การประเมินสภาพผสมเข้ากันได้ระหว่างอีฟาวิเรนซ์กับพอลิเมอร์สำหรับการเตรียมสารละลายของแข็งโดยการอัดรีดแบบหลอมร้อน

นายสรณัฐ เชษฐสุรกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาวิทยาการเภสัชกรรมและเภสัชอุตสาหกรรม
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2555

MISCIBILITY EVALUATION OF EFAVIRENZ AND POLYMERS FOR SOLID SOLUTION PREPARATION BY HOT MELT EXTRUSION

Mr. Sorranut Chetsurakul

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy Program in Industrial Pharmacy
Department of Pharmaceutics and Industrial Pharmacy
Faculty of Pharmaceutical sciences
Chulalongkorn University
Academic Year 2012

Thesis Title	MISCIBILITY EVALUATION OF EFAVIRENZ AND POLYMERS FOR SOLID SOLUTION PREPARATION BY HOT MELT EXTRUSION
By	Mr. Sorranut Chetsurakul
Field of Study	Industrial Pharmacy
Thesis Advisor	Jittima Chatchawalsaisin, Ph.D.
Thesis Co-advisor	Narueporn Sutanthavibul, Ph.D.

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

…..……..…Dean of the Faculty of Pharmaceutical Sciences
(Associate Professor Pintip Pongpech, Ph.D.)

THESIS COMMITTEE

……..Chairman
(Associate Professor Poj Kulvanich, Ph.D.)

…….…….Thesis Advisor
(Jittima Chatchawalsaisin, Ph.D.)

…….. Thesis Co-advisor
(Narueporn Sutanthavibul, Ph.D.)

……..Examiner
(Assistant Professor Walaisiri Muangsiri, Ph.D.)

……..External Examiner
(Assistant Professor Sujimon Tunvichien, Ph.D.)

สรณัฐ เชษฐสุรกุล : การประเมินสภาพผสมเข้ากันได้ระหว่างอีฟาวิเรนซ์กับพอลิเมอร์สำหรับการเตรียมสารละลายของแข็งด้วยกระบวนการอัดรีดแบบหลอมร้อน (MISCIBILITY EVALUATION OF EFAVIRENZ AND POLYMERS FOR SOLID SOLUTION PREPARATION BY HOT MELT EXTRUSION FORMULATION) อ.ที่ปรึกษาวิทยานิพนธ์หลัก : ดร.จิตติมา ชัชวาลย์สายสินธ์, อ.ที่ปรึกษาร่วม : ดร.นฤพร สุตัณฑ์วิบูลย์, 107 หน้า

การศึกษานี้มีวัตถุประสงค์เพื่อประเมินสภาพผสมเข้ากันได้ระหว่างอีฟาวิเรนซ์กับพอลิเมอร์ต่าง ๆ (พอลิไวนิลคาโปรแลคแทมพอลิไวนิลอะซิเตต-พอลิเอธิลีนไกลคอลกราฟท์โคพอลิเมอร์ (Soluplus®) ไวนิลไพรโรลิโดน-ไวนิลอะซิเตตโคพอลิเมอร์ (Kollidon® VA-64) พอลิบิวทิลเมธาครัยเลต-โค-2-ไดเมธิลอะมิโนเอธิลเมธาครัยเลต-โค-เมธิลเมธาครัยเลต (Eudragit® EPO) พอลิไวนิลไพรโรลิโดน (Kollidon® K-30) พอลิไวนิลแอลกอฮอล์ (พีวีเอ) ไฮดรอกซีโพรพิลเซลลูโลส (เอชพีซี) สำหรับการเตรียมให้เป็นสารละลายของแข็งด้วยกระบวนการอัดรีดแบบหลอมร้อน ศึกษาคุณสมบัติของสารที่ผ่านการอัดรีดโดยใช้ดิฟเฟอเรนเชียลสแกนนิงแคลอรีเมทรี (ดีเอสซี) เทคนิคการเลี้ยวเบนของรังสีเอ็กซ์ (เอ็กซ์อาร์พีดี) อินฟราเรดสเปกโทรสโกปีชนิดฟูเรียร์ทรานสฟอร์ม (เอฟที – ไออาร์) และการทดสอบการละลาย ศึกษาความคงสภาพต่อความชื้นในสถานะของแข็งของสารที่ผ่านการอัดรีดโดยใช้เทคนิคไดนามิกเวเปอร์ซอร์ปชัน ผลการคำนวณพารามิเตอร์การละลายพบว่าอีฟาวิเรนซ์สามารถผสมเข้ากันได้กับพอลิเมอร์ที่นำมาศึกษายกเว้นเอชพีซีและพีวีเอ ส่วนผสมของตัวยาต่อพอลิเมอร์ในอัตราส่วน 50:50 สามารถอัดรีดแบบหลอมร้อนที่อุณหภูมิ 20 องศาเซลเซียสเหนืออุณหภูมิกลาสทรานซิสชันของพอลิเมอร์ แต่ส่วนผสมของพีวีเอไม่สามารถอัดรีดได้ สารที่ผ่านการอัดรีดยกเว้นเอชพีซีอยู่ในรูปสารละลายของแข็งเนื่องจากมีลักษณะใส เทอร์โมแกรมจากดีเอสซีไม่แสดงอุณหภูมิของการหลอมเหลวของอีฟาวิเรนซ์และพบว่ามีอุณหภูมิกลาสทรานซิสชันเพียงค่าเดียว รูปแบบการเลี้ยวเบนของรังสีเอ็กซ์ไม่พบลักษณะของความเป็นผลึกของตัวยา สเปกตรัมจากเอฟที – ไออาร์แสดงว่าอาจมีอันตรกิริยาระหว่างตัวยาและพอลิเมอร์ การละลายของอีฟาวิเรนซ์จากสารที่ผ่านการอัดรีดเพิ่มขึ้นอย่างมากเมื่อเปรียบเทียบกับตัวยาเดี่ยว นอกจากนี้พบว่าการดูดซับและคายไอความชื้นไม่ส่งผลต่อสภาวะอสัณฐานและการละลาย ดังนั้นอีฟาวิเรนซ์กับพอลิเมอร์ที่ศึกษายกเว้นเอชพีซีสามารถผสมเข้ากันได้และสามารถเตรียมเป็นสารละลายของแข็งด้วยกระบวนการอัดรีดแบบหลอมร้อน

ภาควิชาวิทยาการเภสัชกรรมและเภสัชอุตสาหกรรม ลายมือชื่อนิสิต.....

สาขาวิชาเภสัชอุตสาหกรรม ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

ปีการศึกษา 2555 ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม.....

5276609433 : MAJOR INDUSTRIAL PHARMACY
KEYWORDS : efavirenz, hot-melt extrusion, miscibility, solid solution
SORRANUT CHETSURAKUL : MISCIBILITY EVALUATION OF EFAVIRENZ AND POLYMERS FOR SOLID SOLUTION PREPARATION BY HOT MELT EXTRUSION. ADVISOR : JITTIMA CHATCHAWALSAISIN Ph.D., CO-ADVISOR : NARUEPORN SUTANTHAVIBUL, Ph.D., 107 pp

The aim of the present study was to evaluate the miscibility between efavirenz and various polymers (polyvinylcaprolactam-polyvinylacetate-polyethylene glycol graft copolymer (Soluplus®), vinylpyrrolidone-vinylacetate copolymers (Kollidon® VA-64), poly(butylmethacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methylmethacrylate) (Eudragit® EPO), polyvinylpyrrolidone (Kollidon® K-30), polyvinyl alcohol (PVA) and hydroxypropyl cellulose (HPC) for the preparation of solid solution by hot-melt extrusion process. The extrudates were characterized by differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), Fourier-transform infrared spectroscopy (FT-IR) and dissolution test. Solid state moisture stability of extrudates was investigated by dynamic vapour sorption technique. The calculated solubility parameters showed that efavirenz were miscible with the polymers studied, except for HPC and PVA. Extrudates containing 50:50 efavirenz/polymer could be prepared by hot melt extrusion at 20 ºC above glass transition temperature (T_g) of each polymer. However, PVA mixture was not possible to be extruded. The extrudates, except for HPC, were found to be in solid solution form according to their transparent appearance. DSC thermograms showed absence of melting endotherm of efavirenz and presence of only single T_g. The XRPD patterns of the extrudates also showed absence of drug crystals. FT-IR spectra suggested possible interactions between efavirenz and polymers. Dissolution of efavirenz from the extrudates was markedly improved, as compared to the drug itself. In addition, the extrudates were stable after exposure to moisture sorption/desorption cycles as their amorphous character and dissolution behavior were marginally changed. Therefore, efavirenz and the polymers studied, except for HPC, were miscible and their solid solutions could be prepared by hot-melt extrusion process.

Department : Pharmaceutics and Industrial Pharmacy Student's Signature…….
Field of Study : Industrial Pharmacy Advisor's Signature……..
Academic Year : 2012 Co-advisor's Signature……..

ACKNOWLEDGEMENTS

The success of this thesis has been attributed to the extensive support and assistance from my advisor, Dr. Jittima Chatchawalsaisin, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University and my deepest gratitude and appreciation is also expressed to Dr. Narueporn Sutanthavibul, thesis co-advisor, for her great help, guidance, valuable suggestions.

I also wish to express deep appreciation to all members of the thesis committee for spending their times to be on my thesis committee and for their suggestion and comments.

I would like to express grateful thanks to the National Metal and Materials Technology Center (MTEC) for providing hot-melt extruder.

I would like to special thanks to the Government Pharmaceutical Organization (GPO) for supplying efavirenz to my study.

Finally, I would like to express my deep gratitude and appreciation to my family for their assistance, care, cheerfulness and encouragement.

TABLE OF CONTENTS

Page

Page

LIST OF TABLES

LIST OF FIGURES

Figure Page

Figure Page

Figure Page

Figure Page

LIST OF ABBREVIATIONS

%	percentage
Δδ	difference of total solubility parameter
^{O}C	degree Celsius (centrigrade)
et al.	et alli, and others
mg	milligram (s)
g	gram (s)
min	minute (s)
ml	milliliter (s)
mm	millimeter (s)
CED	cohesive energy density
DSC	differential scanning calorimetry
DVS	dynamic vapor sorption
FT-IR	Fourier transform infrared spectroscopy
HSM	hot-stage microscope
HME	hot-melt extrusion
HPLC	high-performance liquid chromatography
pH	the negative logarithm of hydrogen ion concentration
R^2	coefficient of determination
RSD	relative standard deviation
SD	standard deviation
SSNMR	solid-state nuclear magnetic resonance
T_g	glass transition temperature
T_m	melting temperature
T_{mo}	melting endotherm onset temperature
T_{deg}	degradation temperature
TGA	thermogravimetric analysis
XRPD	x-ray powder diffraction

CHAPTER I

INTRODUCTION

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of a human immunodeficiency virus (HIV) type 1. In Thailand, there is an announcement about the enforcement of rights under patents called Compulsory Licensing (CL), which are legal measures provided in Thailand medicine Act B.E.2510 resulting in that efavirenz products in Thailand could be produced and people should have more opportunities to access the medicine.

Efavirenz is classified as biopharmaceutical classification system (BCS) Class 2. Its poor solubility could contribute a problem in low bioavailability, resulting in lower efficiency in treatment of acquired immunodeficiency syndrome (AIDS) patients.

There are many ways to increase solubility of poor water soluble drugs such as reducing particles size and hence increasing the surface area to expose solvent (Jim *et al.*, 2007), adding substances such as surfactants (Horter, 2001, Curatoro, 1998), or hydrophilic polymers to improve wettability of drug particles (Sugimoto et al., 1998), forming complexes with some substances such as β-Cyclodextrin to reduce the attraction between molecules of the active ingredient (Chaudhari et al., 2009), forming salts (Serajuddin, 2007), preparing drugs in microemulsion (Panayiotis, 1995), changing chemical structure from crystalline to amorphous (Blagden et al., 2007) and preparing drugs in solid solution or solid dispersion (Win et al., 1971).

Preparation of solid solution or solid dispersion is one of the techniques to increase solubility of poor water solubility drugs. This technique could make the drug to be dispersed at the molecular level or in the carrier particles, cause transformation of crystalline to amorphous solid which is wet easily and preventing aggregation of drug particles or making smaller size of drug particles.

Solid dispersion preparation can be prepared in a number of ways. However, there are generally prepared by two methods: 1) solvent evaporation by dissolving hydrophobic drug and hydrophilic carrier in organic solvents and then removing organic solvents. This technique may be found in spray-drying, vacuum-drying,

fluidized bed and lyophilization processes; 2) melting method (fusion method) by heating the drug and hydrophilic carrier at sufficiently high temperature to fuse both ingredients together and then cooling the product down until it becomes solidified. The drug is covered in a hydrophilic carrier. The solid is ground to powder for loading in a capsule or tableting (Aitken-Nichol et al., 1996).

The important thing of solid dispersion system is miscibility of binary phase system between the drug and polymer. The drug and polymer should be mixed at the molecular level leading to one amorphous solid.

There are many techniques to characterize miscibility of the drug and polymers. These techniques are film casting, solubility parameter calculation, differential scanning calorimetry (DSC), hot-stage microscopy (HSM), Fourier transform infrared spectroscopy (FT-IR), powder X-ray diffractometry (XRPD), dynamic vapor sorption (DVS) and solid-state nuclear magnetic resonance (SSNMR). Film casting is a prelimary way to find out solubility capacity of polymers. Polymer with high solubility capacity tends to be miscible with the drug. Solubility parameters are used to predict the drug and polymer miscibility. DSC is used to find out amorphous phase in the mixture. Hot-stage microscopy is used to observe melting of pure drug and polymer compared with the physical mixture. FT-IR is used to study specific interaction between the drug and polymer. XRPD and DVS are used to prove solid state whether it is in crystalline or amorphous phase (Rumondor et al., 2009). SSNMR is also used to characterize crystal habit of substance. This method focuses on molecular conformation of the drug and polymer. Dipolar interaction between the drug and polymer can be detected by this method.

Recently, hot-melt extrusion technology has taken a role to increase solubility of poor soluble drugs. This technology can be applied in pharmaceutical development of many pharmaceutical dosage forms such as tablets, implants and inserts (Repka et al., 2007). Although the process may be challenged to heat-labile drug, the process is easy to scale up, reproducible and possibly on/in time monitored.

In this study, miscibility of efavirenz and polymers were evaluated by film casting, solubility parameter calculation, DSC, HSM, FT-IR, XRPD and DVS. Solid solution of efavirenz and selected polymers were prepared by hot-melt extrusion (HME). Solid-state characteristics and dissolution of the products were investigated.

Objective of this study

1. To evaluate miscibility of efavirenz and polymers for preparation of solid solution by hot melt extrusion
2. To determine proportions between efavirenz and polymers which form solid solution by hot-melt extrusion
3. To improve dissolution of efavirenz by preparation of solid solution

CHAPTER II

LITERATURE REVIEWS

1. Drug release from solid dosage form

Solid dosages forms are most commonly used because they are convenient to handle and have better stability than liquid dosage forms.

Oral solid dosage forms are designed for the drug to be absorbed through blood system while they transit through the gastrointestinal tract. After exposed to gastrointestinal fluid, solid preparations such as tablets are usually broken to a group of particles called granules. The granules are then separated to fine particles, which are dissolved by gastrointestinal fluid before drug absorption take places.

Drug release, especially for the drugs with low solubility and high permeability, is an important. By enhancing the drug release of these drugs, it is possible to improve bioavailability and reduce side effects (Vasconcelos et al., 2007).

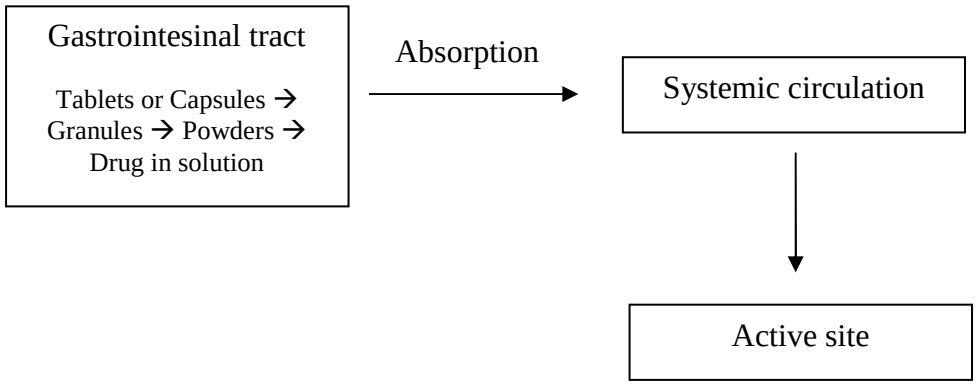


Figure 2-1 Mechanism of drug absorption (modified from [Online]) Available form: http://www.nae.edu/Publications/Bridge/FrontiersofEngineering12256/RecentDevelopmentinNeedle-FreeDrugDelivery.aspx [2012,September 29]

1.1 Factors affecting solubility

Ionic strength

Salt formation leads to better dissolution and absorption. However, salt formation has limitation by concentration of counter ion or ionic strength in the medium. High ionic strength leads to low dissolution rate. Dissolution is also depending on pH. In stomach, which has pH about 1.5-3.0, basic drugs will be dissolved in the stomach better than acidic drugs. On the other hand, small intestine, which has pH about 5.0-7.0, acidic drugs will be dissolved better than basic drugs.

Particle size

Mechanism of drug release can be explained by Noyes-Whitney relationship as the following equation:

$$\frac{dM}{dt} = \left(\frac{DS}{h}\right)(C_s - C_b) \qquad (1)$$

Remarks: M = amount of drug dissolved (mg or mmol)

t = time (seconds)

D = diffusion coefficient of the drug (cm^2/s)

S = surface area (cm^2)

H = thickness of the liquid film

C_s & C_b = concentrations of the drug at the surface of the particle (surface = C_s) and the bulk medium (bulk medium = C_b)

From Noyes-Whitney equation, dissolution rate is directly proportional to the particle surface area of the particles. If particle size is small, effective surface area is increased and dissolution rate is also increased. Reducing the particle size increases surface area. The more surface area of particle size, the more dissolution rate and bioavailability will be increased.

Porosity of particle

Particle with high porosity helps to increase dissolution rate. Dissolution rate from internal porosity is lower than surface porosity.

Crystal habit

Crystalline drugs have lower dissolution than amorphous drugs. Energy to destroy crystalline drugs is higher than amorphous drugs due to crystalline drugs have more intermolecular bonding energy. Hydrate form is freely soluble than anhydrous form.

1.2 Techniques for dissolution/solubility improvement

Many approaches are carried out to increase solubility and dissolution rate of poorly water soluble drugs. These approaches include: chemical modification, physicochemical modification and formulation modification.

Chemical modification

This approach modifies some functional groups of the drug to increase its solubility. The methods are described as follows:

Salt formation

This method is commonly used to increase solubility. Salt form usually dissolves in water than non-salt form. pH adjustment is one way to increase solubility. Solubility of the drug is increased by adding acid to alkaline drugs due to forming acidic soluble salt. On the other hand, solubility of acidic drugs will be increased when adding alkaline. Sodium and potassium salts dissolve more rapidly than other salts.

Prodrug

Prodrug is molecular modification of a drug into a new substance by adding inactive moiety or promoiety to attach with the parent drug. When the prodrug gets into the body, the bonding is broken by enzyme such as esterase. Prodrug is made with ester, carboxylic acid or hydroxyl group. Chemical modification such as prodrug causes solubility and stability changing. Prodrug is also used for prolonged pharmacology effect, toxicity reduction, drug targeting therapy and dissolution improvement. Vollman (2008) added ester to adenosine A2A receptor antagonist MSX-2 to improve the drug solubility.

Physicochemical modification

This approach improves solubility of the drug by modification of its physicochemical properties. The methods are such as particle size reduction, complexation and crystal habit.

Particle size reduction

Particle size reduction leads to increase the surface area of particles. This allows the solubility and dissolution rate of the drug to be increased. The method is achieved by grinding, fluid energy micronization and ball milling. However, this method has several disadvantages such as limitation to control some characters of the final particle such as shape, size, morphology, surface properties and electrostatic charges (Yiyun, 2005).

Solubilization and Complexation

Solubilization of this material including volatile oils, coal tar and resinous material, phenobartital, sulfonamide, vitamins, hormones, dyes and beta-arteether was reported to increase their solubility (Kumar et al., 2011).

Complexation is made by adding some chemical substance such as β-cyclodextrins. β-cyclodextrins have been widely used as solubilizing and stabilizing agent in pharmaceutical dosage forms. The advantages of β-cyclodextrin are good

disintegration agents and low toxicity. β-Cyclodextrin makes inclusion complex by binding water soluble ligand. Complexation leads to increase solubility of the drug (Kumar et al., 2011).

Crystal structure

The various polymorphic forms of the same chemicals generally differ in many physical properties. The arrangement of internal molecular structure is characterized as amorphous solid or crystalline solid.

Amorphous solid

Amorphous state is a solid habit which lack of forms, no order of molecular packing. Amorphous solid has higher internal energy, greater thermodynamic properties, higher entropy, increased mobility due to longer intermolecular distances and higher free energy than crystalline solid. In addition, amorphous solid have lower stability than crystalline solid. Also, amorphous solid is usually more soluble than crystalline form.

Amorphous solid have two states, glassy state and rubbery state. The glassy state has lower solubility and dissolution rate but higher stability than rubbery state. Glass transition temperature (T_g) is a temperature at which phenomenon causes glassy state to convert to rubbery state.

Crystalline solid

Crystalline state is a solid habit in which molecules are arranged in order, having repeating patterns. Crystalline solid has lower internal energy. Hence, it has higher stability than amorphous solid. Crystalline solids can be divided into polymorphs and solvates/hydrates. The uses of metastable forms generally result in higher solubility and dissolution rates than the respective stable crystal (Kumar et al., 2011).

Polymorphism is an occurrence in different crystalline forms of the same substance (Yu et al., 2003). Because of difference in molecular arranging, the

physicochemical properties are also different such as dissolution rate, stability and bioavailability.

Solvates/hydrates are forms of crystalline solid which have certain solvent called solvate or water called hydrate in structure. Their solubility and dissolution rate is lower than anhydrous form.

Many attempts have been conducted to improve drug dissolution by particle size reduction (Liversidege, 1995), complexation (Chaudhari et al., 2007), polymorph and amorphous formation (Hancock et al., 1997).

Formulation modification

An addition of some substances such as surfactant (Horter, 2001), co-solvent (Seedher, 2009) and hydrophilic polymers (Sugimoto et al., 1998) leads to reduce surface tension and causes drug particles to be wetted better. These substances are such as sodium lauryl sulfate (SLS), polyethylene glycol (PEG), hydroxylpropyl methylcellulose (HPMC) and polyvinyl pyrrolidone (PVP).

2. Solid dispersion

In 1961, the solid dispersion technique was invented to reduce particle size and improve dissolution. Sulfathiazole and urea were prepared to solid dispersion by Sekiguchi and Obi (Sekiguchia and Obi, 1961). This solid dispersion was prepared as eutectic mixture.

In 1965, β-carotine was prepared in the colloidal solid dispersion by Tachibana and Nakamura (Tachibana and Nakamura, 1965). Polymer carrier was dissolved in organic solvent and then the solvent was evaporated.

Today, much more research has been conducted on solid dispersion technique. The new technologies have a role in increase drug dissolution of poorly water-soluble drugs. In biopharmaceutical classification system (BCS), the drug with low solubility but high membrane permeability is categorized as Class II. Hence, solid dispersion techniques are particularly useful to improve dissolution and the bioavailability of BCS Class II drugs (Dhirendra, 2009).

Solid dispersion is defined as one or more solid ingredients dispersed in an inert carrier. In other words, it consists at least two different components, i.e. matrix and the drug. The matrix can be either crystalline or amorphous. The drug is dispersed molecularly, in amorphous substance or crystalline substance (Chiou, 1971).

Solid dispersion may include solid solution and eutectic mixture. Solid dispersions can be classified according to the interaction between drug and carriers in the solid dispersion. If drug and carrier are miscible and completely dissolved, the drug and carrier have extremely high interaction energy resulting true solution such as solid solution or glass solution. In amorphous solid solutions, polymers are often used in preparation of true solid solution. The crystalline drug is dissolved in polymer. It becomes a homogeneous system on a molecular level. This method receives amorphous product with only one phase (Vasconcelos et al., 2007).

Solid solution is classified based on miscibility systems including continuous solid solution, discontinuous solid solution, substitutional solid solution and interstitial solid solution. If the carrier is the polymer, the system will be in amorphous solid due to that chain of polymer is amorphous and the drug acts as plasticizer leading to reduction of glass transition temperature of the polymer.

The first generation of solid dispersion contains one or more active ingredients fused in an inert carrier matrix. This method produces faster release and higher bioavailability than other solid preparations. The particle size gets better wettability. Because the carrier is crystalline, it produces crystalline solid dispersions which are more thermodynamically stable and hence slower release than amorphous solid dispersions.

The second generation contains amorphous carriers instead of crystalline carrier. Most of amorphous carriers are polymers such as povidone, polyethyleneglycols, polymethacrylates, hydroxypropyl methylcellulose, ethylcellulose, hydroxypropyl cellulose and cyclodextrins. The drugs are molecularly dispersed in inert polymers which enhance drug solubility.

Recently, the third generation of solid dispersions has been developed. Researchers used the surfactant carrier such as Tween-80, docusate sodium, Myrj-52, Pluronic-F68 and sodium lauryl sulfate (Ghebremeskel et al., 2006). It has self-emulsifying properties. The dissolution profile was improved than crystalline and

amorphous polymers carriers. The third generation of solid dispersions is intended to improve solubility of poorly soluble drugs, stabilize the solid dispersion, avoid drug recrystallization and achieve the highest bioavailability.

Solid dispersion technique has many advantages. The advantages are such as easy to produce, more applicable to patients, more efficient in particle size reduction techniques, improved wettability, high porosity, increased the glass transition temperature (T_g) leading to high stability in room temperature, greater dissolution rate and improve bioavailibity (Serajuddin, 1999).

There are some disadvantages of solid dispersion. Solid dispersion techniques are not commonly used in commercial product because of temperature and humidity stress. Humidity leads to instability because moisture will increase drug mobility which can promote drug recrystallization, phase separation, crystal growth and conversion to crystal form. This may lead to instability, decreasing solubility and dissolution rate.

Solid dispersion technique is an effective way to increase the dissolution rate of poorly water-soluble drugs. However, very few amorphous solid dispersion preparations have been successfully marketed. The reason is poor physical stability in the amorphous state (Serajuddin, 1999). Other problems are the cost of preparation and difficult to scale-up to production (Hancock and Zogra, 1997, Kearney et al 1994).

Techniques in solid dispersion/solution preparation to enhance bioavailability of poorly water soluble drugs are such as lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technology, use of surfactant, electrostatic spinning method and supercritical fluid technology (Kumar et al., 2011). These techniques can be grouped to the solvent method and the fusion method (Vasconcelos et al., 2007).

Solvent method

In solvent method, the drug and the carrier are dissolved together in organic or inorganic solvents and then the solvent was removed by evaporation technique. Tachibana and Nakamura (Tachibana and Nakamura, 1965) was the first who

dissolved β-carotene and polyvinylpyrrolidone (PVP) in an organic solvent and then evaporated the solvent under vacuum to produce a solid solution.

The important thing for the manufacturing solid dispersion by using the solvent method is both the drug and the carrier are sufficiently to dissolve in the solvent. The solvent is removed by evaporation. Temperatures are used for solvent evaporation technique in a range of 23-65 ^{o}C (Zein, 1998). Solvent removal is carried out by freeze-drying (Betageri, 1995) or spray-drying (Lo, 1996). It is important that organic solvents are removed since organic solvents are toxic.

Many researches have been conducted by solvent evaporation method to produce solid solution such as griseofulvin-polyvinylpyrrolidone, sulfathiazole-polyvinylpyrrolidone (Leuner and Dressman, 2000), steroid-polyvinylpyrrolidone (Chiou, 1971), reserpine-deoxycholic acid (Malone et al., 1966).

The advantage of solvent evaporation method is easy to produce. However, the disadvantages are high cost production, hard to remove organic solvent, toxicity from organic solvent and low stability of product.

Fusion method (Melting method)

Because of some limitation of solvent evaporation method as described above, the fusion method was created by Sekiguchi and Obi (Sekiguchia and Obi, 1961) and commonly used in 1970s (Leuner and Dressman, 2000). The fusion method was used to melt the drug within the carrier by heating and quenching cool to obtained product (Vasconcelos et al., 2007). Fusion method was used to produce solid solutions such as sulphathiazole and urea (Sekiguchi, 1961).

The adventages of fusion method are simplicity, economy, avoiding solvent or water and preventing oxidation of the drug and carrier. However, the disadvantages are that fusion method is only applied when the drug and the carriers are miscible and decomposition of the thermolabile drugs and the carrier does not occur (Vasconcelos et al., 2007).

Hot melt extrusion process was invented and now is the current method of choice for manufacturing solid dispersions to avoid long exposure of drug to high temperature in the process causing degradation of the drug and polymers.

Examples of the drug that have been prepared to solid dispersions are such as itraconazole (Kapsi, 2001), prednisolone (Palanisamy, 2011), indomethacin (Bogdanova et al., 1998) and fenofibrate (Sheu et al., 1994). Example of marketed solid dispersion products are griseofulvin-polyethylene glycol solid dispersion (Gris-PEG®, Sandoz-Wander) and nabilone-PVP (Cesamet®, Eli-Lilly).

Dissolution improvement in solid dispersion may result from reduced particle size, improved wettability and/or changed crystal habits.

3. Hot-melt extrusion (HME)

Hot-melt extrusion is the process to melt and mix solid materials directly. HME has been used in other industries, rather than pharmaceutical industry more than 50 years.

At the beginning of 1930s, hot-melt extrusion was applied in plastic industries. Speiser and Huttenrach (1971) adapted process to use HME in pharmaceutical field (Leuner and dressman, 2000). HME is carried out by heating active ingredient and carrier and forcing the molten mixture through die cell to form the uniform shape product under specific condition (Breitenbach, 2002). It is a continuous process with consistent flow and high throughput rate.

In pharmaceutical fields, HME has been used for granulation, taste masking, solubility improvement, preparation of sustained release products and implants. Process parameters of HME affecting product properties are such as screw mixing time and temperature zone settings and feed rates. HME is scalable, from lab scale, pilot scale, plant-scale, and commercial production scale.

HME have two types of screws, single screw and twin screws. Twin screw extruder is better than single screw. HME have many heating zones along the process for applying different temperature in each processing section for various formulation requirements. The processing steps including melting, dispersive mixing, distributive mixing, degassing and pressure build-up, can be controlled very selectively and effectively. The important factors in preparing solid dispersions through HME are using optimized screw configuration and temperature profile for optimization.

HME have a numerous advantages over other melt processing methods, including such as minimal thermal stress on heat sensitive drugs because of short residence time in HME, high reproducibility, great mixing, continuous process and high throughput rate.

3.1 Hot-melt extrusion process

The process of hot-melt extrusion consists of four steps: mixing the power of drug and excipients, heating powder blend, shaping drug particle in the molten polymer through die cell, congealing powder blend.

The hot-melt extrusion process is summarized as diagram in figure 2-2

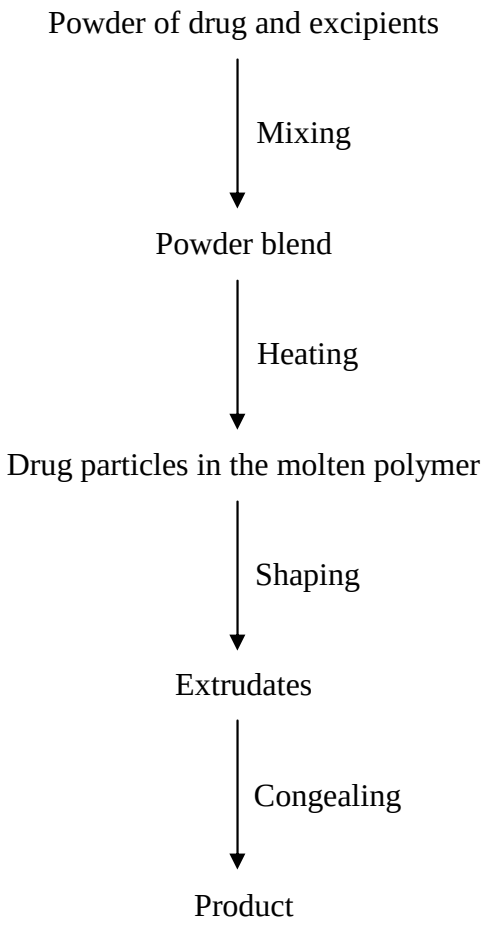


Figure 2-2 Hot-melt extrusion process (modified from Breitenbach, 2003)

3.2 Equipment

Hot-melt extrusion consists of an extruder, auxiliary equipment, downstream equipment and monitoring tools. The extruder consists of four distinct parts.

First part is opening section in which the materials including the drug, polymer and plasticizer enter to the barrel through a gravimetric solid feeder. Physical mixtures are fed into the upstream feeding zone and continue to second part.

Second part is conveying section. This part carries the mixture along the barrel. The barrel and screws help to mix the materials together. Some of HME model, the drug can be added nearly at the end of the previous part to decrease the thermal stress on the drug.

Third part is devolatilisation section which is placed before the end of the process of HME. This section is used to devolatilize the final product. The devolatilisation zone must be completely sealed to prevent product discharging through the vent. This part is also used for mixing of the mixture which has not been incorporated from upstream zones completely.

Fourth part is downstream section. The shaping and cooling was happening at this section. The conveying line is designed to transfer material passing through orifice which helps shaping material before leaving the extruder. Dies are available to shape the melt before it solidifies. Downstream processing also includes cooling equipment to cooling the melt to solid (Kruder, 1985).

3.3 Material used in hot-melt extrusion process

Materials used in hot-melt extrusion process are similar to those in others solid preparation. Materials must have physical, chemical and thermal stability properties. Thermal stability of all materials must be sufficient to withstand melting temperature in the process. The formulation usually consists of three components including active ingredient, carrier and plasticizer.

Active ingredient

Active ingredient must have thermal stable property. Therefore, thermal assessment of active ingredient is very important. Active ingredient should be completely dissolved in carrier.

