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ABSTRACT

ASSESSMENT OF A MARINE POLYSACCHARIDE FOR USE AS EXCIPIENT IN PHARMACEUTICAL HOT-MELT EXTRUSION

by
Qing Ye

Pharmaceutical Hot Melt Extrusion (HME) is currently investigated by both industry and academia as a method for manufacturing solid oral dosages with improved bioavailability of poorly-water soluble active pharmaceutical ingredients (APIs) and control drug release of water-soluble APIs. Although HME is traditionally utilizing synthetic polymers to produce such dosages, biopolymers constantly gain ground by virtue of renewability, biocompatibility and in some cases biodegradability. In this work, the possibility of using Keltone, a marine polysaccharide derived from brown seaweed, as a polymeric excipient for pharmaceutical HME is explored. Keltone is insoluble in acidic pH and soluble in basic pH, therefore making it suitable for intestinal drug release. The processability of Keltone by extrusion using water and Eudragit EPO as plasticizers, and Diphenhydramine Hydrochloride and Clotrimazoleas as active pharmaceutical ingredients is assessed. The amount of residual water in the extrudates is determined by thermogravimetric analysis. The thermal transitions of the extrudates are determined by Differential Scanning Calorimetry.

ASSESSMENT OF A MARINE POLYSACCHARIDE FOR USE AS EXCIPIENT IN PHARMACEUTICAL HOT-MELT EXTRUSION

by
Qing Ye

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APPROVAL PAGE

ASSESSMENT OF A MARINE POLYSACCHARIDE FOR USE AS EXCIPIENT IN PHARMACEUTICAL HOT-MELT EXTRUSION

Qing Ye

Dr. Costas G. Gogos, Thesis Advisor Date
Distinguished Research Professor of Chemical, Biological and Pharmaceutical Engineering, NJIT

Dr. Piero M. Armenante, Committee Member Date
Distinguished Professor of Chemical, Biological and Pharmaceutical Engineering, NJIT

Dr. Robert B. Barat, Committee Member Date
Professor of Chemical, Biological and Pharmaceutical Engineering, NJIT

Dr. Nicolas Ioannidis, Committee Member Date
Research Engineer of Polymer Processing Institute

BIOGRAPHICAL SKETCH

Author: Qing Ye

Degree: Master of Science

Date: May 2014

Undergraduate and Graduate Education:

- Master of Science in Pharmaceutical Engineering,
  New Jersey Institute of Technology, Newark, NJ, 2014

- Bachelor of Science in Pharmacy
  Guangdong Pharmaceutical University, Guangzhou, P. R. China, 2012

Major: Pharmaceutical Engineering

I dedicate this to my beloved family.

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CHAPTER 1

INTRODUCTION

1.1 Objective

Pharmaceutical Hot-melt Extrusion (HME) is currently pursued by both industry and academia as a "green", solvent-less process technology for manufacturing oral dosage formulations and medical devices in a continuous and controlled fashion (Crowley et al., 2007). In this work, the possibility of using Keltone, a marine polysaccharide derived from brown seaweed, as a polymeric excipient for pharmaceutical HME was explored. Keltone is insoluble in acidic pH and soluble in basic pH, therefore making it suitable for intestinal drug release. The processability of Keltone by extrusion using water and Eudragit EPO as plasticizers, Diphenhydramine Hydrochloride and Clotrimazoleas active pharmaceutical ingredients (APIs) were assessed.

1.2 Background Information

HME is primarily utilized to improve the bioavailability of poorly-water soluble, crystalline active pharmaceutical ingredients (APIs) by dissolving them into water-soluble polymer excipients. At the same time, controlled-release oral dosages can be manufactured by dispersing water-soluble APIs into water-insoluble or swellable dissolution rate-controlling polymers (Terife et al., 2012). Combinations of the above can also be realized. Moreover, compared to traditional pharmaceutical processing methods, HME is appreciably less expensive manufacturing process and has the advantage of shorter and more efficient times to the final product through reduction of the processing steps involved (Repka et al., 2007).

Although HME and other pharmaceutical manufacturing methods utilize predominantly synthetic polymers as excipients, biopolymers or naturally occurring polymers constantly gain ground by virtue of renewability, biocompatibility and in some cases, biodegradability. The quest for a green technologies and the growing public awareness of climate changes stimulate the surging demand for green and renewable products with a low carbon foot-print. Moreover, the rapidly growing world population, aspires to a higher quality of life. Ultimately, this will lead to drastically increased demand for energy and resources. In this way, biopolymers play a prominent role (Mulhaupt, 2014). They are made from renewable materials, and so do not use up fossil fuel resources and should result in fewer overall greenhouse gas emissions. And many of them are naturally biodegradable and so will not litter the environment after use (Evans, 2014). According to figure published last year by European Bioplastic, global biopolymer production capacity increased from 250,000 tons in 2009 to almost 1.4 million tons in 2012, and is predicted to rocket to almost 6.2million tons by 2017.

In this work, the possibility of using a sodium alginate, Keltone, as an excipient to manufacture oral dosage formulations with delayed release properties via HME are being explored. Sodium alginate is an anionic polysaccharide that is found in the cell walls of brown algae (Sperger et al., 2011). It is a linear co-polymer with homopolymeric blocks of (1-4)-linked β-D-mannuronate (M) and α-L-guluronate (G) covalently linked together in different sequence blocks. The monomers can appear in homopolymeric blocks of consecutive G-residues, consecutive M-residues or alternating M- and G-residues (Soares et al., 2004). Alginate is one of the most popular hydrogels and has been successfully employed for many applications in the human body, including tissue implants. Several

commercial products containing ultrapure alginate (in accordance with GMP/ISO 9000 guidelines) are extensively used as excipients in the pharmaceutical industry (Dornish et al., 2001).

Keltone is a pH-depended solubility (insoluble in low pH, soluble in basic pH) material, which makes it a good candidate for intestinal drug delivery. Besides, Keltone is of high hydrophilicity biopolymer, which may play an important role in the targeting of gastrointestinal tissue in the development of orally administered drugs. Epithelial cells in gastrointestinal tissue are always covered by protective mucus. A feasible approach is to delay the transit through the gut, increasing the likelihood of contact between the delivery device and the tissue (Castro et al., 2008). By this way, Keltone can be a potential candidate of excipient for controlled-release drug.

However, as a biopolymer, Keltone has two major drawbacks: Poor thermal properties (although crystalline, it has no practical melting point as it thermally degrades before it melts) and high water content that restrict it to a number of main applications. As a result, these properties can make it difficult to process the biopolymers into the final product. In this work, the possibility of using Keltone as an excipient to manufacture oral dosage formulations via HME was examined, in an effort to investigate the possibility of expanding its uses in pharmaceutical product applications.

CHAPTER 2

LITERATURE REVIEW

2.1 Pharmaceutical Hot-melt Extrusion

Hot-melt Extrusion (HME) is an emerging continuous processing technology for the development of various solid dosage forms and drug delivery systems. In the last few decades HME has attracted increased attention from both the pharmaceutical industry and academia. Pharmaceutical Hot-melt Extrusion (HME) is a term that the pharmaceutical sector adopted to differentiate it from traditional oral dosage producing techniques, such as direct compression and tableting. HME is primarily utilized to improve the bioavailability of poorly-water soluble active pharmaceutical ingredients (APIs) by dissolving them into water-soluble polymers. At the same time, its potential of manufacturing controlled-release oral dosages by dispersing water-soluble APIs into water-insoluble or rate-controlling polymers make it a promising technology in pharmaceutical industry.

Due to its versatility in embracing a wide spectrum of applications, HME offers many advantages over conventional pharmaceutical production. HME is a solvent-free process, waiving the need for additional production stages (e.g., time-consuming drying steps), which also makes the process environmentally friendly. There exists a wide range of dosage forms which can be manufactured via HME (granules, pellets, tablets, films, sheets, rings, etc.), depending on the shape of the die and/or the post-processing technique (pelletizing, milling, calendering, injection molding, etc.). A uniform dispersion of API in the molten polymer result from the intense mixing and agitation imposed by the rotating screw during extrusion. The drug release profile offered by HME products via proper selection of the polymers used during HME is highly versatile. Solid solutions are an

efficient approaching the delivery of Biopharmaceutics Classification System (BCS) class II compounds because of the improved absorption and therapeutic efficacy. On the other hand, HME is also an excellent tool to create sustained-release formulations when, for example, a hydrophobic polymer is extruded with a highly water-soluble drug. In this case, API is leached from the matrix much slower than compared to an equivalent compressed tablet (Gogos et al., 2012).

The main drawback of HME is related to the thermal processing, limiting its application for thermo labile components. Degradation of the drug (API) and excipients may occur during HME because of high processing temperatures and heating due to viscous energy dissipation. However, changes in the configuration of the equipment (screw configuration, twin-screw extruders) or the addition of plasticizers can reduce process temperature and residence time to avoid thermal degradation during processing (Gogos et al., 2012). Additionally, there is a shelf-life stability concern arising from the thermodynamic tendency of the API to revert to its crystalline form at ambient temperatures. This will be resisted by the very low mobility of the dissolved API molecules in the Glassy excipient polymer matrix.

HME involves the use of single or more commonly twin rotor extruders for the melting of usually water-soluble polymeric excipients, mixing them with APIs and pumping the homogeneous mixture through a die to form an extrudate. Processes of pharmaceutical HME can be classified into two categories. Case I, where the processing temperature is above the melting temperature (semi-crystalline polymer) or the glass Transition temperature of an amorphous polymer(Tg>50–100◦C) but below the melting point of a crystalline API. Case II, the processing temperature is above both the melting or

glass transition temperature of semi-crystalline or amorphous polymers, respectively, and above the melting point of the API (Gogos et al., 2012).

2.1.1 Elementary Polymer Processing Steps Taking Place in HME

From a polymer processing perspective, HME involves five elementary steps: handling of particulate solids, melting, pressurization and pumping, mixing, and devolatilization and stripping (Tadmor and Gogos, 1979). For HME pharmaceutical processing, *dissolution* of the API in the molten excipient is an additional and most important elementary step, along with melting which precedes it and mixing which assists and speeds up dissolution.

As co-rotating twin-screw extruders (co-TSEs) are more commonly used in HME process development and industrial practice, the following briefly reviewed features of the elementary steps of HME concern co-TSEs.

2.1.1.1 Particulate Solids Handling (PSH). In co-rotating twin-screw extruders (co-TSEs), which are commonly used in HME process development, the particulate solid ingredients are fed gravimetrically or volumetrically controlled at constant rates. These rates are smaller than those needed to fully fill the parallel channels of the co-TSE, resulting in 'starve-fed' processing. Particulate solids handling in co-TSEs may result in spatial particle segregation if the relative sizes or shapes of the API and the excipient are very different, due to different air resistive forces and different particle/wall kinematic friction coefficients. It is also worth noting that polymer excipients are commonly hygroscopic, so they may have to be dried prior to dry mixing with the API particulates.

2.1.1.2 Melting. The available melting mechanisms of co-TSEs are conductive melting of the starve-fed loose particulates by the hot barrel, which is significant for the small

co-TSEs used in HME development, where the surface-to-volume ratio is large. However, for larger-diameter co-TSEs, reverse-screw or reverse-kneading elements are used to create a filled section in which the packed particulates undergo repeated volume-wide deformations before exiting the fully filled region. During this process, the very powerful melting mechanism of plastic energy dissipation (PED) is important and possibly dominant. It is also worth pointing out that the repeated large compressive deformations taking place in full kneading blocks generate heat by PED, but also induce particulate-to-particulate frictional heating and localized melting because of frictional energy dissipation (FED) (Tadmor, 2001) (Gogos, 1998).

2.1.1.3 Devolatilization. Devolatilization refers to the removal of low levels of volatiles of the order of 1000 ppm, dissolved in the molten matrix. It is carried out in co-TSEs in partially filled sections isolated from both the upstream and downstream sections by 'melt seals' so that vacuum can be applied. Under vacuum conditions, the dissolved molecules cause bubbles to be formed in the flowing melt stream (much like the bubbles formed by opening a carbonated refreshment container) which, when they reach the melt–vacuum interface, burst and are removed (Tadmor and Gogos, 2006).

2.1.1.4 Pumping and Pressurization. After the accomplishment of all the other elementary steps, the molten charge need to be pumped through a die which shapes the exiting streaming operations such as pelletization and sheet, film, tube or profiled cross-sectioned products. Drag-induced pumping and pressurization is the flow mechanism enabling both co-TSEs and SSEs to be the pumps of choice for viscous fluids. As co-TSEs are fully intermeshing (and self-wiping, which is an advantage for HME

operations), they are ‘locked in’ with wide channels which are incapable of generating as high pumping pressures as single screw extruders, which can have shallow channels.

2.1.1.5 Dispersive and Distributive Mixing. The mixing process in single- and twin-screw extruders, which is the most important elementary steps in the processes of HME, is generally categorized into two types: (a) dispersive mixing and (b) distributive mixing.

Dispersive mixing refers to the process involving the particle size reduction of cohesive components such as solid fillers (by de-agglomeration) or liquid droplets (by droplet deformation and break-up). Distributive mixing refers to distributing de-agglomerated particulates uniformly throughout space, or stretching the interfacial area between the components lacking a cohesive resistance and distributing them uniformly throughout the product volume. Dispersive mixing is dictated by the magnitude of the laminar shear and extensional stresses and the type of flow generated by the processing equipment, whereas distributive mixing is dictated only by the flow-generated strains. According to these definitions, the mixing of miscible liquids is regarded as distributive mixing, whereas mixing of hard solid agglomerates, immiscible liquids, and soft agglomerates is regarded as dispersive mixing (Tadmor and Gogos, 2006).The dispersive and distributive mixing of solid agglomerates is schematically shown in Figure 2.1.

