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VERSATILITY OF HOT-MELT EXTRUSION FOR DOSAGE FORM DESIGN

A
DISSERTATION SUBMITTED IN THE PARTIAL FULFILLMENT OF REQUIREMENTS
FOR THE DOCTORAL OF PHILOSOPHY DEGREE IN PHARMACEUTICS
THE UNIVERSITY OF MISSISSIPPI

by

SULTAN MOHAMMAD ALSHEHRI

December 2015

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ABSTRACT

Recently, Hot Melt Extrusion (HME) has attracted the attention of pharmaceutical companies and scientists as a technique for manufacturing a variety of dosage forms. In this research, HME was applied in different ways to achieve different goals, such as solubility enhancement, taste masking, solid state stability enhancement, and sustained release formulations for oral drug delivery, using one model drug, mefenamic acid. For solubility enhancement and taste masking formulations, Eudragit EPO was blended with MA in different ratios (20, 25, 30, and 40% of drug loads) and processed by a hot melt extruder to produce a solid dispersion system. FT-IR analysis suggested hydrogen bonding between the drug and the carrier up to 25% drug loading. SEM images indicated aggregation of MA at over 30% drug loading. Based on the FT-IR, SEM, and dissolution results for the extrudates, two optimized formulations (20% and 25% drug loads) were selected to formulate orally disintegrating tablets (ODTs). ODTs were successfully prepared with excellent friability and rapid disintegration time, in addition to the desired taste-masking effect.

In chapter 3, HME was applied to enhance the solubility of class II drugs by making solid dispersion systems by mixing MA with hydrophilic polymers (polyvinylpyrrolidone, PVP) in different ways as follow: (1) to demonstrate the effect of polyvinylpyrrolidone (PVP) matrices on the release of the poorly water-soluble drug, MA was prepared using the hot-melt extrusion technique, (2) to investigate the effect of PEG as a plasticizer and swelling agent in dissolution studies, (3) to study the influence of MgO as an alkalizer on the modification of the

microenvironmental pH of the matrices, and (4) to investigate the combined effect of PEG and MgO on the drug release behavior of the formulations.

In addition, we have also studied the ability of HME techniques to produce sustained release formulations for oral drug delivery. Various drug loads of MA and Kollidon[®] SR as a polymeric carrier were blended and extruded using a twin-screw extruder (16-mm Prism EuroLab, ThermoFisher Scientific) to prepare a solid dispersion system. Thermal analyses were used to confirm thermal stability, miscibility and to select the optimum processing conditions for extrusion. Sustained release tablets were successfully prepared with excellent tablet characteristics of these formulations. The drug release from the 40% drug-loaded extrudate reached 20% within 2 hours and 80% within 12 hours, compared to more than 80% drug release of the corresponding physical mixture, and 100% of the pure drug and formulations with higher drug loads of 60% and 80% within 2 hours. Therefore, the drug release of MA was further retarded by increasing the concentration of this polymer, which indicates Kollidon[®] SR has a significant effect on MA sustained release formulations.

DEDICATION

This dissertation is dedicated to my beloved parents, Mr. Mohammad Alshehri and Mrs. Thnowa Alshehri, my brothers and little sister Amal, to my lovely wife Aseel Alshehri and two daughters, Shahad and Seba for all their support, help and affection all through these years. They all have made me what I am today with their unending encouragement and guidance in every aspect of my life.

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CHAPTER 1

INTRODUCTION

1.1. Solid dispersion:

The most common and preferred route of drug administration is the oral route, due to the ease and convenience of intake compared to other routes of administrations such as parenteral drug delivery. However, the oral route of drug delivery has many limitations for a few reasons, which affect many active pharmaceutical ingredients. Poor drug absorption leads to poor bioavailability, which is a major concern when delivering the drug through the oral route. In addition, poor drug solubility and/or limited drug permeability result in restricted and insufficient drug absorption from the gastrointestinal tract inside the body. Consequently, poor water solubility of a drug will lead to slow or limited dissolution and limited absorption. In addition, drugs with poor permeability will limited the drug particles' ability to cross through the GIT membrane, thus limited the drug absorption (Dhirendra, Lewis, Udupa, & Atin, 2009; Serajuddin, 1999).

To overcome these problems, various solubilization technologies have been developed, including solid dispersion, salt formation, nanocrystals, and cyclodextrin complexes. Recently, research into solid dispersions has attracted the pharmaceutical companies and increased the products that have been approved by the FDA. Solid dispersion is broadly used to improve the oral absorption and bioavailability of the Biopharmaceutical Classification System (BCS) class II

drugs, which is described as low solubility with high permeability, specifically drugs with high dosages and/or high propensity for re-crystallization (Y. Huang & Dai, 2014). The research projects covered by this dissertation mainly uses solid dispersions of a poorly water-soluble drug in several different hydrophilic polymeric carriers.

1.1.1 Definition of solid dispersion:

The definition of a solid dispersion has been clarified by Chiou and Riegelman as “the dispersion of one or more ingredients in an inert carrier or matrix, where the active ingredients could exist in finely crystalline, solubilized or amorphous state”(Chiou & Riegelman, 1971). Therefore, the solid dispersion system usually consists of two or more materials, a hydrophobic drug and a hydrophilic carrier in a solid state. The drug particles can be dispersed in amorphous particles, forming clusters, or in crystalline particles.

1.1.2. Advantages and Disadvantages Solid dispersions:

Solid dispersion has recently become used extensively as a successful technique for solubility enhancement of poorly water-soluble drugs. This great increase in the solubility caused by solid dispersion is the result of decreasing the particle size of the drug, which forms a higher surface area and improves the wettability, which then decreases the thickness of the diffusion layer, consequently increasing the dissolution rate and therefore the bioavailability. It has been reported that solid dispersion has the highest degree of porosity, though this depends on the carrier properties. In addition, converting the crystalline form of the drug to the high-energy amorphous form enhances solubility and bioavailability. Thus, the dissolution rate is specified by the dissolution rate of the polymeric carrier. Subsequently, selecting a suitable carrier will

improve the dissolution rate of poorly soluble drugs (Leuner & Dressman, 2000; Vasconcelos, Sarmiento, & Costa, 2007).

However, solid dispersion does have disadvantages, including drug precipitation and recrystallization. Drug precipitation occurs because the drug particles are dispersed in a hydrophilic carrier, which can then leach out fast without the drug during the dissolution process. The amorphous drugs are physically unstable and have the tendency to revert back to the stable, crystalline form, due to their high-energy states. Also, the hydrophilic polymers have the ability to absorb moisture with time and this increase in the volume of the matrix can lead to recrystallization.

1.1.3 preparation of solid dispersions:

Many methods have been developed to manufacture solid dispersion systems including fusion and melt methods, solvent evaporation, hot melt extrusion, and spray drying. The fusion method is considered to be the first solid dispersion invented for pharmaceutical applications, developed in 1961 by Sekiguchi and Obi, using sulfathiazole and urea as a matrix. However, the major drawback of this technique is that the drug and the carrier have to be compatible and mix well before melting in order to prevent phase separation during the heating and cooling process (Dhirendra et al., 2009). The solvent evaporation technique is the most common and easiest way to form solid dispersions. The solvent evaporation process consists of two simple steps: first, dissolve the drug and the carrier in a suitable solvent, and then dry the solvent to form a solid dispersion system. Unfortunately, most of the organic solvents are toxic and require a large amount of the solvent, which makes this method impractical and highly expensive to manufacture (O'Donnell & McGinity, 1997). Spray drying is a technique that is widely used to manufacture dry powder solid dispersions in the food and pharmaceutical industries. It is a

process of producing a dry powder from a liquid or suspension by rapidly drying it with hot gas. This technique uses a one-step process and is preferred for thermally sensitive materials. This technique suffers from disadvantages that the equipment needed for the process is costly and as well as expensive to maintain. (Jain Manu et al.). For these reasons, hot melt extrusion is now the technique of choice and gets more attention from the pharmaceutical industry and the academic fields as a method for manufacturing solid dispersion systems.

1.2. Hot melt extrusion:

Hot-melt extrusion (HME) is a technique that has been used since the 1930s mostly in the manufacturing of plastic materials. After that, specifically in the early 1970s, HME was applied to the pharmaceutical industry to formulate and manufacture solid oral dosage forms. HME is a technique of pumping raw materials through a feeder to a rotating screw (or screws) under suitable heat, then pushing it through a die to form product extrudates of various shapes and sizes. This technique is used to manufacture amorphous solid dispersion systems where the API particles are melted and dispersed within a matrix carrier to generate and stabilize the amorphous form of the API's particles. The resulting extrudates could be a final product like pellets, mini-tablets, or films, or they could be milled and filled into capsules or compressed into tablets after adding tablet excipients. (Crowley et al., 2007; Repka et al., 2007).

HME offers many advantages over other traditional pharmaceutical techniques. It is a continuous process which gives it a shorter and more effective time, and it is water and solvent free, therefore reducing the number of manufacturing steps as well as the drying process, which makes it beneficial to the environment (Table 1)(Patil, Tiwari, & Repka, 2015). Therefore, HME has attracted the pharmaceutical field with more than 100 papers published and an increase in the

number of patents over the last two decades. HME has proved itself as a new technique to manufacture solid oral dosage forms such as capsules, tablets, pellets, films and implants.

Table 1-1: Advantages and Disadvantages of Hot-Melt Extrusion Technology:

Advantages	Disadvantages
Continuous process	May not be applicable for heat sensitive drugs
No water or organic solvents are needed	High energy input
High production outcomes	Limited number of heat stable polymers
Less labor and equipment demands	
Favorable product cost	
Can produce "solid solutions or dispersions" that may lead to increased solubility and bioavailability	
Shorter and more efficient processing times	

1.2.1. Hot melt extrusion equipment and process:

There are two types of extruders commonly used for pharmaceutical applications, the screw extruder and the ram extruder. The ram extruder works with a positive displacement piston that is able to create high pressure to push materials through the die. The screw extruder, which is the most commonly used in the pharmaceutical industry, consists of a feeder, screws inside a

barrel, control panel, torque sensors, heating/cooling device, divers dies, and downstream auxiliary equipment (fig. 1-1). In addition, the screw extruder could be further classified according to the number of screws, the size, and the direction of the rotation of the screws (co- or- counter rotating screws)(Shah, Maddineni, Lu, & Repka, 2013).

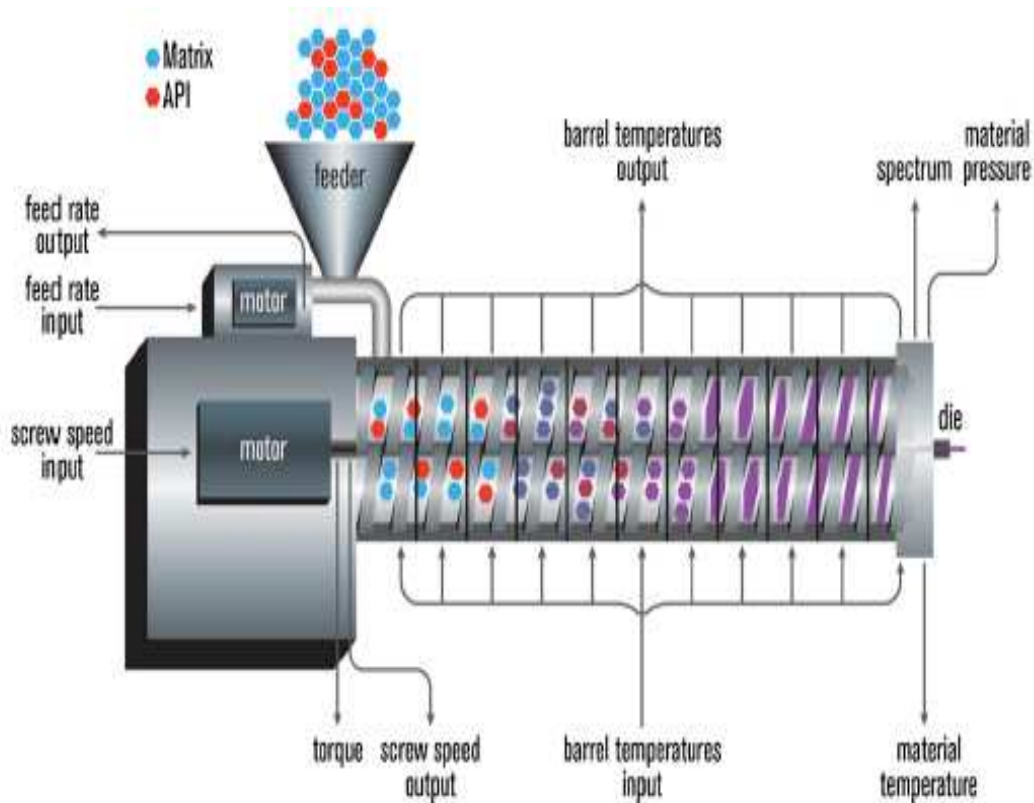


Fig. 1-1: Schematic of typical extruder system(Patil, Tiwari, & Repka, 2015).

The screw extruder is classified according the number of screws inside the barrel as follows: single screw extruders, twin screw extruders and multi screw extruders. The single screw extruder is the most widely used extruder in the industry; it consists of one screw that rotates inside the barrel. This screw serves multiple functions, conveying, melting, pumping and

shaping outputs. The raw materials are placed in the feed hopper (flood fed) then mixed and conveyed through a screw in the barrel. The rate of output from the die is controlled by the speed of the screw. This type of extruder is considered the simplest and least expensive compared to the others (Crowley et al., 2007; Maniruzzaman, Boateng, Snowden, & Douroumis, 2012).

The second common type of screw extruder is the twin screw extruder. As the name indicates, the twin screw extruder has two screws in a parallel position inside the barrel. These screws can rotate in the same direction, which is called co-rotating, or can rotate in opposite directions, which is called counter-rotating screws. The twin screw extruder has many advantages over other extruders which make it the favored choice in the pharmaceutical industry. These advantages include easier feeding, efficient mixing and dispersion of the excipient, decreased heat generation, de volatilization and reduced residence time of the materials inside the extruder. The ultimate choice between co-rotating or counter-rotating screws depends on several factors such as the material properties and the intended application. Counter-rotating screws can be used when there will be high shear and intense mixing as the materials are pressed through the space between the screws when they rotate. However, this system may have some drawbacks, such as high pressure and heat generation that may lead to product degradation, air entrapment and low screw speed with low outcomes. On the other hand, co-rotating twin screw designs usually feature intermeshing screws which are self-cleaning. This type of extruder can maintain uniform mixing even though it operates at high speeds, thus achieving a high output which makes it the most preferred type of extruder in the industry (Chokshi & Zia, 2010; Jani & Patel, 2015; Patel et al., 2013).

There are two types of extrusion processes: wet extrusion and dry extrusion, and which is used depends on the properties of the raw materials. In the wet process, the excipients are wetted

and softened with by a solvent such as water or alcohol to form wet mass, which works as a binder or plasticizer to facilitate the extrusion process and produce more uniform extrudates compared to the dry process. This technique is used when working with heat sensitive materials because the wet extrusion process produces less heat and pressure than the dry process. On the other hand, dry extrusion works with no solvent, making it the process of choice with materials that can handle the process. The API is mixed with a thermoplastic agent (in a powder form), which softens and melts because of the fractional heat during extrusion. The rotating screws force the mixture forward towards the die and, it solidifies when exiting the extruder (Fielden, Newton, & Rowe, 1992).

1.2.2. Materials used in hot melt extrusion:

The raw materials for the HME process must have some requirement and characteristics as follow (Crowley et al., 2007; Patil, Tiwari, & Repka, 2015):

- 1- They must have thermoplastic behavior, which is the ability to deform easily during extrusion and solidify upon exiting the die.
- 2- They must have the same degree of purity and safety as those used for manufacture by traditional methods.
- 3- These materials must have been used previously in the production of other solid dosage forms.
- 4- They must exhibit thermal stability as well as physical and chemical stability. This is a prerequisite for each compound used in the HME process, although decreasing the processing times used in this process may not limit all thermolabile compounds.

Generally, the dosage forms produced by hot melt extrusion techniques consist of a blend

of active pharmaceutical ingredients and functional excipients. These excipients could be classified as matrix carriers, plasticizers, release modifying agents, bulking agents, antioxidants, thermal lubricants, and miscellaneous additives. Thermoplastic carriers (polymers) must withstand shear and high temperatures, form pores or provide to the matrix specific physico-mechanical properties that facilitate the HME process. Adding a plasticizer to the formulations may reduce the processing temperatures, thus decreasing the drug polymer degradation.

1.2.3. Analytical characterizations of hot melt extrusion:

Analytical evaluations of hot melt extrudates, particularly amorphous solid dispersions, is used to determine solid-state drug polymer miscibility, kinetics of solid-state phase separation and nucleation (re-crystalline behavior), thermal stability or drug polymer degradation, and release studies. There are several analytical techniques, which have been applied for characterization of hot melt extruded products that list in table 1-2. Basically, the choice of evaluation methods depends on the physico-chemical properties of the materials and the purposes of the underlying study (Lu et al., 2014; Shah et al., 2013).

Table 1-2: Analytical techniques commonly used in HME:

Method	Evaluations
HPLC	To analyze drug content and dissolution samples.
TGA	Moisture analysis and thermal stability.
LOD	Moisture analysis and thermal stability.
DSC	Physical state (crystalline/amorphous state, polymorphic form).
FTIR	Interaction between drug and matrix.
XRD	Physical state (crystalline/amorphous state, polymorphic form).
PLM	Crystalline/amorphous state of the particles.
SEM	Crystalline state, shape, size, surface morphology.
HSM	Crystalline state, surface morphology.
Dissolution	<i>In vitro</i> drug release.

1.3. Model drug: Mefenamic acid:

Mefenamic acid [N-(2,3-dimethylphenyl) anthranilic acid] is a non-steroidal anti-inflammatory drug (NSAID) that acts by inhibiting the activity of cyclo-oxygenase-2 and thereby the production of prostaglandin, and is also a member of the fenamate group (Zeinolabedini Hezave, Khademi, & Esmaeilzadeh, 2012)(Fig. 1-2). Mefenamic acid (MA) is used as an anti-inflammatory, antipyretic, and potent analgesic agent to treat rheumatoid arthritis, osteoarthritis, dental pain, and dysmenorrhea (Abdolmohammad-Zadeh, Morshedzadeh, & Rahimpour, 2014; Kormosh & Matviychuk, 2013; Sriamornsak, Limmatvapirat, Piriyaprasarth, Mansukmanee, &

Huang, 2014). Recent studies also show that MA could be used to treat Alzheimer's disease (Sevgi, Kaynarsoy, Ozyazici, Pekcetin, & Ozyurt, 2008).

According to the biopharmaceutical classification system (BCS), MA is a class II drug that exhibits high permeability and low water solubility (i.e. 20 mg/l, which is practically insoluble in water). This low solubility affects its rate of absorption from the GI tract and thus consequently decreases its oral bioavailability (Alshehri et al., 2015; Sriamornsak et al., 2014). It is an odorless white or light gray powder with a melting point of 230°-231°C, with an unpleasant taste, which could lead to patient compliance issues (Adam, Schrimpl, & Schmidt, 2000; Mudit Dixit, Kulkarni, KR, & PRASAD, 2011). MA has a relatively short half-life of 2 hours with a usual oral dose of 250 or 500 mg which is prescribed three times daily (Ibrahim, 2013). Like other NSAIDs, and due to the free carboxylic acid group in the chemical structure, MA has broad gastrointestinal side effects, which could lead to serious patient incompliances (Sevgi et al., 2008).

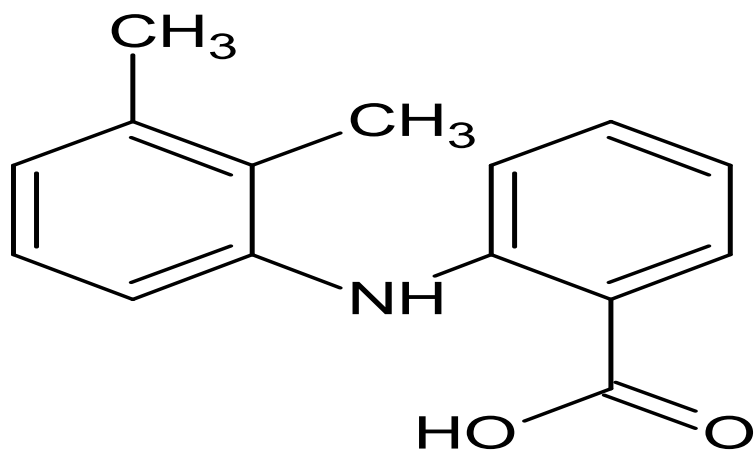


Fig. 1-2: Chemical structure of Mefenamic acid [N-(2,3-dimethylphenyl)] anthranilic acid]

According to the literature, there have been many scientist tried to enhance solubility of the poorly water soluble drug mefenamic acid by producing solid dispersion systems through many techniques, such as the fusion method (Owusu-Ababio, Ebube, Reams, & Habib, 1998; Serajuddin, 1999), thermal cross-linking microsphere (Roy et al., 2009), the cryogenic grinding method (Kojima et al., 2012), solvent evaporation method (Nagabhushanam & Rani, 2011), and the spray drying method (M Dixit, Kini, & Kulkarni, 2010). In addition, sustained release MA microcapsules prepared with acrylic polymers, MA beads based on cellulose acetate phthalate, MA microspheres, and MA matrix tablets have all been studied in the literature (Güngör, Yıldız, Özsoy, Cevher, & Araman, 2003; Sevgi et al., 2008). However, according to our knowledge, no HME studies have been conducted for this drug, there are no MA orally disintegrated tablets available on the market, and there are no taste-masking studies reported in the literature regarding the bitter taste of MA. Also, there is no commercial MA sustained release product available on the market. Therefore, we found that MA is a very unique choice for a model drug to be studied and processed by hot melt extrusion, as illustrated and studied in the following chapters.

CHAPTER 2

MEFENAMIC ACID TASTE-MASKED ORAL DISINTEGRATING TABLETS WITH ENHANCED SOLUBILITY VIA MOLECULAR INTERACTION PRODUCED BY HOT MELT EXTRUSION TECHNOLOGY

Objectives:

The objectives of the present study were to mask the bitter taste and to enhance the solubility of MA using HME solid dispersion techniques, and to optimize the HME processing conditions to manufacture stable orally disintegrating tablets by incorporating milled extrudates. In this study, we have selected Eudragit[®] E PO (aminoalkyl methacrylate copolymer) and explored its solubilizing and taste making potential for MA by HME.

Abstract:

The objective of this study was to enhance the solubility as well as to mask the intensely bitter taste of the poorly soluble drug, Mefenamic acid (MA). The taste masking and solubility of the drug was improved by using Eudragit[®] E PO in different ratios via hot melt extrusion (HME), solid dispersion technology. Thermogravimetric analysis (TGA) demonstrated the stability of both the drug and polymer at the employed processing temperatures. The physical mixtures (20, 25, 30, and 40% of drug loads) were successfully extruded using a co-rotating

twin-screw extruder at 110°C with a screw speed of 100 rpm. Differential scanning calorimetry (DSC) studies demonstrated that MA and E PO were completely miscible up to 40% drug loads. Powder X-ray diffraction (PXRD) analysis indicated that MA was converted to its amorphous phase in all of the formulations. Additionally, FT-IR analysis indicated hydrogen bonding between the drug and the carrier up to 25% of drug loading. SEM images indicated aggregation of MA at over 30% of drug loading. Based on the FT-IR, SEM and dissolution results for the extrudates, two optimized formulations (20% and 25% drug loads) were selected to formulate the orally disintegrating tablets (ODTs). ODTs were successfully prepared with excellent friability and rapid disintegration time in addition to having the desired taste-masking effect. All of the extruded formulations and the ODTs were found to be physically and chemically stable over a period of 6 months at 40°C/75% RH and 25 °C/ 60% RH.

Keywords: Hot-melt extrusion; Orally disintegrating tablets; Solid dispersion; Solubility enhancement; Taste masking effect; Molecular interaction.

2.1. Introduction:

The oral route of drug administration has many advantages over other routes (i.e. simple self-administration, painlessness compared to the parenteral route, and often excellent patient compliance) and, is generally considered to be the most important route for a drug delivery system (Chaudhary, Gauri, Rathee, & Kumar, 2013; Hearnden et al., 2012; Park, Lim, Kang, & Lee, 2013; Sattar & Lane, 2014). However, some patients may find it difficult to swallow intact tablets or capsules. This is particularly true for both pediatric and geriatric populations, who have a tendency to suffer from dysphagia, or among those who suffer from certain mental disorders. These problems could be overcome, in part, by developing orally disintegrating tablets (ODT). These tablets have the capability to dissolve in the mouth rapidly without the need of additional water, or they can be dispersed directly in water to make a suspension which is then administered as a liquid (Abdelbary et al., 2005; M. Huang et al., 2012). The U.S. FDA has defined ODTs as “A solid dosage form containing medical substance or active ingredient which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue” therefore the disintegration time for ODT’s are limited from seconds up to a minute (Narmada, Mohini, Prakash Rao, Gowrinath, & Kumar, 2009). In addition to rapid disintegration concerns, ODT formulations must also provide sufficient taste masking as the tablet dissolves in the oral cavity thereby allowing the drug to come into direct contact with the patient’s taste buds. The bitter taste of the drug could be prevented from coming in direct contact with the patient’s tongue, via the formulation of a solid dispersion system (J.-I. Kim et al., 2013).

According to the drug discovery field, more than 50% of the active pharmaceutical ingredients (APIs) belongs to class II of Biopharmaceutical classification system (BCS), characterized as poorly soluble compounds resulting in low bioavailability, which is a major

disadvantage in oral drug delivery systems (Liu, Cao, Zhang, & Ping, 2013). The bioavailability can be enhanced by increasing the apparent solubility of the API (Shah et al., 2013; P. H.-L. Tran et al., 2013; Vo, Park, & Lee, 2013). Various strategies for improving solubility of poorly water soluble drugs have been developed, such as micronization, chemical modification, pH adjustment, solid dispersion formation, complexation, co-solvency, micellar solubilization, hydrotrophy etc (Vemula, Lagishetty, & Lingala, 2010). Amorphous solid dispersion formulation is a technique that leads to the conversion of the crystalline lattice to the amorphous phase and disperses the drug molecules in a suitable carrier in order to enhance the solubility of the drug (Khan, Kotta, Ansari, Sharma, & Ali, 2014). High drug load in the drug delivery system, especially in solid dispersion systems, is crucial when high dosing is required. Thus, the present study has employed hot-melt extrusion (HME) technology to improve the solubility and to mask the bitter taste of the API in the ODT formulations with maximized drug load.

Over the last decade, HME has been used as a processing technique in the pharmaceutical industry for the formulation of oral solid dosage forms. HME has multiple inherent advantages such as elimination of organic solvents and fewer processing steps compared to the other pharmaceutical technologies (Crowley et al., 2007; Madana & Madanb, 2012). HME has been used to form solid dispersions in order to increase the bioavailability of many drugs by increasing their solubility. This is especially true for BCS class II drugs (Mohammed et al., 2012; Park, Kang, et al., 2013; Reintjes, 2011). Also, HME has been utilized for taste masking purposes (Maniruzzaman, Boateng, Bonnefille, et al., 2012). Mefenamic acid (MA) [2-(2,3-dimethyl phenyl) aminobenzoic acid], is a non-steroidal anti-inflammatory agent, which acts by inhibiting the activity of cyclo-oxygenase-2 and thereby the production of prostaglandin (Zeinolabedini Hezave et al., 2012). It is an odorless white or light gray powder with a melting

point of 230°-231°C, with an unpleasant taste, which could lead to patient compliance issues (Adam et al., 2000; Mudit Dixit et al., 2011) was used as a model drug.

Based on our knowledge, there is no MA ODT available on the market. In addition, there are no taste masking studies reported in the literature regarding the bitter taste of MA. Therefore, the objectives of the present study were to mask the bitter taste and to enhance the solubility of MA using HME solid dispersion techniques, and to optimize the HME processing conditions to manufacture stable orally disintegrating tablets by incorporating milled extrudates. In this study, the authors selected Eudragit® E PO (aminoalkyl methacrylate copolymer) and explored its solubilizing and taste making potential for MA by HME.

