Materials Properties of Pharmaceutical Formulations for Thin-Film-Tablet Continuous Manufacturing

by

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Submitted to the
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Abstract

The development of manufacturing tablets in a continuous way has been possible greatly to the fabrication of polymer based thin-films. It is estimated that the pharmaceutical industry loses as much as a 25% on revenues based on the currently employed batch manufacturing method. Here we studied a continuous way of manufacturing tablets based on API/based polymer formulations that are cast and subsequently rolled into a tablet. Selections of two active pharmaceutical ingredients (SPP-100 and Acetaminophen) were studied into how well it forms mechanical robust, chemical and physical compatible HPMC polymer based films. As well, HPMC polymer based films with no drug loading were compared to measure out the dispersion of the drug on the film. Physiochemical studies were performed by DSC, XRD, FT-IR, and SEM. Moisture content was measured out by Karl Fischer Titration and mechanical properties such as tensile strength were measured for all API/HPMC and placebo films. It was found that the mechanical and physiochemical properties of SPP-100/HPMC films were regarded as the most promising thin film tablet candidate and it is further being tested for other mechanical properties such as bonding, friction, and compression.

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I wish to thank the whole Novartis-MIT CCM for their support throughout this project, especially Salvatore Mascia. Finally, I would like to thank from the bottom of my heart my family and friends that have always been there throughout my years at MIT. Mom, Yolauri, and Dad---this is for you!

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Chapter 1
Continuous Manufacturing in Pharmaceuticals and Motivation for Formulations

1.1 Introduction to Continuous Manufacturing

The most common forms of oral drug delivery systems are tablets and capsules. Approximately 80% of current pharmaceutical dosages exist in this form because of convenience, low manufacturing costs, and acceptable form [1]. The current manufacturing process for tablets is divided into two parts: an *upstream set* of steps and a *downstream processing* of events. As illustrated in Figure 1.1.1, a series of *upstream steps* are carried out to synthesize the chemicals and make the drug substance. As soon as the active pharmaceutical ingredient (API) is produced, the drug substance is ground into a solid powder, followed by subsequent procedures of granulation and milling for appropriate sizing. The addition of an excipient (drug carrier) and further blending is finalized into a final tablet form. An excipient is a pharmaceutically inert substance that functions as a carrier for active pharmaceutical ingredients. Excipients can include diluents for size and volume control, disintegrating agents for absorption into the human body, binders for adhesion, and stabilizers for shelf-life control [2]. These steps are usually referred to as *downstream processing.*

The aforementioned procedure has been used in the pharmaceutical industry since the late 1880's. Although it has been used since the late 1800's, the procedure is a series of disconnected batch steps. The earliest advantage of batch production was the reduction of initial capital outlay because a single production line could be used to produce several products. Batch production, though, can be extremely beneficial for small businesses who cannot afford to run continuous productions lines. For example, if a retailer buys a batch of a product that does not sell, then the producer can cease production without having to sustain huge losses. In addition, batch production

is beneficial for a factory that only makes seasonal items (i.e. products for which it is difficult to predict demand, a set of trial runs for production, or products that have a high profit margin.)

However, batch-based tablet production also brings disadvantages for the current pharmaceutical industry. These processes are costly, inefficient, and have a longer production time than current continuous manufacturing alternatives. For example, in batch-based tablet production equipment must be stopped, re-configured, and test its output before the next batch can be produced.

Currently, several industries in the pretrochemical, chemical, polymer, and food sectors have moved onto continuous processing technologies in manufacturing due to cost and quality considerations [3]. The lack of flexibility in batch processing in response to increasing levels of growth has been cited as the primary driver for industries to shift towards continuous processing technologies [4]. Moreover, current batch manufacturing methodology in pharmaceuticals involves the separation of chemical and drug-product manufacturing at different facilities, locations, and sometimes even countries. The entire process can take up to 300 or more days before the intermediate chemical can be converted into a final drug product. A continuous process, where all the steps are carried out at one facility and eliminate costs such as transportation and time, could be achieved in 10-30 days [5].

The continuous tablet manufacturing process has numerous advantages when compared with the conventional batch-based method such as costs, flexible output control, faster market introduction, production speed, uniformity of API and excipient, and real time quality inspection [6].

The Novartis-MIT Center for Continuous Manufacturing (NVS-MITCCM) is a research initiative that was launched with the primary goal of transforming the pharmaceutical industry from a conventional batch-based tablet method into a continuous process. Currently, the development of a continuous method that employs polymeric thin-film formulations for *downstream processing* through a continuous tableting system as proposed in *Padhey et al. (2012)* is being researched at the NVS-MITCCM. As illustrated in Figure 1.1.2, one way the NVS-MITCCM has been working on this is by using thin films to create tablets. Here, the API is mixed with the excipient, solvents, and plasticizer to make a liquid formulation. The solution is then casted into a thin film, where stacked layers of the thin film can be compacted into a tablet.

In this study, a novel process of fabricating thin films from several formulations is presented. The rheological data of the different formulations was evaluated first to determine whether the formulations can be casted into thin films. An understanding of the physiochemical properties was studied by differential scanning calorimetry, Raman Spectroscopy, X-Ray Diffraction, Scanning Electron Microscopy, and Karl Fischer Titration. Finally, the mechanical properties of the thin films were also evaluated.

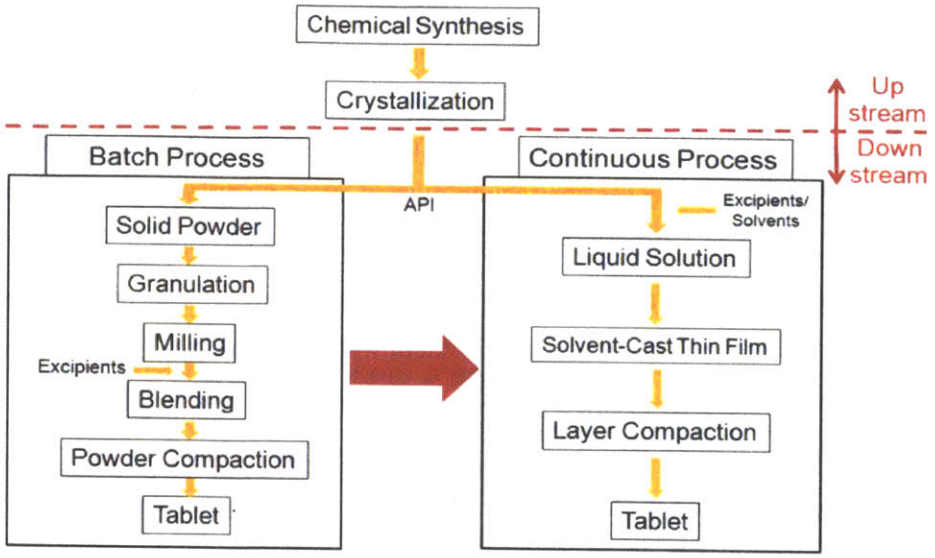

Figure 1.1.1: Schematic of Tablet Manufacturing Process. Batch-based tablet process (left), Continuous based process (right) [1].

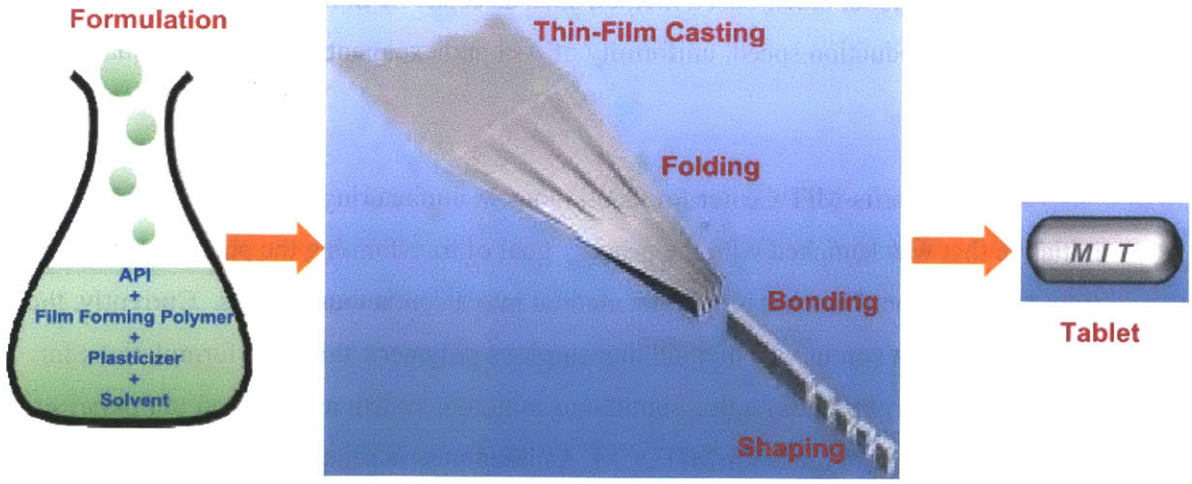

Figure 1.1.2: Schematic of the thin film process for continuous tablet processing developed at the NVS-MITCCM [7].

Chapter 2
Thin-Film-Tablet Continuous Manufacturing in Pharmaceuticals- Materials and Methods

2.1 Introduction

The formation of different polymeric based thin-films has been researched by the Novartis-MIT Center for Continuous Manufacturing. The thin-films are to be rolled into tablets and will revolutionize the way tablets are produced by switching to a continuous manufacturing. In this study various materials and methods were used to make the different thin-films formulation and produce the polymeric/API based thin-films.

2.2 Thin-Film Making Procedure

This section describes the thin-film making procedure adopted in this study. In this study, three different API-based thin-films were produced: (a) 20% Acetaminophen/ 10% Polyethylene Glycol 400, (b) 10% Acetaminophen/ 10% Polyethylene Glycol 400, and (c) 10% SPP-100/ 10% Polyethylene Glycol 400. In addition, a placebo-based film was produced: (a) 9% Hydroxylpropyl Methylcellulose/ 10% Polyethylene Glycol 400. In order to produce a formulation based on 20% Acetaminophen/ 10% PEG 400, 40 grams of Acetaminophen (Paracetamol; Sigma Aldrich Ultra minimum 99.0%) was measured. Furthermore, those 40 grams of ACM were dissolved in 55 grams of Ethanol. 15 grams of Methocel E3 HPMC (Dow Chemical Methocel), and 15 grams of Methocel E15 HPMC (Dow Chemical Methocel) were added to the ACM-Ethanol solution. Finally, 55 grams of deionized water and 20 grams of PEG 400 (Sigma Aldrich PEG 400) were added to the solution, respectively. The formulation was allowed to stir for 24 hours on a magnetic

stirrer to ensure homogeneous mixing. The formulation was allowed to degas for 3 hours to get rid of air bubbles in vacuum (VMR 1400E).

For the formation of 10% ACM/ 10% PEG 400 and 10% SPP-100 /10% PEG 400 formulations an identical approach was followed. Tablet 2.2.1 shows the respective amounts added for each formulation. SPP-100 was supplied by Novartis with a purity of 99.63% (Aliskirien Hemifumarate)

Table 2.2.1: Thin-film formulations considered in this study.