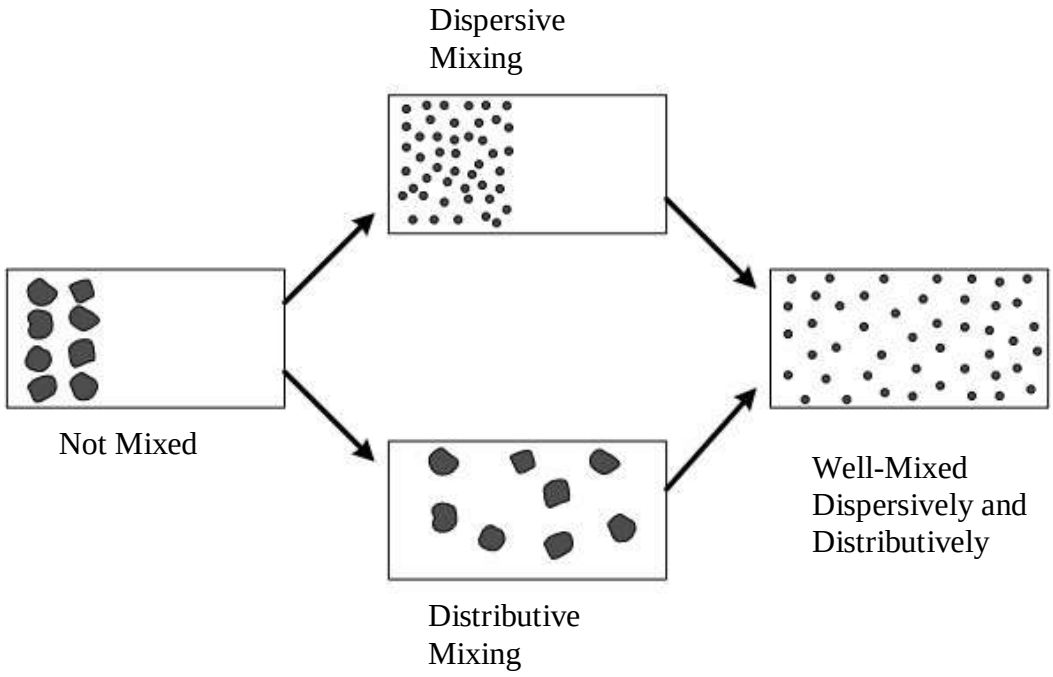

Figure 2.1 Dispersive mixing and distributive mixing of solid agglomerates and immiscible liquid droplets (Tadmor and Gogos, 2006).

Source: Tadmor Z., Gogos C.G., 2006.Principles of Polymer Processing.2nd edition. Wiley-Interscience, New Jersey.

2.1.2 Melting and Dissolution in Extrusion.

In the process for pharmaceutical HME, dissolution of the API in the molten excipient is an additional and most important elementary step, along with melting and mixing.

The physical mechanisms that can bring about melting or heating of any substance are included in the terms of the thermal energy balance (Tadmor and Gogos 2006).

$$\rho \frac{Du}{Dt} = -\boldsymbol{\nabla} \cdot \boldsymbol{q} - P(\boldsymbol{\nabla} \cdot \boldsymbol{v}) - (\tau : \boldsymbol{\nabla v}) + \dot{S} \qquad (2.1)$$

The internal energy of a material can be raised by four sources as indicated in Equation 2.1, where ρ is the density, u is the internal energy and t is the time. ($-\boldsymbol{\nabla} \cdot$

$\boldsymbol{q}$)presents the net rate of internal energy increase per unit volume from an outside source by heat conduction; $P(\boldsymbol{\nabla} \cdot \boldsymbol{v})$presents the (reversible) rate of internal energy increase per unit volume by compression; $[-(\tau : \boldsymbol{\nabla v})]$presents the (irreversible) rate of internal energy increase by flow and deformation; and Ṡ presents an additional possible homogeneous energy source.

Melting of polymers is generally classified into conduction melting, compressive melting, deformation melting and homogeneous internal melting. Conduction melting is the most common mode, which raises the temperature of a solid and melts it. As the surface temperature of the solid is raised, a molten layer is formed and it grows with time. Thermal conductivity, attainable temperature gradients, and available contact area between the heating source and the melting solid are the rate-controlling factors of conduction melting.

For polymers which have with low thermal conductivity and temperature sensitivity, the conduction melting is inefficient. However, in flood-fed single screw extruders, drag-induced melt removal takes place. The SSE quickly removes the freshly molten material from the vicinity of the high temperature zone, which reduces the risk of degradations. Also, it generates heat via viscous energy dissipation, which increases the efficiency of melting.

Deformation melting involves irreversible conversion of mechanical energy to heat. It is significant, in viscous liquid, especially when the shear rates under processing condition are high. In the melting step of polymer processing, repeated deformation is imposed on a compacted bed of particulate solids, which generates significant, but non-homogeneous heat energy, called plastic energy dissipation (PED) and frictional energy dissipation (FED) for individual polymeric particles undergoing repeated

deformations and generating heat within the particle and the mechanical energy dissipated into heat via inter-particle friction, separately. PED and FED play predominant role in processing equipment, in particular in co-rotating twin screw extruders (Co-TSEs). In this case, the thermal energy equation can be written as (Tadmor and Gogos, 2006):

$$\rho_s C_S \frac{DT}{Dt} = -\boldsymbol{\nabla} \cdot \boldsymbol{q} + PED + FED \tag{2.2}$$

where ρ_s is the density of solid, C_S is specific heat of solid. DT/Dt presents change of temperature. $(-\boldsymbol{\nabla} \cdot \boldsymbol{q})$ is rate of internal energy addition by conduction per unit volume. Since the fact that polymer solids and melts are virtually incompressible and other homogeneous internal melting, like dielectric heating, are limited in polymer processing practice, according to criteria of avoiding thermal degradation and achieving high processing rates, the melting mechanisms for polymers are summarized as: conduction melting with forced melt removal (by SSE), plastic energy dissipation (PED) and frictional energy dissipation (FED) (by twin rotor devices), and dissipative mix-melting (DMM) (by twin rotor co- and counter- rotating devices) (Tadmor and Gogos, 2006).

Co-rotating twin screws with only conveying elements act similarly to single screw, which convey and compress the PM by a drag-induced mechanism, then melt by a drag-induced melt removal mechanism. However, because of their unique time-varying screw-to-screw interactions taking place, additional physical mechanisms emerge, which may primarily affect the elementary step of melting and mixing. In other configurations of TSEs, due to the addition mechanisms, melting and mixing steps are carried out more efficiently and uniformly, thus narrowing the residence time distribution (RTD) in the

molten state. In SSEs, on the other hand, some of the polymer melts early in the extruder and some at the very end, and hence, the RTD in the molten state is rather broad.

Melting in Co-TSEs with intense kneading blocks takes place primarily and most commonly in the kneading elements where particulates are fully compacted because of a flow restriction. The evolution of melting in such filled kneading-elementary channels was studied experimentally by Kim and Gogoset.al (Gogos et al., 1998). They found that inter-particles FED takes place early and does not require full compaction. At full compaction, PED becomes dominant melting mechanism.

HME processes can be generally classified into two categories(Gogos et al., 2012):Case I: in which the processing temperature is above the melting temperature (semi-crystalline polymer) or the softening temperature of an amorphous polymer (Tg>50–100◦C) but below the melting point of a crystalline API. Case II: in which the processing temperature is above both the melting or softening temperature of semi-crystalline or amorphous polymers, respectively, and above the melting point of the API.

Case I provides a viable dissolution path which minimizes or circumvents the thermal degradation issue of drugs resulting in a desirable polymer-drug solid dispersion or solid solution, in which the solid API acts as a solute dispersion and the polymer excipient melt acts as a highly viscous solvent. On the other hand, it is expected that the dissolution rates and the solubility are larger in the case that the processing temperature is higher. Figure 2.2 shows its physical model schematically.

The premixed drug (black) and polymer particles (white) are fed into the batch mixer or an extruder. The polymer particles start melting due to the conductive heat from

the mixer or extruder barrel and frictional and plastic energy dissipation for co-TSEs, leading to the solid drug particles being suspended in a continuous polymer melt matrices. While suspended at the processing temperature, which favors dissolution assuming intermolecular forces compatibility between the API and the excipient, the drug molecules start dissolving and create a mass-transfer boundary layer around each drug particles. This layer is continuously wiped away and replaced by fresh polymer melt around each API particulate by the laminar distributive flow of the mixer. The same laminar mixing flow helps the drug molecules to diffuse and mix distributively into the molten excipient. The size of suspended drug particles diminishes as the diffusion continues until the particles disappear and a homogeneous solution formed or until the limit of API solubility at the processing temperature is reached. In the latter case, they reach a minimum average size and remain suspended. The dissolution of the drug in the polymer melt in an extruder is achieved by laminar forced convective mass transfer involving the dissolving and dissolved API molecules.

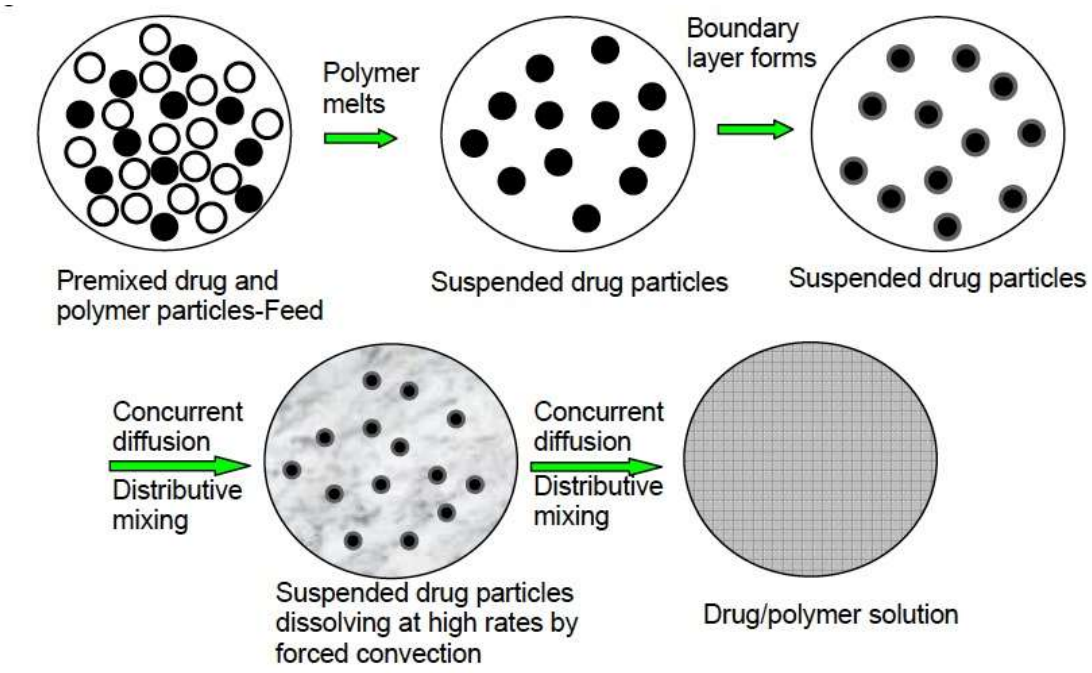

Figure2.2 Schematic representation of the morphological changes of the drug and polymer system in the solution formation process (Case I).

Source: C. G. Gogos, H. Liu and P. Wang, "Laminar Dispersive and Distributive Mixing with Dissolution and Applications to Hot Melt Extrusion", Chapter 12 in Hot Melt Extrusion: Pharmaceutical Applications,D. Douroumis Ed., John Wiley and Sons Ltd, 2012

The main task of Case I is to completely dissolve drugs in polymeric melt within the shortest possible residence time without raising the processed stream melt temperature.

Case II involves liquid – liquid mixing between miscible or partially miscible components. The morphology changes are shown in Figure 2.3.

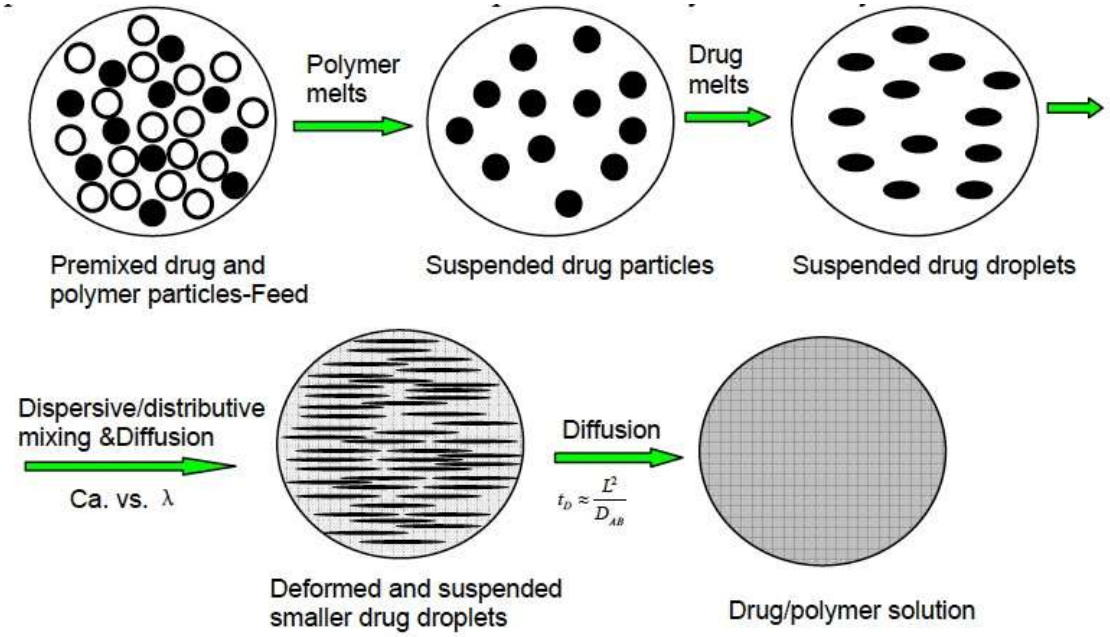

Figure 2.3 Schematic representation of the morphological changes of the drug and polymer system in the solution formation process (Case II).