Carrier

Carrier in hot-melt extrusion process must be compatible and miscible with active ingredient. The carrier is mainly polymers, such as polyvinylpyrrolidone, polyvinylpyrroidone-vinyl acetate, poly(ethylene-co-vinyl acetate), polyethylene glycol, cellulose ethers, acrylate, polyethylene oxides, poly methacrylate and poloxamers or starch (Chokshi, 2004). Polymer must have thermo plasticity properties in order to enable the hot-melt extrusion process and must be thermally stable at the extrusion temperatures. Suitable glass transition temperature (T_g) or melting temperature (T_m) of polymer is 50 – 180 °C. Polymer should be low hygroscopicity and no toxicity (Forster, 2000). Polymers with a high solubilization capacity are particularly suitable because large quantities of drugs can be dissolved. The solubility parameter can be used to determine whether active ingredients and polymers are miscible (Forster, 2000). Extrusion temperature is determined by glass transition or melting temperature. Polymers with high molecular weight generate a high melt viscosity and are difficult to extrude (Chokshi, 2005). A high T_g or T_m requires high processing temperatures, which can degrade sensitive drugs. Extrusion processes can be run at temperatures 20 – 40 °C above glass transition (Breitenbach, 2002, Lakshman et al., 2008, Prodduturi et al., 2006, Khatry, 2011). An extrusion temperature range of 90 – 140 °C for a drug containing polymer seems to be prefered (Kolter et al., 2007).

Plasticizer

Plasticizers in hot-melt extrusion process are typically low molecular weight substances such polyethylene glycol and citrate ester. Plasticizer makes polymer

soften and more flexible. Plasticizers decrease T_g and melt viscosity, therefore plasticizer helps facilitate the extrusion process. Some actives ingredients may also have a plasticizing effect (Ghebremeskel, 2006). Viscosity of polymers depends on type and amount of plasticizer.

Hot-melt extrusion is used to prepare solid dispersion or solid solution of poorly water soluble (Crowley et al., 2002). Polymers are in amorphous state. The HME process requires sufficiently high temperature to soften the polymer but the degradation temperature of the active ingredient is not reached. The temperature could be set a few degrees higher than melting point of semi-crystalline polymers. In the case of amorphous polymers, the melting temperature should be above the polymer glass transition temperature. If the interval between glass transition temperature of polymer and the degradation temperature of the drug is very narrow, the heating process of HME must be carefully controlled. The drug can be either dissolved or dispersed in an amorphous or crystalline state. Solid solution is formed when the drug is dissolved below saturation solubility in the polymer. Solid dispersion was obtained when the drug concentration exceeds the saturation solubility. Solid dispersion or solid solution will change the dissolution and biopharmaceutical properties of the drug.

3.4 Pharmaceutical applications of hot-melt extrusion

Hot-melt extrusion is used for many various purposes such as improving dissolution rate and bioavailability, modifying drug release and taste masking. Hot-melt extrusion has been applied to prepare granules, pellets, tablets and films.

3.4.1 Granules and pellets

Sato et al. (1997) prepared control release granules of diclofenac by hot-melt extrusion. They used a twin-screw extruder to prepare solid dispersion granules of diclofenac with carnauba wax. Dissolution was carried out and compared with hydroxypropylcellulose, methacylic acid co-polymer.

Liu et al. (2001) prepared wax based granules by hot-melt extrusion. Phenylpropanolamine hydrocholoride was an active ingredient. Carriers are Precirol® and Steotex®. Other excipients were microcrystalline cellulose, lactose and Emcompass®. The result found that at the same amount of Precirol®, drug release from tablets decreased in the order of using microcrystalline cellulose (MCC), lactose and Emcompress. When changing Precirol® with Sterotex®, the dissolution rates was increased.

McGinity and Koleng (1997) prepared acetaminophen rapid release granules by hot-melt extrusion process. The granules were compressed with excipients. The results showed that drug release of tablets with 15% polyethylene glycol was improved greater than 80% after 30 minutes.

Perissutti et al. (2002) prepared carbamazepine rapid release granules by ram extruder. The excipients were polyethylene glycol 400 and lactose. Extrudate disintegrated rapidly and dissolution rate was improved.

Hulsmann et al. (2000) prepared solid dispersion of 17-estradiol hemihydrate. They used polymers such as polyethylene glycol 6000, polyvinylpyrrolidone or vinylpyrrolidone-vinylacetate copolymer and excipients such as Sucroester® WE15 or Gelucire® 44/14. Solid dispersion showed increased dissolution rate of pure drug and physical mixture. The formulation containing 10% 17-estradiol hemihydrate, 50% PVP and 40% Gelucire® 44/14 showed 30-fold increasing dissolution rate.

Young et al. (2002) prepared spherical theophylline pellets by hot-melt extrusion and spheronization process. Theophylline, microcrystalline cellulose and polyethylene glycol 800 were blended and extruded by hot-melt extrusion. After that, extrudate was spheronized by spheronizer. The pellets exhibited diffusion-controlled drug release.

Miller et al. (2006) prepared micronized particles of itraconazole by hot-melt extrusion stabilized with polyvinylpyrrolidone or hydroxypropyl methylcellulose and extruded with poloxamer 407 and polyethylene oxide 200M. Dissolution rate of all extrudate was improved.

3.4.2 Tablets

Zhang and McGinity (1999) prepared chlorpheniramine maleate matrix tablets by single screw of hot-melt extrusion. Polyethylene oxide was a drug carrier. Chlorpheniramine maleate was extruded in large diameter rods and cut into tablets. Polyethylene glycol 3350 was plasticizer. They found that if concentration of polyethylene glycol 3350 was increased, drug release form matrix tablets was also increased.

Bruce et al. (2005) prepared 5-aminosalicylic acid using Eudragit® S100 as polymer. Triethyl citrate was used as the plasticizer to reduce glass transition temperature of polymer. Triethyl citrate influenced the release rate of 5-aminosalicylic acid from extruded tablets.

3.4.3 Films

Aitken-Nichol et al. (1996) prepared lidocaine hydrochloride films by hot-melt extrusion process. Eudragit® E100 was the polymer and triethyl citrate was plasticizer. The authors found that lidocaine hydrochloride could act as a plasticizer.

Repka et al. (1999) prepared chlopheniramine maleate and hydrocortisone films by hot-melt extrusion process. Hydroxypropyl cellulose was a polymeric carrier. These researchers found that chlopheniramine maleate extruded films were stable up to 12 months but chemical stability of hydrocortisone was found to be function of residence time and processing temperature in extruder (Repka, 1999).

4. Method to determine miscibility of drug and carrier

Several methods are available to characterize physical properties of solid dispersion. In each method, there are advantage and disadvantage. Two or more methods are required to combine to justify formation of solid solution or solid dispersion. Some methods are listed as follows:

4.1 Film casting

Film casting is used to predict miscibility between the drug and polymer. Solubilization capacity was determined by film casting experiments using the drug and polymers with or without plasticizer combinations. Polymers, having high solubilization capacity, tend to be miscible to the drugs because large quantities of drugs can be dissolved. The solubilization of the drug in the solid solutions of the polymers was determined using film casting.

4.2 Solubility parameters calculation

Solubility parameters are used to predict the drug and carrier miscibility. The concept of solubility parameter is based on cohesive energy density (CED). The CED is the total attractive forces which hold the molecule of substances within a condensed state material together. In addition, The CED represents in a term of energy which is needed to separate the atoms or molecules of substance. The CED is the net energy of the intermolecular interactions including Van der Waals interactions, covalent bonds, ionic bonds, hydrogen bonds, electrostatic interactions, induced dipole and permanent dipole interactions (Hancock et al., 1997).

The CED for a material can be used to predict whether the material is dissolved in the other materials. Solubility parameters are developed by Hildebrand and Scott (Hildebrand and Scott, 1950). The concept of solubility parameters is originally developed from liquid mixtures. It is extended to complex mixture such as gases, solid and supercooled liquid. It is based on non-polar molecules with weak dispersion forces and polar molecules. The total solubility parameters are described by Hansen (Hansen, 2007). The Hansen solubility parameters are calculated based on chemical structures using the approaches of Hoftyzer/Van Krevelen (Van Krevelen, 1990). The solubility parameter was related to the CED according to equation 1.

$$\delta = \sqrt{CED} \qquad (1)$$

The total solubility parameters are divided into three terms of interatomic/intermolecular forces (hydrogen bonds (δh)), dispersion forces (δd), 'polar' interactions (δp) according to equation 2 (Van Krevelen, 1990).

$$\delta t = \sqrt{\delta d^2 + \delta p^2 + \delta h^2} \quad (2)$$

The calculation of Hansen solubility parameters were described by Hoftyzer and Van Krevelen equation. The Hansen solubility parameters were determined by a molecular functional group which was contributed to other functional groups. The reference lists of functional group could be found in Barton's handbook solubility parameters (Barton, 1991). Hoftyzer and Van Krevelen calculation was calculated by molar attraction constant due to dispersion component (F_{di}) and polar component (F^2_{pi}), the hydrogen bonding energy (E_{hi}) and the molar volume from Hildebrand analysis (V). The relationship of Hoftyzer and Van Krevelen parameters were shown in equation 3, 4 and 5

$$\delta d = \frac{\sum F_{di}}{V} \quad (3)$$

$$\delta p = \frac{\sqrt{\sum F_{pi}^2}}{V} \quad (4)$$

$$\delta h = \sqrt{\frac{\sum E_{hi}}{V}} \quad (5)$$

The calculations carried out for the drug and polymers. The Hoftyzer/Van Krevelen values have been used to calculate δ. Compounds with similar δ values are expected to be miscible together which can be grouped into three categories using the difference between the solubility parameters of the compounds (Δδ). Categories 1, compounds having Δδ below 7.0 $MPa^{1/2}$, are likely to be miscible and tend to form glass solutions. Categories 2, compounds having Δδ between 7.0-10.0 $MPa^{1/2}$, are

likely to show some miscibility. And Categories 3, compounds having $\Delta\delta$ over 10 $MPa^{1/2}$, are likely to be significantly immiscible and are not expected to form glass solution (Forster et al., 2001).

4.3 Thermal analysis

Thermal analysis is one of common approaches to study interaction between two or more compounds. This technique relies on the principle of changing thermal energy to investigate miscibility. The behavior of active ingredient was present in crystalline or amorphous state. If two compounds are miscible, it consists of single homogenous phase. Crystallization leads to immiscible and separate into two phases. Miscibility is important thing in solid dispersion. Thermal analysis is an approach to identify how many phases are present. If two phases are present, two glass transition temperatures are observed.

Cooling-curve method

Physical mixtures are heated to get homogeneous melt. The temperature is recorded as a function of time to plot a temperature-time curve in the phase diagram. This method has some disadvantages. It is time-consuming. It also uses a large quantity of samples. This method cannot be used to characterize the sample which is decomposed after melting. In addition, it is difficult to detect the samples which have low content.

Thaw-melt method

Physical mixtures are gradually heated in capillary tube to thaw point which is referred to the temperature between the solid state and liquid state. This method uses stirring device in capillary tube to attain the homogenous system. This method has some disadvantages as it depends upon subjective observation at thaw point by researcher. Therefore, it is not highly reproducible.

Thermomicroscopic method

Physical mixtures are heated in polarized microscope by a hot-stage controller. Physical mixtures are placed on a glass slide with a cover slid. Physical mixtures are heated until they are completely liquid. The melting point is determined by observation under polarized microscope. It uses only a small amount of samples. However, it has some disadvantages such as subjective observation, limitation of thermal stability compounds and inhomogeneous by mixing (Lloyd, et al., 1997)

Differential thermal analysis (DTA)

DTA is one of an effective thermal analysis method to check miscibility of compounds. The differential temperature is recorded as a function of temperatures and time between pure substance and inert material substance. Phase transition or chemical reaction is found by absorption of heat. Changing of sample such as melting, evaporation, sublimation and desolvation is observed. The advantages of this method are highly reproducible in constructing phase diagram. A small amount of sample is used in this method. However, there are some disadvantages of this method. DTA thermograms is influenced by heating rate and thermal conductivity of sample container.

Differential scanning calorimetry (DSC)

DSC is a common technique to evaluate miscibility of two phase systems. The presence of single T_g signal refers to miscibility. However, the presence of more than one T_g signal refers to lack of miscibility.

DSC is a thermal analytical technique by which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. By using this technique, it is possible to observe melting point depression, enthalpy of fusion and glass transition temperature (Paul, 1998).

4.2 Spectroscopic Method

X-ray powder diffraction method (XRPD)

X-ray diffraction or reflection intensity is recorded as a function of diffraction angles. X-ray diffraction is one of tools to study the physical nature of substance. It is used to characterize solid dispersion systems. In amorphous solid is halo characteristic. It is also used to study quantitatively the concentration of crystalline compound in mixture. The x-ray spectrum of solid dispersion is different from that of pure substance.

Fourier transform infrared spectroscopy (FT-IR)

FT-IR is a technique which is used to obtain an infrared spectrum of absorption, emission, photoconductivity. Infrared studies are conducted to find out interaction between drug and polymer in formulation of solid dispersion. Appearance of some interaction peaks such as hydrogen bonding interaction indicates miscibility between two compounds.

Solid-state nuclear magnetic resonance (SSNMR)

Solid-state nuclear magnetic resonance (SSNMR) is one of instruments which can be used to characterize crystal habit of substance. SSNMR gives the detailed information of molecular structure, dynamics and domain morphology in a molecule. SSNMR is detection of ^{13}C. This methods have been used to evaluate a correlation between the ^{13}C line width of the drug and polymers. It enables prediction for solubility of the drug in polymers. Multivariate analysis of ^{13}C SSNMR spectrum of the solid dispersion is useful to predict recrystallization behavior of the drug. Structure analysis of amorphous solid dispersion can be observed by ^{13}C SSNMR spectrum. This method also focuses on molecular conformation of the drug with hydrogen bond. Dipolar correlation methods can predict the interactions between amorphous substance and small molecules by measuring of direct dipolar interaction

spin diffusion and ^{13}C spin-lattice (T_1) relaxation times. ^{13}C spin-lattice in polymers is used to detect amorphous dispersions from spray-drying and hot-melt extrusion process (Pham, 2010). The ^{13}C spin-lattice detection is the detection of ^{13}C spin diffusion of aromatic protons which is commonly found in the drugs with dipolar interaction. Miscibility between the drug and polymers in solid dispersion was evaluated by this method. The distances of interfering aromatic groups between the drug and polymer is used to determine whether solid dispersion state occurs. If the distance of interfering aromatic group is in the range from 5-10 Å, it is classified to glass solutions. If the distance of interfering aromatic group is in the range more than 100 Å, it is classified to suspension (Pham, 2010).

5. Materials

5.1 Efavirenz

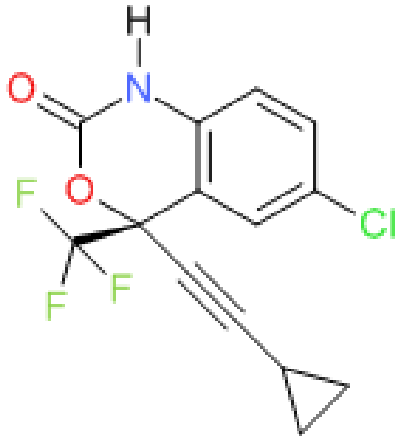


Figure 2-3 Chemical structure of efavirenz [Online]. Available form: (http://en.wikipedia.org/wiki/Efavirenz [2012,September 29]

Efavirenz, $C_{14}H_9ClF_3NO_2$, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and used in part of highly active antiretroviral therapy (HAART) for treatment of human immunodeficiency virus (HIV). It is practically insoluble in water, freely soluble in methanol. Efavirenz is metabolized in the liver and inducer of cytochrome P450 Cyp2B6 and 3A4. Peak plasma concentrations of 1.6-9.1 μM were reached by 5 hours. The bioavailibity is increased by high-fat meals. Efavirenz appears as white to slightly pink powder. It has molecular weight of 315.675 g/mol and melting range of 139-141 °C.

Sathigari et al. (2009) prepared inclusion complexes of efavirenz with β-cyclodextrin to improve the drug solubility. The results showed that inclusion complexes of efavirenz was higher dissolution that pure efavirenz.

Madhavi et al. (2011) prepared efavirenz in solid dispersion by solvent evaporation technique method and PEGylation techniques by using polyethylene glycol as the hydrophilic carrier. The results showed that dissolution of efavirenz was improved by solid dispersion technique.

5.2 Soluplus®

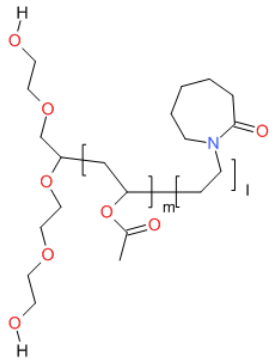


Figure 2-4 Chemical structure of Soluplus® (Soluplus® Technical Information, BASF, 2009)

Soluplus® is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. It appears as white to slightly yellowish granule with a free flowing properties and has molecular weight of 90,000 – 140,000 g/mol. The glass transition temperature of Soluplus® is approximately 70 °C. Soluplus® is soluble in water, acetone (up to 50%), methanol (up to 45%), ethanol (up to 25%) and dimethylformamide (up to 50%). Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure, which was developed as matrix polymer for solid solutions. Moreover, Soluplus® is capable of solubilizing for poorly soluble substance. Hence, it is used to increase the bioavailability of poorly soluble drug. Soluplus® is a well extrudable polymer. The pure polymer can be extruded on a twin-screw extruder. Soluplus® showed no chemical degradation even after extrusion at 180 °C. Incorporation of a drug can lead to lower extrusion temperatures to 120 °C.

Mendiratta et al. (2011) used Soluplus® to enhance solubility of lansoprazole. Solid dispersion of lansoprazole was prepared using Soluplus® by solvent evaporation method. The results showed that the dissolution of lansoprazole in distilled water was remarkably improved.

Nagy et al. (2012) used Soluplus® to enhance solubility of spironolactone. Electrospinning was performed to compare with extrusion process. The results showed that Electrospinning and extrusion processes resulted significantly improved dissolution of spironolactone.

5.3 Kollidon® VA-64

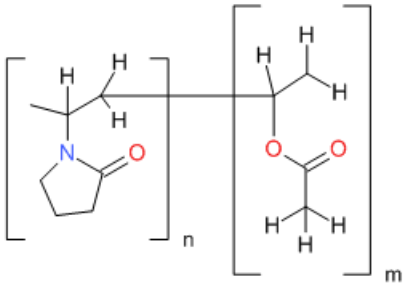


Figure 2-5 Chemical structure of Kollidon® VA-64 (Kollidon® VA-64 Technical Information, BASF, 2008)

Kollidon® VA-64 is vinylpyrrolidone-vinyl acetate copolymers. It appears as white or slightly yellowish with a free flowing properties and practically no taste and has molecular weight of 45,000-70,000 g/mol. The glass transition temperature of Kollidon® VA-64 is approximately 101 °C. It is dissolved in all hydrophilic solvents such as water, ethanol, isopropanol, methylene chloride, glycerol and propylene glycol. It is used in pharmaceutical and cosmetic industries. Kollidon® VA-64 is used as binder in tablets and granules by wet granulation process. It is also used as excellent dry binder in direct compression process. It is suitable for application of roller-compaction. It is a film former which are soluble at all pH values. Plasticizers are not required in film coating of Kollidon® VA-64. It is used as a matrix material for immediate release and sustained or controlled release dosage forms. It could be freeze-dried and hot-melt extruded to produce granules, pellets and melted products.

Kadir et al. (2011) used Kollidon® VA-64 to enhance solubility of ibuprofen by preparing solid dispersion by co-precipitation method. The results showed that when the amount of Kollidon® VA-64 was increased, the dissolution of ibuprofen was also improved.

Ranzani et al. (2011) used Kollidon® VA-64 to enhance solubility of cannabinoid type 1 (CD-1) with solid solution system by hot-melt extrusion. Hansen's solubility parameters were calculated to check miscibility between the drug and Kollidon® VA-64. The results showed that the dissolution rate of CD-1 was improved around 1.8-fold when compared with pure drug.

5.4 Eudragit® EPO

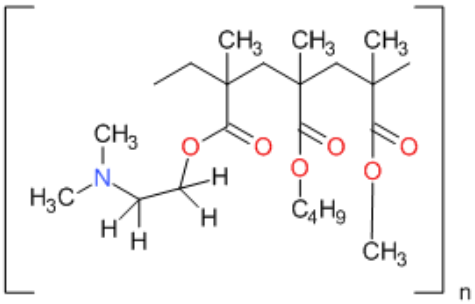


Figure 2-6 Chemical structure of Eudragit® EPO (Eudragit® EPO Technical information, Evonik industry, 2008)

Eudragit® EPO is poly(butyl methacylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) in a ratio of 1:2:1. It appears as white powder with a characteristic amine-like odour and has molecular weight of 47,000 g/mol. The glass transition temperature of Eudragit® EPO is approximately 48 °C. Eudragit® EPO is dissolved in methanol, ethanol, isopropyl alcohol, acetone, ethyl acetate, methylene chloride. Eudragit® EPO is used in many applications such as pH-dependent controlled drug release, protection of active ingredient from gastric fluid, moisture protection of sensitive active ingredients, taste masking, smooth surfaces and good color coating. Eudragit® EPO is used to prepared solid solutions/solid dispersion by solvent evaporation method and hot-melt extrusion method.

Six et al. (2003) used Eudragit® EPO to enhance solubility of itraconazole with solid dispersion system by using a co-rotating twin-screw hot-stage extruder. The results showed that the extrudates of itraconazole and Eudragit® EPO were completely miscible and dissolution rate was significantly increased.

Tang et al. (2011) used Eudragit® EPO to enhance solubility of genistein, isoflavone. Genistein were prepared in nanoparticle by precipitation technique using Eudragit® EPO as carriers. The results showed that genistein nanoparticles has two times greater dissolution rate than conventional capsules (Tang et al., 2011).

5.5 Kollidon® K-30

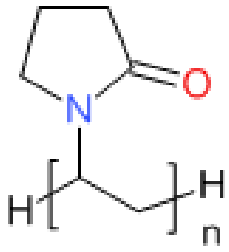


Figure 2-7 Chemical structure of Kollidon® K-30 (Kollidon® Technical Information, BASF, 9th Revision, 2008)

Kollidon® K-30 is vinylpyrrolidone. It appears as free-flowing white or yellowish-white hydroscopic powders with very little taste and has molecular weight of 60,000 g/mol. The glass transition temperature of Kollidon® K-30 is approximately 149 °C. Kollidon® K-30 is widely used in a various industry. Kollidon® K-30 is dissolved in all hydrophilic solvents such as water, ethanol, isopropanol, methylene chloride, glycerol and propylene glycol. It is soluble in water and organic solvents. It has affinity to both hydrophobic and hydrophilic compound. Kollidon® K-30 is used as excellent binder in wet granulation process. Kollidon® K-30 is also used in dry granulation and direct compression process. Kollidon® K-30 is used to improve dissolution rate and bioavailability of active ingredient by solid solutions/solid dispersion systems by spray-drying, vacuum-drying, freeze-drying, cogrinding and hot-melt extrusion.

Yu et al. (2010) used Kollidon® K-30 to enhance solubility of acetaminophen using electrospinning process. Solid dispersion was successfully prepared in this process. The results showed that dissolution of acetaminophen was released 93.8% in 2 minutes. It showed dramatically better dissolution than pure drug.

Hasnian et al. (2012) used Kollidon® K-30 to enhance solubility of ibuprofen by solid dispersion technique. Solid dispersion were prepared by solvent evaporation technique. The results showed that dissolution was improved. XRPD patterns showed reduced crystallinity of the drug.

5.6 Polyvinyl alcohol (PVA)

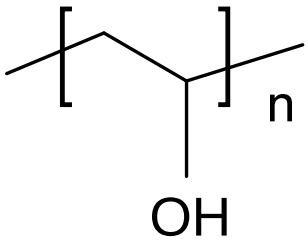


Figure 2-8 Chemical structure of polyvinyl alcohol (Pharmaceutical excipients, 3th Revision, 2006)

Polyvinyl alcohol (PVA) appears as water-soluble synthetic resin, odorless, white to cream-colored granular powder and has molecular weight of high viscosity about 130,000–200,000 g/mol, medium viscosity about 130,000 g/mol and low viscosity about 20,000 g/mol. The glass transition temperature of PVA is approximately 85 °C. PVA is dissolved in water, slightly soluble in ethanol, insoluble in organic solvents.

PVA is used in topical pharmaceutical and ophthalmic formulations. In topical lotions, PVA is used about 2.5% w/v in formulation. In ophthalmic solutions, PVA is used about 0.25-3.00% w/v. It is used as a stabilizing agent for emulsions in concentration of 0.25–3.0% w/v. It is also used as a viscosity enhancing agent. It is used in artificial tears and contact lens solutions. It is also used in sustained-release formulations for oral administration and transdermal patches.

Tapas et al. (2010) used PVA to enhance the dissolution rate of felodipine by spherically agglomeration technique. The results showed that the spherical agglomerates of felodipine with PVA were dramatically increased in dissolution rate.

Alanazi et al. (2011) used PVA to enhance the dissolution rate of albendazole prepared as microparticles by spray dried technique. The results showed that the dissolution rate of albendazole was improved extremely by spray dried microparticles when compared with the physical mixtures.

5.7 Hydroxypropyl cellulose (HPC)

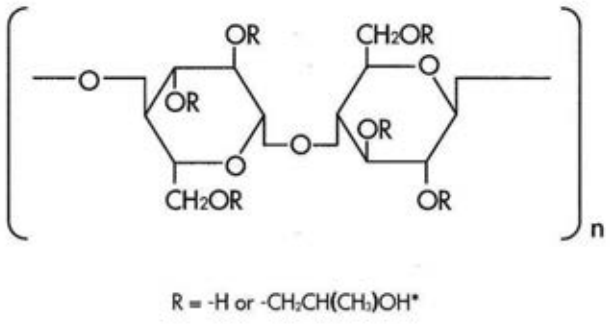


Figure 2-9 Chemical structure of hydroxypropyl cellulose [Online]. Available form: (http://www.harke.com/index.php?id=1409 [2012,September 29]

Hydroxypropyl cellulose (HPC) appears as white to slightly yellow-colored powder, odorless and tasteless and has molecular weight of 50,000–1,250,000 g/mol. The glass transition temperature of HPC is approximately 105 °C. HPC is dissolved in 1:10 in dichloromethane, 1:2.5 in ethanol, 1:2 in methanol 1:5, in propan-2-ol, 1:5 in propylene glycol, 1:2 in water.

HPC is used as binder, film-coating, controlled release matrix in tablet formulations. HPC at concentrations of 2–6% w/w is used as binder in wet granulation, dry granulation and direct-compression tableting processes. HPC at concentrations of 15–35% w/w is used as extended drug release control agent. The release rate of the drug increases when viscosity of hydroxypropyl cellulose decreases. HPC at concentrations of 5% w/w of hydroxypropyl cellulose in solution preparation is used to film-coat tablets. HPC is also used in microencapsulation processes, transdermal patches and ophthalmic preparations.

You et al. (2008) used HPC to enhance the dissolution rate of nitrendipine by solvent evaporation method. The results showed that dissolution rate of nitrendipine were greatly improved with HPC.

Onoue et al. (2010) used HPC to enhance the dissolution rate of cyclosporine using high-energy amorphous solid dispersion system. This system was prepared with wet-mill employing zirconia beads. The results showed that dissolution rate of cyclosporine were improved with HPC (Onoue et al., 2010).

CHAPTER III

EXPERIMENTAL

1. Materials

The following materials obtained from commercial sources were used.

1.1 Drugs and Excipients

- Efavirenz (Batch No. 41031820, Hualian Pharmaceutical Factory, Changzhou, China, supplied by Thailand Government Pharmaceutical Organization)
- Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®, Lot.No. 20777268E0, Ludwigshafen, Germany, supplied by BASF (Thai) Ltd.)
- Vinylpyrrolidone-vinyl acetate copolymers (Kollidon VA-64®, Lot.No. 28769724U0, Ludwigshafen, Germany, supplied by BASF (Thai) Ltd.)
- Polyvinylpyrrolidone (Kollidon K-30®, Lot No. 15248888Q0, Ludwigshafen, Germany, supplied by BASF (Thai) Ltd.)
- Dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate copolymer (Eudragit EPO®, Lot.No. G050731088, New Jersey, United States of America, supplied by JJ Degussa (Thai) Ltd.)
- Polyvinylalcohol, M.W. = 22,000 (PVA, Lot No. AH512105, Chem sources, Bangkok, Thailand)
- Hydroxypropylcellulose , M.W. = 50,000 (HPC, Lot No. PD300936, Chem sources, Bangkok, Thailand)
- Ammonium dihydrogen phosphate (Lot no. 0912491, Ajax finechem, Ontario, Canada)
- Ortho-phosphoric Acid (Lot no. 1003346, Ajax finechem, Ontario, Canada)
- Acetonitrile HPLC Grade (Lot No. L54A1H, Burdick&Jackson Honeywell, Seoul, Korea)

- Methanol HPLC Grade (Lot No. LBAG2H, Burdick&Jackson Honeywell, Seoul, Korea)
- Deinoized water
- 95% Ethyl alcohol (Ayudthaya Spirit Factory, Excise Department, Thailand)

2. Equipment

- Analytical balance (Model PB3002, Mettler Toledo, Zürich, Switzerland and Model A200s, Sartorius Gmbh, Goettingen Germany)
- Hot air oven (Model UL 80, Memmert, Schwabach, Germany)
- Differential scanning calorimetry (Model PB822e, Mettler Toledo, Zürich, Switzerland)
- Thermo gravimetric analyzer (TGA Model DSC/TGA1, Mettler Toledo, Columbus, United States of America)
- Polarizing optical microscope (Model Eclipse E200, Nikon, Tokyo, Japan)
- Digital camera (Model Coolpix4000, Nikon, Tokyo, Japan).
- Hot-stage microscope (Model FP82HT, Mettler Toledo, Columbus, United States of America)
- Hot-melt extrusion (Model HAAKE MiniLab II Micro Compounder, Thermo Scientific, Karlsruhe, Germany)
- X-ray diffractrometer (Model Miniflex II, Rigaku, Tokyo, Japan)
- Fourier transform infrared spectroscopy (Model Spectrum 100, Perkin Elmer , Massachusetts, United states of America)
- Dynamic vapor sorption analyzer (Model Intrinsic, SMS, London, United Kingdom)
- pH meter (model Orion 210A+, Thermo Scientific, Karlsruhe, Germany)
- USP dissolution apparatus II (Model VK 7000, Vankel, Maryland, United states of America)
- High-performance liquid chromatography (LC-20AC, Shimatsu, Tokyo Japan) with a reverse phase column Hypersil C-18 column (Thermo Scientific, Karlsruhe, Germany)

3. Methods

1. Solubility parameter calculation

The calculation of Hansen solubility parameters of efavirenz and polymers were carried out by Hoftyzer and Van Krevelen equation (Hoftyzer et al., 1974) to evaluate drug-polymer miscibility in this study. The calculations were carried out to evaluate efavirenz and polymers miscibility. The solubility parameters were calculated using Van Krevelen method (Hoftyzer et al., 1974). Van Krevelen equation is according to equation 1

$$\delta t = \sqrt{\delta d^2 + \delta p^2 + \delta h^2} \quad (1)$$

When δt is total solubility parameter; δd is contribution from dispersion forces; δp is contribution from polar forces and δh is contribution of hydrogen bonding;

Whereas;

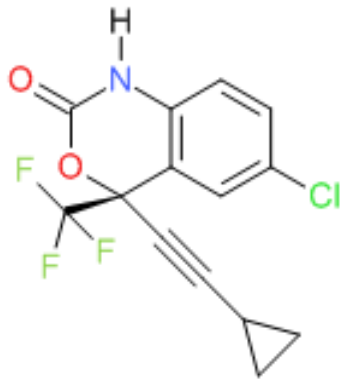
$$\delta d = \frac{\sum F_{di}}{V} \quad (2)$$

$$\delta p = \frac{\sqrt{\sum F_{pi}^2}}{V} \quad (3)$$

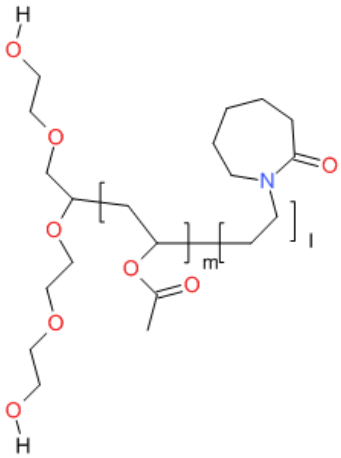
$$\delta h = \sqrt{\frac{\sum E_{hi}}{V}} \quad (4)$$

When F_{di} is molar attraction constant due to dispersion component; F_{pi} is molar attraction constant due to polar component; E_{hi} is hydrogen bonding energy and V is molar volume.

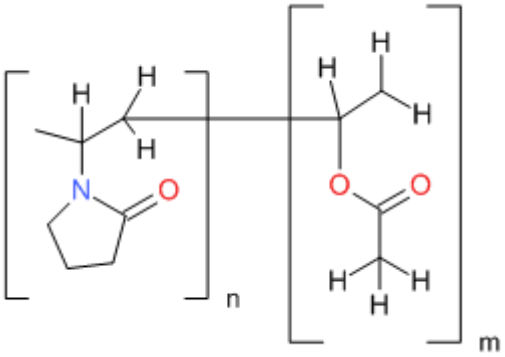
For various terms, the values of F_{di}, F_{pi}, E_{hi}, Δe_i, and V (molar volume) are listed in literature. Compounds with similar δ values are expected to be miscible which may be grouped into three categories according to the difference between the solubility parameters of two compounds and drugs ($\Delta\delta$) (Forster et al., 2001). Compounds which having $\Delta\delta$ below 10.0 $MPa^{1/2}$ are likely to be miscible or partially miscibility and form solid solution. Compounds having $\Delta\delta$ over 10 $MPa^{1/2}$ are likely to be significantly immiscible and are not expected to form solid solution.



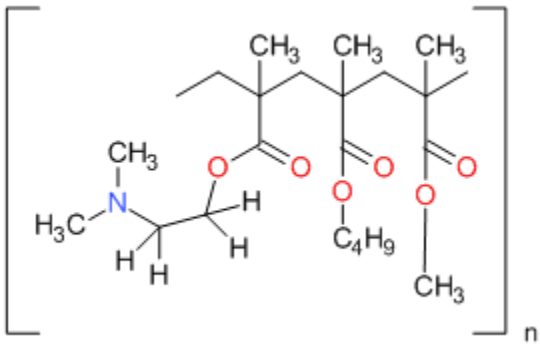
(A)



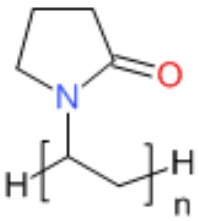
(B)



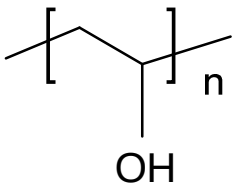
(C)



(D)



(E)



(F)

(G)

Figure 3-1 Chemical structures of (A) efavirenz (B) Soluplus® (C) Kollidon® VA-64 (D) Eudragit® EPO (E) Kollidon® K-30 (F) PVA (G) HPC

2. Film casting

Efavirenz and polymers (Soluplus®, Kollidon VA-64®, Kollidon K-30®, Eudragit EPO®, PVA or HPC) were dissolved in ethanol to obtain 10% w/v solution. Then, the drug and polymer solutions were mixed in proportions of 10:90, 30:70, 50:50, 70:30, and 90:10 by volume, resulting in a clear mixtured solution. After stirring and vortexing, the solution was casted on a 3×3 inches glass plate. Drying was performed at 40 °C for 1 hour in a tray dryer and the glass plate was kept under ambient condition for 24 hours. Observation was performed after 24 hours. Poorly miscible mixture resulted in cloudy film. A solid solution resulted in clear film.