2.2. Materials:

Mefenamic acid (MA) was purchased from Sigma Aldrich (Bellefonte PA. USA); Eudragit® E PO and Aerosil® was gifted by Evonik (Evonik Industries, Germany); Avicel® 200 was gifted by FMC Biopolymers (Philadelphia, PA. USA); Polyplasdone™ crospovidone was gifted by ISP Technologies (ISP Technologies, Inc., Wayne, NJ, USA); Magnesium stearate was purchased from Mallinckrodt (St. Louis, MO, USA). All other chemicals used were of analytical grade.

2.3. Preparation methods:

2.3.1. Preparation and Evaluation of Hot-Melt Extrudates

2.3.1.1. Thermal Gravimetric Analysis (TGA):

The thermal stabilities of Eudragit[®] E PO, Mefenamic acid and the physical mixtures, were determined in the temperature range of 30°C to 250°C, at heating rate of 20°C/min by TGA (Pyris 1 TGA, Perkin Elmer) using Pyris manager software (PerkinElmer Life and Analytical Sciences, 719 Bridgeport Ave., CT, USA). The analysis was performed on samples of approximately 3-5 mg and evaluated as a function of weight loss.

2.3.1.2. Preparation of Hot Melt Extrudates

Mefenamic acid was blended with Eudragit[®] E PO at drug loadings of 20%, 25%, 30%, and 40% using a V-shell blender (GlobePharma, Maxiblend[®], New Brunswick, NJ). The binary mixtures of drug and polymer were extruded using a co-rotating twin-screw extruder (16 mm Prism Euro Lab, ThermoFisher Scientific) at 110°C with a screw speed of 100 rpm. The extrudates were further processed using a comminuting mill (Fitzpatrick, Model L1A), which was sieved by USP mesh (#35).

2.3.1.3. Determination of Drug Loading using Differential Scanning Calorimetry (DSC)

DSC (Diamond DSC, Perkin Elmer) equipped with Pyris manager software, was utilized to determine the physical properties, stability and miscibility of binary mixture of MA with the Eudragit[®] E PO in each physical mixture and the extrudates. Samples were prepared by weighing 2-4 mg each in hermetically sealed aluminum pans and analyzed at a heating rate of 20°C/minute under an inert nitrogen atmosphere at a flow rate of 20ml/min, over a temperature range of 30°C to 250°C.

2.3.1.4. Powder X-Ray Diffraction (PXRD)

PXRD measurements were used to study the crystallinity of the MA in melt extrudates. The PXRD studies were performed using a powder X-ray diffraction apparatus (Bruker AXS,

Madison, MI) at room temperature using CuK α radiation at 15 mA and 30 kV, 4°/min, and diffraction angles (2 θ) of 1-40°.

2.3.1.5. Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectroscopic analysis was performed on the extruded samples to study the drug-polymer interactions and corroborate the miscibility results obtained by DSC. FT-IR was conducted on a Cary 660 bench (Agilent Technologies, Santa Clara, CA.). The bench was equipped with an ATR (Pike Technologies MIRacle ATR, Madison, WI), which was fitted with a single bounce diamond coated ZnSe internal reflection element.

2.3.1.6. Scanning Electron Microscope (SEM)

The surface morphology of the pure drug and milled extrudates were evaluated and studied using SEM. Samples were mounted on adhesive carbon pads placed on aluminum stubs prior to sputter coating. A Hummer[®] 6.2 sputtering system (Anatech LTD, Springfield, VA) in a high vacuum evaporator were used to sputter-coated the samples with gold. SEM (JEOL JSM-5600) operating at an accelerating voltage of 10 kV was used for imaging. Three magnifications (500X, 1000X, 1500X) were used to give more accurate and clear results comparing each blend with pure MA.

2.3.1.7. Quantitative evaluations on extrudates

All of the prepared extrudates were evaluated for content uniformity and dissolution profiles. The milled extrudates were filled into hard HPMC capsules for *in vitro* drug release studies, each capsule containing the equivalent amount of 100 mg MA. The capsule dissolution tests were conducted in 500 ml of acetate buffer (pH 5.5) dissolution medium utilizing a USP apparatus II (Hanson SR8) at 37 \pm 0.5°C for 120 minutes with a rotation speed of 100 rpm (n=3)

(Kojima et al., 2012). All of the samples from the content uniformity test and dissolution studies were analyzed using a Waters HPLC-UV system.

2.3.1.8. HPLC Method

A Waters HPLC (Waters Corp, Milford, MA, USA) and Empower 2 software were used to analyze the samples and data. The stationary phase consisted of a Symmetry Shield C₁₈, 250Å~4.6 mm, 5 µm particle size reverse-phase column. The mobile phase consisted of methanol: water: acetonitrile (80:17.5:2.5 v/v) with the pH adjusted to 3.0 with phosphoric acid (85%). The detection wavelength was set at 225 nm and the mobile phase flow rate was maintained at 1.0 mL/min. The injection volume for all samples was 20 µL (Sultana, Arayne, Siddiqui, & Naveed, 2012). All assays studies were performed in triplicate (n=3).

2.3.2. Preparation and Evaluation for Orally Disintegrating Tablets

2.3.2.1. Tablet Preparations

20% and 25% drug loading extrudates were selected to make ODTs based on the FT-IR, SEM and dissolution results. Selected milled extrudates were mixed with excipients (microcrystalline cellulose, PolyplasdoneTM crospovidone, colloidal silicon dioxide and magnesium stearate) and sieved using US # 35 of mesh size, and compressed at 4-4.1 kN on a manual tablet press (MCTMI, Globe Pharma Inc., New Brunswick, NJ) using a 12 mm flat punch to a final tablet weight of 650 mg (Table 2-1).

Table 2-1: Compositions of Mefenamic Acid ODTs

Excipients	20% MA/EPO EXTRUDATES		25% MA/EPO EXTRUDATES	
	% (W/W)	Weight (mg/tablet)	% (W/W)	Weight (mg/tablet)
Mefenamic acid	15.38	100.00	15.38	100.00
Eudragit® E PO	61.53	400.00	46.15	300.00
Avicel® 102	12.58	81.75	27.96	181.75
AEROSIL® 200	5.0	32.5	5.0	32.5
Polyplasdone™ crospovidone	5.0	32.5	5.0	32.5
Magnesium Stearate	0.5	3.25	0.5	3.25
Total	100.00	650.00	100.00	650.00

2.3.2.2. Compressibility Test to Make ODTs

Prior to compression, compressibility test was carried out with the final mixtures. The bulk density (ρ_b) was determined by placing a specific amount of the mixture (M) in 100 ml graduated cylinder to measure the bulk volume (Vb). Bulk density was calculated using the following equation [35]:

$$\rho_b = M/V_b \quad \text{Eq.1.}$$

Tap density (ρ_t) was determined by placing a known amount of the mixture into a 100 mL graduated cylinder and measuring its volume. The mixture was then tapped for 100 times and its

volume was measured again. The tap density was calculated using the following equation [35]:

$$\rho_t = M/V_t \quad \text{Eq.2.}$$

Where M is the amount of the blend and V_t is the tapped volume.

Compressibility index (Carr's index, I) was determined by the following equation [35]:

$$I = (\rho_t - \rho_b) / \rho_t \times 100 \quad \text{Eq.3.}$$

2.3.2.3. Tablet Characterization

The compressed tablets were evaluated for thickness, diameter, hardness, friability and disintegration test. A digital vernier caliper (Fisher Scientific) was used to evaluate the thickness and diameter of the tablets. A hardness tester (VarianVK200, Agilent technologies, 13000 Weston Pkwy, Cary, NC) was used to evaluate the hardness of the tablets (n=6). Friability studies were performed by Roche friabilator) for 4 min at 25 rpm (n=10, total weight-6.5 g). Disintegration testing was performed on Dr. Schleuniger Pharmatron USP disintegration apparatus (n=6) at $37 \pm 0.5^\circ\text{C}$ [5]. The tablet dissolution test for drug release was carried out using the previously outlined conditions for capsules.

2.3.2.4 *In vitro* taste masking evaluation of OTDs

In vitro dissolution studies were carried out by two different methods to analyze the taste-masking efficiency. *In vitro* oral drug release was conducted in 150 ml of simulated saliva fluids adjusted to pH 6.8 (Table 2-2). A dissolution apparatus II (Hanson SR8), which equipped with UV-Vis probes (Rainbow Dissolution Monitor, pION) set at 225 nm with collecting samples every 5 seconds for 120 seconds, was used and maintained at $37 \pm 0.5^\circ\text{C}$ with a shaft rotation speed of 100 rpm (n=3). In addition, a 500 ml of water using USP apparatus II (Hanson SR8) at

37 ± 0.5°C with a rotation speed of 50 rpm (n=3) was conducted and samples were collected at time points of 0.5, 1, 2, 3, and 5 minute.

Table 2-2: Composition of artificial saliva media adjusted to pH 6.8

	Compounds	Concentration (g/L)
1)	CaCl ₂ .2H ₂ O	0.228
2)	MgCl ₂ .6H ₂ O	0.061
3)	NaCl	1.017
4)	K ₂ CO ₃ .1.5H ₂ O	0.603
5)	Na ₂ HPO ₄ .7H ₂ O	0.204
6)	NaH ₂ PO ₄ .H ₂ O	0.273

2.3.3. Stability Studies

Stability testing was performed over a period of 6 months at accelerated conditions and a year at normal conditions to evaluate the physical and chemical stability of the extrudates and ODTs. The extrudates and ODTs samples were stored in closed glass vials at 40°C/75%RH and 25 °C/60% RH, respectively. DSC, FT-IR, and XRD were utilized to determine the influence of the temperature and humidity conditions on the physical stability of the formulations. The extrudates and ODTs samples were evaluated for chemical stability by measuring drug content and content uniformity, which were compared with fresh ones. Additionally, the *in vitro* drug

release studies in aqueous and 0.1 M acetate buffer media were also performed on the samples and the release profiles were compared with the fresh ones using the similarity factor (f_2 value) (J.-Y. Kim et al., 2012). All of the samples from the drug content, content uniformity test and dissolution studies were analyzed using a Waters HPLC-UV system.

2.4. Results and discussion:

2.4.1. Thermal Analysis

TGA thermogram demonstrated the thermal stability of pure MA and all physical mixtures at the employed processing temperatures (Fig. 2-1). Mefenamic acid and all of the physical mixtures showed no significant degradation up to 200°C. Less than 2% of degradation was considered as residual water of MA and other excipients. Therefore, all of the formulations were assumed to be thermally stable during the hot melt extrusion process.

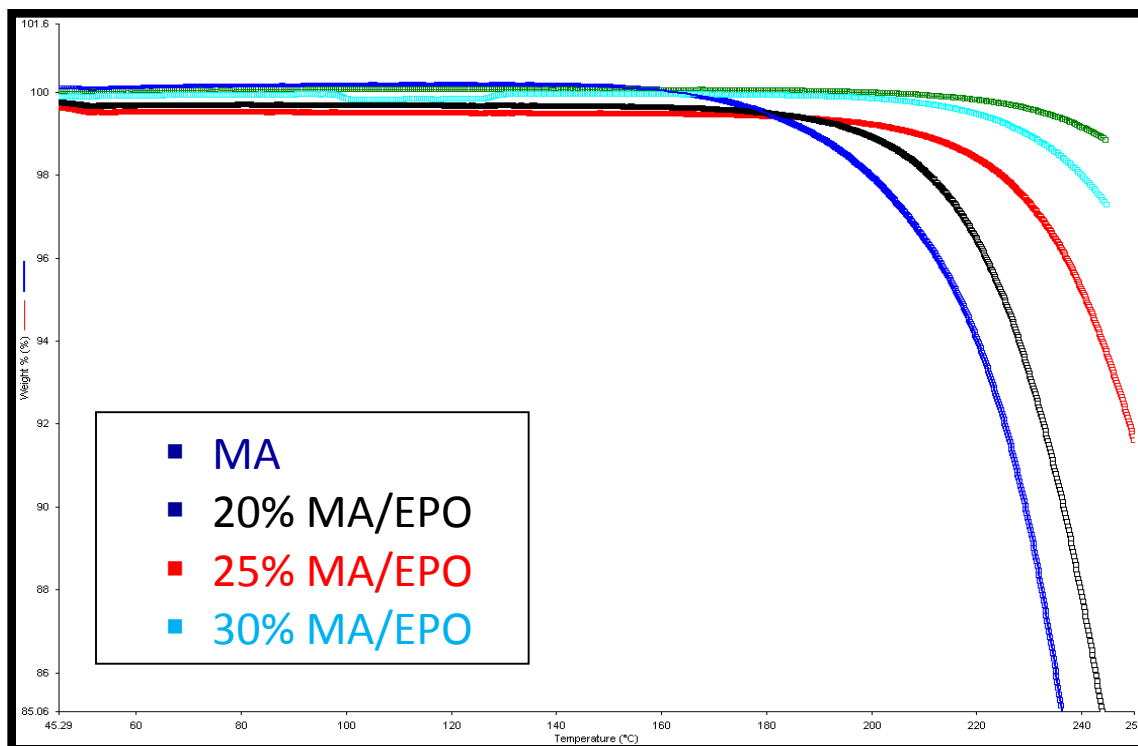


Fig. 2-1: Thermogravimetric analysis of various MA/EPO mixtures

DSC studies of the physical mixtures and the extrudates showed complete miscibility between the MA and Eudragit[®] E PO at 20%, 25%, 30%, and 40% of drug loadings (Fig. 2-2). Moreover, the DSC studies revealed that MA exhibited an endothermic peak at 230°C. However, the disappearance of the MA melting peak in both of the physical mixtures up to 40% drug load and the melt extrudates confirmed the formation of amorphous solid dispersions of MA in Eudragit[®] E PO. Additionally, the absence of the melting peak in the thermograms indicates that the drug was completely solubilized in the melt-extruded matrices [27].

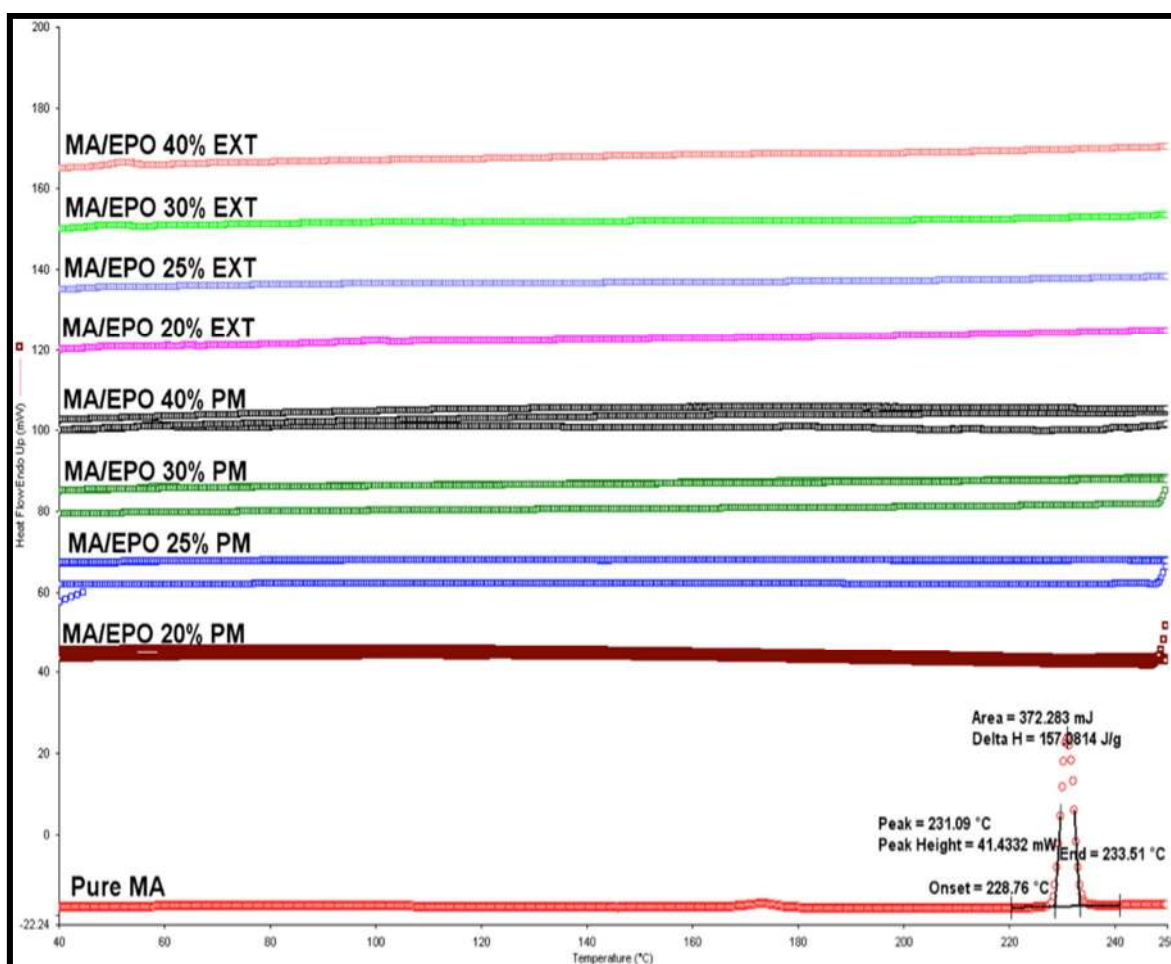


Fig. 2-2 : MA/EPO miscibility studies using DSC at temperatures of 30-250°C and heating rate of 20 °C/min

2.4.2. Hot Melt Extrusion Process

The hot melt extrusion process is affected by the different physical and chemical properties of the drug and the carrier, which also affects the final product as well (Repka et al., 2012; Sarode, Sandhu, Shah, Malick, & Zia, 2013). Thus, the process condition should be adjusted and optimized according to the physicochemical properties of both the API and the excipients. Based on the TGA and DSC studies as well as other preliminary studies, the extruder temperature and screw speed seemed to be well adjusted. Therefore, four drug loads (20%, 25%, 30%, and 40%) were extruded at 110°C with a screw speed of 100 rpm to produce uniform rod extrudates. All of the extruded formulations possessed exceptional drug content (>98%) as well as content uniformities (<3% RSD) after hot melt extrusion processing. This is indicative of a robust formulation and process. However, 20% and 25% of drug loaded extrudates were transparent in appearance, whereas 30% and 40% drug loaded extrudates were opaque due to increasing the amount of drug and decreasing the fraction of the Eudragit® E PO.

Eudragit® E PO is a cationic copolymer, consists of dimethyl amino ethyl methacrylate and neutral methacrylic acid ester, which is in the amorphous form. According to the literature on solid dispersion, E PO has multiple uses in the pharmaceutical field such as taste and odor masking [36]. In this work E PO has been selected as a primary carrier due to its cationic nature, which forms counter ionic intermolecular interaction with the weakly acidic drug (Figure 2-3). The interaction between Eudragit® E PO and MA was later confirmed by FT-IR analysis. This interaction may have aided in improving taste masking efficiency as well as drug release. The advantage of using E PO is that it is very stable thermally, and has a very low glass transition temperature, which is beneficial during HME processing (Kojima et al., 2012; Madana &

Madanb, 2012). MA has a high melting point of 230 °C. However, the binary mixtures could be extruded at a low temperature of 110 °C without the addition of a plasticizer, which indicates that MA acted as a plasticizer with E PO.

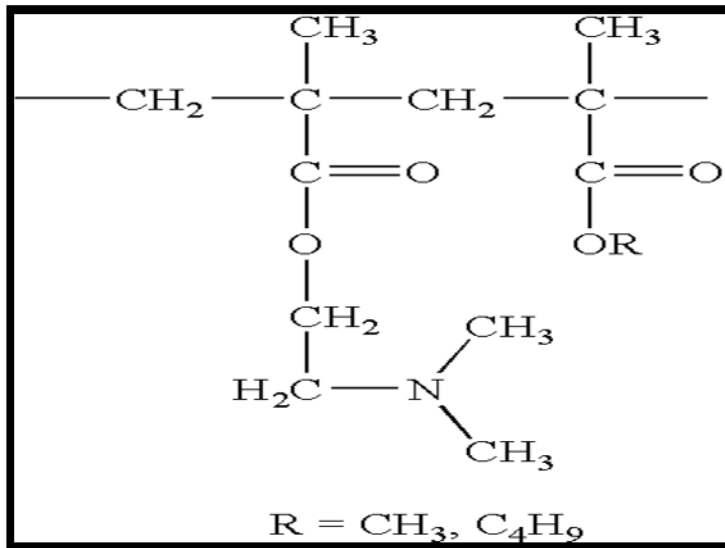


Fig. 2-3: Chemical structure of Eudragit® E PO.

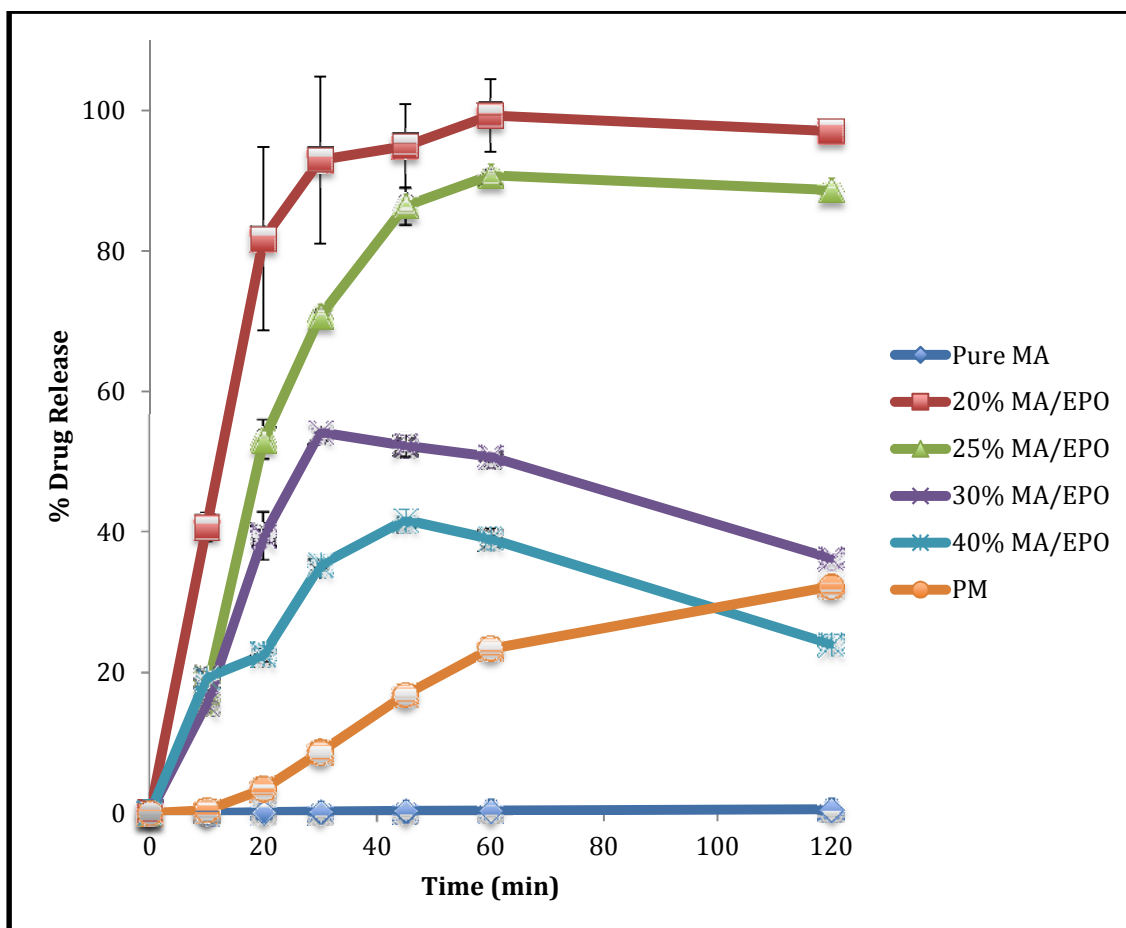


Fig. 2-4: *In vitro* dissolution profiles of MA/EPO extrudates in 0.1 M acetate buffer (pH 5.5) dissolution media.

2.4.3. *In Vitro* Dissolution Studies on Extrudates

Mefenamic acid is known to be increasingly soluble when raising the buffer's pH from pH 1.2 to 9.0. MA is a weak acid ($pK_a=4.32$) and easily ionizes at higher pH (Klose et al., 2011). Thus, the US Pharmacopeia recommended pH 9.0 buffer as a dissolution media to produce sink conditions. E PO is basic material (butylated methacrylate copolymer) with high solubility in the gastric media (1.2-5.0 pH), which cannot dissolve or swell above pH 5. This property of E PO makes it an attractive copolymer for taste masking applications. Therefore, choosing acetate

buffer of pH 5.5 as a dissolution media is a reasonable choice for this extruded formulation, and has been previously reported in the literature (Kojima et al., 2012). Drug release studies were performed to understand the dissolution behavior of MA from the binary solid dispersion matrices.

According to the *in vitro* dissolution studies, drug release from all of the extruded formulations (acetate buffer) demonstrated improved dissolution as compared to the pure drug. The drug release from the 20% and 25% drug loaded extrudates reached more than 85% within 40 minutes, whereas less than 1% drug release within 40 minutes was observed for the pure drug, and less than 15% release for the physical mixture (20% of drug load) under the same conditions (Figure 3). However, the 20% drug loaded formulation demonstrated approximately 99% release within 60 minutes. Thus, the dissolution of MA was greatly enhanced by increasing the portion of Eudragit[®] E PO, and up to 25% drug loading. This indicates that the melt extruded molecular dispersion with Eudragit[®] E PO plays an integral role in enhancing the dissolution rate of MA. The mechanism by which the drug release was enhanced in these formulations is discussed in greater detail in the ‘physico-chemical properties of extrudates’ section.

2.4.4. Physico-Chemical Properties of Extrudates

The characteristic PXRD peaks of crystalline MA were observed at $2\theta = 6.3, 21.4,$ and 26.3 . These peaks indicated that the pure MA is in a crystalline state. Eudragit[®] E PO showed no characteristic peaks, indicating the amorphous structure of the polymer. The MA peaks were absent in the hot melt extruded binary formulations with up to 40% drug loading (fig. 2-5). These results confirm that crystalline MA was transformed into the amorphous phase during the HME processing with Eudragit[®] E PO.

