cumulative distribution function $F(t)$

$$F(t) = \int_0^t E(t) \, dt \quad (12)$$

which can likewise be expressed in a dimensionless form

$$F(\theta) = \int_0^\theta E(\theta) \, d\theta \quad (13)$$

In highly idealized systems, the RTD of a twin screw extruder can be modeled as a tubular laminar flow reactor [15]. This laminar flow is characterized by a parabolic velocity profile, with the centerline velocity equal to the maximum velocity. The complete RTD function for laminar flow is

$$E(t) = \begin{cases} 0 & t < \frac{\tau}{2} \\ \frac{\tau^2}{2t^3} & t \geq \frac{\tau}{2} \end{cases} \quad (14)$$

or in a dimensionless form

$$E(\theta) = \begin{cases} 0 & \theta < 0.5 \\ \frac{1}{2\theta^3} & \theta \geq 0.5 \end{cases} \quad (15)$$

The dimensionless cumulative distribution function is given by

$$F(\theta) = 1 - \frac{1}{4\theta^2} \quad \theta \geq 0.5 \quad (16)$$

The laminar flow model assumes no diffusion in the longitudinal or radial directions.

A series of stirred tanks in series (nCRSTs) is a single parameter model frequently used to simulate behavior of non-ideal extruders [21]. The extruder is replaced by $n$ equal sized reactors whose total volume is equal to that of the extruder. The RTD function for a series of CSTRs is

$$E(\theta) = \frac{n(n\theta)^{n-1}}{(n-1)!} \exp(-n\theta) \quad (17)$$

The cumulative distribution function can be determined numerically using the definition of $F(\theta)$. 
The single parameter, $n$, can be estimated using several techniques. The maximum value of the $E(\theta)$ can be used to approximate $n$ with an error of less than two percent if $n > 5$ as shown in Figure 27. The maximum value of dimensionless time ($\theta$) can likewise be used to estimate $n$.

![Diagram of RTD curve for $n$ CSTRs in series (adapted from Levenspiel [12]). Note the expression relating $E(\theta)_{\text{max}}$ to the number of tanks, $n$, is valid if $n > 5$.]

The value of $n$ can also be determined using the variance response of the extruder to a pulse input.

\[
\sigma^2_{(\nu)^2} = \frac{1}{n} \tag{18}
\]

or

\[
n = \frac{1}{\left(\sigma^2_{(\nu)^2}\right)} \tag{19}
\]

The conversion of Molecule A to degradation products can be predicted using the previously determined $n$ value. The CSTR design equation for a first order reaction can be extended to include $n$ reactors to give

\[
f = 1 - \frac{1}{\left(1 + \frac{k_\tau}{n}\right)^n} \tag{20}
\]

where $f$ is the fractional conversion of Molecule A converted to degradation products. Fractional conversion is defined as

\[
f = \frac{C_n - C}{C_0} \tag{21}
\]
The axial dispersion model characterizes mass transport in the axial direction in terms of an effective dispersion coefficient, $D$. The effective dispersion coefficient accounts for mixing by molecular diffusion and turbulent eddies and vortices [10]. The RTD function can be derived assuming Fickian molecular diffusion for $\frac{D}{uL} > 0.01$ where $u$ is velocity in the axial direction and $L$ is the length along the extruder axis.

$$E(\theta) = \frac{1}{\sqrt{4\pi \left( \frac{D}{uL} \right)}} \exp \left( -\frac{(1-\theta)^2}{4\theta \left( \frac{D}{uL} \right)} \right)$$

(22)

$\frac{D}{uL}$ is the inverse of the non-dimensional Peclet number (Pe). A large Pe indicates convection dominance while a small Pe number indicates diffusion dominated dispersion in the extruder.

The magnitude of $\frac{D}{uL}$ can be estimated by evaluating the variance of the experimental data for a pulse tracer input [10]

$$\sigma^2 = \int_0^\infty t^2 \left( \frac{dF(t)}{dt} \right) dt - \bar{t}^2$$

(23)

The inverse Peclet number can then be calculated once the variance has been determined as follows

$$\sigma^2 = 2\bar{t}^2 \left[ \frac{D}{uL} + 4 \left( \frac{D}{uL} \right)^2 \right]$$

(24)

A material balance evaluated about any section of the extruder including degradation reaction results in the following

$$u \frac{dC}{dL} - D \frac{d^2C}{dL^2} + kC = 0$$

(25)

where $k$ is the reaction rate constant and $i$ is the reaction order. For a first order reaction, this equation has an analytical expression

$$f = 1 - \frac{4\beta \exp(\beta uL/2D)}{(1+\beta)^2 \exp(\beta uL/2D) - (1-\beta)^2 \exp(-\beta uL/2D)}$$

(26)

where

$$\beta = \left[ 1 + 4k \left( \frac{D}{uL} \right) \frac{L}{u} \right]^{-1/2}$$

(27)
6.4. Results and Discussion

6.4.1. Degradation Kinetics

Molecule A undergoes a degradation reaction at high temperatures to produce a synthesis precursor (C) and a degradation product (Degradant B) as shown in Figure 28. The reaction is driven by entropic minimization as temperature increases. While other degradation products appear during HPLC analysis of the final product, Degradant B is the only detectable degradation product with significant concentration changes with increasing temperature.

\[ \text{Molecule A} \rightarrow \text{Degradant B} + C \]

Figure 28: Degradation of Molecule A at high temperatures.

The concentration of Degradant B, for purity reasons, must be present in no greater than 0.2 area percent according to HPLC analysis. During melt extrusion, material is exposed to high temperatures, which leads to the creation of Degradant B. Figure 29 indicates an increase in Degradant B concentration as the temperature is increased and the time exposed to each temperature is increased. The creation of Degradant B can be quantified with an activation energy and frequency factor.

Figure 29: Creation of Degradant B as a function of temperature and time.

We assume that the concentration of Molecule A is only decreased due to the reaction represented in Figure 28, neglecting all other degradation reactions that may be occurring. There are additional degradation products created according to HPLC chromatographs, but for the purpose of this study, Degradant B will be considered the only degradation product. This assumption is quite reasonable because Degradant B concentrations are up to 10 times the concentration of other degradation products detected as determined by HPLC analysis of the final extruded product.
The natural log of Molecule A concentration was plotted against time at given temperatures to allow for an estimation of a first order rate constant. The linearity of the data plotted in Figure 30 indicates that a first order reaction assumption is reasonable. Values for the rate constant at each temperature are summarized in Table 7.

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>k (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>378</td>
<td>1.2 x 10⁻⁵ ± 0.1 x 10⁻⁵</td>
</tr>
<tr>
<td>383</td>
<td>2.6 x 10⁻⁵ ± 0.3 x 10⁻⁵</td>
</tr>
<tr>
<td>388</td>
<td>4.1 x 10⁻³ ± 0.2 x 10⁻⁵</td>
</tr>
</tbody>
</table>

Figure 30: The natural log of Molecule A concentration versus time exposed to a specified temperature.

The activation energy for the degradation reaction of Molecule A was estimated by assuming an Arrhenius form of the reaction rate constant. A plot of the natural log of the reaction rate constant versus inverse temperature gives a linear result as seen in Figure 31.
Figure 31: Natural log of the reaction rate constant versus inverse temperature for the graphical determination of the activation energy.

The calculated value of the activation energy is $35 \pm 5$ kcal/mol. This value indicates that at low temperature, the reaction is largely temperature independent in terms of Degradant B creation, but highly thermally dependent at high temperatures. The implications are significant for pharmaceutical applications. The degradation products or by-products must not be present at levels above 0.2 area percent as determined by HPLC.

Now that the reaction kinetics have been successfully characterized, the melt extrusion of Molecule A can be approached with more knowledge about the interplay of temperature and the creation of Degradant B. Likewise, the estimated values of the first order reaction rate constants can be incorporated into RTD modeling, which is discussed in the following section.

6.4.2. Residence Time Distribution

Carmine, a red pigment, was selected as a tracer material because it is easy to detect both visually and using UV-vis. Molecule A does not interfere with the UV activity of carmine and the melting temperature of carmine is well above 300°C, ensuring that it will not melt at the processing temperatures used. Following a pulse input of carmine to the extruder operating at steady state conditions, the concentration of carmine in the extrudate was measured as a function of time (Figure 32). Carmine first exited the extruder at approximately four minutes and reached near zero level concentration after 60 minutes of operation. The mean residence time of the experimental data is 14 min with a variance of 36 min$^2$. The relatively large variance value indicates a good deal of mixing action within the extruder, which is typical for twin screw extruders. The long tailing section following the peak concentration is also typical for twin screw extruders and indicates adhesion, small dead spaces, and low backmixing within the extruder[22].

The experimental data were transformed to give the RTD function, $E(\theta)$, and the cumulative distribution function, $F(\theta)$ (Figure 33 and Figure 34).

![Normalized carmine concentration in the extrudate as a function of time](image)

**Figure 32:** Normalized carmine concentration in the extrudate as a function of time, where time zero corresponds to the pulse input of carmine.