3. Preparation of physical mixture

Efavirenz and polymers (Soluplus®, Kollidon VA-64®, Kollidon K-30®, Eudragit EPO®, PVA, and HPC) were accurately weighed in a proportional of 10:90, 30:70, 50:50, 70:30 and 90:10 and pulverized thoroughly in a mortar with a pestle. The physical mixtures were kept in a desiccator for further investigation.

4. Hot-melt extrusion (HME)

Efavirenz and polymers in a proportional of 50:50 were accurately weighed and blended in a mortar and pestle. The dry mixture was further mixed in a plastic bag for about 5 min. HME was performed by double-cone hot-melt extruder at the temperature 20 °C above each glass transition temperature of each polymer. The screw speed was kept at 80 rpm. The extrusion was carried out at 5 grams per run. The extrudate was cooled at ambient temperature and stored in a desiccator.

5. Characterization of physical mixtures and products

5.1 Thermal Analysis

5.1.1 Thermogravimetric analysis (TGA)

The decomposition temperatures of efavirenz and polymers were investigated by thermogravimetric analysis. The sample was heated from 25 to 280°C at a heating rate of 10°C/min under a nitrogen purge at 60 ml/min.

5.1.2 Hot-stage microscope (HSM)

Thermal behavior of efavirenz, polymers and physical mixtures in a proportion of 10:90, 30:70, 50:50, 70:30 and 90:10 was investigated using polarizing optical microscope with attached digital camera. The sample about 5–10 mg was placed between a glass slide 1×3 inch and a cover glass and then fixed on a hot-stage. The sample was heated from 25 to 180 °C at a heating rate of 10 °C/min.

5.1.3 Differential scanning calorimetry (DSC)

Thermal behaviors of efavirenz, polymers and physical mixtures of the drug and polymer in the proportions of 10:90, 30:70, 50:50, 70:30 and 90:10 and the extrudate were investigated using DSC. The sample of 5-6 mg was weighed into a DSC pan. The experiment was performed under a nitrogen purge at 60 ml/min. Glass transition temperature (T_g) of individual component and physical mixtures was determined by heating the sample from 25 and 180°C at a heating rate of 10 °C/min. After the sample was kept at 180 °C for 5 min, the melt was rapidly cooled to -20°C at a cooling rate 20 °C/min. The cooled melt was kept at -20°C for 5 min before reheated to 180 °C at a heating rate at 10 °C/min. If the drug and polymer were completely miscible, one glass transition temperature would be found in third round of DSC. For an immiscible mixture, two glass transition temperatures (T_g of efavirenz and polymer) would be found. Partial miscibility, glass transition temperature would

also result in two glass transition temperatures where at least one is shifted (Forster et al., 2001).

To investigate thermal behavior of the extrudate, the samples were ground and heated in DSC pan. The samples were heated from 25 to 180 °C at a heating rate of 10°C/min under a nitrogen purge at 60 ml/min.

5.2 X-Ray powder diffraction (XRPD)

Efavirenz, polymers, physical mixtures of the drug and each polymer were blend in mortal and pestle. The extrudates were ground. Crystallinity of efavirenz, polymers, physical mixtures and ground extrudate were investigated by X-ray powder diffractometer with Cu-Kα radiation. The experiments were performed from 5-40^{o} 2θ at a rate of 1 degree/min.

5.3 Fourier transform infrared spectroscopy (FT-IR)

Efavirenz, polymers, physical mixture were blend in mortal and pestle. Extrudates were crushed to be the powder. Fourier transform infrared spectroscopy patterns of the physical mixtures and ground extrudate were investigated by using potassium bromide disks. The detection was scanning at the range from 4000 to 400 nm^{-1}.

5.4 Dynamic vapor sorption (DVS)

The moisture sorption analysis of extrudate were investigated by dynamic vapour sorption (DVS). Extrudates were crushed to be the powder. The study was carried out under humidity controlled with twin microbalance apparatus. Humidity was controlled with nitrogen purge at 100 ml/min. Samples of approximately 15 mg was placed on one side of pan. The temperature was set at 30 °C. The humidity was set to start at 0% relative humidity (RH) in 10 minutes and then raised each step up to 90% RH with 10% RH interval. With each raising humidity time, the humidity was set to hold at each %RH interval by *dm/dt* for completely equilibrium. In this

experiment, *dm/dt* was set less than 0.05% in 30 seconds. The absorption/desorption cycle was carried out from 0% RH to 90% RH and vice versa for four cycles on the same sample.

6. Assay

6.1 High-performance liquid chromatographic technique for drug analysis

Chromatographic conditions

According to Indian Pharmacopoeia 2007 (IP), efavirenz can be analyzed by high- performance liquid chromatographic (HPLC) technique. The HPLC system used for method validation was Shimadzu model HPLC LC-20AC with one isocratic pump. Analysis of efavirenz was carried out on a reverse phase column Hypersil C-18 250 x 4.6 mm internal diameter. The mobile phase comprised a mixture of buffer ammonium dihydrogen phosphate and acetonitrile in proportion of 50:50 v/v. The pH of the mixture was adjusted to 3.0 with ortho-phosphoric acid. The ammonium dihydrogen phosphate buffer was prepared by dissolving 8.6 g of ammonium dihydrogen phosphate in one liter of filtrated ultrapure water. The mobile phase was filtered through 0.45-micron membrane filter, degassed in ultrasonic bath and pumped from the respective solvent reservoir to the column at a flow rate of 1.5 mL/min. The column temperature was maintained at 40°C and the detection wavelength was 254 nm. The injection volume was 20 μL. The column was equilibrated for 60 min with mobile phase prior to the injection of the drug solution

Preparation of standard solution

The standard stock solution of efavirenz 1.0 mg/mL was prepared by dissolving efavirenz working standard in methanol. The standard solution of 0.1 mg/mL was prepared by dilution using stock standard solution in mobile phase.

Preparation of sample solution

Efavirenz were weighed and transferred into a clean and dry mortar, which was then ground. A sample equivalent to 12 mg of efavirenz was taken in 100 mL volumetric flask with adding of 100 mL of methanol and then soniccated for 10 min to final concentration of 0.12 mg/mL. All the experiments were conducted in triplicate.

6.2 Validation for the quantitative determination of efavirenz

According to United States Pharmacopeia 35–National Formulary 30 (*USP 35–NF 30)*, the analytical methods were evaluated to ensure acceptability the criteria of the United States of pharmacopeia. The analytical method was validated for specificity, linearity, precision and accuracy.

6.2.1 Specificity

Specificity suggests that the signal measured comes from the substance of interest, and that the peaks of other components i.e. polymers must not interfere with the peak of efavirenz. The validation was made by comparing between the standard efavirenz chromatogram and chromatograms of the physical mixture of efavirenz and the polymers solution. In an attempt to develop a stability indicating assay method, efavirenz was treated under different conditions. Heat degradation was carried out by heating the drug at 110°C for 3 hours. Acidic degradation was carried out by adding 5 mL of 0.1N HCl to 5 mL of sample solution of efavirenz. Basic degradation was carried out by adding 5 mL of 0.1N NaOH solution to 5 mL of sample solution of efavirenz. All the degraded drug solutions after appropriate dilutions (0.12 mg/mL) with mobile phase were injected in the chromatographic system.

6.2.2 Linearity

The linearity of efavirenz was verified at seven concentration levels ranging from 0.05-0.15 mg/mL (0.05, 0.08, 0.09, 0.1, 0.11, 0.12 and 0.15 mg/mL). The calibration curve was constructed by plotting mean area response (A) against concentration (C). Linearity is determined by calculating the regression line using a mathematical treatment of the results such as least mean square (R^2). The acceptance criteria assay of least mean square should not be less than 0.995 (*USP 35–NF 30)*.

6.2.3 Precision

Within run precision

Method repeatability (intra-day precision) was evaluated by analyzing in six replicates (n=6) for each of three concentrations of efavirenz standard solution, prepared on the same day. The percent coefficient of variation (%CV) and relative standard deviation (%RSD), which is well within the acceptance criteria between 97.0 and 103.0% and RSD should be not more than 2.0%, was calculated (*USP 35–NF 30)*.

Between run precision

Method repeatability (inter-day precision) was evaluated by analyzing in six replicates (n=6) for one concentration of efavirenz standard solution, prepared on 2 days. The percent coefficient of variation (%CV) and relative standard deviation (%RSD), which is within the acceptance criteria should be between 97.0 and 103.0% and RSD should be not more than 2.0%, was calculated.

6.2.4 Accuracy

Accuracy was determined in three replication (n=3) by applying the developed method to solutions which known amounts of each drug corresponding to

80,100 and 120% of label claim had been added. Average recovery values (mean ± S.D.) for efavirenz from the mixture, which is within the acceptance criteria should be between 98.0 and 102.0%, were calculated.

7. Dissolution studies

Dissolution profiles of efavirenz, the physical mixture between efavirenz and soluplus in the propotional of 50:50 and the extrudates were carried out using USP dissolution apparatus II (Paddle). The stirring speed was set at 100 rpm. Dissolution medium was 900 mL of distilled water of which the temperature at 37 ºC maintained. The sample equivalent to 50 mg of efavirenz was studied. 10 mL of sample was taken at 0, 10, 15, 20, 30, 40, 45, 60, 75 and 90 minutes, respectively. And then, the sample was replenished with 10 mL of distilled water. The sample was analyzed by High-Performance Liquid Chromatography (HPLC) at 254 nm. The study was carried out in triplicates.

CHAPTER IV

RESULTS AND DISSCUSION

1. Solubility parameter calculation

Solubility paramerter were used to evaluate miscibility between efavirenz and polymers. Results of solubility parameters are summarized in Table 4-1. Solubility parameter of efavirenz is 24.55 $MPa^{1/2}$ (Sathigari, 2011). According to Forster et al., 2001, they classified miscibility into 3 groups. If Δδ is less than 7, the drug and the polymer is miscible. If Δδ is between 7-10, the two compounds may be partially miscible. If Δδ is more than 10, they are immiscible. Soluplus®, Kollidon® VA-64, Eudragit® EPO and Kollidon® K-30 showed miscibility with efavirenz. However, PVA and HPC showed immiscibility with efavirenz.

Table 4-1 Solubility parameters of drug and polymers

Drug and Polymers	Solubility Parameters in MPa½	Δδ	Interpretation result by Hansen's method
Efavirenz	24.55 (Sathigari, 2011)		
Soluplus®	19.43 (Maniruzzaman, 2012)	5.12	Miscible
Kollidon® VA-64	19.60 (Maniruzzaman, 2012)	4.95	Miscible
Eudragit® EPO	20.55 (Chokshi, 2005)	4.00	Miscible
Kollidon® K-30	26.28 (Chokshi, 2005)	1.73	Miscible
PVA	41.12 (Chokshi, 2005)	16.57	Immiscible
HPC	11.6 (Choi, 1994)	12.95	Immiscible

2. Film casting

Film casting is one of preformulation screening method to evaluate miscibility between the drug and the polymers. Polymers which have high solubilization capacity are suitable for preparing solid solution because large quantities of drugs can be dissolved. In the present study, solubilization of the drug in the polymers was determined using film casting.

When the amount of efavirenz was increased, the more cloudy film could be observed. Soluplus®, Kollidon VA-64®, Eudragit EPO® and Kollidon K-30® showed the solubilization capacity at 50% drug. While, PVA and HPC showed the solubilization capacity at 30% drug. The results of film casting in drug/polymer 10:90, 30:70, 50:50, 70:30, and 90:10 are shown in Table 4-2 and an example of casted film of efavirenz and Soluplus® is presented in Figure 4-1.

Table 4-2 Solubilization capacity of polymers

Polymer	Efavirenz : Polymer				
	90:10	70:30	50:50	30:70	10:90
Soluplus®	×	×	O	O	O
Kollidon VA-64®	×	×	O	O	O
Eudragit EPO®	×	×	O	O	O
Kollidon K-30®	×	×	O	O	O
PVA	×	×	×	O	O
HPC	×	×	×	O	O

× represents cloudy film
O represents clear film

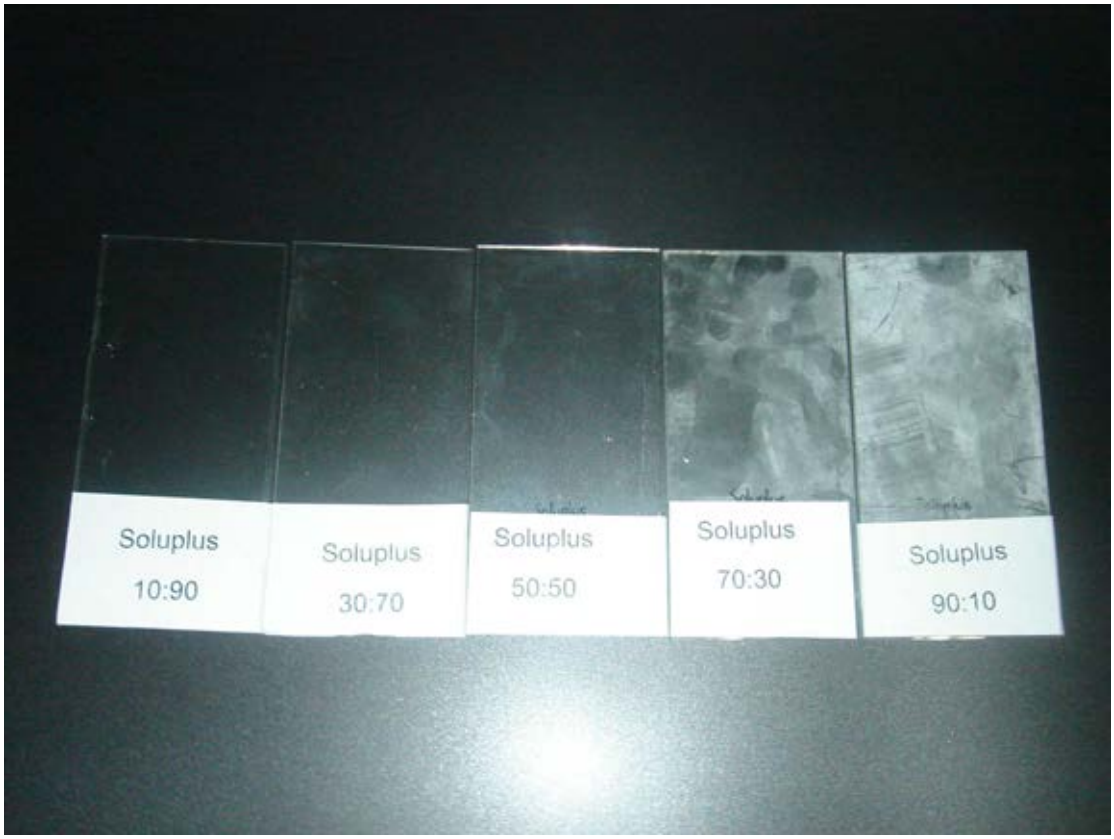


Figure 4-1 Film casting results of varied proportions of efavirenz and Soluplus®

3. Thermal analysis of raw materials and physical mixtures

Thermal analysis is one of many ways to investigate thermal behavior of raw materials. Differential scanning calorimetry **(**DSC) was used to determine melting temperature (T_m) of efavirenz and glass transition temperature (T_g) of pure polymers and physical mixtures. Hot-stage microscopy (HSM) was employed to determine whether the mixtures were miscible. Thermogravimetric analysis (TGA) was applied to find out the decomposition temperature of the drugs and polymer. These methods were carried out to suggest appropriate temperature in hot-melt extrusion process.

3.1 Differential scanning calorimetry (DSC)

DSC and HSM can be used in conjunction to evaluate miscibility of efavirenz and polymers (Forster et al., 2001). Miscibility was evaluated with DSC by glass transition temperature (T_g) of physical mixture and melting endotherm onset temperature (T_{mo}) of efavirenz. DSC data and thermogram of efavirenz and polymers was shown in Table 4-3 and Figure 4-6.

Table 4-3 Glass transition temperature (T_g) data of efavirenz and polymers

Drug : Polymer	T_m		T_g			
	Reported T_m	Measured T_m	Reported T_g	Measured T_g		
				Sample 1	Sample 2	Average (n=2)
Efavirenz	137.7 ± 0.1 (Kolter, 2007)	138.67	37.3 ± 0.2 (Kolter, 2007)	36.15	36.05	36.10
Soluplus	-	-	70 (Kolter, 2007)	72.19	68.21	70.20
Kollidon VA-64	-	-	101 (Kolter, 2007)	105.18	105.98	105.58
Eudragit EPO	-	-	50 (Liu, 2012)	58.53	58.43	58.48
Kollidon K-30	-	-	149 (Kolter, 2007)	155.64	155.25	155.45
PVA	-	-	85 (Strawhecker, 2000)	81.28	81.49	81.39
HPC	-	-	105 (Prodduturi, 2006)	105.52	106.53	106.03

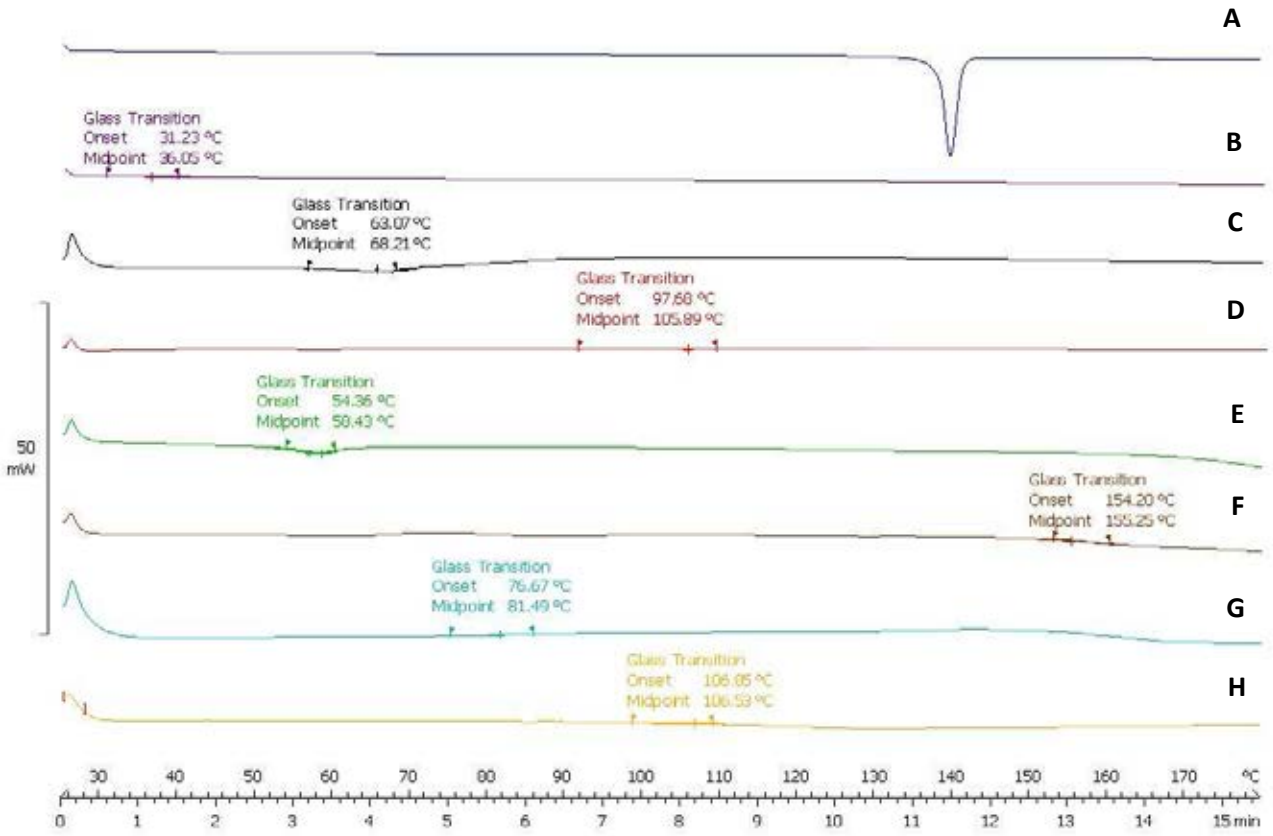


Figure 4-2 DSC thermograms of A) efavirenz (first cycle); B) efavirenz (third cycle); C) Soluplus®; D) Kollidon VA-64; E) Eudragit® EPO; F) Kollidon K-30 G) PVA; H) HPC

Thermal analysis indicated that miscibility of drugs and polymers could be evaluated by decrease in melting endotherms onset temperature (T_{mo}) or presense of only one glass transition temperature (T_g) (Forster et al., 2001). Thermal analysis of physical mixture was investigated and summarized in Table 4-4 and Figure 4-3 to 4-8.

In first cycle of DSC thermogram, efavirenz showed a sharp melting peak at 138.67 °C. This indicated that the starting efavirenz was in crystalline form. The polymer did not show sharp endotherm, hence, it was amorphous in nature.

Table 4-4 Data from heat-cool-heat DSC thermograms for various proportions of drug/polymer mixtures

Substance	**Ratio**	**Melting endotherm onset temperature (T_{mo}) [a] (^oC)**			**Heat of fusion (ΔH) [a] (J/g)**		
		Sample 1	Sample 2	Average (n=2)	Sample 1	Sample 2	Average (n=2)
Efavirenz : Soluplus®	90:10	136.41	135.42	135.92	6.09	5.72	5.91
	70:30	139.19	136.61	137.90	3.96	4.41	4.19
	50:50	130.46	129.38	129.92	3.62	3.87	3.75
	30:70	127.80	127.24	127.52	3.03	3.12	3.08
	10:90	126.96	126.32	126.64	0.43	0.68	0.56
Efavirenz : Kollidon® VA-64	90:10	135.29	135.17	135.23	5.06	5.21	5.14
	70:30	130.82	131.13	130.98	2.85	3.25	3.05
	50:50	124.37	124.02	124.20	2.34	2.46	2.40
	30:70	124.15	124.52	124.34	1.27	1.18	1.23
	10:90	106.75	107.88	107.32	0.60	0.74	0.67
Efavirenz : Eudragit® EPO	90:10	135.81	135.73	135.77	3.80	4.62	4.21
	70:30	135.08	136.46	135.77	4.51	4.24	4.38
	50:50	129.75	130.40	130.08	2.23	2.81	2.52
	30:70	100.97	123.86	112.42	2.21	2.63	2.42
	10:90	115.64	117.14	116.39	0.24	0.82	0.53
Efavirenz : Kollidon® K-30	90:10	135.57	132.94	134.26	8.03	7.32	7.68
	70:30	134.15	130.87	132.51	6.97	6.27	6.62
	50:50	129.49	129.60	129.55	1.41	0.82	1.12
	30:70	132.07	130.66	131.37	0.12	0.41	0.27
	10:90	131.56	130.44	131.00	0.04	0.13	0.09
Efavirenz : PVA	90:10	138.30	134.99	136.65	2.62	4.93	3.78
	70:30	137.20	134.80	136.00	4.88	3.92	4.40
	50:50	137.11	133.16	135.14	3.51	3.56	3.54
	30:70	135.73	132.72	134.23	3.54	3.24	3.39
	10:90	136.13	132.49	134.31	1.29	1.46	1.38
Efavirenz : HPC	90:10	137.83	136.67	137.25	5.2	4.92	5.06
	70:30	137.09	137.11	137.10	4.27	4.18	4.23
	50:50	136.19	136.47	136.33	2.58	3.16	2.87
	30:70	136.25	137.88	137.07	1.26	1.87	1.57
	10:90	135.05	137.31	136.18	0.16	0.51	0.34

[a] determined from first cycle when the sample was melted

Table 4-4 (continue)

Substance	Ratio	Glass transition temperature (T_g) [b] (n=2)		
		Sample 1	Sample 2	Average
Efavirenz : Soluplus®	90:10	38.07 , 69.32	39.42 , 71.97	38.75 , 70.65
	70:30	38.24	38.23	38.24
	50:50	56.11	56.21	56.16
	30:70	61.67	61.67	61.67
	10:90	65.03	64.88	64.96
Efavirenz : Kollidon® VA-64	90:10	37.57 , 107.51	39.98 , 106.05	38.78 , 106.78
	70:30	57.99 , 106.28	57.19 , 106.84	57.59 , 106.56
	50:50	71.51	70.83	71.17
	30:70	86.15	68.59	77.37
	10:90	102.32	102.51	102.42
Efavirenz : Eudragit® EPO	90:10	38.84 , 52.14	37.20 , 53.86	38.02 , 53.00
	70:30	39.15	39.76	39.46
	50:50	41.16	40.80	40.98
	30:70	41.98	42.05	42.02
	10:90	45.51	44.53	45.02
Efavirenz : Kollidon® K-30	90:10	38.08 , 150.62	38.68 , 149.79	38.38 , 150.21
	70:30	48.31 , 151.38	49.03 , 149.21	48.67 , 150.30
	50:50	95.04	95.09	95.07
	30:70	111.17	110.87	111.02
	10:90	123.35	123.74	123.55
Efavirenz : PVA	90:10	35.54 , 80.25	37.45 , 81.77	36.50 , 81.01
	70:30	37.47 , 82.91	38.49 , 81.76	37.98 , 82.34
	50:50	38.47	38.46	38.47
	30:70	38.57	36.52	37.55
	10:90	66.38	66.26	66.32
Efavirenz : HPC	90:10	38.02 , 102.14	38.78 , 101.35	38.40 , 101.75
	70:30	38.97 , 101.61	39.14 , 97.10	39.06 , 99.36
	50:50	38.34	39.47	38.91
	30:70	38.15	38.56	38.36
	10:90	46.31	46.31	46.31

[b] determined from third cycle when the sample was reheated

DSC was used in conjunction with HSM, which allows observation, to evaluate miscibility. The melting endotherm onset temperature (T_{mo}) and heat of fusion (ΔH) were used to investigate miscibility (Forster et al., 2001). DSC thermograms showed that T_{mo} and heat of fusion (ΔH) was decreased when increase amount of Soluplus®, Kollidon® VA-64, Eudragit® EPO and Kollidon® K-30. These showed that efavirenz began to dissolve in molten Soluplus®, Kollidon® VA-64, Eudragit® EPO and Kollidon® K-30 well before the melting point of efavirenz. Decreasing of T_{mo} indicated that efavirenz and Soluplus®, Kollidon® VA-64, Eudragit® EPO or Kollidon® K-30 were miscible. HSM results supported these findings. (Figure 4-10).

PVA and HPC at the entire ratio found that T_{mo} was unchanged when increase amount of polymer. These indicated that PVA and HPC were immiscible with efavirenz. This evidence was also supported by HSM (Figure 4-11).

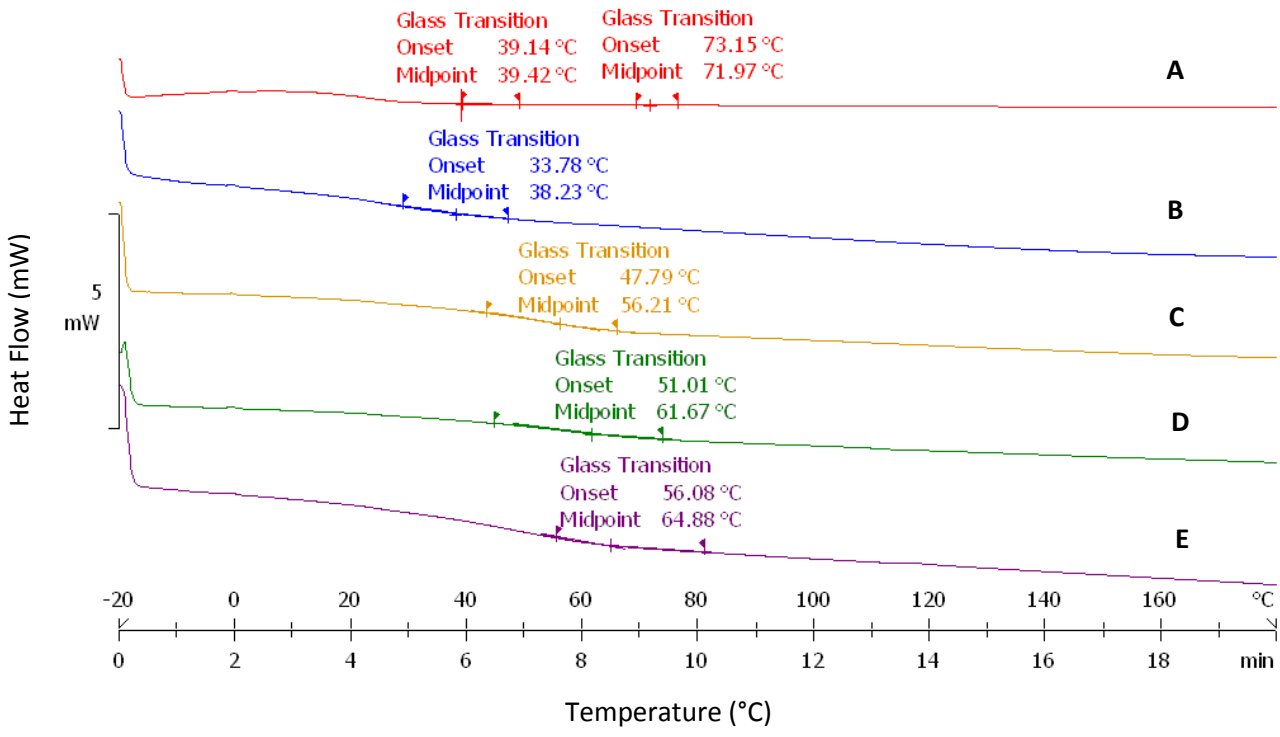


Figure 4-3 DSC thermograms of efavirenz and Soluplus® physical mixture in various proportions A) 90:10; B) 70:30; C) 50:50; D) 30:70; E) 10:90

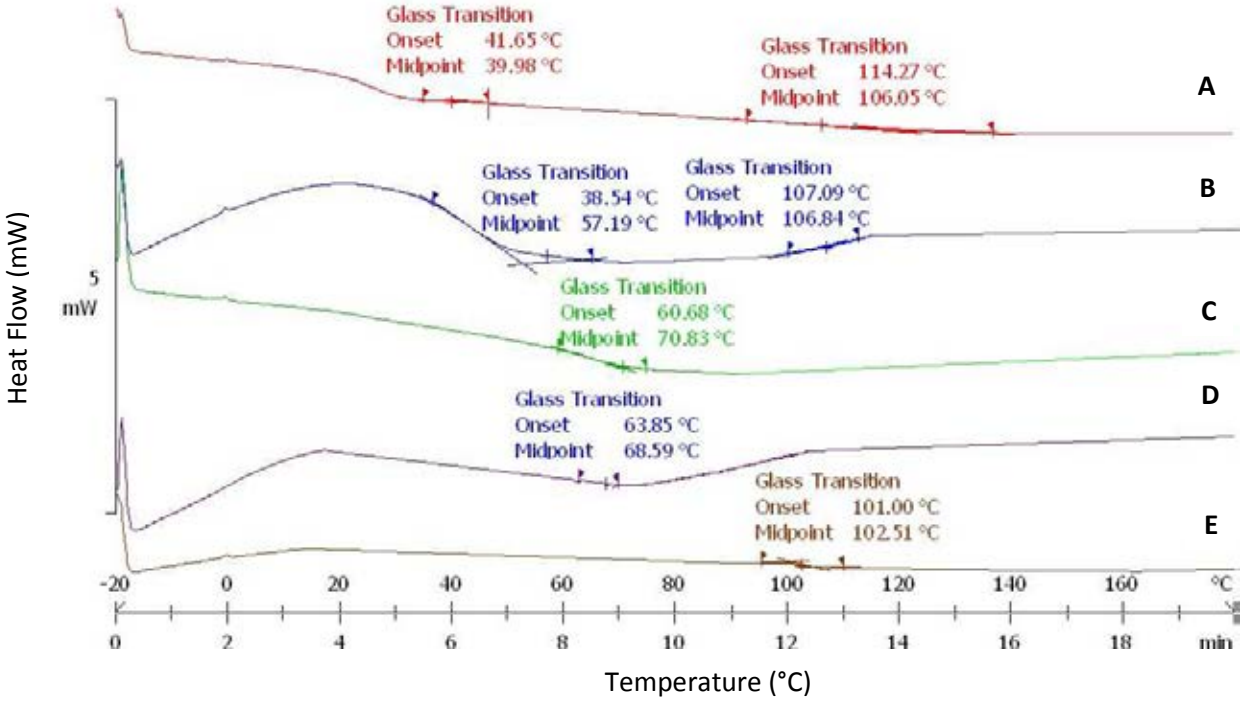


Figure 4-4 DSC thermograms of efavirenz and Kollidon® VA-64 physical mixture in various proportions A) 90:10; B) 70:30; C) 50:50; D) 30:70; E) 10:90