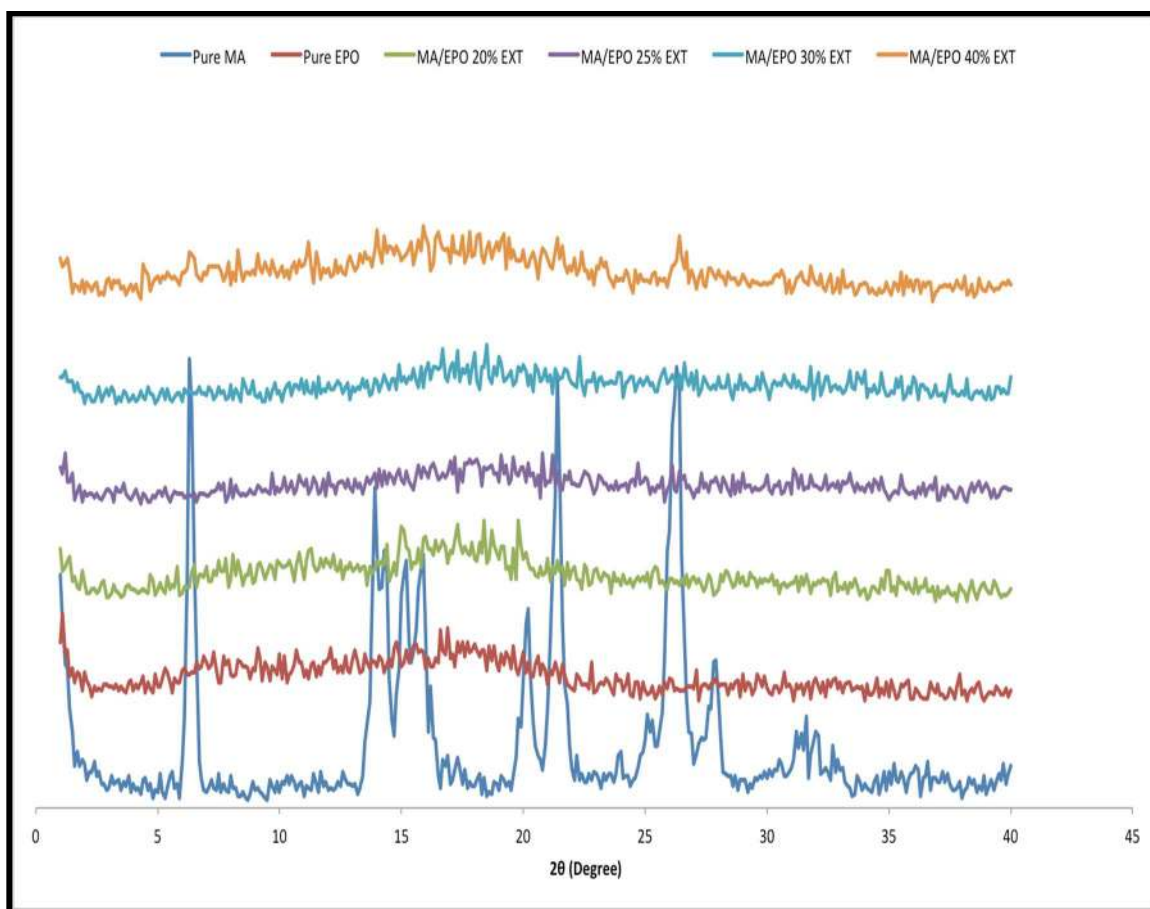


Fig. 2-5: PXR D analysis for pure MA, E PO and various MA/EPO extrudates.

FT-IR analysis was used to observe the drug-polymer interactions usually resulting in peak shifting or the appearance/absence of absorbance peaks. MA showed three significant stretching absorbance peaks at $3,308\text{ cm}^{-1}$, $1,646\text{ cm}^{-1}$, and $1,573\text{ cm}^{-1}$ representative of the functional groups of N-H, C=O, and C=C respectively (fig. 2-6). Additionally, E PO spectra showed one significant peak from the stretching of a carbonyl C=O at $1,730\text{ cm}^{-1}$. Furthermore, from the chemical structure of MA, it can be seen that available carboxyl group (proton-donating group) and the aminoalkyl group (proton-accepting group) in E PO may have a strong interaction. This interaction was confirmed by the absence of the peaks at $1,646\text{ cm}^{-1}$ and $1,573\text{ cm}^{-1}$. Therefore,

FTIR analysis clearly indicated strong intermolecular interactions (hydrogen bonding) were induced between MA and the E PO by HME processing. This interaction is presumed to have led to the enhanced MA release profile. However, the MA peak at $1,646\text{ cm}^{-1}$ reappeared when drug loading increased to 40%. Based on these findings, it is apparent that 30% drug loading saturated the hydrogen bonding capacity of the polymer. Consequently, 30% and 40% of drug loadings showed relatively lower drug release as well as precipitation.

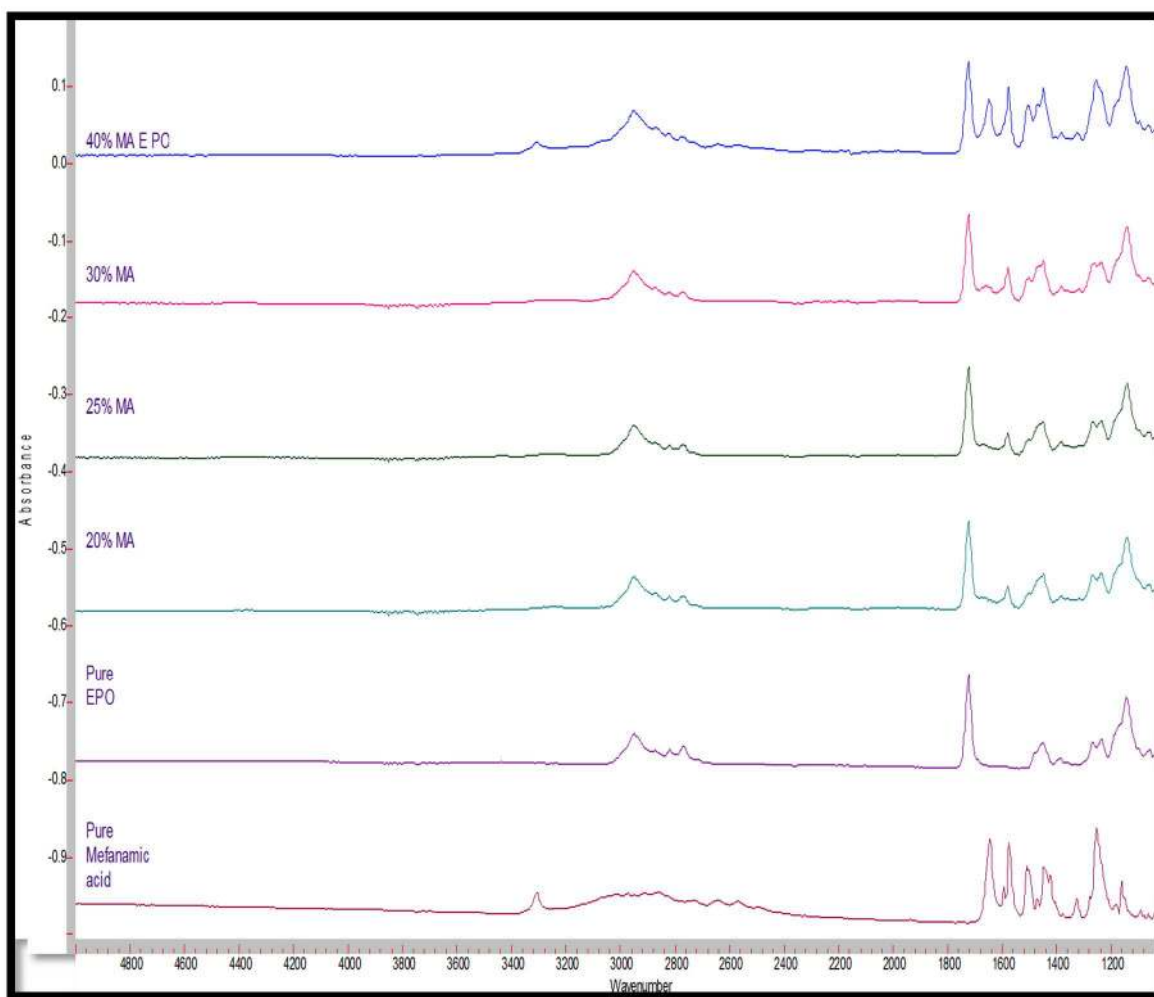


Fig. 2-6: FTIR analysis for pure MA, EPO and various MA/EPO extrudates.

Kojima et al. (2012) used MA and E PO to prepare solid dispersion formulations, which were subsequently stabilized in a supersaturated state utilizing cryogenic milling at -180°C for 90 min. They reported that the strong intermolecular interactions between MA and E PO resulted in enhanced bioavailability as well as long-term storage stability in the solid state (Kojima et al., 2012). In this current research, solid dispersions composed of MA and E PO prepared by hot melt extrusion technology demonstrated the same strong intermolecular interactions, which were made evident by FT-IR analysis.

Scanning Electron Microscope (SEM) showed a remarkable difference between pure MA and processed binary mixtures (fig. 2-7). Pure MA (2-7-e) seemed to consist of microcrystalline aggregates with a coarse surface. On the other hand, 20% (2-7-a) and 25% (2-7-b) drug loaded dispersions exhibited smooth surfaces and no aggregation suggesting a completely miscible single-phase binary solid dispersion system. However, increase in drug loading further results in increase in agglomeration as shown in fig. 2-7-c (30%) and 2-7-d (40%).

The above analysis confirms that the extrudates up to 25% drug loading produced completely miscible systems. Consequently, 20% and 25% of drug loading hot melt extrudates showed very high dissolution rates as compared to the pure API. Though the drug loadings of 30% and 40% were changed to an amorphous phase, there was an occurrence of precipitation and decrease in the drug release which may be due to the weak or absent intermolecular interaction and agglomeration.. Based on these findings, only 20% and 25% drug loadings were chosen for further studies with orally disintegrating tablets (ODT).

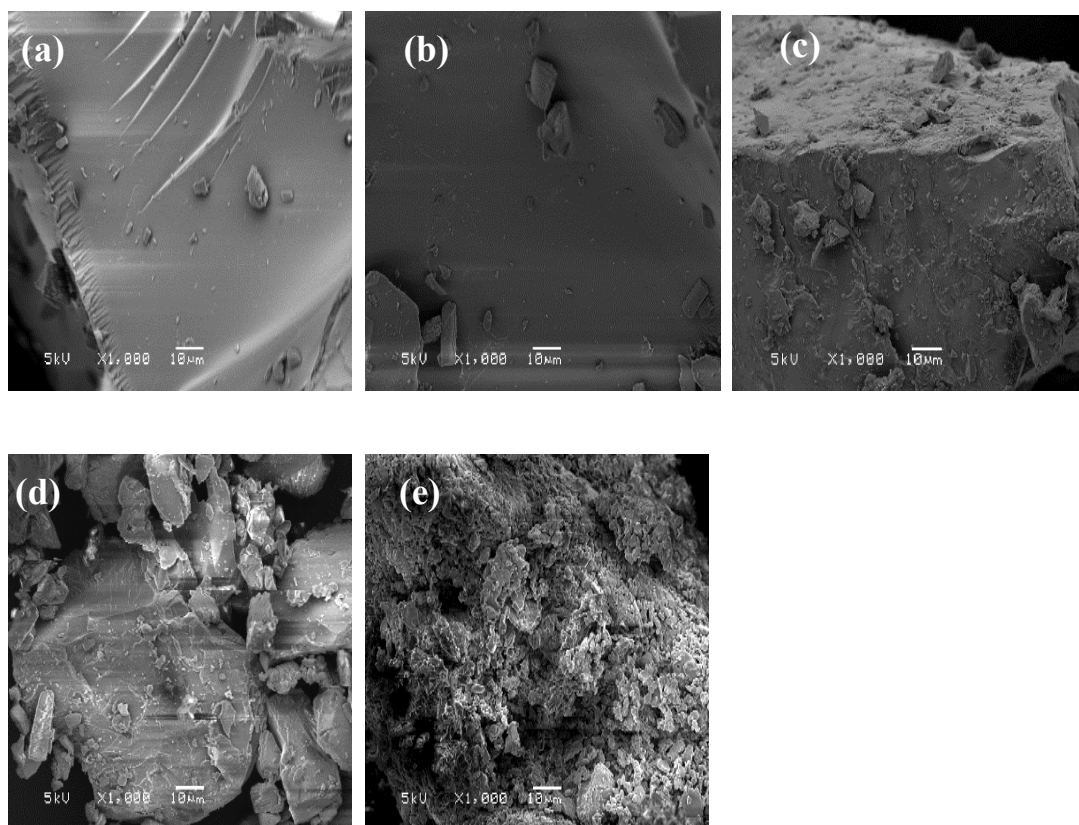


Fig. 2-7: SEM images: (a) 20% MA/EPO extrudate; (b) 25% MA/EPO extrudate; (c) 30% MA/EPO extrudate; (d) 40% MA/EPO extrudate; (e) Pure MA.

2.4.5. Preparation and Characterization of Orally Disintegrating Tablets

Based on the previous findings, 20% and 25% drug loaded hot-melt extrudates were selected to make orally disintegrating tablets. The selected extrudates and corresponding physical mixtures were mixed with tableting excipients (microcrystalline cellulose, colloidal silicon dioxide, polyplasdoneTM crospovidone) for 10 min using V-shell blender (GlobePharma, Maxiblend[®]). Magnesium stearate was added during the final two minutes of mixing. The resulting mixtures were tested for bulk density, tap density and Carr's index (Table 2-3). These

mixtures were compressed into tablets and evaluated by tablet characterization tests. The results of tablet weight, thickness, hardness, friability and disintegrating time were shown in Figure 2-8. The ODT with 25% drug loading showed improved hardness and friability values compared to 20% of drug loading, which may be due to decreasing the amount of extrudate and increasing the amount of microcrystalline cellulose. Both ODT formulations exhibited less than 1% friability, which meets the USP specification. The super-disintegrant, croscopolone, played a key role in disintegration, and consequently, both of the tablets disintegrated in less than 25 seconds. These ODTs showed almost ideal drug content as well as content uniformity for 20% and 25 % drug loaded tablets which were $98.8\% \pm 2.5$ and $102.8\% \pm 1.0$, respectively.

Table 2-3: Physical Properties of Final Blends (n=3)

	20% MA/EPO + Excipients	25% MA/EPO + Excipients
Bulk density (g/cm ³)	0.4	0.38
Tapped density (g/cm ³)	0.5	0.52
Carr's index (%)	20	26.90

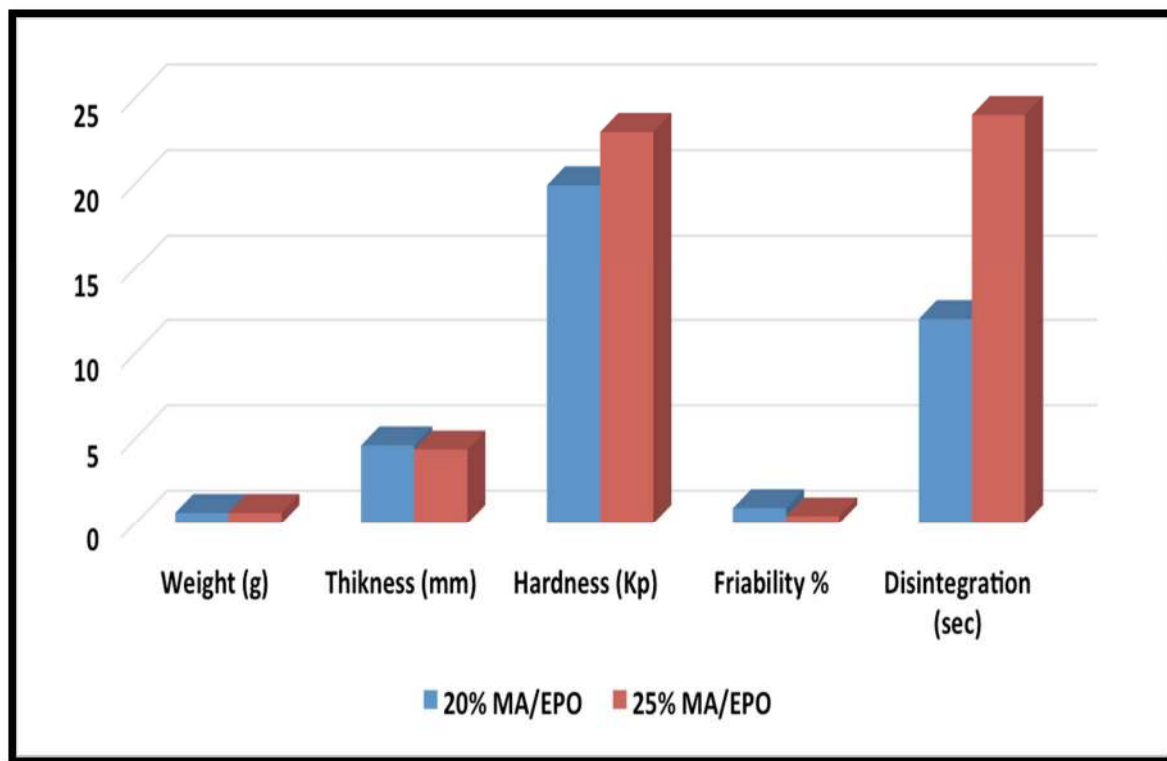


Fig. 2-8: Tablet Properties (weight, thickness, hardness, friability and disintegration time) for 20% and 25% of drug loaded ODTs.

All tablets containing extruded material consistently demonstrated enhanced drug release profiles when compared to tablets containing their corresponding physical mixtures (20% drug load). The drug release from the 20% and 25% drug loaded tablets containing extrudates in pH 5.5 acetate buffer was more than 80% within 5 minutes compared to that less than 10% of drug release was seen with tablets containing physical mixture under the same conditions (Fig. 2-9). However, the drug release from the tablets in the water media for taste masking assessment, which can be placed in a glass of water and administered as a suspension, were less than 2% during the first five minutes (Fig. 2-10) as well as the drug release from the simulated salivary fluid, which can be administered directly into the mouth, were less than 4% during the first 2 minutes (Fig. 2-11) indicating that the bitter taste of the drug was suppressed when processed by

hot melt extrusion [37-40].

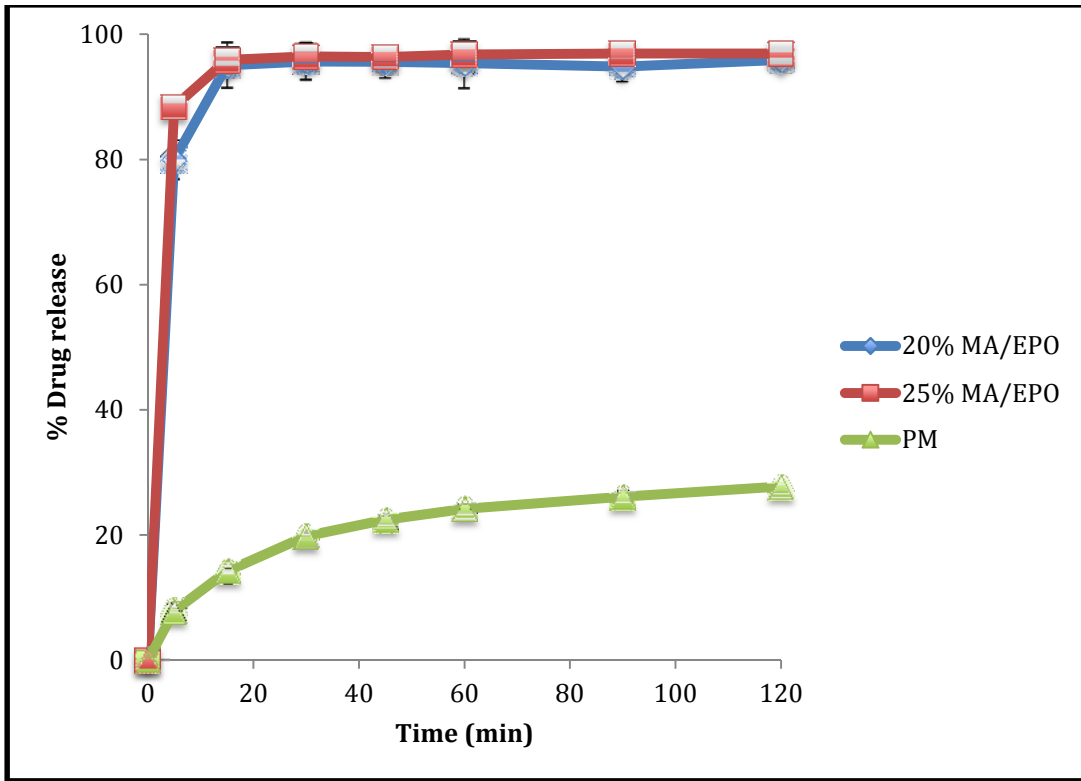


Fig. 2-9: *In vitro* dissolution profiles of ODTs in 0.1 M acetate buffer (pH 5.5).

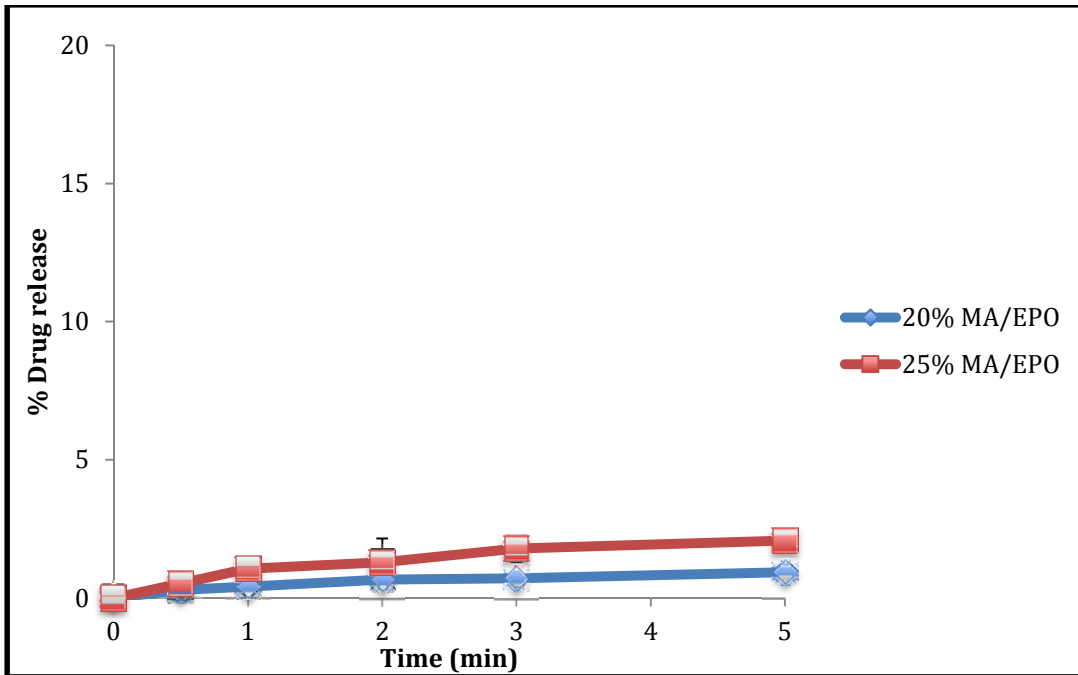


Fig. 2-10: *In vitro* taste masking dissolution testing of ODTs in aqueous media.

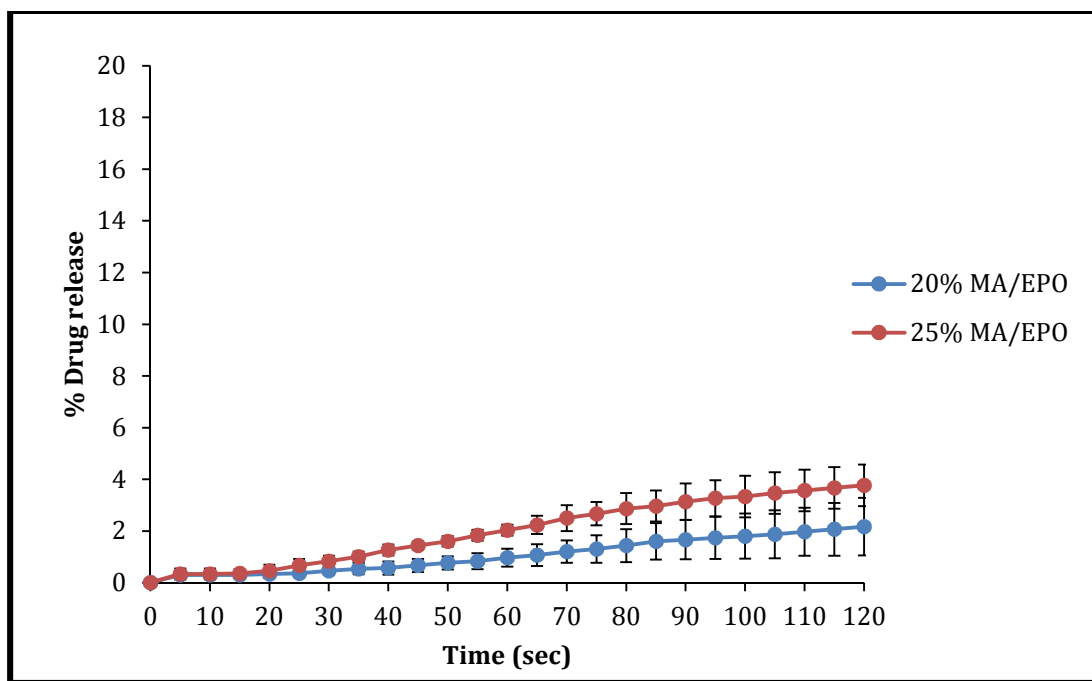


Fig. 2-11: *In vitro* taste masking dissolution testing of ODTs in artificial saliva media (pH 6.8).

2.5. Stability Tests

The rate of recrystallization for amorphous drugs during storage is of considerable concern as they are often physically unstable due to their high-energy states (Ewing, Clarke, & Kazarian, 2014; Keen et al., 2014). Therefore, there are many polymers commercially available that assist in maintaining drugs in the amorphous form for extended periods of time. Drug-polymer interactions may increase the physical stability by increasing their energy barrier for nucleation (Konno & Taylor, 2006; Sathigari, Radhakrishnan, Davis, Parsons, & Babu, 2012). In this work, all of the extruded formulations and ODTs were found to be physically stable when stored under an accelerated stability conditions (40°C/75% RH) and (25°C/60% RH) for a period of 6 months and 12 months, respectively. DSC analysis data showed absence of MA melting endothermic peaks, which confirms the miscibility status of drug, indicating that the MA is still in the

amorphous form even after 6 months (Fig. 2-12-a). Additionally, the MA crystalline peaks in XRD for the extrudates were absent as well (Fig. 2-12-b). The FT-IR results also indicated no differences between, before and after stability testing (data not shown). The contents for two drug loaded extrudates (20% and 25%) after 6 months were identical with the results obtained before the stability study. Dissolution studies were also utilized to verify any post-storage changes. The drug release profiles were assessed by similarity factor (f_2 value), which was developed to evaluate the degree of similarity between two *in vitro* dissolution profiles. If the similarity factor is between 50 and 100, that would suggest that two release profiles are similar (J.-Y. Kim et al., 2012). The f_2 value of 20% and 25% drug loaded extrudates were 59.3 and 62.3 respectively under accelerated condition (40°C/75% RH). The ODTs in 0.1 M acetate buffer media showed more than 85% drug release in 15 minutes, which is considered similar and also it was further supported by f_2 value measurements which were 67 and 64. Also the f_2 values were 88 (20% drug loading) and 82 (25% drug loading) in aqueous media. It can be considered that the drug release profiles after long-term storage under normal and accelerated conditions were similar to the initial ones (Fig. 2-12-c and Fig. 2-13).

Based on these results, the solid dispersions produced via hot-melt extrusion processing were very stable during 6 months at accelerated conditions (40°C/75% RH). Therefore, the molecular interaction between MA and E PO is playing a key role in API phase stability when processed by hot melt extrusion.

