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ABSTRACT

BATCH FOAMING OF HOT MELT EXTRUDED EXCIPIENT/ DISINTEGRANT/ API PHARMACEUTICAL FORMULATIONS AND THE STUDY OF THE EFFECTS OF THE RESULTING CELLULAR STRUCTURES ON API DISSOLUTION

by
Na Yao

This thesis focuses on the impact of a disintegrant included in a foamed immediate release system composed of a polymer excipient and an Active Pharmaceutical Ingredient (API). Indomethacin (INM) is used as model API; Eudragit® EPO (EPO) is used as polymer excipient; AcDiSol and Crospovidone (Cros) are used as two kinds of disintegrant. The main objectives are to gain an understanding of the resulting morphologies, as well as the impact of disintegrants on drug release from foamed polymeric matrices.

In the first part of this research, the Hot Melt Extrusion (HME) process is used to compound the following pharmaceutical formulations: EPO/AcDiSol/INM and EPO/Cros/INM containing different percentages of disintegrant. Comprehensive characterization of this system carried out by Hot-stage Polarized Optical Microscopy (HPOM), Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) shows that in all HME-prepared samples the API is in amorphous form in the polymer excipients, strongly suggesting that the extrudates are solid solutions of INM in EPO. In addition, the DSC results show that the disintegrant is stable in the set temperature range except for the moisture loss. Significantly, the disintegrants, as found from HPOM images, are intact after both HME and batch foaming processing.

In the second part of this research, a batch foaming process is carried out on the milled hot melt extrudated formulations. Scanning Electron Microscopy (SEM) is used to

characterize the resulting cellular structure. The SEM images show that the disintegrants are encaged or embedded in the polymer matrix, which indicates that the polymer and disintegrant are compatible to each other.

In the third part of this research, release profiles of INM are obtained using the dissolution test with the United States Pharmacopeia (USP) Apparatus II (paddle). The concentration of API is determined through an UV absorbance calibration curve. The result strongly indicates that both disintegrants do accelerate the disintegration. In conclusion, the addition of disintegrant in the HME process formulation, which embeds it in the polymer matrix, is a valid method to increase the release rate of the resulting oral dosage extrudate.

BATCH FOAMING OF HOT MELT EXTRUDED EXCIPIENT/ DISINTEGRANT/ API PHARMACEUTICAL FORMULATIONS AND THE STUDY OF THE EFFECTS OF THE RESULTING CELLULAR STRUCTURES ON API DISSOLUTION

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谨以此硕士论文， 献给我亲爱的家人

For my dear family

My grandmother Ruilan Wang (王瑞兰)

My parents Shufan Yong and Hengxiao Yao (雍淑范和姚恒孝)

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CHAPTER 1

INTRODUCTION

The Hot Melt Extrusion (HME) process is currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts (Breitenbach, 2002). A large number of new drugs are poorly water-soluble and their bioavailability can be improved by mixing them with and dissolving them in water-soluble polymers. One way of achieving this is through the use of HME. Meanwhile HME, which is a continuous process, ensures very good manufacturing control and reproducibility. The limited number of processing steps, the absence of use of solvents, and short HME processing residence times, the reduction in labor force lead to a higher economic efficiency (Almeida et al., 2012). The extrudate is air-cooled and ground into fine particulates, which is used most often for pharmaceutical oral dosage form products.

A disintegrant is a substance, or a mixture of substances, added to an oral dosage form to facilitate its break-up or disintegration after oral administration. Chaudhary et al. have studied the phenomena involved using potato starch (disintegrant) and microcrystalline cellulose (excipient) formulations. Higher dissolution rates were observed in tablets with the disintegrant, as compared to the dissolution rate of conventional tablets (Chaudhary et al., 1992).

It has to be mentioned that one of the disadvantages of HME extrudates is that they are less porous extrudate, which may hinder the body fluid, penetrating into the pills or tablets. Hence, some strategies are needed to create pathways inside pills or tablets. Foam

is a material that possesses a closed-cell porous structure with a gas phase dispersed inside. Polymer foams can be found everywhere in modern life and are widely used such as disposable packaging of fast food, insulation material and the cushioning of furniture. Polymeric foams are technologically attractive as well, because they have low cost per volume when compared to un-foamed materials, but also because they have good thermal and acoustic insulation properties and cushioning ability (Sauceau et al., 2011). The first polymer foams made can be dated back in 1931.

In pharmaceutical oral dosages *in vitro* and *in vivo* drug release studies showed that, when biodegradable porous starch (disintegrant) foam was used as a carrier, it allowed immediate release of lovastatin (API) and accelerated the dissolution rate in comparison with crystalline lovastatin and commercial capsules (Wu et al., 2010).

As stated above, disintegrant addition and foaming can be separately used to accelerate the drug release rate. Nevertheless, the combination of the two in a pharmaceutical formulation has not been studied to date.

In this thesis, the main objective is to study the possible enhancement of drug release rate after foaming the HME-prepared API/polymer/disintegrant formulation. HME is a solvent- free continuous process and it may lead to fewer processing steps compared with the traditional drug production process (Liu, 2010).

CHAPTER 2

BACKGROUND

2.1 Oral Dosage Formulation

There are several methods of pharmaceutical product administration, such as oral, sublingual, rectal, intramuscular and intravenous. Among all these, oral administration is the most widely used way. It is generally the least risky and has the fewest negative effects. Tablets and pills are most popular among all dosage forms existing today because of their convenience of self-administration, compactness and easy manufacturing.

2.2 Disintegrants

A disintegrant is a substance or a mixture of substances added to a drug formulation to facilitate its break-up or disintegration into smaller particles after administration, thereby increasing the available surface area and promoting a more rapid release of API. A pharmaceutical tablet dissolves more rapidly than in the absence of disintegrants (Wade, et al., 1994; Alesandro, et al., 2001).

Chitosan has been employed as an excipient in the pharmaceutical industry as a tablet disintegrant. Hou et al. found that granules, formed from chitosan and indomethacin, release the drug faster at pH 7.5 after exposure to acid stomach pH, than if the granules had not been exposed to the low pH. It was thought the reason was the chitosan swelling and gel formation at this low pH (Hou et al. 1985; Illum, 1998).

Gul and Zhu studied the potential of Carbopol® 974P-NF as matrix material in hydrophilic matrix tablets containing a slightly water-soluble drug, ibuprofen (IBF).

The IBF-Carbopol® 974P tablets containing microcrystalline cellulose, as co-excipient, exhibited faster release rates at extended dissolution time periods, as compared to the same type of formulations with respective drug-to-polymer ratios but without microcrystalline cellulose, as well as those containing lactose. The faster release rates and shorter dissolution time observed with microcrystalline cellulose is due to its inherent disintegrant properties, immediate disintegration of the tablets in the dissolution medium, and quick release of the drug from the matrix tablets (Gul and Zhu, 1998).

2.2.1 The Mechanisms of Action of Disintegrants

There are five major mechanisms of the action of disintegrants. They are: (a) swelling, (b) porosity and capillary action (wicking), (c) deformation, (d) repulsion and (e) a combination of any of the above.

Swelling is perhaps the most widely accepted general mechanism of disintegration. By contacting water, the adhesive forces between the other ingredients in a tablet is overcome, causing the tablet to fall apart (disintegrate), as is shown in Figure 2.1.

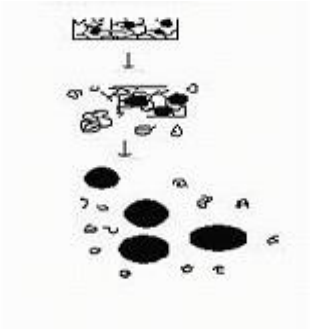


Figure 2.1 The mechanism of swelling causing disintegration.
Source: Kaur, et al., 2011.

Swelling is schematically depicted in Figure 2.1. Particles swell and break up the matrix from within, because of the localized stresses, which spread throughout the whole matrix.

Wicking is another major mechanism of the disintegrant action. When tablets are placed into a suitable aqueous medium, the medium penetrates into the tablet through the pathways provided by the porosity, and replaces the air adsorbed on the particles. As a result, the intermolecular bonds are weakened causing disintegration of the tablet into fine particles. This process is shown schematically in Figure 2.2.

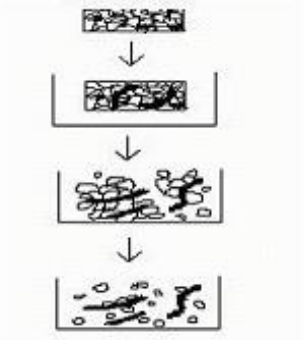


Figure 2.2 The wicking mechanism of disintegration of compressed particulate tablets.
Source: Kaur, et al., 2011.

During tablet manufacture, disintegrated particles are deformed and these deformed particles recover to their normal structure when they are exposed to aqueous media or water. Particles swell to pre-compression size and break up the matrix, which is shown schematically in Figure 2.3.

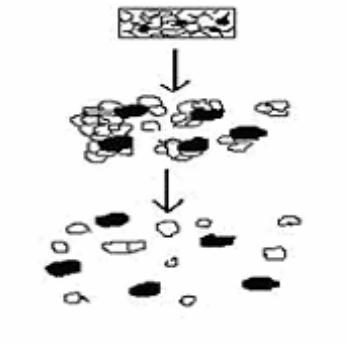


Figure 2.3 The deformation mechanism of tablet disintegration.
Source: Kaur, et al., 2011.

Another mechanism for disintegration has been proposed by Guyot-Hermann. It is based on a particle repulsion theory from experimental observations that non-swelling particles also cause disintegration of tablets. The electric repulsive forces between particles provide the mechanism of disintegration and water is required for it. Figure 2.4 describes, again schematically, this kind of mechanism.

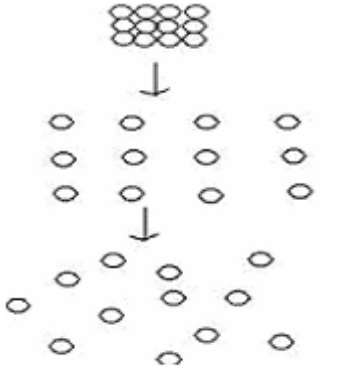


Figure 2.4 The disintegration mechanism of repulsion.
Source: Kaur, et al., 2011.

Besides these four major mechanisms, phenomena such as enzymatic reaction, release of gases, and air expansion facilitate the disintegration.

2.3 Hot Melt Extrusion (HME)

HME is a solvent-free continuous process and it may bring about fewer processing steps (blending, melting, extrusion and shaping in a single-step process) compared with the traditional drug production process (Liu, 2010). Meanwhile, the shorter residence time (maximum of no more than 3-4 minutes) and the reduction in labor force (a higher automation during the process) lead to a promising development in pharmaceutical industrial area (Almeida et al., 2012).

One main potential danger of HME is thermal degradation of the API during its exposure to the elevated processing temperatures during HME processing. Ways of avoiding or eliminating the thermal degradation of the API include changes in the configuration of the equipment (screw configuration, twin-screw extruder) or the addition of plasticizer, both of which can reduce the needed processing temperature. A plasticizer is a polymer additive that serves to increase the polymer's flexibility, elongation or ease of processing. In general, the addition of plasticizer can take the space among the polymer chain, preventing the interactions among chains. The inter-molecular forces between chains are reduced and hence the mobility of polymer chain can be increased, resulting in reduced melt viscosities. Namely, they lower the glass transition temperature during the polymer, which reduces the processing temperature of HME (Almeida et al., 2012).

One of the challenges of the HME process is that the extrudates have no porosity. This may hinder the penetration of gastrointestinal fluids into the tablets or pills (Andrews, Abu-Diak et al. 2010). Therefore, some practical and functional means are needed to increase the porosity of the extrudates, such as foaming, in order to increase the penetration of gastrointestinal fluids.

2.3.1 Active Pharmaceutical Ingredients (APIs)

A very important purpose of drug manufacture is to maximize the therapeutic effect of the Active Pharmaceutical Ingredients (APIs), by making them bio-available, while making their administration convenient to patients. Most of drugs are in crystalline powders, resulting in physical and chemical stability, as compared with the amorphous form. Clearly, for patients, the desirable state is amorphous, which is can be dissolved more readily.

In most cases, formulating crystalline drugs via HME changes their API's morphology from crystalline state to amorphous state, thus increasing solubility in GI fluids (Liu, 2010; Terife et al., 2012; Quinten, 2010).

2.3.2 Bioavailability Improvement

According to the Biopharmaceutics Classification System (BCS) made by U.S. Food and Drug Administration (FDA), drug substances are classified as follows:

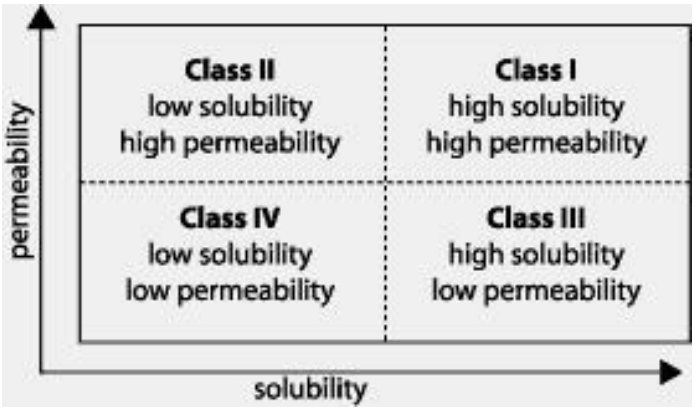


Figure 2.5 The four classes of API compounds according to BCS.

Products in Class I are with ideal properties for oral administration, possessing both high solubility in water and permeability through the enteric tissue into the blood stream.

However, for the drugs in Class II, couples of technologies (including HME) have been proposed and are being developed to improve their low solubility, thus making them bioavailable APIs. For instance, the dissolution rate can be increased by increasing the surface area, which can be achieved through decreasing the particle sizes down to the Nano-scale. Pro-drug strategies are typically used for drug in Class III. The development of Class IV oral dosages is difficult if not impossible (Almeida et al., 2012).

For low solubility and high permeability (Class II) drug, such as indomethacin, the rate of oral absorption is usually controlled by the dissolution rate in the gastrointestinal tract (Nokhodchi, 2005). Therefore, the permeability, the solubility and the dissolution behavior of a drug are key determinants of its oral bioavailability.

2.4 Foaming

There are two major foaming methodologies in the polymeric foam industry: soluble foaming (physical foaming) and chemical (reactive foaming) foaming. The former is related to physical variation in polymer matrix while the latter is caused by chemical reaction. In another words, physical foaming happens when dissolved gas under high pressure forms nucleating cells upon depressurization into the polymer matrix followed by cell growth; chemical blowing agents disintegrate because of chemical instability at processing temperatures causing cell nucleation and growth in the polymer matrix (Lee et al., 2004).

Hile et al. studies on a method for the production of micro-porous poly (D, L-lactide-co-glycolide) foams containing encapsulated proteins using supercritical carbon dioxide. The release and activity of basic fibroblast growth factor from these foams was

determined in vitro and compared with similar porous scaffolds prepared by traditional solvent casting–salt leaching techniques. Total protein release rate was greater from structures made in CO_2 than those made by the salt leaching technique (Hile et al., 2000).

2.4.1 Polymer Foaming

Foam cellular structures result in a substance where air or gas cells are trapped in very small and dispersed phase inside a solid. Polymers, especially thermoplastic polymers possess the material uniqueness of being foamable, by virtue of their rheological properties in the molten state. When foamed, the polymer matrix is transformed from a single phase of dissolved gas in the melt to a two-phase polymer matrix with dispersed gas, because of lowering of the pressure. When cooled this cellular structure becomes stable. The gaseous regions distributed in the polymeric matrix markedly change the structure, morphology, and properties of polymer (Lee et al., 2004). Highly porous foam structures result in low density, favorable to *in vivo* floating behavior of oral dosage forms (Streubel et al., 2002).

2.4.2 Foaming Caused by Dissolved Gas

Soluble foaming (physical foaming) employs a blowing agent, dissolved into the polymer matrix. A sudden pressure reduction, leads to gas phase nucleation and cell growth, by forcing the gas out of solution (Lee et al., 2004; Lee et al., 2007).