Source: C. G. Gogos, H. Liu and P. Wang, "Laminar Dispersive and Distributive Mixing with Dissolution and Applications to Hot Melt Extrusion", Chapter 12 in Hot Melt Extrusion: Pharmaceutical Applications, D. Douroumis Ed., John Wiley and Sons Ltd, 2012

The premixed drug (black) and polymer (white) particles are fed into an extruder and conveyed by the conveying elements. The polymer particles melt first due to the energy input from the barrel and frictional and plastic dissipation. After the polymer particles totally or partially melt, the drug particles suspended in the molten polymer melt rapidly, and the drug droplets begin to be deformed by the mixing laminar flows of the polymer melt rapidly, and the drug droplets begin to be deformed by the mixing laminar flows of the polymer melt. After that, the drug liquid phase breaks up into much smaller droplets due to the competition of surface tension and flow stress. The small droplets are deformed along the shear direction. With numerous very small droplets, which have an enormous surface, diffusion between the droplets and the polymer predominates causing the droplets to disappear, creating drug – polymer solution.

Similarly to the dissolution of drugs in an aqueous medium, the dissolution of drug particulates in molten polymeric excipients during HME can also be described by the Noyes – Whitney equation

$$\frac{dC}{dt} = \frac{D * A * (C_s - C)}{h * V} \tag{2.3}$$

where *D* is the diffusion coefficient; *A* is the total surface area of the drug exposed to the dissolution media; *Cs* is the saturation solubility of the drug in the liquid which (for HME)is the excipient melt; *C* describes the concentration of the dissolved solid phase in the bulk at time *t*; *h* represents the diffusion boundary layer at the solid-liquid interface; and *V* is the volume of the dissolution medium. The variables influencing the dissolution rate of drug particulates in the excipient melt can be grouped into three categories: process, equipment, and material.

In both the diffusion and dissolution cases, the particle sizes of API in the molten excipient – API system play a significant role. The diffusion rate as well as the dissolution rate of drug particulates in polymer melt will increase if the total surface area of the drug particulates exposed to the dissolution media increase. Furthermore, the narrower the drug particle size distribution, the more uniform the total dissolution time distribution needed for complete dissolution of drugs in polymer melt will be (Gogos et al.,2012).

2.2 Characterization Methods

The objective of processing a formulation via HME is to transform thermoplastic materials into homogeneous extrudates with a specific shape. As for a processing of pharmaceutical

formulation, the objective is to dissolve all or partial of the APIs into the polymeric excipient matrixes and fix the mas the amorphous form, then pump them through the die. In order to achieve these objectives, the materials require a substantial energy uptake which is provided by elevated temperatures, high shear forces and pressure to enable the intense mixing of drug and excipient during processing. To characterize the physical nature of extrudates at molecular or microscopic level, several methods can be used. An overview of the most common techniques for physicochemical characterization of HME-processed formulations is provided in the following sections.

2.2.1 Thermo-analytical Methods

Knowledge of the thermal behavior of the drug and polymers incorporated in the formulation is an essential aspect of dosage form development for HME, as product performance in terms of dissolution, bioavailability and stability highly depends on its thermal properties.

The most common application of differential scanning calorimetry (DSC) for HME formulations is the assessment of drug crystallinity following HME processing and during storage, in order to determine its impact on drug release and bioavailability. In DSC tests, it is generally accepted that the absence of endothermic melting peak of the crystalline drug indicates that the drug is present in an amorphous rather than crystalline form. The crystal detection limitation of DSC is about 2% (Leuner, 2000). The DSC device maintains the same programmed temperature in each well and records the power required to achieve this. If a transition takes place in the sample, a characteristic excursion in the measured differential power is observed (Thompson, 1985).

During development of an HME formulation, thermal analysis is essential to determinethe process conditions during HME, based on the thermal stability of the individual components as determined via differential scanning calorimetry (DSC) and/or thermal gravimetric analysis (TGA) .

2.2.2 Microscopy

Optical can help determine the existence of drug crystal regions and the size as well. Although the resolution of polarized light microscopy (PLM) is approximately at 1μm, the birefringence of the crystal drug imparts a sharp and distinct contrast against the amorphous (dark) excipient. Yoo et al. studied the miscibility/stability for 24 binary solid dispersion systems and found that the sensitivity to crystal detection was polarized light microscopy (PLM)> differential scanning calorimetry (DSC)>X- ray Diffraction(XRD) (Yoo, 2009).

Hot stage microscopy (HSM) can be used to visualize the thermal events of sample formulations through a microscope during heating and/or cooling steps. Lloyd et al. found that HSM is far more sensitive to the presence of small quantities of solid drug than DSC (Lloyd, 1997) when studied the preparation of a solid dispersion of acetaminophen and polyethylene glycol (PEG) 4000.

CHAPTER 3

MATERIALS AND METHODS

3.1 Materials

Keltone (LVCR) (FMC Biopolymer), A low viscosity anionic marine polysaccharide was used as a biopolymeric excipient (Figure3.1a). Diphenhydramine Hydrochloride (DMN) (BCS I) (Sigma Aldridge) (Figure3.1b) and Clotrimazole (CLO) (BCS II)(Sigma Aldridge) (Figure3.1c)were used as model APIs, respectively. Distilled water was used as a fugitive plasticizer for Keltone. In some experiments, Eudragit EPO (Figure3.1d) was used as a co-polymer/plasticizer for Keltone. The choice of DMN as API and water as plasticizer was due to earlier solvent casting experiments at Polymer Processing Institute (PPI) where it was showed that DMN forms solid solutions in Keltone in the presence of excess water. Further data to support the use of water as a plasticizer was the incompatibility (recrystallization) of polyethylene oxide (PEO) and the low boiling point of triethyl acetate (~127°C), both commonly used FDA-approved plasticizers in the pharmaceutical industry.

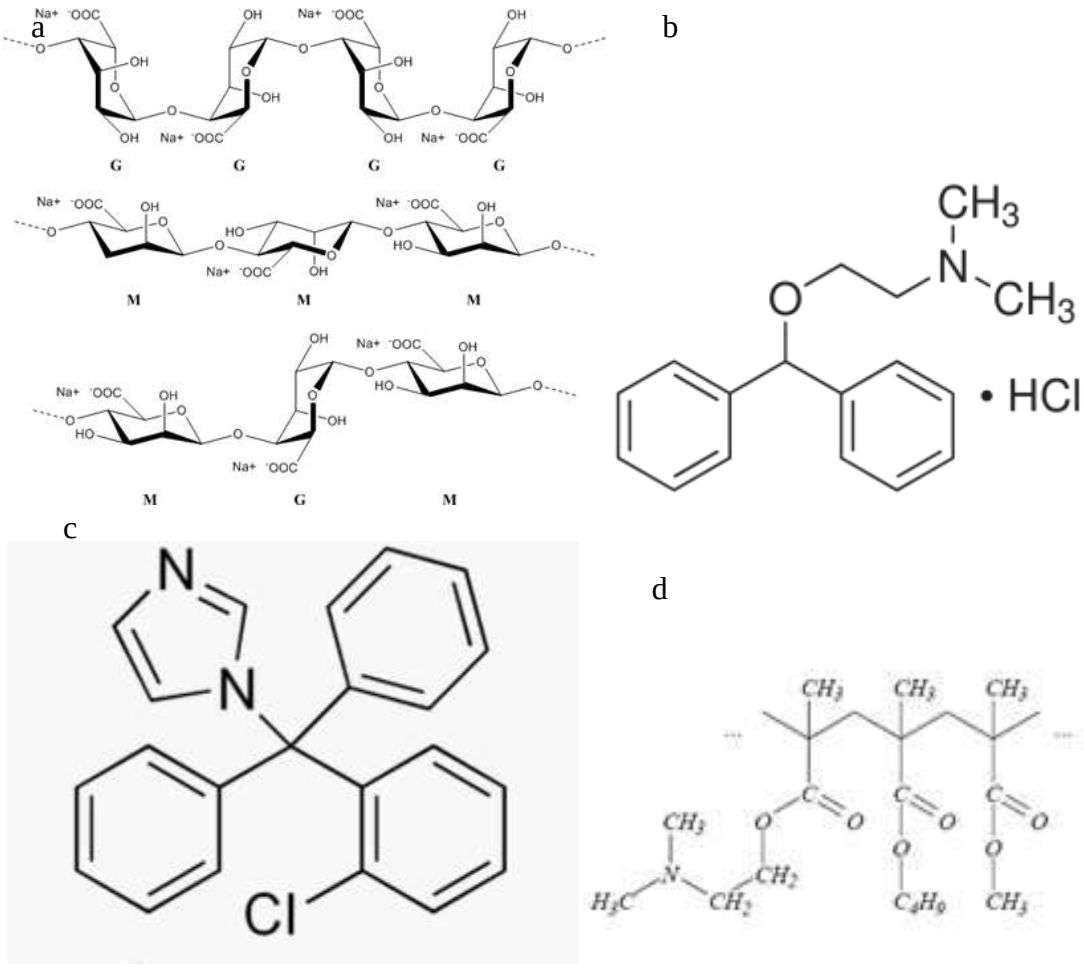

Figure 3.1 Molecular structures of (a) Keltone (sodium alginate), (b) Diphenhydramine Hydrochloride, (c) Clotrimazole, (d) Eudragit EPO.

3.2 Extrusion

Extrusion was carried out in the Leistritz Nano16 Co-TSE (Leistritz). Figure 3.2 shows the appearance of Nano16 Co-TSE. Thisvery small laboratory extruder has two fully intermeshing, co-rotating, 16 mm in diameter screws equippped with neutral kneading blocks, which are shown in Figure 3.3. Nano16 Co-TSE has four heating barrel zones (3 zones + die) while the temperature in the feeding zone can be controlled externally via a jacket. A 1 mm capillary die was used to extrude all formulations.The physical mixture

was fed to the extruder using the AccuRate 102M single-screw volumetric feeder (Schunck Corp).

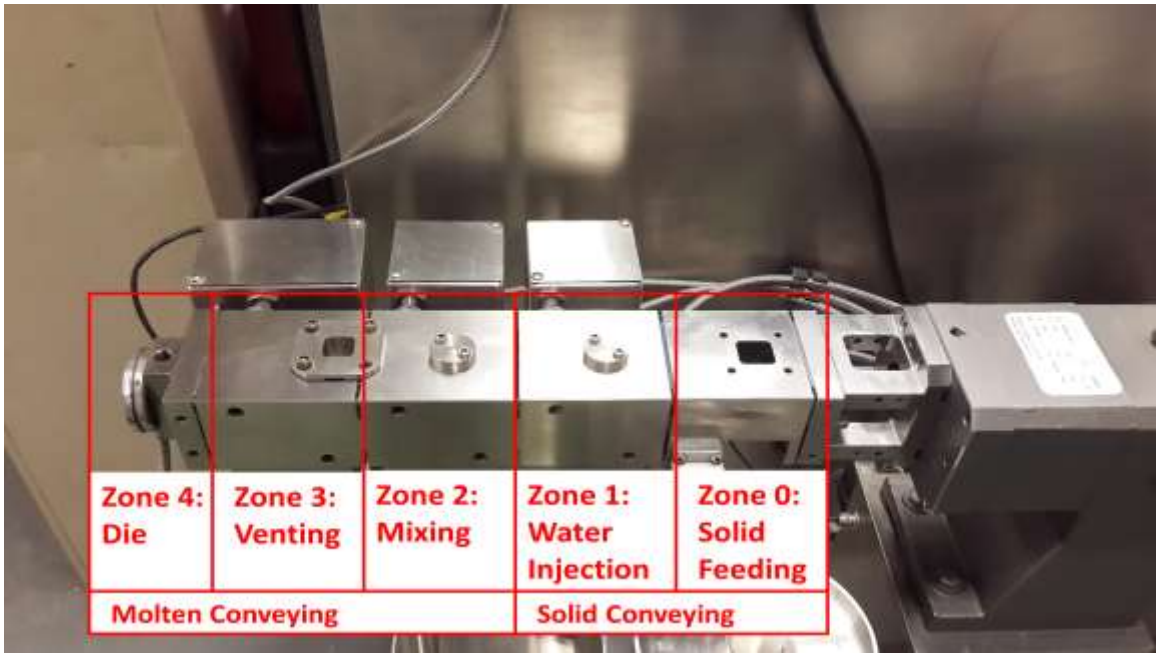

Figure 3.2 Overview of processing zones of Nano16 Co-TSE.

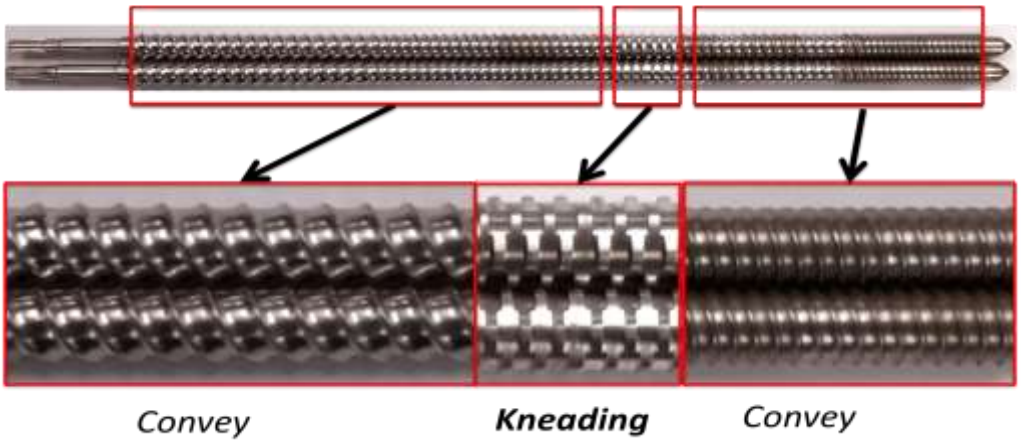

Figure 3.3 Appearance of the co-rotating screws.