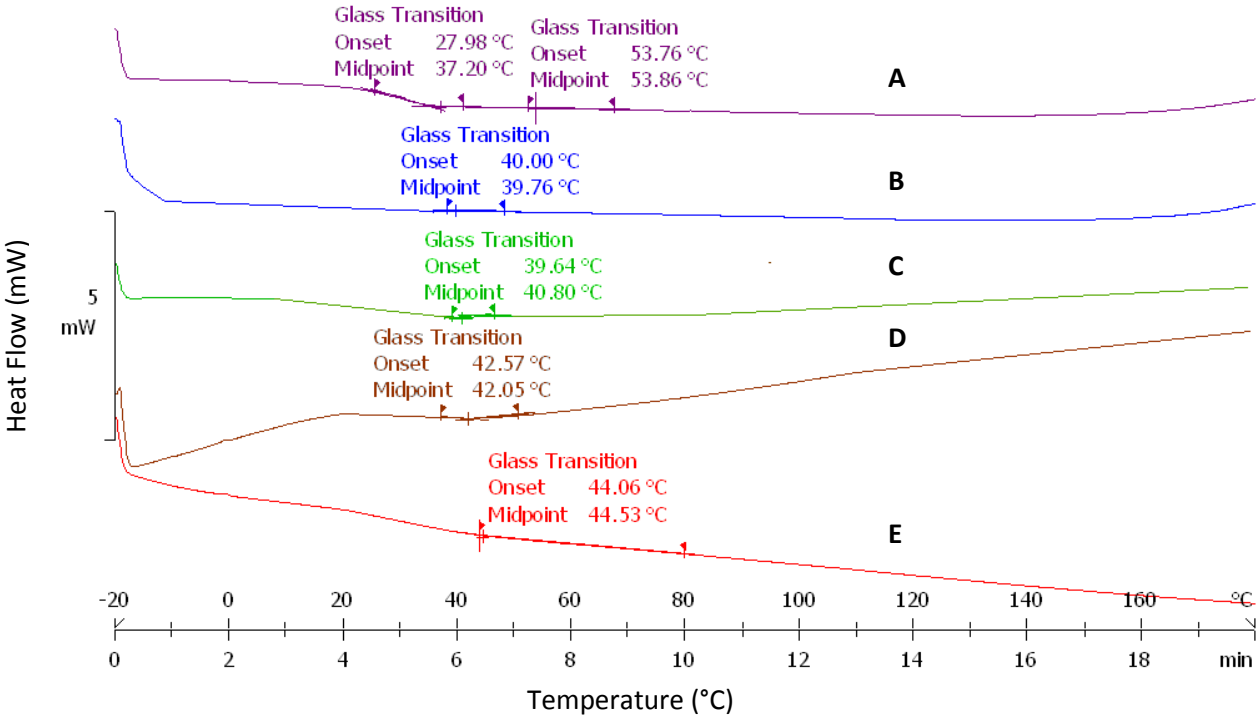


Figure 4-5 DSC thermograms of efavirenz and Eudragit® EPO physical mixture in various proportions A) 90:10; B) 70:30; C) 50:50; D) 30:70; E) 10:90

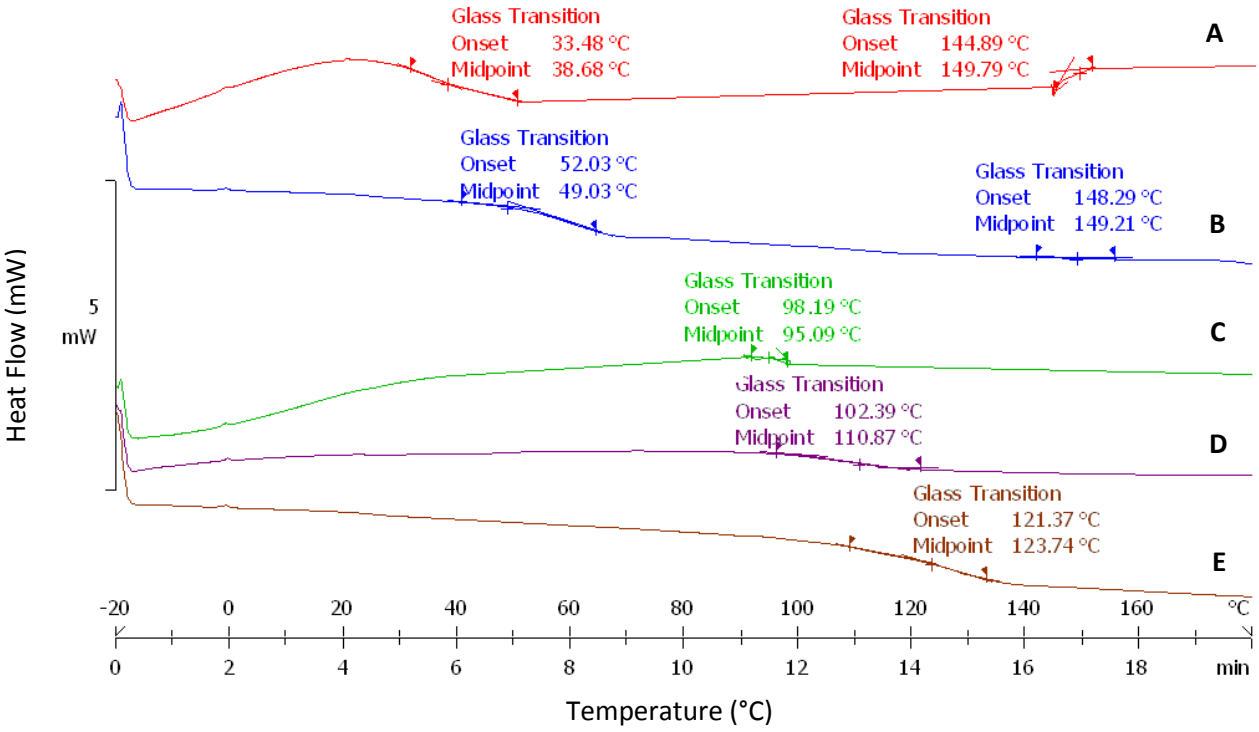


Figure 4-6 DSC thermograms of efavirenz and Kollidon® K-30 physical mixture in various proportions A) 90:10; B) 70:30; C) 50:50; D) 30:70; E) 10:90

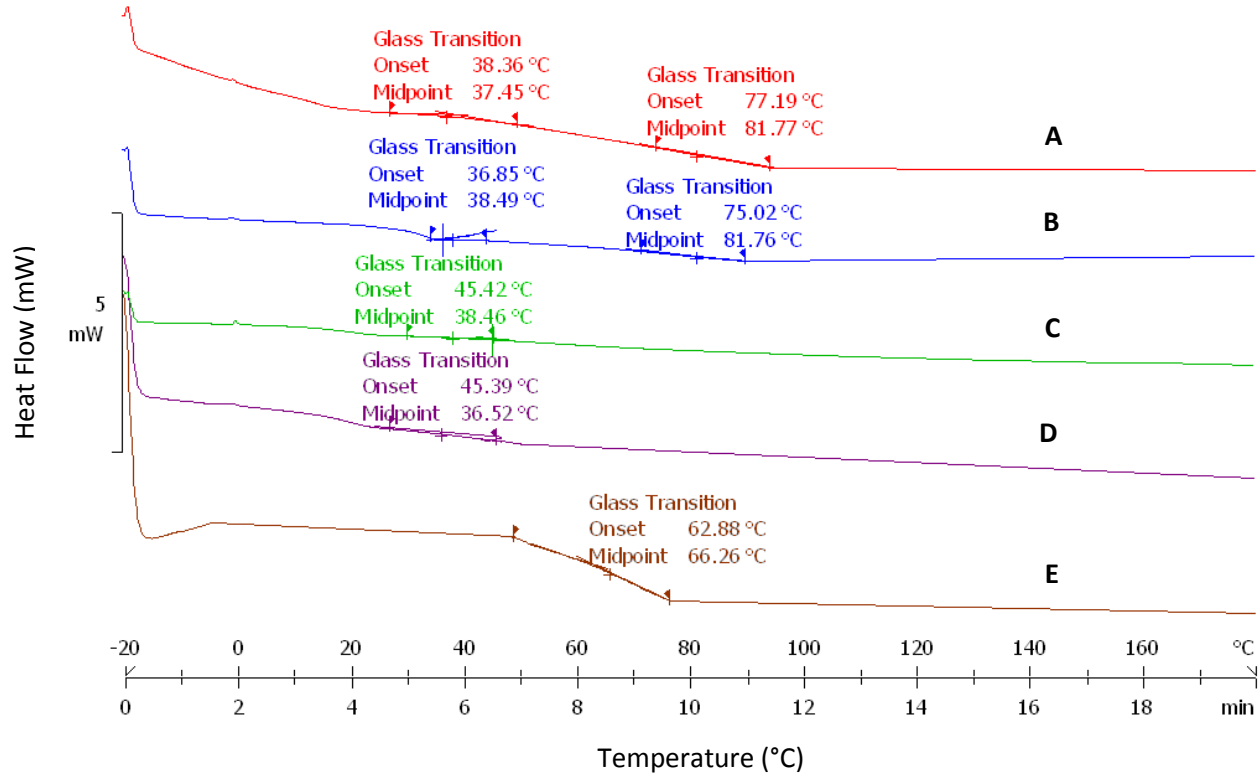


Figure 4-7 DSC thermograms of efavirenz and PVA physical mixture in various proportions A) 90:10; B) 70:30; C) 50:50; D) 30:70; E) 10:90

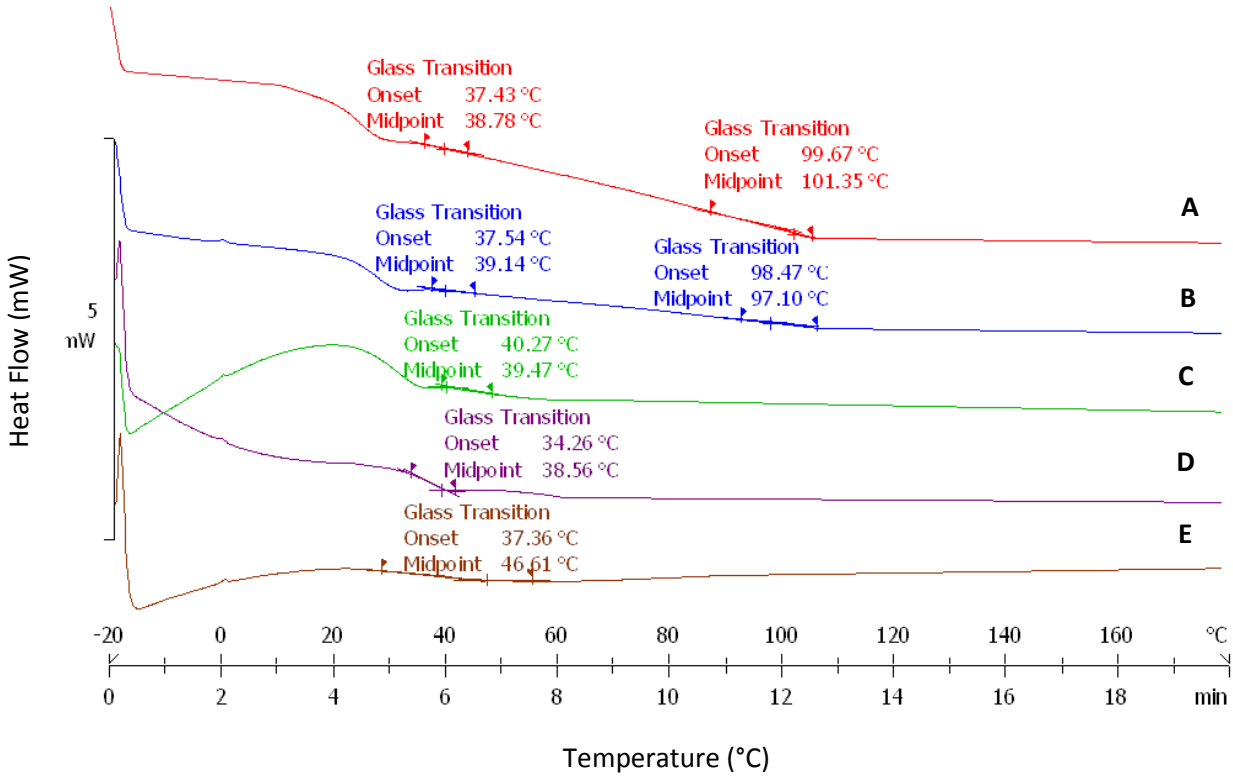


Figure 4-8 DSC thermograms of efavirenz and HPC physical mixture in various proportions A) 90:10; B) 70:30; C) 50:50; D) 30:70; E) 10:90

Glass transition temperature is one of evidence to evaluate miscibility. Only one T_g which between T_g of drug and polymer is an evidence for miscible system (Forster et al., 2001).

DSC thermogram obtained from heating the cooled melt indicated that efavirenz/Soluplus® and efavirenz/Eudragit® EPO showed two T_g at only proportion of 90:10; while the mixture of efavirenz and Kolldion® VA-64, Kollidon® K-30, PVA or HPC remained two T_g at the drug/polymer proportion of 90:10 and 70:30.

A single T_g was found if the mixture between the drug and polymer in each proportion was miscible. This phenomenon showed that there was single phase in the systems (Forster et al., 2001). The phase diagram plotting was shown in Figure 4-9. When the amount of efavirenz was increased, the glass transition temperature of physical mixture would be reduced close to efavirenz.

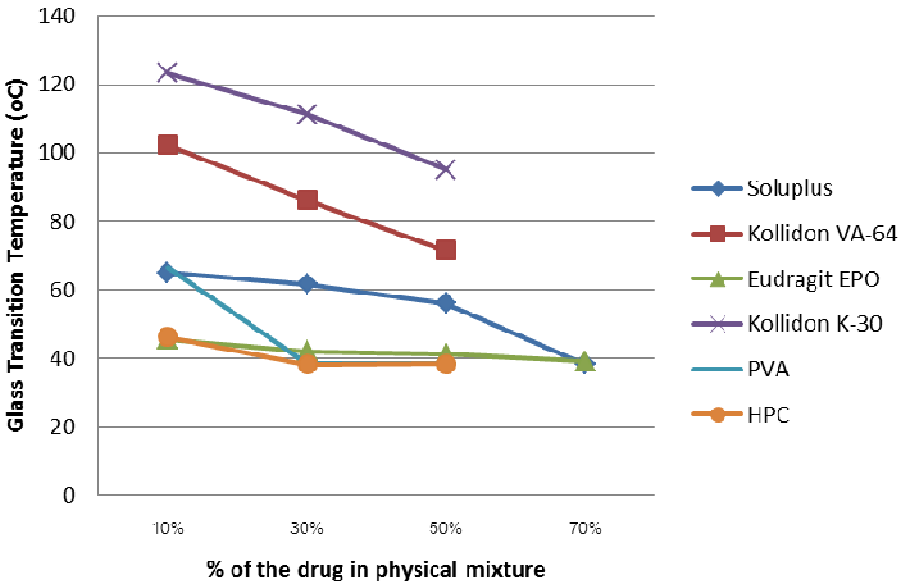


Figure 4-9 Glass transition temperatures of efavirenz/polymer physical mixtures, determined by heat-cool-heat cycles of DSC

3.2 Hot-stage microscope (HSM)

Hot-stage microscope is a helpful instrument which allows visualization of melting event. Analysis of melting endotherm onset temperature (T_{mo}) was used in this study to investigate miscibility in hot stage microscope process. Decreasing in T_{mo} indicated that efavirenz and polymers were miscible. If T_{mo} remained unchanged, this phenomenon indicated a lack of miscibility between efavirenz and polymers. These findings were supported with the HSM results from Forster et al.'s work (Forster et al., 2001).

HSM showed that change in the physical mixture of Soluplus®, Kollidon® VA-64, Eudragit® EPO and Kollidon® K-30 was observed at the temperature of 90 ºC, 115 ºC, 65 ºC and 125 ºC, respectively. The drug started to melt but remained mainly crystalline. The crystalline drug completely melted at 135 ºC which was closed to melting point (T_m) of the drug at 138.67 °C (Figure 4-10). The results agree with melting endoterm onset temperature of the physical mixture of drug and these polymers, which were lower than 135 °C. However, physical mixture of PVA and HPC at the temperature of 135-140 ºC was not completely melted which is melting point of efavirenz (Figure 4-11).

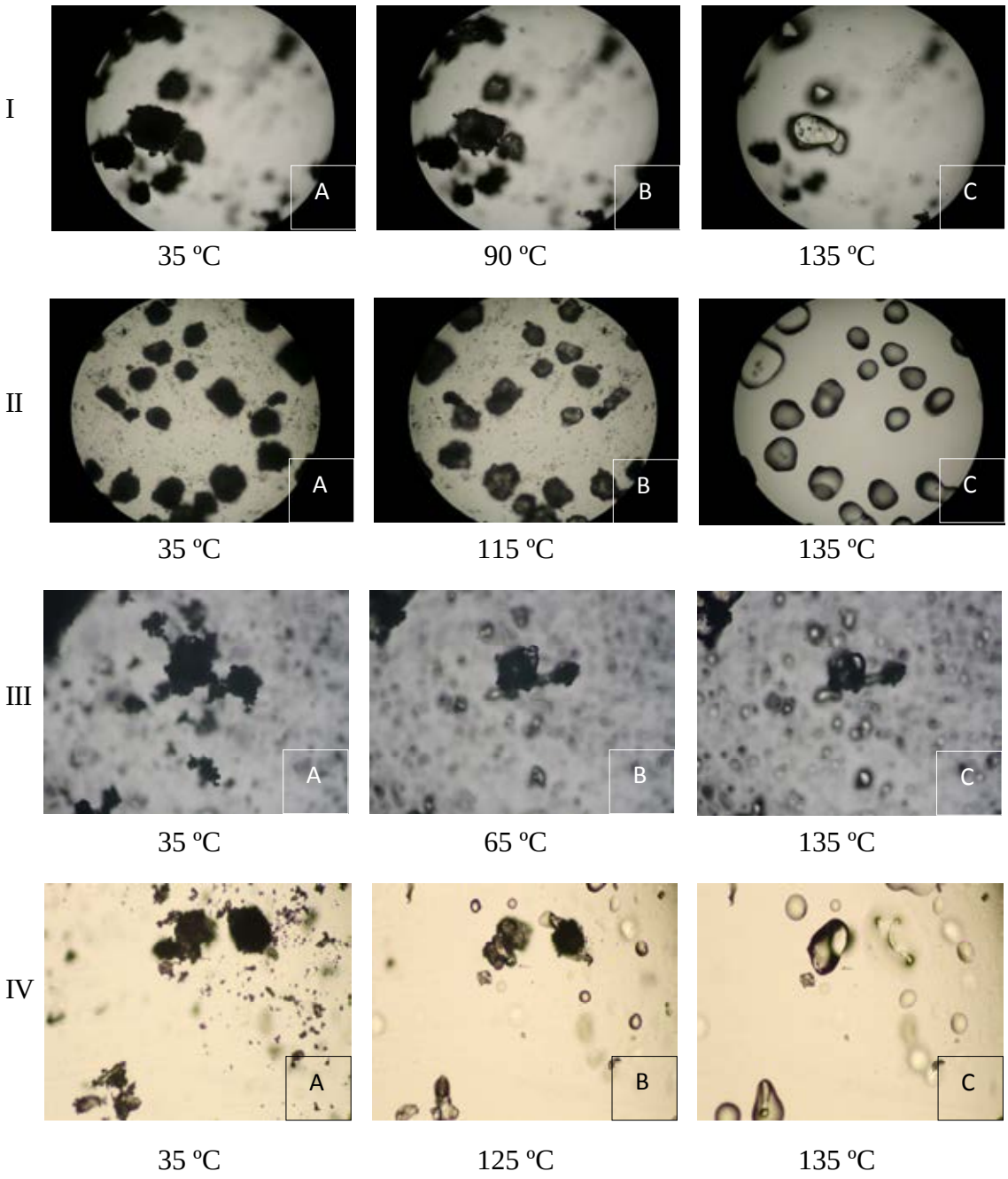


Figure 4-10 I Hot-stage photomicrographs of efavirenz and Soluplus® (50:50) mixtures at A) 30 ºC; B) 90 ºC; C) 135 ºC; II Hot-stage photomicrographs of efavirenz and Kollidon® VA-64 (50:50) mixtures at A) 30 ºC; B) 115 ºC; C) 135 ºC; III Hot-stage photomicrographs of efavirenz and Eudragit® EPO (50:50) mixtures at A) 30 ºC; B) 65 ºC; C) 135 ºC; IV Hot-stage photomicrographs of efavirenz and Kollidon® K-30 (50:50) mixtures at A) 30 ºC; B) 125 ºC; C) 135 ºC.

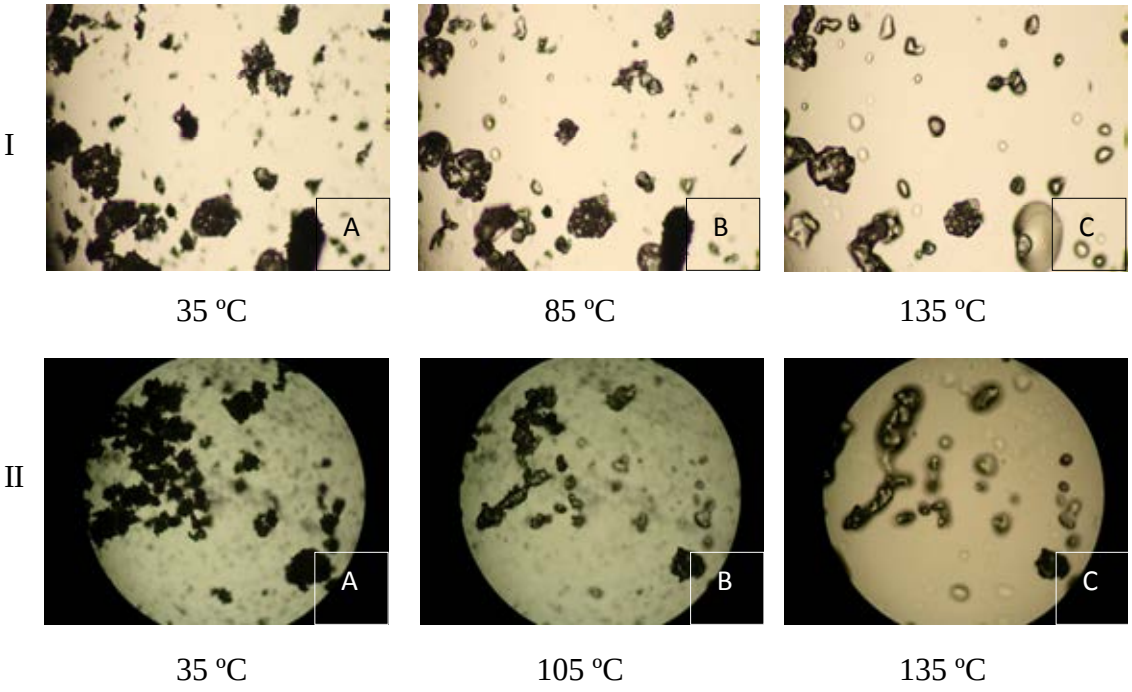


Figure 4-11 I Hot-stage photomicrographs of efavirenz and PVA (50:50) mixtures at A) 30 ºC; B) 85 ºC; C) 135 ºC; II Hot-stage photomicrographs of efavirenz and HPC (50:50) mixtures at A) 30 ºC; B) 105 ºC; C) 135 ºC**.**

3.3 Thermogravimetric analysis (TGA)

To ensure that the temperature that extrusion process was carried out would not cause degradation of the drug, thermal stability of the drug was investigated. The result from thermogravimetric profile showed that efavirenz was stable up to 247°C (Figure 4-12 and 4-13). The degradation temperature (T_{deg}) of polymers was summarized in Table 4-5. This suggested that extrusion process could be performed without causing drug degradation at the temperature above T_g of polymers 20 ºC.

Table 4-5 Degradation temperature (T_{deg}) of pure polymers

Polymer	Reported T_{deg} (°C)	Measured T_{deg} (°C)
Soluplus®	250 (Kolter, 2007)	268.38
Kollidon VA-64®	230 (Kolter, 2007)	262.97
Eudragit EPO®	Above 250 (Liu, 2012)	262.15
Kollidon K-30®	175 (Kolter, 2007)	192.45
PVA	Between 300-325 (Strawhecker, 2000)	above 280
HPC	Between 200-250 (Prodduturi, 2006)	227.32

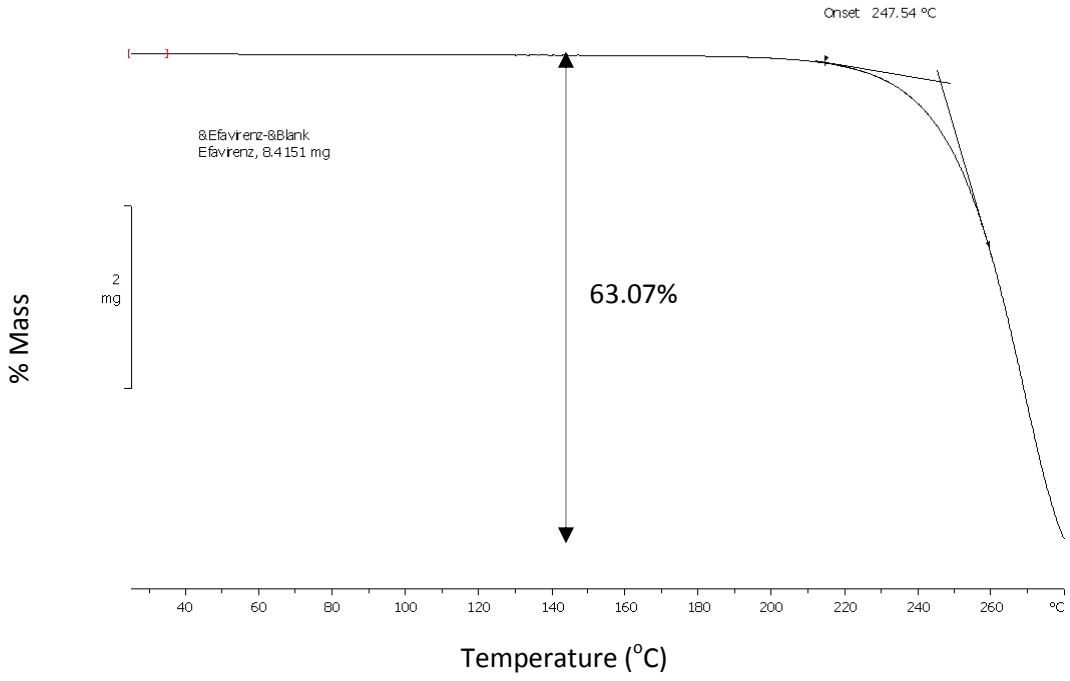


Figure 4-12 Thermogram of efavirenz by thermogravimetric analysis (TGA)

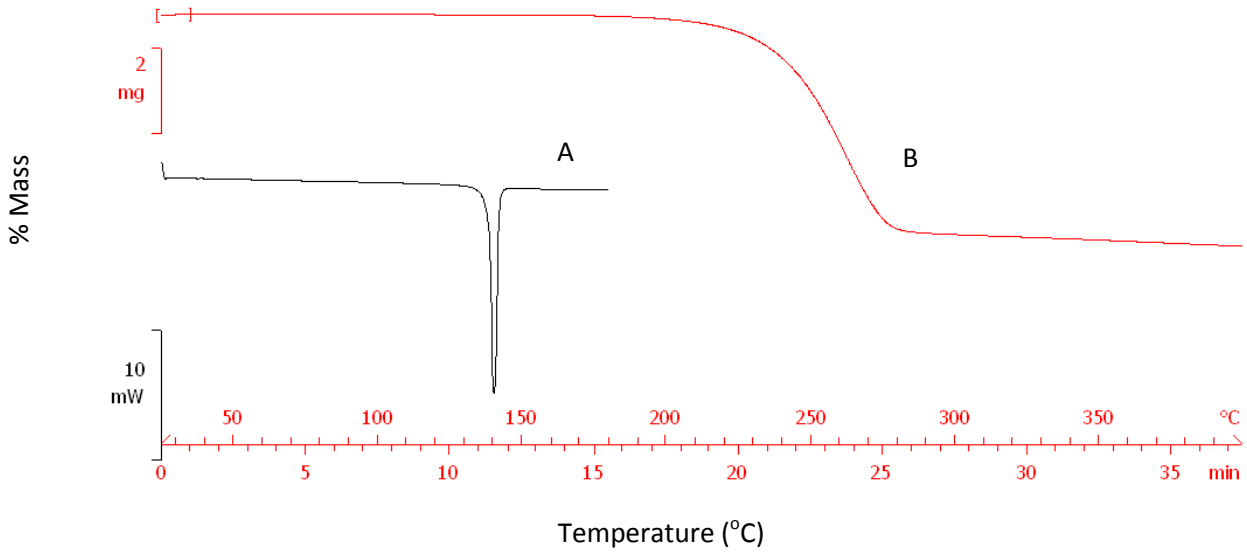


Figure 4-13 Thermogram of efavirenz by (A) Differential scanning calorimetry (DSC) (B) Thermogravimetric analysis (TGA)

Film casting technique, solubility parameters and thermal analysis was suggested to predict miscibility of the drug and polymers (Forster et al., 2001, Kolter, 2007). Overall, Soluplus®, Kollidon® VA-64, Eudragit® EPO and Kollidon® K-30 could be miscible with the drug and maximum solubilization capacity was 50% drug loading. Difference in the solubility parameter of efavirenz and that of the polymers (Δδ), Soluplus®, Kollidon® VA-64, Eudragit® EPO and Kollidon® K-30 were 5.12, 4.95, 4.00 and 1.73, respectively which were below 7. HSM of physical mixtures showed completely melted at 135 ºC.

In opposition, PVA and HPC showed poor miscibility due to solubilization capacity was 30% drug loading. Difference of total solubility parameter (Δδ) between efavirenz and PVA and HPC (Δδ) were 16.57 and 12.95 which were above 10. HSM of physical mixtures were not completely melted at 140 ºC.

Table 4-6 Summary table of the drug and excipients miscibility

Excipients	Solubility parameters	Film Casting[a]	Maximum drug to polymer ratio that showed single T_g	HSM at 135-140 ^oC	Extrudate
Soluplus®	Miscible	50:50	70:30	O	Transparent
Kollidon® VA-64	Miscible	50:50	50:50	O	Transparent
Eudragit® EPO	Miscible	50:50	70:30	O	Translucent
Kollidon® K-30	Miscible	50:50	50:50	O	Transparent
PVA	Immiscible	30:70	50:50	×	N/A
HPC	Immiscible	30:70	50:50	×	White Opaque

[a] maximum drug to polymer ratio that which caused clear film
O represents miscible
× represents immiscible

4. Hot-melt extrusion

Hot-melt extrusion could be performed under below the melting point of the drug. The amount of polymer should be at least 20% w/w in hot-melt extrusion process (Lakshman, 2008). Hot-melt extrusion should be performed at temperature about 15-60 ºC above their T_g of polymers (Prodduturi, 2006, Crowley, 2002). At these temperatures the polymers would be in rubbery state. This condition was carried out to ensure that the polymer allowed the crystalline drug to be easily dispersed in the structure (Khatry, 2011, Ghebremeskel, 2006, Jagtap, 2012).

In this study, hot-melt extrusion of 50:50 drug to polymer ratio was carried out at 20 ºC above T_g of polymers and below the drug degradation temperature, 247.54 ºC, determined by TGA. The extrusion temperatures were summarized in Table 4-7. The

mixture of the drug and polymers studied except for PVA could be extruded at the designated temperatures. When extrusion was carried out at 20 ºC above melting point of efavirenz, the extrudate of drug/PVA was not possible to produce through die cell of extrusion.

Table 4-7 Extrusion temperature for the mixture of drug and polymer in the propotion of 50:50

Polymer	Extrusion temperature (°C)
Soluplus®	92
Kollidon VA-64®	125
Eudragit EPO®	79
Kollidon K-30®	176
PVA	101
HPC	126

The extrudate of drug/soluplus® appeared as transparent glass, while the extrudate of drug/Kollidon® VA-64 or Kollidon® K-30 appeared to be yellowish and transparent. The extrudate of drug/Eudragit EPO was translucent. This suggested that the drug was completely solubilized in the polymers, resulting in solid solution. The extrudate of drug/HPC appeared to be white and opaque. This indicated that the drug was not completely solubilized in the polymers at the ratio of 50:50 and the extrudate was solid dispersion.

Figure 4-14 Raw materials and extrudates of 50:50 drug/polymer from hot-melt extrusion; A) Soluplus®; B) Kollidon® VA-64; C) Eudragit® EPO; D) Kollidon® K-30; E) HPC

5. Characterization of extrudates

Characterization of extrudate was carried out to evaluate miscibility between the drug and the polymers. Miscibility between drug and polymers suggests solid dispersion system. If the drug and the polymer are miscible, it leads solid solution extrudate.

The characterizations of extrudate were carried out with differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), Fourier transform infrared spectroscopy (FT-IR) and dynamic vapour sorption (DVS).

5.1 Differential scanning calorimetry (DSC)

DSC thermograms of the extrudates of efavirenze and various polymers, Soluplus® , Kollidon® VA-64, Eudragit® EPO, Kollidon® K-30 and HPC showed absence of melting endothermic peak of the drug and the presence of only single T_g endotherm at 57.85 ºC, 69.55 ºC, 44.25 ºC, 71.41 ºC and 63.91 ºC, respectively. The results suggested complete miscibility of the drug molecules within the polymer (Figure 4-15 to 4-19). T_g of extrudate was summarized in Table 4-8. The result of single T_g for drug/HPC extrudate which was opaque in character of solid dispersion may be due to that heat introduced by DSC could be efficiently transferred to an extrudate sample allowing the drug to be miscible in the polymer.

Table 4-8 Glass transition temperature (T_g) of extrudate of various polymers

Extrudate	**T_g (ºC)**		
	Sample 1	Sample 2	Average (n=2)
Soluplus®	53.51	53.78	53.65
Kollidon VA-64®	69.55	62.05	65.80
Eudragit EPO®	44.25	44.03	44.14
Kollidon K-30®	71.41	72.64	72.03
HPC	63.91	59.07	61.49

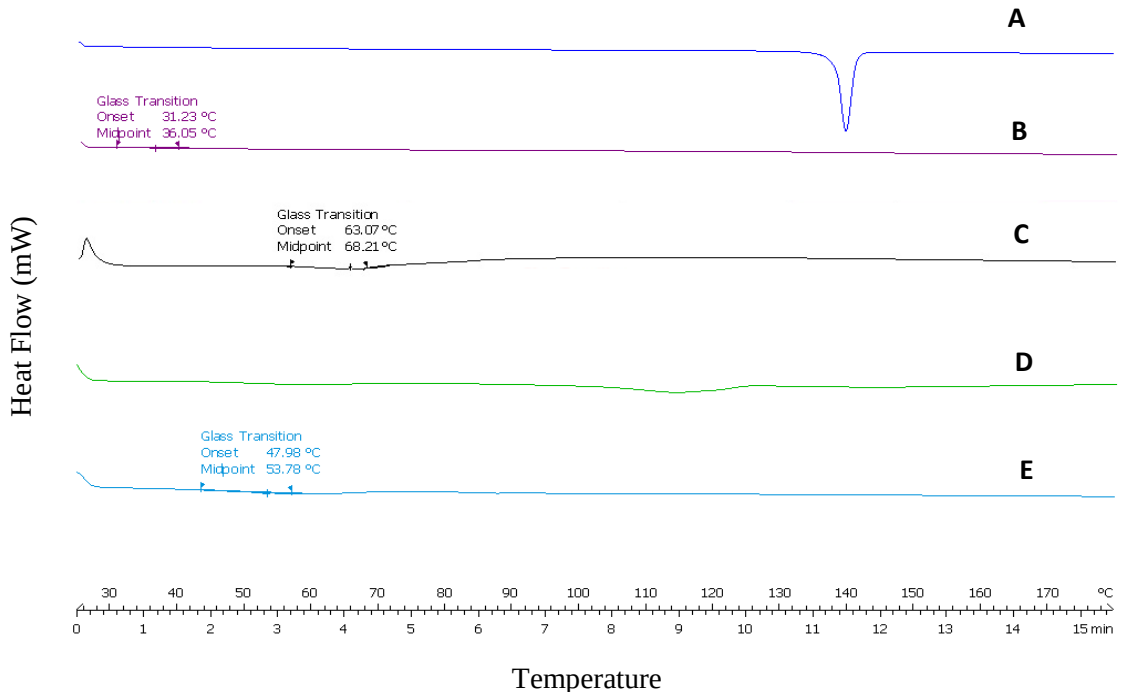


Figure 4-15 DSC thermograms of A) efavirenz in first cycle when the sample was melted; B) efavirenz in third cycle when the cooled melt was reheated; C) Soluplus®; D) physical mixture of efavirenz/ Soluplus® (50:50); E) extrudate.

