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DESIGN AND DEVELOPMENT OF DRUG DELIVERY SYSTEMS FOR IMMEDIATE AND
SUSTAINED RELEASE UTILIZING HOT MELT EXTRUSION TECHNIQUES

A Dissertation

presented for the Doctor of Philosophy degree in the Department of Pharmaceutics

The University of Mississippi

Abhilasha Singh

July 30th 2011

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ABSTRACT

Polymers have indispensable role in pharmaceutical formulation development. Polymer choice is a critical factor to obtain the desired drug-release profile during formulation development for HME (Hot melt extrusion). Many commercially available, pharmaceutical-grade polymers can be used in HME formulations. The suitable polymer choice facilitates processing in the extruder. When choosing a polymer to use in a formulation, processing conditions and processing attributes of the active pharmaceutical ingredients (APIs) should be considered. The physicochemical and the mechanisms of drug release from drug delivery systems prepared by utilizing HME with various polymeric carriers were investigated.

Amorphous forms of API can have as much as 10-1600 fold higher solubility than their crystalline forms. HME technology is extensively been used to convert crystalline form to amorphous form of drug with increased solubility with polymeric matrices as carriers. Efavirenz (EFZ) and Carbamazepine (CBZ) are crystalline lipophilic model drugs used in the studies. These are class II drugs (low solubility, high permeability) according to the BCS guidance by the FDA.

Various polymers for example cellulose ethers (HEC, HPC and HPMC), hypermellose ester derivatives (HPMCAS and HPMCP) and acrylic polymer (Eudragit[®] EPO) with pH dependant solubility were examined for suitability as solubility enhancers for EFZ and processability in melt extrusion processes. To determine suitable polymeric carrier, different tools like solubility parameter calculation, Thermogravimetric analysis (TGA), Differential scanning calorimetry

(DSC) and Dissolution were employed. The physicochemical characteristics of the extruded formulations were compared to the respective physical mixtures to examine the effect of the extrusion process. Furthermore, HME formulations were evaluated for drug polymer interaction utilizing Fourier transform infrared spectroscopy (FTIR).

Sugar alcohols were used as carriers in solid dispersions, since it is known that glass formation is common in many polyhydroxy substances, presumably due to their strong hydrogen bonding which may prevent re-crystallization of the amorphous form of drug molecules. Furthermore, they possess the advantage of high thermal stability and absence of browning reactions. The sugar alcohols (Mannitol, Sorbitol, and Xylitol) investigated in this study proved to be very effective in forming solid dispersions and enhancing solubility of CBZ form III. Xylitol exhibited good processability.

Chlorpheniramine Maleate (CLPM) and Diltiazem Hydrochloride (DTZ) were used as a model API to design a sustained release pellet formulations utilizing Ethocel™ (EC). EC is also studied as matrix former with lipophilic processing aids (Stearic acid, Tristearin and Trimyristin) for HME sustained release pellets. The purpose of this project was to study the effect various levels of processing aid with Ethyl cellulose matrices utilizing melt extrusion techniques. All of the processing aids decreased the T_g of Ethocel™, which facilitated the extrusion process. With addition of Stearic acid (10%w/w), the T_g of the EC matrix decreased from 132.6±2.5°C to 125.4±1.7°C. FTIR spectra of extruded pellets of EC with lipophilic processing aids indicated

band shift when compared to the spectra of pure EC suggesting intermolecular interaction between EC and lipophilic processing aids.

DEDICATION

I would like to dedicate my doctoral dissertation to my family. I am grateful to my parents Dr. Tejvir Singh and Mrs. Kiran Kumari, my brothers Mr. Amit Singh and Mr. Sumit Singh for unconditional love, and support, my husband Mr. Harinder Singh for his continuous encouragement and patience

ACKNOWLEDGMENT

I would like to thank my advisor Dr. Michael A. Repka for the giving me the opportunity of working in his lab. Thanks for your patience, encouragement and support throughout the PhD program.

My appreciation is extended to my committee members: Dr. Soumyajit Majumdar for constructive criticism and guidance, Dr. Seonbong Jo and Dr. John O'Haver for taking time in reviewing my dissertation.

I would like to thank Dr. Kwame Nti Addae, Dr. Setu Roday and Dr. Chong-Hui Gu for supervising and mentoring me during my internships at Vertex Pharmaceuticals.

I would also like extend my thanks to Dr. Amar Chittiboyina for the help with FTIR and NMR samples and Dr. Vijaysankar Raman with SEM analysis.

I am thankful to Dr. Deepthi Pabbisetty, Dr. Harsha Vinnakota and Dr. Venkat Tumuluri for their friendship and support. Weibin Deng and Dr. Noorullah Naqvi Mohammed are gratefully acknowledged for their support and help in the lab.

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CHAPTER – 1 INTRODUCTION

Hot melt extrusion (HME) is an established manufacturing process that has been used in the plastics and food industry since 1930s (1). A number of research groups have demonstrated the HME process as being a viable technique for the preparation of a variety of pharmaceutical drug delivery systems including granules, pellets, sustained release tablets, transdermal and transmucosal drug delivery systems and implants.

Table 1-1: Examples of solving pharmaceutical challenges via HME (2-3).

S. No.	Issues	Solutions by HME
1	Poor (Unreliable/low) bioavailability due to poor API solubility	Use of HME to prepare solid solution and solid dispersion (enhanced dissolution).
2	Poor taste of API	Use of HME to prepare taste masked dosage forms.
3	Unreliable sustained release action	Uses of HME to prepare sustained release dosage forms (single or multiple units).
4	Manufacturing films	Use of HME to prepare oral strips or dermal patches.

1.1 Extruder Assembly

For the present studies we used a co-rotating twin screw extruder with a screw diameter of 16 mm and a barrel length of 640 mm. The length of the screws in the extruder is given in terms of L/D ratio (length of the screw to the screw diameter), which in this case is 40:1 (Figure 1-1). This extruder can be operated at maximum screw speed of 500 rpm, operating temperature up to 300 °C and maximum operating pressure of 100 bars (4).The extruder consists of two screws

which are designed to move in co-rotating manner and are driven by an AC drive. These two screws are assembled with the standardized screw elements, mainly involved in conveying and kneading or mixing (5). The conveying elements are installed at the beginning and end of the extruder, working jointly to transport the melted material to the die plate (Figure 1-1 and 1-3). The kneading elements are assembled in the middle of the extruder at various angles to generate shear forces through mechanical energy input, support the melting process and the homogenization of the melt. In general, kneading elements with a higher advance angles have higher mixing and shearing properties than the ones with lower angle (5). The first kneading unit consists of four elements with three increasing twist angles of 30°, 60°, and 90° which result in an optimum mixing and shearing of the powder blend (Figure 1-2).

In the current research, powder ((carrier with active pharmaceutical ingredient (API)) was fed into the extruder through feeding zone 1. The material was heated with initial melting/softening in the initial zones. Thereafter the material was mixed and homogenized by kneading elements and was then transported by conveying elements to the end of the extruder through a die which can shape the extruded material into films or rods etc.

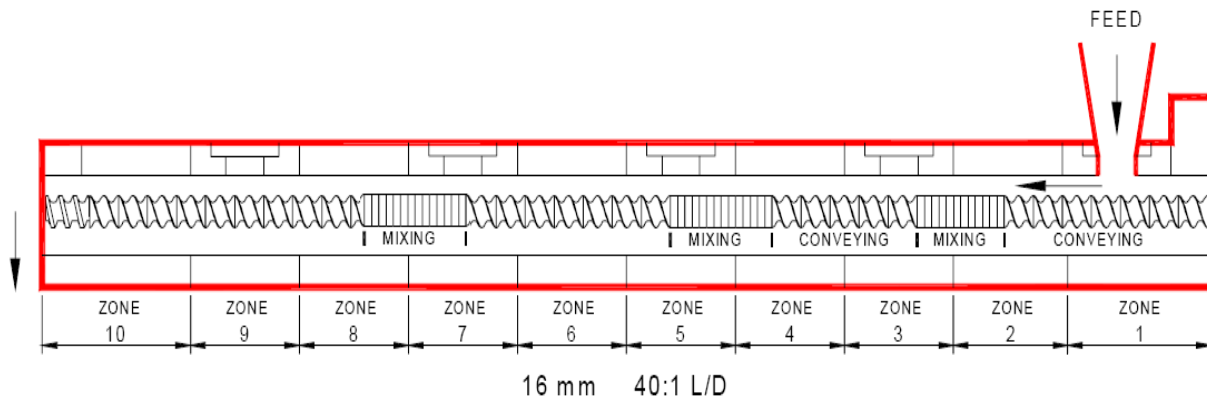


Figure 1-1: Twin screw extruder (4)

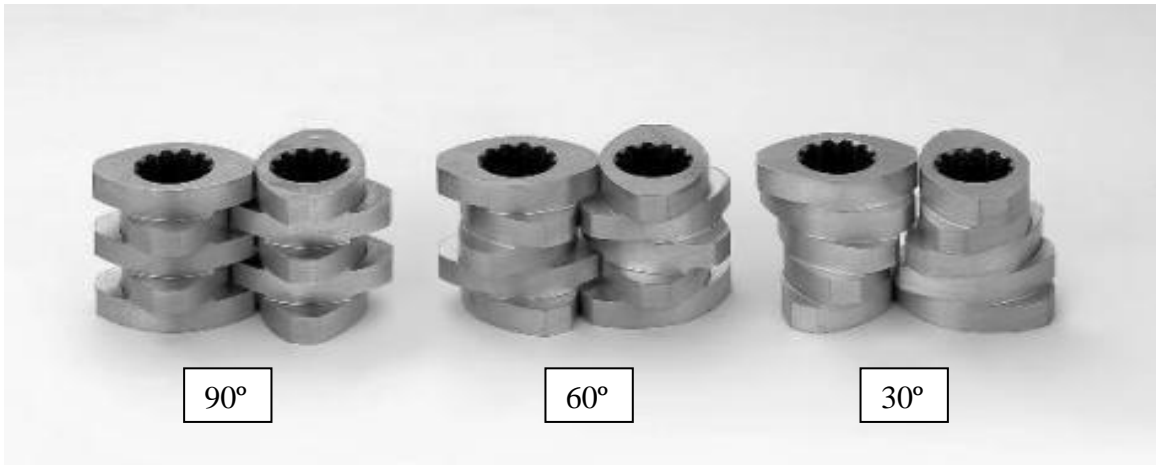


Figure 1-2: Kneading or mixing elements of advance angles (5)



Figure 1-3: Conveying elements (5)

Extruded films were cooled over chill rolls (Figure 1-4 and 1-5). In addition, the chill rolls facilitated collection of the films. Thickness of the films can be adjusted using the speed of upper and lower chill rolls. These films were mainly studied for trans-mucosal drug delivery systems. The rod shaped extrudates were cut into a specific pellet length by means of a pelletizer (Figure 1-6). The pellets or milled extrudates were filled into the capsules or further pulverized and compressed into tablets.

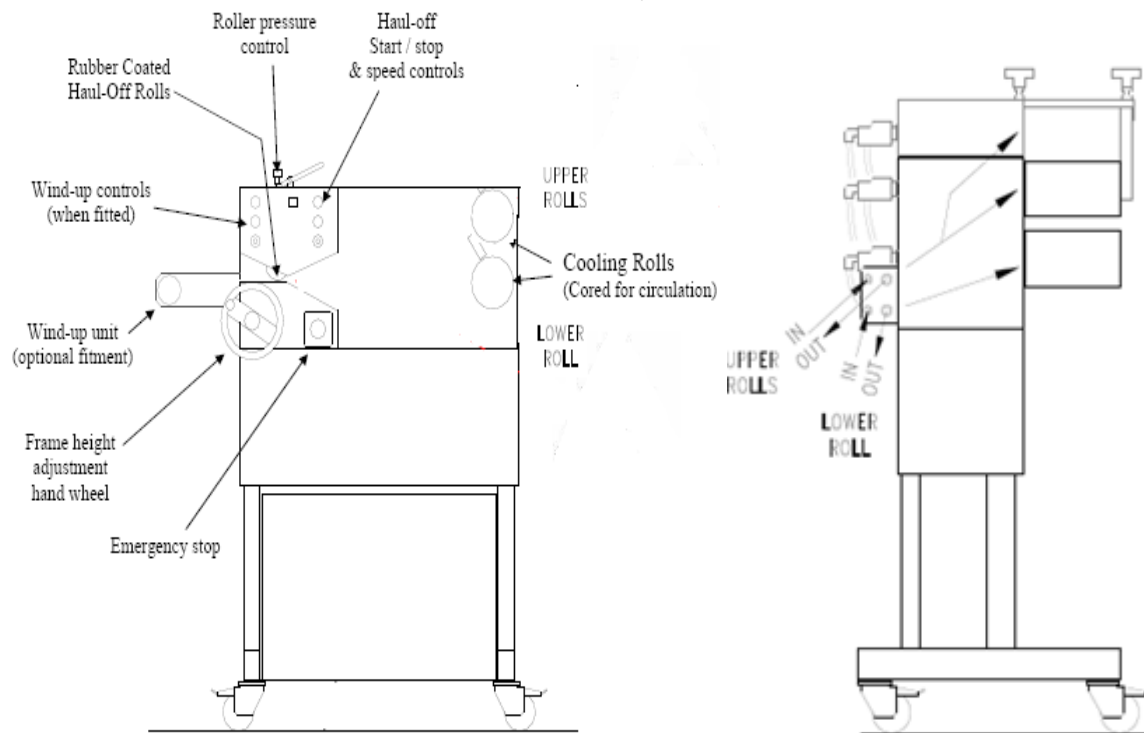


Figure 1-4: Chill rolls for cooling extruded films (4)

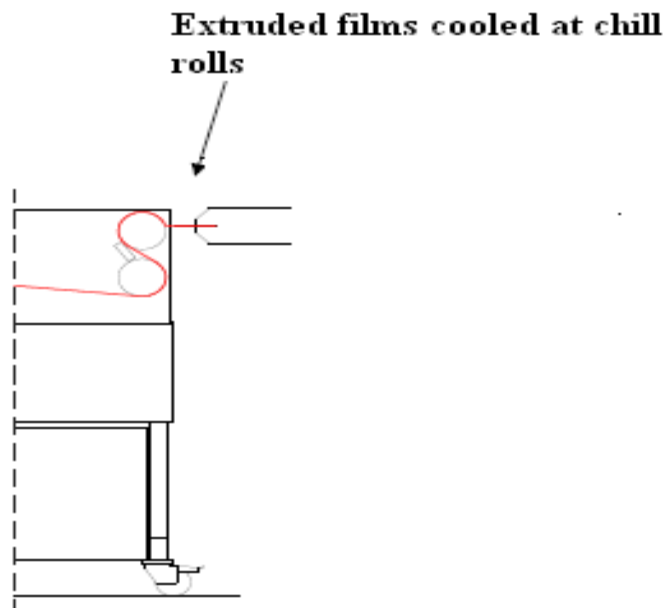


Figure 1-5: Schematics of extruded films utilizing chill rolls (4)

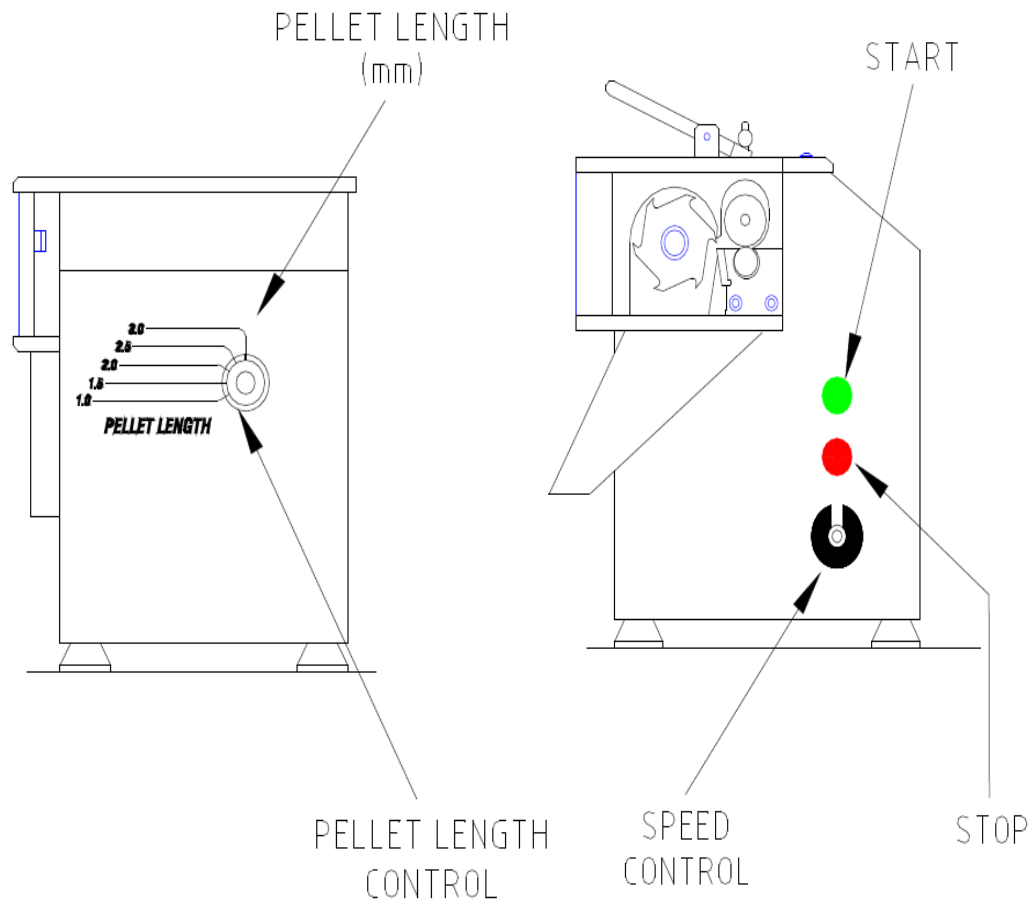


Figure 1-6: Pelletizer (4)

1.2. Investigation of Cellulose ethers, Hypromellose esters and Sugar alcohols, as solid dispersion carrier matrix utilizing HME

Solid dispersion is defined as the dispersion of an API in one or more inert carrier(s) or a hydrophilic matrix in the solid state. Solid dispersions have widely been used in clinical formulation development as a successful approach to deliver poorly water soluble APIs and improve the exposure in both experimental animals and human subjects (6). There are a variety of approaches to prepare solid dispersions (Figure 1-7) using the polymers as carriers, such as hot-melt extrusion (HME), freeze drying (FD) and solvent co-precipitation (CP) (7-8).

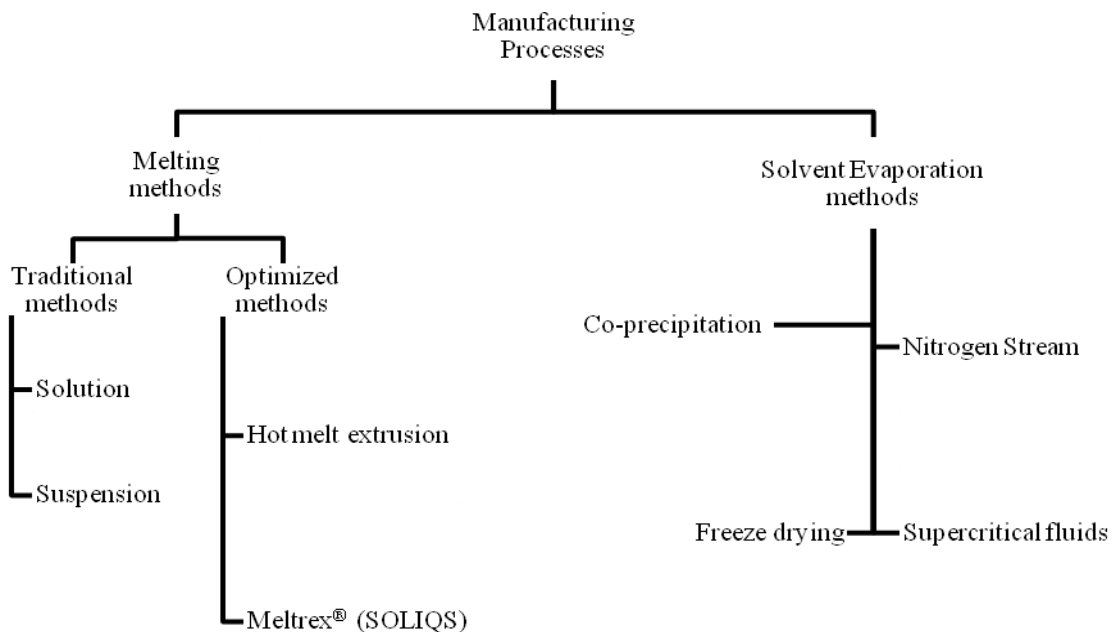


Figure 1-7: Manufacturing processes chart used to produce solid dispersions (7).

HME is a viable method to prepare solid dispersions without using organic solvents. It represents an efficient and continuous manufacturing process with no further drying or discontinuous process steps as involved in FD and CP, respectively.

Polymeric carriers have been the most successful excipients for solid dispersions attributed to their ability to form amorphous solid solutions (7). In the present study, Efavirenz (EFZ) (Figure 1-8) was used as a model API to design formulations to enhance solubility of EFZ utilizing water soluble cellulose ethers-Hydroxy ethyl cellulose (HEC, M.W~90,000 g/mol), Hydroxy propyl cellulose (HPC, M.W~80,000 g/mol) and Hydroxy propyl methyl cellulose or Hypromellose (HPMC, M.W~95,000 g/mol) to form solid dispersions via hot melt extrusion (HME). Hypromellose ester derivatives-Hypromellose acetate succinate (HPMCAS, M.W~18,000 g/mol) and hypromellose phthalate (HPMCP, M.W~45,600 g/mol) were investigated as carriers for the ease of processability, physical stability and dissolution behavior of model API. These synthetically modified natural cellulose polymers are traditionally used as enteric-coating agents,

film-forming agents and more recently as solubility enhancing agents. The results obtained from our studies could provide us a wide choice of polymers in HME formulation development. EFZ is an approved HIV-1 reverse transcriptase inhibitor for the treatment of HIV-1 infections in combination with other anti-retrovirals. It is a crystalline, non-hygroscopic and lipophilic (log P of 5.4) material with an aqueous solubility of 9.2 µg/mL (pH 8.7) at 25 °C (9). EFZ was extruded with water soluble carriers to form a number of solid dispersions. These solid dispersions were then characterized for release profiles and solid state characteristics using Differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD) and Fourier Transform Infra-red Spectroscopy (FTIR).

Table 1-2: Classification of Solid dispersions (10-11)

	Glassy solid solution	Solid solution	Glassy suspension		Eutectic	Amorphous Precipitation
Phases	1	1	2	2	2	2
Drug	Molecularly dispersed	Molecularly dispersed	Amorphous	Crystalline	Crystalline	Amorphous
Carrier	Amorphous	Crystalline	Amorphous	Amorphous	Crystalline	Crystalline

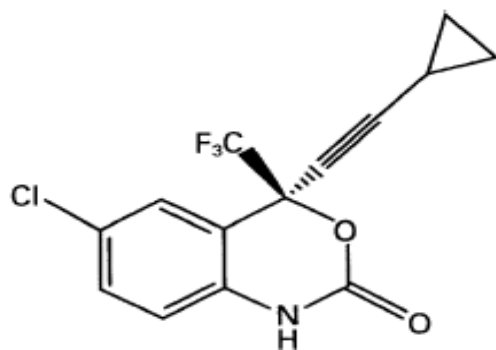
The molecular weights of the cellulose derivative polymers used in solid dispersions are literature values determined using size exclusion chromatography. In polymer industry cellulose derivative polymers, molecular weight is not routinely measured. This is probably because the direct measurement of molecular weight generally requires an expensive and complicated analytical system. Instead, solution viscosity, which is related to molecular weight, is usually employed to monitor quality because it is a simple, easy and reproducible method.

Water-soluble carriers such as sugar alcohols (Mannitol, Sorbitol and Xylitol) have recently attracted a considerable interest in improving the dissolution rate, and hence possibly bioavailability of hydrophobic drugs. However, their utility as a primary matrix in melt extrusion

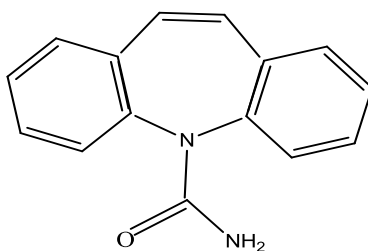
has not been studied. The present work also focuses on the formulation of the poorly water-soluble drug Carbamazepine (CBZ, Figure 1-8) using sugar alcohols as carriers. CBZ is an imperative anti-epileptic agent that has been in use for over 30 years. It is an example of a water-insoluble drug that requires relatively high dosing (>100 mg/day) to attain a therapeutic effect (12). CBZ poses multiple challenges for oral drug delivery, including a narrow therapeutic window, auto induction of metabolism and dissolution-limited bioavailability. CBZ crystallizes in at least four anhydrous polymorphic modifications and has been shown to form several solvates, including a stable dihydrate from aqueous solutions. A marketed formulation of CBZ such as Tegretol[®] contains its pharmaceutically acceptable P-monoclinic or form III (12).

1.3 Taste masking utilizing HME

Another drawback with EFZ pharmacotherapy is that it irritates oral mucosa. The burning mouth syndrome (BMS) leads to an unplanned interruption of antiretroviral pharmacotherapy (13). In this study, we have designed formulations using Eudragit[®] EPO (M.W= 47000 g/mol) as carriers for solid dispersions. Eudragit[®] EPO is a copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters (14). It is soluble below pH 5.5. This polymer matrix can prevent the release of the water soluble drugs in saliva (pH 6.8–7.4) and readily dissolves in the gastric fluids (pH 1.0–1.5) (14). It is a very popular polymer for moisture protection and masking bitter or unpleasant tastes.



Efavirenz



Carbamazepine

Figure 1-8: Chemical structures of model poorly water soluble drugs

1.4 Development of sustained release pellets using HME

A modified release dosage form is one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Controlled or modified release systems are characterized by their ability to either control the rate or the area of drug release. With respect to oral drug delivery, the release can either be sustained during the transit of the dosage form in the gastro-intestinal tract (extended, sustained or prolonged drug release), or delayed to regions subsequent to the stomach including the small intestine or the colon (delayed release) (14).

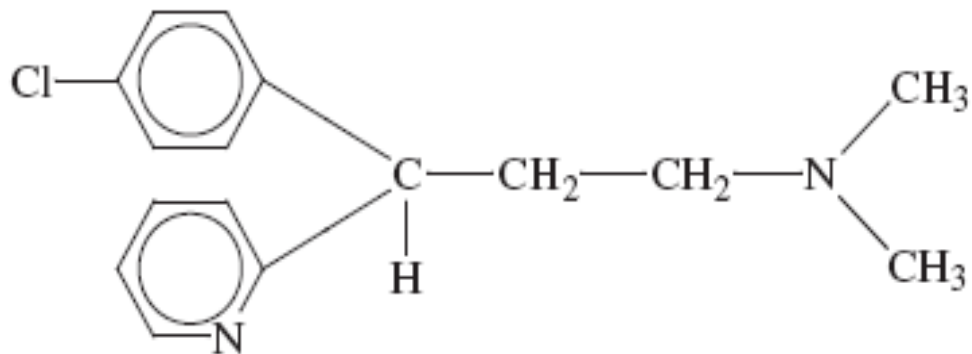
Sustained release (SR) delivery systems for oral dosing are effective in achieving ideal therapy with drugs that are eliminated rapidly or have a narrow effective range of the blood concentration. The drug may be embedded in a release-controlling matrix (matrix systems) or inside a core surrounded by release-controlling shell or a membrane (reservoir system) (15).

Controlled delivery dosage forms can further be classified as single-unit (monolithic) or multiple-unit systems. Multiple-unit dosage forms with modified release properties yield advantages over monolithic systems in terms of beneficial pharmacokinetic properties and formulation flexibility. Multiparticulate oral dosage forms offer several advantages over monolithic systems (15). The pellets disperse rapidly and more uniformly along the gastro-intestinal tract, reducing food effects on drug absorption and avoiding high local drug concentrations. The bioavailability of certain drugs can be enhanced in terms of increased absorption and minimized inter- and intra-subject variability. Enteric or sustained release pellets can either be matrix type or the reservoir type. The drug containing a core of reservoir-type pellets is traditionally produced by wet-mass extrusion/spheronization or by layering of the drug

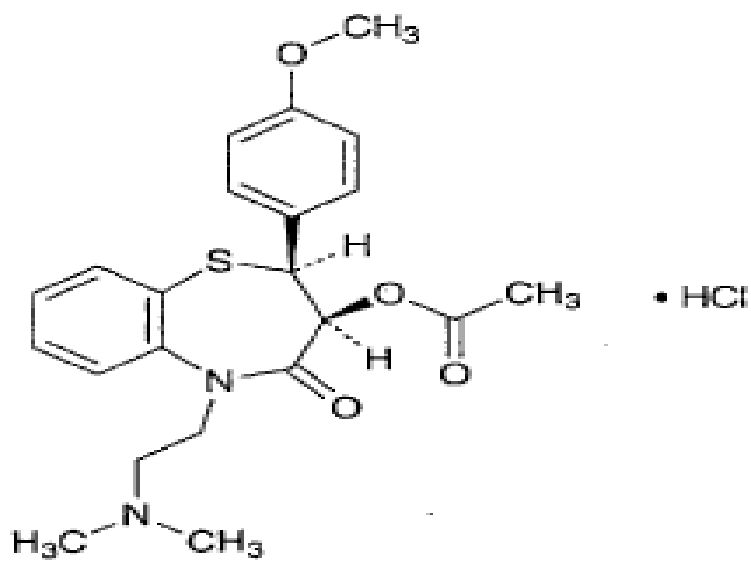
onto nonpareils. A functional coating is then applied to the pellets in subsequent steps. Matrix systems may be produced by wet-mass extrusion and spheronization, melt granulation or hot-melt extrusion using control-release carriers (15).

During hot-melt extrusion, a blend consisting of a drug, a thermoplastic carrier and further optional excipients is transported through a heated barrel by one or two rotating screws. The drug is homogeneously dispersed in the softened carrier and then extruded under high pressure through a product-shaping die to yield a matrix-type dosage form. The initial porosity of melt extruded matrices is low due to the high degree of carrier coalescence during thermal compounding as compared to wet-massed or directly compressed matrices, minimizing percolation effects and hence drug diffusion.

Ethyl cellulose (EC) is a hydrophobic, thermoplastic polymer used in sustained release drug delivery systems. EC is available in various molecular weights, and has a T_g of 129–133 °C and a crystalline melting point 180 °C. EC is a good candidate for extrusion because it exhibits thermoplastic behavior at temperatures above its glass transition temperature and below the temperature at which it exhibits degradation (250 °C). The use of plasticizers in HME formulation with polymers reduces the T_g of polymers with high T_g's and therefore permit processing at lower temperatures. These plasticizers may also increase the release rate by increasing flexibility of extruded pellets or films. In present studies, Ethylcellulose (Ethocel™ 7FP, Viscosity~7cps) was studied as matrix former with lipophilic processing aids (Stearic acid, Tristearin and Trimyrustin) for HME sustained release pellets. The use of lipophilic plasticizer was found to be efficiently lower the required processing temperatures and maintain the sustained release. Chlorpheniramine Maleate (CLPM, Figure 1-9) and Diltiazem Hydrochloride (DTZ, Figure 1-9) were used as a model APIs.



Chlorpheniramine Maleate



Diltiazem Hydrochloride

Figure 1-9: Chemical structures of model water soluble drugs.

CHAPTER - 2

OBJECTIVE

2.1 Solid Dispersions utilizing HME

Solid dispersions utilizing HME present the pharmaceutical industry with endless possibilities with regard to the formulation of poorly soluble drugs. These systems provide pharmaceutical scientists with several opportunities to elucidate their physicochemical characteristics. The solid dispersions are formulated with hydrophilic polymers as carriers, which greatly influence processability in HME, release characteristics and crystallization rate of APIs. Thus, the primary goal of this research was to investigate the viability and suitability of cellulose ethers and ester derivatives polymers, as well as sugar alcohols as carriers in designing solid dispersions. The studies were aimed to elucidate of the mechanism of drug release from extruded formulations, the prediction of drug carrier miscibility, and the stability of melt extruded systems. The behavior of the HME formulations was compared to the behavior of the respective physical mixtures to examine the effect of the processing on API solid state and release characteristics. The solid state of API in the extrudates was evaluated with differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier Transform Infrared (FTIR).

2.1.1. To investigate cellulose ethers (hydroxyl ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC) and hydroxyl propyl methyl cellulose (HPMC)) as carriers for solid dispersions of Efavirenz utilizing hot melt extrusion.

2.1.2. To evaluate Hypromellose (Hydroxypropyl methyl cellulose, HPMC), Hypromellose ester derivative (Hydroxypropyl methyl acetate succinate, HPMCAS and Hydroxypropyl methyl

phalate, HPMCP) polymers as carriers for solid dispersion of Efavirenz utilizing hot melt extrusion.

2.1.3. To study the utility of sugar alcohols (Mannitol, Sorbitol and Xylitol) as solid dispersion carriers for a poorly water soluble drug (Carbamazepine).

2.1.4. To develop taste masking formulations of Efavirenz with Eudragit[®] EPO utilizing hot melt extrusion (HME).

2.2. Sustained release pellets

2.2.1. To develop ethyl cellulose based matrices with lipid based processing aids for sustained release with the water-soluble model drug (Chlorpheniramine Maleate and Diltiazem Hydrochloride).

CHAPTER - 3
CELLULOSE ETHERS (HYDROXYL PROPYL CELLULOSE, HYDROXYL ETHYL
CELLULOSE AND HYDROXYL PROPYL METHYL CELLULOSE) AS CARRIERS
FOR SOLID DISPERSION OF EFAVIRENZ UTILIZING HOT MELT EXTRUSION

3.1. ABSTRACT

The objective of the present research was to utilize hot melt extrusion (HME) techniques to convert the crystalline form of Efavirenz (EFZ) to a more soluble amorphous form by employing hydrophilic matrices of cellulose ethers (HEC, HPC and HPMC). The solid state characteristics of EFZ in pre-extrusion physical mixtures and post-extrusion in extruded formulations in cellulose ether matrices were studied utilizing FTIR, DSC and PXRD. The results of this study indicate that formulations of EFZ in HPMC matrices exhibited the most optimal release characteristics followed by HEC and HPC. This may be attributed to the aqueous solubility and/or swelling behavior of the selected polymers. The relationship between the swelling and erosion process of the polymeric matrices and release pattern of EFZ from the solid dispersions was evaluated. The physical and chemical stability of EFZ under various storage conditions (4 °C, 25 °C/60% RH and 40 °C/75% RH) were studied. In conclusion, HPMC was found to be the most promising of the three polymers tested as it provided a stable solid dispersion with enhanced dissolution compared to HEC and HPC. However, based on the DSC studies, the re-crystallization of the EFZ was observed in formulations with 50% w/w after 6 months in HPMC

formulations. Drug load exhibited a profound effect on release characteristics and stability of these solid dispersions.

Keywords: Cellulose ethers; Hot melt extrusion; Swelling and Erosion process; Recrystallization.

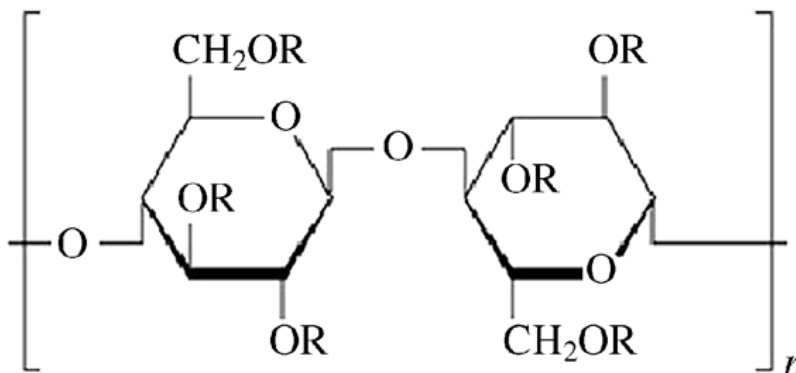
3.2. INTRODUCTION

Water-soluble cellulose ether polymers are used in a broad variety of industrial applications such as food products, adhesives, paints, textiles and paper. In the pharmaceutical industry, cellulose ethers have also found a widespread use. Over 4000 pharmaceutical products listed in the Physician's Desk Reference are formulated with cellulose ethers (16). In solid dosage forms, they are primarily used as tablet binders, film-coating agents and serve as matrix for controlled release formulations. Water soluble cellulose ethers, such as methylcellulose (MC), hypromellose or hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC) are effective in forming hydrophilic matrix in various dosage forms(16). Water insoluble ethylcellulose (EC) has been mainly used as a hydrophobic coating material or matrix former for modifying the release of drugs from oral dosage forms.

For drugs with low aqueous solubility in crystalline form, formulation with respective amorphous forms present the possibility of improving their solubility, dissolution rate and bioavailability. The rationale behind this strategy is that highly disordered amorphous materials have a lower energy barrier to overcome in order to enter into solution than a regularly ordered crystalline solid. For solid dispersion applications, the aliphatic-hydroxyl groups of natural cellulose and synthetic 2-hydroxypropyl groups are capable of forming hydrogen bonds to APIs with hydrogen-bond accepting groups. The backbone of HEC, HPC, and HPMC, whose

molecular structures are shown in Figure. 3-1, is cellulose, which is composed of glucose residues joined by β -1,4 linkage.

The carefully formulated solid dispersion of poorly soluble APIs may enhance solubility as well as improve the bioavailability in GIT milieu. The API is highly dispersed in the polymer matrix (usually at the molecular level or in microcrystalline phase); solid dispersion systems provide a large surface area of the compounds for dissolution process, which greatly improves the dissolution. Therefore, the absorption of these compounds can be improved, if intestinal permeability is not the limiting factor, *i.e.* biopharmaceutical classification system (BCS) class 2 compounds. The model drug EFZ is classified as BCS class II compound. In the present study, hydrophilic matrices comprising of three different cellulose ethers HEC, HPC and HPMC were compared utilizing HME for solubility enhancement of EFZ via solid dispersion. The cellulose ethers have the potential to form hydrogen bonds with EFZ and therefore become stable within the amorphous form.



HEC: R is H or $-(CH_2CHO)_mH$
HPC: R is H or $-[CH_2CH(CH_3)O]_mH$
HPMC: R is H, CH_3 , $-CH_2CH(OH)CH_3$

Figure 3-1: Structures of Cellulose ethers

3.3. MATERIALS

Natrosol[®] hydroxyethylcellulose (HEC), Natrosol[®] 250 L Pharm , Benecel[®] hypromellose (HPMC), Benecel[®] Pharm Type 2910 E 5 and Klucel[®] hydroxypropylcellulose (HPC), Klucel[®] EF, were provided by Ashland Aqualon (Wilmington, DE). Efavirenz (EFZ) was purchased from Shreeji Pharma International, India. Silicon dioxide (Aerosil[®] 200) was provided by Degussa Röhm America (Piscataway, NJ). Microcrystalline cellulose (Avicel[®] PH-112) and croscarmellose sodium (Ac-Di-Sol[®] SD 117) was supplied by FMC Corporation (Newark, DE).

3.4 METHODS

Cellulose ethers (HEC, HPMC and HPC) were geometrically blended with EFZ at 25% w/w and 50% w/w, respectively. The blends were manually fed through a hopper into an extruder barrel (16mm Prism Euro Lab, Thermo Fisher Scientific, Staffordshire UK) and processed at temperatures between 90 and 150 °C. The screw speed was set to a 70 rpm, while torque maintained below 70 N, and the pressure 60 psi. The formulation strands were manually collected, and stored at 4 °C. These strands were pelletized using pelletizer in Chapter 1, Figure 1-6. The pellets were pulverized using a sieve mesh size “22” according to US ASTM standards in a comminuting mill (FITZPATRICK, Model “L1A”). The milled extrudates so obtained, were blended with the excipients listed in Table 3-1 and filled in soft gelatin capsules (size # 2).

Table 3-1: Capsule formulation in cellulose ether matrix used *in vitro* release studies.

S. No.		Function	% w/w
1	Extruded milled powder/Physical mixtures	API carrier	83
2	Microcrystalline Cellulose	Dispersing agent	8
3	Silicon dioxide	Anti-adherent	2
4	Sodium Coscarmellose	Super-disintegrant	7

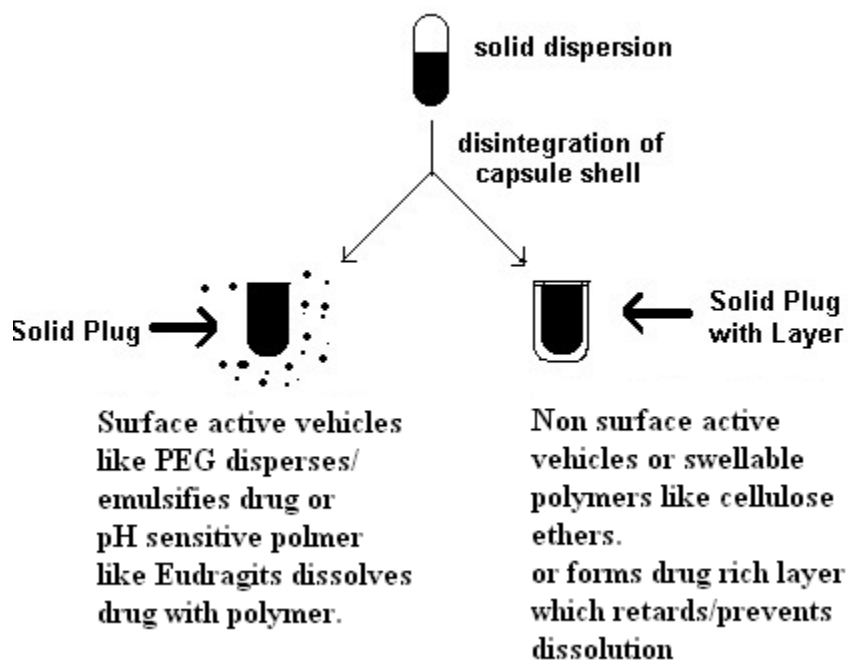


Figure 3-2: Comparative dissolution of poorly water soluble drug from surface active carrier vs non surface active vehicles (6).

3.5. DETERMINATION OF MISCIBILITY OF EFZ IN POLYMERIC MATRICES

When two substances completely mix with each other to form a homogeneous solution, they are termed miscible.(17) Miscibility is complete solubility. Solubility can be measured whereas miscibility is absolute. The solubility and miscibility of active pharmaceutical ingredients (APIs) in polymeric matrices has long been of interest in the design of pharmaceutical dosage forms (18). Amorphous molecular levels of dispersion of API in polymeric matrices is one of the examples of such dosage forms. The term miscibility is used to refer to the formation of a single phase amorphous system through liquid/liquid mixing, where one liquid is an amorphous polymer and the other liquid is an amorphous API (17, 19). Molecular level mixing can be achieved either by dissolving of each component in a mutual solvent followed by solvent removal or by directly mixing the two liquids. The latter method is normally accomplished by melting the crystalline API and mixing the melt with the polymer using a technique such as melt extrusion (20-21). In order to form a one-phase mixture during the preparation stage, the two liquids have to be thermodynamically miscible. The system must re-equilibrate at the post-processing conditions and may remain a single phase or become metastable or unstable. In order to modify the physical stability of the API, molecular level mixing with the polymer is desirable, thereby altering the local environment of the API. If the two components are immiscible, the properties of the pure amorphous solid will largely dominate the crystallization behavior of the mixture and effects of the polymer on physical stability will be limited (20).

DSC thermograms (n = 3) of physical mixtures of EFZ and cellulose ethers with different drug loads (10% to 90%) were analyzed using a two step method: Initial heating step at 10 °C/min. followed by cooling at 40 °C/min. and a second heating at 10 °C/min. after cooling the samples. The instrument was calibrated for temperature and heat flow using high purity standards of

indium and zinc, respectively. DSC can be used for the estimation of the miscibility of solid drugs dispersed in polymeric matrices (22). The method was based on the simple principle that the fraction of a drug solubilized within the matrix does not contribute to the melting endotherm associated with the dispersed drug fraction (23-24).

3.6. POWDER X-RAY DIFFRACTION

The studies were performed on a D-8 Advance X-ray Diffractometer (Bruker-Axs) equipped with a Sol x detector and Diffrac Plus1 software. The generator voltage and current were 40 kV and 40 mA respectively. The step size was 0.01° and the dwell time at each step was 1 sec. The crystallinity of the EFZ in the hot-melt extruded pulverized powder and their respective physical mixtures was analyzed using X-ray Diffractometer. The generator operating voltage and current were 40 kV and 40 mA, respectively. The scanning speed was 2°per min, and the 2θ scanning range was from 5° to 50°.

3.7. SOLUBILITY PARAMETERS

The cohesive energy of a material is the energy which holds that substance together. It is the amount of energy required to separate the constituent atoms or molecules of the material to an infinite distance, and hence it is a direct measure of the attraction that its atoms or molecules have for one another. Cohesive energy is the net effect of all the inter atomic/molecular interactions including Van der Waals interactions, covalent bonds, ionic bonds, hydrogen bonds, electrostatic interactions, induced dipole and permanent dipole interactions (25).

Cohesive energies are especially important to the pharmaceutical material scientists because they determine many of the critical physico-chemical properties (e.g. solubility, melting point) of drugs and excipients. The cohesive energy of a material can be quantified in a number of ways. The most common approach is to use the solubility parameter (δt).

The solubility parameter (δ) is an intrinsic physicochemical property of a substance. Various authors have sub-divided the total solubility parameter into components which express the contributions from the different types of interatomic/intermolecular forces (e.g. dispersion forces (δ_d), hydrogen bonds (δ_h), 'polar' interactions (δ_p)). Solubility parameter calculations were performed using Molecular Modeling Pro software (Chem SW Inc., Fairfield, CA) utilizing group contribution approaches (Molecular Modelling Pro., 2006). For cellulose ethers, solubility parameters were calculated based on the single repeating monomer unit.

The difference between the solubility parameters ($\Delta\delta_t$) of two materials gives an estimation of the likelihood that they will be miscible. Compounds with similar values for δ_t are likely to be miscible because the energy of mixing from intramolecular interactions is balanced with the energy of mixing from intermolecular interactions. Greenhalgh et. al. demonstrated that compounds with $\Delta\delta_t < 7 \text{ MPa}^{1/2}$ were likely to be miscible and compounds with $\Delta\delta_t > 10 \text{ MPa}^{1/2}$ were likely to be immiscible (26).

3.8. FOURIER TRANSFORM INFRARED (FTIR) SPECTROSCOPIC ANALYSIS

Fourier transform infrared (FTIR) spectra for the EFZ and cellulose ethers were obtained using a Perkin-Elmer spectrometer (Perkin-Elmer Life and Analytical Sciences, Shelton, CT, USA). A spectrum was collected for each sample within the wave number region $4,000\text{--}650 \text{ cm}^{-1}$. For analysis the samples of EFZ in cellulose ethers, physical mixtures and pellets with various drug load (25 and 50% w/w) were accurately weighed containing equivalent amount of Efavirenz in all the samples. The spectrums were analyzed for the absence or shift in the wave numbers of the characteristic peaks. FTIR studies were done to detect the possible interactions between the EFZ and cellulose ethers in the solid dispersions (27).

3.9. *IN VITRO* RELEASE STUDIES

In vitro release studies were performed according to USP 31 apparatus I using discriminatory dissolution medium comprised of 1000 ml of 0.2% SLS in distilled water. Hanson SR8-plus™ dissolution test station (Chatsworth, CA) was used at $37\pm 0.5^{\circ}\text{C}$ and paddle speed was maintained at 50 rpm. An amount (250 mg) equivalent to 50 mg and 100 mg of EFZ from both the physical mixtures and the milled extrudates with 25% and 50% w/w drug loads respectively, were blended with the excipients listed in Table 3-1 and filled in gelatin capsules (size # 2). The sinkers were used to immerse the capsules, avoid the floating on surface, and minimize sticking to the walls of the dissolution vessel. Samples were collected at predetermined time intervals, using 0.2-micron nylon filter tips attached to a 1 ml syringe. These samples were analyzed using HPLC/UV. All the results were reported as the average of 3 replicates \pm SD. Dissolution profiles were compared using similarity factor (f_2). An f_2 value larger than 50 indicates that the two dissolution profiles are similar (29).

3.10. POLYMER SWELLING AND EROSION STUDIES

In general, upon contact with dissolution medium, cellulose ethers in formulations start to swell, forming a gel layer around the dry core (28). The dry core of cellulose ethers polymers is glassy; the drug contained in them cannot diffuse unless swelling takes place. On swelling, drug molecules dissolve in water and are released by diffusion or erosion (Figure 3-2). Swelling and water sorption of polymer is a function of polymer chemical structure and polymer water interaction (29). Also, following HME, the extrudates have reduced porosity (30-31).

The rate of dissolution medium uptake by the polymer were determined by equilibrium weight gain method (Swelling studies), and the erosion studies were performed by method similar to Bhisle et al (32). Both the studies were conducted using the same conditions for in vitro release studies. The pre-weighed milled extrudates (approx 200 mg) (W1) were filled into the gelatin capsules, immersed in 1000 ml of 0.2% SLS maintained at 37 ± 0.5 °C in the dissolution vessel and paddle speed set to 50 rpm. The milled extrudates subjected to this study were removed from the dissolution baskets at predefined time intervals the excess water on their surfaces would be blotted with a tissue paper, and the swollen matrix would be reweighed (W2) (32). These matrices were dried to a constant weight in a hot-air oven at 60 °C, and the dried matrix would be reweighed (W3). The percentage swelling (S), and the percentage matrix erosion (E) at time, t were calculated using equations 3-1 and 3-2, respectively.

$$S = \frac{(W2-W1)}{W2} \times 100 \quad \text{Equation 3-1}$$

$$E = \frac{(W3)}{W1} \times 100 \quad \text{Equation 3-2}$$

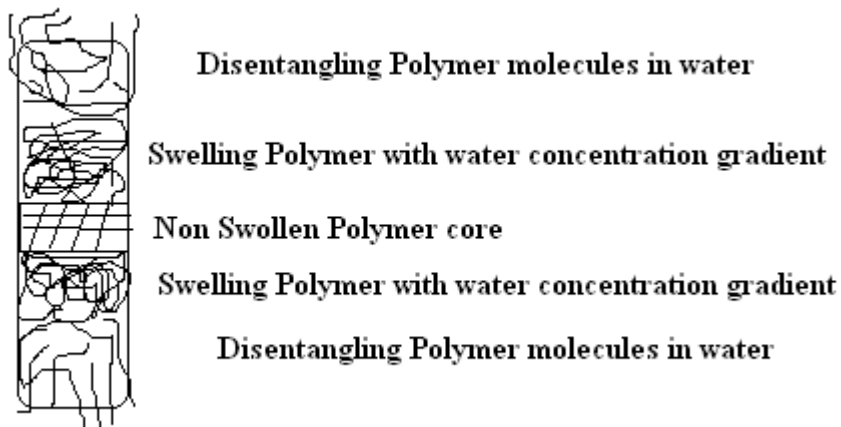


Figure 3-3: Schematic of solubilization of solid dispersions with cellulose ethers as carrier polymers in a capsule (33).

3.11. STABILITY STUDIES

The sample of each of the solid dispersions were transferred to HDPE bottles and placed inside humidity chambers pre-equilibrated to 25 °C/60% RH and 45 °C/75% RH. At specific time interval during the course of study 6 months, the HDPE bottles assigned for each time point would be removed. The solid dispersions of EFZ with cellulose ether matrices were characterized using DSC and *in vitro* release studies.

3.12. RESULTS AND DISCUSSION

3.12.1. MISCIBILITY OF EFZ IN CELLULOSE ETHERS

During the first heating cycle, physical mixtures containing 30% w/w EFZ in HPC matrix did not demonstrate a melting peak (Figure 3-6). This indicates that EFZ is completely soluble within the polymer matrix with drug load 30% w/w. In Figure 3-7, the thermograms indicate absence of the melting endotherm corresponding to EFZ in the physical mixtures containing 20% w/w EFZ in HPMC matrix. The thermograms of physical mixtures containing 30-50% w/w EFZ in HPMC

matrix exhibited diffused endotherm corresponding to EFZ indicating partial solubility. Therefore, this study indicated that at drug loads below 20% w/w of EFZ is completely soluble in the HPMC matrix and drug loads below 30% w/w of EFZ is completely soluble in the HPC matrix. The drug hence will form saturated solid solutions when the drug load is above 20% w/w in HPMC matrix and 30% w/w in HPC matrix. However, the thermograms of HEC and EFZ physical mixtures demonstrated endothermic peaks at 10-90% w/w in the first heating cycle in Figure 3-4. This data is instrumental in prediction of EFZ miscibility and solubility in cellulosic matrices.

3.11.2. SOLUBILITY PARAMETER

The difference in the solubility parameters ($\Delta\delta_t$) of EFZ with cellulose ethers is lower than the proposed value of $<7 \text{ MPa}^{1/2}$ which is required for the polymer–drug miscibility (26). HPC and HPMC would be expected to form stable glass solutions with EFZ (Table 3-4). HEC may be immiscible above certain concentration (25-26). EFZ solubility parameter was calculated as follows:

$$\delta_d = 22.6, \quad \delta_p = 5.9 \quad \text{and} \quad \delta_h = 7.5$$

$$\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \quad \text{Equation 3-3}$$

$$\delta_t = 24.5$$

Table 3-2: Calculated solubility parameters for EFZ and Cellulose Ethers

S. No.		δ_t	$\Delta\delta_t$
1	EFZ	24.5	0
2	HEC	30.3	5.8
3	HPC	23.1	1.4
4	HPMC	25.6	1.1

3.12.3. THERMAL ANALYSIS

The DSC thermogram of EFZ exhibited a sharp endothermic peak between at 137-139°C corresponding to its melting point. DSC analysis of crystalline EFZ showed a single sharp endothermic peak in the temperature range of $137.54 \pm 0.7^\circ\text{C}$ and $\Delta H_f = 51.1 \pm 2 \text{Jg}^{-1}$ at a heating rate of $10^\circ\text{C}/\text{min}^{-1}$. Quench-cooled EFZ exhibited a glass transition temperature of $34.45 \pm 2.1^\circ\text{C}$ (onset T_g) and no other exothermic peak of crystallization or endothermic peak of melting was observed. When amorphous EFZ is heated above T_g at a rate as low as $1^\circ\text{C}/\text{min}$, amorphous EFZ does not crystallize spontaneously. The glass-forming tendency is related to the ease with which the glassy state can be obtained. A measure of glass forming tendency is given by the ratio T_g/T_m , and for an “excellent glass former”, $T_g/T_m > 0.7$. Therefore, EFZ, with $T_g/T_m = 0.82$, is expected to be an excellent glass former. The following properties of amorphous EFZ are amenable for the preparation of solid dispersions containing amorphous EFZ: high apparent aqueous solubility, glass forming tendency and reasonable physical stability.

In a solid dispersions with cellulose ethers, there are several possibilities for the distribution of EFZ, depending on the solid-state solubility in the polymer, a molecular glassy solid solution or a suspension may be formed. The thermograms of extrudates with 25% and 50% w/w EFZ in HEC and HPC matrix indicated absence of crystalline endothermic peak (Figure 3-7 and 3-8). However, the extrudates with 50% w/w in HEC and HPC exhibited the T_g at the same temperature as pure drug (Figure 3-4). The extrudates with 50% w/w EFZ in HPMC matrix demonstrated increase in T_g to $47.84 \pm 0.67^\circ\text{C}$, suggesting antiplasticizing effect of HPMC.