**Axial Dispersion Model**

The axial dispersion model parameter ($D/uL$) was estimated using Equation 24, which gave a value of 0.069. The Peclet number has a value of 15, indicating a convection dominance and minimal backmixing. This conclusion agrees with the those drawn from the data in Figure 32. The Peclet number was also estimated using non-linear regression to give a value of 21, which reasonably matches the variance estimation. The RTD function for the axial dispersion model with $D/uL = 21$ is compared to experimental data in Figure 33, where the correlation index is 0.90. The cumulative distribution function is also presented for comparison in Figure 34.
Figure 33: RTD function, $E(\theta)$, for experimental data and three models. Note ADM = axial dispersion model where $Pe = 21$, CSTR = a series of $n$ CSTRs where $n = 10$, and LF = laminar flow.

The axial dispersion model is able to fit the data well, including the tailing behavior, which is notoriously difficult to model [19]. The RTD function allows for easier qualitative comparison than the cumulative distribution curve because the $F(\theta)$ curve integrates effects giving a smoothed curve that may hide significant real effects [12].

Figure 34: Cumulative distribution function, $F(\theta)$, for experimental data and four models. Note ADM = axial dispersion model where $Pe = 21$, CSTR = a series of CSTRs where $n = 10$, and LF = laminar flow.
A sensitivity analysis was performed for the single parameter axial dispersion model. Figure 35 demonstrates that if \(D/uL\) is increased to a value of 0.07, the correlation index \((R^2)\) drops to 0.86. Similarly, if \(D/uL\) is decreased to 0.03, \(R^2\) becomes 0.082. These results indicate the importance of proper parameter estimation.

![RTD function for experimental data and the axial dispersion model evaluated at three different D/uL values.](image)

**Figure 35:** RTD function for experimental data and the axial dispersion model evaluated at three different D/uL values.

**CSTRs in Series**

The number of CSTRs that best model the system was determined to be approximately six. The equations in Figure 27 were also used, giving 9 CSTRs according to \(\theta_{\text{max}}\) and 12 CSTRs according to \(E(\theta)_{\text{max}}\). In addition, non-linear regression resulted in 10 CSTRs. The estimation of the number of reactors varies significantly for each method, so the value predicted by non-linear regression was used because it falls near the mean of the other predicted values.

The RTD function and the cumulative distribution curve for a series of CSTRs are presented in Figure 33 and Figure 34, respectfully. The correlation index for the \(E(\theta)\) comparison with experimental data \((n = 10)\) is 0.99. When the number of reactors is increased to 12 (an estimate according to \(E(\theta)_{\text{max}}\)), the correlation index drops to 0.98. If the number of reactors in decreased to 6, the correlation index is 0.93. The results are shown graphically in Figure 36. When compared with the axial dispersion model, a series of CSTRs is less sensitive to the single parameter input \((n)\), which indicates a greater robustness for the series of CSTRs model.
1.4

$n = 10$

$n = 6$

$n = 12$

Figure 36: RTD function for experimental data and a series of CSTRs evaluated at three different n values.

As the number of CSTRs increases, the model approaches ideal plug flow behavior. In other words, a series of CSTRs is approaching flow in a tubular reactor as described by the axial dispersion model. For this reason, the results from these models are often very similar when using proper parameter values [12]. Choosing between models becomes a matter of preference or ease of physical representation, but only after this similarity has been confirmed.

Laminar Flow Model

The laminar flow model has no adjustable parameters. The $E(0)$ curve is presented in Figure 33. Qualitatively, the shape of the curve does not mimic experimental data. The curve peaks early and tails off prematurely. The assumptions inherent in the laminar flow model, namely no diffusion in the longitudinal or radial directions, do not properly describe the extrusion system. Note that while the $E(0)$ curve displays the poor fit provided by the laminar flow model, the cumulative distribution curve (Figure 34) suggests a better fit, a consequence of the derivation of $F(0)$.

Conversion by Degradation Reaction

The conversion of Molecule A to degradation products was determined experimentally with HPLC. The fractional conversion is 0.0034. The fractional conversion predicted by the series of CSTRs (10 reactors) and axial dispersion ($D/u_L = 0.05$) are both 0.003. This agreement is a strong indication that using a relatively simple single parameter model for the hot melt extrusion of Molecule A can accurately predict chemical conversion due to a temperature driven degradation reaction a priori if the chemical reaction kinetics are known.

6.5. Conclusions

Melt extrusion of Molecule A can be modeled using a simple one parameter RTD model. Once established, the model along with reaction rate kinetics has the ability to predict the amount of
product lost to temperature driven degradation. The axial dispersion model and a series of CSTRs both model the experimental data well, with a series of 10 CSTRs giving the highest correlation index ($R^2$). The laminar flow model, a zero parameter model, did not sufficiently model the data. The reaction rate kinetics were calculated by assuming a first order reaction with an Arrhenius form of the reaction rate constant. When the kinetics and RTD models were combined, the resultant fractional conversion agreed well with the experimentally determined conversion.

![Diagram](image)

**Figure 37:** Process and requirements for predicting the amount of API degradation.

### 6.6. Bibliography

7. Physical Stability of Melt Extruded Molecule A

The physical properties of 100% melt extruded, amorphous Molecule A are affected by water absorption (as Molecule A is hygroscopic) and instability of the non-equilibrium amorphous state. The following sections outline the characterization of these phenomena and suggest solutions for the prevention of physical instabilities.

7.1. Enthalpy of Relaxation

7.1.1. Introduction

The amorphous physical state created during melt extrusion has the ability to increase the solubility of poorly soluble drug substances because of a decreased energy barrier to dissolution when compared to a crystalline drug substance. However, there are critical drawbacks associated with the amorphous state. A major obstacle for amorphous Molecule A in particular is physical stability. In the amorphous state, the material is not in its lowest energy state (i.e., not in thermodynamic equilibrium). Molecular motions occur as the material attempts to orient itself into a more stable, supercooled liquid state [1]. This change is referred to as “physical ageing” [2] and has been well documented in materials such as polycarbonates [3] and epoxies [4]. The molecular motions lead to decreases in free volume (densification), configurational entropy, and free energy, plus a small heat loss [2]. The physical ageing process as a function of time can be monitored by following changes in thermodynamic, mechanical, or dielectric properties in response to the application of their respective oscillations [5].

Figure 38 graphically represents physical ageing. The material is initially in the liquid state during extrusion, corresponding to the upper right-hand portion of the figure.

![Figure 38: Enthalpy versus temperature for a glassy material.](image-url)
As the temperature is decreased, the enthalpy of the material decreases along the upper curve and comes to rest in the amorphous state along the horizontal line labeled “Glass.” As time increases, enthalpy is lost to the physical ageing process. If the temperature is increased to regain the liquid state, the enthalpy lost is regained at the glass transition temperature \( T_g \) and manifested as an endothermic peak in a plot of temperature versus heat flow. This region where equilibrium is regained is called enthalpy of relaxation [2]. When the aged sample is near the glass transition temperature, the “thermal history” (i.e., ageing history) is erased and subsequent increases in temperature performed before ageing restarts will reveal a typical glass transition without an additional peak.

Physical ageing and enthalpy of relaxation for melt extruded, amorphous Molecule A were characterized using differential scanning calorimetry (DSC). A model, discussed below, was used to fit the experimental data. The conclusions drawn then aided the modification of physical ageing behavior.

7.1.2. Results and Discussion

Physical ageing was initially noted while monitoring the DSC thermogram of amorphous Molecule A as a function of time. After approximately three days post processing, the DSC data displayed an endotherm near the glass transition temperature of Molecule A (approximately 55 - 60°C). The source of this endotherm was investigated thoroughly to rule out recrystallization. Specifically, x-ray powder diffraction (XRD) and hot-stage microscopy confirmed that the material maintained its amorphous character as shown in Figure 39 and Figure 40, respectively. The endotherm at the glass transition temperature therefore is due to the material regaining thermodynamic equilibrium by the absorption of heat previously lost during the physical ageing process.

![Figure 39: XRD of 100% melt extruded Molecule A as a function of ageing time.](image)
Figure 40: Hot stage microscopy images of extruded Molecule A as a function of temperature at day 14. Note that the particle structure is maintained as the temperature increases. The white bar on the left hand side was added for reference and is 100 μm.

As ageing time increased, the intensity of the endothermic peak captured by DSC increased as shown in Figure 41. The area under the peak corresponds to the enthalpy change associated with each particular material. Several strategies are used in the literature for the calculation of the area under the peak. It can be determined by evaluating the area encompassed by a non-aged base peak (reference peak) and the peak of the aged sample [6, 7]. This area is found by superimposing the DSC scans for each sample. This technique requires matching of the DSC scans above and below the glass transition temperature and often leads to inaccurate representations of the data [6]. Others have drawn a tangent from the point of peak recovery [1, 8]. Both of these described methods have been used successfully, but the second strategy described here was utilized in this study to eliminate the possibility of inaccurately representing the data associated with the first method. The enthalpy change was quantified as show in Figure 42.

![Differential scanning calorimetry of a melt extruded 100% Molecule A sample aged at ambient conditions for different amounts of time.](image)

Figure 41: Differential scanning calorimetry of a melt extruded 100% Molecule A sample aged at ambient conditions for different amounts of time.