The limit of solubility is the controlling parameter during the process, which is strongly dependent on the processing pressure, temperature and interaction of the gas with the polymer. The Flory-Huggins (F-H) equation is a good guideline to calculate how much gas can be dissolved in the polymer (Lee et al., 2004), which is expressed as:

$$F_m = kT(n_g \ln\phi_g + n_p \ln\phi_p + \chi n_g \phi_p) \quad (2.1)$$

Where-

ΔF_m is the free energy of mixing,

k is the Boltzmann constant, which is a physical constant relating energy at the individual particle level with temperature,

T is the absolute temperature,

n is the molar fraction,

ϕ is the volume fraction,

p is short for polymer,

g is short for gas,

χ is the interaction parameter, which can be calculated by the formula shown below:

$$\chi = 0.3 + V_g / \mathrm{RT}(\delta_p - \delta_g)^2 \quad (2.2)$$

Where-

V_g is the molar volume of gas,

$\mathbf{R}$ is the ideal gas constant,

δ is the solubility parameter.

2.4.3 Solubility of CO_2 in Polymer

Two major factors can influence the solubility and diffusivity of CO_2 in polymers. One is the polymer morphology (crystalline or amorphous, related with free volume), and the other is molecular structure (the interaction between CO_2 and molecular chains) (Davies, 2007). Moreover, the former plays a more vital role in CO_2 solubility (Shah et al., 1993).

2.4.4 The Foaming Mechanism

The foaming mechanism involves two steps, which are illustrated in Figure 2.6. They are: the gas diffusion (step I), governed by gas solubility, the cell nucleation (step II), which can be homogeneous or heterogeneous, and the cell growth and stabilization (step III).

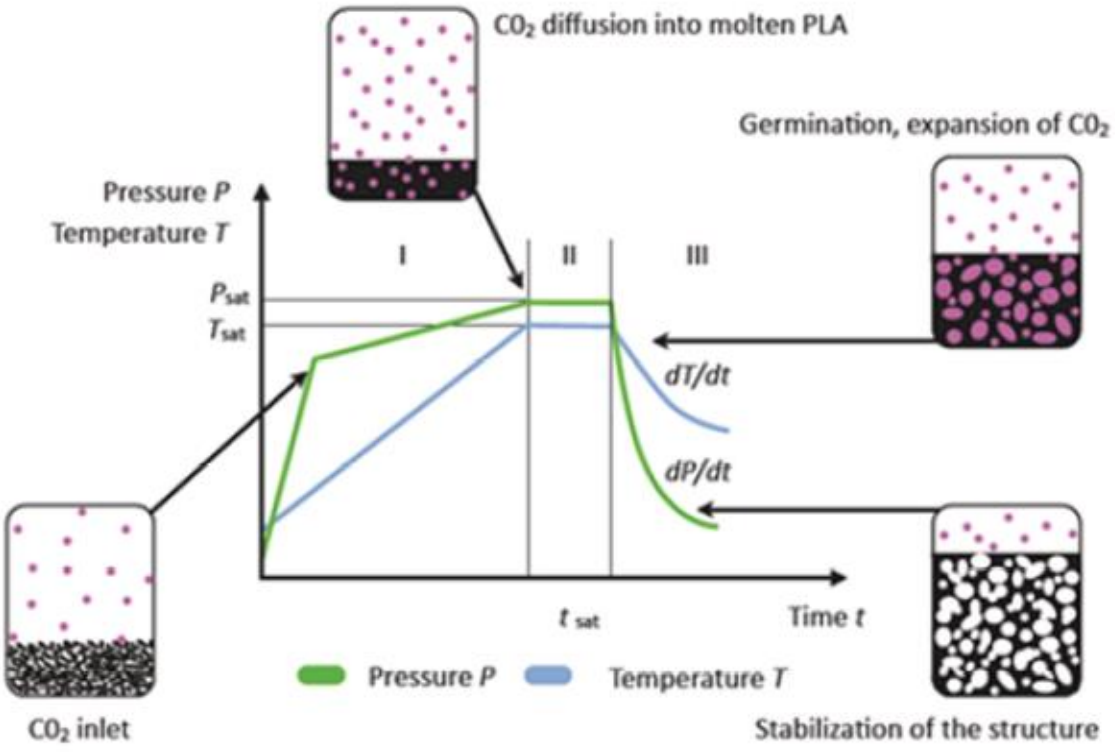


Figure 2.6 Schematic pressure and temperature changes during the foaming process and their effect on the foaming mechanisms.

Source: SustainComp, 2011.

During step I and II in Figure 2.6, the gas is dissolved in the matrix, while both pressure and temperature are increased to reach the desired gas solubility saturation conditions, T_{sat} and P_{sat}. The diffusivity and solubility of the gas, temperature and pressure are the main parameters that control the gas dissolution in the molten polymer. The diffusion time depends not only on the processing temperature and pressure, but on the sample diffusion length (usually the half thickness), as well as the polymer viscosity (Park et al., 1996).

In the saturation state, the whole system is metastable. Every temperature or pressure change will cause another equilibrium state and may possibly lead to a two-phase system. Meanwhile, upon de-pressurization the pressure difference between the interior of a gas-nucleated site and exterior of the pore leads the cell growth. A sudden pressure release or temperature decrease is enough to induce the cell nucleation, which is shown in the step III in Figure 2.6 (SustainComp, 2008).

2.4.5 Nucleation Theory

In nucleation process, a gas cell must overcome the free energy barrier. By increasing the supersaturation of the solution, the activation barrier is lowered, causing a higher rate of nucleation (Tomasko et al., 2009).

Nucleation has generally described by the classical nucleation theory (Laaksonen et al., 1995) which can be applied in polymer foaming. The nucleation rate, J is given by

$$J = J_0 r e^{-W/k_B T} \tag{2.3}$$

Where-

k_B is the Boltzmann factor,

T is the absolute temperature,

J_0 is a kinetically determined constant,

W is the work required to form a critical nucleus, which can be derives from the formally rigorous equation given by Gibbs:

$$W = \frac{16\pi\sigma^3}{3(\Delta P)^2} \tag{2.4}$$

Where-

σ is the surface tension between the metastable polymer mixture and the nucleating phase,

ΔP is the difference between two pressures: one is the nucleation phase if it were in the bulk at the same temperature and chemical potential of the metastable phase; the other is the metastable phase itself.

2.4.6 Cell Growth Processes

The growing cells cause a concentration gradient in the system leading to the gas diffusion out of the polymer solution, which in turn boosts the cell growth (Lee, et al., 2004; Lee et al., 2007).

2.4.7 Foaming Stability

Several conditions are needed to produce foam: there must be mechanical work, surface-active components (surfactants) that reduce the surface tension, and the formation

of foam faster than its breakdown. To create foam, work (W) is needed to create and increase the surface area (ΔA):

The formula

$$W = \gamma * \Delta A \tag{2.5}$$

Where-

W is the mechanical work, and ΔA is the surface area.

ɣ is the surface tension of liquids that gives their surfaces a slightly elastic quality and enables them to form into separate drops. It is caused by the interaction of molecules at or near the surface that tend to cohere and contract the surface into the smallest possible area.

CHAPTER 3

EXPERIMENTS

3.1 Materials

The model API for this study is Indomethacin (INM), whose chemical structure is shown in Figure 3.1. INM is a non-steroidal anti-inflammatory drug. Its melting temperature is 161±0.3 ℃; its glass transition temperature is 46.3±0.1 ℃. The ionizable character of the carboxylic group leads to the solubility of INM in an aqueous solution is pH dependent (Terife et al., 2011).

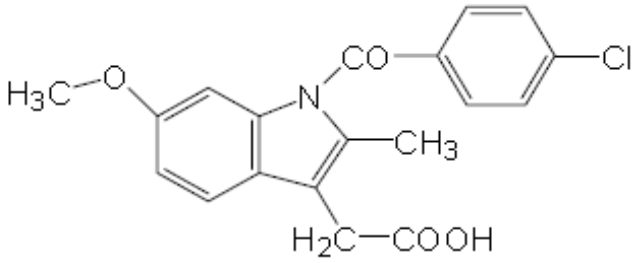


Figure 3.1 Chemical structure of Indomethacin.

Eudragit® EPO (EPO) was chosen as excipient polymer. The chemical structure of the excipient is shown in Figure 3.2. Amorphous EPO is a cationic terpolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It is soluble up to pH=5 and above this pH value, it is only swellable. It is widely employed in the pharmaceutical industry.

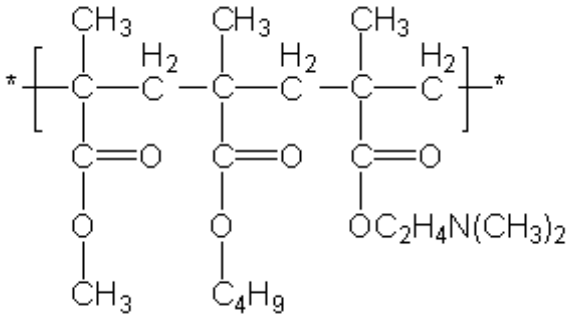
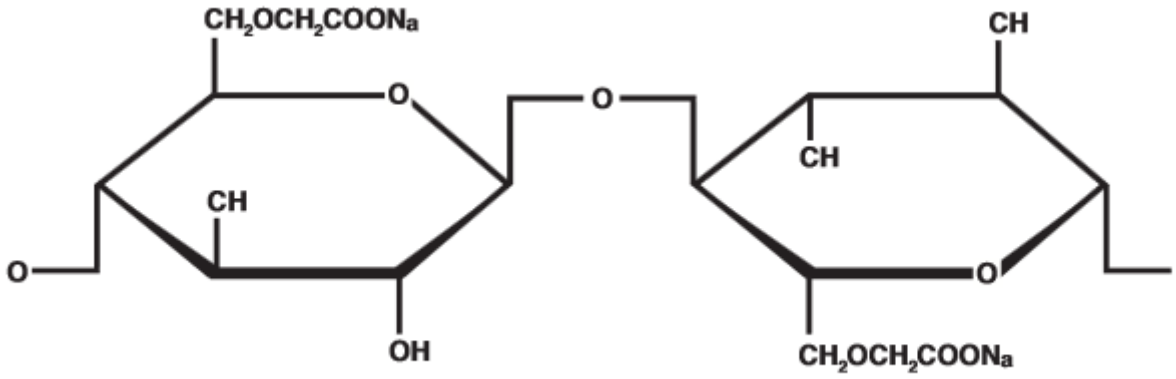
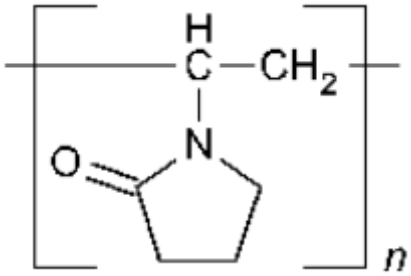


Figure 3.2 Chemical structure of EPO.

Two disintegrants used here were (Ac-Di-Sol) AcDiSol and Crospovidone (Cros). The chemical structures of the two disintegrants are shown in Figures 3.3 (a) (b), respectively. AcDiSol is cross-linked sodium carboxymethylcellullose (CMC). It is a cellulose derivative and it is generally used as a disintegrant. Cros is a cross-linked polyvinylpyrrolidone (PVP), white or yellowish white, and a free-flowing powder practically without odor. Because it is cross-linked, it is insoluble in water, alkali, acid and common solvents. It has good swelling characteristics in water without forming a gel.



(a)



(b)

Figure 3.3 Chemical structures of (a) AcDiSol and (b) Cros.

3.2 Hot Melt Processing

3.2.1 Particulate Premixing

A physical mixture of the INM, EPO and disintegrant was prepared by random distributive mixing at room temperature for 1 hour at 200 rpm at a rolling jar mill (JRM 2"x 24", Paul O. Abbe Inc.). In each formulation of this study, the concentration of INM is 30%. After processing, it is totally dissolved into molten EPO (Liu et al., 2011). Seven formulations (Excipient/Disintegrant/API) were made using this method. They are shown in Table 3.1.

Table 3.1 Composition of the Seven Formulations Extruded

Formulation (#)	Excipient/Disintegrant/API	Composition (%(w/w))
1	EPO/AcDiSol/INM	68/2/30
2	EPO/AcDiSol/INM	64/6/30
3	EPO/AcDiSol/INM	62/8/30
4	EPO/ Cros / INM	68/2/30
5	EPO/ Cros / INM	64/6/30
6	EPO/ Cros / INM	62/8/30
7	EPO/INM	68.3/31.7

The control formulation (#7) is EPO/INM with the ratio is 68.3/31.7, which is the average ratio EPO/INM in each formulation #1-3 (or #4-6).

3.2.2 Hot Melt Extrusion (HME)

In this study, a co-rotating twin-screw extruder, Leistriz's Nano 16, was used to extrude the seven formulations. The two screws are equipped with 30 °forward kneading blocks. The diameter of the screws is 16mm. The barrel consists of four heating zones (three zones and a die) while the temperature in the feeding zone can be controlled externally via a circulation chiller, which is shown in Figure 3.4. Meanwhile the temperature of each zone can be set separately.

Figure 3.4 The Leistriz's Nano 16 Twin-Screw Extruder (the numbers shown in the picture denote the four heated barrel zones).

Each formulation was fed into the extruder using a volumetric feeder (SCHENCK AccuRATE® 102M). Because of flowability and bulk density differences, feeder setting needed for each formulation should be determined separately. The processing conditions for this study are listed in Table 3.2.

Table 3.2 Extrusion Conditions for EPO Solid Solutions

Formulation	Screw Speed (rpm)	Melting Point (℃)	Zone 4 (Die) (℃)	Zone 3 (℃)	Zone 2 (℃)	Zone 1 (℃)	Feeding Zone (℃)	Residence Time (min)	Die Diameter (mm)
EPO solid solutions	300	~138	130	130	130	85	10	<1	3

3.3 Foaming

3.3.1 Sample Preparation

Around 20 g of each extrudate was milled for 2 minutes using a coffee grinder to produce fine powders, which were used for characterization of the extrudates as well as batch foaming process.

3.3.2 Batch Foaming

CO_2 was used as the Physical Blowing Agent (PBA) for this batch foaming process. The temperature and the pressure were 85 ℃ and 2.759 MPa (400 psi), respectively. The dwell time was set for one hour. The experimental setup used is shown schematically in Figure 3.5 (Terife et al., 2012). The mold and the size of pill are shown in Figure 3.6 schematically as well. As it is shown in the Figure 3.6, four pills can be made at the same time. The density of pills is 0.2 g/cm^3, and the volume of each pill is 0.68 cm^3, therefore around 0.136 g powder were placed inside each cavity of mold, which was preheated to 85 ℃. Air in the cavity was removed using vacuum pump for around 5 minutes. The CO_2 was injected into the air-evacuated cavity and the system was pressurized for one hour, allowing the CO_2 to dissolve into the polymer matrix. A sudden decompression of the cavity was then created by opening the release valve to the atmosphere, causing a thermodynamic instability. After that, the mold and the sample were cooled down to 0 ℃ using ice bath and allowed several minutes for the cell structure to be fully stabilized.

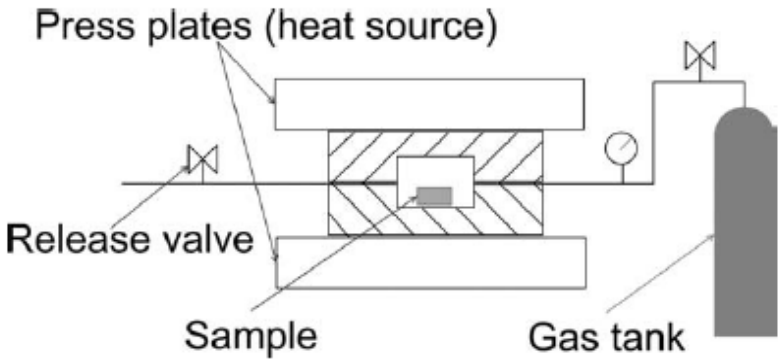


Figure 3.5 Schematic representation of the batch foaming device.