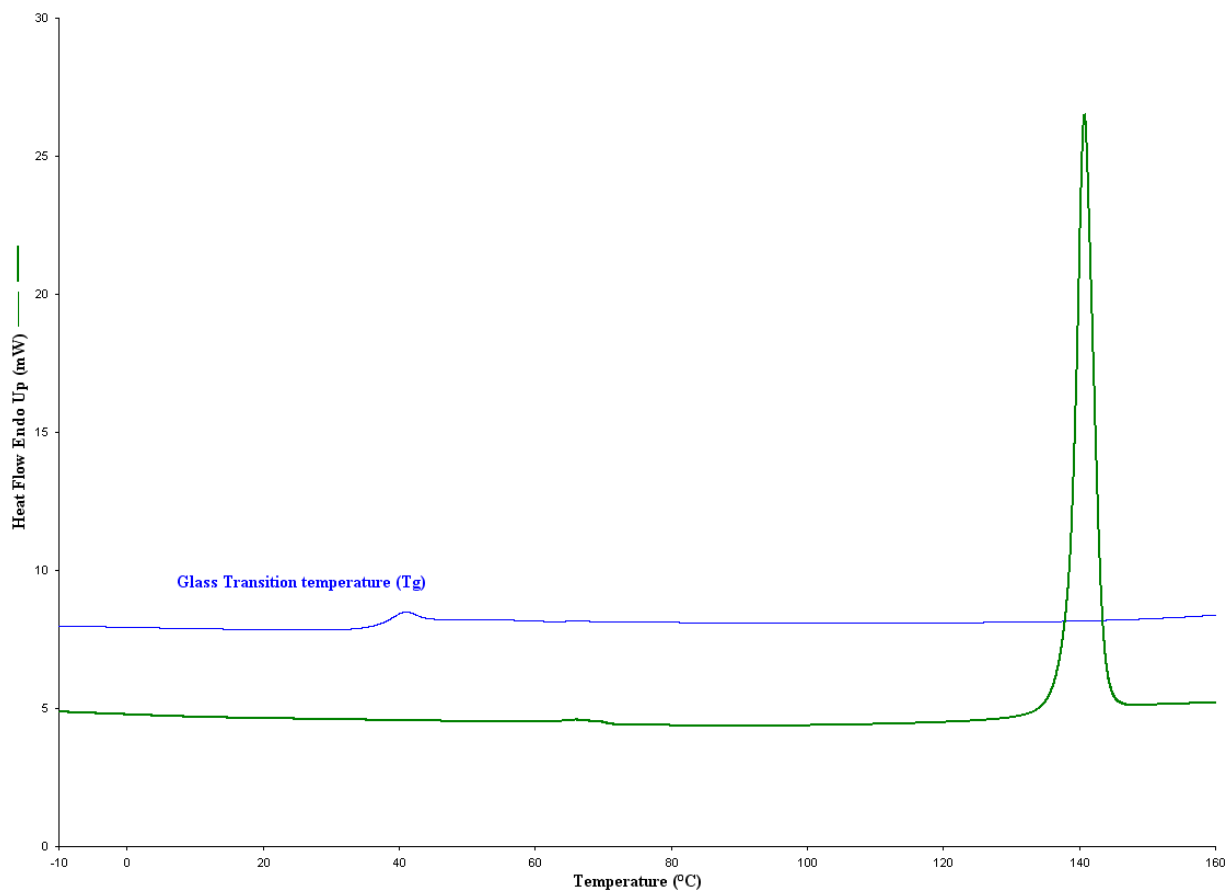


Figure 3-4: DSC profile of crystalline Efavirenz. The sample (~5 mg) was heated from -10 to 180 °C with a heating rate of 10 °C/min, cooled at 40 °C/min to -10 °C and then heated again -10 to 180 °C with a heating rate of 10 °C/min.

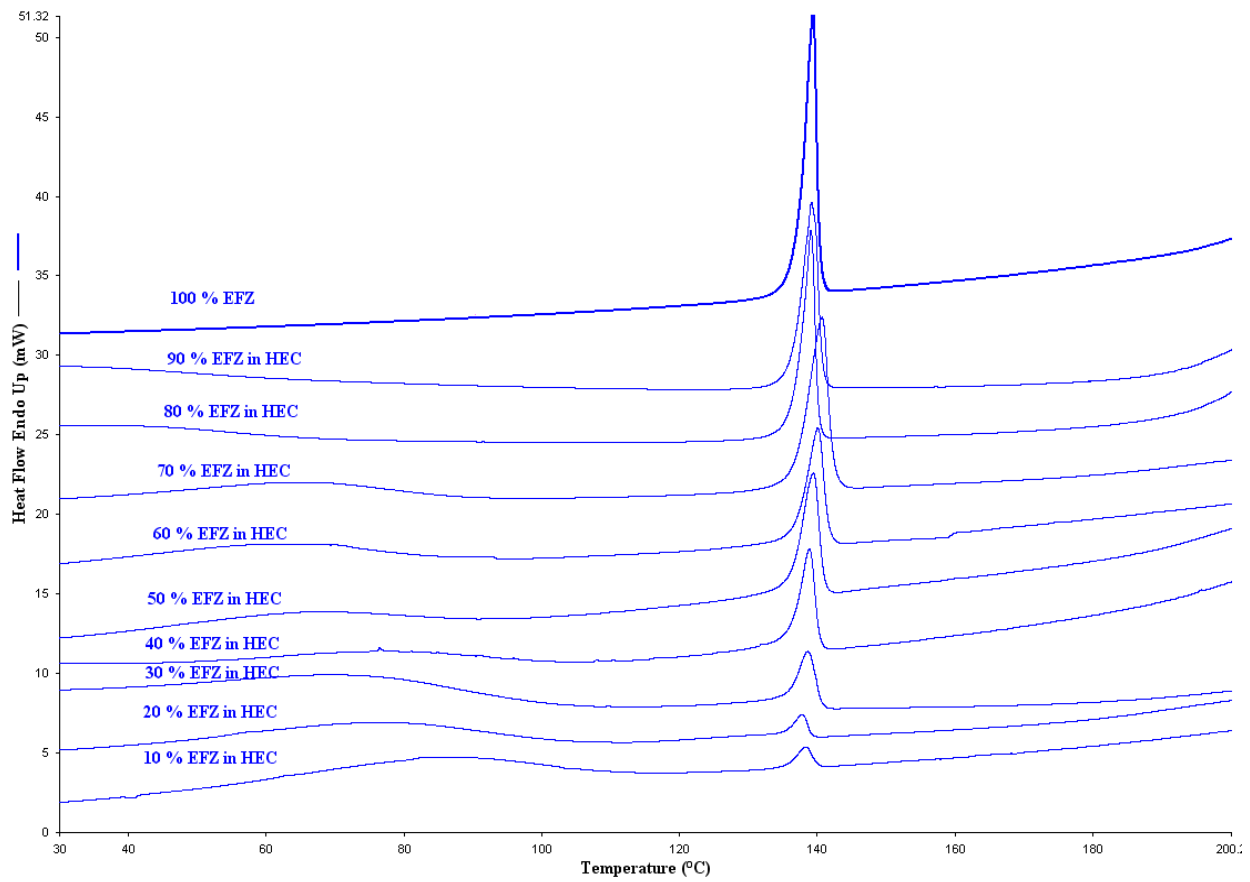


Figure 3-5: First Heating cycle from 30 °C to 200 °C at 10 °C/min of EFZ with different drug loads with HEC.

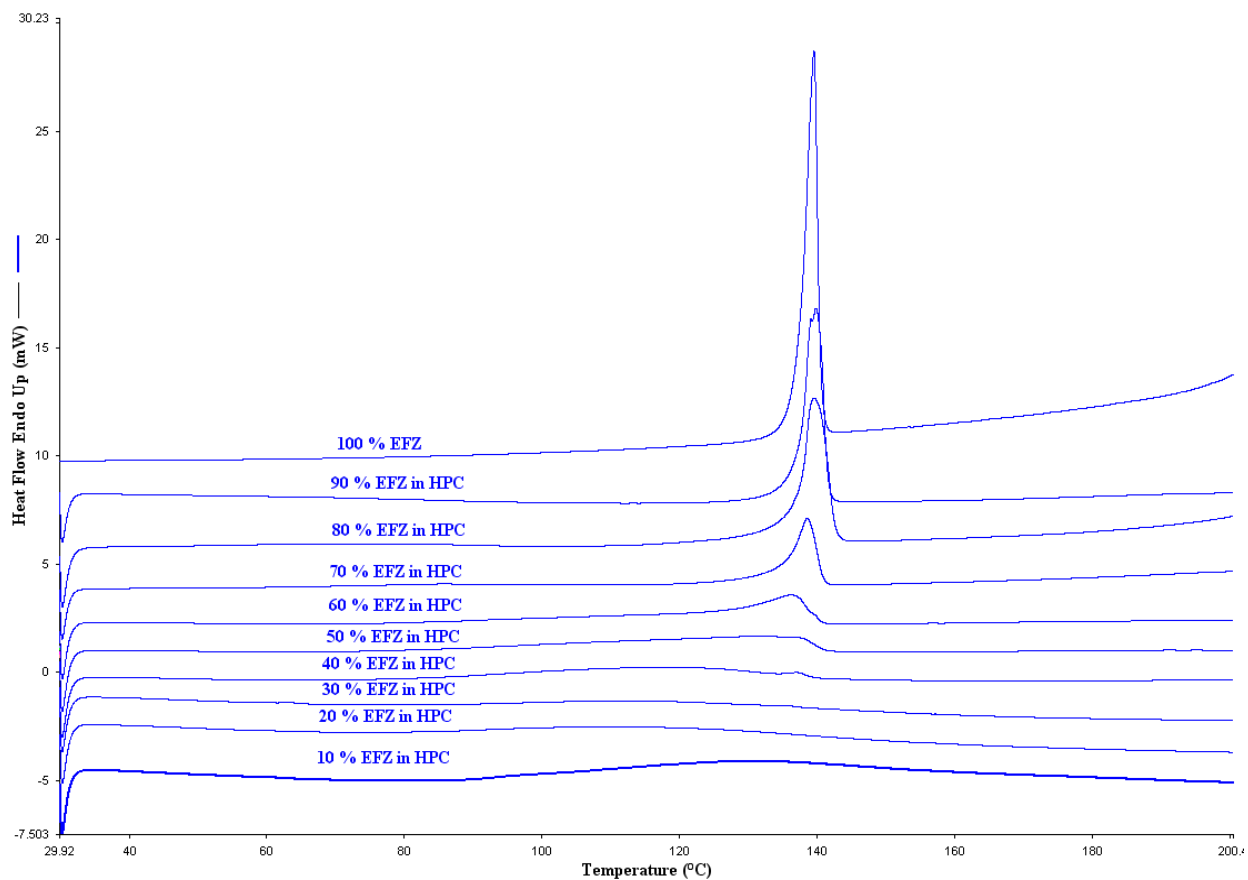


Figure 3-6: First heating cycle from 30 °C to 200 °C at 10 °C/min of EFZ with different drug loads with HPC.

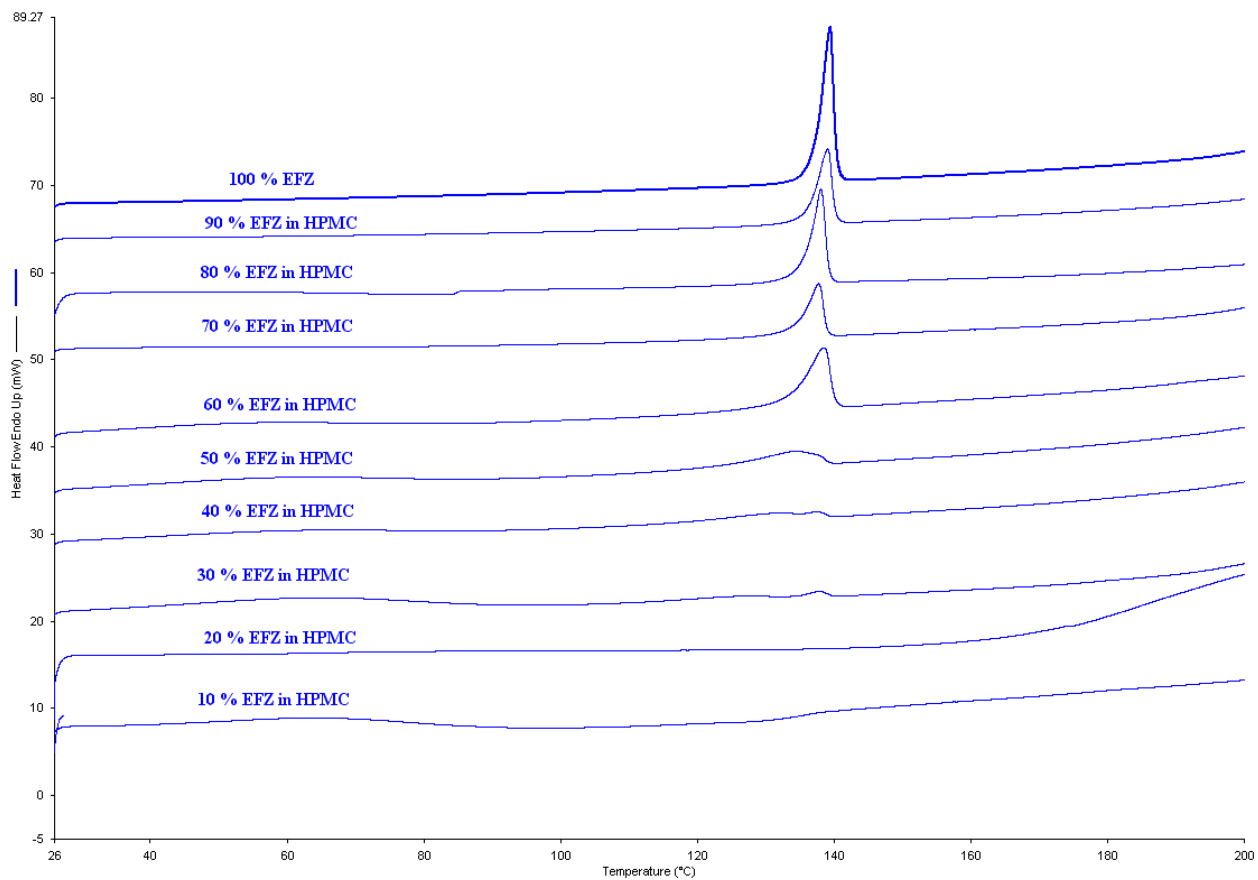


Figure 3-7: First Heating cycle from 30 °C to 200 °C at 10 °C/minute of EFZ with different drug loads with HPMC.

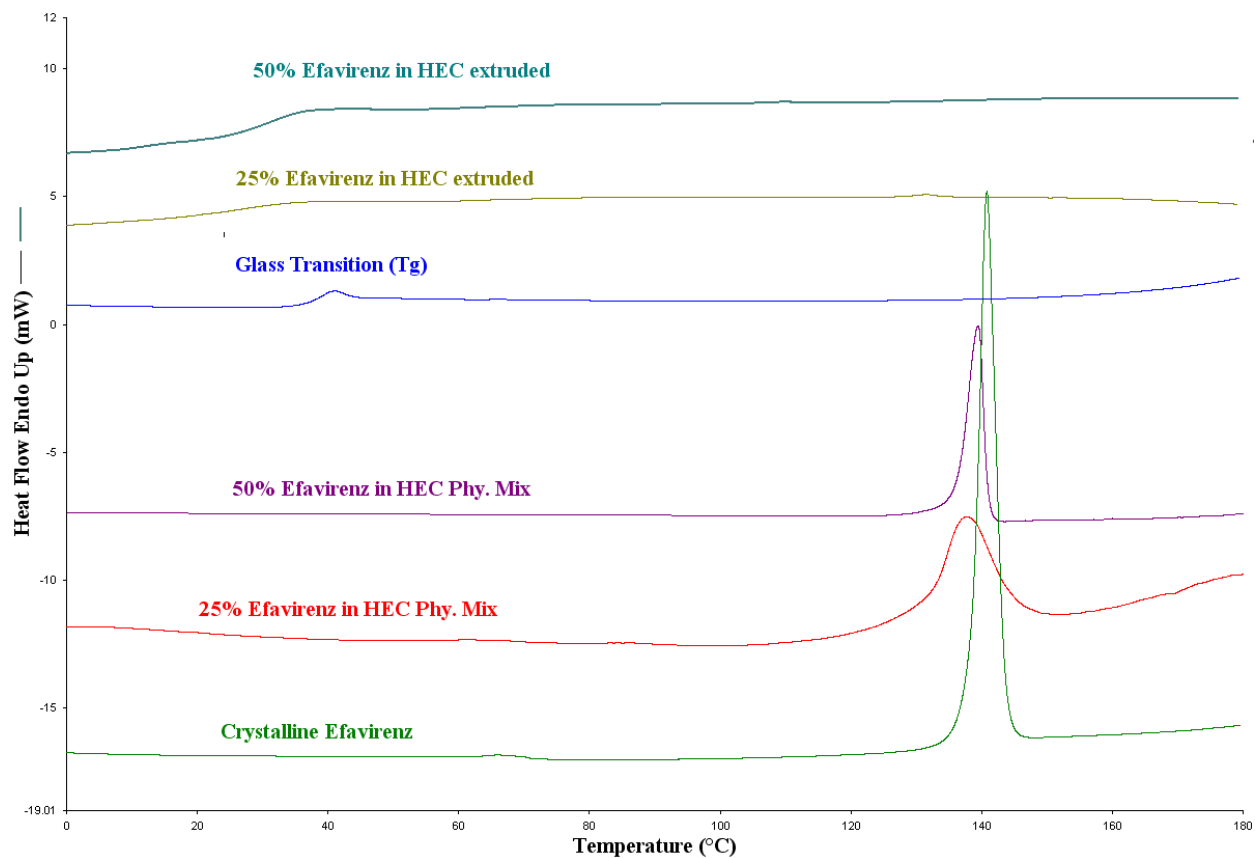


Figure 3-8: DSC thermograms of extruded and physical mixtures (Phy.Mix.) of EFZ with drug loads, 25% and 50% w/w in HEC matrix.

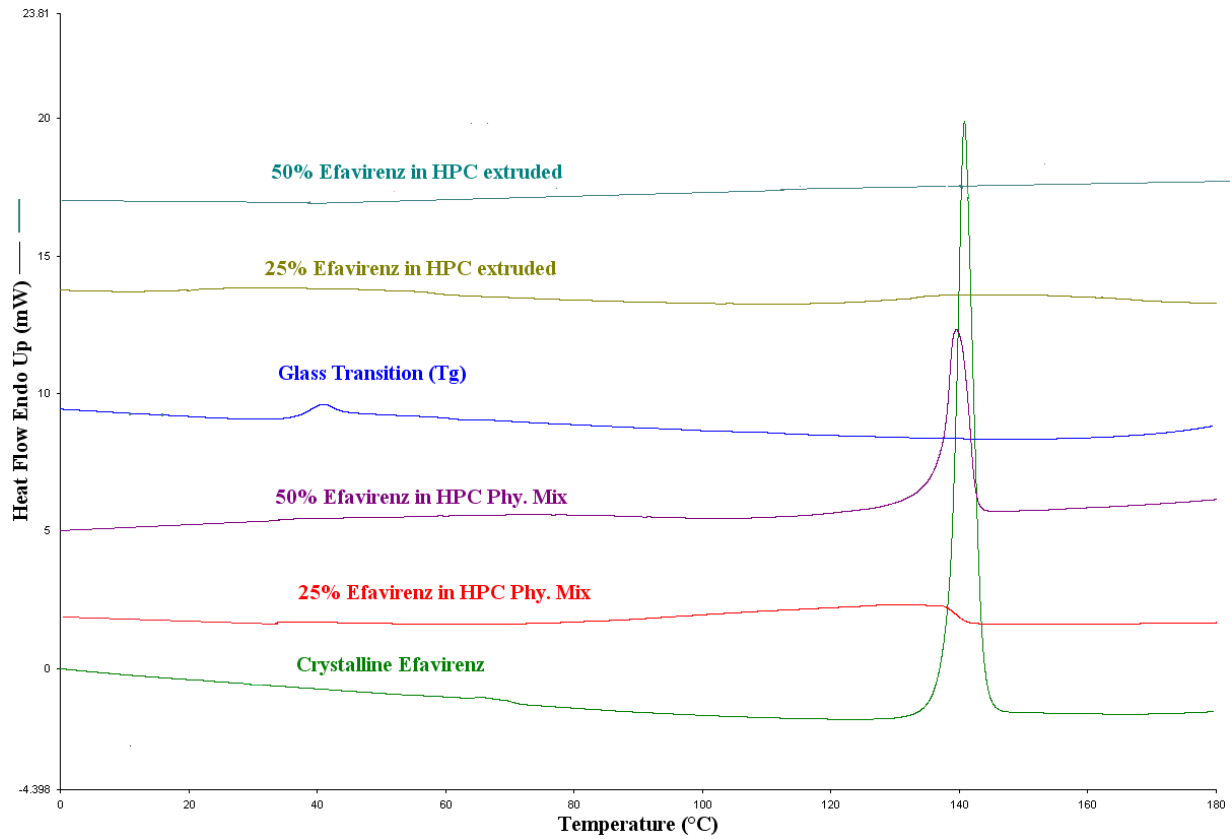


Figure-3.9: DSC thermograms of extruded and physical mixtures (Phy.Mix.) of EFZ with drug loads, 25% and 50% w/w in HPC matrix.

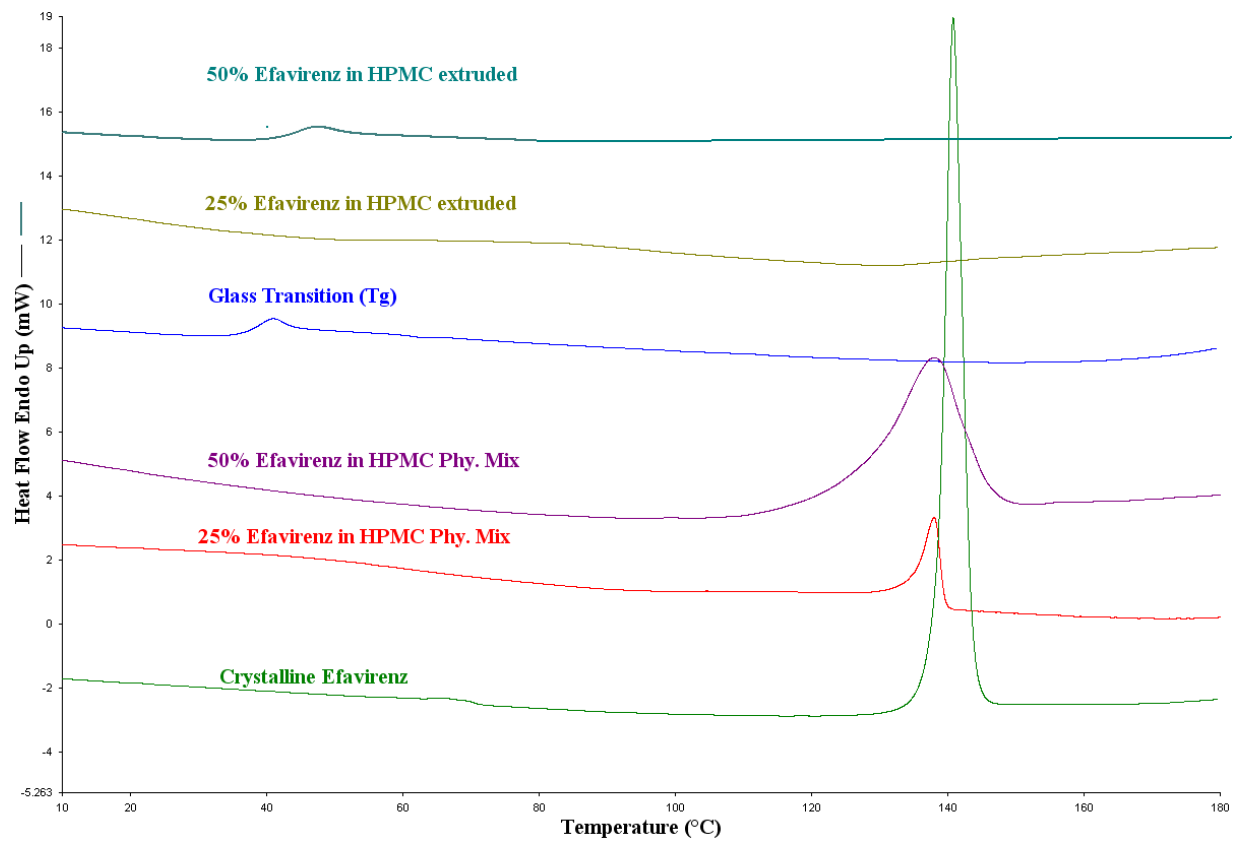


Figure 3-10: DSC thermograms of extruded and physical mixtures (Phy.Mix.) of EFZ with drug loads, 25% and 50% w/w in HPMC matrix.

3.12.4. POWDER X-RAY DIFFRACTION (PXRD)

The crystalline Efavirenz is characterized by a PXRD pattern comprising of 2 Theta values of 6.8 ± 0.2 , 10.3 ± 0.2 , 10.8 ± 0.2 , 14.1 ± 0.2 , 16.8 ± 0.2 , 20.0 ± 0.2 , 20.5 ± 0.2 , 21.1 ± 0.2 and 24.8 ± 0.2 (34). The drug was found to be in amorphous state within the extrudates. The PXRD patterns of the extrudates showed no crystalline peaks corresponding to EFZ compared to corresponding physical mixtures (Figure 3-11 to 3-13). These findings are in agreement with thermal analysis results.

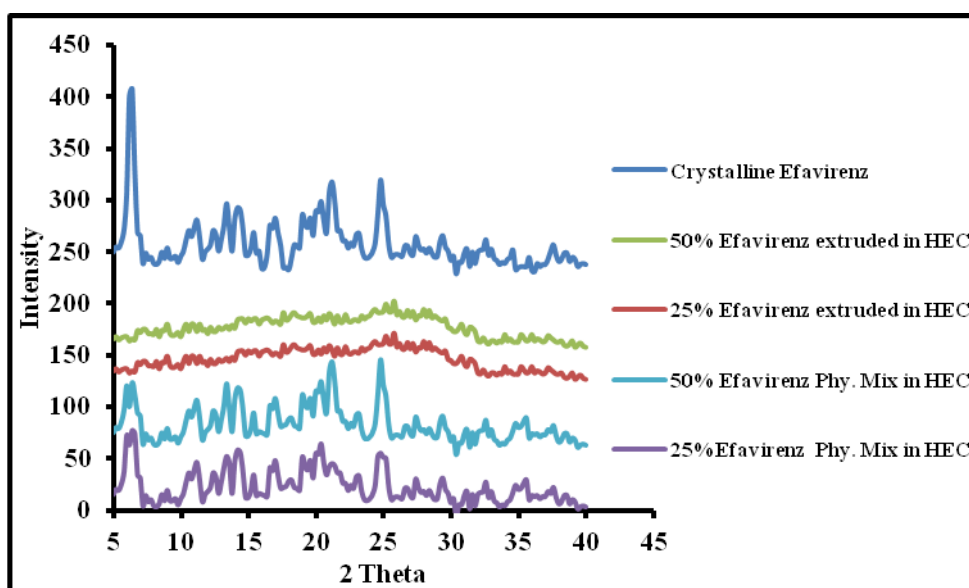


Figure 3-11: PXRD patterns of hot melt extruded pellets and physical mixtures with 25% and 50% w/w drug load in HEC matrix.

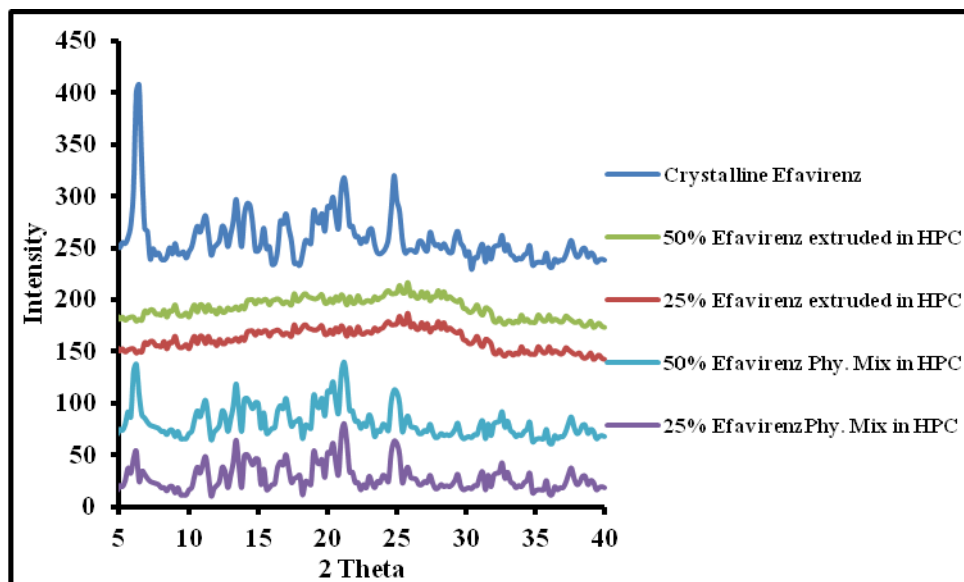


Figure 3-12: PXRD patterns of hot melt extruded pellets and physical mixtures with 25% and 50% w/w drug load in HPC matrix.

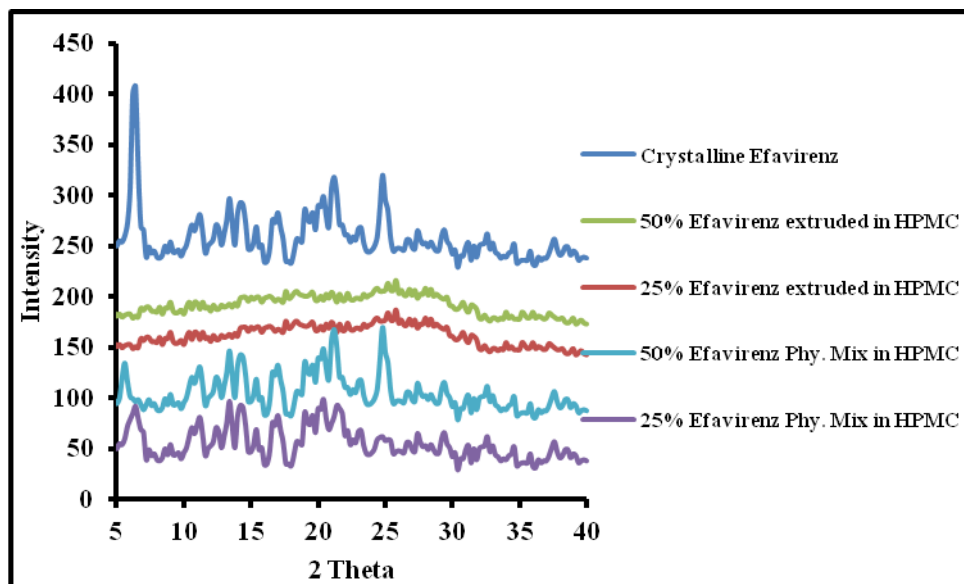


Figure 3-13: PXRD patterns of hot melt extruded pellets and physical mixtures with 25% and 50% w/w drug load in HPMC matrix.

3.12.5. FOURIER TRANSFORM INFRARED SPECTROSCOPY

FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements for different solid-state forms of an organic compound. Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational frequencies, leading to frequency shifts and splitting in absorption or transmittance of peaks.

The chemical interactions between EFZ and cellulose ethers in the solid dispersions may stabilize amorphous state of EFZ. There are several reports in literature of cellulose ethers interaction potential with drugs [35]. The crystalline EFZ shows characteristic bands at 3311.33 cm^{-1} , 2249.86 cm^{-1} , 1602.29 cm^{-1} , 1745.42 cm^{-1} , 1241.11 cm^{-1} and 1316.13 cm^{-1} attributed to N-H stretching vibrations, aromatic C-H stretching vibration, C \equiv C stretching vibration, C=O stretching vibration, C-F stretching vibration, C-O-C stretching vibration, respectively. The bands corresponding to C=O vibrations and N-H stretching became broadened and diffused in case of amorphous form as shown in Figure 3-15 (1728.69 cm^{-1} and 3260.09 cm^{-1} , respectively). This may indicate the participation of -NH and C=O groups in intermolecular hydrogen bonding between EFZ molecules. The spatial arrangement of EFZ molecules in the crystal lattice does not allow intermolecular hydrogen bonding which starts to occur once the orderliness of crystalline lattice is disturbed by formation of amorphous form. These intermolecular hydrogen bonds are relatively weak and amorphous form tends to revert back to the crystalline form.

Cellulose ethers shows the characteristic strong bands due to ether C-O-C stretch at 1150-1060 cm^{-1} in all three spectras in Figure 3-14. Also, HPC and HPMC contain secondary alcohol group's absorption at 1150-1075 cm^{-1} . This band is also found for the secondary alcohol groups

of HEC, but HEC has an additional shoulder due to their primary alcohol groups. Only, HPMC exhibits absorption due to methoxy groups at 1200-1185 cm^{-1} (Figure 3-14).

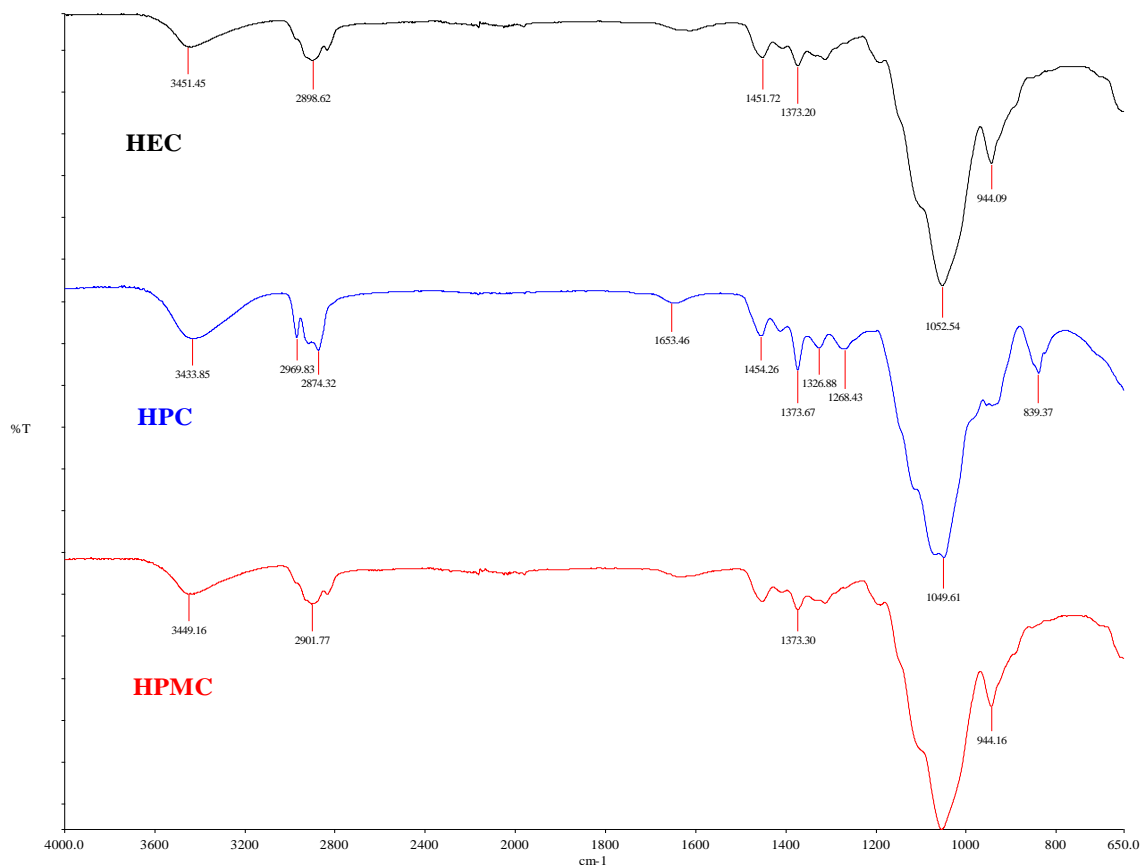


Figure 3-14: An overlay of FTIR spectra of cellulose ethers (HEC, HPC and HPMC).

In Figure 3-15, extruded formulation with 25 and 50%w/w EFZ in HEC matrix showed summation of individual components of IR spectra similar to the physical mixture. The characteristic peaks at 3311.83 cm^{-1} corresponding to N-H stretching and 1744.61 cm^{-1} corresponding C=O stretching vibration indicating the absence of specific interaction with HEC. However, the band at 3311.33 cm^{-1} corresponding to the symmetrical N-H stretching vibrations of the EFZ seen in the pure drug was replaced by a broader band at the 3400 cm^{-1} in the extrudates with HPC and HPMC. This indicates the possible involvement of $-\text{NH}_2$ groups in

hydrogen bonding with the –OH groups of HPC and HPMC. In addition, the carbonyl group band showed shift to higher wave numbers from 1745.42 cm⁻¹ to 1755 cm⁻¹ or higher in extruded pellets spectrum (Figure 3-16 and 3-17). These results suggest that the N–H and C=O functional groups of EFZ interact with the –OH groups of HPC and HPMC at 25% and 50% w/w drug load at the molecular level in solid dispersions, resulting in extended intermolecular interactions in the extruded pellets of EFZ. These results are in agreement with our DSC miscibility studies.

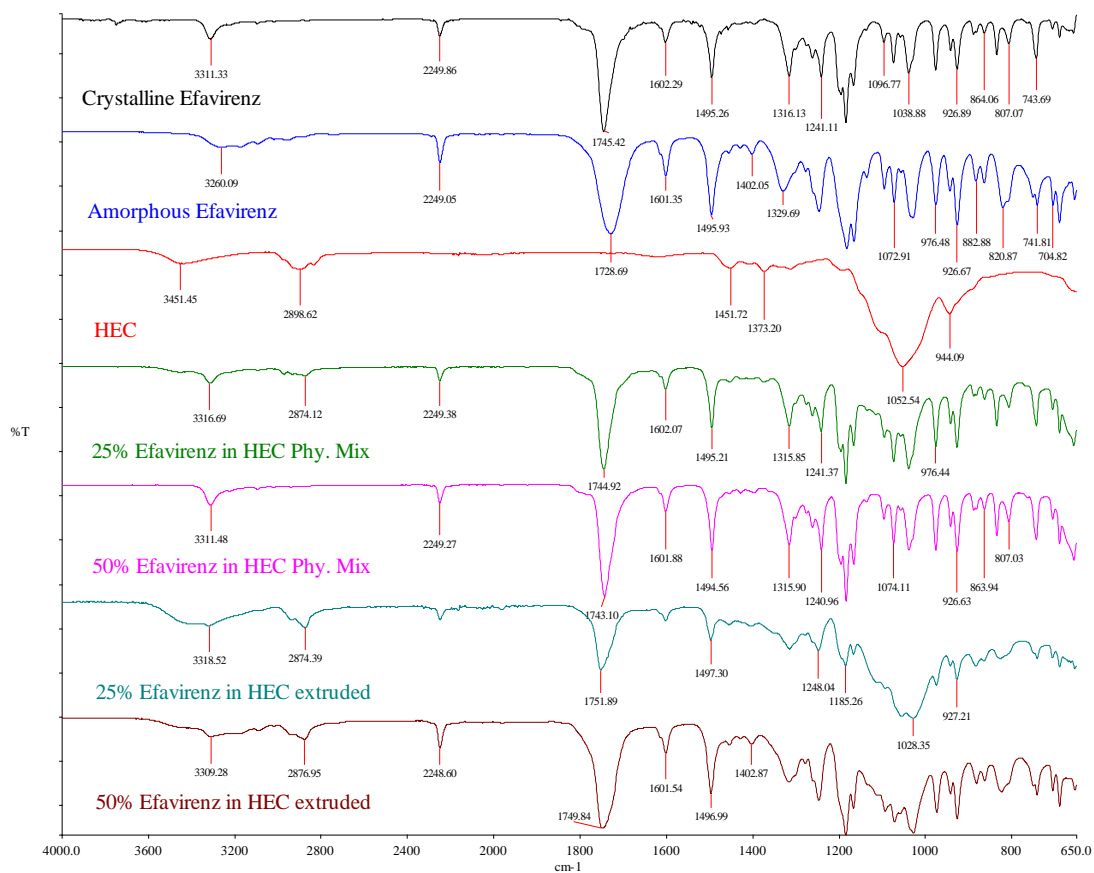


Figure 3-15: An overlay of FTIR spectra of Crystalline Efavirenz, amorphous Efavirenz and HEC at drug loads 25 and 50% w/w.

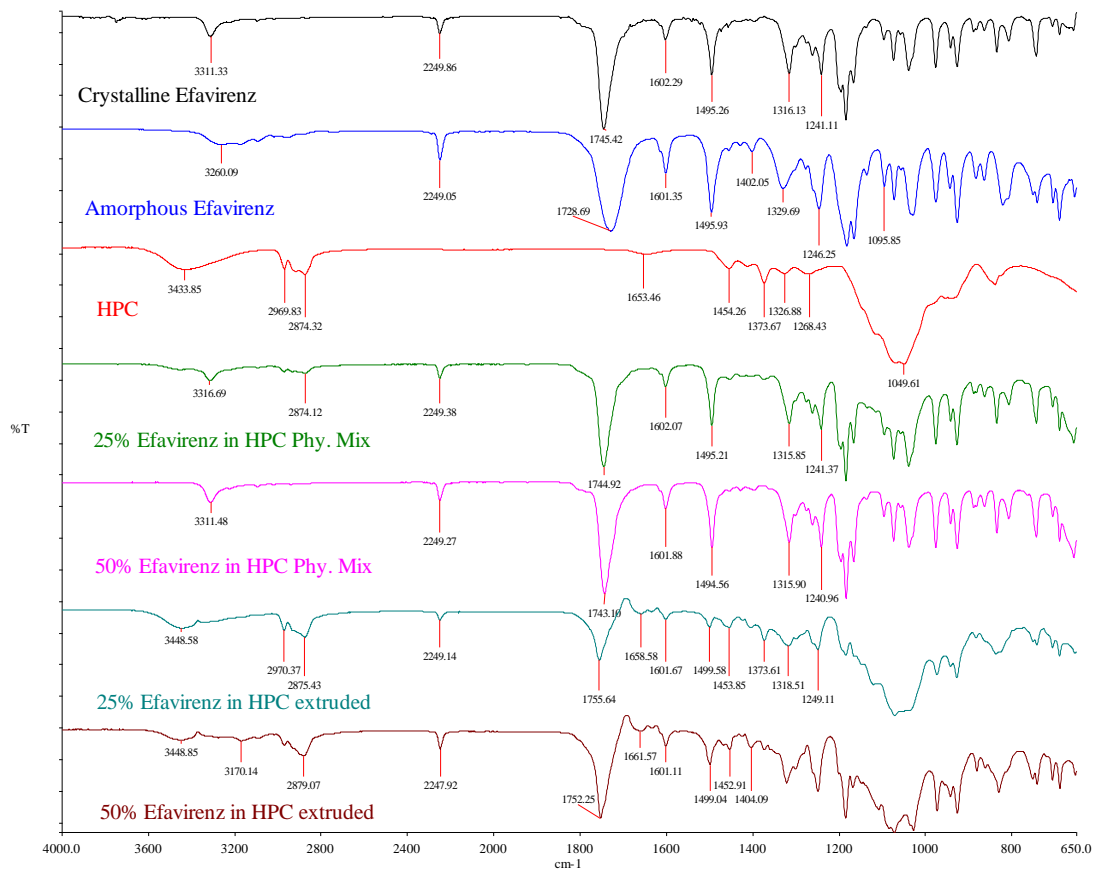


Figure 3-16: An overlay of FTIR spectra of Crystalline Efavirenz, amorphous Efavirenz and HPC at drug loads 25 and 50% w/w.

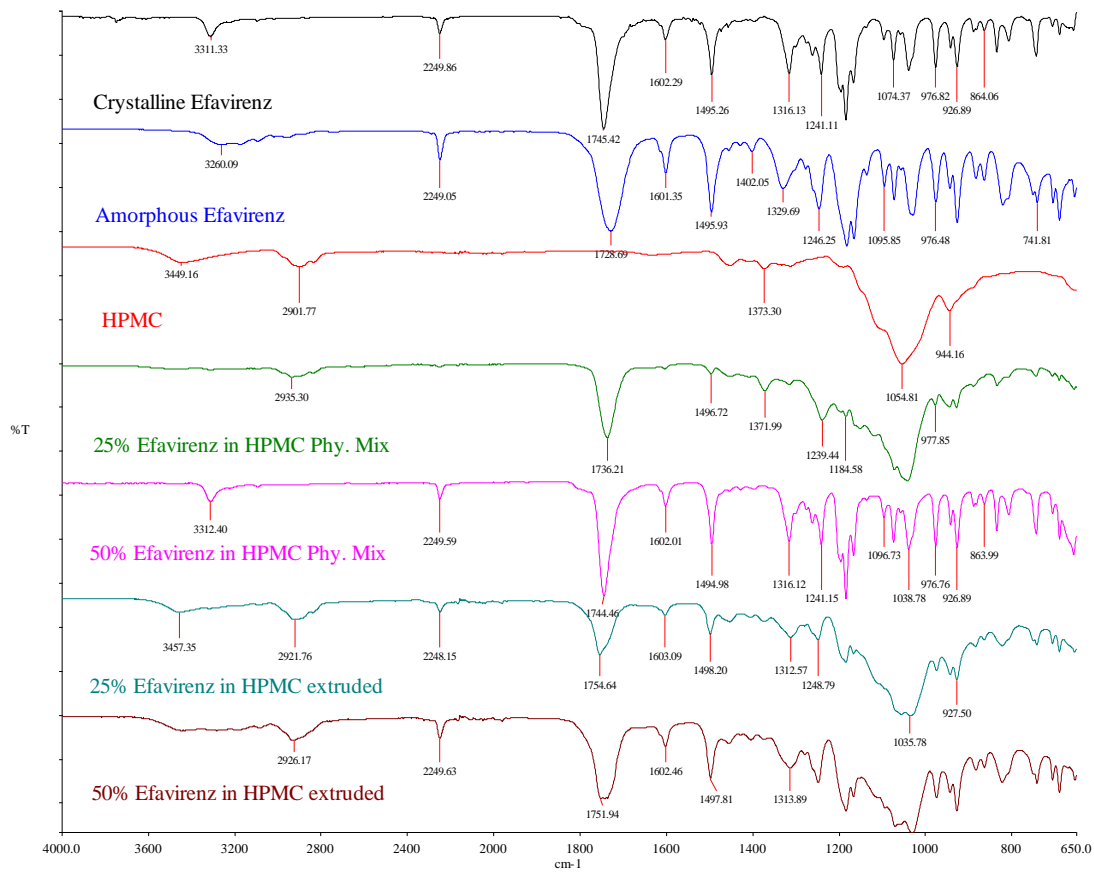


Figure 3-17: An overlay of FTIR spectra of Crystalline Efavirenz, amorphous Efavirenz and HPMC at drug loads 25 and 50% w/w.

3.12.6. RELEASE STUDIES

The extrudates were milled and blended with excipients in order to minimize the delay in drug diffusion due to swelling of the cellulose ether matrix in Table 3-1. *In vitro* release studies (Figure 3-14 to 3-16) of the extrudates were found to be superior in comparison to their corresponding physical mixtures and pure drug (EFZ, Crystalline Efavirenz). HEC and HPMC melt extruded formulations demonstrated faster drug release profiles when compared to those containing HPC ($p < 0.05$), which might be attributed to the aqueous solubility or hydrophilicity and swelling behavior of the HPC (Table 3-5). The Figure 3-2 shows the possible retarding effect

Table 3-3: Literature values of measurement of Cellulose Ethers Hydrophilicity

S. No.		% water content at 70% RH	Surface Tension (mN/m)	Hydrophilicity
1	HEC	21.7	61	High
2	HPMC	14.0	50	Medium
3	HPC	10.9	45	Low

of HPC matrix on the drug release. The formation of solid plug was observed with HPC solid dispersions. The delay in penetration of dissolution medium (Figure 3-15) may provide conditions for conversion of amorphous to crystalline form. HPMC is reported to increase the micro-environment viscosity and prevent re-crystallization of amorphous API.

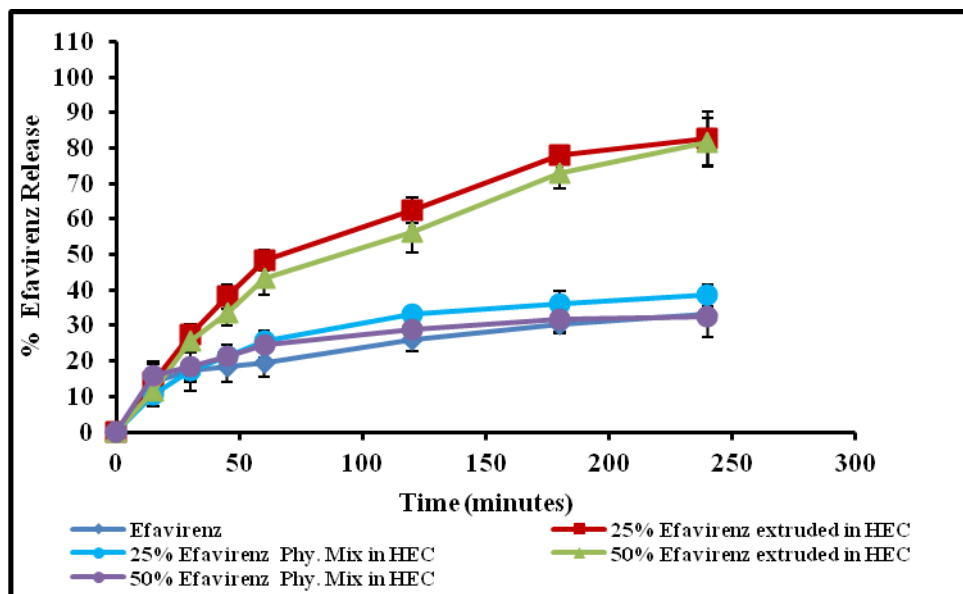


Figure 3-18: Comparison of the *in vitro* release profiles of the 25% and 50%w/w melt extruded and physical mixture capsule formulations in HEC matrix.

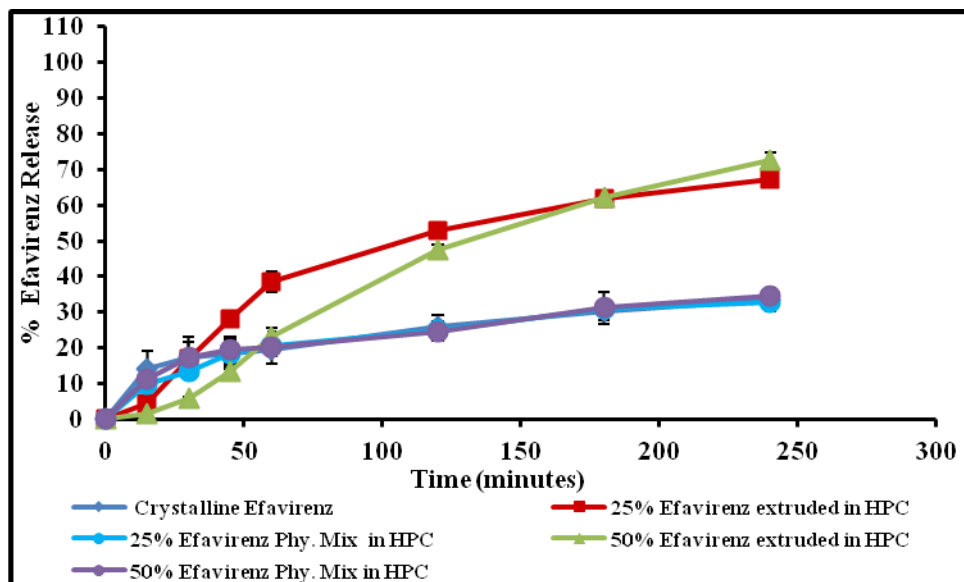


Figure 3-19: Comparison of the *in vitro* release profiles of the 25% and 50%w/w melt extruded and physical mixture capsule formulations in HPC matrix.

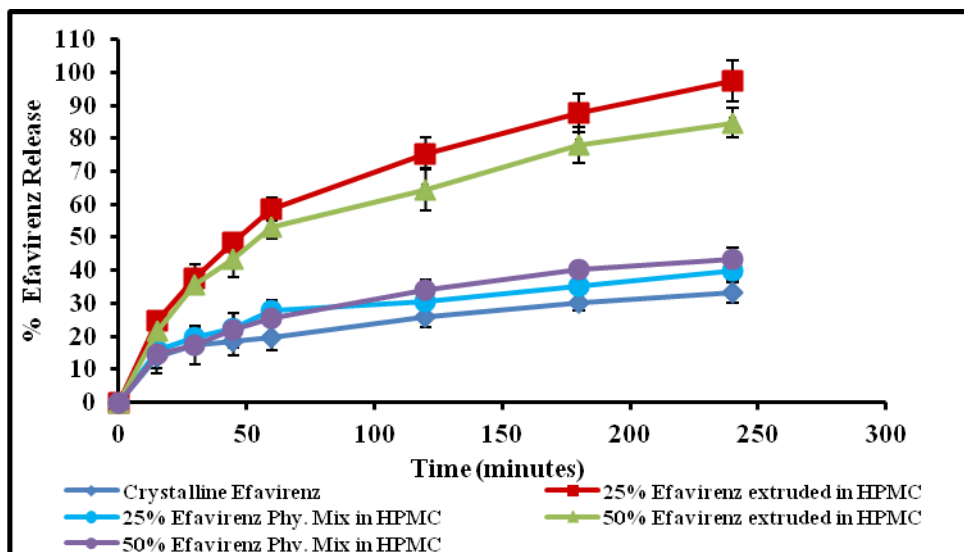


Figure 3-20: Comparison of the *in vitro* release profiles of the 25% and 50%w/w melt extruded and physical mixture capsule formulations in HPMC matrix.

3.12.7. SWELLING AND EROSION STUDIES

In aqueous medium, cellulose ethers tend to form hydrogels. Individual particles swell and their macromolecular chains start entangling, thus creating diffusional spaces that are controlled by the molecular weight and hydrophilic characteristics of the carrier polymers. Evidently, the average distance between consecutive physical entanglements, tight junctions, or tie points in these physical networks is a most important molecular parameter that will control not only the integrity of the formed swollen network (hydrogel) but also the diffusion characteristics of the drug diffusing through it and being released (35). According to literature, the number of entanglements per chain, are lowest for HPMC, followed by, HEC and HPC. Moreover, the molar substitution of HPC polymer was 3.7, indicating that most hydroxyl groups are substituted with hydrophilic hydroxypropyl groups, providing many possibilities for interactions.

The results of swelling and erosion studies presented in Figure 3-21 demonstrated that extrudates of HEC and HPMC matrices rapidly absorb dissolution medium and increase in weight over time until its complete disintegration around 4 hours. However, the extrudates with HPC matrices showed minimum swelling or erosion and their weight remained constant after 4 hours. These results can be correlated to our drug release data.

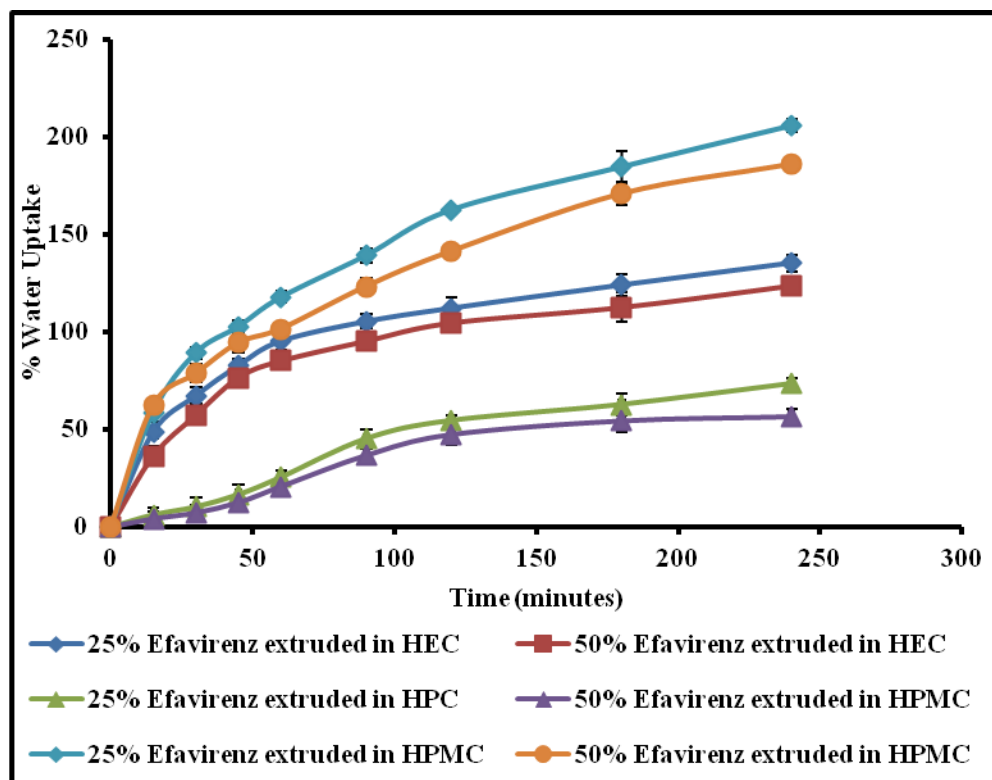


Figure 3-21: Swelling profiles of the 25% and 50% w/w EFZ in melt extruded formulations in cellulose ethers (HEC, HPC and HPMC) matrix.