The enthalpy of relaxation increased until it began to level off at approximately 30 days (Figure 43). For comparison with experimental data, the maximum possible enthalpy change was
estimated assuming that the change in heat capacity at the glass transition temperature ($\Delta c_p$) was independent of temperature [9].

$$\Delta h_r = \Delta c_p \left( T_g - T_{storage} \right)$$ (1)

Here, $\Delta h_r$ is the limiting enthalpy of relaxation and $T_{storage}$ is the storage temperature during the ageing process. The change in heat capacity at the glass transition temperature was calculated using DSC software from TA Instruments (TA Universal Analysis) to give a value of 0.35 J/g°C. At a storage temperature of 25°C, the value of $\Delta h_r$ was 10.0 J/g as calculated using Equation 1. This estimate is an over approximation, but is of comparable magnitude to the overall amount of enthalpy relaxation experimentally measured for Molecule A as shown in Figure 43.

Figure 42: Enthalpy calculation from DSC curve.

In addition to a change in the enthalpy as a function of ageing time, the temperature at which the endothermic peak appears also increases with ageing time (Figure 44). This phenomenon has been observed in epoxy resins [6, 9]. As the amount of ageing time increases for a sample, the molecules become increasingly dense as the free volume and molecular mobility decrease as shown schematically in Figure 45. When the sample is tested using DSC, the temperature required to obtain the equilibrium conditions above the glass transition temperature increases to overcome the relatively tight packing of Molecule A molecules. Figure 44 indicates a linear relationship between the endothermic peak temperature and the ageing time over the course of experimentation. The trend begins to level off as the time increases and the molecules arrange themselves into a more stable orientation.
Figure 43: Enthalpy change as a function of ageing time for amorphous melt extruded 100% Molecule A. An exponential fit is shown for reference.

Figure 44: Temperature of the endothermic peak occurrence as a function of ageing time.

The extent of physical ageing, and thus enthalpy of relaxation, is a function of ageing temperature as well as time. Several studies indicate that if a material is maintained at a temperature of at least 50°C below its glass transition temperature, then molecular motions are negligible because of high viscosity, and thus no ageing effects will be detected [7, 10-12]. This guideline has been accepted as a general rule, but has not been tested on a wide variety of materials.
The enthalpy data may be represented in terms of a relaxation function ($\phi$) with respect to the calculated $\Delta H_\infty$ value [13].

$$\phi(t_{\text{ageing}}) = 1 - \frac{\Delta H_1}{\Delta H_\infty}$$  \hspace{1cm} (2)

Here $\phi$ represents the extent of physical ageing. The relaxation function for Molecule A is presented in Figure 46. The relaxation decays exponentially as a function of ageing time. The relaxation function is often modeled using the Kohlrausch-Williams-Watts (KWW) equation (Equation 3) [8]. The KWW equation is empirically determined and expresses the relaxation as a stretched exponential with time constant $\tau$ and stretch parameter $\beta$.

$$\phi(t_{\text{ageing}}) = \exp\left[\left(-\frac{t}{\tau}\right)^\beta\right]$$  \hspace{1cm} (3)

The KWW fit is shown in Figure 46 along with the experimental data. Overall, the KWW equation mimics the general shape of the data, but does not accurately represent the data from point-to-point. The fit can be improved by using a three parameter model, but adding an additional parameter is not helpful for the physical interpretation of the data. Using non-linear regression, the KWW fit to the data gave $\tau = 45$ days and $\beta = 0.5$. The value of the time constant is representative of shelf life for a material [11]. A time constant on the order of years is desirable, but in the case of Molecule A, the approximate shelf life is 45 days at 25°C. A shelf life on the order of years is needed for safety and patient compliance.
Figure 46: Relaxation function ($\phi$) for Molecule A as a function of ageing time. The Kohlrausch-Williams-Watts (KWW) equation is shown for comparison with $\beta = 0.5$ and $\tau = 45$ days.

The KWW model assumes that $\tau$ is constant throughout the ageing process. Intuitively the value of $\tau$ would decrease as the ageing time increases, i.e., as the system approaches its equilibrium state. In fact, a study by Mao et al. [14] found that a system undergoing physical ageing is better represented using a variable $\tau$ value as suggested by Angell [15, 16]. Angell proposed the use of a fragility parameter ($D$), which is representative of the deviation of the relaxation kinetics from Arrhenius behavior. Amorphous materials exhibiting Arrhenius-like behavior are classified as “strong” glass formers and typically have a three-dimensional network of covalent bonds, whereas materials exhibiting non-Arrhenius behavior are classified as “fragile” glass formers and typically consist of molecular interaction through non-directional and non-covalent interactions [17]. In other words, strong glass formers are less likely to experience physical ageing than fragile glass formers. A fragility parameter greater than 30 is considered strong and a value less than 10 is considered fragile [18].
Figure 47: Temperature versus relaxation time for fragile and strong materials. Strong materials have a linear relationship indicating a small deviation from Arrhenius behavior, while fragile materials have a strong deviation from a linear relationship indicating a large deviation from Arrhenius behavior. (adapted from Angell [19]).

Fragile behavior can be accounted for by the presence of co-operative molecular motions [20].

The fragility parameter is derived from an Adam-Gibbs equation derived from statistical mechanics (Equation 4):

$$
\tau = \tau_0 \exp \left( \frac{\Delta \mu s^*_c}{k_B T S_c(T)} \right)
$$

where $\tau_0$ is the pre-exponential factor, $T$ is absolute temperature, $S_c(T)$ is the configurational entropy at temperature $T$, $k_B$ is Boltzmann's constant, $s^*_c$ is the entropy of the smallest cooperative molecular region, and $\Delta \mu$ is the activation energy of cooperative rearrangement. This equation can be modified to describe non-equilibrium relaxation in the glass state as a function of the fragility parameter [21]. The calculation of the fragility parameter is based on the Vogel-Tammann-Fulcher (VTF) equation (Equation 5), which describes the non-linear temperature dependence of relaxation

$$
\tau = \tau_0 \exp \left( \frac{D T_0}{T(1 - T_0/T_f)} \right)
$$

where $T_f$ is the fictive temperature, and $T_o$ is an additional parameter describing deviation from the linear Arrhenius behavior function. The fragility parameter can be calculated by measuring shear viscosity or dielectric properties of a material as a function of temperature. For pharmaceutical materials, these measurements are usually difficult to obtain given the inherent high viscosity and required sample preparation methods [18]. An alternative method was
proposed by Moynihan et al. [22, 23], which uses thermal measurements to estimate the effect of temperature on relaxation time and thus a prediction of fragility can be made. The heating rate can be related to the activation enthalpy at the $T_g$ ($\Delta H^*$) using Equation 6.

$$\frac{\Delta H^*(T_g)}{R} = \frac{d \ln q}{d(1/T_g)} \quad (6)$$

The heating rate ($q$) is varied during DSC and the corresponding glass transition temperature is measured. The results are shown in Figure 48. As the heating rate increases, the glass transition temperature also increases. A high heating rate allows the sample to stay in the glassy state for a greater temperature range, delaying the glass transition temperature as the molecules rearrange to obtain the equilibrium liquid state [17]. A low heating rate allows the glassy molecules to rearrange over a longer time range so that the liquid state is reached at a lower temperature.

To symbolically express the fragility parameter in terms of estimated quantities, we make use of a second parameter, $m$, which is defined as follows

$$m = \frac{\Delta H^*(T_g)}{\log(10)RT_g} \quad (7)$$

The parameter $m$ can be related to the fragility parameter, $D$, by combining Equations 5 and 7 to give Equation 8.

$$m = \frac{D/T_g}{(\ln 10)(1-T_0/T_g)^2} \quad (8)$$

The minimum relaxation time can be estimated as the timescale of atomic vibrations at $10^{-14}$ s [14]. Now that the value of $\tau_0$ has been estimated, $m_{\text{min}}$ is calculated as 16 (unitless).

$$m_{\text{min}} = \frac{\Delta H^*_{\text{min}}}{\ln(10)RT_g} = \log\left(\frac{\tau(T_g)}{\tau_0}\right) \quad (9)$$

This value of $m_{\text{min}}$ is used in fragility parameter calculations. Finally, the fragility parameter can be calculated using Equation 10.

$$D = \frac{(\ln 10)m_{\text{min}}^2}{(m - m_{\text{min}})} \quad (10)$$

The fragility parameter for Molecule A is $14 \pm 1$. A value of $D$ between 7 and 15 is typical for small molecule pharmaceuticals [18] and is likely due to a lack of physical entanglements often seen in polymeric materials. Crowley et al. [18] have suggested that the fragility parameter of
pharmaceutical materials can be predicted based on the ratio of their glass transition temperature to melting temperature ($T_g/T_m$).

![Figure 48: Inverse glass transition temperature ($T_g$) as a function of the natural log of heating rate, ln($q$), as determined by DSC.](image)

Molecule A is compared with other active ingredients in Table 8. Hydrochloro-thiazide and polythiazide (both diuretics) have $T_g/T_m$ ratios similar to Molecule A and similar fragility parameters. This results confirms that Molecule A is comparable with other active ingredients based on its $T_g/T_m$ ratio.

