คณะเภสัชศาสตร์

ทุนวิจัยทางเภสัชศาสตร์

รายงานผลการวิจัย

ระบบกระจายตัวของแป้งชนิดปลดปล่อยเร็วของไนเฟดิพีน

โดย

สุชาดา ชุติมาวรพันธ์

มิถุนายน 2542

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Project Title Fast Release Solid Dispersion System of Nifedipine

Name of the Investigator Suchada Chutimaworapan

Year 1999

Abstract

Nifedipine solid dispersions in polyethylene glycols (PEG4000 and PEG6000), poloxamers (poloxamer188, poloxamer288 and poloxamer407), β-cyclodextrin (BCD) and 2-hydroxypropyl-β-cyclodextrin (HPBCD), at the drug:carrier ratio of 1:1, 1:3, 1:5 and 1:10 were investigated. The systems were prepared by melting, solvent and kneading method and compared to physical mixtures. It was found that the drug:carrier ratio of 1:10 and by melting and solvent methods showed most conspicuous dissolution rates in most systems ($p<0.05$). The most markedly improved rate was exhibited from the poloxamers. The prominently increased dissolution rates and the time for 80% drug dissolved of only 15 min were obtained in poloxamer 188 and poloxamer 407 from melting method at the 1:3, 1:5 and 1:10 ratios. PEG 4000 and PEG 6000 exhibited a very close dissolution rates when compared within the same method and ratio. Whereas BCD and HPBCD showed only a slightly increase of dissolution rate constants. Physicochemical characterizations showed that the possible key mechanism for fast release was the amorphous transformation of nifedipine in carriers, which shown via X-ray diffraction and differential scanning calorimetry. The marked improved wettability and solubility of nifedipine also gave beneficial effects. The intermolecular H-bonding between nifedipine and carriers was exhibited from the infrared spectral analyses.

ชื่อโครงการวิจัย ระบบกระจายตัวของแข็งชนิดปลดปล่อยเร็วของไนเฟดิพีน

ชื่อผู้วิจัย สุชาดา ชุติมาวรพันธ์

เดือนและปีที่ทำวิจัยเสร็จ สิงหาคม 2542

บทคัดย่อ

การศึกษาไนเฟดิพีนโซลิดดิสเพอร์ชันในกลุ่มโพลีเอทธีลีนไกลคอล (พีอีจี 4000 และพีอีจี 6000) กลุ่มโพล็อกซาเมอร์ (โพล็อกซาเมอร์188, โพล็อกซาเมอร์288 และโพล็อกซาเมอร์407) บีตาไซโคลเด็กซ์ตริน และไฮดรอกซีโพรพิลบีต้าไซโคลเด็กซ์ทริน) โดยใช้อัตราส่วนของตัวยาต่อตัวพาเท่ากับ 1:1, 1:3, 1:5 และ 1:10 และเตรียมโดยวิธีการหลอมเหลว การใช้ตัวทำละลายและการนวดผสมเปรียบเทียบกับของผสมทางกายภาพ พบว่าอัตราส่วนของตัวยาและตัวพา 1:10 และเตรียมโดยวิธีหลอมเหลวและการใช้ตัวทำละลายของระบบส่วนใหญ่จะให้ค่าอัตราการละลายสูงกว่าระบบอื่น ($P<0.05$) อัตราการละลายเพิ่มขึ้นสูงสุดในกลุ่มโพล็อกซาเมอร์ อัตราการละลายที่เพิ่มขึ้นสูงเด่นชัดและเวลาที่ยาละลายได้ 80 % ในเวลาเพียง 15 นาที สามารถได้จากการใช้โพล็อกซาเมอร์188 และโพล็อกซาเมอร์407 โดยวิธีการหลอมเหลวในอัตราส่วน 1:3 1:5 และ 1:10 อัตราการละลายของพีอีจี 4000 และพีอีจี 6000 มีค่าสูงใกล้เคียงกันมากเมื่อเปรียบเทียบระหว่างวิธีการเตรียมและอัตราส่วนเดียวกัน สำหรับกลุ่มบีต้าไซโคลเด็กซ์ทรินและไฮดรอกซีโพรพิลบีต้าไซโคลเด็กซ์ทรินให้ค่าคงที่ของอัตราการละลายเพิ่มขึ้นเพียงเล็กน้อย การศึกษาลักษณะทางเคมีฟิสิกส์พบว่ากลไกสำคัญของการปลดปล่อยเร็วคือการเกิดรูปอสัณฐานของนิเฟดิพีนในตัวพาซึ่งแสดงจากเอกซ์เรย์ดิฟแฟรกชันและดิฟเฟอเรนเชียลสแกนนิงแคลอริเมตรี การเพิ่มการเปียกน้ำและค่าการละลายมีผลดีต่อการเพิ่มอัตราการละลายเช่นกัน จากการศึกษาอินฟราเรดสเปกโทรสโคปีพบการเกิดพันธะไฮโดรเจนระหว่างโมเลกุลของไนเฟดิพีนและตัวพา

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CONTENTS

LIST OF TABLES

Table **Page**

Table **Page**

Table **Page**

Table **Page**

LIST OF FIGURE

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

Figure **Page**

LIST OF ABBREVIATIONS

°C	=	degree Celsius
HPBCD	=	2-hydroxypropyl-β-cyclodextrin
ANOVA	=	analysis of variance
BCD	=	β-cyclodextrin
cm	=	centimeter
DSC	=	differential scanning calorimetry
g	=	gram
IR	=	infrared
KV	=	kilovolt
LSR	=	Least significant range
mA	=	milliampere.
mg	=	milligram
min	=	minute
ml	=	milliliter
mm	=	millimeter
nm	=	nanometer
PEG	=	polyethylene glycol
psi	=	pound per square inch
r^2	=	coefficient of determination
SEM	=	scanning electron microscopy
SMG	=	simulated gastric fluid without pepsin
SSR	=	Significant studentized ranges.
UV	=	ultraviolet
XRD	=	X-ray diffraction
μg	=	microgram
μm	=	micrometer

CHAPTER I

INTRODUCTION

Nifedipine, a highly active calcium channel blocker,is used in the treatment of angina pectoris and hypertension (Reynold, 1989). However, nifedipine is only slightly water soluble (11 μg/ml at 37°C) as a result of which the drug may exhibit poor absorption characteristics and bioavailability after oral administration.

Fincher (1968) reported that the rate limiting step of gastrointestinal absorption of nifedipine is the dissolution rate. Therefore, the improvement of nifedipine dissolution from its oral solid dosage forms is an important issue for enhancing its bioavailability and therapeutic efficiency.

Various strategies have been conducted in order to increase nifedipine dissolution; of which is the use of solid dispersions. Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting, solvent, or melting-solvent methods (Chiou and Riegelman, 1971a).

The formation of amorphous forms to increase drug solubility, reduction of particle size to expand the surface area for dissolution, and a decrease in interfacial tension with

the aid of water soluble carriers are among possible mechanisms for increasing dissolution rate, and improving the bioavailability.(Abdou, 1989).

Even though the dissolution of drug from solid dispersion depends on the method employed to prepare the dispersion, the proportion and property of the carrier used should be concerned. Several carriers have been investigated to enhance the dissolution behavior, polyethylene glycols (PEG) are popular water soluble polymers, extensively used to enhance nifedipine dissolution rate.(Law et al, 1992, Save and Venkitachalam, 1992, Suzuki and Sunada, 1997 and Suzuki and Sunada, 1998)

Cyclodextrins, commonly used in the formation of inclusion complex, have been proven to attain positive outcomes when used as a carrier for solid dispersions. Two keys of cyclodextrins are β-cyclodextrin (BCD) and 2-hydroxypropyl-β-cyclodextrin (HPBCD). There are a number of studies have been published on applications of cyclodextrins in nifedipine solid dispersion systems (Acarturk, Kislal and Celebi,1992 and Hirayama, Wang and Uekema,1994).

Another carrier of interest is poloxamers, a novel group of nonionic surfactants. Some poloxamers were found to inhibit crystal growth and change crystal habit hence improve dissolution rate (Reddy, Khalil and Gouda, 1976, Luhtala, 1992 and Mackella et al.,1994). Thus, it is interesting to investigate this group of carrier in this study.

Since an investigation of physicochemical properties of the nifedipine solid dispersion systems would gain the understanding of the mechanisms that enhance drug dissolution. This would allow the prediction for other poorly soluble drugs. This study will focus on the nifedipine-carrier solid dispersion system in depth to elucidate the specific mechanism involving dissolution enhancement. The preparation by melting, solvent and kneading methods, the proportion and types of carriers are investigated. PEGs, poloxamers and cyclodextrins are selected as carriers in this experiment. These carriers are well accepted as nontoxic carriers which extensively used in the pharmaceutical areas.

Objectives: The purposes of this study are as follows.

1. To prepare nifedipine solid dispersions by melting, solvent and kneading methods.

2. To investigate the effects of types of carriers, mixing ratios between drug and carrier and preparation methods on dissolution of nifedipine compared to their corresponding physical mixtures.

3. To examine the characteristics of the obtained solid dispersions by infrared absorption spectroscopy (IR), differential scanning calorimetry (DSC), powder X-ray diffractometry (XRD) and scanning electron microscopy (SEM).

4. To elucidate the mechanism(s) of enhanced dissolution of nifedipine solid dispersions.

CHAPTER II

LITERATURE REVIEW

Principles of Solid Dispersion

The term solid dispersion was first used by Mayersohn and Gibaldi (1966). "Solid-state dispersion" was employed to increase dissolution rate of water-insoluble drugs. Thereafter the clear definition of solid dispersion was introduced by Chiou and Riegelman (1971a), as a system which one or more ingredients were dispersed in an inert carrier or matrix in the solid state prepared by melting (fusion), solvent (coevaporation) or melting-solvent method.

The dissolution rate of an active ingredient in solid mixture containing more than one component is influenced by other components. The choice of carrier plays an important role to the dissolution rate of the active ingredient in solid dispersion system. Some carriers release the active ingredient faster than the others. From this point of view, solid dispersion can be applied for both sustained release and fast release.

1. Preparation method of solid dispersion.

1.1 Melting method (Fusion method)

Sekiguchi and Obi (1961) were the first group that employed this method. Sulfathiazole and Urea were first physically mixed. Then the mixture was heated until thoroughly fused. Rapid cooling in an ice bath was applied to entrap

sulfathiazole particles in the urea matrix. This procedure was used extensively thereafter. The cooling rate was found important in such a way that the size of crystal and physical state of active ingredients depend upon. Usually the faster cooling, the better dissolution rate.

Several cooling methods were studied e.g. iron plate containing circulated cold air/water (Chiou and Riegelman, 1969; 1971b), and cooled aluminium plate (Pederson and Rassino, 1990)

Mcginity et al. (1984) studied on tolbutamide–urea solid dispersion and found that tolbutamide formed more amorphous state in the process with fast cooling than that with slow cooling. In general, a drug in amorphous state has better dissolution than one in crystalline state.

There are three main advantages of this method. Firstly, melt method is simple and economy. Secondly this method does not require any solvent where sometimes may cause toxicity. Lastly, when this method is used in conjuction with quenching (rapid cooling) technique, drug molecules can be supersaturated in the matrix hence finer drug crystallization. These crystals are much finer than those of simple eutectic mixture.

However there are some disadvantages found in this method. Choice of carriers is limited. Carriers with low melting point are preferred. Decomposition of drugs or carriers can be encountered especially at the high temperature during melting. Some

carriers decomposes at the temperature close to their melting points, for instance, succinic acid. Melting in a close container or in the vacuum atmosphere is therefore required for those types of carriers.

1.2 Solvent method (Coevaporation method)

Solvent method is the technique where a selected solvent is used to dissolve both drug and carrier. The mixed solution is then evaporated to remove the solvent. Evaporation can be either done under atmospheric or vacuum condition. The solid obtained after evaporation is the coevaporate of drug and carrier where the drug is suspended in the carrier network.

A number of investigations have been conducted with this method, for example, griseofulvin-PVP (Mayersohn and Gibaldi, 1966), griseofulvin-PEG6000 (Chiou and Riegelman, 1969), miconazole-PEG4000 (Pederson and Rassino, 1990) and probenecid-phospholipid (Habib, Azadi and Akooteran, 1992).

Advantages of this method is the ability of using carriers with high melting point and the less decomposition of drug and carrier. This is because high temperature exposure of the components can be avoided. Generally, most solvents are easily evaporated.

However, there are a number of disadvantages concerning to this method.

a. The preparation cost of solvent method is higher than that of melt method. The main costs are from incorporation and removal of solvent.

b. Too much effort is needed to completely remove liquid solvent.

c. Preparing time is quite long. It is therefore affecting the chemical stability of key ingredient.

d. Cosolvent is difficult to be determined as, in most cases, carriers are hydrophilic whereas drugs are hydrophobic.

e. Theoretically, reproducing similar crystal form by this method is hardly possible.

1.3 Melting-solvent method.

This method is meant to overcome the disadvantages of both melting and solvent methods. It is prepared by firstly, dissolving the drug in a solvent. Then incorporating the solution directly into melted water-soluble carrier. Then the solvent is evaporated to gain the solid . However, some issues may occur in this method, for example, the selected solvent or dissolved drug may be immiscible with melted water-soluble carrier. Additionally, polymorphic form of the drug in solid dispersed form can be affected by selection of solvent used in the first stage.

The key advantage of this method is the appropriateness to heat labile drugs. However the method is unsuitable to high dosage drugs (not more than 50 mg) and, the polymorphic form of the drug suspended in a carrier sometimes can be affected by the solvent used.

Some examples of pharmaceutical applications employing this method are spironolactone-PEG6000 (Chiou and Riegelman, 1971a) and miconazole nitrate-sodium hydroxide using ethanol as a solvent (Pederson and Rassino, 1990).

2. Mechanism of solid dispersion formation.

The basic main principle of increasing solubility by using solid dispersion method is the alteration of physicochemical structures. The physicochemical structures of dispersions play an important role in controlling the drug release from matrix. There are six representative structures outlining interaction between the drug and carrier (Ford, 1986).

a. Simple eutectic mixtures

b. Solid solution

c. Glass solution and glass suspension

d. Amorphous precipitation in a crystalline carrier

e. Compound or complex formation

f. Combination

a. Simple eutectic mixtures

Simple eutectic mixtures can be prepared by melting two components followed by rapid solidification. The two components must show complete miscibility in the liquid state and negligible solid-solid solubility. Eutectic systems are characterized as a crystalline component. It can be explained by a phase diagram. Both components are crystallized out simultaneously in very small particle sizes. The increment of specific area is the main contributor to increase the dissolution rate.

b. Solid solution

Solid solution is derived from a solid solute dissolving in a solid solvent. Both of which are crystallized together, usually called mixed crystals, in a continuous one -

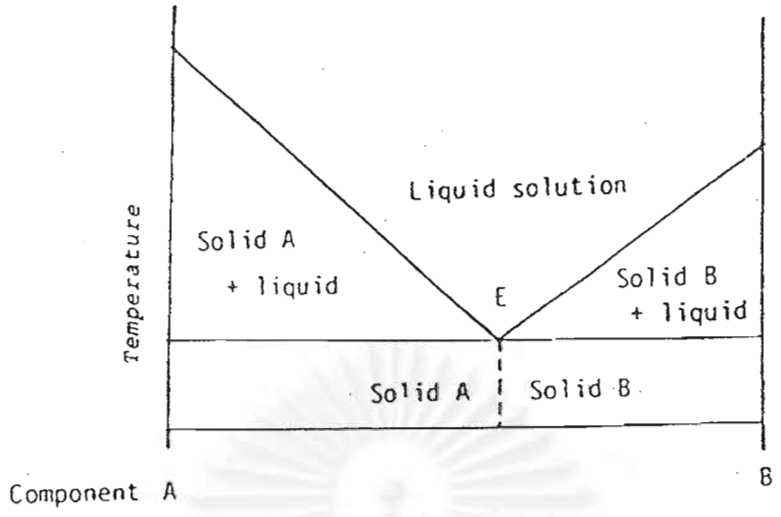


Figure 1 Phase diagram of an eutectic mixture with negligible solid solubility.

E: eutectic point.

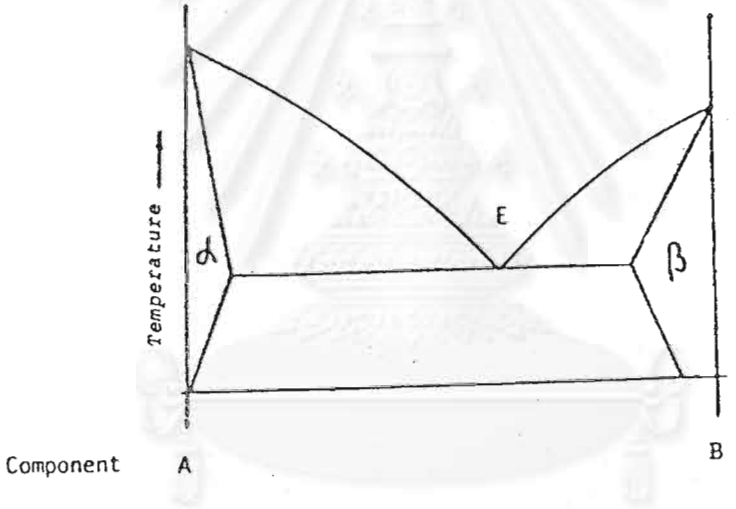


Figure 2 Typical phase diagram of a discontinuous solid solution of binary system A and B. α and β are regions of solid solution formation; E : eutectic point.

phase system. Goldberg, Gibaldi and Kanig (1965) suggested that a slightly water soluble solid drug which was dispersed in a high water soluble carrier will show higher water solubility than that in an eutectic mixture. This phenomenon can be explained by the particle size basis. In the eutectic mixture system, drug particles will be much coarser than that of the solid solution system. This is due to the molecular

dispersion of drug in the system. In addition, the advantage of a solid solution is the lesser solvent needed to dissolve the same amount of solute. Goldberg, Gibaldi and Kanig (1966) demonstrated that the dissolution of griseofulvin-succinic acid solid solution was eight times faster than that of the eutectic mixture system.

Two types of structures are used to represent solid solution. On the basis of their solid miscibility, they may be classified as continuous or discontinuous solid solutions. The main criteria for differentiation of these two structures is the bond strength between the same component versus the bond strength between the different molecules. For continuous solid solution, it possesses the bond strength between the different components greater than the bond strength between the same molecules, and therefore the components are miscible throughout the composition range. This seems to be unrealistic and so far no solid dispersion is classified into this category. Discontinuous solid solution is contrary. Each component is capable of dissolving the other to some extent.

c. Glass solution and glass suspension

Glass solution is a single homogeneous phase containing a solute dissolving in a glass solvent. The glass state is created by melting the glass solvent with the solute and cooling down rapidly. It is often characterized by transparency and brittleness below the glass transforming temperature.

Since the intermolecular bonding between solute and solvent may be increased in solid solutions. For glass solution, the bond is not as strong as lattice bonding of solid

solutions (Chiou and Riegelman, 1969). The bond within the glass solution is just similar to that in the liquid solution. The dissolution rate of the drug in glass solution is therefore theoretically faster than that in the solid solution. Several compounds have been proven to initiate glass solution e.g. sucrose, glucose, ethanol and 3-methylhexane. Molecules with polyhydroxy groups also have potency of glass solution formation. This phenomenon can be explained in terms of the strength of hydrogen bond. These types of molecules have strong hydrogen bonds that help preventing crystallization. Instead they transform into glass solution.

Glass solution is preferred to solid solution when preparing a fast release solid dispersion because of its higher rate of dissolution. The bond between solvent and solute in solid solution is often greater than that in glass solution. Additionally glass solution is more viscous than solid solution. This causes inhibition effect to drug crystallization. As a result, supersaturation level is likely to be achieved. At certain drug to carrier ratios, certain carriers may favor glass solution including PVP, urea and PEG. Glass suspensions rather than glass solution are formed when the drug and carrier do not show interaction and are immiscible in the liquid state.

d. Amorphous precipitation in a crystalline carrier

Instead of forming an eutectic mixture where both drug and carrier crystallize from the melting or solvent method, drug also can behave differently by precipitate out in an amorphous form in the crystalline carrier. The mixture containing long chain polymers may crystallize slowly and because of steric hindrance will never reach 100% crystallinity. Consequently, dispersion in PEGs and other long chain

polymers may show gradual increase in crystallinity of amorphous areas during storage.

In 1961, Sekiguchi and Obi reported that amorphous of sulfathiazole in crystalline urea was the first key factor that enhanced drug absorption in human via oral administration. While Chiou and Riegelman (1971a) obtained precipitated amorphous of iopanoic acid under electron microscopy when PVP10000 was used as the carrier. In 1984 Mcginity, Maincent and Steinfink investigated tolbutamide-PEG system by X-ray diffraction method. It was found that amorphous of tolbutamide presented in the freshly prepared system.

e. Compound and complex formation

This system is very difficult to generalize the influences. This is where some compounds and/or complex are formed. A complex formation is characterized by an enclosure of the drug molecule in the carrier molecule. The hollow space inside a molecule or a group of molecules of the carrier is therefore required. Many soluble carriers readily form soluble complexes with drugs hence improve the drug solubility. Cyclodextrins, microbiologically modified from starch, are one of the current carriers with this property. 'Cyclo' means circle and dextrin means starch. The ring of these dextrins have different internal diameters depending on the number of glucose units present in the molecule.

f. Combination

In any system of solid dispersion, the combined mechanism can occur. This is from where the concept arised. A dispersion may be a combination of drug-carrier interactions. Usually phase interactions are often difficult to qualify because the structures of the dispersions being often dependent on the method of preparation and age of dispersion.

3. Mechanism of increased dissolution rates

The increased dissolution rates from solid dispersions are attributed to the reduction of particle size of the drug within the dispersion, molecular dispersion and wettability.

Particle size reduction is the primary factor in the improvement of dissolution yet not the most powerful factor considered particle size reduction of drug as a predominant factor in controlling the release from chloramphenicol-urea solid dispersion. However particle size reduction has offered to a certain level of increase dissolution rates, which is a minimum level, molecular state is mostly preferred and expected.

A molecular dispersion is where the carrier dissolves intimately with the drug. Molecular dispersions are obtained in glass and solid solutions and possibly in amorphous dispersions as described previously. In some cases, dependent mainly upon the carriers used, a complex can be formed. These are where solid dispersion technique has an advantage over traditionally physical size reduction.

Chiou and Reigelman (1971b), Ford (1986), Bloch and Speiser (1987) and Acarturkl, Kislal and Celebi (1992) reported the mechanisms that enhance solubility in a very similar manner. Following mechanisms are summarized from those reports.

a. Particle size reduction in eutectics

b. Deaggregation and deagglomeration

c. Changing crystallinity of drug into a metastable form

d. Changes in microenvironment of drug

e. Water soluble complex formation

f. Increase wettability

g. Combined effects

a. Particle size reduction

As described earlier, for the eutectic mixtures, the major contribution to enhance drug solubility is the size reduction of crystals. The size of particles liberated from different carriers and compositions are shown in **Table 1** (Ford, 1986).

Table 1 The size of particles liberated from solid dispersions.

Dispersion	Method of preparation	Type of particles liberated	Size (microns)
10% testosterone in PEG6000	Melt	Crystals	1-50
10% testosterone in PEG1000	Melt	Crystals	1-5
10% testosterone in PEG6000	Solvent	Crystals	1-10
10% testosterone in PVP11,500	Solvent	Amorphous	0.5-10.
3% primidone in citric acid	Melt	Crystals	5.2± 0.3
21% primidone in citric acid	Melt	Crystals	4.7± 0.3
5% indomethacin in PEG6000	Melt	Amorphous	0.5-3.0
10% tolbutamide in P 40S	Melt or Solvent	Crystals	3-10

b. Deaggregation and deagglomeration

In general, aggregation and agglomeration reduce the specific surface area thereby reducing accessibility of solvent to the drug. Aggregation describes a group of molecules bind together with strong intermolecular bonds or same type of molecules binding with strong bonds. Whereas agglomeration describes a lump of molecules loosely bind together with weak bond e.g. the bond between different charges. Theoretically, aggregated molecules are more difficult to breakdown than that of agglomeration. Solid dispersion has improved this concern. The drug will be surrounded by the inert carrier which acts as a barrier to prevent aggregation and agglomeration.

c. Changing crystallinity of drug into a unstable form or amorphous

An interest of drug crystalline transformation is mainly studied in two main areas which are polymorph and amorphous.

Polymorph is the term describes solid crystalline phase where at least to two different arrangements are possible (Haleblian and McCrone, 1969). Polymorphism is therefore characterized as any element or compound that has more than one distinct crystal species. Different polymorphs are generally different in structure and properties due to the crystals of two different molecular arrangement. These properties, for instance, are solubility, melting point, density, hardness, crystal shape, optical and electrical properties and vapor pressure.

For solid dispersion system, there are a number of publications illustrating this mechanism. Sulfathiazole-urea, sulfathiazole-povidone and indomethacin-PEG are

some of the illustrations. The change of polymorphism of sulfathiazole dispersing into urea has improved the dissolution rate of sulfathiazole alone (Chiou and Niazi, 1971). In 1976, Simonelli, Mehta and Higuchi identified the form of sulfathiazole that controlled its dissolution rate in the solid dispersion with urea. They considered several forms of sulfathiazole such as polymorph form (Sulfathiazole form I and form II), glassy state and coevaporate form. Solid dispersion of indomethacin and PEG4000 was investigated by Ford (1985). It was found that polymorphism of indomethacin has changed from form I to form II resulting in higher dissolution rate.

Amorphous is the highest energy form of the pure drug. As the third rule of thermodynamics explains that a system with lower energy is more stable than that of higher energy. Amorphous is not an exception. Amorphous will produce faster dissolution than the crystalline whether the crystals are dispersed in a carrier or not.

Simonelli, Mehta and Higuchi (1976) showed in their investigation of sulfathiazole- povidone that an amorphous state of sulfathiazole was the controlling phase for both solubility and dissolution rate.

The form of nifedipine by rolling mixing with PVP was studied by Nozawa, Mizumoto and Higashide (1986). It was found that nifedipine crystals in the roll mixture with PVP at the content PVP 25% seemed to be converted easily to the amorphous state. The X-ray diffraction pattern showed a distinctive peak for the roll mixture with 25 % PVP.

d. Changes in microenvironment of drug

An increase in dissolution can be made by changing the microenvironment of the drug. For instance, when environments surrounding the drug have been improved to be more soluble, the higher drug solubility can be anticipated. The factors that help improve microenvironments include surface tension reduction, viscosity, destruction of hydrogen bond etc.

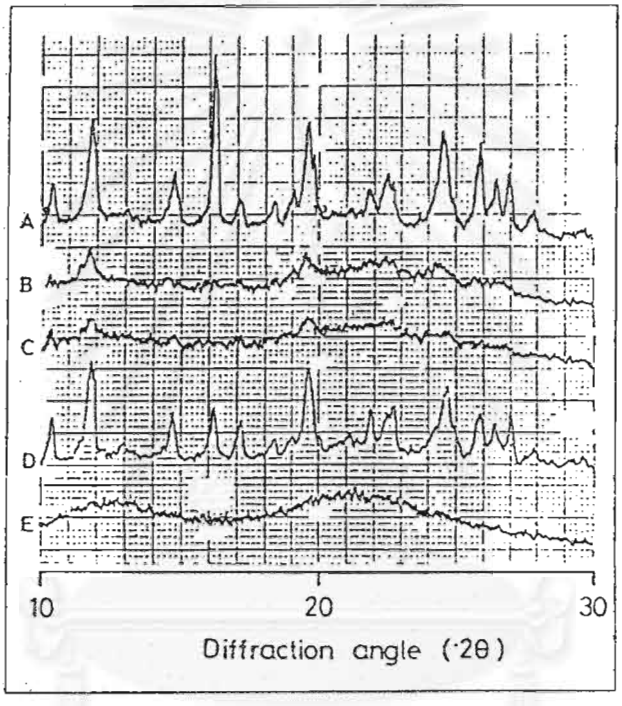


Figure 3 X-ray diffraction pattern of various mixed systems with PVP K-30.

(A) PVP content 50%, physical mixture , (B) 25%, roll mixture, (C) 50%,roll mixture , (D) 25%,coprecipitate (E) 50%, coprecipitate

The surface tensions were evaluated between nifedipine alone, nifedipine with water-soluble gelatin, β-cyclodextrin and egg albumin. It was found that reduction of surface tension is one of the contributing factors to increase dissolution rate (Acarturk, Kislal and Celebi 1992).

Urea is an another carrier which has been proved to destruct the hydrogen bond of water hence increasing enthalpy. As a result, the higher drug level dissolved in the solvent was obtained (Feldman and Gibaldi,1967). Corrigan and Timoney (1975) have also used the similar principle to explain the influence of PVP on the dissolution properties of hydroflumethiazide.

Table 2 Surface tension of samples measured by the ring method

Compound	Surface tension (dyne/cm)		
	Alone	Kneaded mixture	Physical mixture
Nifedipine	65	-	-
Water-soluble gelatin	49	49	60
β-cyclodextrin	69	59	67
Egg albumin	58	56	56

Viscosity has shown the effect on the drug in two ways; positively and negatively. Firstly, it reduces degree of crystallization consequently inducing supersaturated drug in the matrix. This can be simply explained as the matrix can hold higher amount of the drug hence it is called supersaturation. This gives the positive effect to the dissolution rate. Suzuki and Sunada (1998) studied on the influence of water soluble polymer on the dissolution of nifedipine solid dispersion with combined carriers. It was evidenced that the crystallization behavior of nifedipine was inhibited by a supersaturated solution containing hydroxypropyl methylcellulose and PVP. They reported that the use of a polymer with high compatibility and adhesion with nifedipine provided a higher supersaturation level of the drug.

Secondly, viscosity however can reduce the dissolution rate, especially when surfactant is used. Morita and Hirota (1982) studied the effect of polysorbate80, a

nonionic surfactant, on the dissolution rate of benzoic acid. It was reported that the dissolution rate of benzoic acid was initially increased when the percent of polysorbate80 increased. However when the percent of polysorbate80 increased further, the dissolution rate of benzoic acid was decreased as a result of viscosity increment.

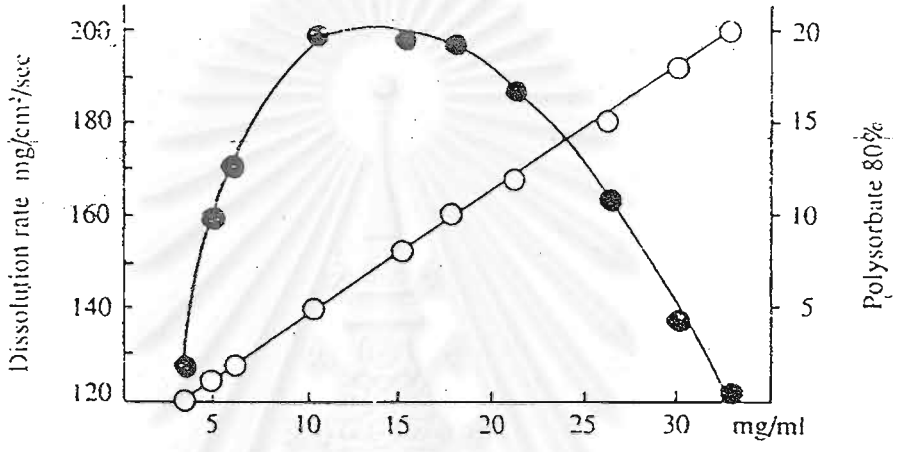


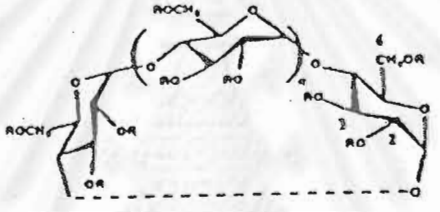
Figure 4 Relationship between dissolution rate of benzoic acid at 25 °C and percent of polysorbate80. -•- dissolution rate, -o- concentration.

e. Water soluble complex formation

As mentioned earlier that water soluble complex can be formed between the drug and certain carriers. β-Cyclodextrin has been studied extensively as it shows a great potential to improve poorly water soluble drugs. Corrigan and Stanley (1982) comprehensively studied the mechanism of drug dissolution rate enhancement from drug-β-cyclodextrin system. β-Cyclodextrin itself is hydrophilic and has a hollow structure where can be filled by certain hydrophobic drugs. It therefore improves hydrophilicity of the drug.

Sometimes the method based on this knowledge is called complex inclusion. There are a number of reports on the applications of these properties (Duchen, Vaution, and Glomot, 1986; Nakai et al., 1990a; Nakai et al., 1990b; Nakai et al., 1991; Acarturk, Kislal and Celedi, 1992; Watanabe et al., 1996; Becirevi-Lacan et al., 1996; Hirayama, Wang and Uekema, 1994; Kedzierewicz, Hoffman, and Maincent, 1990 and Ahmed et al., 1993).

Table 3 General structure of commonly used cyclodextrins and their abbreviated names.



Cyclodextrin	Abbreviation	*R*	*n*
α-cyclodextrin	α-CD	H	4
β-cyclodextrin	β-CD	H	5
γ-cyclodextrin	γ-CD	H	6
Carboxymethyl-β-cyclodextrin	CM-β-CD	CH_2CO_2H or H	5
Carboxymethyl-ethyl-β-cyclodextrin	CME-β-CD	CH_2CO_2H, CH_2CH_3 or H	5
Diethyl-β-cyclodextrin	DE-β-CD	CH_2CH_3 or H	5
Dimethyl-β-cyclodextrin	DM-β-CD	CH_3 or H	5
Methyl-β-cyclodextrin	M-β-CD	CH_3 or H	5
Random methyl-β-cyclodextrin	RM-β-CD	CH_3 or H	5
Glucosyl-β-cyclodextrin	G_1-β-CD	glucosyl or H	5
Maltosyl-β-cyclodextrin	G_2-β-CD	maltosyl or H	5
Hydroxyethyl-β-cyclodextrin	HE-β-CD	CH_2CH_2OH or H	5
Hydroxypropyl β-cyclodextrin	HP-β-CD	$CH_2CHOHCH_3$ or H	5
Sulfobutylether-β-cyclodextrin	SBE-β-CD	$(CH_2)_4SO_3Na$ or H	5

[a] Derivatives may have differing degrees of substitution on the 2, 3 and 6 positions.

f. Increased wettability

Solid dispersion has shown the advantage on wettability over pure drugs. Theoretically, water will diffuse toward the drug so as to wet the drug surface and then diffuses to the center. A poorly water soluble drug prepared by solid dispersion shows an increase in wettability while a carrier which is highly water soluble acts as

a bridge. The drug is surrounded by the carrier which can be easily dissolved in water. This causes the solvent to contact with drug faster.

Mohamnad and Felle (1983) studied the wetting and dissolution rate of phenobarbitone powder and reported that wettability was the first process to occur followed by drug dispersion into liquid phase and solubility. A poor dispersion drug can be improved by incorporation of a surface active agent.

g. Combined effects

Combined effects, a self descriptive, are characterized as the combination of the mechanisms mentioned above. Combined effects are usually found in many cases.

Carriers

1. Selection of suitable carriers

Selection of best carriers is one of the most critical factors to successful increased dissolution rate. A carrier chosen should meet the following criteria (Ford, 1986).

a. The carrier should not be harmful or remaining any toxic residues in the system.

b. It should be water soluble with intrinsic rapid dissolution property.

c. The carrier must fulfil the requirement of specified methods.

Fusion method : The carrier should be chemically, physically and thermally stable with a low melting point. Excessive heat during dispersion process can be easily encounter in fusion method. Low melting point is usually preferred. Chemical interaction between drug and carrier should be also avoided. Ideally the carrier should solidify rapidly and completely into a stable discernable solid. This will help

maintain the drug as a fine crystalline dispersion. Or else the carrier may solidify through a viscous state which help maintain the drug in a near molecular dispersion. Miscibility between drug and carrier is important otherwise subsequent irregular crystallization may occur on cooling which may give variable dissolution.

Solvent method : The carrier should dissolve in a variety of organic solvents. It should be able to pass a vitreous state. This is where the carrier should inhibit or retard drug crystallization. As a result, drug concentration is maintained at or near the molecular dispersion state. Cocrystallization between the drug and the carrier is compulsory otherwise a solid dispersion will not be achieved.

d. As a rule of thumb, a carrier should increase the aqueous solubility of the drug. However there are some studies (Sekiguchi and Obi, 1961 and Chiou and Niazi, 1971) showed that it was not compulsory e.g. sulfathiazole-urea which urea was shown to reduce the aqueous solubility of sulfathiazole.

e. The carrier, in the solid state with the drug, should not form strongly bonded complexes with a strong association constant which may reduce dissolution rates.

f. The carrier should not show any pharmacological effect which may interfere the resultant solid dispersion.

2. Application of selected carriers in solid dispersion system

2.1 Polyethylene glycols (PEGs)

Polyethylene glycols (PEGs) is one of the predominant polymers in this field and has been extensively studied. The molecular weight fraction of PEGs employed for solid dispersion vary from 1000 (soft unctuous solids) to 20000 (hard brittle crystals) (Craig, 1990).

a. Properties of PEGs

The polymers in certain molecular weight range are semi-crystalline, containing both ordered and amorphous components. In the crystalline state, the chains have the structure of double helices. Each repeating unit contains approximately 15 monomers. The helices are arranged as plate-like structures (lamellae) from which the hydroxyl end groups are rejected onto the surface. Therefore PEG is highly water soluble. The chain within the lamellae may be extended or folded, the latter being metastable with respect to the former. The melting characteristics of PEGs have been studied extensively due to the stability of the metastable folded chain forms compared to those of other polymers. Studies using DSC show the folded chain has additional endothermic peaks at temperature below that corresponding to the stable extended chain.

The molecular size of the polymers favor the formation of interstitial solid solution with drugs and their viscous properties at temperature just above their freezing points retard crystallization and favor supercooling of the drug. A shorter cooling time may lead to the higher production of small crystals compared to a longer cooling time. The high viscosity of solid PEG may also lead to a sluggish precipitation of metastable crystals.

b. Solid dispersion of drug-PEG

The early work done by Chiou and Riegelman (1969) showed that the dissolution rate of griseofulvin were increased by dispersion into PEG4000, PEG6000 and PEG20000 using melting and solvent methods. The urinary excretion in dogs for 6-

demethylgriseofulvin revealed 88% absorption from 10% melted griseofulvin-PEG6000 compared with 100% from pure PEG4000 solution, 45% from commercial capsules and 33% from commercial tablets. X-ray diffraction and aqueous solubility studies suggested that the marked enhancement of dissolution and absorption rate of griseofulvin-PEG solid dispersion was primarily due to the reduction of the size of griseofulvin crystals rather than to the formation of solid solution, complexation or metastable polymorphic forms.

On the other hand, Ravis and Chen (1981) suspected that for the system of dicumarol-PEG4000 prepared by melting method, partial polymorphic conversion and solid solution were the attractive explanation to substantial dissolution rate increment.

Allen and Kwan (1969) attempted to determine the ratio of crystalline drug dispersed at the molecular level (a) in a drug-polymer system which behaves as a supercooled liquid solution and (b) in a drug-carrier system which apparently forms true solid solutions. Indomethacin-PEG6000 acted as a supercooled liquid solution whereas sulfathiazole-urea represented a solid solution. In two diverse systems, it was shown that under appropriately chosen conditions, the dissolution rate of the drug was linearly related to its degree of crystallinity at molecular level.

Most other studies emphasized on illustration of increased dissolution rate of sparingly water soluble drugs. Ford (1986) reviewed a number of applications of PEG in solid dispersion, for instance;

-Steriods i.e. prednisolone acetate, 17-methylestosterone, hydrocortisone acetate, betamethasone alcohol and testosterone.

-Sulphonamides.

-Hypoglycemics i.e. chlorpropamide, tolbutamide, acetohexamide.

-Diuretics i.e. hydroflumethiazide, hydrochlorothiazide, bendrofluazide and furosemide.

-Bepridil.

-Phenylbutazone.

-Diazepam.

Current studies include p-aminobenzoates-PEG6000 whose mechanisms of dissolution was reported. Sjokvist-Saers and Craig (1992) found that the aqueous solubility decreased logarithmically with molecular weight of the carrier (PEG6000), whereas a linear increase was found between solubility and initial rate.

Ahmed et al. (1993) studied comparative dissolution between bropirinine-β-cyclodextrin inclusion complex and its solid dispersion with PEG6000 by solvent method. It revealed that the solid complex of bropirinine with β-cyclodextrin exhibited a markedly faster dissolution rate compared to the solid dispersion with PEG6000 for bropirinine.

PEG6000 and β-cyclodextrin have been also applied with hydrochlorothiazide (Simonelli et al.,1994). It was found that both carriers formed amorphous state and increased in dissolution rate over the pure drug. Similar study was done by Veiga and Espanol (1995). Instead of hydrochlorothiazide, oxodipine was used. Guyot et al.

(1995) have also applied those two polymers aimed at improving dissolution of norfloxacin. The achievement was reported.

c. Influence of PEG molecular weight

As there are many grades of PEG available, several studies have attempted to draw a conclusion on the effect of molecular weight on the dissolution rate. In general, the dissolution rates of the pure polymers decreased as the molecular weight increased. When several molecular weights of PEG were applied in different drug-carrier systems, the exact conclusion cannot be drawn. This means that in some cases the lower molecular weight of specific polymers, the worse dissolution rate is obtained and also some cases it may show an opposite result.

The systems where the dissolution rates decrease with decreasing molecular weight of PEG include papaverine, sulphamethoxydiazine and hydrochlorothiazide such phenomenon may be explained as ;

-The higher molecular weight PEGs may form higher viscous solutions thereby further reducing drug crystallization.

-The higher molecular weight PEGs may increasingly favor the incorporation of drug as solid solutions.

-The higher molecular weight PEGs may merely flake more readily during dissolution.

The other system is where the dissolution rate of drug dispersed in PEG decreased as the molecular weight increased. This system includes indomethacin,

hydroflumethiazide, sulphadimadine and tolbutamide. The explanations to such system are probably made on the basis of the dissolution rates of the PEG weight fraction themselves and the incorporation of a drug into the low molecular weight PEG may produce an eutectic temperature below 37 °C hence allowing melting of the dispersion to occur prior to actual dissolution and further enhance dissolution rate (Ford, 1986).

2.2 β-cyclodextrins

a) Properties of β-cyclodextrin.

Cyclodextrins are cyclic oligosaccharide composed of 6-8 glucose units joined through α-1,4 linkage. α-Cyclodextrin contains 6 glucose units while β and γ-cyclodextrins contain 7 and 8 glucose units respectively. **Table 3** is the summary of important characteristics of α, β and γ-cyclodextrins.

Table 4 Some important characteristics of cyclodextrins.

	α	β	γ
Molecular weight	972	1135	1297
$[\alpha]_D^{25}$	+150.5 ± 0.5	+162.0 ± 0.5	+177.4 ± 0.5
$[\alpha]_{334}^{25}$	+1160	+1165	
$[\alpha]_{254}^{25}$	+ 741	+ 798	
Diameter of cavity	4.7–5 Å	6 Å	10 Å
Volume of cavity	176 Å³	346 Å³	510 Å³
Number of water molecules taken up by cavity	6	11	17
Diffusion constant of 40 °C (Craig, Pulley, 1961)	3.443	3.224	3.000
Crystal form (from 60% aq. isopropanol)	Hexagonal plates or blade shaped needles	Monoclinic parallelo-grams	Quadratic plates or prisms
Solubility in water g/100 ml, 25 °C	14.5	1.85	23.2
Molecules per unit cell	4	2	6
Water of crystallization, %	10.2	13.2–14.5	8.13–17.7

In term of cyclodextrin structure, the C-1 chair conformation of the glucose monomers imparts to the molecule, like a cone-shaped structure. The narrow end of the torus contains primary hydroxyl groups on C-6 whereas the another end, the wider, contains the secondary hydroxyl groups on the C-2 and C-3 of the glucose units being located on the torus.

As the interior of the molecule are relatively lipophilic and the exterior relatively hydrophilic, it shows a tendency to form inclusion complex. This is one of the most interesting of cyclodextrins. A molecule which may form inclusion complex only have to satisfy a single condition which is adaptable entirely, or at least partly to the cavity of the cyclodextrins. Most adaptable drugs form1:1 complexes with cyclodextrin.

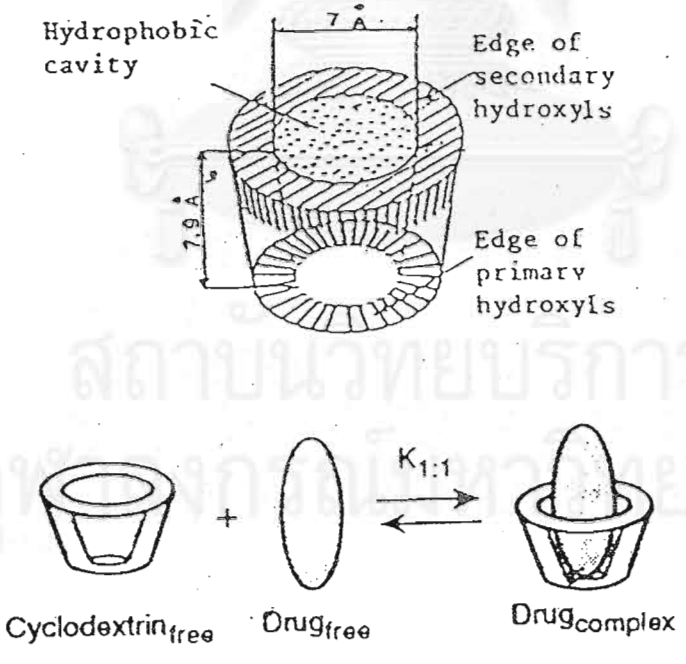


Figure5 Functional structural scheme of cyclodextrin and its association to form a drug-cyclodextrin complex (Stella and Rajewski, 1997)

Inclusion compounds are usually prepared in a liquid medium. In the case of water-soluble materials, a guest drug is added to an aqueous solution of cyclodextrin. The mixture is then heated with continuous agitation for several hours or days depending on type of systems. The inclusion complex precipitates spontaneously or by cooling. The mixture can also be freeze-dried or spray-dried.

For a sparingly water soluble drug, it will be dissolved in the appropriate organic solvent. Drug solution is then added to a hot aqueous cyclodextrin solution with agitation. Crystallization takes place within the following hours or days.

b. Solid dispersion of drug-β-cyclodextrin

β-cyclodextrin has been reported to form inclusion complexes with variety of drugs. In early days, main focus of inclusion complexes was on the complex formation in solution. Until recently the field of study has expanded to those formation in solid state and this is where solid dispersion is involved. Kurozumi, Nambu and Nakai (1975) cited by Corrigan and Stanley (1982) reported the possibility of complex formation by a freeze drying process.

Corrigan and Stanley (1982) have comprehensively explored the mechanism of increased drug dissolution rate from β-cyclodextrin-drug system and freeze dried system. The two classical theories, namely a soluble complex model and a carrier controlled model were reviewed. Physical mixed system and freeze dried system were in comparison.

Their conclusion is that if crystalline drug is dispersed in the carrier, as is the case of physical mixed system, particulate drug will be passively carried into the dissolution medium as the carrier dissolves. This system gives an intermediate dissolution rate.

For the freeze dried system, in this case was bendrofluazide-β-cyclodextrin, the inclusion complex was found. The dissolution rate would follow the soluble complex model. Furthermore, if the freeze drying produce smaller drug crystallites, the drug dissolution rate should be higher than those of the corresponding mechanical mixture.

Mayano et al.(1997) investigated a similar comparison in gliclazide-β-cyclo dextrin system with various preparation methods. For spray dried, the dissolution enhancement was mainly contributed from the formation of an inclusion complex in the solid state and from the reduction of the crystallinity of the products. Whereas the main contributing factor for physical and kneaded mixtures was only due to the wetting effect of the β-cyclodextrin.

Nakai et al. (1990a) studied the interaction of clobazam with cyclodextrin in both solution and solid state. For ground mixture of clobazam with natural cyclodextrin (unmodified), hydrogen bond between the two carbonyl groups of clobazam and hydroxyl groups of natural β-cyclodextrin was detected and yet no inclusion complex was formed. On the other hand, clobazam with heptakis-(2,6-di-o-methyl)-β-cyclodextrin was further employed in inclusion compound formation of benzoic acid (Nakai et al.,1990b and Nakai et al.,1991) and p-nitrophenol (Watanabe et al.,1996).

Other interesting modified β-cyclodextrins is the group of hydroxypropyl-β-cyclodextrins. Becirevic-Lancan et al. (1996) studied the complex formation between nifedipine and β-cyclodextrin and β-cyclodextrin derivatives; hydroxypropyl-β-cyclodextrin and heptakis (2,6-di-o-methyl)- β-cyclodextrin in freeze dried, spray dried and physical mixed systems. Heptakis (2,6-di-o-methyl)-β-cyclodextrin was found to be the best solubilizing agent and freeze dried solid dispersion showed the highest dissolution rate due to high inclusion complex formation. However, similarly to the findings of Mayano et al., 1997, physical mixture was not evident of inclusion complex formation. Other applications of hydroxypropyl-β-cyclodextrin group to other drugs were also studied. Methoxybutropate (Palmieri et al., 1997) and Lonidamine (Palmieri, Wehrle and Martelli., 1998) are some of the examples.

2.3 Poloxamers

a. Properties of poloxamers

Poloxamers can be classified as nonionic surfactant and they consist of a-b-a copolymers of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene). The properties of polyethylene and polyoxypropylene can be altered. This alteration results in change of the total molecular weight and the relative hydrophilicity of the surfactant. The nomenclature given to poloxamers has its own interpretation. The first two numbers multiplied by 100 approximate to the molecular weight of the hydrophobe, whilst the third number multiplied by 10 gives an estimate of the content of polyoxyethylene in percentage.

b. Solid dispersion of drug-poloxamers

In the past few years, a greater attention has been drawn to poloxamer derivatives as another carriers for solid dispersion applications. This is due to a well documented articles have been printed on dissolution improvement of slightly water drugs when poloxamer derivatives were employed.

Reddy, Khalil and Gouda (1976) reported a marked increase in the dissolution rate of digitoxin and digoxin by solid dispersing the drugs into poloxamer188 and deoxycholic acid. The mechanism was thought to be crystalline modifications.

Luhtala (1992) investigated the effect of poloxamer184, a nonionic surfactant, on crystal growth and aqueous solubility of carbamazepine. Poloxamer 184 was found to retard water-mediated phase transformation and the consequent crystal growth. It also changed the crystal habit, more importantly, the solubility properties of carbamazine has been changed.

The more comprehensive study was done on the mechanism of action of poloxamer in changing crystal properties (Mackellar et al.,1994). The experiment was done on ethyl p-hydroxybenzoate as a model drug. Poloxamer resulted in decrease particle size and a change to a prismatic habit. The decrease in particle size of drug crystals was shown to be correlated with the molecular weight of the polyoxyethylene chain in the poloxamer, if the molecular weight of the polypropylene is kept constant. These effect only occurred after a threshold concentration had been stimulated. It was shown that poloxamers do affect solution viscosity and relative supersaturation operating during crystallization. These factors however do not cause

any affect on crystal appearance. Instead, it was proposed that poloxamers adsorbed onto the surface of hydrophilic faces of the crystal to exert this effect on the crystal properties causing a subsequent inhibition of crystal growth.

Nifedipine and Its Properties.

1. Pharmaceutical properties

Chemical structure.

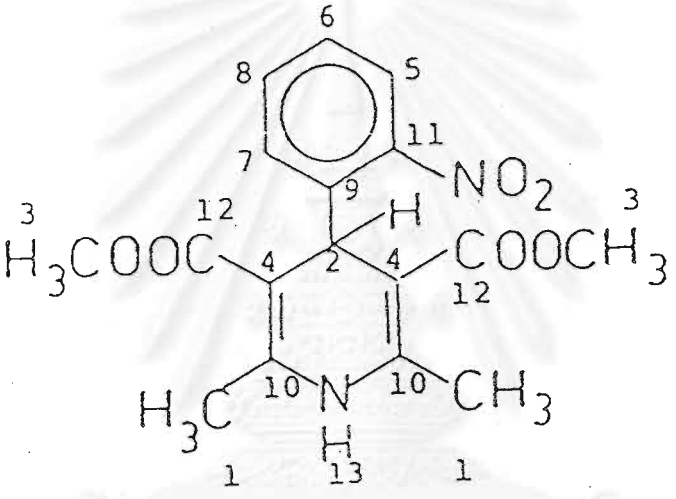


Figure 6 Nifedipine structure.

Empirical formula : $C_{17}H_{18}N_2O_6$

Molecular weight : 346.34

Chemical name : Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine dicarboxylate.

: 3,5-Pyridinedicarboxylic acid1,4-dihydro-2,6dimethyl-4-(2-nitrophenyl)- dimethyl ether (The United States Pharmacopoeial Inc, 1990)

Description : A yellow crystalline powder. Melting point 171 to 175 °C

Solubility	Easily soluble in acetone, chloroform, less soluble in ethanol, practically insoluble in water. Very light senstive in solution (Windholz et al., 1983)

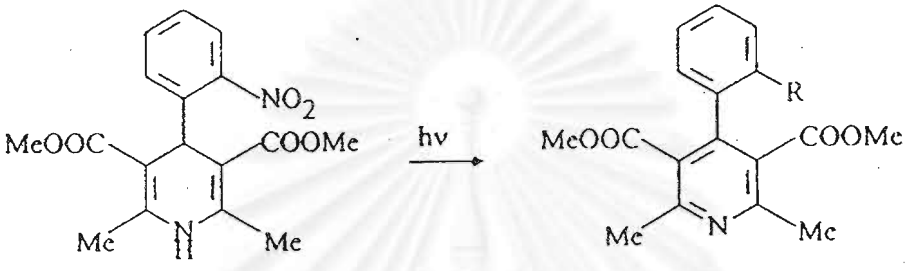
Nifedipine, an oral calcium-blocking agent is widely used clinically as a coronary vasodilator and for the treatment of hypertension, angina pectoris and other cardiovascular disorders (Sorkin, Clissold and Brogden,1985). It shows very slightly water solubility (11 μg/ml at 37°C in distilled water) and exhibits poor dissolution characteristics (Kohri et al.,1987).

Nifedipine physiological action is inhibition of transmembrane influx of extracellular calcium ions across the membranes of myocardial cells and vascular smooth muscle cells, without changing serum calcium concentration (McEvoy, ed., 1989). The usual dose is 10 mg three times daily. It may also be administered by injection via coronary angiography and balloon angioplasty (Reynolds, ed.,1989)

Oral dose of nifedipine is rapidly absorbed from the GI tract approximately 90%. Only 65-75% of the oral dose reaches systemic circulation as unchanged drug since nifedipine is metabolized on first pass through the liver. Peak serum concentration are reached within 0.5-2 hours after oral administration. The therapeutic range in plasma is 25-100 μg/l.

2. Photostability

As nifedipine or 4-(Nitrophenyl)-1,4-dihydropyridines has an aromatic nitro group which is often photoactive, degraded rapidly in sunlight. The nitro group is reduced to nitroso while the ring is oxidized. The product after exposure to sunlight is shown in Figure 7a but under UV irridiation the nitroso group is reoxidized to give b. ($R = NO_2$)



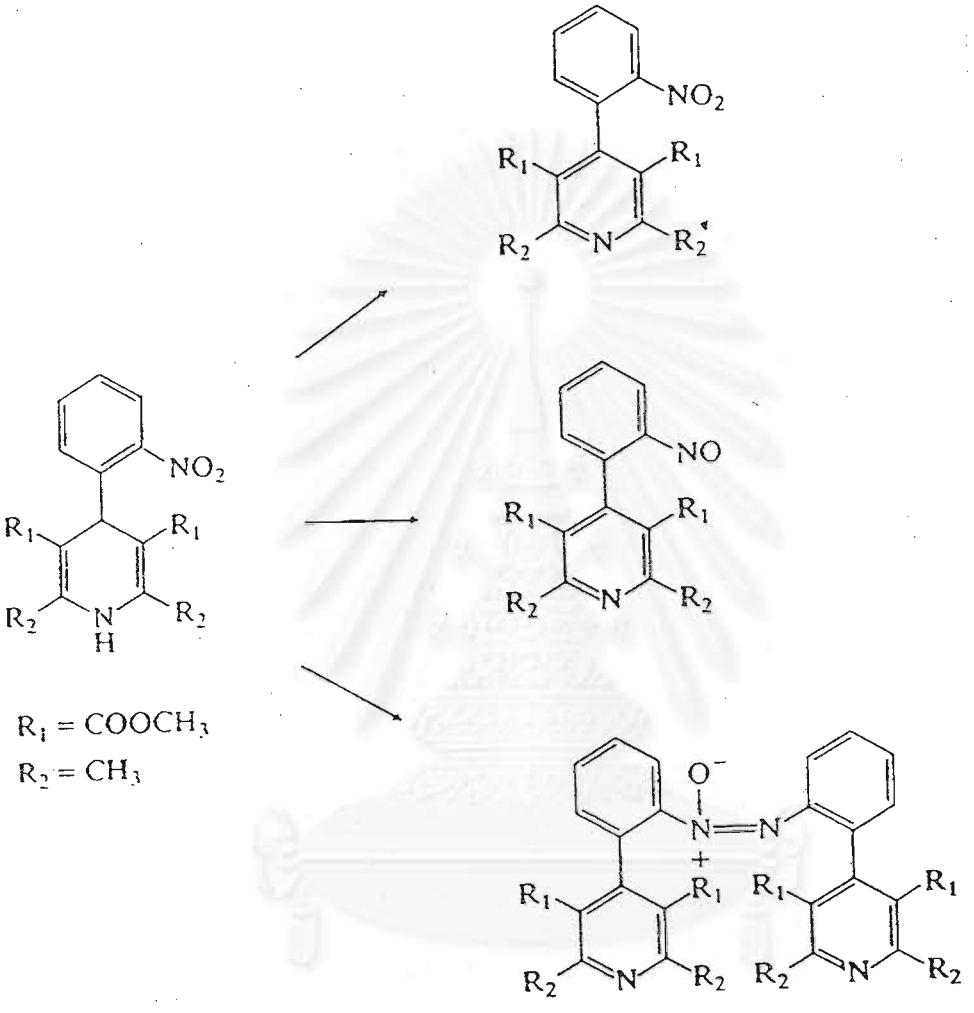
Nifedipine a. R=NO b. $R=NO_2$

Figure 7 Exposured to sunlight and UV products of nifedipine.

Nifedipine is one of the highly unstable drugs. In daylight, nifedipine solution shows high photosensitivity depending on light intensity. Nitrosophenylpyridine and nitrophenylpyridine derivatives are photodegradation products from exposure of nifedipine solution to daylight. Only one minute during the month of May, $t_{90\%}$ is attained compared with $t_{90\%}$ in November (Thoma and Klimek, 1985a and b cited by Tonnesen, 1996). Azoxy derivative is one of the two other decomposition products which has been detected in small amount after irradiation in the solid state **(Figure 8)**.

There was a report on which photodegradation of nifedipine in the crystalline state and in solution were compared. Within 40 minutes, 20% of the crystalline nifedipine decomposed. During the next 80 minutes no further degradation, but

nifedipine solution decomposed completely during this period(**Figure 9**), (Thoma and Klimek, 1985 cited by Tonnesen 1996).



$R_1 = COOCH_3$

$R_2 = CH_3$

Figure 8 Photochemical decomposition products of nifedipine:

(1) nitrophenylpyridine derivative; (2) nitrosophenylpyridine derivative;

(3) azoxy derivative.

In terms of the influence of the wavelength to absorption spectrum of nifedipine, **Figure 10** shows that the solution is stable down to a wavelength of 475 nm. Photolysis starts exactly at the point where nifedipine absorption begins at 450 nm.

Photolysis increase considerably up to about 400 nm. Nifedipine is thus completely degraded by light in the rather long-wavelength region within 10 minutes.

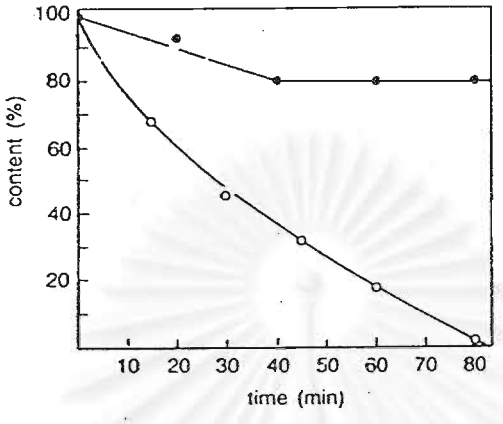


Figure 9 Photoinstability of nifedipine crystals (≤ 5 μm) compared with nifedipine solution :- •- nifedipine crystals; -o- nifedipine solution, C_o = 3mg/50ml

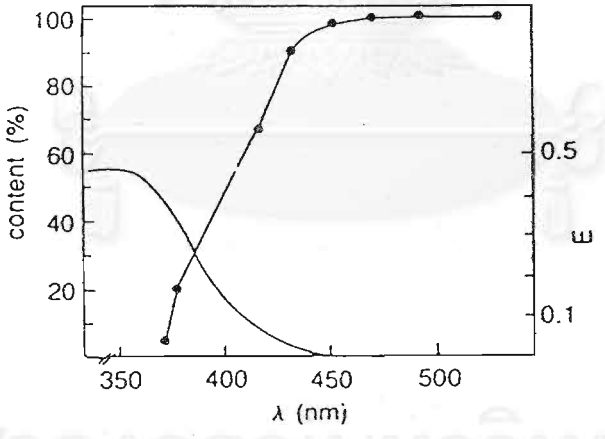


Figure 10 Influnce of the wavelength of the irradation light on the photostability of nifedipine :- •- dependence of the residual concentration on the wavelength of xenon radiation (left ordinate) ; -o- long-wavelength section of the nifedipine adsorption spectrum (right ordinate)

3. Approaches to determine nifedipine concentration

The determination of nifedipine and its oxidized degradation products has been subjected to many investigations. A high performance liquid chromatography procedure for identification and separation of nifedipine and its metabolites in oral nifedipine formulation has been employed for the analysis of the photo-oxidation products of the the drug (Grundy, Kherani and Foster, 1994).

Also, there is a report of using selective gas chromatographic method with electron capture detection analogous to determine nifedipine concentration in plasma (Abrahamsson et al., 1998). The determination of nifedipine concentration was conducted based on one lamda spectrophotometric method (Benita, Barkai and Pathak, 1990 and Yamamura and Rogers, 1996).

However a direct and simple spectrophotometric method for simultaneous determination of both nifedipine and its oxidized degradation products were proposed despite their overlapping UV absorption spectra (Al-Turk et al., 1989). The analysis of both nifedipine and its oxidized degradation products in this investigation is based on the measurement of absorbance values at two wavelengths. The subsequent calculation of the concentrations of the two components in the mixture is required by solving for two simultaneous equations.

4. Applications of Solid Dispersion Used in Nifedipine System

Several attempts were made to improve dissolution rate of nifedipine by applying solid dispersion techniques. Sugimoto et al. (1980) are one of those early candidate worked in this area. Nifedipine was coprecipitated in polyvinylpyrolidone. It was

claimed that amorphous form was found at the drug to the carrier of 1 to 3. X-ray diffraction patterns of those containing 1:3 and 1:9 weight ratio of nifedipine to PVP was found to be different and were suspected an occurance of amorphous, This was confirmed by DTA result when the endothermic peak accompanied with the melting point of nifedipine (171°C) was disappeared in the coprecipitate containing 1:3 ratio of nifedipine to PVP. However DTA result was not actually shown in the publication, only X-ray diffraction results were found. The mechanism proposed was not clearly visualized.

The effect of particle size of solid dispersion was also reported. The 12-16 mesh size, 48-60 mesh size and less than 145 mesh size.were found to have little effect on the dissolution rate of the drug. The study in beagle dogs was shown that the C_{max} and AUC were 5-fold and 3-fold increased respectively for the drug to the carrier ratio of 1:3.

Nifedipine–PVP system was further studied. Nozawa, Mizumoto and Higushide (1986) implemented roll mixing principle to increase dissolution rate of nifedipine. Nifedipine exhibited favorable dissolution rate than those in the system of coprecipitate and physical mixture. Types of PVP used were selected by preparing nifedipine roll mixed with various PVPs: PVP-K15, PVP-K30 and PVP-K90 respectively. PVP K-30 was the most favorable additive for nifedipine system among the three when taking dissolution rate into the consideration. The appropriate roll mixing time was chosen at 60 min. Many diffraction peaks derived from nifedipine crystal almost disappeared overlapped by that of PVP during the roll mixing even for

15 min. The authors suspected that there was an indication of entire crystal changed to an amorphous state. However they have pointed out that disintegration of drug crystal may be attributed to defects of crystal lattice resulted from compression force between rollers. Nevertheless, it was clear that drug crystal in roll mixed system with 25% of PVP-K30 was far more disappeared than that of the coprecipitate system.