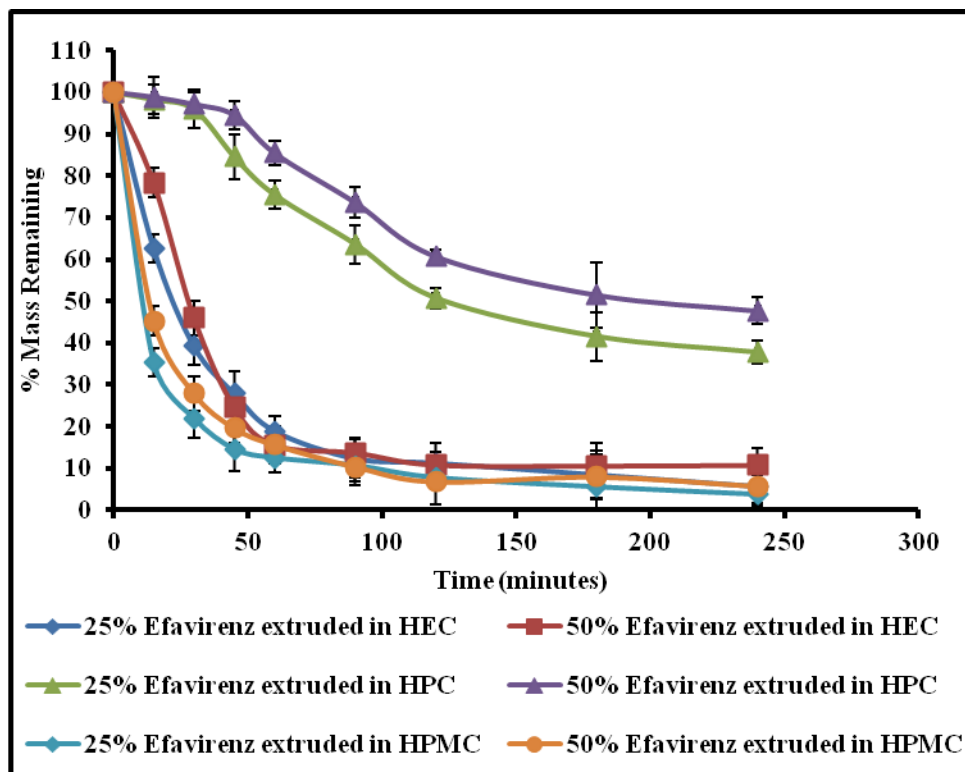


Figure 3-22: Erosion profiles of the 25% and 50% w/w EFZ in melt extruded formulations in cellulose ethers (HEC, HPC and HPMC) matrix.

3. 12.8 STABILITY

Many factors such as glass transition temperature of API, viscosity, plasticization/anti-plasticization, storage temperature, and humidity play an important role in determining the stability of high-energy amorphous solid dosage forms. Cellulose ethers tend to absorb moisture under high humidity conditions. The formulations of EFZ in HEC and HPC demonstrated significant decrease in release over period of time ($f_2 < 50$, Figure 3-21 and 3-22). The solid dispersions of EFZ with HPMC exhibited significant delay in release after 3 months with 50% w/w drug load ($f_2 < 50$, Figure 3-23). These studies would indicate that higher drug load (50% w/w) is prone to re-crystallization at 40 °C/75% RH (Figure 3-24 to 3-26). The moisture may

cause supersaturated regions led by dissolution of the drug at a micro-environmental level in the polymeric matrix, which eventually leads to nucleation and re-crystallization. At lower drug load (25% w/w), drug molecules are surrounded by higher number of polymer molecules which prevent the mobility of drug molecules. The chemical interactions can further impede the motion of drug molecules in polymer matrix and inhibit re-crystallization of EFZ.

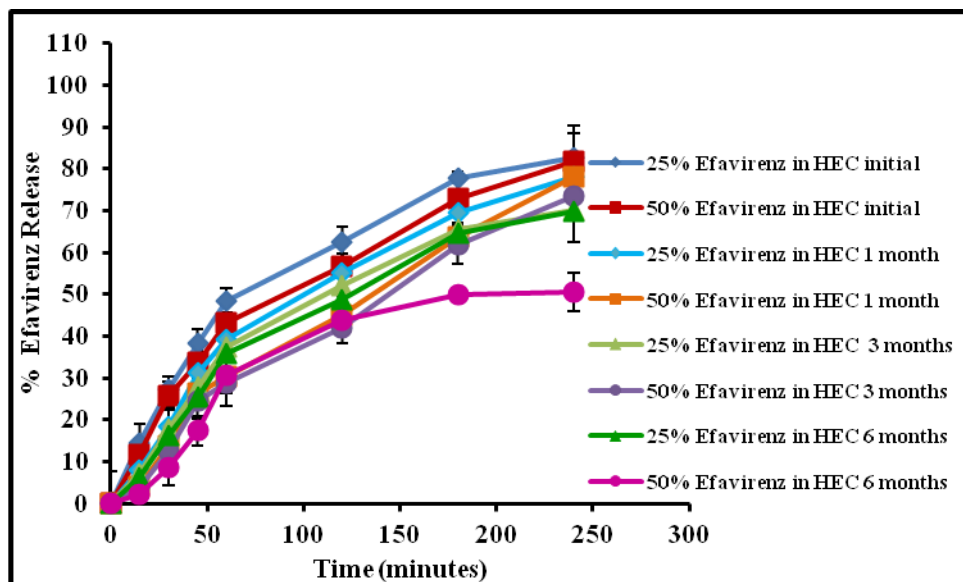


Figure 3-23: Release profiles of the 25% and 50% w/w melt extruded formulations in HEC matrix at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

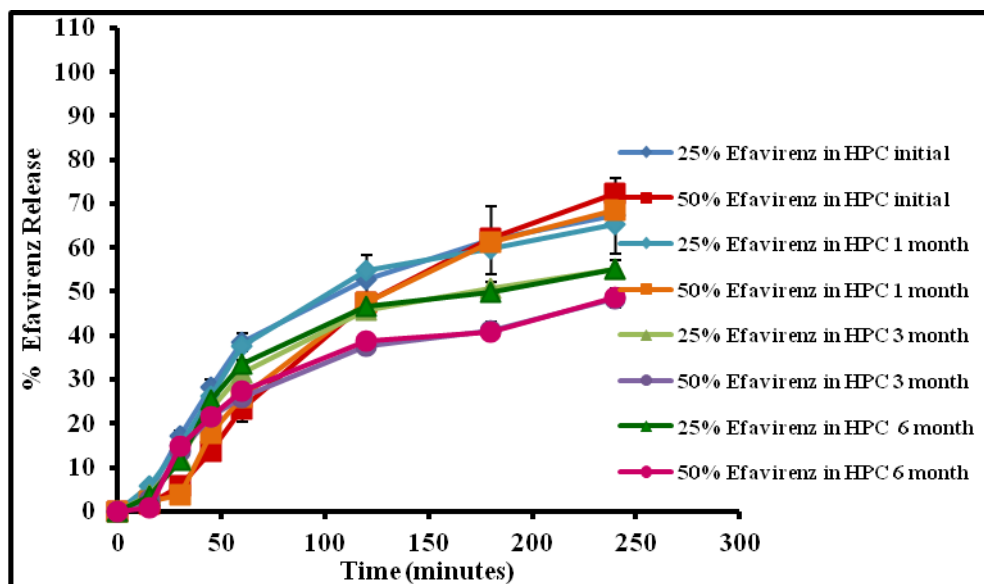


Figure 3-24: Release profiles of the 25% and 50% w/w melt extruded formulations in HPC matrix at the initial, 1, 3 and 6 month time points following storage at 40°C/75% RH.

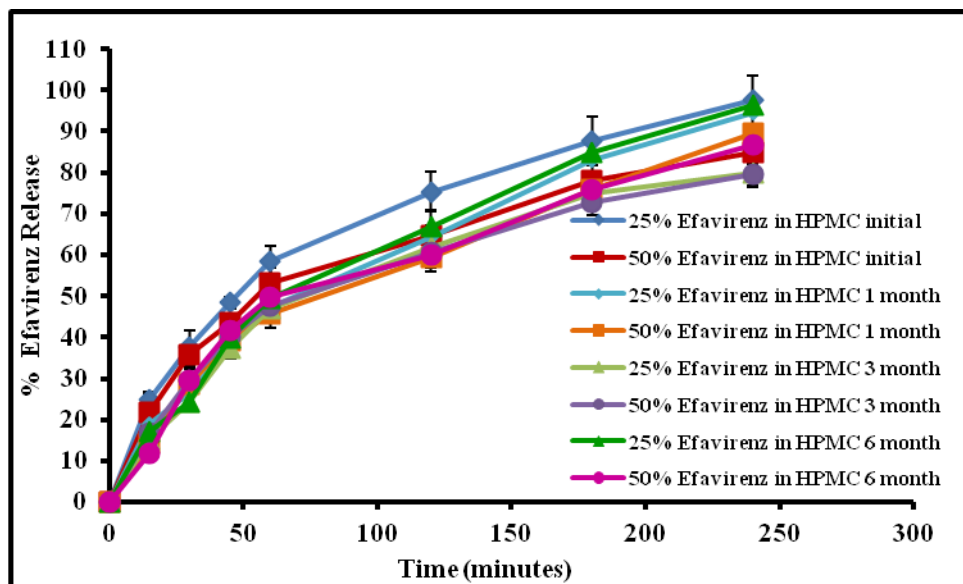


Figure 3-25: Release profiles of the 25% and 50% w/w melt extruded formulations in HPMC matrix at the initial, 1, 3 and 6 month time points following storage at 40°C/75% RH.

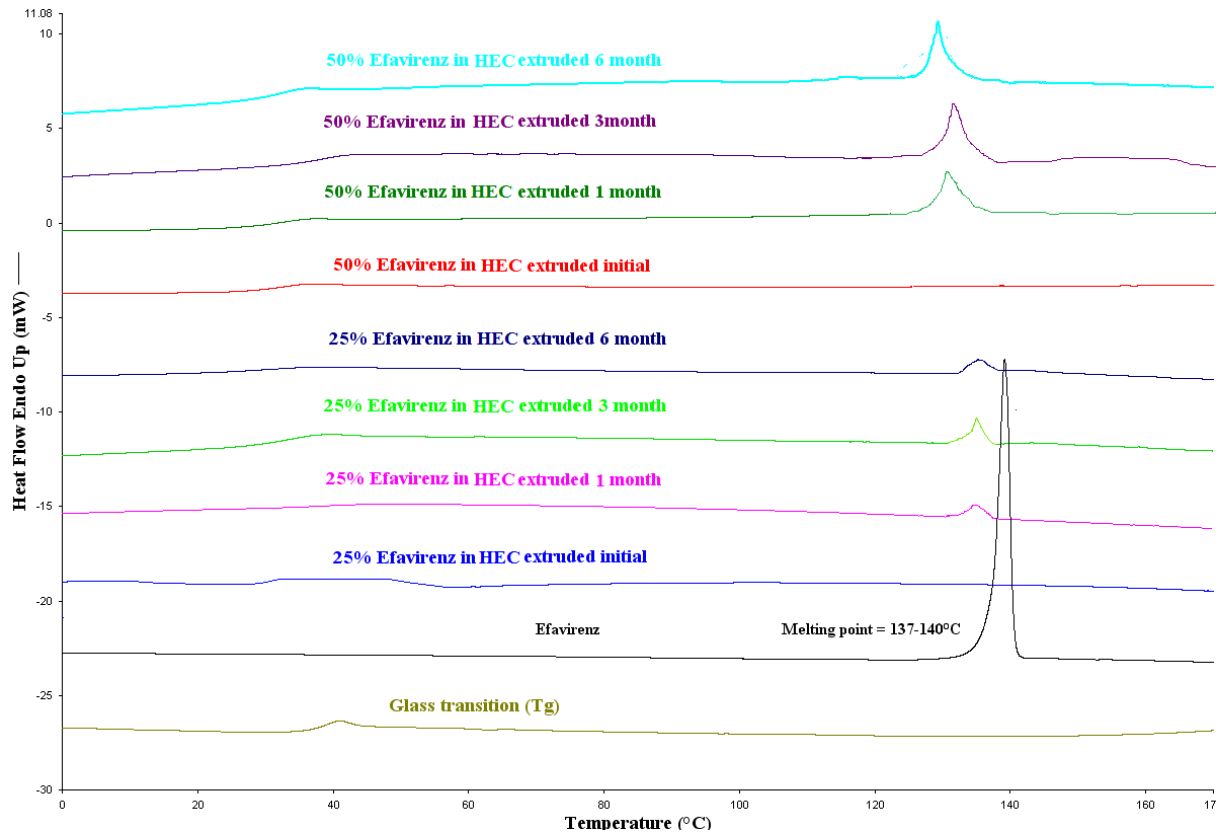


Figure 3-26: DSC thermogram illustrating stability Efavirenz in HEC matrix hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

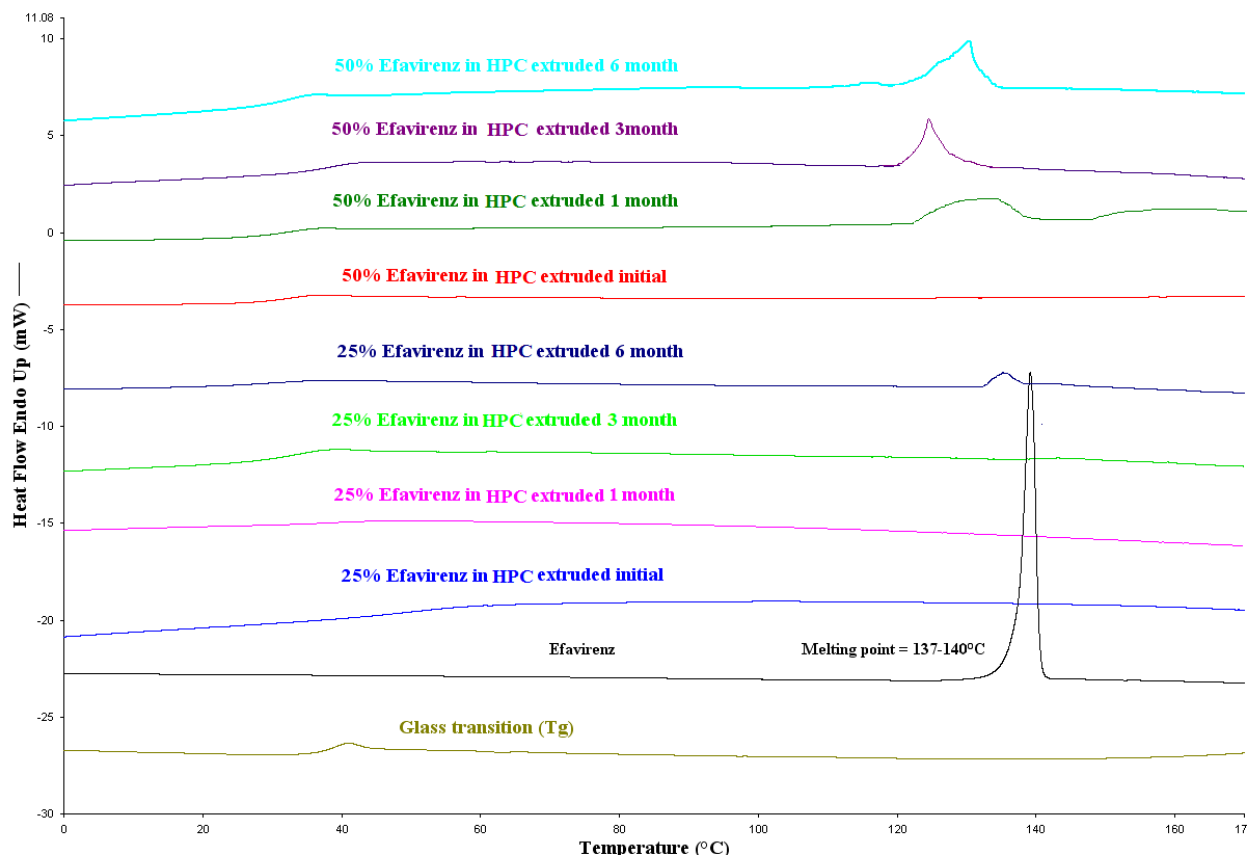


Figure 3-27: DSC thermogram illustrating stability Efavirenz in HPC matrix hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

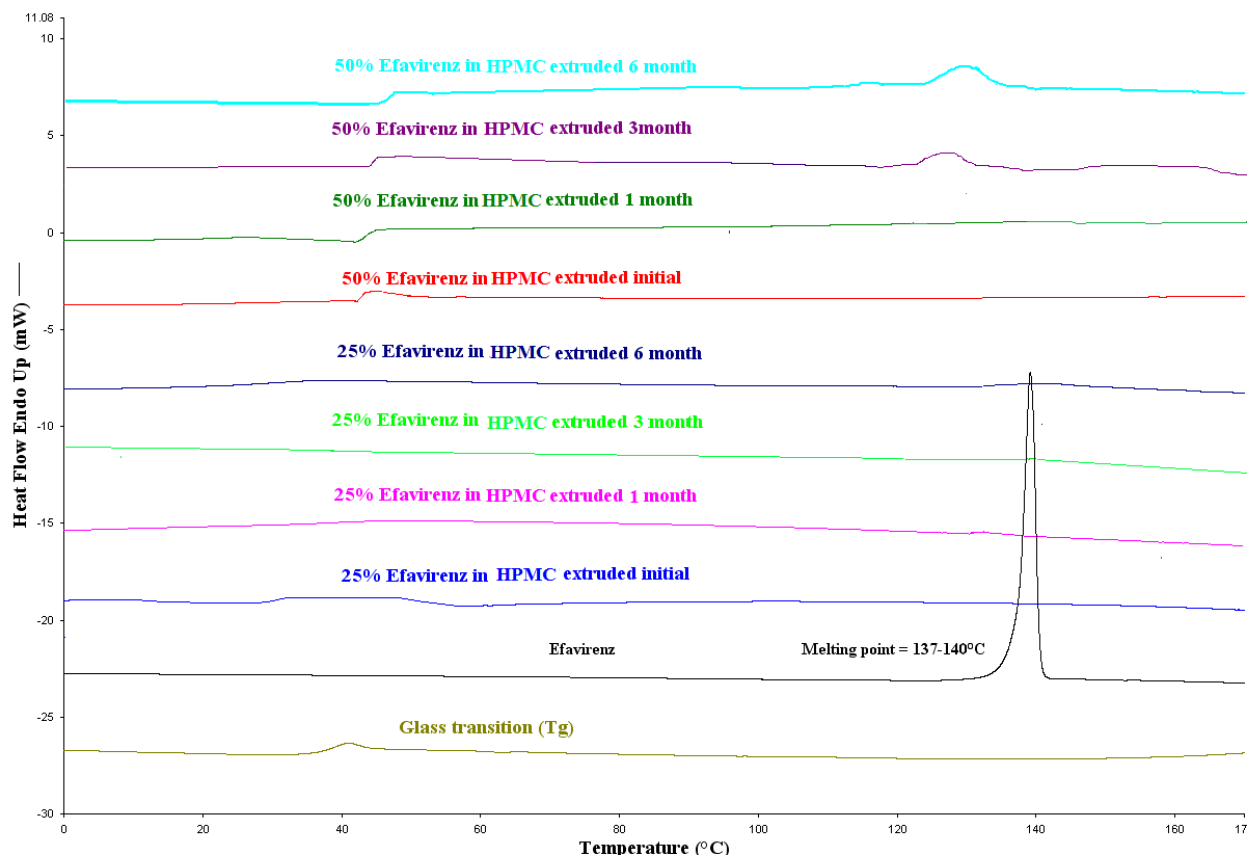


Figure 3-28: DSC thermogram illustrating stability Efavirenz in HPMC matrix hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

3.13. CONCLUSIONS

The present study demonstrated that cellulose ethers can be successfully extruded with EFZ. HPC and HPMC demonstrated promising EFZ solubility in polymer matrix. The data obtained from DSC, PXRD and FTIR studies showed that EFZ is molecularly dispersed in the HPMC and HPC matrices, while EFZ did not exhibit any specific interactions with HEC matrix. HEC based solid dispersions are susceptible to instability due to absence of interactions between EFZ and HEC. However, solid dispersions of EFZ in HPMC matrices exhibited enhanced dissolution rates, attributed to the intermolecular interactions resulting in inhibition of crystallization in dissolution medium and increased wettability. The combination of melt extrusion and

hydrophilic polymers successfully resulted in amorphous solid dispersion systems with enhanced solubility of EFZ although cellulose ethers are susceptible to moisture absorption. This study demonstrates that HME could be considered as an alternative technology to improve the dissolution characteristics of EFZ. Additionally, this research demonstrated that formulation using HPMC via HME may be effective for other poorly soluble drugs.

CHAPTER - 4
**HYPROMELLOSE DERIVATIVE ESTER POLYMERS AS CARRIERS FOR SOLID
DISPERSION OF EFAVIRENZ (EFZ) UTILIZING HOT MELT EXTRUSION**

4.1. ABSTRACT

The current research investigates process-ability; physical stability and dissolution behavior of EFZ solid dispersions prepared using Hypromellose ester derivative polymers (HPMCAS and HPMCP) as carrier matrices in combination with Sodium Lauryl Sulphate (SLS, 2 and 5%w/w). Two different drug loads of 25 and 50%w/w were studied in each polymer system. The chemical interaction between EFZ and Hypromellose ester derivatives was determined using Fourier transform infrared (FTIR). The solid-state characterization of EFZ in the Hypromellose ester derivative matrix was performed using differential scanning calorimetry (DSC), Powder X-ray Diffraction (PXRD). The *in vitro* release of these solid dispersions was evaluated in pH 6.8 phosphate buffer. Although, the drug release from solid dispersions prepared from polymers used for enteric coating (i.e. HPMCP) was higher compared with that of HPMCAS ($p < 0.05$), HPMCAS was found to be easily process-able compared to HPMCP. The interaction between the HPMCAS and EFZ in polymer matrices provided stability to the amorphous EFZ in solid dispersions than its pure form in the amorphous phase. Upon storage at accelerated stability conditions, no phase separation was observed in HPMCAS solid dispersions at the 25 and 50% w/w levels.

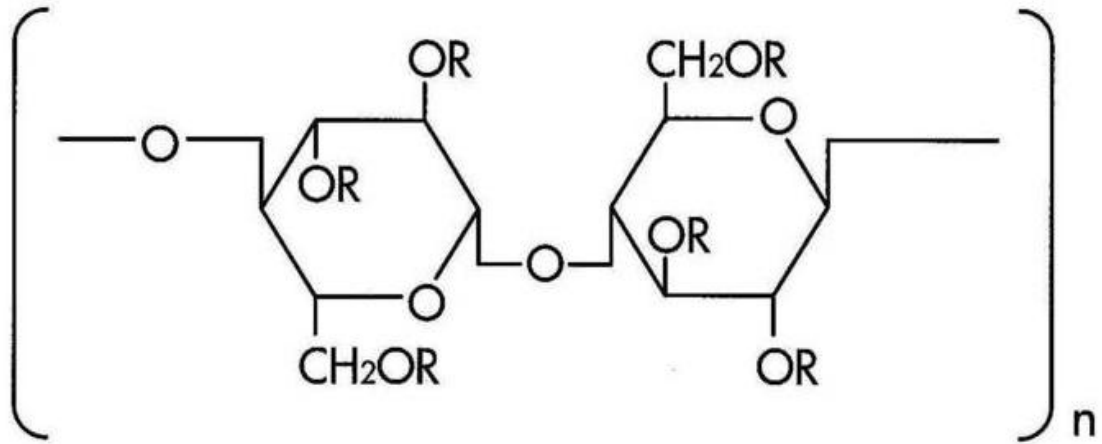
Keywords: Processability; Hypromellose ester derivatives; Phase separation Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), Powder X-ray Diffraction (PXRD).

4.2. INTRODUCTION

Hypromellose (HPMC) is a natural cellulose that is chemically O-methylated and O-(2-hydroxypropylated) cellulose (36). It is available in several grades that vary in viscosity and extent of substitution. Hypromellose has been used as coating agent, dispersing agent, dissolution enhancer, emulsifying agent, tablet binder and thickening agent. Hypromellose acetate succinate (HPMCAS) and hypromellose phthalate (HPMCP) are synthetically modified mixtures of acetic acid, monosuccinic acid esters of hypromellose and 2-hydroxypropyl methyl ether, phthalic acid ester of hypromellose, respectively. These synthetically modified natural cellulose polymers are traditionally used as enteric-coating agents, film forming agents and more recently as solubility enhancing agents in solid dispersions. For solid dispersion applications, the aliphatic-hydroxyl groups of HPMC and synthetic 2-hydroxypropyl groups are capable of donating hydrogen bond to APIs with hydrogen bond accepting groups. In HPMCAS matrix, the acetyl and succinyl groups can accept hydrogen bonds from APIs to stabilize the solid dispersion and in HPMCP matrix phthalyl ester substituent groups are capable of donating strong bonds to APIs with hydrogen-bonds accepting groups. The hydrogen bond accepting carbonyl group ester can resonance to stabilize the carboxylic acid hydrogen bond donating group through the aromatic phthalate. In addition, Hypromellose based solid dispersions are reported to reduce the overall molecular mobility in the system, indicated by an increase in the T_g of the mixed system. A higher T_g value compared to the pure drug will result, or indicate that strong specific interactions between the drug and polymer which may stabilize the solid dispersion.

The objective of this study was to develop a suitable amorphous solid dispersion formulation for a poorly water soluble compound, EFZ with Hypromellose ester derivative as carrier polymers using melt extrusion technique. Hypromellose and Hypromellose ester derivative polymers are

challenging to extrude because of their high glass transition temperature and highly viscous melt generated in the extruder. HPMCAS and HPMCP polymers have glass transition temperatures between 120-135°C and 145-150°C, respectively. However, plasticizers or plasticization by APIs may be necessary to effectively melt extrude HPMC and HPMC ester derivatives. In Chapter-3, HPMC was extruded with EFZ without addition of plasticizers. In the present study, SLS was used as plasticizing agent for HPMCP and HPMCAS matrices. SLS has been reported to exhibit its plasticizing effect by decreasing the melt viscosity and T_g of of the carrier polymers



HPMC (Hypromellose)

R = -H

-CH₃

-CH₂CH(CH₃)OH

HPMCP (Hypromellose Phthalate)

R = -H

-CH₃

-CH₂CH(CH₃)OH

-COC₆H₄COOH

**HPMC-AS (Hypromellose
-acetate succinate)**

R = -H

-CH₃

-CH₂CH(CH₃)OH

-COCH₃

-COCH₂CH₂COCH

-CH₂CH(CH₃)OCOCH₃

-CH₂CH(CH₃)OCOCH₂CH₂COOH

Figure 4-1: Structures of Hypromellose and Hypromellose ester derivatives(36)

4.3. MATERIALS

Hydroxypropyl methylcellulose (Benecel[®], HPMC-E5 PH) was obtained from Ashland Aqualon Ingredients USA, Hydroxypropyl methylcellulose acetyl succinate (AQOAT, HPMCAS-LF) and Hydroxypropyl methylcellulose phthalate (HPMCP, HP55) were obtained from Shin Etsu, USA. EFZ was supplied by Ria International, East Hanover, NJ. All other materials used were of reagent grade.

4.4. METHODS

4.4.1. HOT-MELT EXTRUSION

The polymer with various drug load (25 and 50% w/w) were mixed in a V-cone blender (MaxiBlendTM, GlobePharma) at 25 rpm for 15 minutes and then extruded with a co-rotating twin screw extruder (16 mm Prism EuroLab, ThermoFisher Scientific) into uniform rod extrudates at an extrusion temperature range of 100-150 °C and a screw speed of 70 rpm. The feed rate was adjusted so that the extruder % Torque Indicator was at approximately 60% for optimum extruder performance. The diameter of the extruded rods was approximately 2mm. These extrudates were subsequently processed into pellets of 1mm thickness using a pelletizer (Type L-001-9482, Thermoscientific, Stone, UK).

4.4.2. Thermogravimetric analysis (TGA)

Studies were performed on a Perkin Elmer Pyris 1 TGA equipped with Pyris software. TGA analysis was performed on HPMC, HPMCAS, HPMCP, EFZ and physical mixtures (Phy.Mix) with various drug loads by heating from 30-200 °C at 20° C/min.

4.4.3. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The thermograms were recorded using Perkin-Elmer Pyris 1 DSC equipped with Pyris Manager Software. DSC was used to study solid-state characteristics of EFZ in HPMC, HPMCAS and HPMCP matrix, pre-extrusion in physical mixtures and post-extrusion in extruded pellets. All the samples were heated from -10 °C to 180 °C at 10°C/min, cooled to -10°C (10 °C/min), and then reheated to 180 °C at 10 °C/min. For physical stability studies, samples of extruded pellets, approximately 8–10 mg, were hermetically sealed in an aluminum pan and heated from -10 °C to 180 °C at a linear heating rate of 10 °C/min.

4.4.4. SOLUBILITY PARAMETER

Solubility parameter calculations were performed using Molecular Modeling Pro software (Chem SW Inc., Fairfield, CA) utilizing group contribution approaches (Molecular Modelling Pro., 2006).

4.4.5. CHROMATOGRAPHIC CONDITIONS

A Waters HPLC-UV system (Waters Corp, Milford, MA) and a Symmetry Shield RP C-18 (250×4.6 mm, 5 µm) column was used at a detection wavelength of 245 nm. The mobile phase consisted of acetonitrile and Formic acid in water (pH =4.0) at a ratio of 60:40 (v/v). The mobile phase flow rate was maintained at 1.5 ml/min. EFZ retention time was 7.2±0.43 min under these conditions. Injection volume was 20 µl. All of the HPLC data was analyzed using Empower V. software.

4.4.6. FOURIER TRANSFORM INFRARED (FTIR) SPECTROSCOPIC ANALYSIS

FTIR spectra for EFZ, HPMCP and HPMCAS were obtained using a Perkin-Elmer spectrometer (Perkin-Elmer Life and Analytical Sciences, Shelton, CT, USA). A spectrum was collected for each sample within the wave number region 4,000–650 cm^{-1} . The spectrums were analyzed for the absence or shift in the wave numbers of the characteristic peaks. FTIR studies were done to detect the possible interactions between EFZ and Hypromellose ester derivatives in the solid dispersions.

4.4.7. POWDER X-RAY DIFFRACTION (PXRD)

The crystallinity of EFZ in the hot-melt extruded pellets and their respective physical mixtures were analyzed using X-ray diffractometry. The studies were performed on a D-8 Advance X-ray diffractometer (Bruker-Axs) equipped with Diffrac Plus1 software. The generator operating voltage and current were 40 kV and 40 mA, respectively. The step size was maintained at 0.01° and the dwell time at each step was 1 sec. The scanning speed was 2° per min, and the 2 Theta scanning range was from 5° to 40°.

4.4.8. IN VITRO RELEASE STUDIES

In vitro release studies were performed according to USP 31 apparatus I using discriminatory dissolution medium comprised of 1000 ml of 0.2% SLS in 0.1M HCL (pH 1.2) and 0.2M sodium phosphate buffer (pH 6.8). Hanson SR8-plus™ dissolution test station (Chatsworth, CA) was used at 37±0.5 °C and paddle speed was maintained at 50 rpm. Samples were collected at predetermined time intervals, through a stain-less steel cannula with a 0.2 μm nylon filter tips attached to a 1 ml syringe. These samples were analyzed using HPLC/UV. All the results were reported as the average of 3 replicates ± SD. Dissolution profiles were compared using similarity factor (f_2). An f_2 value larger than 50 indicates that the two dissolution profiles are similar.

4.4.9. STABILITY STUDIES

The impact of temperature and humidity conditions on the physical and chemical stability of EFZ in pellet formulations was determined by storing in closed HDPE bottles at 4 °C, 25°C/60% RH, 40 °C/75% RH and 60 °C. The dissolution profiles, chemical and physical stability of the pellets were examined at initial, 1, 3 and 6 month time points. The dissolution profiles of capsule formulations at different time points were compared using the f_2 similarity factor.

4.4.10. DATA ANALYSIS

In all the cases, statistical analysis was performed utilizing one-way analysis of variance. A statistically significant difference was considered when $p < 0.05$.

4.5. RESULTS AND DISCUSSION

4.5.1. HOT MELT EXTRUSION

The solubility parameters of EFZ, hypromellose phthalate (HPMCP) and hypromellose (HPMC), hypromellose acetate succinate (HPMCAS) are calculated in Table.1. The difference in the solubility parameters ($\Delta\delta t$) are lower than the proposed value of $7 \text{ MPa}^{1/2}$ required for the polymer–drug miscibility indicating that EFZ would likely to be miscible with hypromellose acetate succinate (HPMCAS) and hypromellose phthalate (HPMCP). As discussed earlier plasticizers or plasticization by APIs may be necessary to effectively melt extrude Hypromellose ester derivatives. SLS has been reported to be an instrumental plasticizer, lowering the melt viscosity during extrusion and thereby increasing the drug solubility and homogeneity in the carrier polymer. In this study, two levels (2 and 5% w/w) of SLS were used. HPMCAS and HPMCP could not be extruded without SLS. The extruded pellets were transparent for HPMC and HPMCAS with drug loads of 25 and 50% w/w. The extruded pellets for HPMCP with drug loads of 25 and 50% w/w were turbid or white in color. As discussed in Chapter 3, the clear appearance signify that a solid dispersion was obtained and turbid extrudates may indicate such dispersions are not chemically and physically uniform throughout or comprise more than one phase. HPMCP is reported to form the solid dispersions with super saturated polymer matrix with amorphous API and heterogeneous distribution of API. When all of the EFZ has dissolved in the HPMCAS matrix upon melting during extrusion, a homogenous solution was formed. This solution upon cooling formed a solid solution and exhibited a clear appearance. The clear extrudates indicated a homogenous miscible system upon cooling like the ones obtained with HPMCAS with drug loads of 25 and 50% w/w.

4.5.2. THERMAL ANALYSIS

The thermal stability of physical mixtures of EFZ, HPMC, HPMCAS and HPMCP was determined using (TGA). As shown in Figure 4-2, the results from the TGA study, physical mixtures of EFZ, HPMC, HPMCAS and HPMCP did not begin to show signs of thermal decomposition until reaching approximately 200 °C. TGA thermogram confirmed the thermal stability of physical mixtures of EFZ, HPMC, HPMCAS and HPMCP at the extrusion temperatures at drug loads 25 and 50% w/w.

In Figure 3-4, EFZ exhibited a glass transition temperature of 34.45 ± 2.1 °C. The Tg can be reported as the onset, midpoint ($1/2 \times$ change in heat capacity at the Tg), or the endset (offset) of the glass transition. We used midpoint by placing tangent lines of the step event seen as slight endothermic shifts in the baseline (Figure 4-5). It is often recommended when taking Tg measurements to first heat the sample above its Tg, so as to erase the effects of the sample's thermal history, and cool it down to a temperature well below the Tg and then determine the Tg on the second heating. In the Figure 4-5 to Figure 4-9, Tg of the EFZ significantly increased in extruded formulations with Hypromellose ester derivative polymers compared to EFZ alone.

Table 4-1: Calculated solubility parameters for EFZ and Hypromellose ester derivatives.

S. No.		δ_t	$\Delta\delta_t$
1	EFZ	24.5	0
2	HPMC	25.6	1.1
3	HPMCAS	29.6	5.1
4	HPMCP	30.35	5.85

The anti-plasticization (increase in Tg) effect of polymeric carriers on drugs is considered important for stability. The increase in Tg means molecular mobility of the drug has been reduced which leads to a decrease in nucleation or re-crystallization of drug molecules. A single

T_g (indicating molecular miscibility) was observed for all of the three polymers with T_g ranging from 75 to 82 °C, as measured by DSC, immediately after the manufacture at the two drug loads of 25 and 50% w/w.

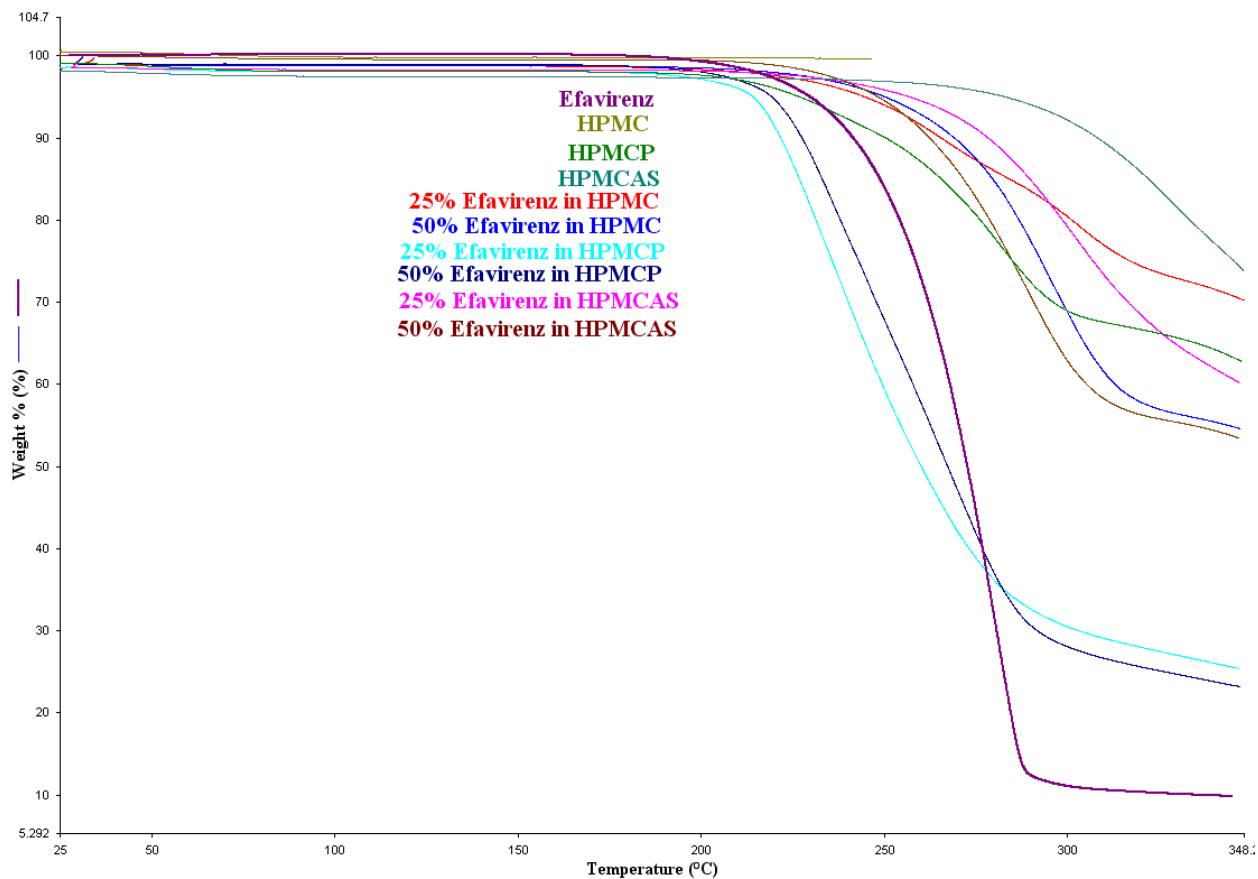


Figure 4-2: TGA of Hypromellose (HPMC) and Hypromellose ester derivatives (HPMCAS and HPMCP) and EFZ at drug loads 25 and 50% w/w.

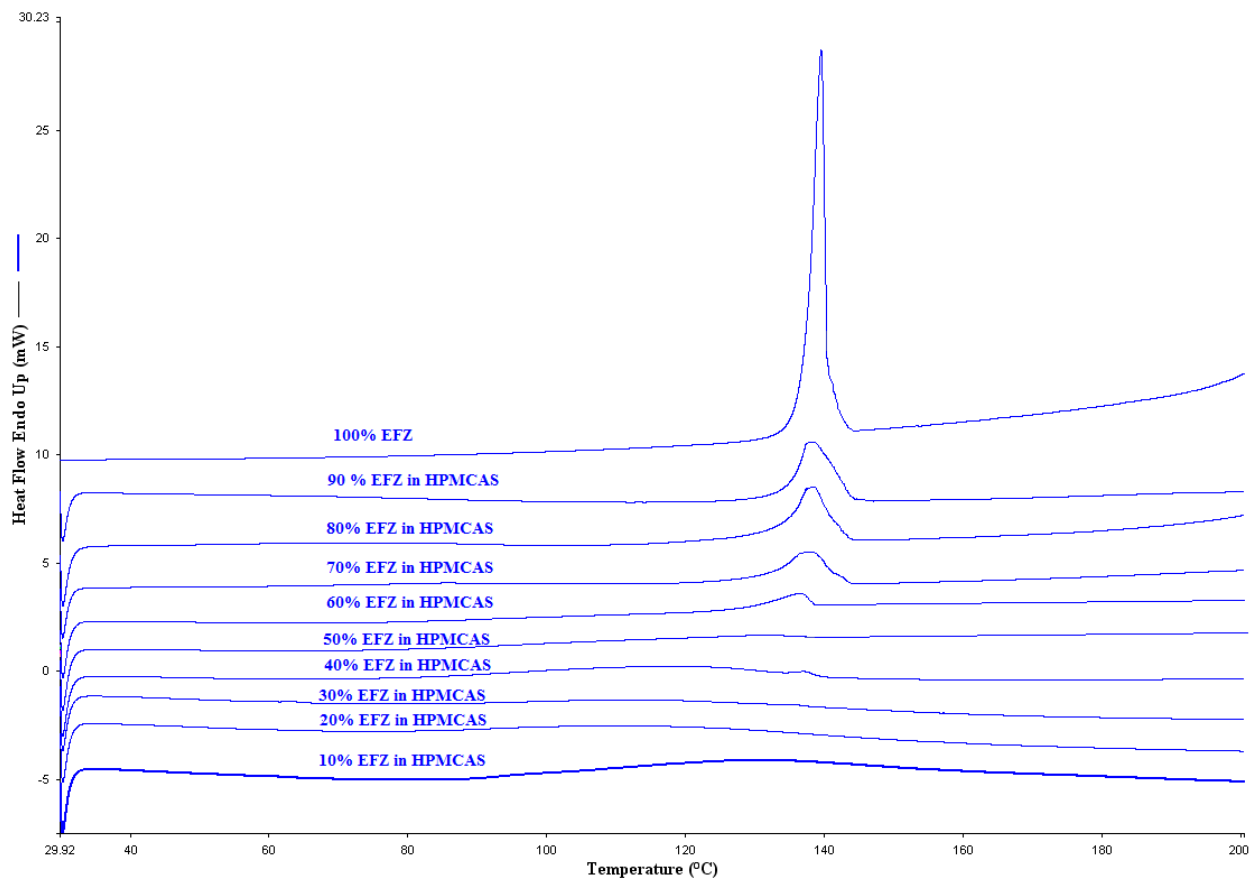


Figure 4-3: First heating cycle of the same sample after cooling from 30 °C to 200 °C at 10 °C/min of EFZ with different drug loads with HPMCAS.

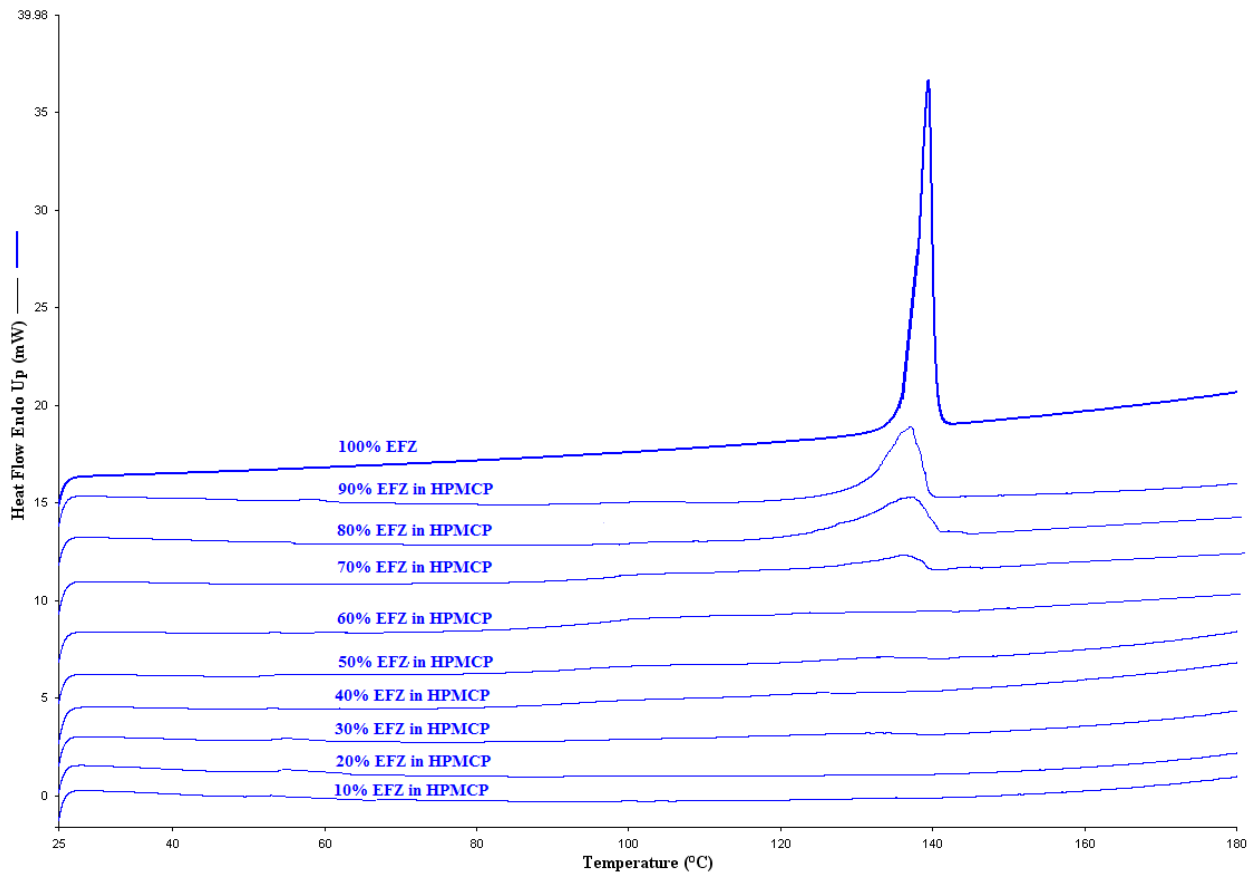


Figure 4-4: First heating cycle of the same sample after cooling from 30 °C to 200 °C at 10 °C/min of EFZ with different drug loads with HPMCP.

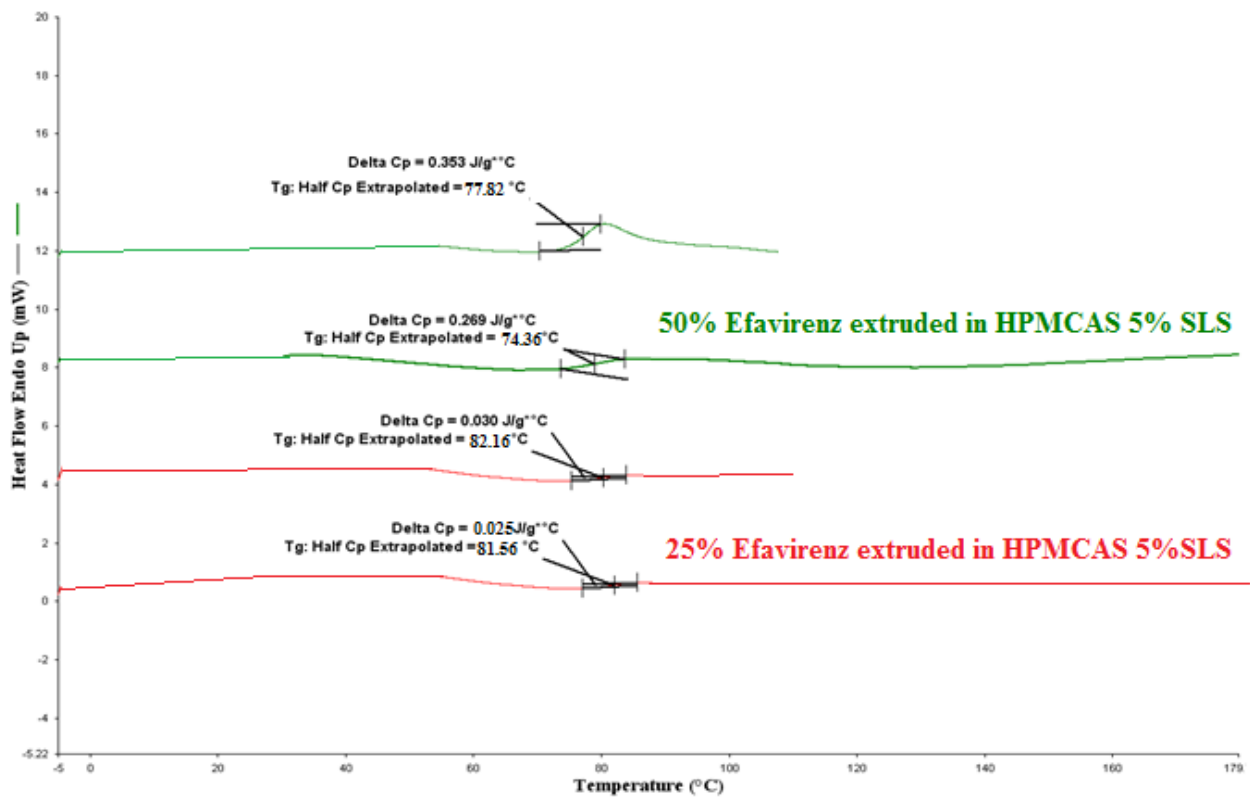


Figure 4-5: DSC thermograms of extruded of EFZ with drug loads 25 and 50% w/w in HPMCAS matrix with 5% SLS; heating step (10 °C/min), followed by cooling step (40 °C/min) and heating step (10 °C/min).

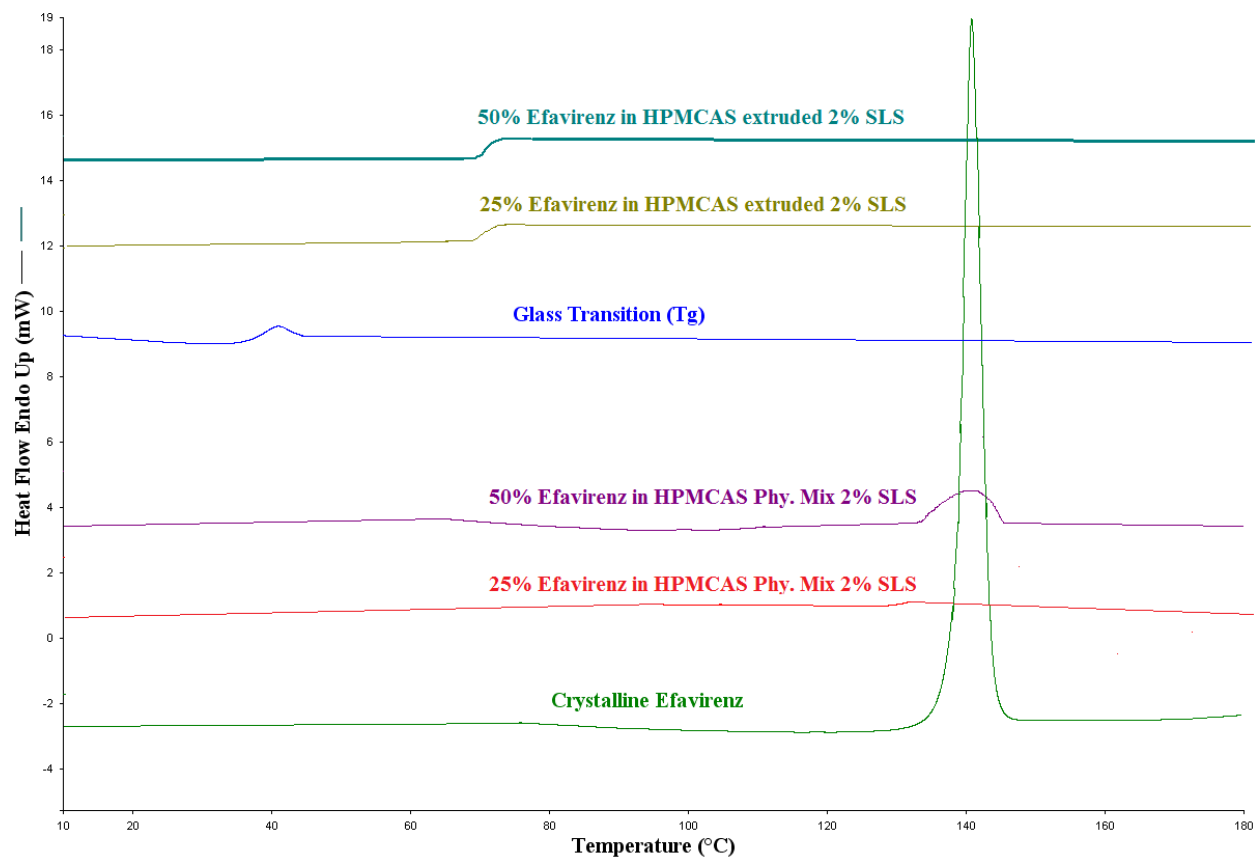


Figure 4-6: DSC thermograms of extruded and physical mixtures (Phy.Mix.) of EFZ with drug loads 25 and 50% w/w in HPMCAS matrix with 2% SLS.