<table>
<thead>
<tr>
<th>Material</th>
<th>$T_g/T_m$</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochloro-thiazide [8]</td>
<td>0.70</td>
<td>12</td>
</tr>
<tr>
<td>Polythiazide [8]</td>
<td>0.70</td>
<td>10</td>
</tr>
<tr>
<td>Molecule A</td>
<td>0.68</td>
<td>14</td>
</tr>
</tbody>
</table>

7.1.3. Conclusions

Physical ageing has been characterized using enthalpy of relaxation data obtained from DSC measurements. The fragility parameter of Molecule A is 14, a typical value for many small molecule drug substances and an indication of glass formation that consists of non-directional molecular interactions versus a three dimensional covalent bond network of a strong glass former. Consistent with this result, the shelf life of 100% melt extruded Molecule A was approximated to be 45 days, which is shorter than the desired shelf life of several years.
7.2. Tuning Enthalpy of Relaxation

Now that physical ageing has been characterized for pure, melt extruded, amorphous Molecule A, we strived to modify the ageing behavior and specifically improve physical stability and shelf life by incorporating additional materials. The materials chosen were polyvinylpyrrolidone K30, hydroxypropyl cellulose, and Eudragit E100 (a methacrylate co-polymer), which are summarized in Table 9. These excipients were chosen because they are pharmaceutically approved and used commonly within the industry. They also are amenable to hot melt extrusion, i.e., they are thermally stable and have an acceptable melt viscosity for processing. In addition, they are water soluble, which keeps the targeted instant dissolution release profile within reach.

Table 9: Excipients used to modify the physical ageing process of Molecule A.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Tg (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinylpyrrolidone (PVP) K30</td>
<td>168</td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose (HPC)</td>
<td>130</td>
</tr>
<tr>
<td>Eudragit E100</td>
<td>50</td>
</tr>
</tbody>
</table>

Molecule A was combined with an excipient in an 80 wt% Molecule A to 20 wt% excipient ratio. A total of 5 grams was mixed using a turbulent mixer for 10 minutes. Then approximately 0.5 grams of the mixture was placed into a small vial and partially submerged in a silicone oil bath at 130 degrees. The contents of the vial were visually monitored and removed from the oil bath once completely melted. The contents were then allowed to cool to room temperature and stored at ambient conditions (approximately 13% RH and 23°C) overnight. The samples were then tested using differential scanning calorimetry. The temperature was equilibrated at 25°C and then ramped up to 200°C at a rate of 10°C per minute. The heat flow was monitored as a function of temperature. This test was performed approximately 24 hours after the mixture was melted. The onset of the glass transition temperature as well as the midpoint of the glass transition temperature was determined using data analysis software from TA Instruments. The results are summarized in Figure 49.
PVP K30, HPC, and Eudragit E100 added to Molecule A at only 20 wt% increase the glass transition temperature of the mixture, indicating the presence of interactions between Molecule A and the excipients. The nature of the interactions are unknown; however, because only one glass transition temperature is present for each mixture, it is likely that a solid solution or molecular dispersion was formed rather than a physical mixture.

Each sample of 80% Molecule A and 20% excipient was stored in a heat sealed moisture barrier bag and allowed to age under ambient conditions. DSC thermograms were again used to test the new bi-component formulation as a function of ageing time. The enthalpy changes were determined by calculating the area under the endothermic peaks and are summarized in Figure 50.

Figure 49: Glass transition temperature onset and midpoint for pure Molecule A (far left) and Molecule A- excipient combinations.
When excipients are added to Molecule A, the change in enthalpy associated with the endothermic peak seen at the glass transition temperature has decreased in all cases. A 20% dilution of pure Molecule A in Figure 50 assumes that the second component does not contribute significantly to the total relaxation [1]. All enthalpy values for mixtures were reduced beyond what is predicted for a non-interacting bi-component mixture. Thus, the addition of a second component leads to molecular interactions with Molecule A and to the coupling to molecular motions. The mobility of the mixture is the net result of the effect of each component on the mobility of the other. In other studies involving mixtures of sucrose and PVP, researchers hypothesize that molecular level interactions occurs via hydrogen bonding of the two components [24]. It appears that the addition of a second component and the subsequent molecular level interactions are important for lowering the observed enthalpy change during ageing.

It seems that molecular level interactions are taking place in the 80% / 20% mixtures, but the extent of these interactions is not fully understood. The mixture may have formed a solid solution or a solid dispersion. The molecules within a solid solution are mixed intimately on the molecular level such that the two components have become essentially indistinguishable. A solid solution is often an indication that the drug substance is miscible in the excipient. On the other hand, a solid dispersion consists of discernable domains of component one and component two. A solid dispersion will have interactions between domains, but not to the extent seen in solid solutions.

Figure 50: Change in enthalpy as a function of ageing time for pure Molecule A (●), with 20% PVP K30 (□), 20% HPC (▲), and 20% Eudragit E100 (○). A physical dilution of 20%(●) is shown for comparison.
If the domain size of the mixture is known, the likelihood of a solid solution versus a solid dispersion can be determined. DSC is often used to detect the presence of a solid solution. This detection is accomplished by ramping the temperature and identifying any glass transition regions. In a two component system, a physical mixture should have two glass transition temperatures. A solid solution will have only one glass transition temperature. The DSC utility is limited, however, to detecting solid solutions in size greater than 30 nm [25]. Solid-state nuclear magnetic resonance (NMR) can be used as a complementary technique to detect domains smaller than 30 nm. Domain sizes are calculated using the following correlation given in Equation 11 [26].

\[ L = (6DT_i)^{0.5} \] (11)

Here, \( L \) is the domain length, \( D \) is the spin diffusivity, and \( T_i \) is time scale obtained from solid-state NMR. A range of \( D \) values was used, spanning rigid to flexible materials (0.5 \( \times \) 10\(^{-16}\) m\(^2\)/s to 8 \( \times \) 10\(^{-16}\) m\(^2\)/s). We assumed that the diffusivity of our material was in this range. The time constant, \( T_i \), describes the diffusion that occurs over a length, \( L \). If the domain of the drug substance or excipient is smaller than the domain outlined by \( L \), then all \( L \)-sized domains will look the same and one value of the time constant will be measured. If the domain of the drug substance or excipient is the same size or larger than \( L \), then the two types of \( L \)-sized domains will look different and two values of the time constant will be measured.

To determine the time constant using solid-state NMR, a negative magnetization is applied to the sample and the spin diffusivity is monitored as the sample regains its original state. The spectrum for 80% Molecule A / 20% PVP K30 is presented in Figure 51 as a function of time.
Figure 51: Solid-state NMR spectra for a 80% Molecule A / 20% PVP K30 solid sample (frequency versus absorption). Times listed indicate the time allowed for spin diffusion to occur after a negative magnetization is applied.

The peak intensities in Figure 51 can be normalized and the time constants extracted. The data are presented in Figure 52. The average $T_1^H$ for PVP K30 peaks (in black) are $1.73 \pm 0.05$ s and the average $T_1^H$ for Molecule A peaks (in red) are $1.17 \pm 0.05$ s.
The results for domain sizes are displayed in Table 10. When a physical mixture of amorphous Molecule A and PVP K30 is examined using solid-state NMR, the domain size is on the order of 20 – 90 nm. Similarly, the domain size for the 80% Molecule A / 20% PVP K30 sample is 20 – 90 nm. These results are a clear indication that the Molecule A sample is a solid dispersion rather than a solid solution. This result is not surprising given the relatively high amount of Molecule A in the sample. With only 20% PVP K30, there is simply not enough polymer for the drug substance to interact with. However, regardless of domain size and conclusions drawn from these data, we can be sure that some molecular level interaction is reducing the enthalpy change as ageing time increases.

Note that only the Molecule A/PVP K30 mixture was examined using solid-state NMR. The expected findings for the HPC and Eudragit E100 samples are believed to yield similar results. PVP K30 is frequently used for its strong solid solution forming abilities. Thus if PVP K30 does not form a solid solution, it is likely that the other mixtures will not form solid solutions either.

Table 10: Domain size and time constant comparison for pure Molecule A, pure PVP K30, amorphous physical mixture of Molecule A and PVP K30 used as a reference, and 80% Molecule A / 20% PVP K30 sample.

<table>
<thead>
<tr>
<th></th>
<th>Molecule A</th>
<th>PVP K30</th>
<th>Amorphous Physical Mixture</th>
<th>Molecule A / PVP K30 Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (1H) (s)</td>
<td>0.90s +/- 0.04</td>
<td>2.36 +/- 0.05</td>
<td>1.71 +/- 0.10 and</td>
<td>1.73 +/- 0.05 and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.72 +/- 0.08</td>
<td>1.17 +/- 0.05</td>
</tr>
<tr>
<td>Domain (nm)</td>
<td>20-70</td>
<td>30-110</td>
<td>20-90</td>
<td>20-90</td>
</tr>
</tbody>
</table>

Figure 52: Normalized $T_1$ data for a 80% Molecule A / 20% PVP K30 sample. Peaks corresponding to PVP K30 are in black and peaks corresponding to Molecule A are in red.
The enthalpy of relaxation data for the two component systems were next modeled using the KWW equation as explained previously. The values of the relaxation time constant, $\tau$, were on the order of years for all excipient combinations. This is a drastic improvement over the pure Molecule A sample which had a time constant of 45 days. The relaxation functions are shown in Figure 53.

![Graph showing relaxation functions for different excipient combinations](image)

**Figure 53:** Relaxation function for pure amorphous Molecule A, 80% Molecule A and 20% PVP K30, 80% Molecule A and 20% HPC, and 80% Molecule A and 20% Eudragit E100.