Water was injected at a constant rate via a siringe pump connected to zone I (after the feeding zone). The total feeding rate (Particulates and water) to the extruder was kept constant during the processing of all formulations at 2 g min^{-1}.

Physical mixtures of excipient and API were prepared by tumbler mixing at 50 rpm for one hour.

3.3 Thermo Gravimetric Analysis (TGA)

The Perkin Elmer Thermogravimetric Analysis 7 was used in this work. The ramp mode was used to determine the water content of Keltone and residual water content of the extrudates. The samples were placed in an aluminum pan and heated from 30°C to 250°C at a heating rate of 10°C/min under air. Preliminary experiments in the TGA under both air and nitrogen atmospheres, showed that the degradation of Keltone and its physical mixtures (PMs) is thermal so there was no need for a nitrogen blanket during processing. Isothermal mode was used to determine the stability of the materials at the processing temperature. In isothermal heating tests, powders were quickly heated to 150°C at a rate of 40°C/min and held isothermally for 10 minutes.

3.4 Differential Scanning Calorimetry (DSC)

The thermal transitions of raw materials, PMs and extrudates during heating were determined using a Metler Toledo Polymer DSC.

3.5 Hot-Stage, Polarized Light Microscopy (PLM)

A hot stage (Mettler FP90) was used in conjunction with a Carl Zeiss microscope (Thornwood, NY)to observe morphology evolution of extrudate samples under polarized light. The heating rate was set 20°C/min from 30 to 160°C. Pictures were taken every 10°C.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Background

Previous work at PPI had showed that (a) Keltone could not be extruded by itself unless a plasticizer (PEO in this case) was added. In addition it was found that Indomethacin (IND) could not be dissolved in Keltone by itself. It may be a result from that both Keltone and IND are anionic materials. IND was found to dissolve in a formulation with both Keltone and PEO, however the product was found to be unstable following extrusion (both PEO and IND recrystallized). To determine if the dissolution ability of Keltone is related to its charge, we used Diphenhydramine Hydrochloride (DMN), which is a cationic drug. Based on literature(M. Pavli et al., 2009), anionic polymers like carrageenans (very similar in structure to sodium alginates) can form solid solutions with cationic drugs by solvent casting in excess of water. To further investigate the ability of Keltone to form ionic complexes with oppositely charged molecules, Eudragit EPO, a cationic polymer was used as a plasticizer for Keltone.

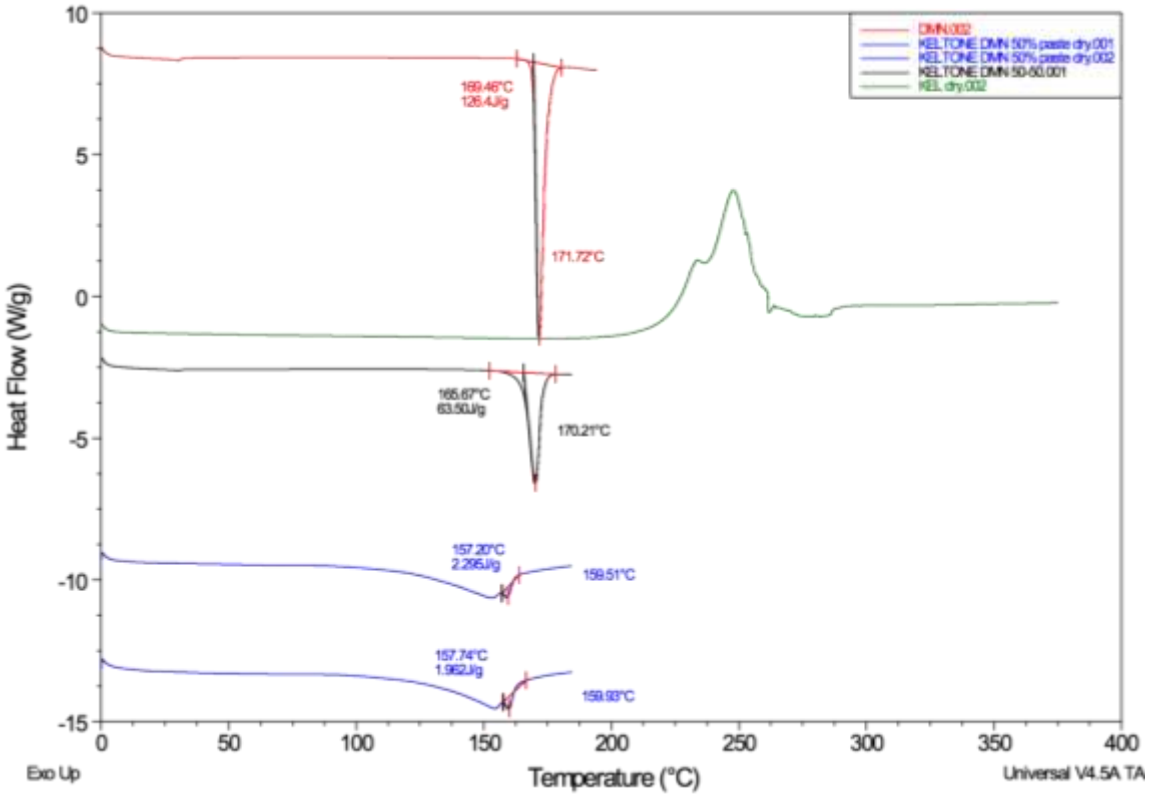

Figure 4.1 Ramp heating of DMN, Keltone, Keltone/DMN PM and Keltone/DMN solvent-casted film.

Figure 4.1 shows the DSC ramp heating of Keltone/DMN 50:50 PM and solvent casted film as well as of the raw materials of this formulation. The endothermic enthalpy of DMN in the PM is very close to the melting enthalpy of the pure drug suggesting the absence of any interaction between the two components (black tracer). However, when the solvent-casted film was heated there is a very small endotherm (~2 J/g) ~10°C lower than the melting point of pure DMN that may be related to the dissolution of DMN in KELTONE (blue tracer). The above strongly suggest that ~50% of DMN was dissolved in Keltone and remained in solution following the removal of water from the formulation.

4.2 Characterization of Raw Materials

The thermal properties and morphologies of the raw materials were characterized in this Section. The characteristic thermal transition temperature of Keltone, Eudragit EPO, DMN and CLO are presented in Figures 4.1 and 4.2. DSC was used to get characteristic thermal transition temperatures, including the glass transition temperature of Eudragit EPO, the melting temperature of DMN and CLO.

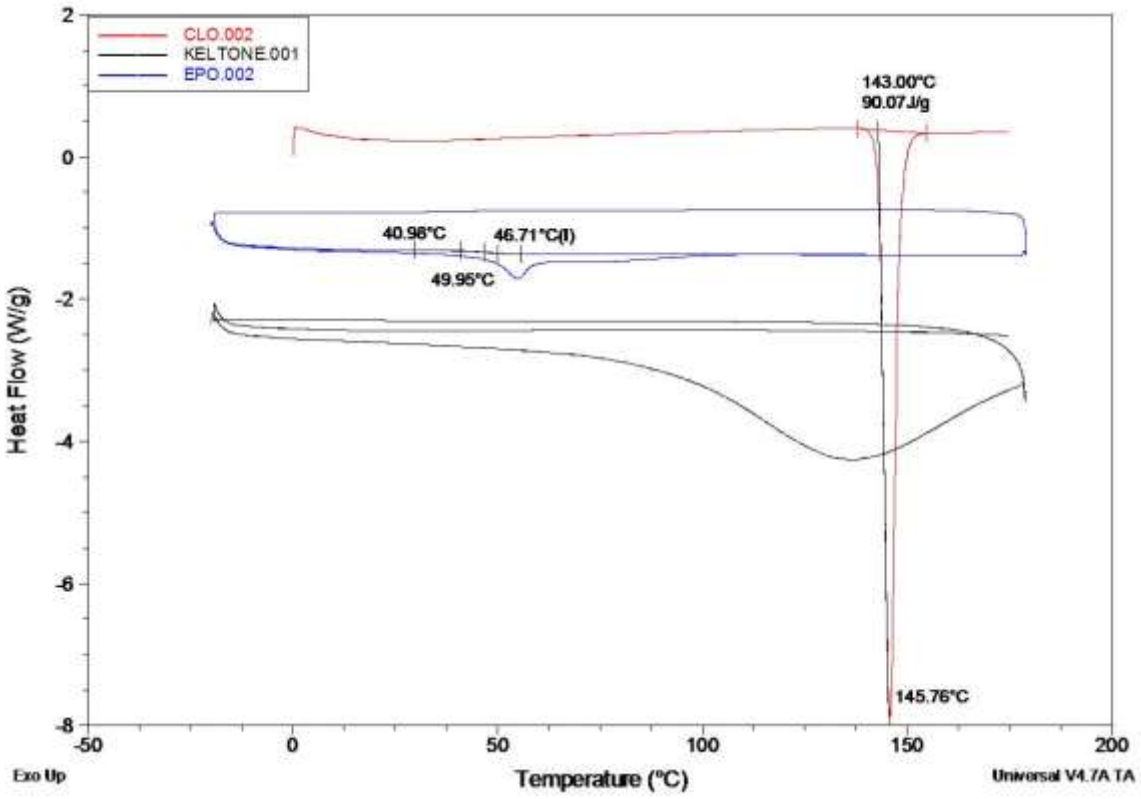

Figure 4.2 Heat-cool-heat scan of Keltone and Eudragit EPO, ramp heating of CLO.

The melting point of DMN is ~ 171°C whereas Clotrimazolemelts~145°C. The Tg of EPO form the second heating is ~ 46°C.Keltone lacks any characteristics transition in the temperature range examined in this work. The large endotherm during the first heating is due to the evaporation of water (~13% as detected by TGA).

The TGA ramp and isothermal heating as well as thermal stability based on color change of Keltone are presented in Figure 4.3 The onset temperature of weight loss in the TGA ramp heating tests is above 200°C. This test was also conducted under N_2 to determine whether the degradation was oxidative in nature. Since no difference between the two ramp tests was detected, there is no need to process Keltone under N_2. The isothermal TGA was conducted to further examine the thermal stability a function of time. The isothermal TGA at the HME barrel temperature (150°C) was conducted to further examine the thermal stability of CLO, as shown in Figure 4.4.The sample was processed for 10min at 150°C, showing less than1% weight loss at 150°C.

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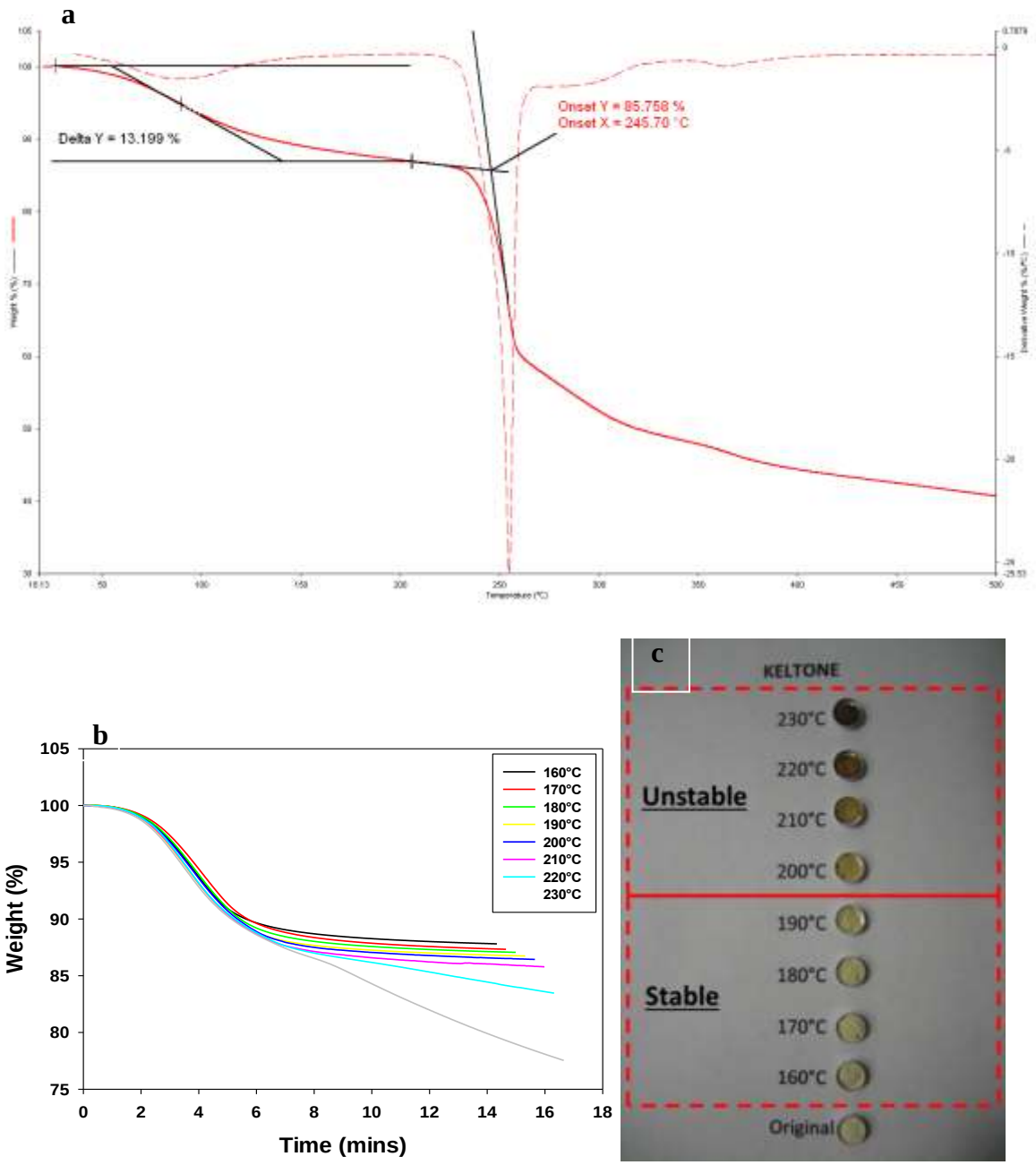

Figure 4.3 (a)Ramp heating of Keltone under air, (b) isothermal heating for 10 min, (c) degradation-induced color change relative to the original material.