Name	HPMC(e3,e15) (g)	PEG-400 (g)	API (g)	H_2O (g)	EtOH (g)
20% ACM, 10 % PEG	**15, 15**	**20**	**40 (ACM)**	**55**	**55**
10% ACM, 10 % PEG	**15, 15**	**20**	**20 (ACM)**	**65**	**65**
10% SPP, 10 % PEG	**15, 15**	**20**	**20 (SPP-100)**	**65**	**65**
9% HPMC/ 10%PEG	**15,15**	**22**	**None**	**96**	**96**

2.3 Thin-Film Casting

Preparation of thin-films was carried out using a casting apparatus comprising of: (a) an adjustable-height knife (to control film thickness), and (b) a stainless steel plate. The casting apparatus was custom made at MIT with specific geometries. A stainless steel plate and polyester film placed on top were used as casting substrates, as illustrated in Figure 2.3.1. Polyester was used as the substrate for the films because appropriate liners are considered a crucial factor in obtaining good uniform films [8]. The polyester sheets acts as a non-sticky substrate for the formulation solution. The formulation solution is then poured over the substrate and dragged across the aluminum plate to form a thin liquid film. In our study, 95 microns was chosen as the knife height for the formulations. Since drying time is important for the thin-films, a sufficient amount of time was allowed for the films to dry (more than 6 hours). Once dry, thin-films were peeled off of the substrate and cut into separate pieces and sealed using a VACUPACK Lite vacuum sealer.

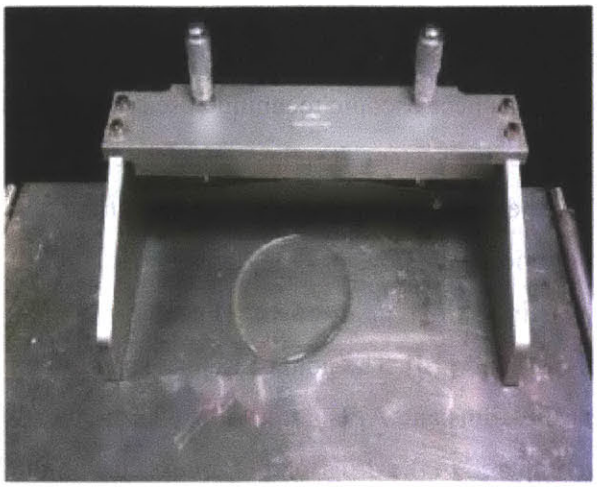

Figure 2.3.1: Example of solution casting for thin-film fabrication.

2.4 Thin-Film Characterization Methods

Here we describe the techniques used for materials characterization of the different formulation and thin-films considered in this study. The goal of this study is to see the variation of different APIs in HPMC forming thin films on the physiochemical, mechanical, and rheological properties of formulations and thin-films.

2.4.1 Formulation Viscosity

The viscosity of the solution was measured using a Discovery HR-3 hybrid rheometer. An estimation of the solution viscosity is valuable because it gives an indication whether or not a formulation can be used for casting thin films. Currently, the viscosity range requirement for NVS-MITCCM thin-film system is between 0.06-9 Pa-s. An extremely low viscosity solution (viscosity lower than 0.06 Pa-s) or an extremely high viscosity (higher than 15 Pa-s) solution would exhibit difficulties when casting into a thin-film.

2.4.2 Karl-Fischer Titration

Karl Fischer titration is a classic titration method in analytical chemistry that helps determine trace amounts of water in different solid or powder materials. In this study, the residual water concentration in the solvent-cast thin films was determined using a Mettler Toledo V20 Volumetric Karl Fischer Titrator. The measurements for all thin films casted and APIs are listed as weight percent (%). This measurement is extremely important because water can act as a plasticizer and have an effect on the physiochemical and mechanical properties of the thin films and also affect the chemical stability of the API.

2.4.3 Raman Spectra

Raman spectroscopy is a spectroscopic technique used to study the vibrational, rotational, and other low-frequency modes in a system. It relies on inelastic scattering of monochromatic light, usually from a laser in the visible, near infrared, or near ultraviolet range [9]. The laser light interacts with molecular vibrations, phonons or other excitations in the system, resulting in the energy of the laser photons being shifted up or down. The shift in energy gives information about the vibrational modes in the system [10]. The goal of Raman spectroscopy was to obtain a fingerprint of the different thin-films and APIs and evaluate its chemical form. The state of the drug in its pure state was compared to the drug loading in the thin film to verify a well solid dispersion of the drug in the thin film.

2.4.4 X-Ray Diffraction (XRD)

X-ray scattering techniques are a family of non-destructive analytical techniques which reveal information about the crystal structure, chemical composition, and physical properties of materials and thin films. Here, all samples were studied using a Pananalytical X'Pert Pro scanning x-ray powder diffractometer with radiation generated by a copper Kα filter at 45 kV and 40 mA. All samples were scanned from 5-40□ C 2θ. The step size was 0.02 degrees. For the purpose of this study, the crystal or amorphous form of the API and thin-films were investigated.

2.4.5 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry is a thermo analytical technique in which the difference of heat required to increase the temperature of the sample pan and its corresponding reference is measure. Powder or thin-film samples (2-10 mg of weight) were sealed in aluminum pans and analyzed under N2 dry conditions using a TA Instruments Q2000.

2.4.6 Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) was performed using a JEOL 6320FV filed emission high-resolution SEM at an acceleration voltage of 10kV. SEM studies were thankfully done by the support of the Institute of Soldier Nanotechnologies at MIT. SEM images were analyzed to study the drug dispersion in the thin-film and characterize its surface properties.

2.1.7 Mechanical Testing

Tensile testing is one of the most commonly employed techniques to characterize the strength of a material. The uniaxial tensile test provides properties such as ultimate tensile strength, maximum elongation and reduction in area. The Young's modulus, yield strength, and strain hardening characteristics can all be extrapolated from such results. Mechanical testing helps determine (a) the influence of plasticizer on the thin-film and (b) predict the behavior of thin-films under loading. All samples were measure using the INSTRON machine with a 1 kN cell load.

Chapter 3
Thin-Film-Tablet Continuous Manufacturing in Pharmaceuticals- Results and Discussion

2.3 Introduction

This chapter provides an analysis on the characterization and materials properties of the different API-based thin-films and placebo-based thin-film. An analysis of thin-film formulation making is discussed, as well as all the physiochemical and mechanical properties of the films. It was found that 2 API-based formulations with 10% drug loading were able to be casted and fabricated into a thin-film, while 20% drug loading was a highly viscosity solution not able to form films. A comparison of the API-based thin-films with the placebo-based thin-film is also discussed.

2.4 Thin-Film Formulation Analysis

The key ingredients for API-based formulations to be casted into thin-films are:

(a) Active Pharmaceutical Ingredient (API) i.e. the real drug substance for the medication.

(b) Excipient- a pharmacologically inactive substance that is used as a carrier for the API.

(c) Plasticizer, which is a also a pharmacologically inactive substance and plays a key role in altering the mechanical properties and bonding behaviors of the thin-films.

(d) Solvents- help to dissolve and mix: API, Excipient and Plasticizer to form a homogeneous

solution.

All mentioned ingredients must be suitable for the good manufacturing practices. Additionally, the excipient and plasticizer, along with the API, must be soluble in the volatile solvent and water mixture being used. Finally, a stable solution with desired viscosity range should be formed in order to form an appropriate thin film with robust mechanical properties and stable physiochemical properties of the API in the thin film.

In this study, we have employed Methocel E3 and E15 PRM IV (Dow Chemical Methocel products are Hydroxypropyl Methylcellulose rheology modifiers: E3 has a viscosity of 3 mPa *s s at 20 C; E15 has a viscosity of 15 mPa *s at 20C) as the excipient. HPMC is the thermoplastic film former commonly used for oral pharmaceutical products [1;12] As well, HPMC was a suitable candidate because it is compatible with both APIs used in the study, and it is also mechanically robust. HPMC films can also be folded into tablets [8]. Polyethylene glycol 400 (Sigma Aldrich PEG 400) was used as the liquid plasticizer. PEG 400 is compatible with both APIs and HPMC and is also miscible in both water and ethanol. The addition of the plasticizer prevents the formulation from becoming brittle when casted. Furthermore, both ethanol and distilled water were used as the volatile solvents. Finally, for the purpose of the study we have tested two different APIs in our formulations: Acetaminophen (Paracetamol; Sigma Aldrich Ultra minimum 99.0%) and Aliskirien hemifumarate (SPP 100; supplied by Novartis with a purity of 99.63%). For the purpose of the study, two different types of drugs were analyzed to show the range of thin-film making process. Acetaminophen is a crystalline drug that has well studied physiochemical properties. In addition, SPP 100 was used as the amorphous structure for the formulations. This allowed a comparison between drug structure and the ability to prove thin film formation for different types of drugs. SPP 100 is hygroscopic that is both soluble in water and ethanol. Figure 3.2.1 shows the chemical structures of both SPP 100 and Acetaminophen.

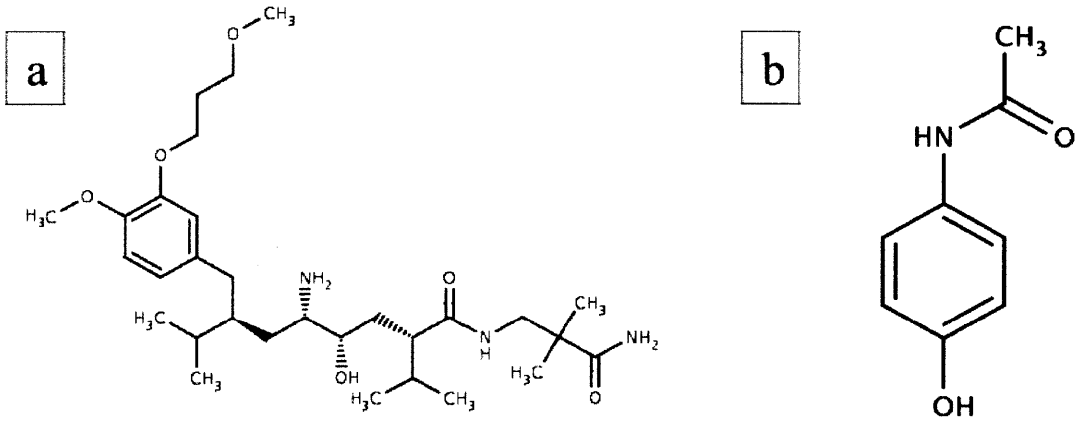

Figure 3.2.1: Chemical structures for (a) SPP 100 and (b) Acetaminophen

As illustrated in Figure 3.2.2, the formulation should be clear and solid dispersion should not be seen. This is a good representation of a formulation that could be casted into a thin film. The success of a homogeneous solution formation depends upon exact compositions of ingredients. At higher concentration of solute, complete dissolution does not occur and it is difficult to obtain homogeneity even with a higher time allowed. For example, Figure 3.2.3 illustrates a formulation when excess amount of solution exists and complete dissolution does not happen. Additionally, Figure 3.2.4 shows an attempt in which thin-films were made from an unclear formulation and it illustrates how this is a bad choice that should be avoided.