The KWW results via DSC data and the conclusions from solid state NMR experiments indicate that molecular level interactions are responsible for the change in molecular mobility via van der Waals interactions and/or hydrogen bonding. With the addition of a second component at a relatively low level (20 wt%), the high Molecule A loading is maintained and physical ageing is slowed.

### 7.2.1. Conclusions

The addition of a relatively small amount of excipient to amorphous Molecule A can extend the shelf life from 45 days to several years. Interaction between Molecule A and the excipients on a molecular level restrict the molecular movements that cause physical ageing.

### 7.3. Water Uptake and Moisture Barrier Coatings

#### 7.3.1. Water Uptake

Molecule A is a hygroscopic material, which readily absorbs water from the atmosphere. The water absorbed can be monitored as a function of relative humidity using a dynamic vapor sorption (DVS) machine. Unprocessed, crystalline Molecule A was held at room temperature
and exposed to a pre-programed cycle of relative humidities as shown in Figure 54. The data show two water uptake regions. At low relative humidity, the slope of the weight % line is relatively linear, representing hydrogen bonding of water to Molecule A. At approximately 60% relative humidity, the slope increases indicating the accumulation of water clusters (i.e., all Molecule A polar groups are saturated). Melt extruded, amorphous Molecule A is presented for comparison.

In general, amorphous materials have the ability to uptake more atmospheric water than their crystalline counterparts because an amorphous material is limited only by the overall sample mass rather than the surface area. As shown in Figure 54, the amorphous material does indeed gain more water than the crystalline sample.

![Graph showing weight % and relative humidity over ageing time](image)

*Figure 54: Dynamic vapor sorption profiles for unprocessed Molecule A and 100% melt extruded Molecule A. Sample weight is measured as a function of time at a constant temperature of 25°C. The relative humidity is increased as a function of time and is plotted accordingly.*

When water enters a tablet core, it can cause premature dissolution, plasticization, and/or degradation. Molecule A is vulnerable to all three phenomena. Plasticization and degradation was observed while monitoring 100% amorphous Molecule A tablets stored at 40°C and 75% relative humidity. Molecule A tablets were placed into a film sealed plastic container and monitored for two months. The tablets, when first produced, appeared as shown in Figure 55. They were cylindrical with a diameter of 9 mm and a height of 4 mm. The tablets appeared glass-like, similar in appearance to ice. Following two months at high temperature and humidity, the tablets had completely transformed. The original cylindrical shape was lost and a spherical shape with extended sides was observed. The glass-like appearance was also lost, as the tablets took on an opaque, wax-like appearance.
Figure 55: 100% melt extruded Molecule A tablets stored at 75% relative humidity and 40°C for two months in a sealed container. Note the previously cylindrical shaped tablets have experienced significant material rearrangement.

Figure 56: Weight percent water content as determined by Karl Fischer titration for Molecule A tablets maintained at various combinations of temperature and humidity for three days.

The influence of temperature and relative humidity on Molecule A tablets was investigated by following the water content and visual appearance of the tablets exposed to different conditions. The conditions used are summarized in Figure 56. Tablets were exposed to these conditions without packaging, i.e., in an open vessel. The water content was measured using Karl Fischer titration, and the results are summarized in Figure 56. At low relative humidity, regardless of temperature, the water content remained at the level of fresh tablets. The visual appearance also is unchanged at 15% relative humidity. At 75% relative humidity, the water content of the tablets rises significantly, with more water content at 40°C than 23.5°C. Visually these tablets appear similar to the tablets aged for 2 months at 75% relative humidity and 40°C (Figure 57).
At 23.5°C and 75% relative humidity, the tablet has retained a shape, but has lost its surface definition. The tablet exposed to 40°C and 75% relative humidity became a disk, taking on the shape of the bottom of the container. These results indicate the importance of relative humidity on the shelf life Molecule A, and will be discussed in detail later. The effect of temperature can be understood in connection with molecular mobility. As the temperature is increased, more energy is added to the system, allowing the molecules to move faster than at low temperatures. This molecular movement contributes to the overall tablet shape change.

The chemical stability of Molecule A tablets were assayed using HPLC. As the storage time increased, the degradation products and byproducts increased in both number and quantity. The results are most easily presented as the area percent Molecule A as a function of ageing time (Figure 58). This was true of both the coated and uncoated amorphous Molecule A tablets. Some peaks which have been commonly detected in previous HPLC analysis have been identified, but the majority of the peaks have not been identified. Without the chemical identification for all peaks, the reaction mechanism responsible for the degradation of Molecule A is not easily determined. A technique such as mass spectrometry can be used in conjunction with liquid chromatography, but this investigation is outside the scope of this work.
7.3.2. Moisture Barrier Coatings

The moisture sorption of hygroscopic drug products can be minimized by carefully selecting appropriate excipients [27] or by the use of moisture resistant packaging [28]. Prinderre et al. suggest that the application of a polymer based coating designed to create a moisture barrier is preferable because of cost and the option to tailor permeability for drug products physical property requirements [29]. Coating materials for moisture protection are commonly selected to be water soluble for rapid disintegration, but also hydrophobic for moisture barrier functionality [30]. Formulators have attempted to combine both of these properties by using a water soluble film polymer incorporated with materials with moisture repellent or scavenging abilities, or alternatively soluble hydrophilic polymers that uptake water and strongly bind to hold water in the coating.

Commonly used moisture barrier coating polymers with moisture scavenging properties include hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), and poly(methylacrylate-methylmethacrylate) [31]. These commercially available coatings are listed in Table 11 according to polymer base material.

<table>
<thead>
<tr>
<th>Commercial Name</th>
<th>Polymer Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepifilm LP</td>
<td>Hydroxypropyl methyl cellulose</td>
</tr>
<tr>
<td>Opadry AMB</td>
<td>Polyvinyl alcohol</td>
</tr>
<tr>
<td>Eudragit</td>
<td>Poly(methylacrylate-methylmethacrylate)</td>
</tr>
</tbody>
</table>

Sepifilm LP and Opadry AMB formulations have a higher water sorption capability due to the higher number of hydroxyl group in the polymer base and constituent polymers (HPMC and
micro crystalline cellulose for Sepifilm LP or PVA and xanthan gum for Opadry AMB). The polymer base for Opadry, PVA, is shown in Figure 59 hydrogen bonding to water. Work by Mwesigwa et al. investigated moisture sorption and permeability of moisture barrier films and found that when coated lactose monohydrate tablets were exposed to high relative humidity, Eudragit coated tablets absorbed the least amount of water and Sepifilm LP coated tablets absorbed the most water [32]. The results of this study are presented in Figure 60. Opadry also holds onto moisture more strongly than the other coatings as the relative humidity is decreased.

Figure 59: Polyvinyl alcohol hydrogen bonding with water.

Conflicting conclusions were drawn from the work of Bley et al. [31]. Bley conducted a similar experiment with coated garlic tablets and found that Opadry coated tablets absorbed less moisture than Eudragit coated tablets at short exposure times (Figure 61). This experiment may more closely imitate actual high humidity conditions because the relative humidity is maintained rather than ramped. The change in the rate of water uptake for Opadry AMB coated tablets after six days is due to a rubbery to glassy state transition in the coating material [31]. Mobility in the glassy state is lower than in the rubbery state according to free volume diffusion theory, so the probability for a water molecule to jump from one cavity to another is lower and thus the penetration rate of water is decreased [33]. These findings indicate that maintaining the glassy state for Opadry coatings during storage may produce the best moisture barrier properties.
Figure 60: Moisture sorption profiles for a lactose monohydrate tablets uncoated and coated with moisture barrier coatings. The data were collected at 25°C and held at each relative humidity for 300 minutes. Tablet coating thickness ranged from 50 – 80 μm. (Adapted from Mwesigwa et al. [32]) Note: Opadry = Opadry AMB.

Figure 61: Water uptake as a function of time for coated 100 mg garlic tablet samples exposed to 75% relative humidity and room temperature (Adapted from Bley et al. [31]). Note: Methocel = HPMC = Sepafilm.
The storage conditions required to maintain the glassy state of the Opadry coating material were determined by varying the relative humidity at 25°C and monitoring the water absorption (Figure 62 (A)). Similarly, the water absorption was monitored at a constant relative humidity of 75% and varying temperatures as shown in Figure 62 (B). Linear equations were fit to the experimental data. The intersections of these fit lines indicate a critical value below which the glassy state was maintained and above which the rubbery state was dominant. Results indicated that at 25°C the relative humidity should be limited to 66% or lower for optimal moisture barrier properties. Likewise, at 75% relative humidity, the temperature should be below 16°C.

![Graph](image)

Figure 62: Opadry AMB water uptake at (A) room temperature and increasing relative humidity, (B) 75% relative humidity and increasing temperature (Adapted from Bley et al. [31]).

Adsorbed moisture on the surface of hydrophilic coatings disrupts intermolecular and intramolecular hydrogen bonding [32]. Subsequently, the integrity of the polymer coating is decreased and permeation of water through the polymer layer may be enhanced. Atmospheric water may either hydrogen bond to polar groups within the coating polymers and/or cluster in pockets once polar sites of the polymer become saturated. In the glassy state, water largely hydrogen bonds to the coating, disrupting inter-polymer hydrogen bonding and thus inducing chain relaxation and swelling. In the rubbery state, water clusters within the coating and is marked by exponential sorption of environmental water.