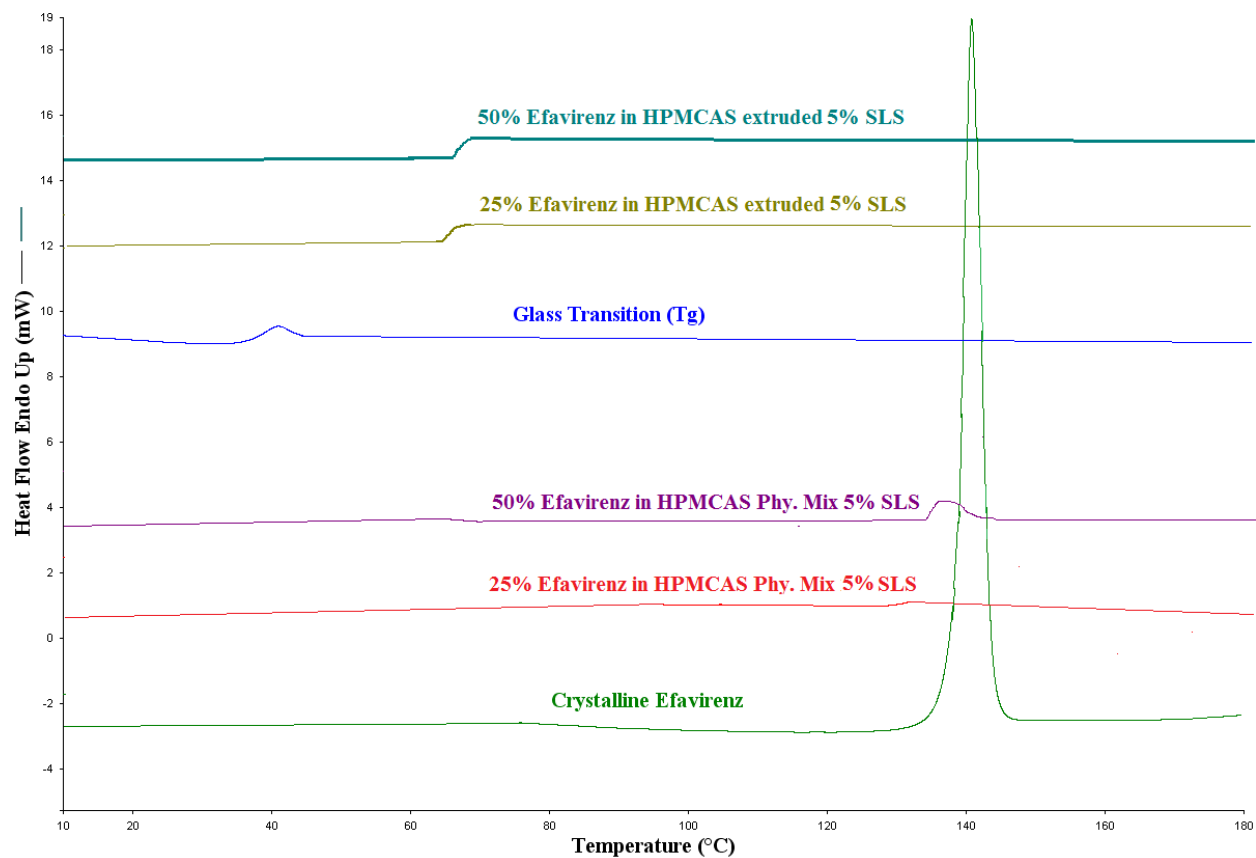


Figure 4-7: DSC thermograms of extruded and physical mixtures (Phy.Mix.) of EFZ with drug loads 25 and 50% w/w in HPMCAS matrix with 5% SLS.

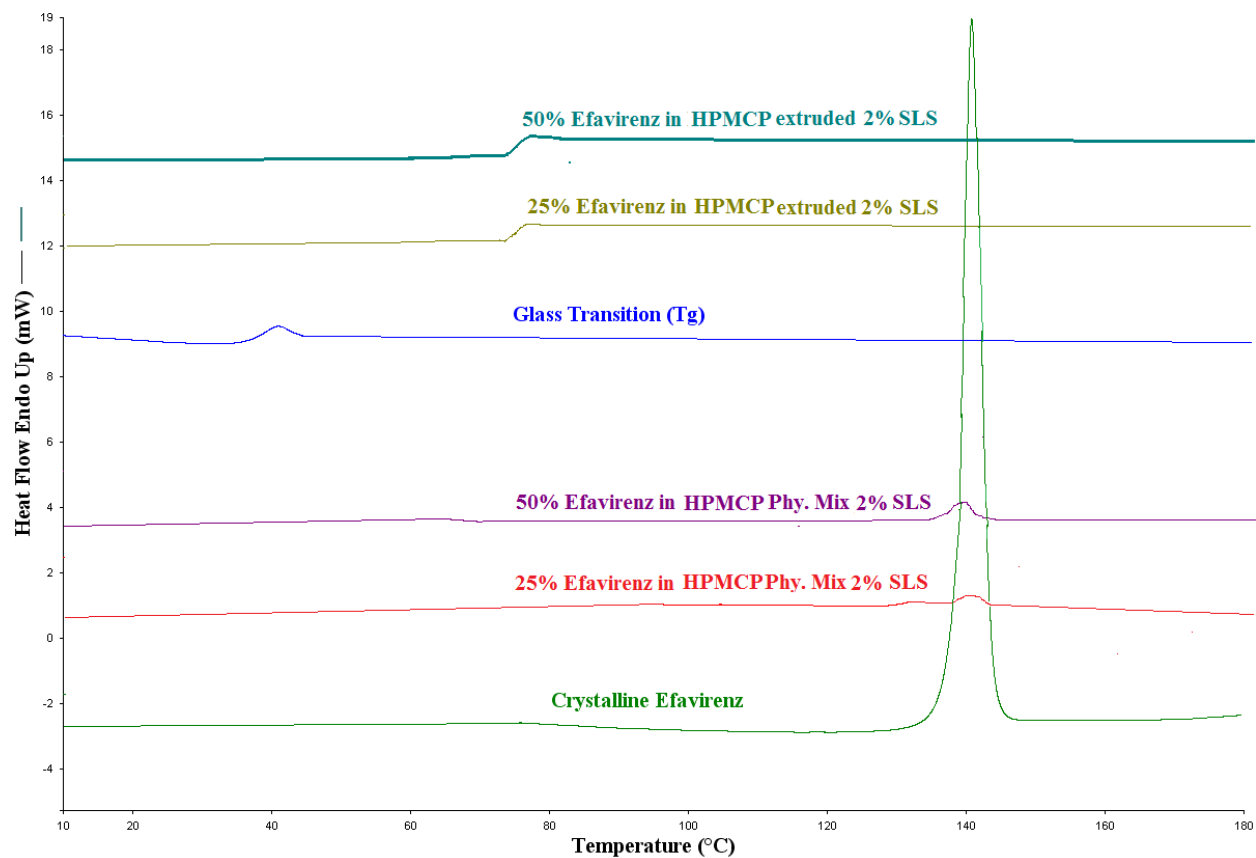


Figure 4-8: DSC thermograms of extruded and physical mixtures (Phy.Mix.) of EFZ with drug loads 25 and 50% w/w in HPMCP matrix with 2% SLS.

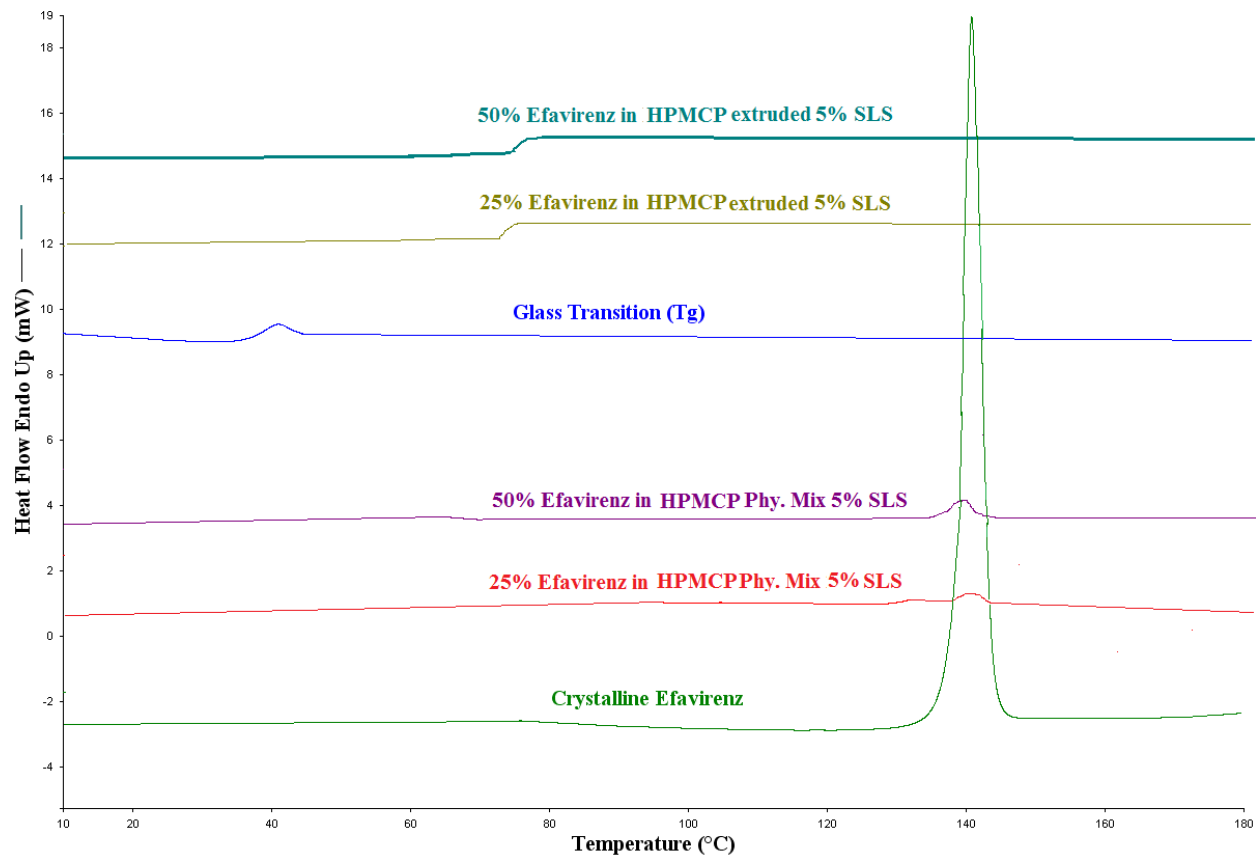


Figure 4-9: DSC thermograms of extruded and physical mixtures (Phy.Mix.) of EFZ with drug loads 25 and 50% w/w in HPMCP matrix with 5% SLS.

4.5.3. POWDER X-RAY DIFFRACTION (PXRD)

The crystalline EFZ is characterized by a PXRD pattern comprising of 2 Theta values of 6.8 ± 0.2 , 10.3 ± 0.2 , 10.8 ± 0.2 , 14.1 ± 0.2 , 16.8 ± 0.2 , 20.0 ± 0.2 , 20.5 ± 0.2 , 21.1 ± 0.2 and 24.8 ± 0.2 . The drug was found to be in amorphous state within the extrudates. The PXRD patterns of the extrudates with Hypromellose ester derivatives matrices showed no crystalline peaks corresponding to EFZ compared to corresponding physical mixtures (Figure 4-10 and 4-11). These findings are in agreement with thermal analysis results.

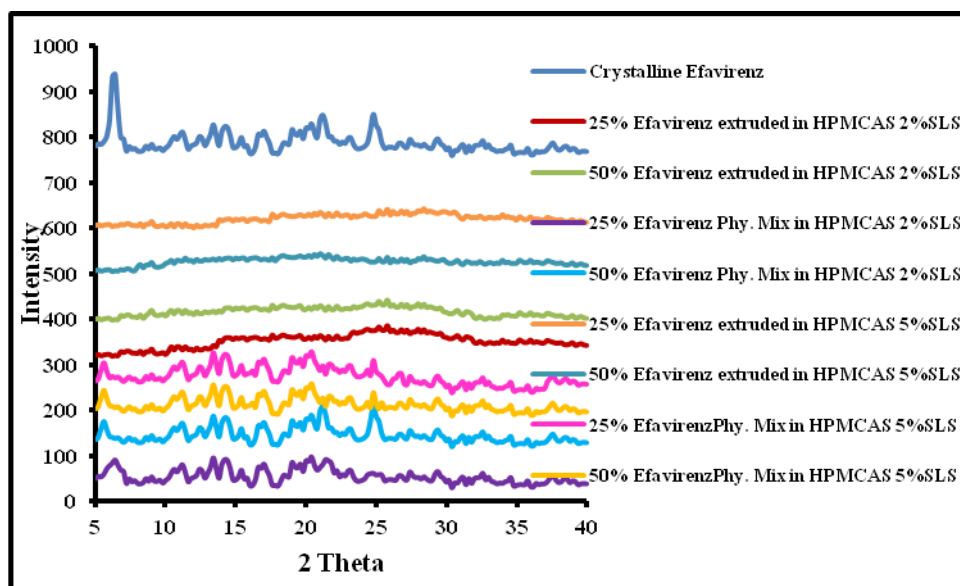


Figure 4-10: PXRD patterns of hot melt extruded pellets and physical mixtures with 25 and 50% w/w drug load in HPMCAS matrix with 2 and 5% SLS.

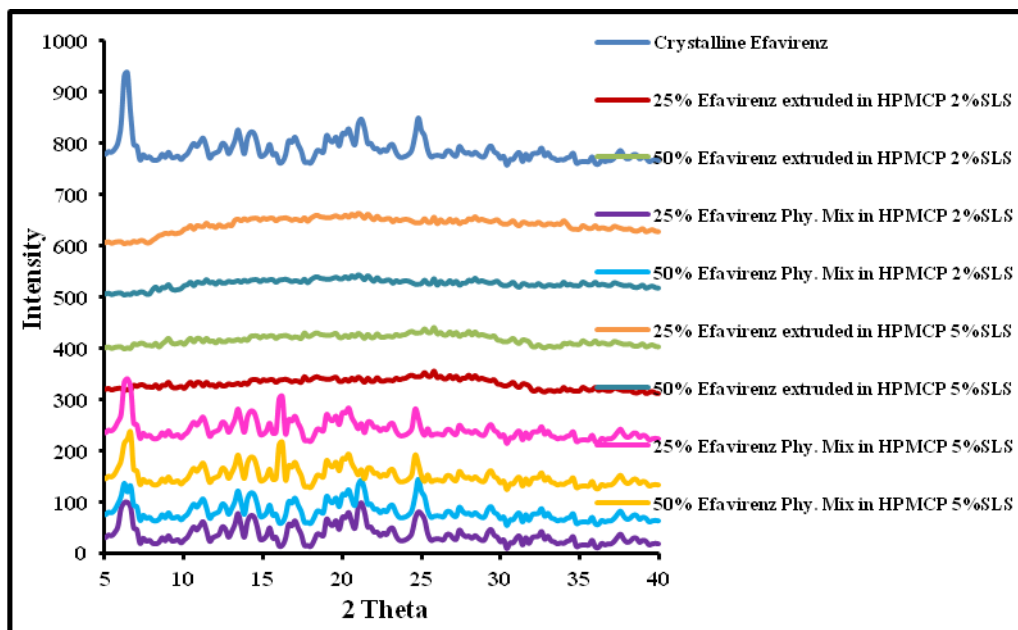


Figure 4-11: PXRD patterns of hot melt extruded pellets and physical mixtures with 25 and 50% w/w drug load in HPMCP matrix with 2 and 5% SLS.

4.5.4. FOURIER TRANSFORM INFRARED SPECTROSCOPY

The chemical interactions between EFZ and Hypromellose ester derivative polymers in the solid dispersions may stabilize amorphous state of EFZ. There are several reports in the literature of Hypromellose ester derivative interaction potential with drugs. As mentioned earlier, the crystalline EFZ shows characteristic bands at 3311.33 cm^{-1} , 2249.86 cm^{-1} , 1602.29 cm^{-1} , 1745.42 cm^{-1} , 1241.11 cm^{-1} and 1316.13 cm^{-1} attributed to N–H stretching vibrations, aromatic C–H stretching vibration, C=C stretching vibration, C=O stretching vibration, C–F stretching vibration, C–O–C stretching vibration, respectively. The bands corresponding to C=O vibrations and N–H stretching diffused in case of amorphous form as shown in Figure-4a (1728.69 cm^{-1} and 3260.09 cm^{-1} , respectively). This may indicate the participation of –NH and C=O groups in intermolecular hydrogen bonding between EFZ molecules. The spatial arrangement of EFZ molecules in the crystal lattice does not allow intermolecular hydrogen bonding which starts to

occur once the orderliness of crystalline lattice is disturbed by formation of amorphous form. These intermolecular hydrogen bonds are relatively weak and amorphous form tends to revert back to the crystalline form. For pure HPMC, the absorption band of hydroxyl group at 3449 cm^{-1} , Hypromellose ester derivative polymers (HPMCP and HPMCAS) shows the characteristic bands of the ester groups at $1150\text{-}1190\text{ cm}^{-1}$, 1239.23 cm^{-1} and 1268.22 cm^{-1} , as well as the C=O ester vibration at $1720\text{-}1740\text{ cm}^{-1}$. The physical mixtures of EFZ in Hypromellose ester derivatives showed summation of EFZ and polymers IR spectra. In extruded pellet formulations with EFZ in HPMCAS (Figure 4-10 and 4-11), the band at 3311.33 cm^{-1} corresponding to N–H stretching in crystalline EFZ spectra disappeared. In the spectra of extruded pellets, the bands corresponding to C=O ester vibrations in HPMCAS exhibited shift in the intensity of bands at $1736\text{-}1739\text{ cm}^{-1}$. This may indicate presence of intermolecular interaction between C=O group of HPMCAS and –NH group of EFZ. The increase in concentration of SLS did not affect the interaction.

In the Figure 4-12 and 4-13, with EFZ in HPMCP matrices, the band at 3311.33 cm^{-1} corresponding to N–H stretching in crystalline EFZ spectra disappeared. In the spectra of extruded pellets, the bands corresponding to C=O ester vibrations in HPMCP exhibited a shift in intensity of the bands at $1755\text{-}1757\text{ cm}^{-1}$ and split in the band at 1721 cm^{-1} . This may indicate the presence of intermolecular interaction between the C=O group of HPMCP and –NH group of EFZ. The increase in concentration of SLS did not affect these interactions.

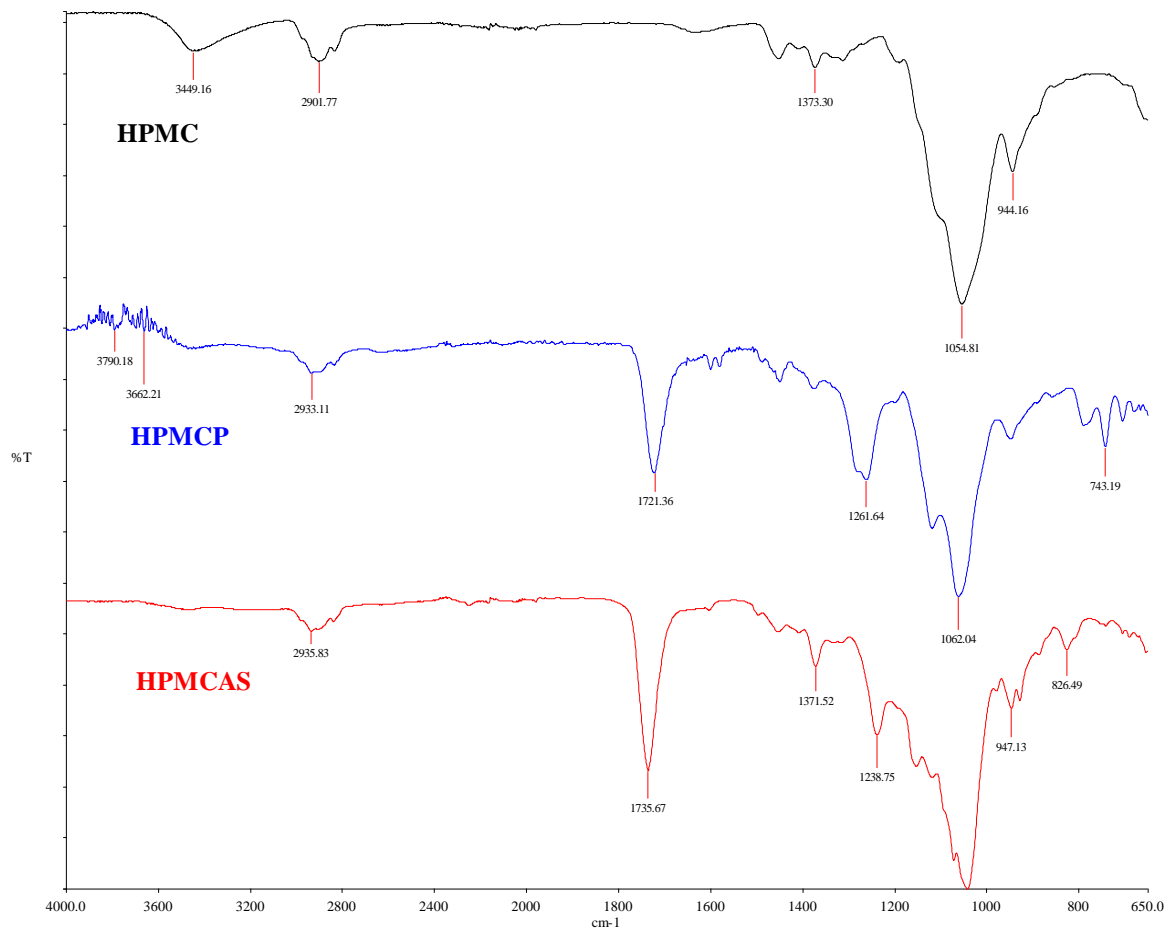


Figure 4-12: An overlay of FTIR spectra of cellulose ethers (HPMC, HPMCAS and HPMCP).

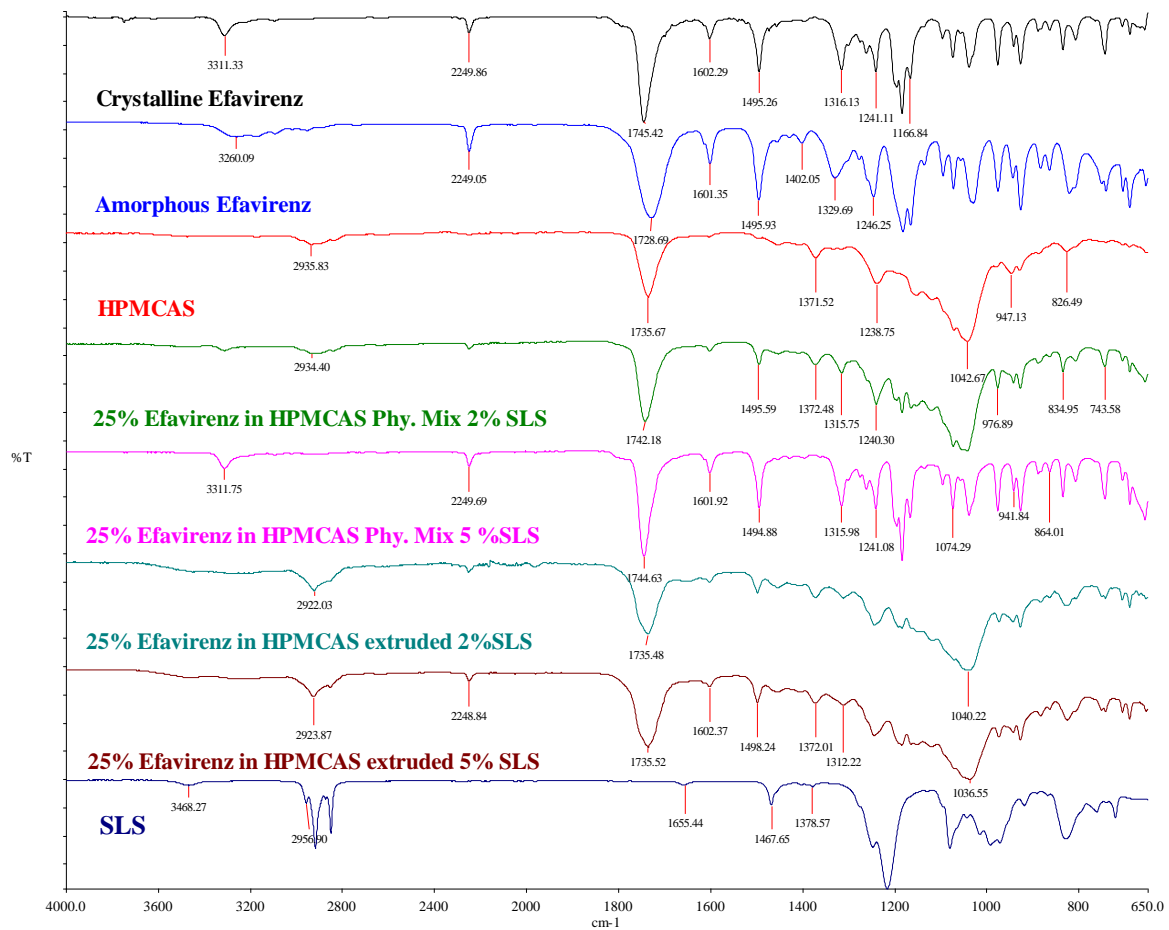


Figure 4-13: An overlay of FTIR spectra of Crystalline Efavirenz, amorphous Efavirenz and HPMCAS at drug loads 25 % w/w with SLS (2 and 5% w/w).

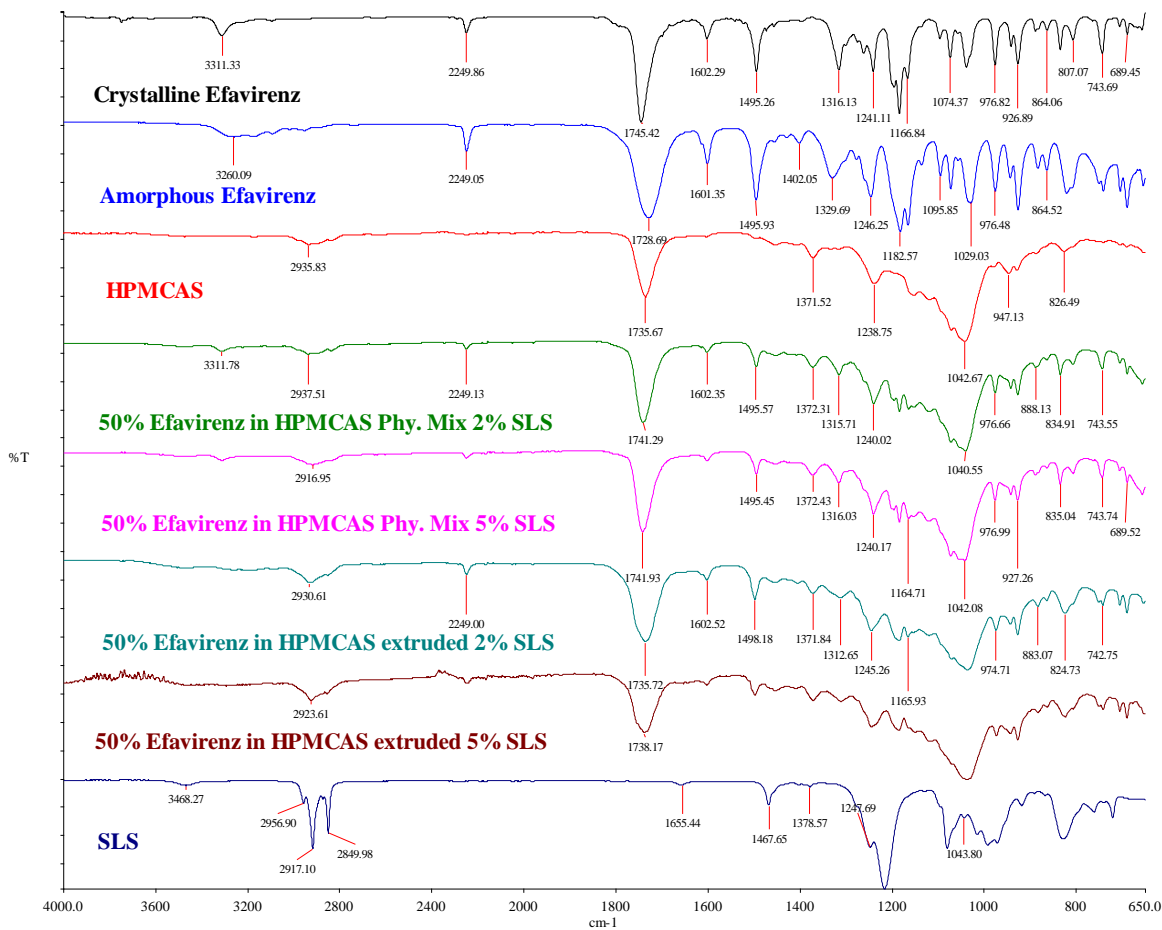


Figure 4-14: An overlay of FTIR spectra of Crystalline Efavirenz, amorphous Efavirenz and HPMCAS at drug loads 50 % w/w with SLS (2 and 5% w/w).

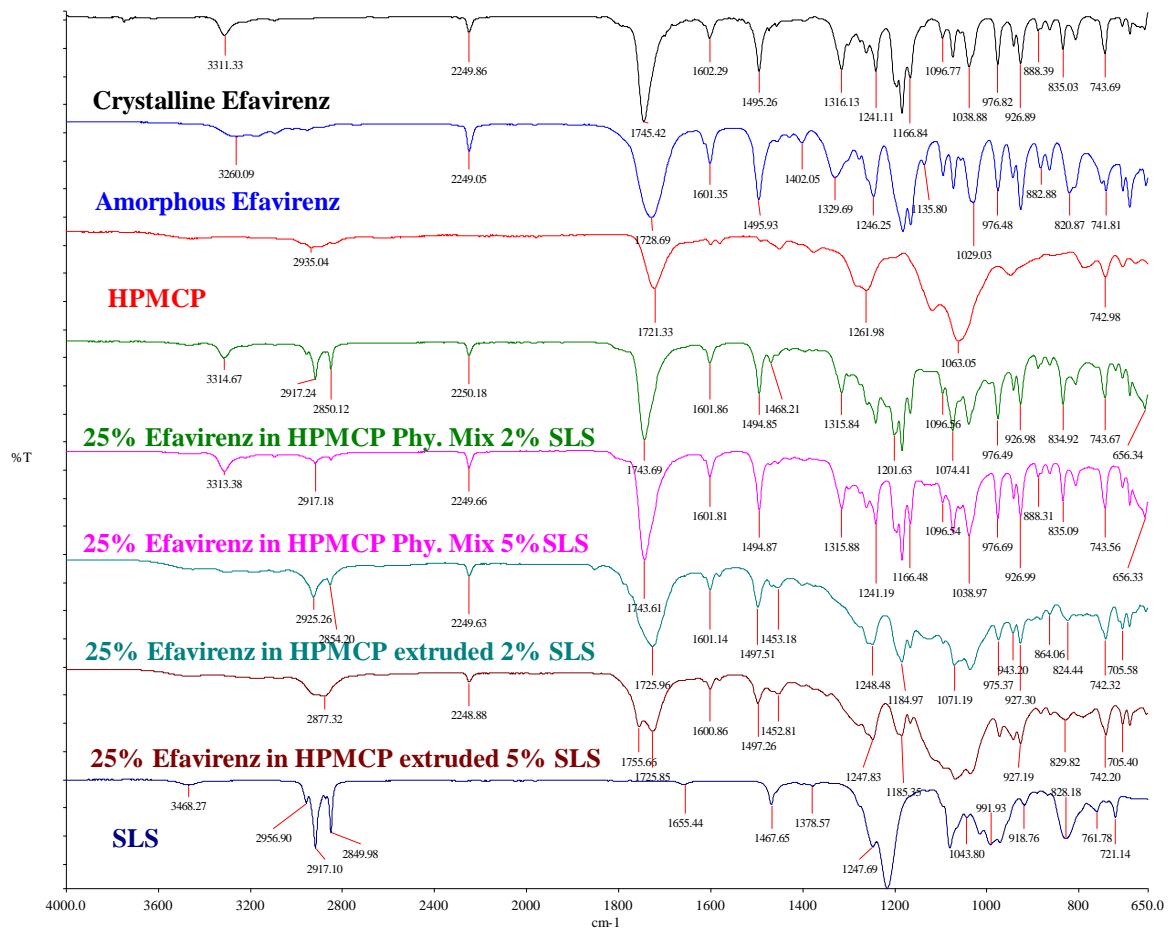


Figure 4-15: An overlay of FTIR spectra of Crystalline Efavirenz, amorphous Efavirenz and HPMCP at drug load 25% w/w with SLS (2 and 5% w/w).

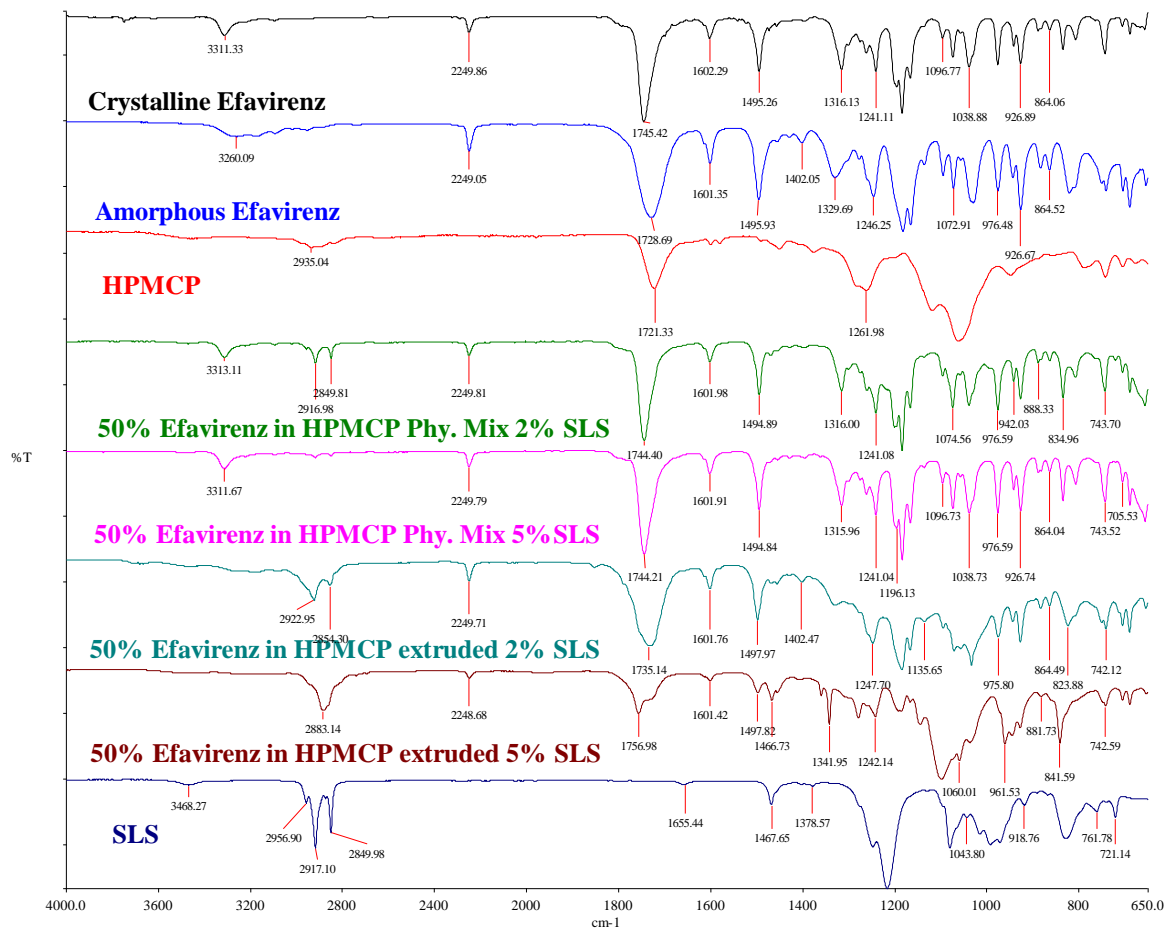


Figure 4-16: An overlay of FTIR spectra of Crystalline Efavirenz, amorphous Efavirenz and HPMCP at drug load 50 % w/w with SLS (2 and 5% w/w).

4.5.6. RELEASE STUDIES

Enteric polymers can be used for a pH-dependent controlled release dosage forms and provide better bioavailability because they prevent re-crystallization of the drug in the gastric juice as well as acid decomposition of drugs (37). Since HPMCAS and HPMCP are enteric polymers and dissolve in basic buffers, they are insoluble in the acidic fluid and in purified water. The extruded pellets were milled and blended with the excipients in Table 4-2. *In vitro* release studies (Figure 4-16 and 4-17) of the extrudates were found to be superior in comparison to their corresponding physical mixtures and pure drug (EFZ, Crystalline Efavirenz). HPMCP and HPMCAS melt extruded formulations significantly improved drug release when compared to those containing HPMC ($p < 0.05$), which might be attributed to the aqueous solubility or hydrophilicity and swelling behavior of the polymers in pH 6.8 dissolution medium. The concentration of SLS (2 and 5% w/w) in HPMCP and HPMCAS matrices had an insignificant effect on release profiles.

Table 4-2: Capsule with Hypromellose ester derivatives formulation used *in vitro* release studies.

S. No.		Function	% w/w
1	Extruded milled powder/Physical mixtures	API carrier and solublizing matrix polymer	83
2	Microcrystalline Cellulose	Dispersing agent	8
3	Silicon dioxide	Anti-adherent	2
4	Sodium Croscarmellose	Super-disintegrant	7

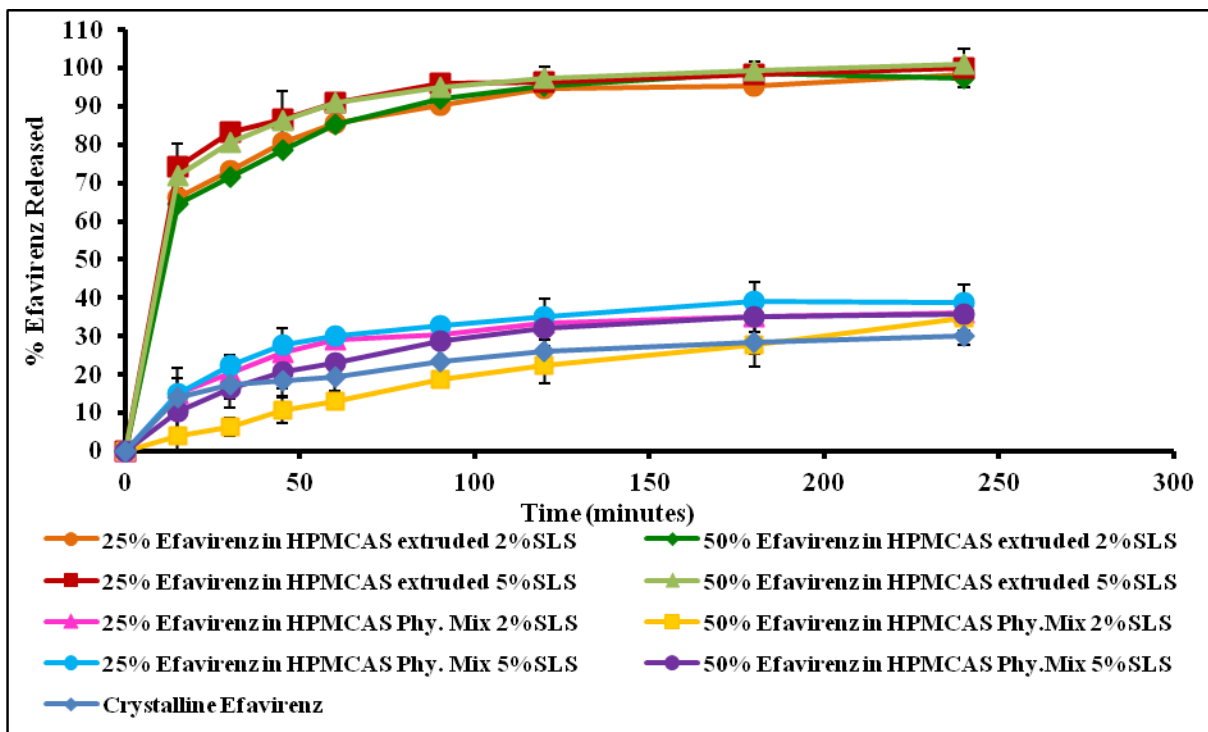


Figure 4-17: Comparison of the *in vitro* release profiles of the 25 and 50% w/w melt extruded and physical mixture capsule formulations with 2 and 5% SLS in HPMCAS matrix in 6.8 pH buffer.

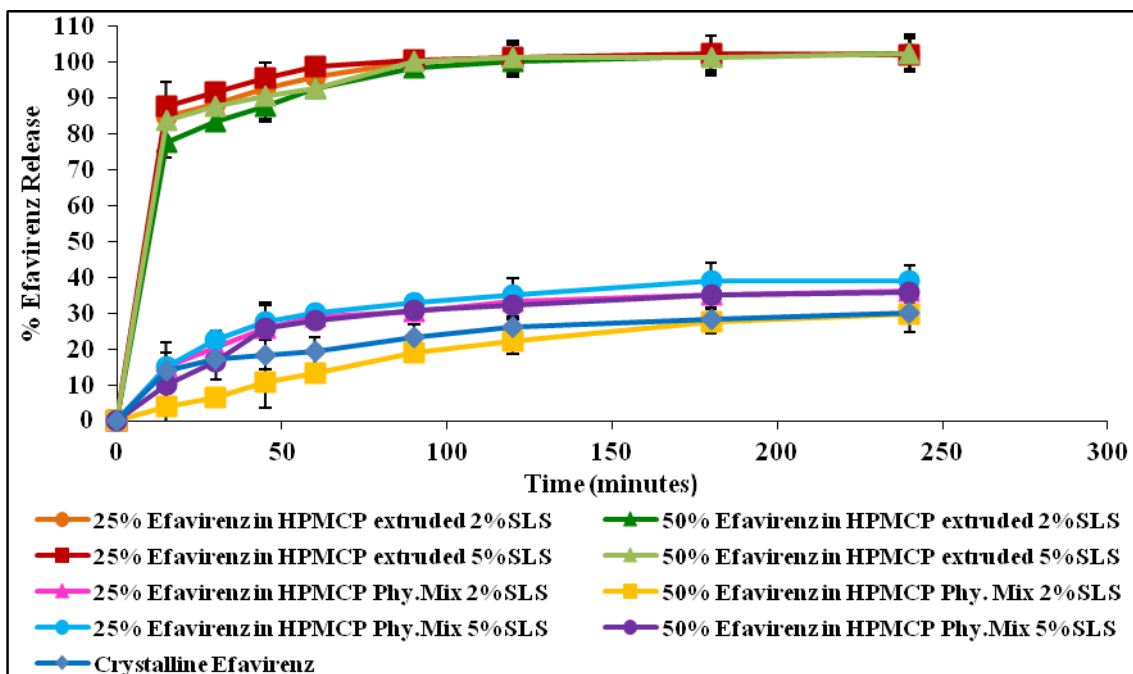


Figure 4-18: Comparison of the *in vitro* release profiles of the 25 and 50% w/w melt extruded and physical mixture capsule formulations with 2 and 5% SLS in HPMCP matrix in 6.8 pH buffer.

4.5.8. STABILITY

Upon moisture exposure in the accelerated condition (40 °C/75% RH), the plasticizing effect of water leads to a reduction in T_g and increase in molecular mobility of the amorphous drug. This may trigger the onset of phase separation and re-crystallization of EFZ as discussed in Chapter 3. HPMCP formulations were discontinued due to their poor process-ability. HPMCAS based solid dispersions were stable over the period of 6 months (Figure 4-18 to 4-21).

The % EFZ content remaining in the formulations was greater than 98.7±0.6%; and the drug release profile ($f_2 > 50$) remained unchanged after 6 month storage at 40 °C/75% RH (Figure 4-20 and 4-21). EFZ melting peak was not detected by DSC even after 6 month storage at 40 °C/75%

RH (Figure 4-19 and 4-20). The stability of the amorphous form of EFZ could be due to interaction with HPMCAS (38).

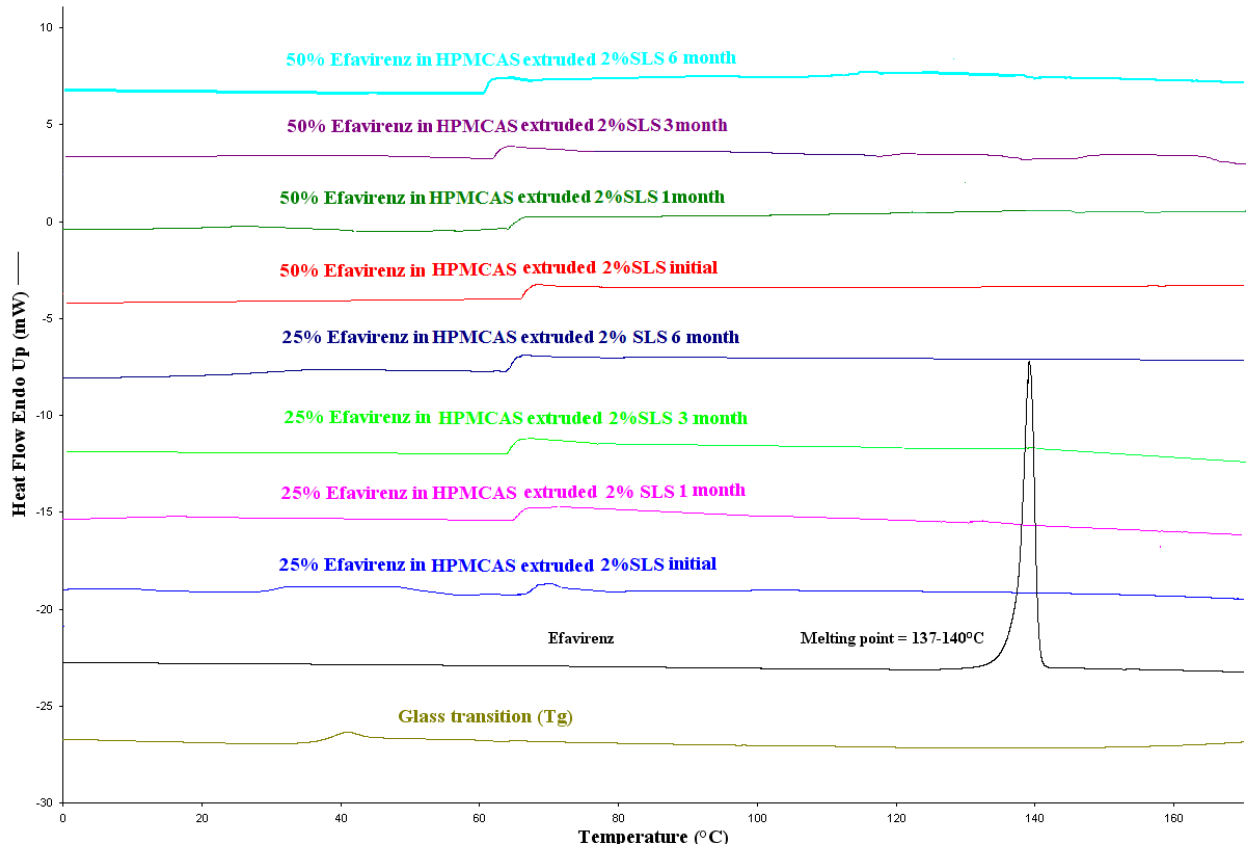


Figure 4-19: DSC thermogram illustrating stability Efavirenz in HPMCAS matrix with 2% w/w SLS hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40°C/75% RH.

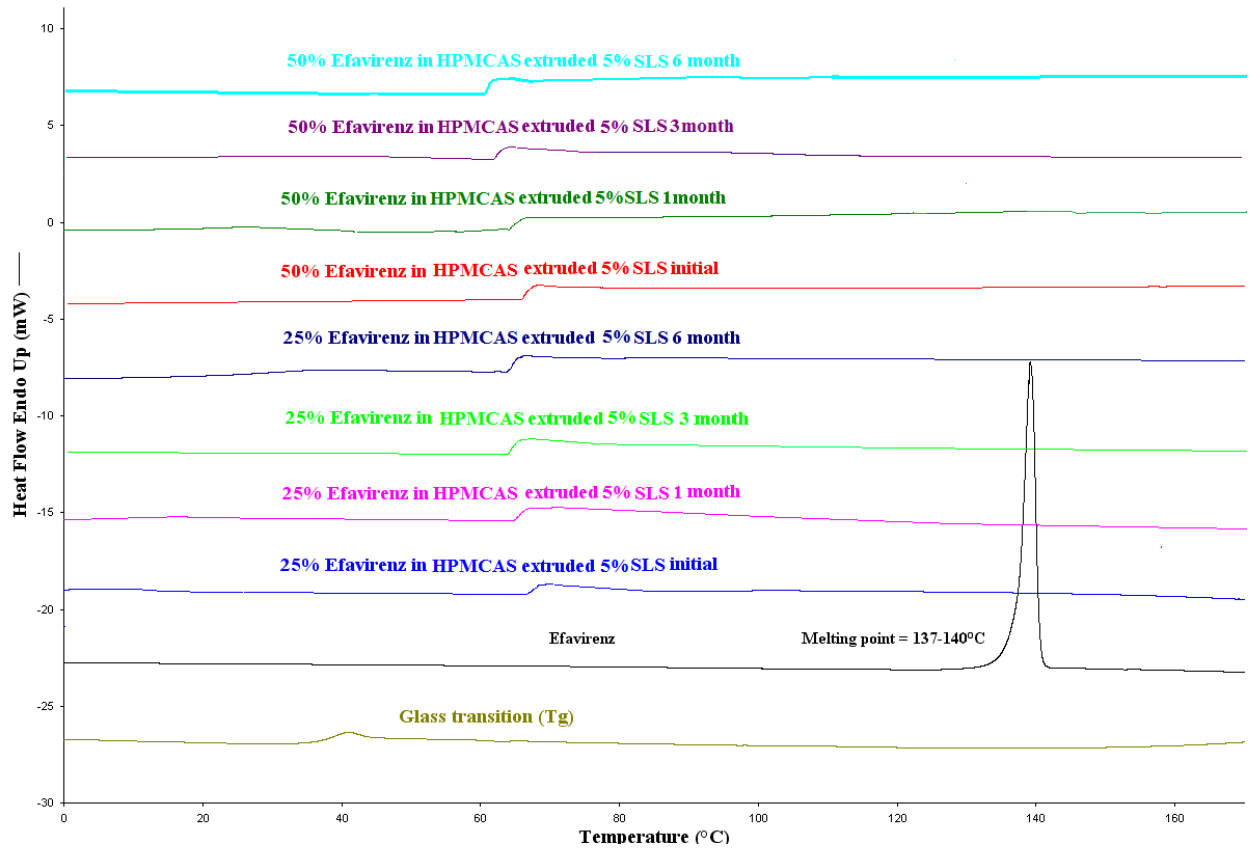


Figure 4-20: DSC thermogram illustrating stability Efavirenz in HPMCAS matrix with 5% w/w SLS hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

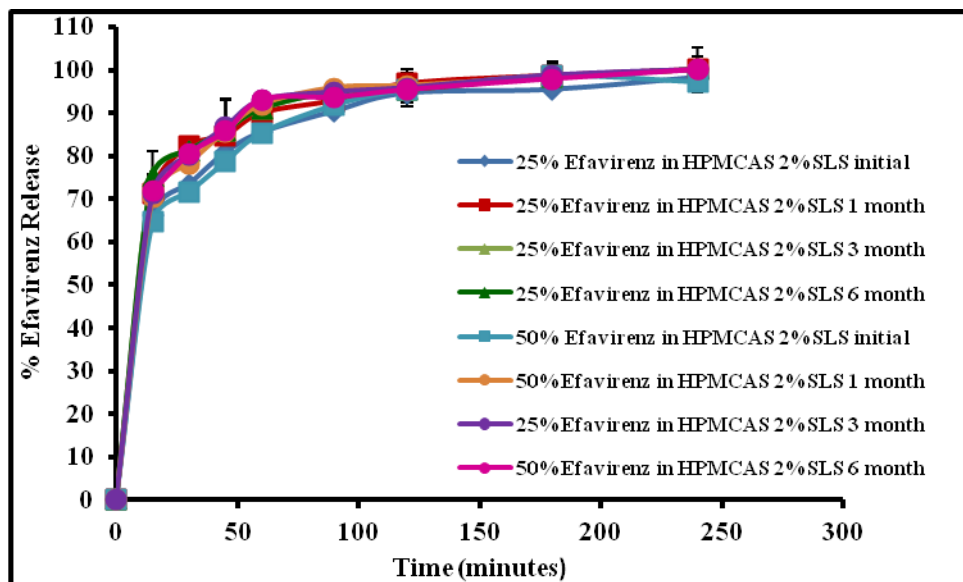


Figure 4-21: DSC thermogram illustrating stability Efavirenz in HPMCAS matrix hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

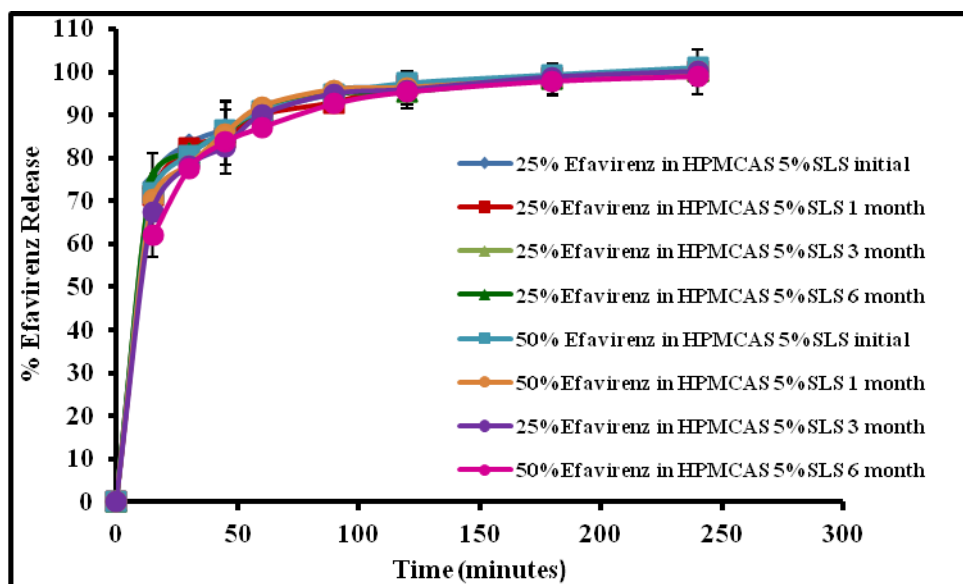


Figure 4-22: DSC thermogram illustrating stability Efavirenz in HPMCAS matrix hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

4.6. CONCLUSIONS

In Chapter 3, the factors affecting the release profiles and stability of high-energy amorphous forms of API such as the aqueous solubility or hygroscopicity and intermolecular interaction of API with polymeric carriers were discussed. In the present study, relatively low hygroscopicity of Hypromellose ester derivatives and ability to form intermolecular interactions with APIs demonstrated stabilizing effect on the amorphous systems (38). The present study showed that Hypromellose ester derivatives can be successfully extruded with EFZ in combination with SLS. HPMCAS and HPMCP matrices demonstrated promising EFZ miscibility. The data obtained from DSC, PXRD and FTIR studies demonstrated that EFZ is molecularly dispersed in HPMCAS and HPMCP matrices. HPMCP based solid dispersions are susceptible to instability due to poor process-ability of EFZ in the matrix. The solid dispersions of EFZ in HPMCAS matrices exhibited enhanced dissolution rates, attributed to the intermolecular interactions resulting in inhibition of crystallization and increased wettability. The combination of melt

extrusion and Hypromellose ester derivatives successfully resulted in amorphous solid dispersion systems with enhanced solubility of EFZ. This study demonstrates that Hypromellose ester derivatives formulation of EFZ via HME may be effective for other poorly soluble drugs.

CHAPTER - 5
DEVELOPMENT AND CHARACTERIZATION OF TASTE MASKED
FORMULATIONS OF EFAVIRENZ UTILIZING HOT MELT EXTRUSION

5.1. ABSTRACT

The objective of this study was to formulate taste-masked pellets and tablets of EFZ with Eudragit® E PO as the matrix polymer utilizing hot melt extrusion (HME) technology. The drug/polymer physical mixtures were extruded as rods with a co-rotating twin-screw extruder and then pelletized. The chemical interaction between EFZ and Eudragit® E PO was determined using Fourier transform infrared (FTIR) spectroscopy. Solid-state characterization of EFZ in the Eudragit® E PO matrix was carried out using differential scanning calorimetry (DSC), Powder X-ray Diffraction (PXRD) and Scanning electron microscopy (SEM) techniques. The solubility of EFZ was improved significantly due to its conversion into a more water-soluble amorphous form. Drug load had a significant effect on EFZ release characteristics from the pellets. *In vitro* release profiles obtained with the extruded pellets at pH 6.8 (simulated salivary medium) indicated that EFZ release would be extremely limited in the saliva, unlike the physical mixture, thus avoiding irritation of the oral mucosa (BMS, burning mouth syndrome). More than 90% drug release in 30minutes was observed in simulated gastric medium (pH 1.2) with the extruded pellets. The dissolution rate of EFZ from the melt extruded pellets was faster than that from the physical mixtures at all drug loads ($p < 0.05$) in simulated gastric medium. Taste masked EFZ pellets were thus successfully developed without affecting the dissolution rate in simulated gastric medium.