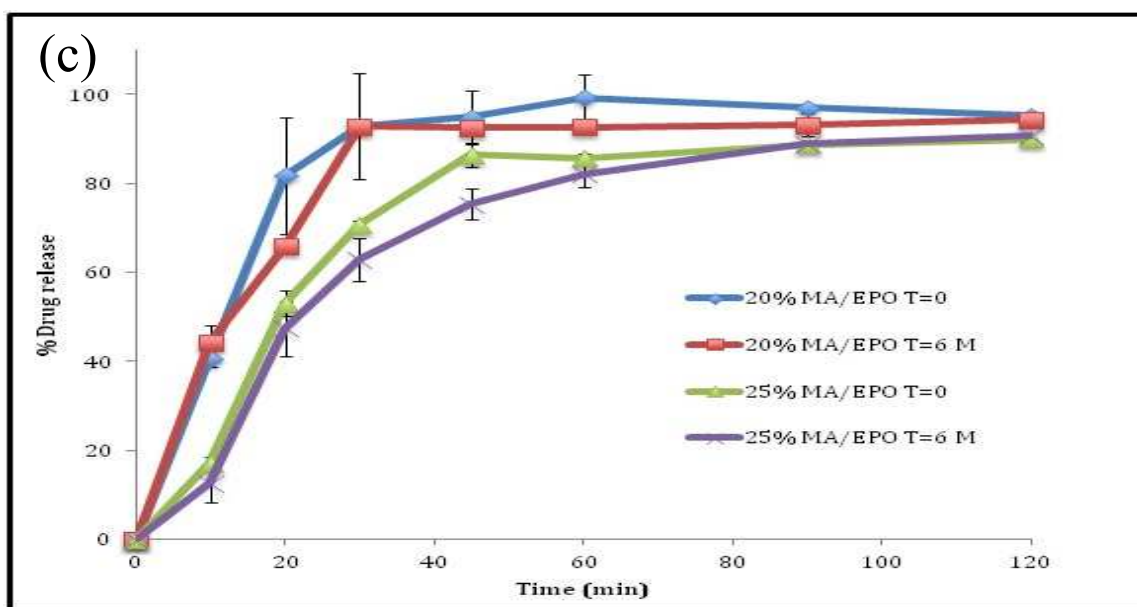
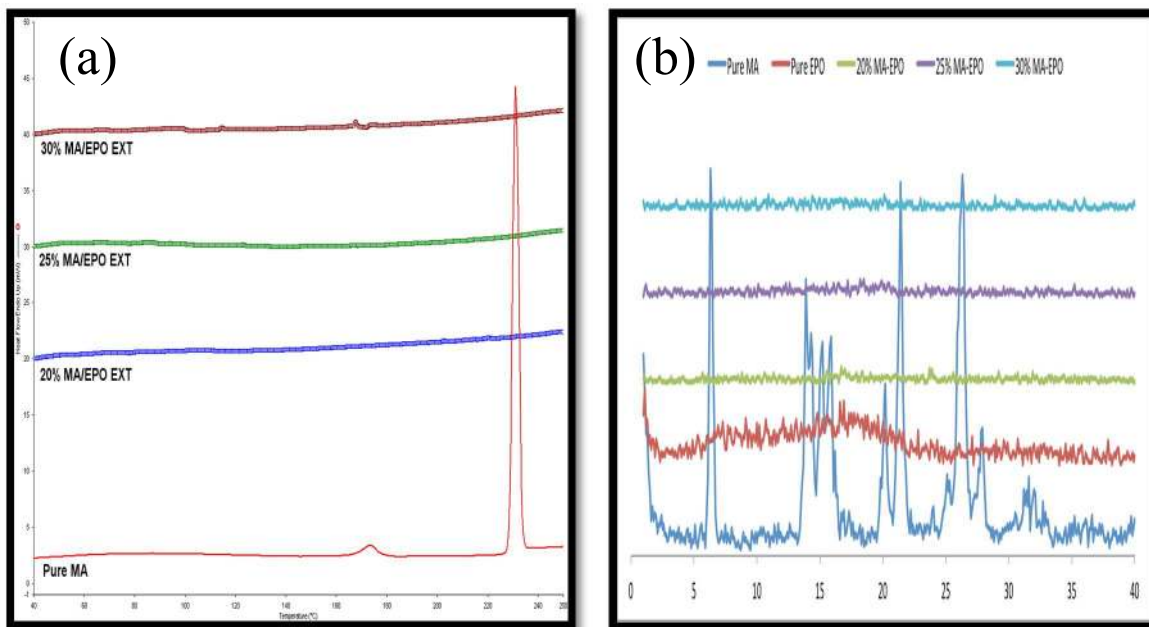
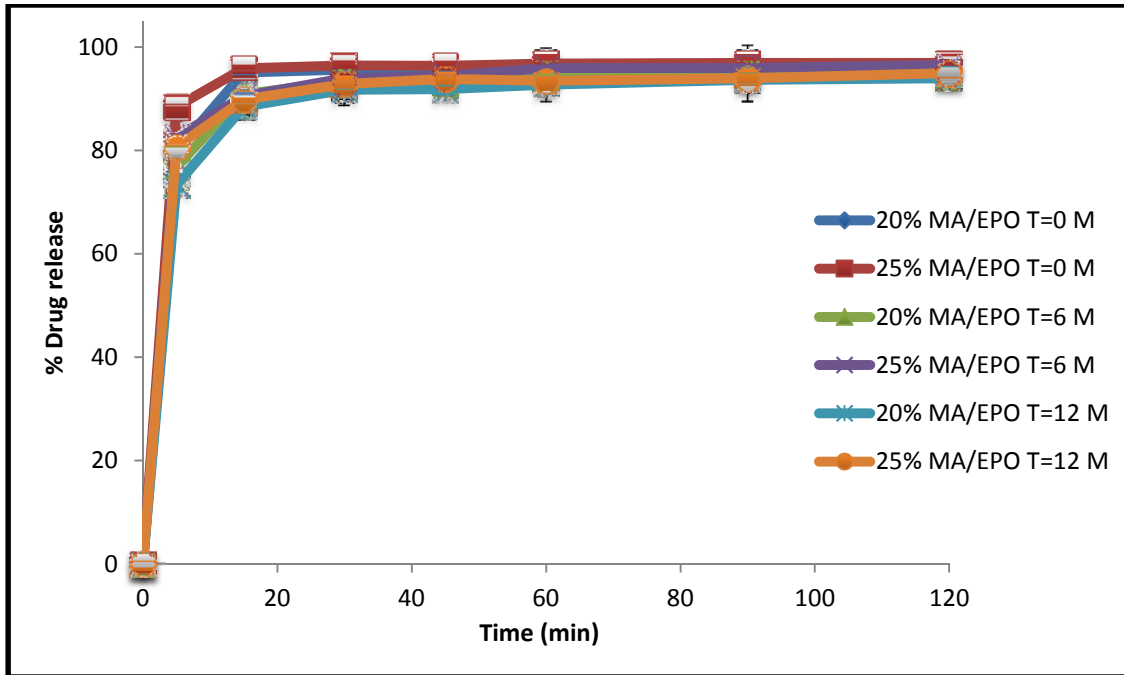


Fig. 2-12: Accelerated stability test (40°C/75% RH) for 6 months of MA/EPO extrudates: (a) DSC results; (b) PXRD data; (c) Drug release of extrudates in 0.1 M acetate buffer (pH 5.5).

(a)



(b)

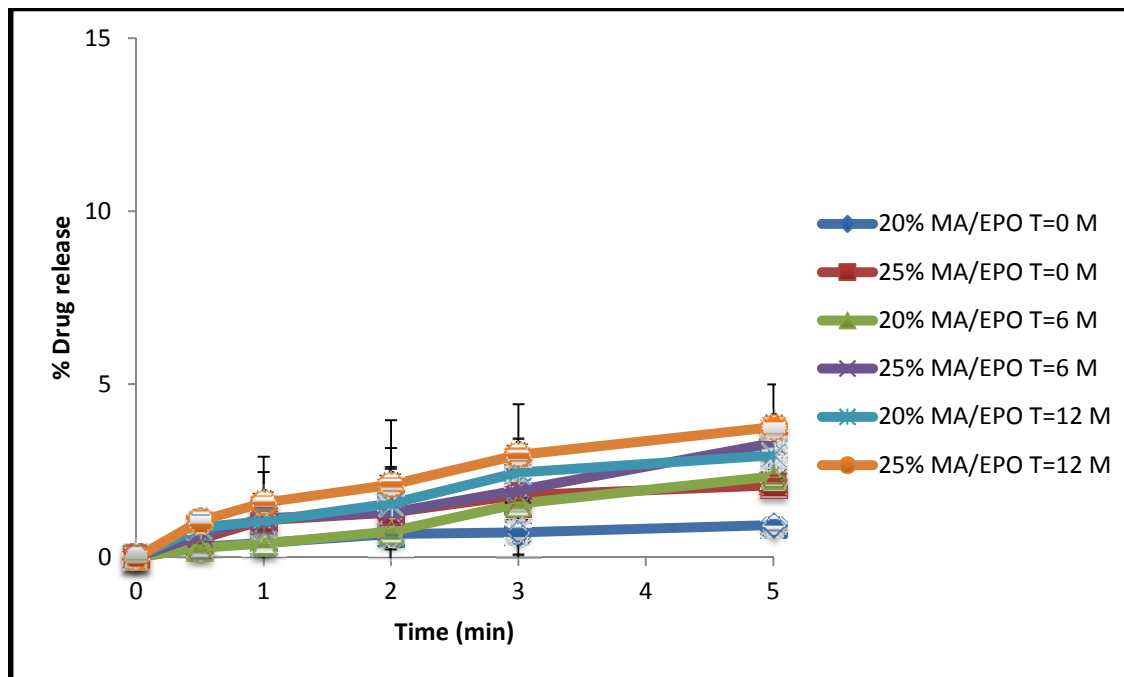


Fig. 2-13: *In vitro* drug release after 6 & 12 months stability at (25 °C/60% RH) of MA/ EPO

ODTs: (a) 0.1 M acetate buffer (pH 5.5); (b) aqueous media

2.6. Conclusion

Mefenamic acid was successfully extruded with the various concentrations of Eudragit[®] E PO using HME technology. The optimized formulations produced very promising solid dispersions for both taste masking and solubility enhancement. The dissolution rate of MA was improved with the increase in the concentrations of Eudragit[®] E PO, indicating that Eudragit[®] E PO is playing an important role in the solubilization of this high melting point, poorly soluble drug. The mechanism of solubility enhancement was investigated using multiple methodologies, including TGA, DSC, PXRD, SEM and FT-IR. Finally, Mefenamic acid ODTs were successfully produced using HME solid dispersion techniques demonstrating short disintegration times, sufficient taste masking and high drug release profiles.

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CHAPTER 3

INVESTIGATIONS OF THE COMBINED EFFECT OF MGO AND PEG ON THE RELEASE PROFILE OF MEFENAMIC ACID PREPARED VIA HOT MELT EXTRUSION TECHNIQUE

Objectives:

The primary aim of this study was to investigate the dual effect of MgO and PEG on the drug release behavior of mefenamic acid (MA)/ polyvinylpyrrolidone (PVP) formulations utilizing hot-melt extrusion technology.

Abstract:

This study aimed to investigate the combined effect of magnesium oxide (MgO) as an alkalizer and polyethylene glycol (PEG) as a plasticizer and wetting agent in the presence of Kollidon[®] 12 PF and 17 PF polymer carriers on the release profile of mefenamic acid (MA), which was prepared via hot-melt extrusion (HME) technique. Various drug loads of MA and various ratios of the polymers, PEG 3350, and MgO were blended using a V-shell blender and extruded using a twin-screw extruder (16-mm Prism EuroLab, ThermoFisher Scientific) at different screw speeds and temperatures to prepare a solid dispersion system. Differential scanning calorimetry and X-ray diffraction data of the extruded material confirmed that the drug existed in the amorphous form, as evidenced by the absence of corresponding peaks. Intermolecular interactions between the drug and polyvinylpyrrolidone were clearly seen in the Fourier transform infrared spectra,

whereas MgO and PEG were not found to be involved in the observed hydrogen bond formation. MgO and PEG altered the micro-environmental pH to be more alkaline (pH 9) and increased the hydrophilicity and dispersibility of the extrudates to enhance MA solubility and release, respectively. The *in vitro* release study demonstrated an immediate release for 2 h with more than 80% drug release within 45 min in matrices containing MgO and PEG in combination with PVP, when compared to the binary mixture, physical mixture, and pure drug.

Keywords: Magnesium oxide, Polyethylene glycol, Mefenamic acid, Hot-melt extrusion, Kollidon® 12 PF and 17 PF.

3.1. Introduction

Mefenamic acid [N-(2,3-dimethylphenyl) anthranilic acid] is a non-steroidal anti-inflammatory drug (NSAID) known to inhibit prostaglandin biosynthesis and is also a member of the fenamate group. Mefenamic acid (MA) is used as an anti-inflammatory, antipyretic, and potent analgesic agent to treat rheumatoid arthritis, osteoarthritis, dental pain, and dysmenorrhea.(Abdolmohammad-Zadeh et al., 2014; Kormosh & Matviychuk, 2013; Sriamornsak et al., 2014) According to the biopharmaceutical classification system (BCS), MA is a class II drug that exhibits high permeability and low water solubility (i.e. 20 mg/l, which is practically insoluble in water). This low solubility affects its rate of absorption from the GI tract and thus consequently decreases its oral bioavailability.(Alshehri et al., 2015; Sriamornsak et al., 2014) Solid dispersion is a promising technique for overcoming this problem; it involves processing the poorly soluble drugs with hydrophilic polymers to change the nature of the drug, i.e. converting the crystalline form of the drug into an amorphous form that subsequently improves drug solubility and further increases drug bioavailability.(Crowley et al., 2007; Kindermann, Mathee, Strohmeyer, Sievert, & Breitreutz, 2011)

Many techniques for formulating solid dispersion systems have been reported. The hot-melt extrusion (HME) technique has attracted attention in the pharmaceutical field as a novel technique with several advantages compared to other conventional techniques.(Morott et al., 2015) HME is a continuous and solvent-free process and thus is considered an economical technique because it reduces processing steps and eliminates drying steps. Extrusion is the process of embedding a raw mixture of the drug, polymers, and other additives into a barrel and then forcing it through a die to produce a molten material of a uniform shape (extrudate).(Crowley et al., 2007; Singhal, Lohar, & Arora, 2011) Poor extrusion processability

is usually an issue since it leads to poor thermoplastic properties and degradation of most drugs. Adding a suitable carrier and/or plasticizer can promote the drug thermal stability by decreasing the processing temperature and enhance the extrusion processability.(Schilling, Bruce, Shah, Malick, & McGinity, 2008) PEG is a chemical synthesis polymer that is usually used in HME to enhance the solubility of a poorly soluble drug or as a plasticizer owing to its high hydrophilicity. This property gives PEGs the ability to increase the porosity, water uptake, and dispersibility of the formulations.(Saharan, Kukkar, Kataria, Gera, & Choudhury, 2009; Stanković, Frijlink, & Hinrichs, 2015)

The solubility of poorly water-soluble drug can be improved by incorporating a hydrophilic carrier into the matrix, such as polyvinyl pyrrolidone, eudragit, or hydroxyl propyl methyl cellulose. However, super saturation or recrystallization may limit the solubilization capacity of a solid dispersion system.(Sikarra, Shukla, Kharia, & Chatterjee, 2012) A pH modifier is a promising agent that increases the solubilization capacity of the drug in the microenvironment pH (pH_M), since most of the active drugs are either weak acids or bases, with pH-dependent solubility.(M. Yang et al., 2014)

In the pharmaceutical field, the pH_M is defined as a very thin layer surrounding drug particles that aids in water adsorption and formation of a saturated solution.(M. Yang et al., 2014) This technique can consequently increase or decrease the pH_M of the matrix by incorporating an alkalizer or acidifier, respectively.(Dvořáčková et al., 2013) This can potentially result in an improvement of the solubility and/or stability of the drug, or achievement of an excellent sustained release formulation as compared to the conventional binary solid dispersion system.(Siepe et al., 2006; T. T.-D. Tran, Tran, Choi, Han, & Lee, 2010) It has been reported that using a small amount of MgO as an alkalizer potentially increases the dissolution of the poorly

soluble drug telmisartan within a solid dispersion of polyethylene glycol 6000.(Phuong et al., 2011; P. H. L. Tran, Tran, & Lee, 2008) In this study, we found that the addition of 5% MgO can modulate the pH_M up to 9.0, thus increasing the drug release of the poorly soluble drug MA from the matrices.

The purpose of this novel study was to: (1) demonstrate the effect of polyvinylpyrrolidone (PVP) matrices on the release of the poorly water-soluble drug MA prepared using the hot-melt extrusion technique, (2) investigate the effect of PEG as a plasticizer and swelling agent in dissolution studies, (3) study the influence of MgO as an alkalizer on the modification of the microenvironmental pH of the matrices, and (4) investigate the combined effect of PEG and MgO on the drug release behavior of the formulations.

3.2. MATERIALS AND METHODS

3.2.1. Materials

Mefenamic acid (MA) was purchased from Sigma Aldrich (Bellefonte PA. USA); Kollidon 12PF and Kollidon 17PF were obtained as gift samples from BASF (PEGPVCLPVA, BASF, Germany). Magnesium oxide and polyethylene glycol 3350 were purchased from Fisher Scientific. All other chemicals used in this study were of analytical grade.

3.2.2. Methods

3.2.2.1. Thermal gravimetric analysis

Thermal gravimetric analysis (TGA) was performed in order to examine the thermal stability

of the pure components and physical mixture at the employed extrusion conditions (TGA, Pyris 1 TGA, Perkin Elmer). Samples weighing around 5-7 mg were placed in a platinum pan before heating from 30°C to 250°C at heating rate of 20°C/min under an inert nitrogen gas purge of 20 ml/min.

3.2.2.2. Loss on drying

For the loss on drying (LOD) test, the moisture analyzer (MB45, Ohaus) was used to measure the amount of moisture in each formulation (physical mixture and pure drug). Each sample was placed in the aluminum dish, accurately weighed on the thermo-balance of moisture analyzer, and further heated electrically at 120°C for 15 min. The moisture analyzer automatically calculated the moisture loss from the sample in this process. The % LOD was calculated using the following equation:

$$LOD(\%) = \frac{\text{Initial weight of the sample}}{\text{Final weight of the sample after drying}} \times 100$$

3.2.2.3. Differential scanning calorimetry (DSC)

DSC (Diamond DSC, Perkin Elmer) studies were performed to evaluate the stability and miscibility of the drug within the matrices before and after the extrusion process. Samples were weighed (2-4 mg) and placed in hermetically sealed aluminum pans before analysis at 10°C/min with a heating rate between 30°C to 250°C under an inert nitrogen gas at a flow rate of 20 ml/min. The obtained data was analyzed using Pyris manager software (Shelton, CT, USA).

3.2.2.4. HPLC analysis

A reverse phase HPLC system was used for the analysis of MA (Waters Corp, Milford, MA, USA). The reverse-phase column consisted of a Symmetry Shield (C₁₈, 250Å~4.6 mm, 5 μm

particle size). The mobile phase comprised methanol, water, and acetonitrile at a ratio of 80:17.5:2.5 v/v, respectively. The pH of the mobile phase was adjusted with phosphoric acid (85%) to 3.0. The mobile phase was degassed under vacuum conditions for 10 min. The injection volume was 20 μ L and the mobile phase flow rate was adjusted at 1.0 mL/min. The detection wavelength was set at 225 nm and all studies were performed in triplicate (n = 3). (Andrews, AbuDiak, & Jones, 2010)

3.2.2.5. Preparation of hot melt extrudates

Before preparing the physical mixture, the polymers were separated using USP mesh screen #35 to remove any aggregations. Various drug loads of MA and various ratios of polymers, with or without PEG 3350 (plasticizer) and MgO (alkalizer), were blended using a V-shell blender (GlobePharma, Maxiblend®) at 25 rpm for almost 10 min (Table 3-1). Each blend was extruded using a twin-screw extruder (16-mm Prism EuroLab, ThermoFisher Scientific) at a temperature range of 100-160°C and screw speed of 100 rpm. The rod-shaped extrudates were milled using a comminuting mill (Fitzpatrick, Model “L1A”), sieved using USP mesh (#35), and stored in glass vials for further analysis.

3.2.2.6. Evaluation of MA capsules

Hot-melt extrudates equivalent to 100 mg MA were filled in HPMC capsules. *In-vitro* release studies were conducted for all of the formulations in 900 ml phosphate buffer (pH 6.8) as the dissolution medium utilizing an USP apparatus II (Hanson SR8) maintained at $37 \pm 0.5^\circ\text{C}$ for 120 minutes with a shaft rotation speed of 50 rpm (n = 3). Sample (1.5 ml) was collected at the following intervals: 10, 20, 30, 45, 60, 90, and 120 min. It was then centrifuged (Centrifuge Eppendorf 5415 R) for 8 min at 13,000 rpm and 25°C , and then analyzed using the Waters

HPLC-UV system. Fresh dissolution media was added to the dissolution vessels, equivalent to 1.5 ml at each time point.

Table 3-1: Formulation Design and processing conditions.

Formulations	MA W/W%	K12 W/W%	K17 W/W%	MgO W/W%	PEG 3350 W/W%	Extrusion Conditions	
						Temp. °C	Speed rpm
F1	20	80	-	-	-	145	100
F2	20	70	-	-	10	110	100
F3	20	75	-	5	-	120	100
F4	20	65	-	5	10	110	100
F5	20	-	80	-	-	150	100
F6	20	-	70	-	10	125	100
F7	20	-	65	5	10	130	100

3.2.2.7. Fourier transform infrared spectroscopy (FT-IR)

Mid-infrared spectra were collected using an FT-IR bench (Agilent Technologies Cary 660, Santa Clara, CA). The bench was equipped with a high-pressure ATR (Pike Technologies MIRacle ATR, Madison, WI), which was fitted with a single bounce diamond-coated ZnSe

internal reflection element. Analysis of the spectra was performed using Resolution Pro Version 5.2.0 (Agilent Technologies) software suite.

3.2.2.8. Scanning electron microscope (SEM)

The surface size, shape, and structure of the pure drug and optimized formulations were evaluated using a JEOL JSM-5600 SEM. In a high-vacuum evaporator, a Hummer® 6.2 sputtering system was used to sputter coat the samples with gold (Anatech LTD, Springfield, VA). Before sputter coating, the samples of interest were mounted on adhesive carbon pads set on aluminum stubs. An accelerating voltage of 5 kV equipped with JSM 5000 software was used for imaging.

3.2.2.9. *In-vitro* media uptake studies

This study was conducted similar to the *in-vitro* dissolution studies described above. Samples were weighed and placed into the dissolution tester. Samples were withdrawn at two time points (10 and 20 min) and the excess liquid was removed by tissue paper. Samples were re-weighed W_o , placed into an oven, and dried for 24 h before re-weighing for a constant weight, W_1 . The percentage media uptake capacity (MUC) was calculated using the following equation:(Kreye, Siepmann, & Siepmann, 2011) (Fig. 3-1)

$$\%MUC = \frac{W_o - W_1}{W_o} \times 100$$

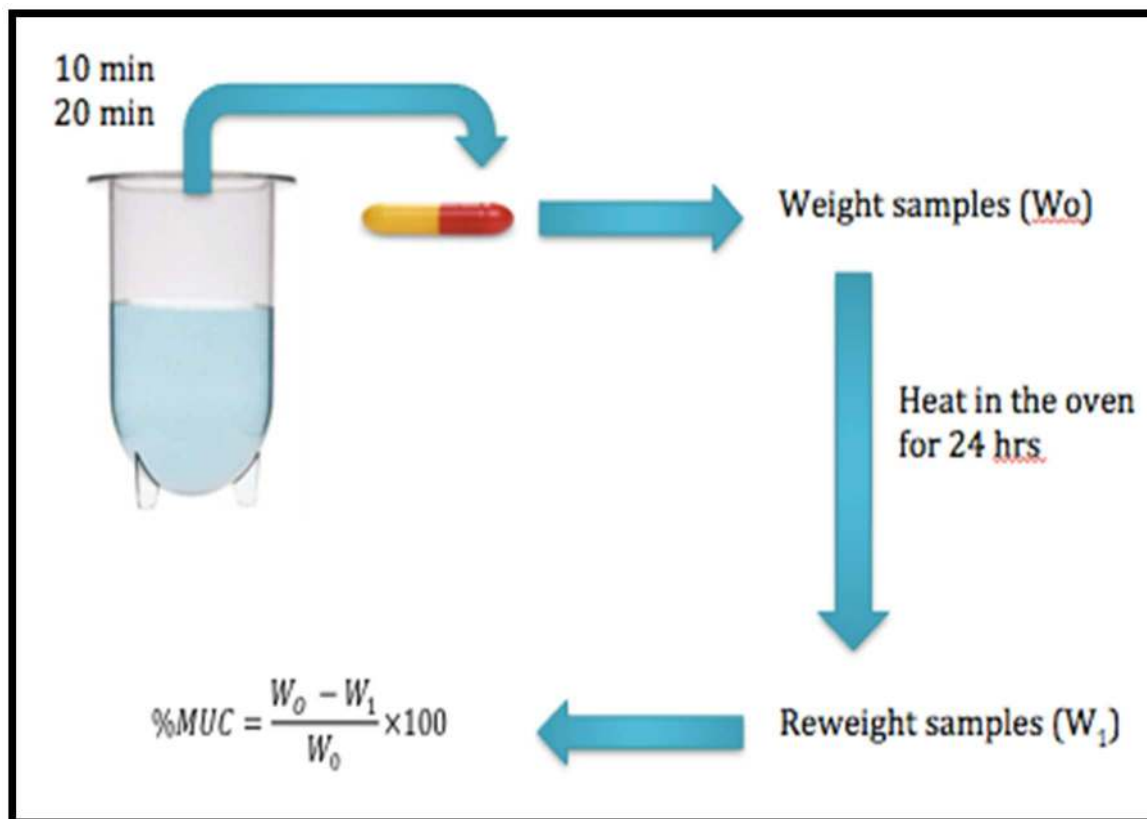


Fig. 3-1: schematic diagram for preparation of media uptake studies.

3.2.2.10. Measurement of microenvironmental pH (pH_M)

To investigate the effect of an alkalizer on the release of MA in the dissolution, the weighed capsules were removed from the dissolution media (pH 6.8) after 10 min time intervals. The non-disintegrated capsules were removed from the dissolution and the water was strained off at ambient temperature. The pH_M for each formulation was measured potentiometrically using an Oakton pH meter (pH Spear, Fisher Scientific) equipped with a contact electrode (Ha, Tran, Tran, Park, & Lee, 2011; Patil, Tiwari, Upadhye, Vladyka, & Repka, 2015; T. T.-D. Tran, Tran, & Lee, 2009) (Fig. 3-2)

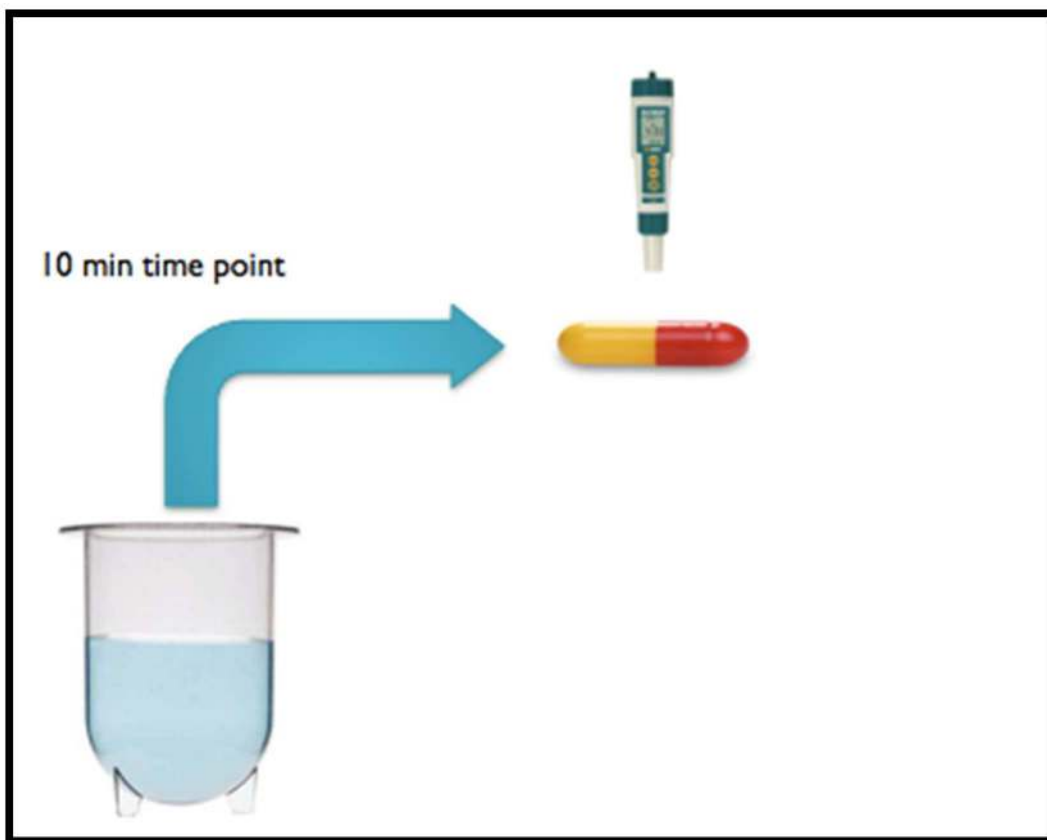


Fig. 3-2: schematic diagram for Measurement of microenvironmental pH (pH_M).