Amorphous Molecule A tablets were coated with 4.5 weight percent of Opadry AMB coating material before being stored at 40°C and 75% relative humidity. The tablets were stored in identical containers as used with the non-coated tablets. The coating added significantly to the physical integrity of the tablets as shown in Figure 63. The tablet shape remained cylindrical in shape, maintaining the original dimensions. The water content in the tablets could not be distinguished from the water content in the Opadry coating due to strong adhesion of the coating material and required sample size for Karl Fischer titration. The Opadry AMB coating works as
a water scavenger, adsorbing water to the coating surface. Measuring the water content of the tablet would not indicate the percentage of water contained within the coating versus the tablet core.

Visually the tablet cores maintained the shape of the original, uncoated tablets at day zero. In comparison, the uncoated tablets stored in high temperature and humidity conditions became opaque over time, representative of the rubber-like state above the glass transition temperature. Due to a high amount of water present in the tablet core, Molecule A was plasticized, decreasing the glass transition temperature such that the storage temperature of 40°C exceeded the plasticized glass transition temperature.

![Figure 63: Pure amorphous Molecule A tablets coated with Opadry AMB and stored at 40°C and 75% relative humidity for three months.](image)

Opadry AMB is a water soluble coating and should not inhibit the dissolution of an instant release tablet. This hypothesis was confirmed by comparing the dissolution of coated and uncoated tablets using the same dissolution procedure. The results are presented in Figure 64. The dissolution behavior of coated tablets with 4.0 and 4.5 wt% of Opadry AMB coating material follow an instant release profile. The initial rate of dissolution is smaller as the coating material dissolves and moves into solution, but the following behavior matches the uncoated tablet closely.
Figure 64: Dissolution of Opadry AMB coated Molecule A tablets. An uncoated tablet and a coated tablet courtesy of Novartis are shown for comparison.

7.3.3. **Conclusions**

Applying a coat of 4.5 wt % Opadry AMB to 100% amorphous Molecule A tablets reduces molecular motions in the tablet core caused by water uptake.

The lessons learned from the study of amorphous Molecule A are summarized in Figure 65. Topics of concern are located at the perimeter of the figure and the subsequent stability problems are at the center.
Figure 65: Stability summary.
&.
8. Dissolution

8.1. Introduction

Dissolution testing is an important measure to ensure that a drug product meets the desired specifications. These specifications may simply require a certain overall release profile (e.g., instant release, sustained release, etc.) or they may require that the release profile for a new solid dosage form matches the release profile of a prior form. If the dissolution behavior can be controlled, years of development work can be saved and regulatory hurdles can be avoided.

Many factors control the dissolution behavior of a solid dosage form, including tablet properties and the properties of the medium in which the tablet is dissolved [1]. The dissolution apparatus and protocol are outlined by the United States Pharmacopeia (USP), which details the size and shape of the dissolution vessel, the temperature of operation, sampling techniques, etc. Thus, the conditions of the dissolution medium are intended to be invariant, leaving the properties of the tablet itself to control dissolution behavior. Some of the most influential properties include the solubility of the drug substance and excipient(s) and the physical form of the drug substance (e.g., crystalline or amorphous). The geometry of a tablet, the particle size of the tablet constituents, and the porosity are also important. A schematic presented in Figure 66 summarizes dissolution behavior influences.

![Figure 66: Important factors influencing dissolution behavior.](image)

A survey of Figure 66 indicates that one variable in particular can control many of the factors influencing dissolution behavior: excipient selection. Changing the formulation of a tablet is convenient, but in practice can prove difficult due to processing requirements (i.e., temperature restrictions) or unwanted interactions with the drug substance. However, if a drug substance is compatible with many excipients and allows for a large operating space, the dissolution behavior can be tailored according to excipient properties.
8.2. Excipient Selection

Molecule A happens to be a good candidate for dissolution tuning by excipient selection. Molecule A’s relatively low melting temperature and required high drug load for bioavailability allow formulations to be processed at low melt extrusion temperatures. For example, polyvinyl pyrrolidone (PVP) has a glass transition temperature \( T_g \) of approximately 165°C. If processed alone, the processing temperature must be above the \( T_g \) of PVP. When PVP is added to Molecule A, the mixture can be processed at a lower temperature because the melted Molecule A essentially acts as a plasticizer for PVP. Five excipient candidates were chosen for incorporation with Molecule A and are summarized in Table 12.

Table 12: Excipients chosen for processing with Molecule A.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Approximate Molecular Weight</th>
<th>Hydrogen Bonding Donor/Acceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene Glycol (PEG)</td>
<td>8,000</td>
<td>Acceptor</td>
</tr>
<tr>
<td>PVP K17</td>
<td>10,000</td>
<td>Acceptor</td>
</tr>
<tr>
<td>PVP K30</td>
<td>45,000</td>
<td>Acceptor</td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose (HPC)</td>
<td>80,000</td>
<td>Acceptor / Donor</td>
</tr>
<tr>
<td>Eudragit E100</td>
<td>150,000</td>
<td>Acceptor</td>
</tr>
</tbody>
</table>

These excipients were chosen based on several criteria. First, they are all pharmaceutically acceptable and are currently used in some capacity in the pharmaceutical industry. For example, PVP is used frequently in formulations that are processed using granulation and tablet compaction. Second, all excipients are heat insensitive at the operating temperatures required for the melt processing of Molecule A. Finally, each of the listed excipients is water soluble. Molecule A requires an instant release dissolution profile and the solubility of the excipients is important to maintain this behavior. Exact solubility values are unknown, but were estimated as follows [2]

\[
\text{PEG 8,000} > \text{Eudragit E100} > \text{PVP (K17 and K30)} \approx \text{HPC}
\]

A mixture containing 50 wt% Molecule A and 50 wt% of excipient was extruded at an operating temperature above the melting temperature of Molecule A for consistency. Tablets were hand molded directly after extrusion into cylindrical shapes, 4 mm high with a 9 mm diameter. The tablets were stored at atmospheric conditions in moisture barrier bags until they were tested to understand their dissolution behavior. Dissolution was conducted using guidelines from the United States Pharmacopeia (USP) paddle method. The dissolution medium was 500 mL of 0.1 M HCl maintained at 37°C. Molecule A absorption was measured using UV-vis at a wavelength of 279 nm. Beer’s law and a calibration curve allowed for the calculation of Molecule A concentrations.

The dissolution results are presented in Figure 67. The dissolution timescale was observed to vary directly with the excipient molecular weight (Table 12). PEG 8000 containing tablets, the lowest molecular weight excipient, reach complete dissolution first. This dissolution behavior is also consistent with the high relatively high solubility of PEG 8000. Both molecular weights of PVP follow with the second and third fastest dissolution time. In this case, the molecular weight of PVP does not substantially change the dissolution behavior of the tablets. The chemical
nature of PVP, i.e., the solubility, drives the dissolution. Total dissolution of Eudragit E100 containing tablets occurs at a longer time. The solubility of Eudragit is greater than PVP, but its molecular weight is an order of magnitude higher, slowing the dissolution process. Finally the HPC containing tablet is the slowest to dissolve, not reaching complete dissolution within the three hours it was monitored. Figure 68 presents the dissolution results at longer times. Note that the other four excipients have reached a steady state before the HPC containing tablets have completely dissolved.

Figure 67: Dissolution results for Molecule A and excipient combinations. The percent of Molecule A dissolved was measured as a function of time using UV-vis spectroscopy. Standard deviation is not presented, but is on average ± 2% for all data.

The dissolution behavior of the HPC containing tablets can be attributed to its relatively high molecular weight and relatively low solubility. However, a more telling insight is HPC’s ability to both accept and donate hydrogen bonds while the other excipients are only hydrogen bond acceptors (Table 12). The presence of hydrogen bond donating and accepting sites indicates the possibility of strong binding between Molecule A and HPC, which retards the dissolution behavior. The combination of HPC and Molecule A, while meeting the requirements for chemical stability and processing ability, does not meet requirements for instant release dissolution behavior (i.e., greater than 80% percent Molecule A dissolved within 30 minutes).
Dissolution data can be analyzed using several methods. Similarity factor and difference factor methods [3] compare dissolution data point-by-point. A degree of similarity is calculated and is used to determine how similar or dissimilar data are. Statistical methods, such as analysis of variance (ANOVA) can also be used. ANOVA results give essentially an estimation of similarity, in the same vein as the similarity factor and difference factor methods. While these methods are easy to utilize, they offer no insight into the dissolution mechanism. A mathematical formula used to express the dissolution results makes analysis simpler.

From a purely qualitative perspective, observing dissolution can give clues to the mechanism of release. Swelling or bulging of the tablet is an indication of bulk erosion of the drug substance. In other words, the drug is exiting from the inner portion of the tablet as the excipient matrix swells and exit passages are created. Alternatively, if a tablet maintains its shape and decreases uniformly in all dimensions, the tablet is likely surface eroding. Drug substance dissolves at the surface of the tablet and moves into the dissolution medium fast enough to ensure a large concentration gradient at the tablet surface only. This behavior is typical of highly water soluble drug substances and excipients.