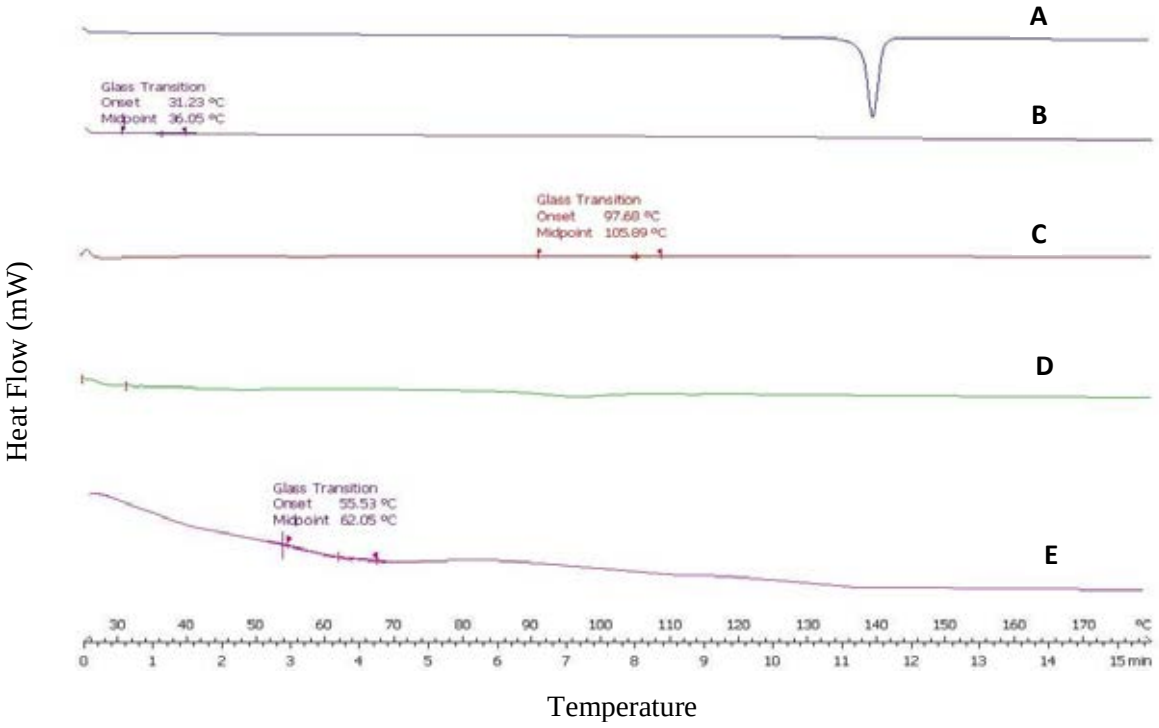


Figure 4-16 DSC thermograms of A) efavirenz in first cycle when the sample was melted; B) efavirenz in third cycle when the cooled melt was reheated; C) Kollidon® VA-64; D) physical mixture of efavirenz/ Kollidon® VA-64 (50:50); E) extrudate.

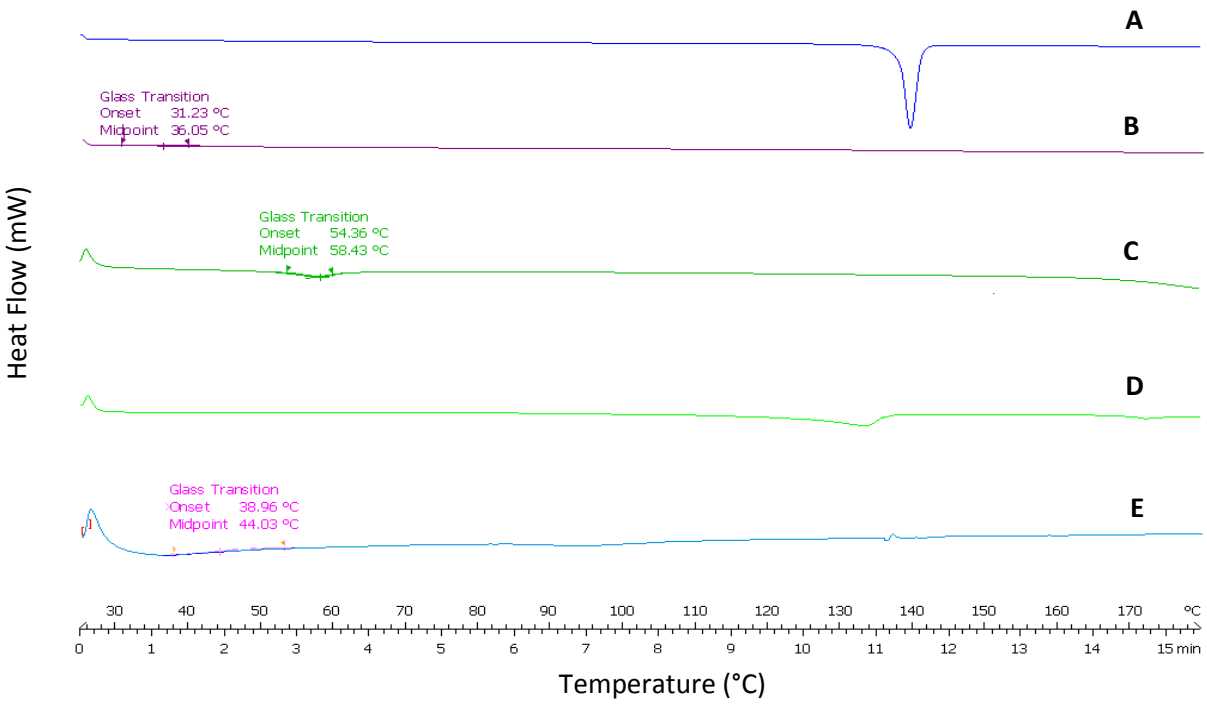


Figure 4-17 DSC thermograms of A) efavirenz in first cycle when the sample was melted; B) efavirenz in third cycle when the cooled melt was reheated; C) Eudragit® EPO; D) physical mixture of efavirenz/ Eudragit® EPO (50:50); E) extrudate.

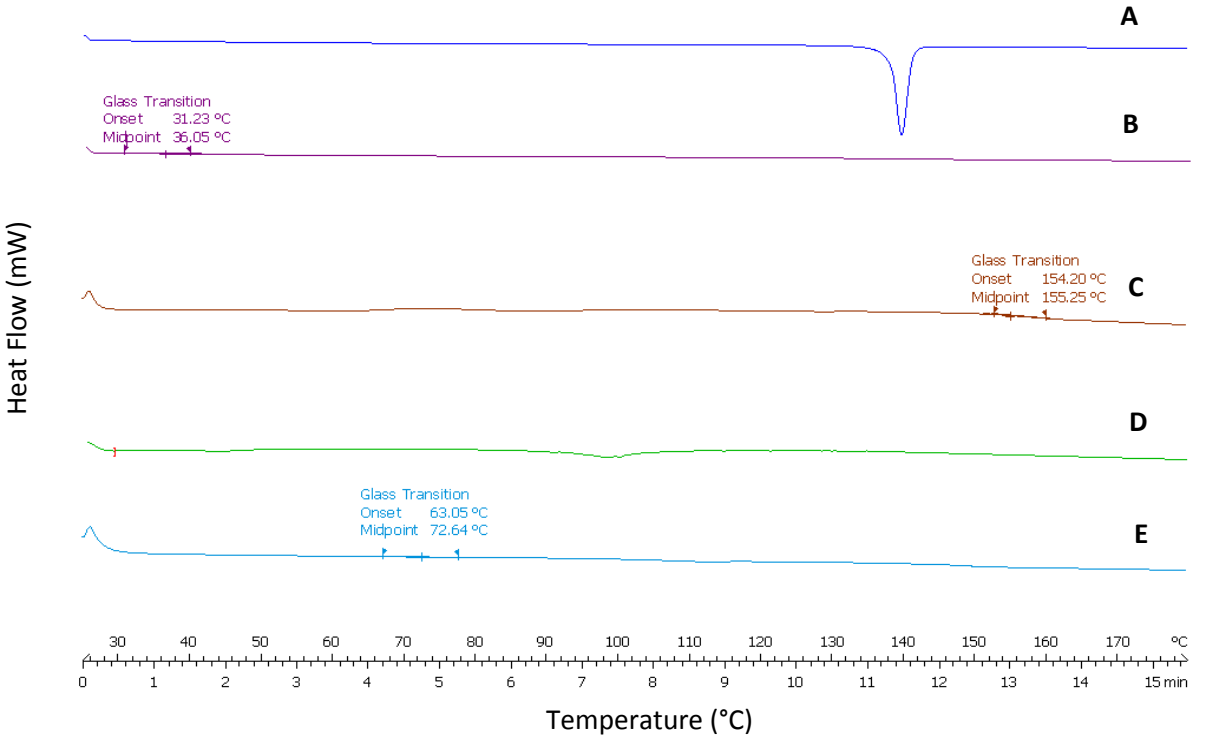


Figure 4-18 DSC thermograms of A) efavirenz in first cycle when the sample was melted; B) efavirenz in third cycle when the cooled melt was reheated; C) Kollidon® K-30; D) physical mixture of efavirenz/ Kollidon® K-30 (50:50); E) extrudate.

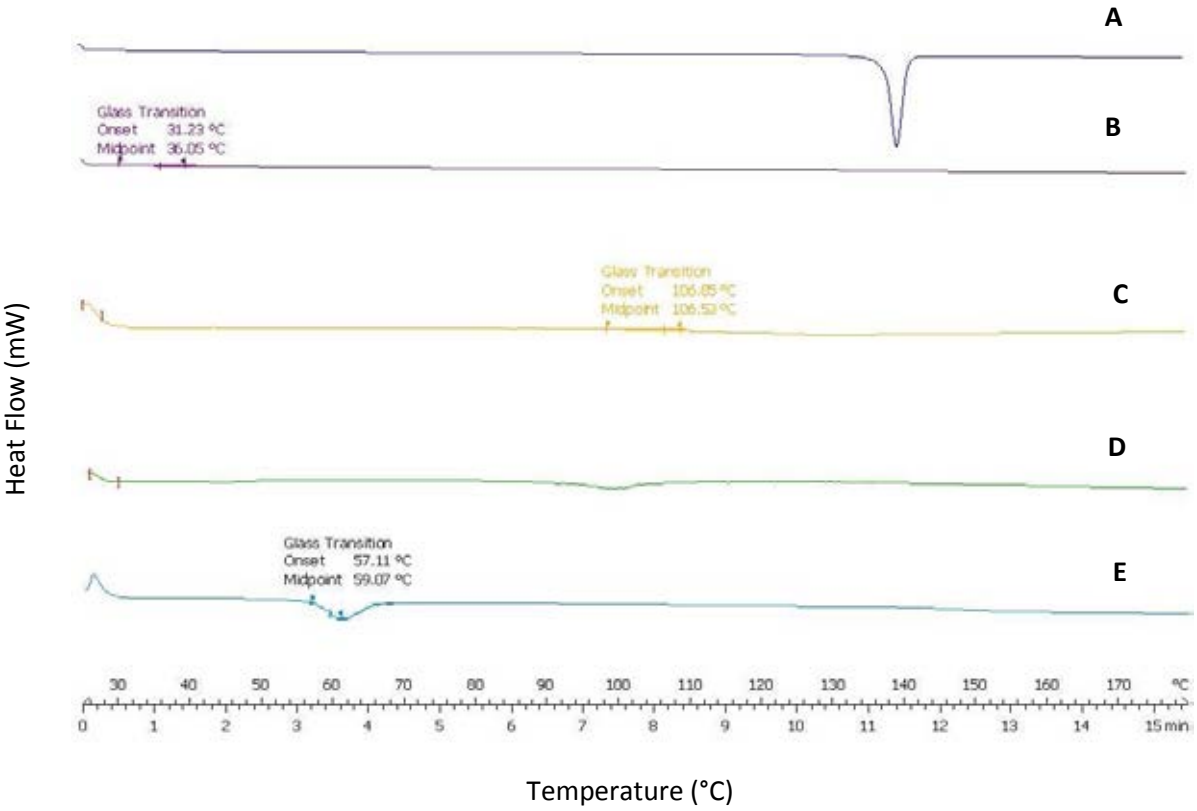


Figure 4-19 DSC thermograms of A) efavirenz in first cycle when the sample was melted; B) efavirenz in third cycle when the cooled melt was reheated; C) HPC; D) physical mixture of efavirenz/HPC (50:50); E) extrudate.

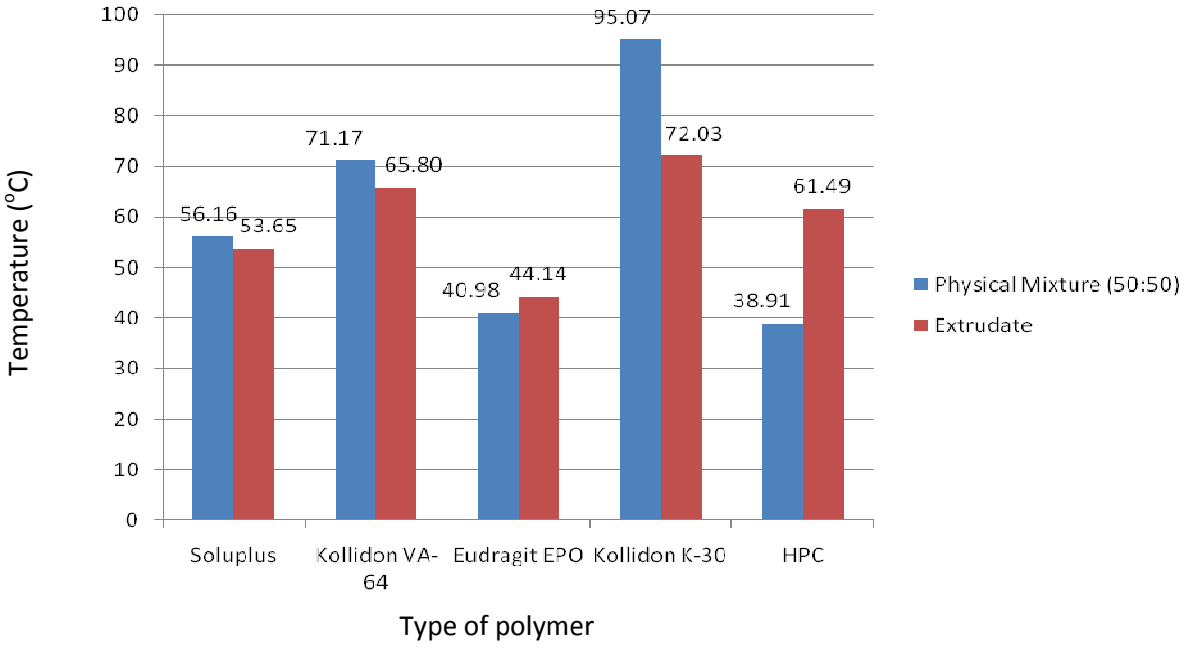


Figure 4-20 Comparison of glass transition temperature of 50: 50 physical mixtures and extrudates

5.2 X-ray powder diffractometry (XRPD)

XRPD pattern of efavirenz showed diffraction peaks indicating crystalline morphology. All polymers had halo characteristic without any sharp peaks indicating amorphous nature. XRPD patterns of the 50:50 physical mixtures of the drug and the polymers were similar to combined diffractograms of the efavirenz and polymer, indicating efavirenz remained crystalline in the physical mixture. It was found that XRPD pattern of the extrudates produced from 50:50 drug-polymer mixtures showed absence of efavirenz crystalline peaks indicating amorphous structure where the crystal lattices of the drug were destroyed (Figure 4-21 to Figure 4-25).

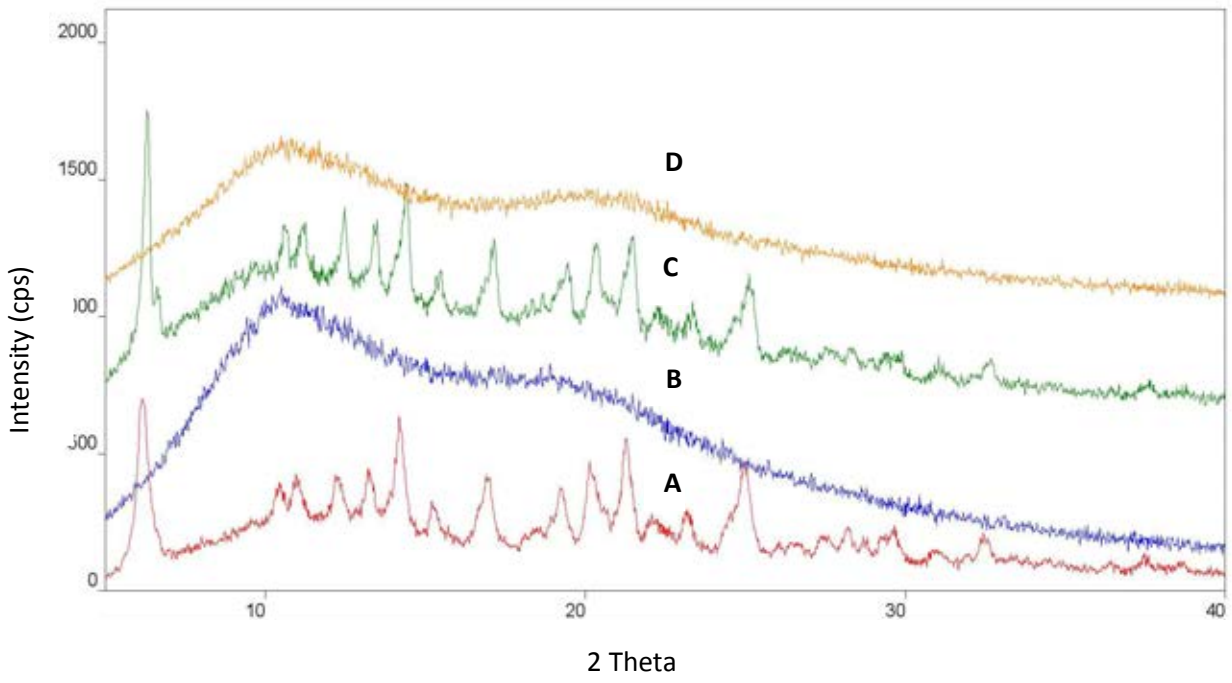


Figure 4-21 X-ray power diffraction patterns of the A) efavirenz; B) Soluplus®; C) physical mixture; D) extrudate

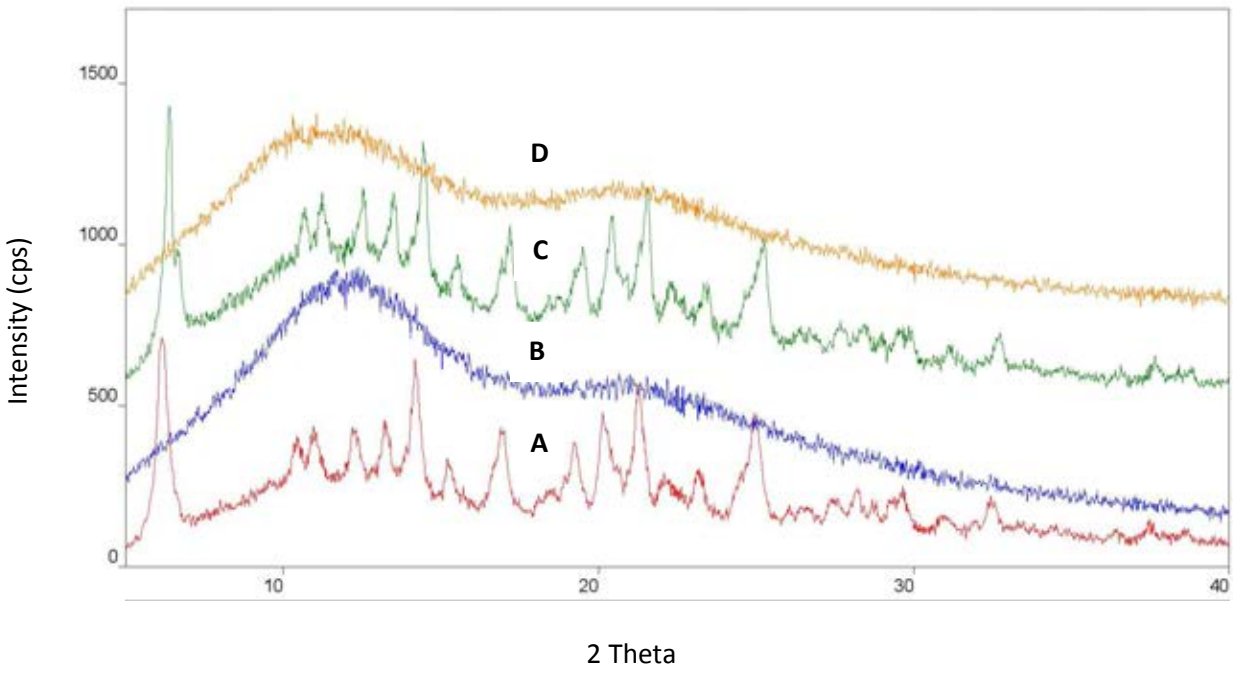


Figure 4-22 X-ray power diffraction patterns of the A) efavirenz; B) Kollidon® VA-64; C) physical mixture; D) extrudate

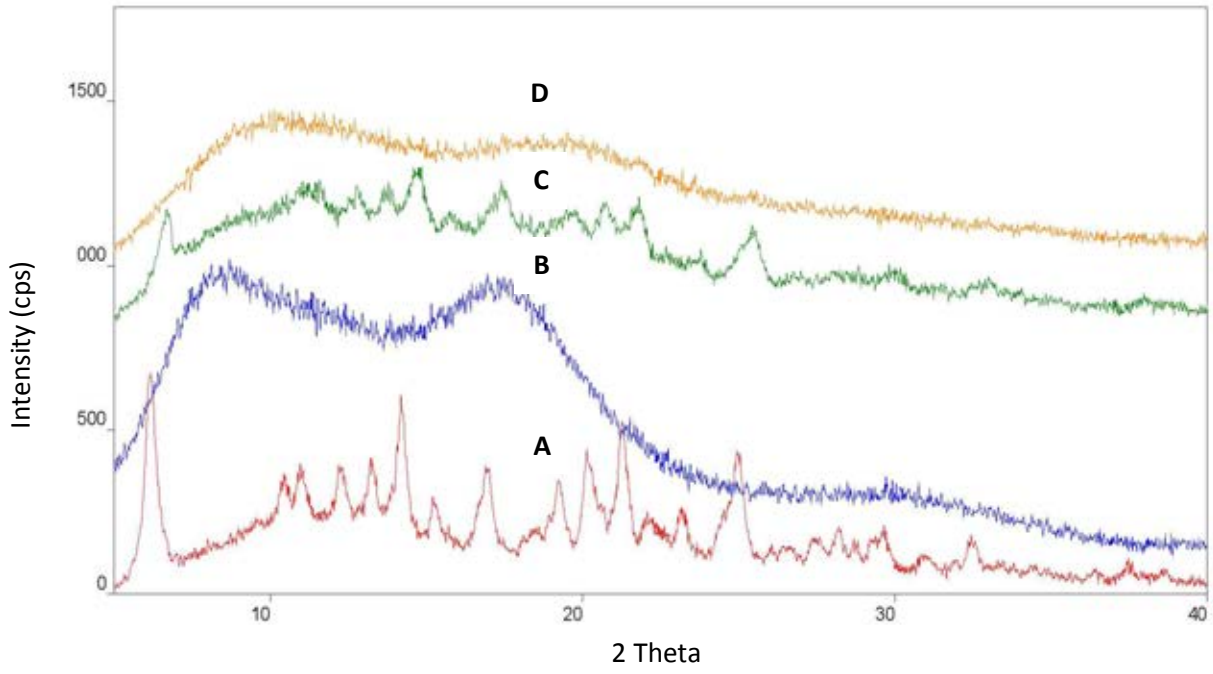


Figure 4-23 X-ray power diffraction patterns of the A) efavirenz; B) Eudragit® EPO; C) physical mixture; D) extrudate

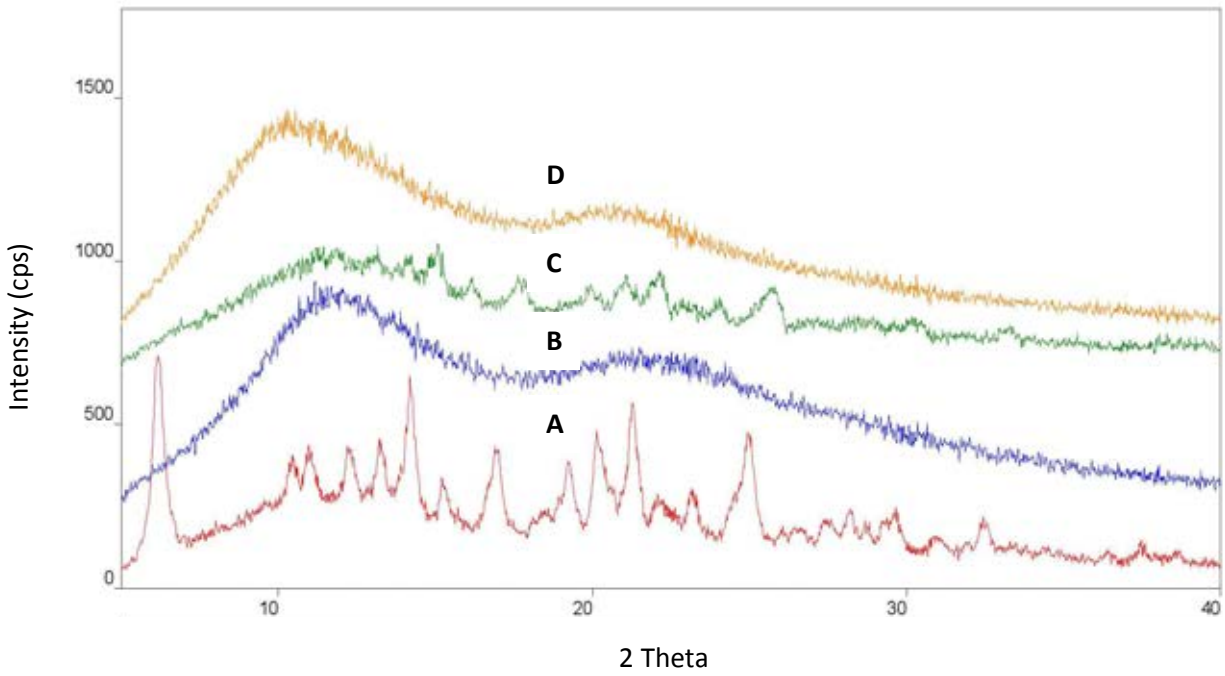


Figure 4-24 X-ray power diffraction patterns of the A) efavirenz; B) Kollidon® K-30; C) physical mixture; D) extrudate

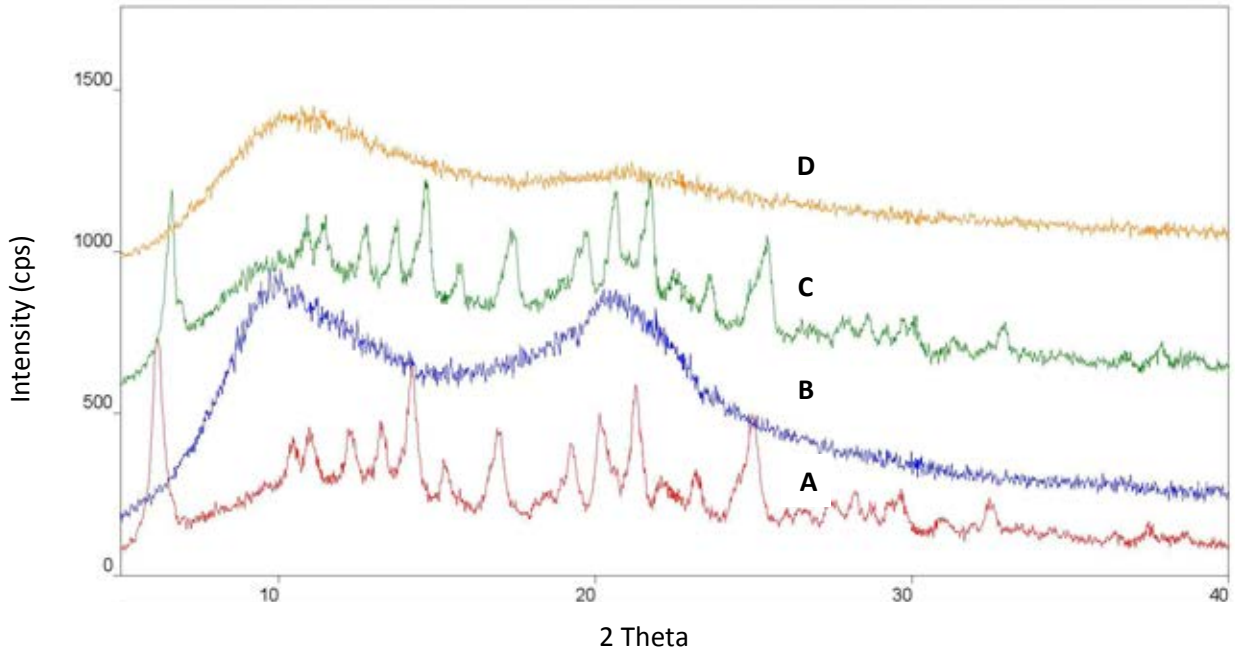


Figure 4-25 X-ray power diffraction patterns of the A) efavirenz; B) HPC; C) physical mixture; D) extrudate

5.3 Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra of efavirenz, polymer, physical mixtures and extrudate were investigated to evaluate interactions between the drug and polymer. Efavirenz showed characteristic peaks with alkyne at around 2250 cm^{-1}, C-F stretching at around 1000–1400 cm^{-1}, N-H stretching at around 3300–3400 cm^{-1} and C-H stretching at around 2850–3000 cm^{-1}.

Soluplus®, Kollidon® VA-64 and Eudragit® EPO showed characteristic peaks with C=O stretching at around 1750 cm^{-1}. Soluplus®, Kollidon® VA-64 and Kollidon® K-30 also showed =N- stretching band at 3070-3350 cm^{-1}. In addition, HPC also attributed to O-H stretching at around 3400 cm^{-1}. These chemical groups of the polymers could form intermolecular hydrogen bonds with efavirenz in the extrudate.

IR spectra of the extrudates of efavirenz/Soluplus®, Kollidon® VA-64 and Eudragit® EPO showed the shoulder of absoption bands at around 1700 cm^{-1} corresponded to hydrogen-bonded carbonyl group. The carbonyl group had potential to form intermolecular hydrogen bonds with efavirenz. These results suggested that Soluplus®, Kollidon® VA-64 and Eudragit® EPO had interaction with efavirenz (Figure 4-26 to 4-28). The N-H stretching bands could also form hydrogen bonding. The N-H stretching bands around 3300–3400 cm^{-1} of Soluplus®, Kollidon® VA-64 and Kollidon® K-30 extrudates were shift to lower wavenumber when compared with physical mixture (Figure 4-26, 4-27, 4-29). These results suggested that Soluplus®, Kollidon® VA-64 and Kollidon® K-30 had interaction with efavirenz through proton donating groups (N-H). The extrudate of HPC also showed hydroxyl band shifted to lower wavenumbers at around 3350 cm^{-1}, indicating an interaction with the drug.