3.2.2.11. Polarized light microscopy (PLM):

Polarized light microscopy was conducted using an optical microscope (Agilent Technologies 620 IR) equipped with crossed polarizers. The images were captured at 5X and 15X magnification. Images were identified using Videum Capture software. Samples of interest were exposed to the dissolution media (pH 6.8 phosphate buffer) and observed at 0 and 30 min to understand dissolution behavior.

3.2.2.12. Powder X-ray diffraction (PXRD)

The PXRD studies were performed using a Bruker AXS D8 ADVANCE XRD instrument (Bruker AXS, Madison, MI) at room temperature using a $CuK\alpha$ radiation current at 40 mA and

generator voltage at 40 kV. The scanning rate was 0.5 deg/min and diffraction angles (2Θ) of 3-40°.

3.2.2.13. Stability studies

Analysis of the physicochemical stabilities of the extrudates was carried out for a period of 6 months to evaluate the influence of the temperature and humidity on the amorphous solid dispersion system. Corresponding samples were stored in stability chambers (Caron 6030 Environmental Test Chamber, Caron Products and Services, Marietta, OH) in closed glass vials at 25°C/60% RH conditions. Physical stability of the formulations was determined by DSC and XRD. Drug content was determined by HPLC analysis to confirm chemical stability. *In-vitro* drug release studies after 3 and 6 months were evaluated and the similarity factor (f_2 value) was applied to compare the dissolution profile at time 0 using the following equation:(Food & Administration, 2000)

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

Where R_t and T_t is the cumulative percentage of drug released from the reference and the test product, respectively, at each of the selected n time points. The f_2 value or similarity factor was calculated to determine whether two dissolution profiles are similar. The two profiles are considered similar when the f_2 value is between 50 and 100.

3.2.2.14. Statistical analysis

Differences between groups were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's test. A difference of $P < 0.05$ was considered statistically significant as compared with the pure MA.

3.3. RESULTS AND DISCUSSION

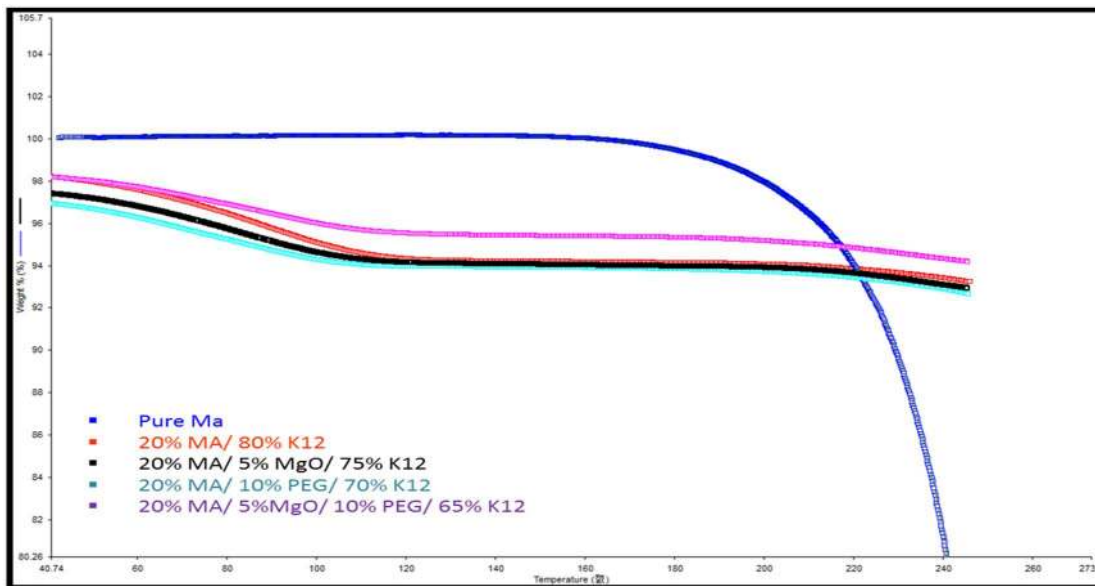
3.3.1. Thermal analysis

TGA analysis is generally performed before running the extrusion process to evaluate the thermal stability of the drug and physical mixture, and to make sure the excipients are thermally stable under the processing extrusion temperatures. These excipients must not degrade either at or below the extrusion processing temperature. Our results show that there was a loss in weight after heating from 30 to 250°C with a heating rate of 20°C/min, which was about 4-5% with k12 formulations and 5-7% with k17 formulations. This is considered high and may be due to drug degradation or water evaporation (Fig. 3-3). To confirm that this loss of weight was due to moisture uptake, because PVP polymers have the ability to absorb water, we applied the LOD moisture analyzer to the mixture for 15 min at a heating temperature of 120°C. The LOD results demonstrated that there was up to 9% moisture uptake, which further supports the TGA results (Table 3-2). Consequently, TGA studies confirmed the stability of the drug and the polymers at the employed extrusion temperatures.

To achieve proper HME outcomes, miscibility studies of the API within the matrix had to be addressed. Solid-state characterization of MA in the matrix was carried out using differential scanning calorimetry. MA exists in two polymorphic forms, I and II.(Romero, Escalera, & Bustamante, 1999) In the present study, form I, crystalline MA, was used. Form I has two endothermic peaks, a small one at 175°C and a more significant, sharp peak at 230°C. The K-series of 12 and 17 polymers display a glass transition temperature at 90°C and 138°C, respectively.(Crowley et al., 2007):³⁴ Polyethylene glycol (PEG 3350) and magnesium oxide

(MgO) have melting point at 53-59°C and 2,852°C, respectively.(Al-Naser, Zhou, Wang, Liu, & Wang, 2015; Oh, Heng, & Chan, 2015) The melting endothermic peaks were not observed in the extrudates in all formulations up to 20% drug load, indicating that the drug was completely transformed into an amorphous state after the extrusion process. Therefore, the DSC studies of the pure drug and the extrudates demonstrated miscibility of drug and PVP polymers, as the corresponding sharp peak representative of the drug's melting point at 230°C was not observed (Fig. 3-4).

a)



b)

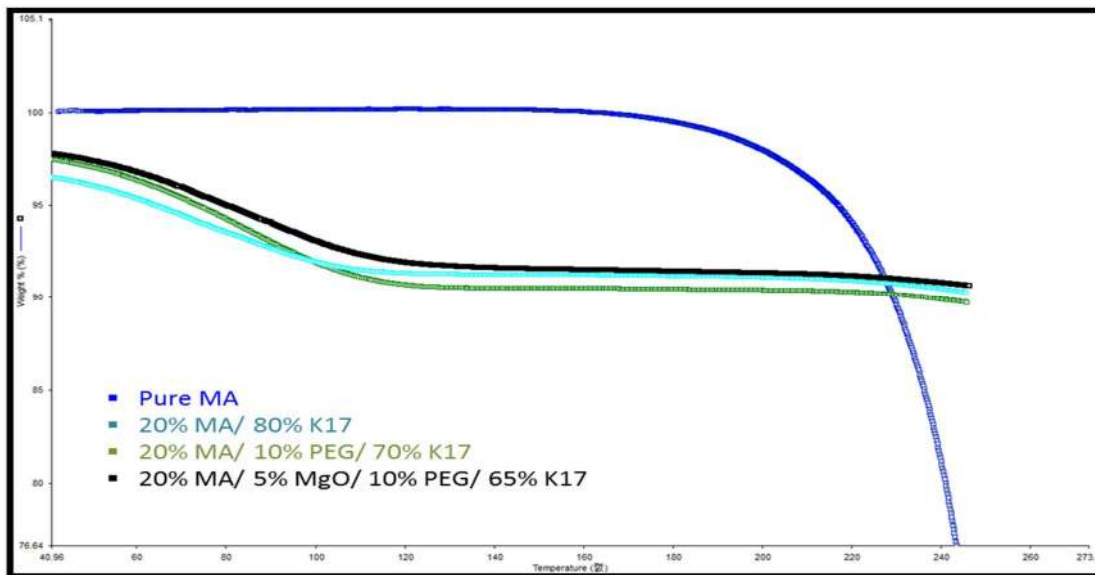
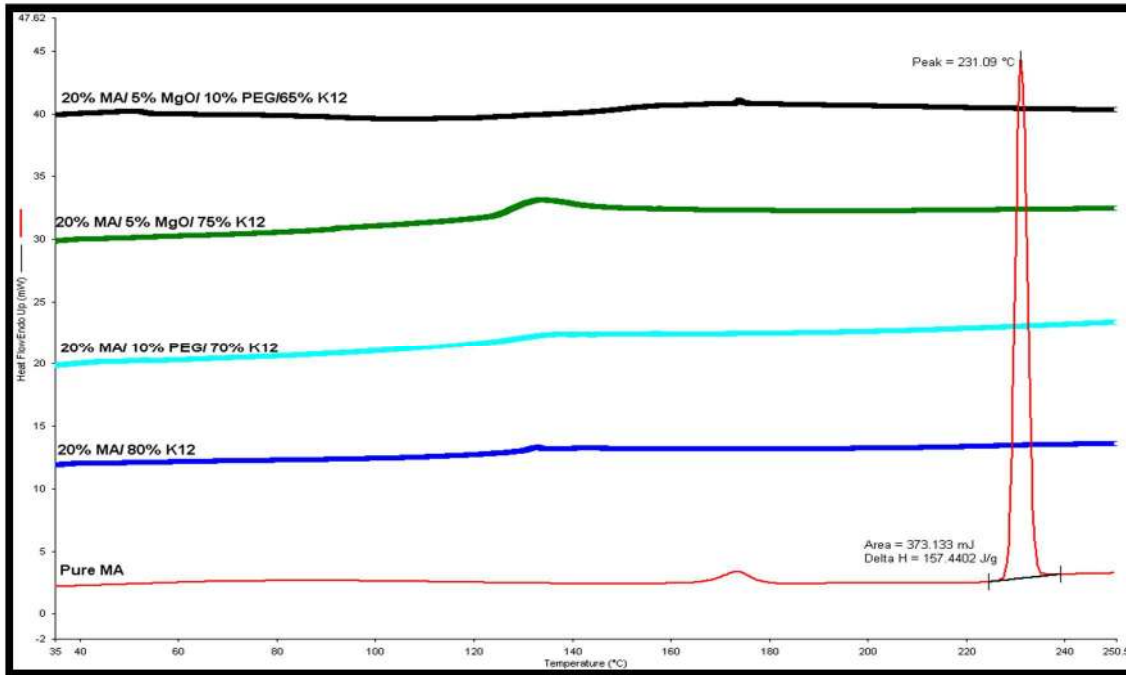


Fig. 3-3: TGA analysis of: a) MA/ K12 formulations, b) MA/ K17 formulations.

Table 3-2: LOD analysis of Pure MA and physical mixture:

Formulations	% LOD
F1	6.64
F2	6.44
F3	8.16
F4	7.24
F5	9.22
F6	8.73
F7	9.17
Pure drug	0.84

a)



b)

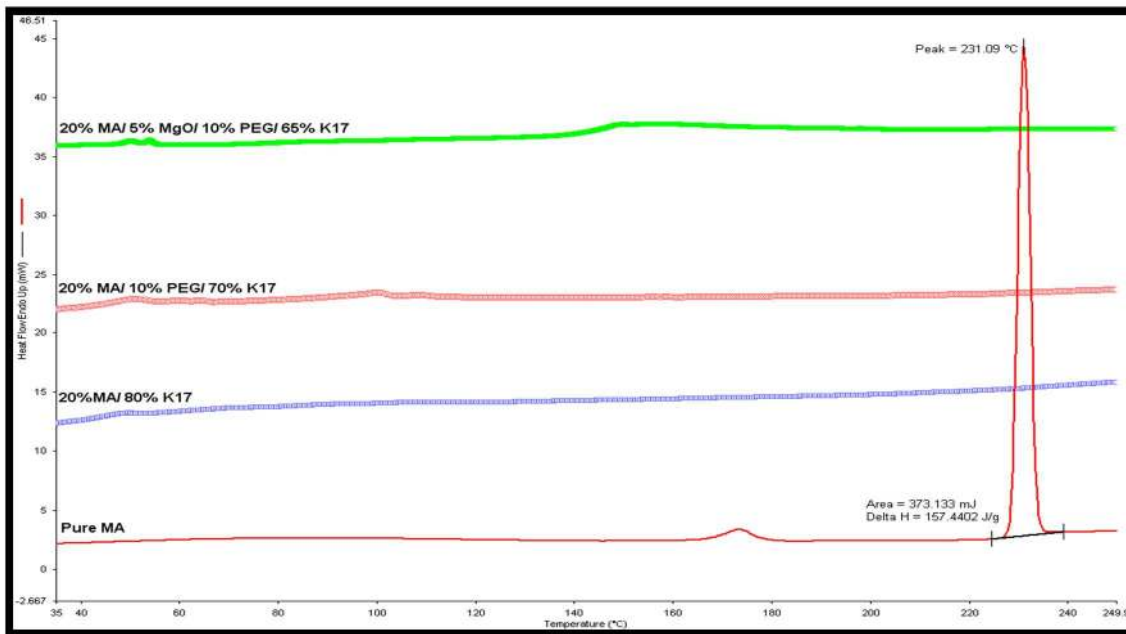


Fig. 3-4: Pure MA and extrudates miscibility studies using DSC at temperatures of 30-250°C and heating rate of 10 °C/min, a) PVP K12 formulations, b) PVP K17 formulations.

3.3.2. Proper hot melt extrusion process with MA

Before beginning the experiment, the HME process could be adjusted and optimized by studying the physical-chemical properties of the API and other materials. Choosing the appropriate excipients is highly recommended in order to formulate suitable HME products. These excipients should have some elastic behavior, i.e. they should be able to deform and pass easily through the extruder during processing and should solidify after extrusion from the die³⁵. MA is considered a challenging drug to process via HME owing to its high melting point (230°C), which indicates high crystallinity and sticking behavior during manufacturing. Two polyvinylpyrrolidone (PVP) grades with various molecular weight and glass transition temperatures were selected as main carriers. They possess amorphous hydrophilic properties that aid in producing solid dispersions via HME technology. PVP is an efficient carrier due to its ability to inhibit drug recrystallization and decrease molecular motion of the amorphous drug, leading to a more stable solid dispersion system.(Andrews et al., 2010) PVP K12 has low Tg (90°C) with a high degradation temperature, which makes it easier to process during HME (Table 3-1).

Adding a plasticizer to the formula reduces the processing temperature and facilitates the extrusion process, thus decreasing the degradation of the drug and polymers. There were no issues during the extrusion process when MgO was added to the formulations owing to the low Tg of the polymer, K12. However, K17 has a high Tg (139°C) with a degradation temperature around 175°C, which makes it difficult to process using HME under 175°C without a plasticizer, especially when MgO is added to the formulations.

Therefore, MA and the polymers with and without a plasticizer were extrudable at the processing conditions previously stated (Table 3-1). However, K17 combined with an alkalizer

was not extrudable without a plasticizer.

3.3.3. *In vitro* drug release studies

The dissolution profile of the pure drug, physical mixture, and solid dispersions in simulated intestinal fluid (pH 6.8) is shown in the figure 3-5. The release of the pure drug was less than 1% within first hour owing to the hydrophobic nature of the drug; the drug particles were not in contact with the media and did not dissolve. However, the binary solid dispersion of MA with K12 and K17 exhibited remarkable drug release, at less than 40% and 20% within 120 min, respectively. In this case, the extrudates had limited effect on the drug release even though the drug was transformed into an amorphous form. This low release was hypothesized to be due to the aggregation and agglomeration of the mixture in the dissolution media, because the drug did not dissolve well in the PVP polymer carrier. The difference in drug release between the two polymers was because of the difference in the viscosity, molecular weight, and water uptake ability. Thus, we hypothesized that adding a wetting or dispersion agent would have a strong effect and reduce or prevent aggregation and agglomeration.

Polyethylene glycols (PEGs) are usually used as a plasticizer in the HME process due to their low melting point, low toxicity, and low cost.(Crowley et al., 2007) It has been reported that PEG has the ability to increase the wettability and dispersibility of the mixture directly after contact with water.(Minhaz, Rahman, Ahsan, Rahman, & Chowdhury, 2012; D. Yang, Kulkarni, Behme, & Kotiyan, 2007) Therefore, PEG 3350 was incorporated into the HME process to facilitate the extrusion process as well as improve drug release by increasing the capability of the matrix to absorb more media and increase drug-polymers dispersibility, leading to increased drug

release. Adding PEG 3350 to the formulations enhances the drug release dissolution to 10-30% of the binary mixture by inhibiting aggregation and agglomeration. In addition, we confirmed our hypothesis by studying how much media the matrix would absorb during the dissolution process. Media uptake results indicate that the pure drug media uptake rate increased from 2.6% to 7-12% with K-Series (12 & 17) PVP polymers. Adding PEG 3350 to the formulations increased the media uptake to 20-23% at the 10 min time point. The media uptake after 20 min of exposure increased from 2.9% to approximately 29% of the pure drug and MA in the extrudates, respectively (Fig. 3-6). The water uptake study corresponded with the dissolution behaviors of the drug and extrudates as a function of time.

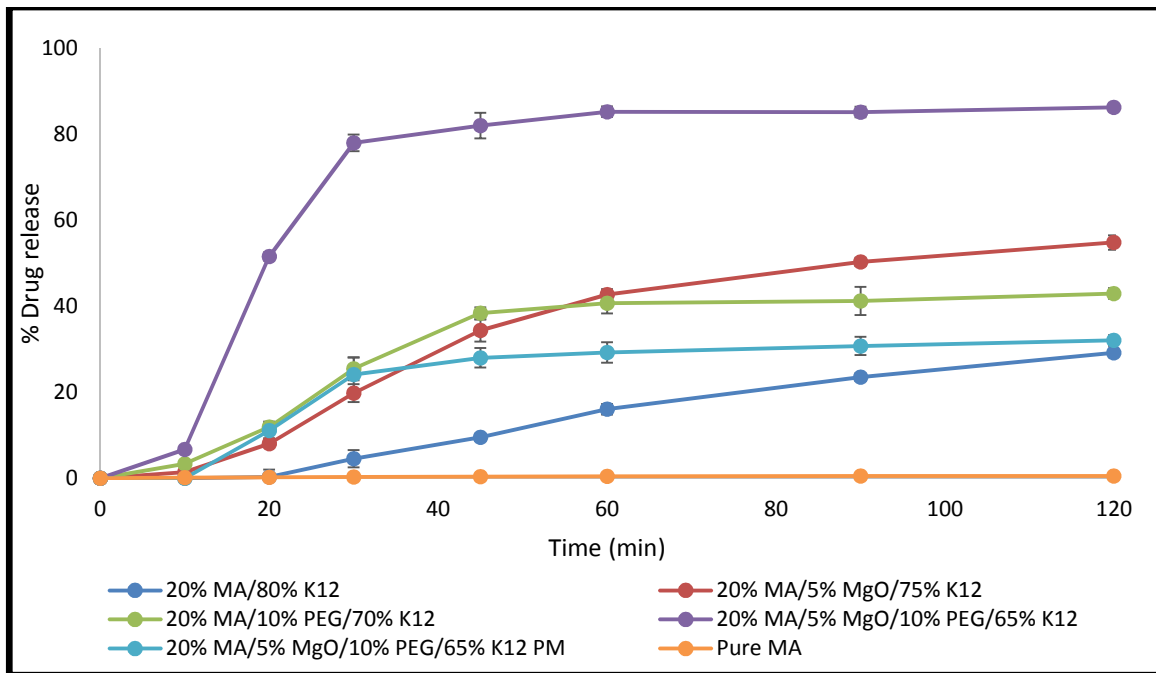
However, increasing water uptake ability is not sufficient to achieve high drug release. It has been reported that modifying the pH_M could have a strong positive effect on the solid dispersion system. Incorporating an alkalizer or acidifier to the formula would modulate the pH_M and thus be beneficial in enhancing the solubility of weakly acidic or basic poorly soluble drugs, respectively.

Tran et al. (2008) has investigated the use of nine alkalizers to modulate the pH_M of a solid dispersion of Telmisartan and PEG 6000. They found that there was no significant increasing in the drug dissolution of the binary solid dispersion without an alkalizer. Moreover, among the nine alkalizers, a small amount of MgO (3%) demonstrated the highest modulation of pH_M , leading to enhancement of drug dissolution.(P. H. L. Tran et al., 2008) Tran et al. (2011) continued their work and studied MgO release behavior and its potential effect on Telmisartan in gastrointestinal tissue. They reported that MgO increases the pH_M and thus increases the release of the insoluble model drug.(T. T.-D. Tran et al., 2010)

MgO was chosen as an alkalizer in the present study owing to its strong alkalizing effect

and thermally stability. Furthermore, it has been reported in the literature to be a powerful agent that can increase pH_M . Incorporating MgO into the binary mixture of MA-K12 increased the dissolution of the drug to around 20%, compared with the binary mixture, and 40% compared to the pure drug MA. We have confirmed these results by measuring the pH_M of the formulations within the dissolution media. We found that incorporation of MgO into the formulations increases the pH_M to about 9, which allows the drug to easily ionize and dissolve since the drug is weakly acidic in nature (Fig. 3-7). The pH of the drug and other formulations was maintained between 6-6.5; it is evident that in the absence of MgO, the pH_M of the formulation would not increase to the pH_M of the alkaline media and ionize the drug, thus decreasing its solubility. However, adding MgO to the binary mixture (MA-PVP) resulted in less than 50% drug release within 2 h, with more than half of the drug remaining undissolved in the dissolution media.

a)



b)

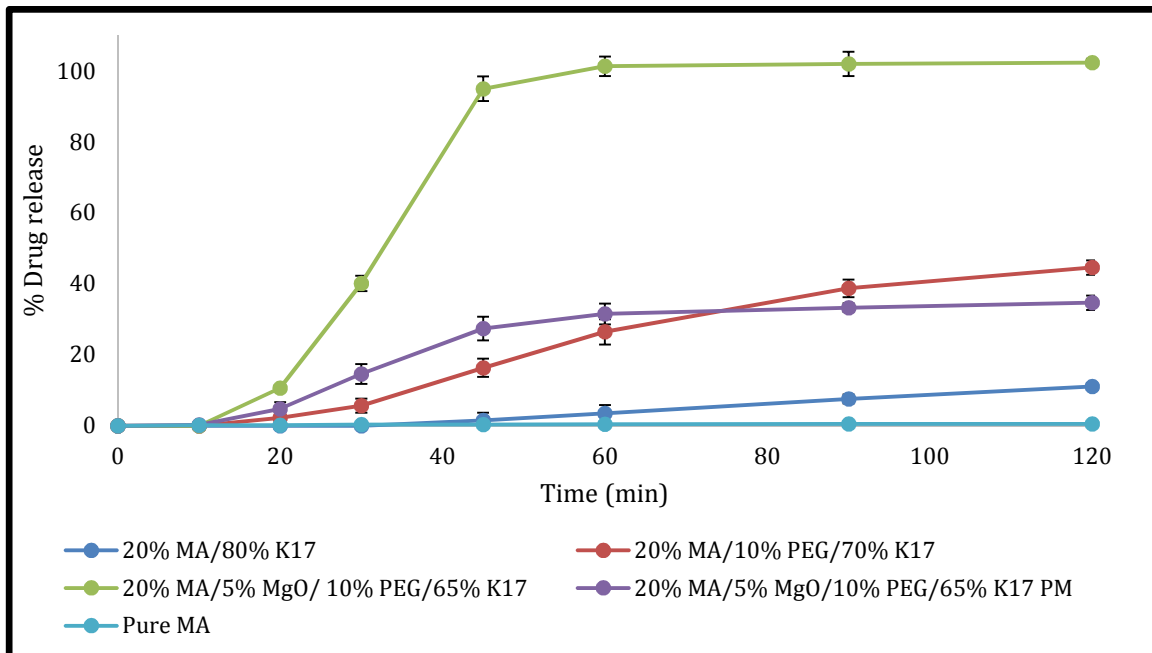
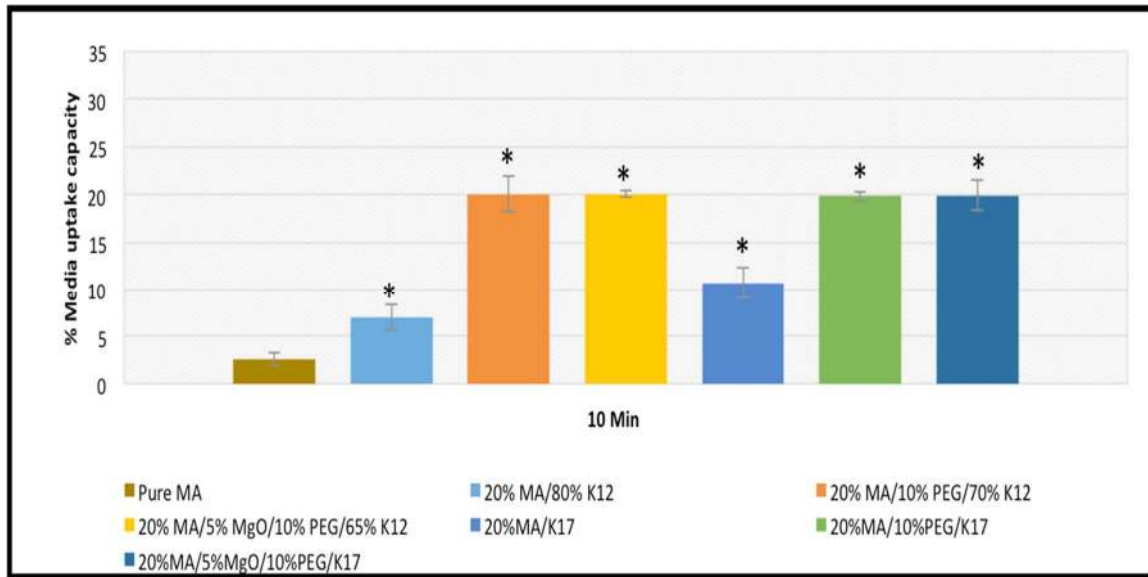


Fig. 3-5: *In vitro* dissolution testing of physical mixture and extrudates in phosphate buffer (pH 6.8), a) PVP K12 formulations, b) PVP K17 formulations.

a)



b)