Molecule A and the incorporated excipients are water soluble and no bulging or swelling of the tablets was observed. Thus, a surface eroding mechanism is highly likely. The dissolution data can be modeled by relating the change in concentration of Molecule A to the concentration of Molecule A via a kinetic model [4]

\[
\frac{dC}{dt} = -kC^n
\]

where \( C \) is concentration, \( k \) is a release rate constant, and \( n \) is an integer \( \geq 0 \). A zero order reaction \( (n = 0) \) can be integrated to the following equation

\[
C(t) = C_o - k_0 t
\]
A zero order kinetic model is well suited to several types of pharmaceutical dosage forms including some transdermal systems, matrix tablets, coated forms, etc. [5]. Zero order release ensures the same amount of drug is released per unit time. A first order kinetic model was first proposed by Gibaldi and Feldman [6] and has been used to model absorption and elimination of some drug substances in addition to tablet dissolution. For a first order reaction, Equation 2 becomes

\[ \frac{dc}{dt} = -k_1 C \]  

which when integrated can be fit to experimental data

\[ C(t) = C_0 e^{-k_1 t} \]

A first order release profile releases drug substance such that the amount released is proportional to the drug remaining in the tablet core. Other mathematical models exist and are used commonly in practice including the Weibull model [7] and the Higuchi model [8] among others. These additional models often incorporate many parameters and are derived for specific scenarios.

The excipient – Molecule A tablets can all be modeled using a zero-order kinetic model. This is consistent with visual observations. Using the model, the release rate constants can be calculated using graphical methods when plotting the amount of Molecule A dissolved versus time. The results for the rate constants are presented in Table 13.

**Table 13: Zero-order rate constants for 50/50 Molecule A/excipient tablets.**

<table>
<thead>
<tr>
<th>Excipient</th>
<th>( k_0 ) (Percent Dissolved / min)</th>
<th>( R^2 ) (Model fit factor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG 8,000</td>
<td>7.2</td>
<td>0.99</td>
</tr>
<tr>
<td>PVP K17</td>
<td>4.0</td>
<td>0.97</td>
</tr>
<tr>
<td>PVP K30</td>
<td>4.2</td>
<td>0.98</td>
</tr>
<tr>
<td>HPC</td>
<td>0.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Eudragit E100</td>
<td>1.6</td>
<td>0.89</td>
</tr>
</tbody>
</table>

The zero-order rates summarized in Table 13 can be used as a library to tailor melt extruded tablet dissolution of Molecule A.

### 8.3. Ratio of Excipient to Drug Substance

Changing the relative amount of a particular polymeric excipient may also be a way to alter dissolution behavior as outlined in Figure 66. PEG 8000 was chosen as the excipient to investigate because of its ability to plasticize a formulation during melt extrusion, thus allowing a high load of Molecule A to be produced. PEG 8000 was combined with Molecule A at three different levels, ranging from 50% PEG 8000 to 30% PEG 8000. The dissolution results are presented in Figure 69.
In addition to comparison of the PEG 8000 tablets, the dissolution behavior of Molecule A as prepared by Novartis was included. Molecule A is prepared by a wet granulation method followed by tablet compaction. These Molecule A tablets have been coated with a non-functional, water soluble coating. The data shown for Novartis prepared tablets matches the data produced during dissolution testing at Novartis.

The dissolution data in Figure 69 indicate that regardless of the amount of PEG 8000 added to the Molecule A formulation, the dissolution behavior remains unchanged. Release of Molecule A follows a zero-order release mechanism with the same rate constant presented in Table 13. The solubility of PEG 8000 is high, negating any affect that may be observed by changing its concentration.

8.4. Coating Material

An Opadry® AMB water soluble coating was applied to the PEG 8000 / Molecule A tablets. Approximately 4.5 wt% of the Opadry coating was applied to each tablet. The dissolution behavior of coated PEG 8000 tablets is also shown in Figure 69. The coated tablets exhibit a slight variation in curve shape as a result of the time required for the coating material to dissolve and expose the Molecule A/PEG 8000 tablet core when compared to the uncoated tablets. This is likely due to the variability in the amount of coating material applied. Coated tablets are compared directly to Novartis produced tablets in Figure 70.

By simply coating tablets with 4.5 weight percent of water soluble Opadry® coating material, the dissolution behavior can be altered to match existing Molecule A products. After the coating material has dissolved, the release rate of the 50/50 Molecule A/PEG 8000 tablet is identical to that of the uncoated tablet. The zero-order rate constants for the coated and uncoated tablets after the coating material has dissolved away are not statistically different.
Figure 70: Dissolution of Molecule A tablets in 500 mL of 0.01 M HCl according to the USP Method #2.

8.5. Conclusions and Implications

The above results show that the dissolution rate can be controlled by adding excipient(s) in the form of coatings. The excipient can also be incorporated into the Molecule A core during extrusion. A number of excipient materials are available, but the excipient must be compatible with the drug substance and water soluble to maintain the instant release dissolution profile. The ability to systematically control dissolution behavior with excipients is a valuable tool. In principle, when a different drug substance is chosen, the proper formulation could be chosen without experimental testing to achieve the desired dissolution.
8.6. **Bibliography**

2. From SciFinder Database - calculated using Advanced Chemistry Development Software.
9. Continuous Melt Extrusion of Molecule A

The previous chapters have outlined research conducted to understand the scientific nature of hot melt extrusion. This chapter addresses the direct application of melt extrusion to the continuous processing of Molecule A. Two formulations will be described, one of which is ready for implementation.

9.1. Introduction

The Novartis-MIT Center for Continuous Manufacturing was created to introduce innovative and continuous processing techniques to the pharmaceutical industry. The pharmaceutical industry has relied on batch processes for decades, but cost-cutting incentives have piqued interest in continuous manufacturing because of its economic advantages. Continuous manufacturing also offers a uniform final product, reduced development time, and the opportunity to incorporate in-line monitoring devices. A small part of the Novartis-MIT Center, called the Redline, is part of that continuous manufacturing effort that focuses on the implementation of the first completely continuous production line from drug substance synthesis to final dosage form. Melt extrusion is an important part of that process because of its ability to reduce the total number of unit operations and powder handling steps.

The current downstream process to manufacture Molecule A utilizes an organic solvent based wet granulation step followed by milling, drying, powder mixing, and tablet compaction. The overall downstream production time is on the order of several days. This process involves many powder handling steps, which is particularly problematic given the poor flow properties and high drug load requirement due to bioavailability constraints.

9.2. Pure Molecule A Extrusion

The properties of Molecule A were determined in order to create a temperature operating space. To determine an upper bound, Molecule A was tested with thermal gravimetric analysis (TGA). The results are shown in Figure 71 for both viable polymorphs of Molecule A.
Figure 71: TGA of Molecule A polymorph A (mod A) and polymorph B (mod B).

Molecule A polymorph A loses approximately one weight percent of residual solvent remaining from its chemical synthesis followed by decomposition at approximately 150°C. Polymorph B has a large amount of residual solvent as demonstrated by the continual drop in weight percent until its decomposition. Polymorph B was manufactured in house at MIT and did not meet residual solvent requirements due to an insufficient drying step. For this reason, Molecule A polymorph A was the focus of this study.

Differential scanning calorimetry was used to determine the melting temperature of Molecule A. The results in Figure 72 show a strong melting endotherm beginning at approximately 95°C. The TGA and DSC data have outlined two different operating zones for Molecule A. To the left of the dotted line in Figure 72, Molecule A can be processed by melt extrusion only with a carrier with a melting temperature below 95°C. To the right of the dotted line, Molecule A can be processed in three different ways:

1. Molecule A and a high melting temperature carrier
2. Molecule A and a low melting temperature carrier
3. Molecule A only
The third option presents an interesting alternative not before seen in the pharmaceutical melt extrusion literature. A small molecule extrusion would decrease the number of unit operations further, relieve the threat of blending inconsistencies, and simplify analysis.

Molecule A was melt extruded using the operating temperatures defined in Figure 73. Molecule A was fed to the extruder using a gravimetric feeder at a rate of 100 g/hr, the rate at which Molecule A is synthesized upstream. The temperature along the barrel was ramped to a final temperature of 85°C. The relatively low temperature near the inlet (50°C) allowed powder to flow into the barrel without prematurely melting. The final temperature of 85°C was chosen to ensure that in addition to heat generated from friction and shearing within the barrel, the overall temperature of the extrudate would not be significantly higher than the melting temperature of Molecule A.

After extrusion, the Molecule A extrudate was hand molded. The crystallinity of the extrudate was determined using X-ray diffraction (XRD). As shown in Figure 74, the extrudate has become amorphous as evidenced by the characteristic amorphous halo. In comparison, the
starting Molecule A material is semi-crystalline (approximately 70%) as shown by the numerous peaks.

![XRD results for Molecule A before and after extrusion.](image)

**Figure 74: XRD results for Molecule A before and after extrusion.**

The dissolution behavior of melt extruded Molecule A tablets was tested to ensure an instant release profile. The profile is presented in Figure 75. Not only do the melt extruded tablets meet the instant release requirement, but they dissolve completely in approximately half the time as the Novartis wet granulation tablets. Faster dissolution can be an advantage when delivery to the patient is the concern, but may be a disadvantage when considering bioequivalence. Bioequivalence mandates that two solid dosage forms of the same drug substance have the same release profile within the body. From the *in vitro* dissolution testing, there is cause to predict a lack of bioequivalence. If bioequivalence requirements are not met, the new drug product must be re-filed with the FDA—a costly and time consuming process. However, from a research perspective, a decrease in time required for dissolution is an interesting tool.