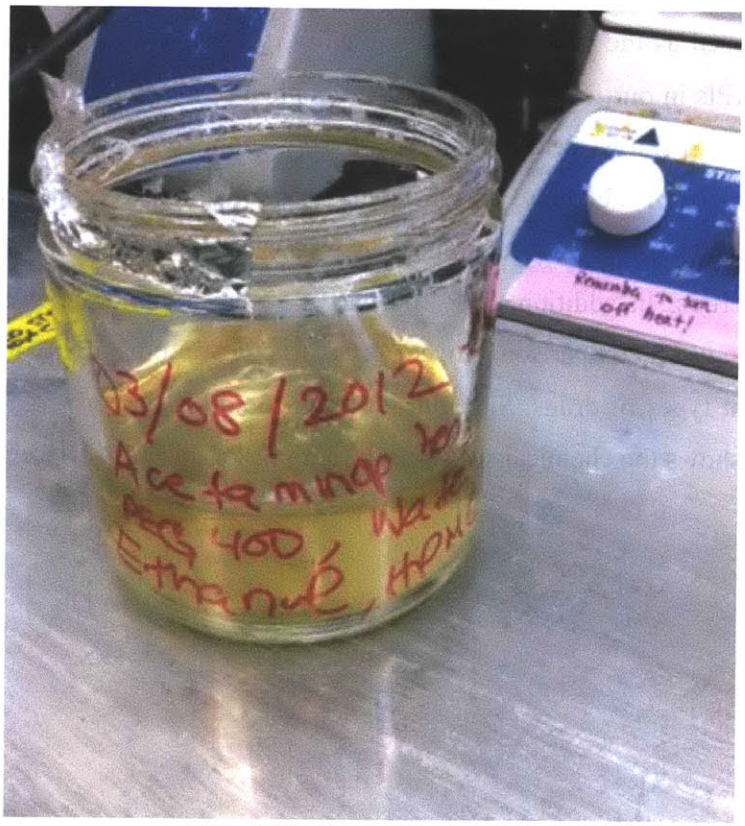

Figure 3.2.2: An example of a homogeneous liquid formulation for thin film preparation after 24 hours of stirring.

From previous studies done, it was found that 9% PEG formulation (15 grams each of HPMC e15 and e3, 96 grams of Water, 96 grams of Ethanol, 22.0 grams of PEG400) [13] showed the most desired mechanical properties for thin-film formation. As mentioned before, PEG 400 was the plasticizer user. Plasticizers are additives that provide additional flexibility and durability to the thin films. Plasticizers have smaller sizes and embed themselves between HPMC polymeric chains, spacing them apart, which will increase its free volume. By increasing the free volume, secondary bonds between chains break apart and create more space for chain motion. In this course of study, the search for solutions and associated films with desired properties was adopted.

Figure 3.2.3: Physical appearance of a non-homogeneous formulation where excess amount of solute exists and homogeneity never occurs.

Figure 3.2.4: Film-casting from unclear solution as represented in Figure 3.2.3.

3.3 Properties of Formulations and Thin-Films

Here we present the results obtained from characterization of solution and thin-films. As stated earlier, we carry out following measurements:

(a) Viscosity and Surface Properties
(b) Moisture Content
(c) Raman Spectroscopy
(d) X-Ray Diffraction
(e) Mechanical Properties
(f) Differential Scanning Calorimetry

3.3.1 Viscosity and Surface Properties

In order for a formulation to be cast into a thin film it must contain the right mechanical and physiochemical properties. In addition, the solution should be in the ideal range necessary for Thin-Film-Tablet-Manufacturing. This ideal range has been determined by *Padhye et al.* 2011 [14] as to be in the range of $0.06 - 6.0$ P a − s. As illustrated in Figure 3.3.1.1, the viscosity, as a function of temperature, for HPMC 9% PEG 400 was determined by *Padhye et al.* 2011. In the curve, the viscosity initially decreases as temperature rises, but after 53 □ C the viscosity starts to increase as temperature increases. This is expected because as the temperature increases the solvent starts evaporating and the solution becomes thicker and thicker thus increasing the viscosity. Moreover, it was imperative to find the appropriate shear rate to measure our solutions

in the rheometer. *Padhye et al.* 2011 stated that thin-films casting were done using a knife with wet thickness of 100 microns at a speed of 5 centimeter/minute. In a non-Newtonian solution, viscosity of solution depends on shear rate. A preliminary analysis was done to identify the appropriate shear rate to be used when casting thin films. According to equation (1), which describes the measurement of shear rate and strain rate, if the height of a wet film is 100 μ-m (Height) and the velocity of casting with the knife is 5 cm/sec (U) then by simplification the shear rate is approximately 20 sec^-1.

$$\tau = \mu \frac{\partial u}{\partial y}$$

(1)

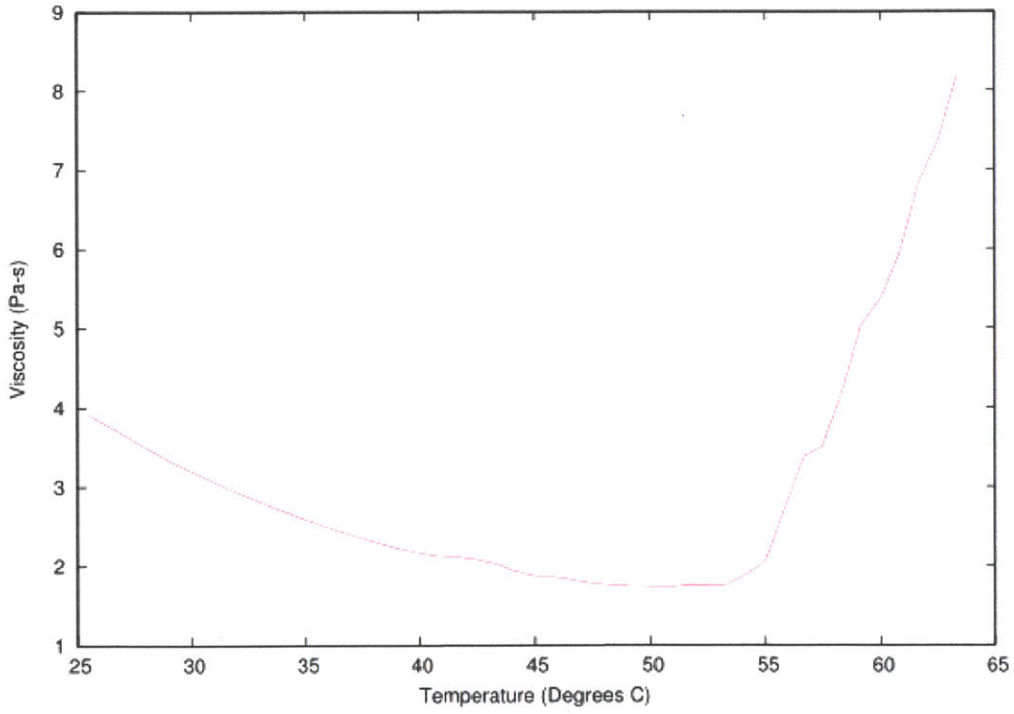

Figure 3.3.1.1: Viscosity as a function of temperature for the reference solution (HPMC 9%PEG 400 formulation) under a temperature ramp of 0-65 □C [14].

Therefore, a shear rate of 25.0 sec^-1 was proposed for all viscosity measurements. The same methodology was applied for all samples in this study. Viscosity measurements under the temperature ramp are presented in Figure 3.3.1.2, Figure 3.3.1.3, and Figure 3.3.1.4. The same trend observed in the ideal formulation HPMC 9%PEG [3] a lowering followed by a rise in viscosity, was observed for all three formulations. As expected, 20% ACM/ 10% PEG 400

solution shows a greater viscosity than 10% ACM/ 10% PEG 400. A higher drug loading constitutes a higher solute loading and therefore a thicker solution with a higher viscosity. Interestingly, it was found that the viscosity of 10% SPP 100/10% PEG 400 was greater than the viscosity of 20%ACM/10%PEG 400 at room temperatures. This may be due to hygroscopicity levels of SPP 100. The water content of SPP 100 as compared to that of Acetaminophen is much higher and therefore it will blend better with the HPMC polymer. Additionally, the chemical structure of SPP-100 might blend better with the HPMC polymer. SPP-100, as mentioned, is a semicrystalline drug and it might increase the viscosity of the formulation due chemical interactions between the drug and polymer. More water content also means the effecting concentration of each component is lower, since water is also one of the solvents into making the formulation.

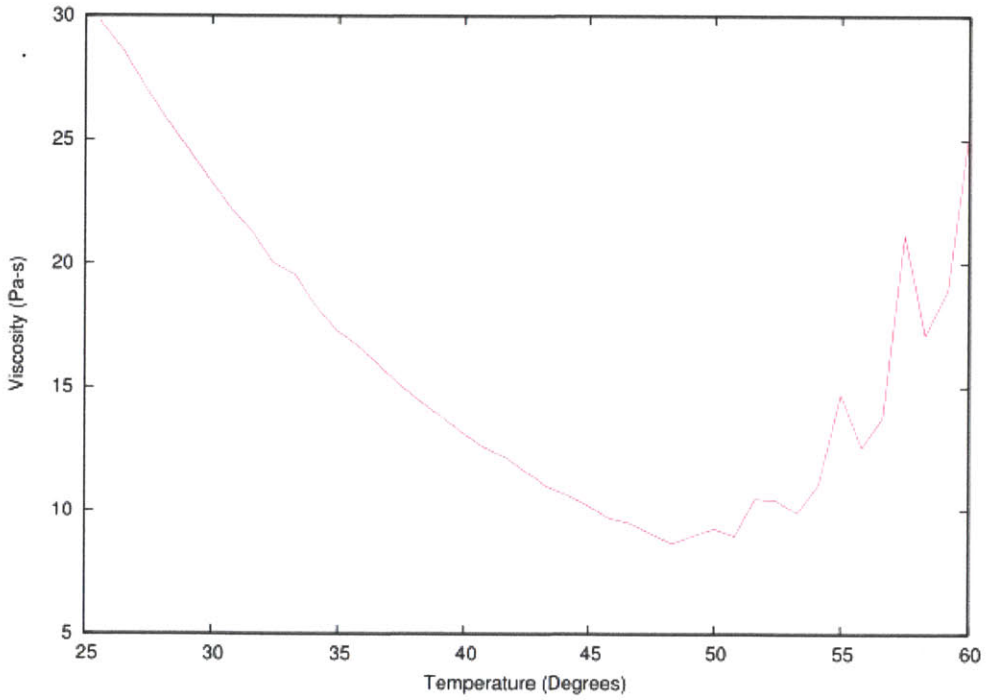

Figure 3.3.1.2: Viscosity measurements as a function of temperature for 20% Acetaminophen/ 10% PEG 400
solution.