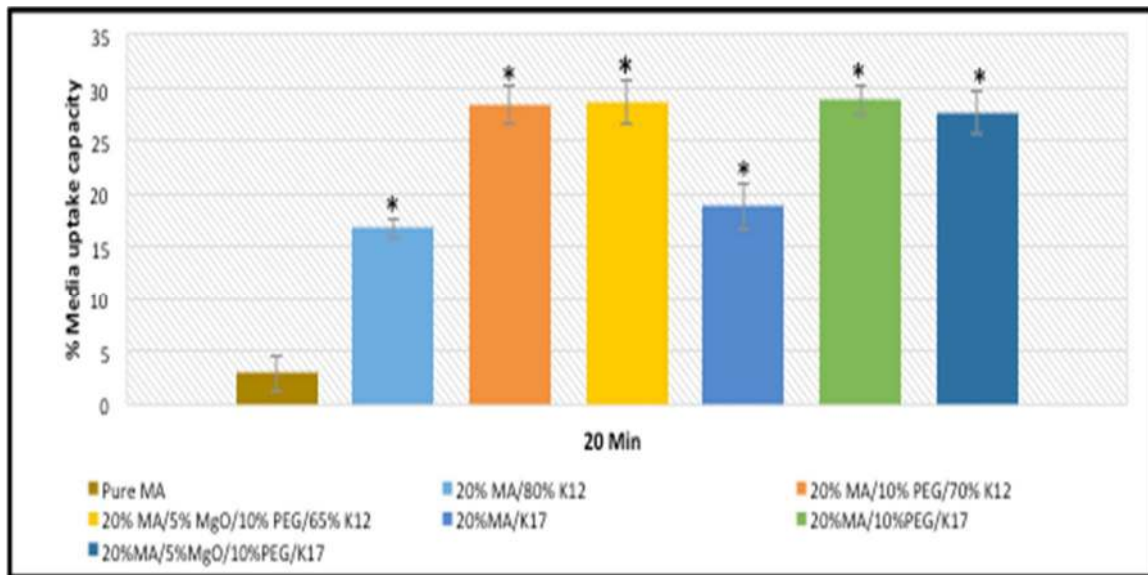
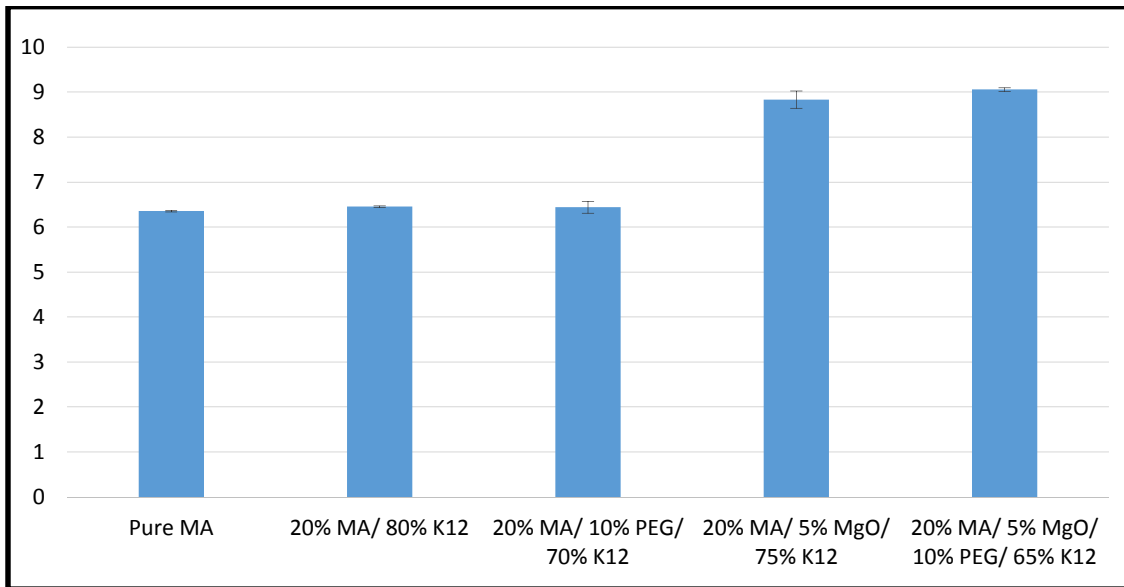


Fig. 3-6: Media uptake studies of pure drug and extrudates after: a) 10 min. and b) 20 min.

a)



b)

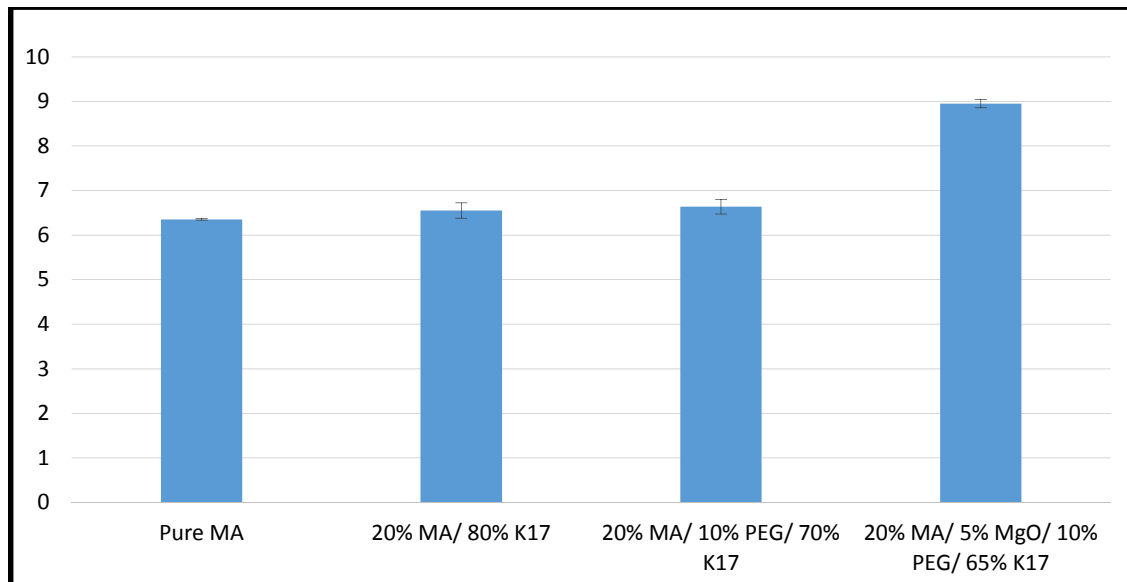


Fig. 3-7: pH analysis of pure drug and extrudates: a) K12 formulations, b) K17 formulations.

Interestingly, we found that incorporating 5% MgO and 10% PEG 3350 together within the binary mixture significantly increased drug release, resulting in more than 80% dissolution within one hour for the binary mixture with both K12 and K17. We also found that the formulation containing K12 (average M_w 2000-3000) had a more rapid release, reaching 85% within 2 h, whereas the other formulation with K17 (average M_w 7000-11000) demonstrated slower release, reaching 100% drug release. This is probably due to the differences in the molecular weight (M_w) and viscosity of the polymers. Increasing the amount of MgO to 10% did not affect the formulation containing K12, but resulted in faster release with K17, since MgO interfered more strongly with the API's particles with rapid modulation of the pH_M .

Therefore, the dissolution rate was found to significantly increase after incorporation of an alkalizer and PEG into the formulations, when compared to that of the pure drug, physical mixture, and binary mixture with PVP. It is evident that PEG 3350 led to an increase in the media uptake and MgO modified the microenvironmental pH inside the extrudate to be highly basic, resulting in an enhanced MA dissolution rate.

3.3.4. Physico-chemical properties of extrudates

The FT-IR, PXRD, SEM, and PLM studies were performed to understand the mechanism of action of the extrudates, as well as to observe the changes after extrusion.

The FT-IR spectra indicate that there is an extrusion-induced intermolecular interaction between MA and the K-Series (12 & 17) PVP polymers. Figure 3-8 displays the individual spectra for the raw materials for comparison with the extruded formulations. The carbonyl in PVP, a most likely hydrogen bond acceptor, was originally centered at 1651 cm^{-1} before making

a noteworthy shift to 1661 cm^{-1} in the extruded formulation. Likewise, there is a complimentary shift in the MA amino group, a likely hydrogen bond donor, from 1574 cm^{-1} to 1580 cm^{-1} . The decrease in the observed absorption intensity from this amino group is attributed to APIs' dilution in the polymer relative to the reference spectrum. It is also possible that the hydroxyl portion of the carboxylic acid group present on MA is also participating in the newly formed bond. However, taking into consideration the strong, broad absorbance of the PVP carbonyl centered near 1650 cm^{-1} , as well as the carrier and API's relative proportions (80% and 20% respectively), it is not possible to distinguish any changes to the hydroxyl's infrared signature due to the stated spectral overlap. In either case, the formation of post-extrusion hydrogen bonds is strongly indicated by these spectral shifts. Additionally, the spectra containing magnesium oxide and PEG did not seem to alter the spectral absorptions in these specified regions and were therefore considered to be uninvolved in the observed hydrogen bond formation (Fig. 3-8). It is also worth noting that these spectral characteristics were apparent in all of the formulations, as the only difference in the carriers was one of molecular weight and not chemical composition.

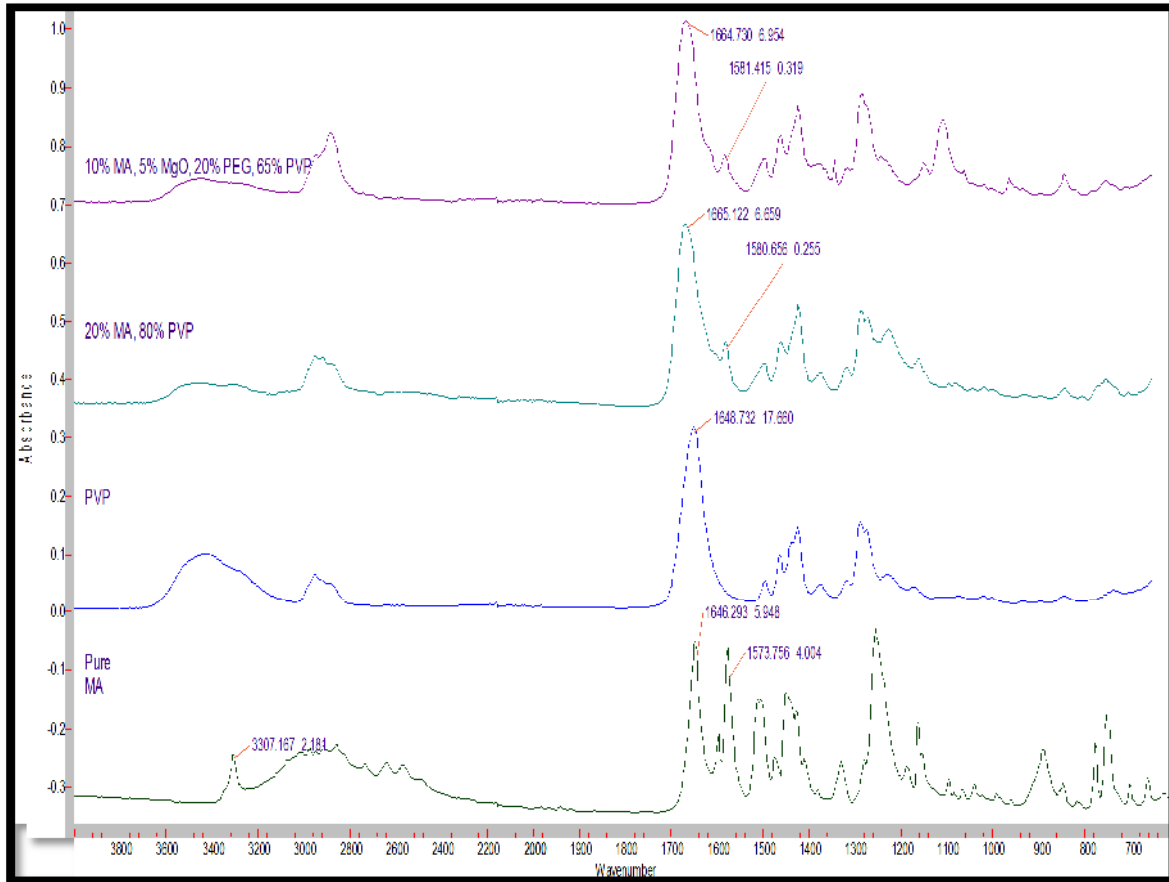
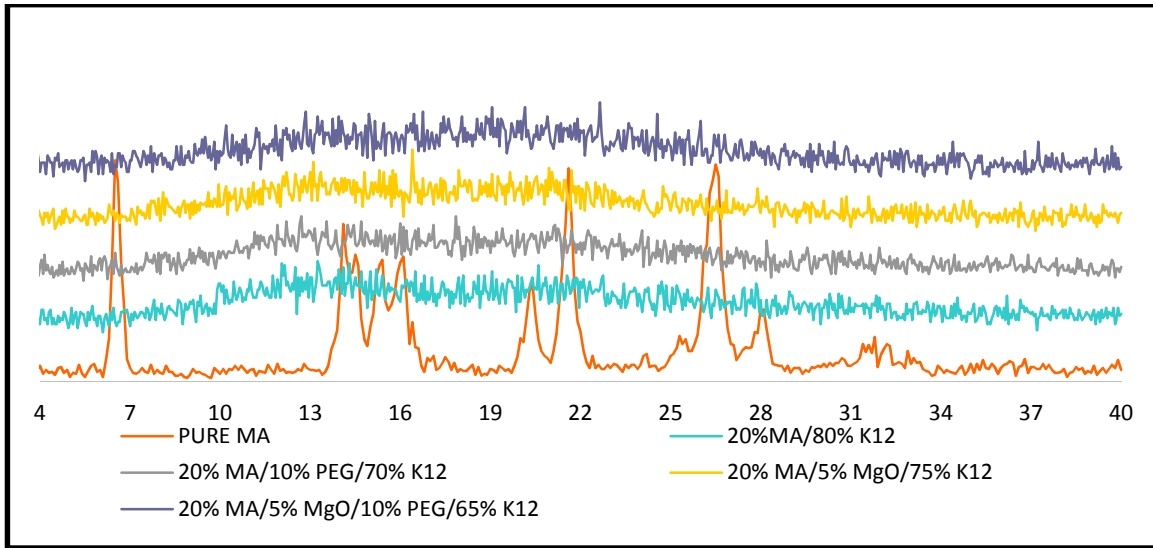


Fig. 3-8: FTIR analysis of pure drug, polymer and extrudates.

Powder X-Ray Diffraction (PXRD) measurements were used to study the crystallinity of the MA in the extrudates. The PXRD diffraction pattern of pure MA demonstrated highly intense and sharp peaks at $2\theta = 6.3, 21.4,$ and 26.3 , confirming the crystalline structure of the pure API. However, the PXRD analysis of various formulations after extrusion did not exhibit any traces of crystallinity as all sharp peaks had disappeared, indicating that the drug had completely transformed into an amorphous structure and had formed a solid dispersion in those matrices (Fig. 3-9). These results further confirm the DSC data, where the absent melting endothermic peaks of MA indicated the formation of a solid dispersion system by HME.

a)



b)

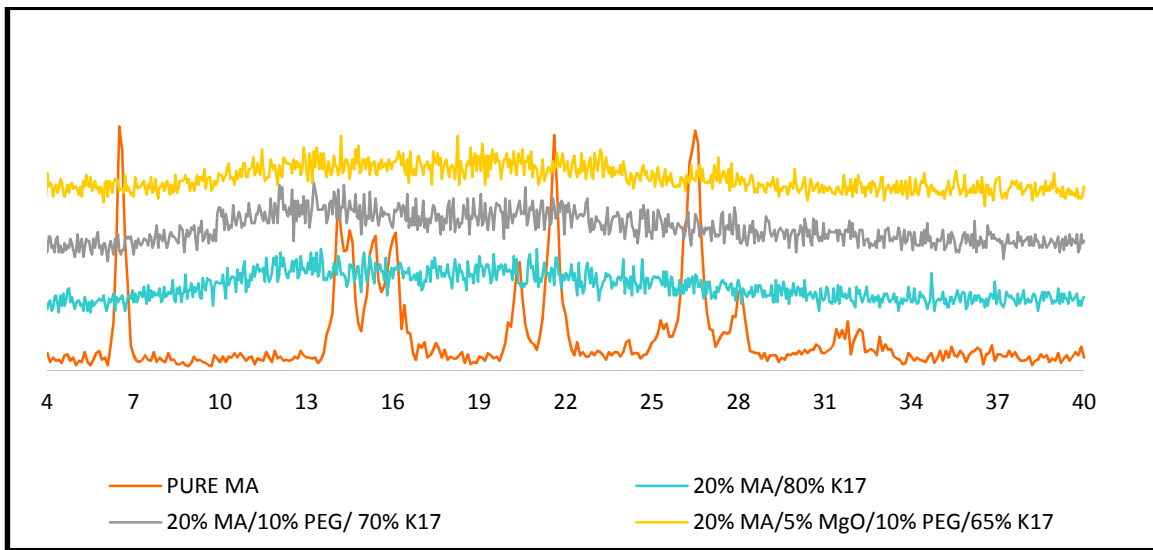
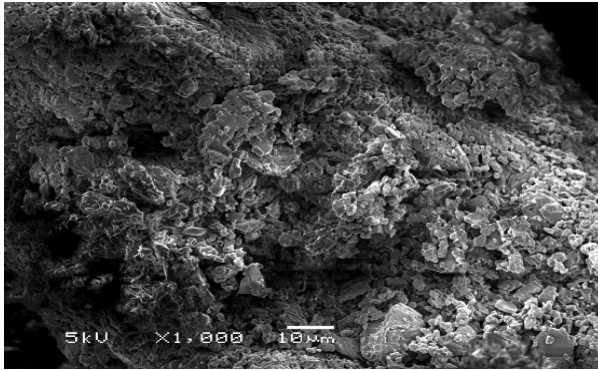


Fig. 3-9: PXRD analysis for pure MA and extrudates, a) PVP K12 formulations, b) PVP K17 formulations.

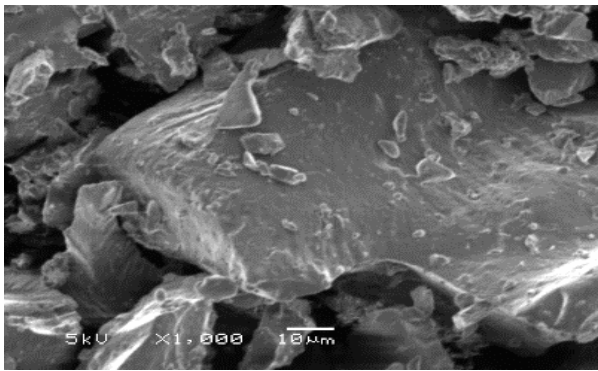
Scanning electron microscope (SEM) was used to investigate the surface morphology of the pure drug and extrudates (Fig. 3-10). The surface morphology of pure MA consists of microcrystalline aggregates with a coarse surface, which explains the hydrophobicity and poor

water solubility of this compound. However, the extrudates, including MgO and PEG within the binary mixture of MA-PVP, showed fewer aggregates, and a large smooth surface.

a)



b)



c)

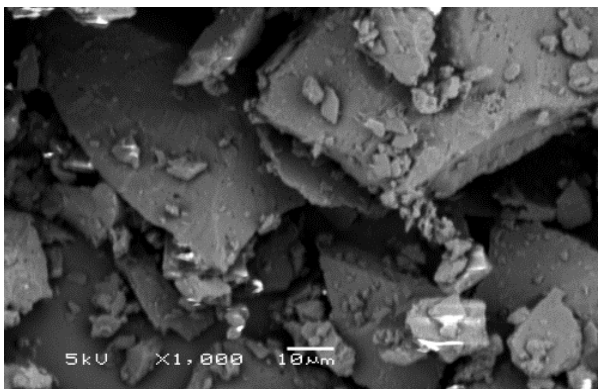
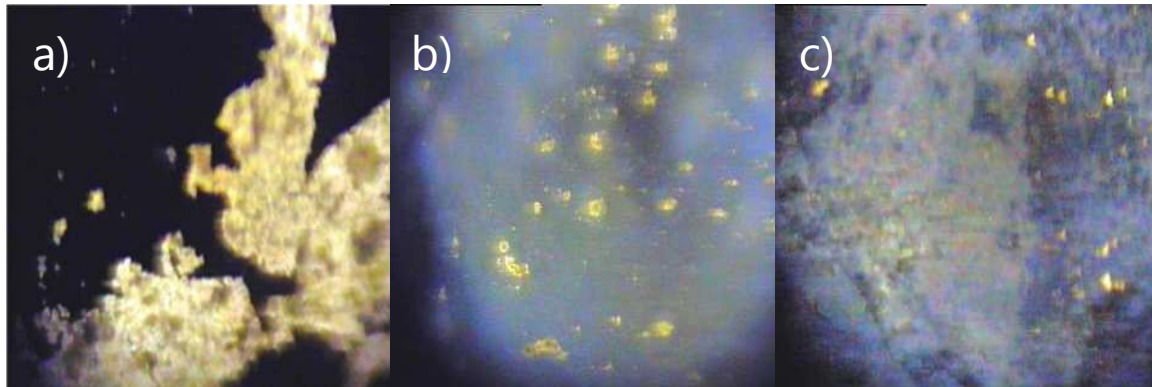


Fig. 3-10: SEM images of a) pure MA, b) 20% MA/ 5% MgO/ 10% PEG/ K12, c) 20% MA/ 5% MgO/ 10% PEG/ K17.

Polarized light microscopy (PLM) is a technique that has been used to differentiate between crystalline and amorphous form of the particles, since crystal structures have different refractive indices that are usually birefringent. They can be determined under polarized light microscope as a brilliant color that cannot be seen in the amorphous form.(Sarode et al., 2013) PLM was applied to compare the pure drug and extrudates and to study the dissolution behavior of the two optimized formulations (20% MA/ 5%MgO/ 10%PEG/ 65%K12 & K17). Figure 9-A shows that the pure drug crystals exhibited large crystal birefringence even after 30-min exposure to phosphate buffer (pH 6.8). Interestingly, extrudates rapidly dissolved once exposed to the dissolution media, with no vivid color, confirming that the drug exhibited in an amorphous form (Fig. 3-11).

i)



ii)

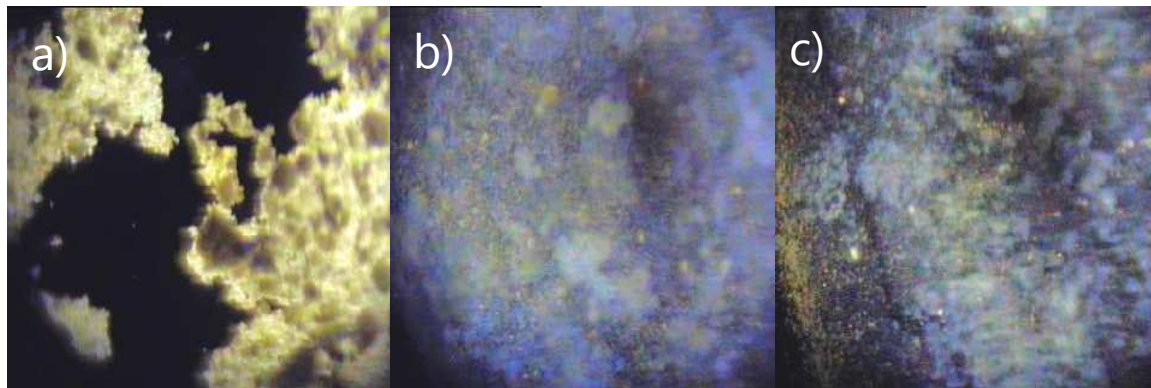


Fig. 3-11: PLM of a) pure MA, b) 20% MA/ 5% MgO/ 10% PEG/ K12, c) 20% MA/ 5%MgO/ 10% PEG/ K17, after exposure to phosphate buffer (pH 6.8) at: i) 0 min, ii) 30 min.

According to these studies of physical-chemical properties, it was determined that after incorporation of PEG 3350 and MgO to PVP-based extrudates, an amorphous solid dispersion with hydrogen bonding was able to be prepared that increased the amount of water uptake and the pH_M , resulting in the rapid and fast dissolution profiles of MA.

3.3.5. Stability studies

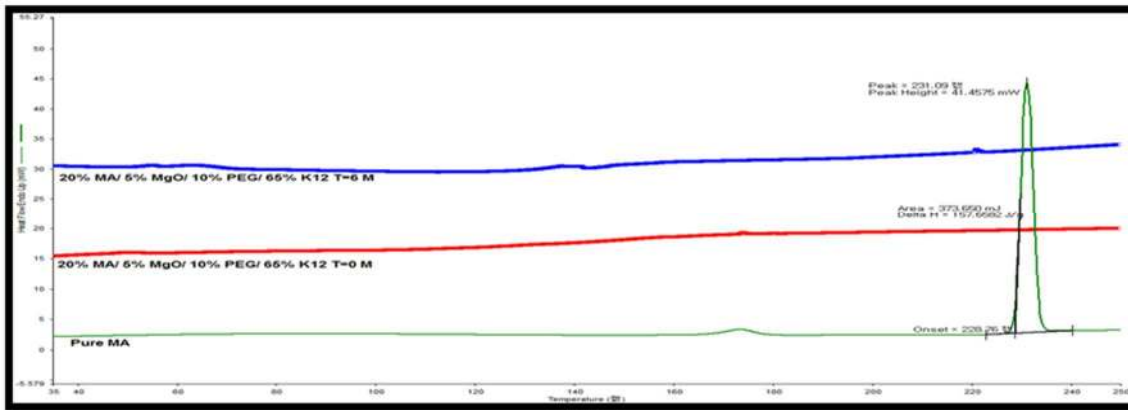
One of the critical problems that can limit the commercial outcomes of solid dispersions is the physical and chemical stability of the blends.(Breitenbach, 2002) Recrystallization of the drug in the amorphous systems usually occurs with aging due to the high free energy of

amorphous molecules compared to the crystalline form. The addition of a suitable polymer can delay this crystallization phenomena according to many studies.(Qian, Huang, & Hussain, 2010) The viscosity of the polymer, as well as the intermolecular interactions (hydrogen bonds) that can occur between the API and the polymer, are most important factors in the stabilization of solid dispersion systems(Breitenbach, 2002) Fitzpatrick et al. (2002) studied the effect of temperature and humidity on the stability of PVP formulations. They found that the PVP formulations at a high temperature and humidity (accelerated conditions) modified it from a glassy to rubbery state. However, this transformation did not occur when PVP was stored over long term conditions (61 weeks) at 30°C/60% RH.(Fitzpatrick, McCabe, Petts, & Booth, 2002)

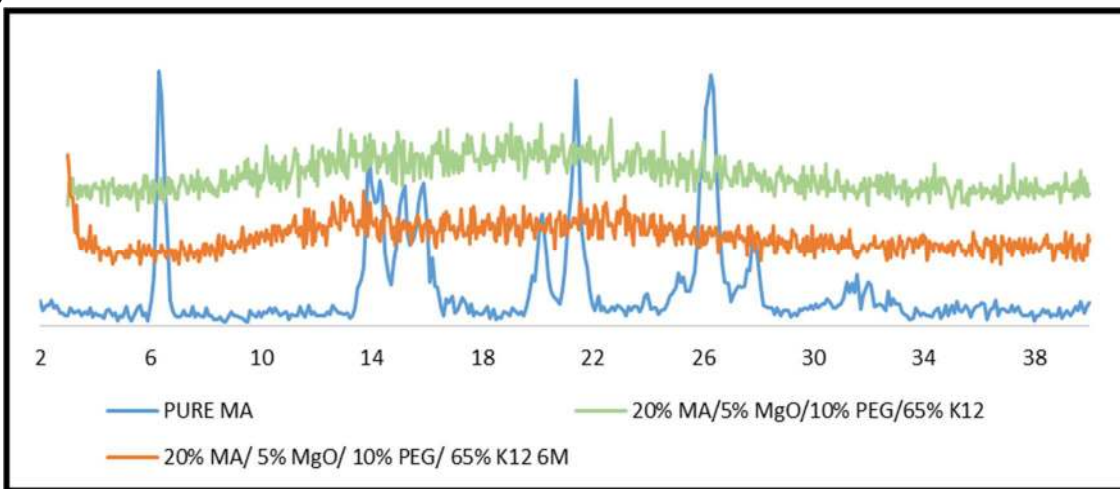
In the present study, we stored our samples of interest for a period of 6 months at normal conditions (25°C/60% RH). Assay of MA in the extrudates confirmed that the extrudates were chemically stable, with no drug degradation when checking for drug content after storage (>99%, within 1% difference). DSC analysis demonstrated that the drug remained in an amorphous form, as the corresponding endothermic peak was not present after 6 months of storage (Fig. 3-12-a & 3-13-a). Furthermore, drug crystalline peaks were absent in XRD, and no recrystallizations were found (Fig. 3-12-b & 3-13-b). In addition, *in-vitro* drug dissolution studies were applied to check for any modifications that might have occurred with time and compare the formulation with fresh ones. The f_2 value for k12 formulations after 3 and 6 months were 57% and 53%, respectively. The k17 formulations after 3 and 6 months of storage time were 59% and 54%, respectively. Therefore, we can conclude that the drug release profiles after long-term storage were similar to the ones at time 0.