Source: Terife et al., 2012

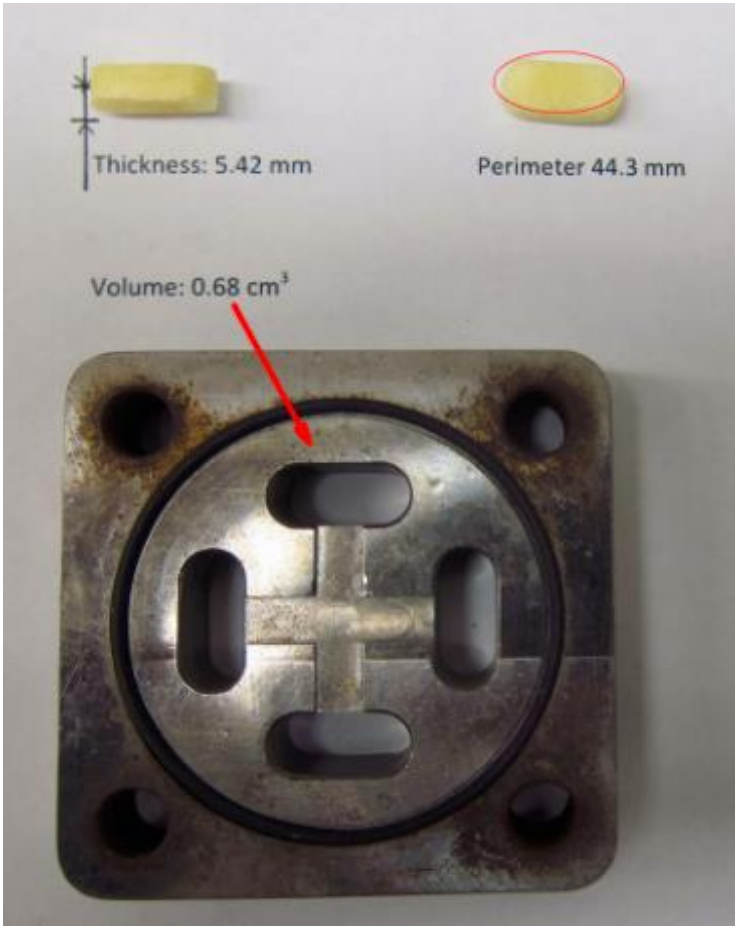


Figure 3.6 Schematic representation of the mold and size of pill.

The study of the cell morphology was carried out using a Leo 1530 Field Emission Scanning Electron Microscope (Carl Zeiss SMT Inc., Peabody, MA). The cross-section of the foamed pills was coated with a thin layer of carbon to enhance its electrical conductivity.

3.4 Characterization

3.4.1 Hot-stage Polarized Optical Microscopy (HPOM)

Optical microscope (Carl Zeiss Universal Research Microscope) was used to evaluate the state of the drug and disintegrant in the polymeric matrix after compounding. The crystalline drug is bright whilst any amorphous material is dark. The Zeiss AxioCam Digital camera has 5MB-pixel resolution. Samples are the powders that were from grinding the extrudates. A temperature ramp was used from 40 ℃ to 180 ℃ at 20 ℃ min^{-1}. Images of the extrudates were captured every 10 ℃ or 30 seconds.

3.4.2 Differential Scanning Calorimetry (DSC)

The thermal transitions during heating of the extrudates were recorded using the DSC Q 100. Samples of raw material, physical mixture and grinded extrudates were accurately weighed and placed in closed aluminum pans. For the extrudates, a temperature ramp from -20 ℃ to 180 ℃ was applied at 20 ℃ min^{-1} heating rate. For the raw materials, a heat-cool-heat cycle from -20 ℃ to 180 ℃ was applied at 20 ℃ min^{-1} heating / 10 ℃ min^{-1} cooling to remove their thermal history. Runs were occasionally performed in duplicate with very good reproducibility. Throughout the study, the chamber of equipment was blanketed with nitrogen at a flow rate of 40 mL/min.

3.4.3 X-Ray Diffraction (XRD)

XRD analysis was carried out in a Philips PW3040 X-Ray diffractometer (Cu Kα radiation, 0.154nm), operated with a power level of 45 KV and 40 mA. It was used to detect the amorphous and crystalline phases of the raw materials and extrudates. Samples were scanned over the 2θ range 5 °-30 ° at step size of 0.02 °/step and scan rate of 1 sec/step.

3.4.4 Scanning Electron Microscopy (SEM)

The morphology of sample was determined by LEO 1530 Field Emission SEM (Carl Zeiss SMT Inc., Peabody, MA). Foamed samples were coated with a thin layer of carbon by sputtering to improve the conductivity using a Bal-Tee Med 020 Sputter Coater.

3.4.5 Dissolution Test

Dissolution test is used by the pharmaceutical industry to characterize the dissolution and release properties of APIs, from a dosage formulation. The release profiles of INM were obtained using a Distek 2100A USP Apparatus II (paddle) (North Brunswick, NJ) in triplicate. The analyses were conducted at 37℃ in 900 mL of pH 1.2 hydrochloric acid buffer solutions. The rotation speed of paddle is 50 rpm. At pre-established time intervals 5 mL samples were withdrawn by syringe from the dissolution medium, filtered through polyvinylidene fluoride (PVDF) filters with pores size of 0.45 μm and then analyzed at 318 nm by a Cole Parmer UV spectroscopy (Cole Parmer Instruments Company, East Hills, IL). The PVDF filters were used here is to confirm the sample, which would be taken the UV test was truly dissolved API, not micellar INM as it was probably blocked during filtration. The concentration of API in the solution was determined through a UV absorbance calibration curve.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Solubility of INM in EPO

One of the objectives of this study is to gain an understanding of the effects of the batch foaming process and cellular structure on the performance of solid solution made from HME. Therefore, it is important to have an understanding of the solubility of INM (API) in the polymer matrix.

The solubility parameters (δ) of EPO and INM are 18.53 $MPa^{1/2}$ and 22.1$MPa^{1/2}$, respectively. The difference in solubility parameters (**Δ**δ) between EPO and INM is 3.57 $MPa^{1/2}$. Greenhalgh et al. (Greenhalgh et al. 1999) proposed that miscible systems have a Δδ between 1.6 and 7.5 $MPa^{1/2}$, which suggests that the system of EPO and INM is a miscible one. Many researchers have proved this conclusion (Greenhalgh et al. 1999; Chokshi et al., 2005; Liu, 2010).

The solubility of INM in EPO was evaluated through Hot-stage Polarized Optical Microscopy (HPOM), Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD).

4.1.1 Hot-stage Polarized Optical Microscopy (HPOM) Result

HPOM was used to directly evaluate the presence of morphology of the milled extrudates following HME with comparison to the formulation of physical mixture. Under the cross-polarizer, amorphous materials appear dark, while crystalline materials appear bright. Of the raw materials used here, EPO and Cros are amorphous whereas INM and AcDiSol are crystalline.

Figure 4.1 and Figures 4.1 (a), (b), (c) showed the morphology evaluation of extrudated and physical mixture EPO/INM/AcDiSol formulations at different hot stage temperature. A temperature ramp was used from 40 ℃ to 180 ℃ at 20 ℃ min^{-1}. Images of the extrudates were captured every 10 ℃ or 30 seconds. Figure 4.1 showed the morphology evolution of physical mixture formulation. In the images, the dissolution of INM in the polymer matrix takes place between 120 ° C and 150 ℃. The onset of disappearance of INM at 120 ℃ suggests that the crystal lattice of INM is disintegrated far below its melting point (162 ℃) (from DSC result), indicating its increased diffusivity in the polymer matrix, due to the decreased viscosity of the polymer, and the formation of strong polymer-drug molecular interactions. After 160 ℃, only intact crystalline AcDiSol can be seen (Figure 4.1) whereas intact Cros is also present but somewhat difficult to detect under the cross-polarizer, as it is amorphous. The morphology evaluation of extrudated and physical mixture EPO/INM/Cros formulations during ramp heating were showed in Appendix A.

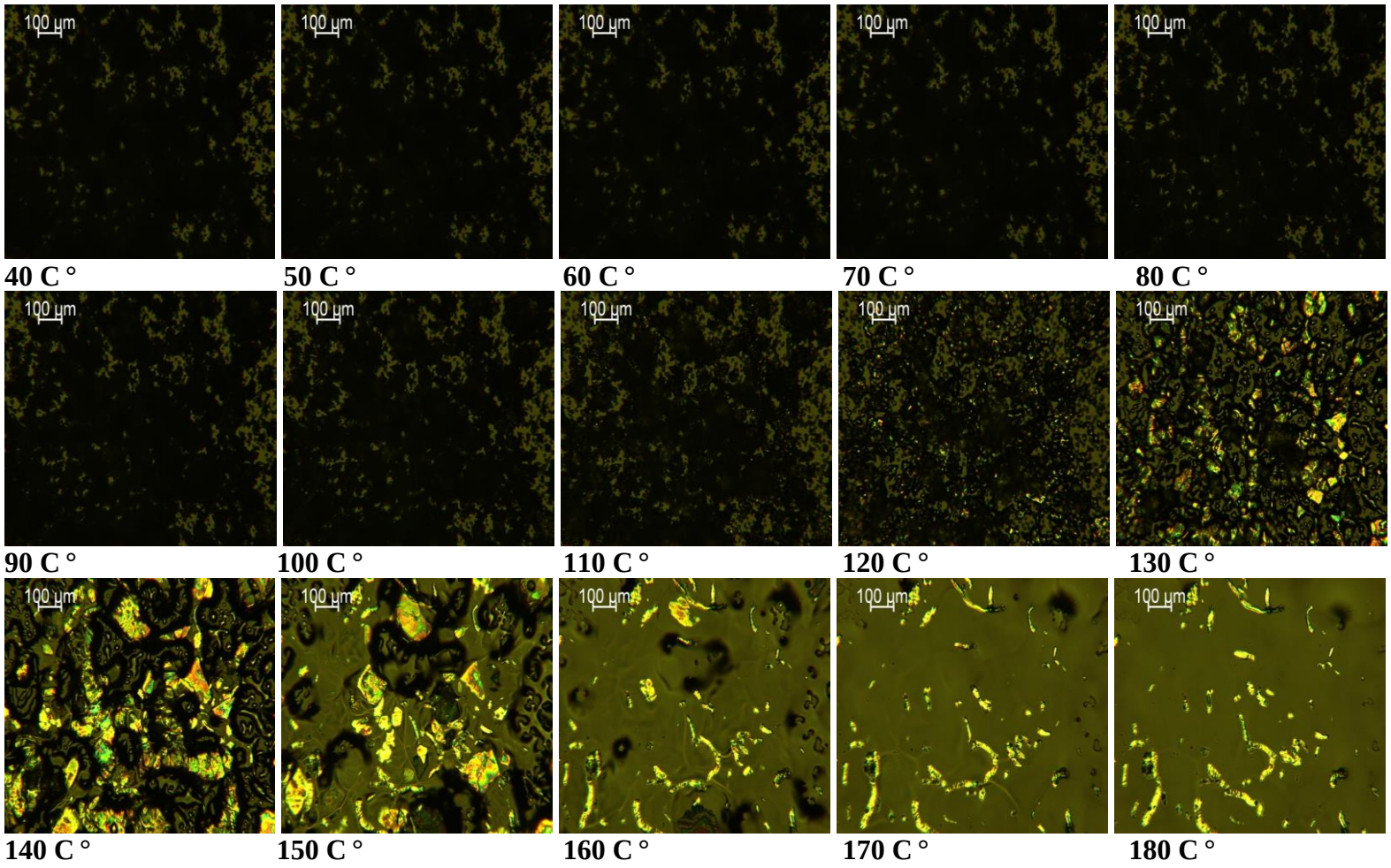


Figure 4.1 Physical mixture: EPO-INM-AcDiSol 66-30-4 @ 20 ℃ min^{-1}.

Contrary to the physical mixture images (Figure 4.1 and Figure A.1), the extrudates (Figures 4.1 (a), (b), (c) and Figures A.1 (a), (b), (c)), showed no evidence of crystalline INM to be present. The only crystalline substance present is AcDiSol (Figures 4.1 (a), (b), (c)) and it remains unchanged during heating of the sample, as it is stable in the range of conditions used here. The above strongly suggest that the extrudates are solid solutions of INM.

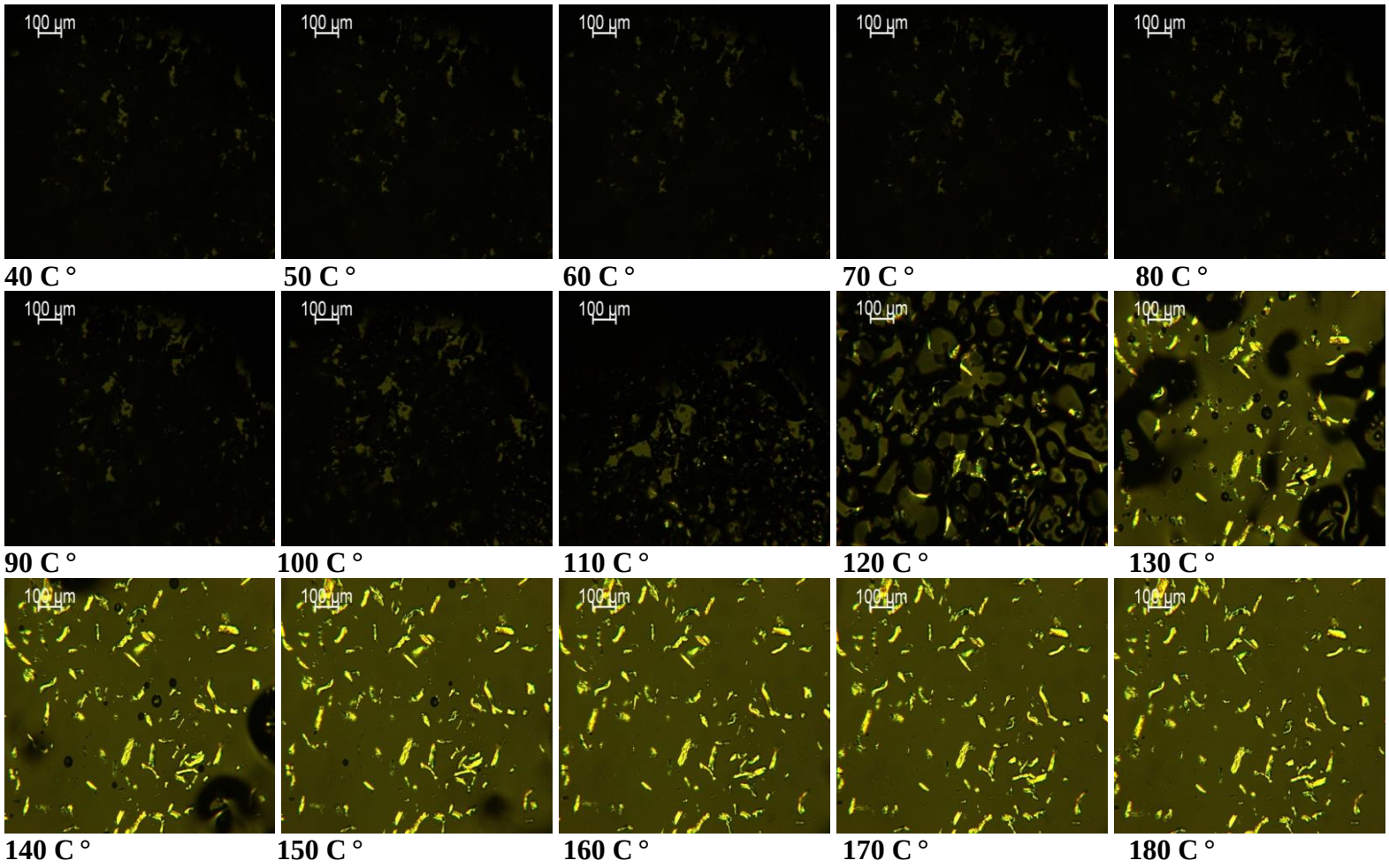


Figure 4.1 (a) Extrudate #1: EPO-INM-AcDiSol 68-30-2@ 20 ℃ min^{-1}.