Keywords: Hot melt extrusion (HME), Eudragit[®] E PO, EFZ, differential scanning calorimetry (DSC), Powder X-ray diffraction (PXRD), Fourier transform Infrared (FTIR), Scanning electron microscopy (SEM).

5.2. INTRODUCTION

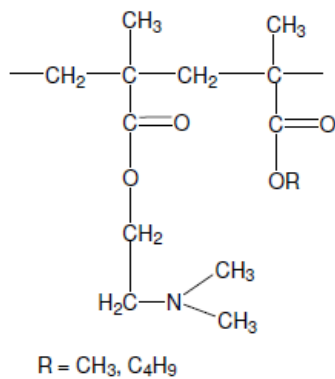
EFZ is an approved first choice HIV-1 reverse transcriptase inhibitor recommended by the World Health Organisation (WHO) for the treatment of children above the age of 3 (39). It is a crystalline, non-hygroscopic and lipophilic (log P of 5.4) material with an aqueous solubility of 9.2 µg/mL (pH 8.7) at 25 °C (40). The extremely low aqueous solubility of the drug leads to limited oral absorption and low bioavailability (40-45%) (41). The inter- and intra-individual variability is found to be relatively high being approximately 55-80% and 19-24%, respectively (41). Another drawback of EFZ treatment is that it irritates the oral mucosa, causing a burning mouth syndrome (BMS). BMS is one of the main causes of unplanned interruption in pediatric treatment (39). It causes vomiting and spitting which might result in EFZ's under-dosing and erratic plasma concentrations due to the partial intake of the administered dose. There have been attempts in the literature to enhance the solubility of EFZ with cyclodextrins (40), surface-modified polypropylene imine (PPI) dendrimers (42), encapsulation within polymeric micelles of linear and branched poly(ethylene oxide)-polypropylene oxide block copolymer (42). However, the scale-up of these formulations is limited by the many discontinuous steps. HME is a continuous process and requires fewer operator interventions and can thus yield improved product quality. HME technology has become easier for the industry to adopt, due to the technical developments of recent years i.e., extruder vendors have begun to produce units designed according to the principles of good manufacturing practice (43).

Hot melt extrusion (HME) technology has become popular for taste masking of bitter drugs, besides its solubility enhancement capabilities, by producing solid dispersion that prevent drugs from coming into direct contact with the patient's taste buds (44). Eudragit® E PO is a cationic

copolymer based on dimethylaminoethyl methacrylate and is soluble at a pH below 5.5 (Figure 5-1). This polymer can thus prevent the release of the drug in the saliva (pH 6.8–7.4) while readily dissolving in the gastric fluids (pH 1.0–1.5). Hence, Eudragit[®] E PO is a suitable matrix for taste masking poorly soluble solid dosage forms. In this study, a co-rotating twin screw extruder with a screw diameter of 16 mm and a barrel length of 640 mm was used. The length of the screws in the extruder is given in terms of length of the screw to the screw diameter (L/D) ratio, which in this case is 40:1. The extruder consists of two screws which are assembled with the standardized screw elements, conveying and kneading elements (Figure 1). The conveying elements are installed at the beginning and end of the extruder working jointly to transport the melted material to the die plate. The kneading elements have various angles and produce higher mixing and shearing. The twin screw variables, for example screw design, barrel layout, screw speed directly affect the process parameters like shear rate, residence time, dispersion of drug in polymeric matrix and color of extrudates

The goal of the present study was to develop and characterize stable, taste masked, hot melt extruded oral pellet formulations of EFZ utilizing various drug: polymer ratios. Multi-particulate oral dosage forms like pellets offer several advantages over monolithic systems (e.g. tablets). The pellets pass through the stomach pylorus rapidly and disperse homogeneously in the gastrointestinal tract, independently of gastric emptying and feeding state, which minimizes inter and intra subject variability. Thus, the pellet formulations can be helpful in improving inter- and intra-individual variability associated with EFZ (14). Importantly, these pellet formulations will allow flexibility of dosing and taste masking of EFZ for pediatric patients. The multiple unit dosage form (pellets) offers a flexible dosing system for pediatric patients (45). Since each individual unit contains a small amount of drug, the dose can be easily adjusted by measuring a

specific weight, or counting the required number of pellets, depending on the patient's body weight. Secondly, pellets also offer an advantage in that they can be sprinkled on food, mixed with fluids (water, milk or jelly) or directly swallowed, improving pediatric patient compliance (45).



Eudragit[®] EPO

Figure 5-1: Structure of Eudragit[®] EPO.

5.3. MATERIALS

The following materials were used as supplied: Efavirenz (Ria International, East Hanover, NJ), Eudragit[®] E PO (E PO, Evonik Industries, Germany). Sodium lauryl Sulphate (SLS), Sodium phosphate monobasic (NaH_2PO_4 ; M.W 119.98 g/mol), Sodium phosphate dibasic (Na_2HPO_4 ; M.W 141.96 g/mol) and Hydrochloric acid were obtained from Spectrum Chemical, Inc., Gardena, CA. The solvents acetonitrile (HPLC grade) and methanol (HPLC grade) were purchased from Fisher Chemicals, NJ. HPLC grade water was freshly prepared in the laboratory by Nanopure system (Barnstead, Dubuque, IA).

5.4. METHODS

5.4.1. HOT-MELT EXTRUSION

EFZ and Eudragit[®] E PO were mixed in various drug loads (10, 25, 50, 60 and 70% w/w) in a V-cone blender (MaxiBlendTM, GlobePharma) at 25 rpm for 15 minutes and then extruded into uniform rods with a co-rotating twin screw extruder (16 mm Prism EuroLab, ThermoFisher Scientific) at an extrusion temperature range of 70-110 °C and a screw speed of 70 rpm (Table 5-1). The feed rate was adjusted so that the % Torque was at approximately 60 % for optimum performance. The diameter of the extruded rods was approximately 2 mm. These extrudates were subsequently processed into pellets of 1 mm thickness using a pelletizer (Type L-001-9482, Thermoscientific, Stone, UK). The extrudates were pulverized using a sieve mesh size “20” according to US ASTM standards in a comminuting mill (FITZPATRICK[®], Model “L1A”). The milled extrudates (HME) were further blended with tablet excipients as shown in Table 5-2. The tablets were prepared with physical mixtures (Phy. Mix) by blending the excipients while maintaining the composition identical to their corresponding HME tablets. The hot melt extruded EFZ tablets and their corresponding physical mixture tablets were compressed using a MTP 1

tablet press equipped with an 8mm round beveled edge punch. The tablets (240 ± 0.26 , 472 ± 0.63 and 942 ± 0.65 mg) equivalent to 50, 100, 200 and 400 mg of EFZ content were produced.

Table 5-1 Processing temperatures for the formulations

Zone	Zone	Zone	Zone	Zone	Zone	Zone	Zone	Zone	Zone	Zone
10	9	8	7	6	5	4	3	2	1	
110	110	120	120	110	110	100	90	80	70	°C



5.4.2. THERMOGRAVIMETRIC ANALYSIS (TGA)

TGA (Perkin Elmer Pyris 1 TGA equipped with Pyris software) analysis of Eudragit[®] E PO, EFZ and physical mixtures (Phy.Mix) with various drug: polymer ratio was studied within temperature range of 30-200 °C at a heating rate of 20 °C/min. The thermal stability of drug and polymer was determined as a function of weight loss.

5.4.3. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Perkin-Elmer Pyris 1 DSC, equipped with Pyris Manager Software, was used to study the solid-state characteristics of EFZ in Eudragit[®] E PO matrix, pre-extrusion physical mixtures and extruded pellets. All samples were weighed approximately 8–10 mg, hermetically sealed in an aluminum pan and heated from -10 °C to 180 °C at a linear heating rate of 10°C/min.

5.4.4. SOLUBILITY PARAMETER

Solubility parameter calculations were performed using Molecular Modeling Pro software (Chem SW Inc., Fairfield, CA) utilizing group contribution approaches (Molecular Modelling Pro., 2006).

5.4.5. FOURIER TRANSFORM INFRARED (FTIR) SPECTROSCOPIC ANALYSIS

FTIR studies were undertaken to detect the possible interactions between EFZ and Eudragit[®] E PO in the solid dispersions. FTIR spectra for the EFZ and Eudragit[®] E PO were obtained using a Perkin-Elmer spectrometer (Perkin-Elmer Life and Analytical Sciences, Shelton, CT, USA). A spectrum was collected for each sample within wave number region 4,000–650 cm⁻¹. Samples of EFZ in Eudragit[®] E PO, physical mixtures and pellets with various drug loads (10, 25, 50, 60 and 70% w/w) were weighed such that they contained an equivalent amount of EFZ in all the samples. The spectrums were analyzed for the absence or shift in the wave numbers of the characteristic peaks.

5.4.6. POWDER X-RAY DIFFRACTION (PXRD)

Crystallinity of EFZ in the hot-melt extruded pellets and their respective physical mixtures were analyzed using X-ray diffractometry. The studies were performed on a D-8 Advance X-ray diffractometer (Bruker-Axs) equipped with Diffrac Plus1 software. The generator operating voltage and current were 40 kV and 40 mA, respectively. The step size was 0.01° and the dwell time at each step was 1 sec. The scanning speed was 2°per min, and the 2 Theta scanning range was from 5° to 40°.

5.4.7. SCANNING ELECTRON MICROSCOPY (SEM) ANALYSIS

The morphology of amorphous EFZ in the pellets was compared against the physical appearance of the pure drug utilizing a scanning electron microscope. The samples were mounted onto an aluminum stage using adhesive carbon tape. Samples were then sputter coated with gold under an argon atmosphere using a Hummer™ 6.2 Sputter Coater (Ladd Research Industries, Williston, VT, USA) in a high vacuum evaporator equipped with an omnirotary stage tray to produce uniformly coated specimens. The processed samples were examined and the images were captured using a JEOL JSM-5600 scanning electron microscope (JEOL USA, Inc., Waterford, VA, USA) operating at an accelerating voltage of 9–13 kV.

5.4.8. CHROMATOGRAPHIC CONDITIONS

A Waters HPLC-UV system (Waters Corp, Milford, MA) and a Symmetry Shield RP C-18 (250×4.6 mm, 5 μm) column was used at a detection wavelength of 245 nm. The mobile phase consisted of acetonitrile and water (0.1% v/v Formic acid, pH=4) at a ratio of 60:40 (v/v). The mobile phase flow rate was maintained at 1.5 ml/min. EFZ retention time was 7.2±0.43 min under these conditions. Injection volume was 20 μl. The HPLC data was analyzed using Empower 2 software.

5.4.9. SOLUBILITY STUDIES

The solubility of pure drug, physical mixtures and pellets with various drug: polymer ratios (10, 25, 50, 60 and 70% w/w) was determined following the standard shake flask method, wherein excess quantities were added to 50 ml of water, freshly prepared dissolution medium 0.2% SLS in 0.1M HCL (pH 1.2, simulated gastric medium) and 0.2% SLS 0.2M sodium phosphate buffer (pH 6.8, simulated salivary medium). To achieve uniform mixing, samples were continuously agitated at 100 rpm at 37 °C, separately, for a period of 24 hour in a reciprocal shaking water bath (Fisher Scientific, USA). At the end of 24 hour, samples were centrifuged (Centrifuge 5415R, eppendorf, USA) at 10,000 rpm for 10 minutes; the clear supernatant was suitably diluted and analyzed for drug content.

5.4.10. *IN VITRO* RELEASE STUDIES

In vitro release studies were performed according to USP 31 apparatus I using discriminatory dissolution medium comprised of 1000 ml of 0.2% SLS in 0.1M HCL (pH 1.2, simulated gastric medium) and 0.2% SLS in 0.2M sodium phosphate buffer (pH 6.8, simulated salivary medium). Hanson SR8-plus™ dissolution test station (Chatsworth, CA) was used at 37±0.5 °C and paddle speed was maintained at 50 rpm. Samples were collected at predetermined time intervals, through a stainless steel cannula with a 0.2 µm nylon filter tip attached to a 1 ml syringe. These samples were analyzed using HPLC/UV. The results were reported as the average of 3 replicates ± SD. Dissolution profiles were compared using similarity factor (f_2). An f_2 value larger than 50 indicates that the two dissolution profiles are similar.

5.4.11. STABILITY STUDIES

The impact of temperature and humidity conditions on the physical and chemical stability of EFZ in the pellets and tablets were determined in HDPE bottles at 4 °C, 25 °C/60% RH, 40 °C/75% RH and 60 °C. The dissolution profiles, chemical and physical stability of the pellets were examined at initial, 1, 3 and 6 month time points. The dissolution profiles of pellet formulations at different time points were compared using the f_2 similarity factor.

5.4.12. DATA ANALYSIS

In all the cases, statistical analysis was performed utilizing one-way analysis of variance. A statistically significant difference was considered when $p < 0.05$.

Table 5-2: Tablet formulation used *in vitro* release studies.

S. No.		Function	% w/w
1	Extruded milled powder/Physical mixtures	API carrier	85
2	Microcrystalline Cellulose	Dispersing agent	6
3	Silicon dioxide	Anti-adherent	1
4	Xylitol	Sweetening Agent	3.5
4	Sodium Coscarmellose	Super-disintegrant	7
6	Sodium Stearyl Fumarate	Lubricant	0.5

5.5. RESULT AND DISCUSSION

5.5.1. HOT MELT EXTRUSION

The solubility parameters of EFZ and Eudragit[®] E PO were calculated to be 24.5 and 19.6 MPa^{1/2}, respectively. The difference in the solubility parameters ($\Delta\delta_i$) is 4.9 MPa^{1/2}, which is lower than the maximum value of 7 MPa^{1/2} required for the polymer–drug miscibility indicating that EFZ would likely be miscible with Eudragit[®] E PO. The percent drug load had a significant effect on the appearance of the extruded pellets. The extruded pellets were clear and transparent up to 60% w/w drug load. When all the EFZ dissolves in the Eudragit[®] E PO matrix during extrusion a homogenous solution is formed. This solution upon cooling forms a solid solution. The transparent characteristic of the extrudates, obtained with the 10, 25, 50 and 60% w/w EFZ loads, signifies the formation of a homogenous miscible system upon cooling. The turbid extrudates obtained with the 70% w/w EFZ indicates solid dispersion formation that is not chemically and physically uniform throughout or comprises of more than one phase. This could presumably be due to the fact that not all of the EFZ has dissolved in the polymer phase (46).

5.5.2. THERMAL ANALYSIS

TGA has frequently been used to assess the thermal stability of drugs and excipients/polymers prior to HME. When heated from 30 °C to 350 °C at a rate of 20 °C/min, less than 2% degradation below 200 °C was observed with the pure drug and physical mixture at the various drug: polymer ratio (Figure 5-2). Additionally, TGA confirmed the thermal stability of Eudragit[®] E PO at the extrusion temperatures used.

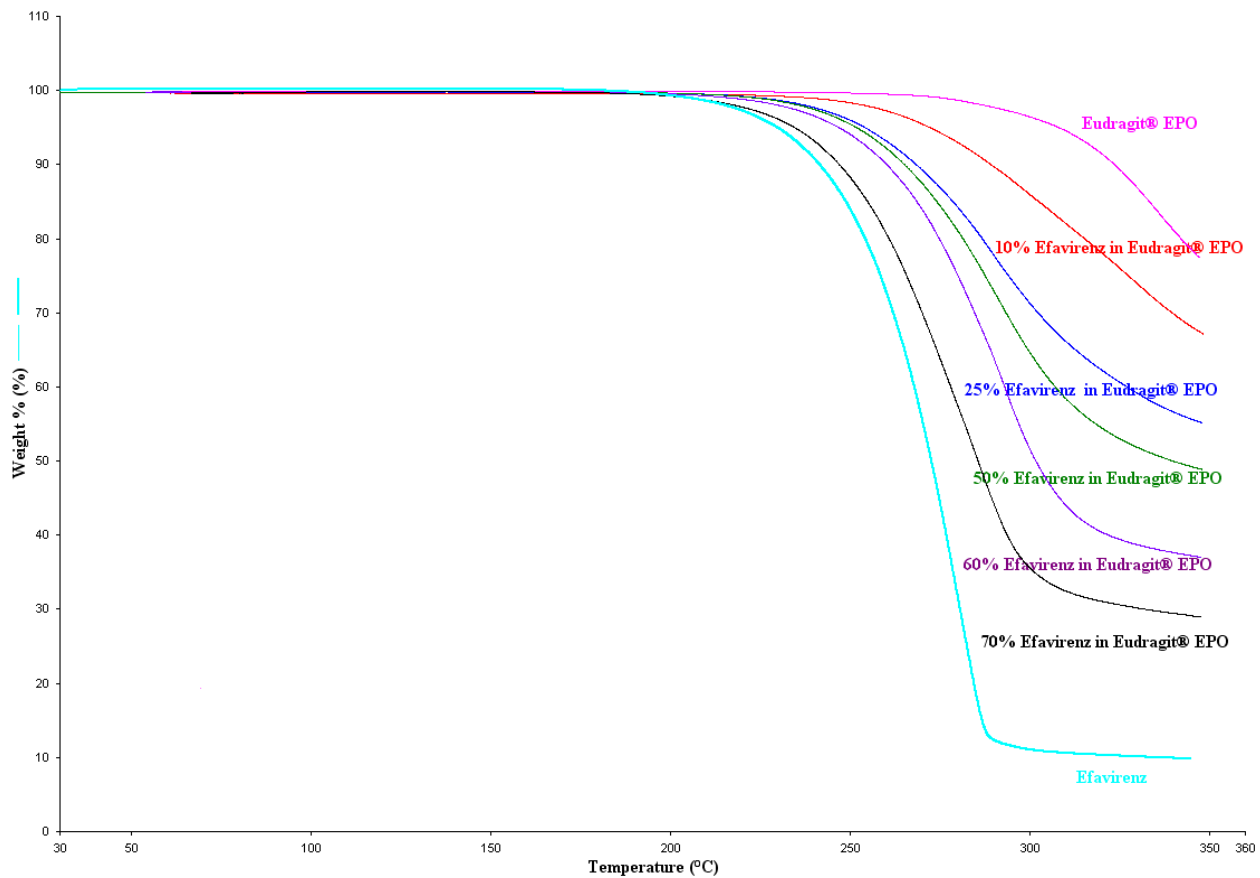


Figure 5-2: Thermal gravimetric analysis (TGA) of Eudragit® EPO and EFZ at various drug loads.

DSC analysis of crystalline EFZ showed a single sharp endothermic peak within the temperature range of 137.54 ± 0.7 °C with $\Delta H_f = 51.1 \pm 2$ Jg⁻¹. Quench-cooled EFZ exhibited a glass transition temperature of 34.45 ± 2.1 °C (onset Tg) and no other exothermic peak of crystallization or endothermic peak of melting was observed (Figure 3-4). A variety of pharmaceutical glass formers or drugs with high Tm/Tg (Kelvins) ratios generally crystallize more rapidly in solid dispersions than drugs with low Tm/Tg values at a given drug load and temperature (47). The Tm/Tg ratio of EFZ is 1.32, a somewhat high value, which indicates formulation with drug load $\geq 50\%$ w/w will be needed to ensure sufficient physical stability (48).

A melting endotherm for EFZ was not observed in the physical mixtures containing 10 to 50% w/w of EFZ indicating that the drug is completely soluble in Eudragit® E PO at these concentrations (Figure 5-3 a). In contrast to physical mixtures the pellets containing up to 60% w/w drug load did not show the EFZ melting endotherm (Figure 5-3 b). However, the pellet formulations at 70% w/w drug load exhibited a Tg and a diffused endothermic peak around 120 - 135 °C indicating partial crystallization of EFZ out of the Eudragit® E PO matrix at this concentration.

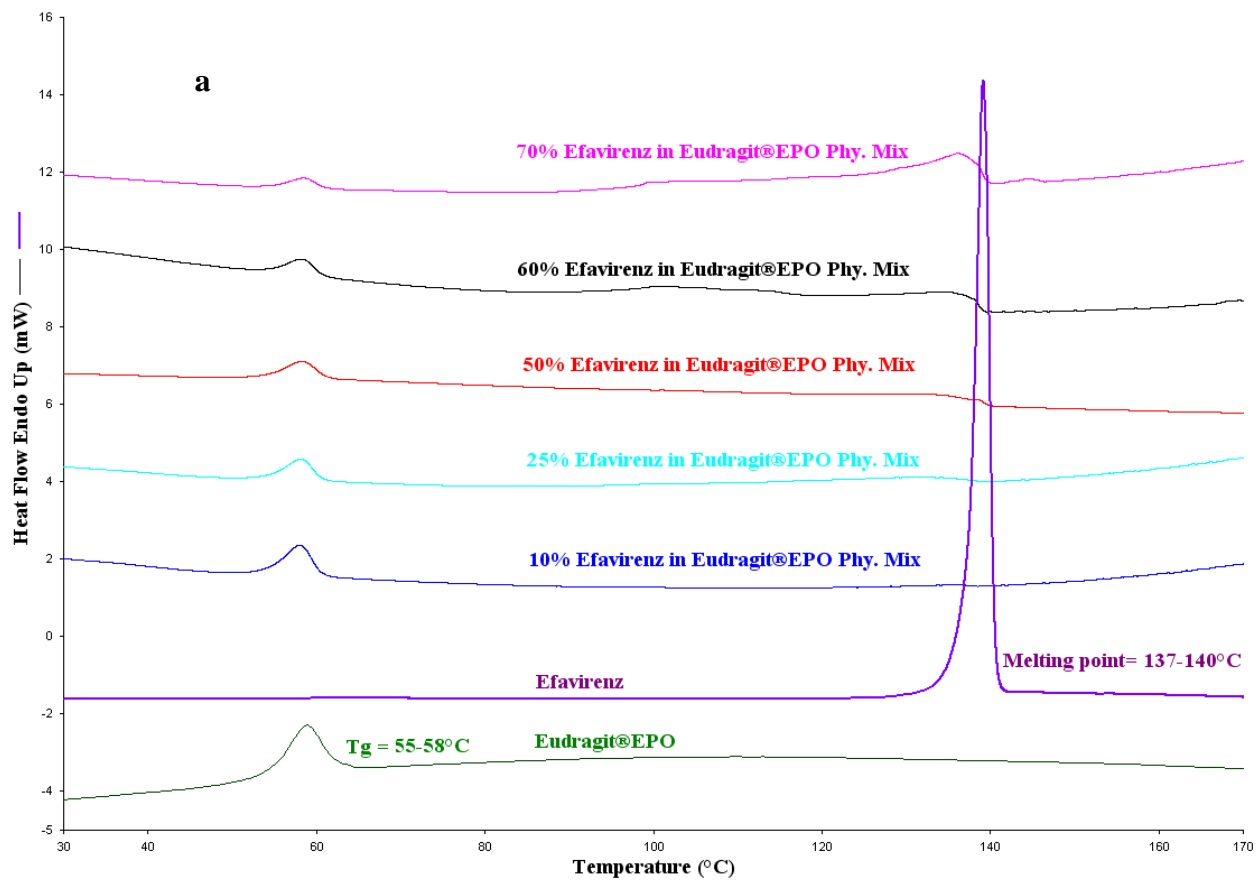
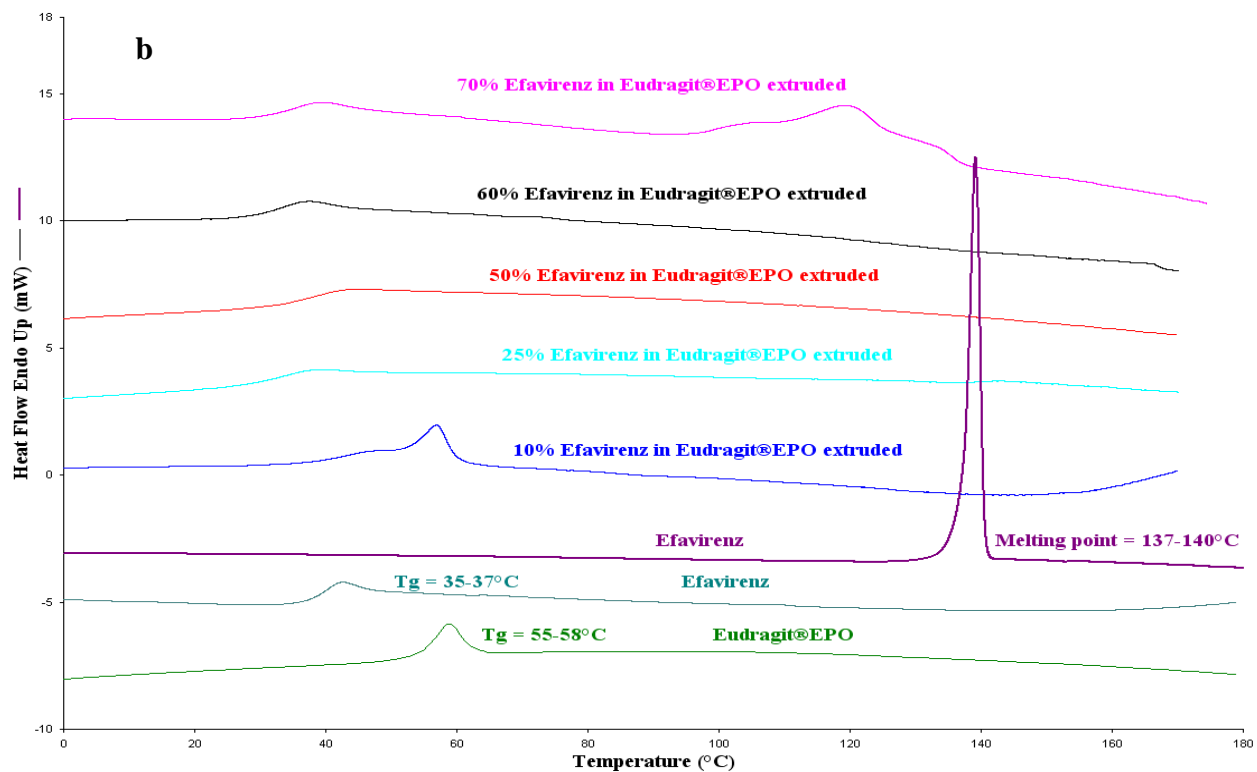


Figure 5-3: Thermal properties of physical mixtures and extruded pellets. **a.** EFZ melting endotherms in the physical mixtures was observable in weight proportions $\geq 60\%$ w/w.



b. The melting endotherm was not observed in extruded pellets $\leq 70\%$ w/w.

5.5.3. FTIR Spectroscopy

FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements of organic compounds. Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational frequencies, leading to frequency shifts and splitting in absorption or transmittance of peaks.

Chemical interactions between EFZ and Eudragit® E PO in the solid dispersions may stabilize the amorphous state of EFZ. Also, taste masking can be achieved through intermolecular forces (e.g., hydrogen bonding and/or ionic interaction) between the active substance and polymer matrix. There are several reports in the literature of potential interaction of Eudragit® E PO with drugs (49). EFZ (pka=9.1) is considered to be a weak acid (50) whereas Eudragit® E PO is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and

methylmethacrylate. EFZ crystals show characteristic bands at 3311.33 cm^{-1} , 2249.86 cm^{-1} , 1602.29 cm^{-1} , 1745.42 cm^{-1} , 1241.11 cm^{-1} and 1316.13 cm^{-1} attributed to N-H stretching vibrations, aromatic C-H stretching vibration, $\text{C}\equiv\text{C}$ stretching vibration, C=O stretching vibration, C-F stretching vibration, C-O-C stretching vibration, respectively. The bands corresponding to C=O vibrations and N-H stretching, at 1728.69 cm^{-1} and 3260.09 cm^{-1} , respectively, became broadened and diffused in the case of the amorphous EFZ (Figure 5-4 a). The spectra suggests the participation of -NH and C=O groups in intermolecular hydrogen bonding between EFZ molecules in the amorphous state. The spatial arrangement of EFZ molecules in the crystal lattice does not allow intermolecular hydrogen bonding which starts to occur once the orderliness of crystalline lattice is disturbed due to the formation of the amorphous form. However, these intermolecular hydrogen bonds are relatively weak and the amorphous form tends to revert back to the crystalline form (51).

Eudragit[®] E PO shows the characteristic bands of the ester groups at $1150\text{-}1190\text{ cm}^{-1}$, 1239.23 cm^{-1} and 1268.22 cm^{-1} , as well as the C=O ester vibration at 1722.79 cm^{-1} . The absorptions at 2770.23 cm^{-1} and 2821.82 cm^{-1} can be assigned to the dimethylamino groups. The physical mixtures of EFZ in Eudragit[®] E PO showed a summation of the EFZ and Eudragit[®] E PO IR spectra. In the extruded pellets containing EFZ and Eudragit[®] E PO matrix, the band at 3311.33 cm^{-1} corresponding to N-H stretching in crystalline EFZ spectra disappeared and the C=O stretching vibration at 1745.42 cm^{-1} shifted to higher wave numbers i.e. $1755\text{-}1758\text{ cm}^{-1}$ (Figure 5-4 a-d). Moreover, the bands corresponding to dimethylamino groups in Eudragit[®] E PO at 2770.23 cm^{-1} and 2821.82 cm^{-1} exhibited decreased intensity in the extruded pellets (Figure 6 b-d). Since dimethylamino group is a proton-accepting functional group, the proton-donating carboxyl group of EFZ formed an intermolecular bond with the dimethylamino group of

Eudragit[®] E PO exhibiting a band shift was observed in the spectra. The extruded pellet formulations containing 70% w/w EFZ in Eudragit[®] E PO matrix showed a summation of the individual components of the IR spectra similar to the physical mixture (Figure 5-4 e). The characteristic bands at 3311.83 cm⁻¹ corresponding to N-H stretching and 1744.61 cm⁻¹ corresponding C=O stretching vibration were observed indicating the presence of crystalline EFZ in the hot melt extruded pellet formulations containing 70% w/w EFZ. This data suggest that EFZ is not completely soluble at this concentration in the Eudragit[®] E PO matrix (Figure 5-4 e).

Satigrahi et al, investigated the formation of amorphous EFZ with Plasdone[®] S-630 and Eudragit[®] E PO systems (1:1) utilizing a small scale extruder (HAAKE Minilab series) (52). According to their studies, EFZ and Eudragit[®] E PO extrudates do not exhibit any specific interaction under the processing conditions used. The observed differences could be because of variation in mixing efficiency of the instruments. In the present study, a co-rotating twin screw extruder with ten heating zones, three mixing zones and a large screw diameter of 16 mm was used. This extruder generates higher shear and achieves dispersion at the molecular level which is not possible with micro compounders such as HAAKE Minilab (Figure 1). The extruder screw design plays crucial role in the dispersion of drug within the polymer matrix. Therefore, the intermolecular interaction of drug with polymer could vary depending on the extruder design.

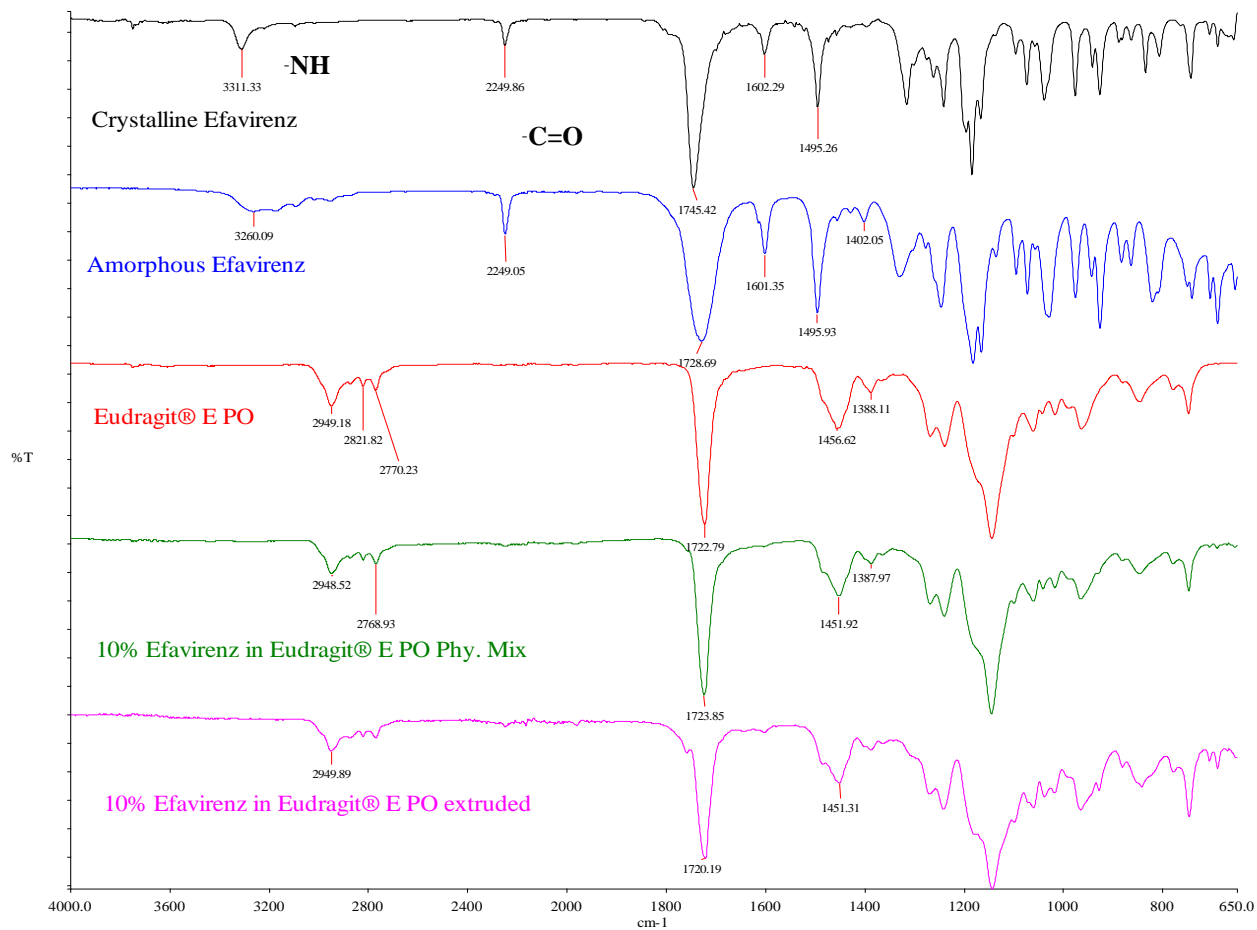
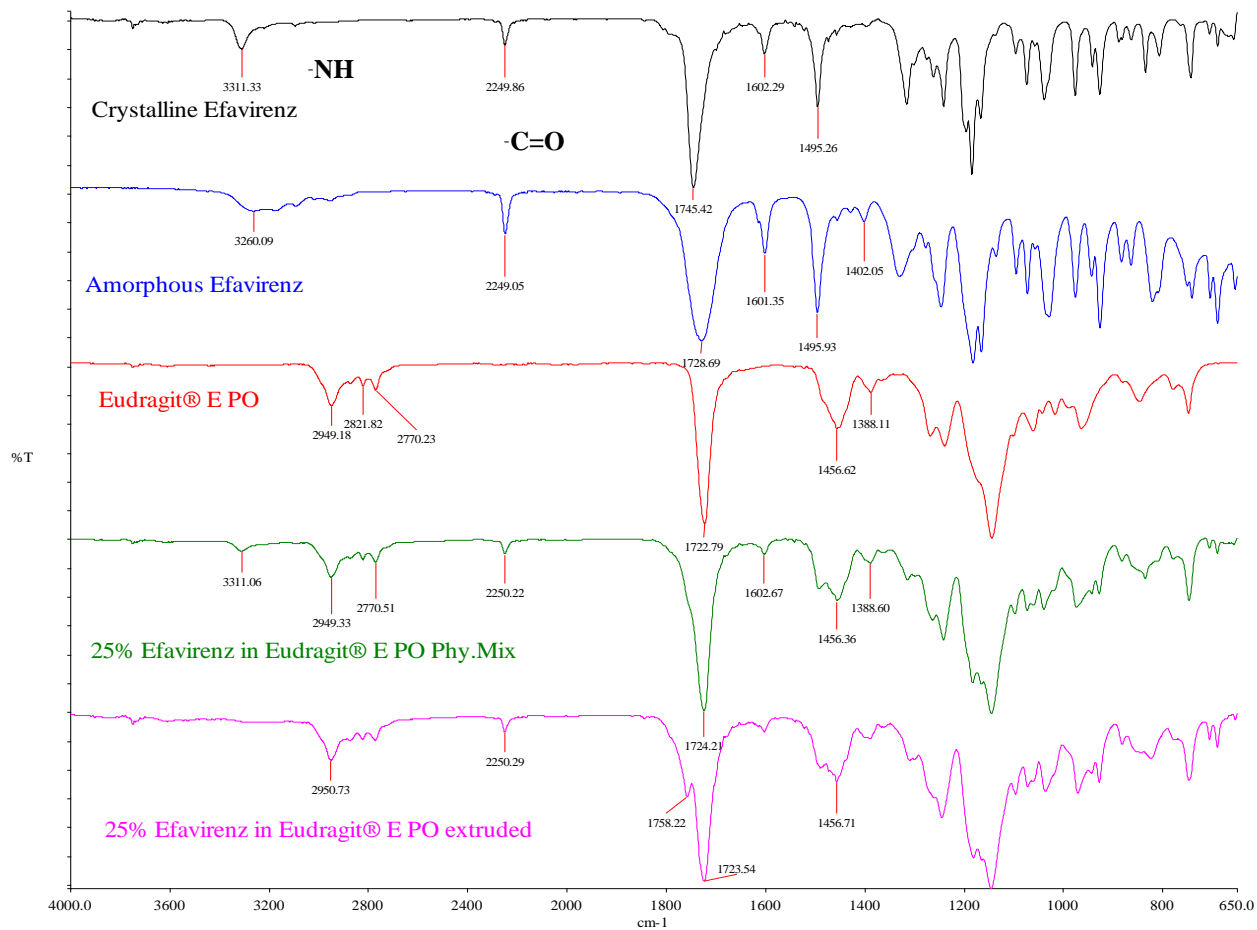
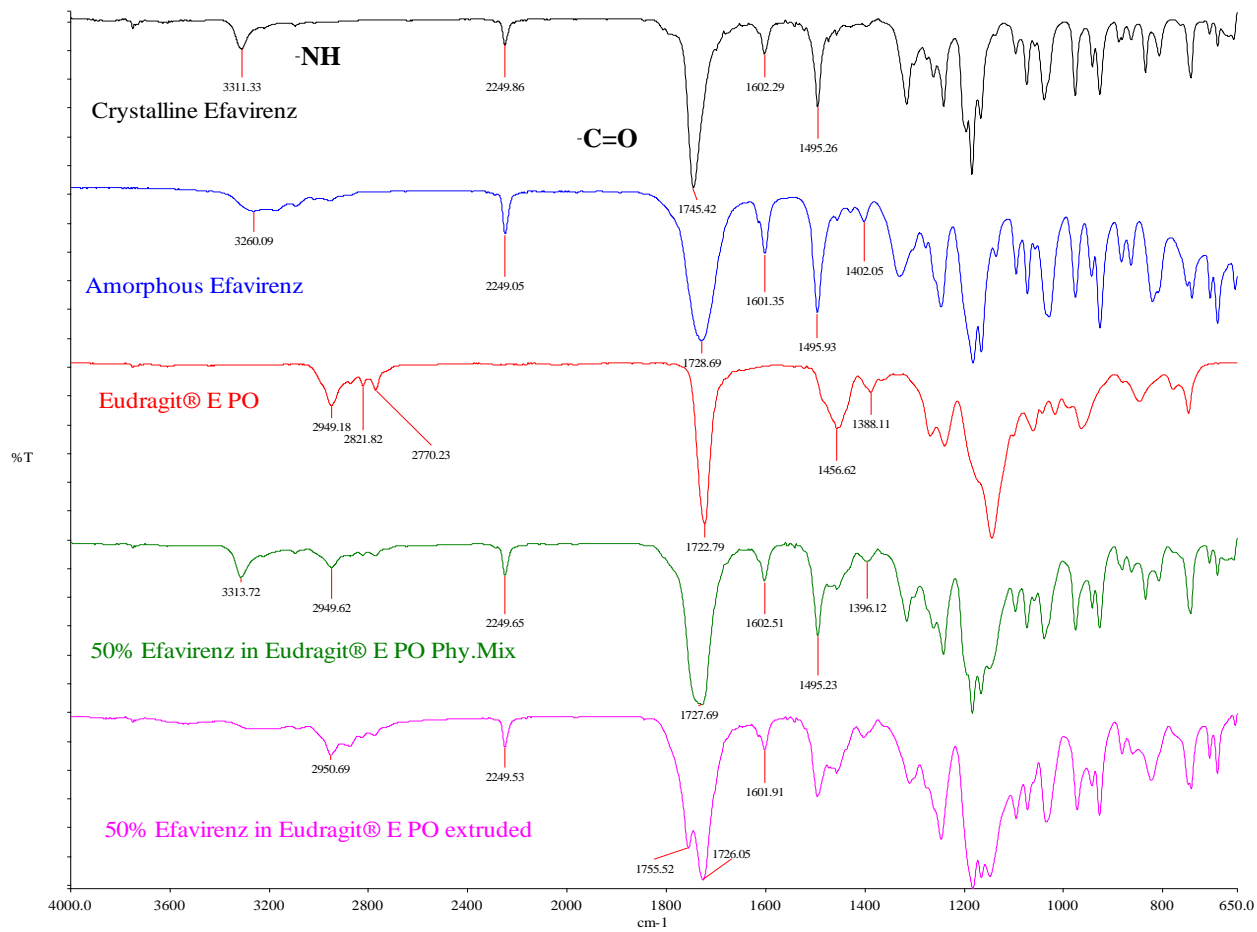


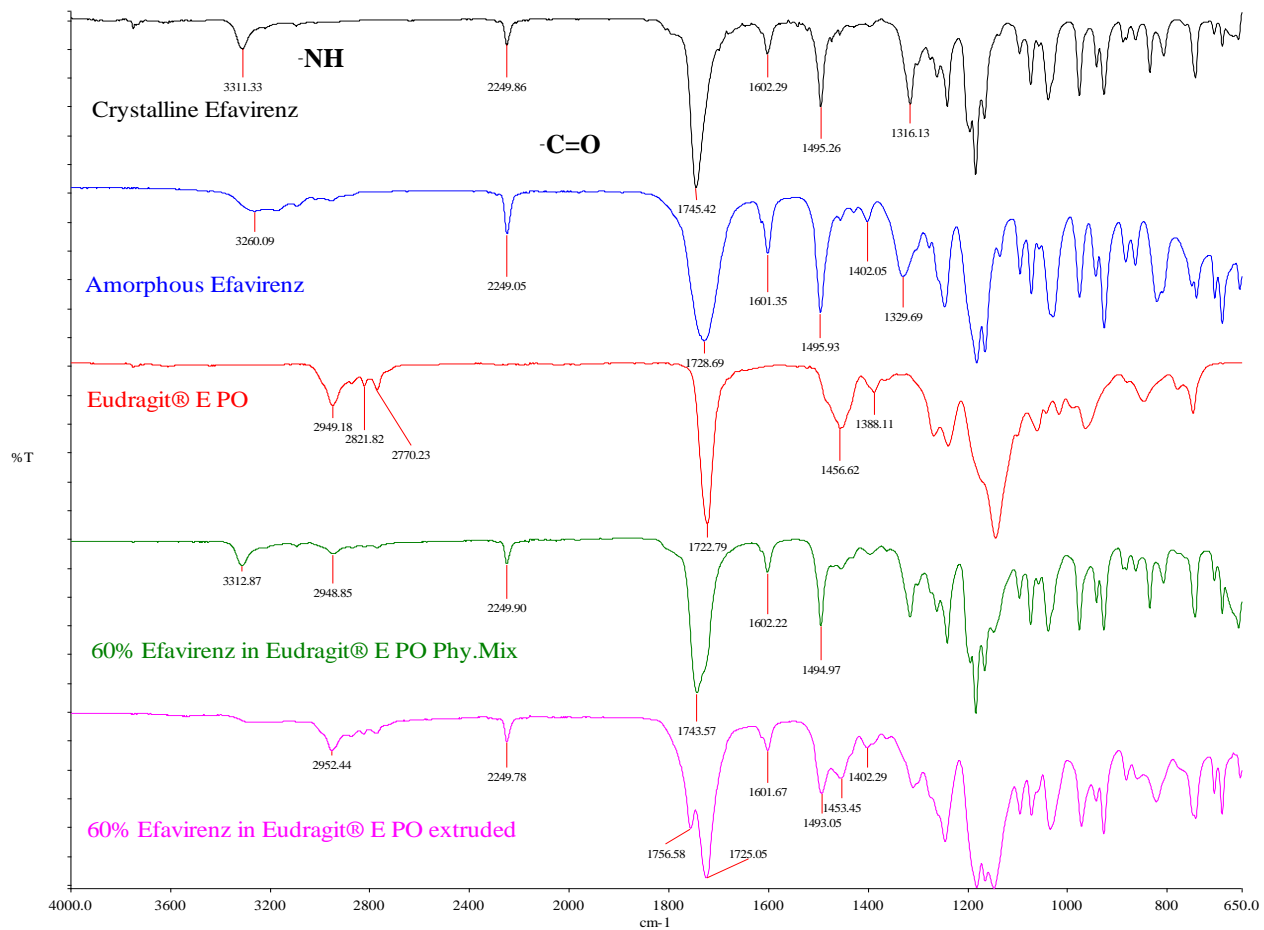
Figure 5-4: An overlay of FTIR spectra of Crystalline EFZ, amorphous EFZ and Eudragit® E PO at various drug loads a. 10% w/w EFZ in Eudragit® EPO matrix,



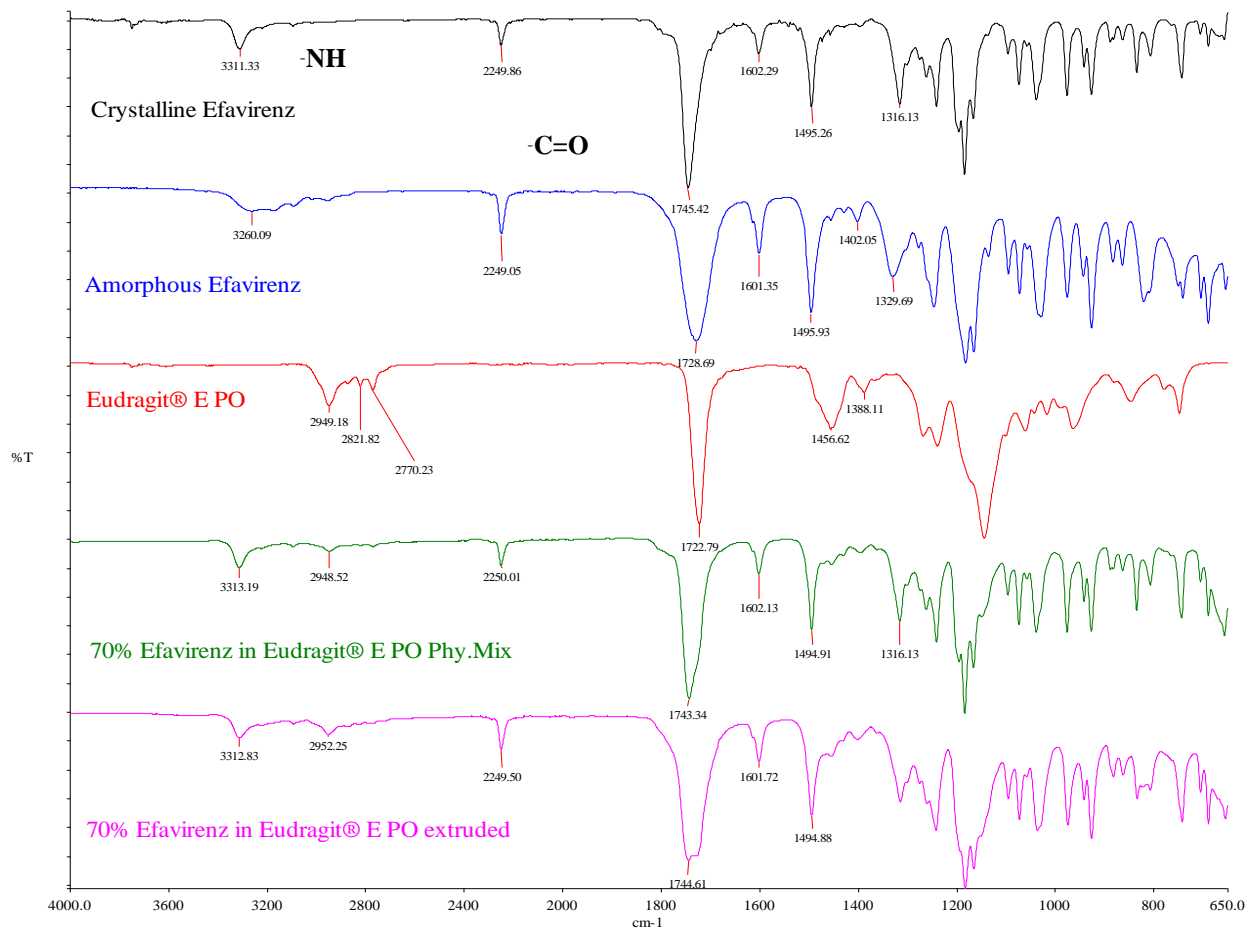
b. 25% w/w EFZ in Eudragit® E PO matrix,



c. 50% w/w EFZ in Eudragit® E PO matrix,



d. 60% w/w EFZ in Eudragit® E PO matrix



e. 70% w/w EFZ in Eudragit® E PO matrix.

5.5.4. POWDER X-RAY DIFFRACTION (PXRD)

Crystalline EFZ PXRD pattern comprises of 2 Theta values of 6.8 ± 0.2 , 10.3 ± 0.2 , 10.8 ± 0.2 , 14.1 ± 0.2 , 16.8 ± 0.2 , 20.0 ± 0.2 , 20.5 ± 0.2 , 21.1 ± 0.2 and 24.8 ± 0.2 (34). The patterns for EFZ, physical mixtures, and HME pellets are represented in the Figure 5-5. There were no crystalline peaks corresponding to EFZ in the HME pellets up to 60% w/w drug load indicating EFZ existed in an amorphous state within the HME pellets. However, crystallization of EFZ was observed within HME pellets containing 70% w/w EFZ (peaks corresponding to 6.8 ± 0.2 and 24.8 ± 0.2).

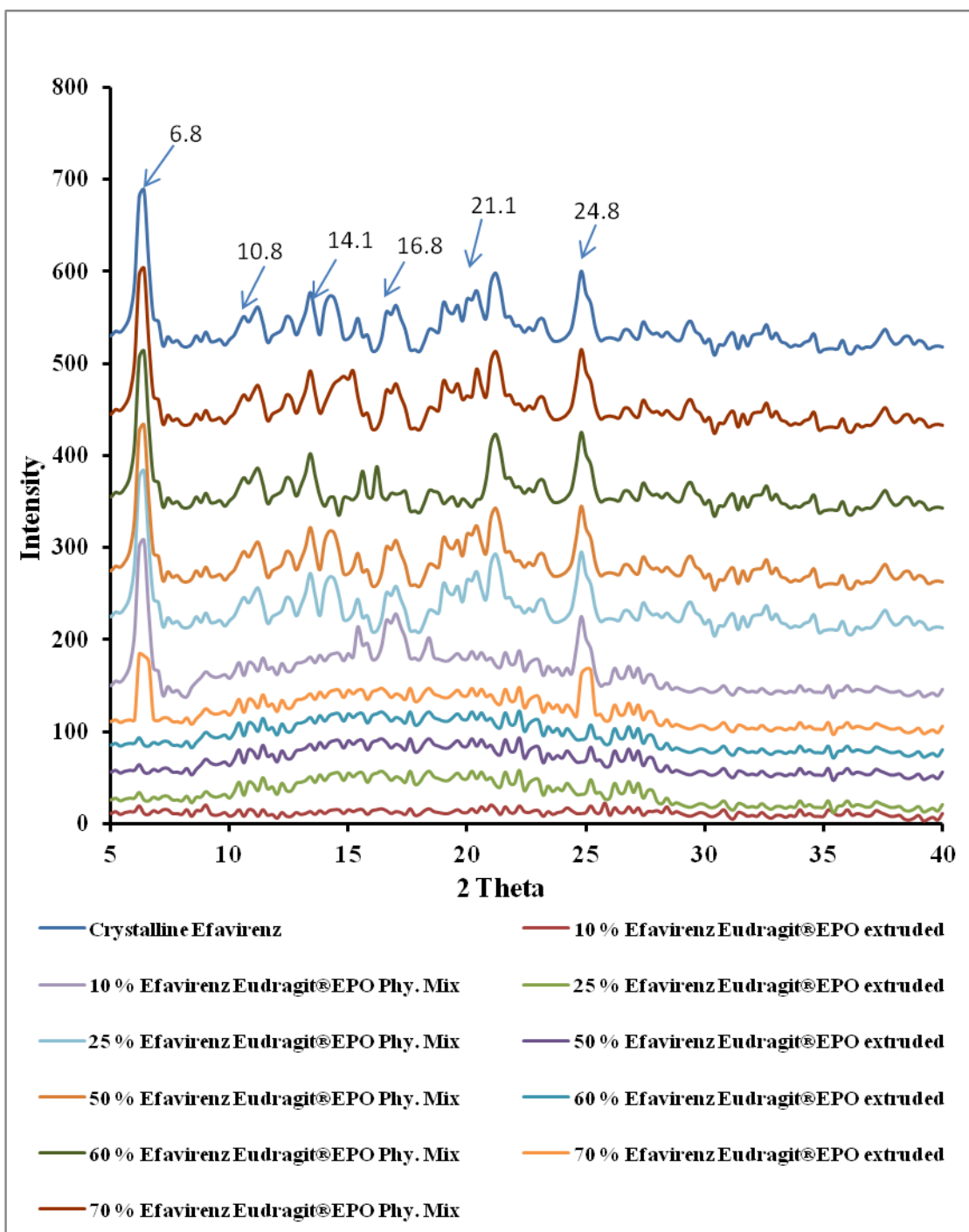


Figure 5-5: PXRD patterns of hot melt extruded pellets and physical mixtures with 10, 25, 50, 60 and 70% w/w drug load. (Arrows indicate the characteristic 2 theta values of EFZ).

5.5.5. SCANNING ELECTRON MICROSCOPY (SEM) ANALYSIS

SEM has been demonstrated to be a highly sensitive method for the detection of drug crystals at the surface of extruded formulations (9, 16). The micrographs (Figure 5-6 a–f) represent pure drug and the surface of the hot-melt extruded pellets. Pure EFZ exists predominantly as broken and fused needles (53) whereas in the melt extruded pellets containing 60% w/w EFZ it appeared as amorphous aggregates. EFZ crystals were seen embedded on the surface of pellets as well as irregular aggregates indicating existence of drug in more than one phase in the polymer matrix containing 70% w/w EFZ (Figure 5-6 f).