Thus, the 6-month stability studies for the hot melt extrudates suggest that the extrudates were physically and chemically stable and identical to the fresh extrudates.

a)



b)



c)

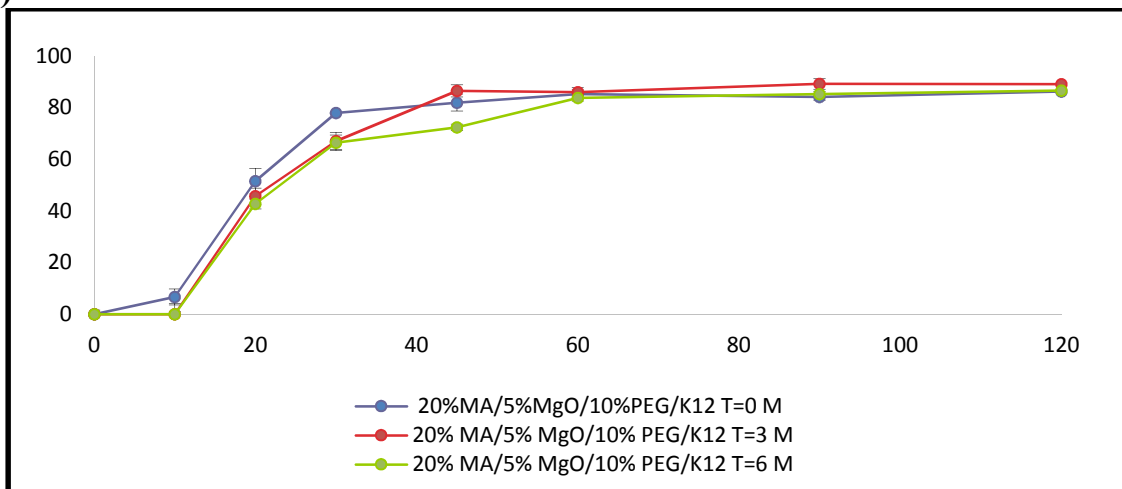
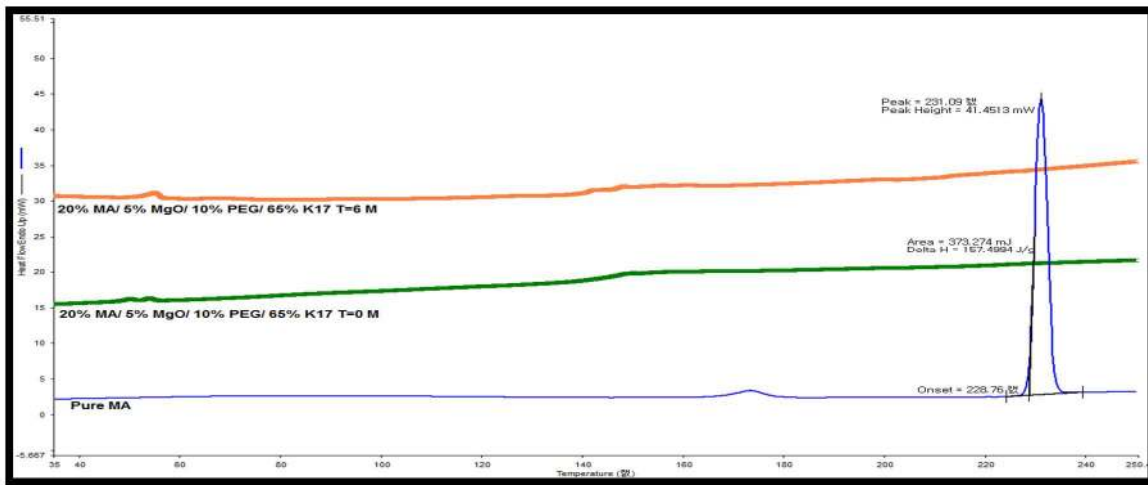
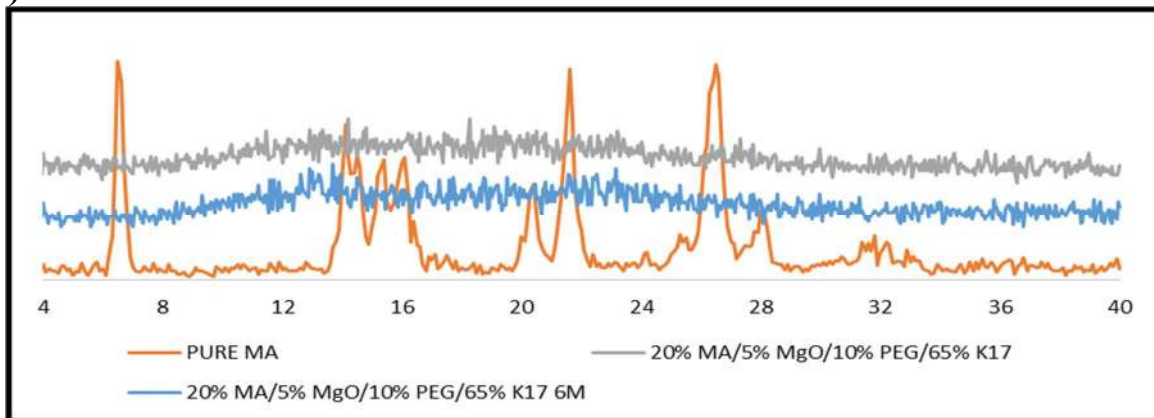


Fig. 3-12: Stability test (25°C/60% RH) for 6 months of MA/PVP K12 extrudates: (a) DSC results; (b) PXRD data; (c) Drug release of extrudates in phosphate buffer (pH 6.8).

a)



b)



c)

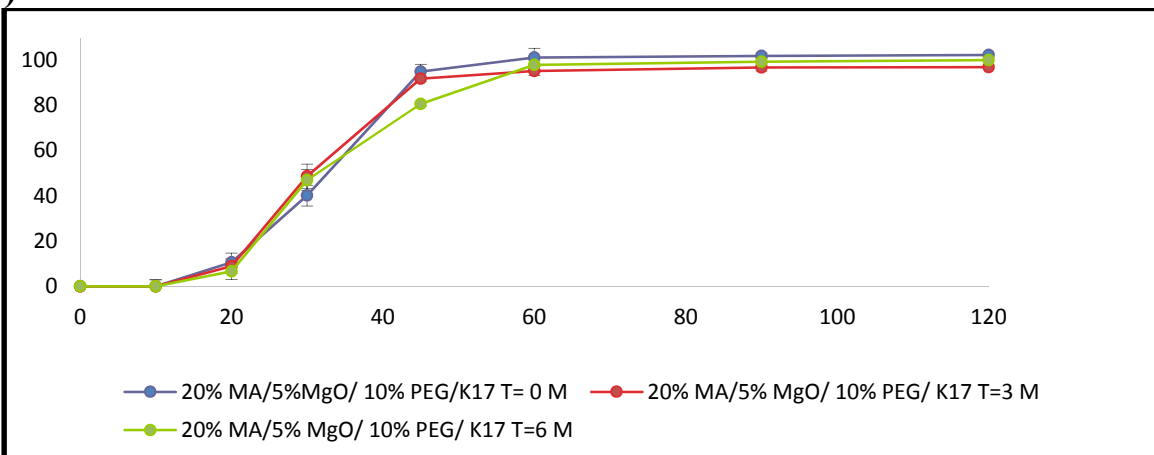


Fig. 3-13: Stability test (25°C/60% RH) for 6 months of MA/PVP K17 extrudates: (a) DSC results; (b) PXRD data; (c) Drug release of extrudates in phosphate buffer (pH 6.8).

3.4. Conclusion

The thermal stability of each blend at the employed extrusion temperatures was confirmed by TGA analysis. All formulations were successfully extruded under the employed extrusion parameters. DSC revealed that the MA was completely miscible up to 20% w/w drug load extrudate. PXRD confirmed that the drug was in an amorphous form after extrusion. The formation of post-extrusion hydrogen bonds is strongly indicated between MA and the K-Series (12 and 17) PVP polymers. Different grades of Kollidon[®] had an effect on the solubility of MA by transforming the drug crystals into an amorphous form to form a solid dispersion system. Moreover, adding an alkalizer to the formulation has a marked positive effect on its dissolution rate by increasing the pH_M to almost 9 and alkalizing the surrounding area. Incorporating PEG 3350 into the formulations significantly increased media uptake, owing to the wettability and dispersability effect of PEG. Kollidon[®] is a promising carrier with which to produce solid dispersion formulations by hot melt extrusion for poorly water-soluble drugs. Furthermore, the addition of an alkalizer with a plasticizer to the formulation had significant influence on the release of this API from the Kollidon[®] matrices.

CHAPTER 4

FORMULATION AND EVALUATION OF MEFENAMIC ACID SUSTAINED RELEASE TABLETS CONTAINING KOLLIDON® SR VIA HOT-MELT EXTRUSION TECHNOLOGY

Objectives:

The main objectives of this study was:

- 1- To formulate and evaluate the effect of Kollidon® SR on the release profiles of mefenamic acid from matrix tablets using hot-melt extrusion technology.
- 2- Formulation of an MA sustained-release dosage form to reduce the frequency of intakes and therefore reduce its adverse side effects.

Abstract:

The aim of this study was to formulate and evaluate the controlled effect of a Kollidon® SR polymer carrier on the release profiles of the poorly soluble drug mefenamic acid from matrix tablets utilizing hot melt extrusion technology. Various drug loads of MA and polymer were blended using a V-shell blender and extruded using a twin-screw extruder (16-mm Prism EuroLab, ThermoFisher Scientific) at a screw speed of 100 rpm, and 150-160 °C extrusion temperature to prepare a solid dispersion system. Differential scanning calorimetry (DSC) studies demonstrated that MA and K SR were completely miscible and transformed to an amorphous structure at drug loads up to 40%. FT-IR confirmed the intermolecular interaction between the drug and the polymer carrier after extrusion process. Sustained release

tablets were successfully prepared with excellent tablet characteristics for these formulations. In addition, the drug release from the 40% drug loaded extrudate reached 20% within 2 hours and 80% within 12 hours, compared to more than 80% drug release of the corresponding physical mixture, and 100 % of the pure drug and higher drug load (60% and 80%) formulations within 2 hours. Finally, the drug release kinetics showed that the drug release from the tablets was controlled by two mechanisms: diffusion and the erosion process.

Keywords: Mefenamic acid, Kollidon[®] SR, Hot Melt Extrusion, Sustained Release Tablets, *In vitro* drug release.

4.1. Introduction:

Recently, sustained/controlled release formulations have become an important issue and have received much attention in the manufacturing process and medical use due their ability to release the drug at a sustained rate over a period of time, which maintains the pharmacological effect of the drug. Long-acting formulations have many advantages, such as improving patient compliance by reducing intake frequency and therefore reducing gastrointestinal side effects (P. H.-L. Tran, Tran, Park, & Lee, 2011). Hot melt extrusion (HME) is one of several techniques that can be used to make sustained-release dosage forms (Almeida et al., 2011). It has been reported that the formulations created by HME show slower drug release rates due to lower porosity, compared to other traditional methods. There are many suitable and safe polymers that have been used to make sustained release formulations, including ethylcellulose, polymethacrylate, polyethylene oxide and polyvinyl acetate/ polyvinylpyrrolidone (Özgüney, Shuwisitkul, & Bodmeier, 2009).

Mefenamic acid (MA), a poorly water-soluble compound, was chosen as a model drug. It has a relatively short half-life of 2 hours and a usual oral dose of 250 or 500 mg which is prescribed three times daily (Ibrahim, 2013). In recent studies, MA also has the potential to be used to treat Alzheimer's disease. As other NSAIDs, and due to the free carboxylic acid group in the chemical structure, MA has broad gastrointestinal side effects, which could lead to serious patient non-compliance. In addition, there is no commercial MA sustained release product on the market (Sevgi et al., 2008). It has been reported that Kollidon SR is a great matrix-retarding agent and it is widely used to develop oral controlled release products. It consists of 80% polyvinyl acetate, which is water the insoluble part, and almost 20% polyvinylpyrrolidone, which is a water-soluble compound (Fig. 4-1). Therefore, when the tablet contacts the dissolution media,

the tablet can maintain its geometric shape till the end of the test because of the superior content of the insoluble part of the polymer; in the same time the povidone can leach out to make pores through the tablet which explains the diffusion drug release mechanism (Buhler, 2008; Sakr, Alanazi, & Sakr, 2011). Kollidon® SR is considered a safe material for oral administration in humans, with no toxicity and no irritation of the skin or mucous membranes of the body. It has been reported that this carrier is barely absorbed orally and mostly excreted in the feces (Arias, Gómez-Gallo, Delgado, & Gallardo, 2009).

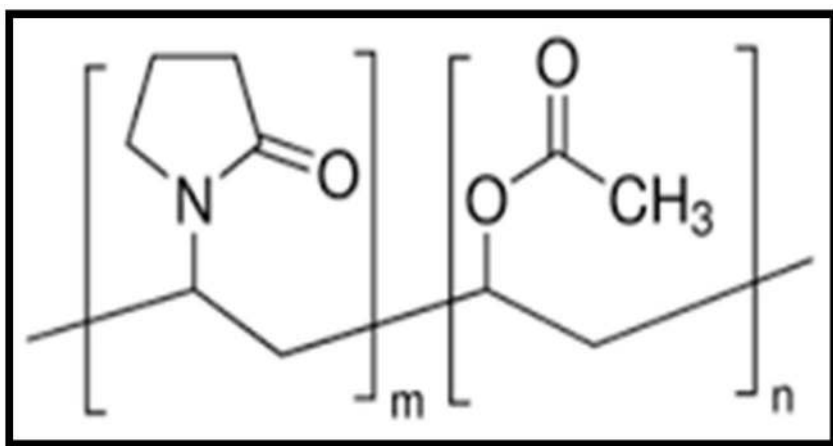


Fig. 4-1: chemical structure of Kollidon® SR.

In this study, various drug loads of mefenamic acid were blended with Kollidon® SR to assess and evaluate its effect on the release profiles of MA from matrix tablets using hot-melt extrusion technology.

4.2. Materials and Methods:

4.2.1. Materials:

Mefenamic acid (MA) was purchased from Sigma Aldrich (Bellefonte PA. USA);

Kollidon SR was obtained as gift samples from BASF (PEGPVCLPVA, BASF, Germany); Microcrystalline cellulose (Avicell PH 101) was gifted from FMC Biopolymer (Philadelphia, PA); Magnesium stearate was purchased from Mallinckrodt (St. Louis, MO, USA). All other chemicals used were of analytical grade (impurities <0.1%).

4.2.2. Perpetration Methods:

4.2.2.1. Thermal Characterization:

4.2.2.1.1. Thermogravimetric (TGA) & Differential Scanning Calorimetry (DSC) Analysis:

Thermogravimetric analysis (TGA, Pyris 1 TGA Perkin Elmer) equipped with Pyris manager software (PerkinElmer Life and Analytical Sciences, 719 Bridgeport Ave., Connecticut, USA) was used to assess the thermal stability of the MA and Kollidon[®] SR in order to select the optimal temperatures for the extrusion process. Each sample of pure MA, pure polymer, and physical mixture weighed from 7-10 mg and was heated from 30 °C to 250 °C at a heating rate of 20 °C/min. The results were collected according to the percentage of weight loss that occurred when increasing the temperature of the samples.

Differential scanning calorimetry (DSC) was performed to study the physical nature of the drug and the polymer and also to study the drug-polymer compatibility. Samples of interest were analyzed using Perkin Elmer Diamond Differential Scanning Calorimeter (DSC) (Perkin Elmer Life and Analytical Sciences, 710 Bridgeport Ave., Connecticut, USA) equipped with Pyris manager software (Shelton, CT, USA). Each sample weighed between 3-5 mg and was hermetically sealed in an aluminum pan then heated, under an inert nitrogen atmosphere, from 30-250 °C at a heating rate of 10 °C/min.

4.2.2.2. Chromatography System and Conditions:

A Waters HPLC system consisting of a Waters 600 binary pump, Waters 2489 UV/ detector, and Waters 717 Plus auto sampler (Waters Technologies Corporation, 34 Maple St., Milford, MA 0157) and Empower 2 software was used to analyze the samples and data. The stationary phase consisted of a Symmetry Shield C₁₈, 250Å~4.6 mm, 5 µm particle size reverse-phase column. The mobile phase consisted of methanol: water: acetonitrile (80:17.5:2.5 v/v) with the pH adjusted to 3.0 with phosphoric acid (85%). The detection wavelength was set at 225 nm and the mobile phase flow rate was maintained at 1.0 mL/min. The injection volume for all samples was 20 µL (Sultana et al., 2012). The drug content samples of the mefenamic acid physical mixture and extrudates were approximately 20mg weighed and dissolved in methanol then diluted 10 times with methanol. After that, samples were filtered and analyzed using the HPLC method stated above. All assays studies were performed in triplicate (n=3).

4.2.2.3. Preparation of hot melt extrudates:

MA and Kollidon[®] SR were blended at drug loads of 20%, 40%, 60% and 80% using a V-shell blender (MaxiBlend[™], GlobePharma, North Brunswick, NJ, USA), at 25 rpm for 10 minutes (Table 4-1). After passing the physical blend through US# 35 mesh screen to remove any aggregates that may have formed, melt extrusion was used for each blend using a twin-screw extruder (16 mm Prism Euro Lab, Thermo Fisher Scientific) at a screw speed of 100 rpm and over the temperature range of 150-160⁰C. The obtained extrudates were further milled using a comminuting mill (Fitzpatrick, Model “L1A”) and then sieved using ASTM #35 mesh.

Table 4-1: Formulation Design and processing conditions.

Formulations	MA w/w%	K SR w/w%	Extrusion conditions	
			Temp. °C	Speed rpm
F1	20	80	150	100
F2	40	60	155	100
F3	60	40	160	100
F4	80	20	160	100

4.2.2.4. Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectroscopic analysis was performed on the extruded samples to study the drug-polymer interactions and corroborate the miscibility results obtained by DSC. FT-IR was conducted on a Cary 660 bench (Agilent Technologies, Santa Clara, CA.) for mid-infrared spectra from 4000–650 cm^{-1} . The bench was equipped with an ATR (Pike Technologies MIRacle ATR, Madison, WI), which was fitted with a single bounce diamond coated ZnSe internal reflection element.

4.2.2.5. Scanning Electron Microscope (SEM)

The surface morphology of the pure drug, mefenamic acid, pure polymer, Kollidon SR, and milled extrudates were evaluated and studied using SEM (JEOL JSM-5600). Samples were mounted on adhesive carbon pads placed on aluminum stubs prior to sputter coating. A

Hummer[®] 6.2 sputtering system (Anatech LTD, Springfield, VA) in a high vacuum evaporator was used to sputter-coat the samples with gold. SEM operating at an accelerating voltage of 10 kV was used for imaging.

4.2.2.6. *In vitro* drug release studies:

Milled extrudates equivalent to 100 mg MA were then filled in hydroxypropyl methylcellulose (HPMC) capsules and used for the dissolution studies. *In-vitro* release studies were performed for 12 hours using a USP apparatus Type-II (Hanson SR8) in 900 ml of 0.5% Tween 80, adjusted pH to 7.4 phosphate buffer maintained at $37 \pm 0.5^\circ\text{C}$ and at a paddle rotation speed of 50 rpm (Güngör et al., 2003). At different time points, the samples were withdrawn (1.5 ml) and an equal amount of fresh medium was added to the continuing dissolution medium vessel. HPLC was used to analyze the samples and the percentage of drug release vs. time (hours) profile was plotted. The dissolution studies were performed in triplicate (n=3). Similarity factor (f_2 values) were calculated in order to evaluate similarity of the release patterns of MA from the optimized extrudate and the tablet of 40% drug load.

4.2.2.7. Preparation and compression of MA sustained release tablets:

Based on the DSC data and dissolution results of the prepared extrudates, 40% drug load was chosen to formulate the sustained release tablets and further mixed with the tablet excipients such as microcrystalline cellulose, used as diluent, and magnesium stearate, used as lubricant. All excipients were mixed using a V-shell blender (GlobePharma, MaxiBlend, New 111 Brunswick, NJ, USA) after passing through ASTM #30 mesh. Magnesium stearate was added when two minutes of blending remained to prevent over-mixing. Then, tablets were manually prepared by direct compression on a single punch tablet press (MCTMI, Globe Pharma Inc., New Brunswick, NJ) by using 10 mm biconcave punches at a compression force of 1.0-1.1 kN,

to create a final tablet weight of 400 mg.

4.2.2.8. Evaluation of tablet properties

Compressed tablets were then evaluated for weight variations, thickness, diameter, hardness, friability and drug content uniformity. Thickness and diameter of the tablets were evaluated using a digital vernier caliper (Fisher Scientific). Ten tablets were randomly selected and tested for hardness using a hardness tester (VarianVK200, Agilent technologies, 13,000 Weston Pkwy, Cary, NC). Friability studies were performed as a percentage weight loss of tablets (weighing 6.5 g) using Roche friabilator for 4 min at 25 rpm (Vankel Industries Inc., Chatham, NJ).

4.2.2.9. Drug release kinetics and mechanism

To understand the mechanism of the drug release from each formulation, the analysis data was determined kinetically by four equations as follow (Higuchi, 1963; Korsmeyer, Gurny, Doelker, Buri, & Peppas, 1983; Patil, Tiwari, Upadhye, et al., 2015):

- Zero order equation:

$$Q_t = Q_0 + K_0t$$

Where Q_t is the amount of the drug release at time t , Q_0 is the initial amount of the drug in the dissolution media and K_0 is the zero order rate constant.

- First order equation:

$$\log Q_t = \log Q_0 - K_1t/2.303$$

Where Q_t is the amount of the drug release at time t , Q_0 is the initial amount of the drug in the dissolution media and K_1 is the first order rate constant.

- Higuchi equation:

$$Q_t = K_H t^{1/2}$$

Where Q_t is the amount of the drug release at time t and K_H is the Higuchi dissolution constant.

➤ Korsmeyer-Peppas equation:

$$Q_t/Q_\infty = K_{kp} t^n$$

Where Q_t is the amount of drug release at time t , Q_∞ is the total amount of the drug in the dosage form, K_{kp} is the Korsmeyer's rate constant which is the release constant, comprised of structural and geometrical characteristics of the tablets, and n is the release exponent that is explained by the drug release mechanism.

4.3. Results and discussion:

4.3.1. Thermal Analysis:

The TGA thermograms of the samples were determined for changes in weight. TGA thermograms confirmed that the pure drug and the physical mixture are thermally stable during the extrusion processing temperature. Pure drug and physical mixtures showed less than 2% weight loss up to 200 °C and that was considered to be from residual moisture of MA and other components. Therefore, all of the formulations were assumed to be thermally stable during the hot melt extrusion process as the extrusion temperatures were less than this temperature (Fig. 4-2).

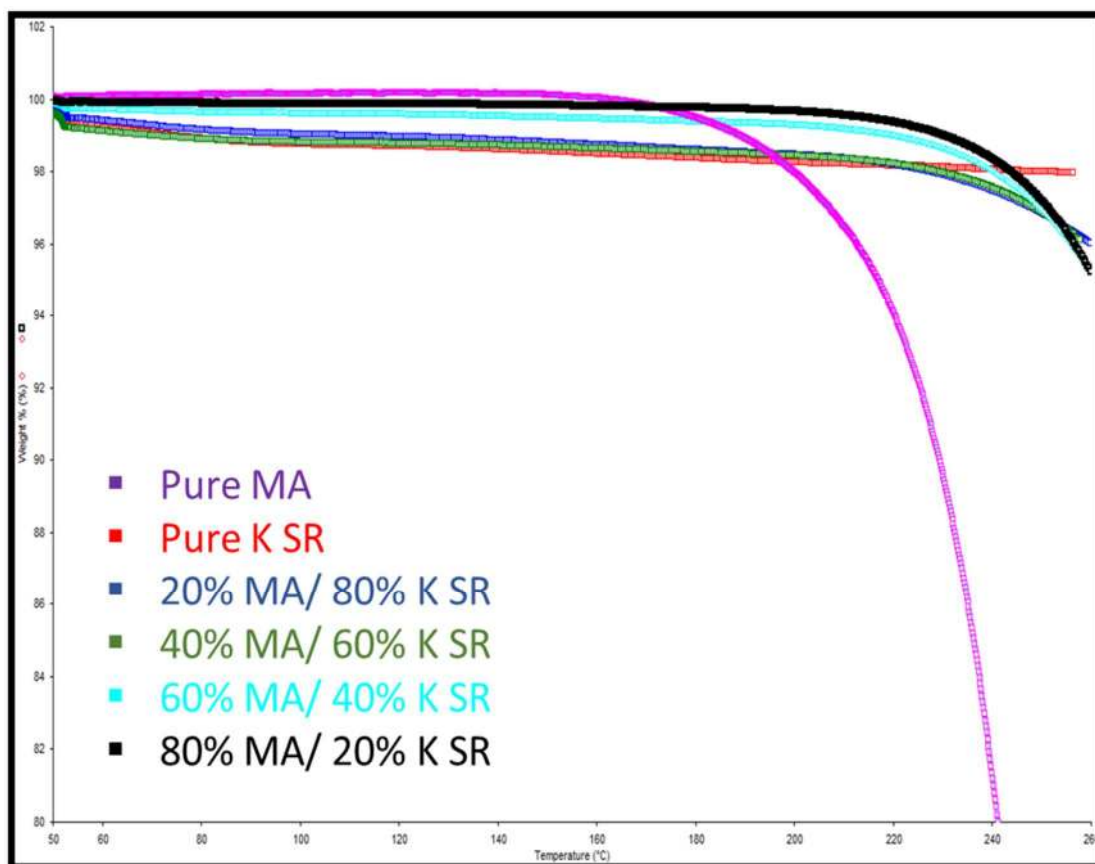


Fig. 4-2: Thermogravimetric analysis of pure MA, pure K SR and various MA/K SR mixtures.

DSC studies were applied to evaluate the physical state of the drug in the polymeric matrix. Pure mefenamic acid exhibited a sharp endothermic peak onset at 230 °C shown in Figure 4-3. DSC data showed that MA was completely transformed to an amorphous form within the polymer matrix up to 40% drug loading, as its endothermic peak at 230 °C was completely absent. However, this peak appeared slightly with 60% and more with 80% drug loading, suggesting that the drug partially exists in the crystalline form (Fig. 4-3). Thus, the DSC results indicate that the molten formulations were able to depress the melting point of MA and manufacture an amorphous solid dispersion after passing through the hot melt extrusion at up to

40% drug loads and this corresponds with the dissolution studies which are explained in the next section.

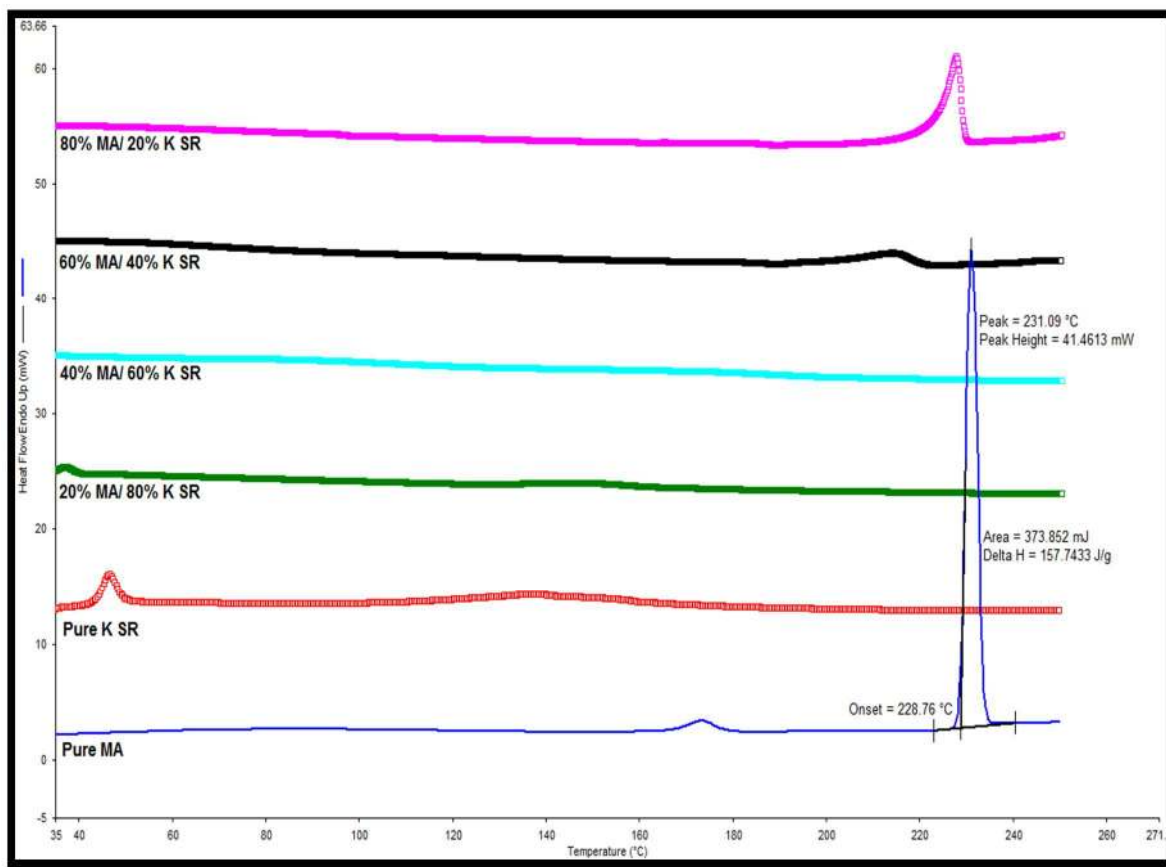


Fig. 4-3: DSC analysis of pure MA, pure K SR and MA/ K SR extrudates at temperatures of 30-250°C and heating rate of 10 °C/min.