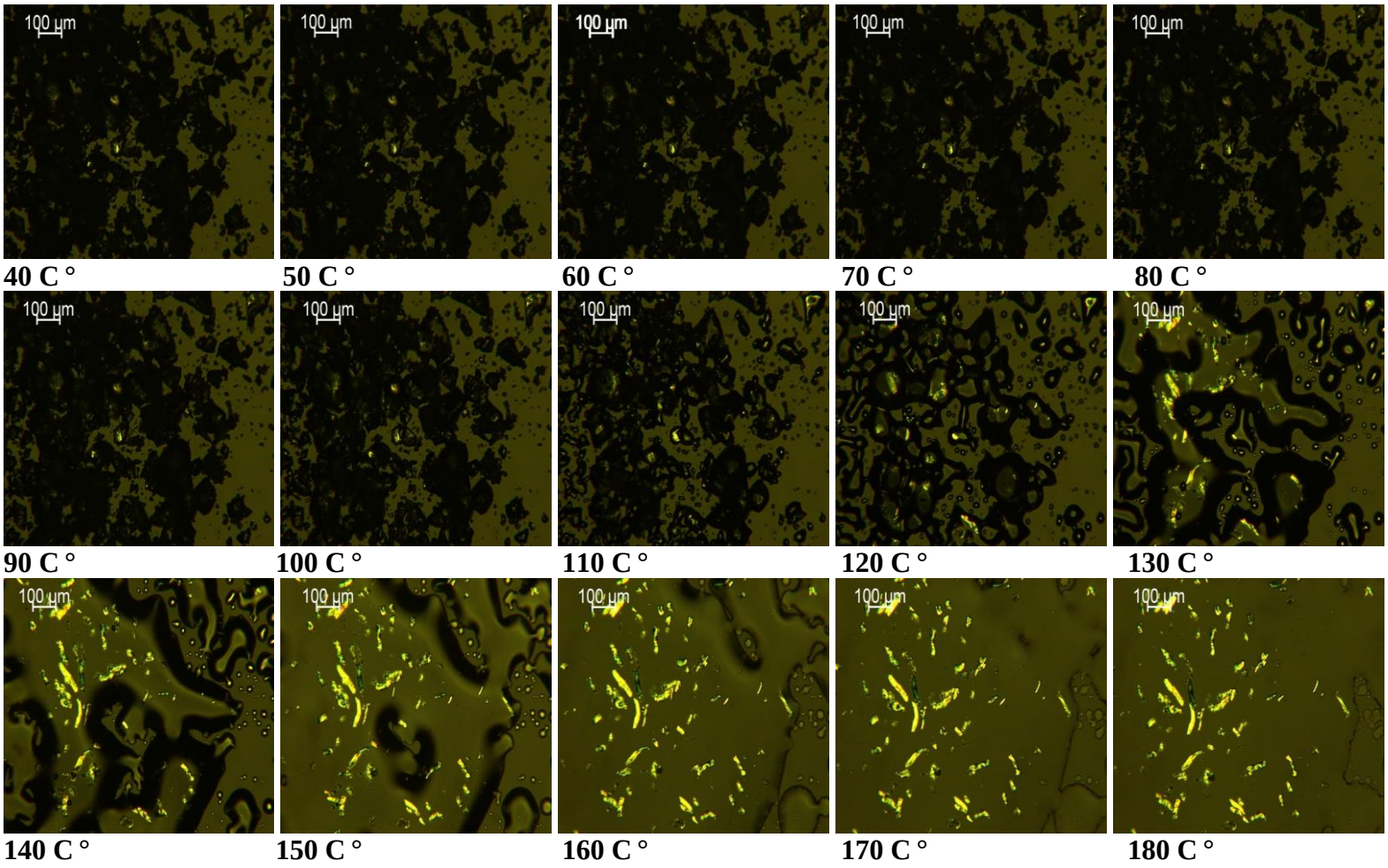


Figure 4.1 (b) Extrudate #2: EPO-INM-AcDiSol 66-30-4@ 20 ℃ min^{-1}.

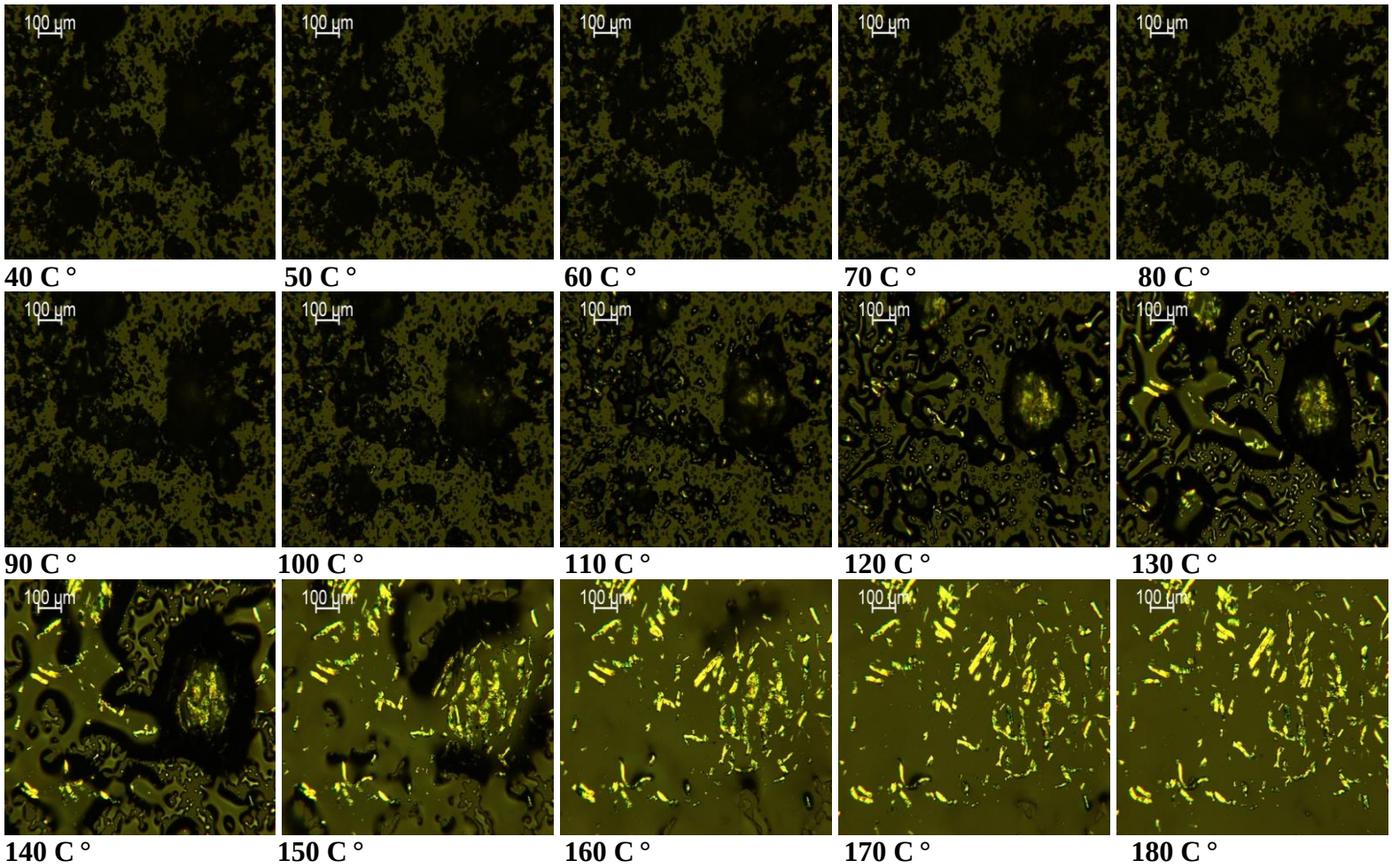
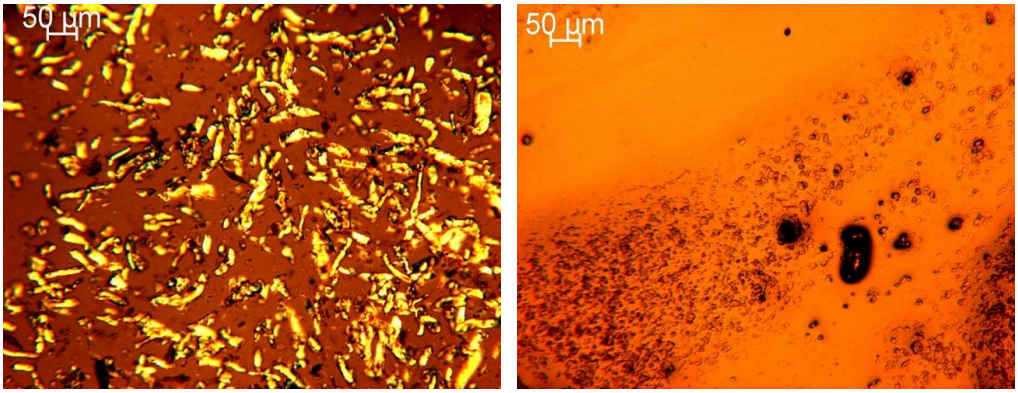


Figure 4.1 (c) Extrudate #3: EPO-INM-AcDiSol 62-30-8@ 20 ℃ min^{-1}.

Figure 4.2 depicted HPOM results of powder from milled foamed EPO/INM/8% disintegrant. The only crystalline substance present in Figure 4.2 (a) were AcDiSol, which were in the same amount compared with Figure 4.1 (c) Extrudate #3, EPO-INM-AcDiSol 62-30-8. The amount of Cros in the Extrudate (Figure A.1 (c)) and Foamed sample (Figure 4.2 (b)) was the same as well but somewhat it was difficult to detect under the cross-polarizer, as it was amorphous.



(a) (b)

Figure 4.2 HPOM results of foamed powder of (a) # 3 EPO/INM/AcDiSol 62/30/8; (b) # 6 EPO/INM/Cros 62/30/8 at 170 ℃.

4.1.2 Thermal Properties

Figures 4.3-4.5 show the thermographs of the raw materials, Physical Mixtures (PM) and Extrudates (EX). For the raw materials, a cyclic scan (heat-cool-heat) was performed whereas for the physical mixtures and extrudates only the first heating is shown. Amorphous EPO shows upon second heating a T_g at around 46.51 ℃ and crystalline INM a shows a T_m at around 162 ℃ and upon second heating a T_g at around 48.61 ℃. These values correlate well with values mentioned in previous research (Chokshi et al., 2005). AcDiSol and Cros upon first heating show a broad endotherm possibly associated with water loss

(Kibbe et al., 2000). However, upon second heating they do not show any characteristic transition, suggesting that, besides moisture loss, they are stable in the temperature range used.

Figure 4.4 shows the heating ramp of EPO/INM/AcDiSol-containing physical mixture and extrudates at 20 ℃ min^{-1}. In the physical mixture thermograph (black trace), there are three endotherms of interest. The first is at around 50 °C, corresponding to EPO's enthalpic relaxation. The second is a broad endotherm ranging from 60 to 110 ℃ corresponding to moisture loss of AcDiSol. The third, the broad endothermic peak ranging from 120 to 165 ℃, is the dissolution/melting of INM in the polymer matrix. The temperature range of this peak is consistent with the dissolution/melting as seen in the HPOM images (Figure 4.1). The thermographs for the three extrudates in Figure 4.4 show the enthalpic relaxation at around 50 ℃, water loss from AcDiSol between 75-125 ℃, however they lack the INM dissolution/melting endotherm between 120 to 165 ℃. This also corresponds with the absence of any INM crystals during the ramp heating of the extrudates using HPOM (Figures 4.1 (a), (b), (c) and Figures A.1 (a), (b), (c)). The same trends were observed for the EPO/Cros-containing formulations (Figures 4.5). The above strongly suggest that all extrudates are solid solutions of INM. Figure 4.5 shows the heating ramp of EPO/INM/Cros-containing physical mixture and extrudates at 20 ℃ min^{-1}, which is similar to Figure 4.5. The PM ramp has one more edotherm of interest compared to the extrudate ramp. That one is the dissolution/ melting of INM in the polymer matrix.

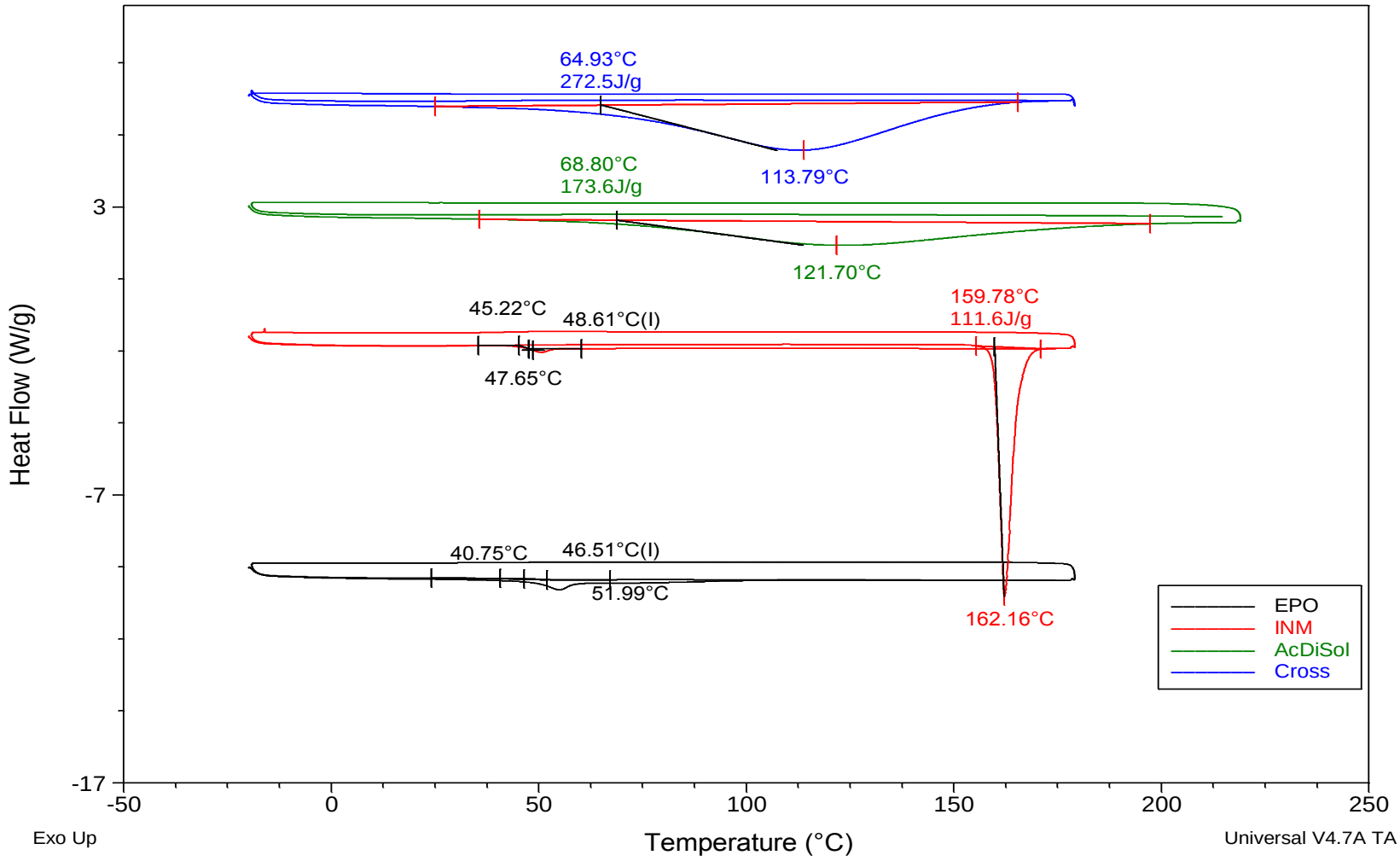


Figure 4.3 DSC heat-cool-heat cycle at 20 ℃ min^{-1} heating / 10 ℃min^{-1} cooling of the raw materials used in this work.