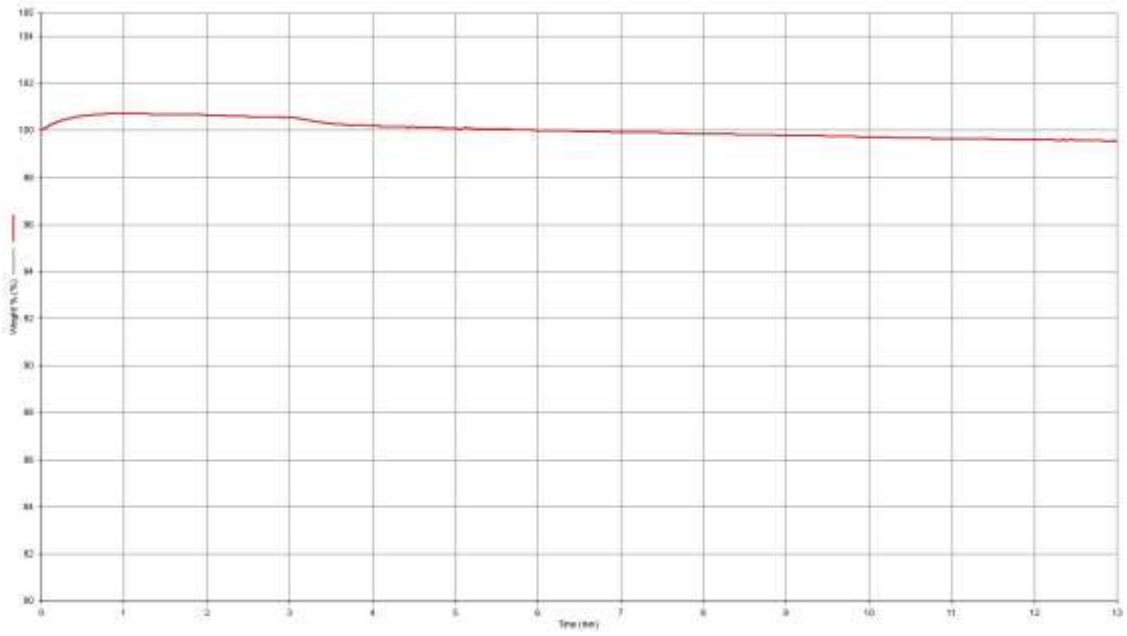

Figure 4.4 Isothermal heating of CLO for 10 min (vertical/ horizontal axes: weight / time).

4.3 Extrusion

In this section, the possibility of Keltone being extruded with water as a plasticizer and DMN as an API was examined. We also extruded Keltone with EPO as a plasticizer and Clotrimazoleas an API. The minimum amount of plasticizer and the processing temperature of Keltone were optimized. TGA tests were conducted to identify the residual water content of extrudates. DSC tests were conducted to determine the thermal transitions of extrudates during heating.

4.3.1 Optimization of Minimum Amount of Plasticizer and Processing Temperature for Keltone Using Water as Plasticizer

Extrusion optimization runs were performed to identify a) the minimum concentration of water as a plasticizer for Keltone and b) the optimum extrusion temperature. Table 4.1 lists the barrel temperatures and compositions used during all extrusion optimzation runs.The

first three combinations (Formulations #1 to #3) of composition/processing temperature resulted into extrudates of acceptable consistency and ease of extrusion. Extrusion of formulation #4 was very unstable and resulted into an extrudate of uneven consistency, because of a combination of high temperature and low water content. Formulation #5 could not be extruded as the amount of water was too low (blockage of the extruder). Based on the preliminary runs without API we decided that the most suitable extruder barrel temperature profile is the following: 120°, 90° , 80°, 80° , 50°C; the die temperature in the range of 124-126°C; and the minimum amount of water as plasticizer allowing extrusion runs is 40%. Formulations #6 and #7 were the two formulations that contained DMN, based on 40% of water as plasticizer. Formulation #6 was not possible to extrude. Formulation #7 was also very difficult to extrude and had very low viscosity (oil-like). Figure 4.5 shows the appearance of extrudates after extrusion.

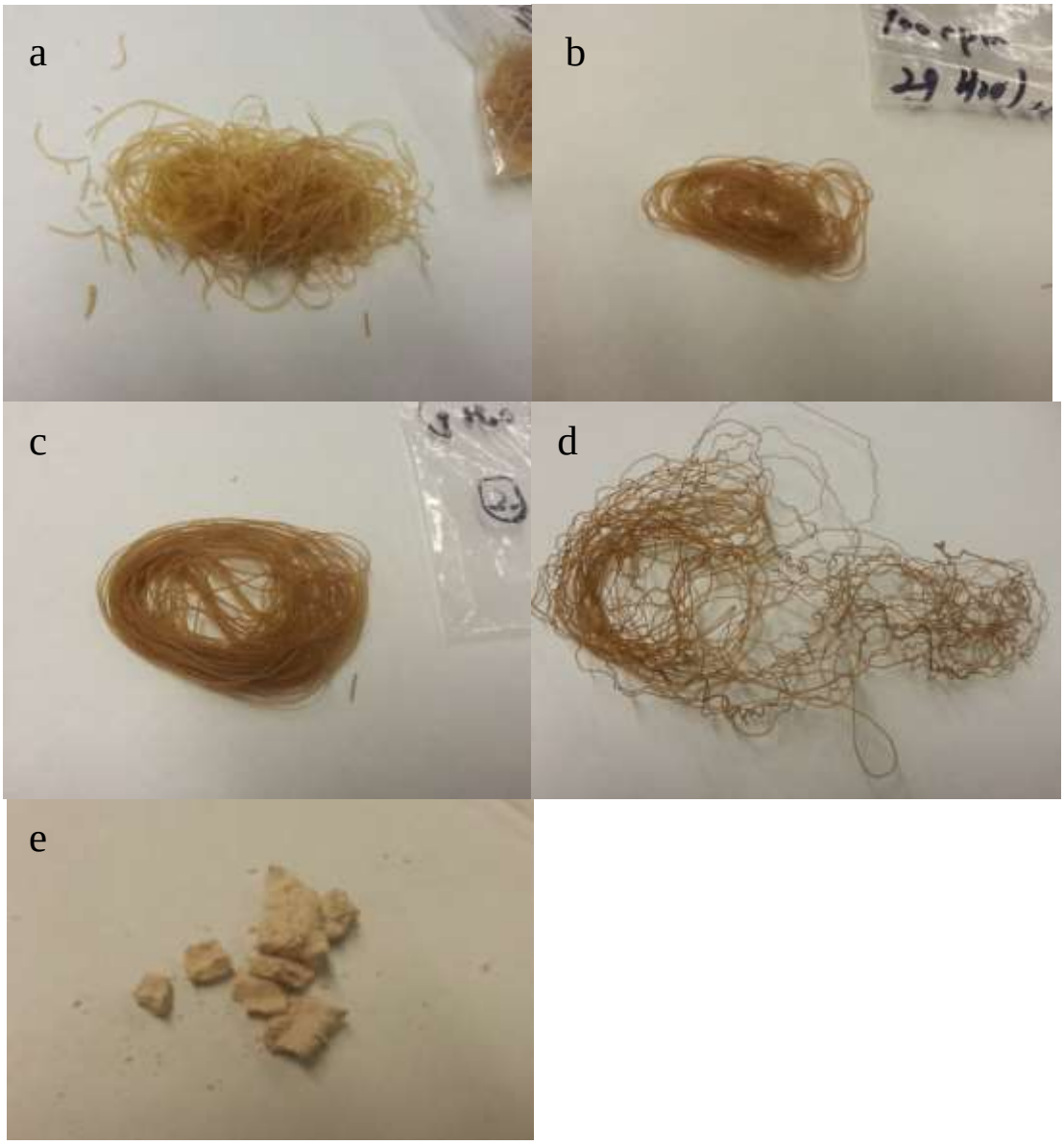

Figure 4.5 Appearance of extrudates after extrusion: (a) formulation #1, (b) formulation #2, (c) formulation #3, (d) formulation #4 and (e) formulation #7 (after drying).

Table 4.1 Formulations and Extrusion Conditionsof Keltone, DMN And Water

Formulation	Composition	Composition	Extrusion conditions					
(#)	(Keltone/DMN/water) (%(w/w))	(Keltone/DMN/total water) (%(w/w)) (adjusted for Keltone water content (~15%))	(C°) M	Z4(D)	Z3	Z2	Z1	Z0(F)
1	42.9/-/57.1	36.1/-/63.9	126°	120°	90°	80°	80°	50°
2	42.9/-/57.1	36.1/-/63.9	124°	130°	100°	80°	80°	50°
3	60/-/40	50.5/-/49.5	125°	120°	90°	80°	80°	50°
4	60/-/40	50.5/-/49.5	126°	130°	100°	80°	80°	50°
5	66.7/-/33.3	56.7/-/43.3	129°	120°	90°	80°	80°	50°
6	42/30/28	35.7/30/34.3	126°	120°	90°	80°	80°	50°
7	52.5/37.5/10	44.6/37.5/17.9	133°	120°	90°	80°	80°	50°

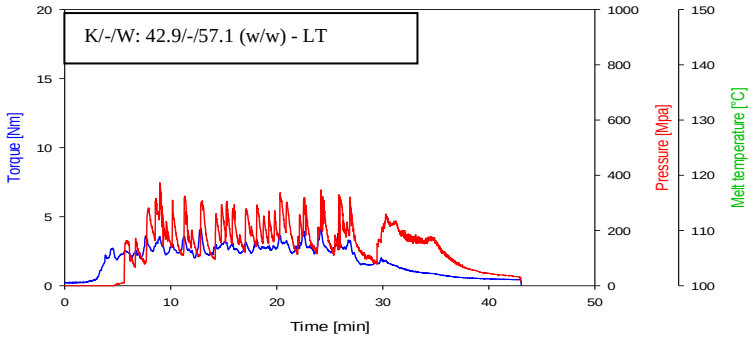

Figure 4.6 Torque, pressure, and melt temperature traces for extrudate #1.

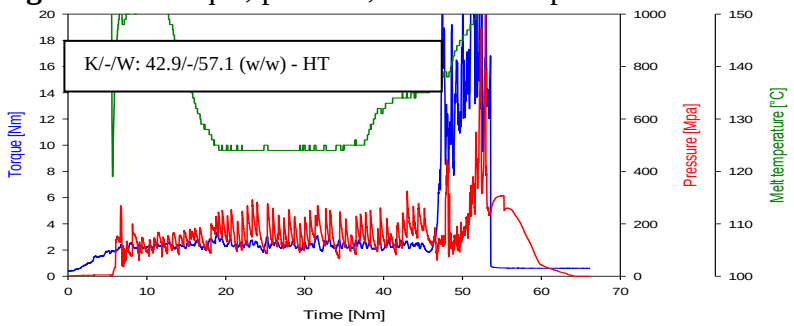

Figure 4.7 Torque, pressure, and melt temperature traces for extrudate #2.

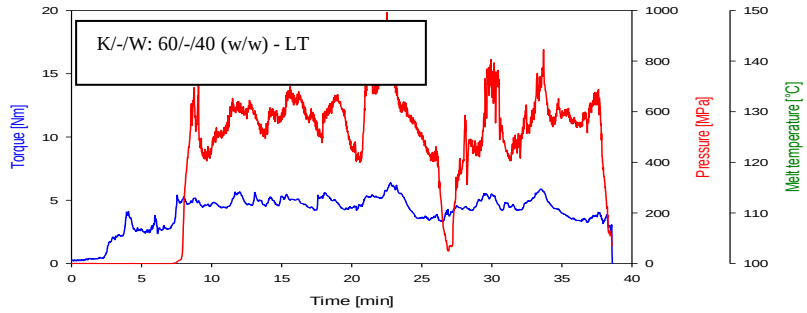

Figure 4.8 Torque, pressure, and melt temperature traces for extrudate #3.

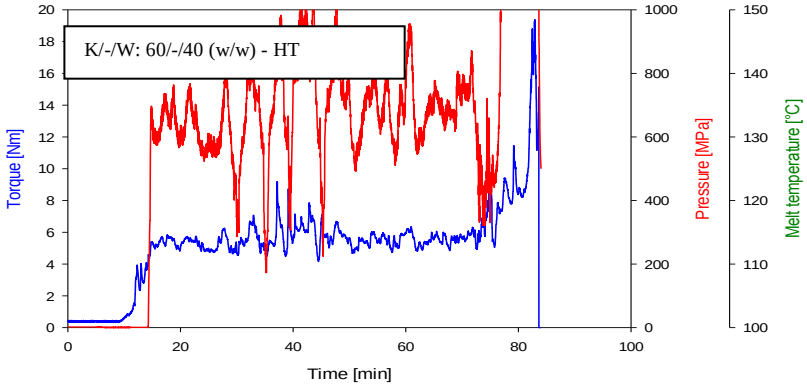

Figure 4.9 Torque, pressure, and melt temperature traces for extrudate #4.