Yamamura and Rogers (1996) comprehensively studied the effect of lattice distortion if nifedipine crystals and an amorphous state of phosphatidylcholine on dissolution behavior of nifedipine in its binary systems with phosphatidylcholine. The physicochemical properties of nifedipine, dipalmitoyl phosphatidylcholine and dimyristoyl phosphatidylcholine in physical mixtures, coprecipitate and ground mixture were investigated in relation with dissolution behavior of nifedipine in such system.

Dipalmitoyl phosphatidylcholine was found existed in an amorphous form in the ground mixture whereas in the physical mixture and coprecipitates dipalmitoyl phosphatidylcholine presented in a crystalline state. This was confirmed by disappearance of both correspondent peak in X-ray diffraction and the correspondent endothermic peak in DSC spectra. From the studies of lattice parameters; C-axis and full-width at half-maximum, of X-ray diffraction suggested that the lattice distortion of nifedipine crystals in the ground mixture was larger than that in the coprecipitate.

It was concluded that the improvement of dissolution rate of nifedipine from nifedipine-phosphatidylcholine ground mixtures is strongly dependent upon the

physicochemical state of both nifedipine and phosphatidylcholine. A distortion of nifedipine crystal lattice and an amorphous state of phosphatidylcholine are some of the contributions to those improvement. However, it should be noted here that phosphatidylcholine itself is not a carrier. It was described as forming colloidal aggregates (liposomes) in the dissolution medium in which drug partitioned and dissolved during dissolution.

Law et al. (1992) have previously incorporated phosphatidylcholine in nifedipine-PEG solid dispersion. It was reported that incorporation of phosphatidylcholine have resulted in a 2.6 and 2.2-fold increase in nifedipine initial dissolution rate and dissolution after 60 minutes respectively. There were two main mechanisms explained. One of which was an amorphous formation of nifedipine. Another factor attributed to the phosphatidylcholine in the solid dispersion system was the formation of lipid vesicles entrapping some dissociated nifedipine molecules. Also the lipid-soluble nifedipine molecules could be accommodated in the bilayer structure of the phosphatidylcholine vesicles, the dissolution rate therefore was enhanced. The latter mechanism was investigated under microscope.

PEGs have also been employed as the other carriers to nifedipine solid dispersion. Save and Venkitachalam (1992) prepared nifedipine-PEG solid dispersion by melt method aimed to improve nifedipine solubility in aqueous. Two types of PEGs; PEG4000 and PEG6000 were used to compare with physical mixture. Both physical mixed and solid dispersion systems showed and increase in dissolution rate of nifedipine. For physical mixture, the explanation was based on the solubility effect

by the carrier operating in the microenvironment of the drug. For a system of solid dispersion PEG, whose gave higher solid dispersion, the mechanisms were primarily contributed to the transformation from crystalline state to the other less stable forms.

The best performing ratio between drug to carrier was found at 1:10. It was suspected that at this ratio the drug might exist in a metastable form at the saturation point, the point at which the system exhibits maximum enhancement in solubility. Above this saturation point, as the percentage of carrier increased, the longer time required for diffusion of the drug from the matrix probably resulted in a slightly decreased dissolution rate.

Suzuki and Sunada (1997) have compared nicotinamide, ethylurea and PEG6000 as carrier for nifedipine solid dispersion prepared by melt and physical mixed materials. From the solubility study of nifedipine in presence of those carriers; nicotinamide showed about 2 times stronger solubilizing effect than those of PEG6000 and ethylurea. Since ethylurea and PEG have amino or hydroxyl groups and hydrophobic groups, it was suspected that both groups interfere with the water structure and the formation of hydrophobic interaction which finally affected the solubilization of the drug.

The dissolution profiles of the solid dispersions clearly showed that the dissolution rate of nifedipine from solid dispersions with ethylurea or PEG was much higher than that from the physical mixtures. However the difference between the physical mixtures and the solid dispersion with nicotinamide was not substantial.

In the X-ray diffraction pattern, the identity peak of 7.9, 10.3 and 11.7 at 2 θ for crystalline nifedipine in both physical mixed and solid dispersed with nicotinamide were found. The intensity of these peaks were similar when compared with the same ratio but different preparation methods, suggesting that the entire amount of the drug exist as a pure crystalline phase in the solid dispersion. The phenomenon was explained by solubilizing effect. It was predicted that the higher the solubilizing effect of a carrier, the smaller the difference in the dissolution rates between physical mixture and solid dispersion.

Solubility enhancement with combined carriers was also studied by incorporating hydroxypropylmethylcellulose into the nifedipine-ethylurea, PEG6000 and nicotinamide. Nifedipine solid dispersion with a single carrier improved the drug dissolution rate, but there was not a remarkable increase in the drug solubility. This may be due to the presence of drug crystallinity. Hydroxypropylmethylcellulose was found effective in forming an amorphous nifedipine in solid dispersion with nicotinamide and ethylurea. The combined carriers were again employed in their later work (Suzuki and Sunada, 1998). It was concluded that the use of a polymer with high compatibility and adhesion with nifedipine provides a high supersaturation level of the drug during dissolution. For the selection of combined carrier, solubility and miscibility if any combined carrier to the primary carrier and the drug are the useful factors to consider.

It should be addressed that the similarity between the findings concerning nifedipine-PEG6000 system by Save and Venkitachalam (1992) and Suzuki and

Sunada (1997). The transformation of crystalline nifedipine to amorphous form was nit found in the work done by Suzuki and Sunada (1997) at the drug-carrier ratio of 1:5. Similarly, Save and Venkitachalam (1992) suggested that the saturation point for metastable from nifedipine was at the drug-carrier ratio of 1:10.

Very few publications reported the solid dispersion of nifedipine with poloxamers. One of which was the study done by Khidr (1994). The result was just briefly mentioned that poloxamer407 had showed a positive outcome in improving dissolution rate of nifedipine.

β-Cyclodextrin and its family have also shown an improvement of nifedipine dissolution rate. Acarturk, Kislal and Celebi (1992) studied that interaction of nifedipine with water soluble gelatin, egg albumin and β-cyclodextrin in solid state prepared by kneading method. β-cyclodextrin and water soluble gelatin were found significantly increase in the dissolution rate of nifedipine as compared to pure drug. The enhanced dissolution rate of nifedipine from nifedipine-β-cyclodextrin system may be caused by the solubility effect. It was reported that the inclusion complex of nifedipine and β-cyclodextrin had not been completely formed in the solid state.

Hirayama, Wang and Uekama (1994) have studied the effect of 2-hydroxypropyl-β-cyclodextrin on crystallization and polymorphic transition of nifedipine in solid state. The key finding was the glassy nifedipine in 2-hydroxypropyl-β-cyclodextrin matrix was converted to the metastable form of nifedipine, form B, in the non isothermal heating. When it was stored below the crystallization and transition

temperatures, metastable form B was converted to the stable form A. As a result, 2-hydroxypropyl-β-cyclodextrin is useful for selection of preparation method of form B as a fast dissolving form of nifedipine.

Method for Determination Characteristic of Solid Dispersion.

1. X-ray powder diffraction.

The diffraction method is the most powerful tool in solid state studies especially for studying the physical nature of solid dispersion. A diffractogram serves as the drug's fingerprint which markedly different from those of the compound or complex formation. In this method, the intensity of the X-ray diffraction from a sample is measured as a function of diffraction angles. Various studies of solid dispersion has been used this method (Portero, Remunan-Lopez and Vila-Jato, 1998; Guyot et al.,1995)

2. Differential scanning calorimetry (DSC).

DSC has proved a powerful tool in evaluating the drug-carrier interaction. The physical or chemical changes are automatically recorded as a function of temperature or time as the substance is heated at a uniform rate. Aging characteristics and stability problems may also be predicted from this method.(Ford and Timmins,1989)

3. Infrared (IR) spectrophotometry.

Infrared spectrophotometry is the method of determination between the interaction of drug and carrier in solid dispersion system. If the IR band do not deviate from the drug, it suggests that there is no interaction between drug and carrier. If the

band is broaden and different from the pure drug, it indicates that there might be some interactions such as complex formation, hydrogen bond.

4. Scanning electron microsopy (SEM).

This is the method where sample was scanned under microscopy. It can actually see what appearances of particles. This method is often used to characterize morphology, particle size, shape, surface and appearance.

CHAPTER III

MATERIALS AND METHODS

Materials

Model drug

Nifedipine (batch no.71/2, MOEHS,S.A., Barcelona, Spain)

Carriers

1. Polyethylene glycol 4000 (lot no.49-4429, BASF, Germany)
2. Polyethylene glycol 6000 (lot no.32-3729, BASF, Germany)
3. Poloxamer 188 (Lutrol F68, lot no.87-0807, BASF, Germany)
4. Poloxamer 288 (Lutrol F98, lot no. WPWT-566B, BASF, Germany)
5. Poloxamer 407 (Lutrol F127, lot no.12-0226, BASF, Germany)
6. 2-Hydroxypropyl-β-cyclodextrin (lot no.369003/1 21697, Fluka, Switzerland)
7. β-cyclodextrin (Ringdex-B® lot no. 23723, Merician Corporation, Japan).

Other substances

1. Absolute ethyl alcohol, analytical grade (lot no. K25846283 844, E.Merck, Germany)
2. Hydrochloric acid 37% (lot no. K25290117 825, E.Merck, Germany)
3. Methyl alcohol (lot no. 980060049, Lab- Scan, Ireland)

4. Acetone (lot no. 98081038, Lab-Scan, Ireland)

5. Sodium chloride (lot no. 47/874, E.Merck, Germany)

6. Potassium bromide (lot no. 378170/1 50398, Fluka, Switzerland)

7. . Putified water

Apparatus

1. Analytical balance (Satorius, GMPH, Germany)

2. Hot air oven (UL 50, Memmert, Germany)

3. Ultrasonic bath (3210, Branson, Swithkline Co., U.S.A.)

4. Vertical rotator apparatus (EWPC 902/T/R/P,Eliwell, Thailand)

5. Rotary evaporator (RE120, Buchi, Switzerland)

6. UV Spectrophotometer (Model 7800, Jasco Corporation, Thailand)

7. Dissolution apparatus (Model AT7, Sotax, Switzerland)

8. Fourier transform infrared spectrometer (Perkin Elmer Spectrum 2000, U.S.A.)

9. X-ray diffractrometer (Rigaku Denki 2027, Japan)

10. Differential scanning calorimetry (Model TA9900,Du Pont, U.S.A.)

11. Scanning electron microscope (JSM-6400, Jeol, Japan)

12. Low pressure sodium lamp (SOX-E XWC121K, Phillips, U.K.)

13. Fluorescent lamp (TFC FL-15D,15 watt, 43 cm., daylight, Taiwan)

14. Full flow™ filters (10□m,VanKel Industries, Inc., U.S.A.)

15. Membrane filters (lot. No.-7295-17, 0.8□m, Domnick hunter, Asypor, U.S.A.)

Methods

As nifedipine is sensitive to light, all experiments were conducted under yellow sodium light which has nonabsorbed wavelength by nifedipine to prevent any influences from photodegradation (Abrahamsson et al., 1998). In addition, containers used for nifedipine were wrapped with aluminium foil, when needed, throughout the experiment.

A. Preparation of solid dispersion

Nifedipine was solid-dispersed in PEG family (PEG4000 and PEG6000), poloxamer family (poloxamer188, poloxamer288 and poloxamer407) and cyclodextrin family (β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin). The ratios between drug and all the carriers were standardized at 1:1, 1:3, 1:5 and 1:10 on the weight per weight basis.

Each combinations were prepared by 3 methods which are melting method, solvent method and kneading method compared to physical mixing. Each method is detailed in 1-4. Then the solidified products were stored in a desiccator overnight. The dried mass was ground with mortar and pestle before passed through 60 mesh sieve. The final products were stored in a desiccator ready for further experiments.

1. Preparation of nifedipine physical mixtures

1.1 The required amount of nifedipine and carrier were accurately weighed in weight ratio as shown in **Table 5.**

Table 5 The weight of nifedipine : carrier in each ratio used in the preparation

Method	Carrier	Drug : Carrier (g)			
		1 : 1	1 : 3	1 : 5	1 : 10
Physical Mixing	PEG4000	5.0:5.0	2.5:7.5	1.67:8.33	0.91:9.10
	PEG6000				
	Poloxamer188				
	Poloxamer288				
	Poloxamer407				
	β-Cyclodextrin				
	2-Hydroxy-β-cyclodextrin				
Melting	PEG4000	5.0:5.0	2.5:7.5	1.67:8.33	0.91:9.10
	PEG6000				
	Poloxamer188				
	Poloxamer288				
	Poloxamer407				
	β-Cyclodextrin	-	-	-	-
	2-Hydroxy-β cyclodextrin	-	-	-	-
Solvent	PEG4000	5.0:5.0	2.5:7.5	1.67:8.33	0.91:9.10
	PEG6000				
	Poloxamer188				
	Poloxamer288				
	Poloxamer407				
	β-Cyclodextrin	-	-	-	-
	2-Hydroxy-β-cyclodextrin	5.0:5.0	2.5:7.5	1.67:8.33	0.91:9.10
Kneading	PEG4000	5.0:5.0	2.5:7.5	1.67:8.33	0.91:9.10
	PEG6000				
	Poloxamer188				
	Poloxamer288				
	Poloxamer407				
	β-Cyclodextrin				
	2-Hydroxy-β-cyclodextrin				

1.2 Both components were thoroughly mixed in glass a mortar with pestle for five minutes as illustrated in **Figure11.**

1.3 The mixture was then screened through a 60 mesh sieve and stored in a desiccator.

2. Preparation of nifedipine solid dispersion by melting method

2.1 The required amounts of nifedipine and carrier were accurately weighed and physically mixed.

PHYSICAL MIXTURE

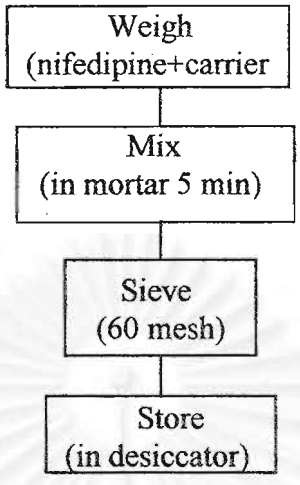


Figure 11 A schematic diagram for preparing nifedipine solid dispersion as physical mixture.

2.2 The mixture was melted on the sand bath. It was continuously stirred until both components were completely melted.

2.3 Rapid cooling was then conducted in an icebath .

2.4 The solid dispersion was placed in a desiccator overnight.

2.5 Solid dispersion was scrapped, grounded, passed through 60 mesh sieve and stored in a desiccator.

β-Cyclodextrin and 2-hydroxypropyl-β-cyclodextrin cannot be prepared by melting method because of too high melting points (about 280°C)of both carriers even though extremely high temperature was applied (about 200°C) which higher than melting point of nifedipine, may be the degradation products of nifedipine will occur.

The procedure was shown in **Figure 12.**

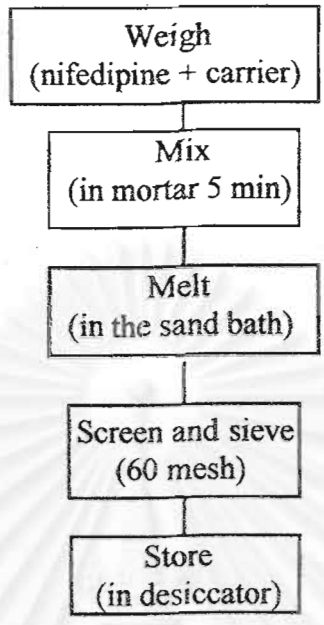


Figure 12 A schematic diagram for preparing nifedipine solid dispersion by melting method.

3. Preparation of nifedipine solid dispersion by solvent method.

3.1 The accurately weighed amount of nifedipine was dissolved in 20 ml of acetone, except for 2-hydroxypropyl-β-cyclodextrin solid dipersion, nifedipine was dissolved in methanol (0.1g: 50 ml).

3.2 Carriers were dissolved in 30 ml of absolute ethanol and sonicated until solution obtained, except for 2-Hydroxypropyl-β-cyclodextrin was dissolved in methanol 40 ml.

3.3 After that the dissolved drug was thoroughly mixed with the dissolved carrier in a round bottom flask.

3.4 The mixture was then evaporated by the rotary evaporator under vacuum condition until solvent completely evaporated. (about 10 hours) and placed in a desiccator overnight.

3.5 The solid dispersion was grounded in a mortar and pestle and screened through 60 mesh and kept in a desiccator

The procedure was shown in **Figure 13** and the types and amount of solvent used in all treatments were summarized in **Table 6**. The solid dispersion of β-cyclodextrin cannot prepared by solvent method, since an appropriate solvent systems at appropriate volume to dissolve both nifedipine and β-cyclodextrin cannot be obtained.

4. Preparation of nifedipine solid dispersion by kneading method.

4.1 The physical mixture of accurately weighed nifedipine and carrier as shown in **Table 5** was made in mortar for 5 minutes.

4.2 The mixture was kneaded with deionized water in the amount of 0.1 times of total weight for PEGs and poloxamers but 0.4 times of total weight for cyclodextrins. Water was gradually added while continuously kneading. Kneading time was controlled at 30 minutes. This should have given the mixture homogeneous texture.

4.3 Purified water can be added during kneading to maintain moist homogeneous texture. The procedures were illustrated in **Figure 14.**

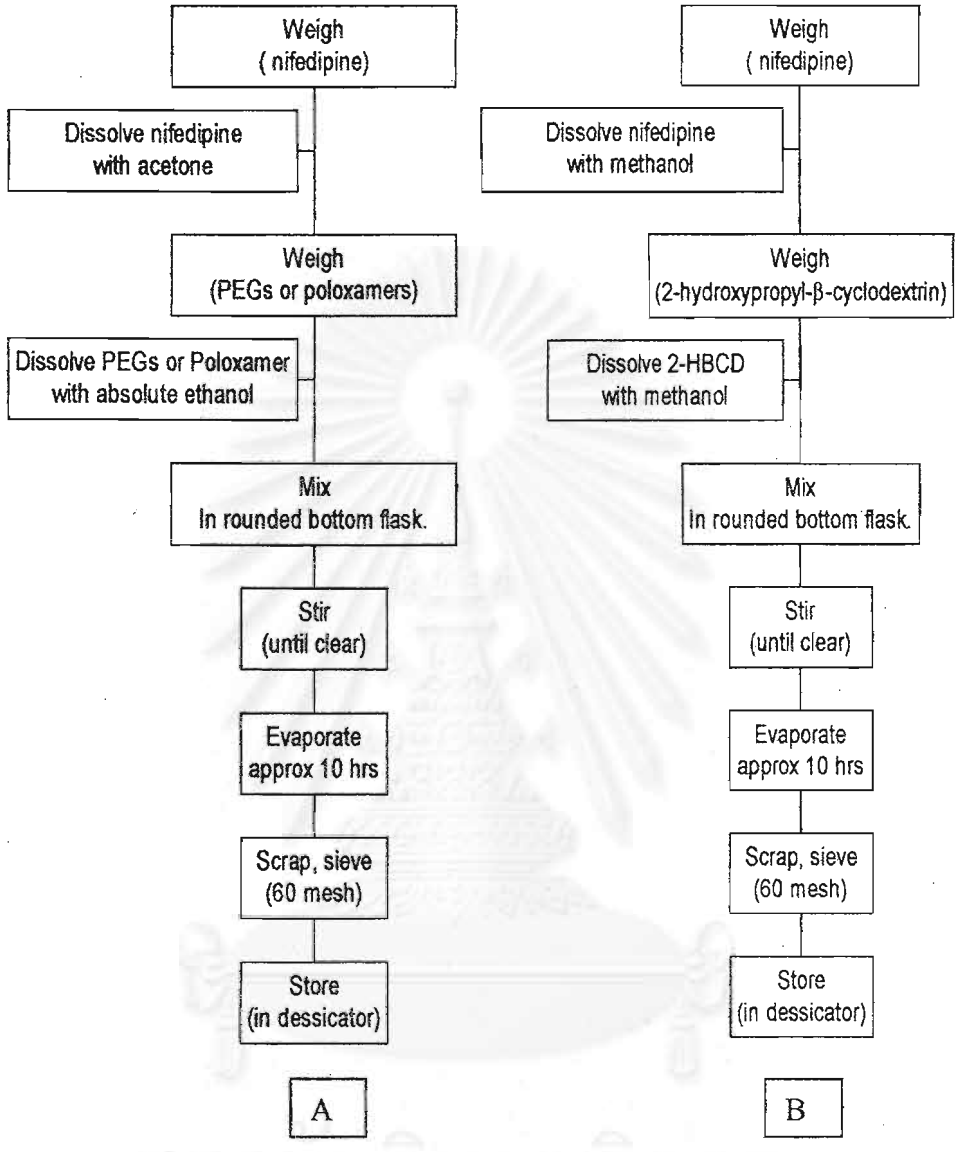


Figure 13 Schematic diagrams for preparing nifedipine solid dispersion by solvent method for PEGs and poloxamers (A) and 2-hydroxypropyl-β-cyclodextrin (B).

Table 6 Types of solvent and volume used in preparation of solid dispersion

Carrier	Solvent used		Solvent used		Drug : Carrier Ratio			
	Carrier	ml	nifedipine	ml	1 : 1	1 : 3	1: 5	1 : 10
PEG4000	absolute ethanol	30	acetone	20	5.0:5.0	2.5:7.5	1.67:8.33	0.91:9.10
PEG6000								
Poloxamer188								
Poloxamer288								
Poloxamer407								
BCD	-	-	-	-	-	-	-	-
2-HPBCD	methanol	40	methanol	0.1g/ 50ml	5.0:5.0	2.5:7.5	1.67:8.33	0.91:9.10

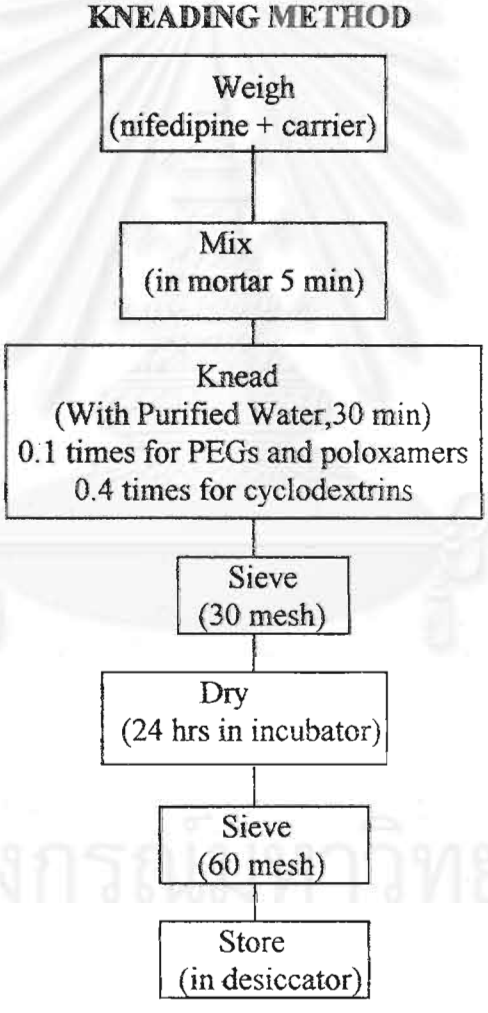


Figure 14 A schematic diagram for preparing nifedipine solid dispersion by kneading method.

B. In-Vitro Evaluation

1. Analysis and calibration curve of nifedipine

1.1 The stock solution of nifedipine was prepared by weighing nifedipine accurately 0.031g into a 100 ml volumetric flask. The solution was diluted to 100 ml using absolute ethanol. Then 10 ml of nifedipine solution was transferred and diluted to 100 ml in a volumetric flask .

1.2 Appropriate dilution of nifedipine standard solutions were made by diluting the stock solution as shown in **Figure 15** using simulated gastric fluid without pepsin as solvent (USPXXIII).

1.3 Absorbances of nifedipine solutions were measured by spectrophotometric method at 238 and 280 nm (maximum wavelength for reduced form and oxidized form respectively). These two wavelengths were previously investigated before and after the solution was irradiated to a 15 watt fluorescent lamp for 4 hours using a double beam spectrophotometer in a 1-cm cell (Al-Turk et al., 1989).

1.4 After initial time measurement, nifedipine solutions were then transferred to a light cabinet which had a 40 cm fluorescent lamp hanging 30 cm above the sample solutions. The intensity of light is about 1000-1300 lux. After 4 hour irradiation , nifedipine was completely oxidized to be nitrosopyridine (Al-turk et al., 1989). Absorbance of each solution was measured again at 238 and 280 nm.

NIFEDIPINE DILUTION FOR CALIBRATION CURVE

Nifedipine 0.031g.

↓

100 ml with absolute ethanol

↓

10 ml of nifedipine solution

↓

100 ml with SMG* (stock solution)

↓

1 ml. ⇓ 10 ml.	1.5 ml. ⇓ 10 ml.	2 ml. ⇓ 10 ml.	2.5 ml. ⇓ 10 ml.	3 ml. ⇓ 10 ml.	4 ml. ⇓ 10 ml.	4.5 ml. ⇓ 10 ml.	5 ml. ⇓ 10 ml.
3.1 µg/ml	4.65 µg/ml	6.2 µg/ml	7.75 µg/ml	9.3 µg/ml	12.4 µg/ml	13.95 µg/ml	15.5 µg/ml

* simulated gastric fluid without pepsin.

Dilution in the table, diluted by simulated gastric fluid without pepsin.

Figure 15 A schematic diagram of nifedipine dilution for calibration curve.

1.5 A linear regression between concentration and absorbance was made to obtain 4 slope values and Y-interceptions (two values before and after irradiation at 238 nm and also two values at 280 nm). An equation was derived as shown in Appendix A by using 4 slopes and Y-interception values for calculating the reduced form of nifedipine in further study of dissolution and determination of percentage drug content. The validation of calibration curve is in the Appendix A.

2. Dissolution study

2.1 The dissolution studies were performed in triplicate with Sotax dissolution test apparatus (USPXXIII, apparatus 2), in simulated gastric fluid without pepsin at 37°C using the paddle method at a rotation speed of 150 rpm. A certain amount of each sample, containing equivalent amount to 10 mg nifedipine was put into a vessel with 900 ml of simulated gastric fluid without pepsin as dissolution medium.

2.2 After 5, 10, 15, 20 min and so on until the dissolution was in steady state, 5 ml of solution were withdrawn through 10 μm filters. The initial volume of the vessel was maintained by adding 5 ml of the same medium after each sampling.

2.3 The withdrawn solution was assayed spectrophotometrically with Jasco UV-spctrophotometer at 238 and 280 nm . The concentration of reduced form of nifedipine present in solution was calculated from the derived equation as previously described in 1.5.

The investigated samples were those prepared from 1:1, 1:3, 1:5 and 1:10 nifedipine–carrier mixing ratios with 7 carriers (PEG4000, PEG6000, poloxamer188, poloxamer288, poloxamer407, β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin) with various methods. The untreated and treated nifedipine were also investigated.

The dissolution profile of % dissolution of nifedipine was plotted against time and dissolution rate constant was analyzed at 30 minutes. Then the statistical significance of dissolution rate constants of each carrier were determined by the two

way analysis of variance at 95% confidence interval (Appendix D). In addition, the time 80% of nifedipine dissolved was also discussed.

3. Solubility Study

Solubility study of nifedipine-carrier were carried out according to the method of Higuchi and Connors (1965). Each concentration of carriers were investigated in triplicate . All steps have to be protected from light .

3.1 An excess amount of nifedipine was added to 5 ml solutions containing different concentrations of carriers and rotated for 24 hours (The preliminary test showed that the equilibrium was obtained at about 24 hours.) by vertical rotator, previously adjusted to $30 \pm 2^{\circ}C$.

3.2 Then, the solution was filtered passed through 0.8 μm membrane filter and suitably diluted with deionized water.

3.3 The solution was analyzed spectrophotometrically at 238 and 280 nm to define the solubility characteristics. Each concentration of carriers were performed in tripicate. All steps of the study have been protected from light.

4. Scanning electron microscope study

Electron photomicrographs of samples were taken with the scanning electron microscopy. The samples were coated with gold before examination, using ion

sputtering. Then they were photographed at appropriate magnification scales. The samples were all ratios of 7 carriers by 4 methods in this experiment except for melting and solvent method β-cyclodextrin and melting method 2-hydroxypropyl-β-cyclodextrin.The samples including nontreated pure nifedipine, treated pure nifedipine by four methods and seven pure carriers.

5. Powder X-ray diffraction study

The powder X-ray diffraction (XRD) pattern was investigated on Rigaku Denki 2027 Diffractometer with target Cu and filter Ni. The measurement condition was as follows:

Voltage	30 KV
Current	5 mA
Scanning speed	4°C/min
Scanning range (2□)	5-40°

6. Differential scanning calorimetry study

Differential scanning calorimetry (DSC) was investigated on a differential scanning calorimeter (DuPont, Model TA9900). The 2-3 mg sample was accurately weighed and placed in a closed aluminum pan. The measurement condition was as follows:

Scanning speed	5°C/min.
Temperature range	35-250 °C
Atmosphere	Nitrogen gas, flow rate 60ml./min.

7. Infrared spectrophotometric study

Infrared (IR) spectra were measured by the KBr disc method using Perkin-Elmer Spectrum 2000 infrared spectrophotometer in the range of 4000-400 cm^{-1}, the characteristic bands were observed.

8. Wettability Study

The wettability of powder samples was investigated by the modified method of Imai et al (1989).

8.1 The sample powder of 200 mg weight was compressed into a cylindrical tablet (11 mm diameter) using a single punch compressing machine at a pressure of 400 psi for 1 min.

8.2 A 20 µl drop of deionized water was placed on the flatted tablet surface using a micropipette.

8.3 After 2 seconds, the drop was photographed, and the contact angle was measured directly from the photographs.

CHAPTER IV

RESULTS

1. Preparation of Nifedipine Solid Dispersion

Nifedipine naturally is yellow crystalline powder and odorless. Polyethylene glycols (PEG4000 and PEG6000) and poloxamers (poloxamer188, poloxamer288, poloxamer407) are white-creamy color with wax-liked surface. Cyclodextrins (β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin) are very brittle, nonhygroscopic and free-flowing powder.

Most nifedipine solid dispersions are easily prepared except melting method for 2-hydroxypropyl-β-cyclodextrin and β-cyclodextrin and solvent method for β-cyclodextrin. For the solvent method, 2-hydroxypropyl-β-cyclodextrin could not readily dissolve in absolute ethanol as in PEGs and poloxamers systems. Methanol was therefore used to dissolve nifedipine and 2-hydroxypropyl-β-cyclodextrin in this method. The kneaded products of 2-hydroxypropyl-β-cyclodextrin and nifedipine at most mixing ratios were prepared by using larger amount of water to wet than those of other carriers. These products then were dried in an incubator and pulverized to obtain brittle and free flowing powder.

The solid dispersions of PEGs and poloxamers were wax-liked, therefore slightly hard to be pulverized. All dispersions were pale yellow powder.

2. The Calibration Curve

Calibration curve of nifedipine in simulated gastric fluid without pepsin using a linear regression plot is presented in appendix A. A high coefficient of determination (r^2) exhibited that the data were fit with this linear plot.

3. Dissolution Study

The dissolution profiles of nifedipine solid dispersions and treated pure drug by various methods namely physical mixing, kneading, solvent, and melting are presented in **Figure 16-41**. The summarized of dissolution results are shown as the time to dissolve 80% of the drug (T80%) (**Table 7**). For the aim of fast release behavior of nifedipine system, the initial dissolution rate constant at the first 30 min. were examined. The rate constant was calculated by the Sigma-minus method (Martin, 1993) since it was found that the dissolution profiles fit the first order plot (Appendix E). The dissolution rate constants of all systems were summarized in **Table 8**. The two way analysis of variance ($\alpha = 0.05$) of the rate constants are presented in Appendix D. All detailed experimental data were given in Appendix B and C.

From two way analysis of variance of dissolution rate constants at initial 30 min, it was found that method, ratio and method-ratio interaction were significantly different in PEG and poloxamer system, but in cyclodextrin system, the statistically significant difference were found in only method and ratio.

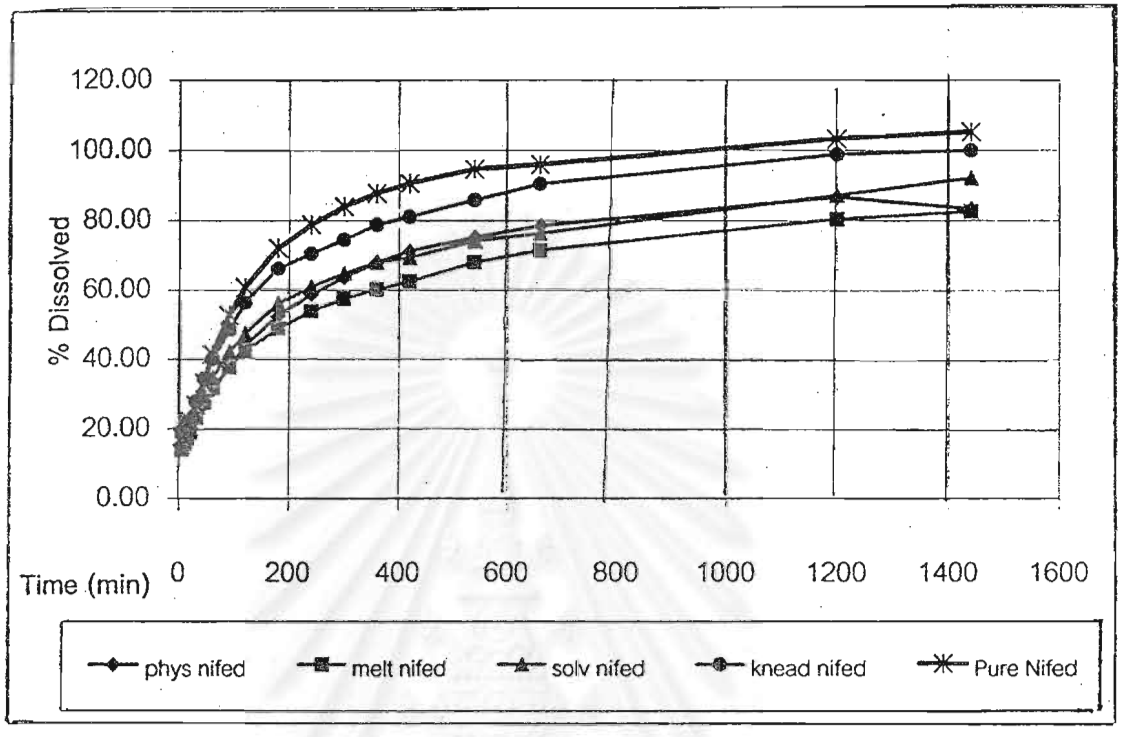


Figure 16 Dissolution profiles of treated and nontreated nifedipine

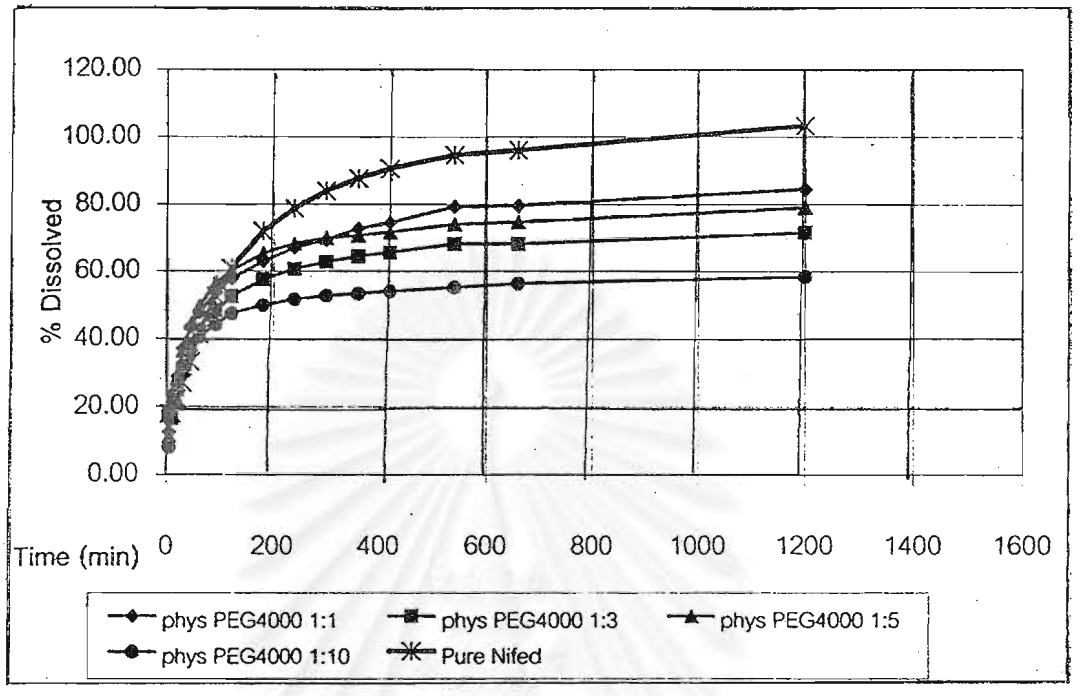


Figure 17 Dissolution profile of nifedipine from nifedipine-PEG4000 physical mixtures.

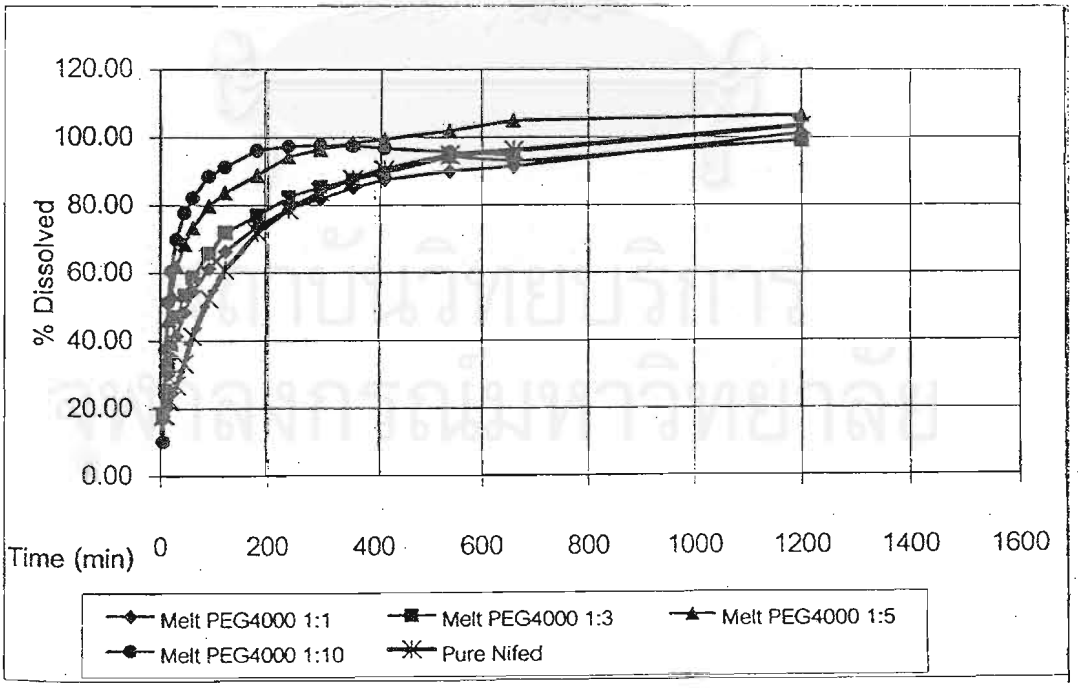


Figure 18 Dissolution profile of nifedipine from nifedipine-PEG4000 melting method.

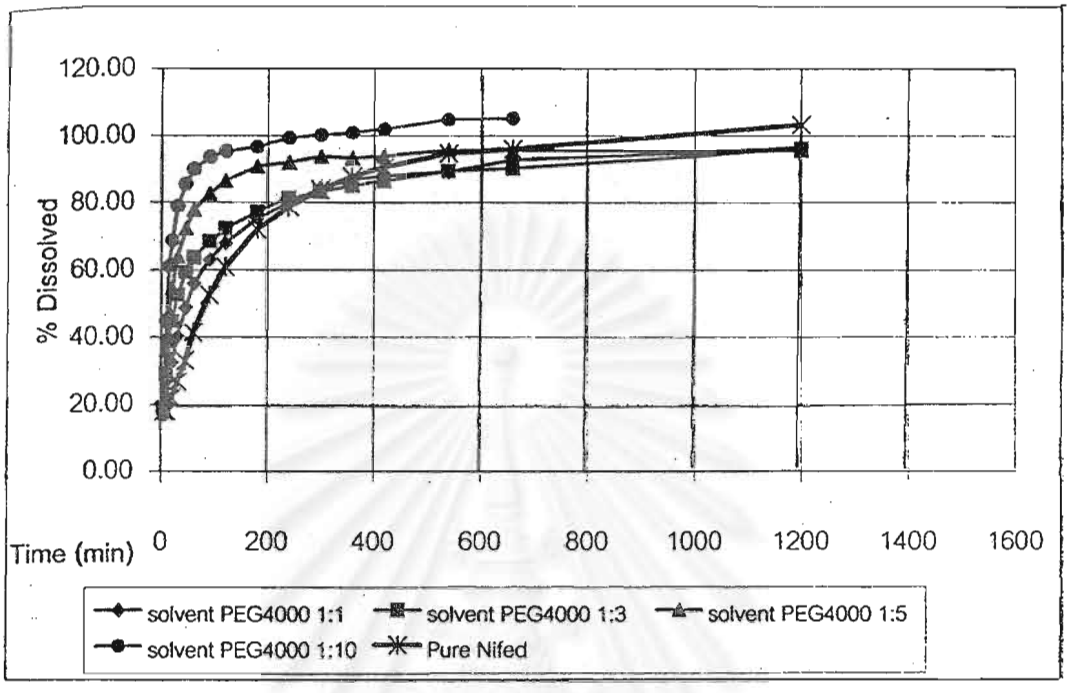


Figure 19 Dissolution profile of nifedipine from nifedipine-PEG4000, solvent method.

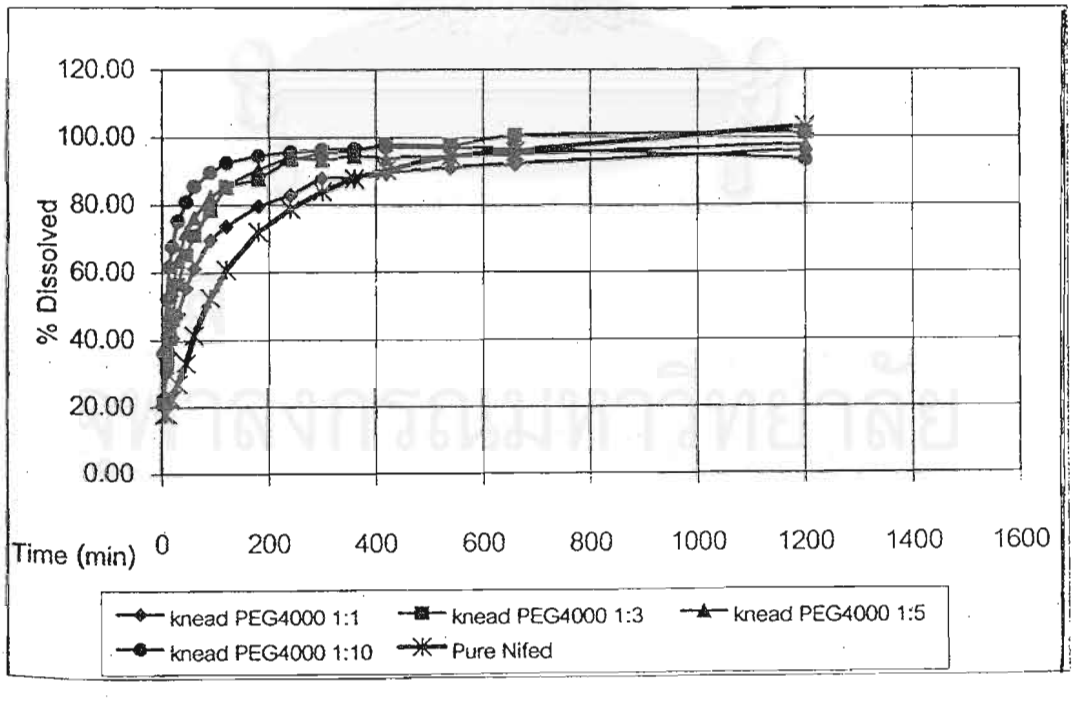


Figure 20 Dissolution profile of nifedipine from nifedipine-PEG4000, kneading method.

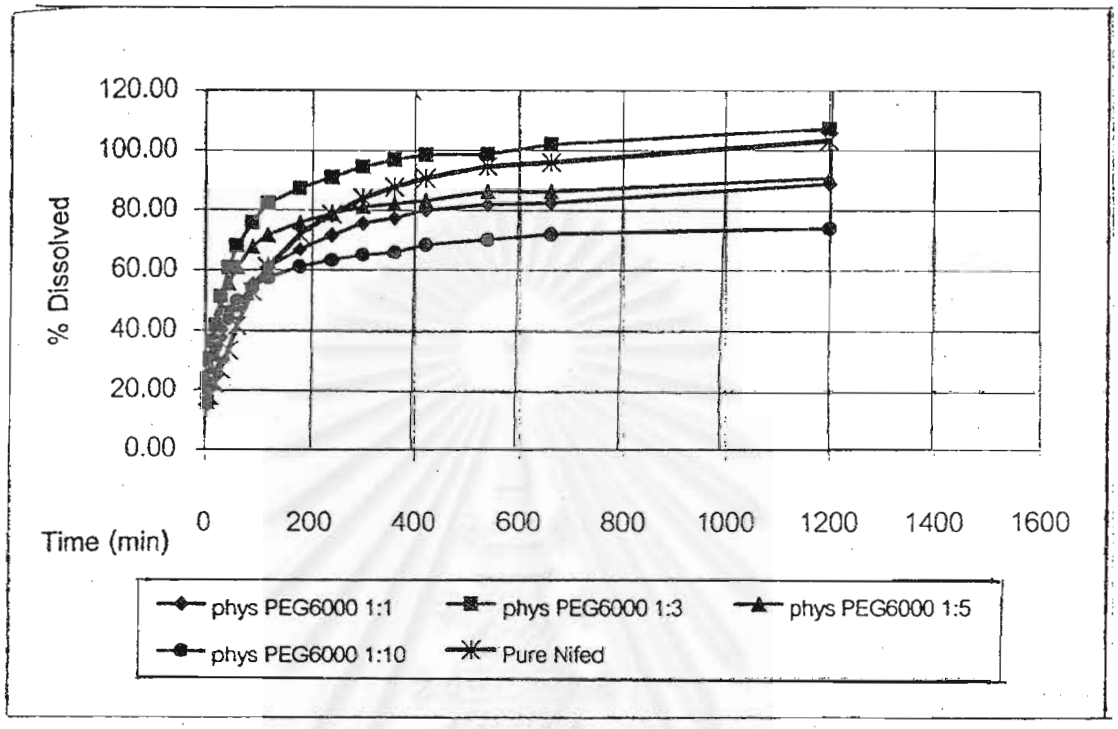


Figure 21 Dissolution profiles of nifedipine from nifedipine-PEG6000 physical mixtures.

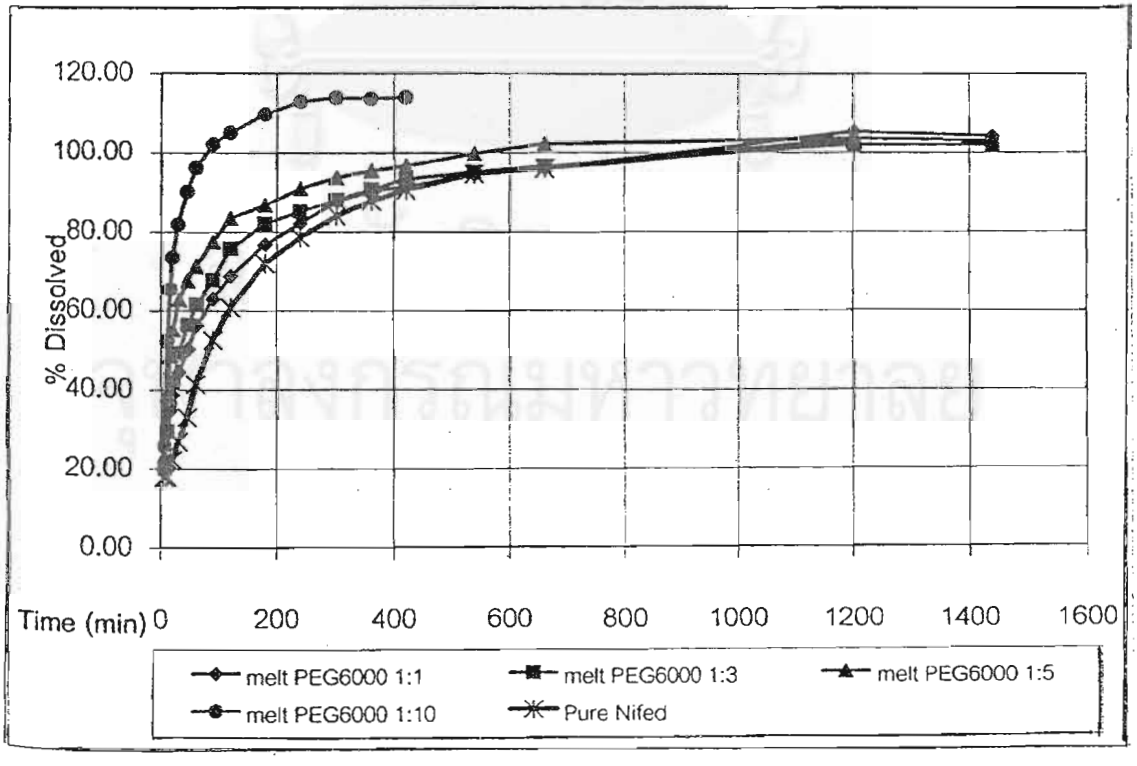


Figure 22 Dissolution profiles of nifedipine from nifedipine-PEG6000 solid dispersions prepared by melting method.

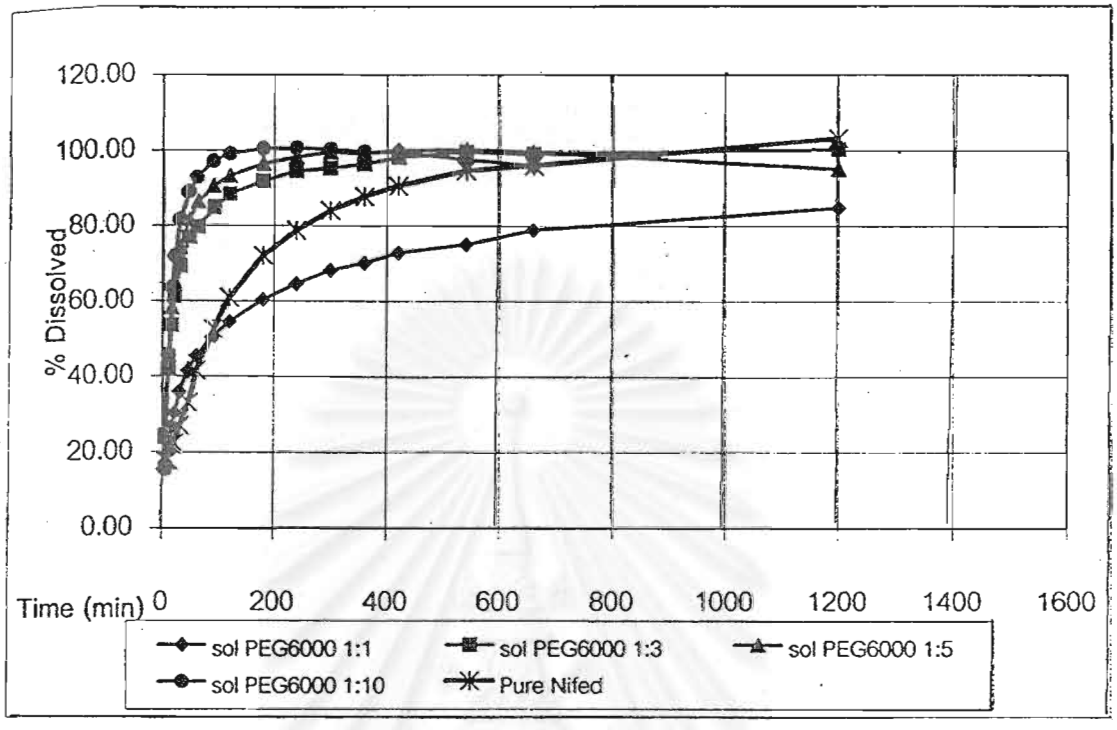


Figure 23 Dissolution profiles of nifedipine from nifedipine-PEG6000 solid dispersions prepared by solvent method.

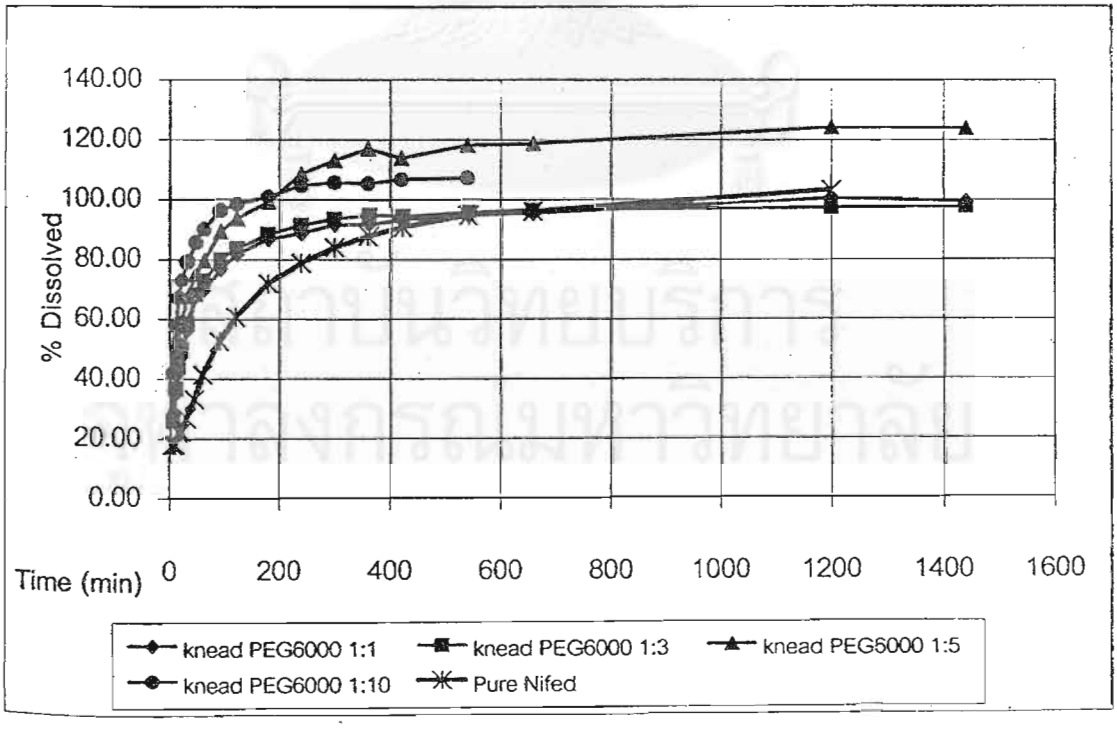


Figure 24 Dissolution profiles of nifedipine from nifedipine-PEG6000 solid dispersions prepared by kneading method.

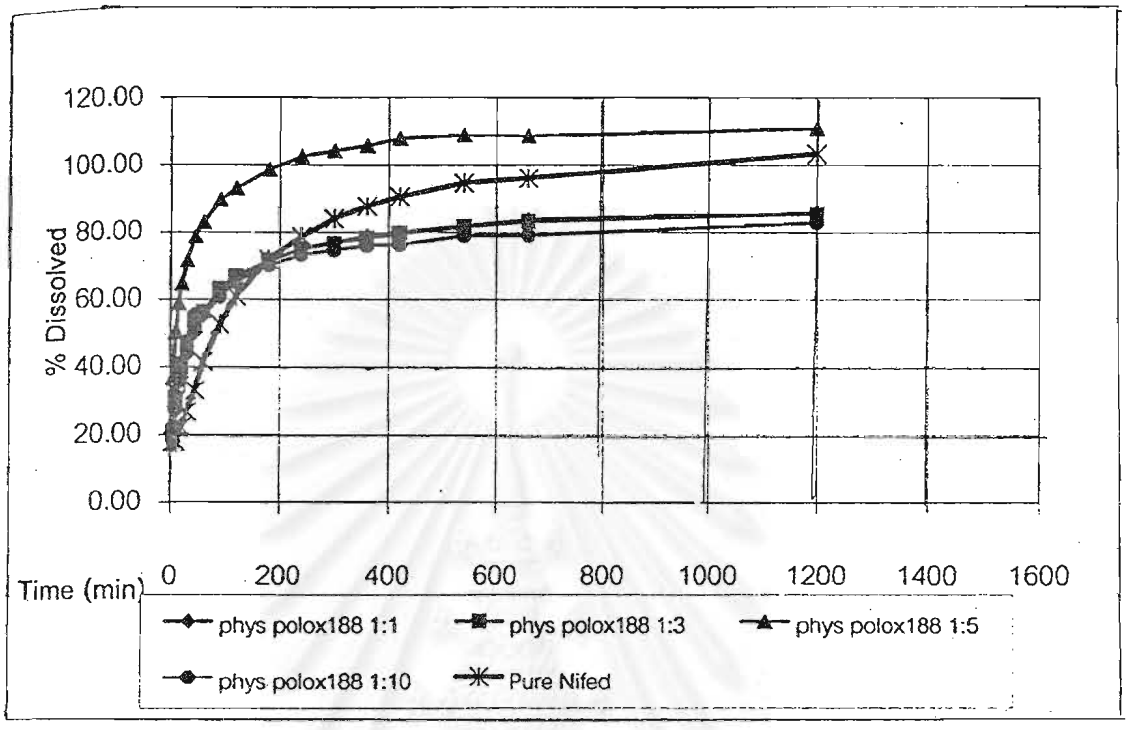


Figure 25 Dissolution profiles of nifedipine from nifedipine-poloxamer188 physical mixtures.

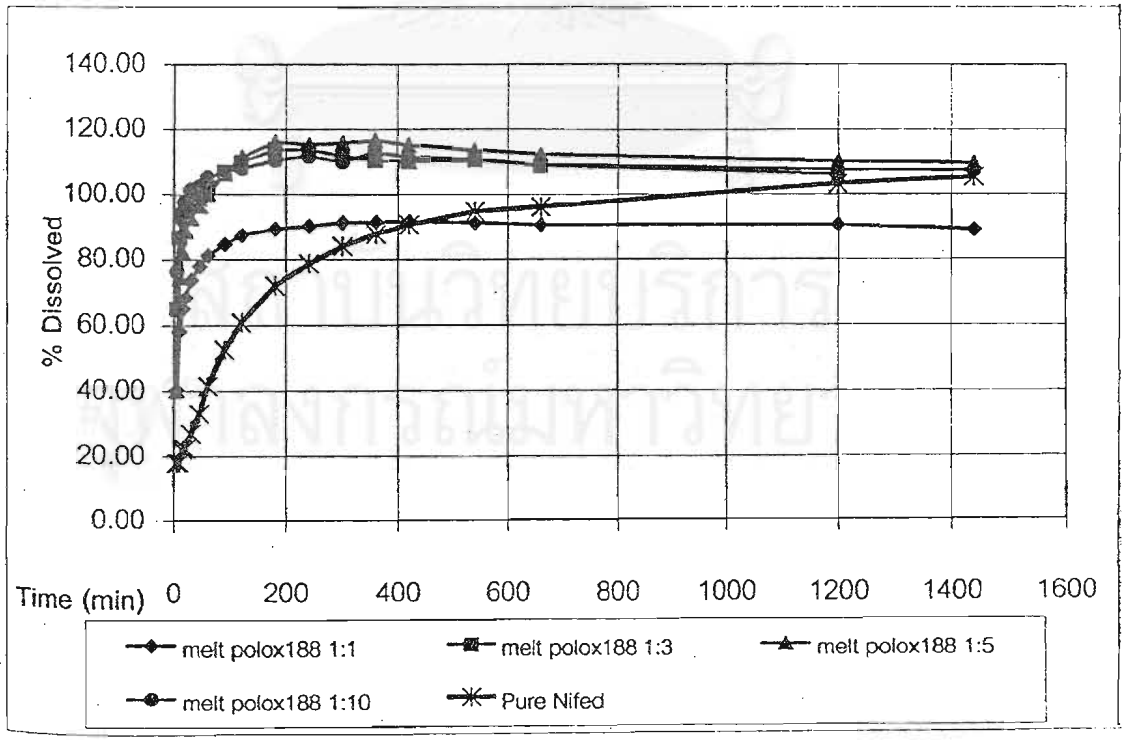


Figure 26 Dissolution profiles of nifedipine from nifedipine-poloxamer188 solid dispersions prepared by melting method.

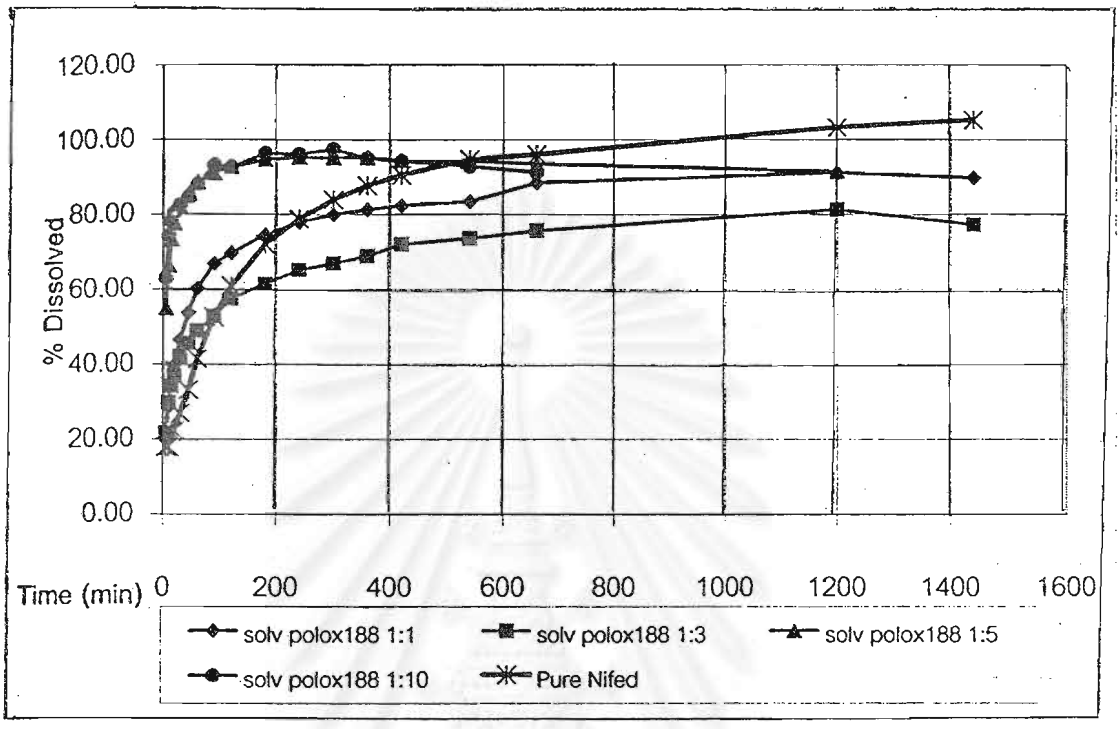


Figure 27 Dissolution profiles of nifedipine from nifedipine-poloxamer188 solid dispersions prepared by solvent method.