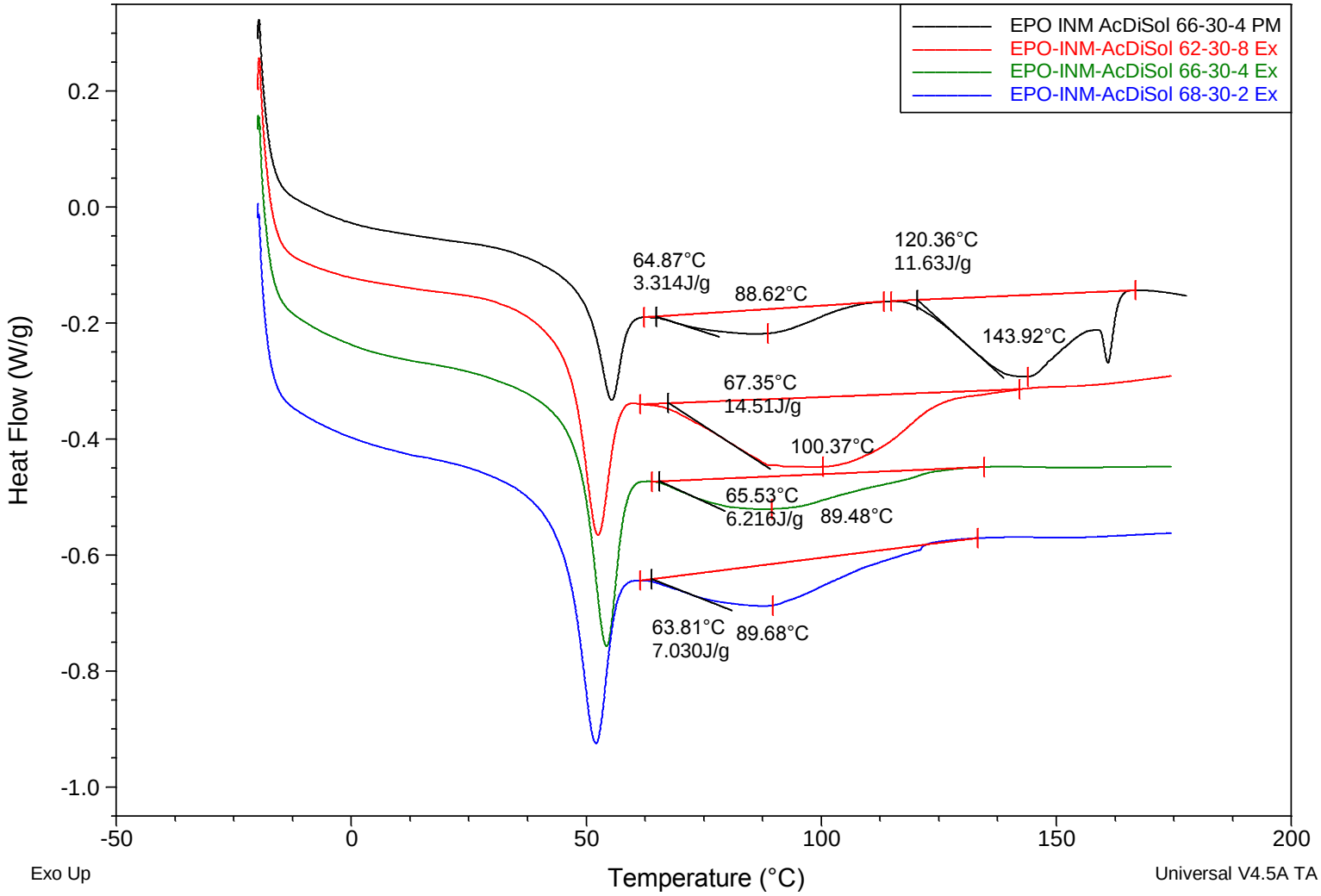


Figure 4.4 DSC temperature ramp of EPO/AcDiSol-containing PM and extrudates at 20 ℃ min^{-1} heating.

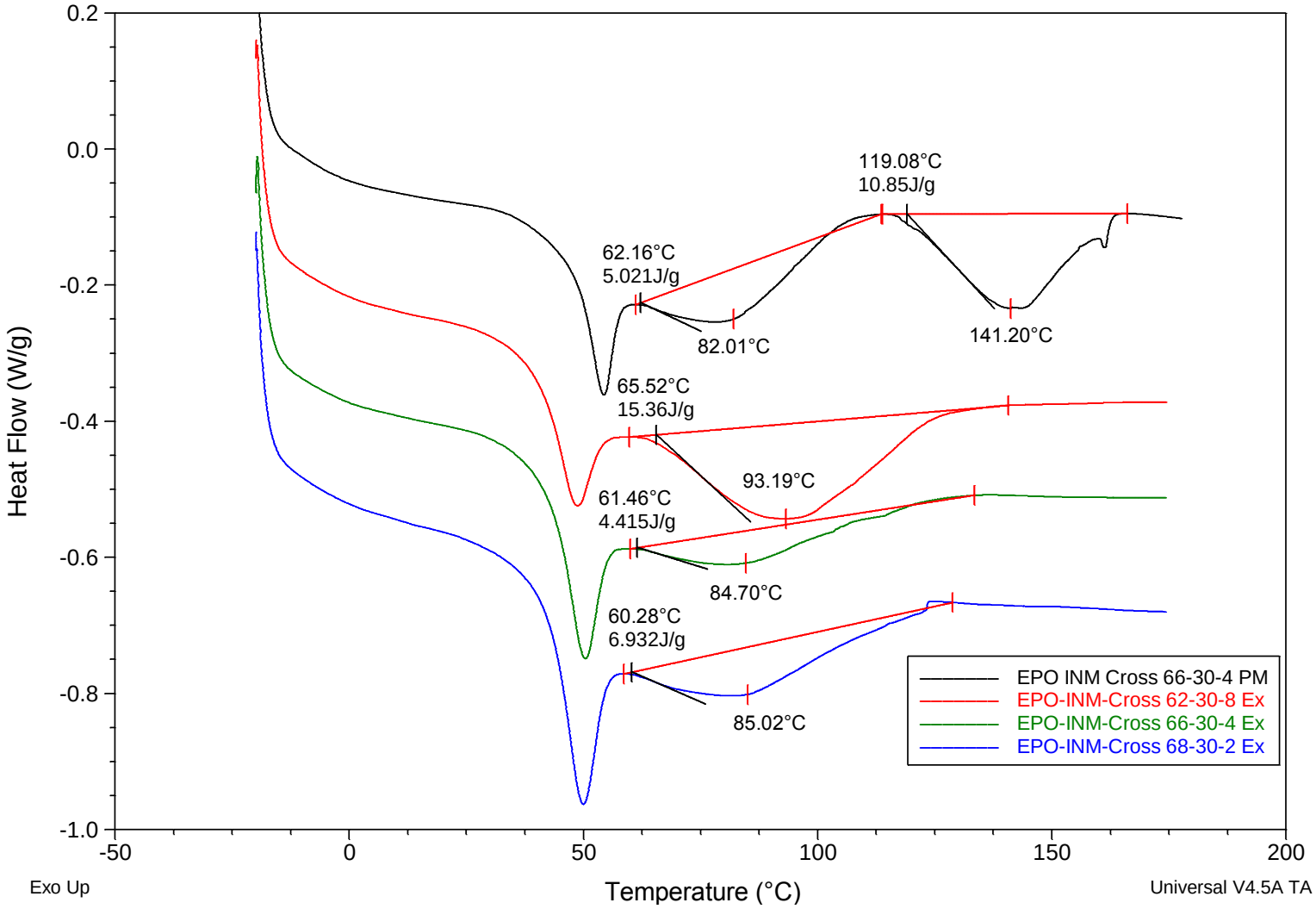


Figure 4.5 DSC temperature ramp of EPO/Cros-containing PM and extrudates at 20 ℃ min^{-1} heating.

4.1.3 XRD Analysis

Figures 4.6-4.7 show the XRD patterns of the raw materials, physical mixtures and extrudates. Fig. 4.12 shows the XRD patterns of raw materials and the EPO/AcDiSol-containing formulations. It can be seen that, the XRD pattern of INM is weaker in intensity in the physical mixture (red tracer) by virtue of dilution of INM by the other two components in the physical mixture. However, in the extrudates, the characteristic peaks of INM are not present, indicating the formation of a solid solution of INM during extrusion. The same trends were observed for the EPO/Cros-containing formulations (Figure 4.7).

Regarding the disintegrants, the amount (2%, 4% and 8% (w/w)) is too low to have a distinct contribution to the XRD patterns of the physical mixture and extrudates.

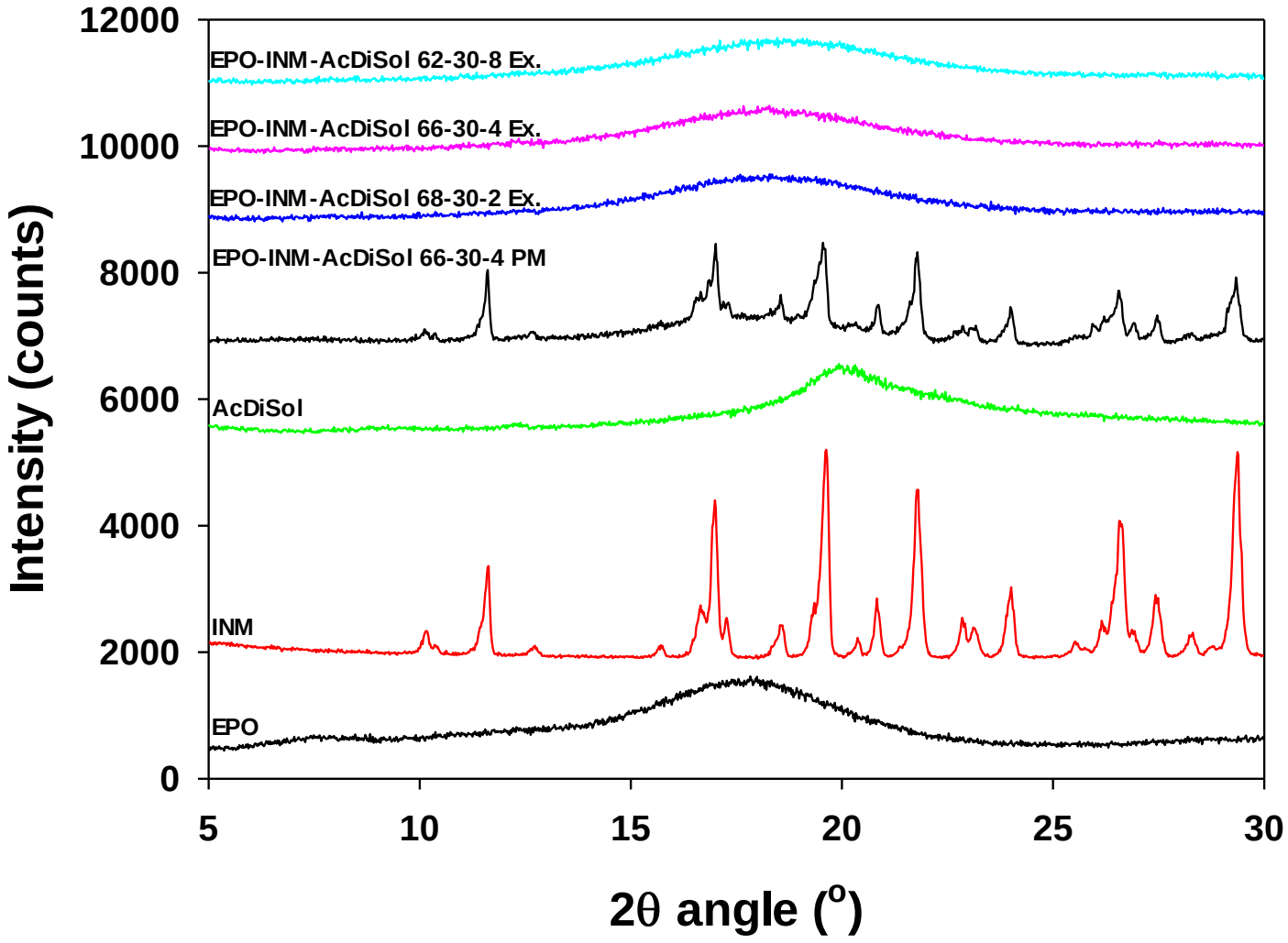


Figure 4.6 XRD of raw materials and EPO/ AcDiSol-containing PM and extrudates.

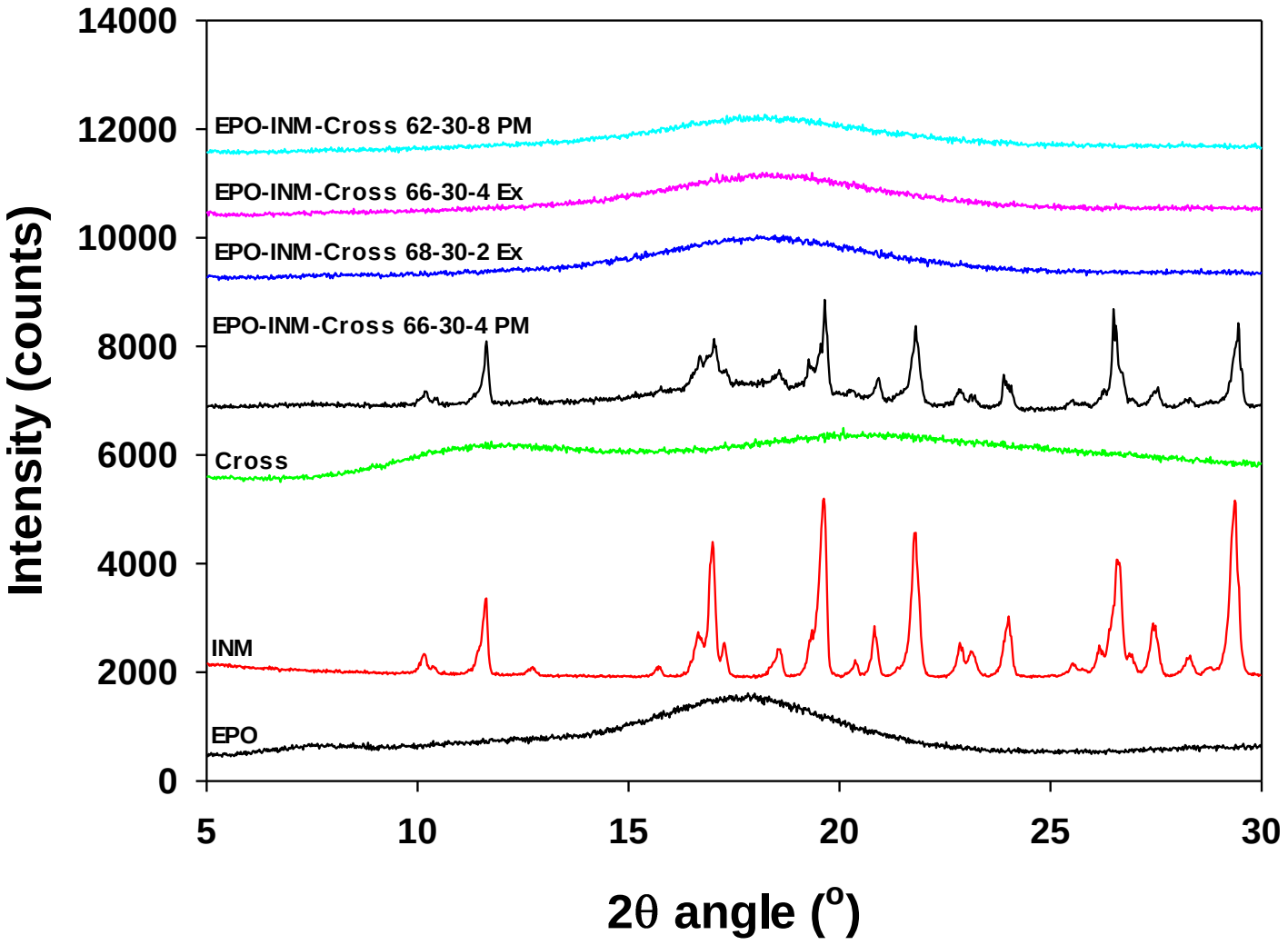


Figure 4.7 XRD of raw materials and EPO/ Cros-containing PM and extrudates.

4.1.4 Summary

With the analyses described above, seven formulations have been produced for evaluation of the intragranular addition of disintegrants during HME. From the hot-melt extrusion point of view, the components that dictate the processing conditions are the amount of polymeric excipient and API, and type of disintegrant in the formulation.

From HPOM images, we were able to follow the dissolution of the drug in the physical mixtures, confirm the absence of any detectable crystals in the solid solution formulations and confirm the stability of the disintegrants in the range 30-180 ℃. After the foaming process, the disintegrant was still intact and INM was still in its amorphous state. In other words, the state of solid solution did not change throughout the foaming process.