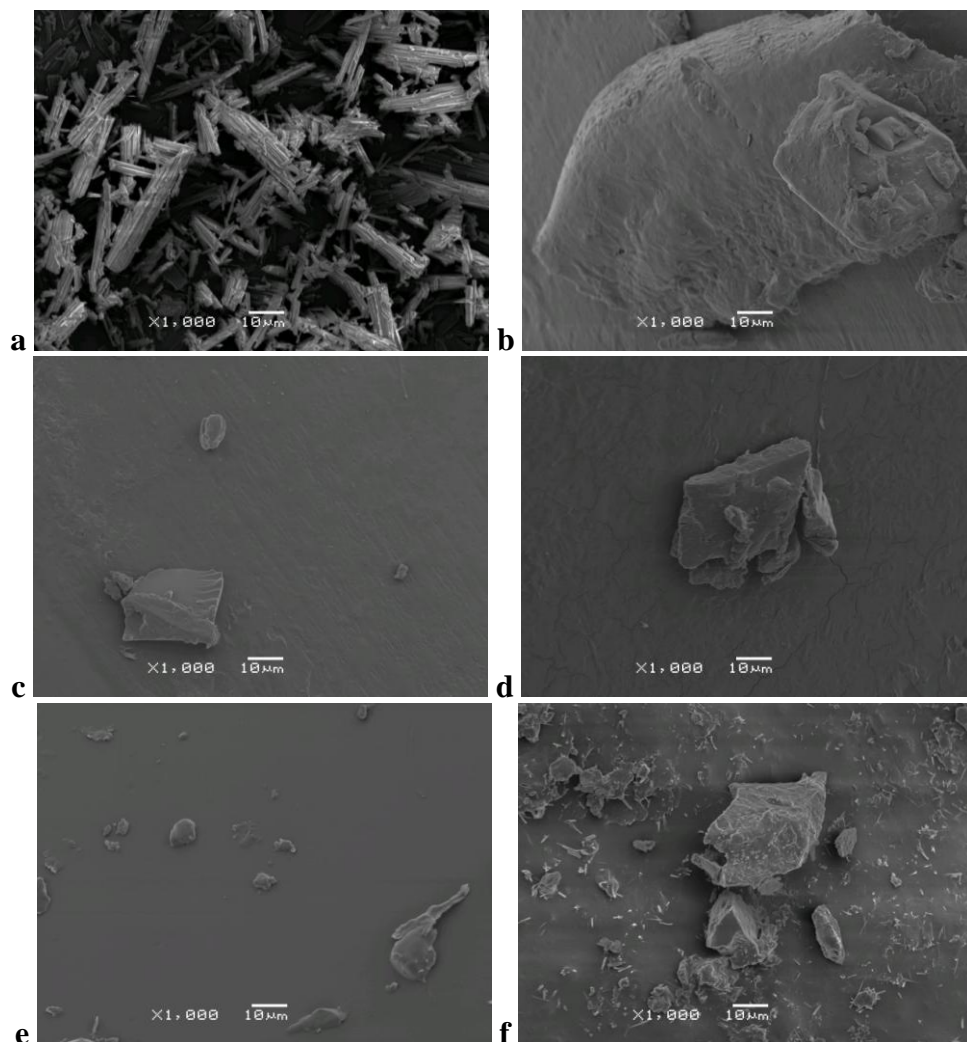


Figure 5-6: **a.** SEM of pure EFZ viewed at 1,000 X magnification **b.** The surface of hot-melt extruded pellets matrix 10% w/w EFZ in Eudragit® E PO matrix **c.** The surface of hot-melt extruded pellets matrix 25% w/w EFZ in Eudragit® E PO matrix **d.** The surface of hot-melt extruded pellets matrix of 50% w/w EFZ in Eudragit® EPO matrix **e.** The surface of hot-melt extruded pellets matrix of 60% w/w EFZ in Eudragit® E PO matrix and **f.** The surface of hot-melt extruded pellets matrix of 70% w/w EFZ in Eudragit® E PO matrix.

5.5.6. *IN VITRO* RELEASE STUDIES

The aqueous solubility of EFZ at 37 °C was found to be 5.26 ± 2.3 µg/ml. The saturation solubility of EFZ at 37°C in 0.2% SLS 0.2M sodium phosphate buffer (pH 6.8, simulated salivary medium) and 0.2% SLS in 0.1M HCL (pH 1.2, simulated gastric medium) was found to be 212.26 ± 3.32 µg/ml and 232.47 ± 4.35 µg/ml, respectively. The pellet formulations containing various drug: polymer ratios, meeting the desired post extrusion drug content ($98.36 \pm 0.47\%$ w/w), were tested for drug release. Dissolution testing was employed to assess the *in vitro* taste masking ability of the hot melt extruded pellet formulations. The pH of the saliva has been reported to be between 6.8- 7.4 and delay in drug release at this pH of even only a few minutes can prevent the unpleasant taste sensation or in the present case, irritation of the oral mucosa (BMS, burning mouth syndrome). The release profiles, obtained with melt extruded pellets in simulated salivary medium indicate that release will be delayed in simulated salivary medium the hot melt extruded pellets with 10, 25 and 50% w/w drug load (Figure 5-7). Hence, the hot melt extruded pellets will provide sufficient taste masking and prevent the BMS. In contrast to the release profile in simulated salivary medium, the hot melt extruded pellet formulations rapidly released EFZ in simulated gastric medium. Also, the dissolution rate of the melt extruded pellets was faster than that of the physical mixtures ($p < 0.05$, Figure 5-8) in simulated gastric medium. For example, 90% drug was released within 30minutes from the hot melt extruded pellets consisting of 10, 25 and 50% w/w drug load in simulated gastric medium. However, with the physical mixtures only 25-30% dissolution took place in 60 minutes. The observed dissolution rate enhancement in simulated gastric medium was due to the conversion of EFZ into an amorphous state, which offers a low thermodynamic barrier to solution, and also due to Eudragit® E PO's solubilizing effect at acidic pH (Figure 5-8).

The pellets containing 60 and 70% w/w EFZ exhibited significantly lower drug release in simulated gastric medium in comparison to pellets from 10, 25 and 50% w/w drug load ($f_2 < 50$). For example, less than 70% drug release occurred in 60 minutes with the 60 and 70% w/w drug loaded melt extruded pellets with in comparison to 100% drug release in less than 60minutes from the hot melt extruded pellets with 10, 25 and 50% w/w drug load. The pellets with 25 and 50% w/w drug load exhibited release profiles similar to that of the marketed formulation of EFZ (micronized and formulated with SLS containing 50 mg EFZ) under the same dissolution conditions ($f_2 > 50$, Figure 5-9). EFZ has a usual daily adult dose of 600 mg and the recommended daily doses in children are between 200 mg and 600 mg (39, 54). Therefore, in the present studies pellets with 25 and 50% w/w drug load were selected for further stability studies. These pellets were used to formulate the tablets (Figure 5-10 to 5-13).

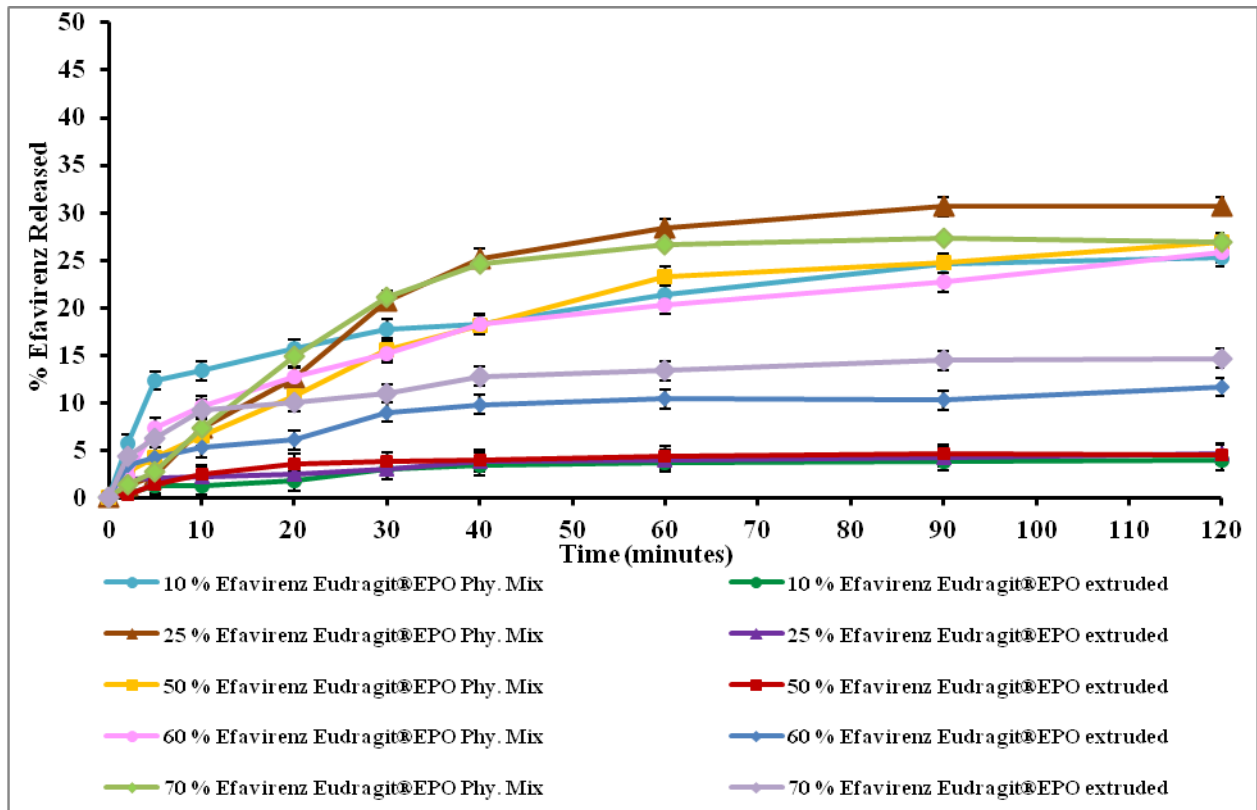


Figure 5-7: Release profile of hot melt extruded pellets and physical mixtures with 10, 25, 50, 60 and 70% w/w drug load equivalent to 200 mg EFZ in pH 6.8 buffer with 0.2% SLS.

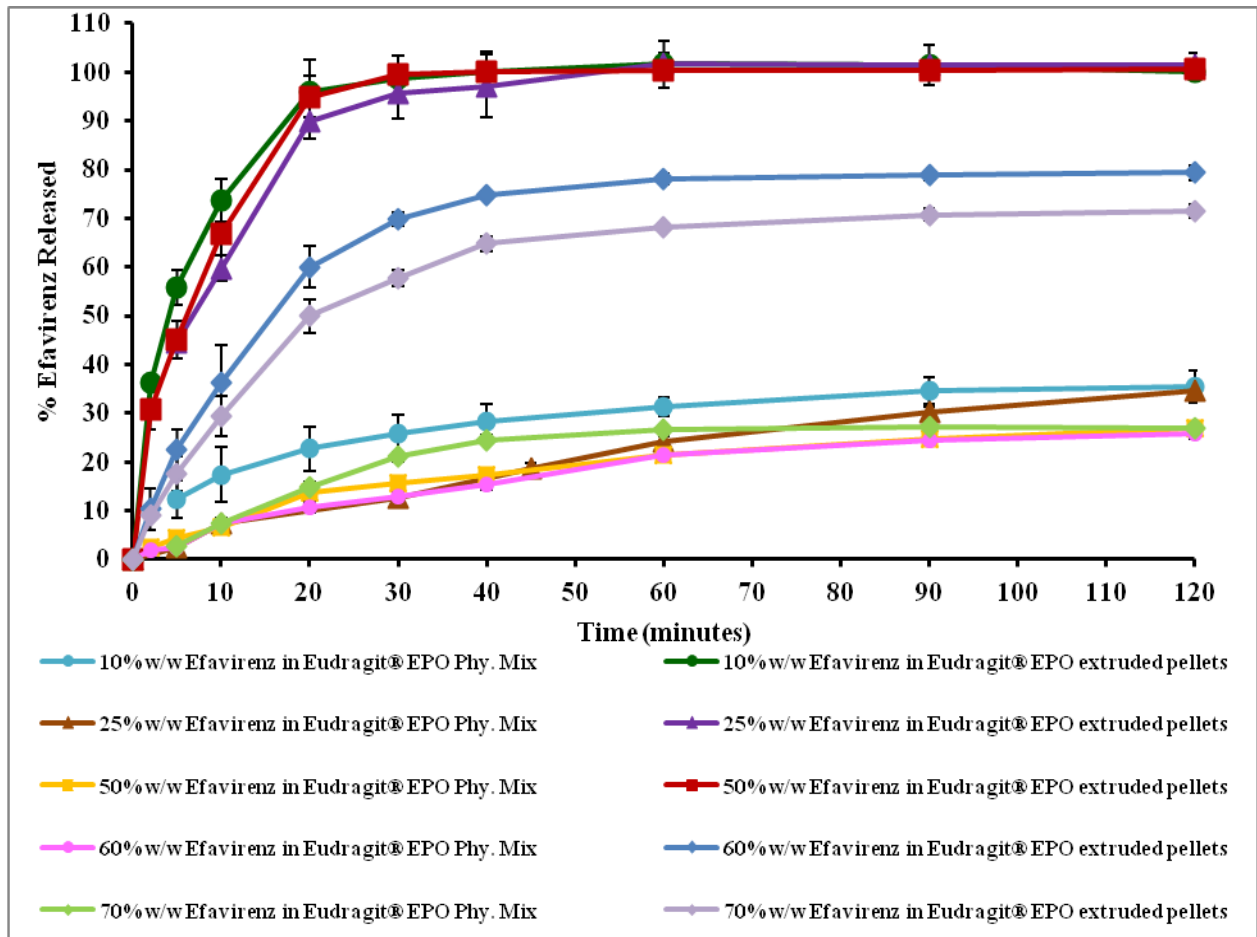


Figure 5-8: Release profile of hot melt extruded pellets and physical mixtures with 10, 25, 50, 60 and 70% w/w drug load equivalent to 200 mg EFZ in 0.1MHCL with 0.2% SLS.

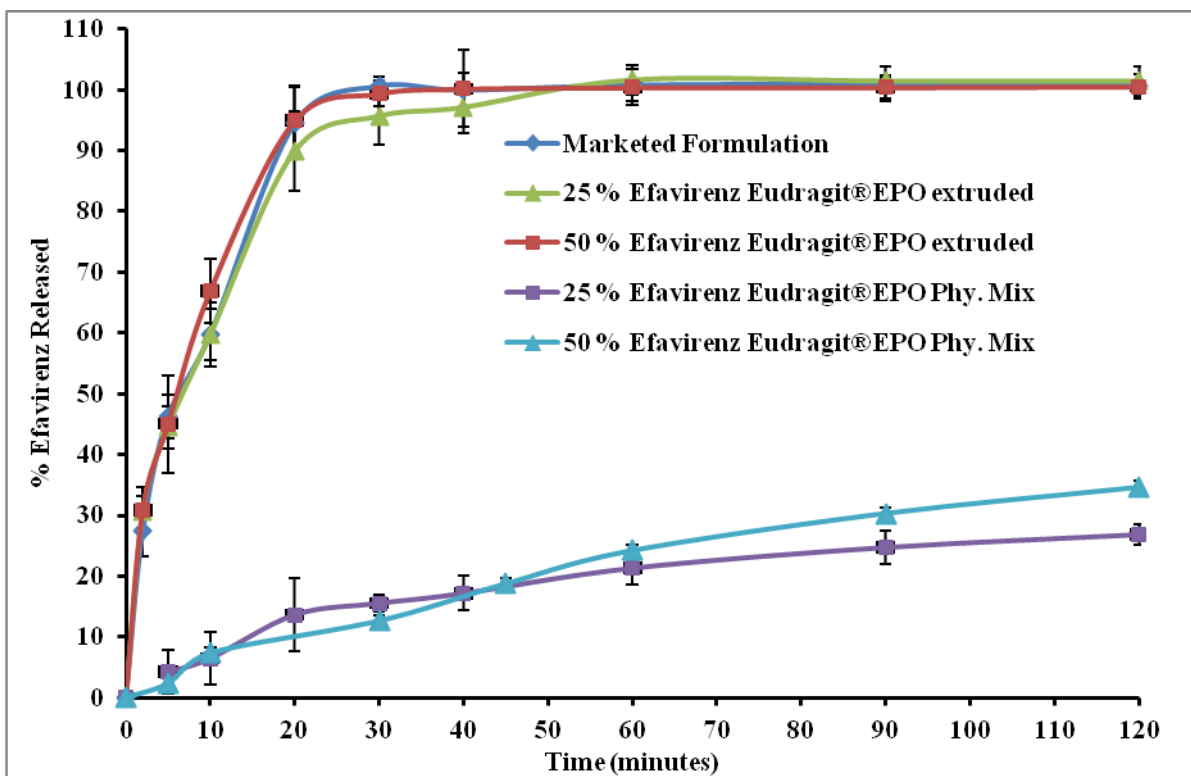


Figure 5-9: Comparison of the release profiles of the 25%w/w and 50%w/w hot melt extruded pellets and physical mixture equivalent to 50 mg with that of marketed formulation 50 mg EFZ capsules.

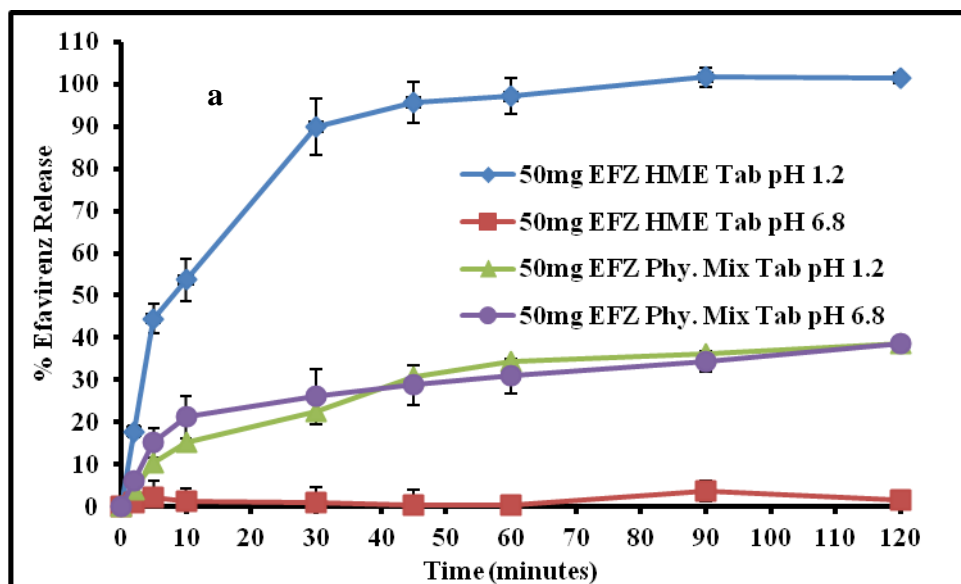


Figure 5-10: *In vitro* release profiles of EFZ tablet weight **a** 240 mg (Dose=50 mg EFZ) and **b** and 472 mg (Dose=100 mg EFZ) with HME and Phy. Mix with 25% EFZ in Eudragit® E PO

matrix (Dissolution conditions: USP type II, 50 RPM, 1000 ml with 0.2% SLS in pH 1.2 or 6.8 buffer at 37 °C).

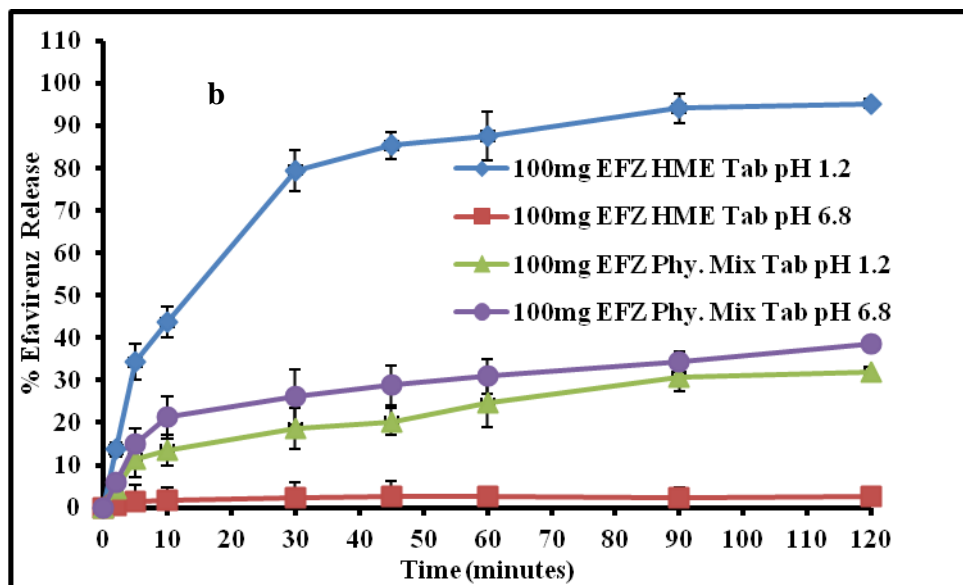


Figure 5-11: *In vitro* release profiles of EFZ tablet weight **a** 240 mg (Dose=50 mg EFZ) and **b** and 472 mg (Dose=100 mg EFZ) with HME and Phy. Mix with 25% EFZ in Eudragit[®] E PO matrix (Dissolution conditions: USP type II, 50 RPM, 1000 ml with 0.2% SLS in pH 1.2 or 6.8 buffer at 37 °C).

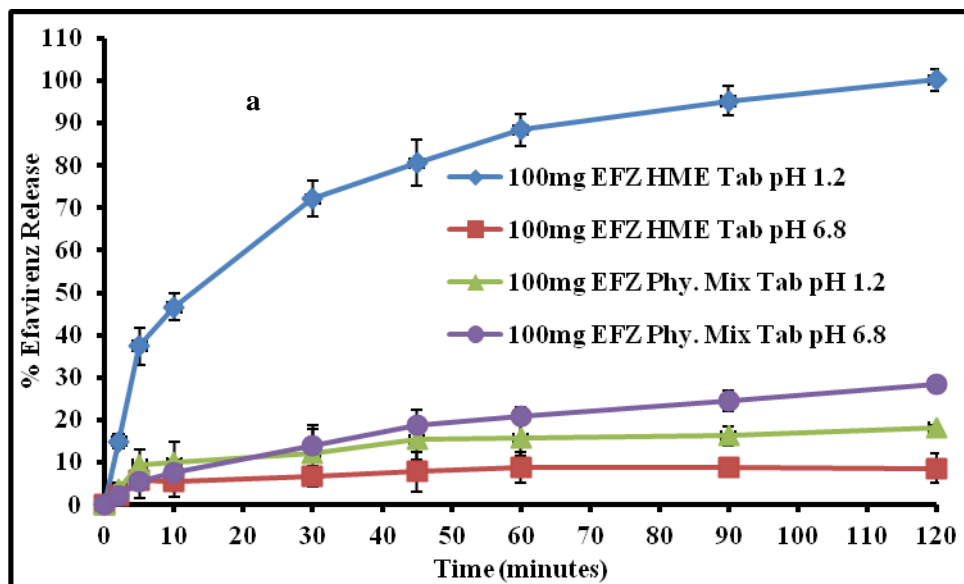


Figure 5-12: *In vitro* release profiles of EFZ tablet weight **a** 240mg (Dose=100 mg EFZ) and **b** 472 mg (Dose=200 mg EFZ) with HME and Phy. Mix with 50% EFZ in Eudragit[®] E PO matrix (Dissolution conditions: USP type II, 50 RPM, 1000 ml with 0.2% SLS in pH 1.2 or 6.8 buffer at 37 °C).

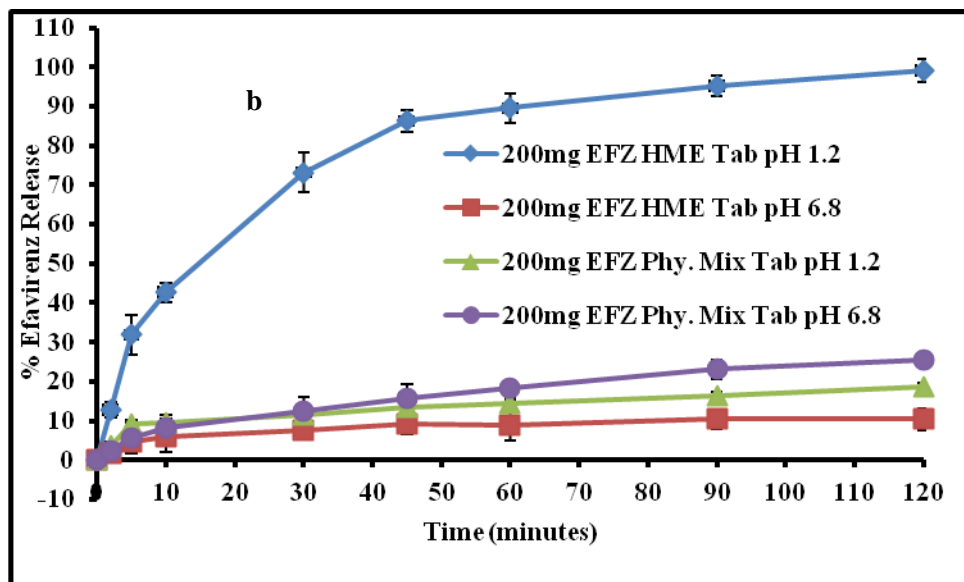


Figure 5-13: *In vitro* release profiles of EFZ tablet weight **a** 240 mg (Dose=100 mg EFZ) and **b** 472 mg (Dose=200 mg EFZ) with HME and Phy. Mix with 50% w/w EFZ in Eudragit® E PO matrix (Dissolution conditions: USP type II, 50 RPM, 1000 ml with 0.2% SLS in pH 1.2 or 6.8 buffer at 37 °C).

5.5.7. STABILITY STUDIES

The 6 month stability study data for pellet formulations with 25 and 50% w/w drug load suggests that the formulation was physically and chemically stable. The % EFZ content remaining in the pellet formulations was greater than 97.5%±0.63, and the drug release profile remained unchanged ($f_2 > 50$) after 6 month storage at 40 °C/75% RH (Figure 5-14). EFZ melting peak was not detected by DSC even after 6 month storage at 40 °C/75% RH (Figure 5-15). The observed stability of the amorphous form of EFZ could be due to its interaction with Eudragit® E PO.

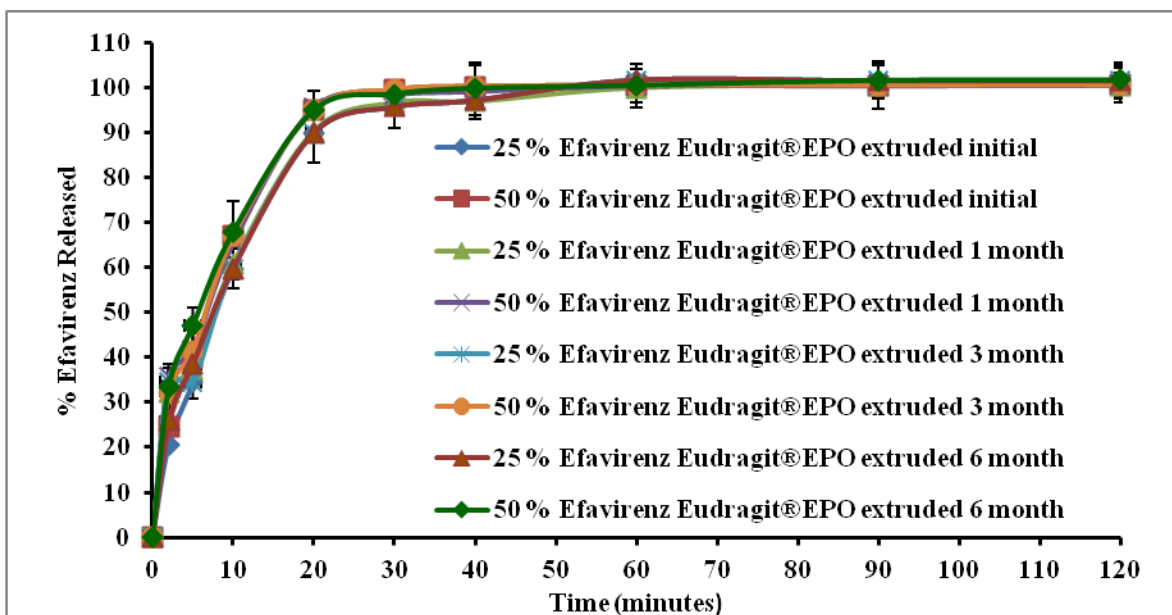


Figure 5-14: Release profiles of 25% w/w and 50% w/w hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

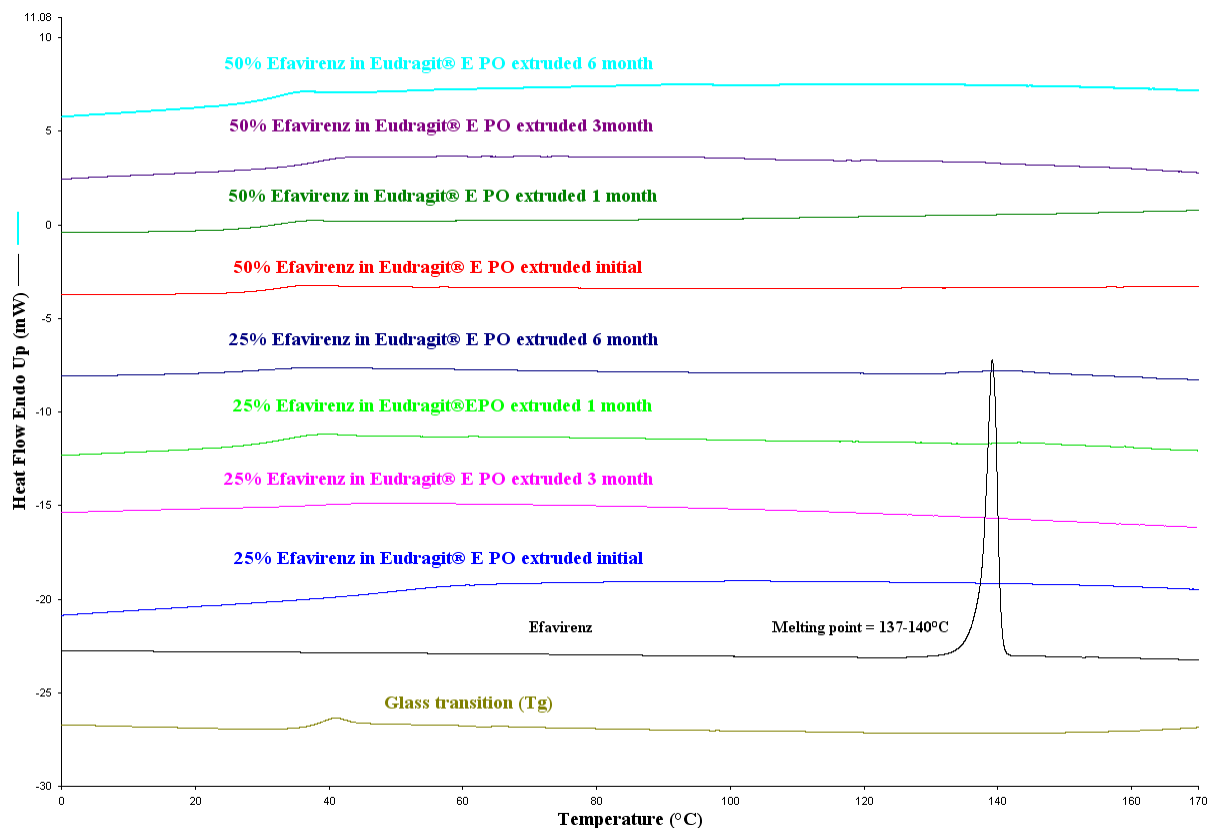


Figure 5-15: DSC thermogram illustrating stability of amorphous form of EFZ in Eudragit® E PO matrix hot melt extruded pellets at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

5.6. CONCLUSION

Hot-melt extrusion is a simple, efficient, and continuous process and has been used in this study to produce immediate-release EFZ pellet formulations. The solid state characteristics of EFZ in the pellets were confirmed using DSC, PXRD and SEM. The dissolution rate of EFZ was significantly improved in simulated gastric medium with HME technology using Eudragit® E PO. *In vitro* release profile in simulated salivary medium confirmed the ability of the Eudragit® E PO to minimize the release of EFZ in the saliva. This will prevent the BMS caused by ingestion of EFZ. The pellet formulation will improve pediatric patient compliance not only by taste masking but also by providing flexibility of dosing. Since each pellet contains a specific

amount of drug; the drug dose can be easily adjusted by measuring a specific weight of pellets depending on the patient's body weight. The administration of pellets is easier in pediatric patients as it can be sprinkled on food, mixed with fluids (water, milk or jelly) or directly swallowed. EFZ exhibited adequate physical stability probably due to the intermolecular interactions with the dimethylamino group of Eudragit[®] E PO. The dissolution profile remained unchanged even after 6 months storage at 40°C/75% RH. The release from melt extruded pellets with drug loads 10, 25, 50% w/w was comparable to that of a marketed formulation, which released 100% drug in less than 60 minutes. This study illustrates that HME could be considered as an alternative technology for improving the dissolution characteristics as well for taste masking of EFZ to improve pediatric patient compliance.

CHAPTER - 6

SUGAR ALCOHOLS AS CARRIERS FOR SOLID DISPERSIONS USING MELT EXTRUSION TECHNIQUES

6.1 ABSTRACT

Hot melt extrusion (HME) technology has become very popular in generation of amorphous solid dispersions of poorly soluble drugs for attainment of increasingly popular immediate release dosage forms. Water-soluble carriers such as sugar alcohols (Mannitol, Sorbitol, and Xylitol) have recently attracted considerable interest as a means of improving the dissolution rate, and hence potential for increased bioavailability of hydrophobic drugs. However, their utility as a primary matrix in melt extrusion has not been studied. Therefore, the present work focuses on the formulation of the poorly water soluble drug Carbamazepine (CBZ) using sugar alcohols as carriers. In all samples, the amorphous structure of CBZ was confirmed using differential scanning calorimetry (DSC) and Powder X-ray diffraction (PXRD). Also, all of the investigated drug/sugar alcohol combinations demonstrated improved solubility and dissolution rates. The increase in dissolution rates was attributed to the presence of the CBZ in its amorphous form.

Keywords: Hot melt extrusion, Sugar alcohols, Carbamazepine, differential scanning calorimetry (DSC), Powder X-ray diffraction.

6.2. INTRODUCTION

A sugar alcohol (also known as a polyol, polyhydric alcohol, or polyalcohol) is a hydrogenated form of carbohydrate, whose carbonyl group (aldehyde or ketone, reducing sugar) has been reduced to a primary or secondary hydroxyl group (55). Sugar alcohols or Polyols are sugar-free sweeteners. Some of them are found naturally in various fruits and vegetables. Sugar alcohols may be used either as sweeteners or as fillers i.e. non-sweetening functions in the food industry or pharmaceuticals. The most widely used polyols are Sorbitol, Mannitol, Maltitol, Isomalt, Lactitol, Xylitol and Erythritol (55).

Sugar alcohols are very useful in formulating solid dosage forms such as tablets, capsules, and granules. Sorbitol powder with its characteristic sweet and cool taste is ideally suited for oral medication such as suckable tablets. Mannitol in various forms (spray dried, directly compressible and granulated) is used for chewable / oral dispersible or effervescent tablets. Isomalt can be used as a filler binder in tablets (56). Sugar alcohols are also known as common excipients for hard coating (57). Hard Coating is the traditional method of coating tablets. It is mainly used to mask unpleasant odors and tastes or to protect actives against light. Maltitol powder successfully replaces traditionally used sugars, and achieving faster coating. A pleasant cooling effect will be produced as some sugar alcohols dissolve. This unique effect is known as the “heat of solution” and is an actual exchange in energy. It can either lower or raise the temperature of a solution when a substance (sugar) is added to water (or saliva). As the heat of solution decreases into negative values, the cooling effect is more intense. Xylitol has been popular for its negative heat of solution which is more pronounced than that of other sugar alcohols, since they produce an intense cooling effect as the crystalline material dissolves (Table

6-1). Xylitol's combination of sweetness and cooling can create product appeal while helping to mask the undesirable taste of many pharmaceutical actives or excipients (58). Due to their properties such as taste, mouth feel, low calorie content, non-carcinogenicity, suitability for diabetics and low hygroscopicity, they offers several advantages when formulated into pharmaceutical dosage forms.

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with the objective to enhance oral bioavailability. Furthermore, the carrier used has, again traditionally, been a water-soluble or water miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as sugars. In solid dispersions, the amorphous drug has a lower thermodynamic barrier for dissolution together with a maximally reduced particle size. The sugar alcohols can also be used as carriers in solid dispersions, since it is known that glass formation is common in many polyhydroxy substances, presumably due to their strong hydrogen bonding which may prevent recrystallization of the amorphous form of drug molecules. Furthermore, they possess the advantage of high thermal stability and absence of browning reactions. The studied sugar alcohols Mannitol, Sorbitol, and Xylitol are used in the manufacture of sugar-free hard candies and dietetic food.

There are a variety of approaches to prepare solid dispersions, such as hot-melt extrusion (HME), spray drying, and solvent co-precipitation. Hot-melt extrusion is a solvent free process. Thus there are no concerns with solvent handling or recovery after processing. Also, there are no requirements on the compressibility of the active ingredients. The intense mixing and agitation by the extruder screw during processing causes suspended drug particles to disaggregate in the

polymer melt, resulting in a uniform dispersion of fine particles. Drug bioavailability may therefore be improved by dispersion of the drug substance at the molecular level in melt extruded dosage forms. During the HME extrusion process, a blend of the active ingredients, the thermoplastic polymers, and other processing aids is fed into the barrel of the extruder through the hopper. The materials are transferred inside the heated barrel by a rotating screw. Temperatures at different zones are controlled by several thermocouples in the barrel. The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. The formulations are subject to heat only a few minutes within the extruder.

Carbamazepine (CBZ) is an important anti-epileptic agent that has been in use for over 30 years. It is an example of a water-insoluble drug that requires relatively high dosing has a high dose requirement (>100 mg/day) to attain a therapeutic effect (59). The aqueous solubility of carbamazepine at 37 °C was determined to be $237.2 \pm 5.2 \mu\text{g/mL}$ and log P value of 2.3. CBZ poses multiple challenges for oral drug delivery, including a narrow therapeutic window, auto induction of metabolism and dissolution-limited bioavailability. CBZ crystallizes in at least four anhydrous polymorphic modifications (Table 6-4) with the energy separation is <0.7 kcal/mol between the most and least stable form and has been shown to form several solvates; including a stable dihydrate from aqueous solutions (60). The marketed formulations such as Tegretol[®] contain the pharmaceutically acceptable P-monoclinic or form III (60-61).

Several attempts have been made by pharmaceutical scientists to improve dissolution profile of CBZ, by using water soluble carriers like polyvinyl pyrrolidone (PVP), polyethylene glycols (PEG) and Hydroxy propyl methyl cellulose (HPMC) (62) to prepare solid dispersions of CBZ, by preparing co-crystals with saccharin (63) or by using mesoporous silica as carriers (59).

However, the preparation method of the solid dispersions or other more water soluble formulations studied in the literature involves organic solvents such as that used in freeze drying or involved with many discontinuous steps that are difficult to be successfully adopted by industry. HME is a continuous process that requires less offline testing. Melt extrusion requires fewer operator interventions and, thus, can yield improved product quality. This technology has become easier for industry to embrace due to the technical developments of recent years (i.e., extruder vendors have begun to produce units designed according to the principles of good manufacturing practice). The present study focuses on the formulation and processing of CBZ utilizing sugar alcohols (Mannitol, Sorbitol, and Xylitol) as HME produced matrices (Figure 6-1). Furthermore, this manuscript proposes solutions for major issues in the development of solid dispersions by industry, such as process adaptability. This novel work demonstrates the utility of sugar alcohols for pharmaceutical dosage forms utilizing HME. The formulations studied were prepared by hot melt extrusion and characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and *in vitro* release studies.

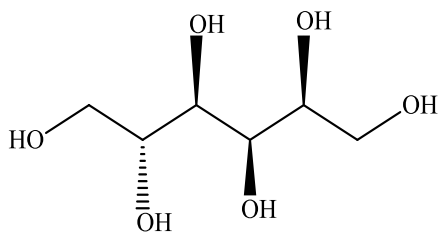
6.3. MATERIALS

Pearlitol[®]PF (Mannitol), Neosorb[®] PF (Sorbitol), and Xylisorb[®]PF (Xylitol) were kindly gifted by Roquette Pharma, RCS Bethune, and France. All the excipients used were of pharmaceutical grade. Crystalline anhydrous Carbamazepine (CBZ) was obtained from Sigma Chemical Co. (St. Louis, MO). Other reagents (HPLC grade) were purchased from Fisher Chemicals, NJ.

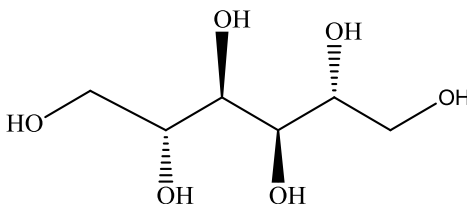
6.4. METHODS

6.4.1. HOT MELT EXTRUSION PROCESSING

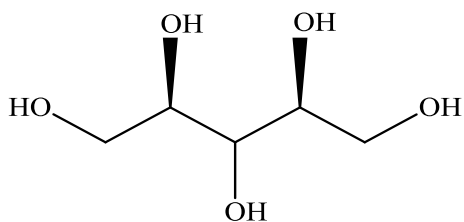
Carbamazepine (CBZ) was blended with the sugar alcohols (Mannitol, Sorbitol, and Xylitol) in two ratios, (1:10, and 1:4) in a V-cone blender for 10 minutes and analyzed for pre- and post-extrusion content uniformity. Rod shaped hot melt extruded (HME) formulations were obtained using a Thermo Scientific HAAKE MiniLab at an extrusion temperature range of 120-175 °C (Mannitol formulations) and 80-100 °C (Sorbitol and Xylitol formulations) and processed at a screw speed of 75 rpm. The system is based on a conical, twin-screw compounder equipped with co rotating screws. The extrudates were pulverized using a sieve mesh size “22” according to US ASTM standards in a comminuting mill (FITZPATRICK, Model “L1A”).



Sorbitol



Mannitol



Xylitol

Figure 6-1: Structures of sugar alcohols studied.

6.4.2. THERMOGRAVIMETRIC ANALYSIS (TGA)

A Perkin-Elmer Pyris-1 TGA (Shelton, CT) was used to determine the thermal stability of the sugar alcohols and CBZ. The samples were heated from 25 to 200 °C at a heating rate of 20 C/min. All TGA runs were performed in an open pan with purge and protective nitrogen gas flow at 40 mL/min.

6.4.3. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The DSC thermograms were recorded using a Pyris 1 Perkin-Elmer Diamond DSC equipped with Pyris -7 Manager Software (Shelton, CT). DSC was used to study the crystallinity and solid-state physical stability of the HME formulations pre- and post-extrusion. Accurately weighed amounts (5-10 mg) of either the physical mixtures or the extrudates of sugar alcohols and CBZ were hermetically sealed in a flat-bottomed aluminum pan and heated from 25 C to 200 C at a linear heating rate of 10 C/min. The pure CBZ samples were tested at three different heating rates 10, 40 and 100 °C/min. An empty pan was used as a reference and calibrations for temperature and enthalpy were performed with indium. Measurements were repeated (n=3) and mean values with the respective standard deviation were determined.

6.4.4. POWDER X-RAY DIFFRACTION (PXRD)

The crystallinity of the drug was analyzed using PXRD. The samples were analyzed using a D-8 Advance X-Ray Diffractometer (Bruker AXS, Madison, WI) equipped with a Sol X detector and Diffrac Plus software. The generator voltage and current was 40 kV and 40 mA, respectively. The 2 Theta scanning range was from 5° to 50°. The step size was 0.02°, and the dwell time at each step was 1 second.

6.4.5. FOURIER TRANSFORM INFRARED (FTIR) SPECTROSCOPIC ANALYSIS

FTIR studies were done to detect the possible interactions between the CBZ and sugar alcohols in the solid dispersions leading to stabilization of amorphous state of CBZ. The FTIR spectra of CBZ corresponded with those previously reported for Form III in the literature. The spectra were analyzed for the absence or shift in the wave numbers of the characteristic peaks and reported.

6.4.6. *IN VITRO* EVALUATION

Two-hundred milligrams of the pulverized extrudates were filled into size '0' capsules. Hence, the formulations with CBZ and sugar alcohols (Mannitol, Sorbitol, and Xylitol) in the two ratios of 1:10 (CBZ equivalent to 20 mg) and 1:4 (CBZ equivalent to 50 mg) were used for analysis. The capsules were used to evaluate *in vitro* release, using a Type 2 apparatus (paddles) 0.5% SLS 900 ml as the dissolution medium at 37 °C and the paddle rotation speed was 75 rpm with a Hanson SR8-Plus dissolution test system (Chatsworth, CA). Samples were collected at predetermined time intervals at 5, 15, 30, 45, 60, 90, and 120 min., filtered using 0.2 micron dissolution filter tips attached to a 1 ml nylon syringe, and analyzed by HPLC. All of the results are reported as the average of 3 replicates \pm SD.

6.4.7. CALCULATION OF HANSEN SOLUBILITY PARAMETER

The cohesive energy of a material is the energy that holds that substance together or the amount of energy required to separate the constituent atoms or molecules of the material. Cohesive energies are especially important to the pharmaceutical materials scientist since he/she determine many of the critical physico-chemical properties (e.g. solubility, melting point) of drugs and excipients.

The cohesive energy of a material can be quantified in a number of ways. The most common approach is to use the solubility parameter (or cohesive energy densities (CED)). The solubility parameter of each component is defined as the square root of its CED, measured as the energy of vaporization per unit volume:

$$\delta = (\text{CED})^{1/2} = (\Delta E_v/V_m)^{1/2} \quad (6-1)$$

The difference between the solubility parameters (δ_i) of two materials provides an estimation of the likelihood that they will be miscible²¹. The solubility parameter (δ_t) is calculated using the equation below.

$$\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \quad (6-2)$$

The partial solubility parameters δ_d , δ_p and δ_h are calculated using group contributions for London dispersion forces, polar forces, and hydrogen bonding forces.

6.4.8. STABILITY STUDIES

The sample of each of the solid dispersions were transferred to HDPE bottles and placed inside humidity chambers pre-equilibrated to 25 °C/60% RH and 45 °C/75% RH. At specific time intervals during the course of the 6 month study, the HDPE bottles assigned for each time point

would be removed. The solid dispersions of CBZ with sugar alcohols were characterized using *in vitro* release studies.

6.4.9. DATA ANALYSIS

In all the cases, statistical analysis was performed utilizing one-way analysis of variance. A statistically significant difference was considered when $p < 0.05$.

6.5. RESULTS AND DISCUSSION

6.5.1. HOT MELT EXTRUSION PROCESSING

Xylitol exhibited best flow properties compared to other sugar alcohols. Mannitol and Sorbitol resulted in very viscous melts within the extruder demonstrating high die pressure and torque values. However, the intimate mixing of sugars and CBZ during the extrusion process resulted in homogenous extrudates for all of the formulations tested (CBZ assay $\geq 100\%$).

Sorbitol ($T_m = 95\text{ }^\circ\text{C}$) is the stereoisomer of Mannitol. It is more hygroscopic compared to the other two sugars, as well as exhibiting less desirable melt flow properties. These properties were problematic for handling sorbitol during the extrusion process. Mannitol has a very high melting point ($T_m = 165\text{-}167\text{ }^\circ\text{C}$). The requirement of processing conditions (above $165\text{-}170\text{ }^\circ\text{C}$) could be problematic for certain drugs. Xylitol ($T_m = 98.5\text{ }^\circ\text{C}$) possesses better flow properties and exhibited good extrudability in comparison to Mannitol and Sorbitol (Table.6-2).

Table 6-1: Comparison of heat of solution of selected sugar alcohols (64).

Sugar Alcohols (Carriers)	Heat of Solution (kJ/kg)
Sorbitol	-106.3
Mannitol	-120.9
Xylitol	-157.1

Table 6-2: Thermal properties of sugar alcohols (65).

Sugar Alcohols (Carriers)	Melting point (T _m) / Glass transition temperature (T _g) (°C)
Sorbitol	85-87/0
Mannitol	160/10.7
Xylitol	95/N.A

Table 6-3: Hilderband total solubility parameter δ_t (H) between sugar alcohols and CBZ (66).

Compound	$\Delta\delta_t$ (H)*	$\Delta\delta$
Carbamazepine	28.1	0
Xylitol	37.1	9
Sorbitol	38.2	10.1
Mannitol	39.1	11

*The $\Delta\delta_t$ values are from the referenced literature.

Table 6-4: Transition Temperatures of the Four Polymorphs of CBZ (60).

	Triclinic Form I	Trigonal Form II	P-Monoclinic Form III	C-Monoclinic Form IV
Peak 1 (°C)	-	140-160	174.8	187.7
Peak 2 (°C)	193.5	192.1	193.2	191.5

6.5.2. CBZ-MISCIBILITY BY SOLUBILITY PARAMETERS

BCS Class II drugs typically have solubility parameters of between 20 and 30 MPa^{1/2}(26). It has been reported that systems with a $\Delta\delta_t$ ranging from 1.6 to 7.5 MPa^{1/2} may show complete miscibility when in a molten state, systems with a $\Delta\delta_t$ from 7.4 to 15.0 MPa^{1/2} may demonstrate immiscibility in the liquid state, and systems with a $\Delta\delta_t$ above 15.9 will most likely exhibit total immiscibility. When the difference in solubility parameters is between 7.4 to 15.0 MPa^{1/2} prediction of glass solution formation is considered only after further experiments are performed with thermal analysis. If the solubility parameters are greater than 10 MPa^{1/2} apart, a partially crystalline or two phase amorphous product is formed (26). The carriers utilized in our studies demonstrated $\Delta\delta_t \geq 9$ (Table 6-3).

Pharmaceutical scientists recognize that there are limitations to the miscibility predictions based solubility parameters (26). Many of the drugs possess several polar and hydrogen bonding groups within the molecule and are most likely capable of interacting with different materials in a number of different ways. The donor-acceptor capacity of hydrogen-bonding groups in drugs and carriers must be considered to maximize interaction between the two materials. One further consideration when using solubility parameters is that they may be modified with temperature. It is possible that different materials will have solubility parameters which change to varying degrees with a change in temperature, such as during the processing conditions utilized during hot melt extrusion. These differences may become significant at high temperatures and may play a role in high melting point drug/carrier systems. It may be possible that the processing conditions during melt extrusion such as high temperature and shear increase the miscibility of drug and carriers.

6.5.3. THERMAL ANALYSIS

Thermal gravimetric analysis (Figure 6-2) of sugar alcohols (Sorbitol, Mannitol, and Xylitol) and CBZ demonstrated thermal stability up to 200 °C. The different heating rates were utilized to confirm CBZ's Form III defined within literature (Figure.6-3). The thermogram at 10 °C/ min demonstrated one endothermic peak occurred at 175.51 °C, followed immediately by an exotherm indicating melting of Form III and crystallization of Form I, respectively (Table. 6-4). A second endotherm corresponding to the melting of Form I appeared at 191.38 °C (60).

The thermograms (Figure 6-4) indicate that the extruded formulations do not exhibit endotherms around the melting point of CBZ. The lack of CBZ melting endotherms in the HME solid dispersions suggests the presence of the drug in an amorphous form within the matrix. This can account for its higher release from the HME dispersions.

The solid state characteristics of carrier sugars also play a role in release performance of solid dispersions. In thermograms, the melting endotherms of Sorbitol and Xylitol were not observed in melt extruded formulation systems (Figure 6-4 a and b). This would indicate the conversion of Sorbitol and Xylitol into an amorphous form. Mannitol based solid dispersions of CBZ can be classified as amorphous precipitation according to Table 1-2 i.e. drug is in amorphous form and carrier is crystalline. The amorphous state of the carriers markedly affects its usefulness as a carrier for formation of solid dispersions. An amorphous carrier in which the molecular arrangement is disordered helps penetration of dissolution media.

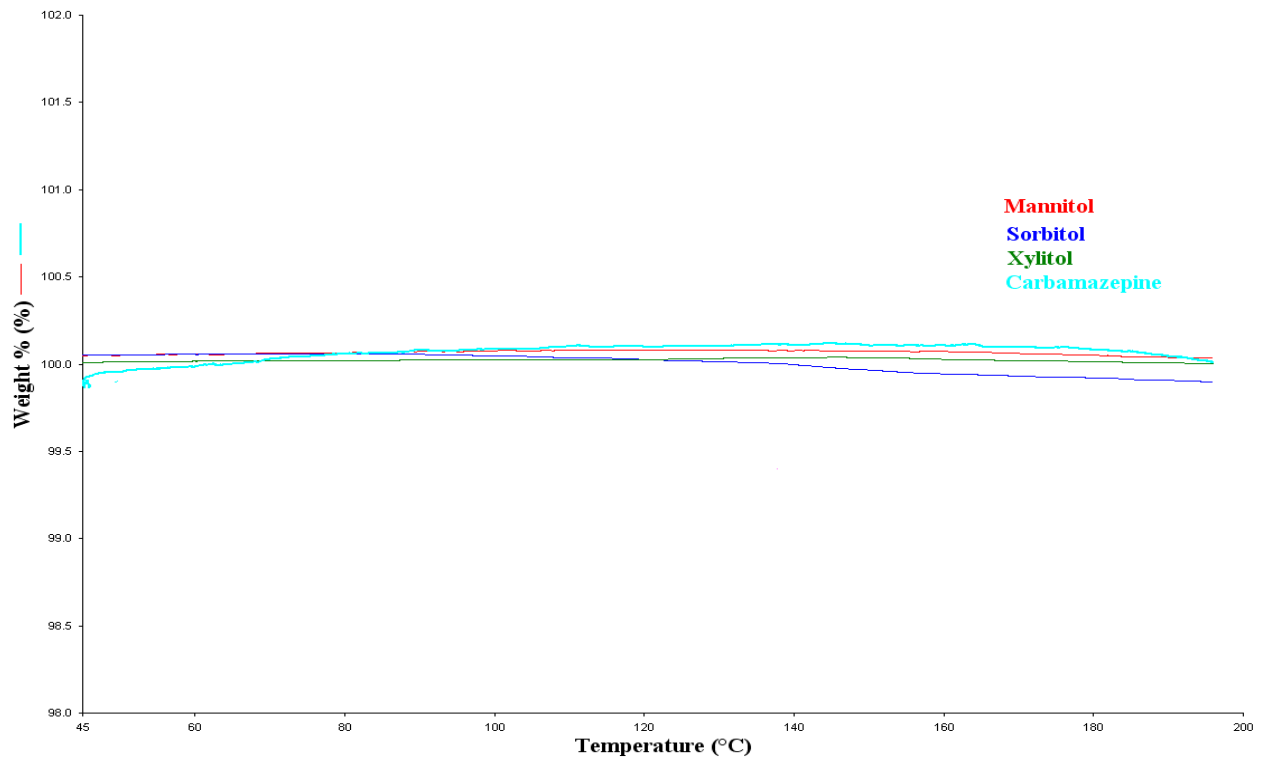


Figure 6-2: Thermal gravimetric analysis (TGA) of sugar alcohols and CBZ.

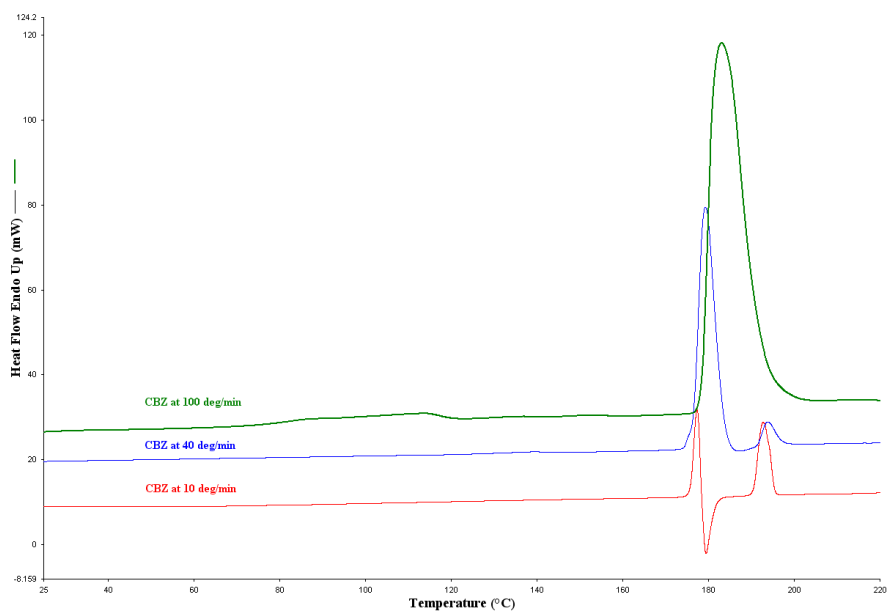


Figure 6-3: DSC thermogram of CBZ at different heating rates (deg /min).