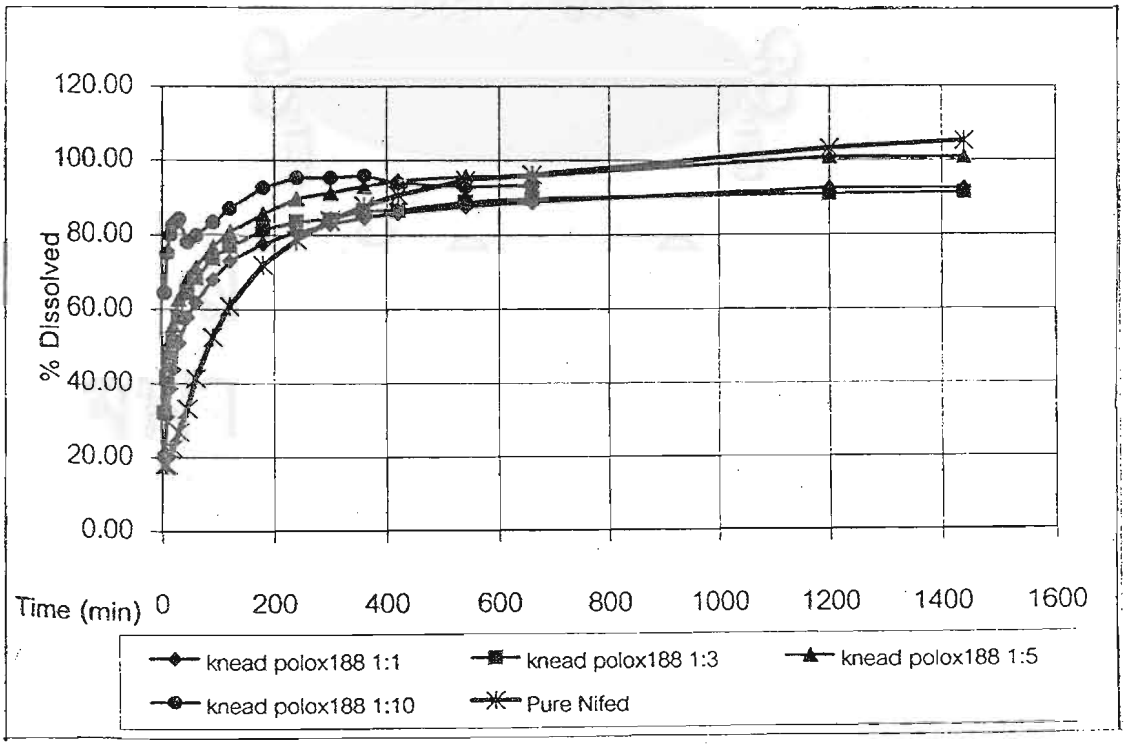


Figure 28 Dissolution profiles of nifedipine from nifedipine-poloxamer188 solid dispersions prepared by kneading method.

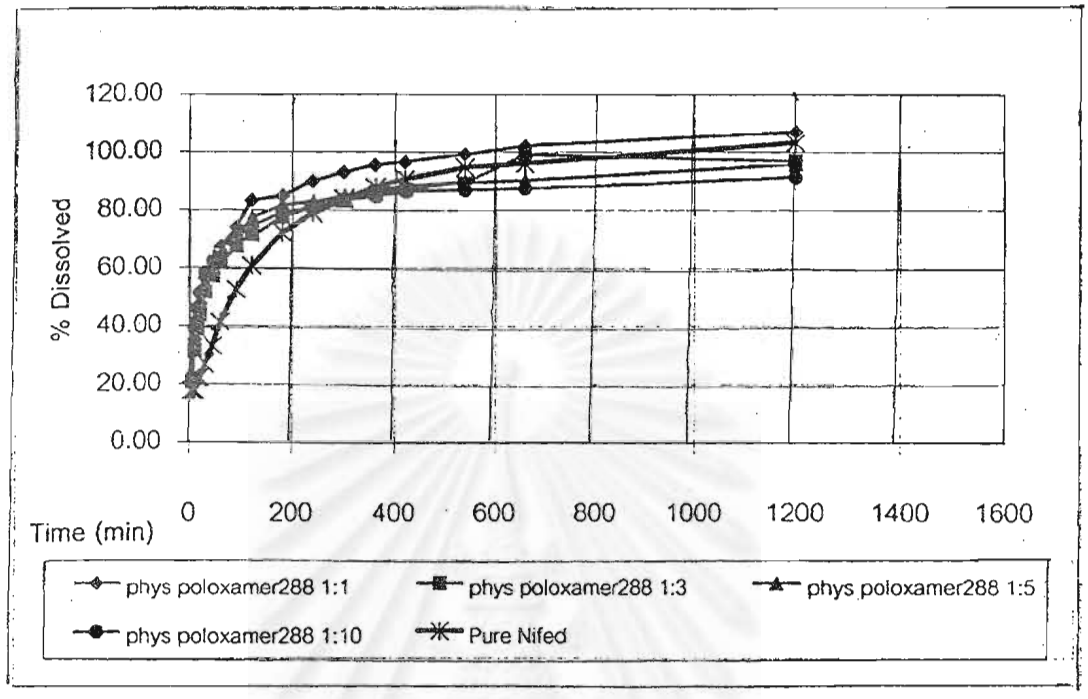


Figure 29 Dissolution profiles of nifedipine from nifedipine-poloxamer288. physical mixtures.

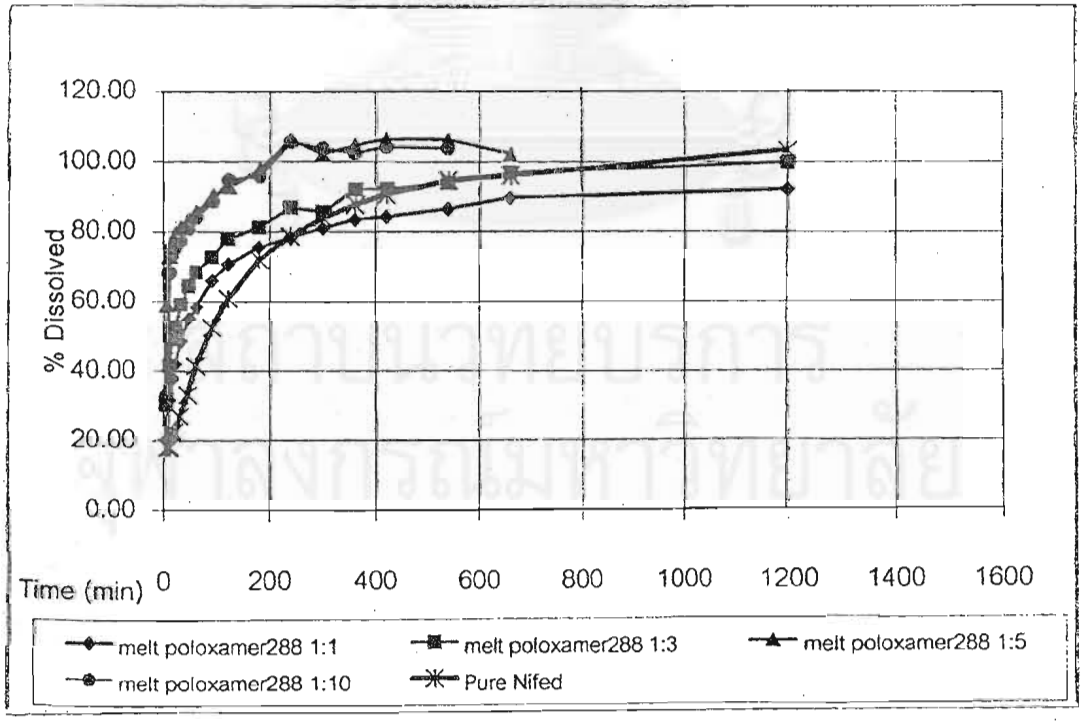


Figure 30 Dissolution profiles of nifedipine from nifedipine-poloxamer288 solid dispersions prepared by melting method.

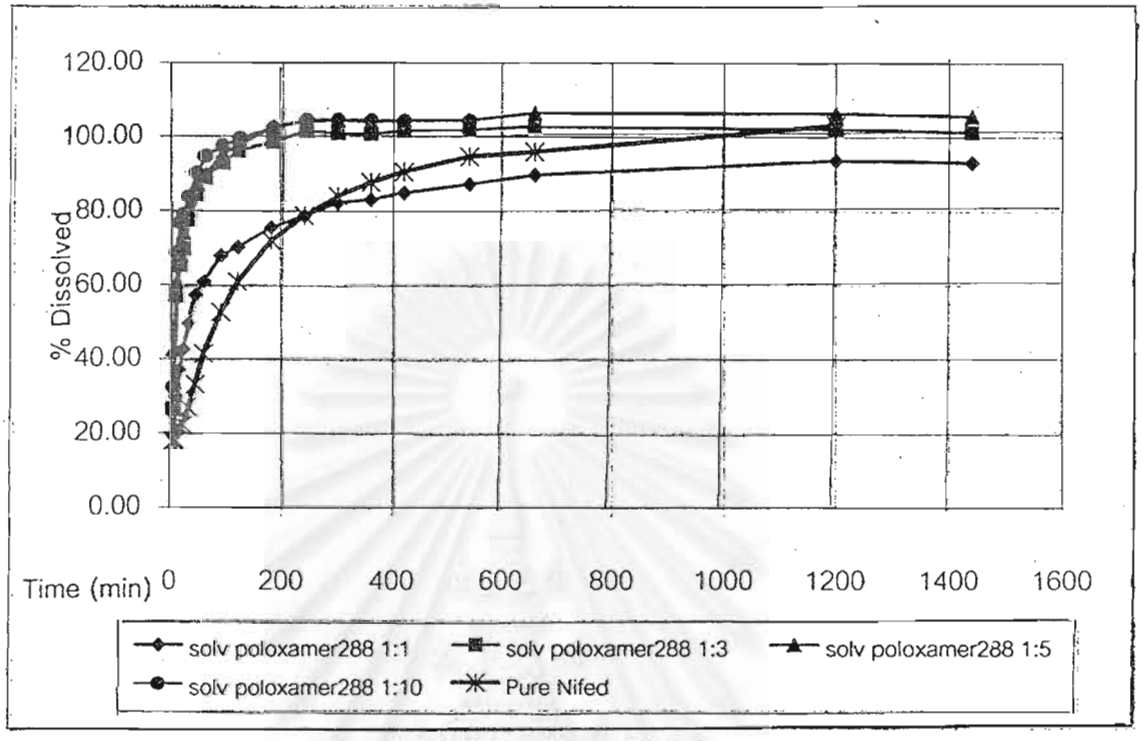


Figure 31 Dissolution profiles of nifedipine from nifedipine-poloxamer288 solid dispersions prepared by solvent method.

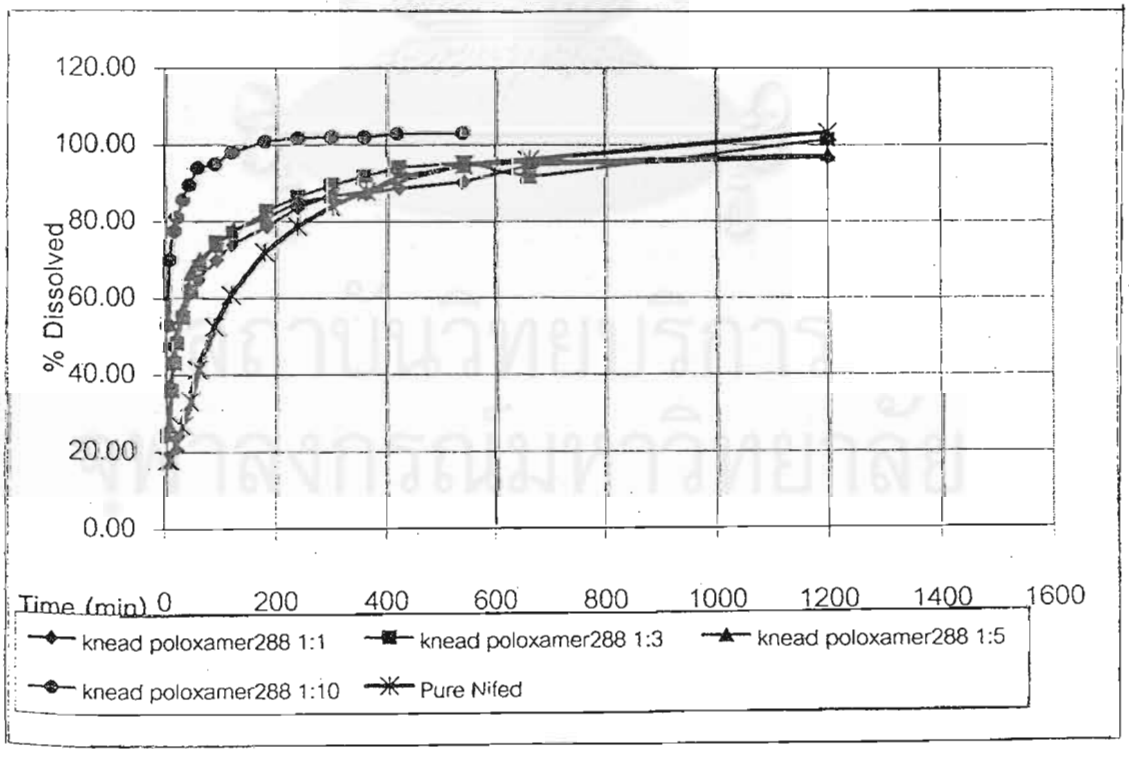


Figure 32 Dissolution profiles of nifedipine from nifedipine-poloxamer288 solid dispersions prepared by kneading method.

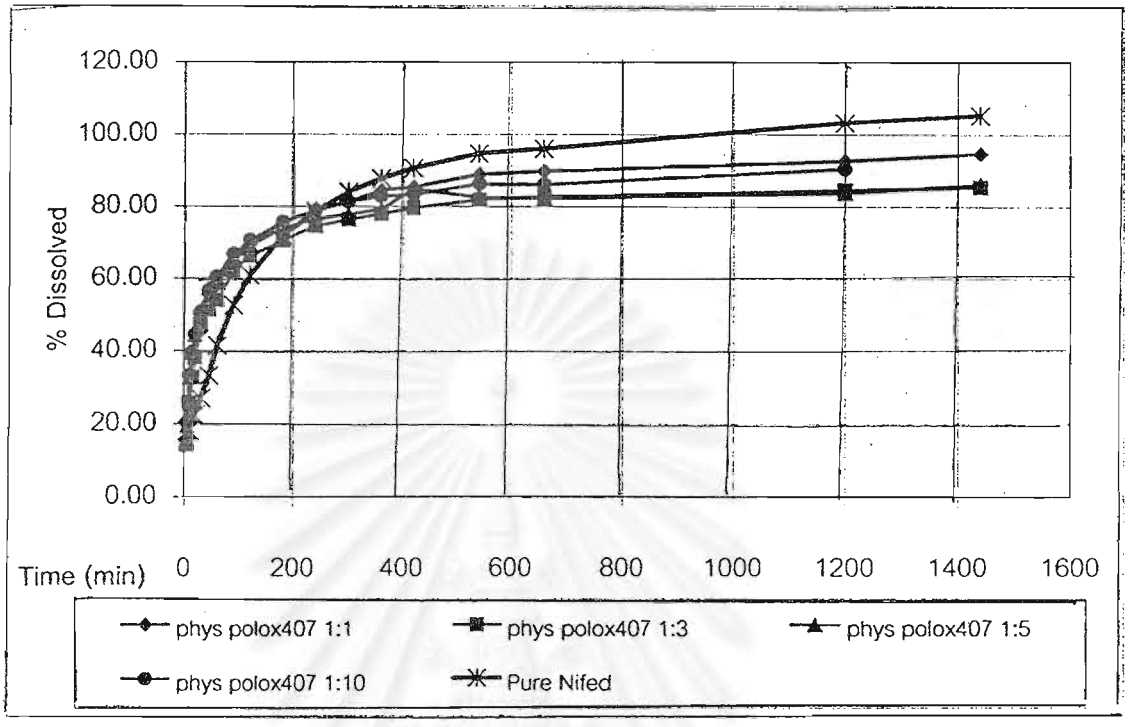


Figure 33 Dissolution profiles of nifedipine from nifedipine-poloxamer407 physical mixtures.

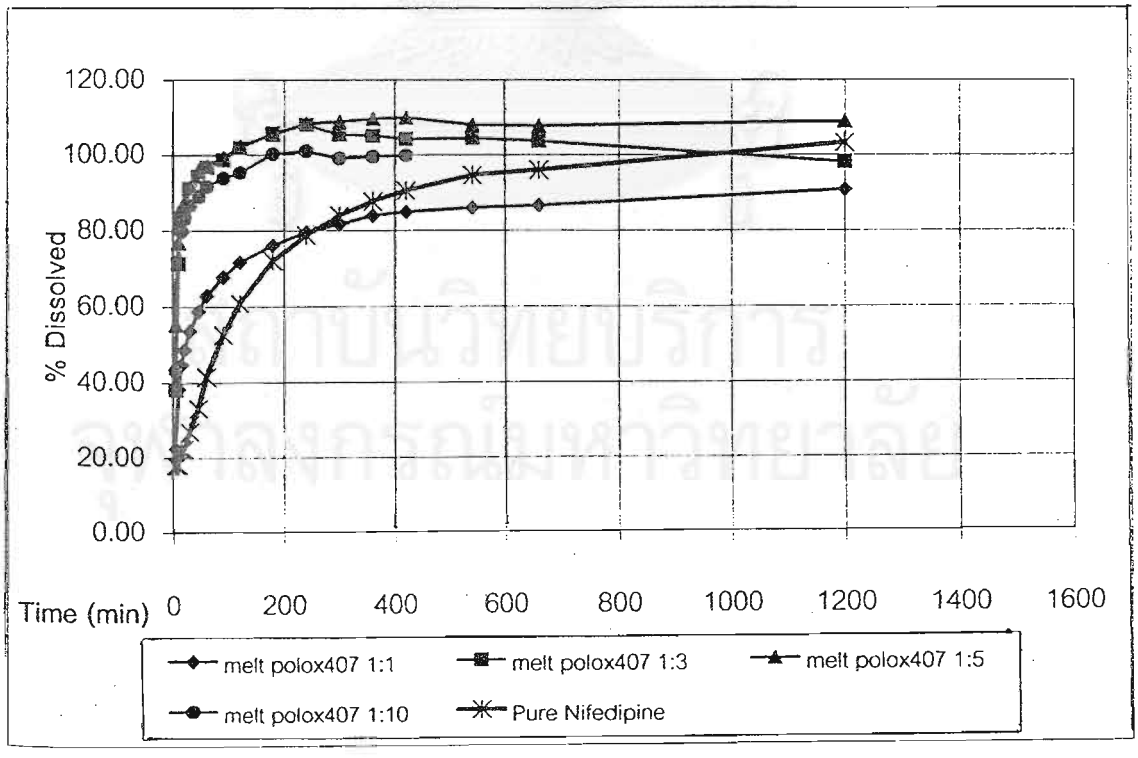


Figure 34 Dissolution profiles of nifedipine from nifedipine-poloxamer407 solid dispersions prepared by melting method.

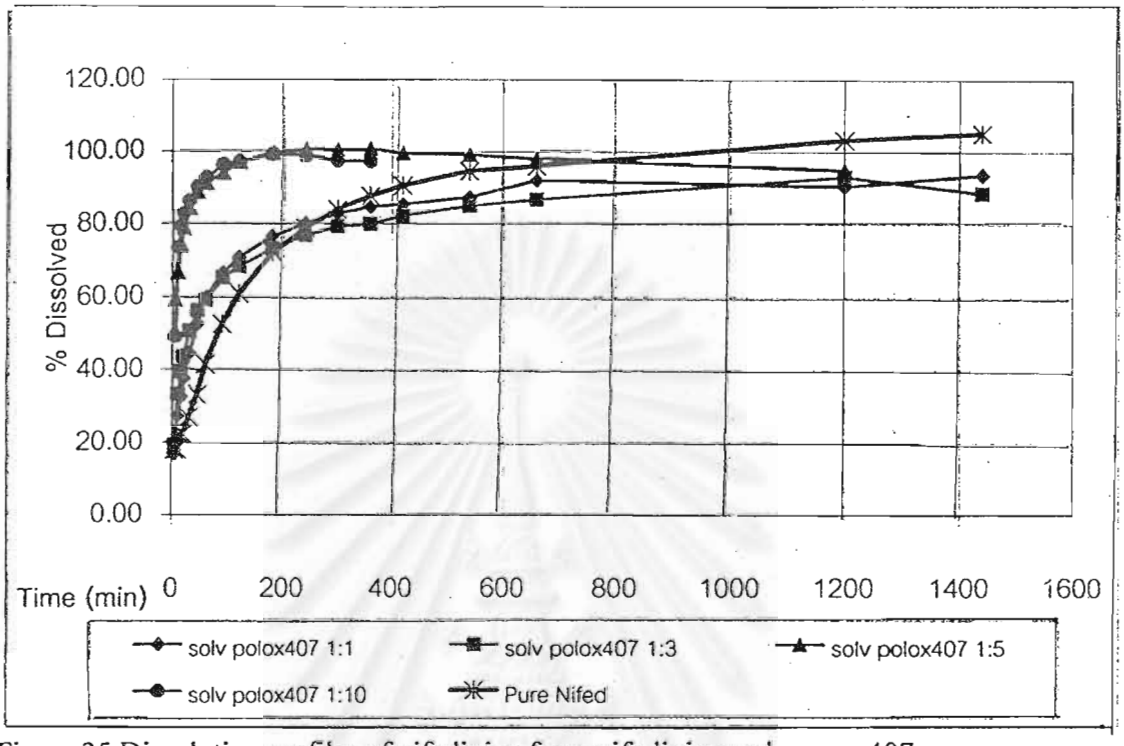


Figure 35 Dissolution profiles of nifedipine from nifedipine-poloxamer407 solid dispersions prepared by solvent method.

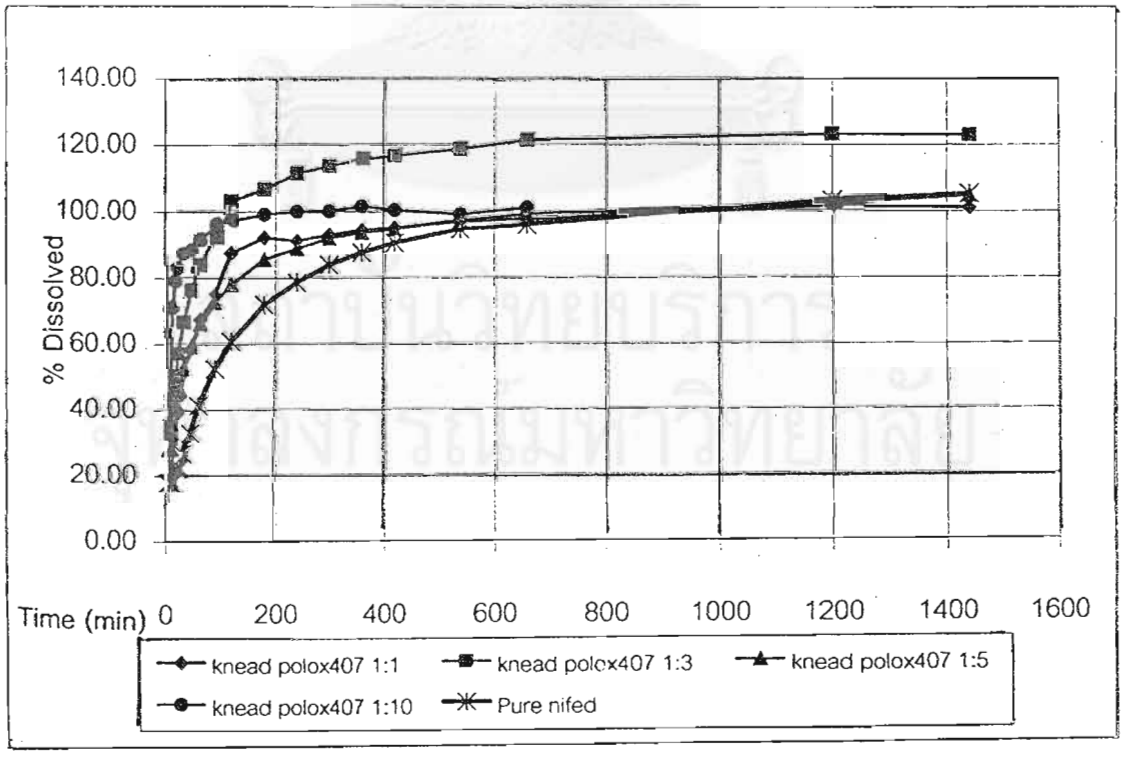


Figure 36 Dissolution profiles of nifedipine from nifedipine-poloxamer407 solid dispersions prepared by kneading method.

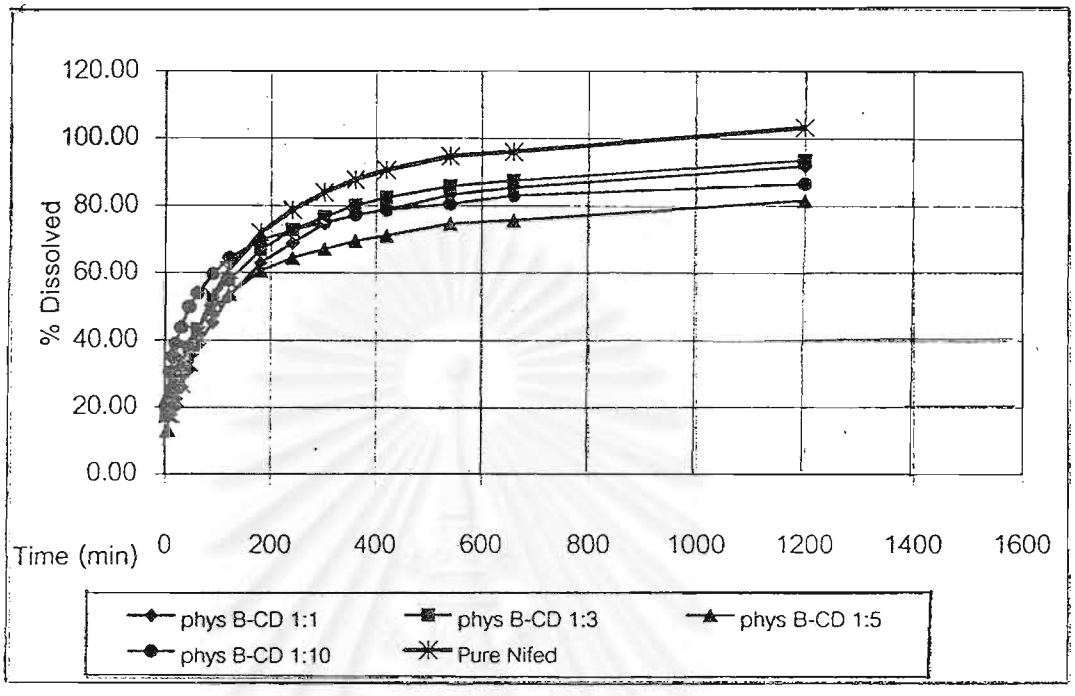


Figure 37 Dissolution profiles of nifedipine from nifedipine-β-cyclodextrin physical mixtures.

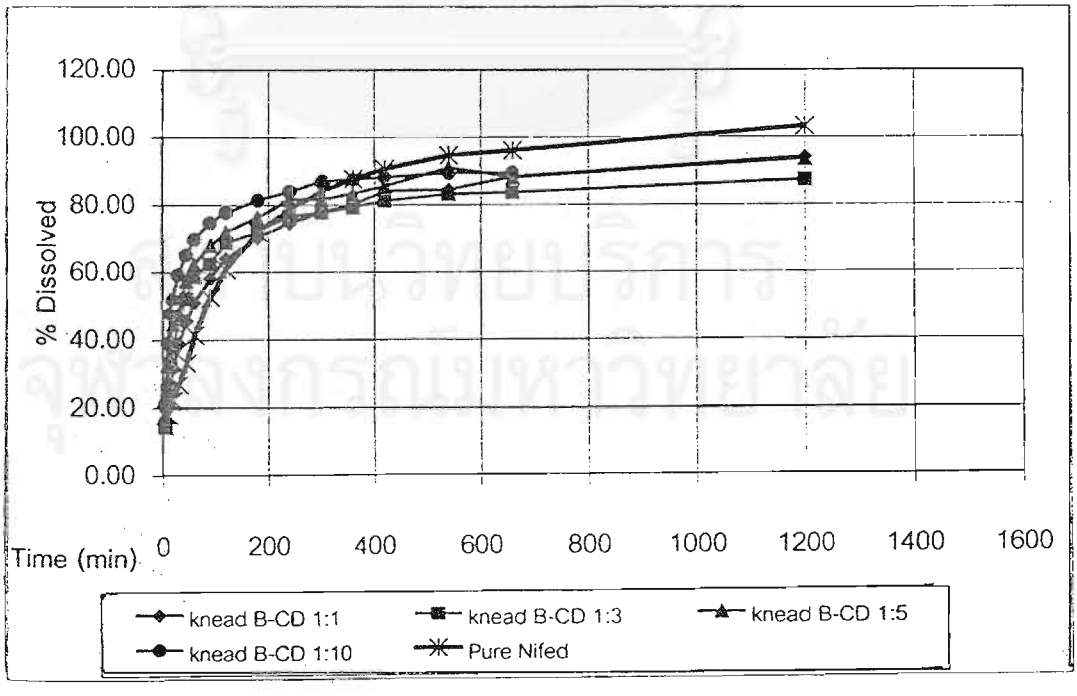


Figure 38 Dissolution profiles of nifedipine from nifedipine-β-cyclodextrin solid dispersions prepared by kneading method.

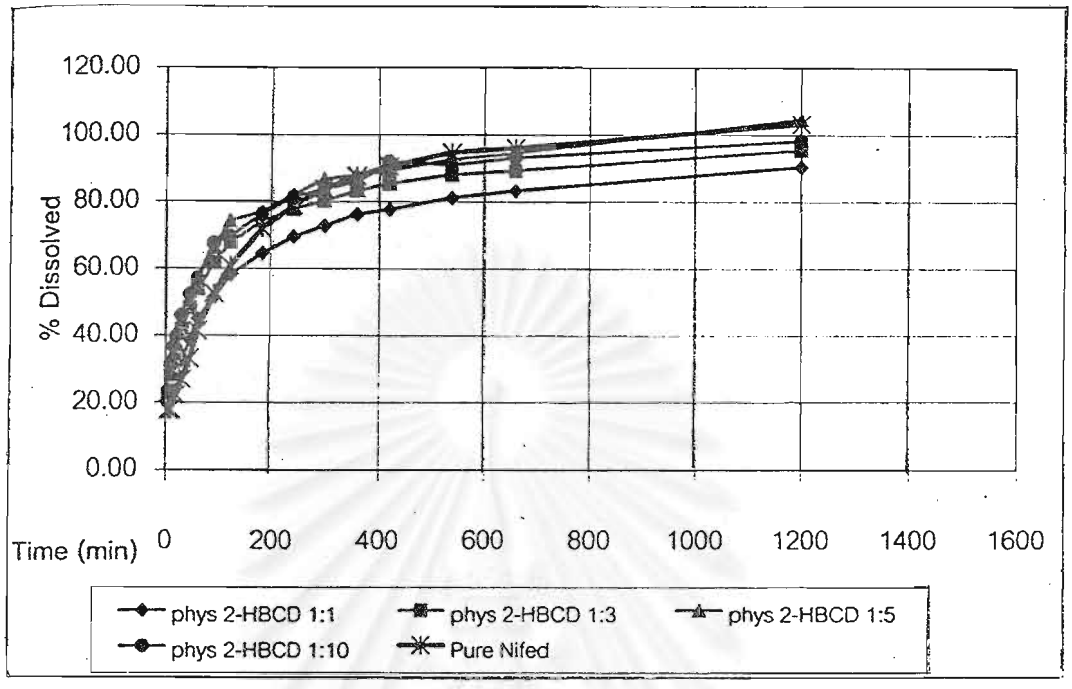


Figure 39 Dissolution profiles of nifedipine from nifedipine –2- hydroxypropyl-β-cyclodextrin physical mixtures.

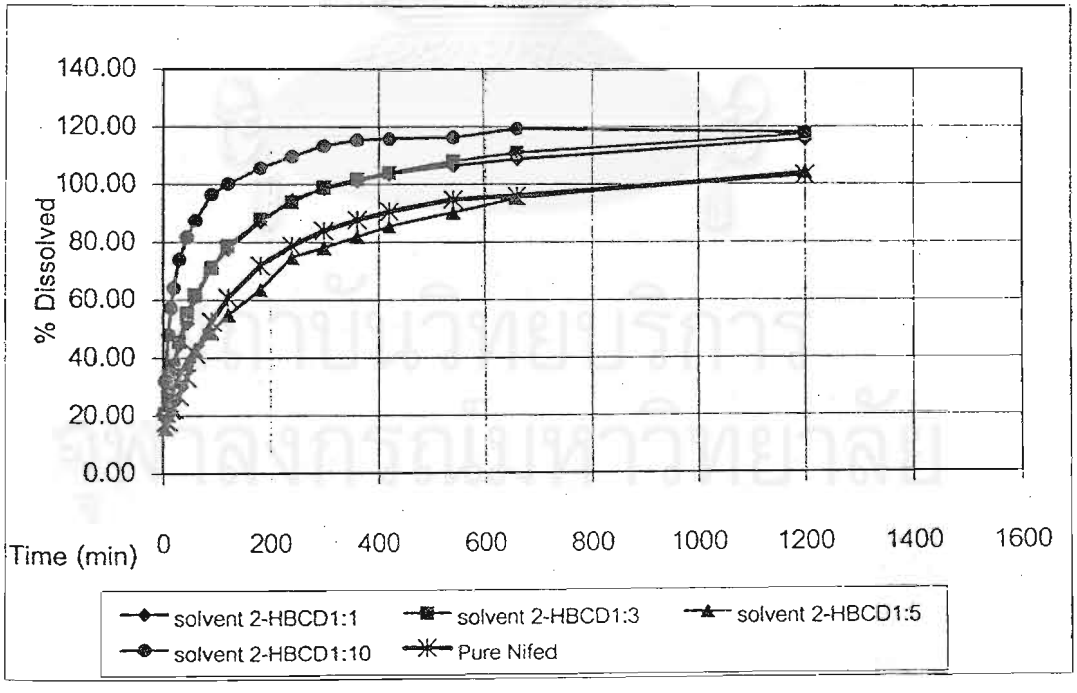


Figure 40 Dissolution profiles of nifedipine from nifedipine- 2-hydroxypropyl-β-cyclodextrin solid dispersions prepared by solvent method.

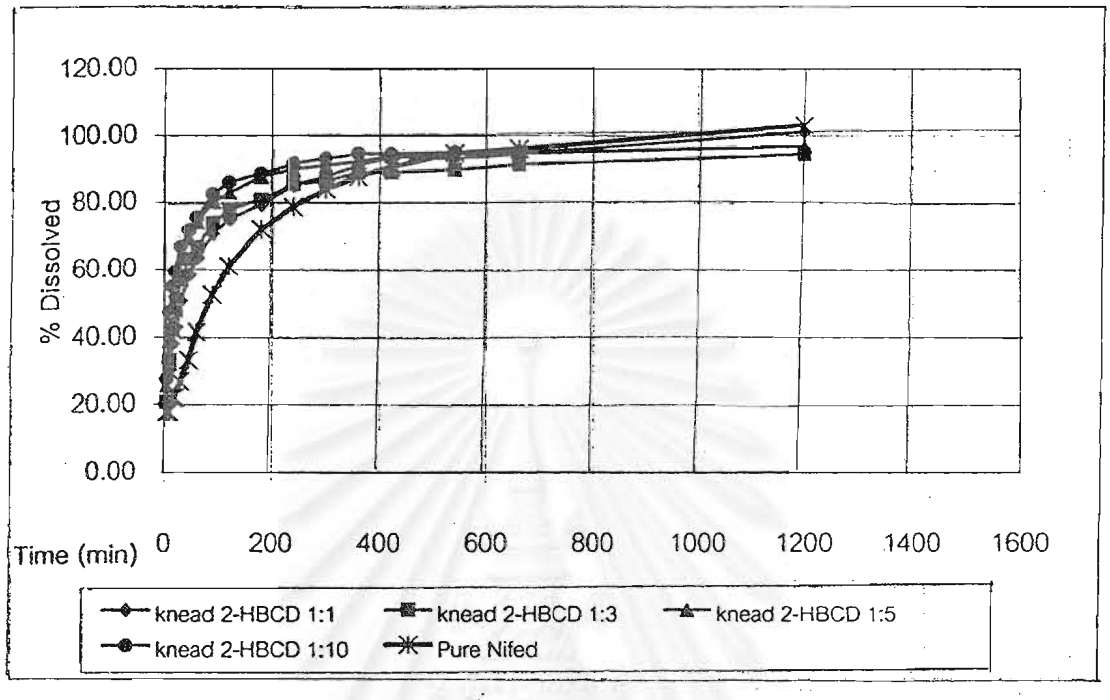


Figure 41 Dissolution profiles of nifedipine from nifedipine-2-hydroxypropyl-β-cyclodextrin solid dispersions prepared by kneading method.

Table 7 The time at 80% of nifedipine dissolved

Carrier	Drug:Carrier Ratio	The time of 80% dissolution (min)			
		Method			
		Physical	Melting	Solvent	Kneading
Nifedipine +	1:0	770	1185	840	395
PEG4000	1:1	660	270	245	195
	1:3	*	215	230	90
	1:5	*	90	75	80
	1:10	*	55	45	45
PEG6000	1:1	420	225	765	105
	1:3	105	160	60	90
	1:5	270	110	45	60
	1:10	*	30	30	30
Poloxamer188	1:1	420	55	300	200
	1:3	420	15	1080	155
	1:5	55	15	33	120
	1:10	780	15	30	20
Poloxamer288	1:1	110	270	260	200
	1:3	225	155	33	150
	1:5	160	30	30	165
	1:10	110	35	25	15
Poloxamer407	1:1	270	260	240	100
	1:3	455	15	350	55
	1:5	375	15	20	130
	1:10	255	15	15	15
BCD	1:1	450	-	-	380
	1:3	360	-	-	355
	1:5	990	-	-	220
	1:10	510	-	-	150
HPBCD	1:1	495	-	330	180
	1:3	295	-	135	165
	1:5	220	-	135	90
	1:10	220	-	40	75

+ T80 % of nontreated nifedipine was 255 min.

* The 80% drug dissolution could not be achieved

- No dissolution profile

Table 8 Dissolution rate constant of nifedipine - various carrier systems

Carrier	Drug:Carrier Ratio	Dissolution rate (min^{-1})			
		Method			
		Physical	Melting	Solvent	Kneading
Nifedipine +	1:0	0.0492	0.0552	0.0287	0.0314
PEG4000	1:1	0.0858	0.0769	0.0855	0.0732
	1:3	0.0815	0.0987	0.0832	0.0546
	1:5	0.1110	0.1038	0.1070	0.0760
	1:10	0.1224	0.1165	0.1053	0.0988
PEG6000	1:1	0.0975	0.0794	0.0807	0.0638
	1:3	0.0921	0.1137	0.0877	0.0844
	1:5	0.1105	0.1152	0.1080	0.0878
	1:10	0.1258	0.1297	0.1188	0.0862
Poloxamer188	1:1	0.1213	0.0913	0.0966	0.0883
	1:3	0.2095	0.0903	0.0933	0.0991
	1:5	0.1754	0.1223	0.1006	0.1062
	1:10	0.1059	0.1483	0.1507	0.0910
Poloxamer288	1:1	0.0962	0.0979	0.1006	0.0921
	1:3	0.1022	0.1241	0.1001	0.0914
	1:5	0.1705	0.1169	0.0999	0.1116
	1:10	0.1996	0.1579	0.1314	0.1093
Poloxamer407	1:1	0.1203	0.0894	0.0949	0.0940
	1:3	0.1445	0.1000	0.0818	0.0899
	1:5	0.1455	0.1019	0.0866	0.1057
	1:10	0.1695	0.1531	0.1585	0.1071
BCD	1:1	-	-	0.0749	0.0503
	1:3	-	-	0.0955	0.0663
	1:5	-	-	0.1055	0.0926
	1:10	-	-	0.1038	0.1031
HPBCD	1:1	-	0.0669	0.0931	0.0635
	1:3	-	0.0767	0.0937	0.0688
	1:5	-	0.0793	0.0936	0.0795
	1:10	-	0.0967	0.1095	0.0865

+ The dissolution rate constant of nontreated nifedipine was 0.0524 min^{-1}.

- No dissolution profile

The results from dissolution profiles and dissolution rate constants revealed that poloxamers, in general, gave the fastest dissolution followed by PEGs and cyclodextrins respectively.

3.1 Dissolution studies of nontreated pure drug and treated pure drug

The dissolution profiles of pure drug treated by various methods revealed that nontreated nifedipine showed better dissolution profile than those of other carrier systems (**Figure 16, Table 8**). The reason was possibly the agglomeration of nifedipine particles in treated drug caused a lower specific surface area, hence, poorer dissolution profiles. This showed that the preparation process itself without incorporation with any carrier did not promote the dissolution of nifedipine, but also delayed dissolution .

3.2 Dissolution studies of nifedipine-PEG4000 solid dispersions

The maximum initial dissolution rate constant at 30 min was obtained at ratio 1:10 by melting method followed by 1:10 solvent method and 1:5 melting method , respectively. However these three values of dissolution rate constant were not statistically significant difference ($p>0.05$). The summary of two way analysis of variance is shown in **Appendix D.**

Comparing within the individual methods, the ratio of 1:10 mostly showed the highest dissolution rate constant whereas the ratio 1:1 usually gave the lowest rate. And among the same ratio, melting method was the most favorable preparation procedure for the system with PEG4000.

From the dissolution profiles (**Figure 17-21**), it was found that physical mixtures showed lower dissolution profile than nontreated pure nifedipine in every mixing ratio. Other methods, behaved differently, gave the better profiles than nontreated

pure nifedipine at every mixing ratio. Consistency with the dissolution rate constants, the ratio of 1:10 exhibited the best dissolution profiles.

3.3 Dissolution studies of nifedipine-PEG6000 solid dispersions

Similarly to the system of PEG4000, the solid dispersions of nifedipine-PEG6000 gave the highest dissolution rate constants at the ratio of 1:10 for solvent, melting and kneading methods respectively. All three values were not statistically different ($p>0.05$). It should be pointed out that for the maximum dissolution rate constants of nifedipine-PEG4000 was from the melting method whereas for the nifedipine-PEG6000 the maximum rate was from the solvent method at the same ratio of 1:10 **(Figure 21-24).**

The solid dispersions of nifedipine-PEG4000 and nifedipine-PEG6000 had the dissolution profile in common. From the dissolution profiles, the ratio 1:10 in all methods gave the highest dissolution rate constant except kneading method. For the kneading method, the ratio of 1:5 gave the best profile because it gave the higher percent dissolved than that of the ratio of 1:10 after 200 minutes. In the physical mixtures, it was found that the profile of ratio 1:3 was higher than the profile of nontreated pure nifedipine whereas the other ratios showed poor dissolution profiles. However these poor profiles still showed that nifedipine dissolved rapidly in the initial period of dissolution profiles.

3.4 Dissolution studies of nifedipine-poloxamer188 solid dispersions

In poloxamer188 system (**Figure 25-28**), the ratio of 1:3 by melting method gave the highest dissolution rate constant among all treatments of poloxamer188 and all carriers. The following descending ranks were the ratios and methods of 1:5 melting, 1:10 kneading, and 1:10 solvent respectively. The ratio of 1:10 solvent method, kneading 1:10 and melting method at the ratio of 1:5 were not statistically different ($p>0.05$) but all were significantly different from 1:3 melting method ($p<0.05$) (**Figure 27**).

From the dissolution profile point of view, the ratio of 1:10 solid dispersion prepared by every method showed good profile and superior to physical mixtures (**Figure 27**). For the melting method, the profile of 1:3, 1:5 and 1:10 seemed to superimposed on one another. For the physical mixtures, the best profile was found at the ratio of 1:5, which other ratios initially higher than nontreated pure nifedipine but showed lower percent dissolved when they reached equilibrium.

3.5 Dissolution studies of nifedipine-poloxamer288 solid dispersions

From two way ANOVA, it revealed that melting 1:10 gave the highest dissolution rate constant at 30 min followed by melting 1:5, solvent 1:10 and kneading 1:10 respectively. Melting method 1:10 was not significantly different from melting 1:5 ($p>0.05$) whereas different from solvent 1:10 and kneading 1:10 ($p<0.05$). And solvent 1:10 ratio was not significantly different from kneading 1:10 ($p>0.05$). The results were shown in **Table 8 and Appendix D**. These showed that the melting method was superior to the solvent and kneading method.

The dissolution profiles shown in **Figure 29-32** of physical mixture depicted that all ratios of them were close to one another but a little higher than nontreated pure nifedipine. The kneading method, 1:10 ratio was obviously higher than the group of other ratios and nontreated drug. In solvent method, all ratios gave superimposed profiles except 1:1 ratio which was close to nontreated drug. Focused on the melting method, the higher mixing ratios of 1:10 and 1:5 ratio were superior to that of 1:3, 1:1 and nontreated pure nifedipine.

3.6 Dissolution studies of nifedipine-poloxamer407 solid dispersions

The highest dissolution rate constant was found in 1:10 ratio by melting method followed by 1:10 ratio of kneading method, 1:10 of solvent and 1:5 ratio by melting method, respectively (**Table 8 and Appendix D**). All of those mentioned above were not statistically different ($p>0.05$).

From the dissolution profiles (**Figures 33-36**), physical mixtures were not different in each ratio and initially higher than nontreated pure nifedipine. The profile of melting method, 1:10, 1:5 and kneading method 1:10 were close to one another and obviously higher than melting method 1:3 and nontreated pure nifedipine. In solvent method, 1:10 and 1:5 ratio were superimposed but higher than group of other ratios and nontreated pure nifedipine. For kneading method, 1:10 ratio showed the highest dissolution in the initial dissolution profile followed by 1:3 ratio. The ratio of 1:1 and 1:5 were almost superimposed, and higher than nontreated pure nifedipine.

3.7 Dissolution studies of nifedipine- β-cyclodextrin solid dispersion

From two way ANOVA, it showed that interaction between method and ratio was not statistically different ($p>0.05$), but the difference was found within group of ratios and methods ($p<0.05$).

In testing the difference among methods, it was found that physical mixture was significantly different from kneading method. Similarly, among the ratio testing when methods were negligible, it showed that the 1:5 ratio was not significantly different from 1:10 ratio but the rest of them were significantly different. The best dissolution rate constant was from the kneading method 1:5 ratio followed by 1:10 and 1:3 ratio, respectively.

From dissolution profile, **Figure 37-38**, all ratios of physical mixtures seemed to be lower than nontreated nifedipine, except the 1:10 ratio that was initially higher than others. The dissolution profiles of kneading method were close to one another and a little higher than nontreated pure nifedipine. However 1:10 ratio was superior to others.

3.8 Dissolution studies of nifedipine-2-hydroxypropyl-β-cyclodextrin solid dispersion

From two way ANOVA, only within group of ratios and group of methods were significantly different ($p<0.05$). Within method testing, the kneading method gave significant different rate constant from solvent method and physical mixture ($p<0.05$). The testing within ratios, the 1:1, 1:3 1:1 were not significantly different ($p>0.05$), but all were significantly different from the ratio 1:10 ($p<0.05$).

The best dissolution rate constant in the group of 2-hydroxypropyl-β-cyclodextrin was the ratio 1:10 of kneading method followed by the 1:10 ratio of solvent method and the 1:3 or 1:5 ratio of kneading method.

The dissolution profiles of physical mixture were the same as β-cyclodextrin physical mixtures that all ratios were so closely and almost superimposed to nontreated nifedipine except 1:1 ratio that seems to be the lowest profile **(Figures 39-41).**

In solvent method, the 1:10 ratio was obviously higher than other ratios and nontreated pure nifedipine. All ratios of kneading method were closely to one another but 1:10 seemed to be the highest and all of them were a little higher than nontreated nifedipine.

3.9 The time of 80% dissolution

The time for 80% nifedipine dissolved ($T_{80\%}$) was chosen to be an additional comparative parameter other than initial dissolution rate constant. The USP XXIII states not less than 80% of the labeled amount of nifedipine dissolved in 20 min.

As shown in **Table 7**, the time at 80% of nifedipine dissolved, obtained from the dissolution profiles (**Figure 16-41**) were presented. The $T_{80\%}$ of all systems varied from the shortest time at 15 min to as high as 1185 min. Certain systems, e.g. 1:3, 1:5, and 1:10 PEG physical mixtures, 1:10 PEG6000 physical mixture could not reach the 80% level of dissolution despite of their plateau levels.

It was interesting that solid dispersions prepared by melting method of poloxamer188 and poloxamer407 gave the shortest $T_{80\%}$ at the ratio of 1:3, 1:5 and 1:10. Moreover, poloxamer407 solid dispersions prepared by all methods, that were melting, solvent and kneading methods at the ratio of 1:10, gave the shortest $T_{80\%}$ as 15 min.

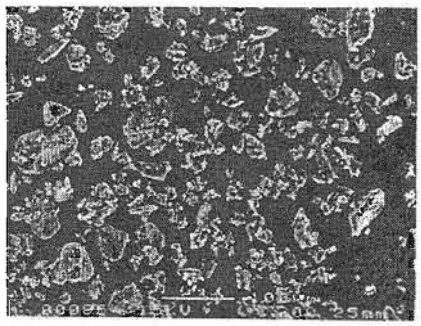
4. Scanning electron micrograph (SEM)

Scanning electron micrographs of nifedipine solid dispersions prepared by various methods and ratios are illustrated in **Figure 42-72** with different magnification factors, x100 or x200 for the low level and x800 for the high level.

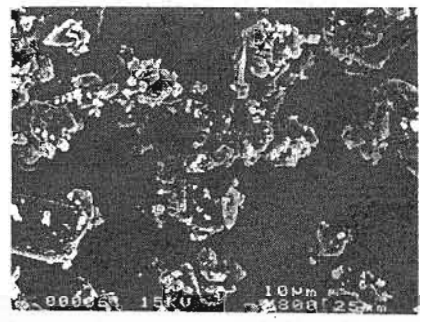
4.1 SEM of pure drug and non treated pure drug

The nontreated nifedipine had smooth surface crystals. Crystalline characteristics of the compound were clearly noticed under the microscope. The treated drug with melting and solvent methods were very similar in term of the roughness of the surfaces except more porous surface was found in the pure drug treated with solvent method. A slightly smooth surface was found in the drug prepared by kneading and physical mixing methods **(Figures 42-43).**

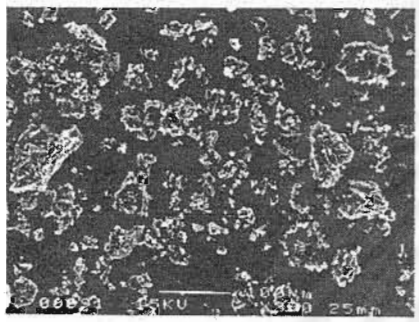
From the comparison of crystal size of nifedipine and the carriers, it was clearly seen that the size of nifedipine particles in the solid dispersion were smaller than carrier particles. This has an advantage in differentiation of drug from carriers once they present in the solid dispersion pattern.



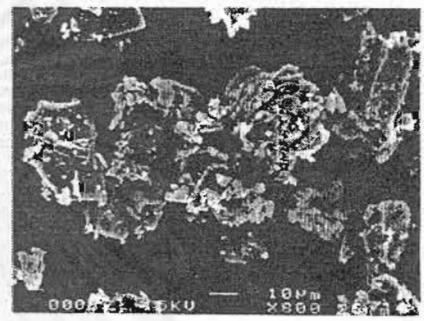
A.



B.



C.



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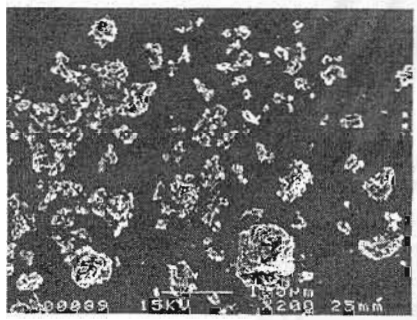

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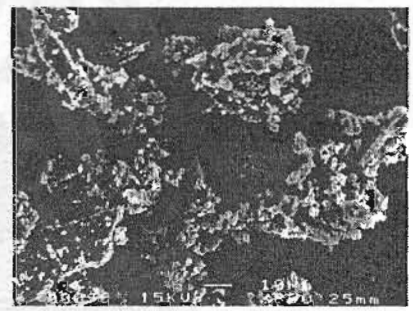


F.

Figure 42 Photomicrographs of nifedine nontreated and treated with various methods.

A and B: Non treated, A. x200, B. x800

C and D: Treated by solvent method, C. x200, D. x800

E and F: Treated by melting method, E. x200, F. x800

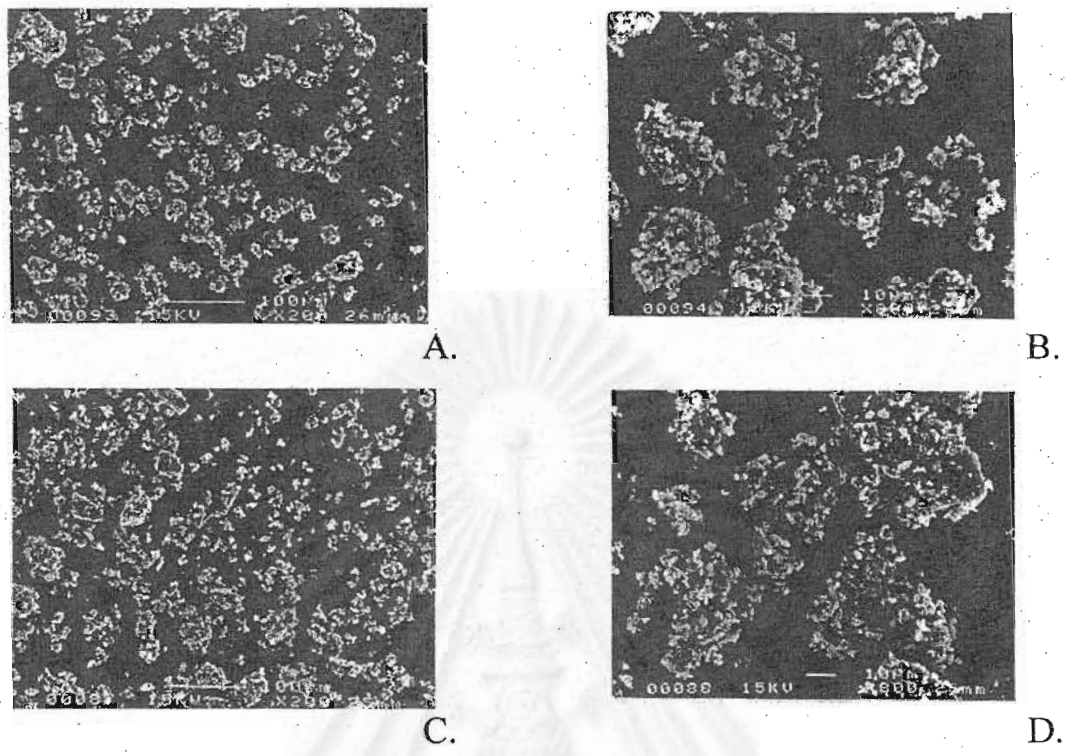


Figure 43 Photomicrographs of nifedipine treated with various methods.

A and B: Treated by kneading method, A. x200, B. x800

C and D: Treated by physical mixing C. x200, D. x800

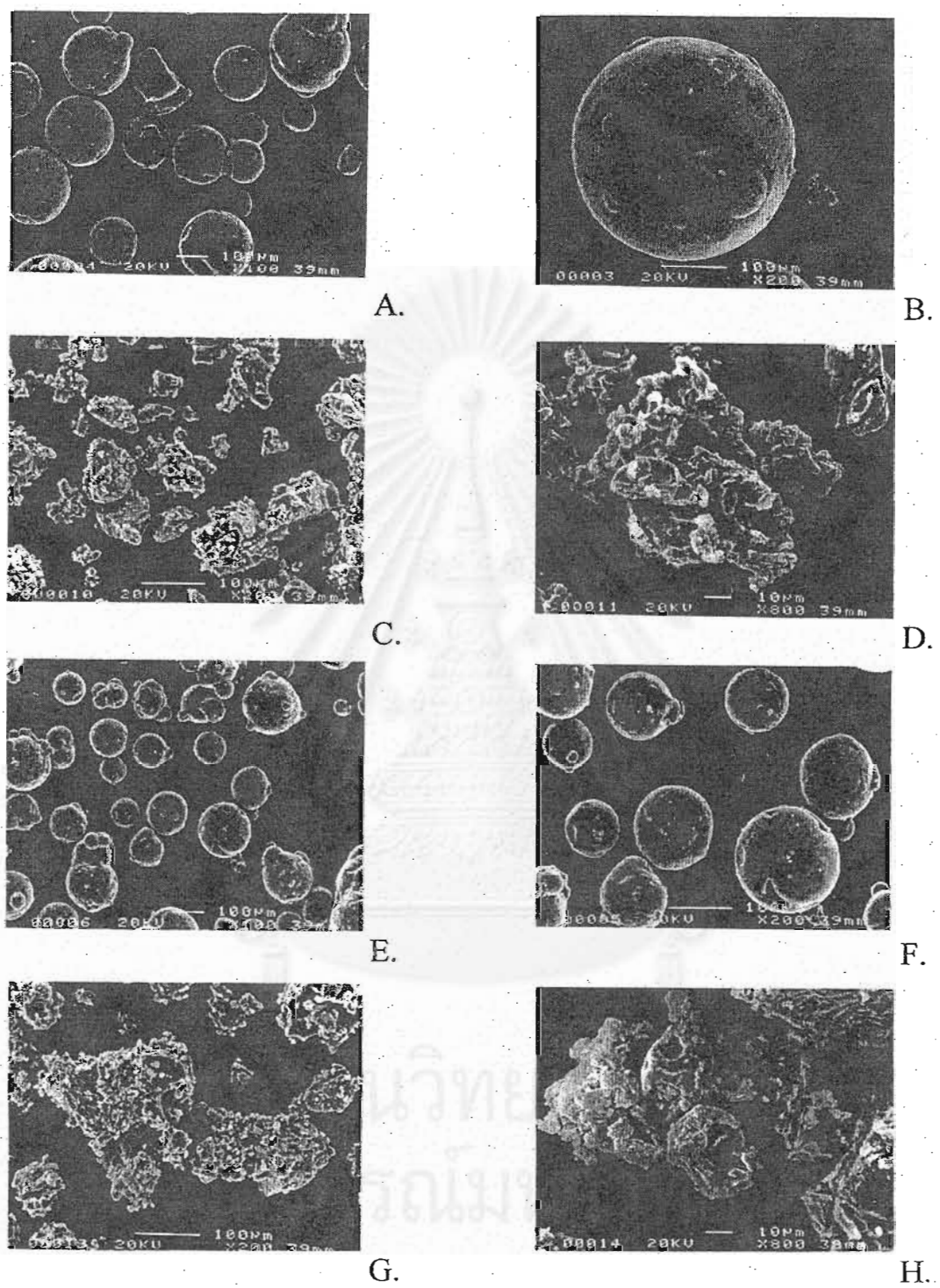


Figure 44 Photomicrographs of pure PEG4000 and PEG6000.

A and B: PEG4000 non pulverized and sieved, A. x100, B. x200

C and D: PEG4000 pulverized and sieved, C. x200, D. x800

E and F: PEG6000 non pulverized and sieved, E. x100, F. x200

G and H: PEG6000 pulverized and sieved, G. x200, H. x800

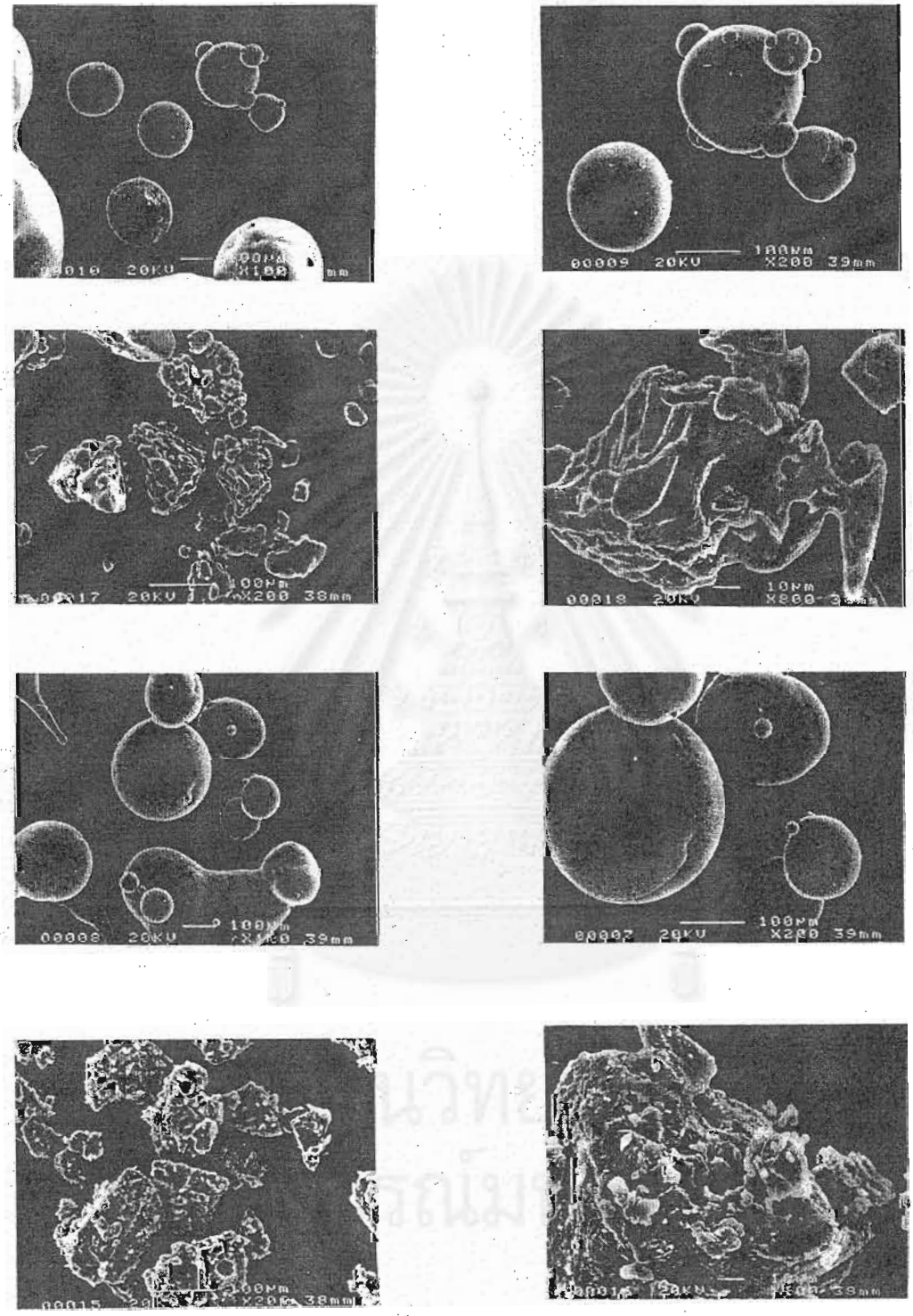


Figure 45 Photomicrographs of pure poloxamer 188 and poloxamer 407.
A and B: poloxamer 188 non pulverized and sieved, A. x100, B. x200
C and D: poloxamer 188 pulverized and sieved, C. x200, D. x800
E and F: poloxamer 407 non pulverized and sieved, E. x100, F. x200
G and H: poloxamer 407 pulverized and sieved, G. x200, H. x800

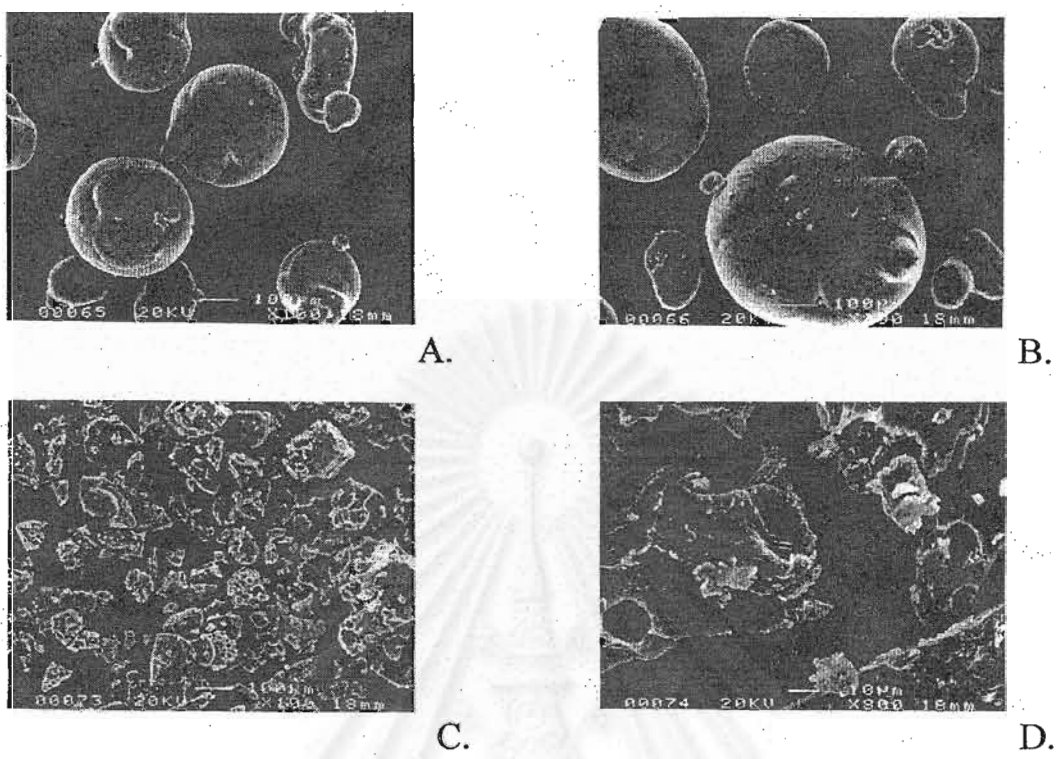
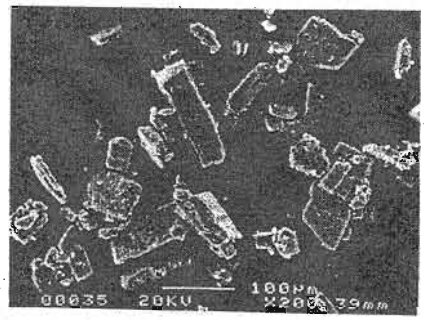


Figure 46 Photomicrographs of pure pluronic F98.