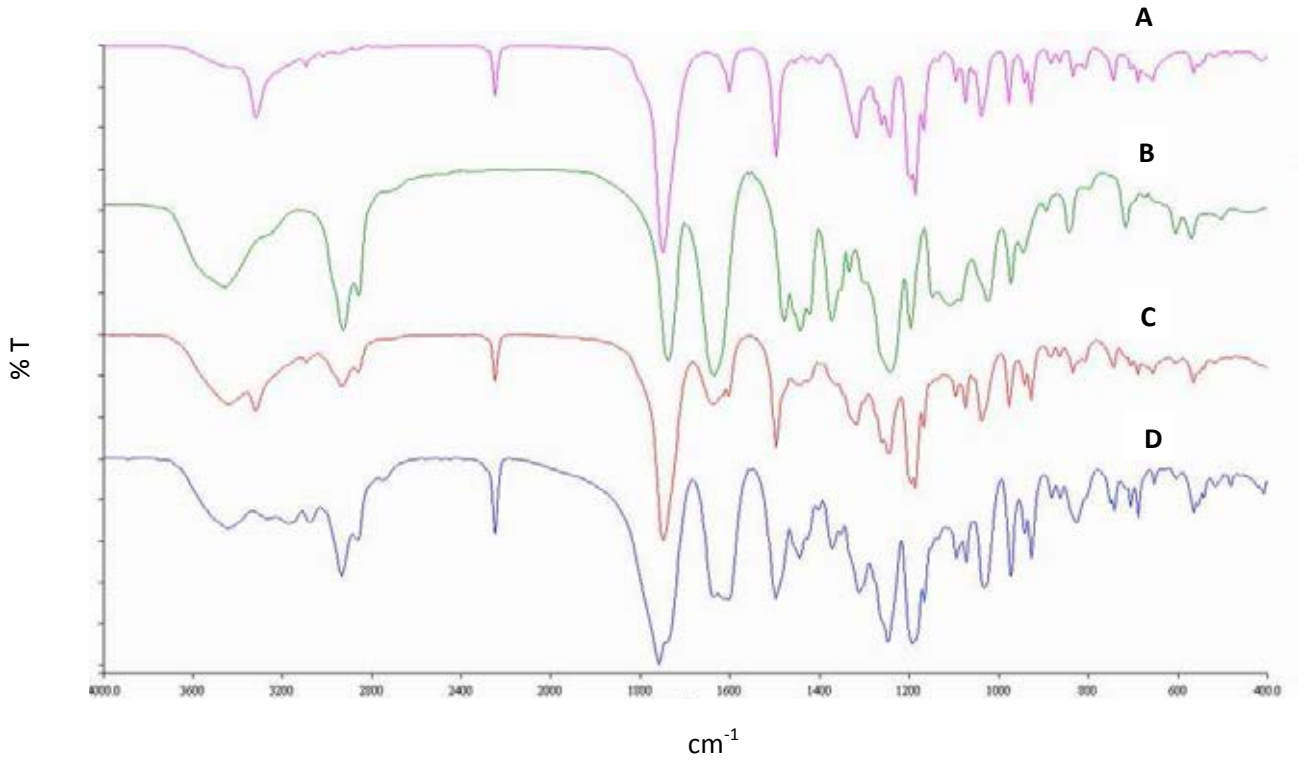


Figure 4-26 FT-IR patterns of the A) efavirenz; B) Soluplus®; C) physical mixture; D) extrudate

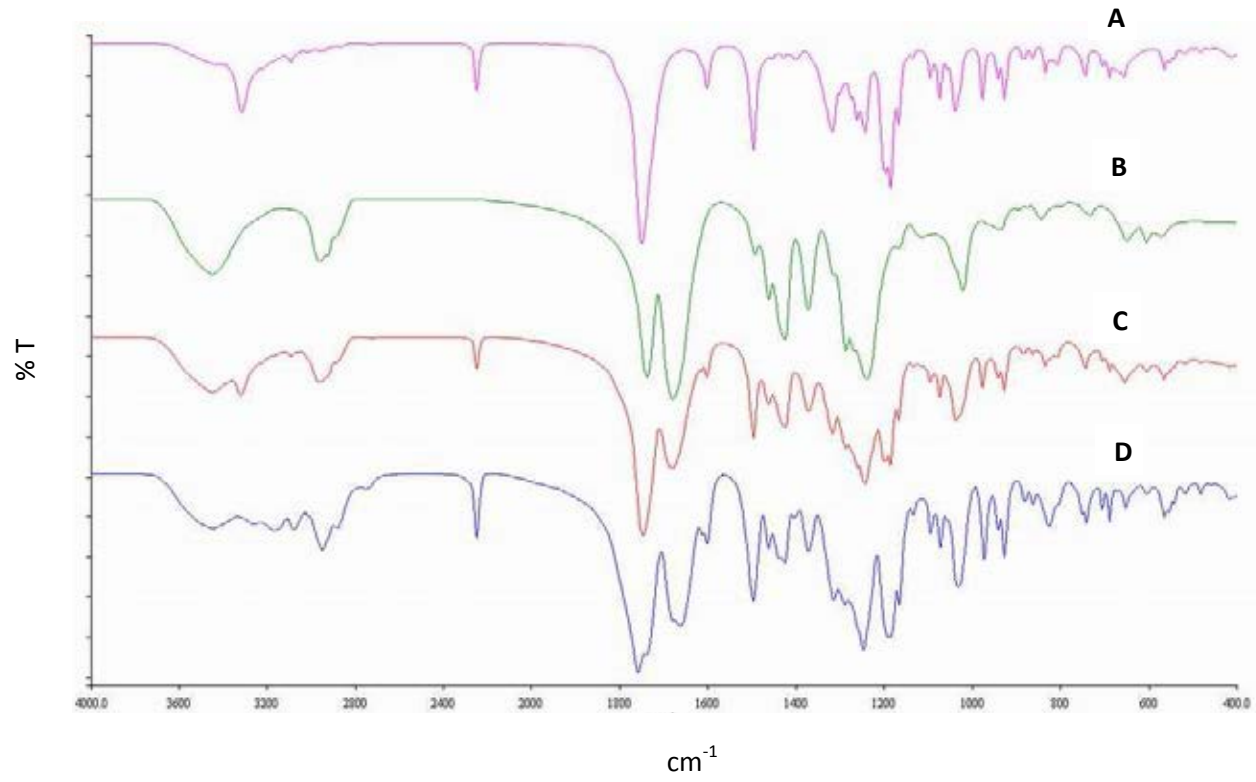


Figure 4-27 FT-IR patterns of the A) efavirenz; B) Kollidon® VA-64; C) physical mixture; D) extrudate

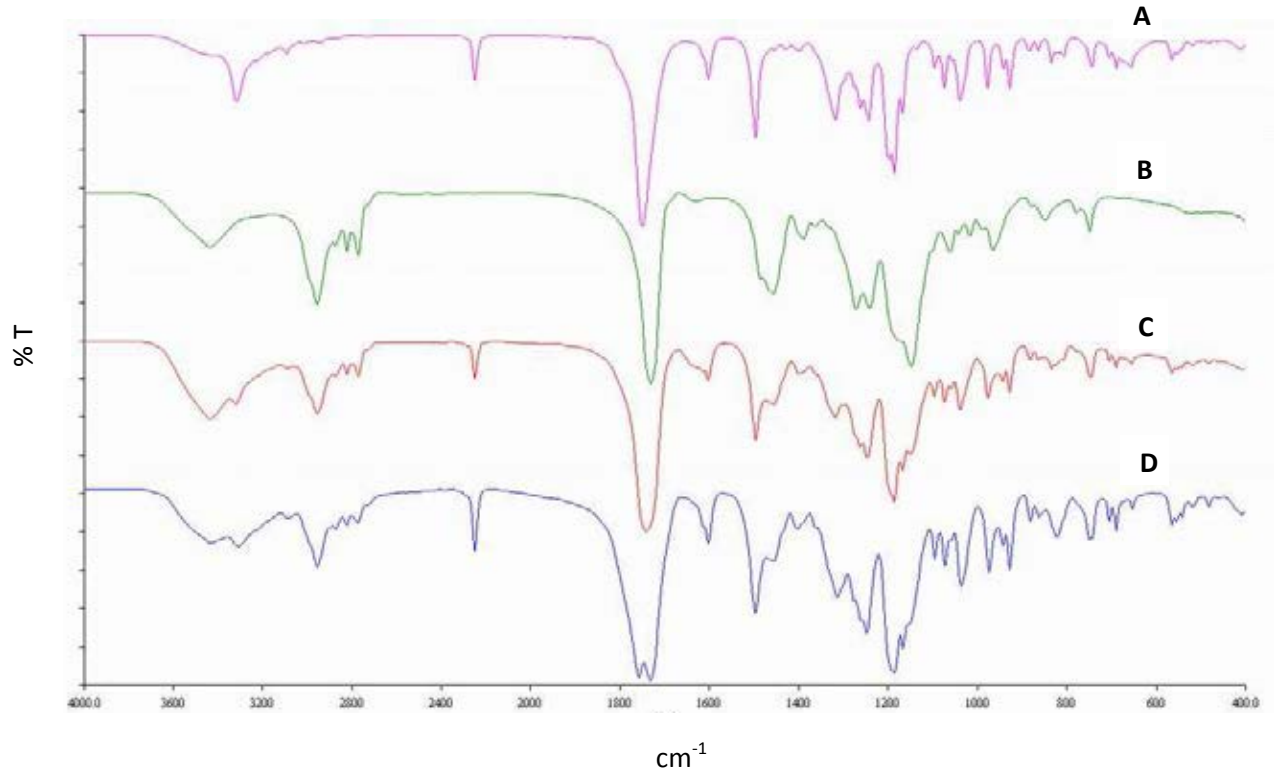


Figure 4-28 FT-IR patterns of the A) efavirenz; B) Eudragit® EPO; C) physical mixture; D) extrudate

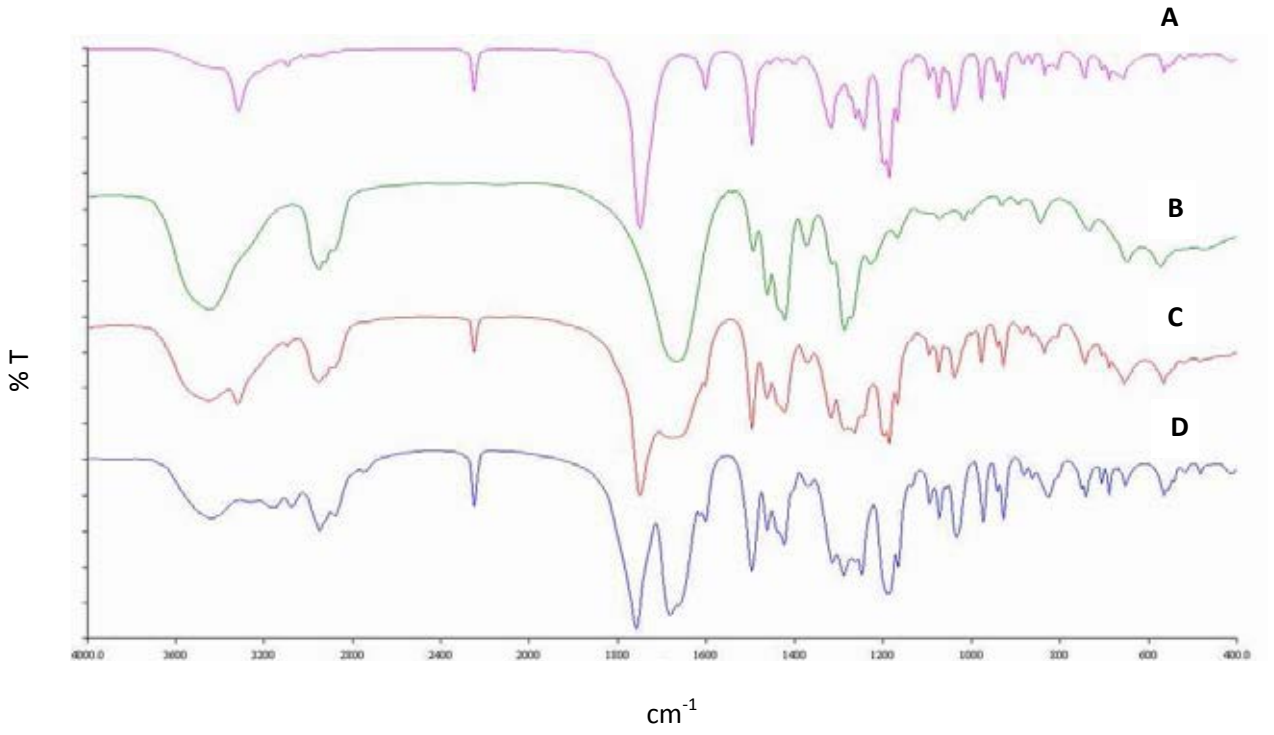


Figure 4-29 FT-IR Spectrum of A) efavirenz; B) Kollidon® K-30; C) physical mixture; D) extrudate

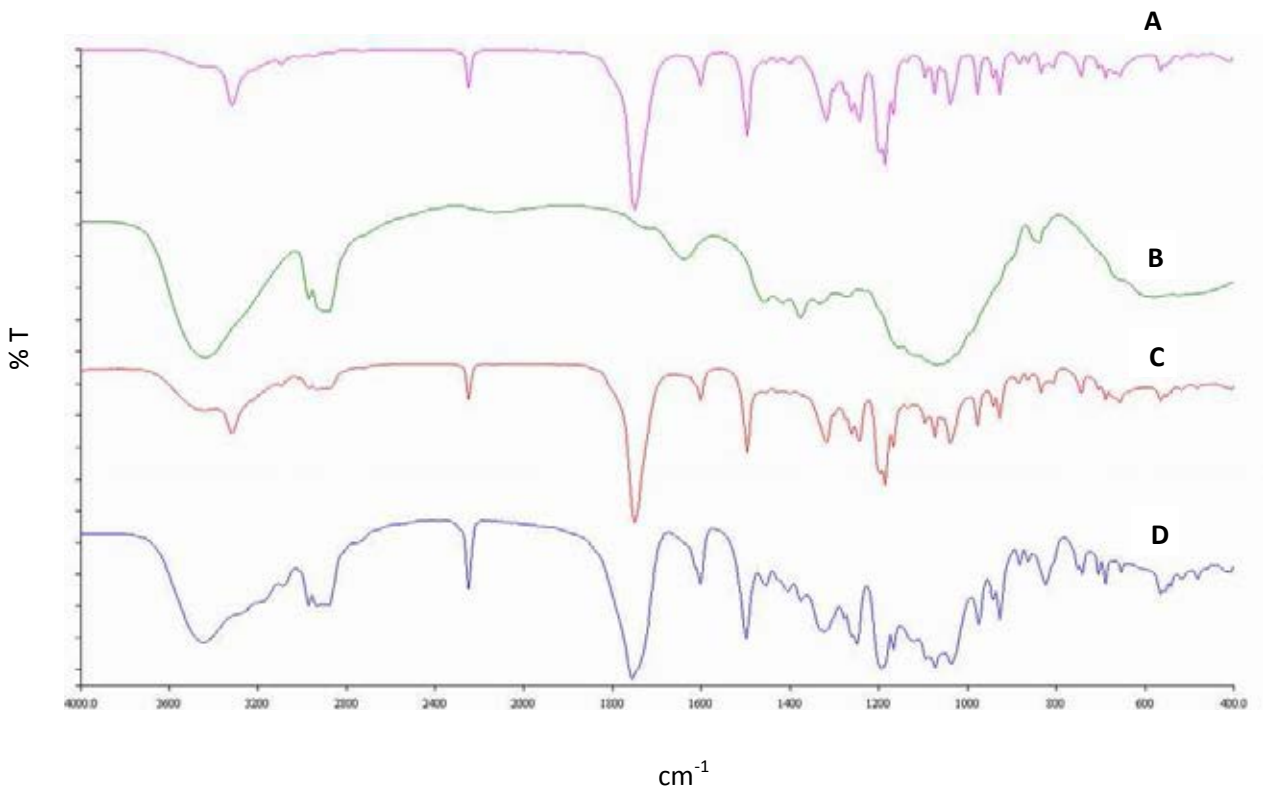


Figure 4-30 FT-IR Spectrum of A) efavirenz; B) HPC; C) physical mixture; D) Extrudate

5.4 Dynamic vapour sorption (DVS)

Dynamic vapour sorption can be used to characterize crystallinity of powder (Buckton, 1995). Extrudates of Soluplus®, Eudragit® EPO and HPC showed a little difference between weight gain in first sorption process and weight gain in the later process (Figure 4-31, Figure 4-33 and Figure 4-35). Otherwise, Extrudate of Kollidon® VA-64 and Kollidon® K-30 showed a significantly difference between weight gain in first sorption process and weight gain in the later process (Figure 4-32 and Figure 4-34).

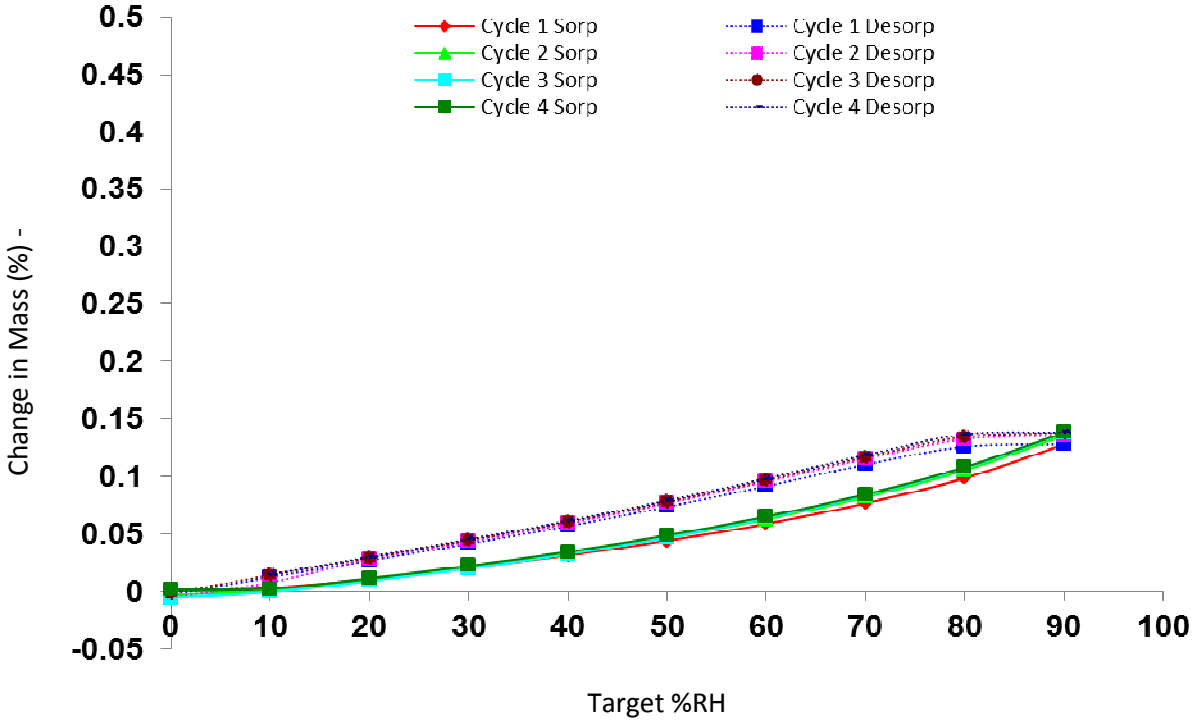


Figure 4-31 Sorption and desorption isotherms for 4 repeated cycles on the extrudate of Soluplus®

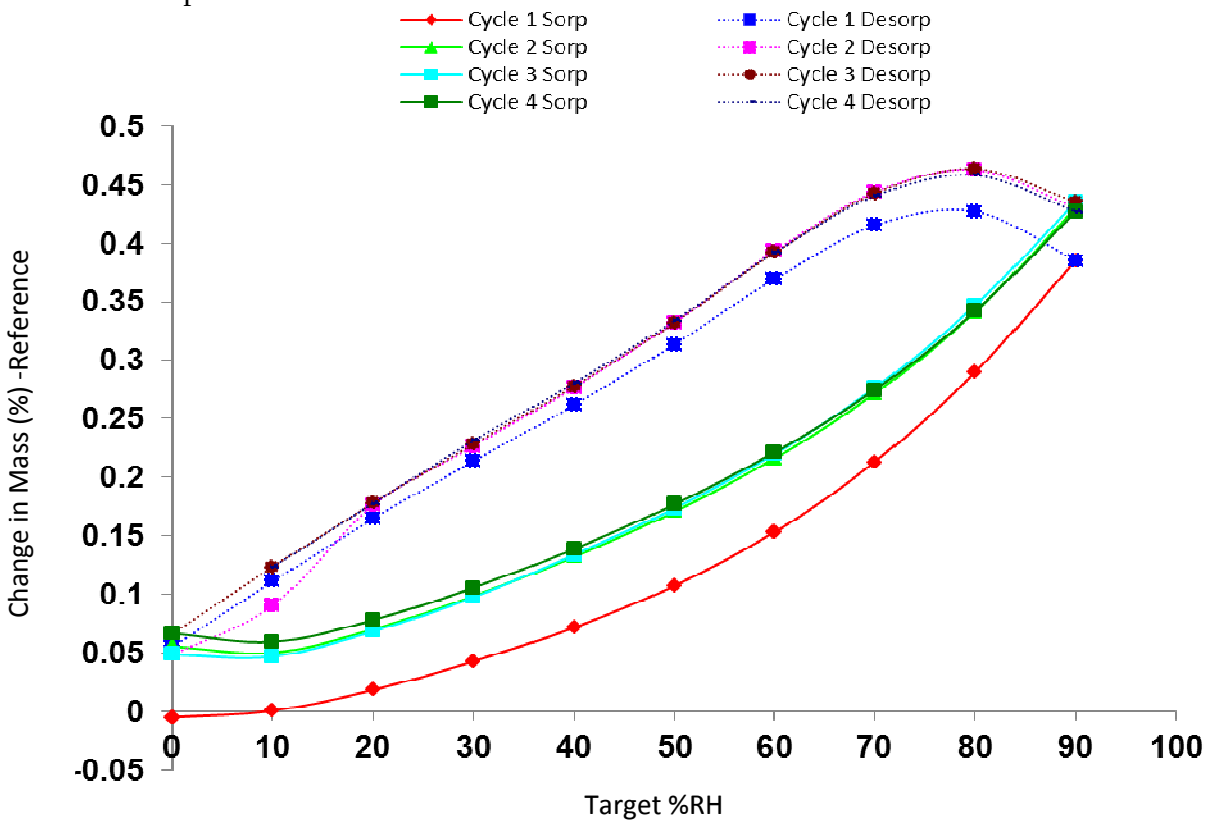


Figure 4-32 Sorption and desorption isotherms for 4 repeated cycles on the extrudate of Kollidon® VA-64

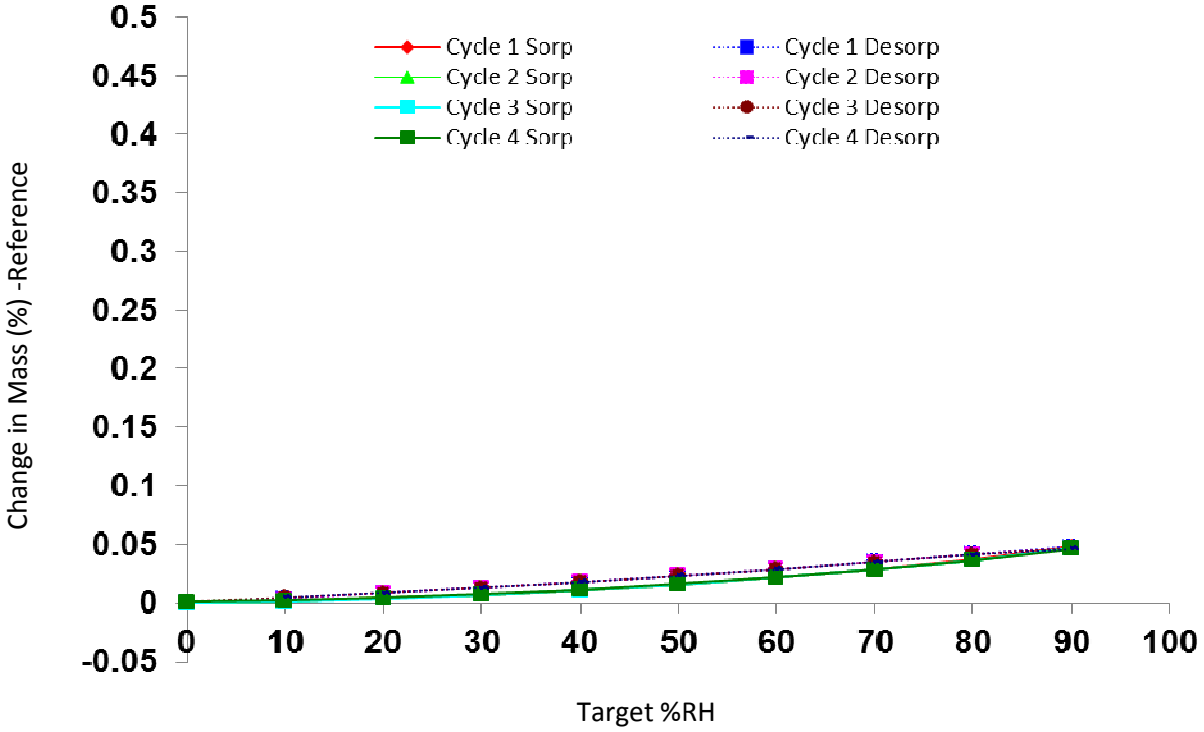


Figure 4-33 Sorption and desorption isotherms for 4 repeated cycles on the extrudate of Eudragit® EPO

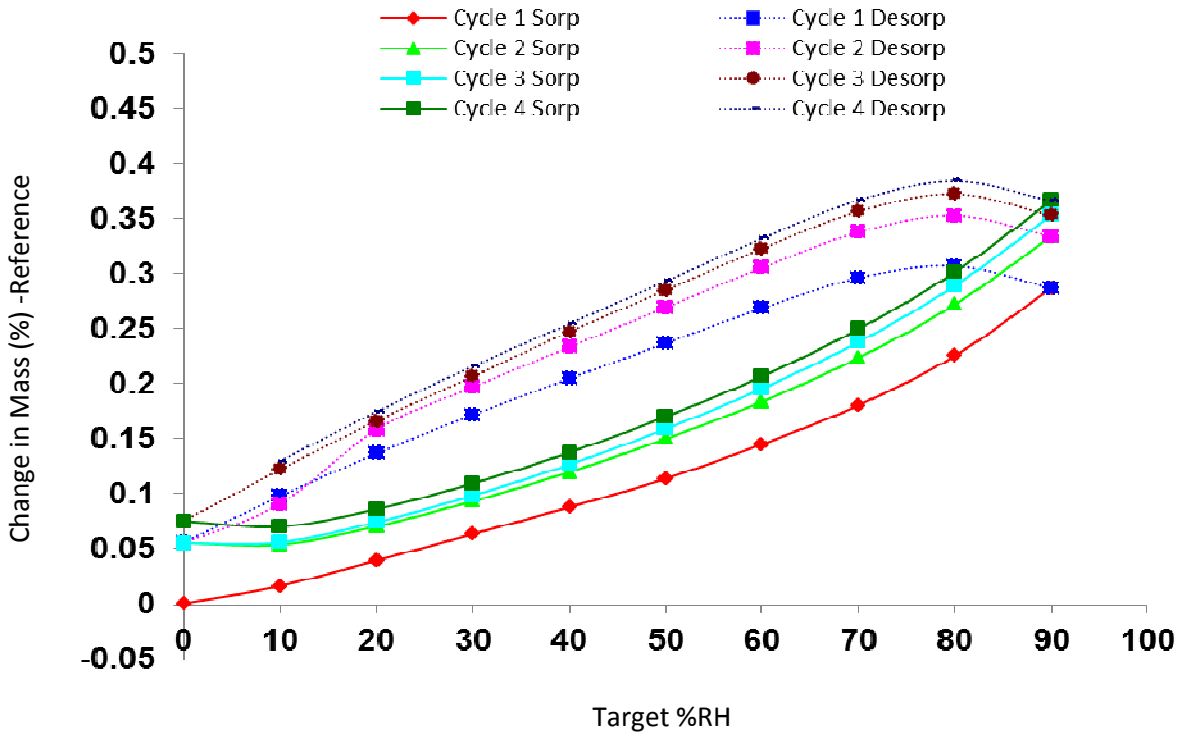


Figure 4-34 Sorption and desorption isotherms for 4 repeated cycles on the extrudate of Kollidon® K-30

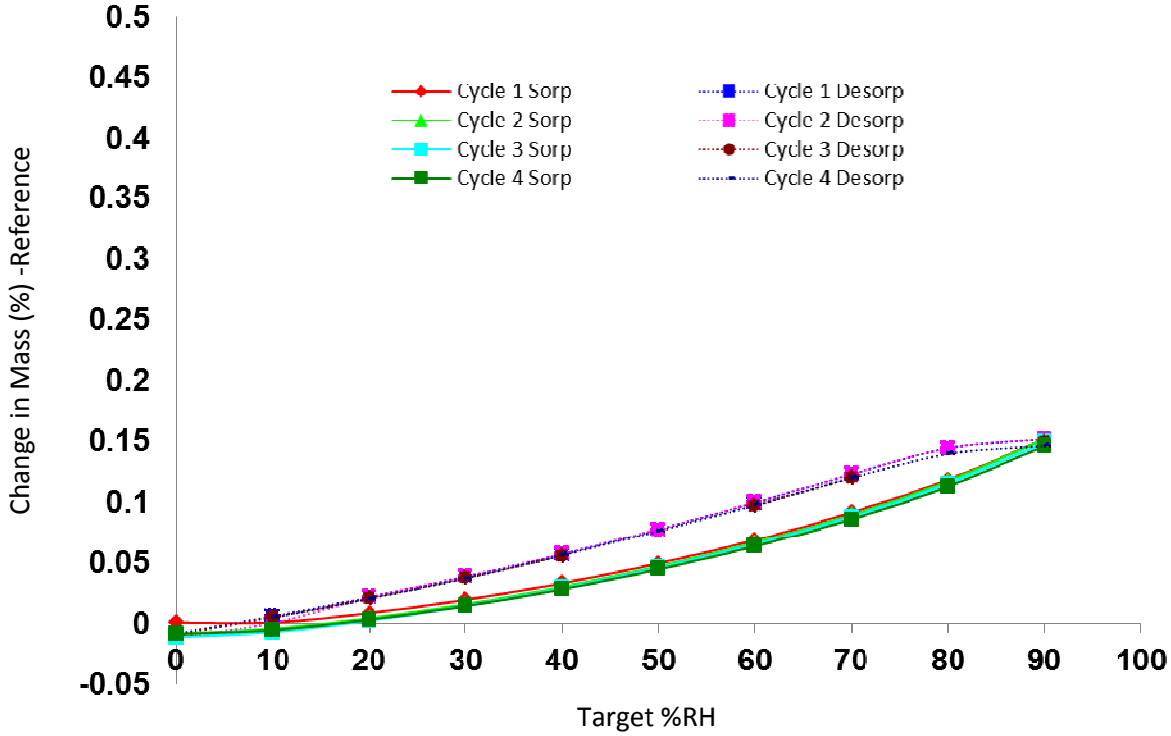


Figure 4-35 Sorption and desorption isotherms for 4 repeated cycles on the extrudate of HPC

6. Assay

One hundred milligrams of the extrudate of Soluplus®, Kollidon® VA-64, Eudragit® EPO, Kollidon® K-30, HPC contained efavirenz 46.23, 45.23, 44.01, 44.87 and 45.51 mg, respectively. % Label amount of efavirenz in Soluplus®, Kollidon® VA-64, Eudragit® EPO, Kollidon® K-30 extrudate was 92.46, 90.46, 88.02, 89.72 and 91.02, respectively.

7. Dissolution study

Dissolution profiles of the drug alone and the physical mixture of efavirenz and Soluplus® dissolved slowly and maximum drug release in 90 min was 2.4% and 20.9%, respectively. The physical mixture showed better dissolution than pure efavirenz, possibly because Soluplus® has the solubilizing function of the polymer.

Dissolution profiles of extrudate of Soluplus®, Kollidon® VA-64, Eudragit® EPO, Kollidon® K-30 and HPC is showed in Figure 4-24. The maximum drug release from the extrudate of Soluplus®, Kollidon® VA-64, Eudragit® EPO, Kollidon® K-30 and HPC was 74.06%, 66.38%, 71.86%, 61.9%, and 64.16%, respectively. It signified that the dissolution of efavirenz was greatly improved. The dissolution was improved by forming solid dispersion or solid solution. Some of extrudate were solid solution, i.e. the extrudate of Soluplus®, Kollidon® VA-64, Kollidon® K-30 and Eudragit® EPO. The extrudate of HPC were solid dispersion due to opaque appearance indicating that the drug was not completely dissolved in the polymer.

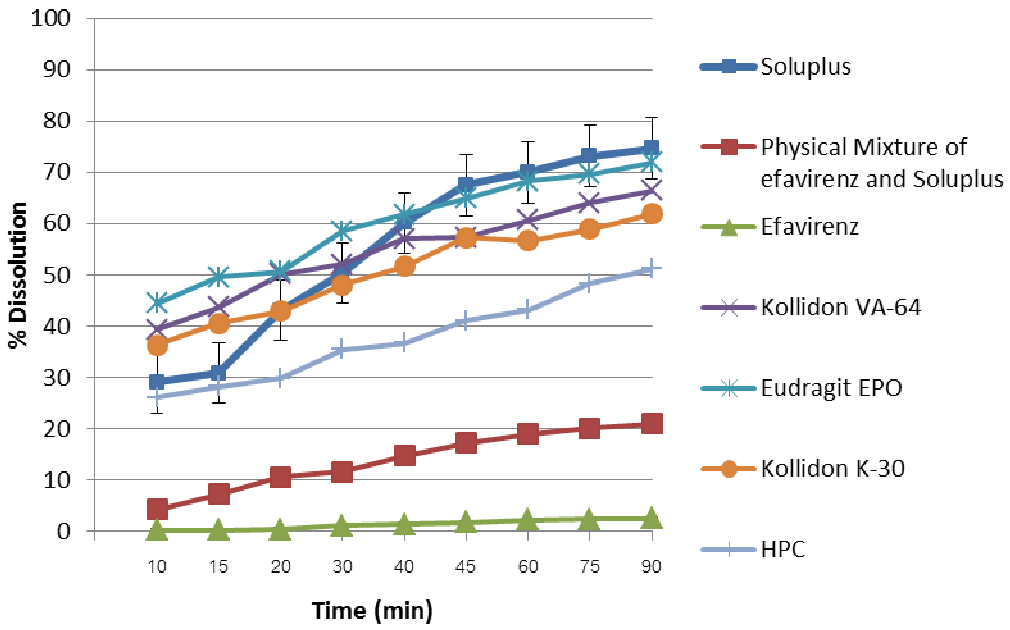


Figure 4-36 Dissolution profile of efavirenz, physical mixture of efavirenz/Soluplus®, extrudates of Soluplus®, Kollidon® VA-64, Eudragit® EPO, Kollidon® K-30, HPC.

8. Effect of water sorption on properties of extrudate

Extrudate was treated under accelerate condition by DVS. After the same extrudates were treated with 4 repeated cycles of water sorption, the samples were investigated using DSC, XRPD and dissolution test.

8.1 Differential scanning calorimetry (DSC)

The treated extrudate tended to raise glass transition temperature. The extrudate of Soluplus® and Kollidon® VA-64 showed very little increase in glass transition temperature at about 5 ºC. Eudragit® EPO showed a little increase in glass transition temperature at about 10 ºC. Kollidon® K-30 and HPC showed increase in glass transition temperature at about 10-20 ºC.

Water sorption of extrudate affected on molecular rearrangement in the chain of polymer. Water sorption made polymer to be more flexible, allowing molecular rearrangement of efavirenz in the extrudates to be in more order. This led to increase glass transition temperature.