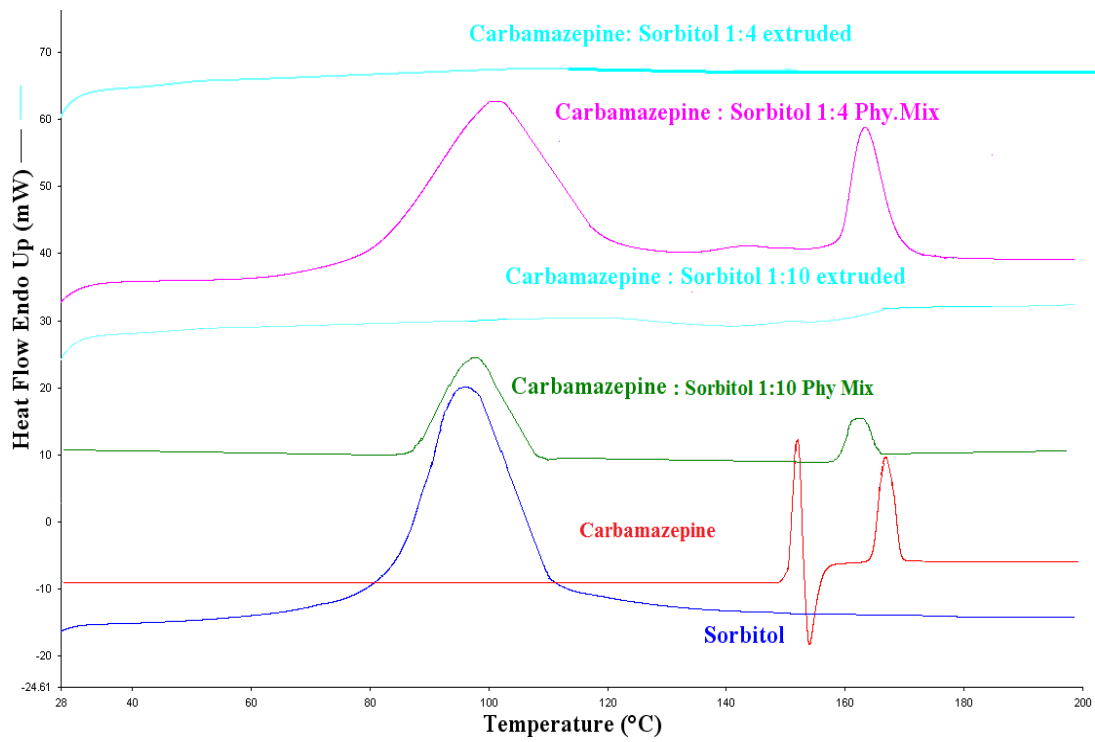


Figure 6-4: DSC thermograms of formulations with Sorbitol and CBZ.

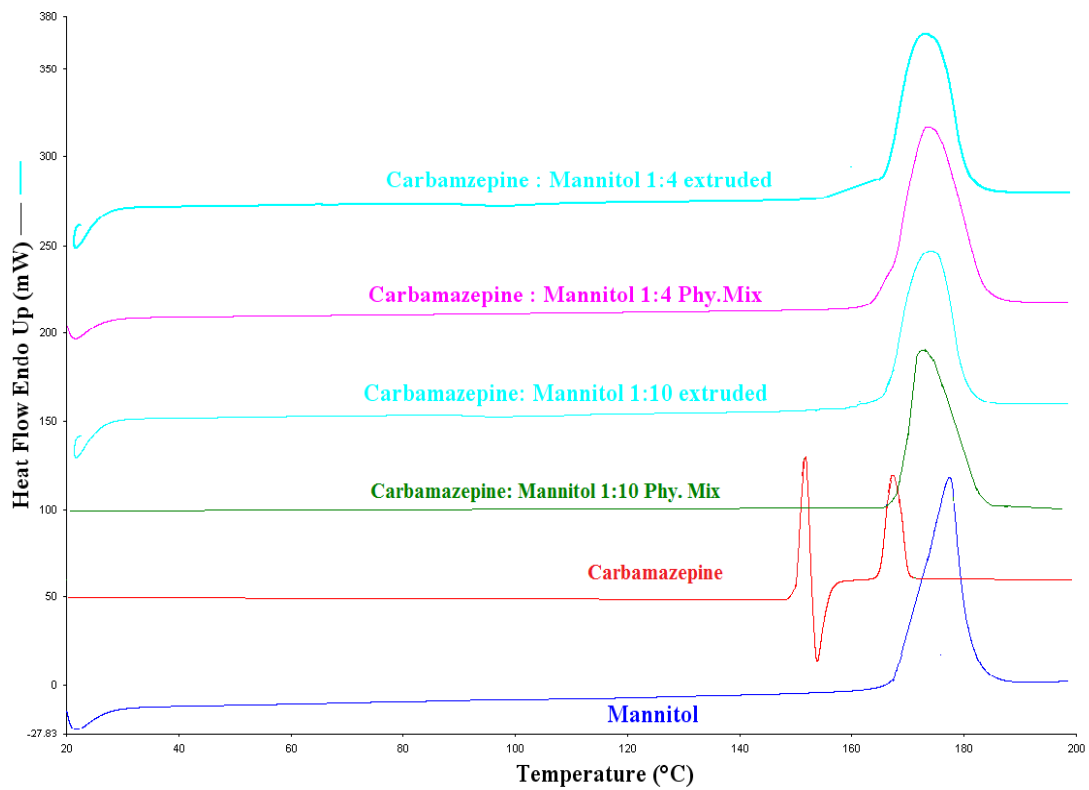


Figure 6-5: DSC thermograms of formulations with Mannitol and CBZ.

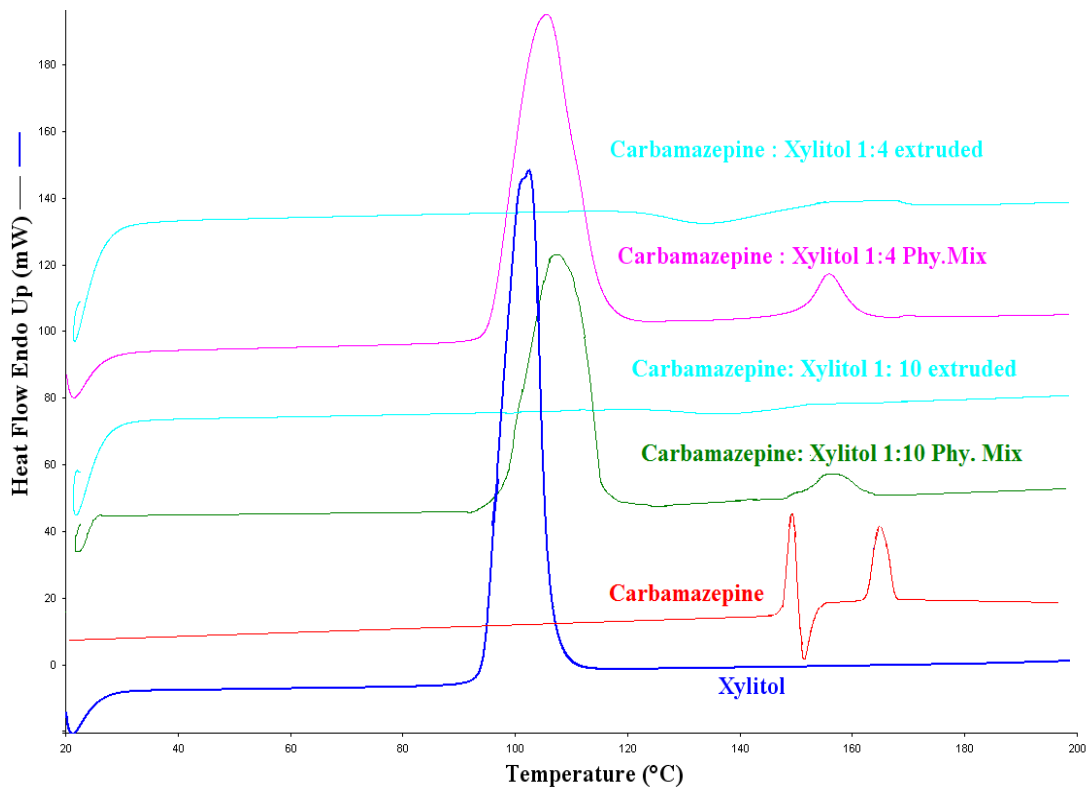


Figure 6-6: DSC thermograms of formulations with Xylitol and CBZ.

6.5.5. PXRD

PXRD is a powerful technique for the identification of crystalline solid phases. Every crystalline solid phase has a unique PXRD pattern, which can form the basis for its identification. CBZ's characteristic high-intensity diffraction peaks were detected at: $2^\circ\theta$ -13.1, 15.4, 15.9, 17.2, 27.2 and 27.5° matching CBZ Form III (62, 67). The PXRD patterns of all of the extruded formulations with sugar alcohols did not exhibit peaks corresponding to CBZ thus indicating that CBZ was in an amorphous form. The PXRD pattern of extrudates demonstrated absence of crystalline peaks in Sorbitol and Xylitol formulations, with the exception of Mannitol. These data corroborated the results from thermal analysis (Figures 6-7 to 6-9).

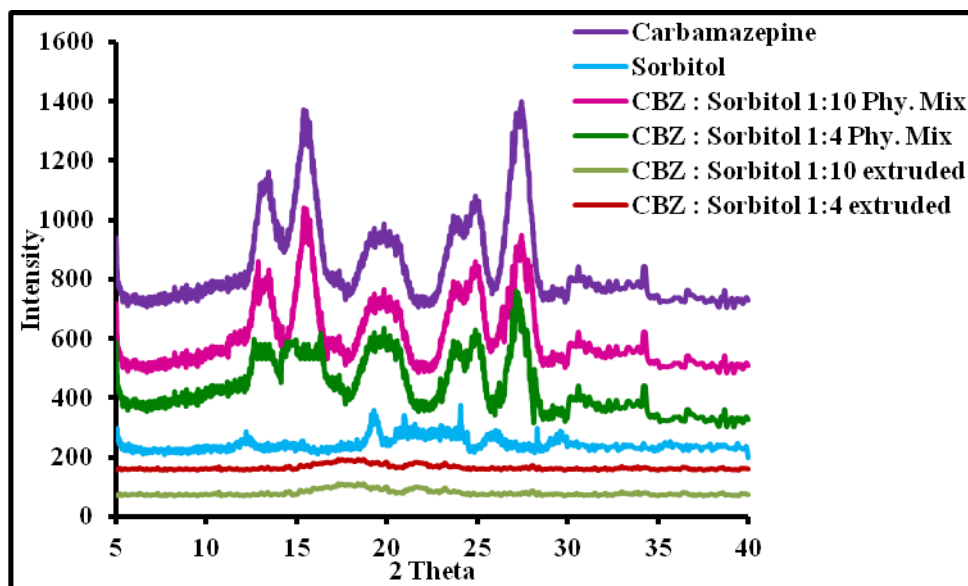


Figure 6-7: Powder X-ray diffractogram of formulations with Sorbitol and CBZ.

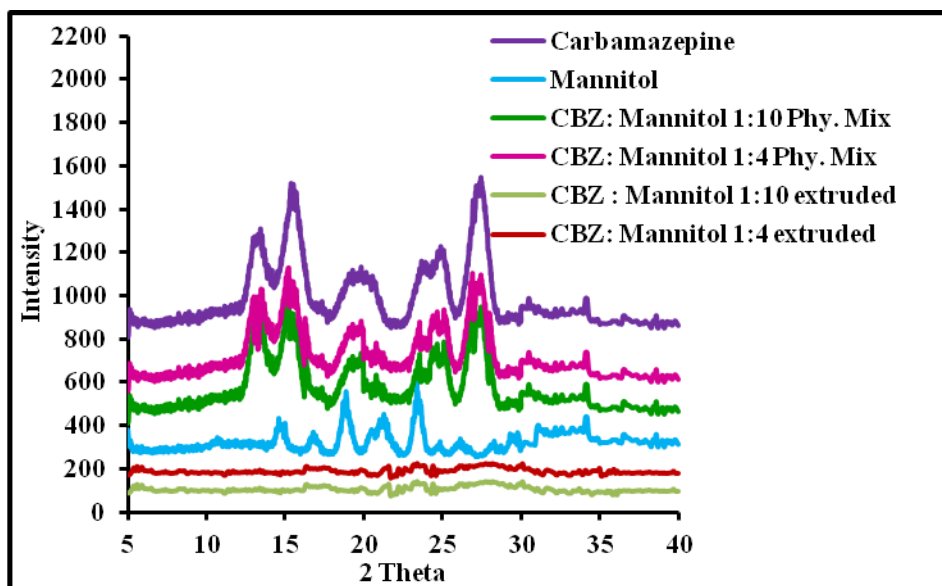


Figure 6-8: Powder X-ray diffractogram of formulations with Mannitol and CBZ.

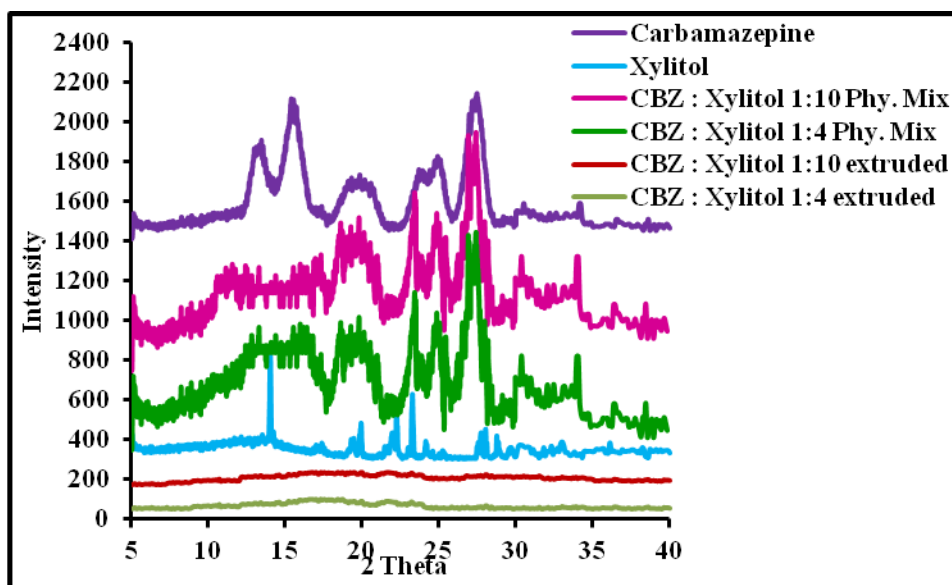


Figure 6-9: Powder X-ray diffractogram of formulations with Xylitol and CBZ.

6.5.4. FOURIER TRANSFORM INFRARED SPECTROSCOPY

FTIR studies were performed to detect the possible interactions between the CBZ and sugar alcohols in the solid dispersions leading to an amorphous state of CBZ. Figure 6-10 to 6-12 shows the IR spectra of CBZ, sugar alcohols and their formulations. The characteristic bands of CBZ polymorph III were found at 3464.86, 3280.79 and 3157.17 cm^{-1} ($-\text{NH}$ valence vibration), 1675.77 cm^{-1} ($-\text{CO}-\text{R}$ vibration), 1604.91 and 1594.38 cm^{-1} (range of $-\text{C}=\text{C}-$ and $-\text{C}=\text{O}$ vibration and $-\text{NH}$ deformation). The FTIR spectra of CBZ corresponded with those previously reported for Form III in the literature (68). Sugar alcohols showed strong bands at 3200-3500 and 1200-1500 cm^{-1} due to OH stretching (56-57). The physical mixtures of CBZ in ratios 1:4 and 1:10 with Mannitol showed summation of CBZ and Mannitol IR spectra (Figure 6-12). However, in solid dispersions of CBZ in ratios 1:4 and 1:10 with Mannitol, the two bands approximately at 3464 and 3280 cm^{-1} corresponding to the symmetrical and asymmetrical N-H stretching vibrations of primary amide groups of CBZ, seen in physical mixture, are replaced by a broader band at 3274 and 3278 cm^{-1} , respectively, indicating the possible involvement of the $-\text{NH}_2$ group hydrogen bonding with OH groups of Mannitol. Sorbitol and Mannitol are isomers and hence have very similar IR spectra. In the case of Sorbitol and Xylitol based solid dispersions with CBZ in ratios 1:4 and 1:10 in addition to broader bands at 3280.79 cm^{-1} and 3157.17 cm^{-1} ($-\text{NH}$ valence vibration), they also exhibited shifts at 1675.77 cm^{-1} ($-\text{CO}-\text{R}$ vibration), 1604.91 and 1594.38 cm^{-1} (range of $-\text{C}=\text{C}-$ and $-\text{C}=\text{O}$ vibration and $-\text{NH}$ deformation) indicating a second point of interaction (Figure 6-10 and 6-11).

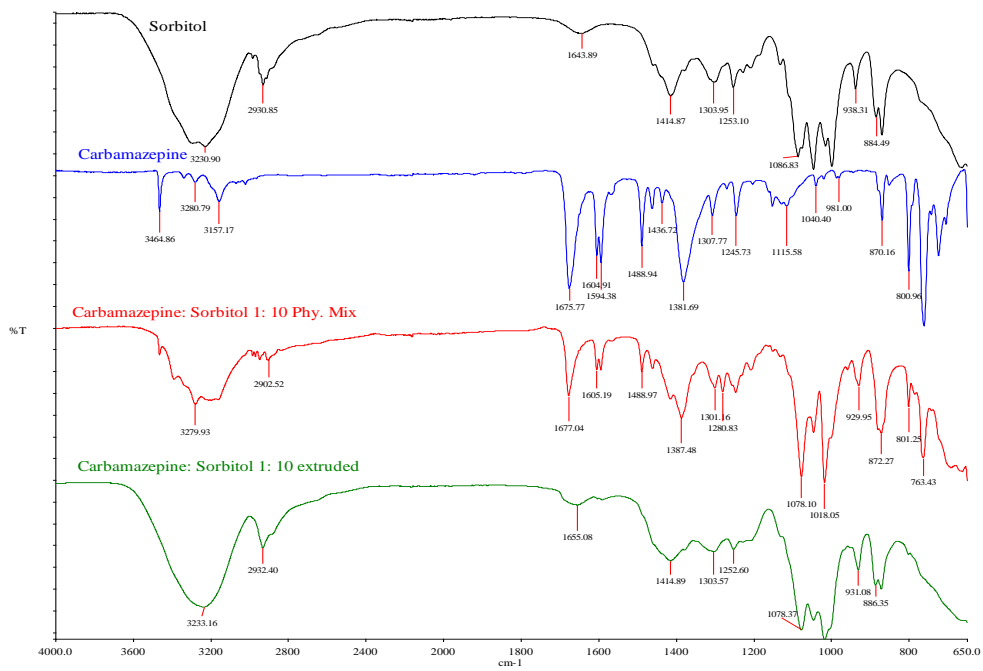


Figure 6-10: a) An overlay of FTIR spectra of Carbamazepine, Sorbitol, physical mixture (Phy. Mix) and extruded formulations in ratio 1:10.

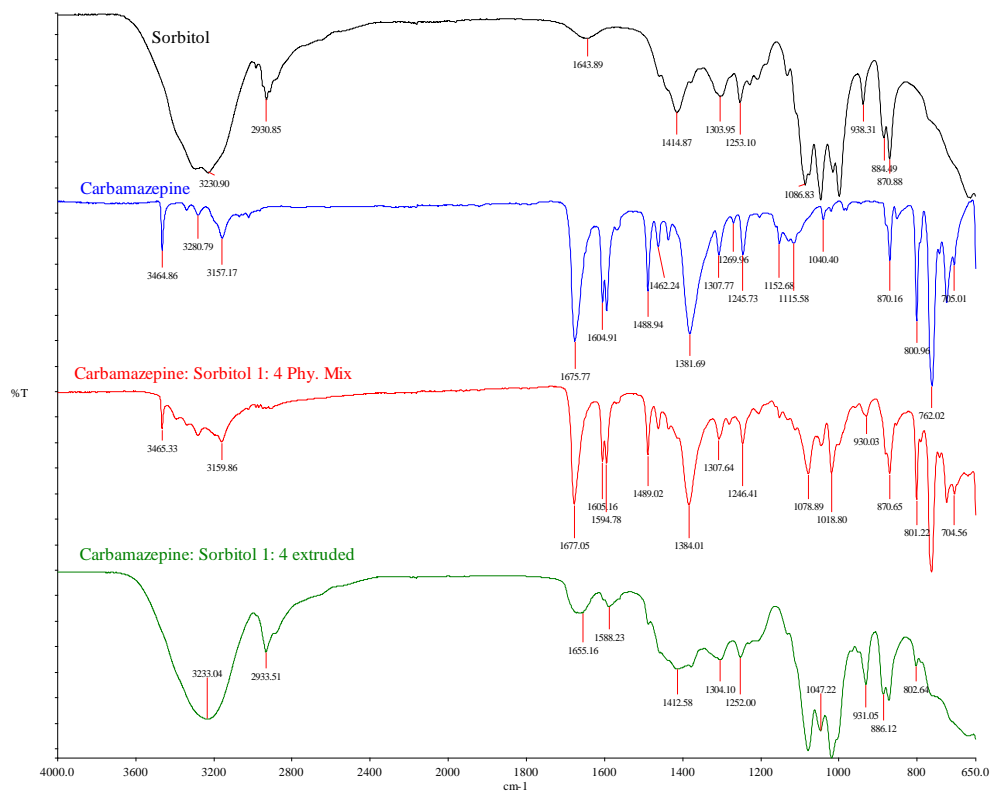


Figure 6-10: b) An overlay of FTIR spectra of Carbamazepine, Sorbitol, physical mixture (Phy. Mix) and extruded formulations in ratio 1:4.

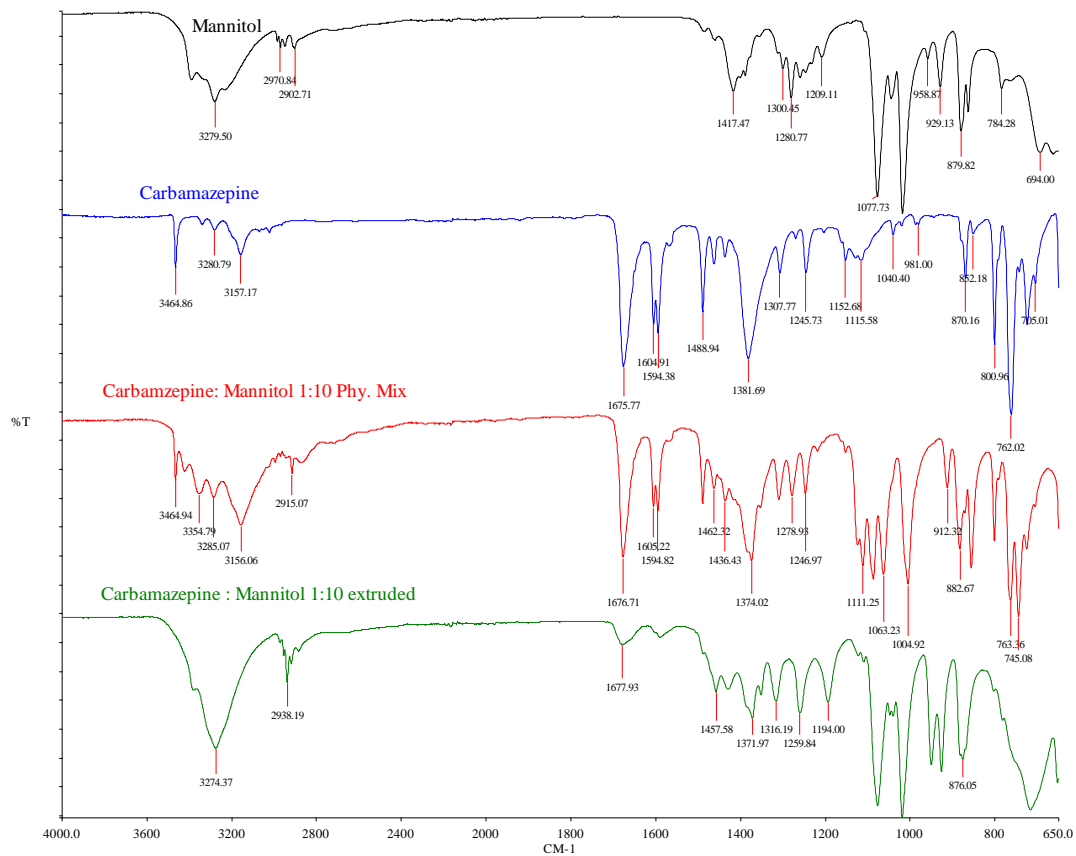


Figure 6-11 a) An overlay of FTIR Spectra of Carbamazepine, Mannitol, physical mixture (Phy. Mix) and extruded formulations in ratio 1:10.

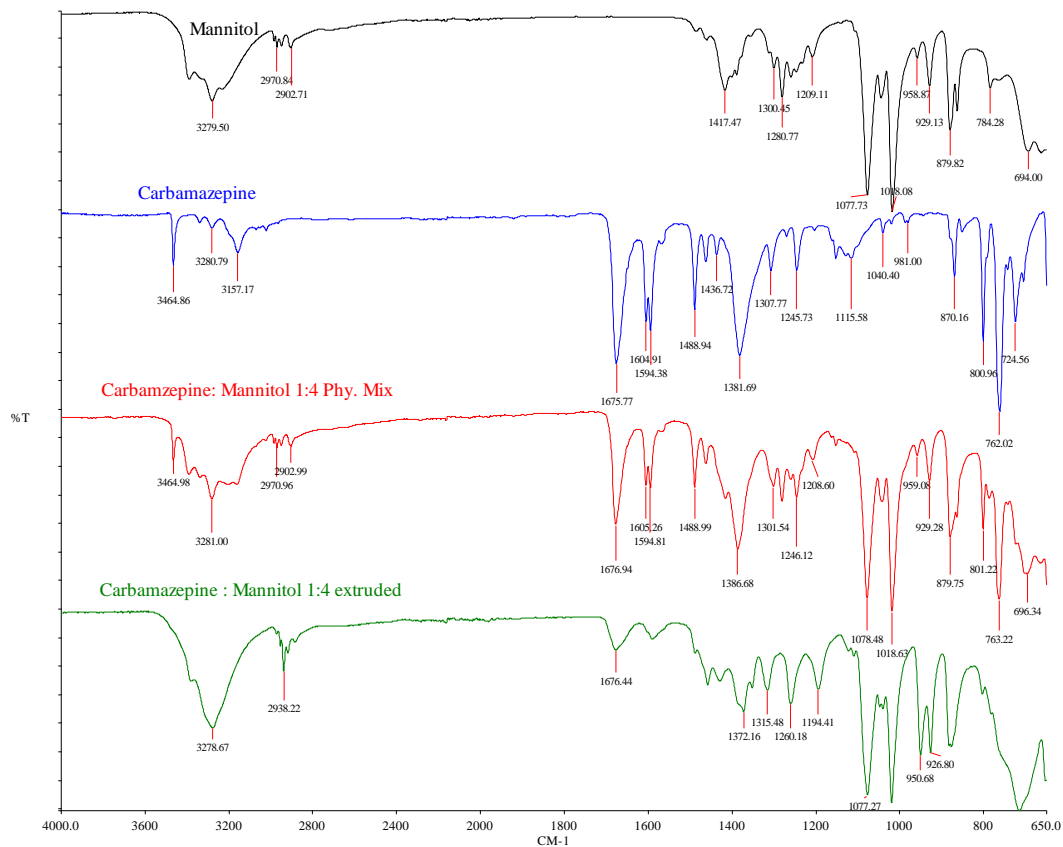


Figure 6-11 b) An overlay of FTIR Spectra of Carbamazepine, Mannitol, physical mixture (Phy. Mix) and extruded formulations in ratio 1:4.

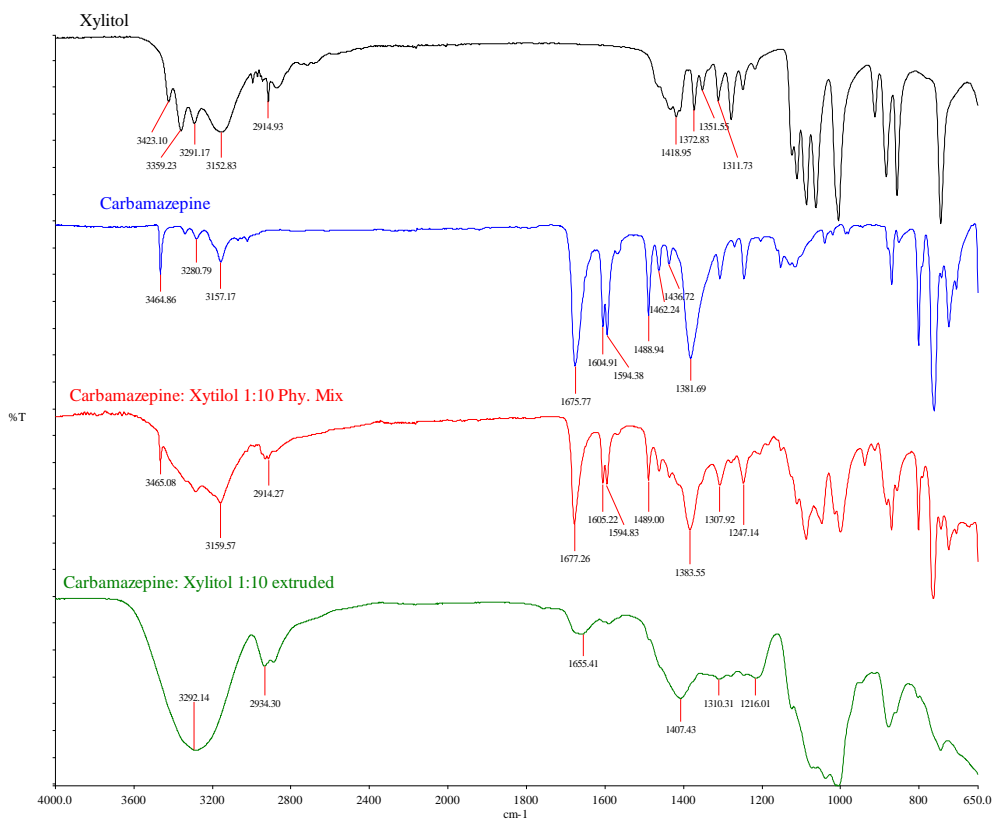


Figure 6-12: a) An overlay of FTIR Spectra of Carbamazepine, Xylitol, physical mixture (Phy. Mix) and extruded formulations in ratio 1:10.

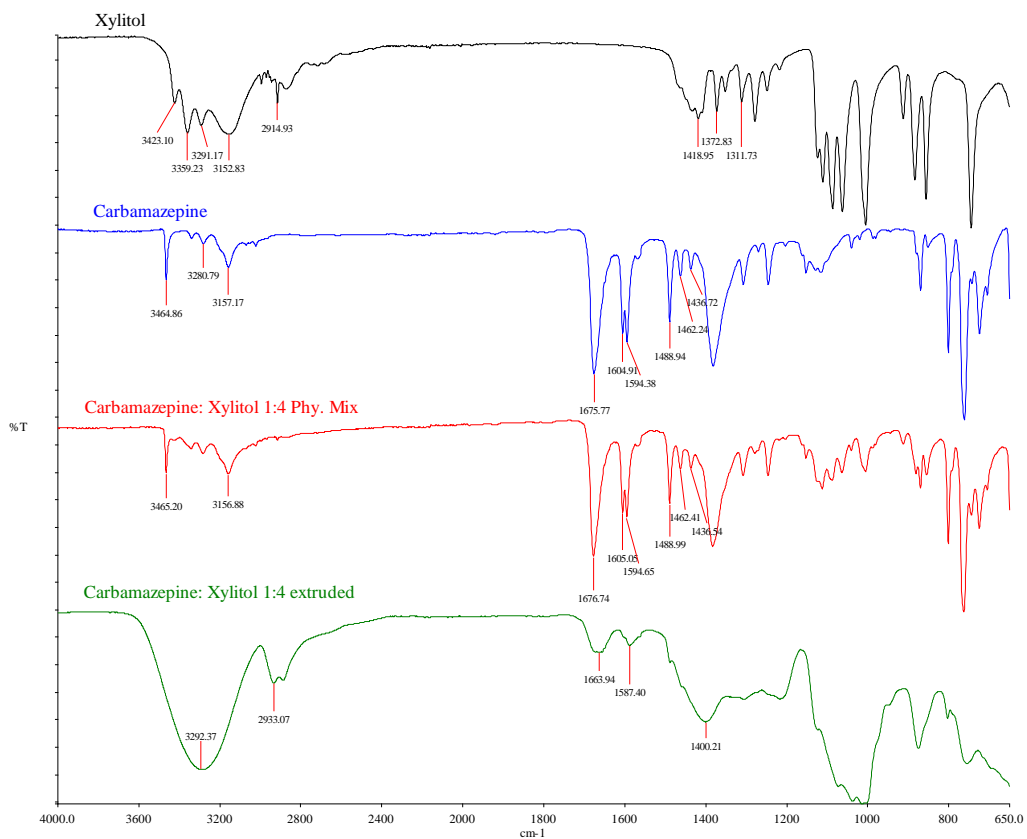


Figure 6-12: b) An overlay of FTIR Spectra of Carbamazepine, Xylitol, physical mixture (Phy. Mix) and extruded formulations in ratio 1:4.

6.5.6. IN VITRO DRUG RELEASE PROPERTIES OF SOLID DISPERSIONS

The dissolution media adopted by the pharmacopeias or recommended by FDA for *in vitro* drug release studies are designed to maximize drug release (69). Thus, the recommended medium for a given marketed drug becomes the quality control standard to ensure that batch-to-batch consistency and continuing product quality and performance are maintained regardless of changes in the manufacturing process.(70) The recommended media for *in vitro* dissolution testing can guide formulation development. It typically does not discriminate between formulation ingredients because a poorly soluble drug's release is usually affected more by the medium than the formulation ingredients. Discriminatory dissolution profiles are highly desirable for distinguishing between products with different pharmaceutical attributes (e.g., formulation or manufacturing process differences) for poorly soluble drugs (70). There are some examples in the literature on selection of discriminatory dissolution medium for CBZ. Therefore, 900 ml with 0.5 % SLS ml as the dissolution medium at 37 °C, USP type II apparatus and the paddle rotation speed of 75 rpm was selected for study.

Sugar alcohols (Mannitol, Sorbitol, and Xylitol) used in this investigation are readily soluble in an aqueous media. Upon exposure of these systems to an aqueous medium, the sugar rapidly dissolved and complete wetting of the drug occurred (64). During extrusion of sugars with CBZ mixtures, the crystalline form of the model drug, CBZ converted to its amorphous form, which is more water soluble. Also, the improvement in the dissolution rate of the drug in the presence of sugar alcohols can be attributed to a state of very fine subdivision attributed to agitation in the extruder.

FDA has set a public standard of f_2 value of '50-100' to indicate similarity between two dissolution profiles (71). Sorbitol formulations did not exhibit statistically significant different release rates at different drug loads (1:10 and 1:4). Mannitol and Xylitol formulations at the two different tested drug loads (1:10 and 1:4) were found to exhibit dissimilar release profile ($f_2 < 50$, Figure 6-14 and 6-15). The release was decreased when CBZ concentration increased in the formulation.

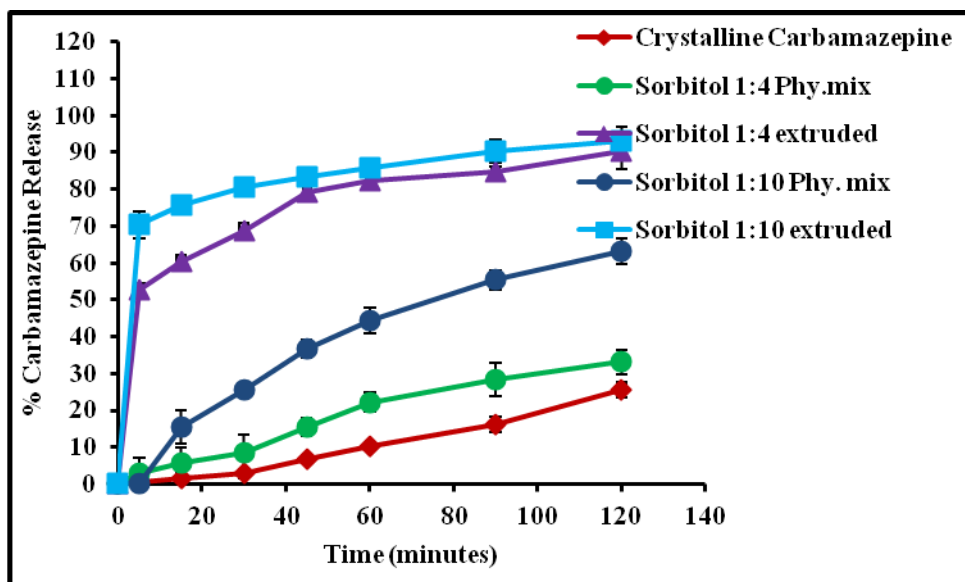


Figure 6-13: Release profile of formulations with Sorbitol in 0.5% SLS.

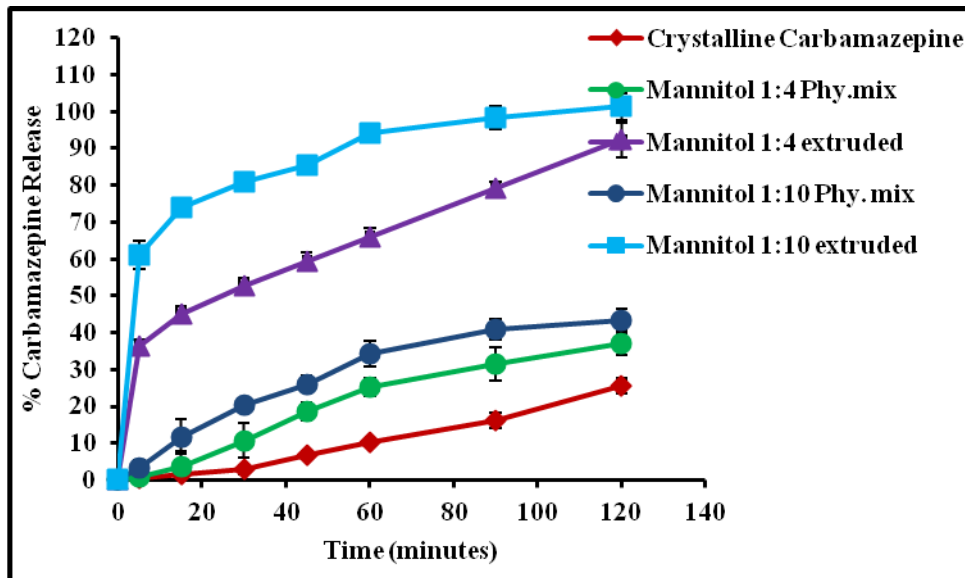


Figure 6-14: Release profile of formulations with Mannitol in 0.5% SLS.

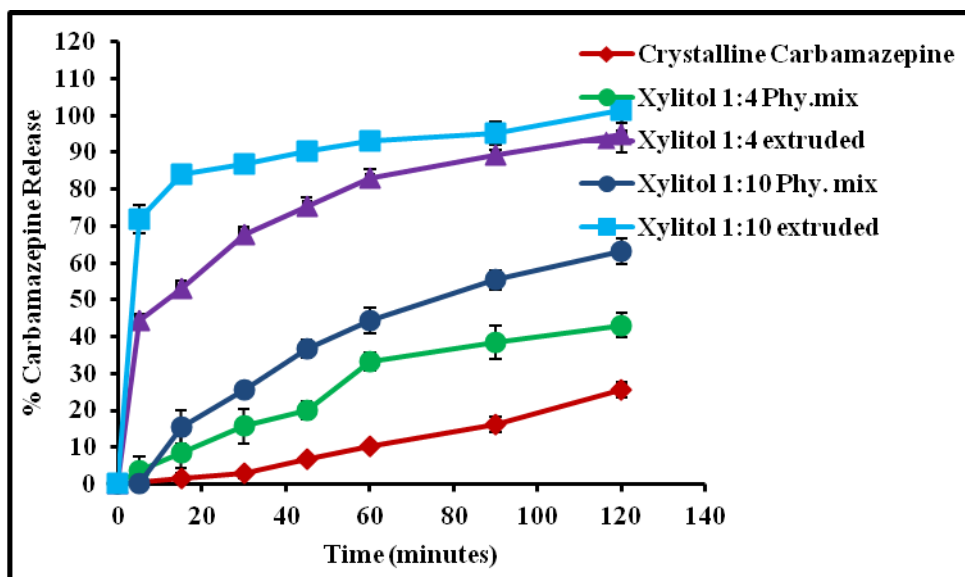


Figure 6-15: Release profile of formulations with Xylitol in 0.5% SLS.

6.5.7. STABILITY STUDIES

The 6 month stability study data for extruded formulations with drug loads (1:10 and 1:4) was stable. The % CBZ content remaining in the pellet formulations was greater than $98.4\% \pm 0.4$ and the drug release profile ($f_2 > 50$) remained unchanged after 6 month storage at $40\text{ }^\circ\text{C}/75\% \text{ RH}$ (Figure 6-16 to 6-18). The stability of the CBZ could be due to intermolecular interactions with sugar alcohols.

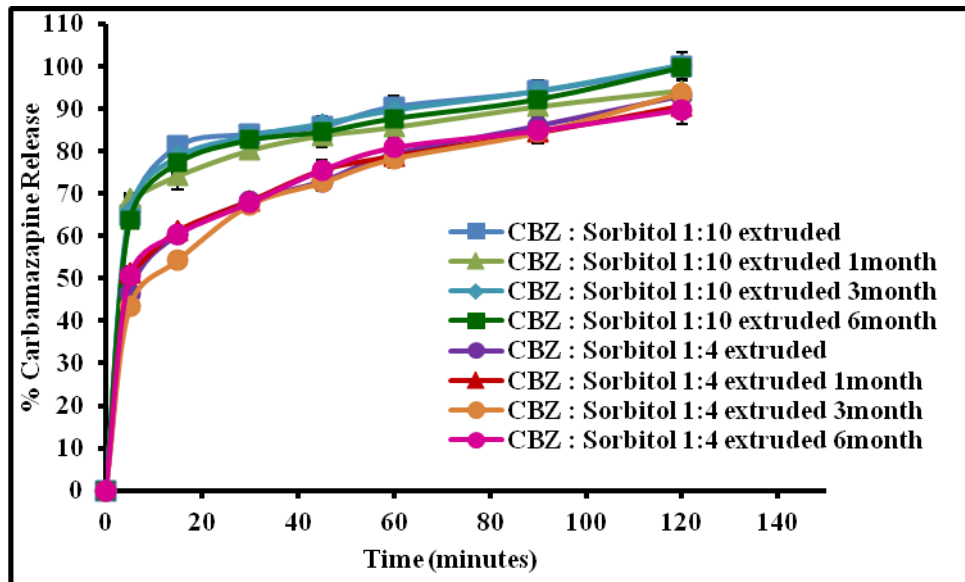


Figure 6-16: Release profiles of hot melt extruded formulations with Sorbitol at the initial, 1, 3 and 6 month time points following storage at 40 °C/75%RH.

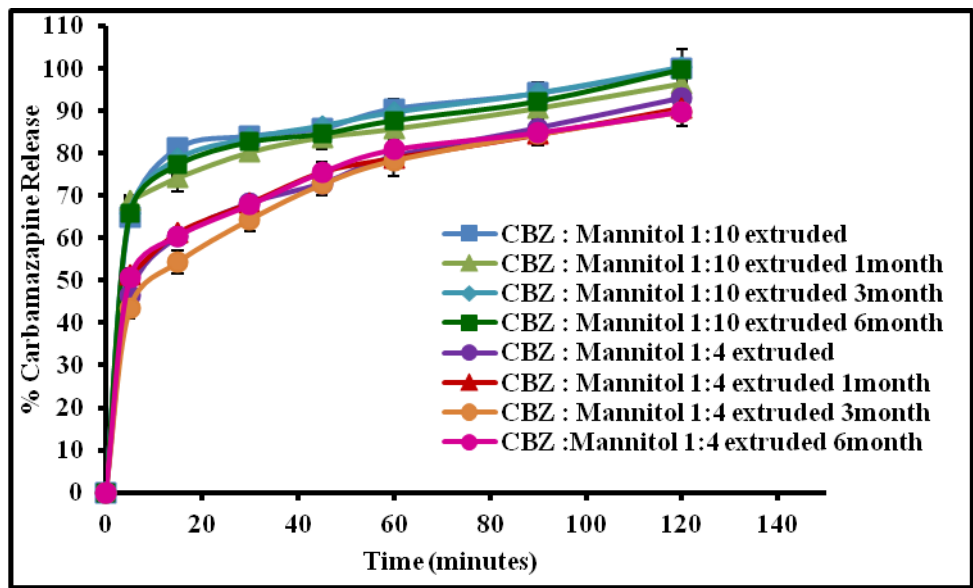


Figure 6-17: Release profiles of hot melt extruded formulations with Mannitol at the initial, 1, 3 and 6 month time points following storage at 40 °C/75% RH.

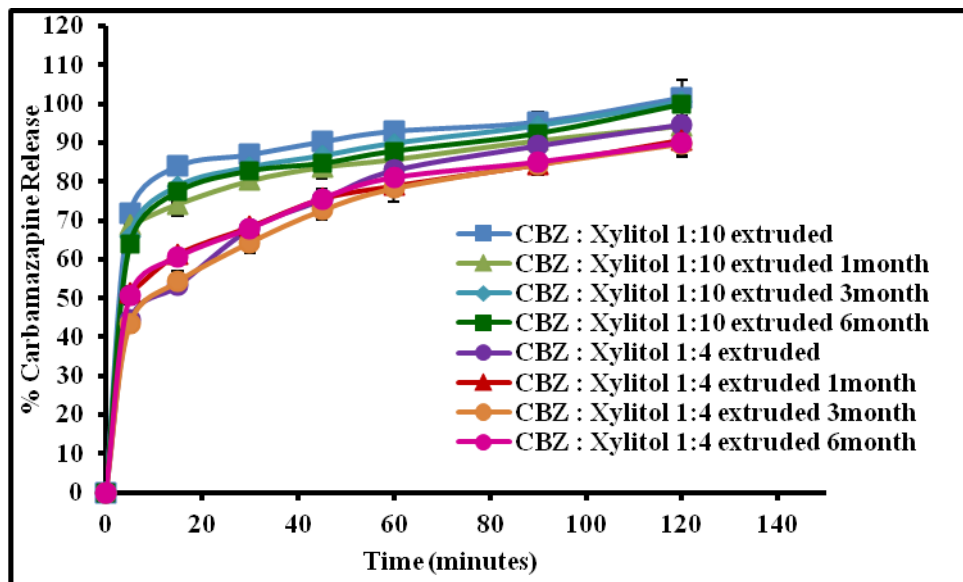


Figure 6-18: Release profiles of hot melt extruded formulations with Xylitol at the initial, 1, 3 and 6 month time points following storage at 40 °C/75%RH.

6.6. CONCLUSION

The hot-melt extrusion process has been proven to be a promising technology for solubility enhancement of poorly water soluble drugs. The present study demonstrates the utility of HME as a method for solubility enhancement of CBZ (a class II BCS drug) using simple GRAS/ FDA approved excipients such as sugar alcohols. Traditionally, sugar alcohols have been utilized as bulking agents, taste-masking agents, and in cosmetic preparations. However, the solubilization potential of sugar alcohols remains largely un-explored. The sugar alcohols (Mannitol, Sorbitol, and Xylitol) investigated in this study proved to be very effective in forming solid dispersions for the BCS class II drug, CBZ. This novel study highlights both the utilization of HME as a process/technology and even more strikingly using sugar alcohols as solubilizers/ carriers to prepare solid dispersions of CBZ for the design of immediate release dosage forms.

CHAPTER - 7

SUSTAINED RELEASE FROM ETHYL CELLULOSE PELLETS WITH LIPID BASED PROCESSING AIDS UTILIZING MELT EXTRUSION

7.1. ABSTRACT

The aim of this study was to investigate the efficiency of lipid based processing aids on an ethyl cellulose polymer in terms of their glass transition temperatures (T_g). Ethyl cellulose (EC) was plasticized with Stearic acid, Trimyristin and Tristearin at different concentration levels (10 to 30% w/w). A significant decrease in T_g of the plasticized polymer was observed, which functioned as an indicator of plasticizing efficiency. The drug release rate was dependent on processing aid concentrations in all of the formulations for both of the model compounds, Chlorpheniramine Maleate (CLPM) and Diltiazem Hydrochloride (DTZ). All of the processing aid decreased the T_g of EthocelTM, which facilitated the extrusion process. With addition of Stearic acid (10% w/w), the T_g of the EC matrix decreased from 132.6 ± 2.5 °C to 125.4 ± 1.7 °C. The pellets containing 10%w/w Stearic acid demonstrated desired sustained release profiles according to USP requirements for both model compounds with 45-51 % release in 6 to 8 hours in simulated intestinal fluid. Tristearin and Trimyristin at concentrations of 10%w/w also demonstrated desired release profiles. The drug release increased with an increase in concentration of lipid based processing aids from EC matrices.

Keywords: Ethylcellulose, EC matrix, Lipid based processing aids, Stearic Acid, Tristearin, Trimyristin.

7.2. INTRODUCTION

Ethocel™ (EC) polymers (ethylcellulose ethers) are a family of inert hydrophobic polymers that have been used as a coating material for tablets and granules, as a tablet binder, in the preparation of microcapsules and microspheres, and as a film/matrix forming material for controlled release formulations (33). Ethocel™ polymers are usually dissolved in an organic solvent during the preparation of the dosage form. Ethocel™ is a good candidate for extrusion as well because it exhibits thermoplastic behavior at temperatures above its glass transition temperature ($T_g = 129\text{--}133\text{ }^\circ\text{C}$) (72). Typically, plasticizers are added to polymers to reduce their T_g and therefore permit processing at lower temperatures (73).

Hot melt extrusion (HME) technology has recently gained significant importance in the pharmaceutical industry for the development of immediate and sustained release dosage forms (pellets, tablets) (1). Its advantages over conventional techniques for manufacturing of sustained release dosage forms (e.g. coating, compression) is the continuity of the extrusion technique as the different process steps (mixing, melting, homogenizing and shaping) are carried out on a single machine with no solvents necessary (74). Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics (75). In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00 mm (14). The objective of this project was to optimize the level of processing aids within EC matrices utilizing melt extrusion techniques for the sustained release (> 8 hours) of the model bioactives, Chlorpheniramine maleate (CLPM) and Diltiazem Hydrochloride (DTZ).

These model bioactives have high aqueous solubility of 160 mg/ml and 590 mg /ml at 25 °C, respectively (76-77).

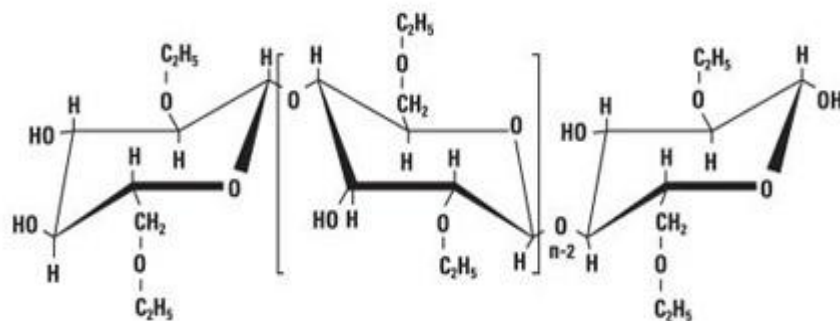


Figure 7-1: Structure of Ethocel™ (Ethylcellulose).

7.2. MATERIALS

Trimyristin (Dynasan[®] 114) and tristearin (Dynasan[®] 118), monoacid triglycerides, were used in the powdered form as received from Sasol North America Inc. (Witten, Germany).

Ethocel™ 7FP was kindly gifted by The Dow Chemical Company, Midland, MI. Chlorpheniramine Maleate and Stearic Acid were obtained from MP Biomedical, LLC (Solon, Ohio). Diltiazem Hydrochloride was purchased from Hawkins Inc., Minneapolis, MN.

7.3. METHODS

7.3.1. MANUFACTURE OF MELT EXTRUDED PELLETS

EC was geometrically diluted and blended with CLPM and DTZ at 10 % w/w and 30 % w/w, respectively. The blends were manually fed through a hopper into an extruder (16 mm Prism Euro Lab, Thermo Fisher Scientific, Staffordshire UK).and processed at temperatures between 110 and 150 °C. The screw speed was set to a 50 rpm, while torque remained below 50-60 Newton, and the pressure was maintained at 60 PSI. The formulation strands were manually collected, and stored at 4 °C. These strands were cut into pellets of 1 mm length using the pelletizer (Chapter 1, Figure 1-6) and filled in capsules.

7.3.2. PLASTICIZATION EFFICIENCY: THERMAL ANALYSIS OF PHYSICAL MIXTURES

DSC thermograms (n = 3) of samples were analyzed using a two step method: Initial heating step at 10 °C/min. followed by cooling at 40 °C/min. and a second heating at 10 °C/min. after cooling the samples. EC was blended with Stearic acid, Trimyristin or Tristearin in 3 levels (10%, 20%

& 30% w/w) and analyzed using DSC for plasticization efficiency. EC blend with CLPM (10% w/w) and DTZ (30% w/w) with and without lipid based processing aids were also analyzed.

7.3.3. DRUG-POLYMER BINDING STUDY

A stock solution of DTZ and CLPM in phosphate buffer pH 6.8 (0.1 mg/ml) was prepared, and aliquots of 50 ml were filled into Erlenmeyer beakers. Increasing increments of EC (0, 10, 20, 40, 60 mg) were added to the beakers, and the suspensions were incubated at 37 °C in an Innova 4300 Incubator Shaker (New Brunswick Scientific Co., Edison, NJ) at 100 rpm. The sample of 1ml were withdrawn, centrifuged, filtered, and analyzed for drug content after 24 hours. Analysis was performed in triplicate (78).

7.3.4. FOURIER TRANSFORM INFRARED (FTIR) SPECTROSCOPIC ANALYSIS

FTIR studied were done to detect the possible interactions between the EC and with Stearic acid, Trimyristin and Tristearin in the HME pellets. The spectra were analyzed for the absence or shift in the wave numbers of the characteristic peaks and reported.

7.3.5. *IN VITRO* RELEASE STUDIES

The pellets were weighed to 160 mg with formulations of CLPM and filled in size zero capsules. The pellets were weighed to 400 mg with formulations of DTZ and filled in size one capsules. These capsules were used for in vitro release studies, performed according to USP 31, using a type II apparatus. The dissolution medium consisted of 500 mL pH 6.8 (simulated intestinal fluid) and pH 1.2 (simulated gastric fluid) with temperature maintained at 37± 0.5 °C. The paddle rotation speed was set at 100 rpm. At predetermined intervals, a 2.0 ml volume samples were removed and centrifuged using an accuSpin TM 3R refrigerated benchtop centrifuge (Fisher Scientific, Pittsburgh, PA) at a speed of 10,000 rpm for 10 minutes at 37 °C. The clear

supernatant was then transferred into vials and injected onto HPLC (Waters Corporation, Milford, MA) and analyzed for CLPM and DTZ.

7.3.6. MODEL DRUG ASSAY

The DTZ concentration in the dissolution medium at each sampled time point and formulations with EC were analyzed by means of HPLC (Waters Inc., Milford, MA). An aliquot of 20 µl was injected onto a C18-reversed phase column (Symmetry Shield C 18 4.6 X 250 mm, particle size 5 µm) and analyzed at a flow rate of 1.0 ml/min using a mixture of phosphate buffer pH 4.0/ acetonitrile/ methanol in a 5:4:1 ratio as mobile phase. The drug content was measured at 237 nm with a UV/Visible detector (2489 Water, Waters Inc., Milford, MA), and peaks were integrated using Empower Version 2.0 software (Waters Inc.).

The CLPM concentration in the dissolution medium at each sampled time point and formulations with EC were analyzed by means of HPLC (Waters Inc., Milford, MA). An aliquot of 20 µl was injected onto a C18-reversed phase column (Symmetry Shield C 18 4.6 X 250 mm, particle size 5 µm) and analyzed at a flow rate of 1.0 ml/min using a mixture of phosphate buffer pH 4.2/ acetonitrile at a 3:7 ratio as mobile phase. The drug content was measured at 261 nm.