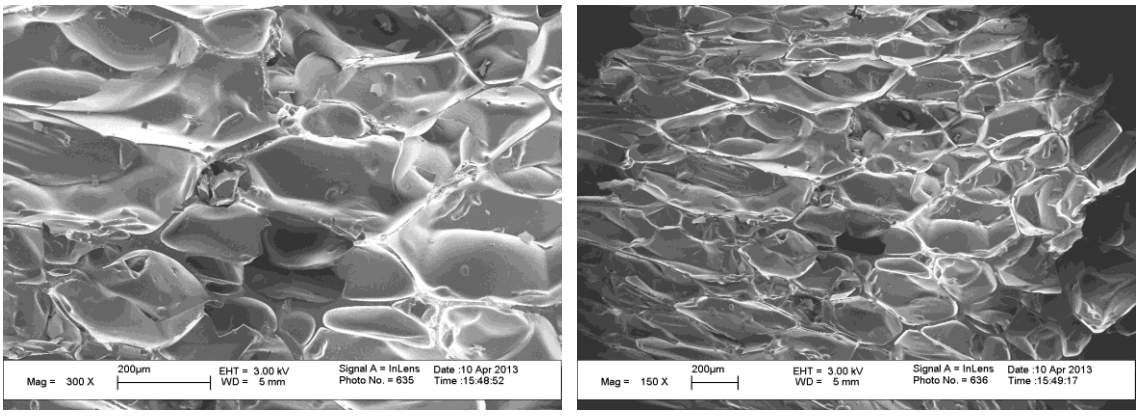
For the solid solution extrudates, DSC showed no dissolution endotherm for INM confirming that the extrudates are solid solutions of INM. DSC on these formulations was also able to detect the remaining moisture of the dissintegrants that was not removed during extrusion.

XRD was able to confirm both the absence and the presence of crystalline drug in the solid solution.

In short, after HME process, the INM was in its amorphous state. Compared with its crystalline state, the dissolution rate is facilitated, as lacking the lattice structure. In other words, for amorphous INM dissolved, there is no need to overcome the lattice energy. Consequently, during the HME process, the morphology of INM changed from crystalline to amorphous state, which is desirable. It has to be mention that the state of solid solution did not change throughout foaming process.

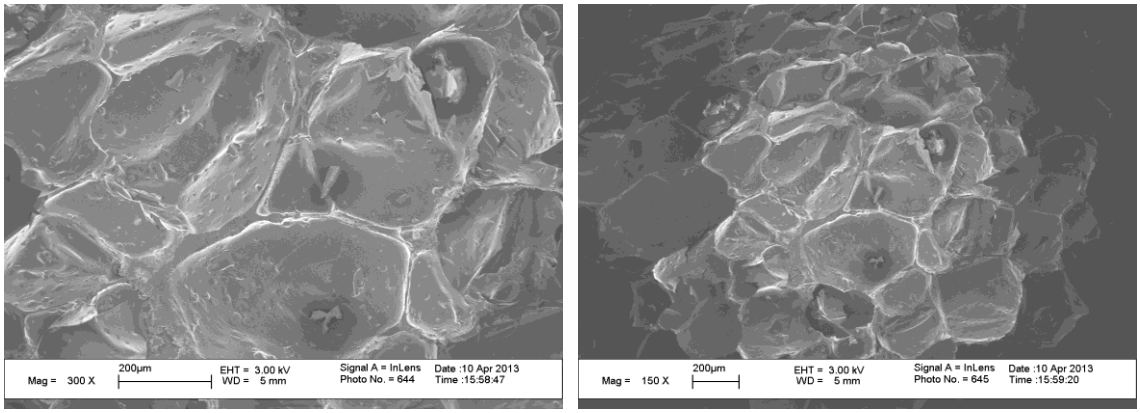
4.2 Cellular Structure Study

As stated before, the batch foaming process was used to improve the porosity of hot melt extrudates, enhancing the permeability of gastric fluids into tablets or pills. Foaming was performed at 85 ℃, which is well above the T_g of polymer. At this foaming temperature, the excipient is in a rubbery state, which is more elastic than viscous and thus not capable of purely viscous flow. Through batch foaming process, using CO_2 as the PBA, cellular structures were produced (Figures 4.8-4.9). The high degree of foaming expansion was induced by the dissolved CO_2 coming out of solution with the sudden decompression. All batch foaming processes were carried out under the same conditions; accordingly, there was not a big difference of the cellular structures (cell size distribution; wall thickness) among all (AcDiSol-containing and Cros-containing) formulations. The cell size range is 83-417 μm and the thickness range is 8-30 μm. All foamed samples have a closed-cell morphology, as it can be seen in all SEM images of the cross-sectional surface of foamed pills. In other words, the cells are not interconnected; with this morphology, the cross-sectional images of the foamed samples have honeycomb-like appearance.



(a) (b)

Figure 4.8 SEM images of cross-sectional surfaces of the EPO/INM/AcDiSol 62/30/8 with a magnification of (a) 300 X and (b) 150X.



(a) (b)

Figure 4.9 SEM images of cross-sectional surfaces of the EPO/INM/Cros 62/30/8 with a magnification of (a) 300 X and (b) 150X.

In Figures 4.8-4.9 and Figures 4.10 (b) (c) (d), some particles (or parts of them) can be seen embedded inside the cell walls of foam. However, no particles can be seen in Figure 4.10 (a) as this is the control sample with no disintegrant particulates. As expected, the number of the particles in the cell walls increases with the concentration of disintegrant (Figure 4.10 and Figure B.1). As seen in the HPOM images (Figure 4.2), the disintegrants are intact after the HME and foaming processing steps. Furthermore, it is evident that the surfaces of the cells of the non-disintegrant containing formulation (Figure 4.10 (a)) are smooth. On the contrary, the cell surfaces of disintegrant-containing formulations have regularly rough patterns, as seen in Figures 4.10 (b) (c) (d). As stated above, at the foaming temperature, the excipient is in a rubbery state, which is quite elastic and supports the stable growth of the cells, without breaking of the cell walls. During cell growth process, the material was subjected to biaxial tension and deformation. The reason of different surface patterns is most probably the intact disintegrants interfere with this biaxial extension and deformation during foaming process. Figure 4.11 describes schematically the cross-section surface of a cell resulting from foaming and how the disintegrants are

embedded or encaged in the polymer matrix. Obviously, the rod-like dissitegrant aligns along the cell wall “membrane” during cell growth.

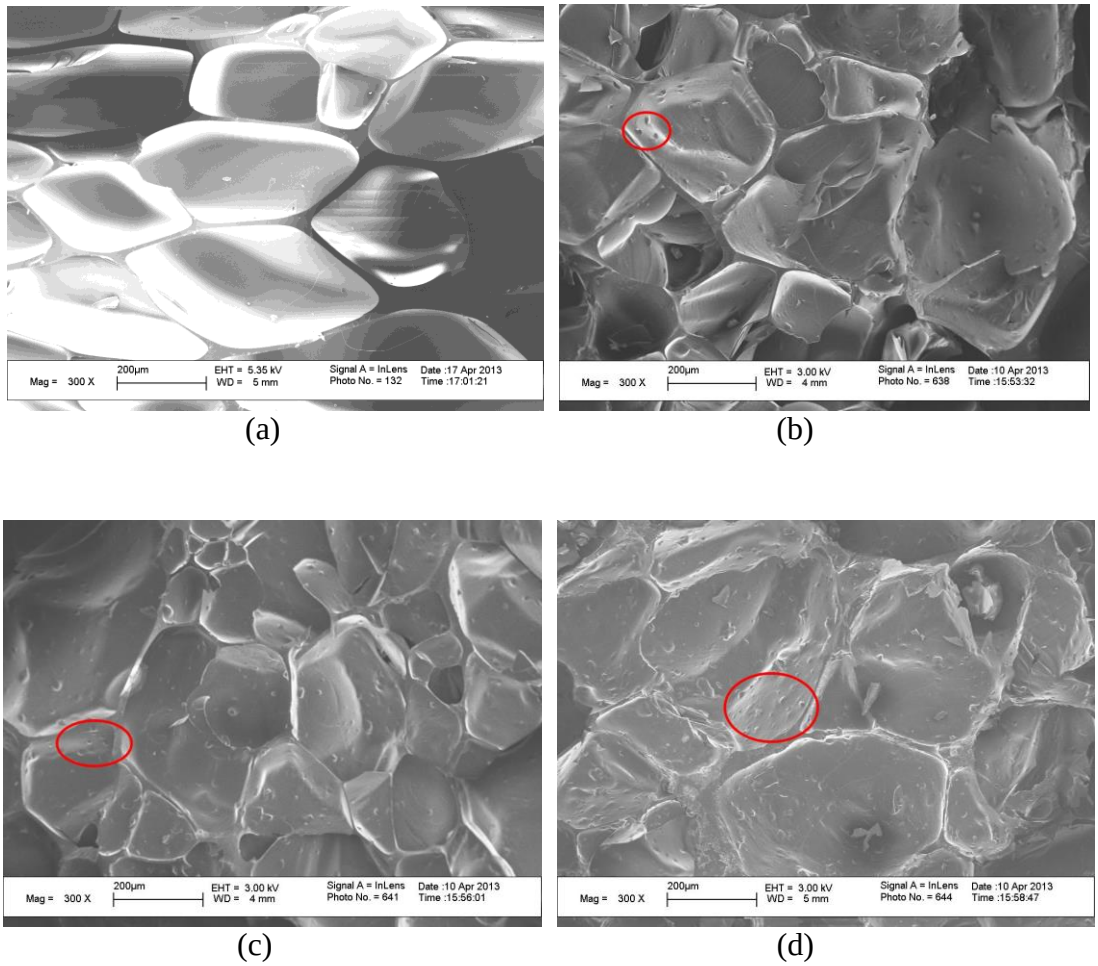


Figure 4.10 SEM images of cross-sectional surfaces of (a) EPO/INM 68.3/31.7, (b) EPO/INM /Cros 68/30/2, (c) EPO/INM /Cros 66/30/4 and (d) EPO/INM /Cros 62/30/8 with a magnification of 300 X.

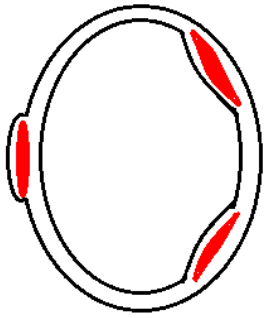


Figure 4.11 Cross-sectional surface of a cell resulting from foaming (the red dots represent disintegrants).

From the perspective of surface tension, the addition of disintegrant can lead to stress concentration forces on the cells, especially in the contact surface, with the cell resulting from foaming possibly breaking due to this unbalance. However, the cell did not break, which indicates that the polymer and disintegrant are compatible avoiding stress concentrations. It will be worth finding a disintegrant incompatible with the excipient to investigate the extent of cell wall ruptures, leading to near-open cell structures.

Finally, the density before and after foaming process changed a lot, which can be seen from Figure 4.12. On the left of this figure was the foamed pill and on the right was the powder used in the batch foaming process. They were of the same weight.

Figure 4.12 Volume difference between the foamed pill and the amount of powder used before batch foaming process.

4.3 *In vitro* Dissolution Test

4.3.1 Release Rate of INM from Foamed Solid Solution

The release profiles of INM from foamed hot melt extruded EPO-containing formulations without disintegrant (AcDiSol; Cros), with 2% (w/w), 4% (w/w), and 8% (w/w) disintegrant were presented in Figures 4.14-4.17. Since the pill was around 0.136g as described in Chapter 3 for the disintegrant-containing pill, the amount of INM is 40.8 mg;

the control sample (without disintegrant) was with an average of around 42.97 mg. Figure 4.15 and Figure 4.17 presented the first 5 minutes of the INM release rate, which clearly described the release rate of INM. The *in vitro* dissolution tests were conducted in a hydrochloric acid buffer solution with pH 1.2 at 37 ℃.

The release profiles in Figure 4.14 and Figure 4.16 clearly indicate that INM was released faster from the foamed pills with disintegrant than those without disintegrant (it is shown as control in the release profile).

In the AcDiSol-containing release profiles (Figures 4.14-4.15), during the first 5 minutes the foamed pills with 2% AcDiSol show the fastest release, 8% AcDiSol-containing foamed pills followed and then the 4% AcDiSol. After 30 minutes, the foamed pills with 8% AcDiSol showed the greatest release among all samples.

In the Cros-containing release profiles (Figures 4.16- 4.17), the foamed pills with 4% Cros-containing resulted in the lowest release rate compared with the other two foamed pills with 2% and 8% Cros-containing. At the first 5 minutes, foamed pill with 8% Cros was the fastest, followed by 2% and finally 4% Cros-containing foamed pills. Nevertheless, after 20 minutes, 2% Cros-containing foamed pills presented the fastest release while the one containing 4% Cros having still the lowest one. It has to be mentioned that at the first 5 minutes among all formulation dissolutions, the rate was not as fast as expected. This is because the polymer excipient has to dissolve first, letting the encaged disintegrant be exposed to buffer solution for disintegration. As it was immersed in buffer solution, the cellular structure seemed to erode and break down, which further contributed to the acceleration of the release rate of the API. Figure 4.13 presents schematically the collapse of the overall cellular structure as polymer dissolved.

Figure 4.13 The breakdown of the cellular structure as polymer dissolves.

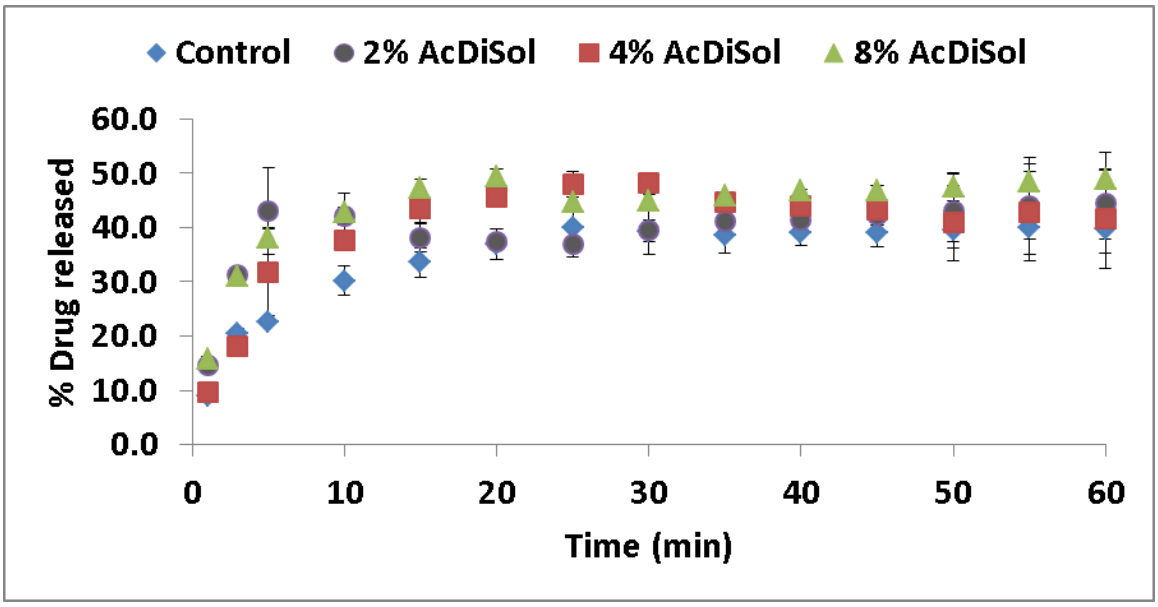


Figure 4.14 Release profiles of INM from foamed hot melt extrudated EPO containing formulations without AcDiSol, with 2% (w/w) AcDiSol, with 4% (w/w) AcDiSol, and with 8% (w/w) AcDiSol.