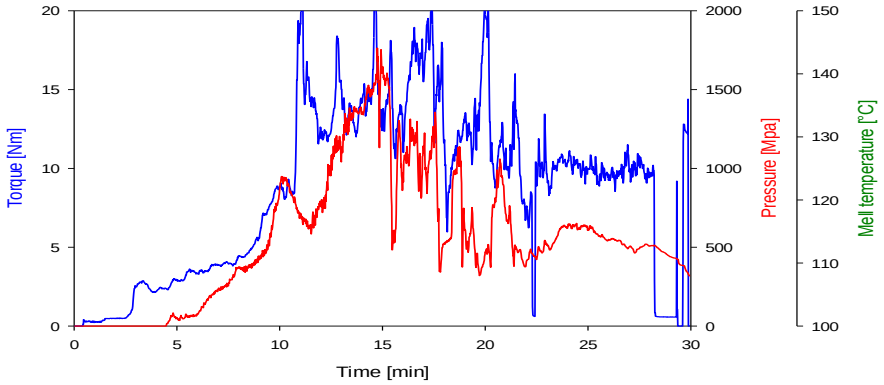

Figure 4.10 Torque, pressure, and melt temperature traces for formulation #5.

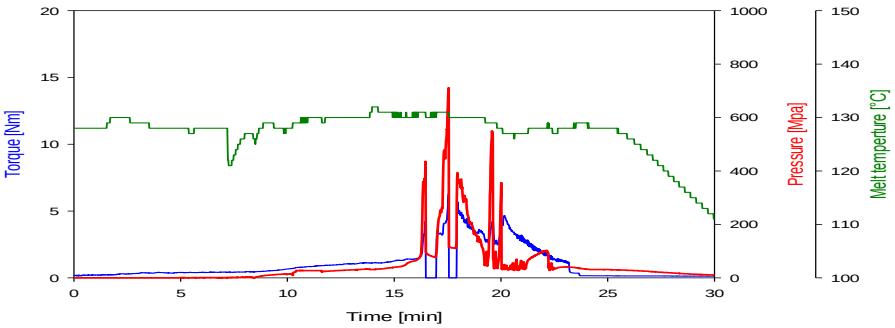

Figure 4.11 Torque, pressure, and melt temperature traces for formulation #6.

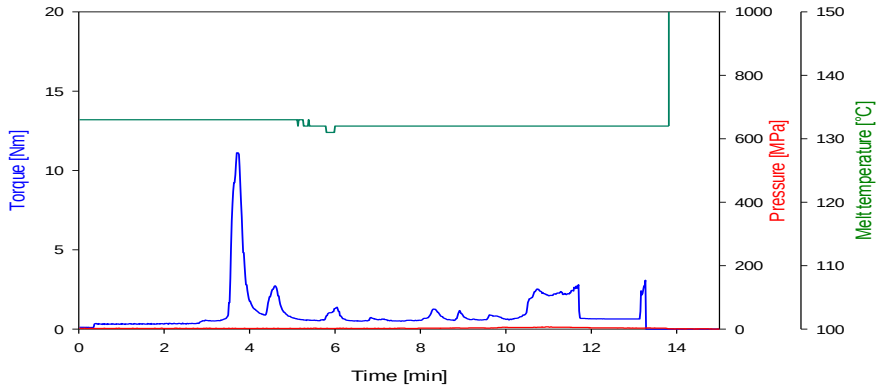

Figure 4.12 Torque, pressure, and melt temperature traces for formulation #7.

Figures4.6-4.12 show the torque, die pressure and melt temperature during extrusion of formulations #1-#6. In all graphs the torque and die pressure are unstable. This is probably a result of the fact that the incorporation of water into Keltone is taking much of the extruder length to complete. Therefore, most of the extruder barrel is filled with what may be mostly a “wet powder” mixture, while true dissolution of Keltone into

water takes place only at the end of the barrel. Including additional kneading elements in the extruder screw to enhance early and adequate mixing of the feed, primarily water incorporation, maybe a way to circumvent torque and die pressure instabilities.

4.3.2 Thermo-Gravimetric Analysis of Extruded Formulations

Water or moisture is undesirable in finished pharmaceutical products since its presence can result in product instabilities (e.g., recrystallization of drug, change of mechanical properties of tablets). For this reason, after extrusion, TGA was used to determine the residual water content of extrudates #1, #2, #3, #4 and #7. For ramp heating, a heating rate of 10°C/min was used to heat the samples from 30°C to 250°C. Runs were occasionally performed in duplicate with good reproducibility.

From the results in Figure 4.13 it can be seen that the more water the formulation initially contains, the more water the extrudates contain. In addition, for the same formulation composition, the higher the extrusion temperature, the less water the extrudates contain. For lower initial water contents (formulation #3 and #4) increasing the temperature by 10°C at the last two zones of the extruder can result in a ~15% reduction in residual water (36% vs 21%). It should be noted that when we attempted to use higher die temperatures (>130°C) to remove all or most of the water at the end of the barrel, the extruder was blocked. This is due to the fact that Keltone and related polysaccharides are crystalline polymers that do not possess a practical melting point (degradation occurs before melting) and as a result they do not flow without a plasticizer when heated.

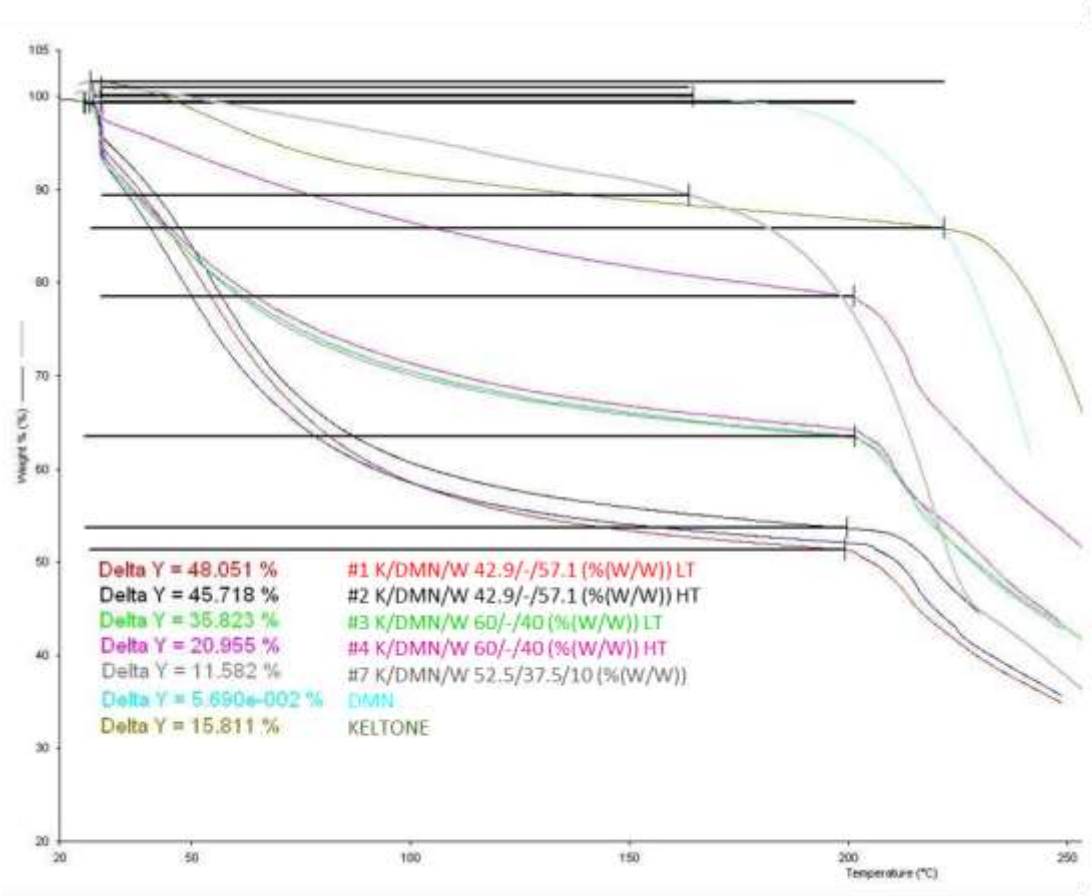

Figure 4.13 TGA ramp heating of pure Keltone, DMN and extruded formulations #1-#4 and #7.

4.3.3 Concluding Remarks

The processability of Keltone extruding with water as a plasticizer was explored. The most suitable extruder temperature profile along the extruder barrel and die (from the screw tip to the hopper)for Keltone using water as a plasticizer is the following: 120° , 90° , 80° , 80°, 50°C, the minimum amount of water as plasticizer allowing extrusion runs is 40%. The residual water contents in extrudate were determined by TGA test, which show that the residual water contents in extrudates were from 21% to 48%. Higher die temperature (>130°C) to remove the water at end of the result in the blockage of the extrusion.

4.3.4 Optimization of Amount of Plasticizer and Processing Temperature of Keltone Using Eudragit EPO as Plasticizer

In this section, extrusion optimization runs were performed to identify a) the optimum amount of Eudragit EPO as a plasticizer for Keltone and b) the optimum extrusion temperature. Table 4.2 lists the barrel temperatures and compositions used during all extrusion optimmzation runs.The first three combinations (Formulations #1 to #3) of composition/processing temperature could not be extruded as the amount of Eudragit EPO was too low (blockage of the extruder) and the processing temperature was too low (materials seem to consolidate). Formulation #4 was succesfully extruded and with ease. However considerable discoloration was observed potentially as a result of thermal degradation. By lowering the processing temperature and increasing the amount of EPO,formulation #5 produced an extrudate with color closer to the original raw materials. Based onpreliminary runs without API, the most suitable extruder temperature profile of Keltone with Eudragit EPO as plasticizer was decidedas the following: 150° 150° 130° 80° 50°C. Control formulation #6 containedonly Eudragit EPO and CLO. Formulation #7 and #8 were the two formulations that contained Keltone, Eudragit EPO and CLO, using the same ratio of EPO/CLO as in formulation #6. Both of the two runs were of good consistency and were easily extruded. Figure 4.14 shows the appearance of extrudates after extrusion.

Table 4.2 Formulationsand Extrusion Conditions of Keltone, CLO and Water

Formulation	Composition	Extrusion conditions					
(#)	(Keltone/CLO/EPO) (%(w/w))	(C°) M	Z4(D)	Z3	Z2	Z1	Z0(F)
1	90/-/10	145°	130°	100°	80°	80°	50°
2	85/-/15	165°	130°	100°	80°	80°	50°
3	70/-/30	161°	150°	140°	120°	80°	50°
4	50/-/50	166°	160°	160°	140°	80°	50°
5	40/-/60	159°	150°	150°	130°	80°	50°
6	-/30/70	157°	150°	150°	130°	80°	50°
7	10/27/63	157°	150°	150°	130°	130°	50
8	20/24/56	157°	150°	150°	130°	130°	50

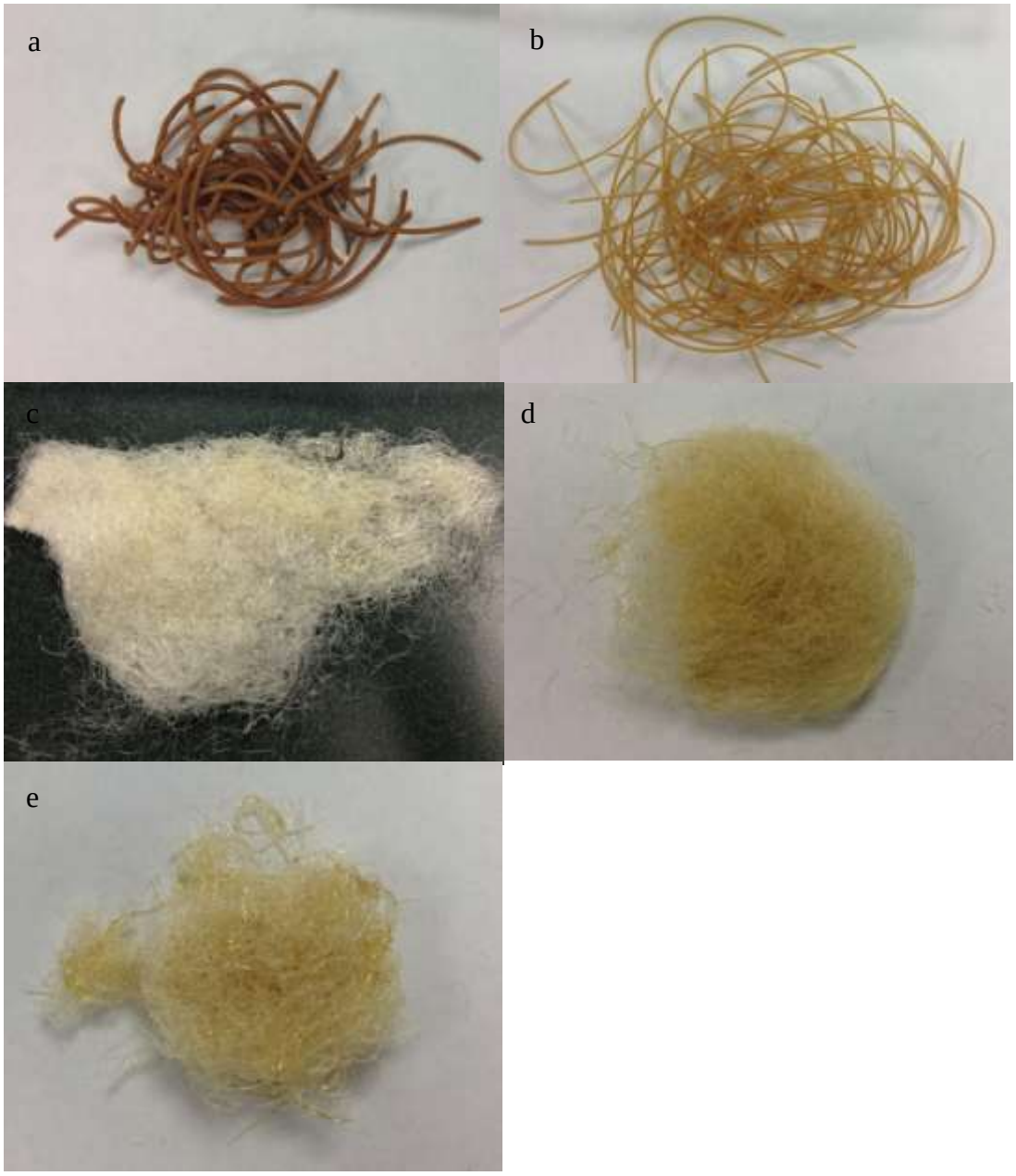

Figure 4.14 Appearance of extrudates after extrusion: (a) formulation #4, (b) formulation #5, (c) formulation #6, (d) formulation #7 and (e) formulation #8 (after drying).