A and B: pluronic F98 non pulverized and sieved, A. x100, B. x200

C and D: pluronic F98 pulverized and sieved, C. x200, D. x800



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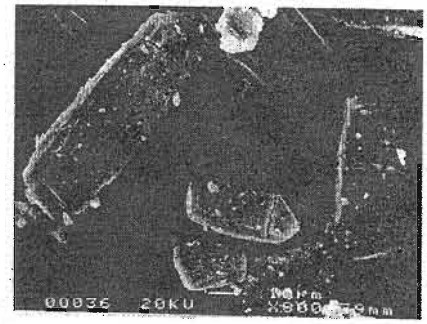

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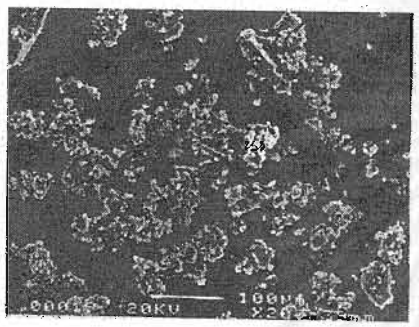

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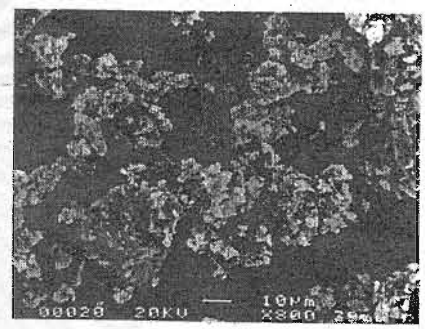

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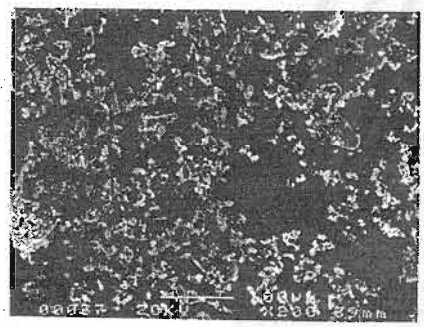

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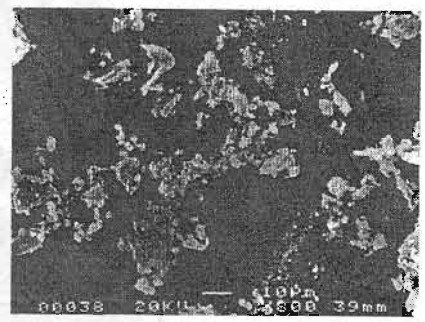

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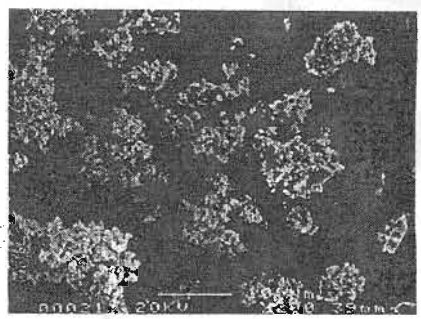

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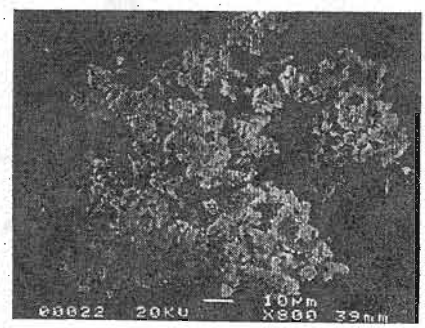


H.

Figure 47 Photomicrographs of β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin.

A and B: β-cyclodextrin non pulverized and sieved, A. x200, B. x800

C and D: β-cyclodextrin pulverized and sieved, C. x200, D. x800

E and F: 2-hydroxypropyl-β-cyclodextrin non pulverized and sieved, E. x200, F. x800

G and H: 2-hydroxypropyl-β-cyclodextrin pulverized and sieved, G. x200, H. x800

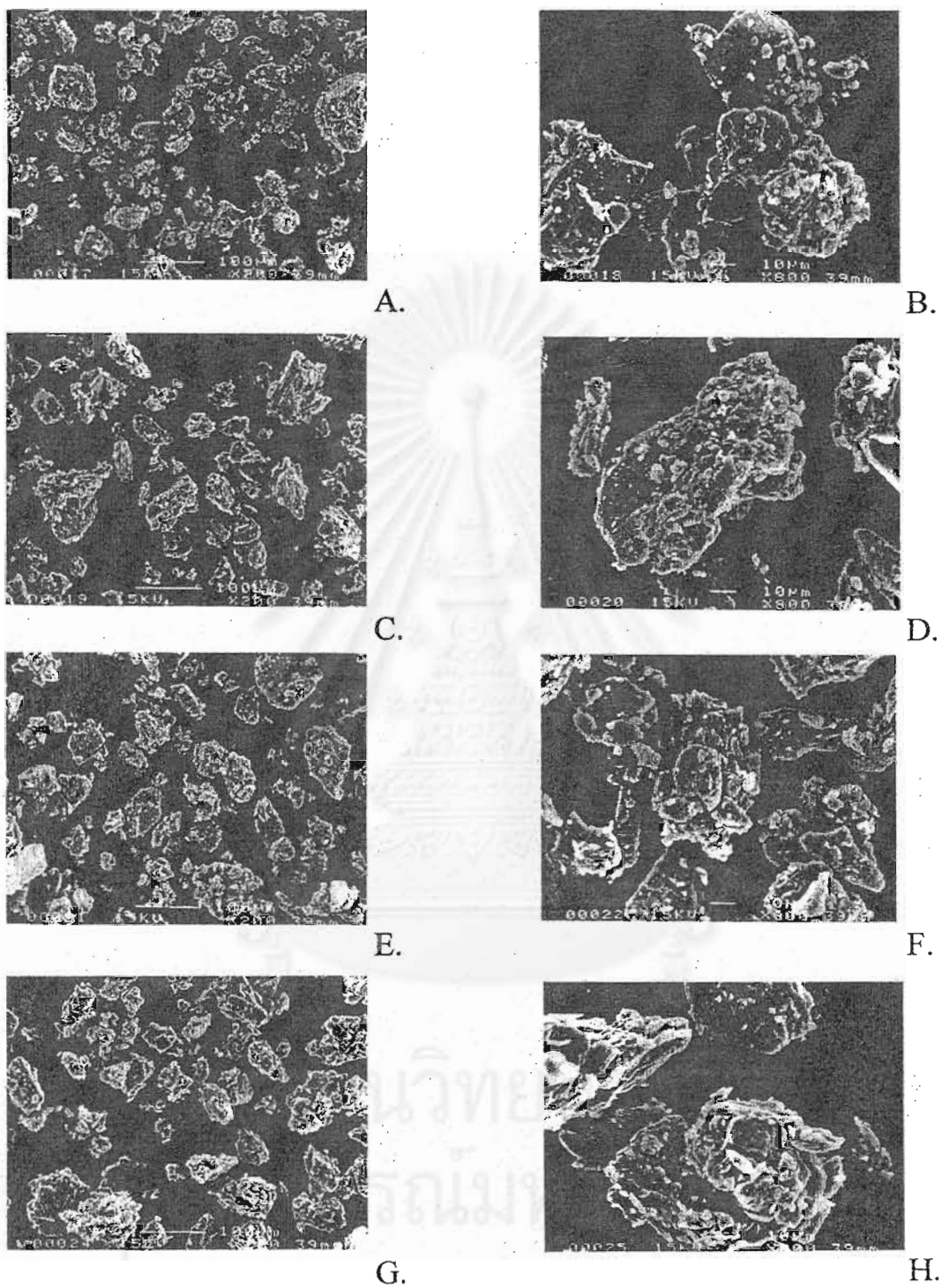


Figure 48 Photomicrographs of nifedine-PEG4000, physical mixture

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

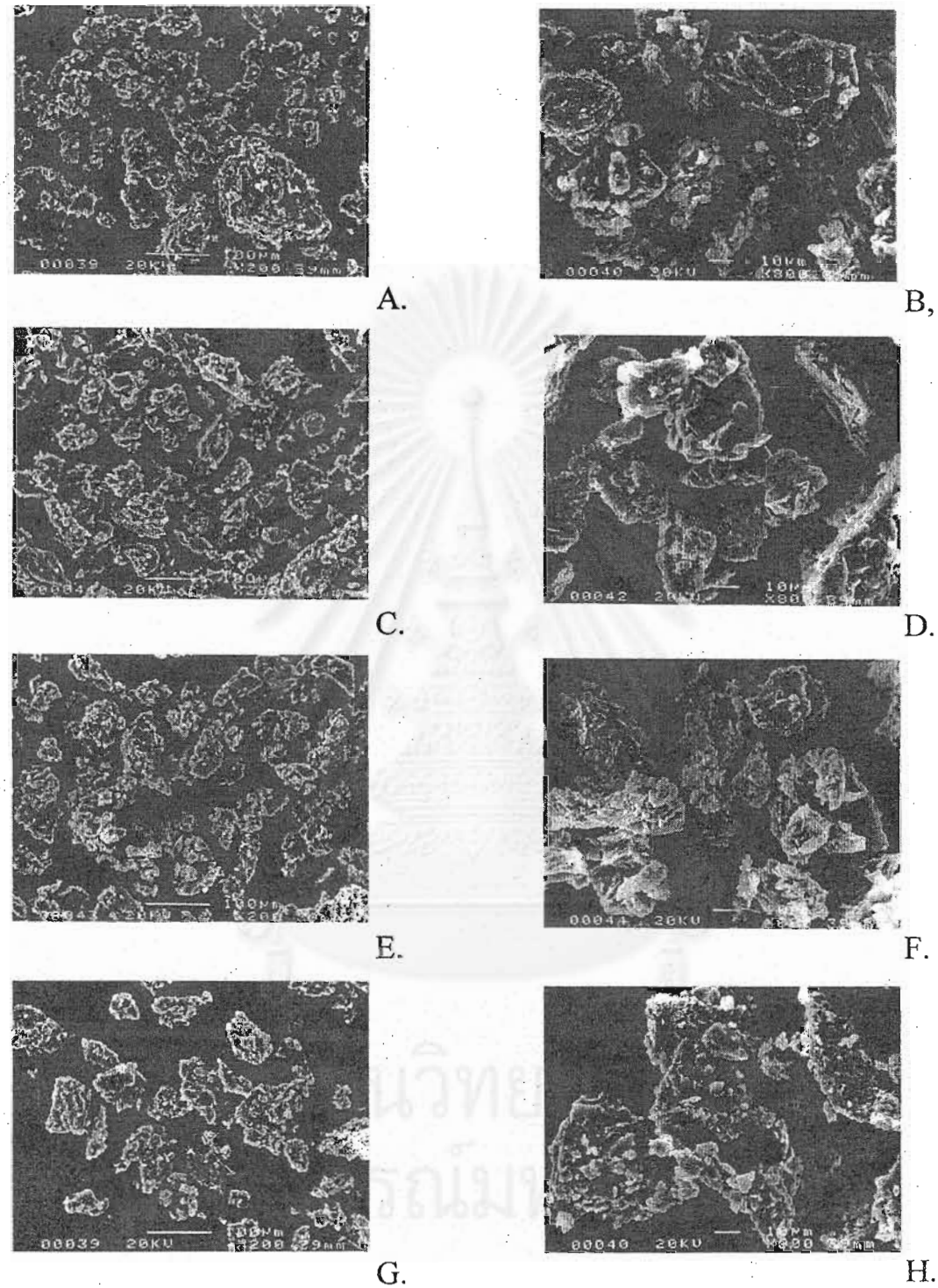


Figure 49 Photomicrographs of nifedine-PEG4000, melting method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

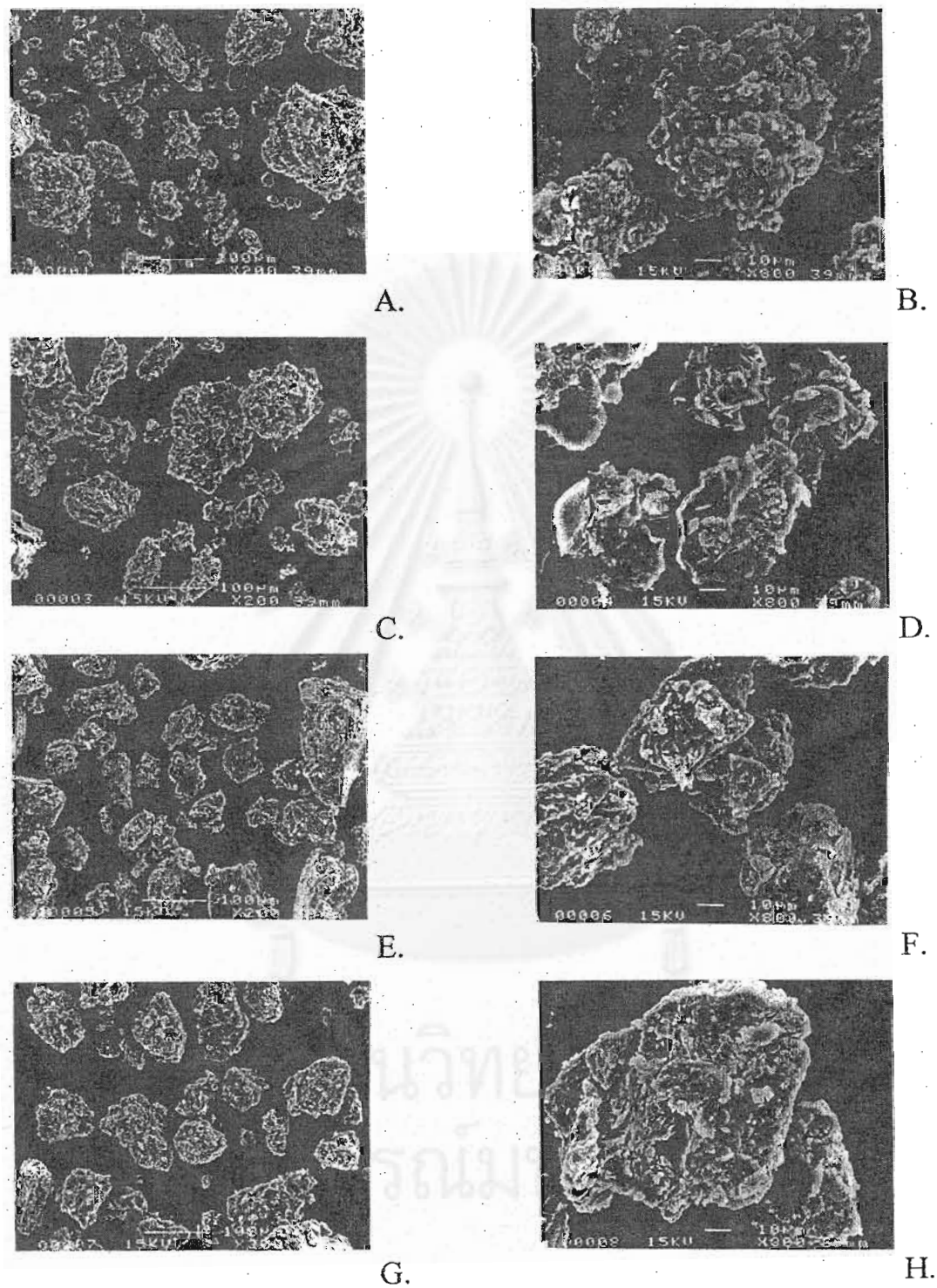


Figure 50 Photomicrographs of nifedine-PEG4000, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

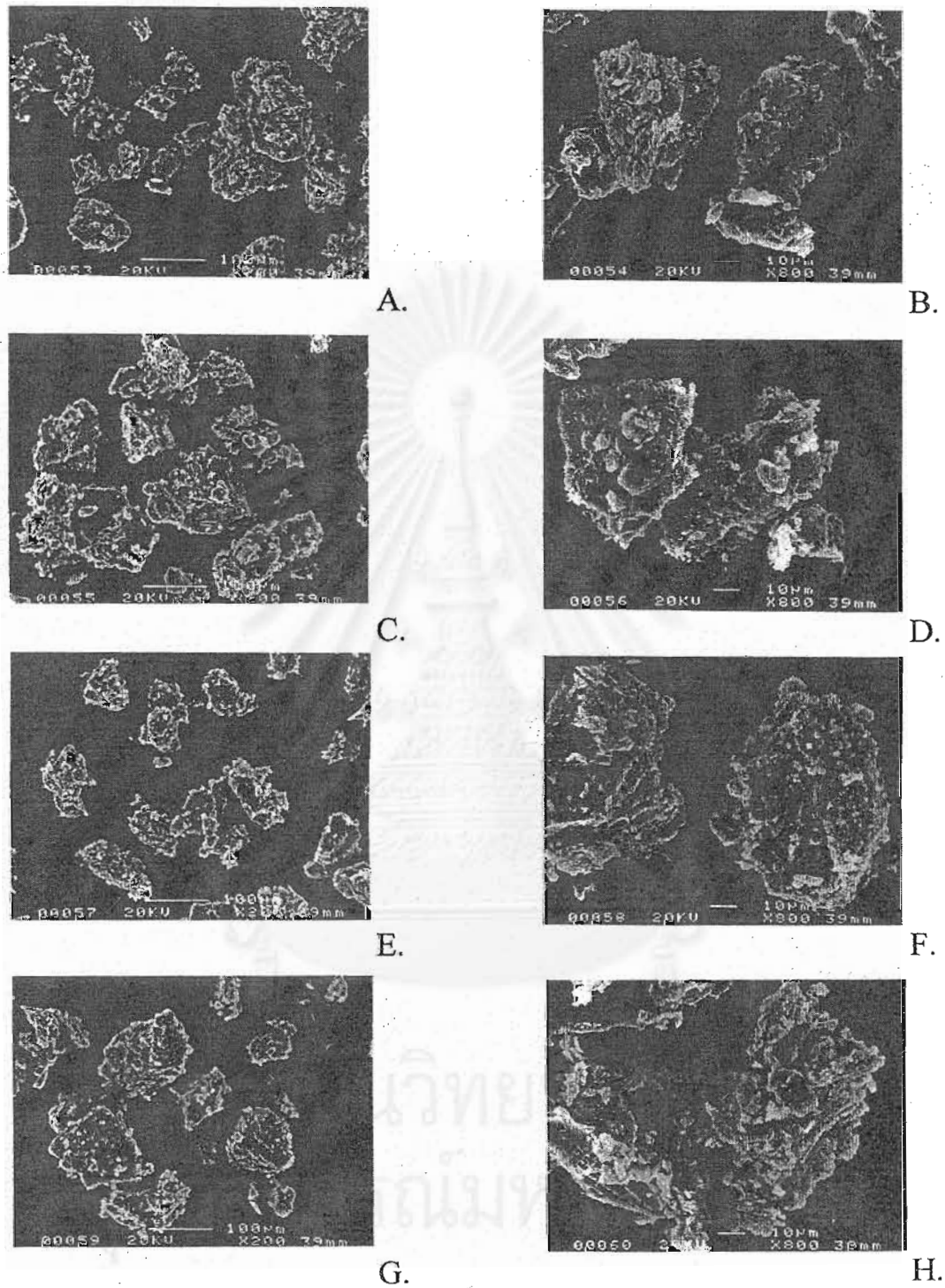


Figure 51 Photomicrographs of nifedine-PEG4000, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

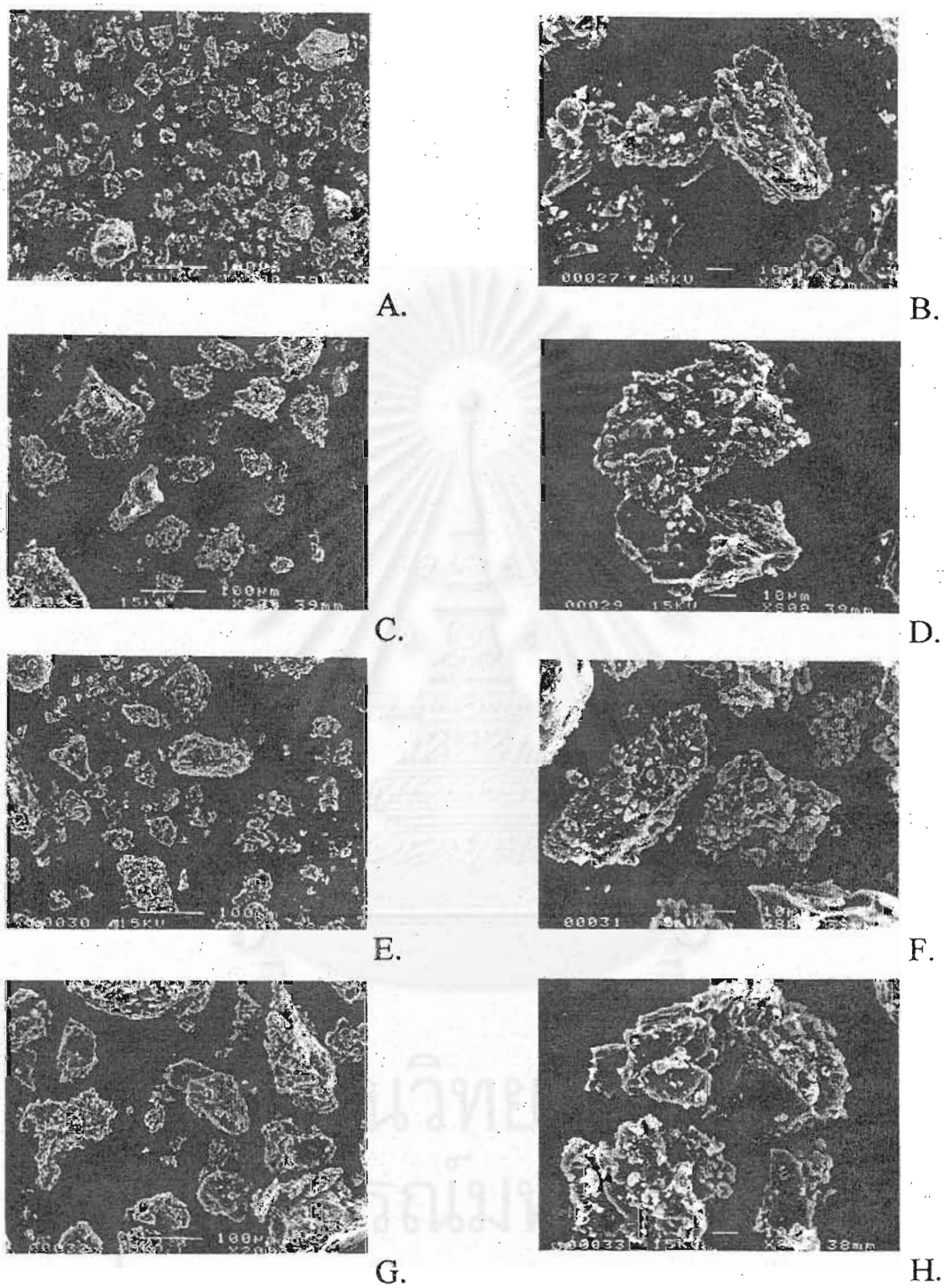


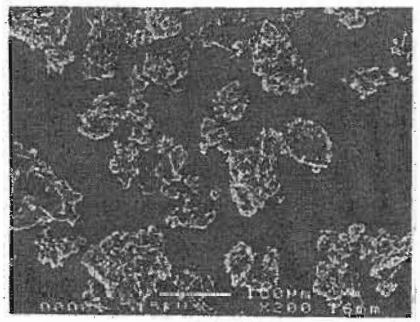
Figure 52 Photomicrographs of nifedine-PEG6000, physical mixture.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

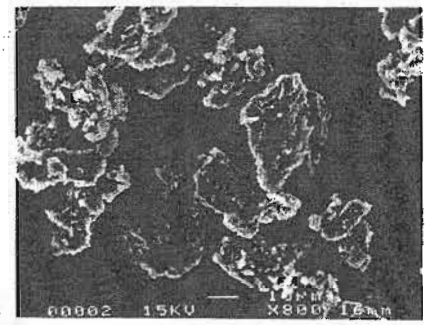
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



A.



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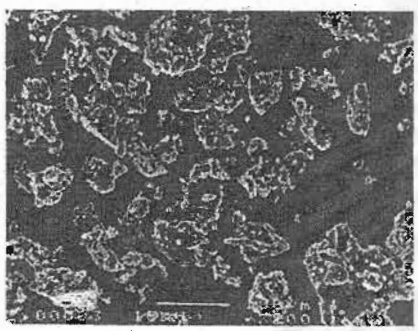

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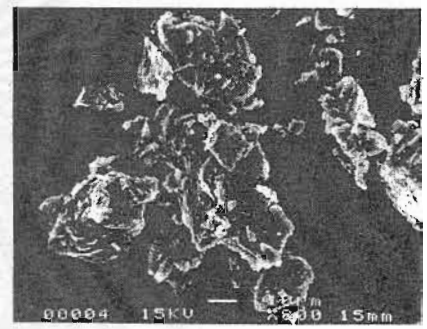
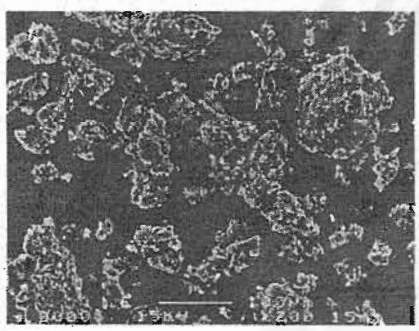
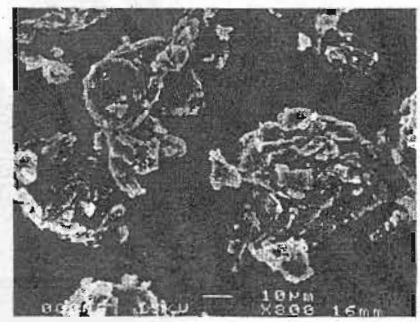


D.



E.



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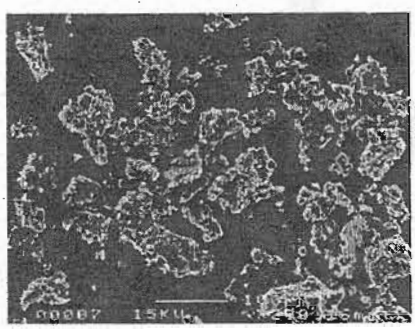
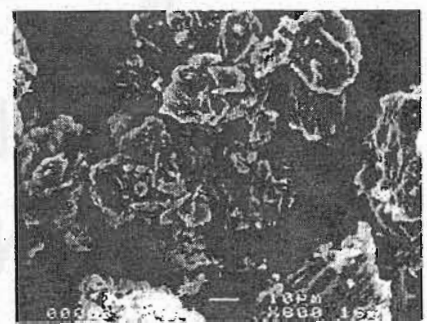


G.



H.

Figure 53 Photomicrographs of nifedine-PEG6000, melting method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

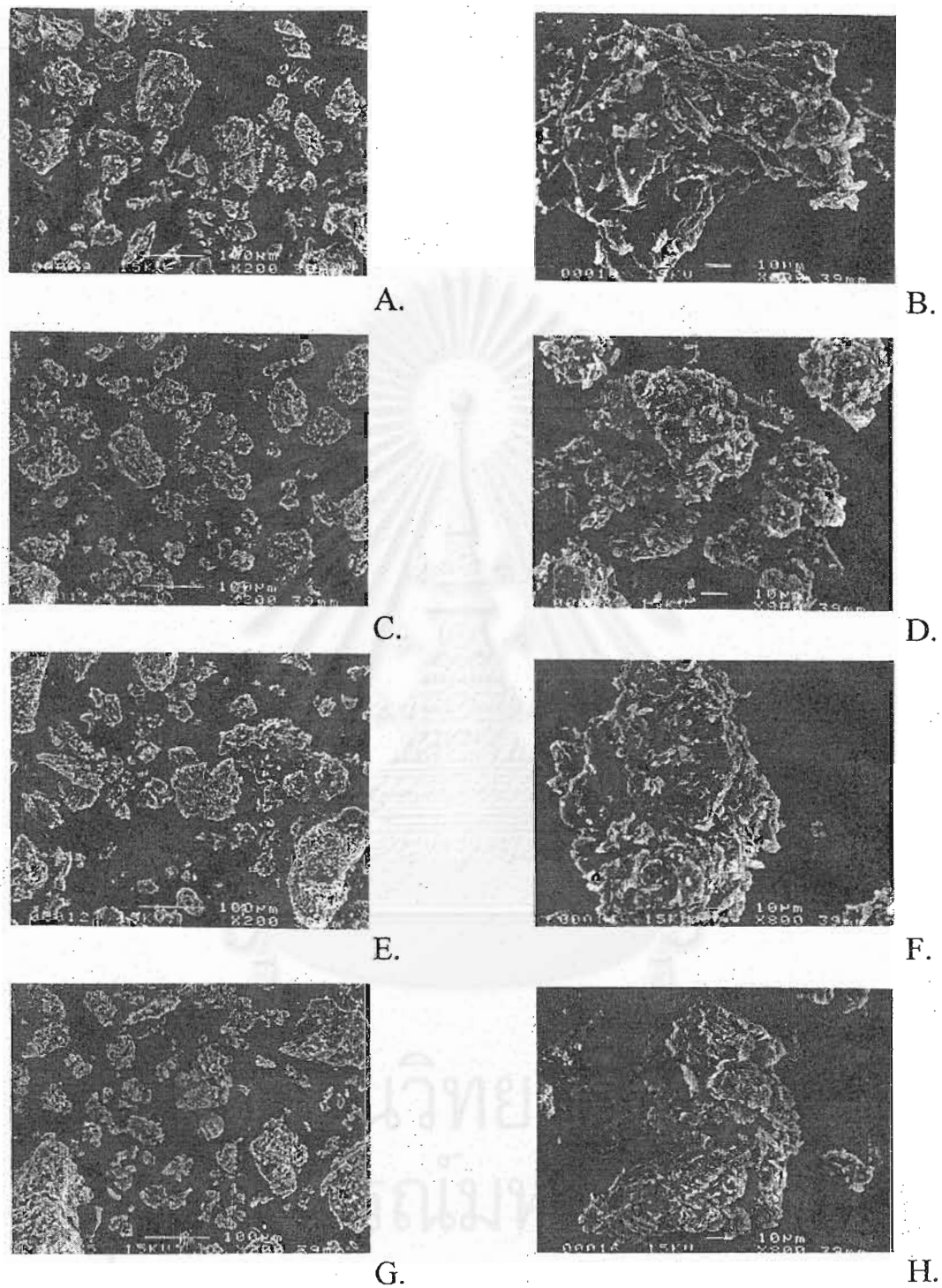


Figure 54 Photomicrographs of nifedine-PEG6000, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

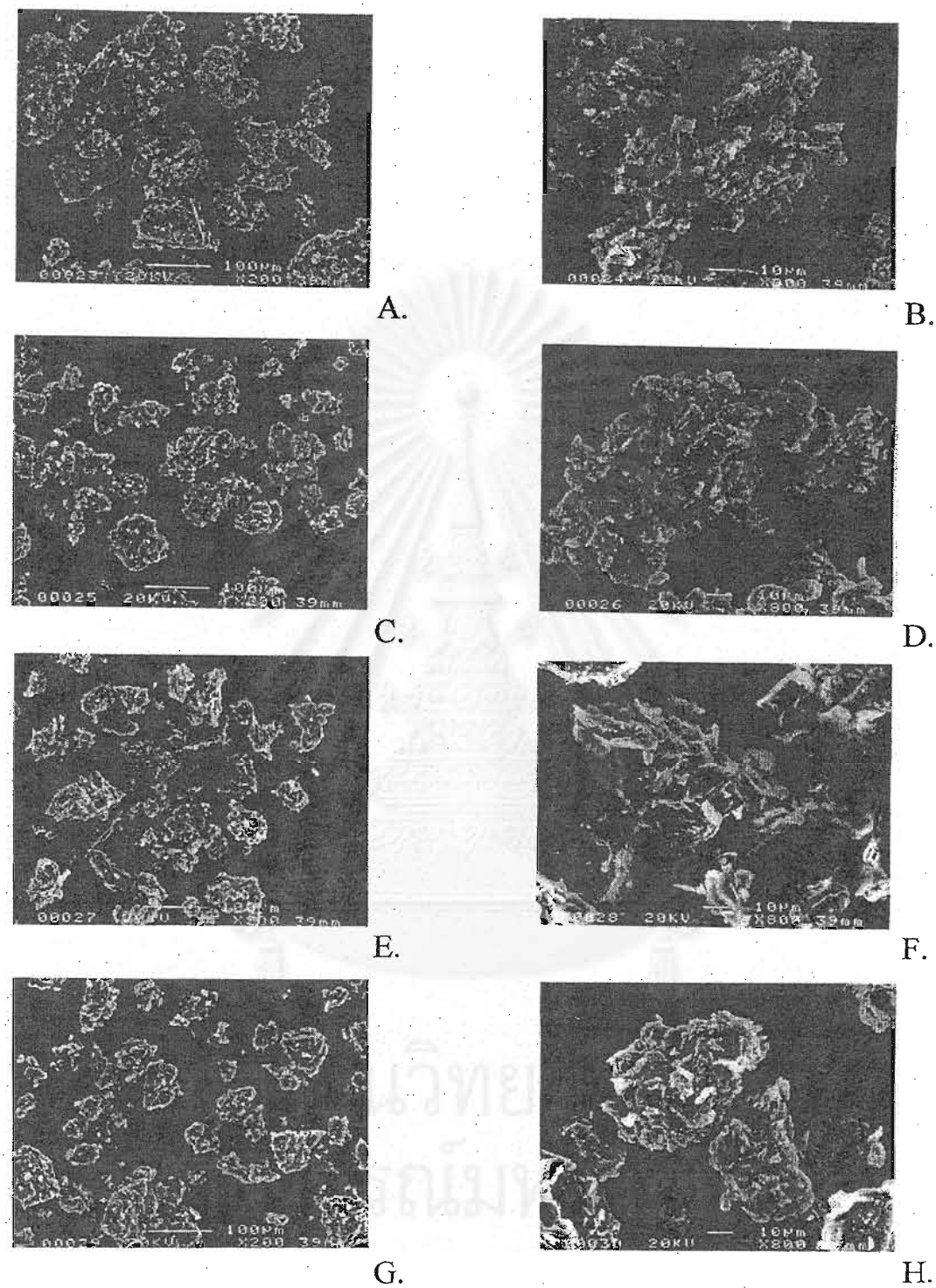


Figure 55 Photomicrographs of nifedine-PEG6000, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

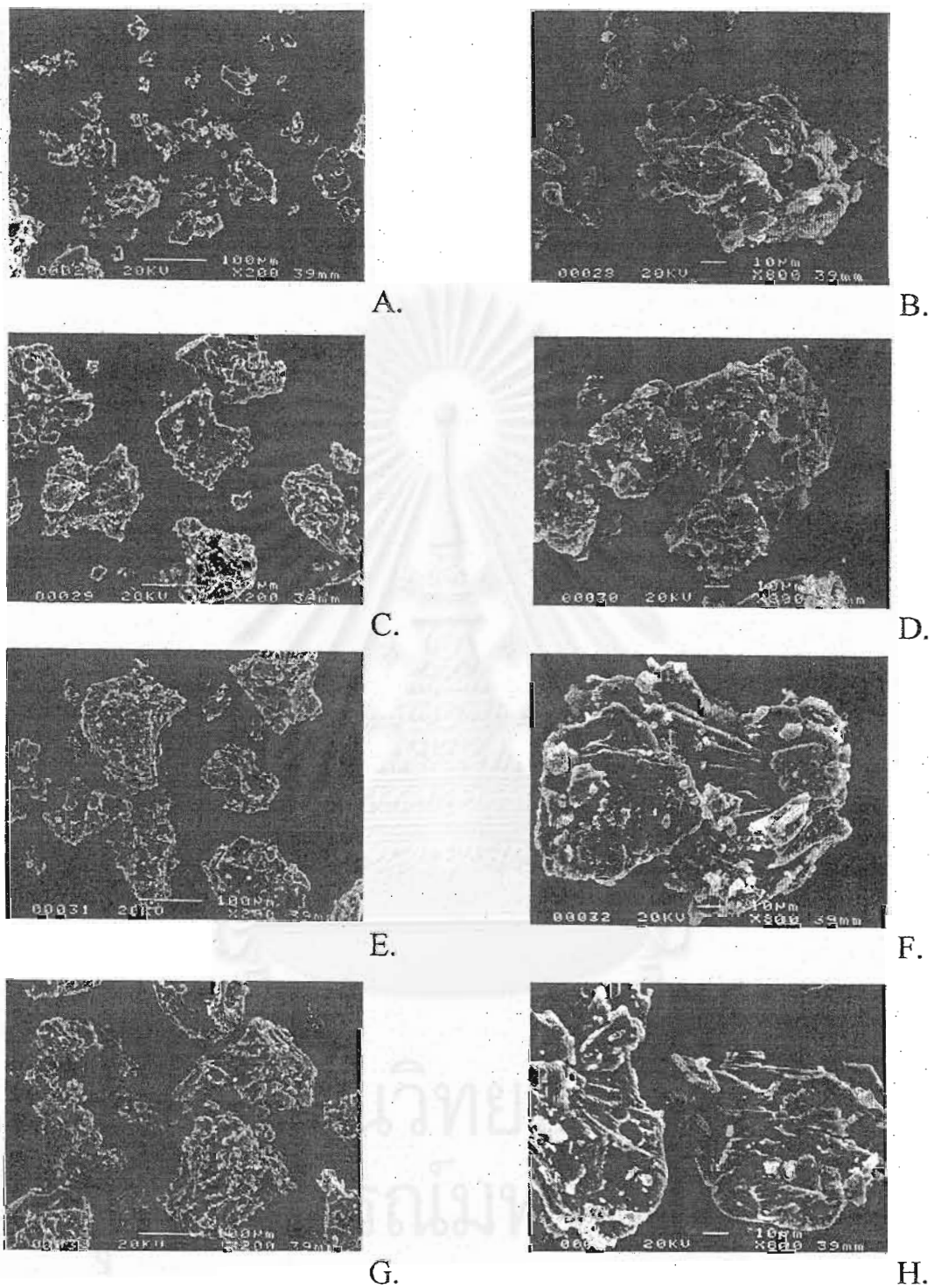


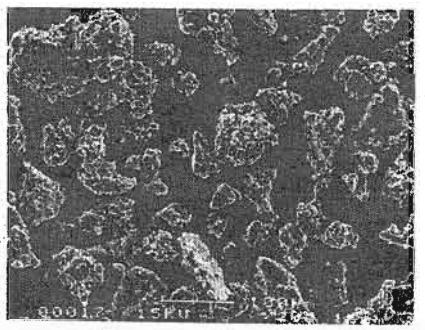
Figure 56 Photomicrographs of nifedine-poloxamer 188, physical mixture

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

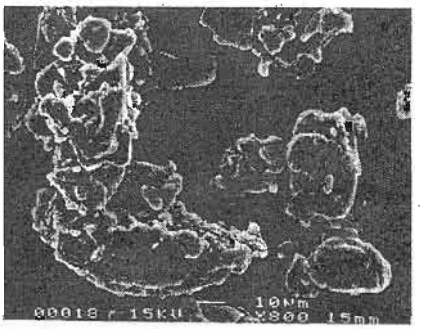
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



A.



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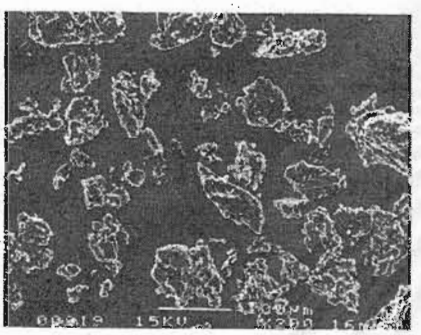
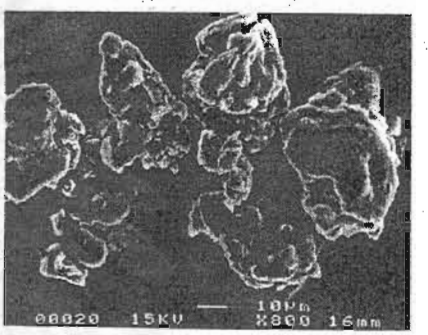
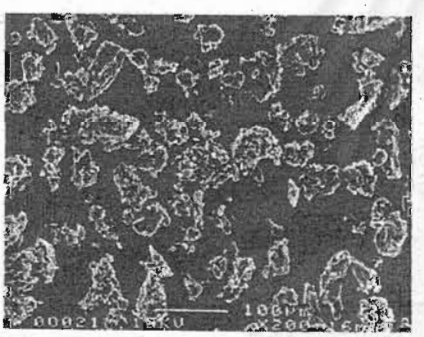


C.



D.



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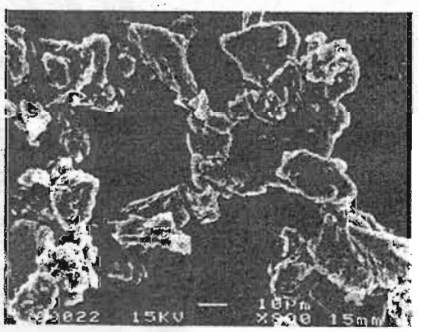
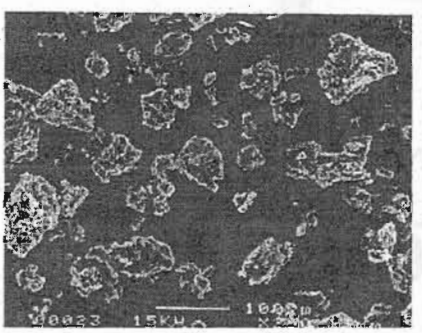
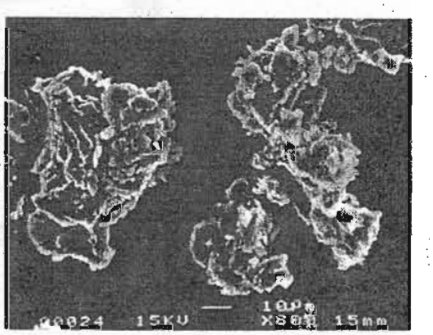


F.



G.



H.

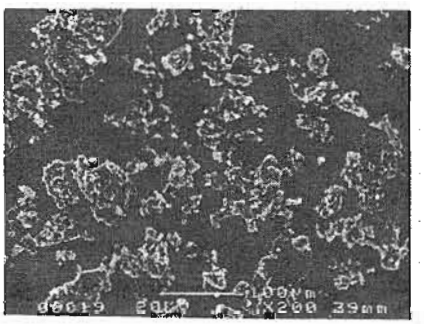
Figure 57 Photomicrographs of nifedine-poloxamer 188, melt method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

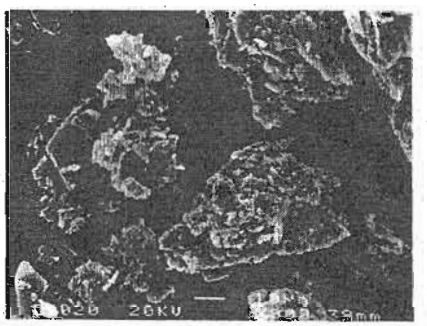
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

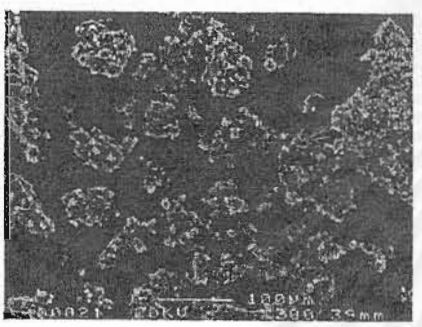
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



A.



B.



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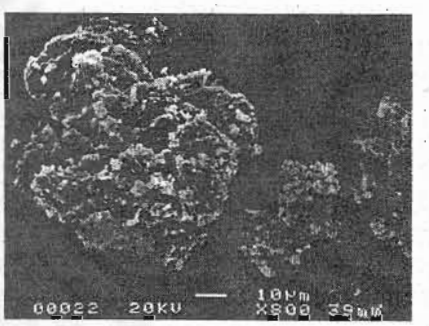
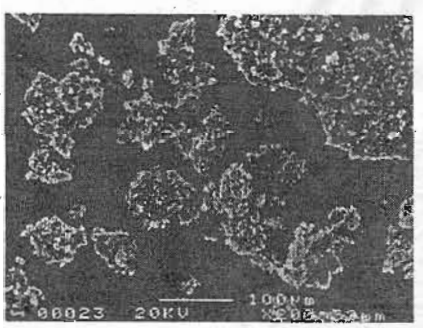


D.



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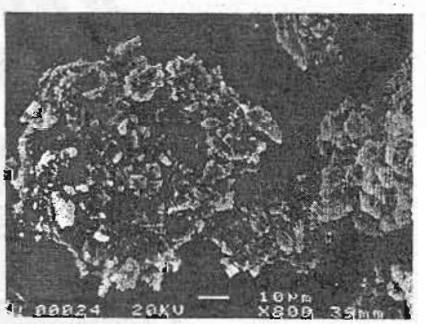
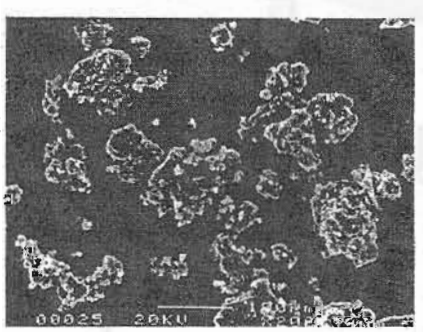
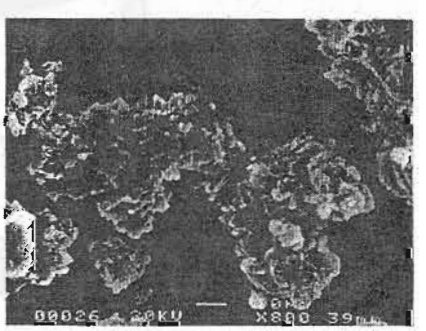


F.



G.



H.

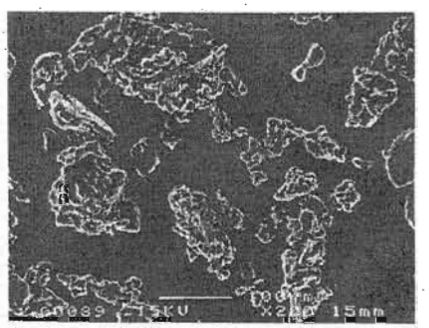
Figure 58 Photomicrographs of nifedine-poloxamer 188, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

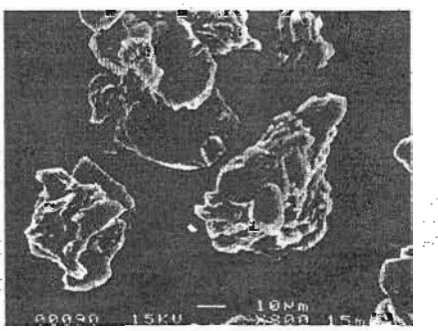
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



A.



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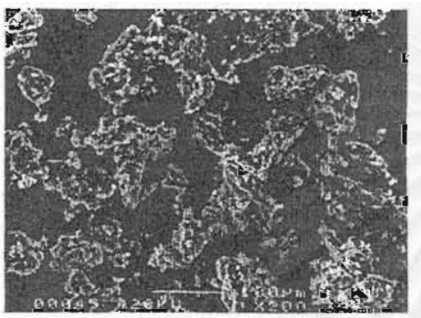
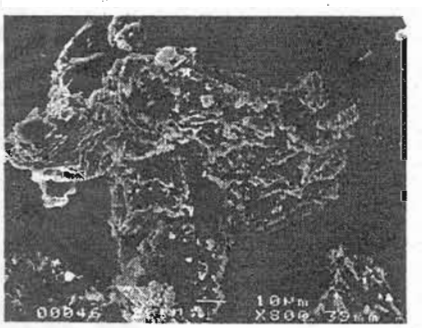
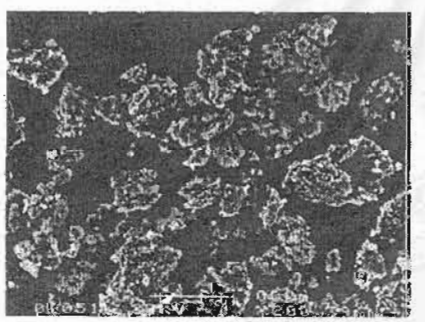


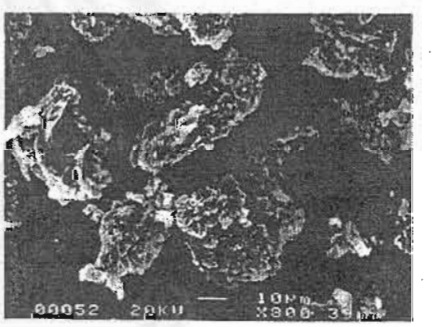
C.



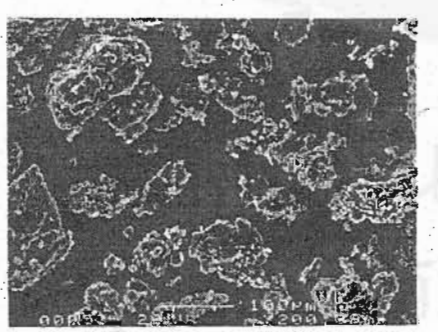
D.



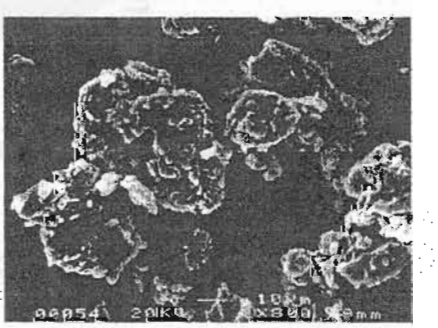
E.



F.



G.



H.

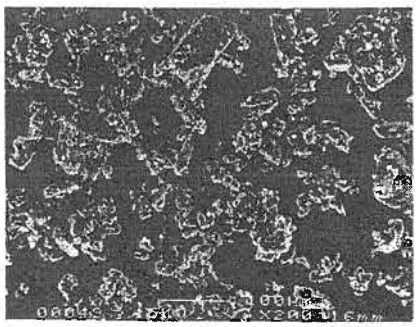
Figure 59 Photomicrographs of nifedine-poloxamer 188, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

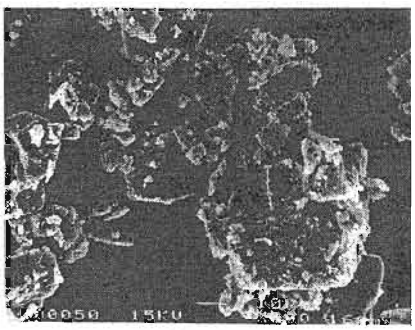
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

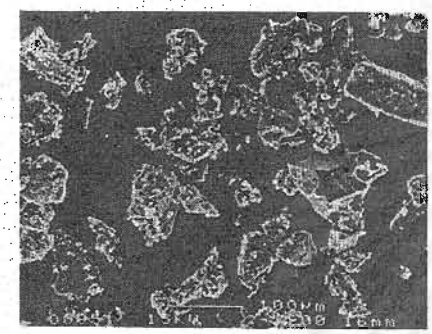
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



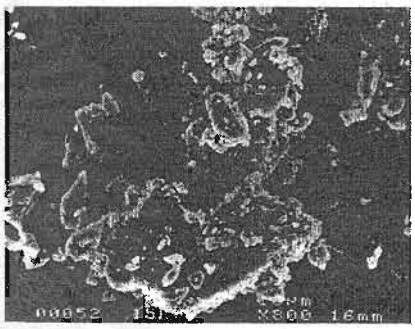
A.



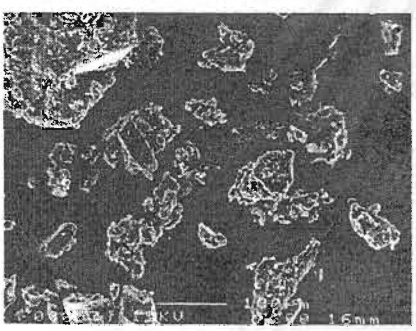
B.



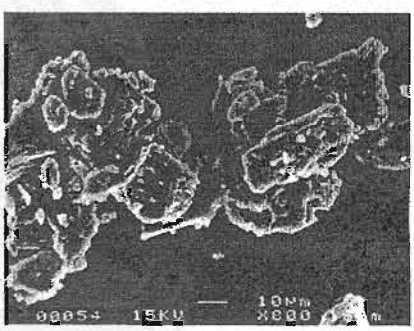
C.



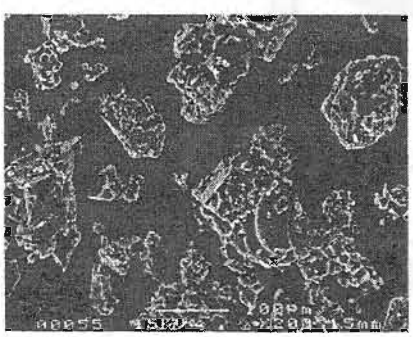
D.



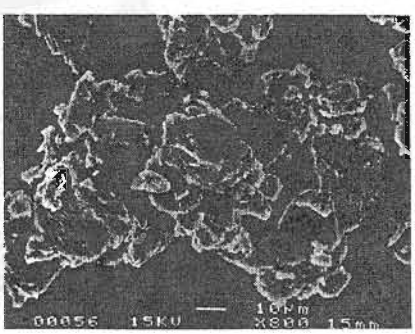
E.



F.



G.



H.