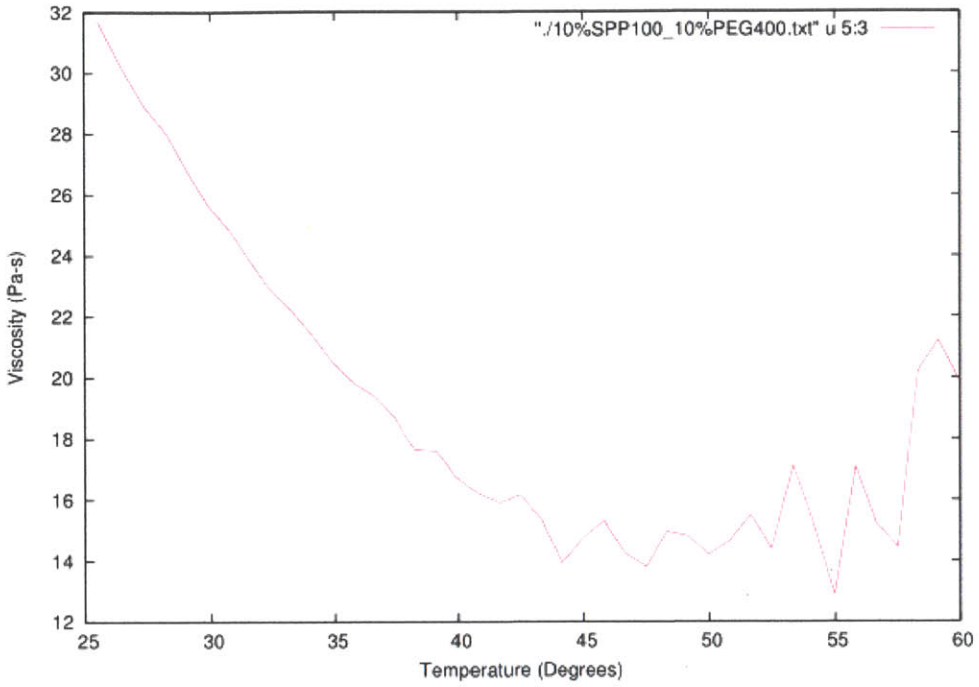

Figure 3.3.1.3: Viscosity measurements as a function of temperature for 10% SPP 100/ 10% PEG 400.

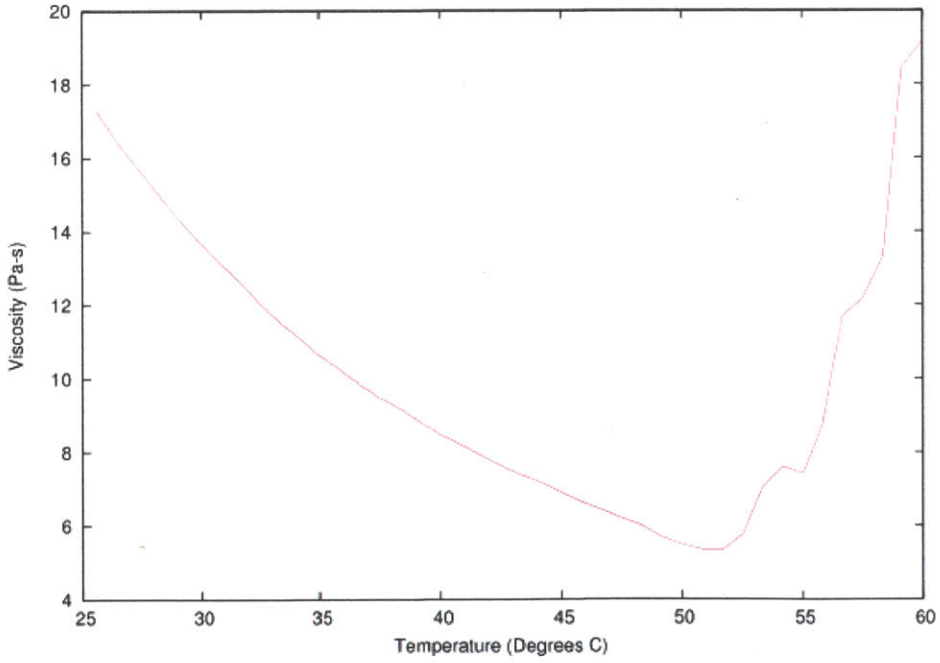

Figure 3.3.1.4: Viscosity measurements as a function of temperature for 10% ACM/ 10%PEG 400

Additionally, it is important to mention how viscosity is extremely important and it is the first step into deciding thin-film casting. As previously shown in Figure 3.2.4, a film cast from a solution where the viscosity is not ideal and not within the range described above, will form a robust, thick film that is not feasible for continuous tablet-film manufacturing. On the other hand, a film that is cast from a solution that falls within the ideal viscosity range can also form films that at times cannot be suitable. For example, 10% ACM/ 10% PEG 400 films had some areas where the film was neither smooth nor flat. This is because Acetaminophen is crystalline and crystalline drugs interact differently than semi-crystalline or amorphous drugs with the polymer. It is important to mention that this non-uniformity did not occur everywhere in the film and some parts were really usable. Figure 3.3.1.5, 3.3.1.6, and 3.31.7 show an Acetaminophen-based film, a SEM micrograph of the Acetaminophen based film, and an SEM micrograph of the SPP-100 based film, respectively.

Figure 3.3.1.5: 10%ACM/ 10%PEG 400 thin-film after being dried overnight.

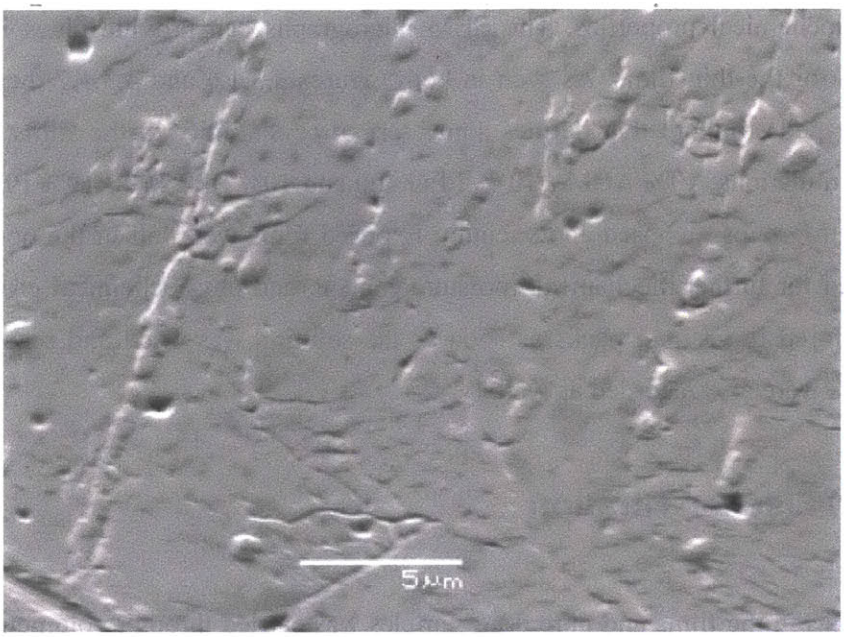

Figure 3.3.1.6: Scanning Electron Microscopy micrograph of 10% ACM/ 10% PEG 400 thin film.

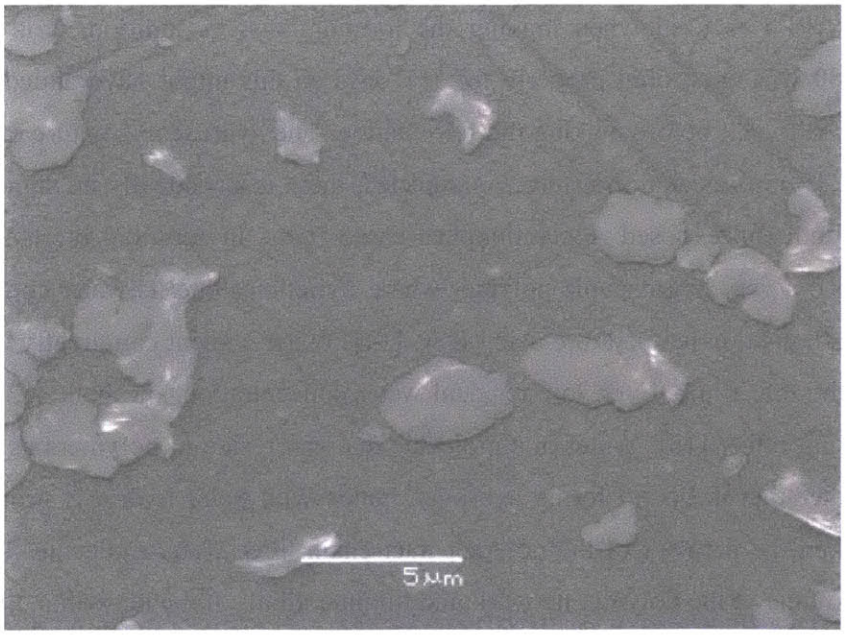

Figure 3.3.1.7: SEM micrograph of 10% SPP 100/ 10% PEG 400 films.

The viscosity of formulations can greatly affect the final surface characteristics and overall appearance of the thin film. As shown in Figure 3.2.4, when the viscosity is too high for a solid dispersion, a film cannot be cast. The ideal solution is to fall within the regime set by the NVS-MIT CCM group. If the solution is within the range, films can be cast and tested further for

mechanical and physiochemical properties. The SEM micrographs can provide clues into the surface characteristics for the thin-films. As seen in both Figures 3.3.1.6 and 3.3.1.7 there is no defined crystal rod-shaped structure that defines some sort of crystallinity in the films. In this study, we cast two formulations: 10% ACM / 10 % PEG 400 and 10% SPP 100 / 10% PEG 400. Films were divided into groups: exposed and vacuum. Exposed films were left in the hood over the weekend and tested for further mechanical, moisture content, and physiochemical properties. Vacuum films were stored in vacuum packs as soon as the solution was dried and ready to be stored. Their properties were also recorded as well.

3.3.2 Karl Fischer Titration

Moisture analysis in the films and pure drug samples was carried through volumetric Karl Fischer titration. Table 3.3.2.1 shows the recorded values obtained for all samples in the study. Please note that no standard deviations or sources of errors produced—the instrument only gives these values and they are manually written). Results indicate some moisture content in the original API itself. This same API was used when making the formulations. In addition, it is worth mentioning that SPP 100 was not stored properly for few days so this might have added some moisture content to the API itself before making the formulation. The hygroscopic nature of SPP-100 is reflected with (7.4%) of residual moisture. As depicted, there is statistically no significant difference between vacuum and exposed Acetaminophen based films. In addition, literature has shown that HPMC is also a very hygroscopic polymer where sometimes due its water content is very hard to find a glass transition temperature using DSC [14]. Water content can greatly impact the final properties of the thin-films. Even low residual water concentration, of about 1-2 wt % can have large plasticizing effect [15]. Water is a molecule that can reside in polymers as either bound or free [16]. Water that is bound forms hydrogen bonds with polar hydroxyl groups of polymer, so it can weaken the network of the polymer inter-chain. Free water molecules can be absorbed into the free volume of the polymer network and fill interstitials of the networks. Finally, the thin-films are very sensitive and are treated very carefully. The impact of residual water can affect the mechanical properties of the film by decreasing its tensile strength, its friction coefficient, and have an effect on the bonding properties of the film when cast.