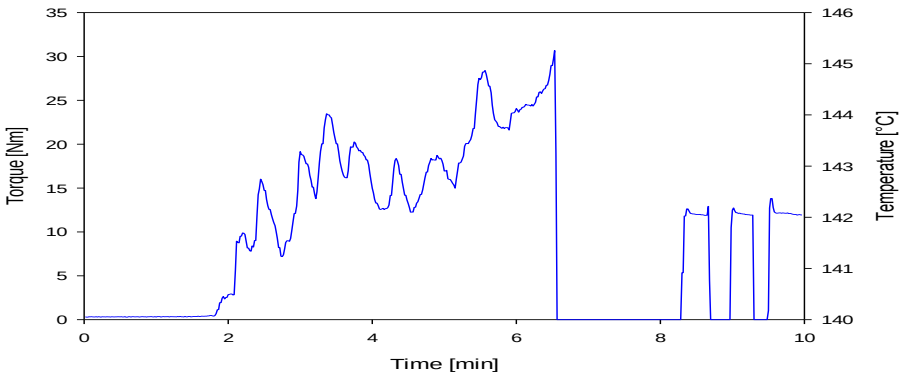

Figure 4.15 Torque, melt temperature traces for formulation #1.

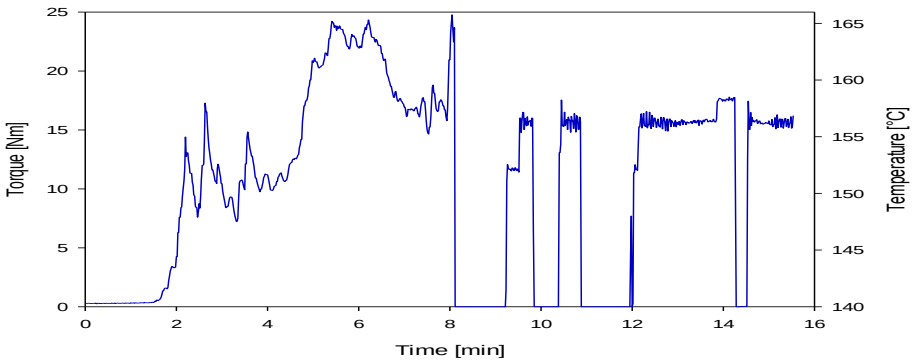

Figure 4.16 Torque, melt temperature traces for formulation #2.

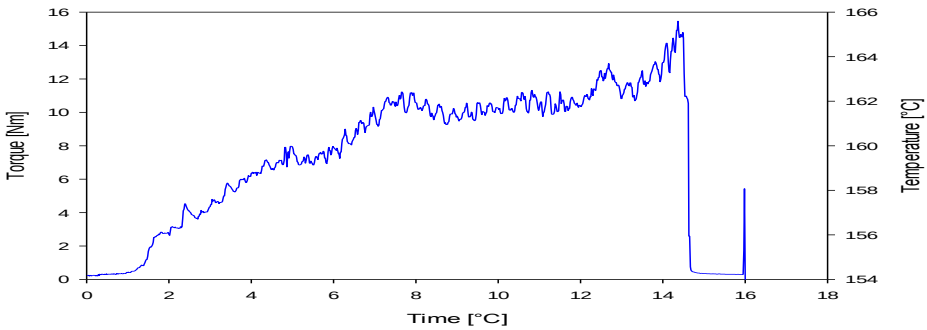

Figure 4.17 Torque, melt temperature traces for formulation #3.

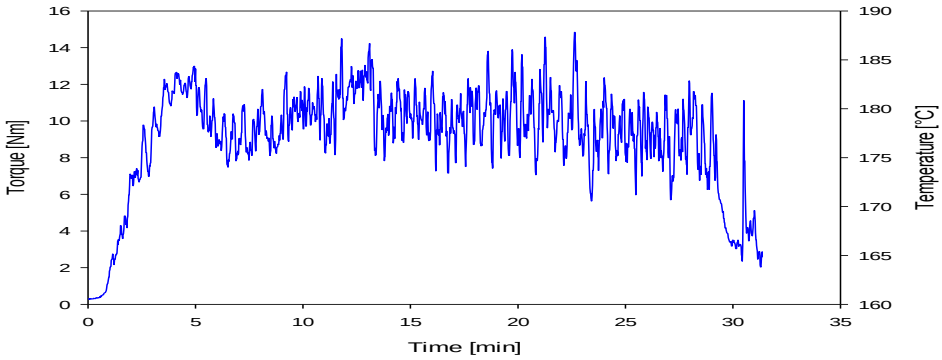

Figure 4.18 Torque, melt temperature traces for formulation #4.

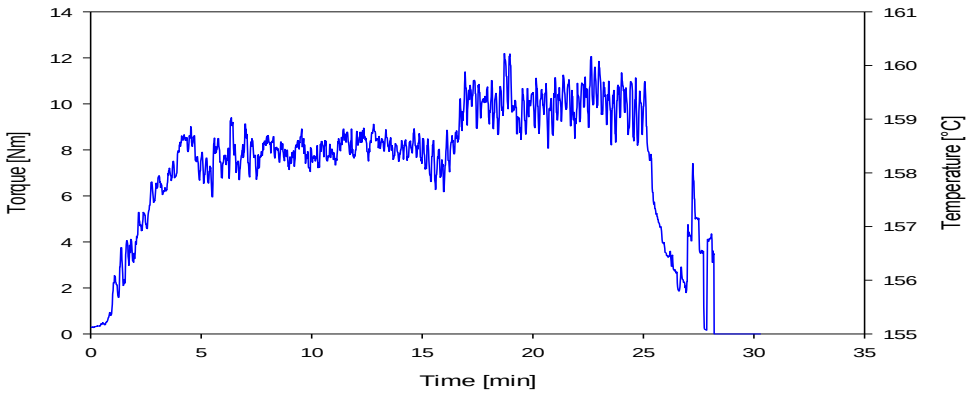

Figure 4.19 Torque, melt temperature traces for formulation #5.

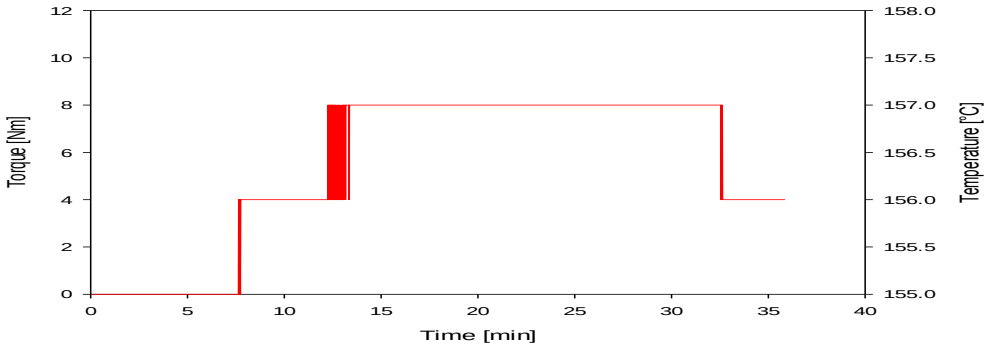

Figure 4.20 Torque, melt temperature traces for formulation #6.

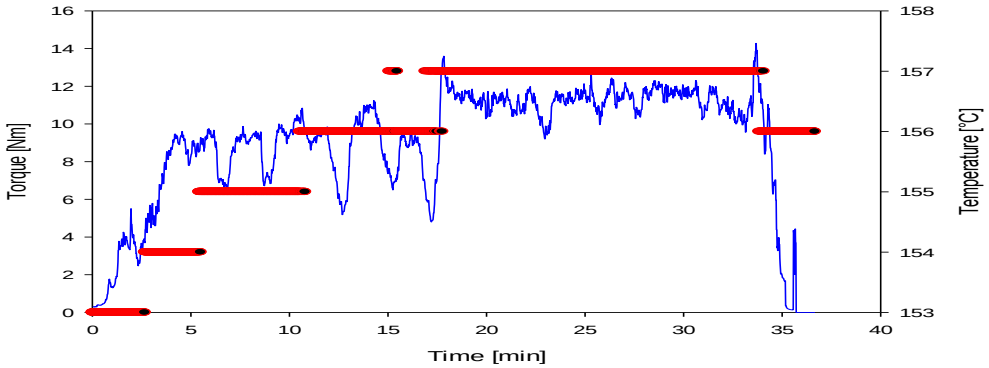

Figure 4.21 Torque, melt temperature traces for formulation #7.

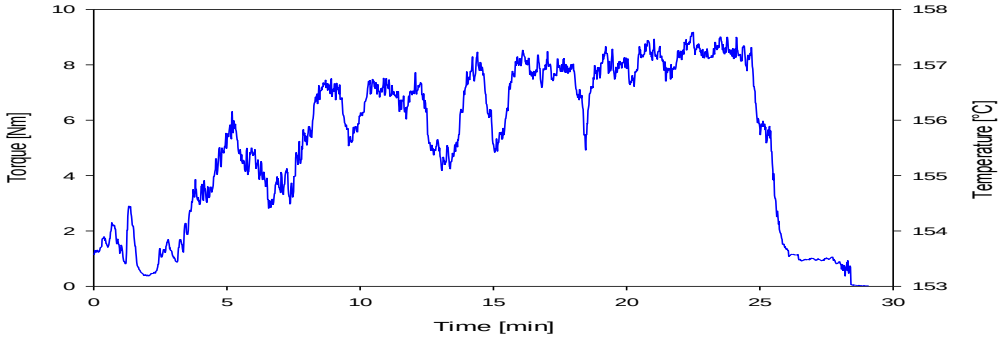

Figure 4.22 Torque, melt temperature traces for formulation #8.

Figures 4.15-4.22 show the torque and melt temperature during extrusion of formulations #1-#8. In Figures 4.15-4.17the torque is unstable. This maybe a result of the fact of the insufficient amount of Eudragit EPO as a plasticizer. In Figures 4.18-4.22, the torque of during extrusion of formulation #4-#8 is of acceptable stability, due to the good consistency of formulation component homogenization during the extrusion.

4.3.5 Observation on Hot Stage Microscopy

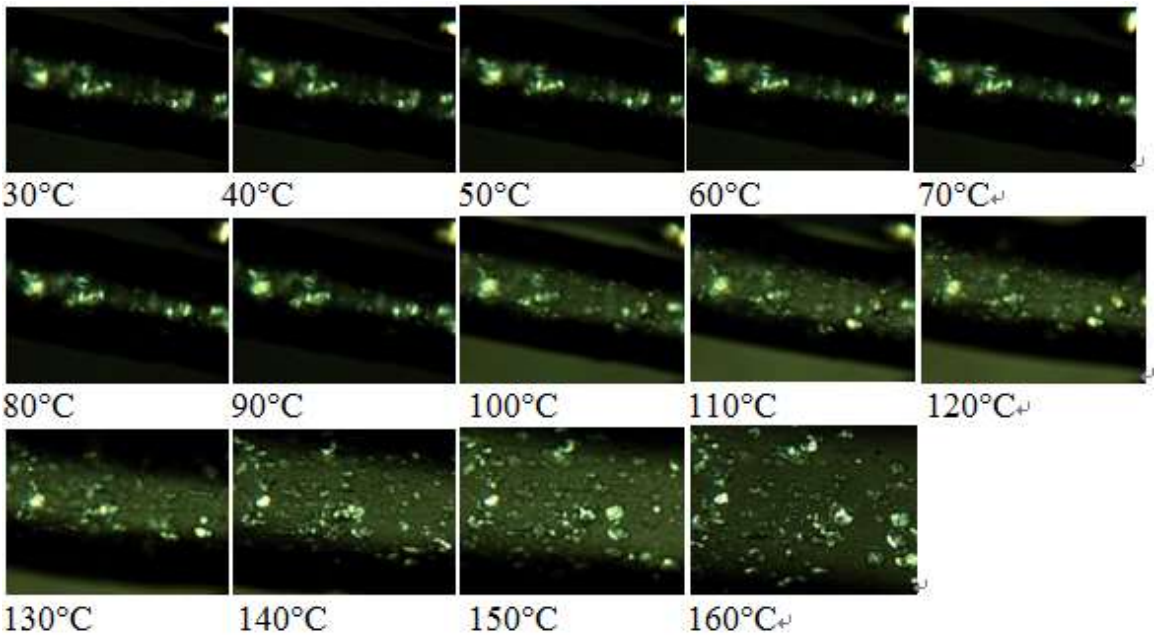

Figure 4.23 Transmission optical microscopy evolutions of EPO/CLO/Keltone (63/27/10), extrudate #7.