Figure 60 Photomicrographs of nifedipine-poloxamer288, physical mixture

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

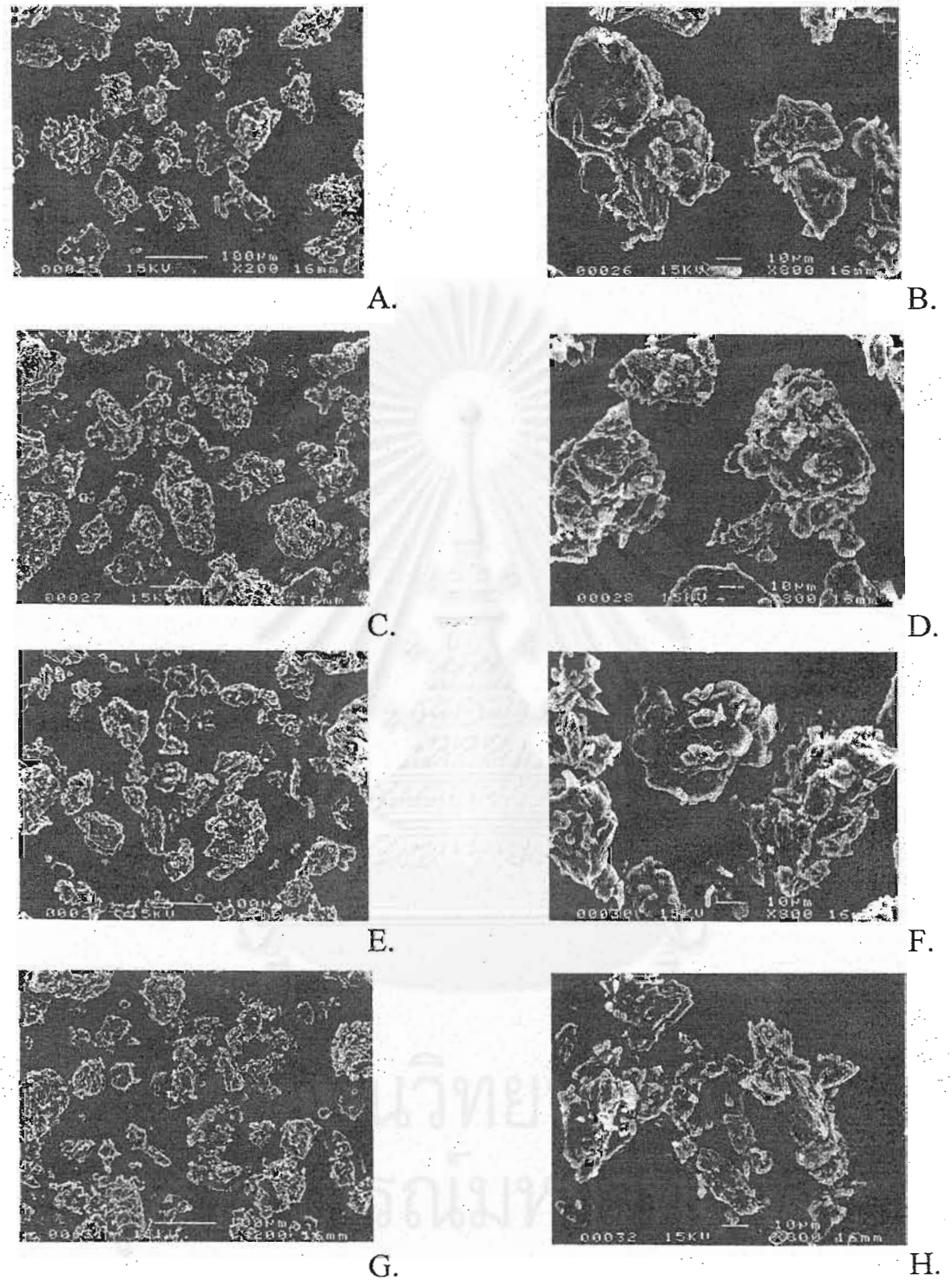


Figure 61 Photomicrographs of nifedipine-poloxamer288, melting method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

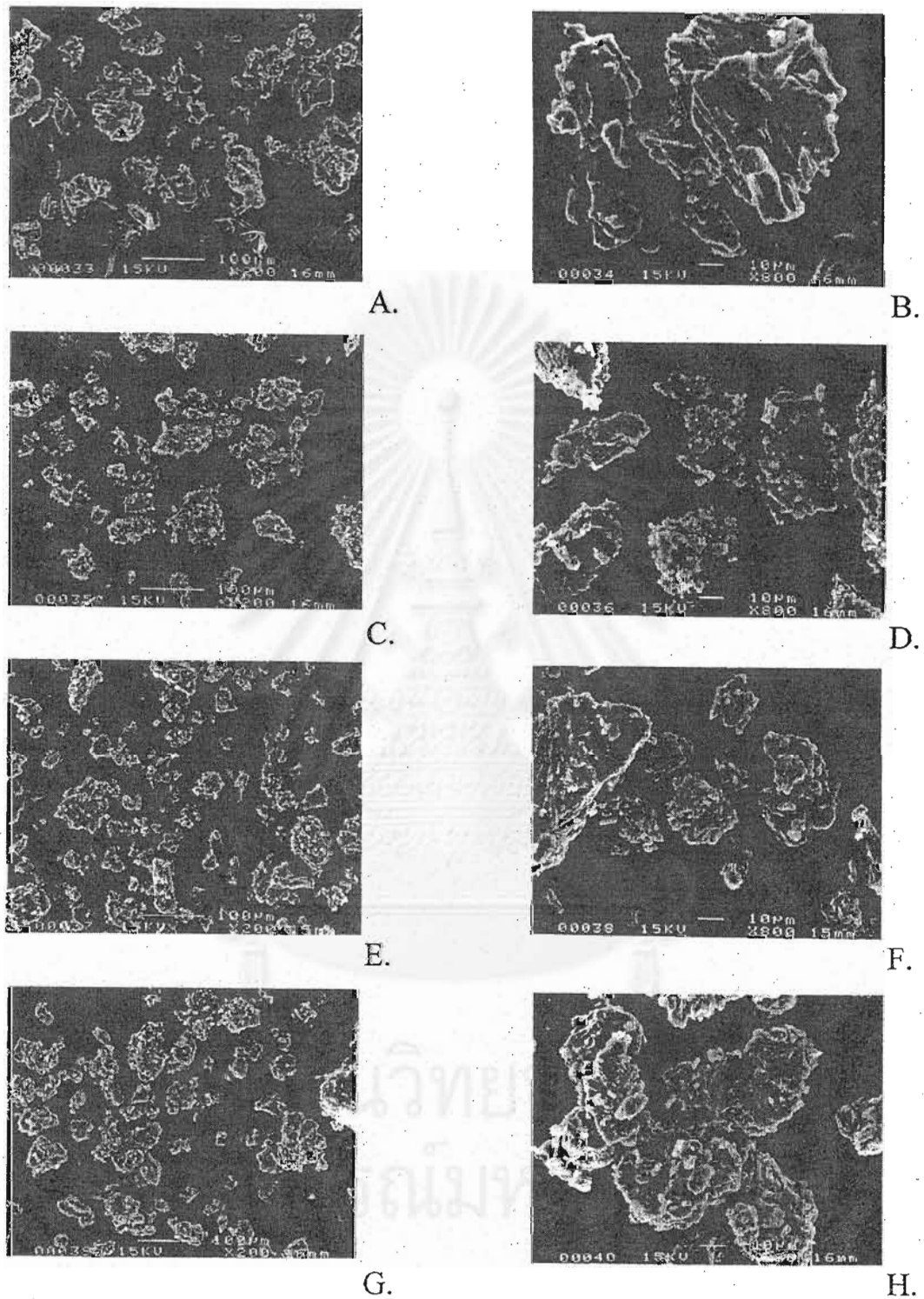


Figure 62 Photomicrographs of nifedipine-poloxamer288, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

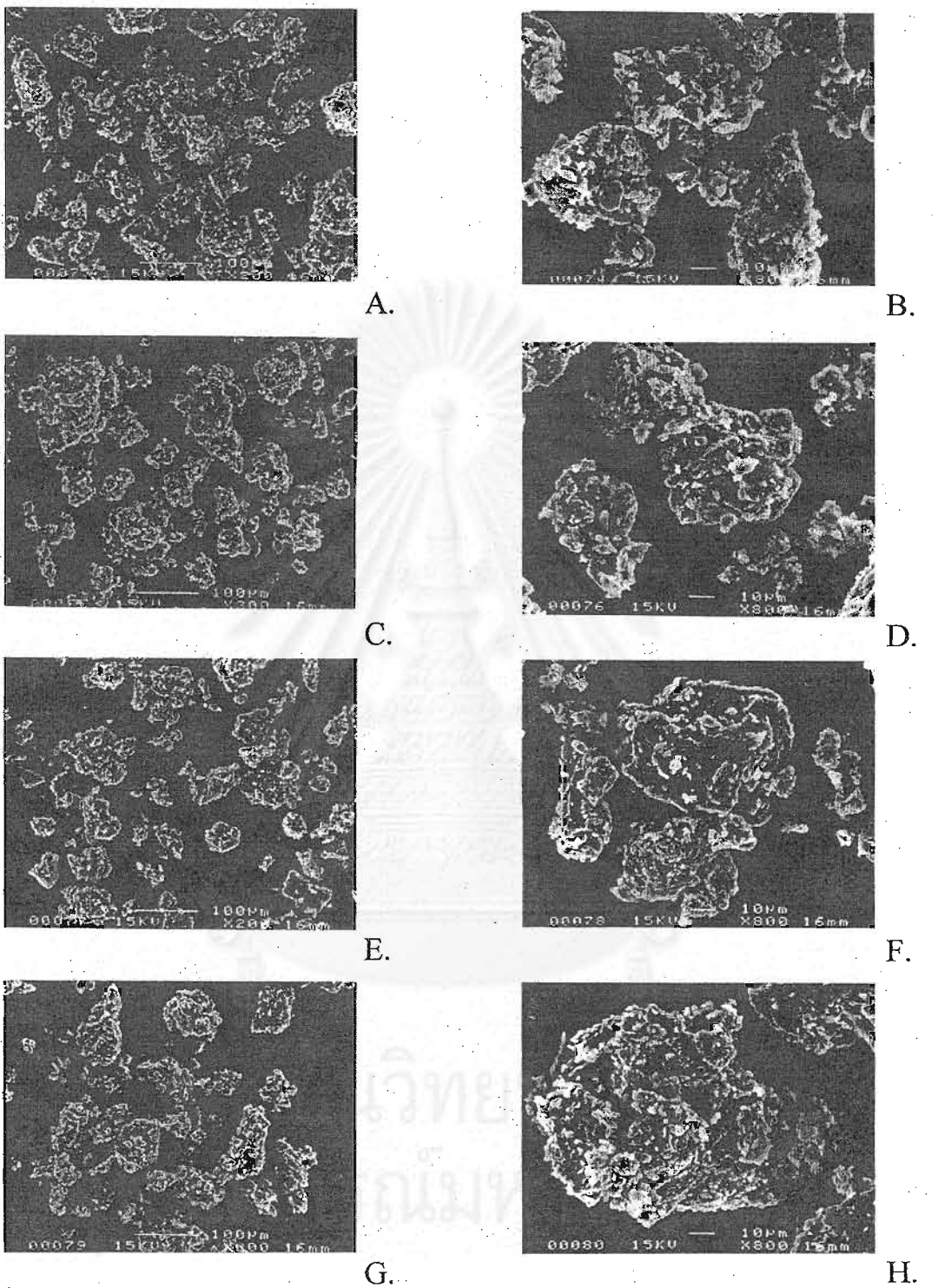


Figure 63 Photomicrographs of nifedipine-poloxamer288, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

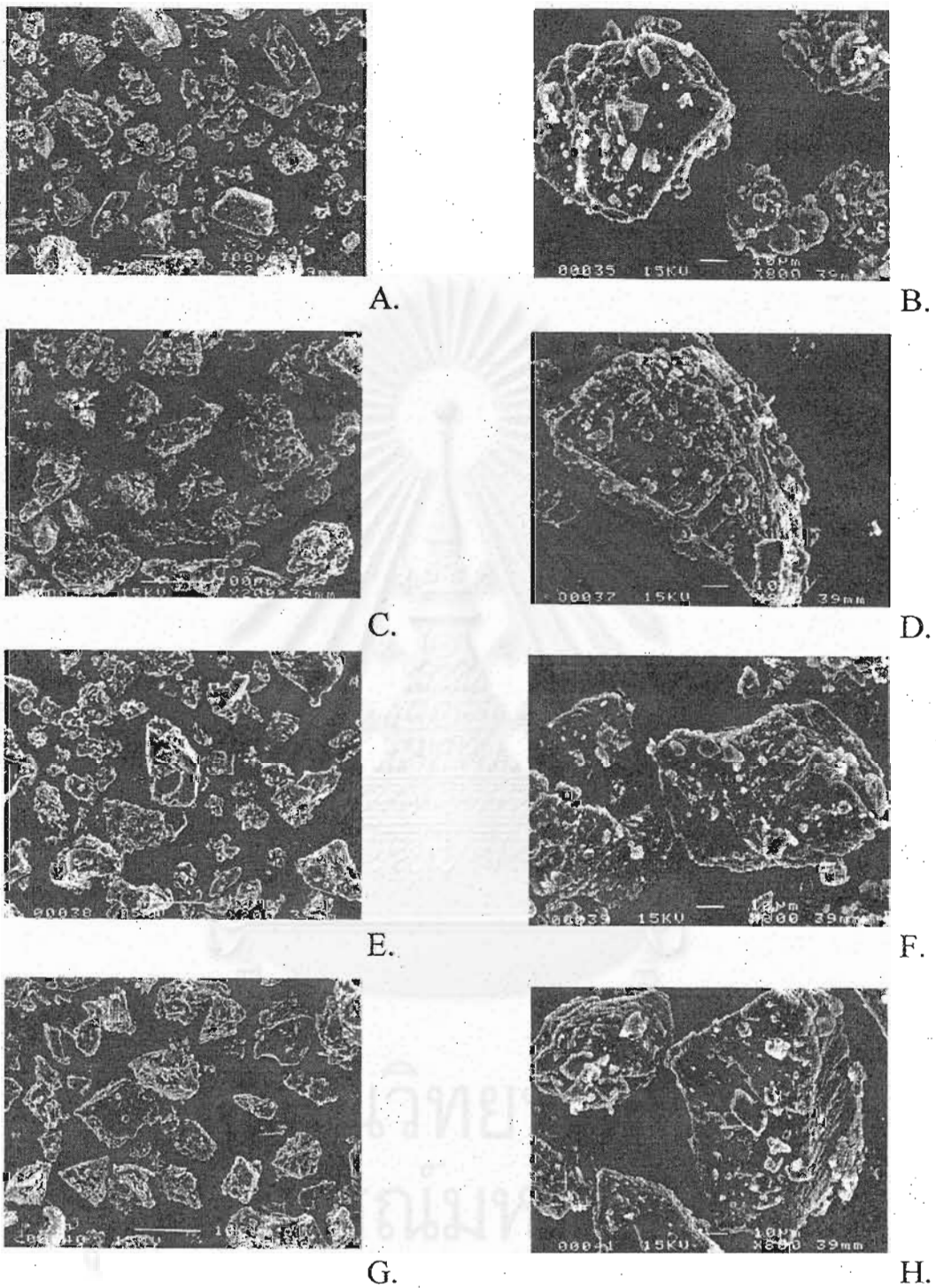


Figure 64 Photomicrographs of nifedine-poloxamer 407, physical mixture

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

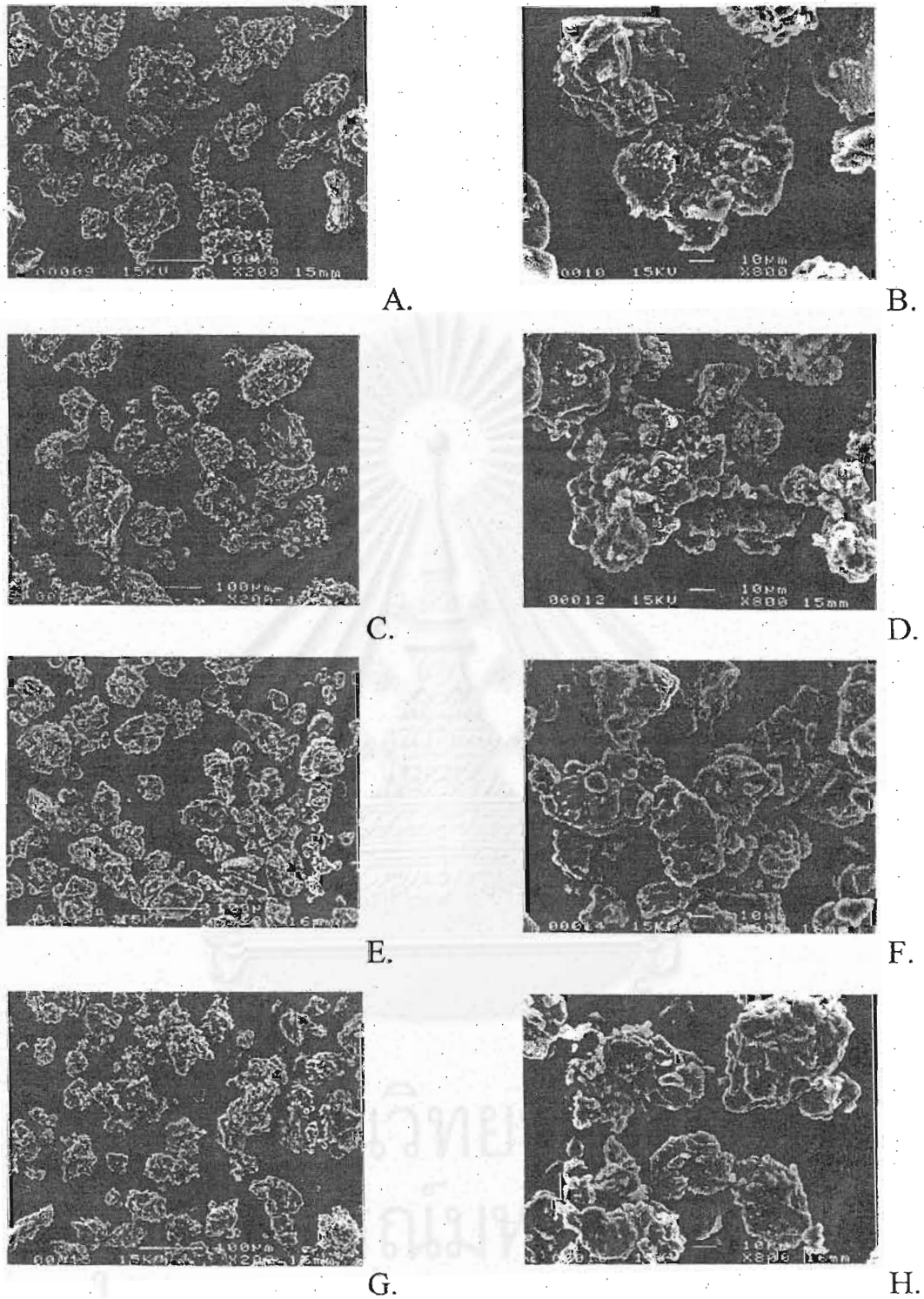


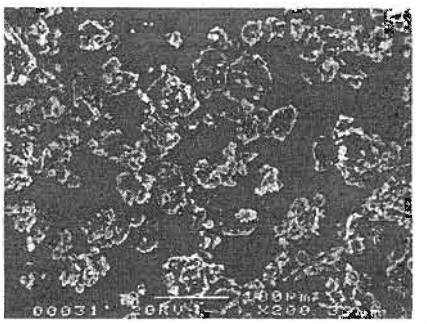
Figure 65 Photomicrographs of nifedine-poloxamer 407, melting method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

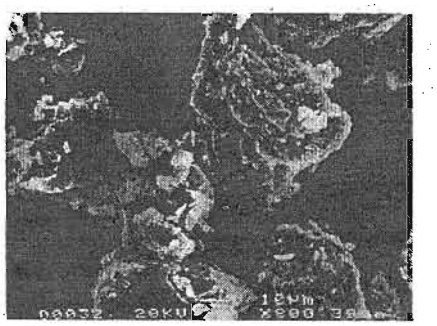
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

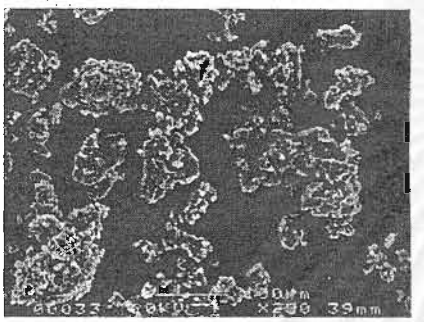
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



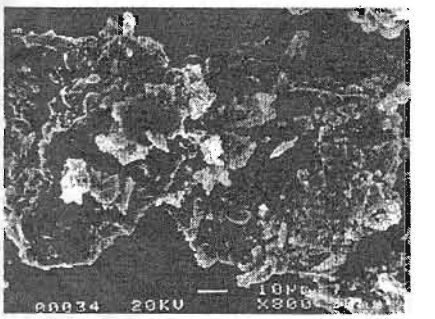
A.



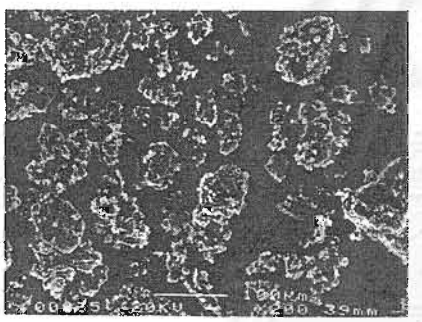
B.



C.



D.



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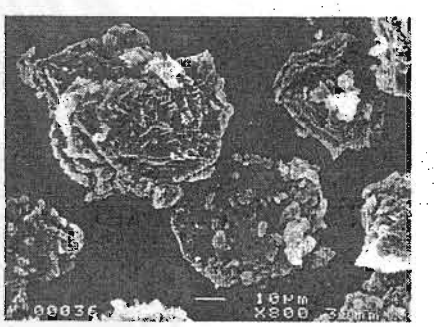

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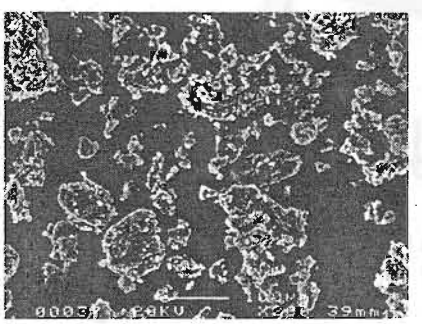
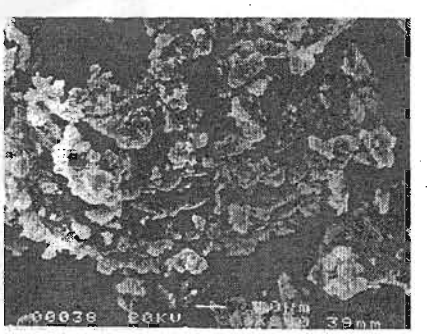


G.



H.

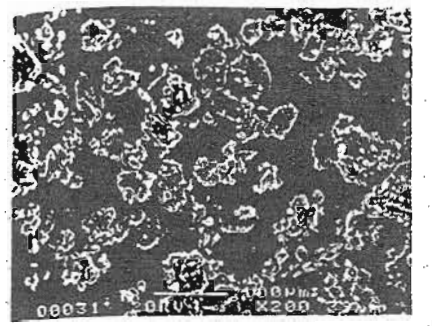
Figure 66 Photomicrographs of nifedine-poloxamer 188, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

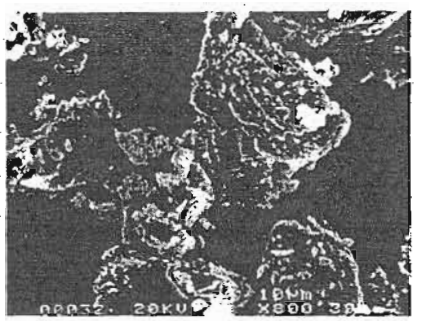
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

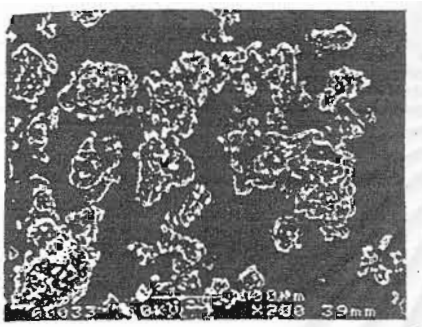
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



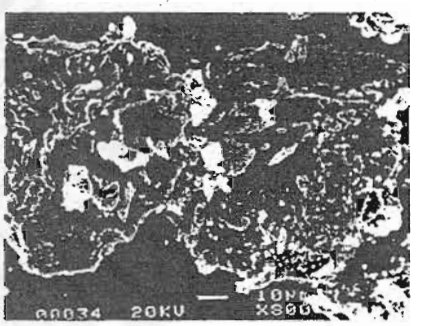
A.



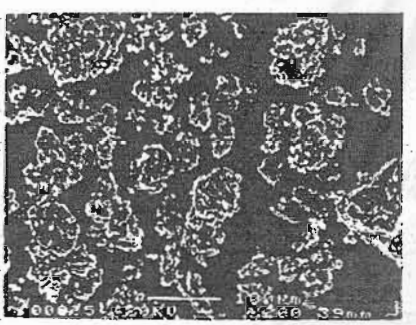
B.



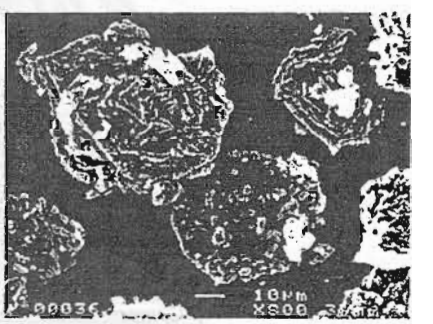
C.



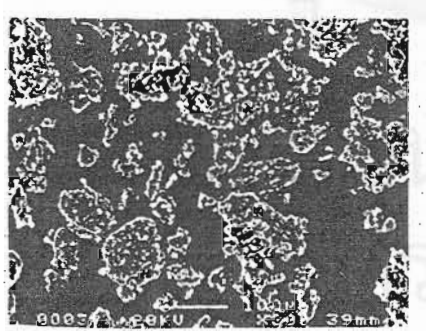
D.



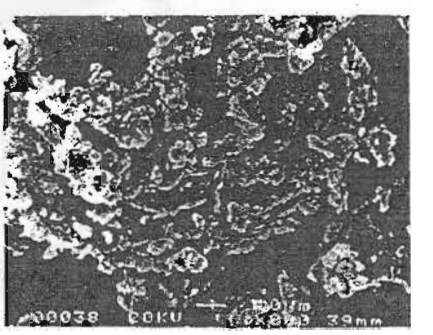
E.



F.



G.



H.

Figure 67 Photomicrographs of nifedipine-poloxamer 407, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

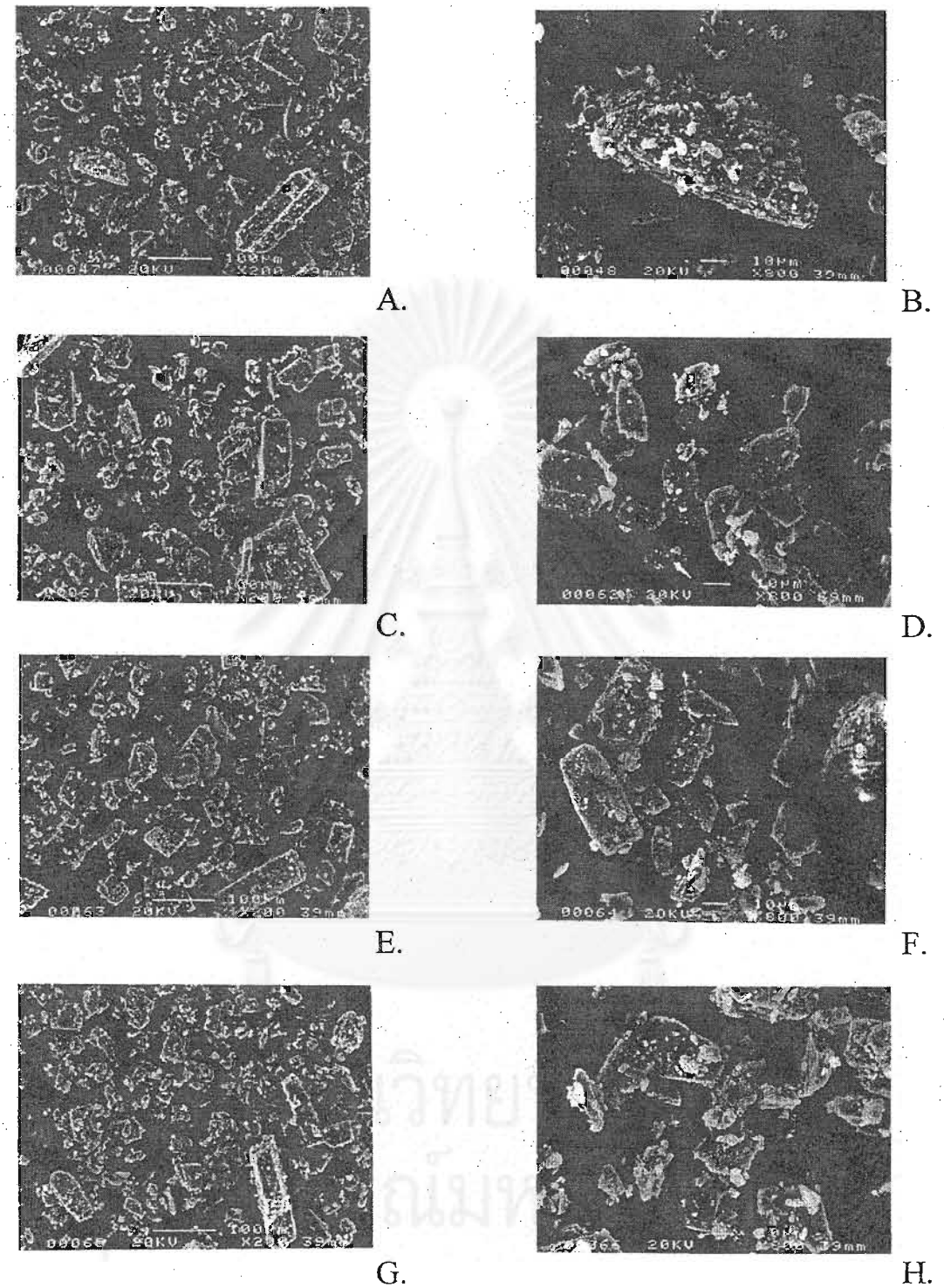


Figure 68 photomicrographs of nifedine-β-cyclodextrin, physical mixture

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

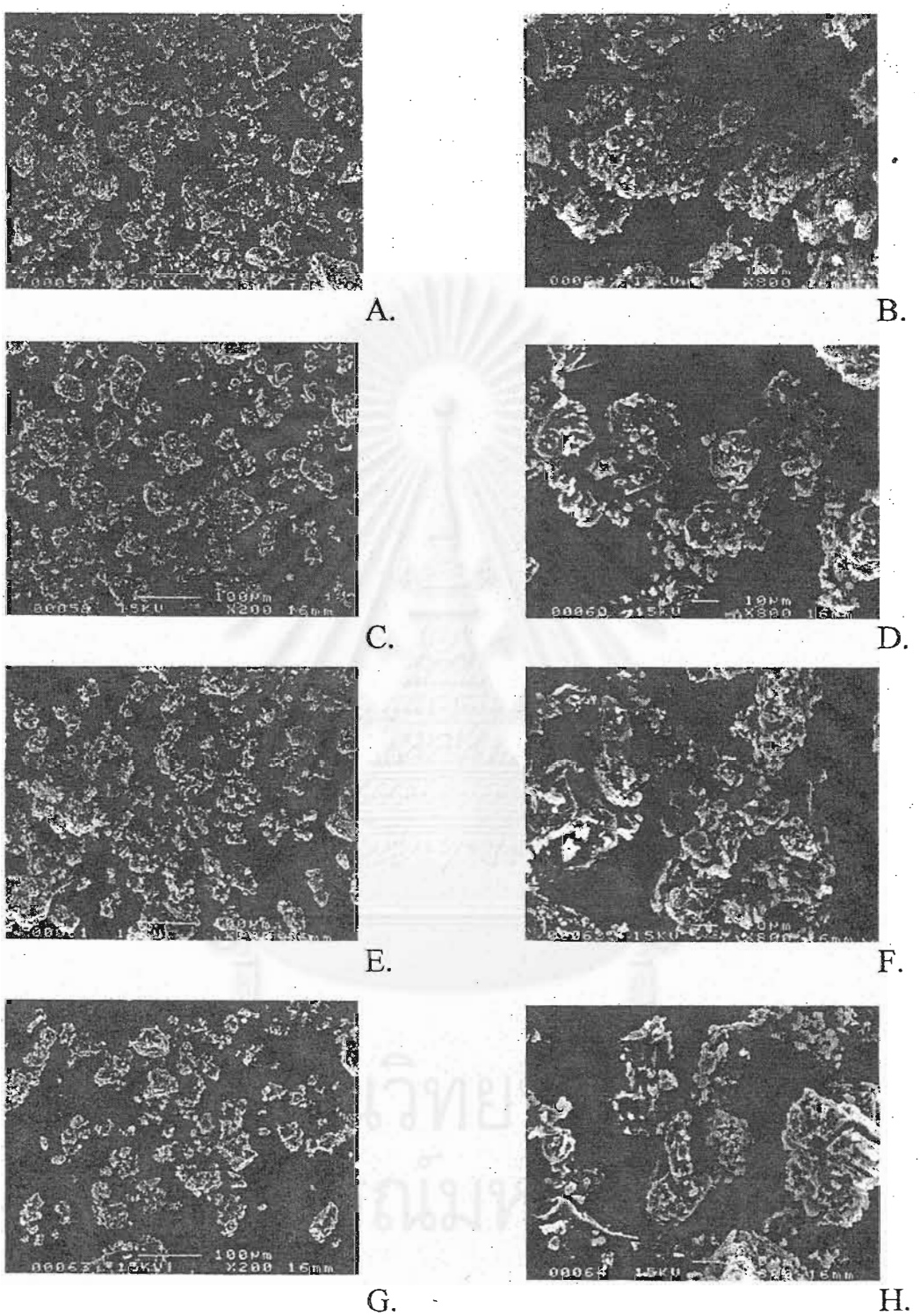


Figure 69 Photomicrographs of nifedine-β-cyclodextrin, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

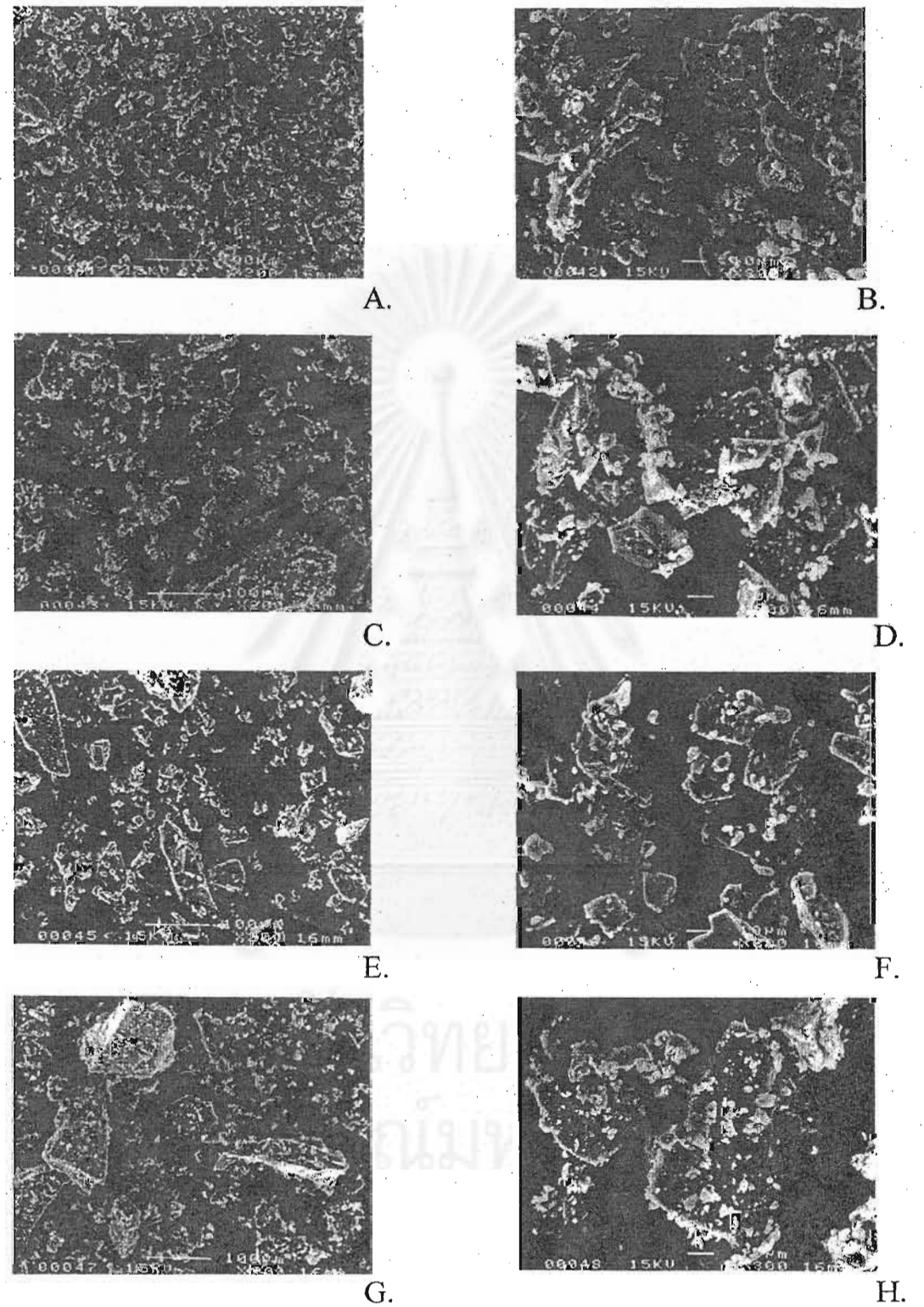


Figure 70 Photomicrographs of nifedine-2-hydroxypropyl-β-cyclodextrin , physical mixture

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

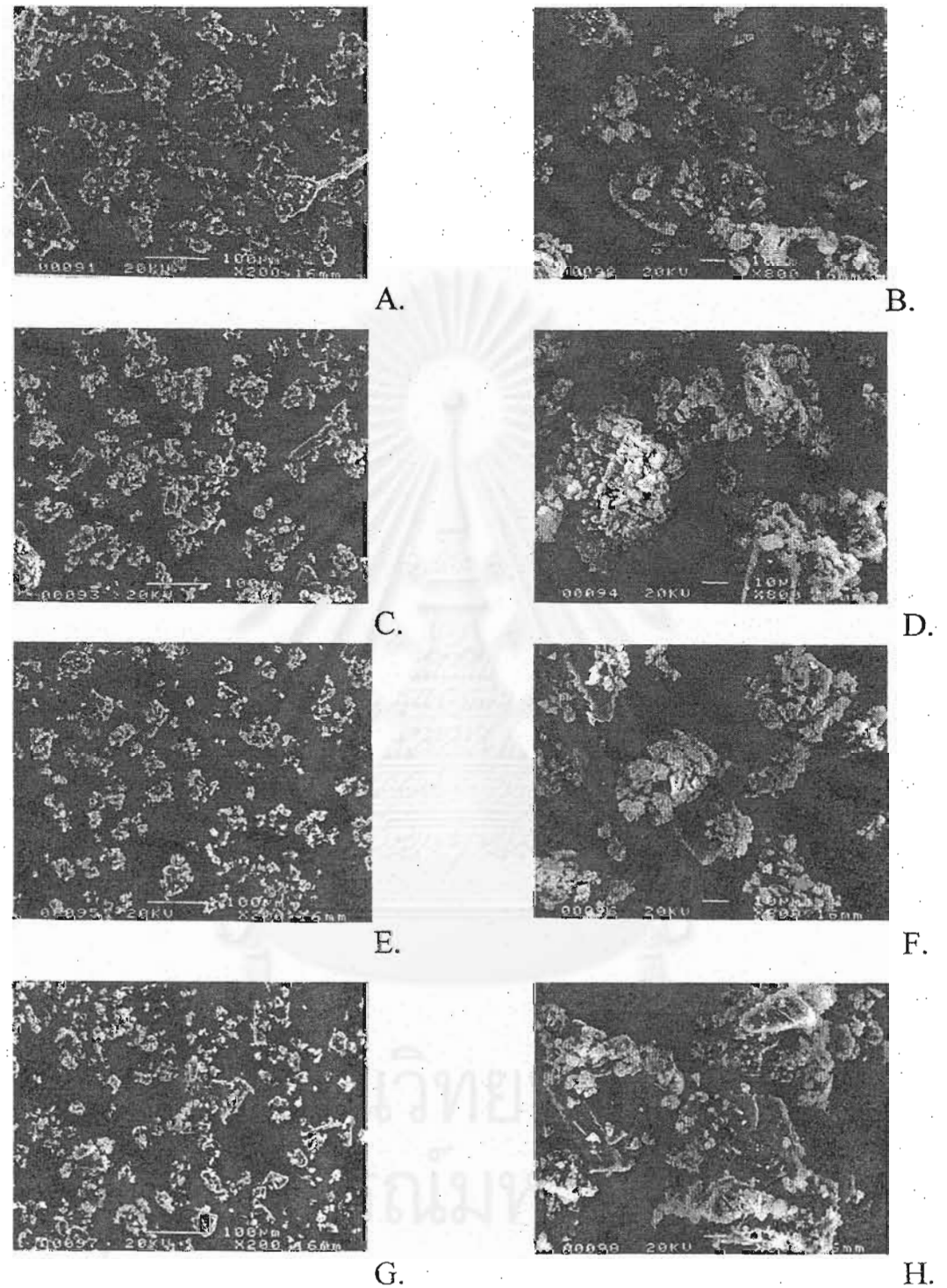


Figure 71 Photomicrographs of nifedine-2-hydroxypropyl-β-cyclodextrin, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

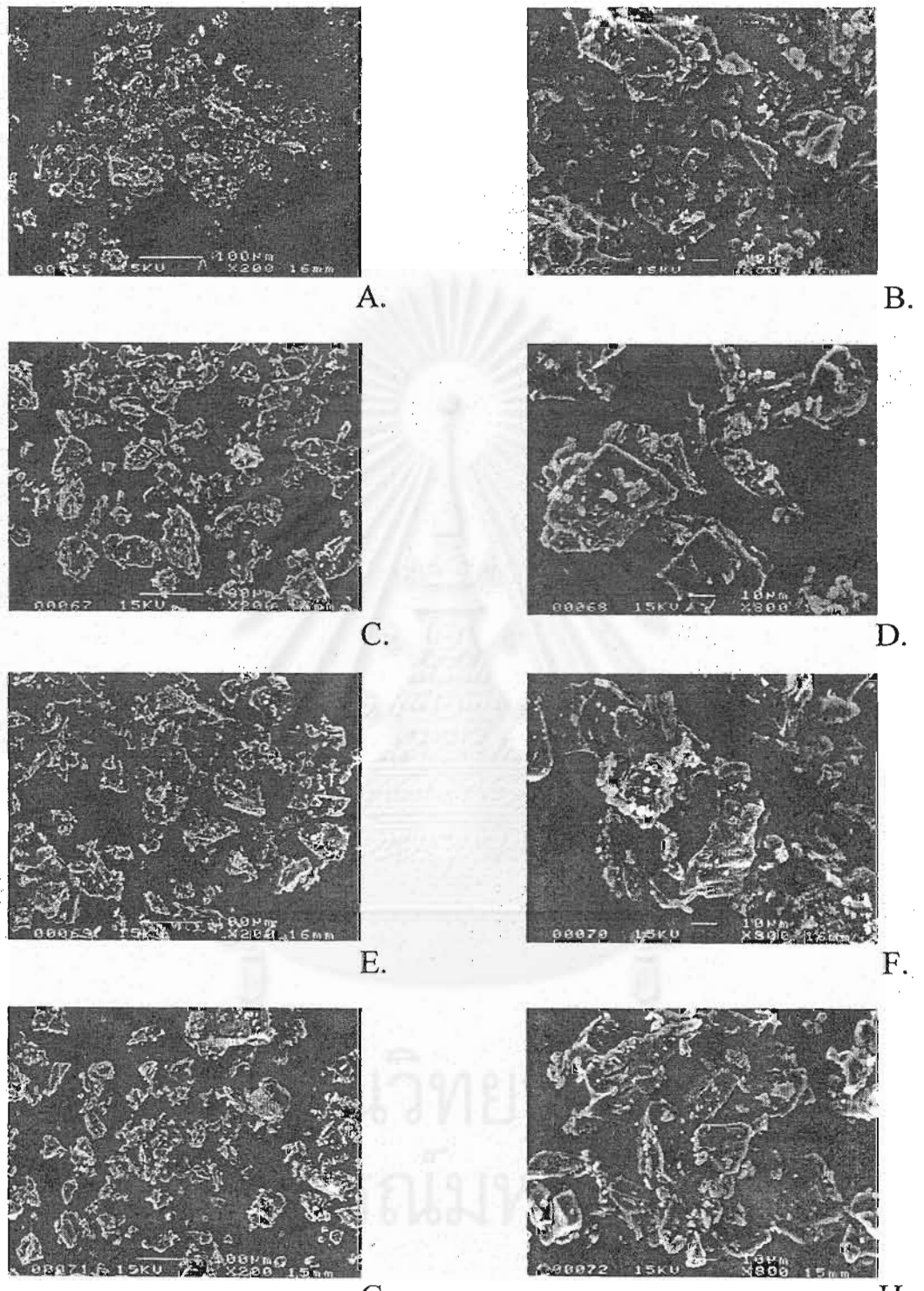


Figure 72 Photomicrographs of nifedine-2-hydroxypropyl-β-cyclodextrin, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

The microscopic appearance of PEG4000, PEG6000, poloxamer188, poloxamer288, poloxamer407, β-cyclodextrin and 2-hydroxypropyl- β-cyclodextrin are illustrated in **Figures 44-47**, respectively.

Photomicrographs of pure PEG4000 and PEG6000 **(Figure 44)** were very identical and showed spherical in shape with smooth surface. The diameters are range of 100-200 μm. However PEG4000 seems to be bigger than that of PEG6000.

The microscopic appearance of poloxamers **(Figure 45-46)** were similar to PEGs, rounded shape, smooth surface, but the range of diameter was wider at about or less than 100 μm for small particles and more than 200 μm for big ones. Some small particles (less than 100 μm) attached to the surface of the big ones.

For β-cyclodextrin **(Figure 47),** it appeared as rod shaped crystals at irregular sizes. In contrast, 2-hydroxypropyl- β-cyclodextrin was fine porous particles.

4.2 SEM of nifedipine-PEGs solid dispersion

The SEM results of PEG4000 **(Figure 48-51)** and PEG6000 **(Figure 52-55)** showed very similar appearances. Descriptions of most treatments were applicable to both carriers. In the melting method, nifedipine was found to be dispersed on the surface of carrier crystals. This result was found similar to solid dispersion prepared by solvent method whose amount of drug particles spread onto the carrier surface were lower. Some drug particles have even implanted on the surface of PEGs particles whereas majority were just physically deposited on the surface.

For physical mixed dispersions, drug particles found spreading on the PEGs surface were lower than those of melting and solvent method. Kneaded products were somewhere in between melting or solvent method and physical mixture.

The surfaces in most methods were rougher than pure carrier. However corners and sides of particles still could be noticed This suggested that carriers were in crystalline state.

Different drug-carrier ratios seemed not to influence the way particles presented in the system. However it affected the degree of roughness of drug particles. This was possible due to the amount of drug was lower at the higher mixing drug : carrier ratio i.e. the ratio at 1:10 contained fewer drug particles than the ratio of 1:3.

4.3 SEM of nifedipine-poloxamers solid dispersion

The nontreated poloxamer188 and 407, like PEGs, were spherical in shape with very smooth surface. While poloxamer288 was small in size, about 10-50 μm, the surface was smooth like melted wax and the particles were irregular shape.

From **Figure 56-59, 60-63 and 64-67**, melting method of nifedipine-poloxamers gave very interesting observation. It was found that the drug particles have embedded into the surface of the carriers, not just deposited on it, resulting in jagged particles from inside but smooth surface from outside. Poloxamer188 was the smoothest with a lot of drug implantation, especially at the ratio of 1:3, followed by poloxamer288 and poloxamer407 respectively. Few drug crystals were found in this treatment.

For nifedipine-poloxamer188 prepared by kneading, the photomicrographs **(Figure 59)** showed that poloxamer188 particles had the smoothest surface among the three poloxamers. In contrast, the surface of poloxamer288 **(Figure 67)** were still rough whereas poloxamer407 **(Figure 63),** the surface was slightly smoother than that of poloxamer228 but not as smooth as poloxamer188. The drug particles spread on the surface of carrier were higher than that of the melting method. This phenomenon became dominant when compared with physical mixture.

The system of nifedipine-poloxamers from solvent method were depicted in **Figure 58.** Some drug particles were embedded into the surface of the carriers whereas some other part of the drug spread out between the carrier particles. In general, the surface of the particles were still rough and most of them were smaller compared with physical mixture at the same ratio.

Drug particle embedding was rarely found in the physical mixtures. Most drug particles spread between the carrier particles. The carrier particles also showed the most rough surface.

4.4 SEM of nifedipine-cyclodextrins solid dispersion

It should be noted here again that β-cyclodextrin could not be prepared by melting and solvent methods and 2-hydroxypropyl- β-cyclodextrin could not be prepared by melting method. SEM of β-cyclodextrin presented in crystalline forms whereas 2-hydroxypropyl- β-cyclodextrin was fine particles.

As pure β-cyclodextrin presented as smooth surfaced and rod shaped crystal, physical mixtures of β-cyclodextrin **(Figure 68),** had nifedipine spread both on the surface and between the carrier particles. Carriers, as well as the drug, were existed in the crystalline form since corners and sides were still clearly observed. Both drug and carrier showed smooth surfaced particles. The drug distribution was high as the drug to carrier ratio increased. However, 2-hydroxypropyl- β-cyclodextrin physical mixtures **(Figure 70)** showed nifedipine particles adsorbed on the carrier surface.

Kneaded products of both carriers still **(Figure 69 and 72)** clearly showed drug and carriers crystals. However, carrier particles were distorted slightly resulting in smoother surface when compared to the physical mixtures. This was possibly the result of compression force during kneading. Drug particles were found deposit on the surface of the carrier.

For the solvent method, only 2-hydroxypropyl- β-cyclodextrin could be appropriately prepared, the surface of 2-hydroxypropyl- β-cyclodextrin particles was smooth. Drug particles were found adsorbed on the surface of the carrier as porous particles.

5. The X-ray Diffractograms

5.1 X-ray diffractogram of nontreated pure drug, treated drug and carriers

Major X-ray diffraction peaks of nontreated and treated nifedipine by several methods were particularly observed at five diffraction angle of 8.0, 11.9, 16.2, 19.5 and 24 at 2 θ **(Figure 73).** PEG4000 and PEG6000 diffractograms showed similar pattern that they were in crystalline form. Their characteristic peaks were particularly observed at 19.5° and 23.5° respectively **(Figures 74-81).** Poloxamer188, poloxamer288 and poloxamer 407 all were also in crystalline form with the characteristic peaks very similar to PEGs peaks of 19° and 23.5° **(Figures 82-93).** A crystalline β-cyclodextrin, in **Figures 94-95,** showed distinguished peaks at 8.5° and 12.5°. In contrary to all other carriers, 2-hydroxypropyl- β-cyclodextrin in **Figure 96-98,** was found to be in amorphous form. Its diffractogram showed a halo pattern.

5.2 X-ray diffractogram of nifedipine-PEGs solid dispersion

The X-ray diffraction pattern of nifedipine-PEGs systems are illustrated in **Figures 74-81**. PEG4000 and PEG6000, in all systems were in a similar manner. The observed major peaks of nifedipine presented at 8°, 11.9°, 15.9° and 16.8°, however at higher ratio of carriers these peak intensity were markedly decreased. At the ratio of 1:10, the distinguished peaks of nifedipine could not be detected, it can be assumed that nifedipine in the system may be in amorphous form. For the dispersion of PEG6000 physical mixtures, it was found that the distinguished peaks of nifedipine could rarely be detected since 1:3 to 1:5 ratio. In each system, two major peaks of PEG4000 or EG6000 can be observed about 19.2° and 23.4°. When compared by method of preparation, it revealed that PEG4000 dispersion by melting method at 1:10 ratio seemed similar to the melt of PEG6000 at 1:10 ratio.

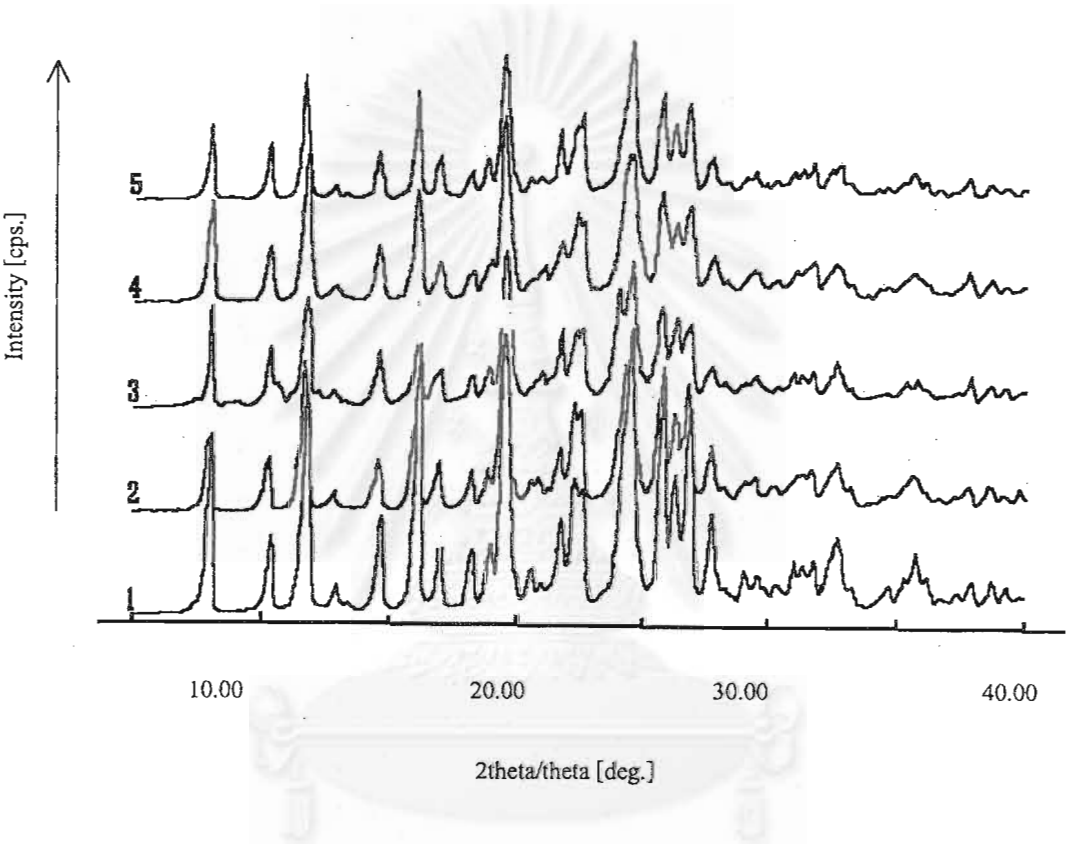


Figure 73 Powder X-ray diffraction patterns of nontreated nifedipine (1) and treated nifedipine by (2) physical mixing , (3) melting method , (4) solvent method and (5) kneading method

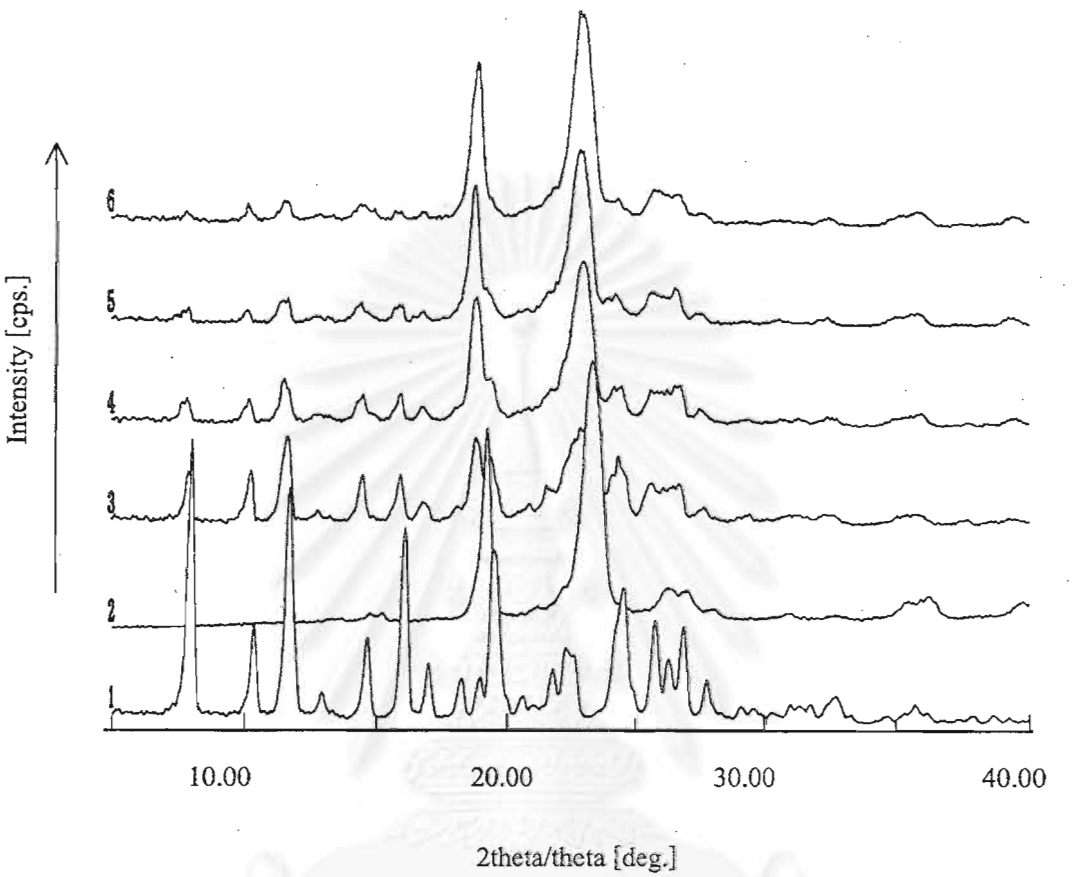


Figure 74 Powder X-ray diffraction patterns of nifedipine-PEG4000 system prepared by physical mixing (1) nifedipine, (2) PEG4000,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

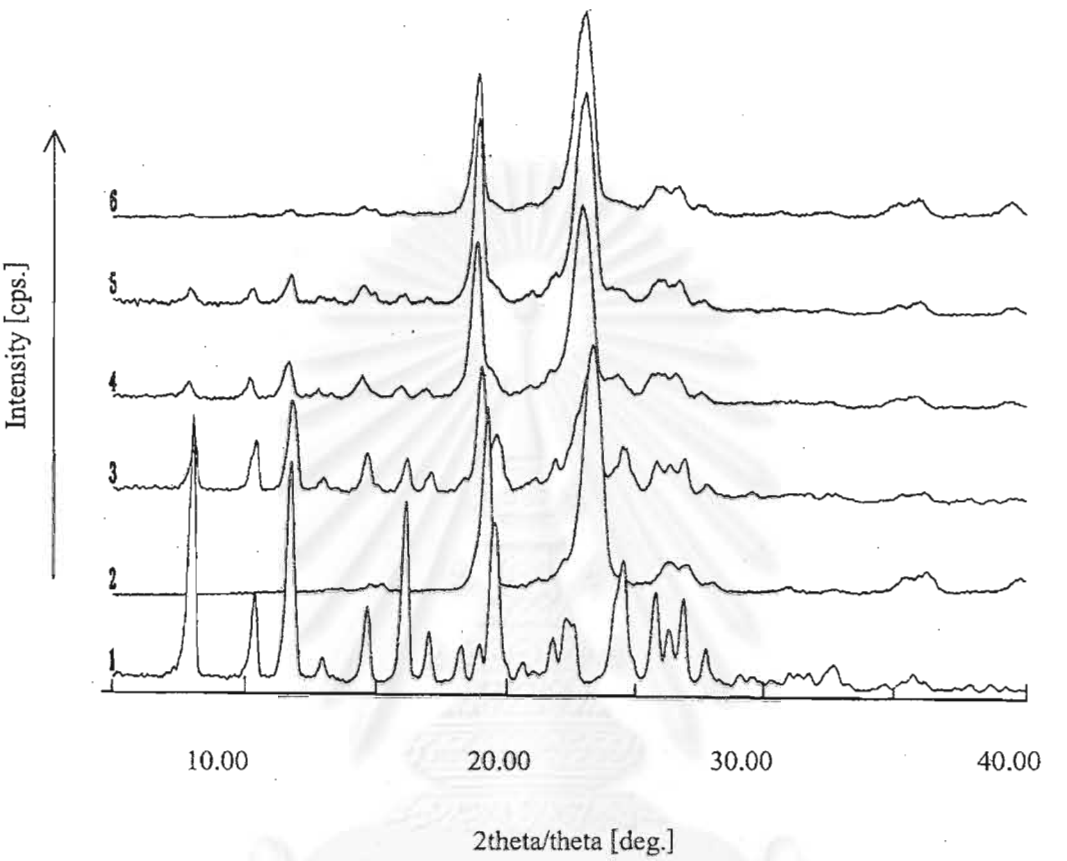


Figure 75 Powder X-ray diffraction patterns of nifedipine-PEG4000 system prepared by melting method (1) nifedipine, (2) PEG4000,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

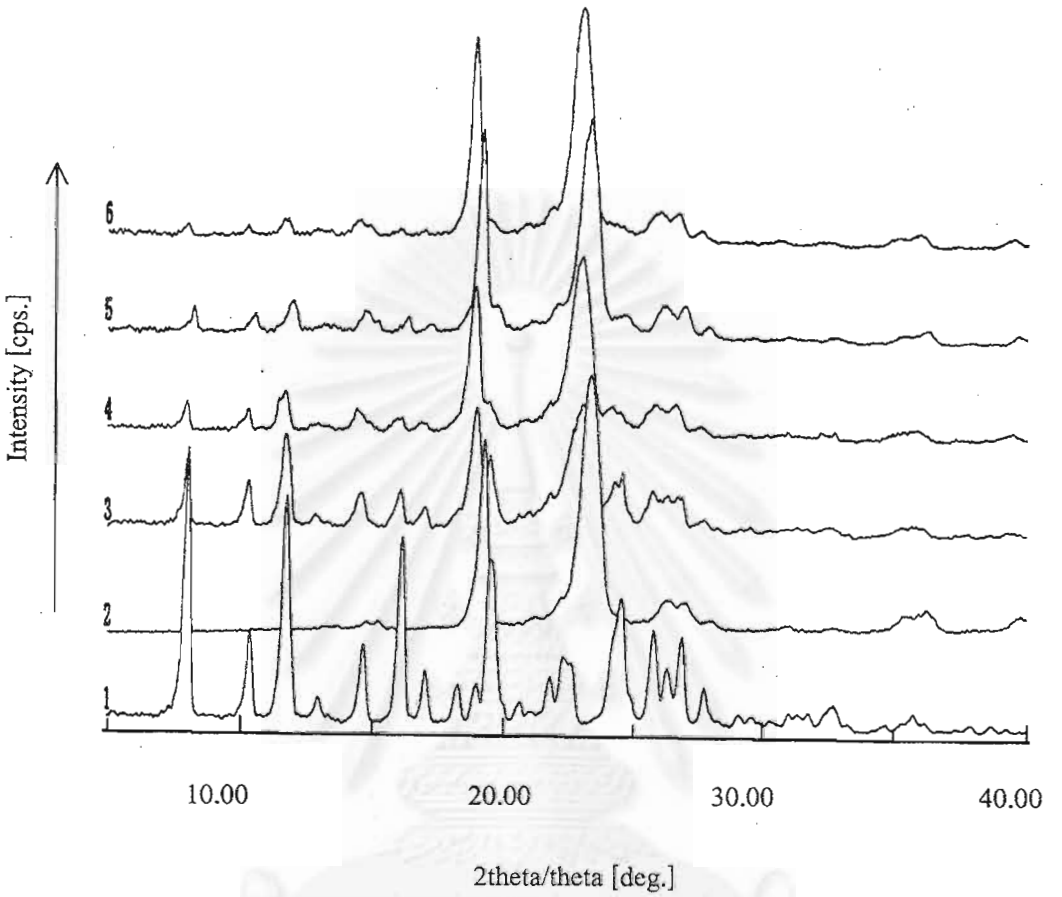


Figure 76 Powder X-ray diffraction patterns of nifedipine-PEG4000 system prepared by solvent method (1) nifedipine, (2) PEG4000,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

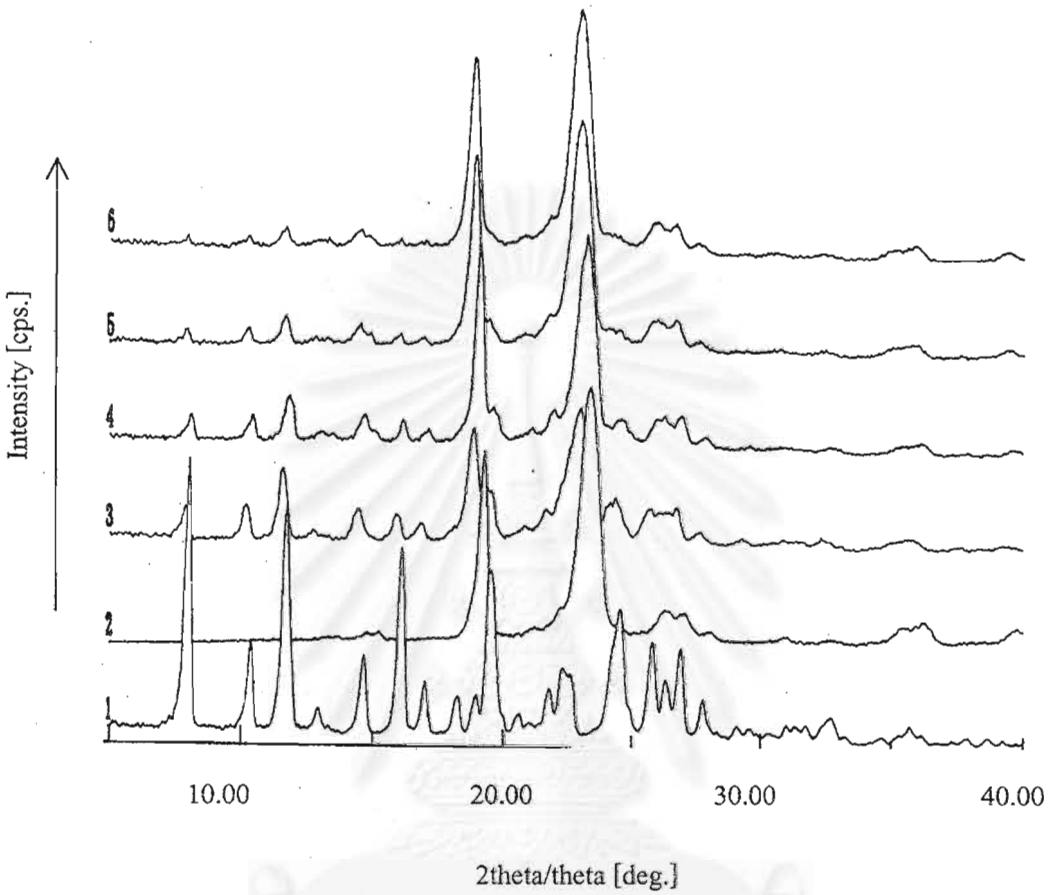


Figure 77 Powder X-ray diffraction patterns of nifedipine-PEG4000 system prepared by kneading method (1) nifedipine, (2) PEG4000,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

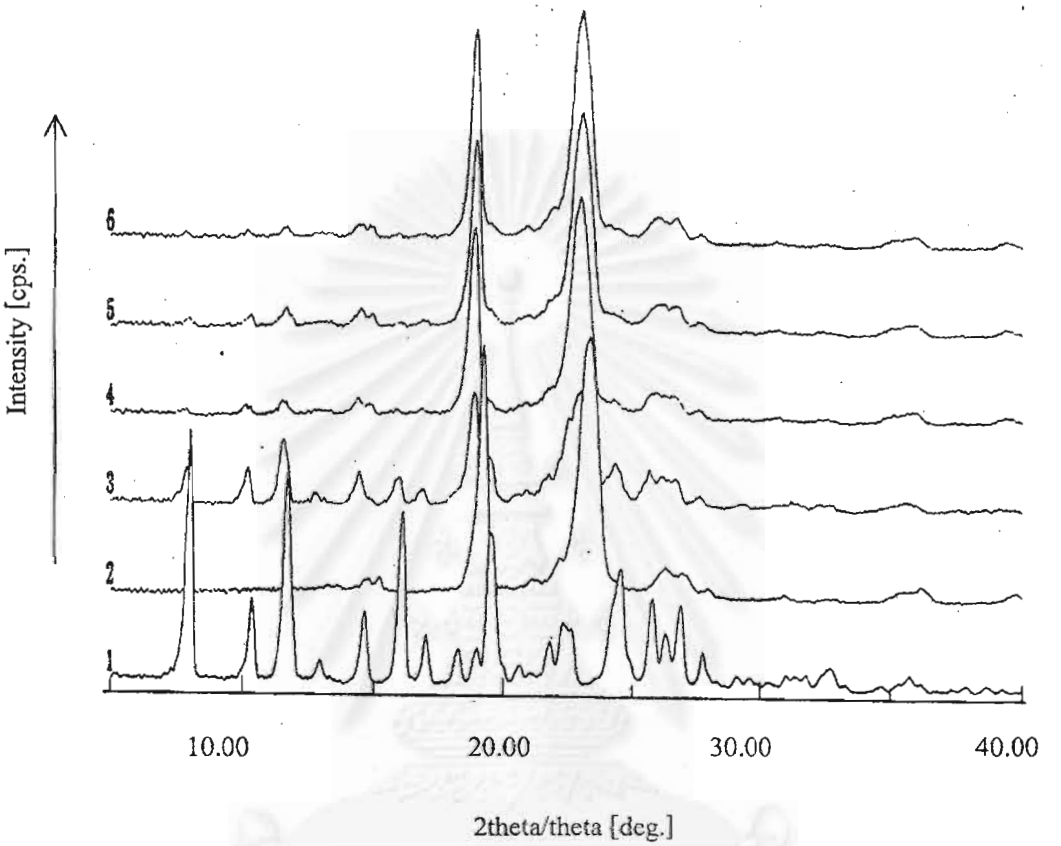


Figure 78 Powder X-ray diffraction patterns of nifedipine-PEG6000 system prepared by physical mixing (1) nifedipine, (2) PEG6000,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

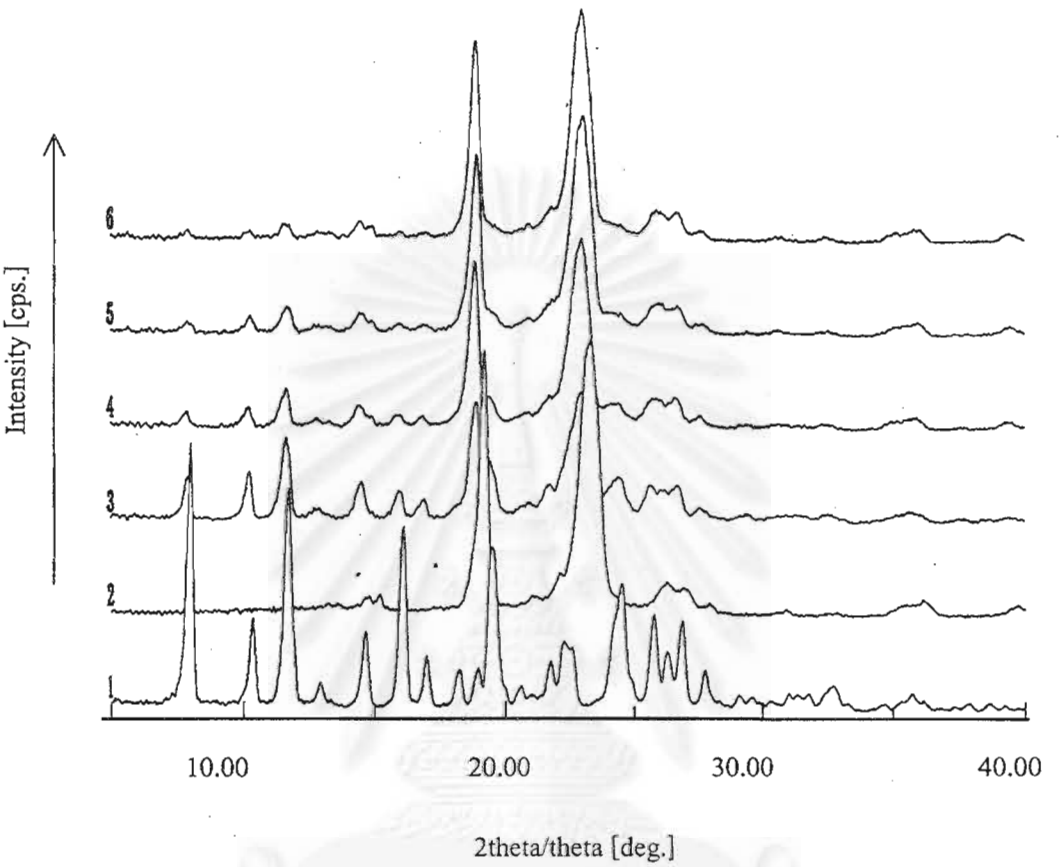


Figure 79 Powder X-ray diffraction patterns of nifedipine-PEG6000 system prepared by melting method (1) nifedipine, (2) PEG6000,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