Table 3.3.2.1: Moisture content (%) of thin-Film formulations and APIs considered (No sources of errors are produced in the instrument—values are recorded manually)

Candidate	Moisture Content (%)
Pure ACM	1.9235%
10% ACM, 10 % PEG Exposed Film	4.28135%
10% ACM, 10 % PEG Sealed Film	4.278328%
Pure SPP-100	4.3%
10% SPP, 10 % PEG Exposed Film	7.35152%
10% SPP, 10 % PEG Sealed Film	2.9218%

3.3.3 Raman Spectroscopy

Raman Spectroscopy provides a fingerprint of the molecule or sample to be investigated. Here, we study the Raman signals from all thin-films and pure APIs. The chemical form of both SPP-100 and Acetaminophen was studied using Raman Spectroscopy. As well, the molecular dispersion of the APIs in the casted films was characterized through Raman. It was found that HPMC is a great polymer for the solid dispersion of SPP-100 and ACM at 10% drug loading. As illustrated in Figures 3.3.3.1 and 3.3.3.2 the spectrum for both Acetaminophen and SPP-100 were obtained, respectively. It was found through Raman Spectroscopy that the Acetaminophen used was ACM Form I. This was also later confirmed through DSC by finding the melting temperature of ACM Form I and compared that to literature. As seen in Figure 3.3.3.1, the peaks corresponding to shifts at 1600, 1200 and 850 cm^{-1} are identical to those reported in *Kauffman et al.* (2008) Acetaminophen I [17]. In addition, the Raman Spectra obtained for Acetaminophen was identical to the spectra illustrated in Figure 3.3.3.2, obtained by postdoctoral associate Inna Myroshnyk in the NVS-MITCCM. On the other hand, as seen in Figure 3.3.3.3 the SPP-100 spectra was obtained as well. It was found that SPP-100 was Form A and it was then verified verbally with postdoctoral associate Haitao Zhang that I indeed received SPP-100 Form A.

However, the spectra does not 100% match to that of the NVS-MITCCM and this is due to moisture absorption and impurities that were included in the form A of SPP 100 used for the films. As mentioned before, SPP-100 was not stored properly and consumed some water absorption which affected the chemical fingerprint of SPP-100.

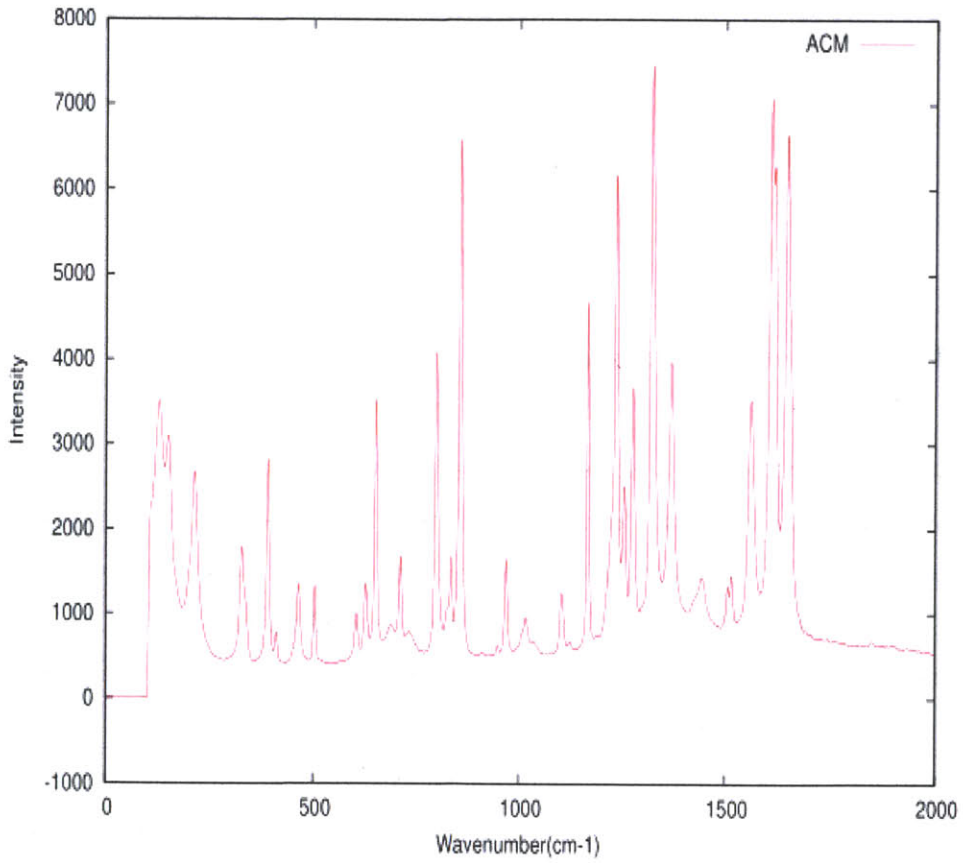

Figure 3.3.3.1: Raman Spectra for Acetaminophen Type I

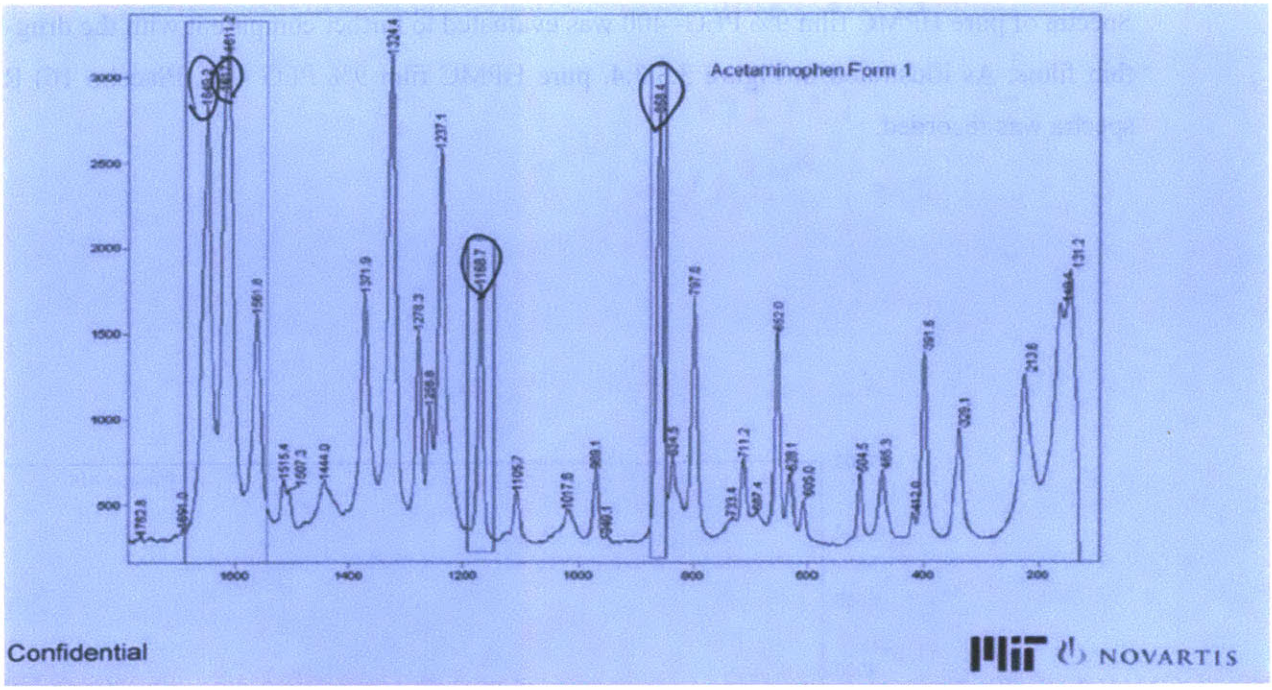

Figure 3.3.3.2: Raman Spectra for Acetaminophen I as analyzed by postdoctoral associate Inna Myroshnyk in the Novartis-MIT Center for Continuous Manufacturing.

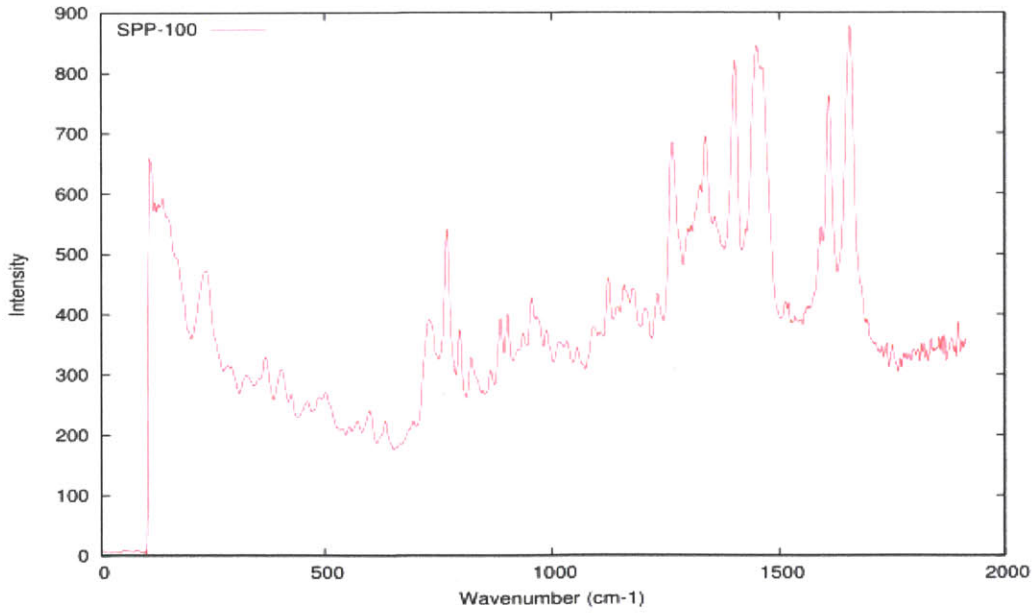

Figure 3.3.3.3: Raman Spectra for SPP-100 Form A.

In order to better assess the solid dispersion of the drug in the HPMC based film, Raman

Spectra of pure HPMC film 9% PEG- 400 was evaluated to further compare it with the drug-based thin films. As illustrated in Figure 3.3.3.4, pure HPMC film 9% PEG 400 (Placebo 16) Raman spectra was recorded.

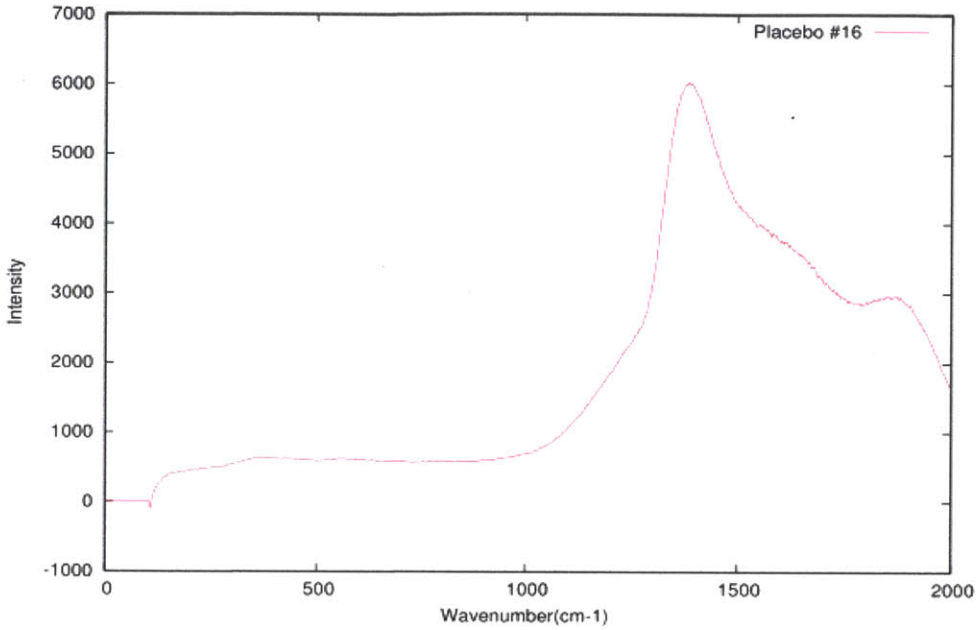

Figure 3.3.3.4: Raman Spectra for Placebo # 16 film.