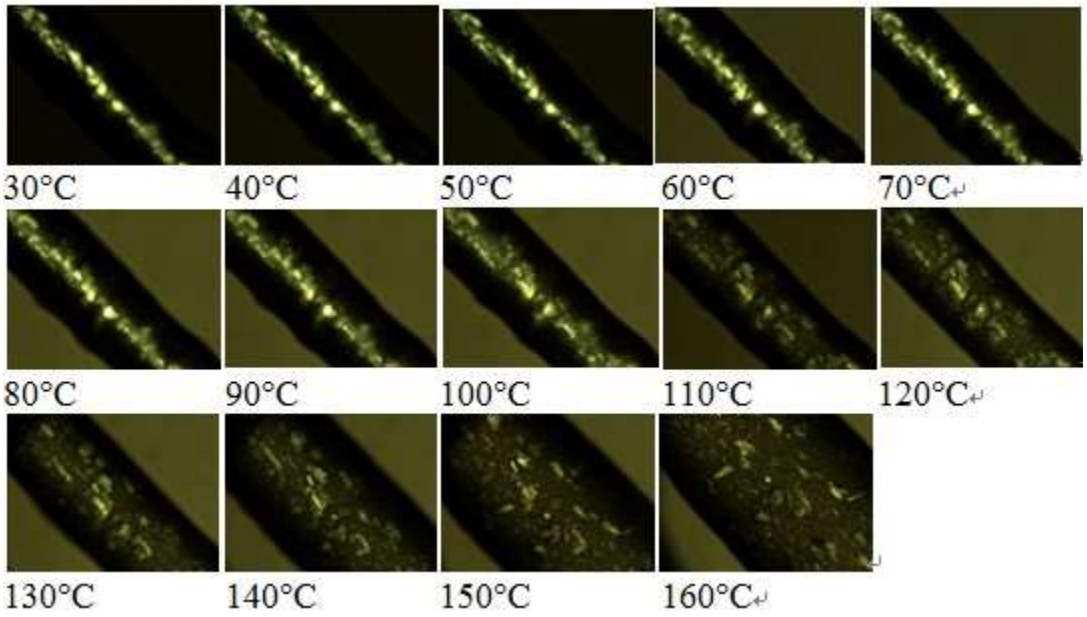

Figure 4.24 Transmission optical microscopy evolutions of EPO/CLO/Keltone (63/27/20),extrudates #8.

A hot stage was used to observe the morphology evolution in conjunction with the optical microscope. Figures 4.19- 4.20 show themorphology evolution of extrudate #7and extrudate #8at the same heating rates, which was set 20°C/min from 30 to 160 °C, conducted on a hot stage microscope. No changes in shapes of the crystals were shown in their morphologies during heating. Since the final temperature is beyond the melting point of CLO, which is 146°C, the crystals seen in these images are crystalline Keltone, indicating that either a portion or all of the Keltone did not consolidate with EPO during extrusion.

4.3.6 Differential Scanning Calorimetry Analysis of Extruded Formulation

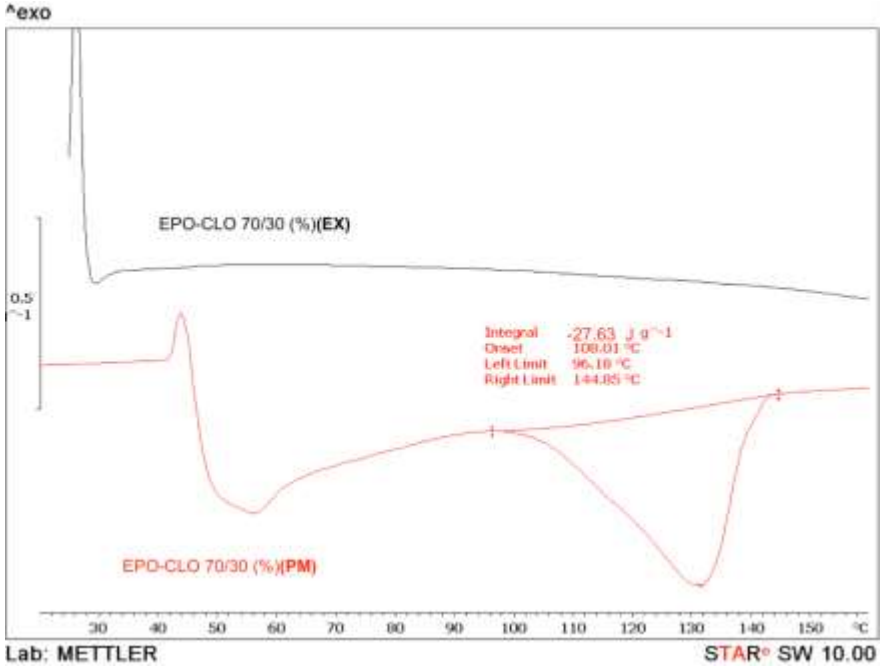

Figure 4.25 Ramp heating of EPO/CLO PM and extrudate.

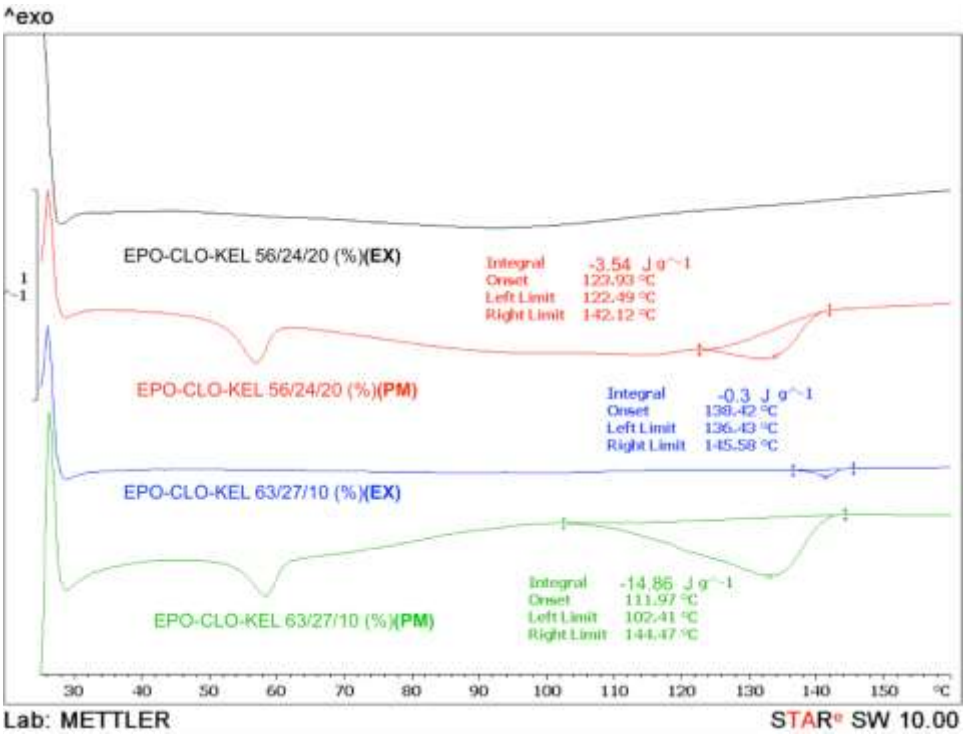

Figure 4.26 Ramp heating of EPO/CLO/KEL PM and extrudates.

Figure 4.25 shows the ramp heating of EPO/CLO 70/30 PM and extrudates that was used as a control for the EPO/CLO/KEL formulations. During the heating of the PM there is an endotherm that corresponds to the dissolution of CLO into EPO. During the heating of the extrudate, there is no endotherm indicating that 30% CLO is dissolved into EPO. In addition no traces of crystalline drug were found when looked at the extrudate under the polarized light microscope (results not shown).

Figure 4.26 shows the ramp heating of the PMs and extrudates of the two formulations with EPO, CLO and KEL. The dissolution endotherm of the CLO in the extrudate with 10% Keltone is larger that the one with 20% Keltone since the former contains more CLO. However, both of the extrudates show no dissolution endotherm for CLO (there is a very small endotherm in the extrudate with 10% Keltone however, the value of 0.3 J/g is extremly small to be taken as indication of undissolved CLO). These results correlate with the absence of any CLO crystals in the PLM images of the extrudates (Figures 4.23 and 4.24). The uncosolidated Keltone seen in these PLM images cannot be detected by the DSC as Keltone lacks any characteristic thermal transitions in the temperature range examined.

CHAPTER 5

SUMMARY AND FUTURE WORK

The work in this thesis has focused on the assessment of the possibility of using Keltone, a marine polysaccharide derived from brown seaweed, as a polymeric excipient for pharmaceutical HME. Water and Eudragit EPO were used as plasticizers, and Diphenhydramine Hydrochloride and Clotrimazole were **us**ed as active pharmaceutical ingredients (APIs). Extrusion was conducted in the Leistritz Nano16 Co-TSE.TGA was used to determineresidual water content of the extrudates. DSC was used to characterize thermal transitions of extrudates during heating. Optical microscopy was used to determine any undissolved API.

In this work, the minimum amount of plasticizer and processing temperature for Keltone using water as plasticizer was optimized. The most suitable extruder temperature profiles is: 120° 90° 80° 80° 50°C, while the minimum amount of water as plasticizer allowing extrusion runs is 40%.Above a certain processing temperature and below a certain amount of water, extrusion of Keltone was not possible. Based on above formulation of Keltone and water, and the suitable processing temperature, extrusions contained DMN were conducted. However, formulation contained DMN could not be extruded in consistency. DMN does not dissolve in the extrudates when heated in DSC, therefore water may play a very important role in this. In the TGA result of the samples extruded using the mos suitable conditions, the residual water is 21%. As water or moisture is undesirable in finished pharmaceutical products because of potential product

instabilities, water may not be a proper candidate as plasticizer for the extrusion of Keltone.

The processability of Keltone by extrusion using Eudragit EPO was also assessed in this work. The most suitable extruder temperature profiles was: 150° 150° 130° 80° 50°C, and the optimal amount of Eudragit EPO was found to be 60% wt. Formulations contained CLO as API were extruded under this condition. The DSC analysis of the extrudates showed no melting peak for CLO, suggesting that this drug only can fully dissolve in the excipient matrix in an amorphous state.

An important summary conclusion is the following: as a result of this work we can state with certainty that Keltone cannot be easily or widely used as polymer excipient.

Future work can be done as follows:

The plasticizer being used is distilled water with a specific pH of four. As Keltone is insoluble in acidic pH and soluble in basic pH, the pH of distilled water can be adjusted to higher one, in which way Keltone may be processed more easily. The combination of water and Eudragit EPO as a plasticizer also has the potential to allow the extrusion of Keltone.

Clotrimazole (CLO) is a weak base with two ionizable nitrogen atoms, which may make CLO exhibit good dissolution behavior under acidic conditions in stomach, but is likely to precipitate further in gastrointestinal tract because of a sharp increase in pH under the condition found in the intestine. This may result in poor and erratic bioavailability. Since the DSC result of extrudates showed that CLO was fully dissolved in the extrudate, the bioavailability CLO may be improved by this way. Moreover,

Keltone is a pH-depended solubility (insoluble in low pH, soluble in basic pH) material, which makes it a good candidate of excipient for target-release of CLO. Further work of dissolution tests can be conducted to verify the dissolution rate of CLO.

REFERENCES

Crowley M.M., Zhang F., Repka M.A., Thumma S., Upadhye S.B., Battu S.K., Mc Ginity J.W., Martin, C., 2007. Pharmaceutical applications of hot-melt extrusion: Part I. Drug Dev. Ind. Pharm., 33, 909-926.

Castro G.R., Panilaitis B., Kaplan L.D., 2008.Emulsan, a tailorable biopolymer for controlled release. Bioresource Technology., 99, 4566–4571

Dornish, M., Kaplan, D., Skaugrud, Ø., 2001. Standards and guidelines for biopolymers in tissue-engineered medical products. Ann. N. Y. Acad. Sci., 944, 388–397.

Evans J., 2014. Bio Beware. J. Plast. Eng., 70, 4-10.

Gogos C.G., Liu H., Wang P.,2012. Laminar dispersive and distributive mixing with dissolution and application to hot-melt extrusion: hot-melt extrusion: pharmaceutical application. D. Douroumis. Chichester, UK: John Wiley & Sons Ltd.

Gogos C.G., Tadmor Z., Kim M.H., 1998. Melting phenomena and mechanisms in polymer processing equipment. Adv. Polym. Technol.,17, 285-305.

Leuner C., Dressman J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm., 50, 47-60.

Mulhaupt R., 2014. Green polymers for sustainability. J. Plast. Eng., 70, 34-36.

Pavli M., 2009. Interaction of biopolymers carrageenans with cationic drug doxazosinmesylate characterized by means of differential scanning calorimetry. J. Die Pharmazie.,65, 525-527.

Repka M.A., Battu S.K., Upadhye S.B., Thumma S., Crowley, M.M., Zhang F., Martin C., Mc Ginity J.W., 2007. Pharmaceutical applications of hot-melt extrusion: Part II. Drug Dev. Ind. Pharm., 33, 1043-1057.

Sperger D.M., Fu S., Block L.H., Munson E.J., 2011. Analysis of composition, molecular weight, and water content variations in sodium alginate using solid-state NMR spectroscopy.J. Pharm. Sci., 100(8), 3441-3452.

Soares J.P., Santos J.E., Chierice G.O. Cavalheiro E.T.G., 2004.Thermal behavior of alginic acid and its sodium salt. Ecl. Quím., São Paulo., 29(2), 53-56.

Terife G., Wang P., Faridi N., Gogos C.G., 2012. Hot melt mixing and foaming of soluplus® and indomethacin. Polym. Eng. Sci. 52(8), 1629-1639.

Tadmor Z., Gogos C.G., 2006.Principles of Polymer Processing.2nd edition. Newark, New Jersey, US: Wiley-Interscience.

Thompson E.V.,1985. Encyclopedia of Polymer Science and Engineering, 2nd edition.,16, 711-747.