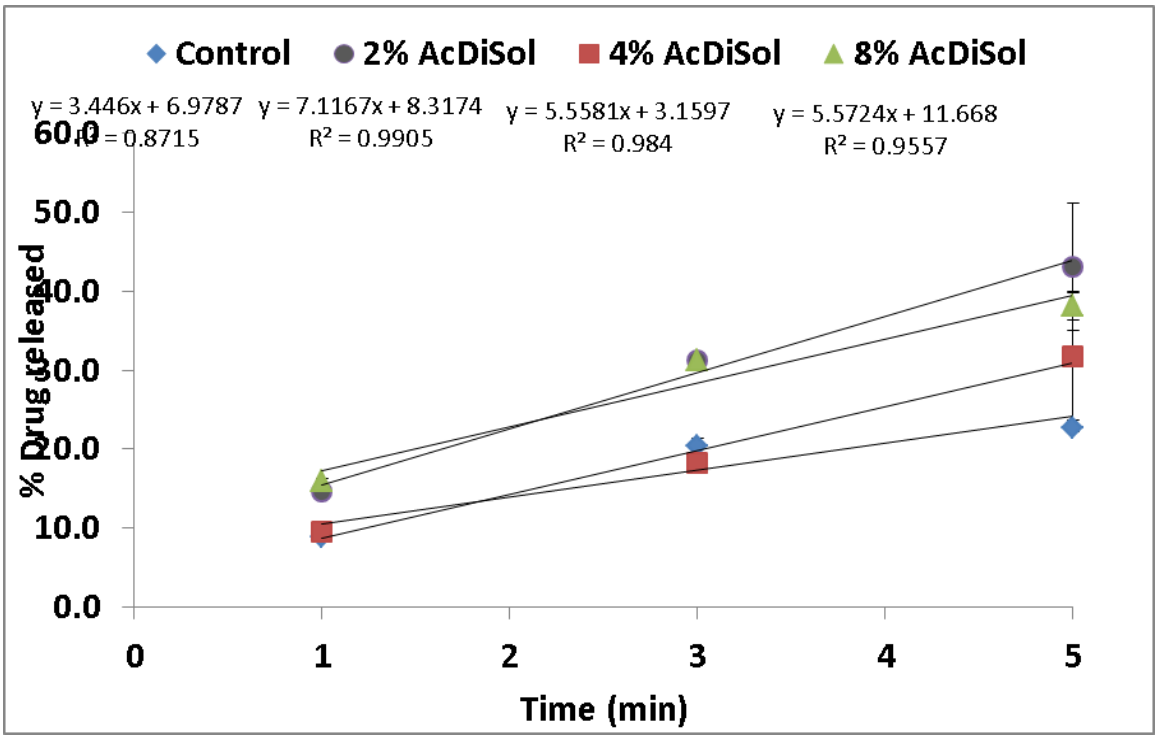


Figure 4.15 The first 5 minutes of the release profiles of INM from foamed hot melt extrudated EPO containing formulations without AcDiSol, with 2% (w/w) AcDiSol, with 4% (w/w) AcDiSol, and with 8% (w/w) AcDiSol.

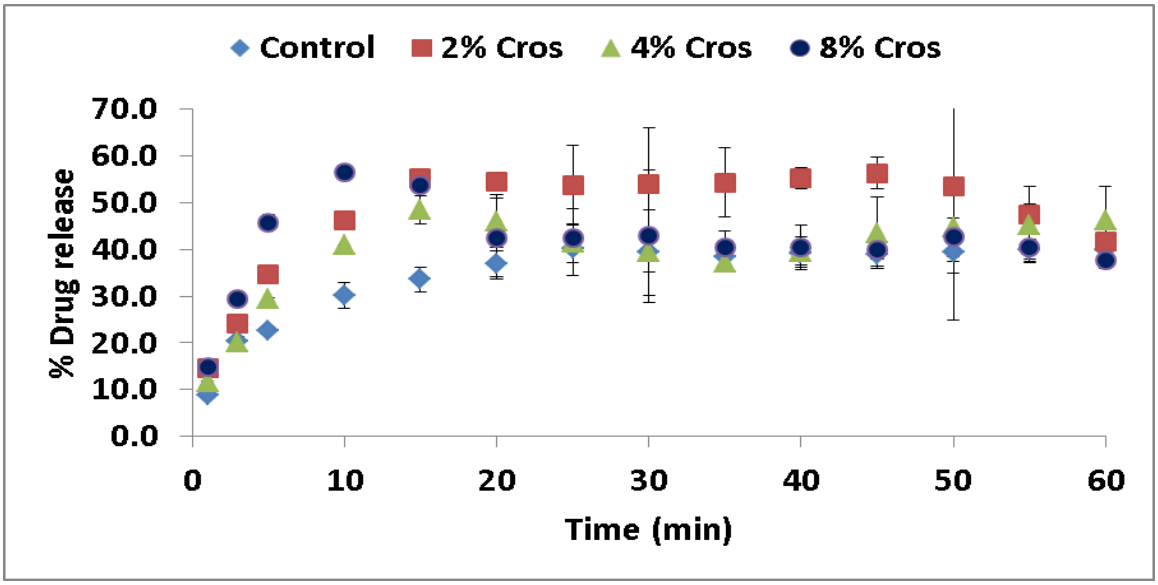


Figure 4.16 Release profiles of INM from foamed hot melt extrudated EPO containing formulations without Cros, with 2% (w/w) Cros, with 4% (w/w) Cros, and with 8% (w/w) Cros.

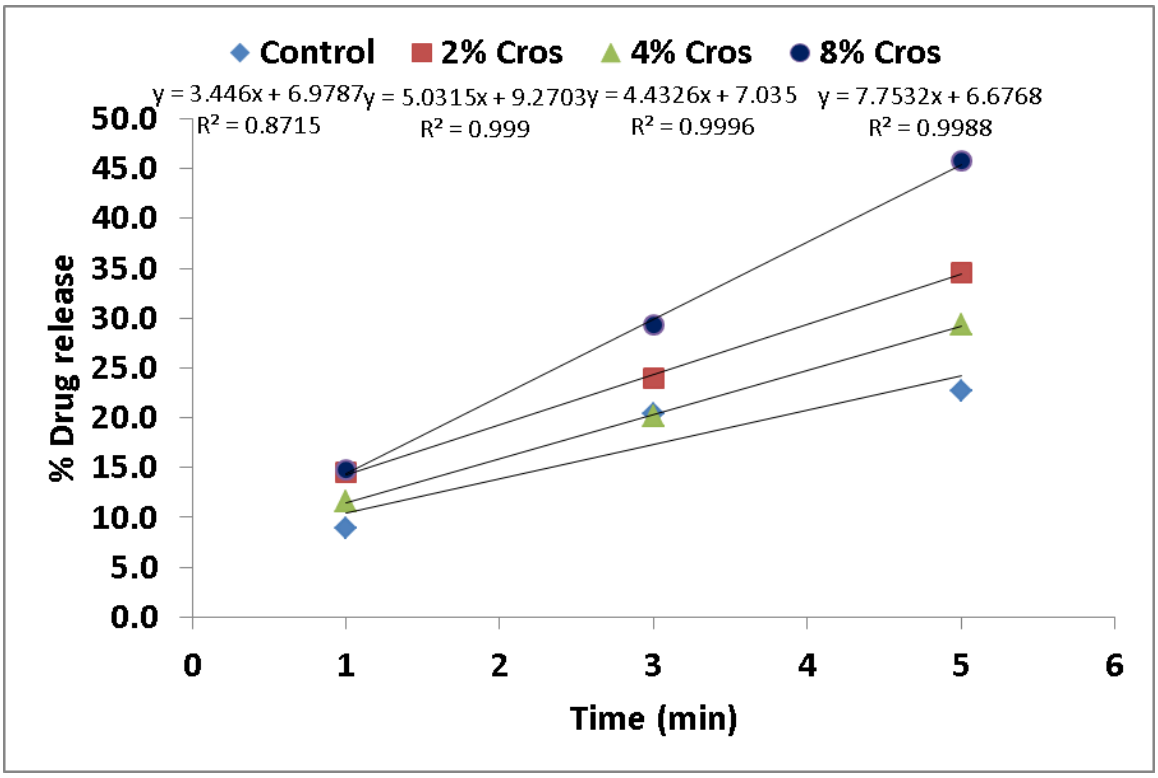


Figure 4.17 The first 5 minutes of the release profiles of INM from foamed hot melt extrudated EPO containing formulations without Cros, with 2% (w/w) Cros, with 4% (w/w) Cros, and with 8% (w/w) Cros.

It has to be mentioned that among all release profiles, the highest amount of INM released occurred in the 8%-Cros containing formulation at the 10th minute (Figure 4.16). This percentage is around 56.5%. Since the amount of INM in the pill is 40.8 mg, the amount of released INM is around 23.05 mg. Liu reported the similar released amount, around 24.08 mg (Liu, 2010). The Figure 4.18 shows the release profile of 8%-Cros containing formulation normalized by the maximum amount of INM appearing to be dissolved in 900 mL of dissolution medium.

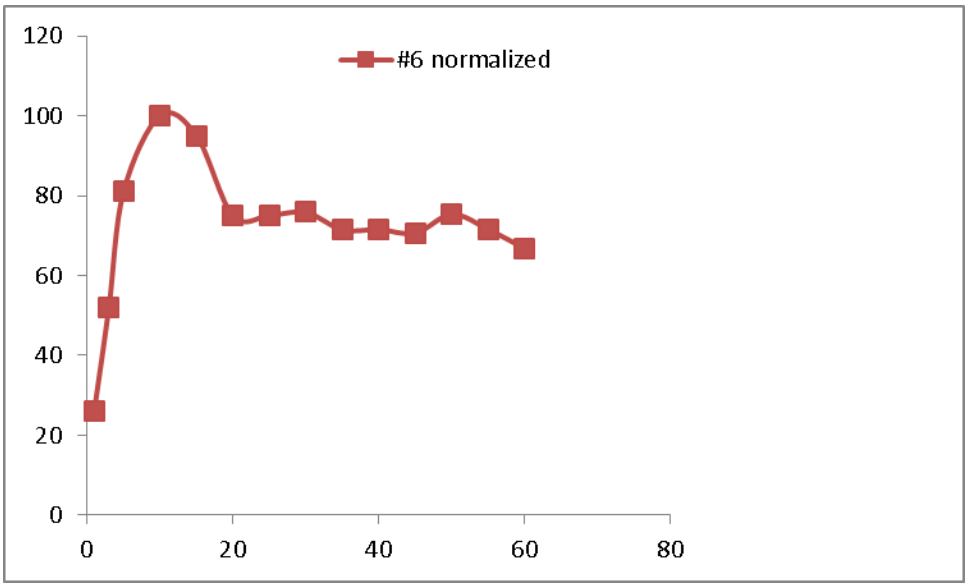


Figure 4.18 The release profile of normalized 8%-Cros containing formulation.

4.3.2 Quantitative Comparison of the Release Profiles from the Pills with and without Disintegrant

In order to establish a quantitative comparison between two release profiles, the USA Food and Drug Administration (FDA) in its Guidance for Industry (FDA, 1997) provide a simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles (Moore, 1996). The difference factor (f_1) calculates the percentage difference between the two curves at each time point and is a measurement of the relative error between the two curves. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measure of the similarity in the percent dissolution between the two curves.

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \, 100 \qquad (4.1)$$

$$f_2 = 50\ log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \cdot 100\right\} \quad (4.2)$$

where n is the number of time points, R_t is the dissolution value of the reference (prechange) batch at time t, and T_t is the dissolution value of the test (postchange) batch at time t. Generally, the closer f_1 's value is to zero, the more alike the two release profiles are. Conversely, a higher value of f_2 indicates that the two curves are more similar to each other. According to FDA's guidance, to consider two API release profiles to be similar f_1 should be less than 15 and f_2 should be greater than 50 (FDA, 1997).

The difference and similarity factors were calculated for each disintegrant-containing and non-disintegrant-containing pairs. The time range for the calculation was chosen from 1-30 minutes. The results are summarized in Table 4.1.

Table 4.1 Calculated Difference Factor (f_1) and Similarity Factor (f_2) for Formulations with and without Release Profile (the number of formulation here is same as in Table 3.1).

Formulations	**#1**	**#2**	**#3**	**#4**	**#5**	**#6**
$\mathbf{f_1}$	36.03	34.87	47.79	45.47	30.56	54.01
$\mathbf{f_2}$	28.34	29.05	22.21	23.29	31.91	19.56

In the results obtained here all the values of f_1 are greater than 15 and all the values of f_2 are less than 50, which means all the formulations with disintegrant are statistically different from the formulations without disintegrant. Among all samples, 8% disintegrant-containing formulation expresses the great difference.

4.3.3 Summary

From the release profile of INM from AcDiSol-containing and Cros-containing foamed pills, it is evident that the two kinds of disintegrants clearly accelerated the disintegration

process. Researchers have conducted studies on the release performance among foamed and un-foamed disks (Terife et al., 2012). It turns out that foamed disks showed a much faster release rate than the un-foamed ones. Souto et al. studies the utility of including superdisintegrants in microcrystalline cellulose extrusion-spheronization pellets. Neither disintegrant caused disintegration of the pellet in drug dissolution medium, however, the disintegrans afforded a modest increase in drug dissolution rate, mainly attributable to their effect on the pellet's pore structure (Souto et al., 2005). Lundqvist et al. reported that the disintegrant pellets clearly did break the tablet; the higher the proportion of disintegrant, the shorter the disintegration time (Lundqvist et al., 1997). Accordingly, it is reasonable that disintegrants added to a foamed pharmaceutical formulation will enhance the release rate of API.

CHAPTER 5

SUMMARY

The Hot Melt Extrusion (HME) process was used to produce seven amorphous Polymer/API/ (Disintegrant) formulations systems. Foamed samples were produced by batch foaming using CO_2 as the PBA. Comprehensive characterization was carried out combining HPOM, DSC, XRD, SEM and *in vitro* dissolution test. These analyses of HPOM, DSC and XRD results show that the extrudates produced by HME are amorphous solid solutions of INM in EPO. In addition, the disintegrants, as found from HPOM images, are intact both after HME and batch foaming processing. The DSC results also show that the disintegrants are stable in the set temperature range except for the moisture loss. From the SEM analysis, the disintegrants are encaged/embedded in the polymer matrix, which indicates that polymer and disintegrant are compatible with each other. Meanwhile, the cellular structure caused by foaming processing provides many pathways for gastric fluids to penetrate to into pills or tablets. From the release profiles of INM from AcDiSol-containing and Cros-containing foamed pills, it is clear that the two kinds of disintegrants did accelerate the disintegration. From the statistical analysis, the 8% disintegrant-containing systems showed the greatest difference compared with the system, which contains no disintegrant. In conclusion, the addition of disintegrant in the HME-produced solid solutions is a good method to increase the release rate.

Based on previous studies in our group, the foamed disks showed a greater release rate than their un-foamed counterparts. This is because the cellular structure provides many pathways for the gastrointestinal fluids to penetrate into the pills or tablets. In this thesis,

the main contribution is the finding that the addition of disintegrants in the HME feed of API and excipient and their incorporation in the API/Excipient solid solution matrix enhances the API release rate.

APPENDIX A

HOPM RESULT OF POWDERED EXTRUDATED CROS-CONTAINING FORMULATION

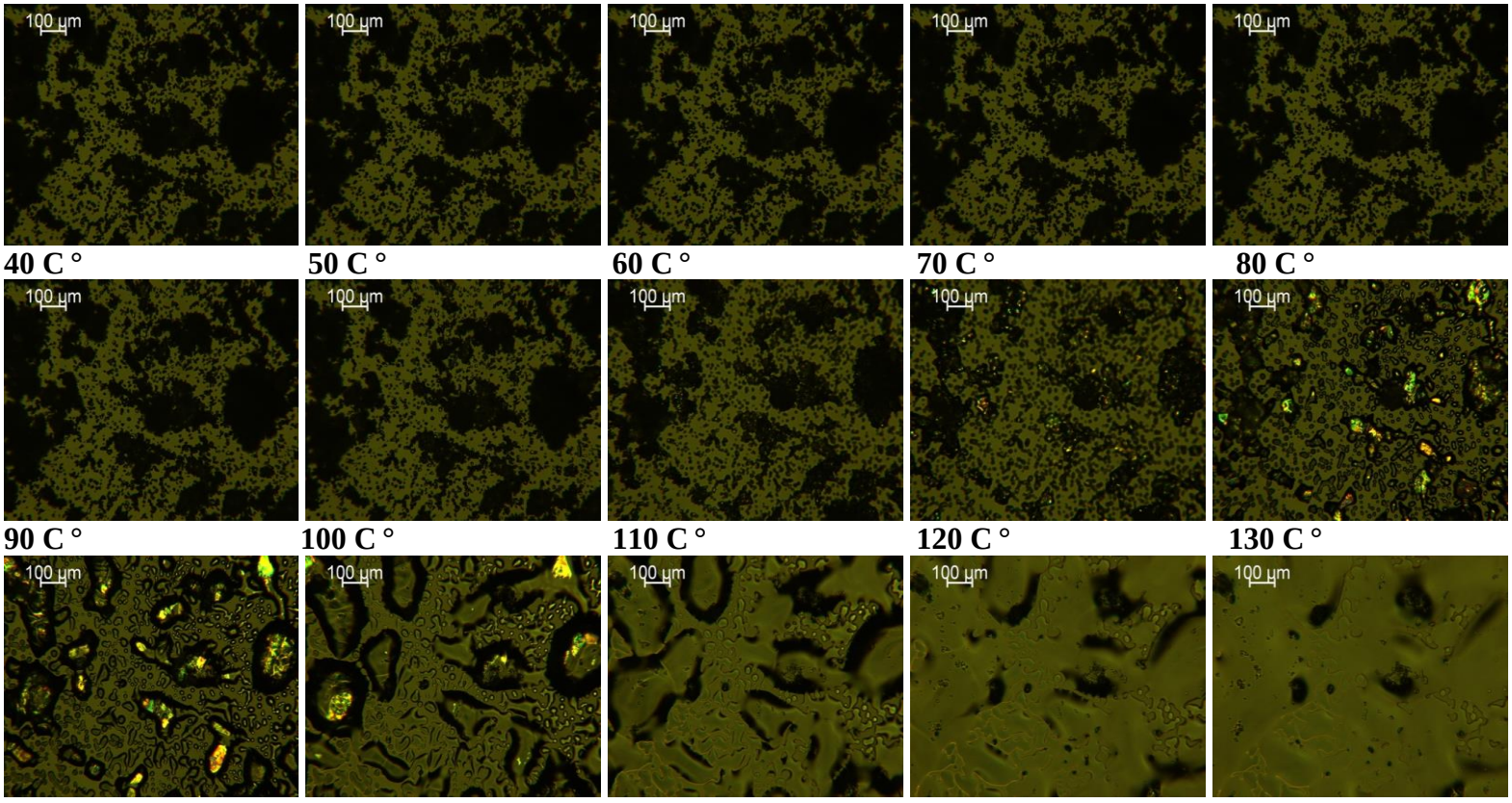


Figure A.1 Physical mixture: EPO-INM-Cros 66-30-4 @ 20 ℃ min^{-1}.