Furthermore, to evaluate the physiochemical properties of the films, Raman Spectroscopy was done for all samples: (a) 10% ACM/ 10% PEG 400 (exposed) and (b) 10% SPP 100/ 10% PEG 400 (exposed and vacuum). Raman spectrum for all samples, regardless of the type of drug used, shows an exact similarity to that of pure HPMC films with no drugs. This verifies the fact that the thin film is HPMC dominated and the API is well dispersed in the thin film. Figure 3.3.3.5 and Figure 3.3.3.6, represent Raman spectrum for 10% ACM/ 10% PEG 400 (exposed) and 10% SPP 100/ 10% PEG 400 (exposed and vacuum), respectively.

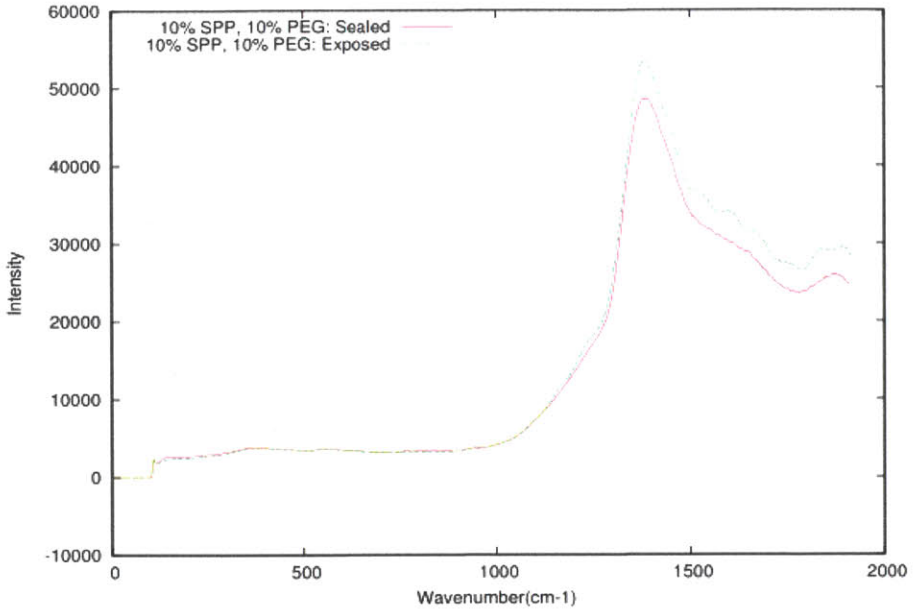

Figure 3.3.3.6: Raman spectrum for 10 % SPP 100/ 10 % PEG 400 (exposed/vacuum)

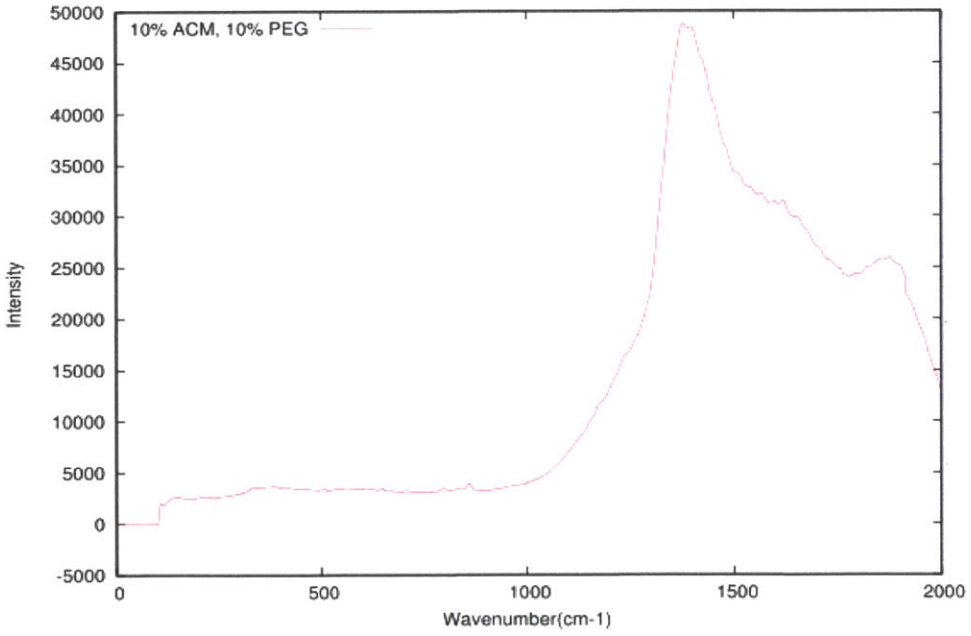

Figure 3.3.3.5: Raman Spectrum for 10% ACM/ 10 % PEG 400 (exposed)

We can depict from all Raman Spectrum when compared to Placebo #16 that all have a significant peak around 1500 cm^1 that might be attributed to the C=O stretching vibration, but most importantly we can conclude that all films are in the HPMC dominated region regardless of

the drug. To further validate this, an extreme formulation, where no films can be casted and the viscosity is extremely high was studied. Here, 20% ACM/ 10% PEG 400 films were studied. As shown before, these films are robust and very rough and do not fit into the category of thin films. As illustrated in Figure 3.3.3.7, a film made from 20% ACM / 10% PEG 400 (where there is a solid dispersion in the formulation) shows a similar Raman spectrum to that of pure ACM, regardless of HPMC also being present. This verifies that the amount of drug loading is really important if API amorphous dispersion is wanted in the film. At higher drug concentration, HPMC does not dominate, but rather the drug states in its crystalline or pure state. This is further validated by X-Ray diffraction results.

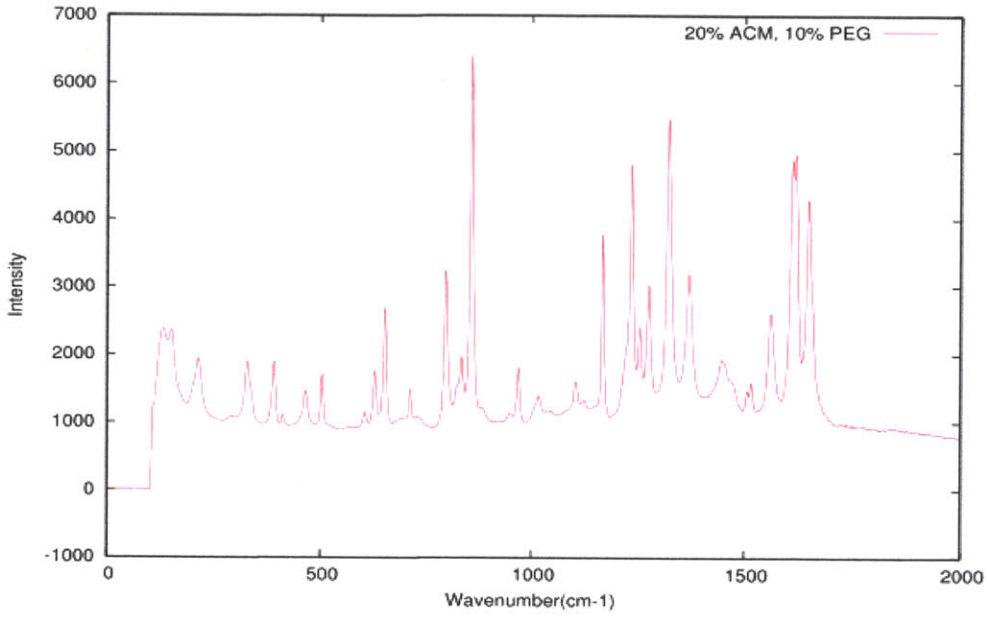

Figure 3.3.3.7: Raman Spectra of 20% ACM/ 10% PEG 400 films

3.3.4 X-Ray Diffraction

To further complete the physiochemical properties of the films and pure APIs, X-Ray diffraction was performed. The goal of X-Ray diffraction is to identify areas of crystalline or amorphous states of both drugs and films. As mentioned before, ACM was identified as Type I

ACM. X-ray diffraction verified this by comparing to that of data obtained by the NVS-MITCCM group. Figure 3.3.4.1 illustrates a reference XRD image of ACM Type I. Figure 3.3.4.2 illustrates that the ACM used in this study matches that of literature and ACM studied before in the NVS-MITCCM group.

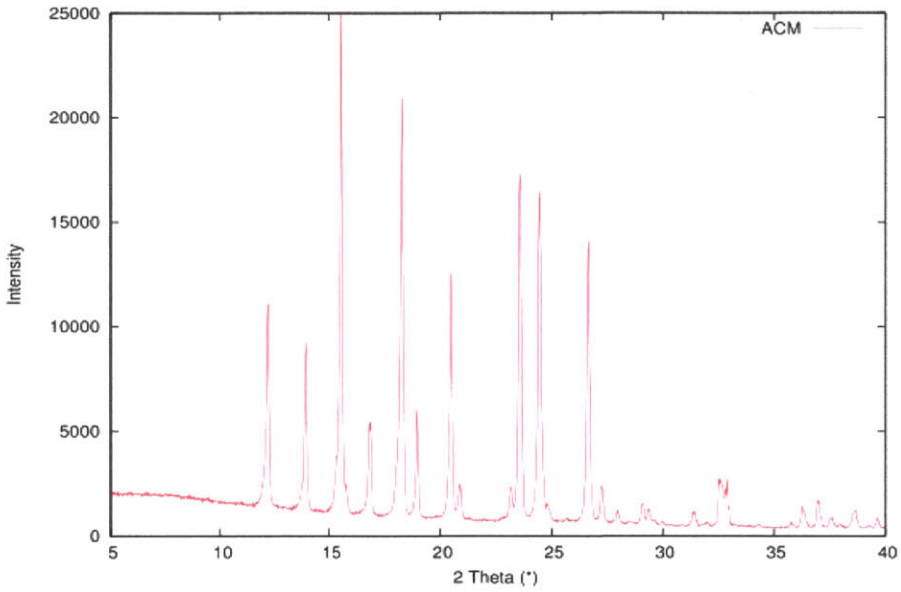

Figure 3.3.4.1: Reference ACM Type I X-ray diffraction data.