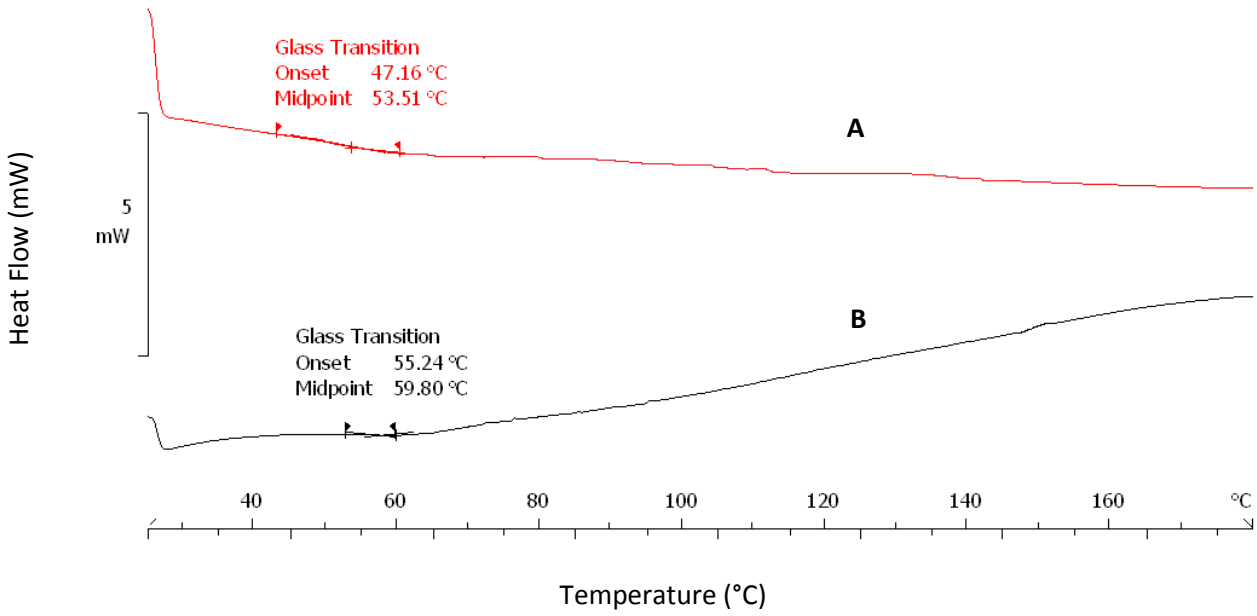


Figure 4-37 DSC thermograms of Soluplus® extrudate: A) untreated extrudate; B) treated extrudate

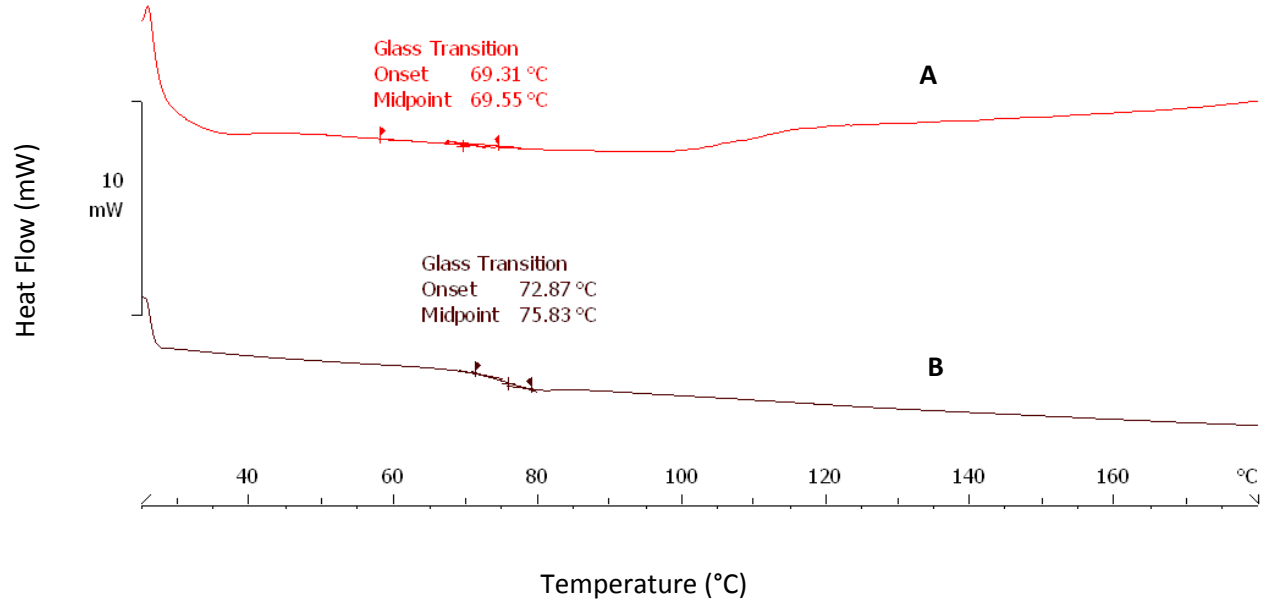


Figure 4-38 DSC thermograms of Kollidon® VA-64 extrudate: A) untreated extrudate; B) treated extrudate

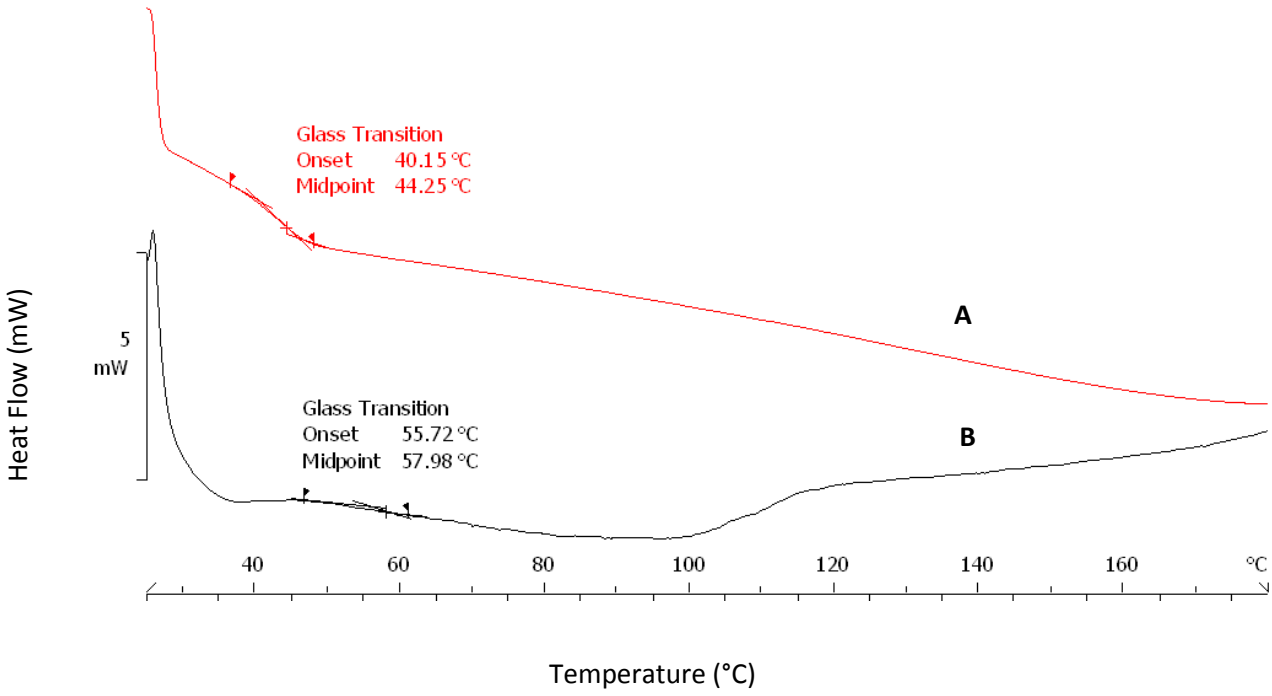


Figure 4-39 DSC thermograms of Eudragit® EPO extrudate: A) untreated extrudate; B) treated extrudate

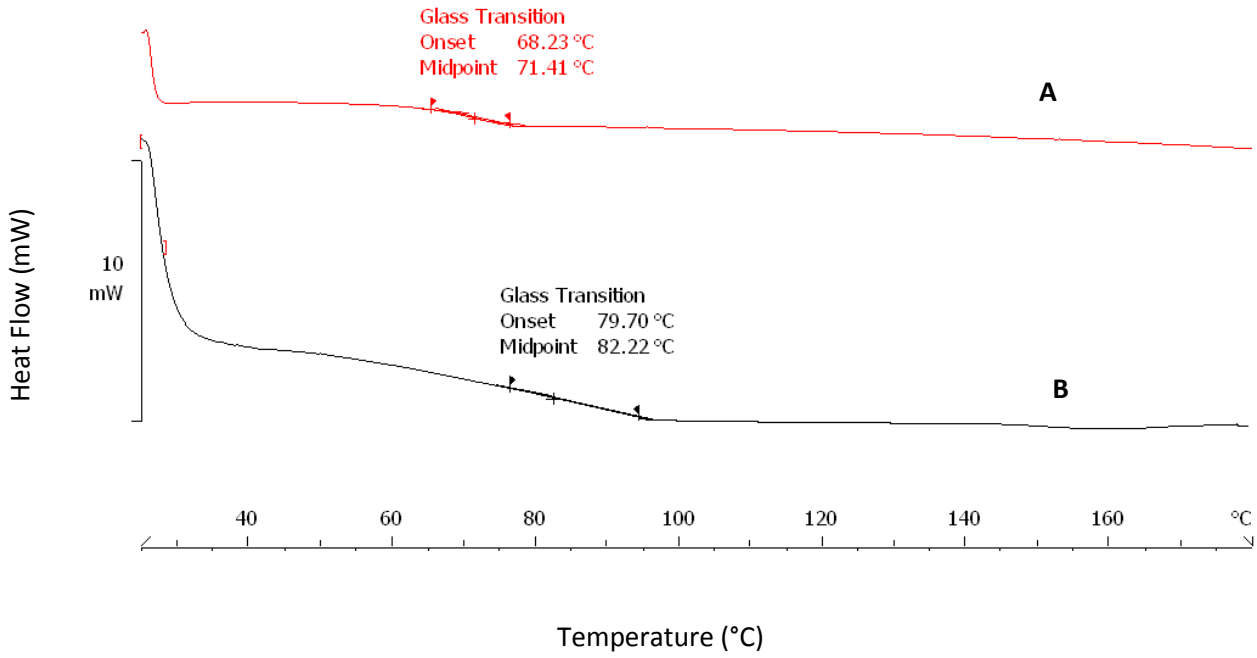


Figure 4-40 DSC thermograms of Kollidon® K-30 extrudate: A) untreated extrudate; B) treated extrudate

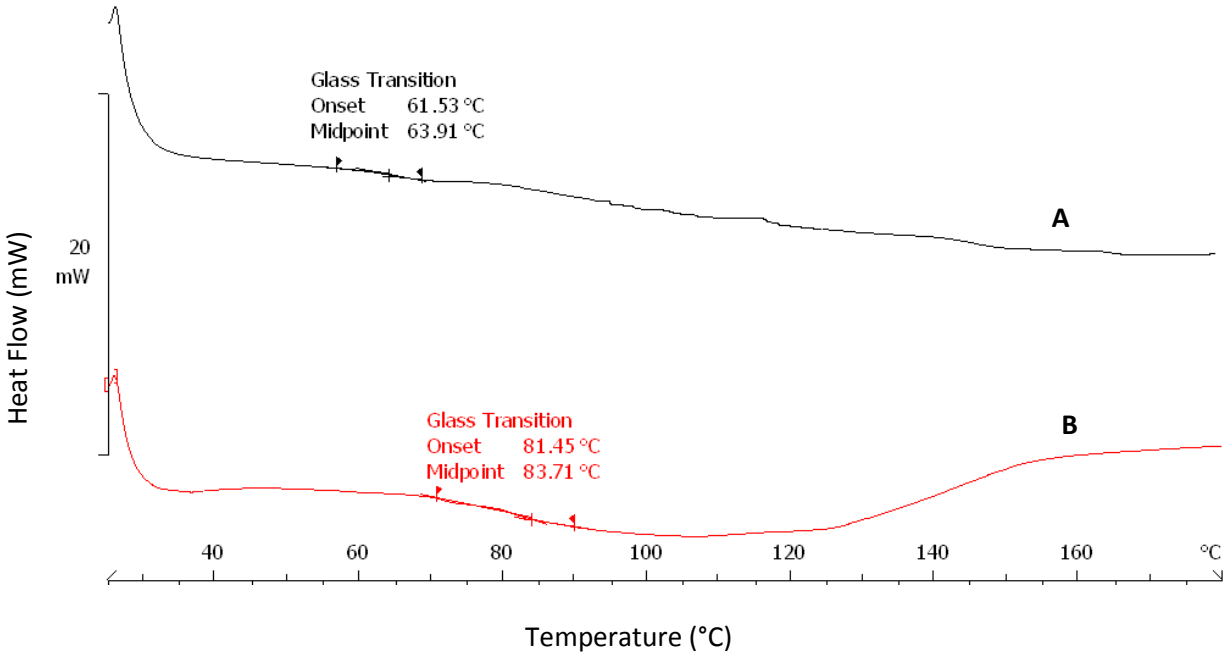


Figure 4-41 DSC thermograms of HPC extrudate: A) untreated extrudate; B) treated extrudate

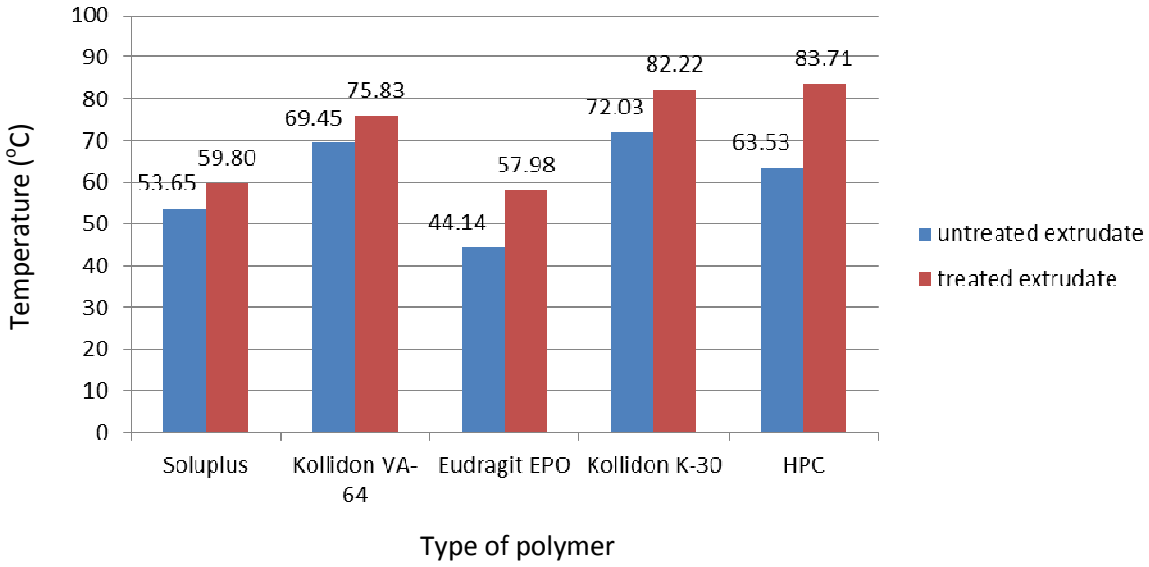


Figure 4-42 Glass transition temperatures of untreated extrudate and treated extrudate

8.2 X-ray powder diffractometry (XRPD)

The extrudate subjected to four cycles of water sorption and desorption. The XRPD pattern showed halo characteristic without any sharp peaks. The patterns were similar to the diffractograms of the untreated extrudate. They showed absence of efavirenz crystalline peaks of efavirenz indicating amorphous structure where the crystal lattices were destroyed. For the conclusion, extrudate showed good stability with under of water sorption process.

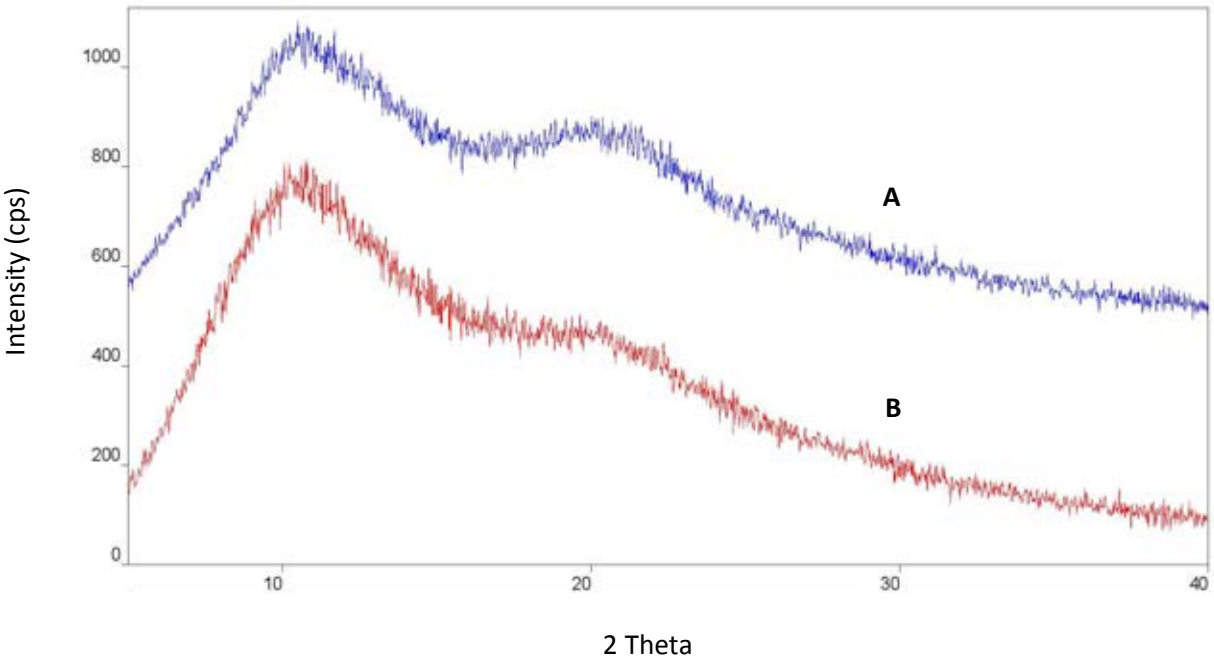


Figure 4-43 X-ray power diffraction patterns of Soluplus® extrudate: (A) untreated extrudate; (B) treated extrudate

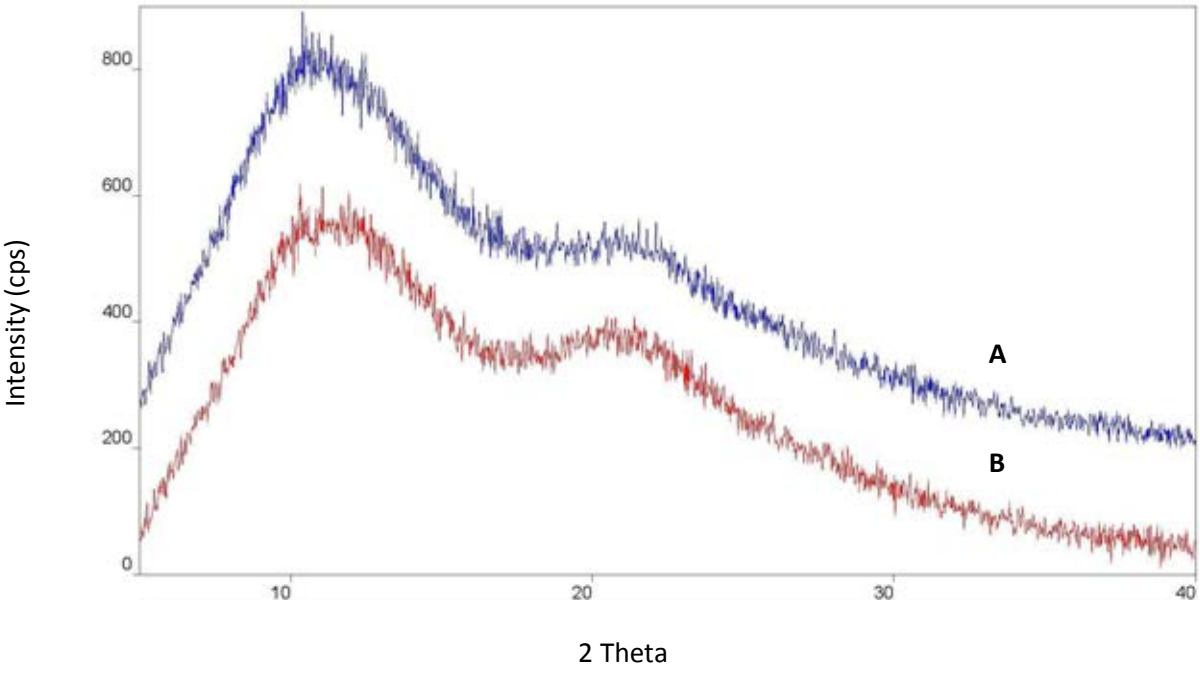


Figure 4-44 X-ray power diffraction patterns of Kollidon® VA-64 extrudate: A) untreated extrudate; B) treated extrudate

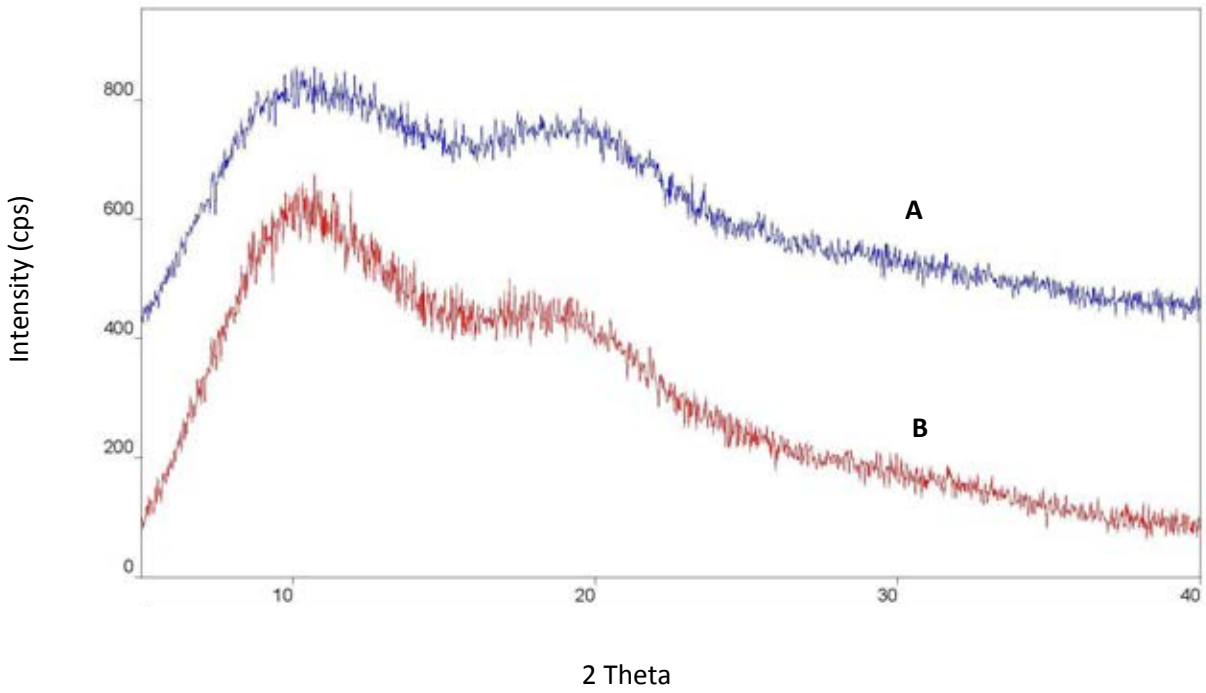


Figure 4-45 X-ray power diffraction patterns of Eudragit® EPO: A) untreated extrudate; B) treated extrudate

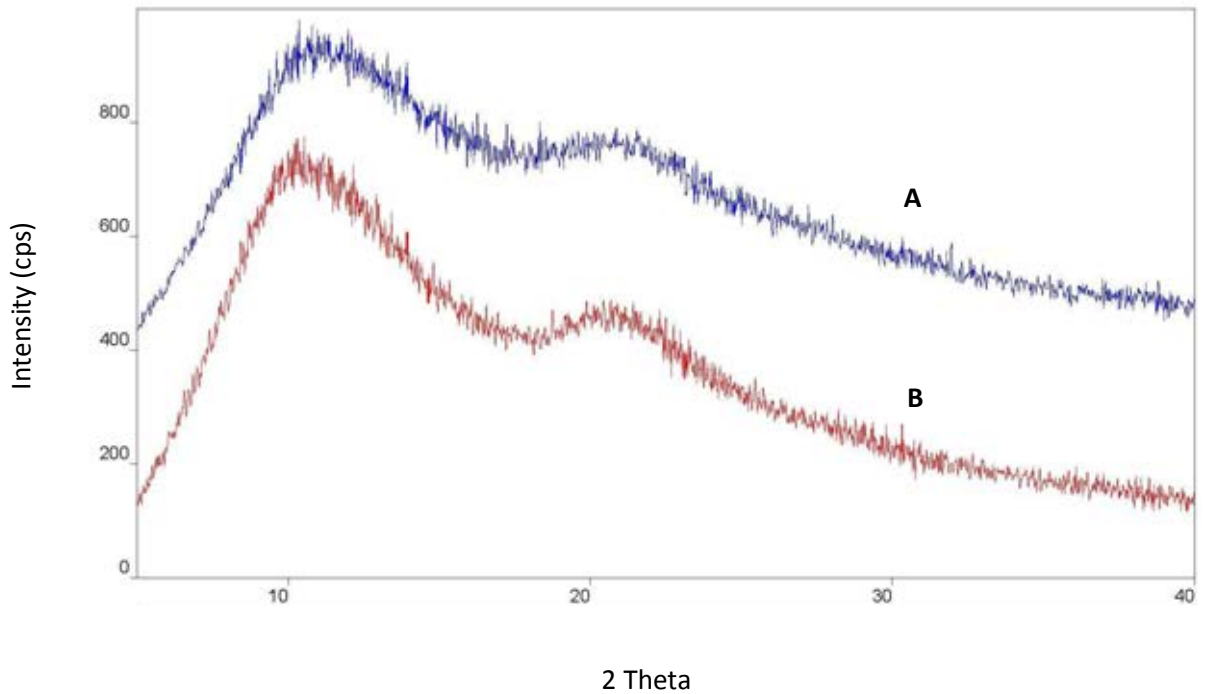


Figure 4-46 X-ray power diffraction patterns of Kollidon® K-30 extrudate: A) untreated extrudate; B) treated extrudate

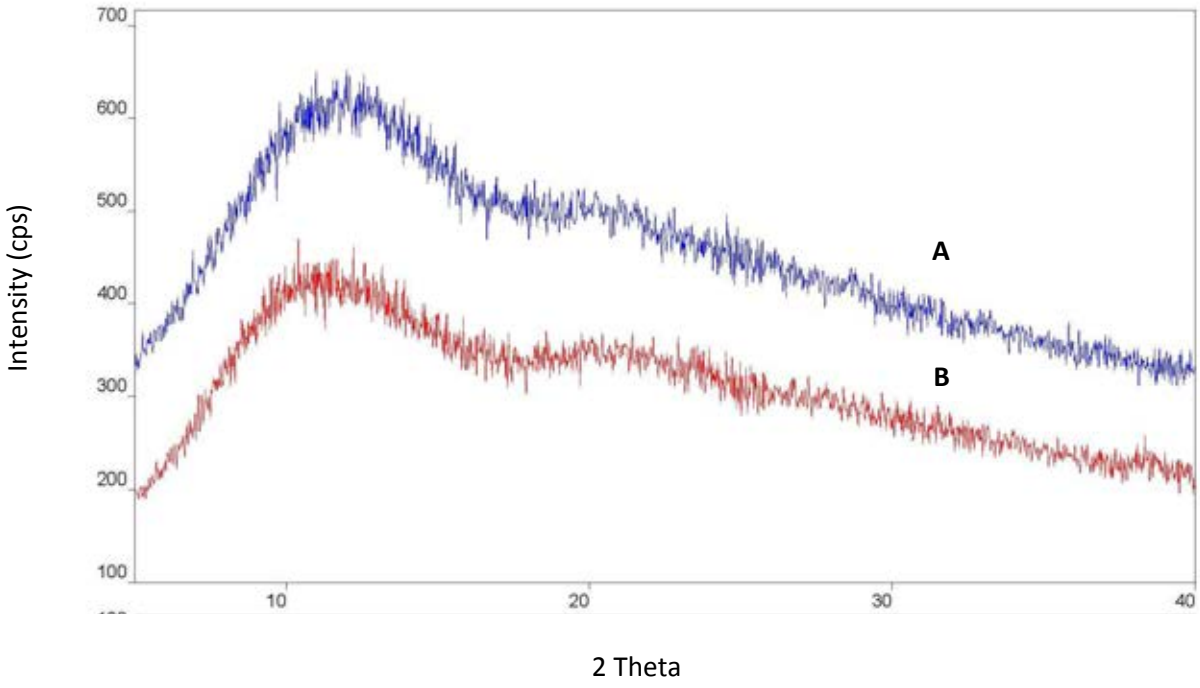


Figure 4-47 X-ray power diffraction patterns of HPC extrudate: A) untreated extrudate; B) treated extrudate

8.3 Dissolution study

Dissolution profiles of treated extrudates was not significantly different comparing those of the untreated. The results indicated that moisture did not affect dissolution behavior of the extrudate.

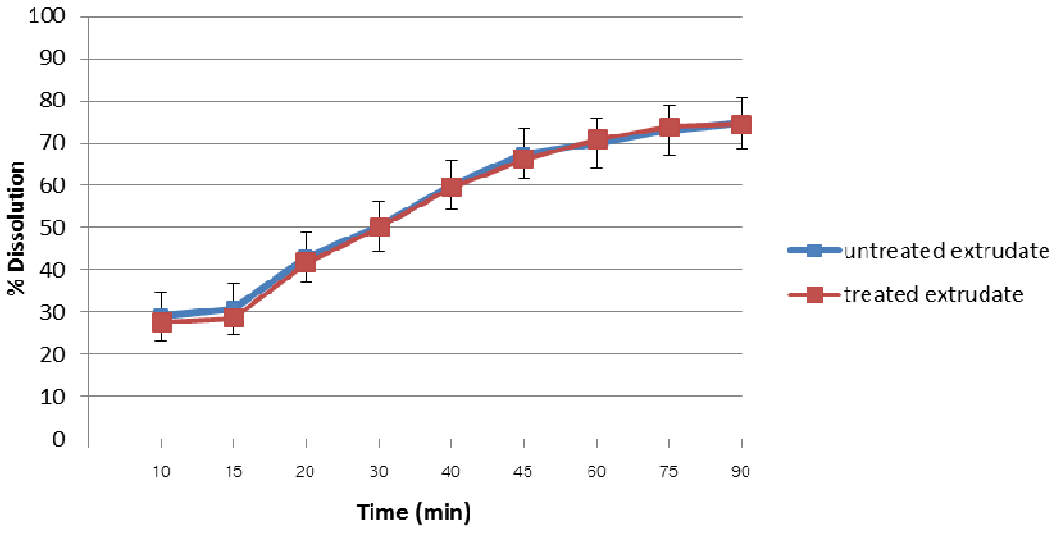


Figure 4-48 Dissolution profiles of untreated and treated Soluplus® extrudate

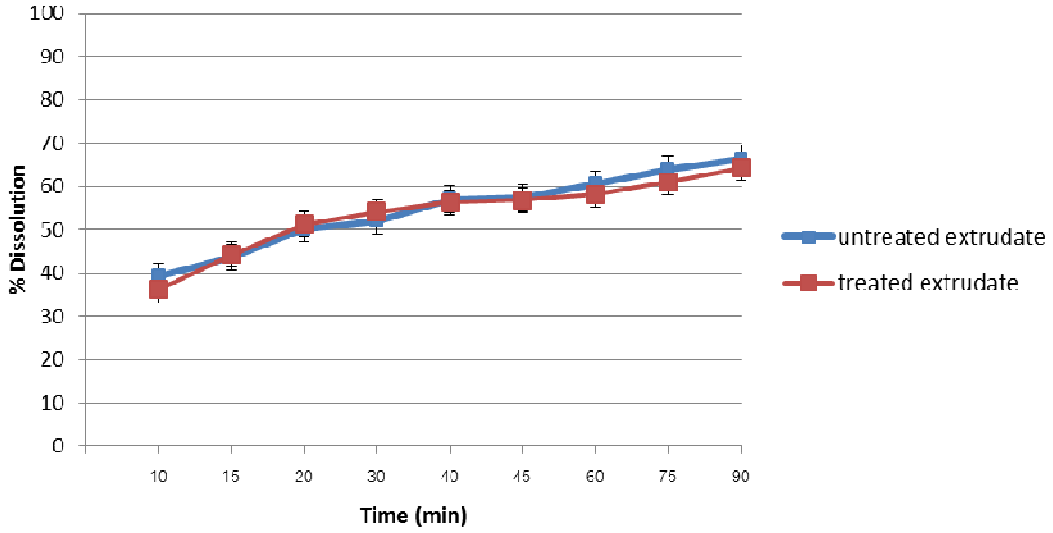


Figure 4-49 Dissolution profiles of untreated and treated Kollidon® VA-64 extrudate

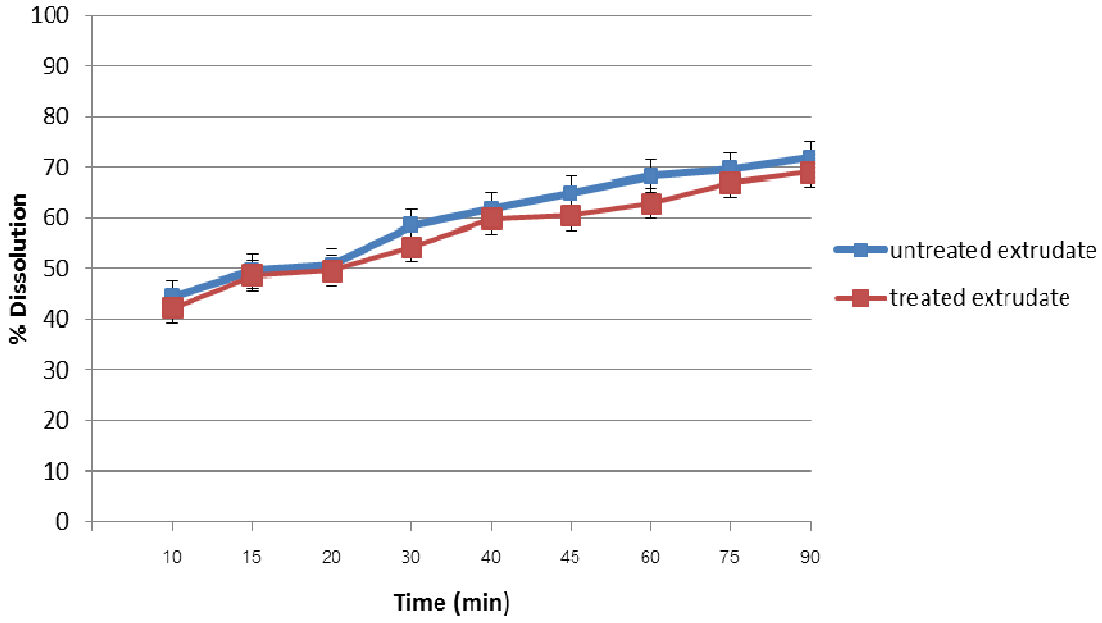


Figure 4-50 Dissolution profiles of untreated and treated Eudragit® EPO extrudate