![Dissolution of Molecule A melt extruded tablets and the Novartis wet granulation formulation.](image)

**Figure 75: Dissolution of 100% Molecule A melt extruded tablets and the Novartis wet granulation formulation.**
Pure Molecule A melt extrusion has been shown to be a viable option for the production of solid dosage forms. However, as described in previous chapters, the amorphous form of Molecule A suffers from chemical and physical instabilities. Next steps recommended for making this formulation successful in terms of stability are summarized in Future Work and Recommendations.

9.3. 50-50 Molecule A-PEG 8000 Extrusion

An alternative formulation for the processing of melt extruded Molecule A is 50 wt% Molecule A and 50 wt% PEG 8000. The extruder is operated at a maximum temperature of 65°C, melting the PEG 8000 but leaving the Molecule A crystalline and dispersed within the polymer matrix. DSC and X-ray diffraction measurements have confirmed these physical states as shown in Figure 76 and Figure 77. Degradation of Molecule A is minimized because the operation temperature is not in the range that leads to significant degradation.

![Figure 76: XRD of 50-50 Molecule A-PEG 8000 extrudate.](image)

![Figure 77: DSC results for 50-50 Molecule A-PEG 8000 extrudate.](image)
Figure 77 reveals an interesting aspect of the 50-50 Molecule A-PEG 8000 extrudate. The endothermic peak at approximately 60°C corresponds to the melting temperature of PEG 8000. The second peak must then correspond to crystalline Molecule A. Figure 72 indicates that Molecule A has a melting temperature onset at 95°C, whereas the peak in Figure 77 occurs at 120°C. The source of this peak is unknown and will be discussed briefly in Future Work and Recommendations, but due to the shape of the endotherm, it is believed that a new, more stable form of Molecule A has been created.

![HPLC results](image)

**Figure 78:** HPLC results presented as area percent of total chromatogram area for 50-50 Molecule A-PEG 8000 extrudate as a function of total extrusion time. The degradation products are listed along the abscissa.

Molecule A and PEG 8000 are added to the extruder from two separate gravimetric feeders. The extent of mixing was tested, giving an overall Molecule A weight percentage of 50% ± 1.5% at a feed rate of 100 g/hr of each component. The variation in drug content leaves room for improvement, but, for a proof of concept, this level of mixing justifies the removal of a pre-mixing step upstream. The degradation products created as a function of time during extrusion remained at acceptable limits during the entire extrusion run as shown in Figure 78.

A complete stability test has been performed at two different conditions: 40°C / 75% relative humidity and 25°C / 60% relative humidity. No significant changes were noted in the chemical composition, the physical form, the dissolution behavior, or tablet hardness. Thus, this 50-50 formulation is ready for implementation into the continuous manufacturing production line.

### 9.4. Molding and Extrudate Forming

Initial studies have been conducted using a prototype extrudate molding design. This molding device relies on the pressure created by the extruder drive rather than a piston as is often used in a traditional injection molding process. This "strip" mold is indexed such that once a mold cavity is filled, the device advances to the next mold cavity. The mold was fabricated and designed in collaboration with David Dow of the mechanical engineering department at MIT and is shown in Figure 79.
Figure 79: “Strip” molding device fabricated in house at MIT. The mold interfaces with the extruder die using the part at the top of the picture. The indexed mold cavities are shown at the bottom.

Tablets of the 50-50 mixture of Molecule A and PEG 8000 were produced successfully. Figure 80 shows the 150 mg, 9 mm diameter molded tablets.

Figure 80: Molded 50/50 Molecule A/PEG 8000 tablets.

The chemical composition and physical attributes of the molded tablets were similar to tablets molded by hand indicating no additional degradation products were created in the molding operation and that the crystalline structure of Molecule A was maintained.

9.5. Conclusions and Implications

- Melt extrusion parameters and formulation have been chosen for the continuous operation of the Novartis-MIT Redline.
- The system has been successfully operated at steady state for approximately 6 hours.
- The mixing achieved by the extruder is sufficient to eliminate a pre-mixing unit operation.
- The stability of the chosen formulation meets all physical and chemical criteria.
• A prototype molding device has been built and successfully implemented for uniform tablet production.
• The overall melt extrusion / molding process fits seamlessly into the Redline, producing consistently uniform tablets for a coating process downstream.
10. Future Work and Recommendations

- Identifying the source of degradation products during Molecule A melt extrusion

The extrusion of 100% Molecule A at a maximum operation temperature of 85°C produces temperature driven degradation products. While the amount created during the extrusion process itself is within the acceptable range, the amount of degradation increases when tablets are stored at accelerated stability conditions (e.g., 40°C and 75% relative humidity). Not only does the amount of degradation product increase, but new degradation products appear on HPLC chromatographs. Many of the new degradation products have not been seen previously during processing. However, they have been encountered when Molecule A was processed in the amorphous form for the production of a thin film and stored at the same accelerated stability conditions.

The first step in identifying the source of degradation products during storage is to identify chemical structures. This can be accomplished using a combination liquid chromatography – mass spectrometry (LCMS). Once the chemical structures have been identified, the underlying chemistry can be investigated. This work should be carried out in collaboration with our chemistry colleagues.

- Overcoming physical instabilities in 100% amorphous Molecule A

A solution to physical ageing was proposed by adding an additional component to the Molecule A formulation. Molecular level interactions slow the movement of amorphous Molecule A as a more stable thermodynamic state is approached. Solid state NMR results and DSC data give an indication of the specific interactions occurring, but there is no evidence to support the occurrence of a particular interaction. Understanding the molecular level interactions would aid in the engineering of an amorphous Molecule A system that is resistant to physical ageing.

- Identifying the endothermic peak from DSC data of 50-50 Molecule A-PEG 8000 extrudate

A single endothermic peak present in DSC data collected for 50-50 Molecule A-PEG 8000 extrudate indicates the presence of a component not encountered before. There are several explanations for this peak. First, Molecule A may be soluble in molten PEG 8000 during extrusion and recrystallizes into a more stable, higher melting temperature form following the cooling process. Second, PEG 8000 may interact with Molecule A to form a new co-crystal with a higher melting temperature. A third option is that a contaminant with a melting temperature of 120°C has entered the system. This option is unlikely because the endothermic peak has been detected several times, spanning different batches and different operating conditions.

X-ray diffraction (XRD) can be used to identify the lattice structure of Molecule A in the extruded mixture. It is possible that the lattice parameters will not match any existing data, confirming the presence of a new crystalline form.
• Extrusion process optimization

The melt extrusion operating conditions used throughout the course of this thesis work were maintained at constant values. The temperature values were chosen based on the physical properties of Molecule A and aimed to minimize extended exposure to high temperature and reduce temperature driven degradation product production. Likewise, the screw speed and screw design were selected to reduce torque requirements associated with the processing of Molecule A. These parameter selections were not optimized and further work could heavily influence degradation, physical state, etc.

The variables listed here, namely temperature profile, screw speed, screw design, all influence the way in which material flows through the extruder barrel and consequently the localized temperature and shear profiles of the material. A thorough understanding of this process requires a factorial design of experiments as well as computational fluid dynamics (CFD) modeling. Measured variables should include temperature dependent viscosity, shear, and a measure of tackiness.
11. Conclusions

Specific conclusions drawn from this work are summarized below.

- **The residence time distribution for melt extrusion has been characterized and degradation reaction kinetics have been estimated**
  - These conclusions are important for the processing of Molecule A that will meet purity requirements
- **Amorphous Molecule A is a fragile material, especially prone to molecular rearrangement of the non-equilibrium glassy state**
  - Physical ageing has been identified as the source for physical instability during storage
  - Change in enthalpy can be tuned by introducing a second component. The molecular level interactions contribute to the overall enthalpy change.
- **Coating Molecule A tablets with a polyvinyl alcohol based coating material will minimize moisture uptake and premature dissolution**
- **The dissolution behavior can be controlled by the addition of a water soluble excipient/coating**
  - A library of rate constants has been constructed for future use when designing new dosage forms
- **The overall melt extrusion / molding process produces consistently uniform tablets**
  - The stability of the chosen formulation meets all physical and chemical criteria
  - The mixing achieved by the extruder is sufficient to eliminate a pre-mixing step

These conclusions are not unique to Molecule A. The quantification and scientific understanding can serve as a toolkit for the practical application of pharmaceutical hot melt extrusion. Table 14 outlines the advantages of these contributions. The row labeled “Trial and Error” describes a traditional approach to problem solving, whereas the row “Contribution” identifies specific conclusions drawn from this thesis that enhance problem solving skills through scientific understanding.
Table 14: Contribution to the manufacture of pharmaceutical materials with hot melt extrusion.

<table>
<thead>
<tr>
<th></th>
<th>Temperature Sensitivity</th>
<th>Physical Stability</th>
<th>Extrudate Processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial and Error</td>
<td>High temperature degrades API</td>
<td>Amorphous form changes as a function of time</td>
<td>Rely on often used unit operations</td>
</tr>
<tr>
<td>Contribution</td>
<td>RTD characterization and modeling with kinetic parameter estimation</td>
<td>API fragility and enthalpy of relaxation tuning</td>
<td>Continuous manufacturing using melt extrusion and forming built on scientific principles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Application of moisture barrier coating and relative humidity studies</td>
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