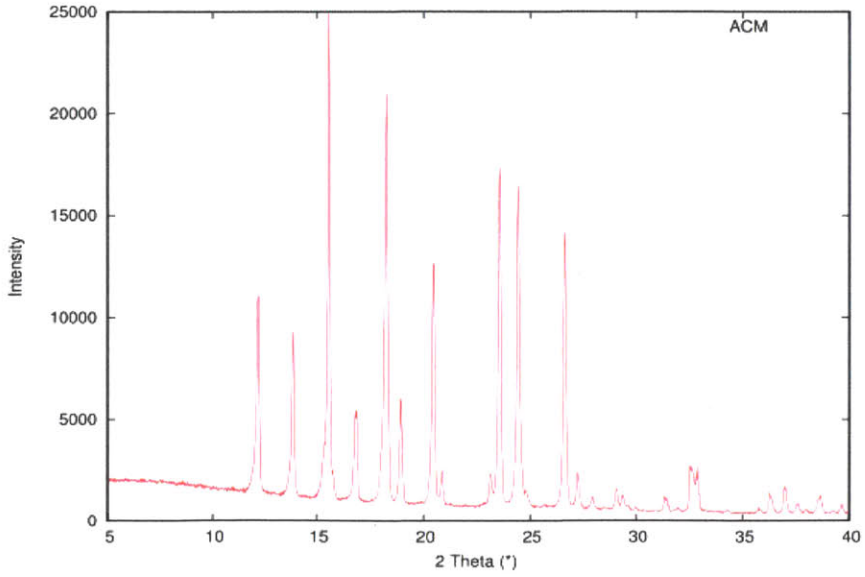

Figure 3.3.4.2: X-ray diffraction data on ACM Type I used in this study.

The same trend was observed for pure SPP-100. As expected, SPP-100 in this study shifted somewhat to that of referenced data due to water content and drug purity in our API. The X-Ray data confirms SPP 100 was received as Form A. Figure 3.3.4.3 and Figure 3.3.4.4 illustrate x-ray data for SPP-100 data as received and as used in our study, respectively. The peaks of SPP-100 form A suggest this drug is semi-crystalline and it was verified it is 50/50 crystalline/amorphous and due to its highly hygroscopic nature is recommended to be stored carefully to avoid discrepancies as seen here.

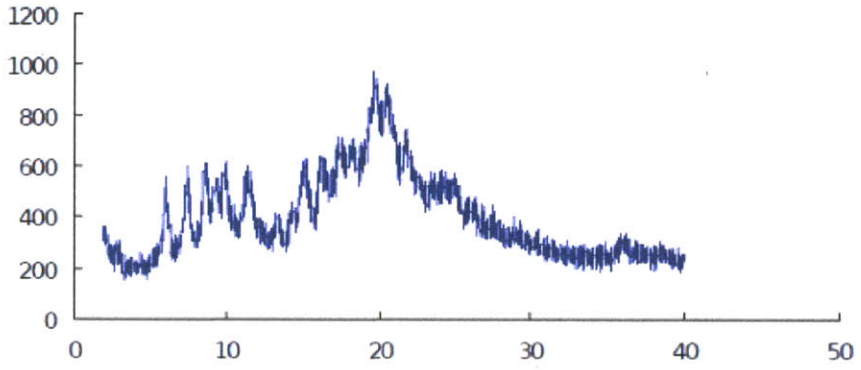

Figure 3.3.4.3: NVS-MITCCM Reference X-Ray data on SPP-100

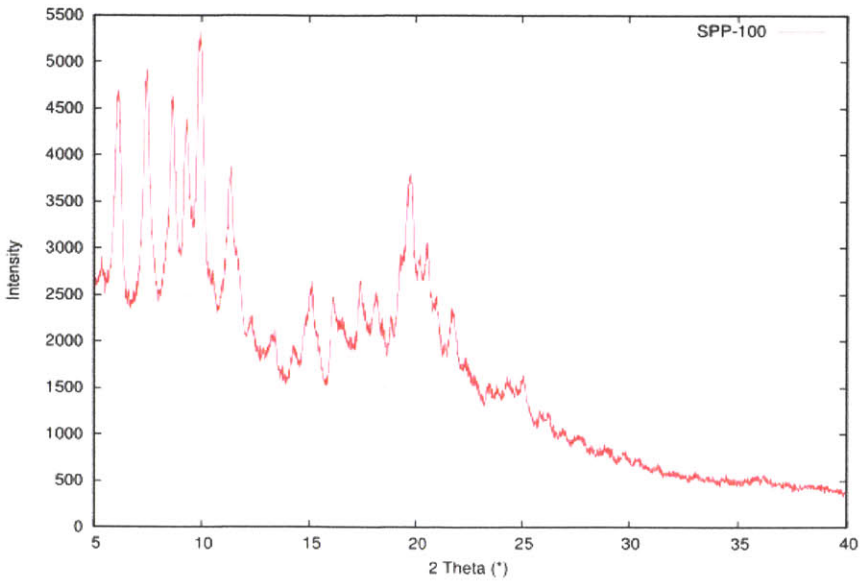

Figure 3.3.4.4: X-ray data on SPP 100 as used in the study.

Finally, X-ray diffraction was performed on the thin films to verify the drug nature in the film. As expected, none of the films showed a crystalline peak and verify the solid dispersion of the drug in the film and as such HPMC dominates. It is expected, though, a sample like 20% ACM/ 10% PEG 400 to show crystalline peaks due to the high drug loading and visible solid particles in the formulation.

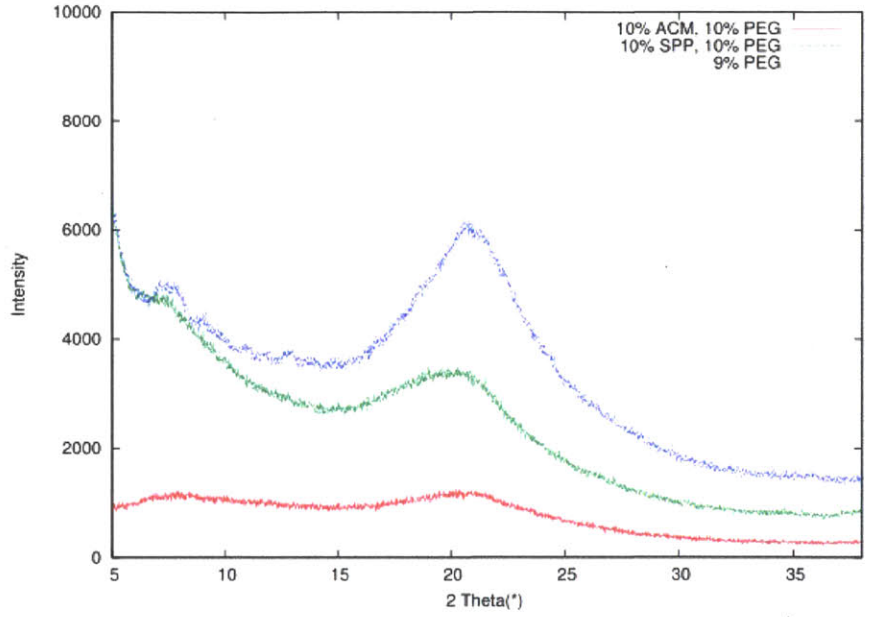

Figure 3.3.4.5: X-ray diffractions on 10%ACM/10%PEG 400 and 10% SPP100/10%PEG 400 films.

3.3.5. Mechanical Properties

Finally, in this study mechanical characterization was performed for all films. Samples were 1 inch wide and 2 inches long. The thickness of the samples was measure and inputted in the Instron software. The cross head speed was kept at 5 mm/min. This section aims to compare the mechanical properties of the thin films with respect to the ideal film (HPMC 9% PEG 400) as suggested in *Padhye and Trout* (2011b) [3]. However, a direct comparison of results obtained here with those presented in *Padhye and Trout* (2011b) [3] is not entirely accurate based on the experimental variables that were different. It is expected water content to affect the mechanical

properties, as mentioned before, and for that the properties of both sealed and exposed films were obtained. Stress and strain curves for all samples are shown in Figures 3.3.5.1- 3.3.5.4.

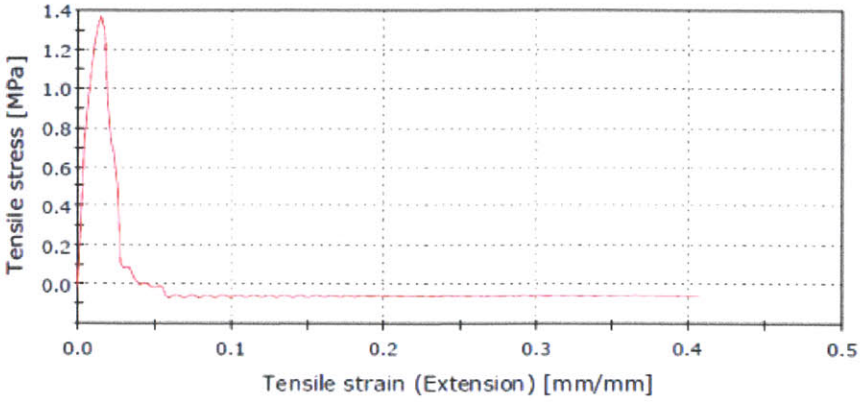

Figure 3.3.5.1: Stress and strain curve for 10% ACM/ 10% PEG 400-sealed

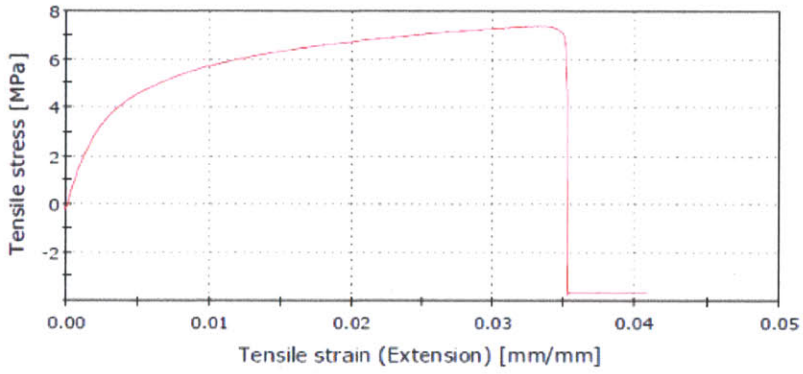

Figure 3.3.5.2: Stress and strain curve for 10%ACM/10%PEG 400-exposed.

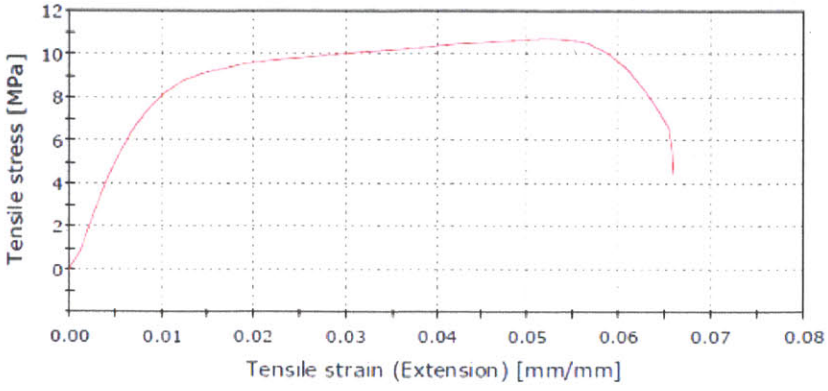

Figure 3.3.5.3: Stress and strain curve for 10% SPP 100/ 10% PEG 400-sealed

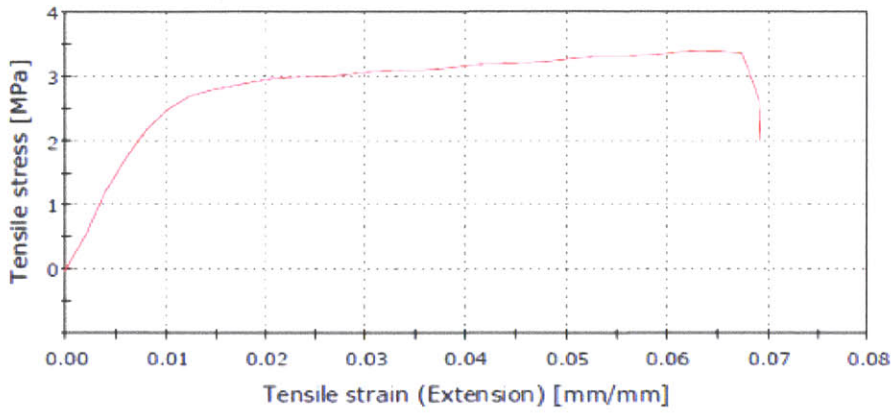

Figure 3.3.5.4: Stress and strain curve for 10%SPP100/10%PEG 400-exposed

Based on mechanical figures it can be concluded that:

(1) For both APIs, the exposed films showed a greater plastic deformation region when compared to the sealed one. This can be attributed to the fact that absorbed moisture in the exposed films acts as a plasticizer.