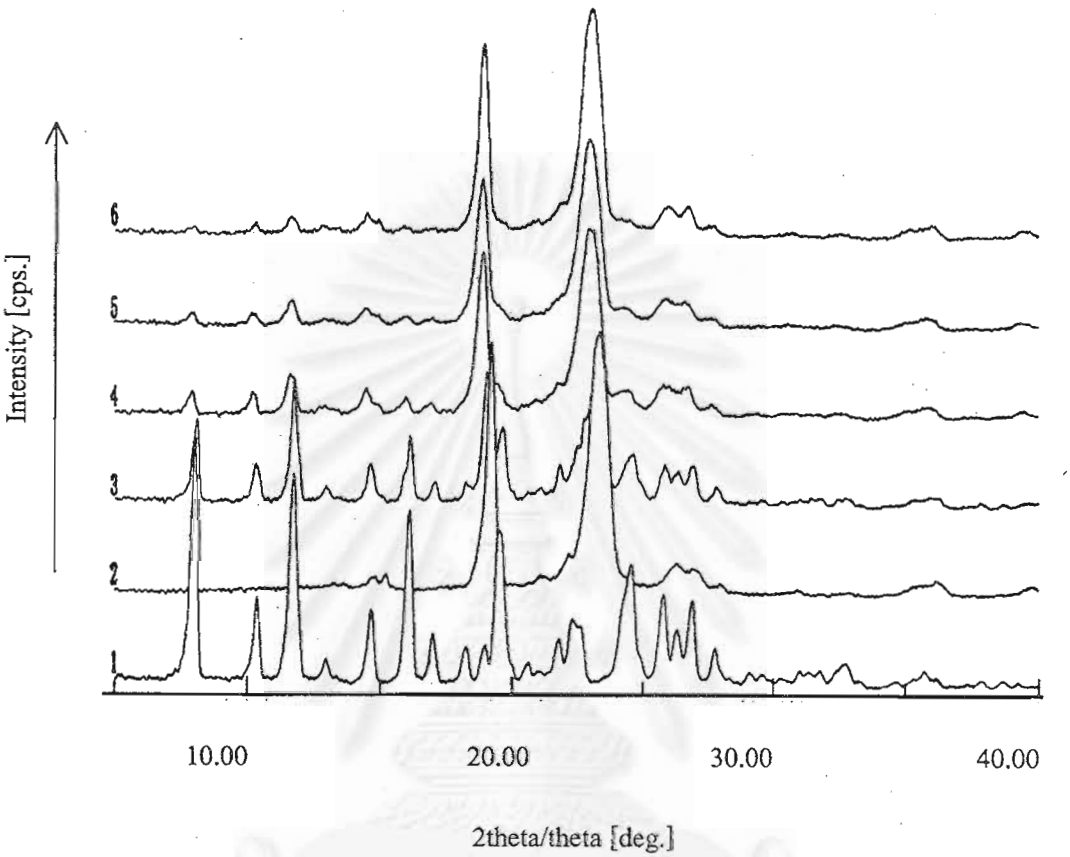


Figure 80 Powder X-ray diffraction patterns of nifedipine-PEG6000 system prepared by solvent method (1) nifedipine, (2) PEG6000,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

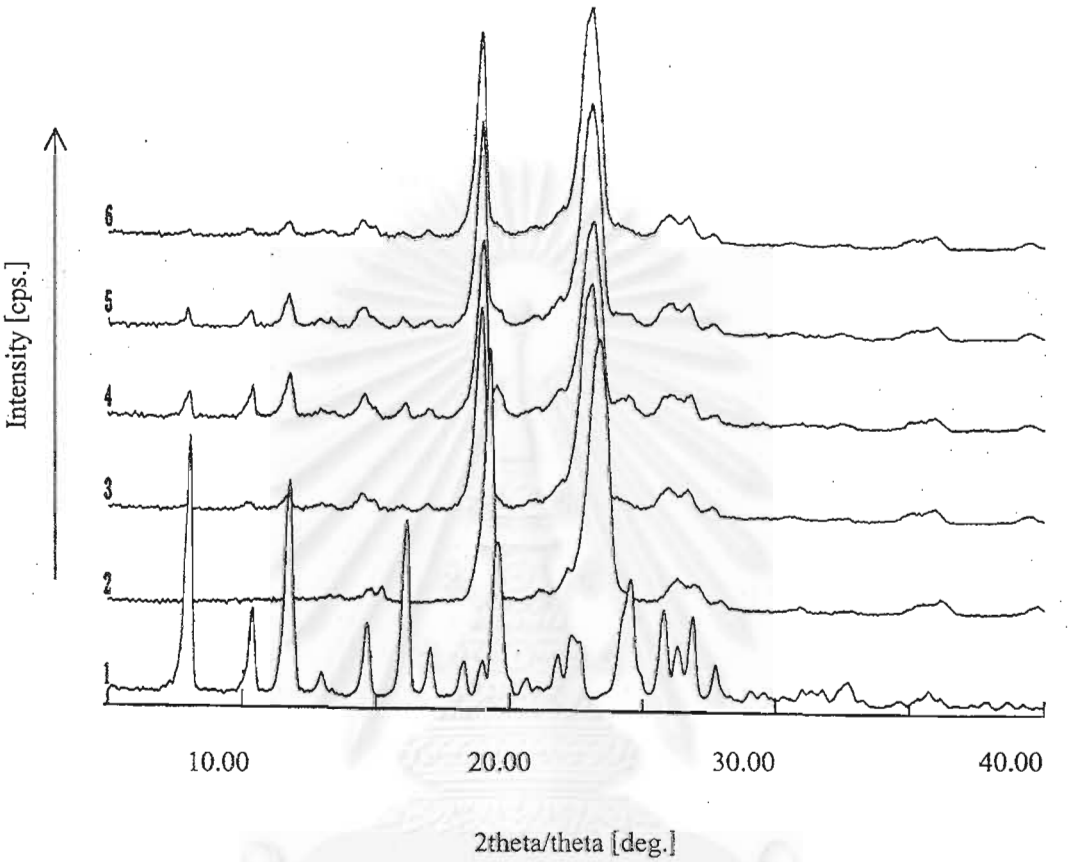


Figure 81 Powder X-ray diffraction patterns of nifedipine-PEG6000 system prepared by kneading method (1) nifedipine, (2) PEG6000,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

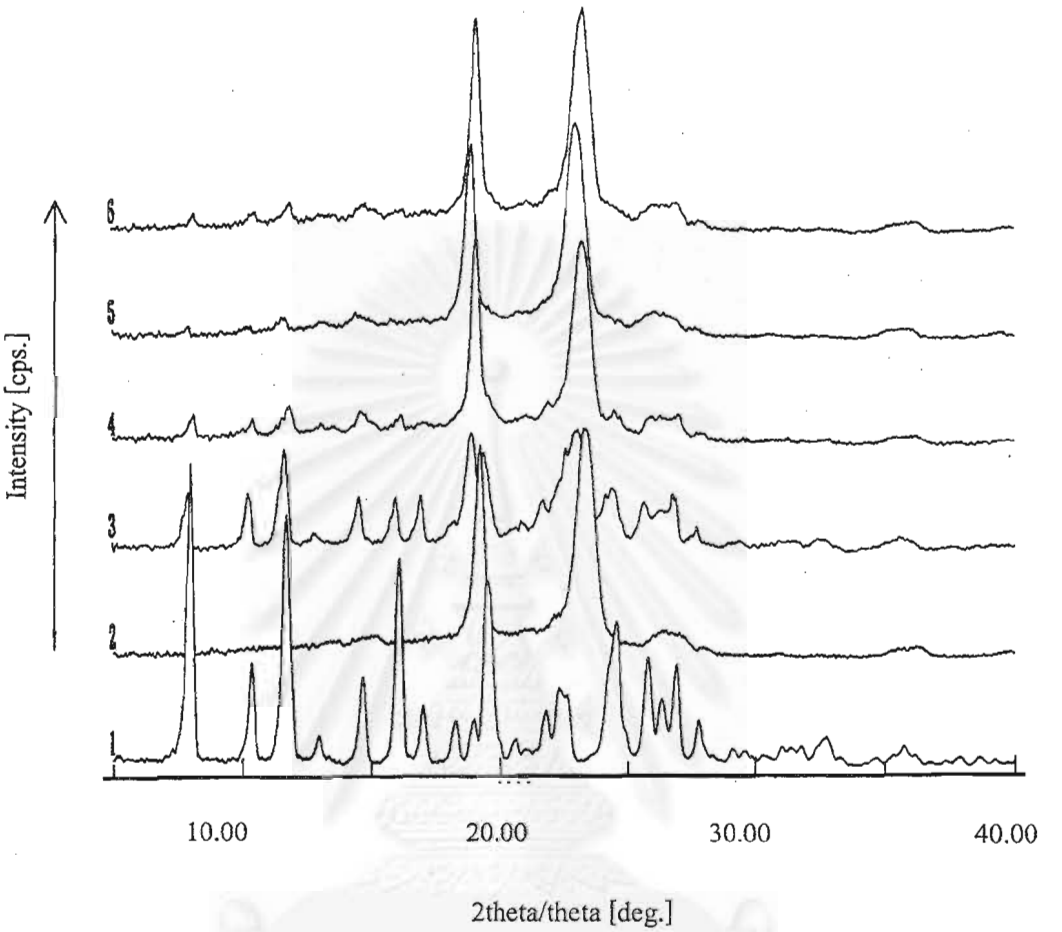


Figure 82 Powder X-ray diffraction patterns of nifedipine-poloxamer 188 system prepared by physical mixing (1) nifedipine, (2) poloxamer 188,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

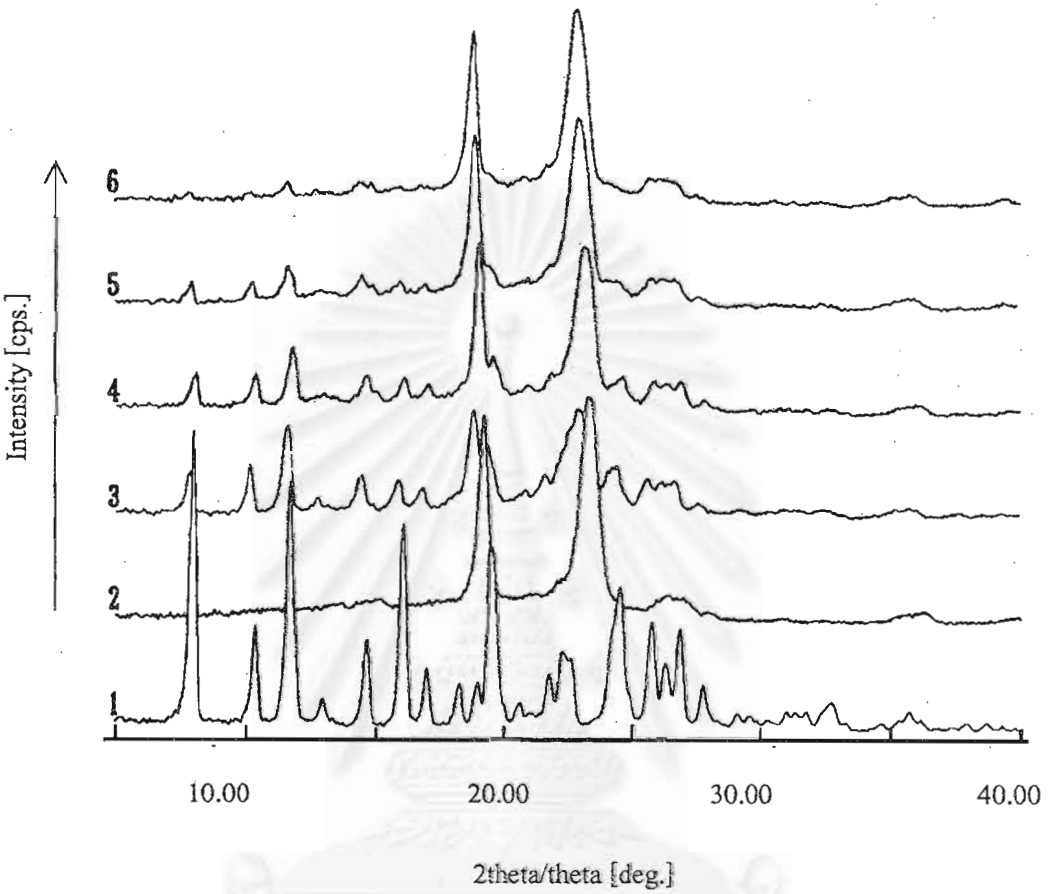


Figure 83 Powder X-ray diffraction patterns of nifedipine-poloxamer 188 system prepared by melting method (1) nifedipine, (2) poloxamer 188,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

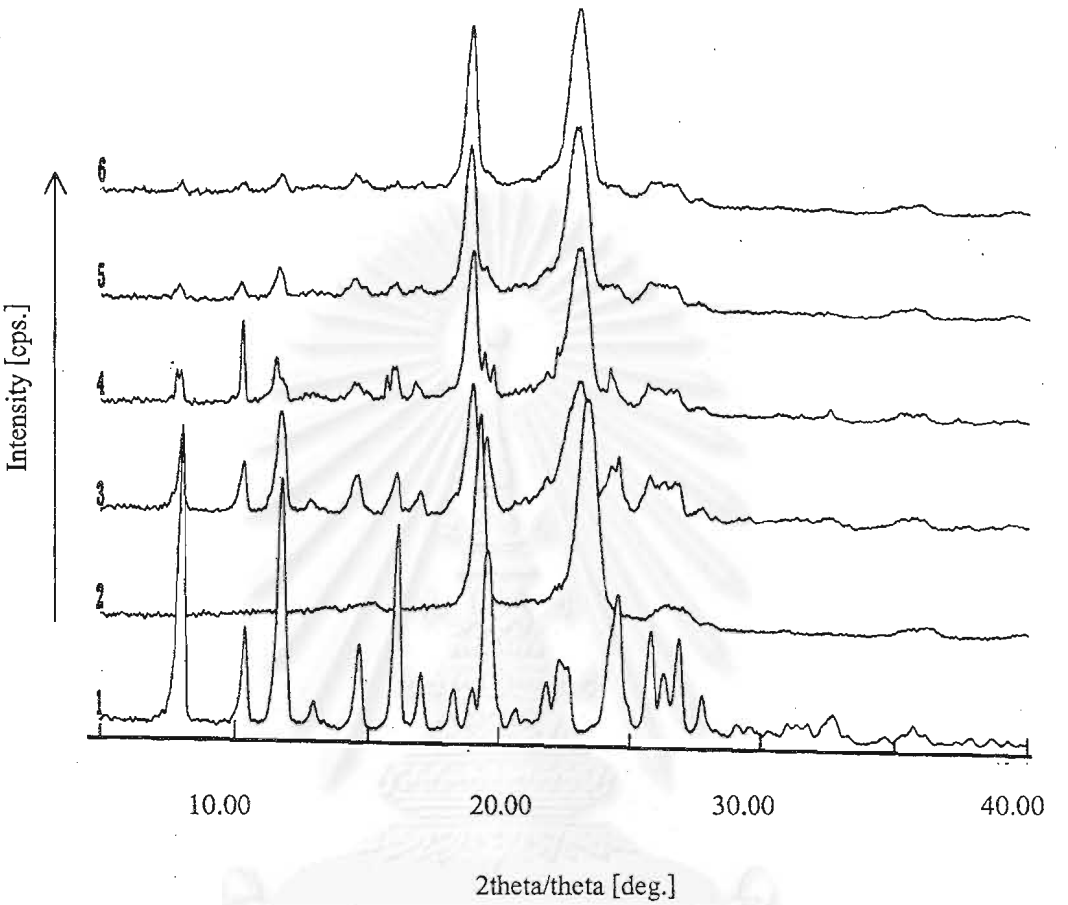


Figure 84 Powder X-ray diffraction patterns of nifedipine-poloxamer 188 system prepared by solvent method (1) nifedipine, (2) poloxamer 188,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

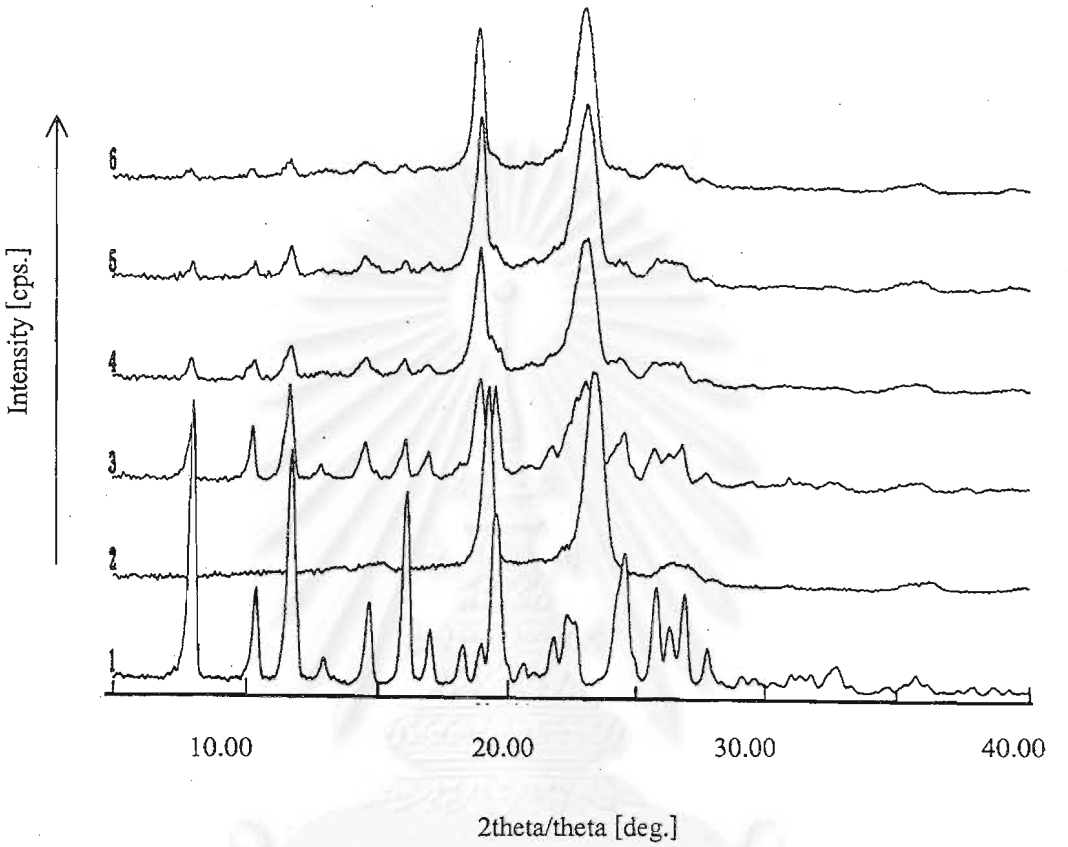


Figure 85 Powder X-ray diffraction patterns of nifedipine-poloxamer 188 system prepared by kneading method (1) nifedipine, (2) poloxamer 188,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

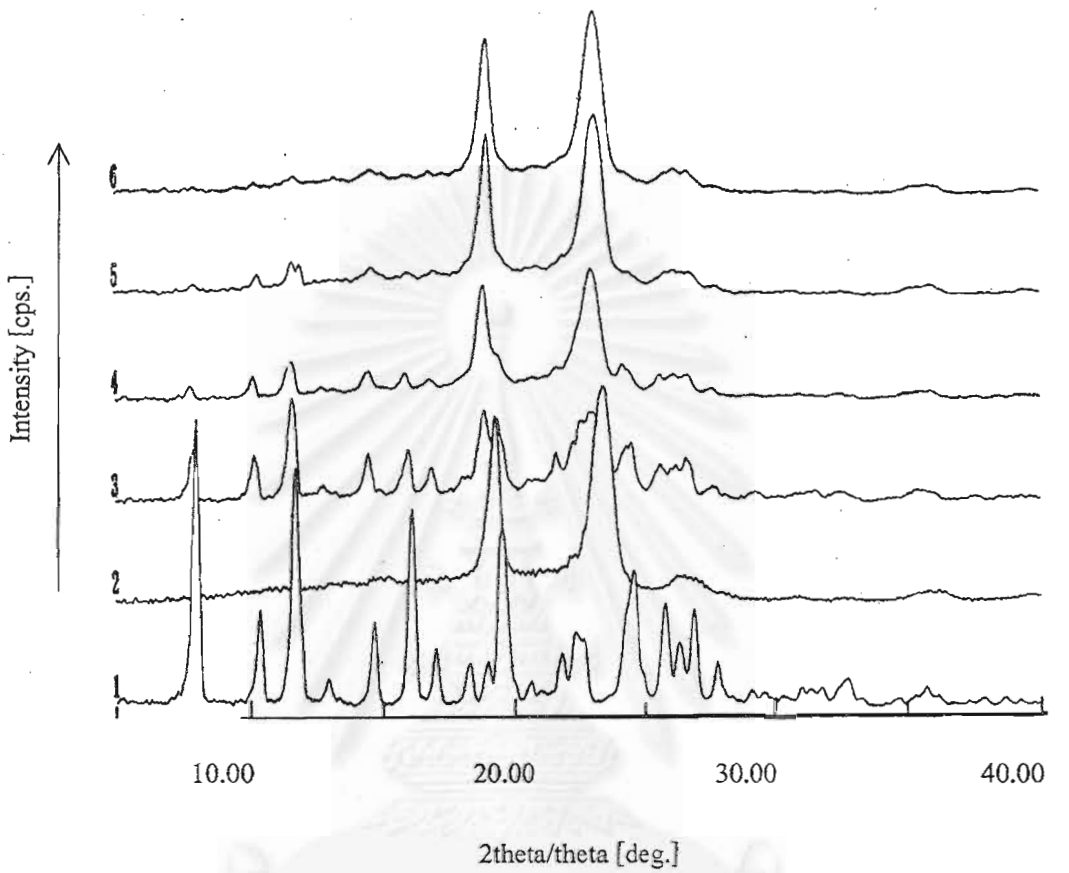


Figure 86 Powder X-ray diffraction patterns of nifedipine-poloxamer 407 system prepared by physical mixing (1) nifedipine, (2) poloxamer 407,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

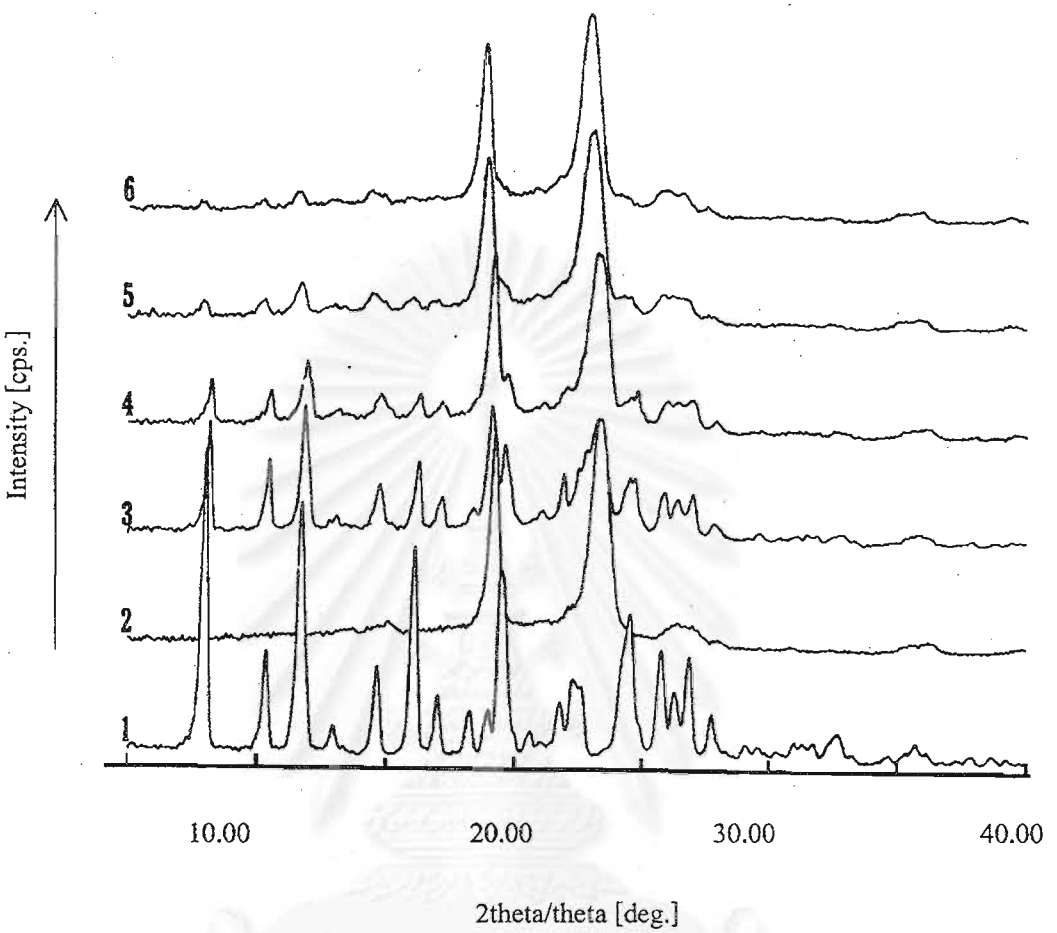


Figure 87 Powder X-ray diffraction patterns of nifedipine-poloxamer 288 system prepared by melting method (1) nifedipine, (2) poloxamer 288,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

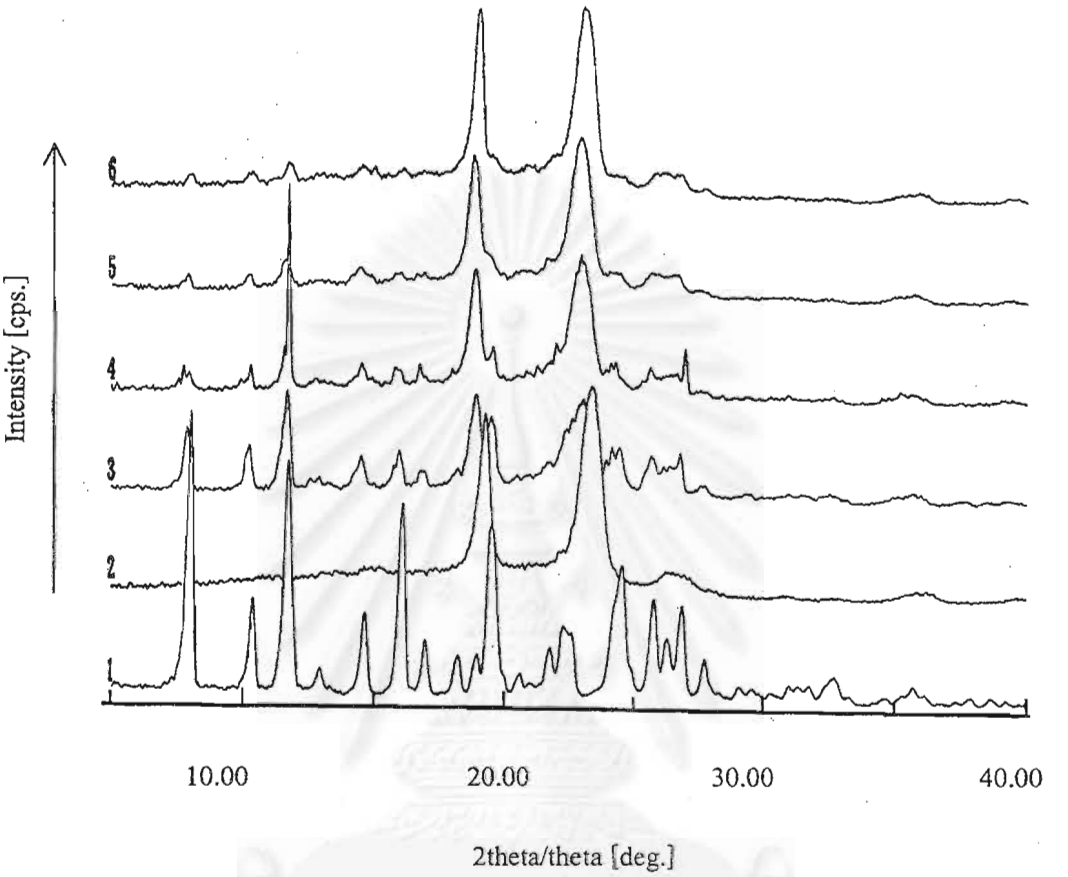


Figure 88 Powder X-ray diffraction patterns of nifedipine-poloxamer 407 system prepared by solvent method (1) nifedipine, (2) poloxamer 407,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

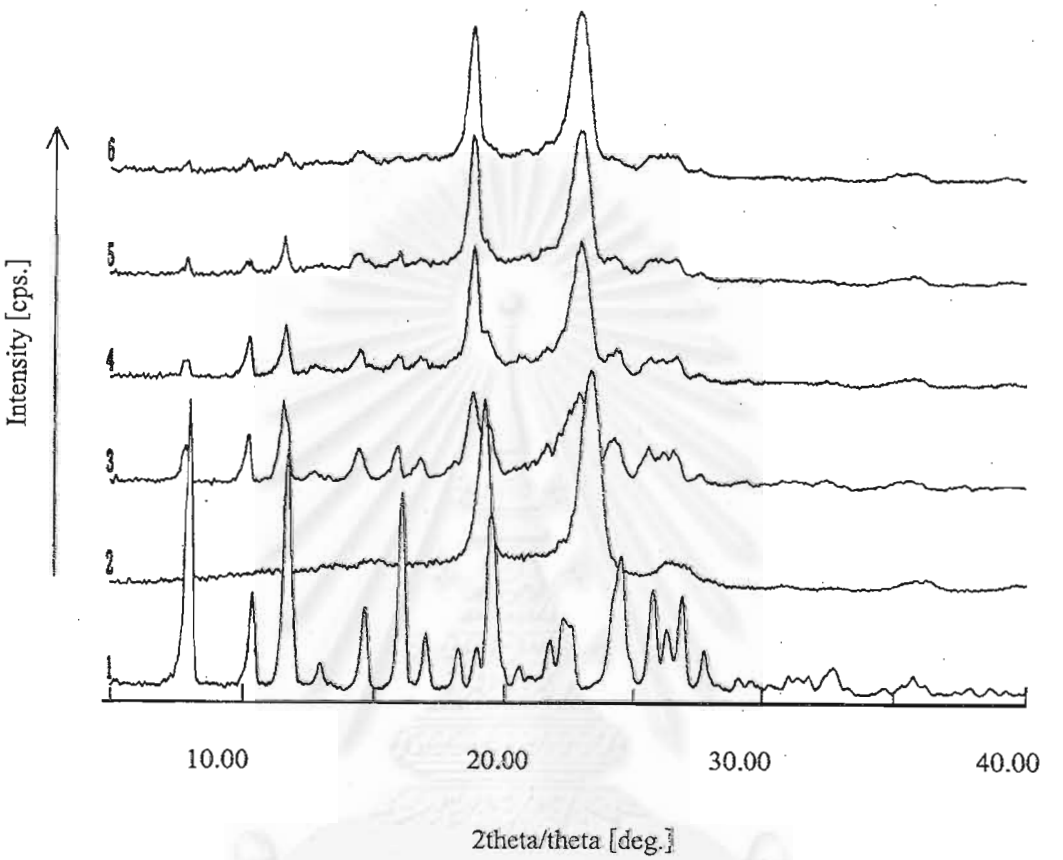


Figure 89 Powder X-ray diffraction patterns of nifedipine-poloxamer 407 system prepared by kneading method (1) nifedipine, (2) poloxamer 407,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

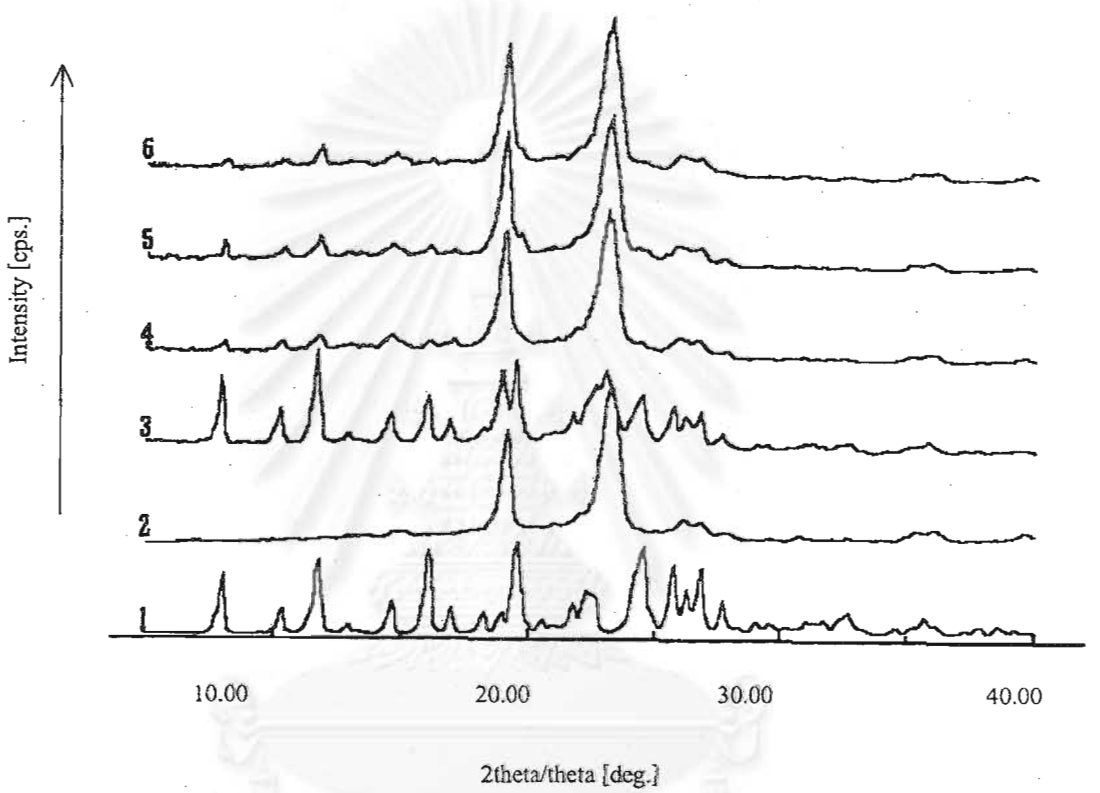


Figure 90 Powder X-ray diffraction patterns of nifedipine- poloxamer98 system prepared by physical mixing (1) nifedipine, (2) poloxamerF98, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

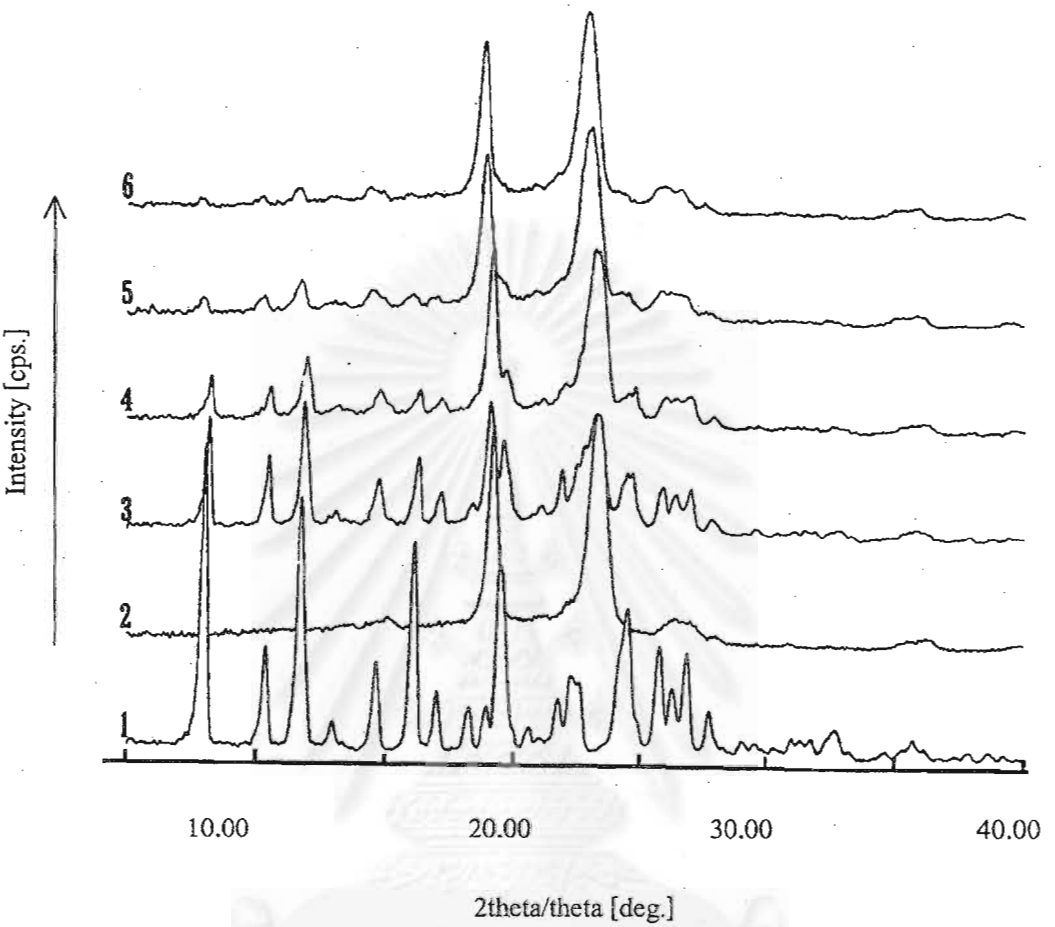


Figure 91 Powder X-ray diffraction patterns of nifedipine-poloxamer 98 system prepared by melting method (1) nifedipine, (2) poloxamer 98,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

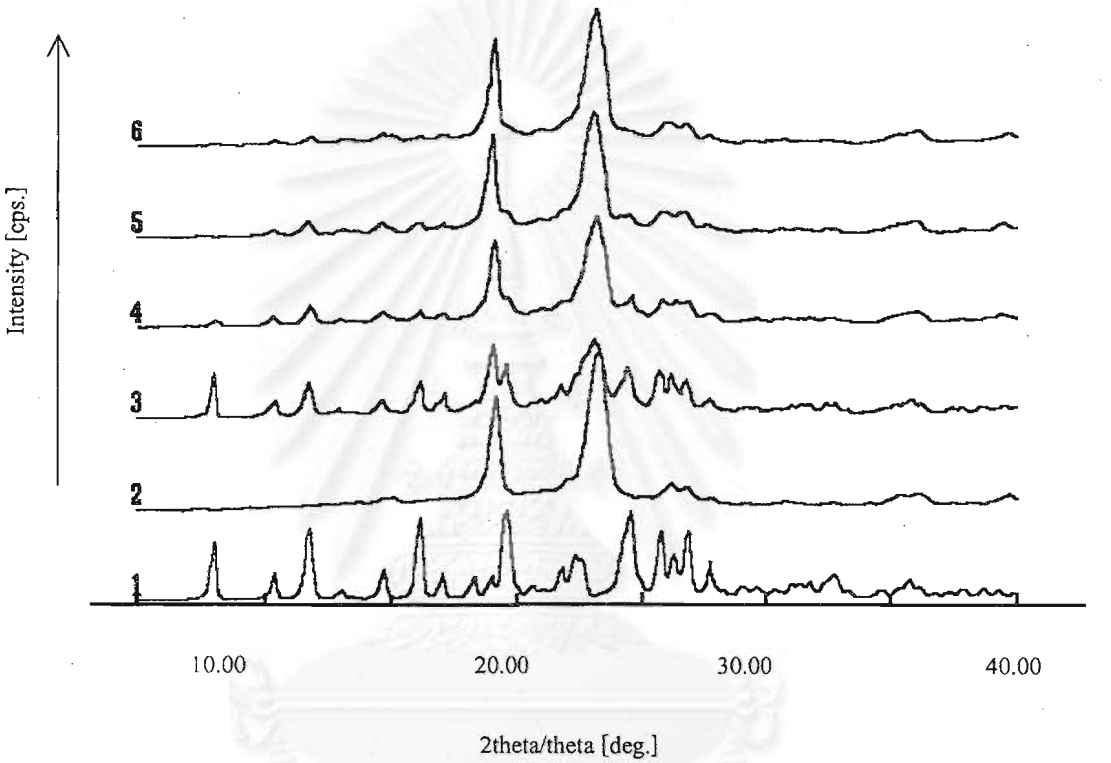


Figure 92 Powder X-ray diffraction patterns of nifedipine-poloxamer98 system prepared by solvent method (1) nifedipine, (2) poloxamerF98,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

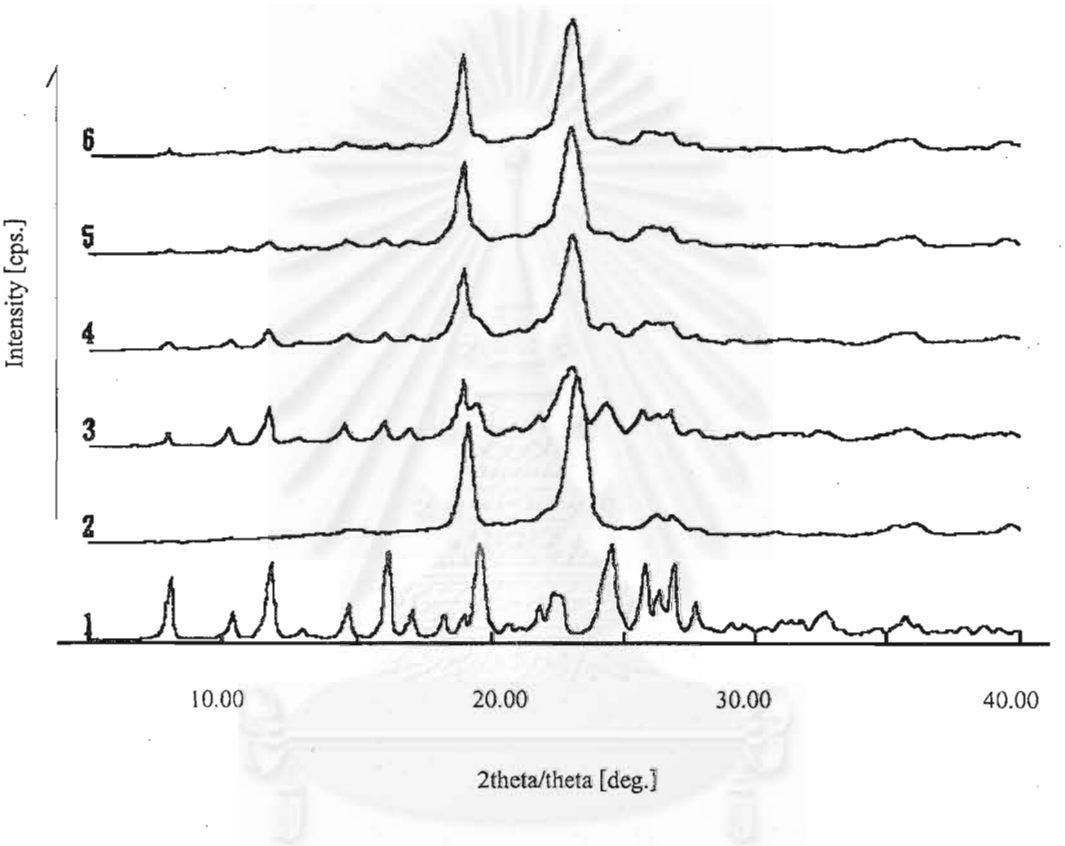


Figure 93 Powder X-ray diffraction patterns of nifedipine-poloxamer98 system prepared by kneading method (1) nifedipine, (2) poloxamerF98,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

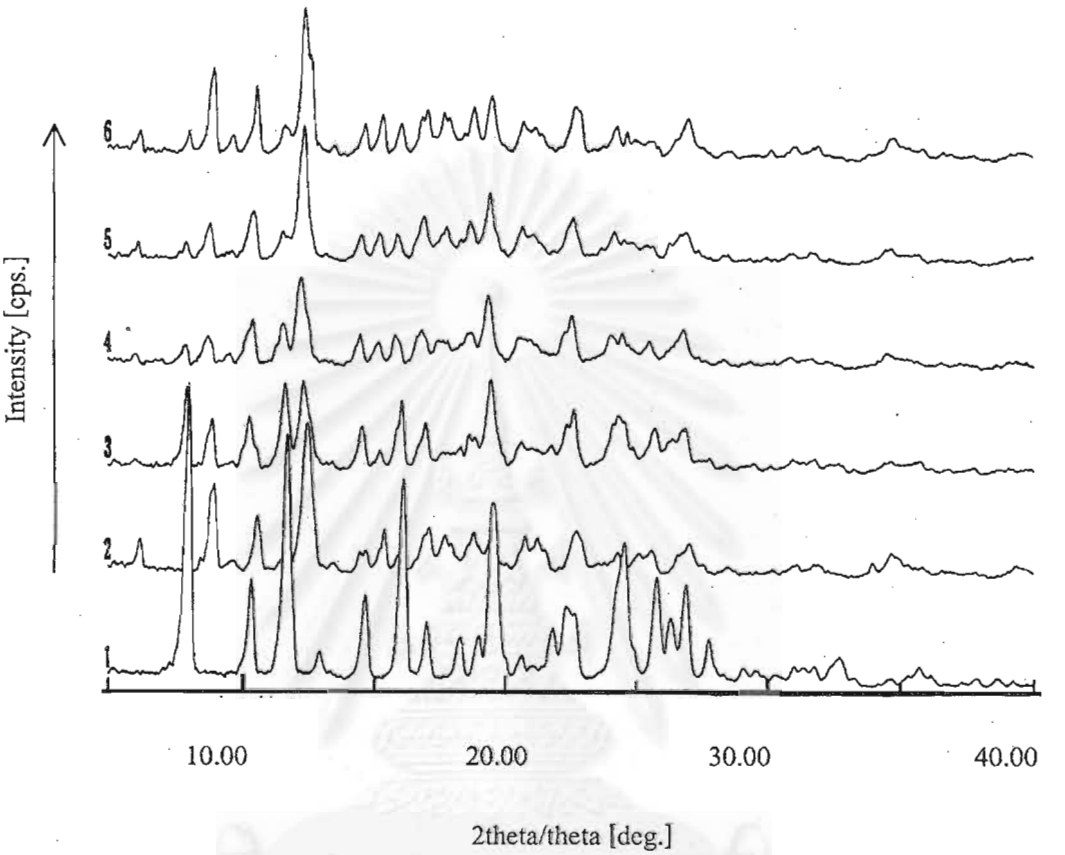


Figure 94 Powder X-ray diffraction patterns of nifedipine-betacyclodextrin(BCD) system prepared by physical mixing (1) nifedipine, (2) BCD,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

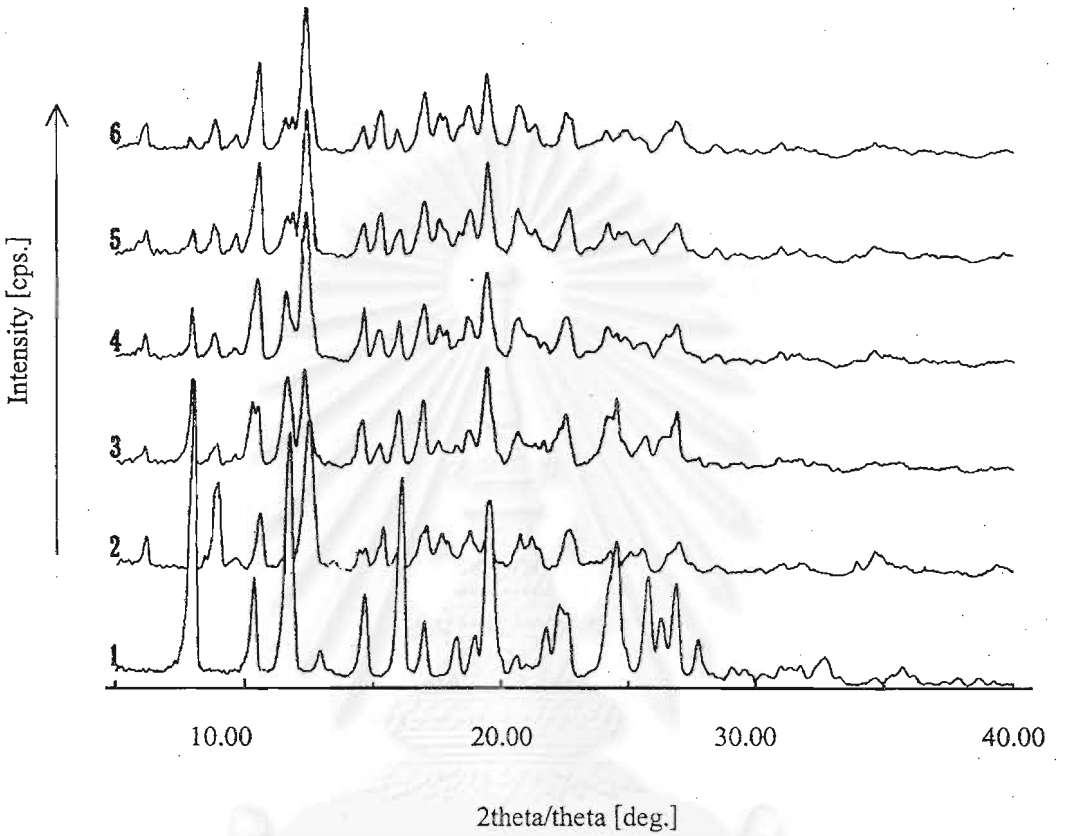


Figure 95 Powder X-ray diffraction patterns of nifedipine-betacyclodextrin(BCD) system prepared by kneading method (1) nifedipine, (2) BCD,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

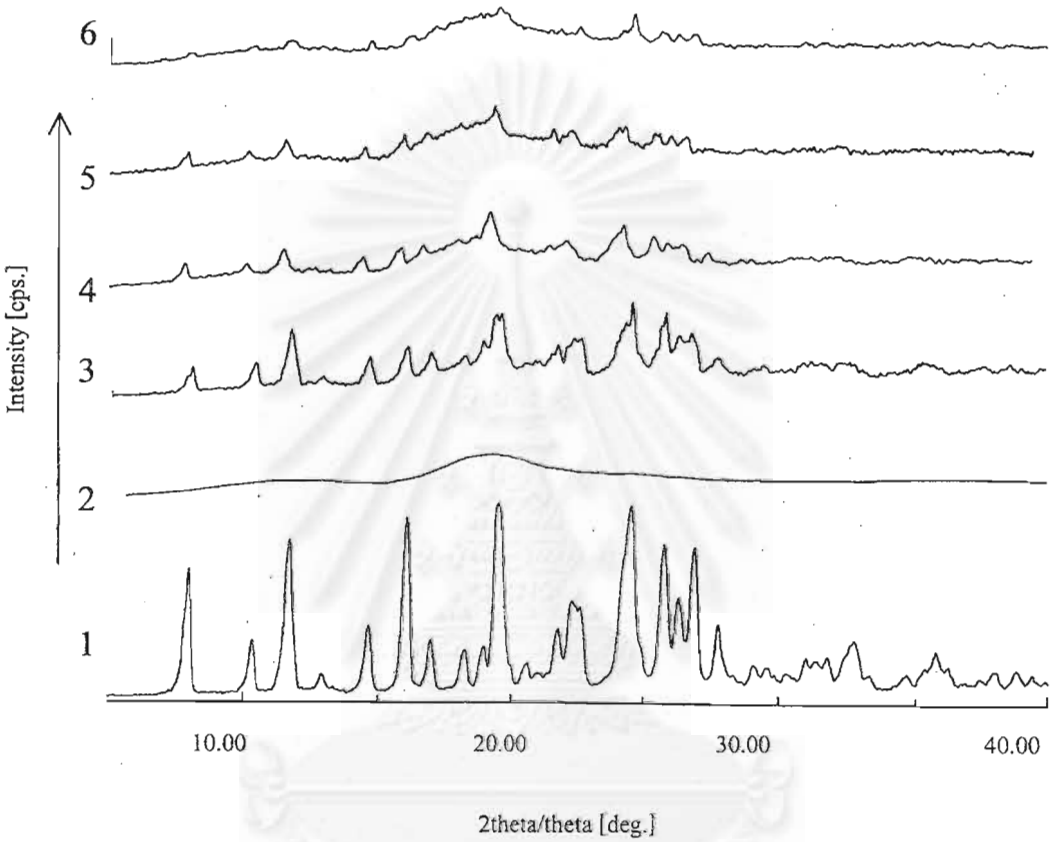


Figure96 Powder X-ray diffraction patterns of nifedipine-2-hydroxypropyl betacyclodextrin system prepared by physical mixing (1) nifedipine, (2) HPBCD,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

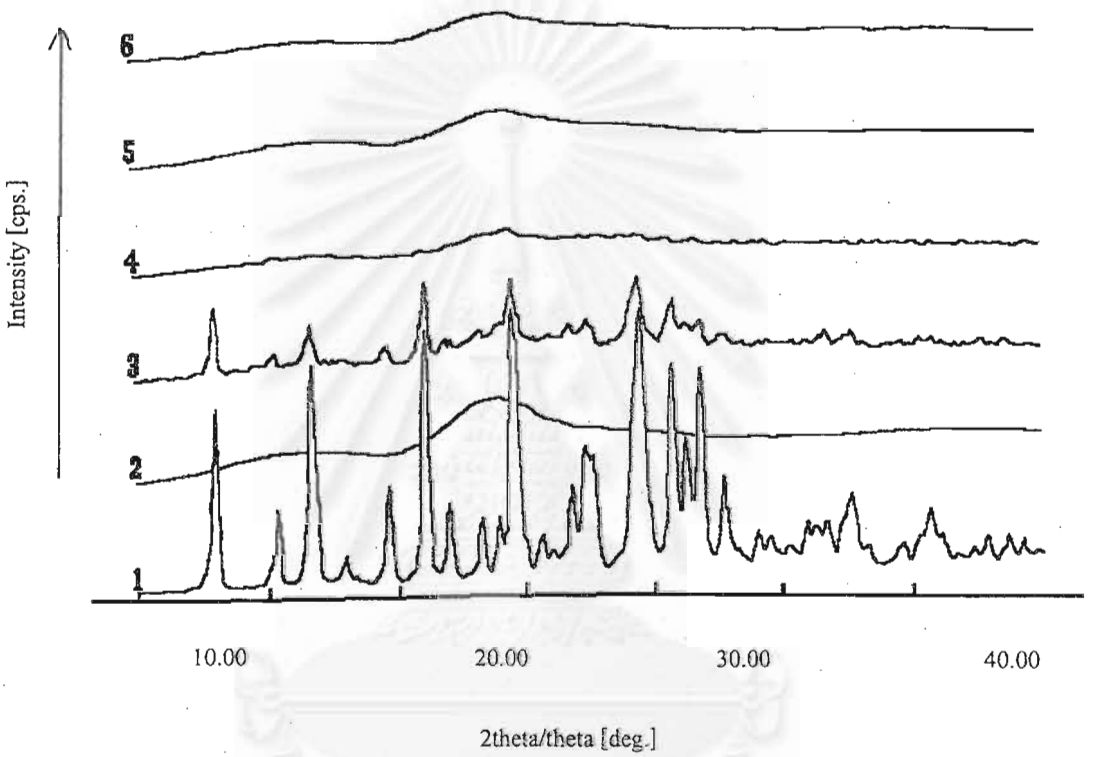


Figure97 Powder X-ray diffraction patterns of nifedipine-2-hydroxypropyl beta-cyclodextrin system prepared by solvent method (1) nifedipine, (2) HPBCD, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

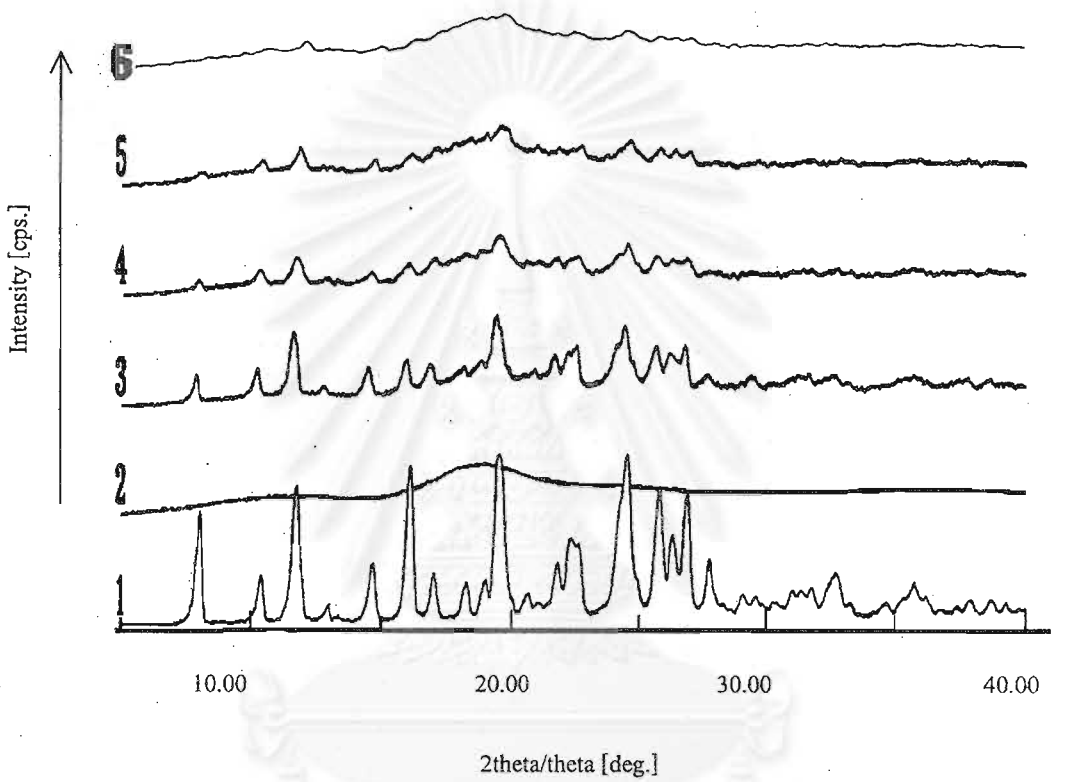


Figure98 Powder X-ray diffraction patterns of nifedipine-hydroxypropyl betacyclodextrin system prepared by kneading method (1) nifedipine, (2) HPBCD, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

5.3 X-ray diffractogram of nifedipine-poloxamers solid dispersion

The X-ray diffractograms of poloxamer system are demonstrated in **Figures 82-93.** In the case of poloxamers, the result in the system was similar to PEG systems that when the mixing ratio of carrier was increased, the major peaks of nifedipine gradually decreased. However, these peaks did not completely disappeared since they could be observed as very little ones even in the 1:10 ratio. Obviously, it showed that the crystalline peaks of poloxamer188, poloxamer288 and poloxamer407 were stilled observed very similarly at 19.3° and 23.4° throughout all dispersion systems non regarding to mixing ratios and preparation methods.

5.4 X-ray diffractogram of nifedipine-cyclodextrins solid dispersion

It was revealed that each mixing ratio in physical mixture and kneading of β-cyclodextrin, the diffraction peaks of nifedipine could still be found but 2-3 times less intensity than nontreated nifedipine. Moreover the crystalline peaks observed in all systems additionally resulted from the crystallinity of β-cyclodextrin itself. Diffraction peaks at 8.9°, 10.6°, and 12.5° were the major peaks of β-cyclodextrin **(Figures 94-95).** In contrary, 2-hydroxypropyl- β-cyclodextrin itself **(Figures 96-98)** showed no diffraction peak as the holo pattern that revealed that it was in amorphous form. Physical mixtures of nifedipine with 2-hydroxypropyl- β-cyclodextrin at every mixing ratios even at the 1: 10 ratio, only nifedipine diffraction peaks could be found (**Figure 96**). From the dispersions of solvent method, the characteristic diffraction peaks of nifedipine disappeared at the ratio of 1:5 and 1:10. Thus, only the holo pattern of 2-hydroxypropyl- β-cyclodextrin could be found. For the kneading

method, the diffraction peaks of nifedipine showed an obvious decrease mostly to be a halo pattern. However, very little diffraction peaks could still be observed.

6. The Differential Scanning Calorimetry (DSC)

The DSC curves of pure nontreated nifedipine, treated nifedipine, pure carriers, physical mixtures and solid dispersions of nifedipine prepared with various ratio of carriers and various methods are illustrated in **Figures 99-124.**

6.1 DSC thermorams of pure nifedipine and pure carriers

The DSC curves of pure nontreated nifedipine **(Figure 99)** showed the characteristic melting endotherm at 174.8 °C. Nifedipine treated by physical mixing, melting, solvent and kneading method showed the similar melting endotherms at 174.6, 174.6, 174.4 and 174.6 °C respectively.

The thermogram of PEGs displayed the endothermic peak approximately at 62.0 °C for PEG4000 and 62.2 °C for PEG6000 **(Figures 100-107).**

For poloxamers, the endothermic peaks showed the melting point at 54.6 °C for poloxamer188, 60.5 °C for poloxamer288 and 57.5 °C for poloxamer407 **(Figure 108-119).**

β-Cyclodextrin **(Figure 120-121)** showed a broad endothermic peak of dehydration at 155.7 °C while 2-hydroxypropyl- β-cyclodextrin, **(Figure 122-124)** showed no endothermic peak in the experimental temperature range.