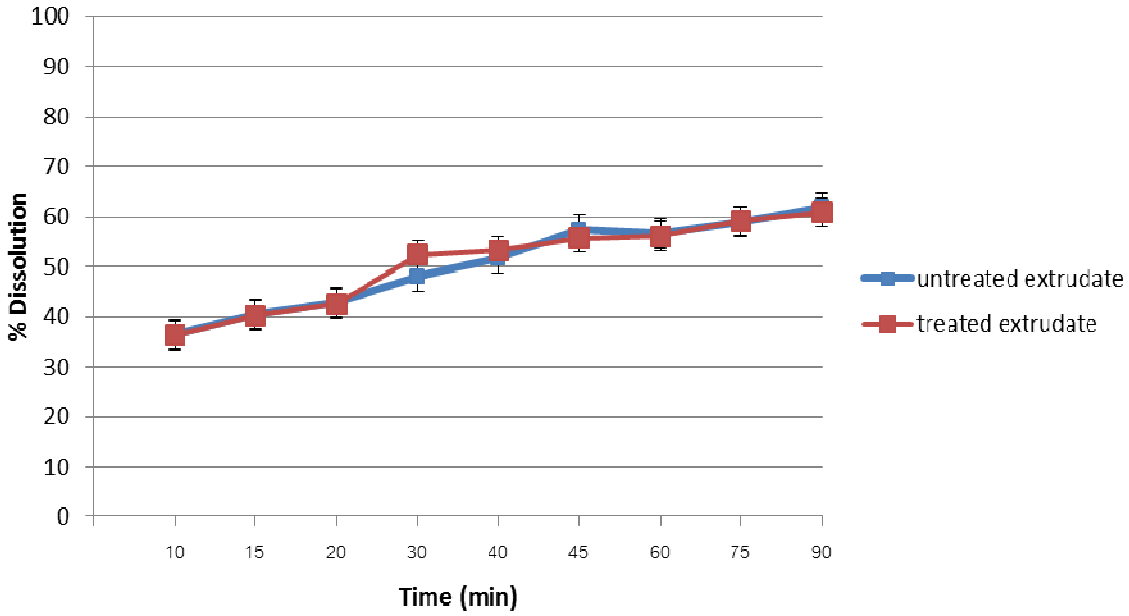


Figure 4-51 Dissolution profiles of untreated and treated Kollidon® K-30 extrudate

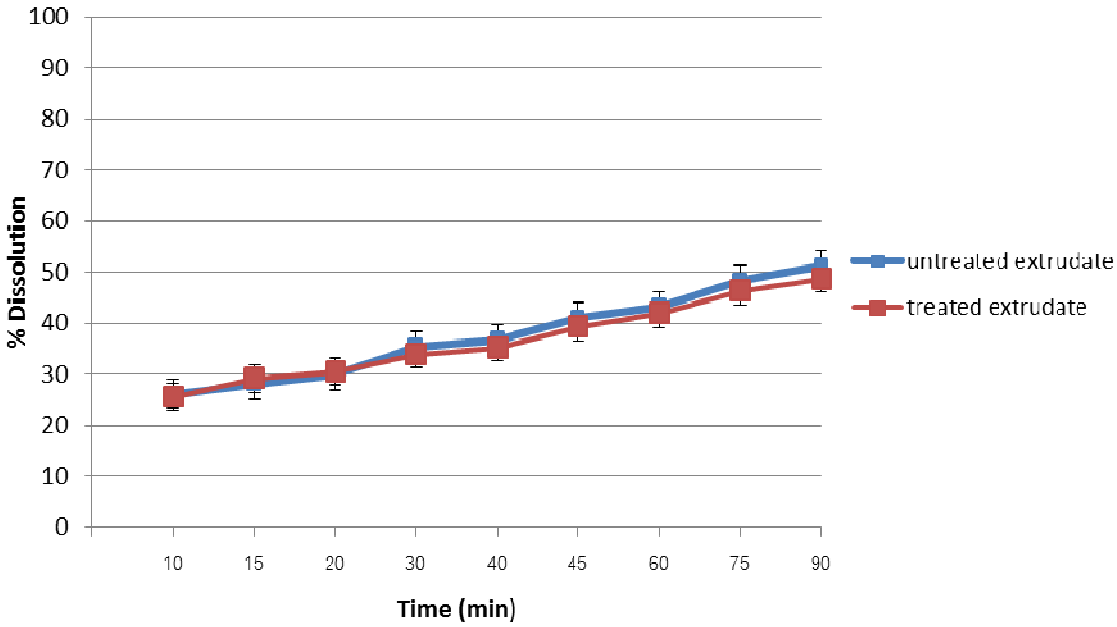


Figure 4-52 Dissolution profiles of untreated and treated HPC extrudate

CHAPTER V

CONCLUSION

Miscibility of efavirenz and the polymers (Soluplus®, Kollidon VA-64®, Eudragit EPO®, Kollidon K-30®, polyvinyl alcohol and hydroxypropyl cellulose (HPC)) could be predicted by solubility parameter calculation, film casting, hot-stage microscopy (HSM) and differential scanning calorimetry (DSC). Overall, the results indicated that the drug and the polymers studied, except for HPC, were miscible.

The 50:50 drug/polymer mixtures, except for polyvinyl alcohol, could be extruded by conical twin screw extruder at the temperature 20 ºC above glass transition temperature (T_g) of the polymers.

Characterization of the extrudates with DSC and X-ray powder diffractometry (XRPD) indicated that they were solid solution, except for efavirenze/HPC extrudate. The DSC thermograms showed absence of melting endothermic peak of efavirenz and the presence of only single T_g. XRPD patterns showed absence of efavirenz crystalline peaks and the presence of board halo characteristics. IR spectra implied that there were interactions between the drug and polymers.

The results of dynamic vapor sorption technique (DVS) suggested that miscible drug in all extrudates was stabilized against stressed condition induced by moisture. However, the DSC thermograms showed gradual increase in T_g of the solid solution due to possible molecular rearrangement in the chain of polymer during the sorption/desorption cycles.

As for efavirenze/HPC extrudates, they also exhibited the same charactertistics obtained by various solid state analytical techniques, i.e. DSC, XRPD, FT-IR and DVS, as previously described. However, it could not be concluded that efavirenze/HPC extrudate was a solid solution due to the extrudate's opaque appearance. The extrudate was found to be a dispersion of efavirenz in the HPC matrix.

The dissolution profile of the drug alone and that of every extrudates were significantly different. This signified that the dissolution of efavirenz was greatly enhanced by forming solid solution of the polymer studied or solid dispersion in the case of HPC.

REFERENCES

Aitken-Nichol, C., Zhang, F., and McGinity, J. W. Hot-melt extrusion of acrylic films. Pharmaceutical Research 13 (1996): 804-808.

Alanazi, F. K., El-Badry, M., Ahmed, M. O. and Alsarra, I. A. Improvement of albendazole dissolution by preparing microparticles using spray-drying technique. Scientia Pharmaceutica 75 (2007): 63-79.

Barton, A. F. M. **CRC Handbook of solubility parameters and other cohesion parameters**. Florida: CRC Press Inc., 1991

Betageri, G. V. Enhancement of dissolution of glyburide by solid dispersion and lyophillization techniques. International Journal of Pharmaceutics 126 (1995) :155-160.

Blagden, N., Matas, M. D., Gavan, P. T., and York, P.. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advance Drug Delivery Reviews 59 (2007): 617-630.

Bogdanova, S., Sidzhakova, D., Karaivanova, V. and Georgieva, S. V. Aspects of the interactions between indomethacin and nicotinamide in solid dispersion. International Journal of Pharmaceutics 163 (1998): 1-10.

Breitenbach, J. Melt Extrusion: form process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics 54 (2002): 107-117.

Bruce, L. D., Shah, N.H., Waseem, M.A., Infeld, M.H. and McGinity, J.W. Properties of hot-melt extruded tablet formulations for the colonic delivery of 5-amino salicylic acid. European Journal of Pharmaceutics and Biopharmaceutics 59 (2005): 85-97.

Buckton, G. The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. International Journal of Pharmaceutics 123 (1995): 265-271.

Chaudhari, P., Sharma, P., Barhate, N., Kulkarni, P. and Mistry, C. Solubility enhancement of hydrophobic drugs using synergistically interacting cyclodextrins and cosolvent. Science Current. 92 (2007): 1586-1591.

Chiou, W. Pharmaceutical applications of solid dispersion systmes. Journal of Pharmaceutical Sciences 60 (1971): 1281-1302.

Choi, P., Kavassalis, T. A. and Rudin, A. Estimation of Hansen solubility parameters for hydroxyethyl and hydroxypropyl cellulose through molecular simulation. Industrial and Engineering Chemistry Research 33 (1994): 3154-3159.

Chokshi, R., Sandhu, H. K., Iyer, R. M., Shah, N. H., Malick, A. W. and Zia, H. Characterization of physico-mechanical properties of indomethacin and polymers to assess their suitability for hot-melt extrusion process as a means to manufacture solid dispersion/solution. Journal of Pharmaceutical Sciences 94 (2005): 2463-2474.

Chokshi, R. Hot-melt extrusion technique: A Review. Iranian Journal of Pharmaceutical Sciences. 3 (2004): 3-16.

Crowley, M. M., Zhang, F., Koleng, J. J. and McGinity, J. W. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Biomaterials 23 (2002): 4241-4248.

Crowley, M. M., Zhang, F., Repka, M. A., Thumma, S., Upadhye, S. B., Kumar, S., McGinity, J.W. and Martin, C. Pharmaceutical applications of hot- melt extrusion: Part I. Drug Development and Industrial Pharmacy 33 (2007): 909-926.

Curatolo, W. Physical chemical properties of oral drug candidates in the discovery and exploratory development settings. Pharmaceutical Science & Technology Today 1 (1998): 387-393.

Dhirendra, K., Lewis, S., Udupa, N. and Atin, K. Solid dispersion: A review. Pakistan Journal of Pharmaceutical Sciences. 22 (2009): 234-246.

Forster, A., Hempenstall, J., Tucker, I., and Rades, T. Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis. International Journal of Pharmaceutics 226 (2001): 147-161.

Forster, A., Hempenstall, J. and Rades, T. Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophillic amorphous polymers. Journal of Pharmacy and Pharmacology. 53 (2000): 303-315.

Ghebremeskel, A. N., Vemavarapu, C. and Lodaya, M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Stability texting of selected solid dispersions. Pharmaceutical Research 23 (2006): 1928-1936.

Greenhalgh, D. J., Williams, A. C., Timmins, P. and York, P. Solubility parameters as predictors of miscibility in solid dispersions. Journal of Pharmaceutical Sciences 88 (1999): 1182-1190.

Hancock, B. C., York, P. and Rowe, R. C. The use of solubility parameters in pharmaceutical dosage form design. International Journal of Pharmaceutics 148 (1997): 1-21.

Hancock, B. C. and Zogra, G. Characteristics and significance of the amorphous state in pharmaceutical systems. Journal of Pharmaceutical Sciences 86 (1997): 1-12.

Hansen, C. M. **Hansen solubility parameters: A user's handbook**. Florida: CRC Press Inc., 1991

Hasnain, B. Solubility and dissolution enhancement of ibruprofen by solid dispersion technique using PEG 6000-PVP K30 combination carrier. Bulgarian Journal of Science Education 21 (2012): 118-132.

Hildebrand, J. H. and Scott, R. L. **The solubility of nonelectrolytes**. New York: Reinhold Pub. Corp., 1950.

Horter, D. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Advanced Drug Delivery Reviews 46 (2001): 75-87.

Hulsmann, S., Backensfeid, T., Keitel, S. and Bodmeier, R.. Melt extrusion – an alternative method for enhancing the dissolution rate of 17β-estradiol hemihydrate. European Journal of Pharmaceutics and Biopharmaceutics. 49 (2000): 237-242.

Jagtap, P. S., Jain, S. S., Dand, N., Jadhav, K. R. and Kadam, V. J. Hot melt extrusion technology, approach of solubility enhancement: A brief review. Pharmaceutical Letter 4 (2012): 1-8.

Jim, W. M., Michael, A. R., and John, J. K. Hot-Melt Extrusion Technology. Encyclopedia of Pharmaceutical Technology 3 (2007): 2004-2020.

Kadir, M. F., Sayeed, M.S.B., Khan, R.I, Shams, T. and Islam S. Study of binary and ternary solid dispersion of ibuprofen for the enhancement of oral bioavailability. Journal of Applied Pharmaceutical Science 1 (2011): 103-107.

Kapsi, S. Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailibility. International Journal of Pharmaceutics 229 (2001): 193-203.

Khatry, S. Melt extrusion - An overview. International Journal of Pharmaceutics and Technology 3 (2011): 685-703

Krevelen, V. **Properties of polymers**. New Jersey: Elsevier Science, 1990.

Kolter, K., Karl, M., Nalawade, S. and Rottmann, N. Hot-melt extrusion with BASF Pharma. Polymers 35 (2007).

Kruder, G. A. **Encyclopedia of polymer science and engineering**. New York: Herman Francis Mark, 1985.

Kumar, S. D., Bihari, G. V. and Suresh, P. Solubility improvement using solid dispersion; strategy, mechanism and characterization: responsiveness and prospect way outs. International Research Journal of Pharmacy 1 (2011): 55-60.

Kearney, A. S., Gabriel, D. L., Mehta, S. C. and Radebaugh, G. W. Effect of polyvinylpyrrolidone on the crystallinity and dissolution rate of solid dispersions of the anti-inflammatory CI-987. International Journal of Pharmaceutics 104 (1994): 169–174.

Lakshman, J. P., Cao, Y., Kowalski, J. and Serajuddin, A. T. M. Application of melt extrusion in the development of a physically and chemically stable high energy amorphous solid dispersion of a poorly water-soluble drug. Molecular Pharmacology 5 (2008): 994-1002.

Leuner, C., and Dressman, J. Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics 50 (2000): 47-60.

Liu, J., Zhang, F. and McGinity, J. W. Properties of lipophillic matrix tablets containning phenylpropanolamine hydrochloride prepared by hot-melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics. 52 (2001): 181-190.

Liu, H., Zhang, X., Suwardie, H., Wang, P. and Gogos, C.G. Miscibility studies of indomethacin and Eudragit® EPO by thermal, rheological, and spectroscopic analysis. Journal of Pharmaceutical Sciences 101 (2012): 2204-2212.

Liversidege, G. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. International Journal of Pharmaceutics 125 (1995): 91-97.

Lloyd, G. R., Craig, D. Q. M., and Smith, A. An investigation into the production of paracetamol solid dispersions in PEG 4000 using hot stage differential interference contrast microscopy. International Journal of Pharmaceutics 158 (1997): 39-46.

Lo, W. Dissolution behavior of griseofulvin solid dispersions using polyethylene glycol, talc and their combination as dispersion carriers. Drug Development and Industrial Pharmacy. 22 (1996): 231-236.

Madhavi, B., Kusum, B., Chatanya, C. K., Madhu, M. N., Harsha, V. S. and Banji, D Dissolution enhancement of efaivrenz by solid dispersion and PEGylation techniques. International Journal of Pharmaceutical Investigation 1 (2011): 29-34.

Malone, M. H., Hochman, H. I. and Nieforth, K. A. Desoxycholic acid enhancement of orally administered reserpine. Journal of Pharmaceutical Sciences 55 (1966) : 972-974.

Martin, A., Wu, P. L., Liron, Z. and Cohen, S. Dependence of solute solubility parameters on solvent polarity. Journal of Pharmaceutical Sciences. 74 (1985): 638-642.

Maniruzzaman, M., Rana, M. M., Boateng, J. S., Mitchell, J. C. and Douroumis, D. Dissolution enhancement of poorly water-soluble APIs processed by hot-melt extrusion using hydrophilic polymers. Drug Development and Industrial Pharmacy 1 (2012): 1-10.

McGinity, J. W., and Koleng, J. J. preparation and evaluation of rapid-release granules using a novel hot-melt extrusion technology. 16th Pharmaceutical technology Conference, Athens (1997): 153-155.

Mendiratta, C., Kadam, V. and Pokharkar, V. Lansoprazole solid dispersion using a novel amphiphillic polymer Soluplus®. Journal of Chemical Pharmaceutical Research 3 (2011): 536-543.

Miller, D. A., Yang, W., Williams, R. O., McGinity, J. W. Hot-melt extrusion for enhanced delivery of drug particles. Journal of Pharmaceutical Sciences. 96 (2006): 361-376.

Nagy, Z. K., Balogh, A., Vajna, B., Farkas, A., Patyi, G., Kramarics, A. and Marosi G. Comparison of electrospun and extruded Soluplus® - based solid dosage forms of improved dissolution. Journal of Pharmaceutical Sciences. 101 (2011): 322-332.

Onoue, S., Sato, H. Ogawa, K., Kwabata, Y., Mizumoto, T., Yuminoki, K. Hashimoto, N. and Yamaha, S. Improved dissolution and pharmacokinetic behavior of cyclosporine A using high-energy amorphous solid dispersion approach. International Journal of Pharmaceutics 399 (2010): 94-101.

Palanisamy, M. Solid dispersion of prednisolone: solid state characterization and improvement of dissolution profile. Drug Development and Industrial Pharmacy 37 (2011): 373-386.

Panayiotis, P. C. Lipid microemulsions for improving drug dissolution and oral absorption: Physical and biopharmaceutical aspects. Pharmaceutical Research 12 (1995): 1561-1572.

Paul, G. R., Duncan, Q. M. C., and Christopher, D. Characterization of the Glass transition of an amorphous drug using modulated DSC. Pharmaceutical Research 15 (1998): 1117-1121.

Perissutti, B., Newton, M., Podczeck, F. and Rubessa, F. Preparation of extruded carbamazepine and PEG4000 as a potential rapid release dosage form. European Journal of Pharmaceutics and Biopharmaceutics. 49 (2002): 237-242.

Pham, T. N., Watson, S. A., Edward, A. J., Chavda, M., Clawson, J. S., Strohmeier, M. and Vogt, F. G. Analysis of amorphous solid dispersions Using 2D solid-state NMR and 1H T1 relaxation measurement. Molecular Pharmacology 7 (2010): 1667-1691.

Prodduturi, S., Urman, K. L., Otaigbe, J. U. and Repka, M. A. Stabilization of hot melt extrusion formulations containing solid solutions using polymer blends. AAPS Pharmaceutical Science Technology 8 (2006): 1-10.

Ranzani, L. S., Font, J., Galimany, F., Santanach, A., Gomez-Gomar, A.M., Casadevall, G. and Gryczke, A. Enhanced *in vivo* absorption of CB-1 antagonist in rats via solid solutions prepared by hot-melt extrusion. Drug Development and Industrial Pharmacy 37 (2011): 694-701.

Repka, M. A., Gerding, T. G., Repka, S. L., and McGinity J. W. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylmethylcellulose films prepared by hot-melt extrusion. Drug Development and Industrial Pharmacy 25 (1999): 627-635.

Repka, M. A., Battu, S. K., Upadhye, S. B., Thumma, S., Crowley, M. M., Zhang, F., Martin, C. and McGinity, J. W. Pharmaceutical applications of hot-melt extrusion: Part II. Drug Development and Industrial Pharmacy 33 (2007): 1043-1057.

Rumondor, A. C. F., Ivanisevic, I., Bates, S., Alonzo, D. E. and Taylor, L. S. Evaluation of drug-polymer misicibility in amorphous solid dispersion systems. Pharmaceutical Research 26 (2009): 2523-2534.

Sato, H., Miyagawa, Y., Okabe, T. Miyajima, M. and Sunada, H. Dissolution mechanism of diclofenac sodium from wax matrix granules. Journal of Pharmaceutical Sciences. 86 (1997): 929-934.

Sathigari, S. K. **Dissolution Enhancement of Poorly Water Soluble Drugs**. Doctoral dissertation, Graduate School, Auburn University, 2011.

Sathigari, S. K., Chadha, G., Lee, P., Wright, N., Parsons, D. L., Rangari, V. K., Fasina, O. and Babu, J. Physicochemical characterization of efavirenz cyclodextrin inclusion complexes. AAPS Pharmacuetical Science Technology. 10 (2009): 81-87.

Seedher, N. Co-solvent solubilization of some poorly-soluble antidiabetic drugs. Pharmaceutical Development and Technology. 14 (2009): 185-192.

Sekiguchi, K and Obi, N. Studies on absorption of eutectic mixtures. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chemical and Pharmaceutical Bulletin 9 (1961): 866-872.

Serajuddin, A. T. M. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. Journal of Pharmaceutical Sciences 88 (1999): 1058-1066.

Sheu, M. T., Yeh, C. M. and Sokoloski, T. D. Characterization and dissolution of fenofibrate solid dispersion systems. International Journal of Pharmaceutics 103 (1994): 137-146.

Six, K., Berghmans, H., Leuner, C., Dressman, J., Werde, K. V., Mullens, J., Benoist, L., Thimon, M., Meublat, L., Verreck, G., Peeters, J., Brewster, M. and Mooter, G. V. D. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extursion, Part II. Pharmaceutical Research 20 (2003): 2003.

Strawhecker, K. E. and Manias, E. Structure and properties of poly(vinyl alcohol)/Na+ montmorillonite nanocomposites. Chemical Materials 12 (2000): 2943-2949.

Sugimoto, M., Okagaki, T., Narisawa, S., Koida, Y. and Nakajima, K. Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water-soluble polymer. International Journal of Pharmaceutics 160 (1998): 11-19.

Tachibana, T. and Nakamura, A. A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: Dispersion of β-carotene by polyvinylpyrrolidone. Colloid and Polymer Science 203 (1965): 130-133

Tang, J., Xu, N., Ji, H., Liu, H., Wang, Z. and Wu, L. Eudragit nanoparticles containing genistein: formulation, development, and bioavailability assessment. International Journal of Nanoparticles 6 (2011): 2429-2435.

Tapas, A. and Sakarkar, D.M. Polymeric recrystallized spherical agglomerates of felodipine by quasi-emulsion solvent diffusion method. Der Pharmacia Sinica 1 (2010): 136-146.

Vasconcelos, T., Sarmento, B. and Costa, P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovory Today 12 (2007): 1068-1075.

Vollmann, K., Qurishi, R., Hockemeyer, J. and Muller, C. E. Synthesis and properties of a new water-soluble prodrug of the adenosine A2a recepter antagonist MSX-2. Molecules. 3 (2008): 348-359.

Win, L. C. and Sidney, R. Pharmaceutical applications of solid dispersion systems. Journal of Pharmaceutical Sciences. 60 (1971): 1281-1302.

Yiyun, C., Tongwen, X. and Rongquang, F. Polyamidoamine dendrimers used as solubility enhancers of ketoprofen. European Journal of Medicinal Chemistry 40 (2005): 1390-1393.

You, B., Liang, N., Wang, L., Cui, F. Comparison of methods to improve the dissolution rate of nitrendipine. Asian Journal of Pharmaceutical Sciences 3 (2008): 102-109.

Young, C. R., Koleng, J. J. and McGinity, J. W. Production of spherical pellets by a hot-melt extrusion and spheronization process. International Journal of Pharmaceutics 242 (2002): 87-92.

Yu, L. X., Furness, M. C., Raw, A., Outlaw, K. P. W., Nashed, E. N., Ramos, E., Miller, S. P. F., Admas, R. C., Fang., R., Patel, R. M., Holcombe, F. O., Cuiu, Y. and Hussian, A. S. Scientific considerations of pharmaceutical solid polymorphism in abbreviated new drug applications. Pharmaceutical Research 20 (2003): 531-536.

Yu, D., White, C.B., White, K., Li, X., Zhu, L. Dissolution improvement of electrospun nanofiber-based solid dispersions for acetaminophen. AAPS Pharmacuetical science technology. 11 (2010): 809-817.

Zein, H. E., Riad, L. and Elbary, A. A. Enhancement of carbamazepine dissolution *in vitro* and *in vivo* evaluation. International Journal of Pharmaceutics 168 (1998): 209-230.

Zhang, F. and McGinity, J. W. Properties of sustained-release tablets prepared by hot melt extrusion. Pharmaceutical Development and Technology 4 (1999): 241-250.

APPENDIX

Analysis of efavirenz and HPLC method validation

1. High-performance liquid chromatographic technique for drug analysis

The quantitative analysis of efavirenz was carried out by HPLC technique according to Indian pharmacopoeia 2007 (IP). Analysis method was validated for specificity, linearity, precision and accuracy according to acceptance criteria of United States Pharmacopeia 35–National Formulary 30 (USP 35–NF 20).

HPLC chromatogram of efavirenz found retention time at 12.084 minutes. (Figure 1A)

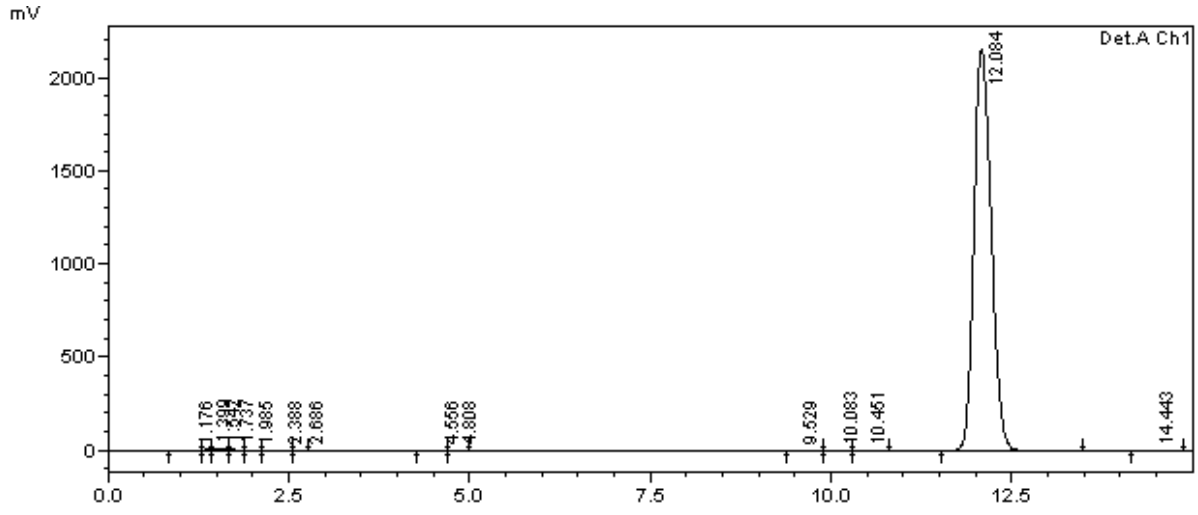


Figure 1A The retention time of efavirenz was found at 12.084 minutes

2. Validation for the quantitative determination of efavirenz

The validation process result are described in table 1A

Table 1A Analytical method validation parameter of HPLC for efavirenz

Parameter	Result value	Limit
1. Specificity	No other peak interfere major peak	No other peak interfere major peak
2. Linearity (Correlation coefficient)	0.9997	>0.9995
3. Precision		
3.1 Within Run (%RSD)	0.459%	<2.00%
3.2 Between Run (%RSD)	0.452%	<2.00%
4. Accuracy		
4.1 Recovery (%)	101.99%	98-105%
4.2 % RSD	1.335%	<2.00%

1.1 Specificity

HPLC chromatogram of efavirenz has a good resolution. The comparisons were taken out between efavirenz solution 100 mg/mL and efavirenz 100 mg/mL with polymer (Soluplus®, Kollidon VA-64®, Eudragit EPO®, Kollidon K-30® and HPC) solutions in a concentration of 100 mg/mL. The area under the curve of efavirenz solution was not significantly different with efavirenz and Soluplus®, Kollidon VA-64®, Eudragit EPO®, Kollidon K-30® and HPC (p-value = 0.297, 0.201, 0.140, 0.249, 0.352, respectively). There was no other peak interfere the major peak at 12.084 minute. The degradation study was performed at temperature of 110 ^{o}C for 3 hours, 0.1 N HCl and 0.1 NaOH. It was shown that heat, acid and base did not affect to stability of efavirenz. The results were summarized in Table 1C.

Table 1C Specificity validation of efavirenz

Concentration (mg/mL)	Sample	Peak area
Efavirenz 100 mg/mL	1	36542530
	2	35432487
	3	35634185
Efavirenz + Soluplus®	1	36457482
	2	36757534
	3	35345975
Efavirenz + Kollidon® VA-64	1	36253185
	2	36324538
	3	36123581
Efavirenz + Eudragit® EPO	1	36543982
	2	36434861
	3	35935275
Efavirenz + Kollidon® K-30	1	36133254
	2	36234539
	3	36135378
Efavirenz + HPC	1	35723576
	2	36137942
	3	36437381
Efavirenz (110 ^{o}C, 3 hours)	1	36135742
	2	36048982
	3	36095234
Efavirenz + 0.1 N HCl	1	36234237
	2	35934789
	3	35683424
Efavirenz + 0.1 NaOH	1	35937650
	2	35801769
	3	36135752

1.2 Linearity

Linearity of efavirenz was validated with concentration of the standard solutions of 150, 120, 110, 100, 90, 80, 50 mg/mL. The correlation coefficient (R^2) between average of area under the curve and concentrations were 0.9997. The results were summarized in Table 1D and Figure 1B.

Table 1D Linearity of analytical method of efavirenz

Concentration	**Peak Area**			**Average**
(mg/mL)	1	2	3	
150	51344605	47821936	48611561	49259367.33
120	41548772	41546441	40475080	41190097.67
110	38842998	39365936	36529820	38246251.33
100	36598605	36212867	35039012	35950161.33
90	32311744	33661658	32518838	32830746.67
80	31916617	29282096	29877842	30358851.67
50	22978494	22439054	21703145	22373564.33

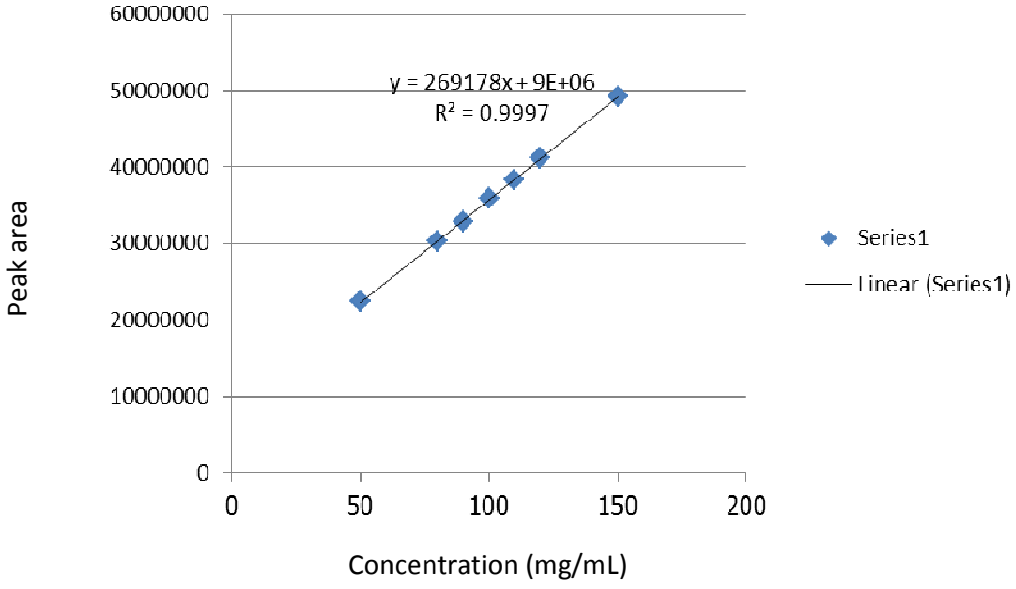


Figure 1B The calibration curve of efavirenz

1.3 Precision

Precision of efavirenz was validated under within run and between run conditions. Within run condition was validated with concentrations of the standard solution at 110, 100 and 90 mg/mL. The percentage relative standard deviation for the concentration of 110, 100 and 90 mg/mL was 0.617, 0.367 and 0.392, respectively. Between run condition was validated with concentrations of the standard solution at 100 mg/mL on 2 days. The percentage of relative standard deviation for day 1 and day 2 was 0.535 and 0.344, respectively. The results were summarized in Table 1E and Table 1F.

Table 1E Within run precision of analytical method of efavirenz

Concentration	**Peak Area**			**Average**	**SD**	**% RSD**
(mg/mL)	1	2	3			
110	38622481	38159116	38478789	38420128.67	237186.76	0.617
100	36609977	36480002	36342294	36477424.33	133860.11	0.367
90	32747111	32995579	32931310	32891333.33	128967.78	0.392
Average				35929628.78	166671.55	0.459

Table 1F Between run precision of analytical method of efavirenz

Day	**Peak Area**			**Average**	**SD**	**% RSD**
	1	2	3			
Day 1	38507939	38318581	38098210	38308243.33	205060.02	0.535
Day 2	38176903	38387664	38419665	38328077.33	131894.94	0.344
Average				38318160.33	167875.50	0.452

1.4 Accuracy

Accuracy of analytical method was validated with concentrations of the standard solution at 80, 100 and 120 mg/mL. Recovery percentage of the standard solution at 80, 100 and 120 mg/mL was 103.54, 103.68 and 98.76, respectively. The percentage of relative standard deviation for the standard solution at 80, 100 and 120 mg/mL was 1.626, 1.400 and 0.980, respectively. The results were summarized in Table 1G.

Table 1G Accuracy validation of analytical method of efavirenz

Conc (mg/mL)		**Area**	**Average**	**SD**	**% RSD**	**% Recovery**
80	1	25499791	25906757	421349	1.626	103.54
	2	26341149				
	3	25879331				
100	1	31916617	32429255.33	454096.5	1.400	103.68
	2	32780995				
	3	32590154				
120	1	36956709	37068110	363091.3	0.980	98.76
	2	37473850				
	3	36773771				
Average			31801374.11	412845.6	1.335	101.99

VITA

Mr. Sorranut Chetsurakul was born on April 18, 1985. He received his Bachelor Degree in Pharmacy, B.Sc. (in Pharm), in 2007 from the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand. He worked at Medica Innova, Co., Ltd. as medical writer for 1 year after graduation.