7.3.7. STABILITY STUDIES

The sample of each pellet formulation were transferred to HDPE bottles and placed inside humidity chambers pre-equilibrated to 25 °C/60% RH and 45 °C/75% RH. At specific time interval during the course of study 6 months, the HDPE bottles assigned for each time point would be removed. The pellet formulations were characterized using *in vitro* release studies.

7.3.7. DATA ANALYSIS

In all the cases, statistical analysis was performed utilizing one-way analysis of variance. A statistically significant difference was considered when $p < 0.05$.

7.4. RESULT AND DISCUSSION

7.4.1. PLASTICIZATION EFFICIENCY OF LIPID BASED PROCESSING AIDS ON EC

Plasticizers are traditionally low molecular weight compounds that are added to polymers to modify their physico-mechanical properties. Plasticizer-polymer compatibility is defined as the ability of the plasticizer to form a homogeneous phase with the polymer without exudation (liquid plasticizers) or crystallization (solid-state plasticizers). The extent of Tg reduction in the presence of a plasticizer can be used as a parameter to assess the plasticization efficiency. The Tg of the EC was reduced from 133.5 ± 0.8 °C to 115.4 ± 2.8 °C at 30% w/w Stearic acid concentration (Figure 7-2). The EC matrix with 10 % w/w CLPM, the Tg was reduced to 110.3 ± 1.3 °C. Trimyristin and Tristearin also demonstrated reduction in Tg of EC with and without CLPM. CLPM has been reported to act as processing aid in HME for HPC and Eudragit® RSPO (79). In the case of EC matrices with 30% w/w DTZ, DTZ did not contribute in reduction of the Tg of EC (Figure 7 3).

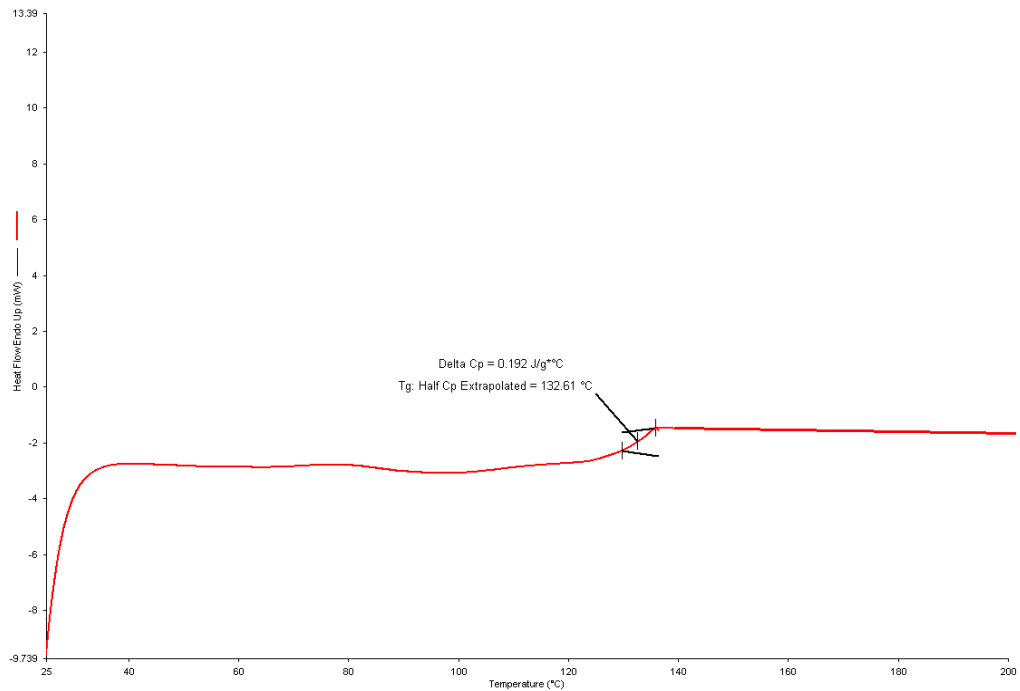


Figure 7-2: Thermogram of second heating cycle of EC. The sample was heated from 25 to 200 °C with a heating rate of 10 °C/min, cooled at 40 °C/min to -10 °C and then heated again 25 to 200 °C with a heating rate of 10 °C/min.

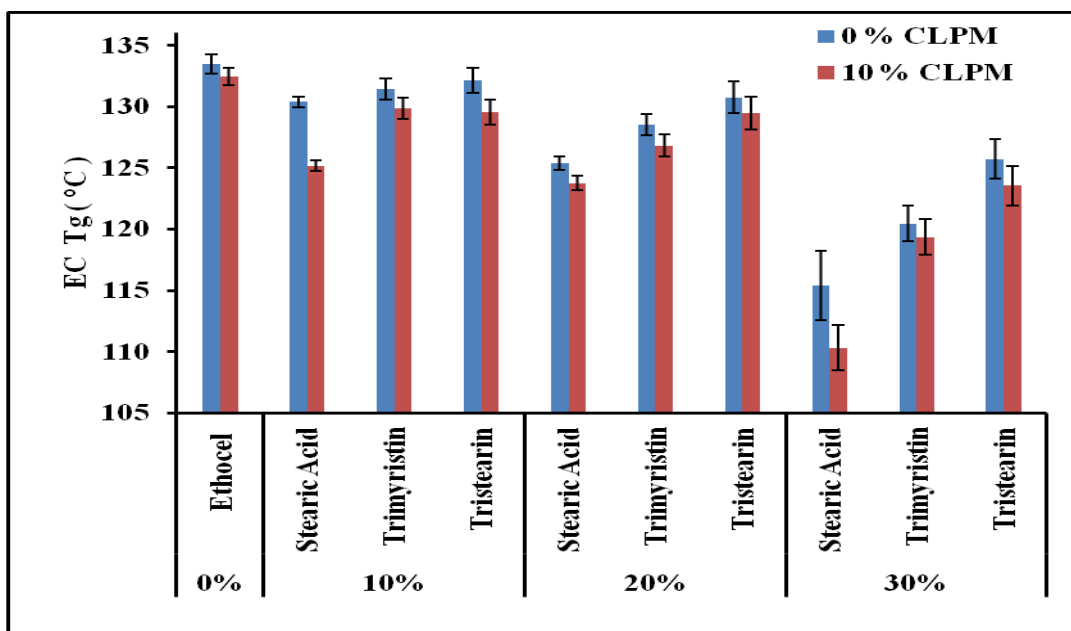


Figure 7-3: The effect of lipid based processing agents and CLPM on the Tg of EC.

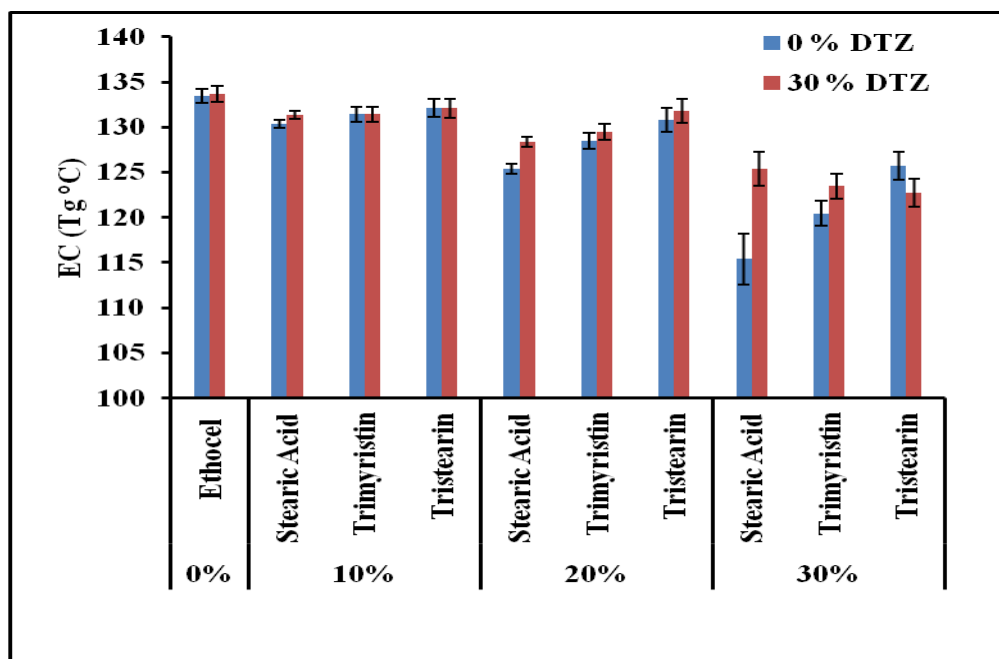


Figure 7-4: The effect of lipid based processing agents and DTZ on the Tg of EC.

7.4.2. DTZ AND CLPM BINDING TO EC

Drug adsorption to the polymeric carrier may account for incomplete drug release from the matrix dosage forms. Within the literature, there has been a report of a complex formation between methacrylates and salts of acidic drugs in phosphate buffer solutions, which was mainly attributed to electrostatic interaction (78). In addition, non-electrostatic binding due to hydrogen bonding or van der Waals forces may lead to adsorption. This study results indicate (Figure 7-1) a statistically insignificant adsorption of DTZ on EC. CLPM demonstrated interaction potential with EC.

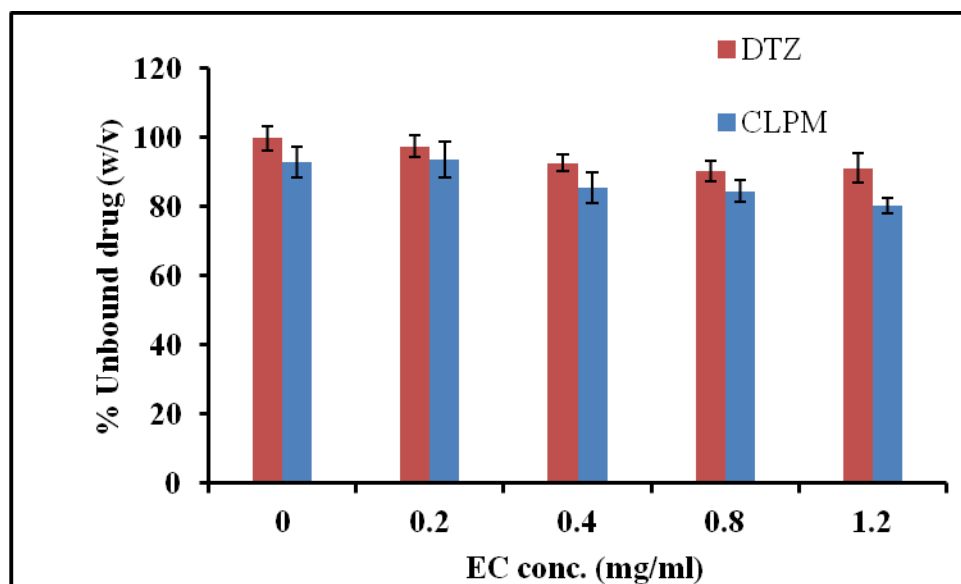


Figure 7-5: Binding of DTZ and CLPM to EC.

7.4.3 FTIR SPECTROSCOPY

The spectrum of EC polymer in Figure 7-6 to 7-8 showed distinct absorption bands at 1052.70 cm^{-1} for $-\text{C}-\text{O}-\text{C}$ stretching vibration in cyclic ether and the asymmetric bands seen around 2869 and 2973 cm^{-1} may be due to the $\text{C}-\text{H}$ stretching (80). The band at 1052.70 cm^{-1} in pure EC and physical mixtures polymer shifted to lower wavenumbers 1030 to 1023 cm^{-1} in HME pellets which is the indication of hydrogen bonding between them. This intermolecular interaction may be the reason in reduction of T_g of EC.

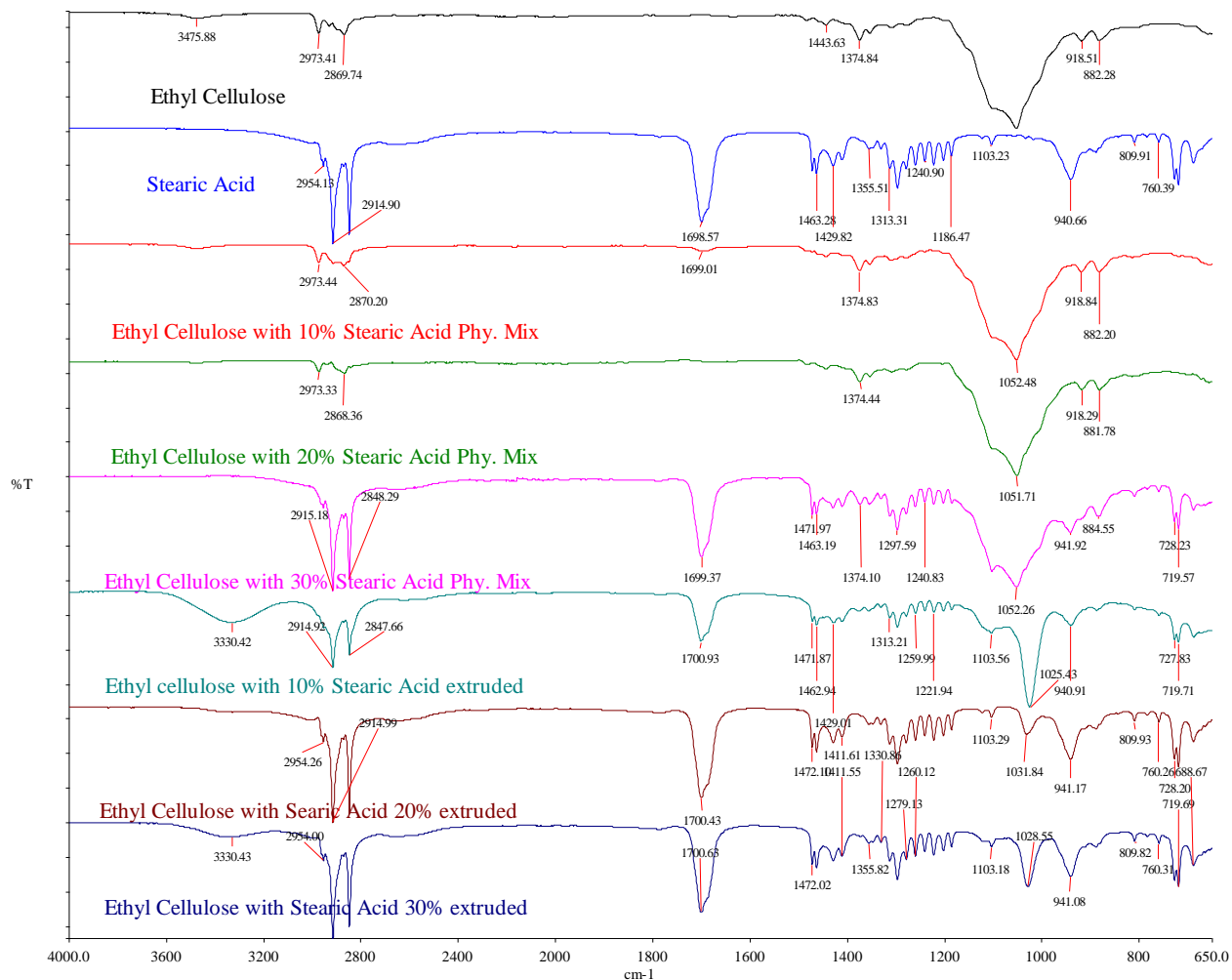


Figure 7-6: An overlay of FTIR spectra of Ethylcellulose, Stearic Acid and Ethylcellulose containing Stearic Acid 10-30 % w/w in physical mixtures (Phy. Mix) and extruded matrix.

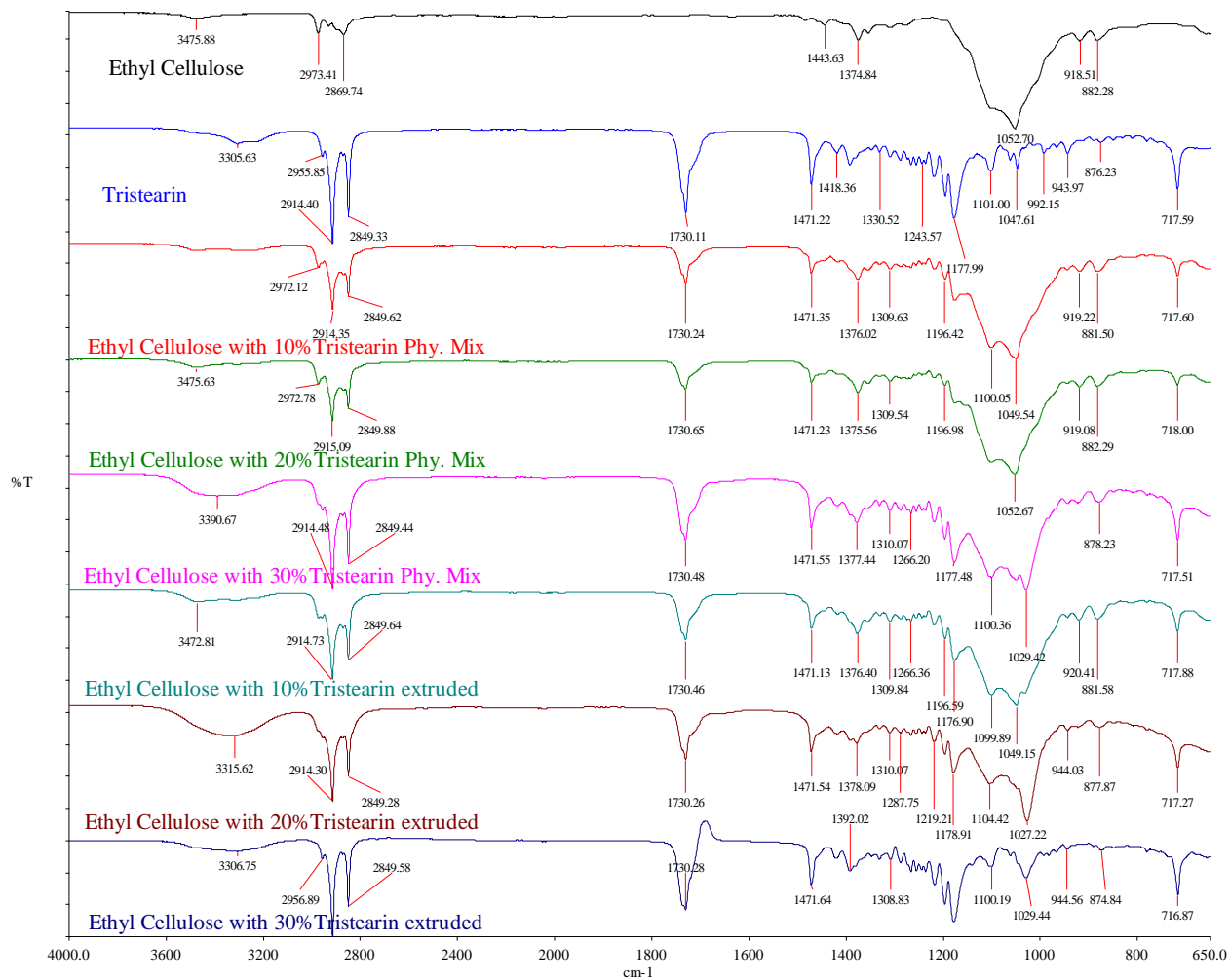


Figure 7-7: An overlay of FTIR spectra of Ethylcellulose, Tristearin and Ethylcellulose containing Stearic Acid 10-30 % w/w in physical mixtures (Phy. Mix) and extruded matrix.

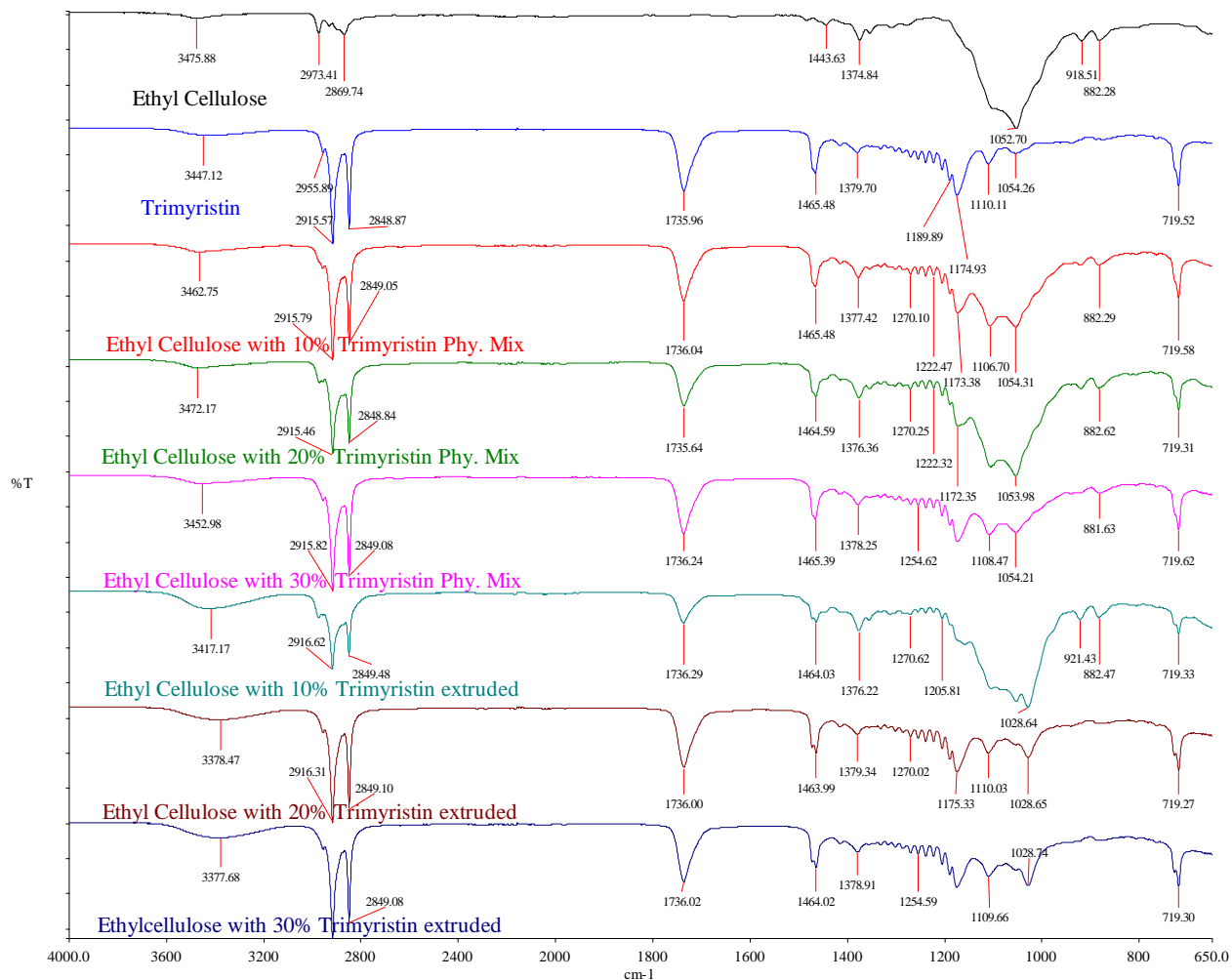


Figure 7-8: An overlay of FTIR spectra of Ethylcellulose, Trimyrustin and Ethylcellulose containing Trimyrustin 10-30 % w/w in physical mixtures (Phy. Mix) and extruded matrix.

7.4.1. RELEASE STUDIES

Sustained release is an outcome of a dissolving drug having to diffuse through a network of channels that exist between compacted polymer particles (81). The drug release rate and mechanisms from matrix-type delivery systems are influenced by a multitude of factors. These include matrix porosity, permeability, swelling behavior and solubility of the polymer, load of soluble compounds in the formulation, drug solubility, drug solid-state and particle size, plasticizer type and level and dosage form geometry and surface area (82). The drug release from

insoluble carrier materials including polymers and lipids is mainly governed by diffusion, which can be understood as a three-step process:

1. Water ingress into the matrix,
2. Drug dissolution and
3. Drug diffusion through the matrix into the dissolution medium.

Each of the steps can be rate controlling, depending on the properties of the matrix. If the polymer swells or dissolves in the dissolution medium, further release mechanisms come into play. Generally, in matrix systems, there are two major factors that control the rate of release of the drug from the matrix. One is the rate of aqueous medium infiltration into the matrix followed by a relaxation process (hydration, gelation or swelling) and the other is the rate of erosion of the matrix (83). As a result of these simultaneous processes, two fronts are evident, a swelling front (glassy polymer / gel interface) and an eroding front (gel /medium interface). The distance between the two fronts (diffusion layer thickness) depends on the relative rates at which the swelling and eroding fronts move in relation to each other. Various mathematical equations were used to evaluate drug release mechanisms from the formulations tested (Figure 7-4 -7-9). The zero order Equation 7-1, describes systems in which the drug release rate is independent of its concentration. The first order Equation 7-2 describes the release from systems where release rate is concentration dependent. The release of drugs from an insoluble matrix can be described as a square root of time dependent process based on Fickian diffusion, Equation (7-3). The mechanism of drug release from matrices containing swellable polymers is complex and not completely understood. Some systems may be classified as either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms (84).

$$Q_t = Q_0 + K_0t \quad \text{Equation 7-1}$$

$$\ln Q_t = \ln Q_0 - k_1.t \quad \text{Equation 7-2}$$

$$Q_t = K.S \sqrt{t} = k_H .\sqrt{t} \quad \text{Equation 7-3}$$

The Korsmeyer–Peppas model is used to analyze drug release from pharmaceutical dosage forms when the release mechanism is not well known or when more than one type of release phenomena is involved. The exponent, termed the release exponent or n value, was studied to characterize different drug release mechanisms (83).

CLPM release kinetics from the pellets

The release profiles of all the formulations in both pH buffers were plotted according to various release kinetic models and correlation coefficient values (r^2) are listed in Table 7-3 and 7-4. The model demonstrating the highest value of r^2 was selected as best fit to explain drug release mechanisms. The formulation with Stearic acid (10% w/w) followed zero order release kinetics. With the increase in concentration of Stearic acid (20-30% w/w), the release profile seem to best fit the first order release kinetics. In 6 hours, 35-45% CLPM and after 10 hours more than 80% CLPM release was observed with pellet formulation in simulated intestinal fluid and simulated gastric fluid with 10%w/w processing aids. In summary, for the lipid processing aids (Stearic acid, Tristearin and Trimyrustin), the 10%w/w levels incorporated in EthocelTM matrices exhibited desired release profiles according to USP requirements for CLPM extended release capsules (Table 7-1). Therefore, for designing successful sustained release of CLPM, the optimum concentration of Stearic acid would be 10% w/w (Figure 7 10a to7 15a). The systems with Trimyrustin (10-30% w/w) followed first order release and the Higuchi model in pH 6.8 (simulated intestinal fluid) and pH 1.2 (simulated gastric fluid). The Higuchi model describes the diffusion of drug from an insoluble matrix. This may indicate diffusion of drug from the EC

matrix is dependent on the concentration gradient. The drug release from the matrix was the result of penetration of dissolution medium through pores or channels and leaching out of the drug. Hence, Trimyristin created these pores or channels and facilitated the drug release. The systems with Tristearin (10–30% w/w) also followed first order release kinetics.

DTZ release kinetics from the pellets

The model demonstrating the highest value of r^2 in Table 7-5 and 7-6 was selected as best fit to explain DTZ release mechanism from all of the formulations. It is observed that DTZ release kinetics from the matrix demonstrates the combination of mechanism is has the highest value of r^2 when fitted to the first order release model. With the increase in concentration of processing aids (20-30% w/w), the release profile demonstrated the highest r^2 (0.998-0.997) value when fitted to Higuchi model. The release was combination of Higuchi and First order model, which indicates the diffusion and erosion of the matrix. In 3 hours, 35-45% DTZ and after 8 hours more than 80% DTZ release was observed with pellet formulation in simulated intestinal fluid and simulated gastric fluid with 10%w/w processing aids (Figure 7 10 b to 7 15 b) . In summary, for the lipid processing aids (Stearic acid, Tristearin and Trimyristin), the 10%w/w levels incorporated in EthocelTM matrices exhibited desired release profiles according to USP requirements for DTZ extended release capsules (Table 7-2).

Table 7-1: USP requirements for CLPM extended release capsule formulation.

Time (Hours)	Amount Dissolved
1.5	Between 15 % and 40 %
6	Between 50 % and 80 %
10	Not less than 70 %

Table 7-2: USP requirements for DTZ extended release capsule formulation.

Time (Hours)	Amount Dissolved
1	Not more than 15 %
3	Between 45 % and 70 %
8	Not less than 80 %

Table 7.3: Dissolution kinetics of pellets with CLPM 10 % w/w in EC matrix in pH 6.8 buffer.

Formulations		Zero order	First Order	Higuchi Model	Peppas–Korsmeyer	
		r ²	r ²	r ²	r ²	n
Stearic Acid	10%	0.998	0.989	0.947	0.962	1.250
	20%	0.991	0.994	0.978	0.987	0.124
	30%	0.949	0.984	0.984	0.949	0.323
Trimyristin	10%	0.988	0.995	0.984	0.994	0.171
	20%	0.964	0.987	0.994	0.969	0.291
	30%	0.952	0.983	0.992	0.966	0.347
Tristearin	10%	0.971	0.998	0.993	0.986	0.210
	20%	0.946	0.999	0.996	0.983	0.342
	30%	0.943	0.985	0.995	0.973	0.392

Table 7-4: Dissolution kinetics of pellets with CLPM 10 % w/w in EC matrix in pH 1.2 buffer.

Formulations		Zero order	First Order	Higuchi Model	Peppas–Korsmeyer	
		r ²	r ²	r ²	r ²	n
Stearic Acid	10%	0.992	0.979	0.973	0.962	0.082
	20%	0.986	0.996	0.986	0.991	0.211
	30%	0.937	0.993	0.995	0.976	0.445
Trimyristin	10%	0.936	0.995	0.993	0.967	0.281
	20%	0.918	0.994	0.988	0.956	0.352
	30%	0.884	0.997	0.980	0.954	0.528
Tristearin	10%	0.936	0.996	0.997	0.993	0.384
	20%	0.963	0.915	0.994	0.969	0.417
	30%	0.883	0.972	0.979	0.947	0.536

Table 7-5: Dissolution kinetics of pellets with DTZ 10 % w/w in EC matrix in pH 6.8 buffer.

Formulations		Zero order	First Order	Higuchi Model	Peppas–Korsmeyer	
		r ²	r ²	r ²	r ²	n
Stearic Acid	10%	0.975	0.993	0.981	0.985	0.123
	20%	0.966	0.997	0.998	0.989	0.270
	30%	0.945	0.992	0.992	0.973	0.372
Trimyristin	10%	0.989	0.999	0.984	0.993	0.204
	20%	0.952	0.987	0.986	0.944	0.338
	30%	0.955	0.982	0.995	0.979	0.379
Tristearin	10%	0.965	0.999	0.996	0.996	0.259
	20%	0.961	0.997	0.997	0.973	0.300
	30%	0.935	0.998	0.993	0.993	0.403

Table 7-6: Dissolution kinetics of pellets with DTZ 10 % w/w in EC matrix in pH 1.2 buffer.

Formulations		Zero order	First Order	Higuchi Model	Peppas–Korsmeyer	
		r ²	r ²	r ²	r ²	n
Stearic Acid	10%	0.979	0.995	0.978	0.974	0.121
	20%	0.954	0.995	0.996	0.961	0.306
	30%	0.955	0.992	0.993	0.968	0.375
Trimyristin	10%	0.991	0.997	0.981	0.964	0.195
	20%	0.965	0.992	0.991	0.971	0.335
	30%	0.955	0.979	0.995	0.991	0.390
Tristearin	10%	0.951	0.995	0.996	0.969	0.336
	20%	0.928	0.998	0.994	0.982	0.435
	30%	0.912	0.974	0.989	0.967	0.551

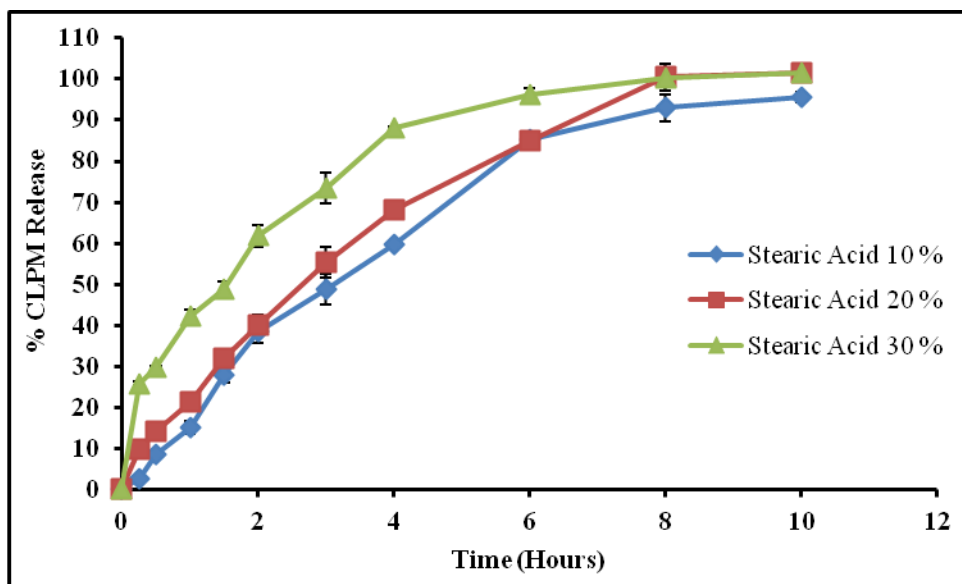


Figure 7-9 a: Release profiles of CLPM from EC pellets with Stearic acid in pH 1.2 buffer.

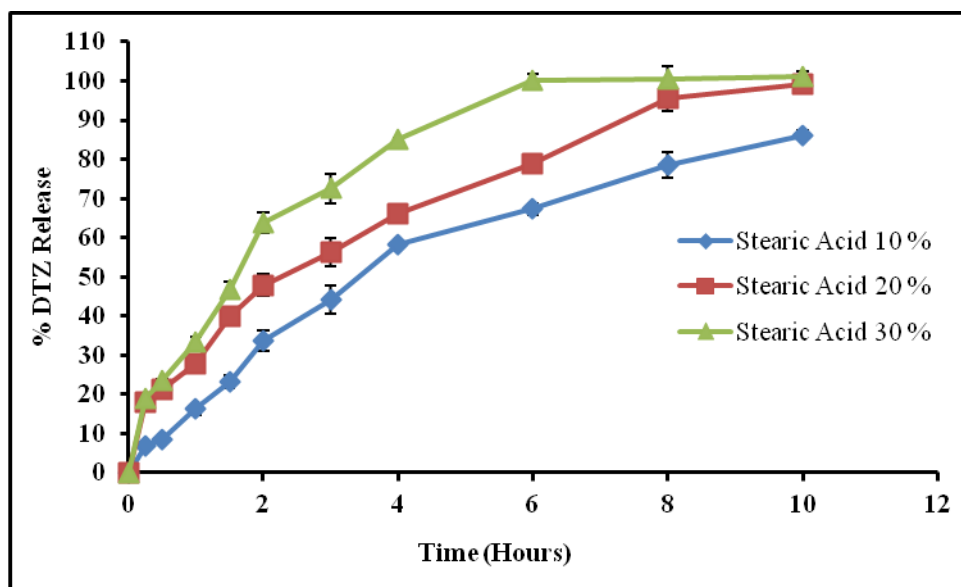


Figure 7-9 b: Release profiles of DTZ from EC pellets with Stearic acid in pH 1.2 buffer.

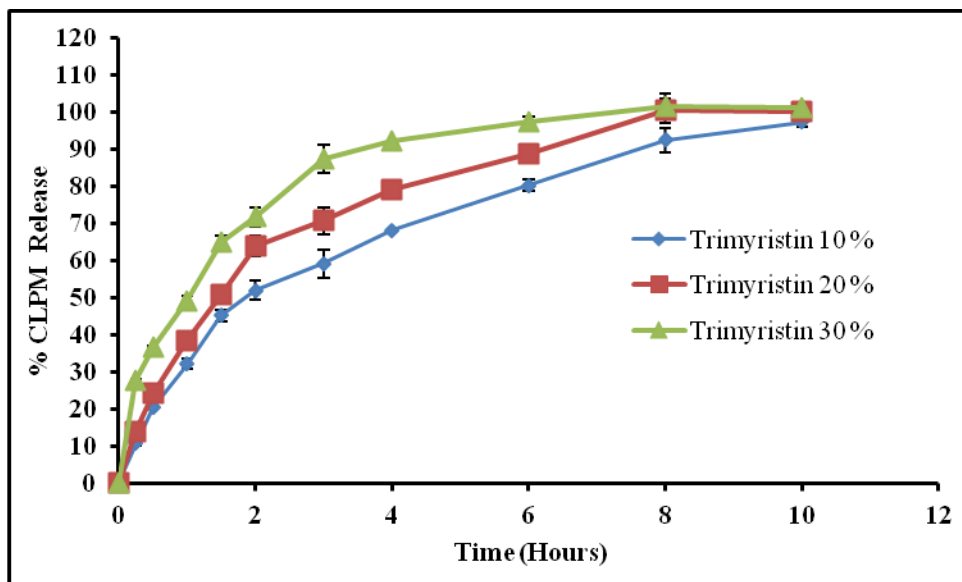


Figure 7-10 a: Release profiles of CLPM from EC pellets with Trymyristin in pH 1.2 buffer.

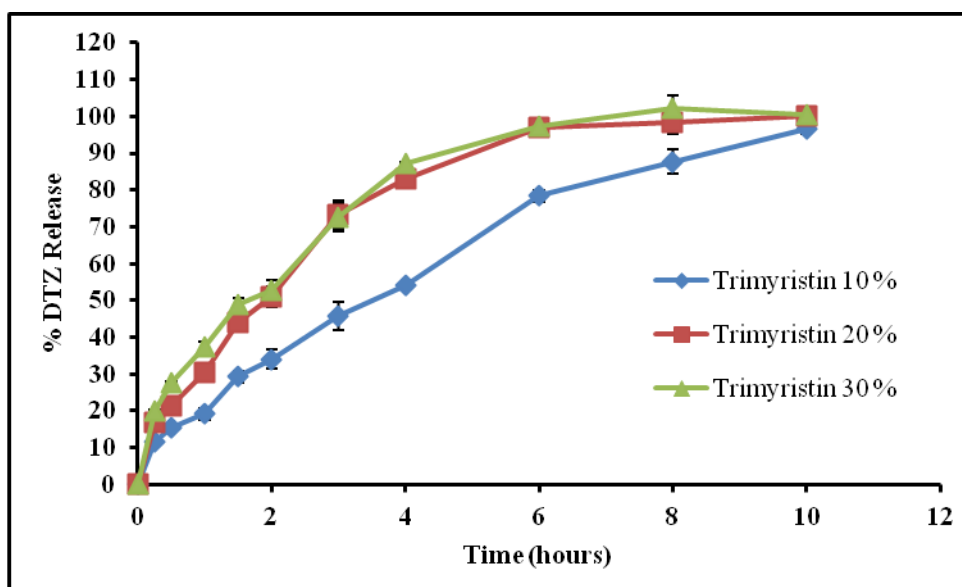


Figure 7-10 b: Release profiles of DTZ from EC pellets with Trymyristin in pH 1.2 buffer.

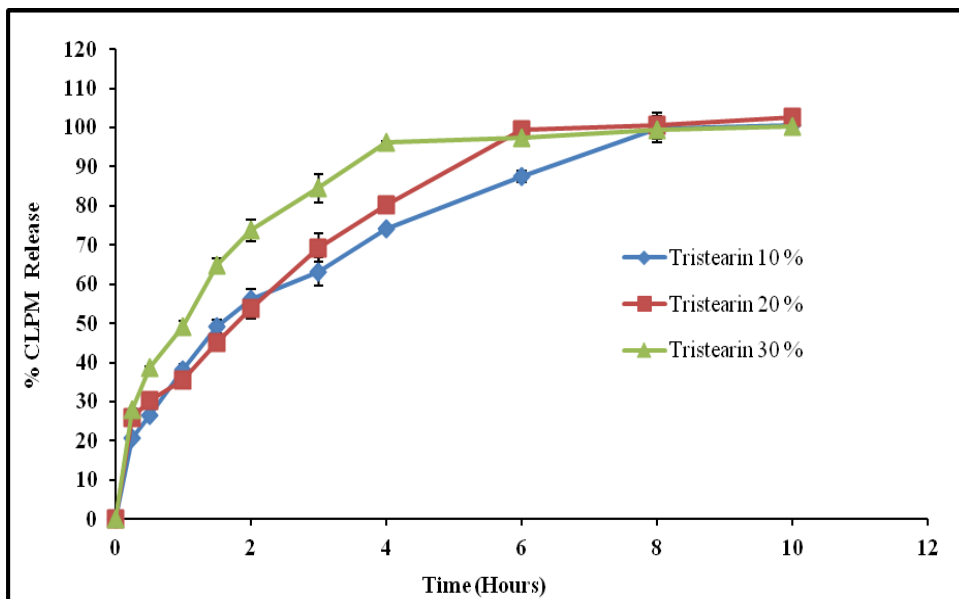


Figure 7-11 a: Release profiles of CLPM from EC pellets with Tristearin in pH 1.2 buffer.

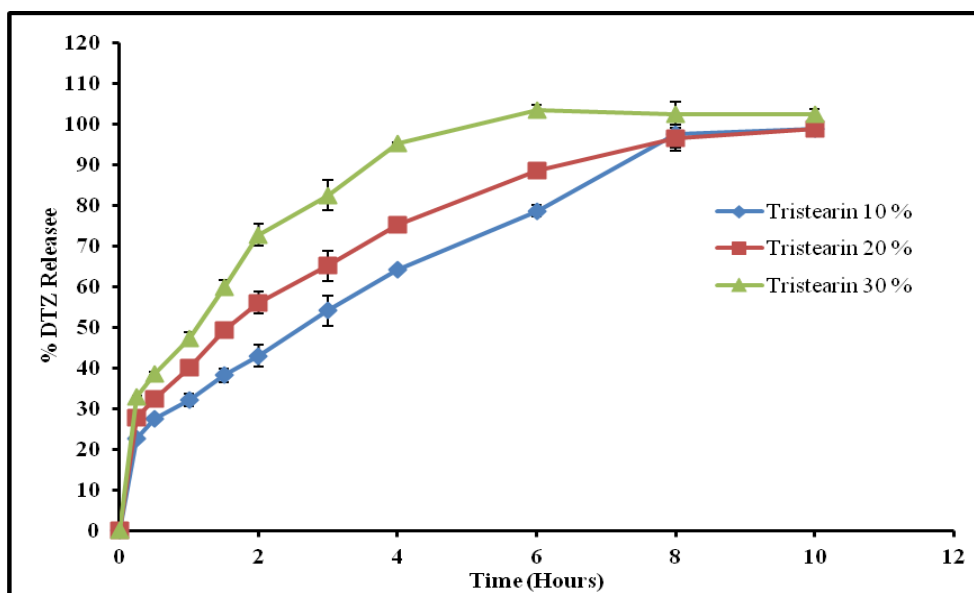


Figure 7-11 b: Release profiles of DTZ from EC pellets with Tristearin in pH 1.2 buffer.

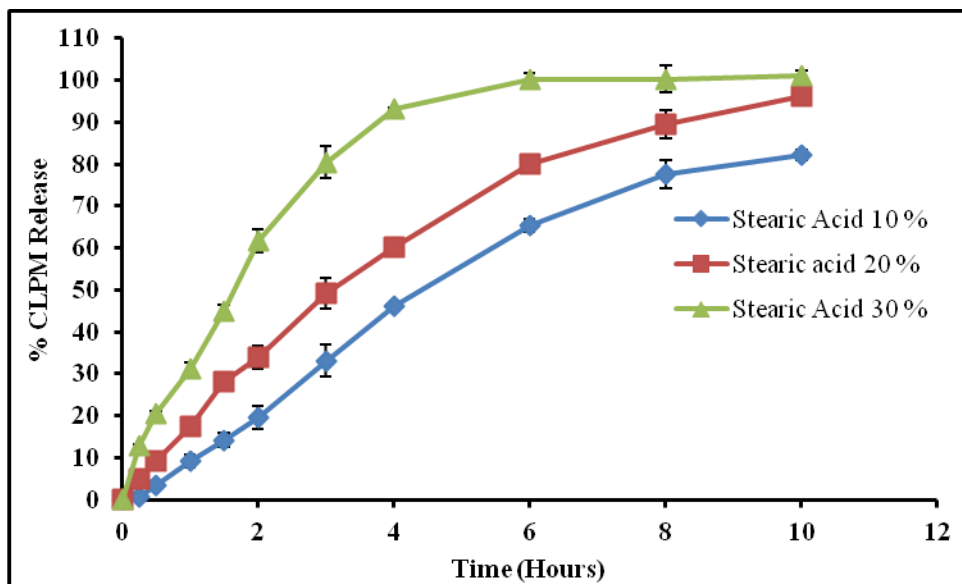


Figure 7-12 a: Release profiles of CLPM from EC pellets with Stearic acid in pH 6.8 buffer.

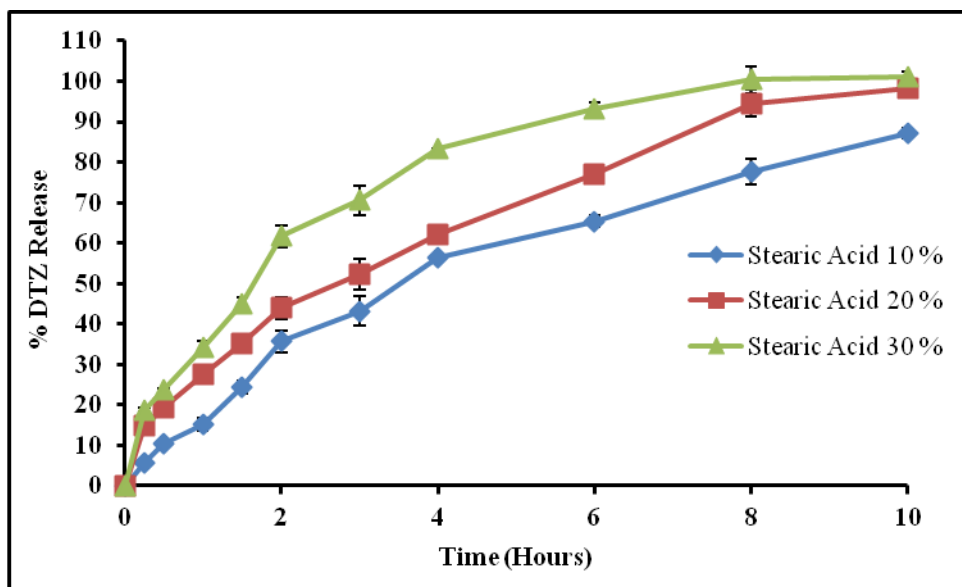


Figure 7-12 b: Release profiles of DTZ from EC pellets with Stearic acid in pH 6.8 buffer.

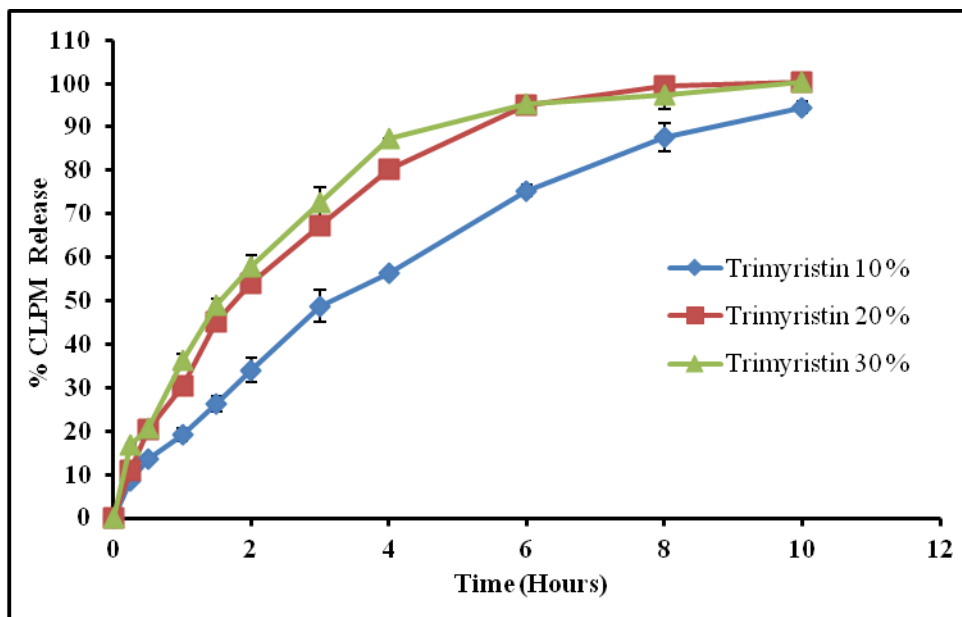


Figure 7-13 a: Release profiles of CLPM from EC pellets with Trimyristin in pH 6.8 buffer.

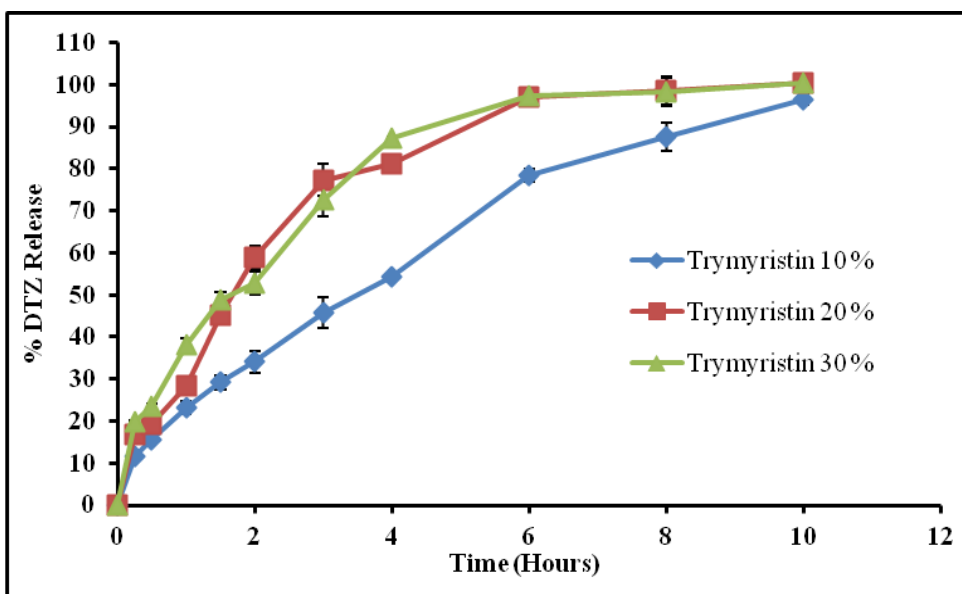


Figure 7-13 b: Release profiles of DTZ from EC pellets with Trimyristin in pH 6.8 buffer.

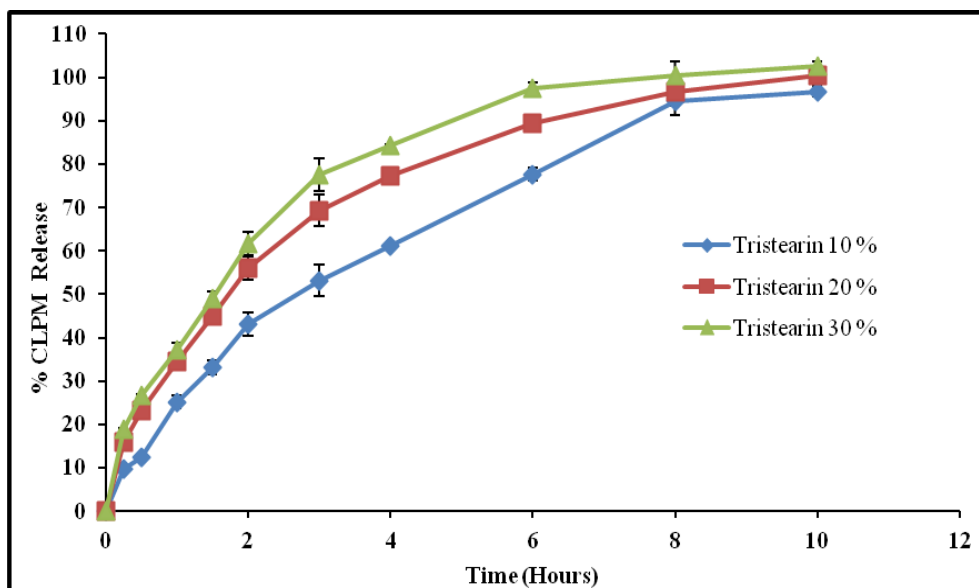


Figure 7-14 a: Release profiles of CLPM from EC pellets with Tristearin in pH 6.8 buffer.

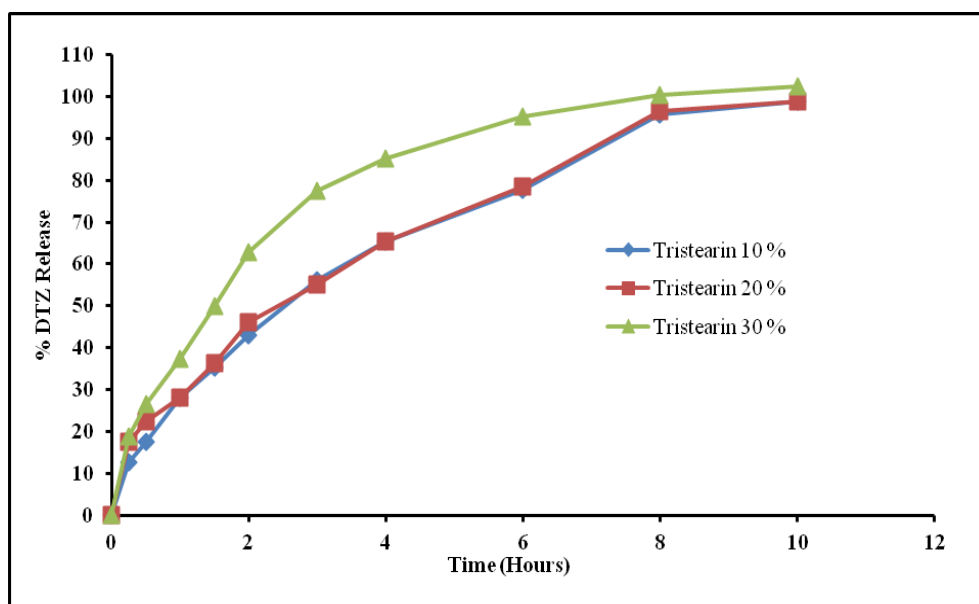


Figure 7-14 b: Release profiles of DTZ from EC pellets with Tristearin in pH 6.8 buffer.

7.5. CONCLUSION

Sustained release matrix pellets could be successfully prepared by hot-melt extrusion when plasticized EC was employed as the matrix material. Lipid based processing aids efficiently lowered the required processing temperatures, by reducing Tg of EC and melt viscosity. Stearic acid demonstrated superior plasticization efficiency. Trimyristin and Tristearate were investigated for the first time as processing aids. With 10% w/w incorporated into EC matrices, the desired release profiles of the model drugs were achieved. With addition of Stearic acid (10% w/w), the Tg of the EC matrix decreased from 132.6 ± 2.5 °C to 125.4 ± 1.7 °C. The pellets containing 10% w/w Stearic acid demonstrated desired sustained release profiles according to USP requirements for both model compounds with 45-51% release in 6 to 8 hours in simulated intestinal fluid. Tristearin and Trimyristin at concentrations of 10% w/w also demonstrated desired release profiles. The drug release increased with an increase in concentration of lipid based processing aids from EC matrices. CLPM also reduced the Tg of EC whereas DTZ did not exhibit a significant effect on the Tg of polymeric matrix. The present study demonstrated utilization of HME as viable technique for development of sustained or extended release formulations utilizing lipid based processing aids plasticized EC matrices.

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