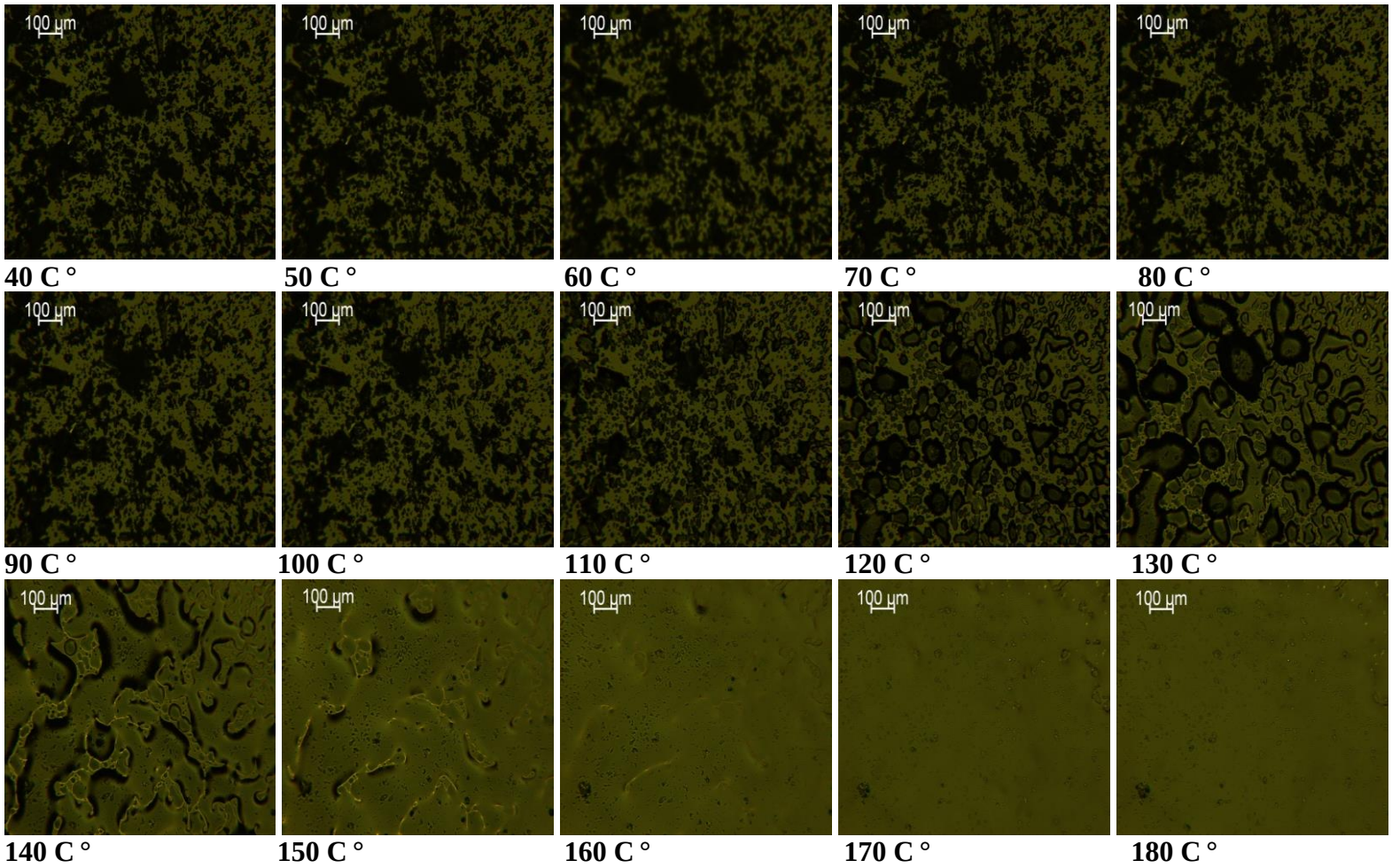


Figure A.1 (a) Extrudate #4: EPO-INM-Cros 68-30-2@ 20 ℃ min^{-1}.

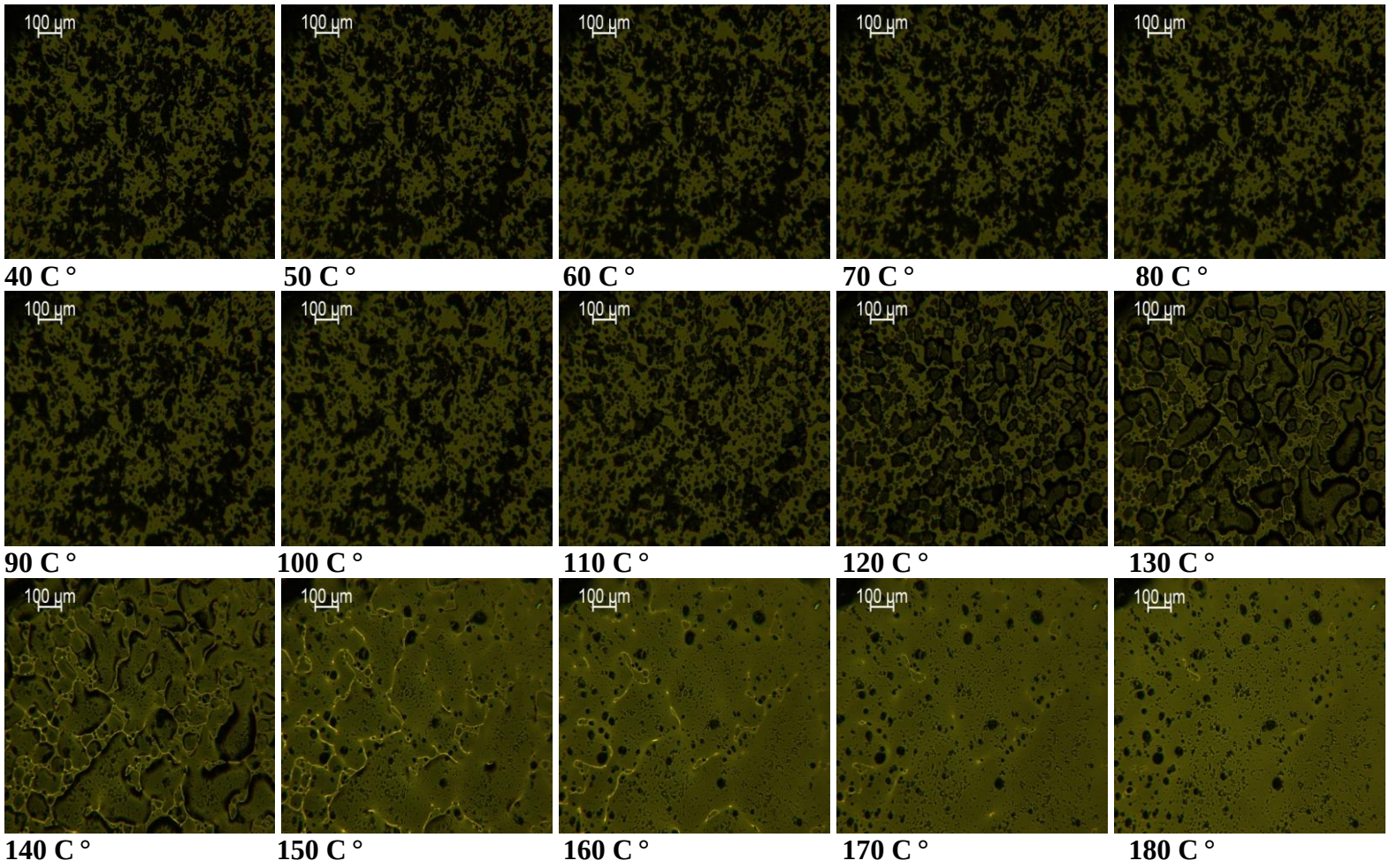


Figure A.1 (b) Extrudate #5: EPO-INM-Cros 66-30-4@ 20 ℃ min^{-1}.

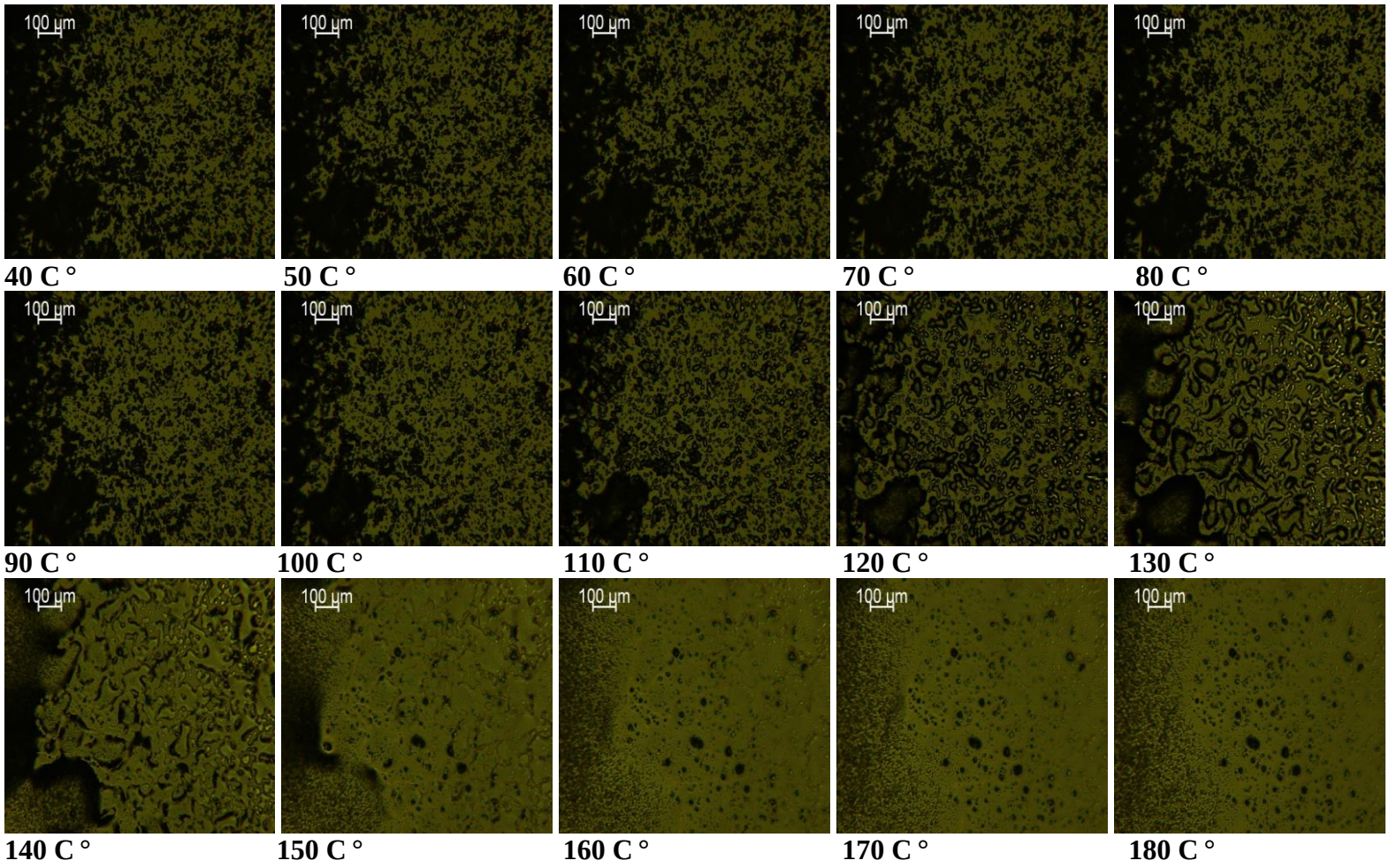
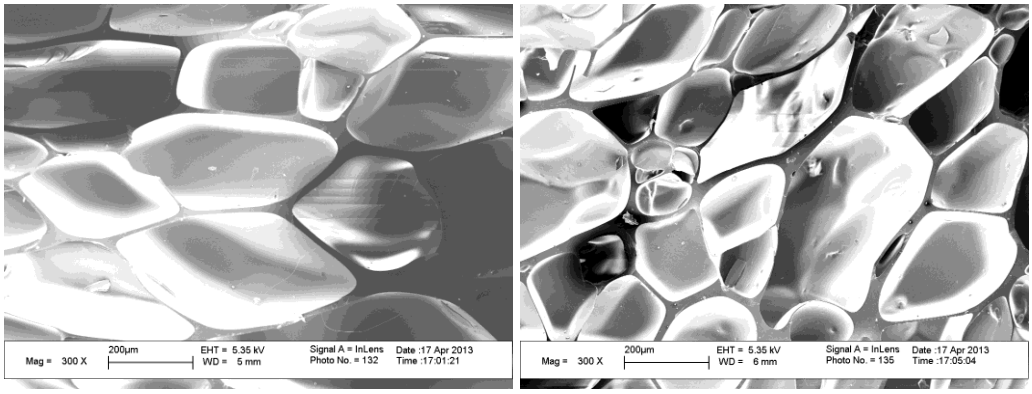


Figure A.1 (c) Extrudate #6: EPO-INM-Cros 62-30-8@ 20 ℃ min^{-1}

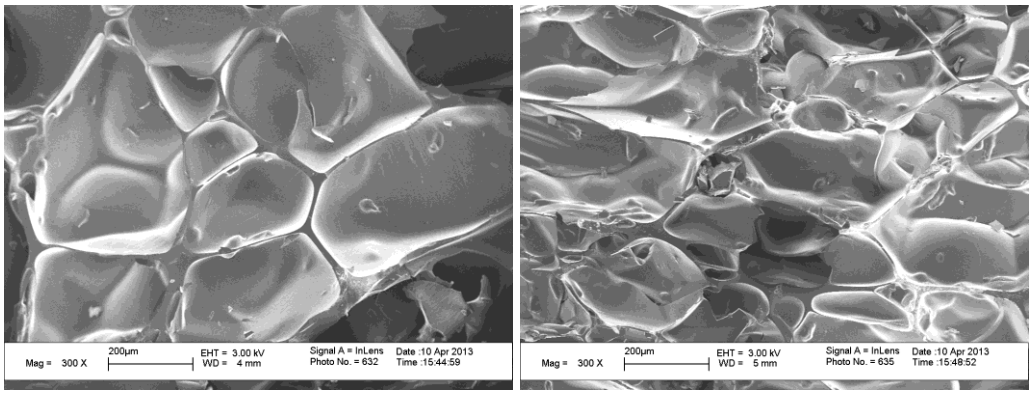
.

APPENDIX B

SEM RESULT OF ACDISOL-CONTAINING GROUP



(a) (b)



(c) (d)

Figure B.1 SEM images of cross-sectional surfaces of (a) EPO/INM 68.3/31.7, (b) EPO/INM /AcDiSol 68/30/2, (c) EPO/INM / AcDiSol 66/30/4 and (d) EPO/INM / AcDiSol 62/30/8 with a magnification of 300 X.

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