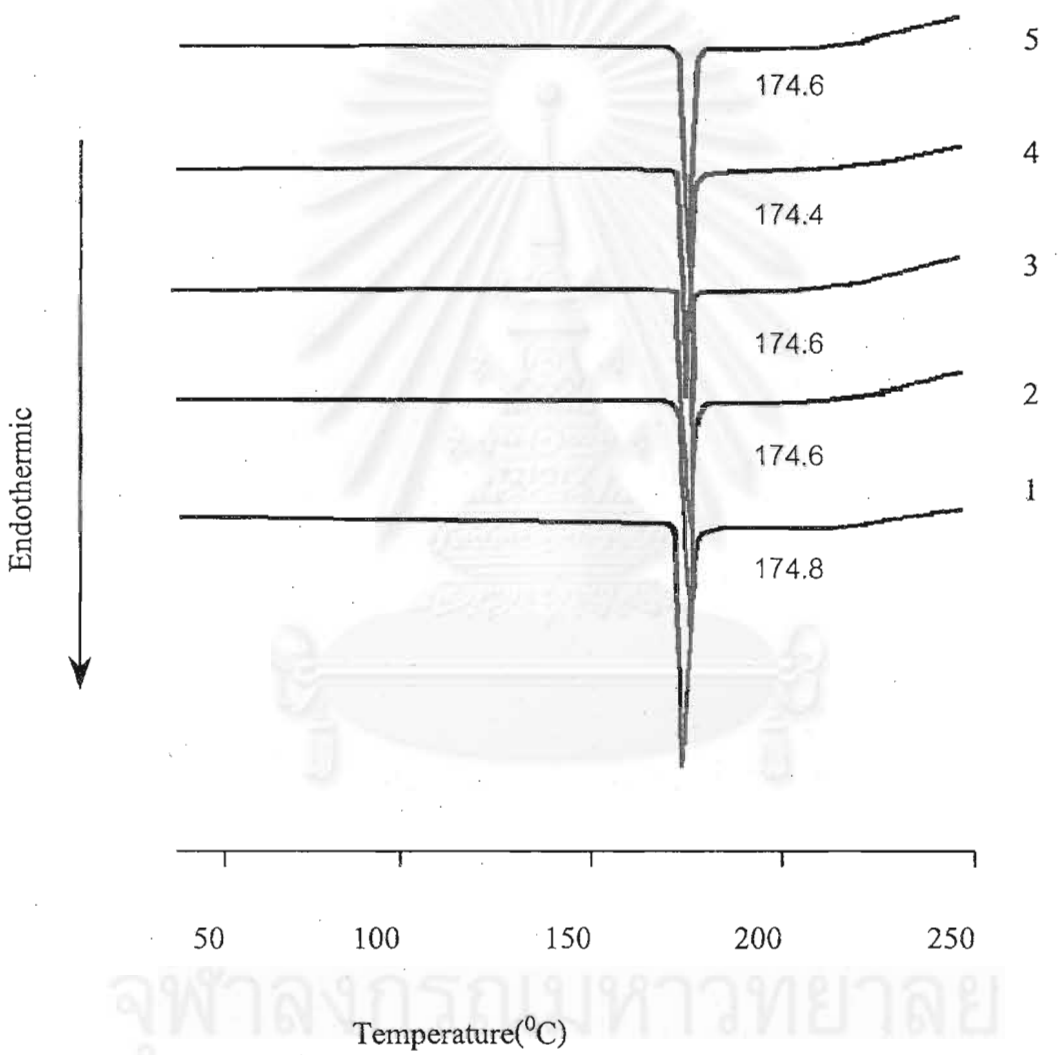


Figure 99: DSC curves of nontreated nifedipine (1) and treated nifedipine by (2) physical mixing , (3) melting method , (4) solvent method and (5) kneading method.

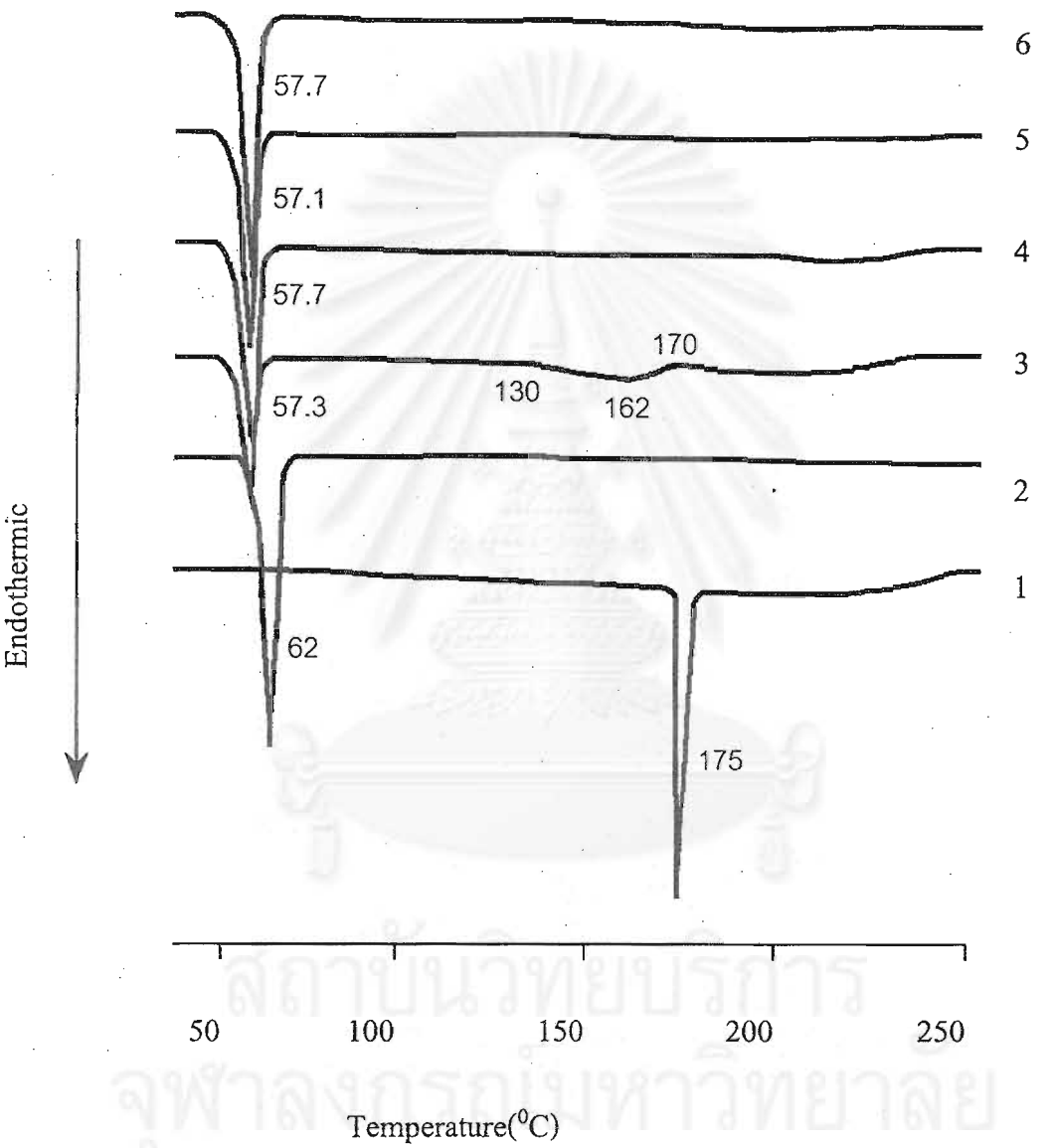


Figure 100: DSC curves of nifedipine - PEG 4000 physical mixtures containing nifedipine (1), PEG4000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

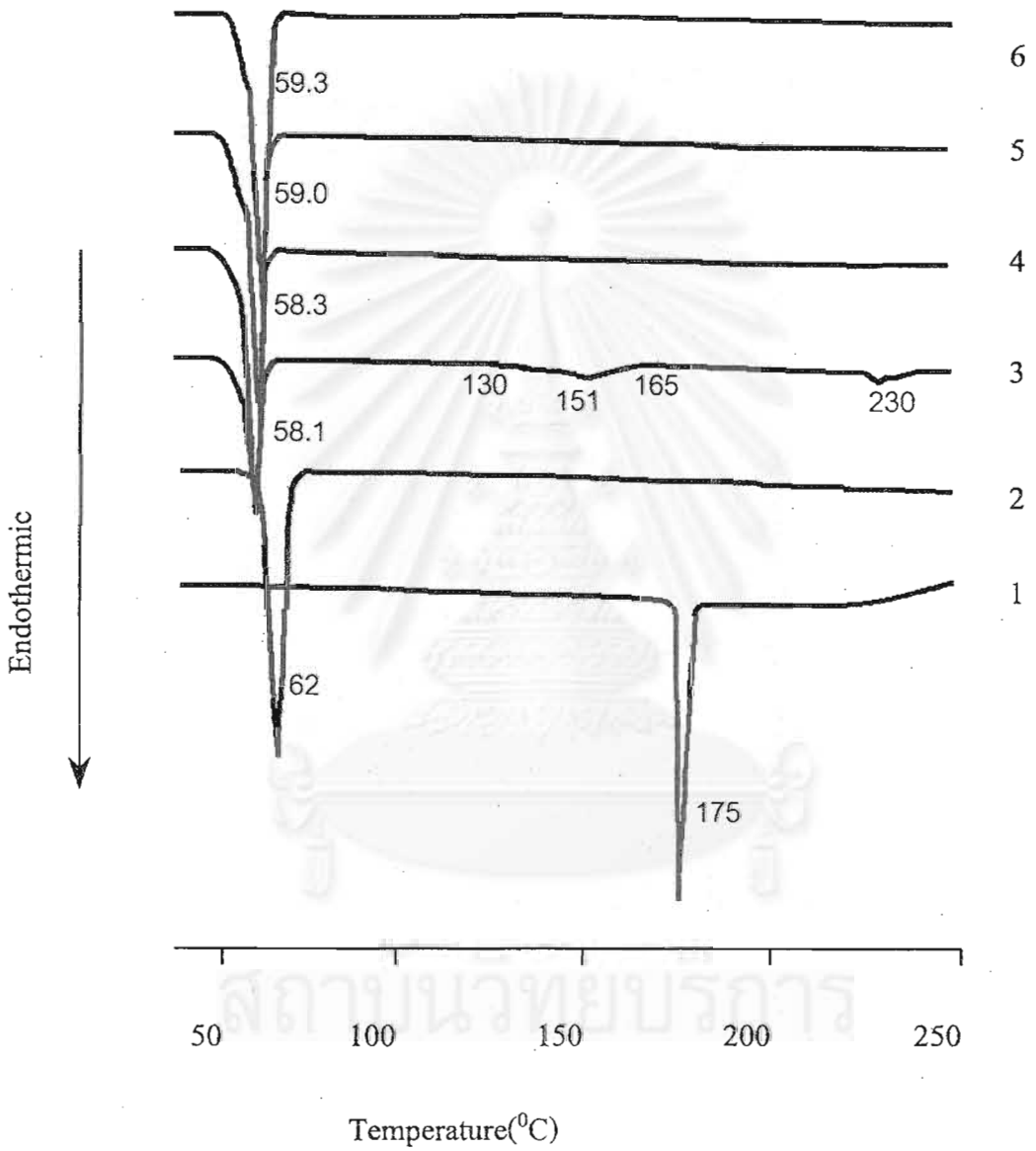


Figure 101: DSC curves of nifedipine - PEG 4000 solid dispersions prepared by melting method containing nifedipine (1), PEG 4000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

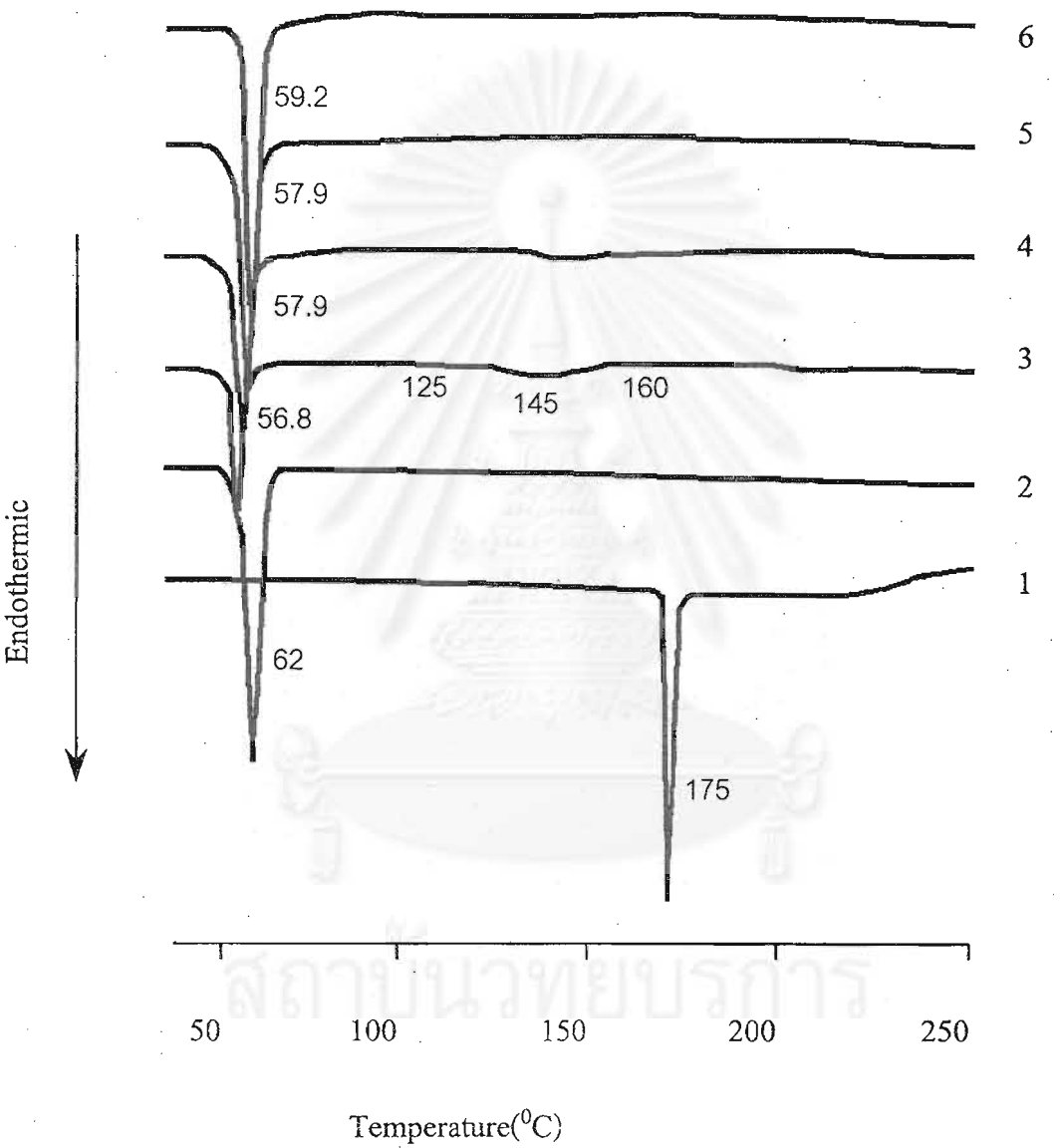


Figure 102: DSC curves of nifedipine - PEG 4000 solid dispersions prepared by solvent method containing nifedipine (1), PEG4000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

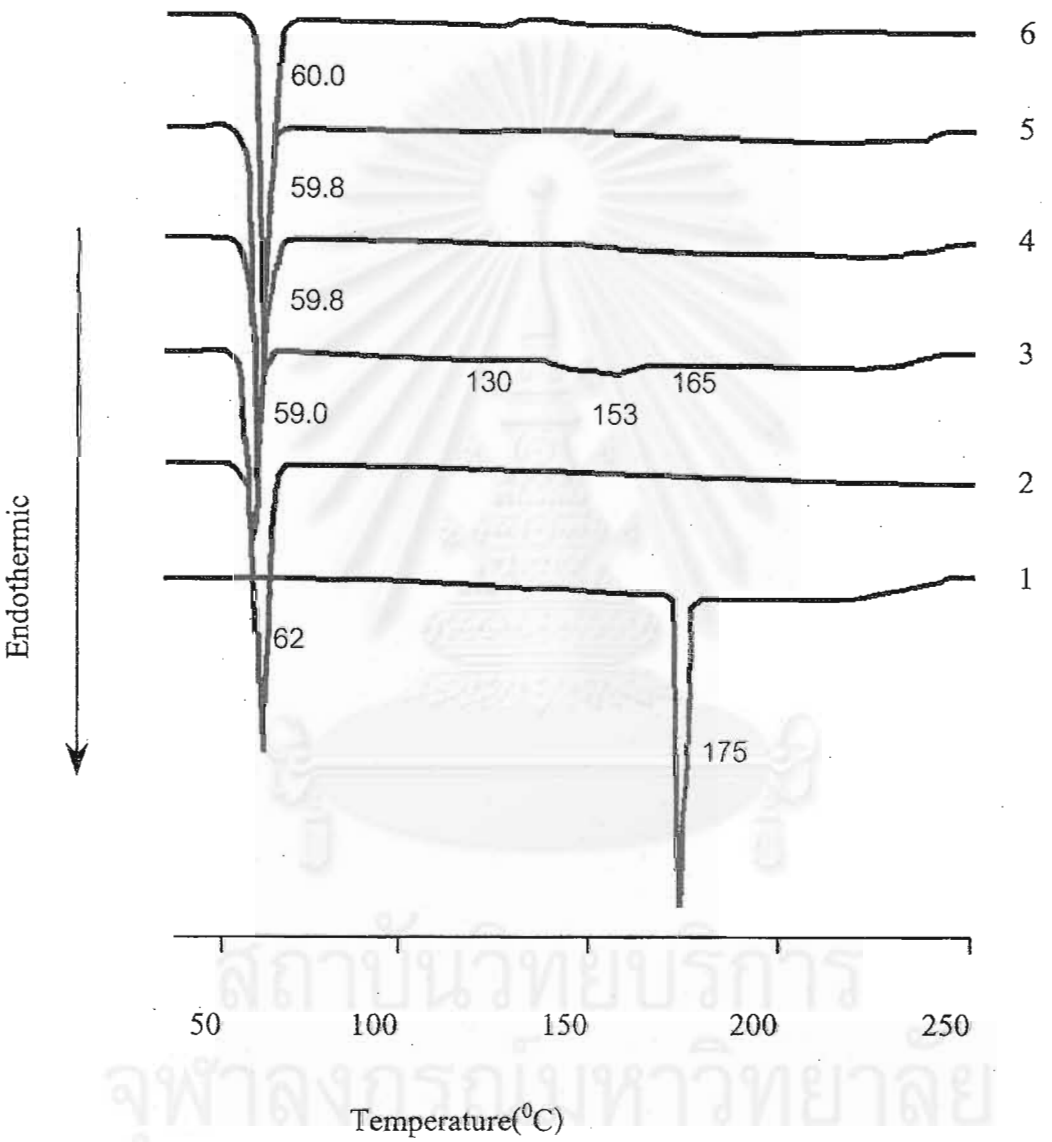


Figure 103: DSC curves of nifedipine - PEG 4000 solid dispersions prepared by kneading method containing nifedipine (1), PEG4000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

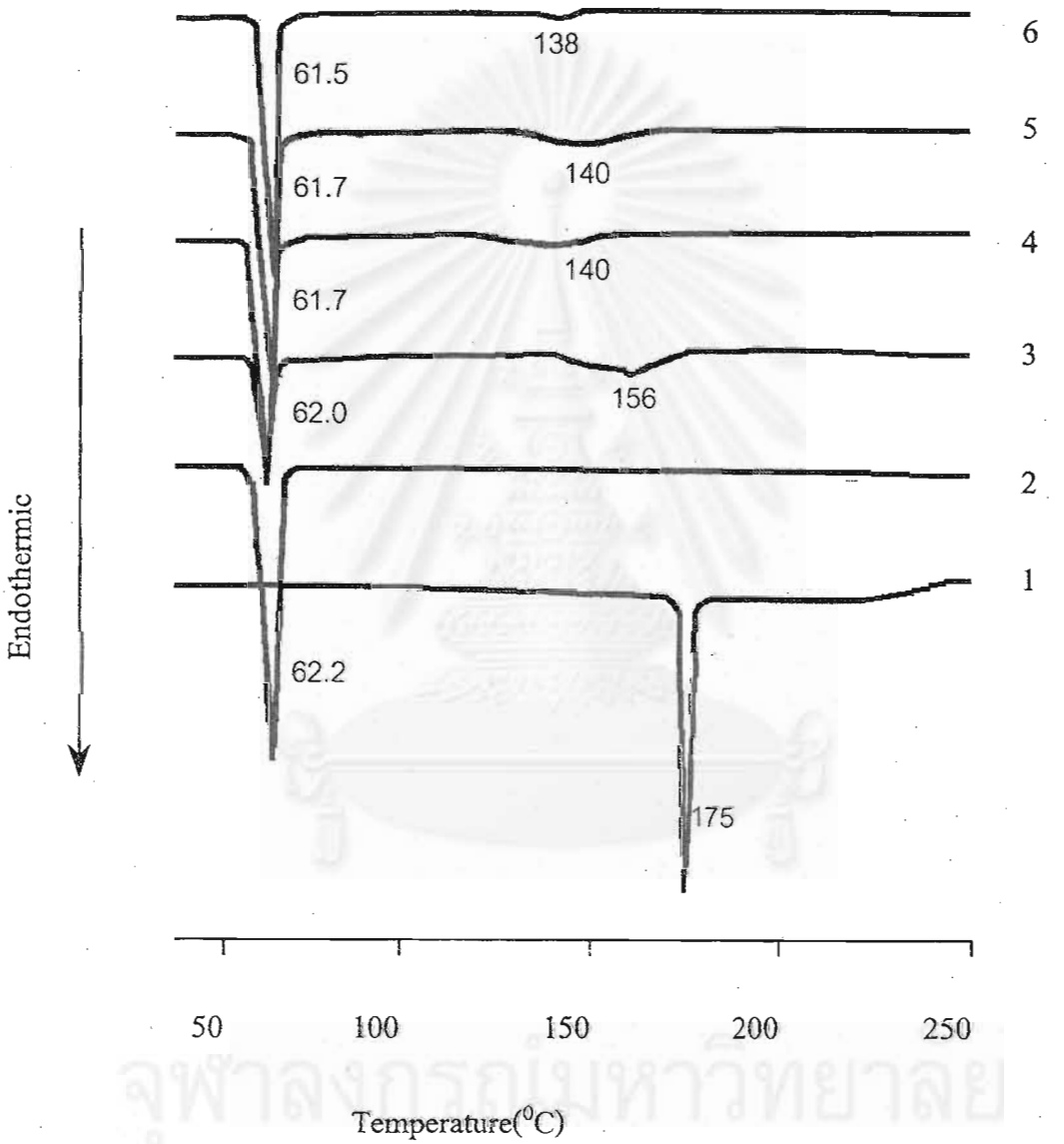


Figure 104: DSC curves of nifedipine - PEG 6000 physical mixtures containing nifedipine (1), PEG6000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

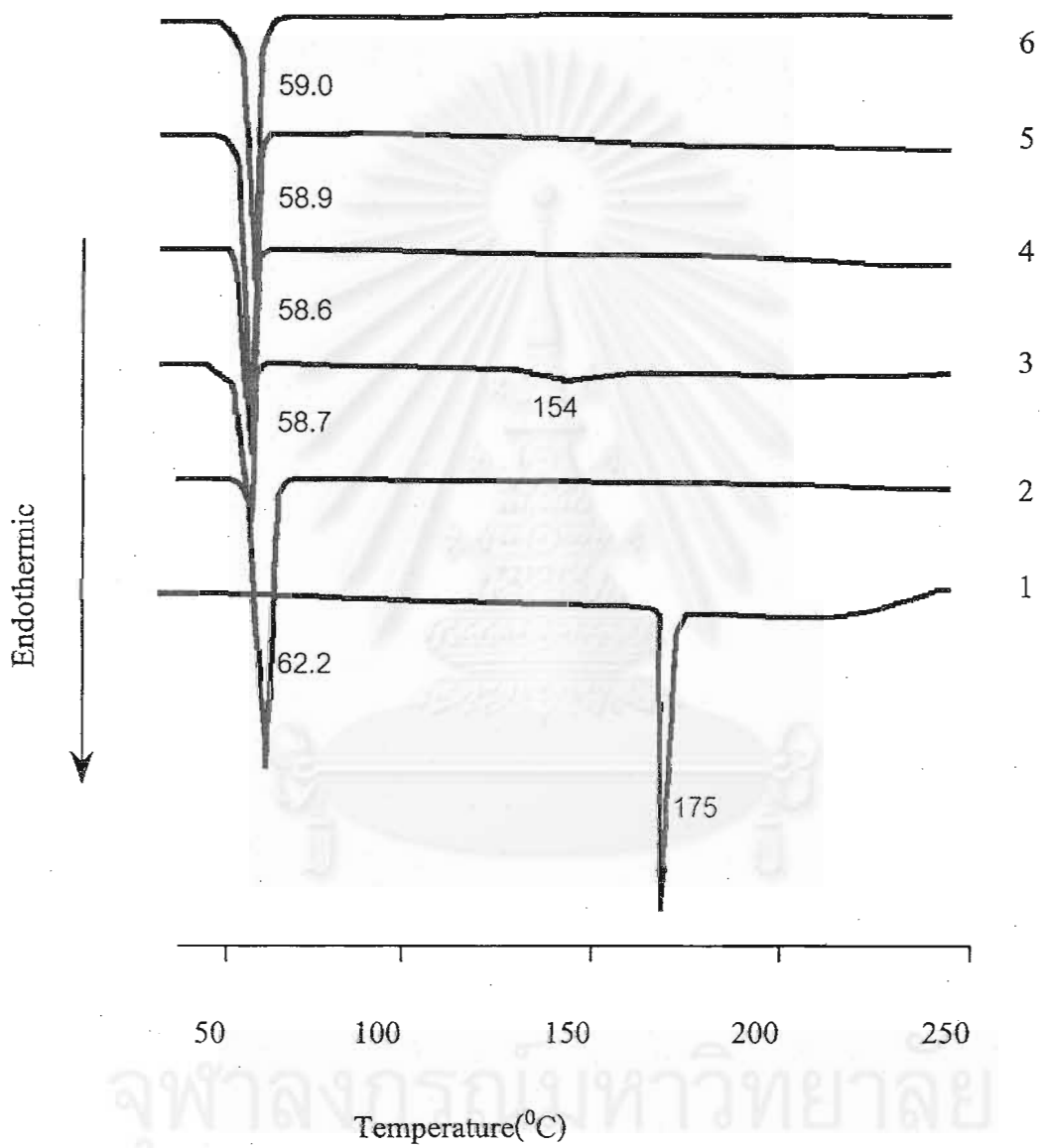


Figure 105: DSC curves of nifedipine - PEG 6000 solid dispersions prepared by melting method containing nifedipine (1), PEG6000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

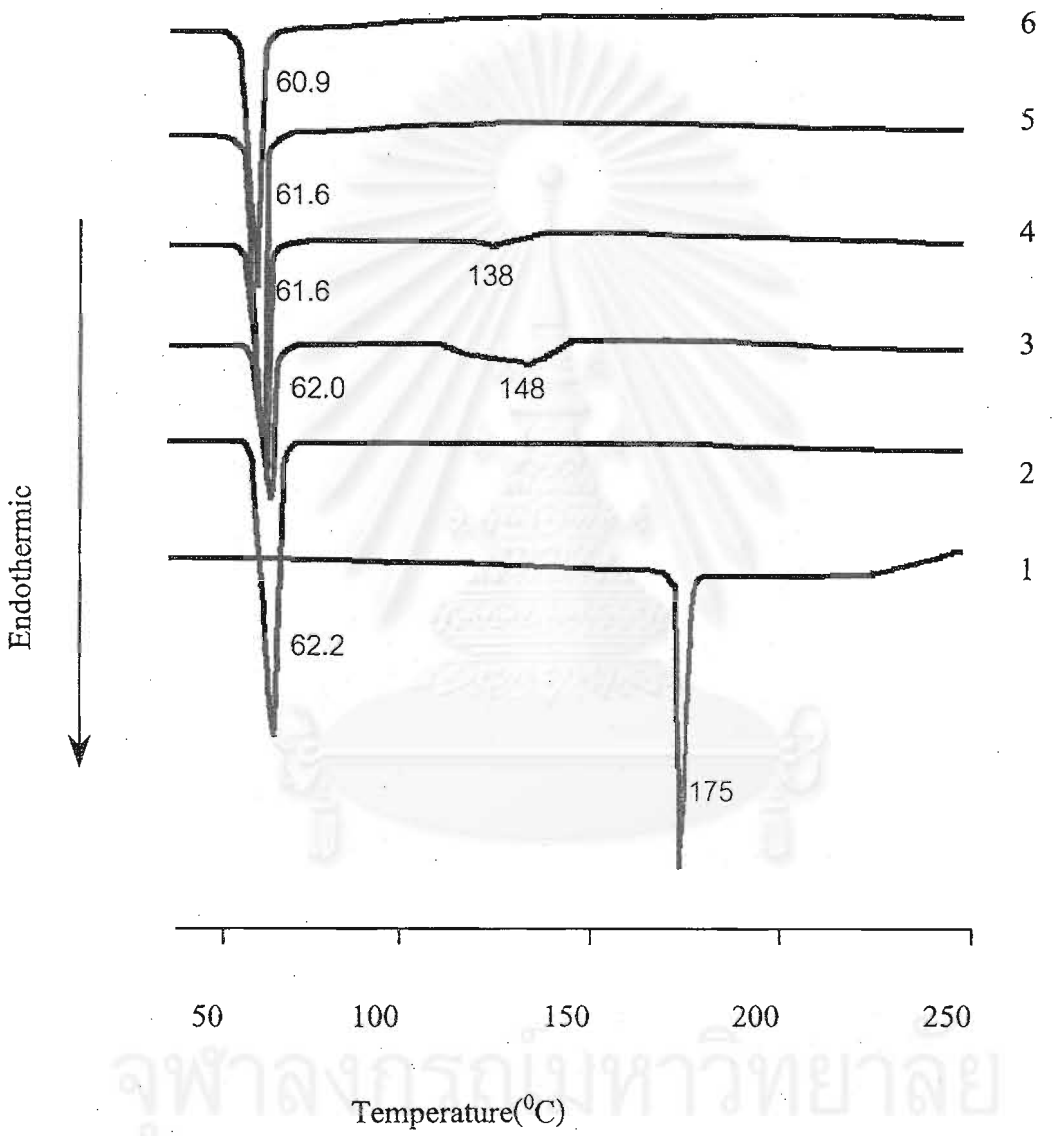


Figure 106: DSC curves of nifedipine - PEG 6000 solid dispersions prepared by solvent method containing nifedipine (1), PEG6000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

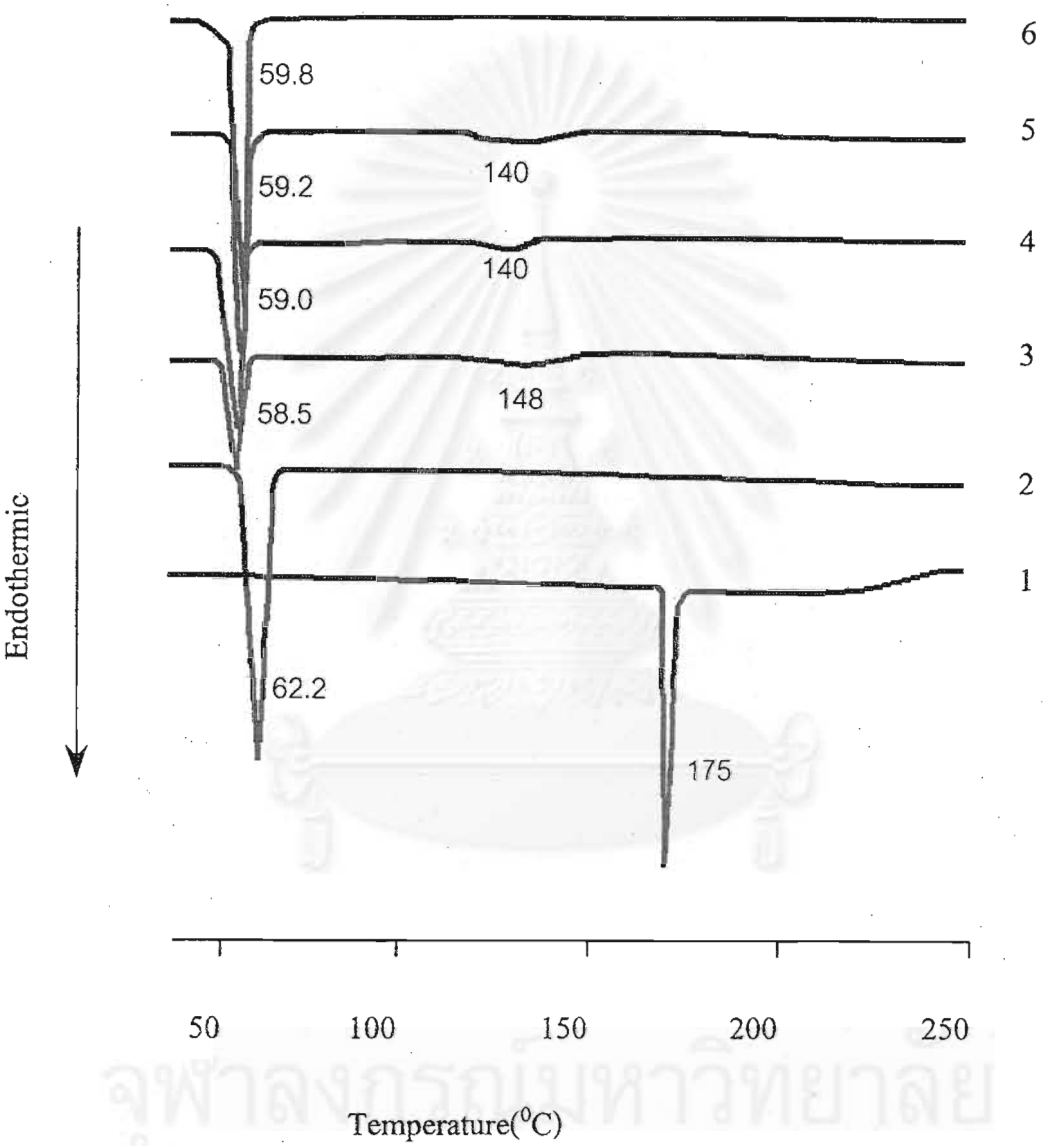


Figure 107: DSC curves of nifedipine - PEG 6000 solid dispersions prepared by kneading method containing nifedipine (1), PEG6000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

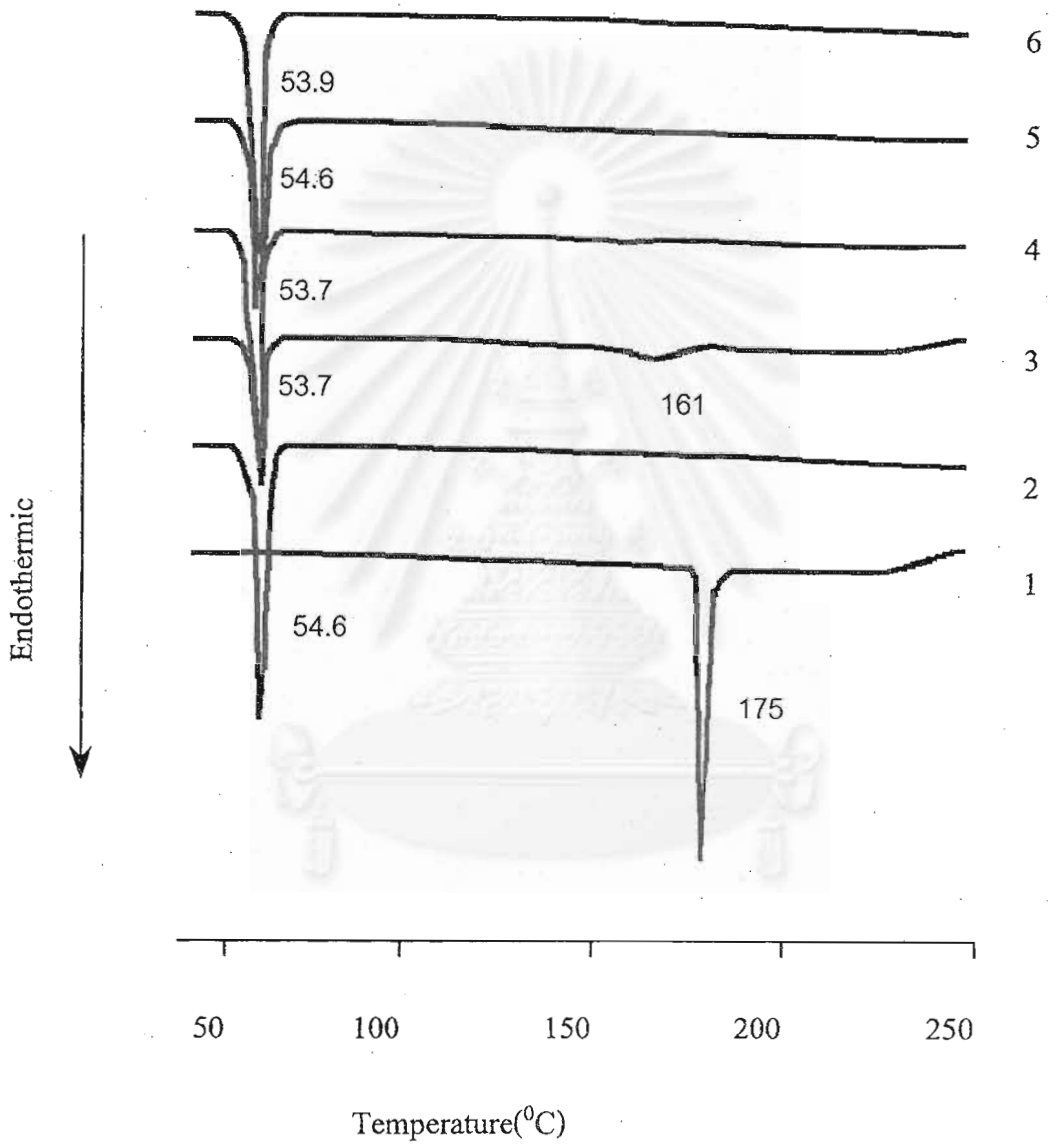


Figure 108: DSC curves of nifedipine - poloxamer 188 physical mixtures containing nifedipine (1), poloxamer 188(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

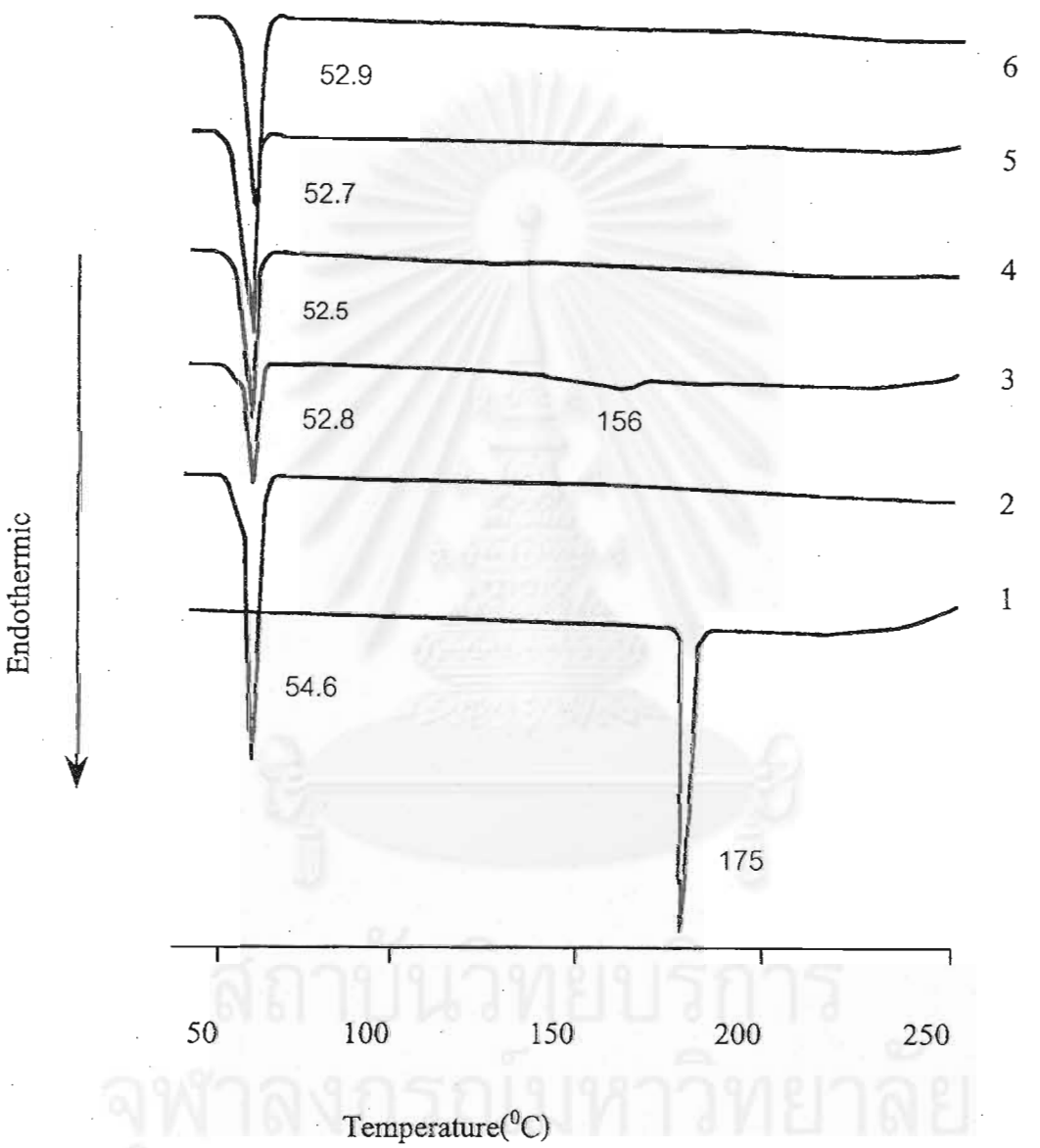


Figure 109 : DSC curves of nifedipine - poloxamer 188 solid dispersions prepared by melting method containing nifedipine (1), poloxamer 188(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

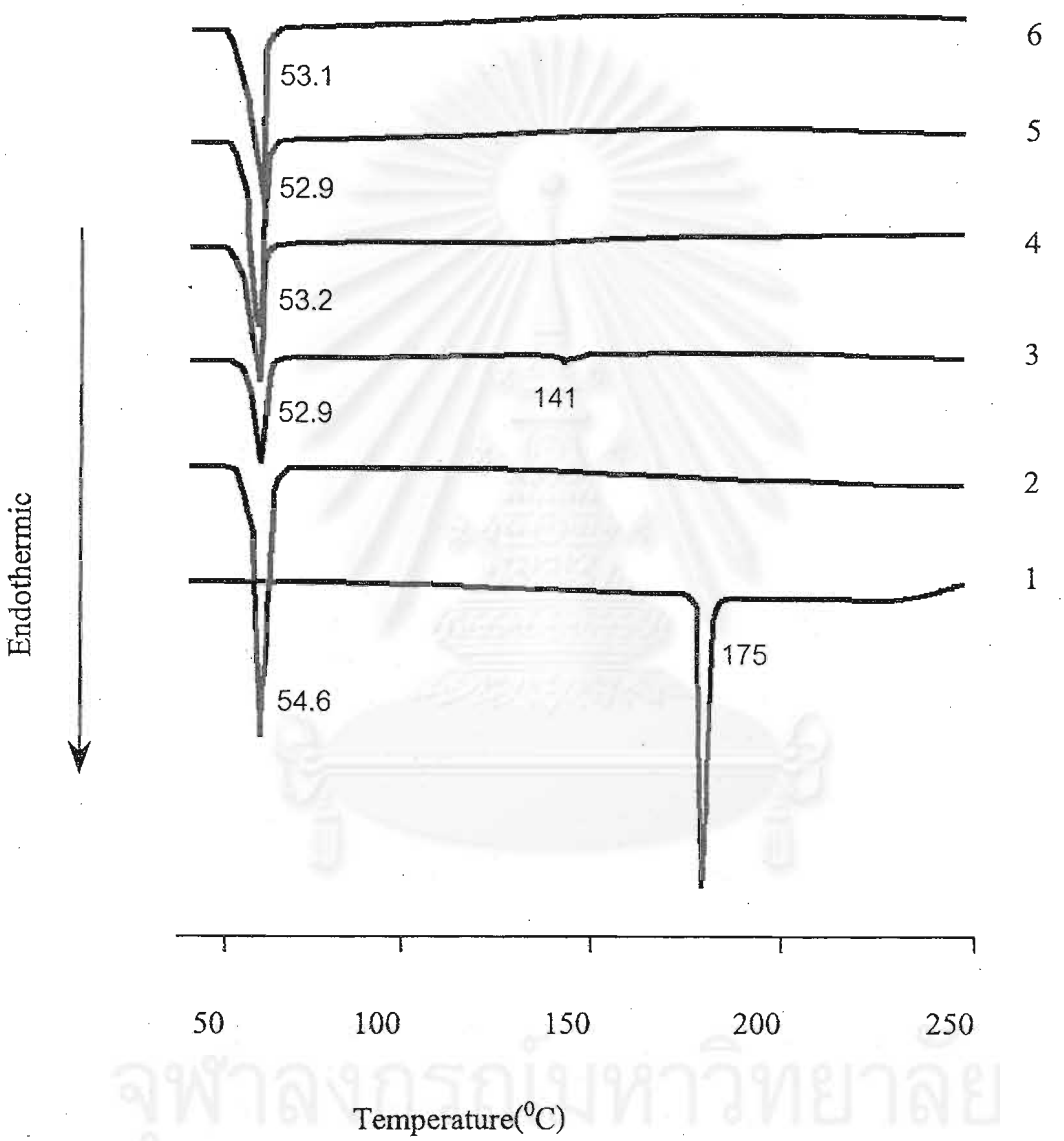


Figure 110: DSC curves of nifedipine - poloxamer 188 solid dispersions prepared by solvent method containing nifedipine (1), poloxamer 188(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

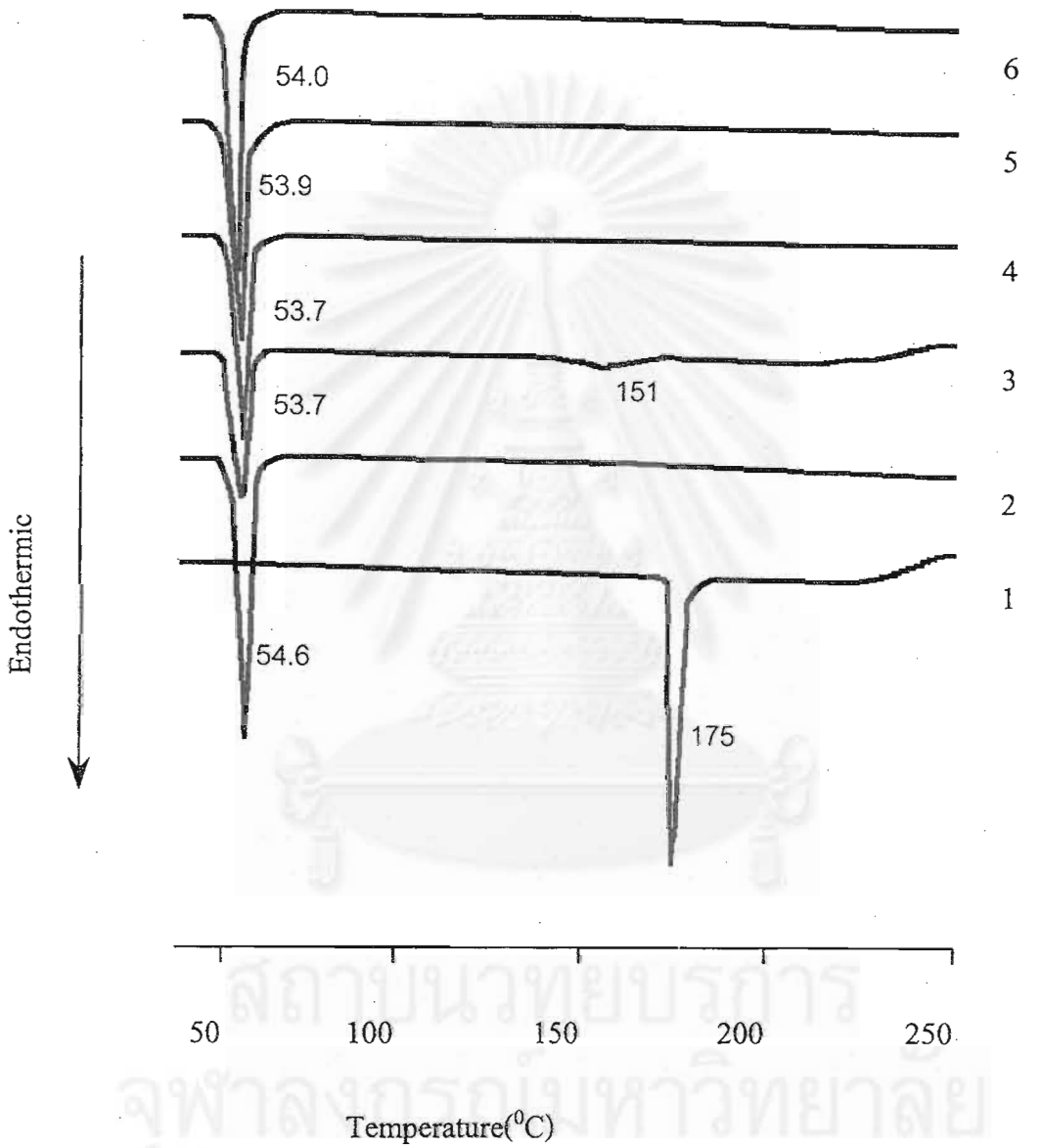


Figure 111: DSC curves of nifedipine - poloxamer 188 solid dispersions prepared by kneading method containing nifedipine (1), poloxamer 108(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

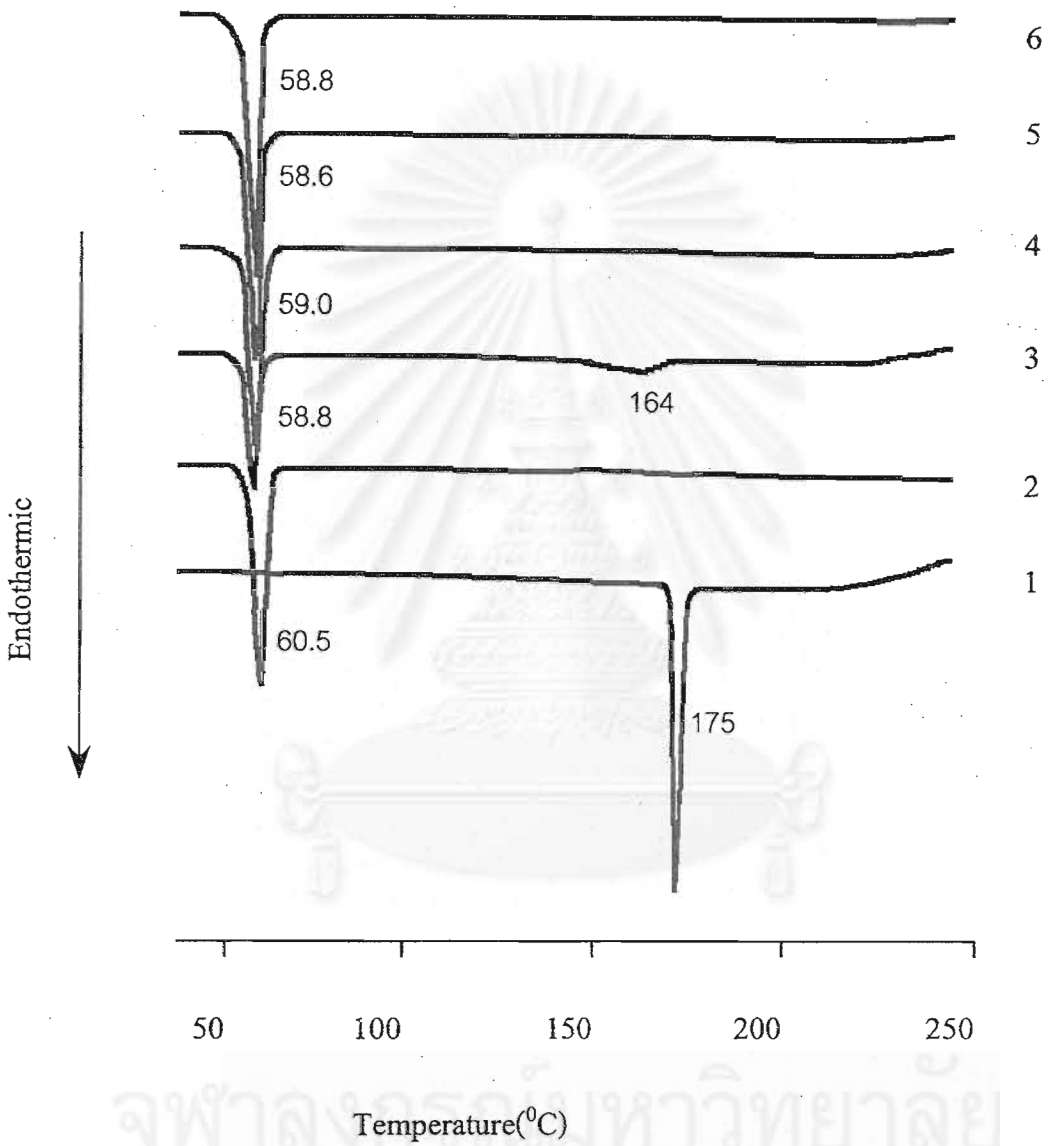


Figure 112 : DSC curves of nifedipine - poloxamer288 physical mixtures containing nifedipine (1), poloxamer288(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

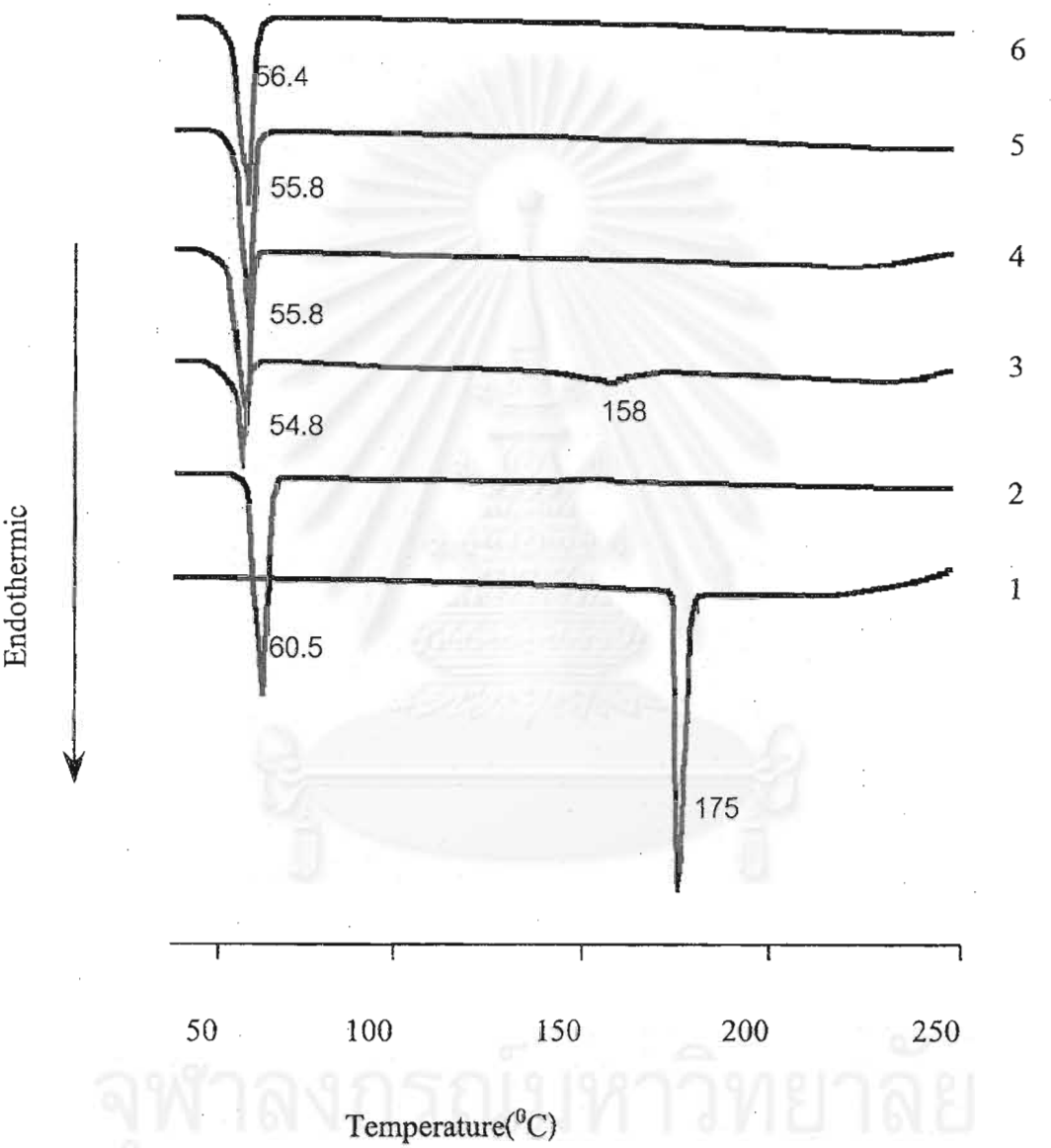


Figure 113: DSC curves of nifedipine - poloxamer288 solid dispersions prepared by melting method containing nifedipine (1), poloxamer288(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

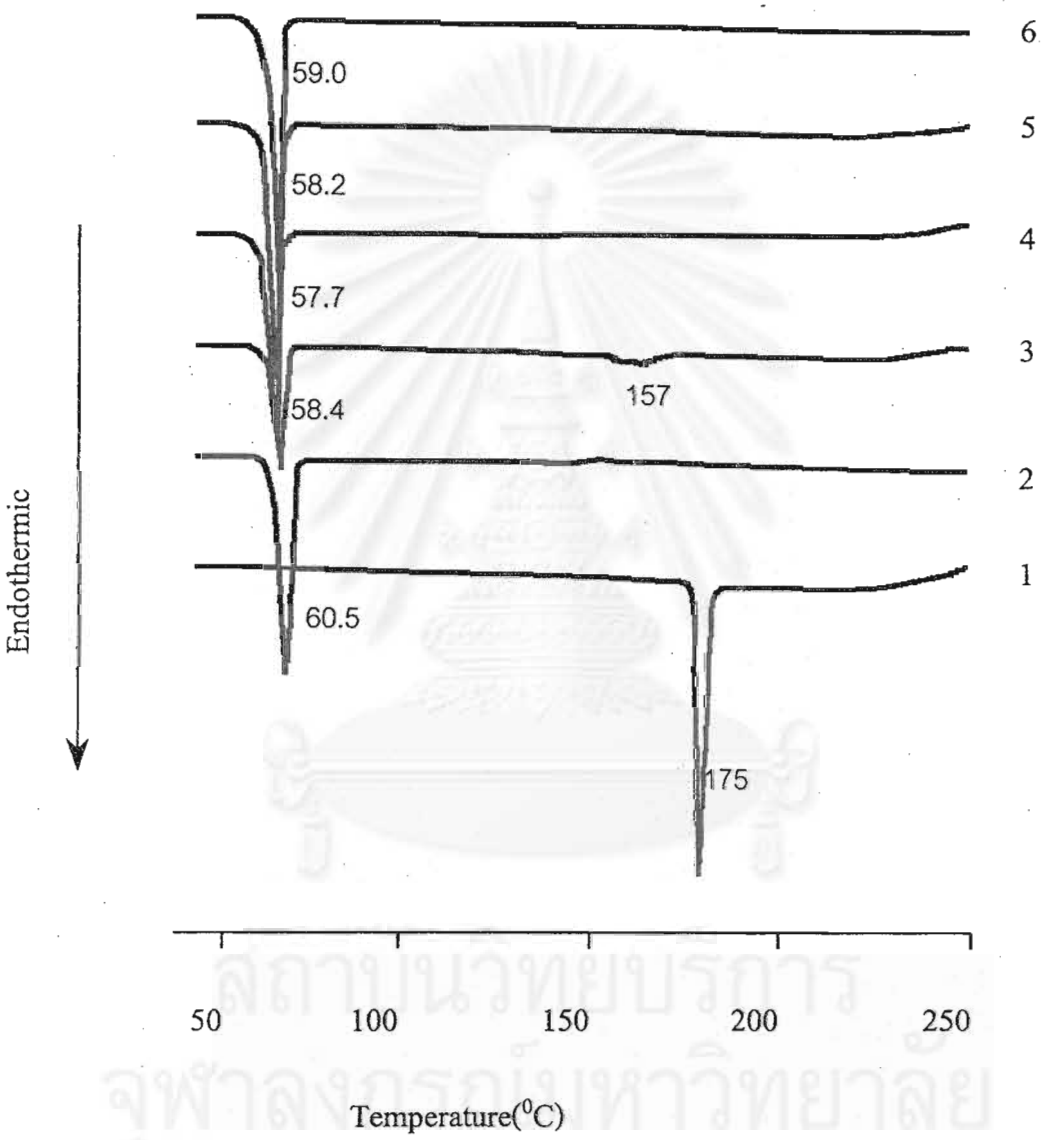


Figure 114: DSC curves of nifedipine - poloxamer288 solid dispersions prepared by solvent method containing nifedipine (1), poloxamer288(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

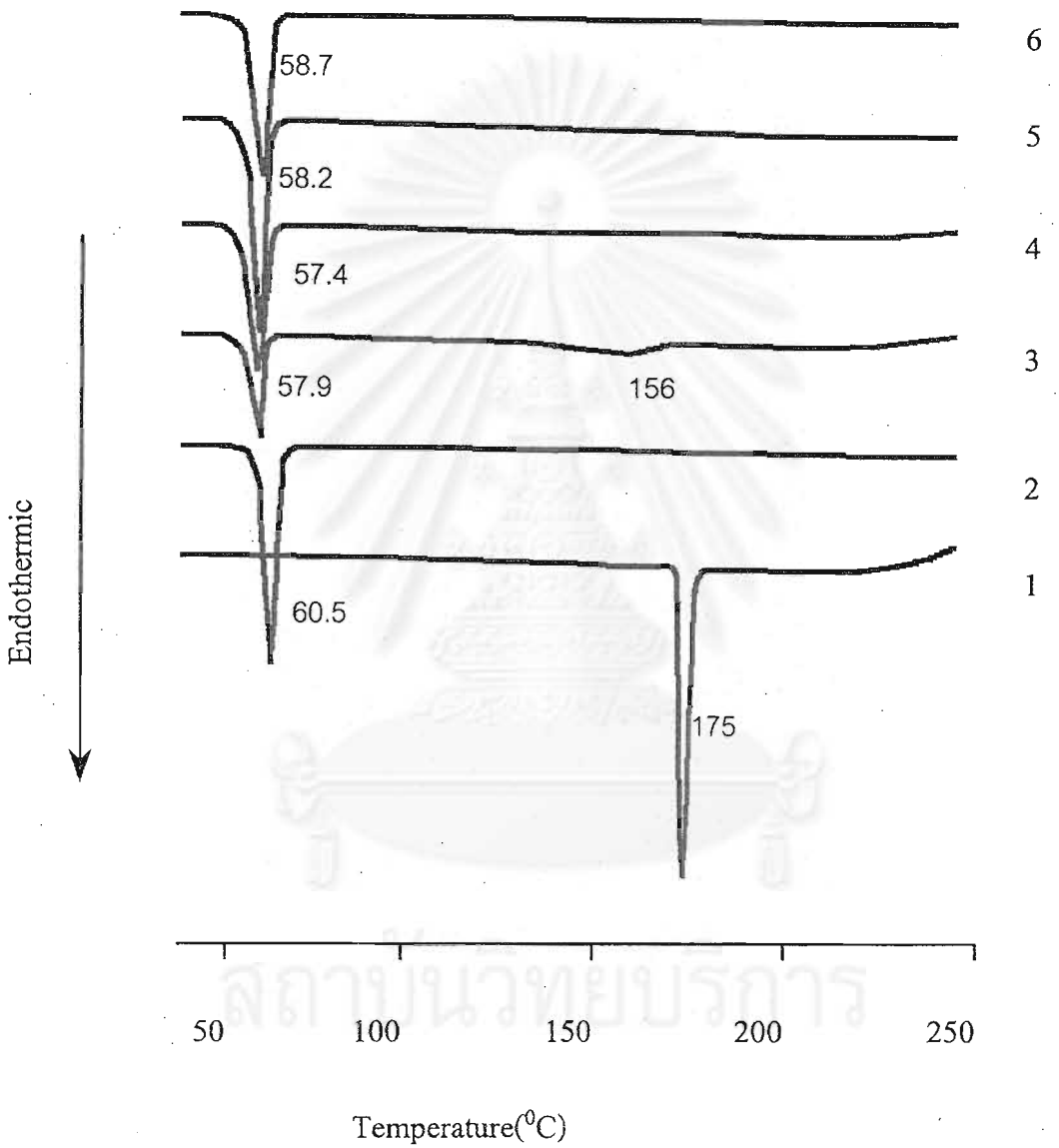


Figure 115: DSC curves of nifedipine - poloxamer288 solid dispersions prepared by kneading method containing nifedipine (1), poloxamer288(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