(2) SPP 100 films showed a greater yield and tensile strength when compared to the ACM based films. The fracture strain was also greater for SPP-100 films. This can be attributed to homogeneity of SPP-100 in the films and the fact that its crystalline structure is subdued. Whereas Acetaminophen crystals maintain their characteristic structure. From classical mechanics, a crystal substance does not show great regime of plastic deformation.

3.3.6 Differential Scanning Calorimetry

The melting point of both pure drugs, SPP-100 and Acetaminophen was measured to verify its form. The DSC for the films was attempted, but as mentioned before, it is very hard to measure the glass transition temperature of the films. The glass transition temperature is masked by the water content and a Tg was never obtained even when different measurements were made. Different protocols were followed to get rid of excess moisture in the film, but none showed a success into obtaining a glass transition temperature. Therefore, only the measurements for pure drugs are analyzed. As seen in Figure 3.3.5.1, the melting point of Acetaminophen matches to that

to the literature melting point of ACM type I [20], verifying the results from Raman and X-Ray Diffraction. The same was observed for the melting point of SPP-100 Form A (Figure 3.3.5.2).

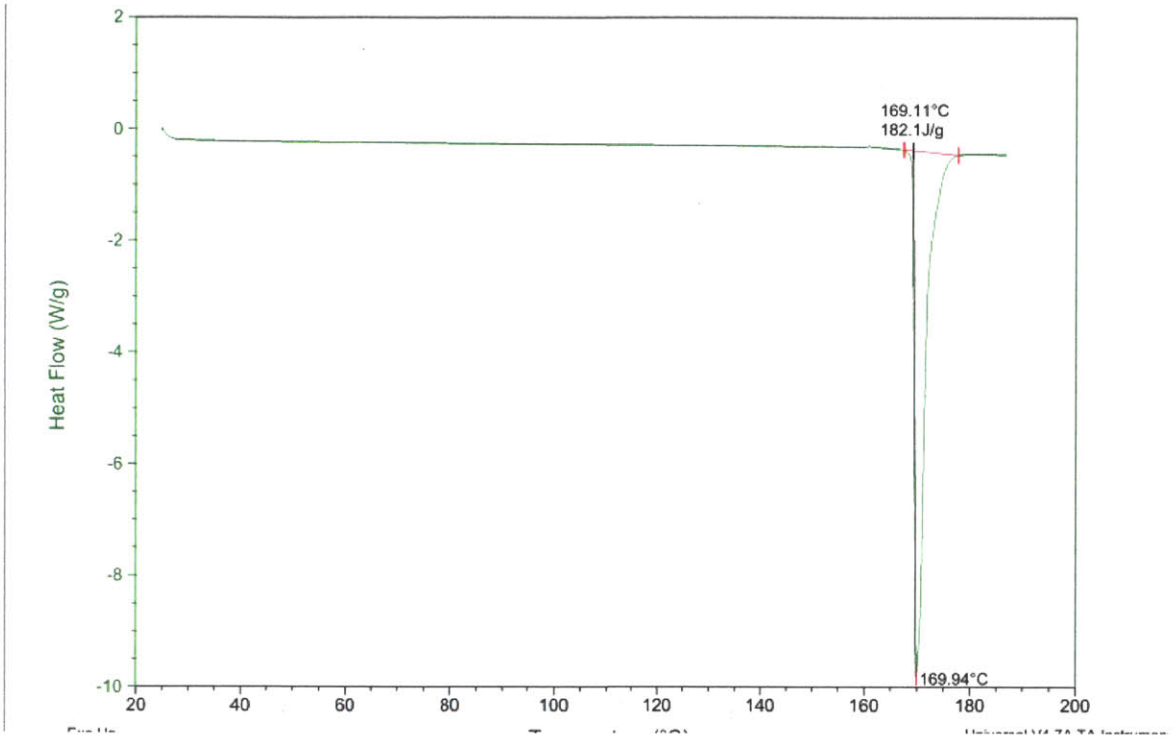

Figure 3.3.6.1: DSC measurement for pure Acetaminophen. The melting point was found to be 169.94 □C.

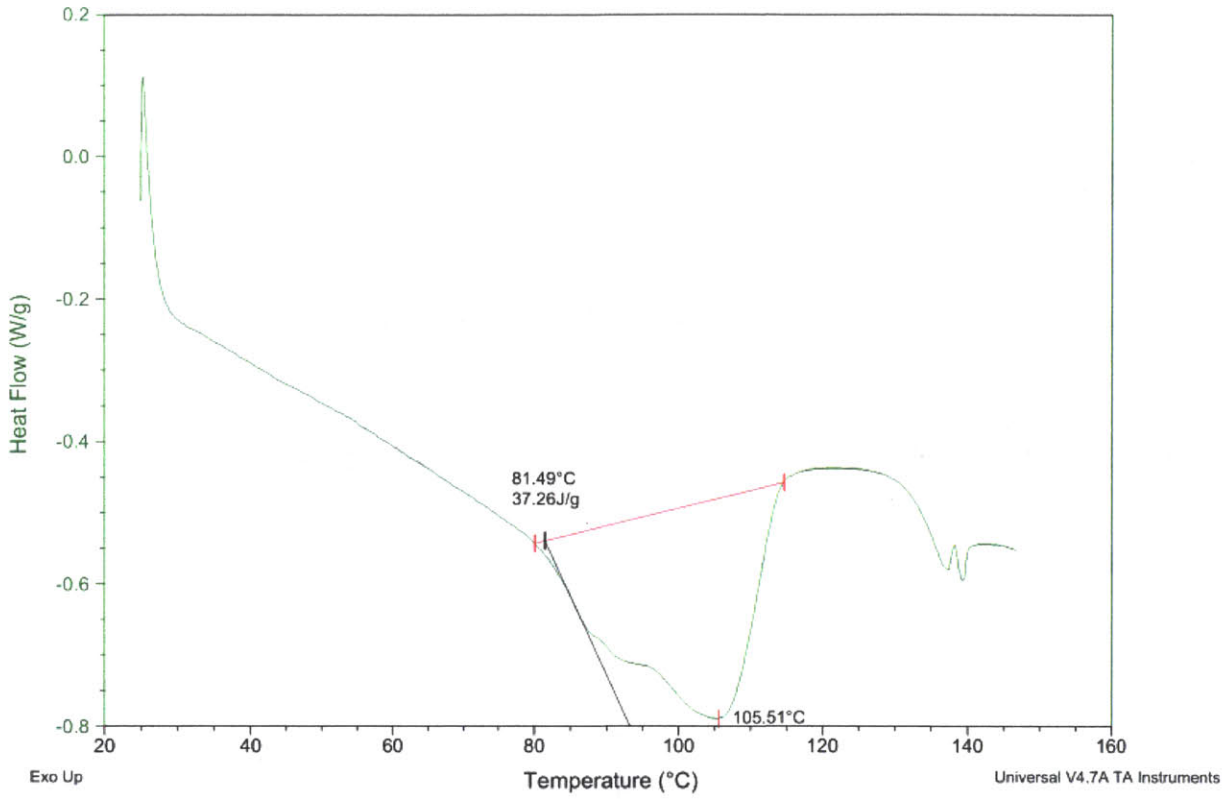

Figure 3.3.6.2: DSC measurement for SPP-100. The overall skewness of the graph is due to the water content found in SPP-100. Melting point found to be 105.51 □C.

3.3.6. Conclusion

It was found that both 10% SPP-100/ 10% PEG 400 and 10% ACM/ 10% PEG 400 formulations had the appropriate viscosity to be cast into films. Both films were characterized by various techniques such as Karl Fischer Titration, Raman Spectroscopy, X-Ray Diffraction, Instron Testing, and Differential Scanning Calorimetry. Both films showed a degree of residual water content and both were HPMC dominated (meaning good dispersion) as observed by Raman and XRD results. Films made from 10% SPP-100/ 10% 10% PEG 400 showed better results in the mechanical testing and are preferred than those of 10% ACM/ 10% PEG 400. ACM-based films tend to crumble when cast and are extremely thin. Additionally, spectroscopy, DSC, and X-ray data confirmed the chemical stability of both drugs: SPP-100 and ACM.

Chapter 5

Thin-Film-Tablet Continuous-Manufacturing: Conclusions and Future Work

5.1 Summary of Thesis and Future Work

The overall goal of this study has been to find optimal formulations of Acetaminophen and SPP-100 capable to be cast into polymer based thin-films with the right mechanical and physiochemical properties for tablet forming. Here we considered thin film formulations based on HPMC and PEG, as a plasticizer. Only two APIs were used in the study: Acetaminophen and SPP-100. In order to find the most workable thin-film, various characterization techniques were used to analyzed the properties of the polymeric thin-films such as Karl-Fischer titration for water content, Raman Spectroscopy for a fingerprint chemical image of the film, SEM for surface properties, rheology for viscosity measurements, X-Ray diffraction for crystallinity, DSC for melting temperatures, and Instron testing for mechanical properties. All films analyzed were compared to a placebo film where no drug loading existed. Regardless of API, 10% drug loading/ 10% PEG 400 showed to be the promising as the thin-films were molecularly dispersed and HPMC dominated. On the other hand, 20% drug loading/ 10% PEG 400 proved to be a high viscosity solution where films could not be cast. Therefore, API content, moisture content, and physiochemical properties are all correlated to the desired mechanical robustness for film folding and tablet formation. Mechanical data proves that SPP/HPMC thin-films obtained a greater yield and tensile strength when compared to ACM/HPMC thin-films. It is believed that ACM/HPMC thin-films crystallize over time and how fast it happens depends on the ACM content. Therefore, the right API/Plasticizer content was found for thin-film formulations and further work needs to be done in regards to the mechanical properties of the thin-films.

It was found that the thin-films obtained the appropriate physiochemical properties for tablet forming. Nevertheless, future work needs to be done to better understand the mechanical

properties of the films. Currently, the films are being tested for compaction pressure, friction against stainless steel and aluminum blocks, and bonding. Without the correct mechanical properties, the thin-films would not be able to be rolled into tablets continuously.

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