4.3.2. Drug content and *In vitro* drug release studies on extrudates:

The uniformity of drug content was calculated before and after extrusion to confirm uniformity of mixing and to evaluate the chemical stability of mefenamic acid. Each formulation was analyzed using HPLC for drug content and content uniformity. All of the extruded blends

and tablets showed excellent drug content and content uniformity (98%-102%) after processing by hot-melt extrusion, thus exhibiting a robust process and product outcome, indicating that mefenamic acid is chemically stable with no degradation or weight loss in any formulation after extrusion, further confirming the TGA results.

In vitro dissolution studies were performed by a modified dissolution method that has been reported in the literature, as currently there are no regulatory (USP or FDA) guidelines available to evaluate mefenamic acid sustained release tablets in the dissolution media. We choose this media as a discrimination media to compare between the pure drug and other formulations and also to show the powerful effect of this polymer to sustain the drug release of poorly soluble drugs. The formation of solid dispersions tends to sustain the release of poorly water-soluble drug when they are extruded with Kollidon[®] SR at various drug loads. The dissolution results displayed show that the pure drug release showed fast and high release compared to all formulations with this polymer. Clearly from figure 4-4, we can observe that the drug release from the 40% drug loaded extrudate reached 20% within 2 hours and 80% within 12 hours compared to more than 80% drug release of the corresponding physical mixture, 100 % of the pure drug and higher drug loads 60% and 80% formulations within 2 hours (Fig. 4-4). Therefore, Kollidon[®] SR demonstrated the ability to sustain the drug release up to 12 hours in the dissolution study.

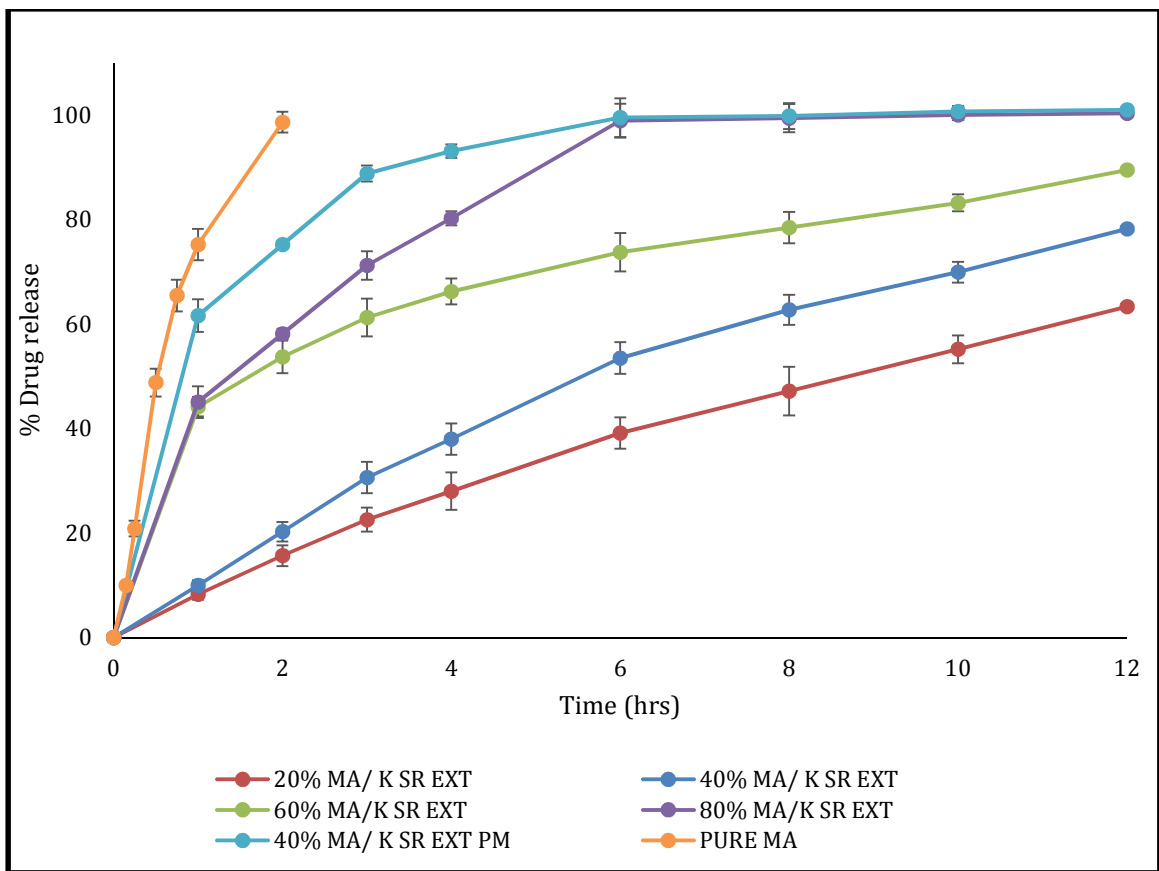


Fig. 4-4: *In vitro* dissolution profiles of pure MA and MA/K SR extrudates in buffer (pH 7.4)

4.3.3. Fourier Transform Infrared Spectroscopy (FT-IR)

It is believed that physical stability and solubility were improved by manufacturing solid dispersion systems through making intermolecular interactions such as hydrogen bonding interactions between the API and the polymeric carrier. In order to confirm this hypothesis, FT-IR studies was used to demonstrate the drug-polymer intermolecular interaction, resulting in peak shifting, or the appearance or absence of the absorbance peaks. The FT-IR analyses were conducted on the pure component, physical mixture and extrudates. The model drug, MA,

showed two significant stretching absorbance peaks of N-H functional group at 3308 cm^{-1} and C=O absorbance functional group at 1646 cm^{-1} . The polymeric carrier, K SR, consisting of polyvinyl acetate (PVA) and polyvinyl pyrrolidone (PVP) showed three significant peaks at 1740 cm^{-1} , which correspond to the carbonyl stretching vibration of the ester group and that belongs to the PVA part. The N-H and C=O functional groups showed absorbance peaks around 3470 and 1664 cm^{-1} corresponding to the PVP part. As shown in Figure 4-5, no peak shifting, or appearance or absence of the absorbance peaks was detected in the physical mixture. However, in the extrudates, the stretching absorbance peak of N-H was shifted and the intensity was decreased indicating the hydrogen bonding (drug-matrix interactions) could be formed between the N-H group of mefenamic acid and C=O group of K SR after processing utilizing HME technology.

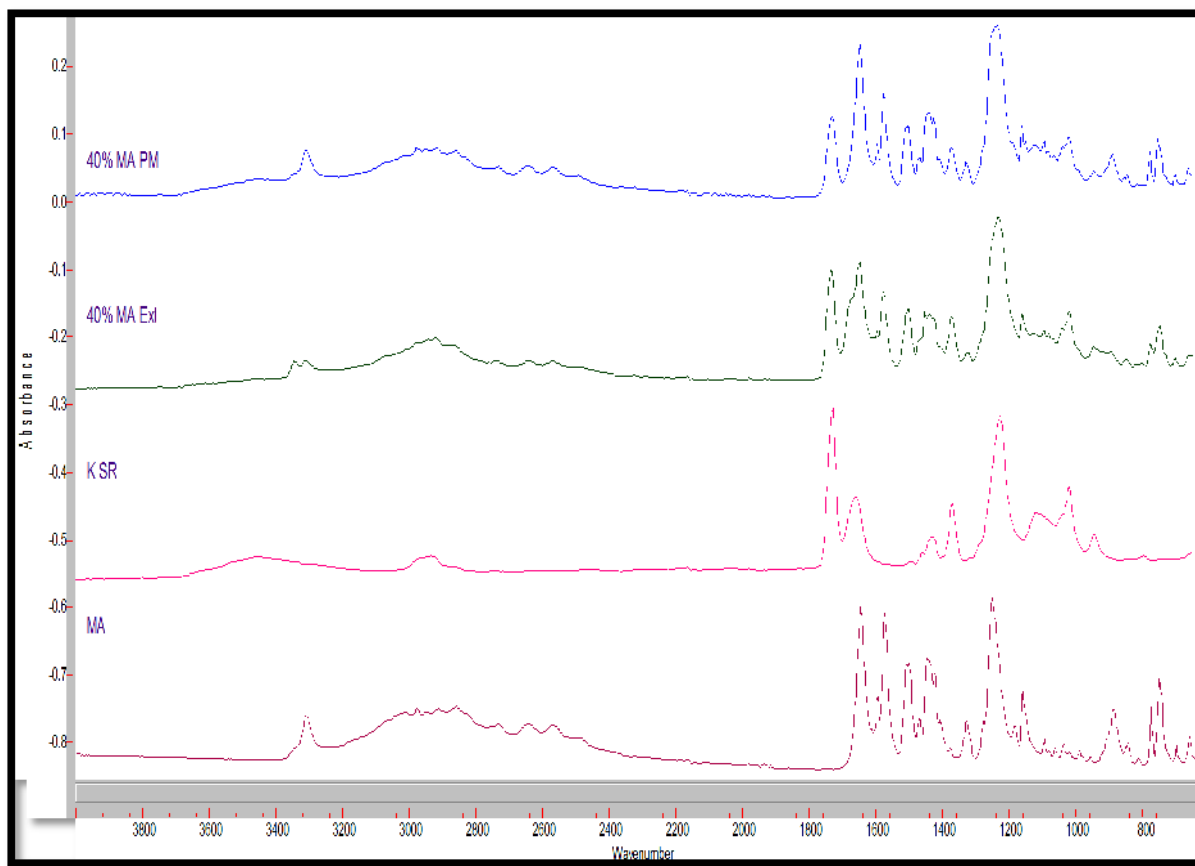


Fig. 4-5: FT-IR analysis of pure MA, pure K SR, MA/ K SR physical mixture and extrudates.

4.3.4. Scanning Electron Microscope (SEM)

Due to the high resolution and magnification of the SEM machine, it has been used to characterize the solid-state conditions of substances in the pharmaceutical field. Kollidon® SR polymeric carrier loaded with mefenamic acid was studied by scanning electron microscope to understand the morphological and the particle size changes that may have occurred after the extrusion process. Figure 4-6 shows remarkable variances between the pure API and other formulations. Pure MA seems to consist of microcrystalline aggregates with a coarse texture while Kollidon® SR shows spherical shapes with smooth surfaces, which indicates the amorphous state of the polymer. However, the aggregates and coarse morphology become less

when extruded with Kollidon SR, especially when the portion of the polymer is increased and the drug load is decreased. 20% and 40% drug loads exhibited smooth surfaces which were interspersed with fissures; this explains the sustained-release behavior of these two drug loads in the dissolution studies. Therefore, the morphology and surface properties were found to be affected by different Kollidon SR concentrations.

4.3.5. Preparation and characterization of sustained release tablets:

Tablets showed good hardness and excellent friability which was related to the polymeric carrier, K SR. Tablet characterization test results exhibited an average weight of 401.5 mg, a thickness of 5.9 mm, and a hardness of 10.8 kp. The most important factor here is the friability of 0.25%, which fit the USP specifications (Fig. 4-7). In addition, drug release from 40% drug loaded tablets at 1.0-1.1 kN compression force showed almost the same as the corresponding extrudates with the similarity factor (f_2 value) of 71, which is considered similar when the f_2 value is between 50 and 100 (Fig. 4-8).

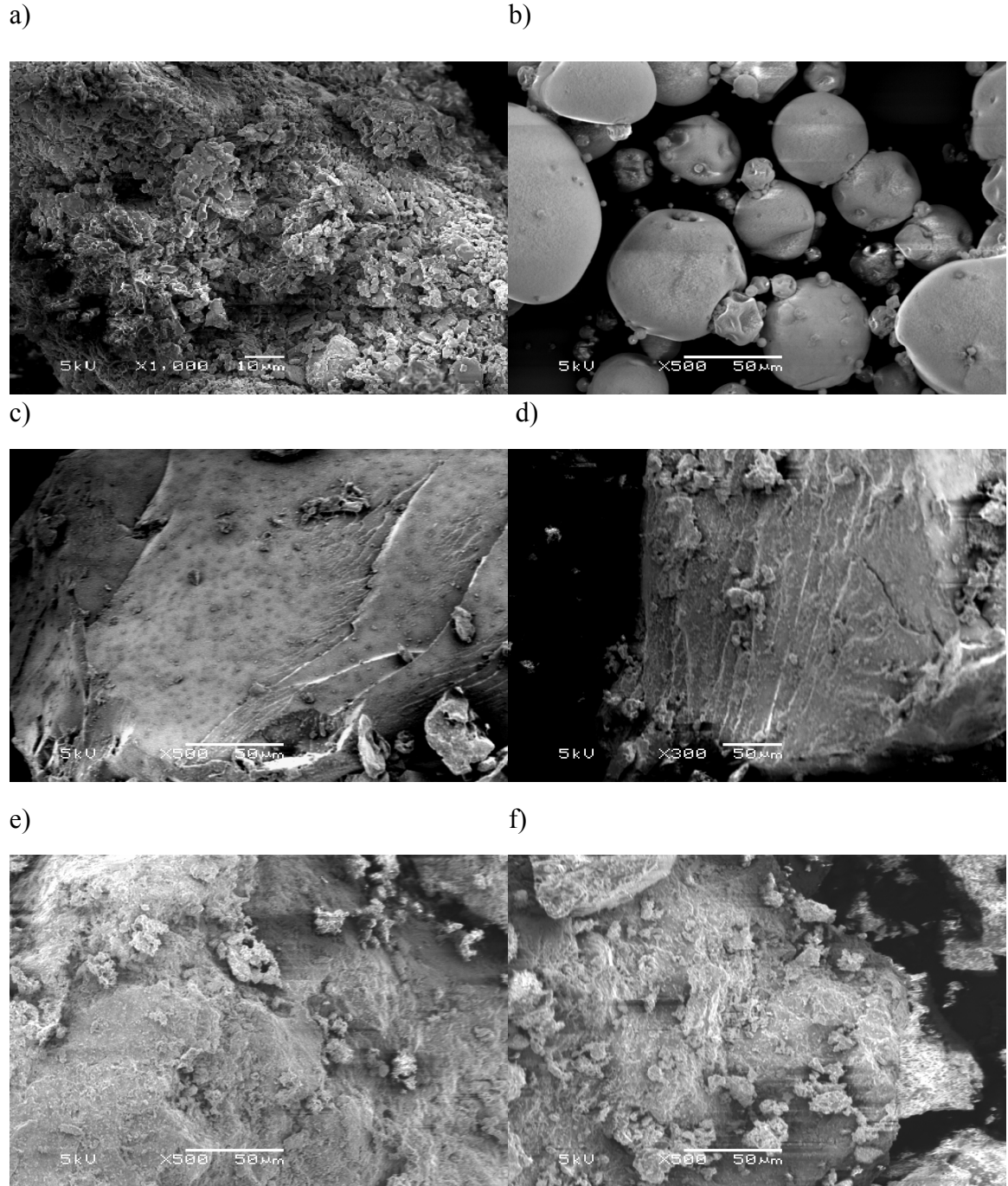


Fig. 4-6: SEM analysis of: a) pure MA, b) pure K SR, c) 20% MA/K SR extrudates, d) 40% MA/K SR extrudates, e) 60% MA/K SR extrudates, f) 80% MA/K SR extrudates.

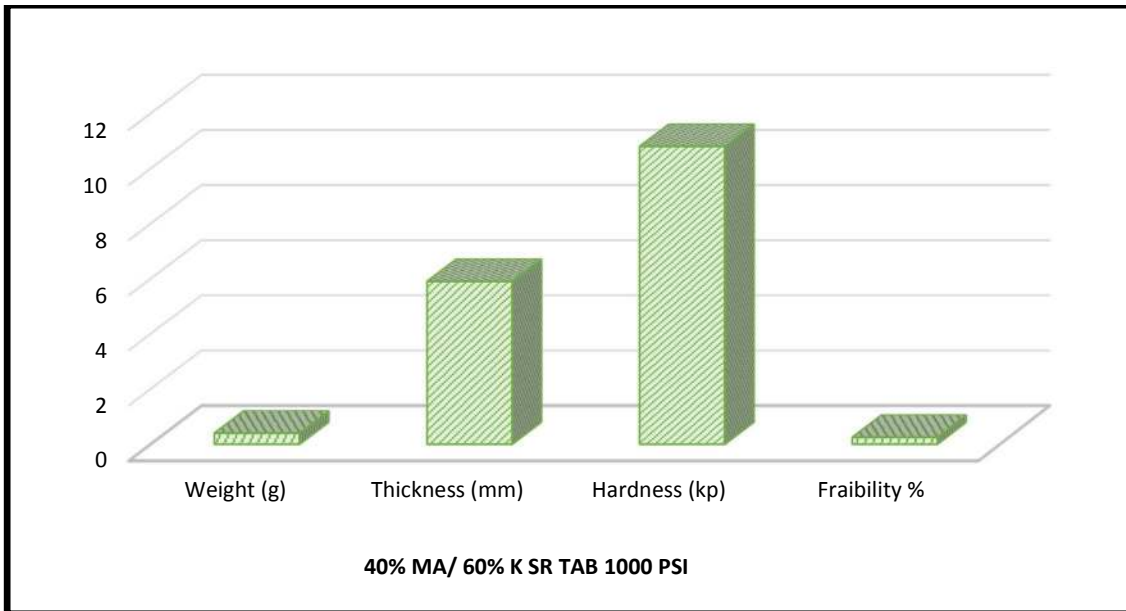


Fig. 4-7: Tablet Properties (weight, thickness, hardness and friability) for 40% MA/ 60% K SR tablet at 1000 PSI.

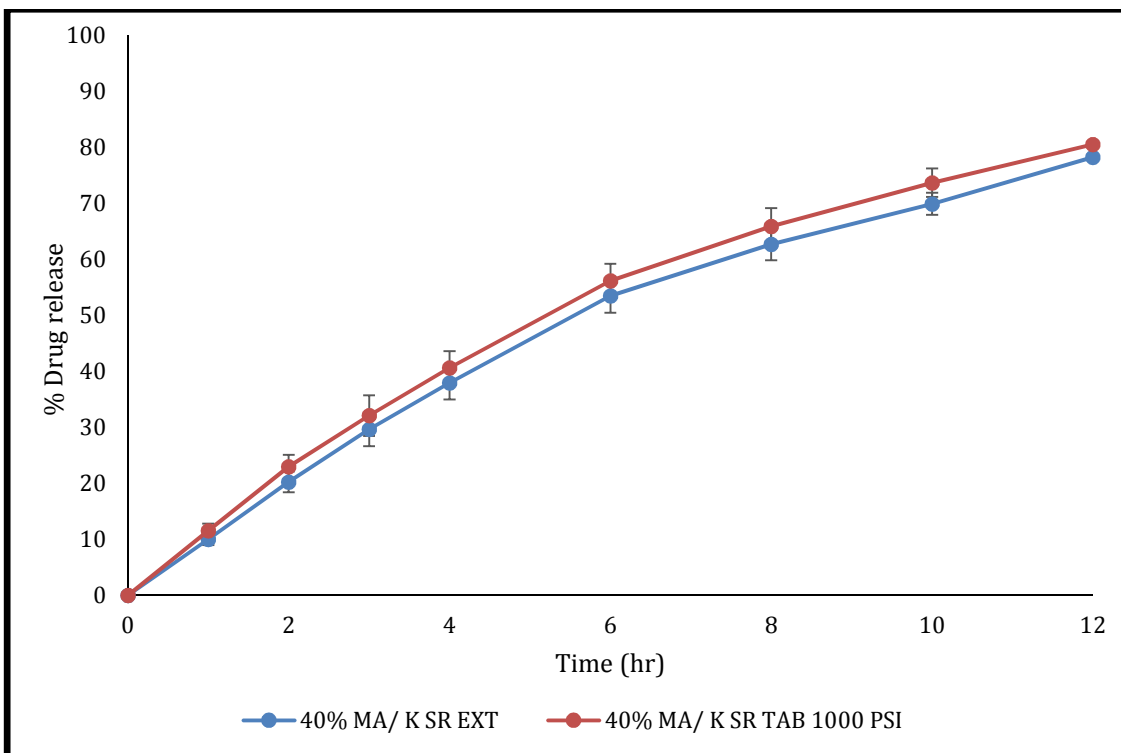


Fig. 4-8: *In vitro* dissolution profiles of 40% MA/ K SR extrudate and tablet in buffer (pH 7.4).

4.3.6. Determination of drug release kinetics:

In order to understand the release mechanism of MA from various formulations, the dissolution profiles were plotted according to several kinetic equations such as zero-order, first-order, Higuchi and Korsmeyer-Peppas. The regression coefficient values of various release kinetic equations for all performed formulations were compared as shown in Table 4-2.

Table 4-2 clearly indicates that all formulations did not follow zero order patterns. However, 20% and 40% drug loads of extrudates and tablets showed high linearity of first order release with regression values of 0.9987, 0.9982, and 0.9915, respectively which indicates that the drug release is highly governed by the diffusion process. To confirm the diffusion mechanism, data were plotted in the Korsmeyer–Peppas equation. The release exponent (n) found for these formulations were more than 0.5 (0.81, 0.89, and 0.84), which indicates that the combined effect of diffusion and erosion mechanisms for the drug release. Thus the drug release was controlled by both diffusion and erosion processes.

Table 4-2: Mathematical modeling and release kinetics of MA from the prepared formulations:

Formulations	Zero order plots (R^2)	First order plots (R^2)	Higuchi plots (R^2)	Korsmeyer-Peppas plots	
				Correlation coeff. (R^2)	Diffetional exponent (n)
20% MA/60% K SR EXT	0.9831	0.9987	0.9666	0.9964	0.81
40% MA/60% K SR EXT	0.9964	0.9982	0.9705	0.9963	0.89
60% MA/60% K SR EXT	0.7174	0.9471	0.9278	0.9986	0.3
80% MA/60% K SR EXT	0.7036	0.8548	0.9178	0.94574	0.41
40% MA/60% K SR EXT PM	0.5148	0.9858	0.7901	0.98905	0.33
40% MA/60% K SR TAB	0.9578	0.9915	0.9763	0.9937	0.84

4.4. Conclusion

TGA thermograms confirmed that the pure drug and the physical mixture are thermally stable during the extrusion processing temperature. DSC data showed that MA was completely transformed to an amorphous form within the polymer matrix up to 40% drug loading, as its endothermic peak at 230 °C was completely absent. All of the extruded blends and tablets

showed excellent drug content and content uniformity (98%-102%) after processing by hot-melt extrusion, thus exhibiting a robust process and product outcome. The formation of intermolecular interaction between the drug and the carrier were confirmed by FT-IR. Sustained release formulations with an exceptional tablet characteristic of this API can be produced by hot-melt extrusion processing using Kollidon[®] SR as a polymeric carrier. Kollidon[®] SR exhibited superior flowability and compressibility as well as excellent hardness and friability. The drug release of MA was further retarded by increasing the concentration of this polymer, which indicates Kollidon[®] SR has a significant effect on MA sustained release formulations.

CHAPTER 5

SUMMARY AND CONCLUSIONS

2- Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology:

- Mefenamic acid was successfully extruded with the different ratios of Eudragit[®] E PO using hot melt extrusion technology.
- The optimized formulations produced very promising solid dispersions for both taste masking and solubility enhancement.
- The dissolution rate of MA was improved with the increase in the concentrations of Eudragit[®] E PO, indicating that Eudragit[®] E PO is playing an important role in the solubilization of this high melting point, poorly soluble drug.
- The mechanism of solubility enhancement was investigated using multiple methodologies, including TGA, DSC, PXRD, SEM and FT-IR.
- Mefenamic acid ODTs were successfully produced using HME solid dispersion techniques demonstrating short disintegration times, sufficient taste masking and high drug release profiles.

3- Investigations of the combined effect of MgO and PEG on the release profile of Mefenamic acid prepared via hot melt extrusion technique:

- DSC revealed that the MA was completely miscible up to 20% w/w drug load extrudate.
- PXRD confirmed that the drug was in an amorphous form after extrusion.
- The formation of post-extrusion hydrogen bonds is strongly indicated between MA and the K-Series (12 and 17) PVP polymers.
- Different grades of Kollidon[®] had an effect on the solubility of MA by transforming the drug crystals into an amorphous form to form a solid dispersion system.
- Adding an alkalizer to the formulation has a marked positive effect on its dissolution rate by increasing the pH_M to almost 9 and alkalizing the surrounding area.
- Incorporating PEG 3350 into the formulations significantly increased media uptake, owing to the wettability and dispersability effect of PEG.
- Kollidon[®] is a promising carrier with which to produce solid dispersion formulations by hot melt extrusion for poorly water-soluble drugs. Furthermore, the addition of an alkalizer with a plasticizer to the formulation had significant influence on the release of this API from the Kollidon[®] matrices.

4- Formulation and Evaluation of Mefenamic Acid Sustained Release Tablets Containing Kollidon[®] SR via Hot-Melt Extrusion Technology:

- TGA thermograms confirmed that the pure drug and the physical mixture are thermally stable during the extrusion processing temperature.
- DSC data showed that MA was completely transformed to an amorphous form within the polymer matrix up to 40% drug loading, as its endothermic peak at 230 °C was completely absent.
- All of the extruded blends and tablets showed excellent drug content and content

uniformity (98%-102%) after processing by hot-melt extrusion, thus exhibiting a robust process and product outcome.

- Sustained release formulations with an exceptional tablet characteristic of this API can be produced by hot-melt extrusion processing using Kollidon® SR as a polymeric carrier.
- Kollidon® SR exhibited superior flowability and compressibility as well as excellent hardness and friability.
- The drug release of MA was further retarded by increasing the concentration of this polymer, which indicates Kollidon® SR has a significant effect on MA sustained release formulations.

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VITA

Sultan Mohammad Alshehri, proud son of Mrs. Thnowa Alshehri and Mr. Mohammad Alshehri, was born in Riyadh, Saudi Arabia on October 3, 1985. He attended the School of Pharmacy at King Saud University, Riyadh, Saudi Arabia, and received his Bachelor's degree in 2009, and since that time he has been a registered pharmacist with The Saudi Commission for Health Specialties. Immediately after graduation, he was chosen for the faculty of the Department of Pharmaceutics in the School of Pharmacy at King Saud University, and awarded a full scholarship to get his Ph.D. degree in the United States of America. In 2010, Mr. Alshehri was accepted into the Ph.D. program of Pharmaceutical Science with an emphasis on Pharmaceutics and Drug Delivery at the University of Mississippi, which is the one of the best programs in the US. He is an active member of the American Association of Pharmaceutical sciences (AAPS). His work has been presented at national as well as international conferences. He received his Doctor of Philosophy in Pharmaceutical Sciences in December of 2015 under the supervision of Dr. Michael A. Repka.