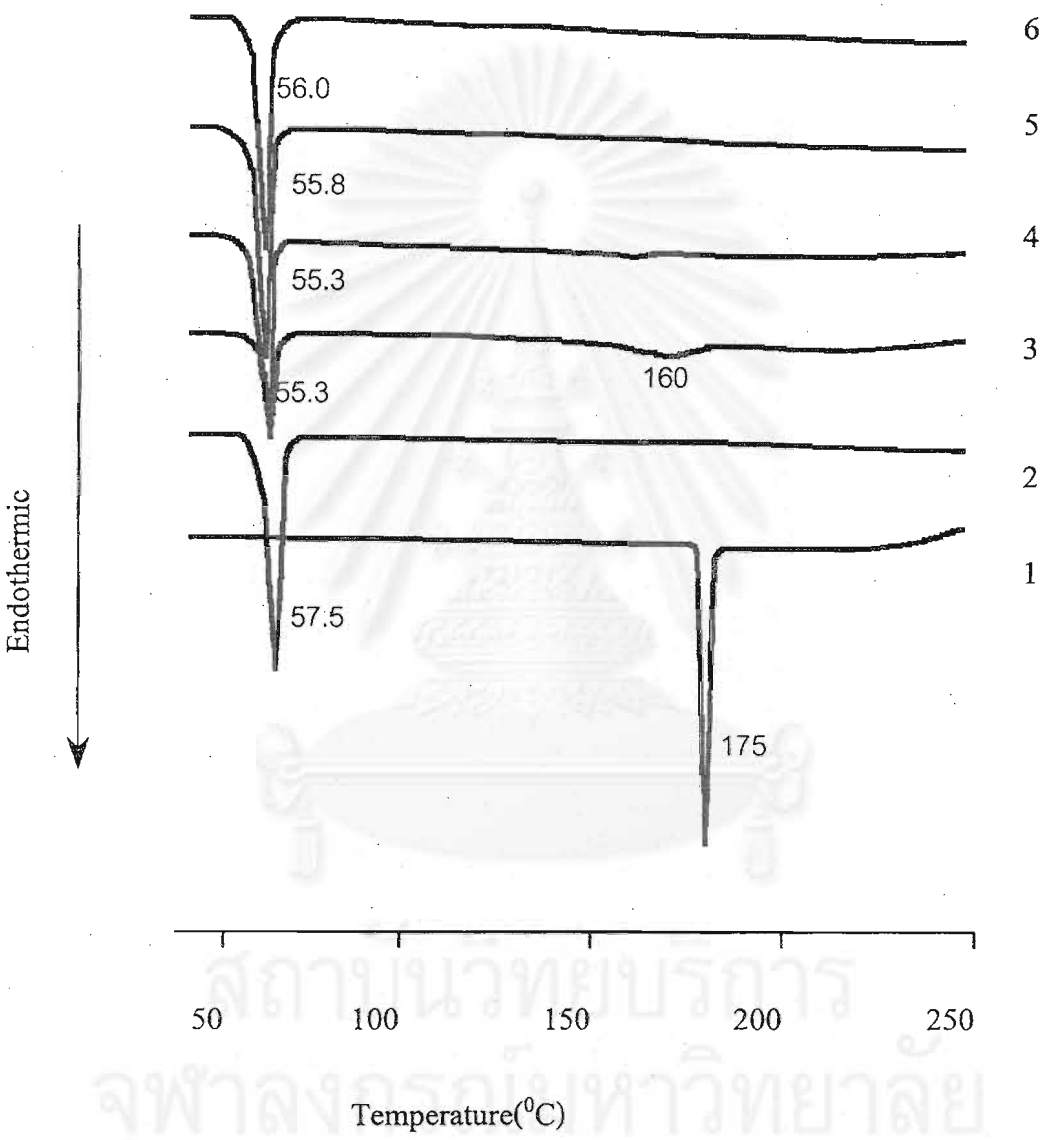


Figure 116: DSC curves of nifedipine - poloxamer 407 physical mixtures containing nifedipine (1), poloxamer 407(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

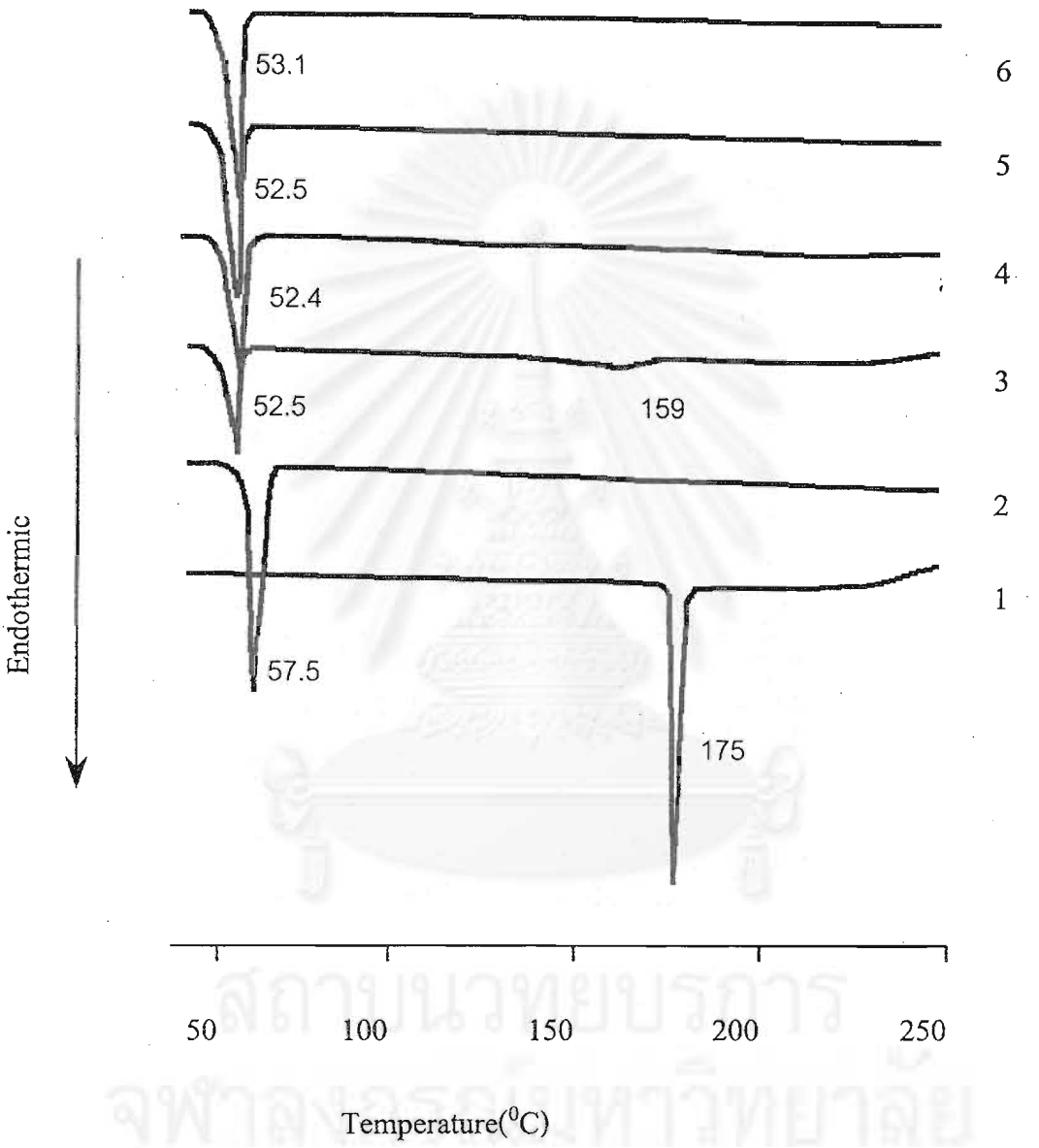


Figure 117: DSC curves of nifedipine - poloxamer 407 solid dispersions prepared by melting method containing nifedipine (1), poloxamer 407(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

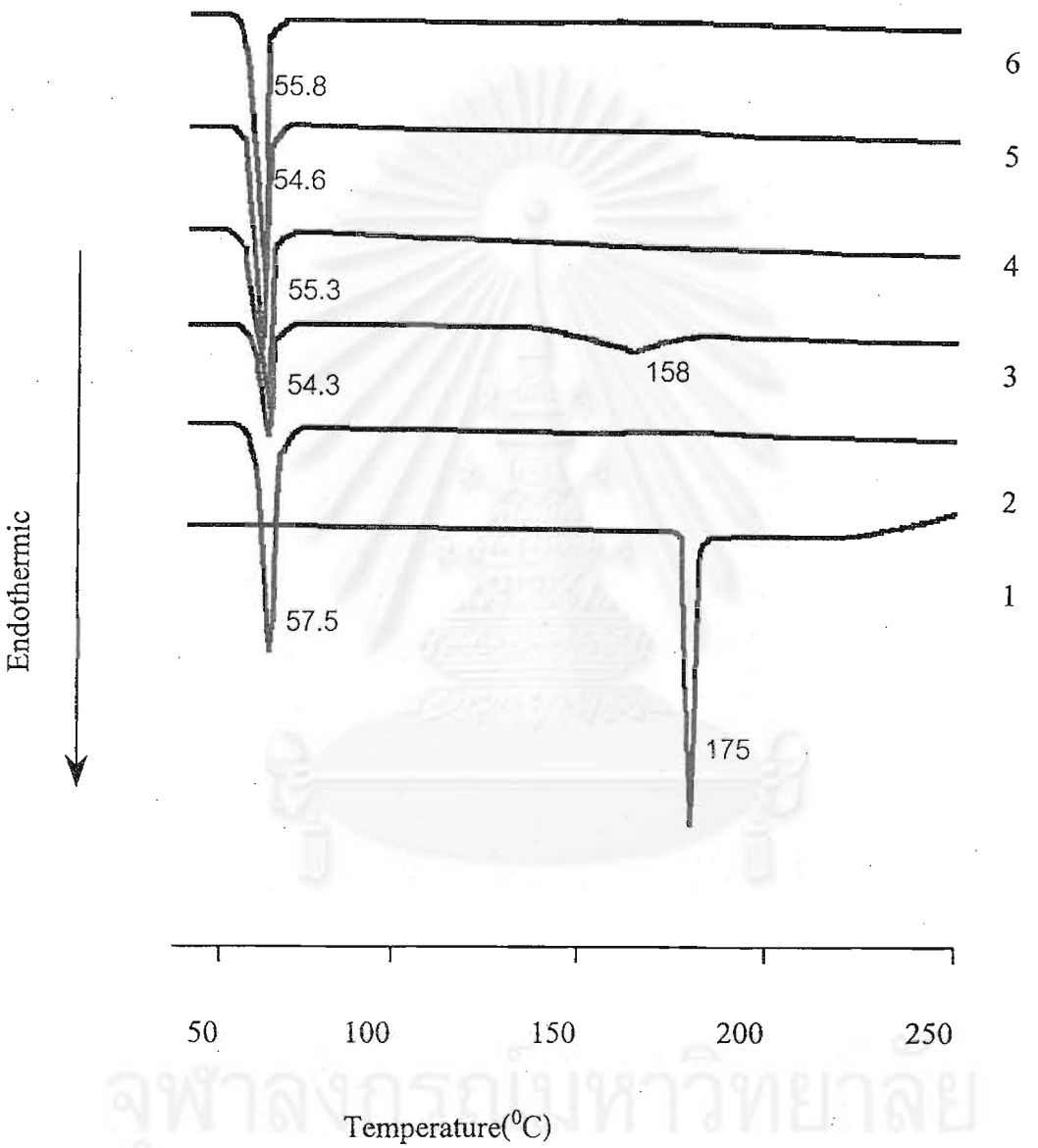


Figure 118: DSC curves of nifedipine - poloxamer 407 solid dispersions prepared by solvent method containing nifedipine (1), poloxamer 407(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

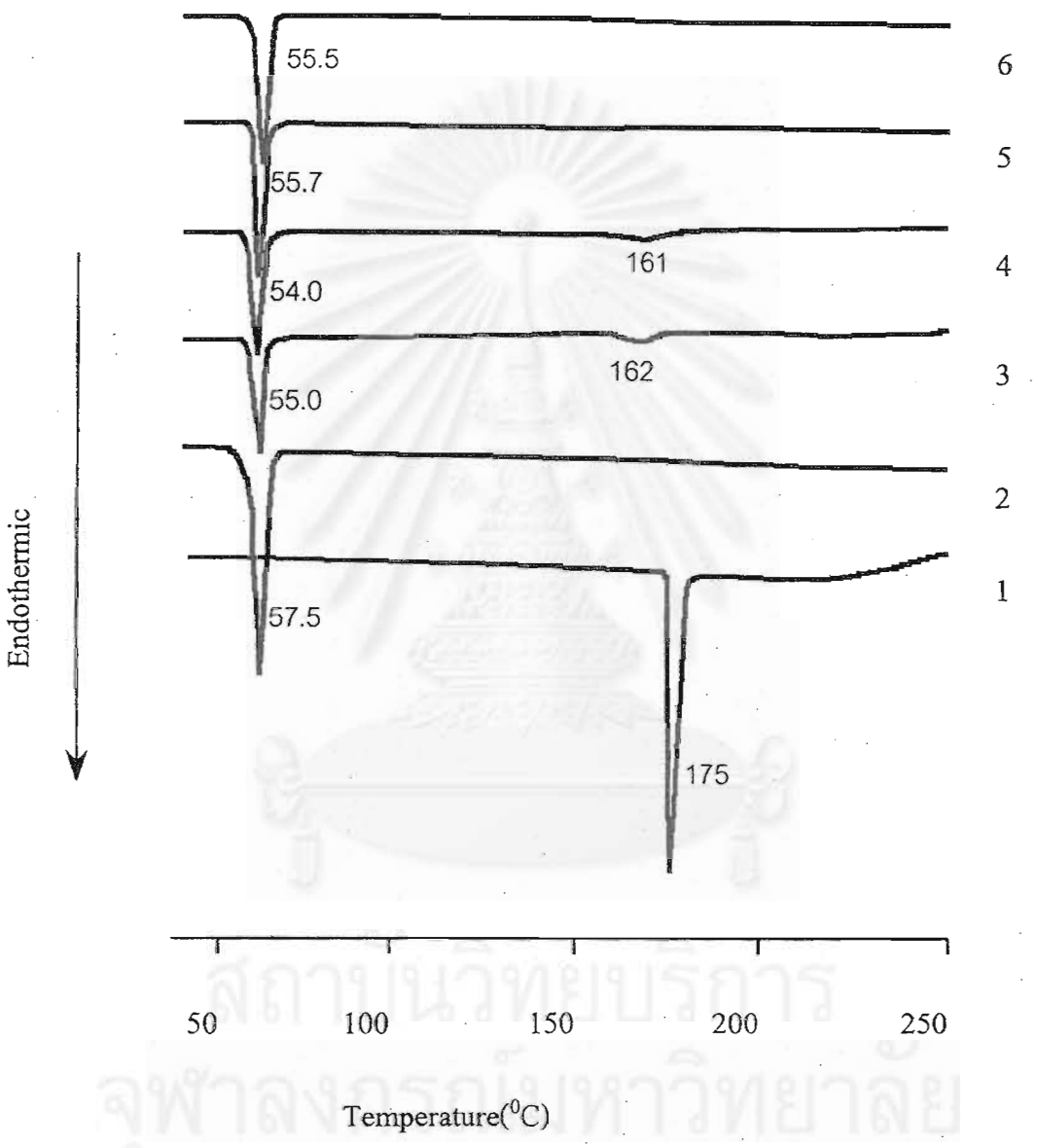


Figure 119: DSC curves of nifedipine - poloxamer 407 solid dispersions prepared by kneading method containing nifedipine (1), poloxamer 407(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

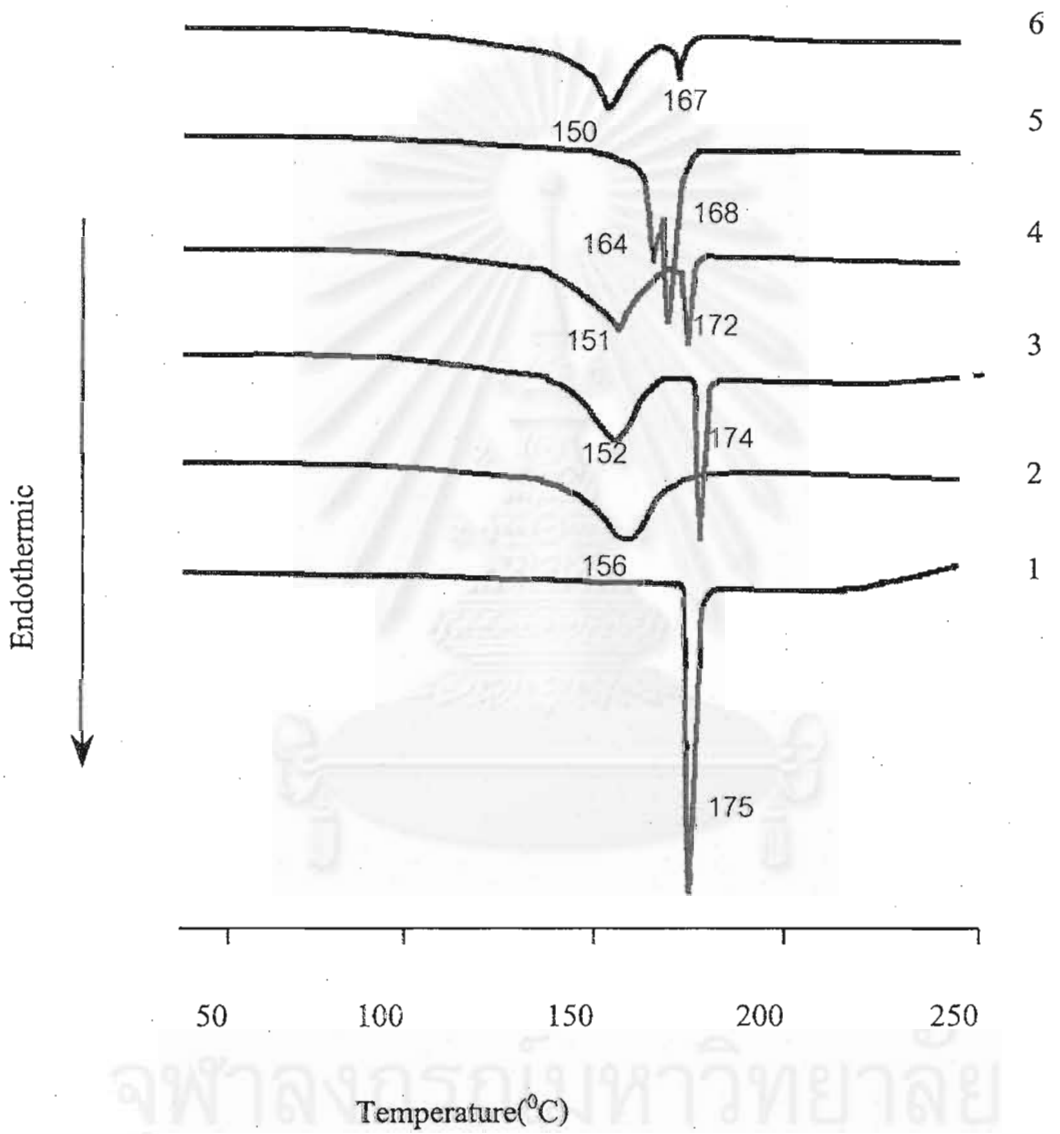


Figure 120: DSC curves of nifedipine - betacyclodextrin physical mixtures containing nifedipine (1), BCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

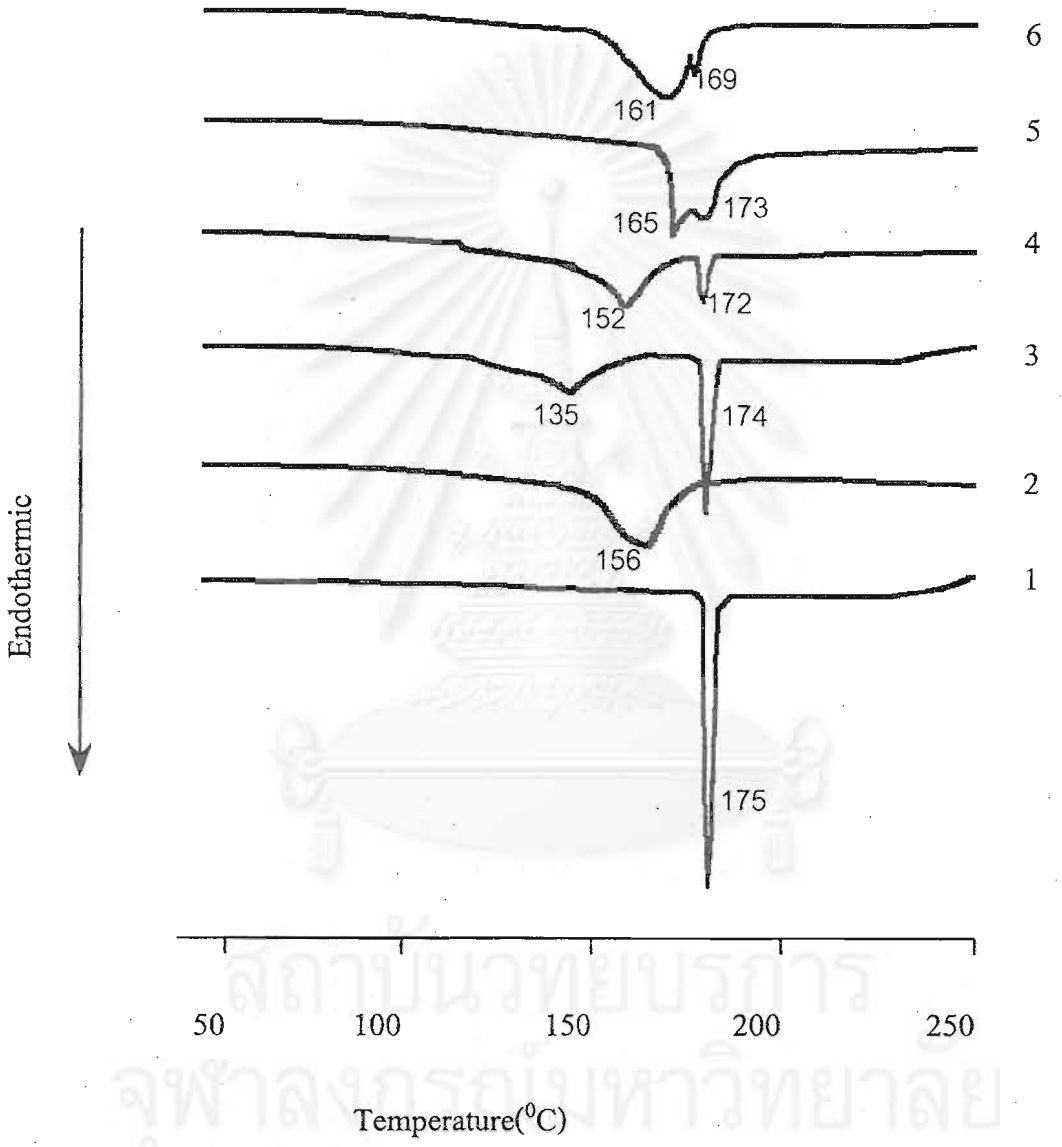


Figure 121: DSC curves of nifedipine - betacyclodextrin solid dispersions prepared by kneading method containing nifedipine (1), BCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

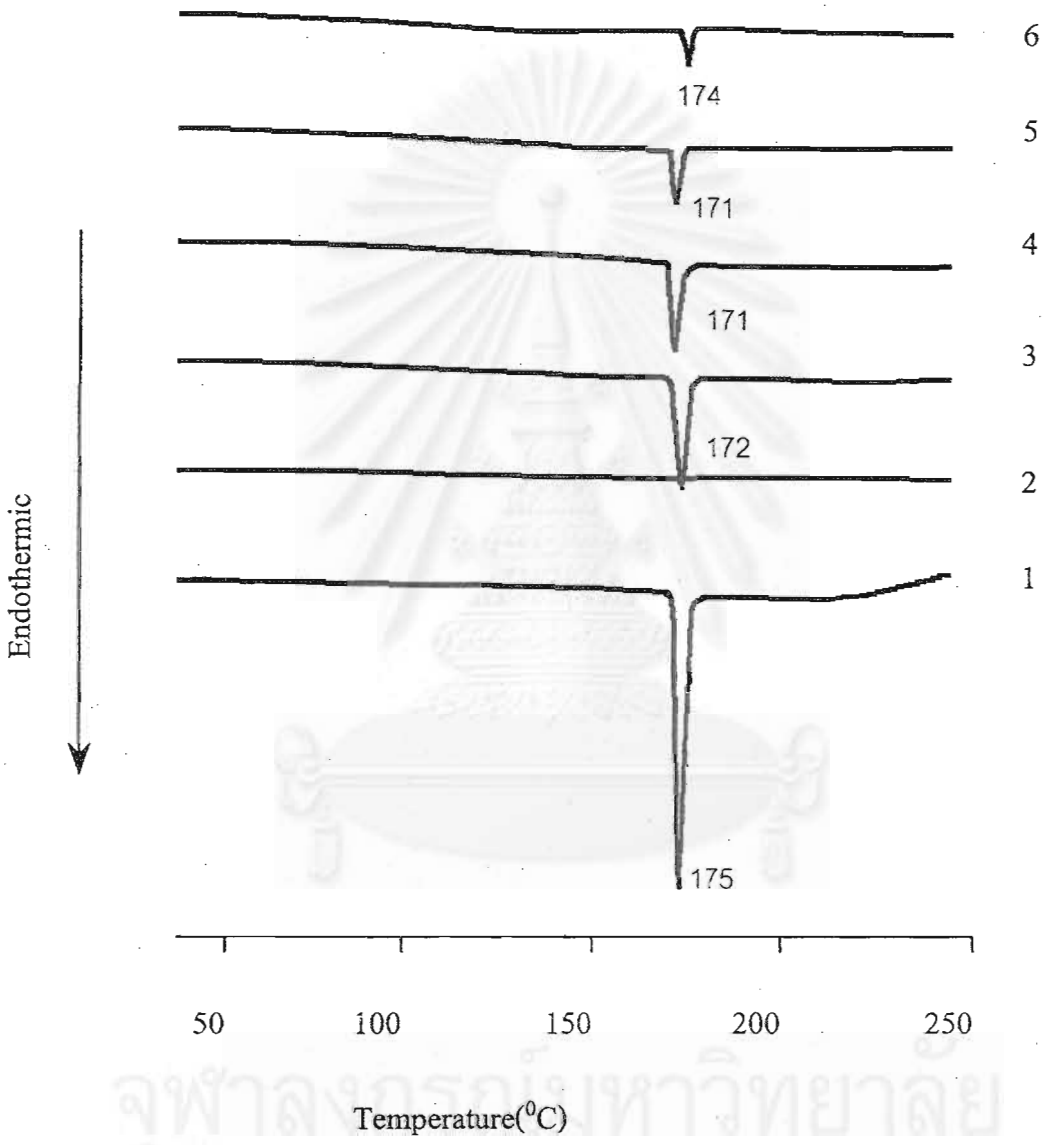


Figure 122: DSC curves of nifedipine- 2- hydroxypropyl betacyclodextrin physical mixtures containing nifedipine (1), 2-HBCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

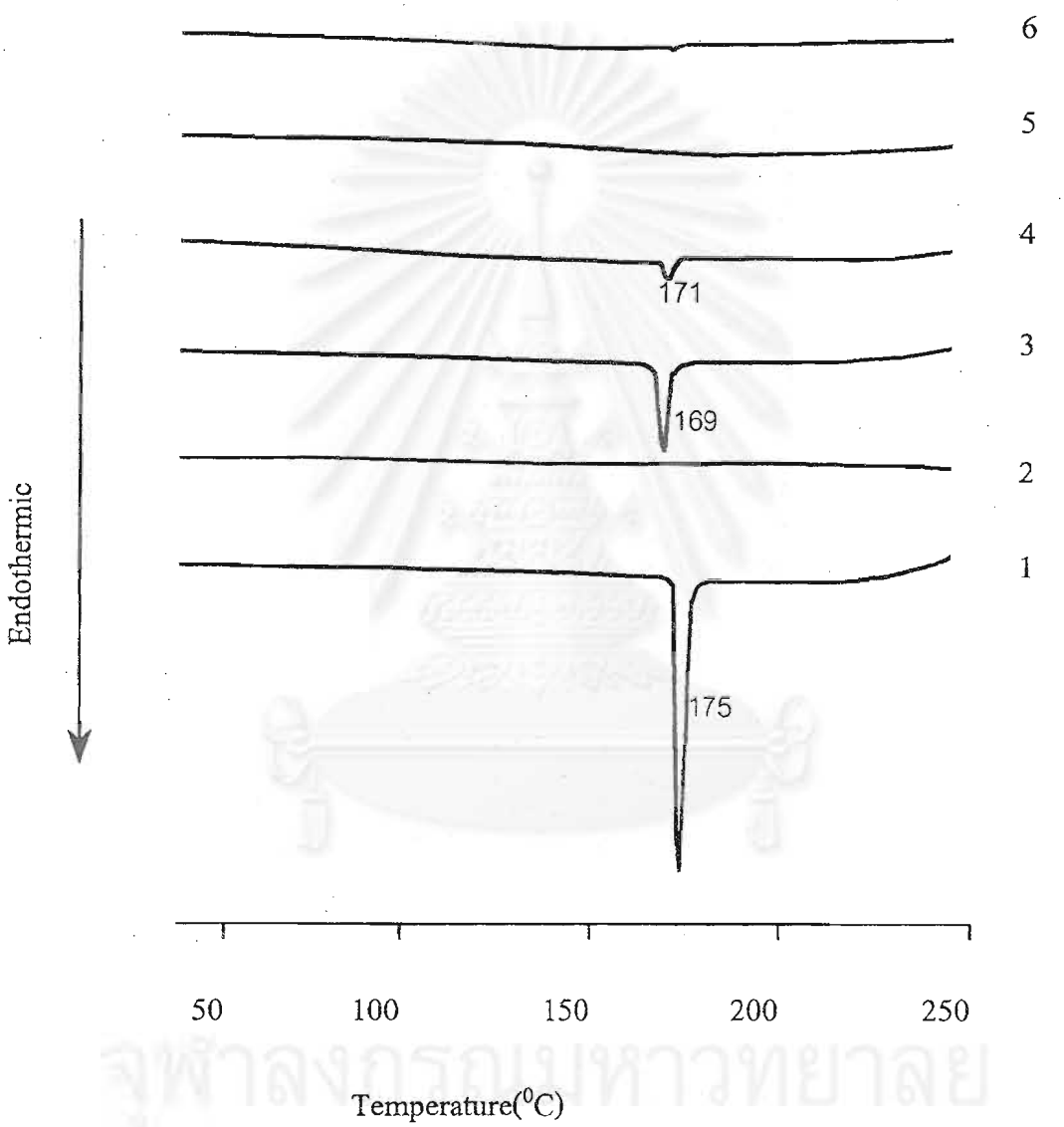


Figure 123: DSC curves of nifedipine- 2- hydroxypropyl betacyclodextrin solid dispersions prepared by solvent method containing nifedipine (1), 2-HBCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

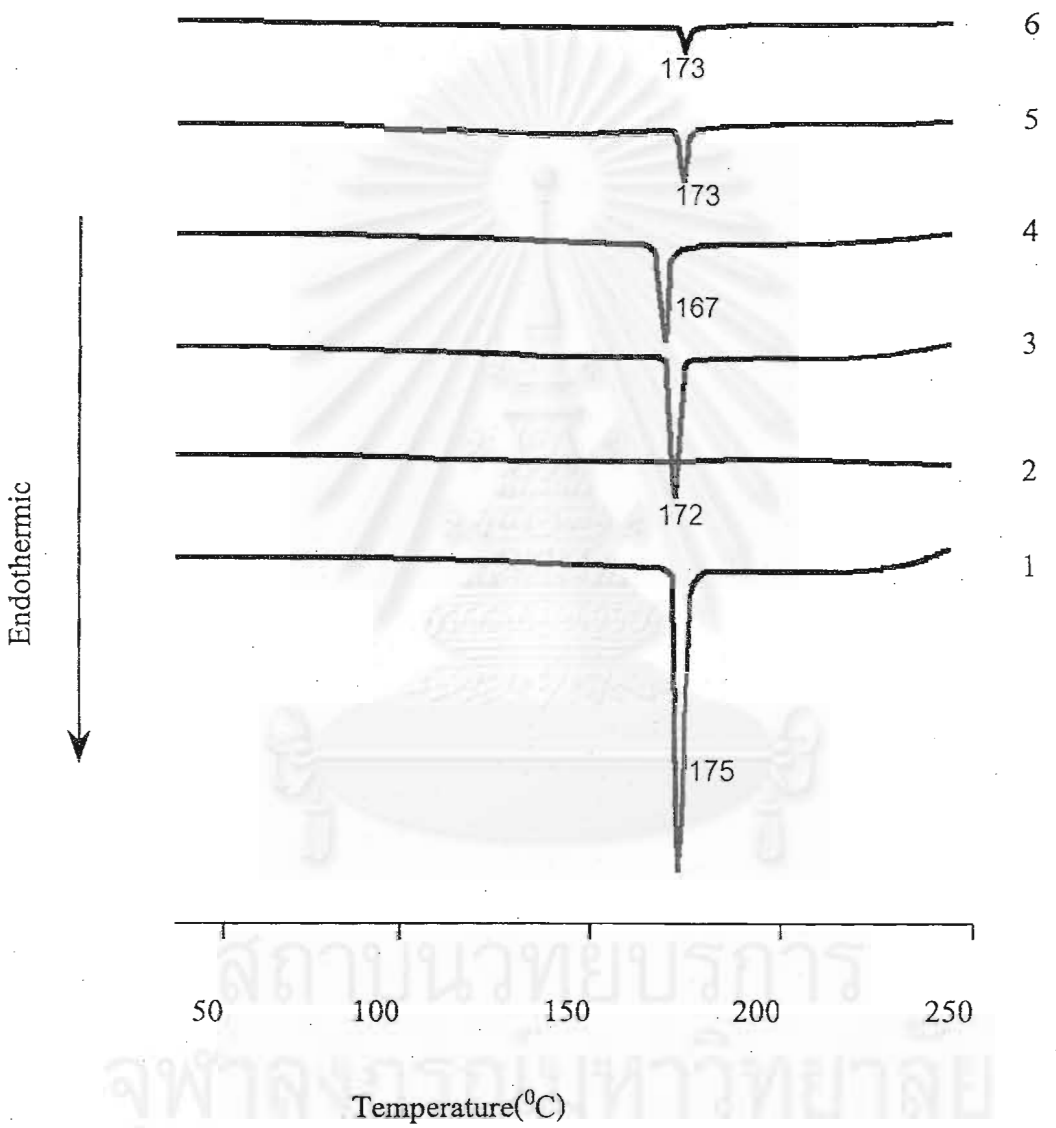


Figure 124: DSC curves of nifedipine- 2- hydroxypropyl betacyclodextrin solid dispersions prepared by kneading method containing nifedipine (1), 2-HBCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

6.2 DSC thermograms of nifedipine-PEGs solid dispersions

The thermogram of nifedipine-PEG4000 systems were illustrated in **Figure 99-107.** The nifedipine-PEG4000 physical mixtures **(Figure 100)** at all mixing ratios displayed the melting endotherm of PEG 4000 at 57.1-57.7°C. Only at the 1:1 mixing ratio, the thermogram showed a broad endothermic peak at 162°C. As the proportion of PEG4000 increased (at 1:3, 1:5 and 1:10 ratios), this broad peak could not be observed.

Similar DSC thermograms could also be observed in the solid dispersions prepared by melting, solvent and kneading methods.

The melts showed sharp melting endotherms of PEG4000 at 58.1-59.3°C **(Figure 101).** The broad melting endotherm of nifedipine could be observed only in the melt of 1:1 ratio at 151°C. In addition, a small endothermic peak was observed at 230°C.

The coevaporates showed sharp melting endotherms of PEG4000 at 56.8-59.2°C **(Figure 102).** The broad nifedipine melting endotherm was detected at 1:1 ratio at 145°C. Lastly, the kneaded mixtures showed sharp melting peaks of PEG4000 at 59.0-60.0°C. The broad endothermic peak of nifedipine were found at 153°C **(Figure 103).**

The DSC thermograms of nifedipine-PEG6000 systems were presented in **Figure 104-107.** The PEG6000 physical mixtures **(Figure 104)** showed two endothermic peaks. One was a sharp melting endotherm of PEG6000 at the temperature slightly lower than that of pure carrier. The melting point of PEG6000

were lowered at 61.5-62.0°C. The other was a broad melting endotherm of nifedipine at 156, 140, 140 and 138°C for 1:1, 1:3, 1:5 and 1:10 ratios, respectively.

The solid dispersions prepared by melting method showed PEG6000 melting points in the range of 58.7-59.0°C **(Figure 105).** Melting endotherm of nifedipine was found only at the 1:1 ratio at 154°C.

The coevaporates of PEG6000 displayed PEG6000 melting endothermic peaks at 60.9-62.2°C **(Figure 106).** Nifedipine melting could be observed in the 1:1 and 1:3 ratios at 148° and 138°C, respectively.

For the kneaded solid dispersions, PEG6000 melting appeared at 58.5-59.8 °C. Broadened peaks of nifedipine melting were found in the kneaded mixtures at 1:1, 1:3 and 1:5 ratios at 148°, 140° and 140°C, respectively **(Figure 107).**

6.3 DSC thermogram of nifedipine-poloxamers solid dispersion

The DSC thermograms of nifedipine-poloxamers system were illustrated in **Figure 108-119**. In all poloxamer188 system **(Figure108-111)**, displayed poloxamer188 sharp melting endothermic peaks at the temperatures ranges lower than that of pure poloxamer188 itself at 54.6 °C. Physical mixtures, showed poloxamer188 melting points in the range of 53.7-54.6 °C, the melt mixtures at 52.5-52.9 °C, the coevaporates at 52.9-53.2 °C and the kneaded mixtures at 53.7-54.0 °C.

Broadened endotherms of nifedipine could be found only at 1:1 ratio of physical mixtures, melts, coevaporates and kneaded mixtures at 161, 156, 141 and 151°C, respectively.

Similarly, in all systems of poloxamer288 **(Figure 122-115),** showed poloxamer288 melting endotherms at the temperature ranges slightly lower than that of pure poloxamer288 at 60.5°C. Physical mixtures displayed poloxamer288 melting points at 58.6-59.0 °C, the melts as much lower at 54.8-56.4 °C, coevaporates at 57.7-59.0 °C and the kneaded mixtures at 57.4-58.7 °C.

Only at the 1:1 ratio of poloxamer288 systems that nifedipine melting could be observed at broadened peaks at 164, 158, 157, and 156 °C in physical mixtures, melts, coevaporates and kneaded mixtures, respectively.

For all nifedipine-poloxamer407 systems (**Figure116-119**), similar observations to the other two poloxamers were found. Poloxamer407 melting endotherms could be observed at the temperature ranges slightly lower than that of its pure poloxamer407 at 57.5 °C. Physical mixtures showed poloxamer407 melting point at 55.3-56.0 °C, the melts as much lower range at 52.4-53.1 °C, the coevaporates at 54.2-55.8 °C and the kneaded mixtures at 54.0-55.7 °C.

Only the 1:1 ratio that nifedipine melting could be observed as broadened peaks at 160, 159, 158, and 162 °C in physical mixtures, melts, coevaporates and kneaded

mixtures. However, a small broadened peak of nifedipine melting could be detected also in the 1:3 ratio of kneaded mixture at 161 °C.

6.4 DSC thermogram of nifedipine-cyclodextrins solid dispersion

The thermograms of β-cyclodextrin systems were illustrated in **Figure 120-121**. The physical mixtures exhibited two characterized endotherms which referred to that of water and nifedipine **(Figure 120).** Nifedipine melting could be observed in all ratios of physical mixture at the slightly lower temperature than that of pure nifedipine at 167-174 °C.

Similarly results were obtained in the kneaded mixture of β-cyclodextrin systems that two melting endotherms could be detected (**Figure 121**). It was noticed that at the ratios of 1:5 and 1:10 that two endotherms became more closely and partially fused. However, nifedipine melting could be detected at the temperatures at 167-168 °C.

The thermograms of 2-hydroxypropyl- β-cyclodextrin systems were shown in **Figure 122-124**. As the endothermic peak of nifedipine could be detected in all ratios of physical mixtures at the temperatures slightly lower than that of pure nifedipine, at 171-174°C.

However, nifedipine melting disappeared in the coevaporates of 2-hydroxypropyl-β-cyclodextrin, at the ratio of 1:5 and 1:10. While the kneaded mixtures exhibited

similar thermograms to those of their physical mixtures. Nifedipine melting exhibited at the temperature range 167-173 °C as a small endothermic peak.

7. The IR Spectra

The IR spectra of pure nontreated nifedipine, treated nifedipine, carriers, physical mixtures and solid dispersions of nifedipine with various ratios of carriers are illustrated in **Figure 125-150.**

7.1 The IR spectra of pure drug and nontreated pure drug

The IR spectra of nontreated and treated nifedipine by physical mixing, melting, solvent and kneading method were shown in **Figure 125.** The IR spectra of all nifedipine samples showed characteristic absorption bands of N-H stretching vibrations at 3331-3332 cm^{-1}. The peak at 3102 cm^{-1} indicated C-H aromatic vibration and at 2954 cm^{-1} referred to C-H-aliphatic stretching. The major peaks of carbonyl C=O stretching showed at 1689 and 1680 cm^{-1} and C-O ester stretching at 1228 and 1122 cm^{-1}. The sharp peaks of NO_2 stretching was noticed at 1530 cm^{-1}.

After being treated by different methods nifedipine showed the IR spectra pattern including the fingerprint region below 1300 cm^{-1} which were quite similar to the untreated drug.

7.2 The IR spectra of nifedipine-PEG4000 solid dispersions

The IR spectra of PEG4000, as shown in **Figure 126B-129B**, showed characteristic broad peaks of O-H stretching vibration from 3300 to 3600 cm^{-1}, C-H

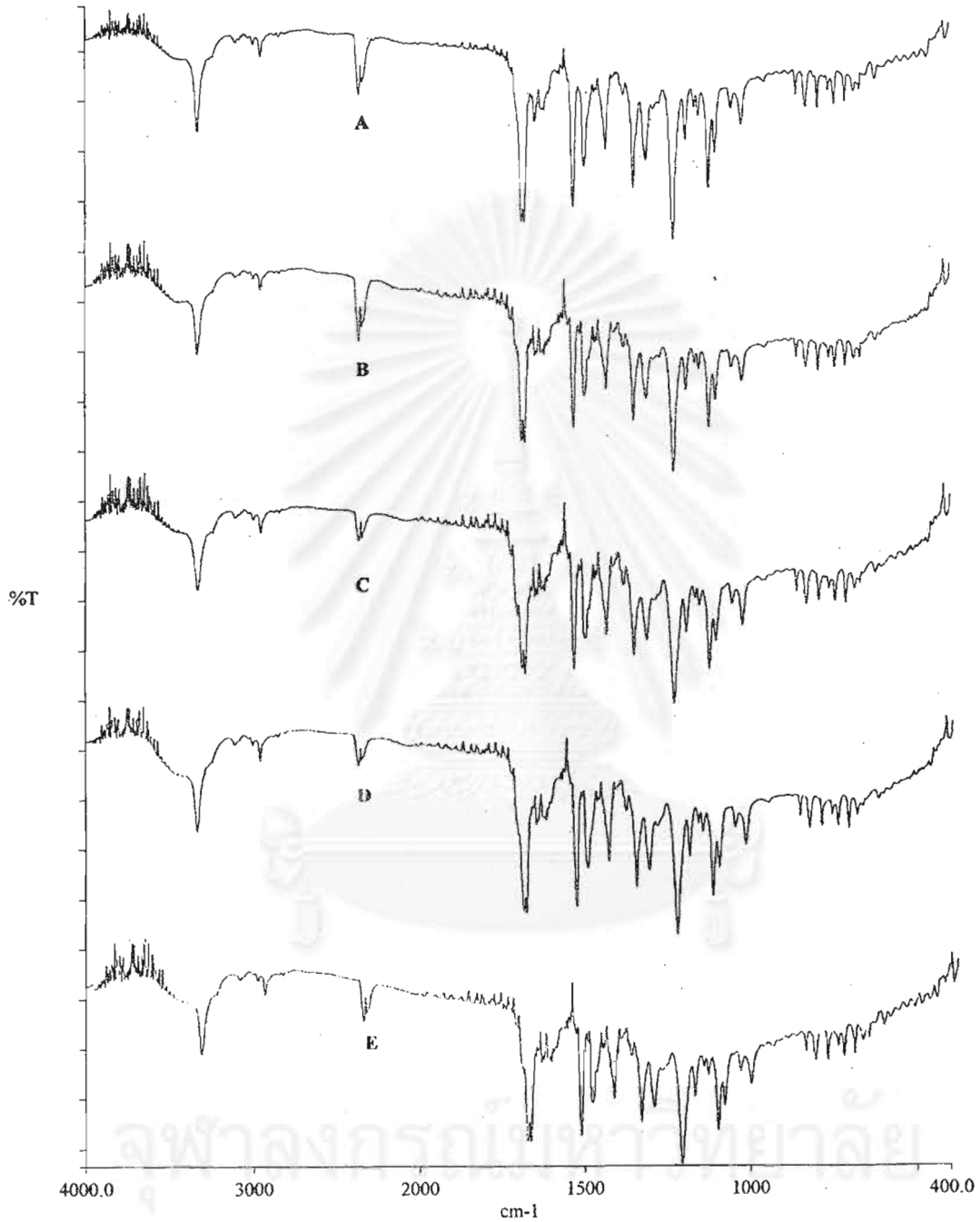


Figure 125 IR spectra of nontreated and treated nifedipine with various methods.

A: Nontreated nifedipine B: Treated by physical mixing

C: Treated by melting method D: Treated by solvent method

E: Treated by kneading method

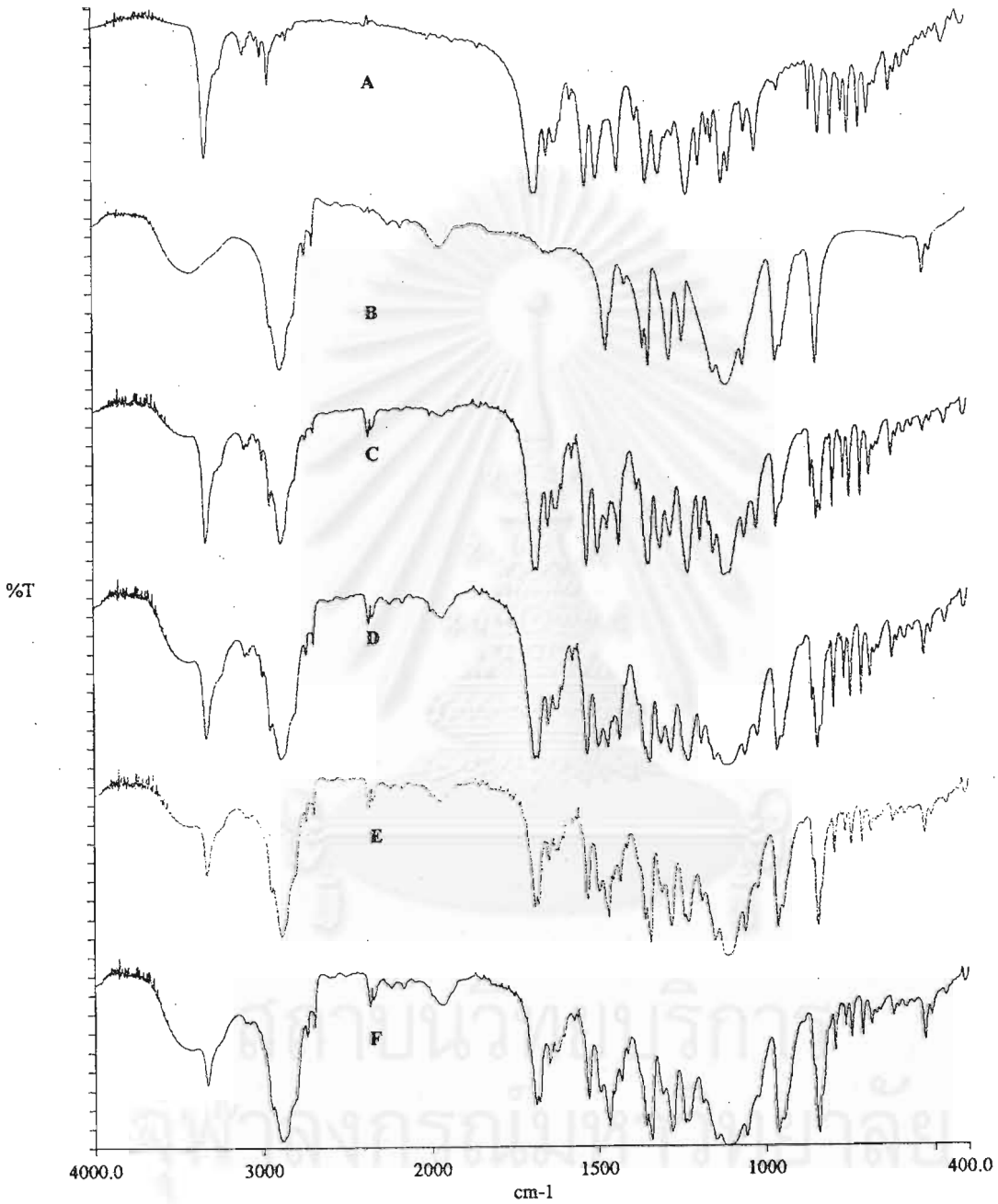


Figure 126 IR spectra of nifedipine-PEG4000 prepared by physical mixing

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

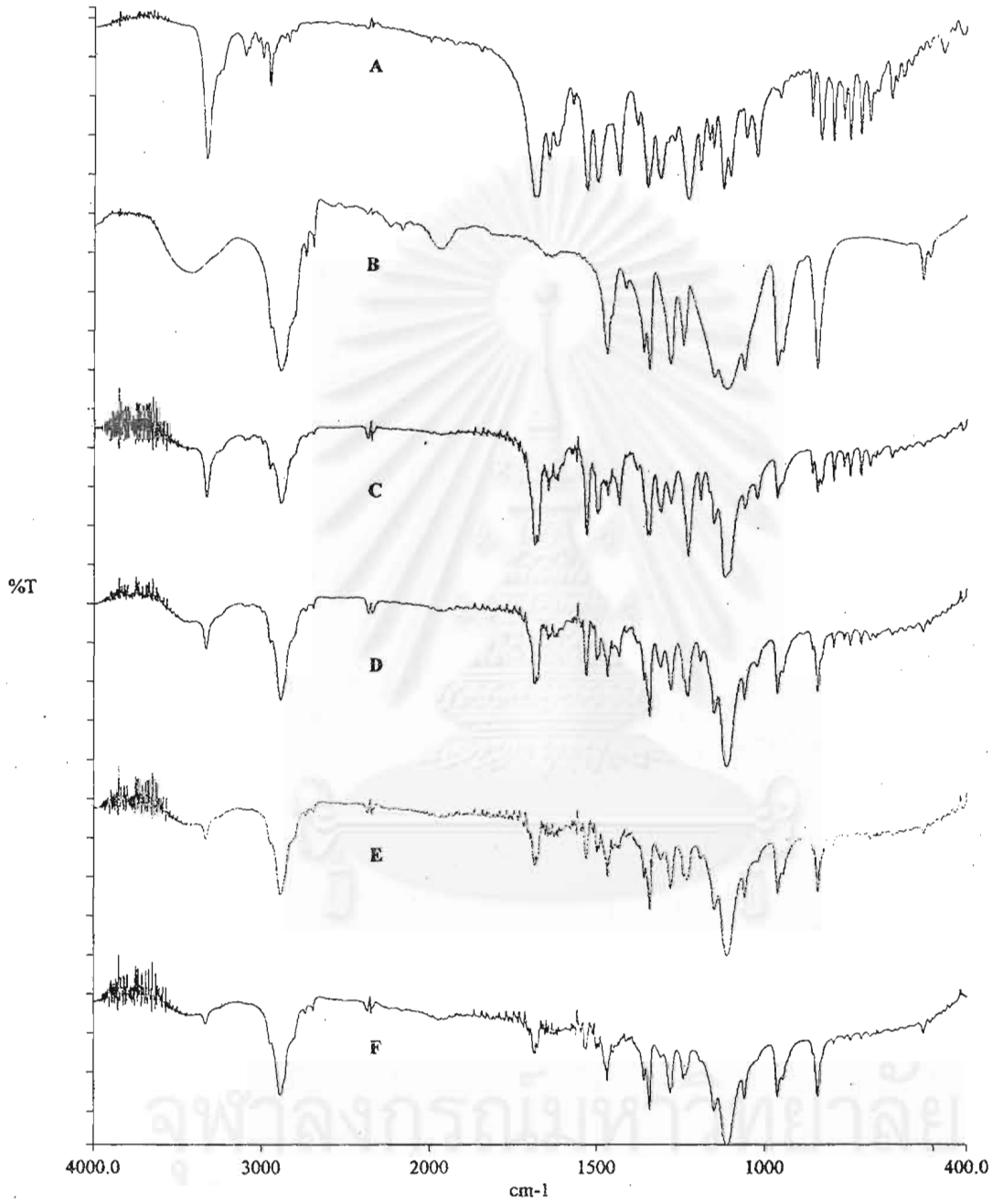


Figure 127 IR spectra of nifedipine-PEG4000 prepared by melting method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

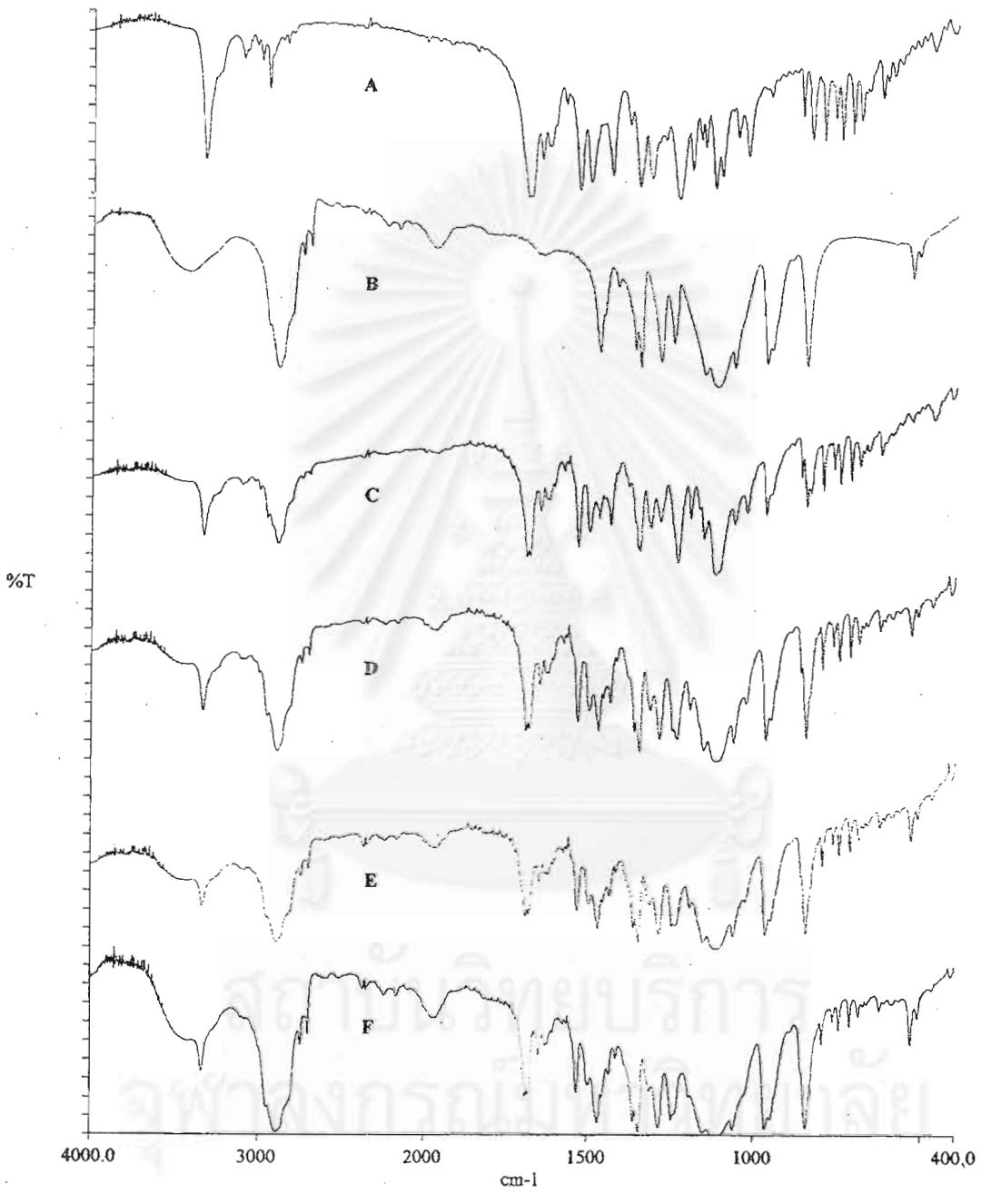


Figure 128 IR spectra of nifedipine-PEG4000 prepared by solvent method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

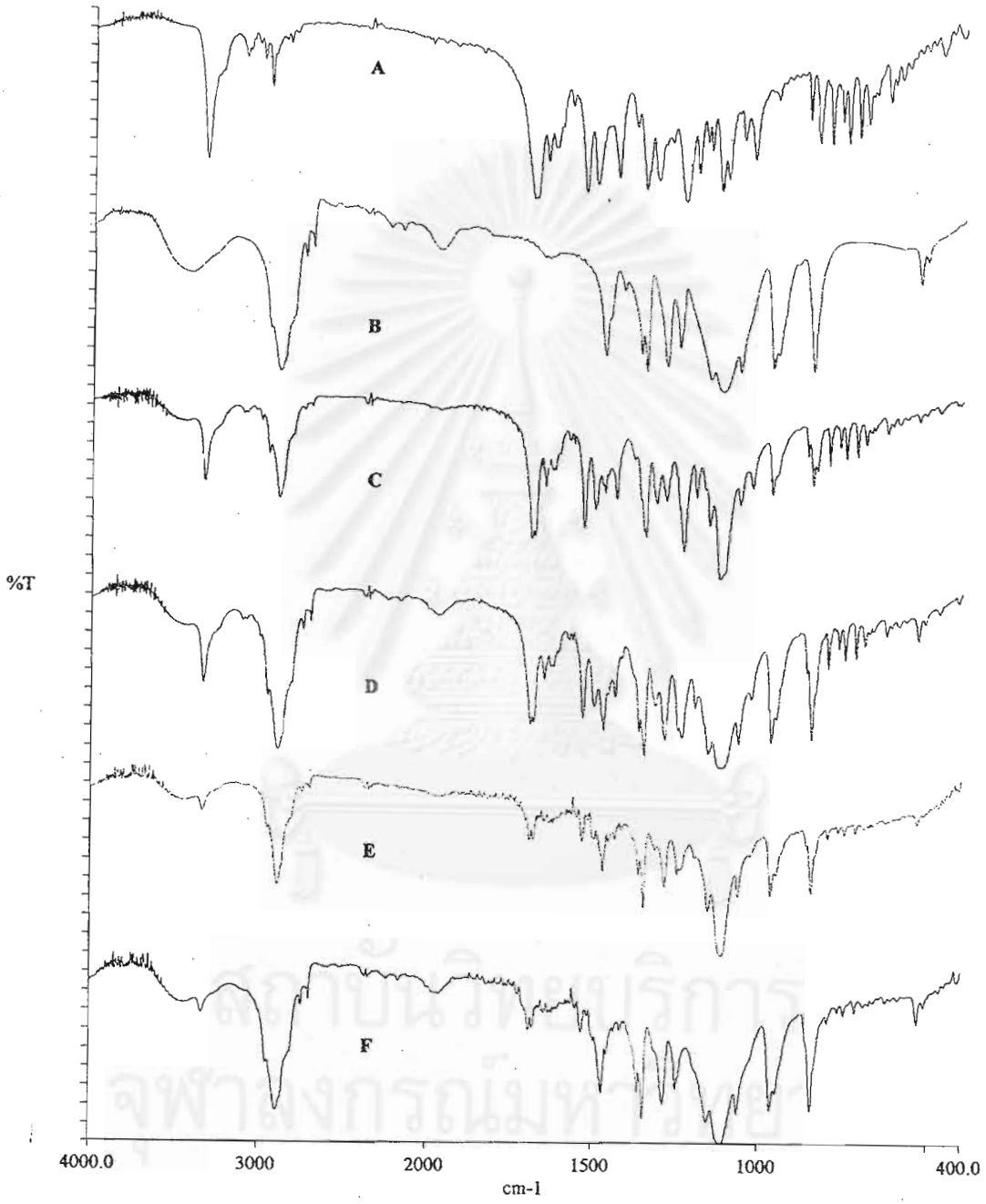


Figure 129 IR spectra of nifedipine-PEG4000 prepared by kneading method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

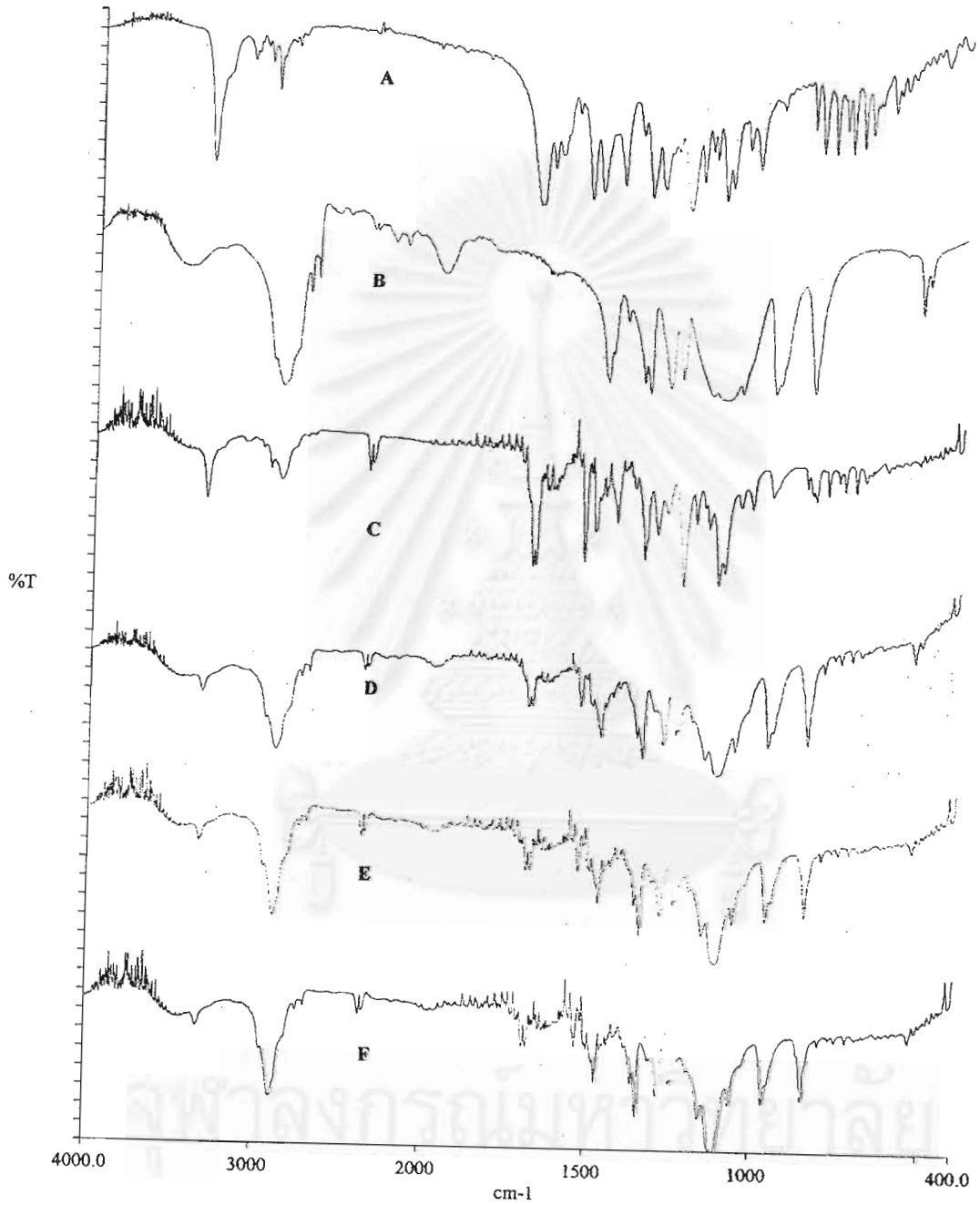


Figure 130 IR spectra of nifedipine-PEG6000 prepared by physical mixing.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

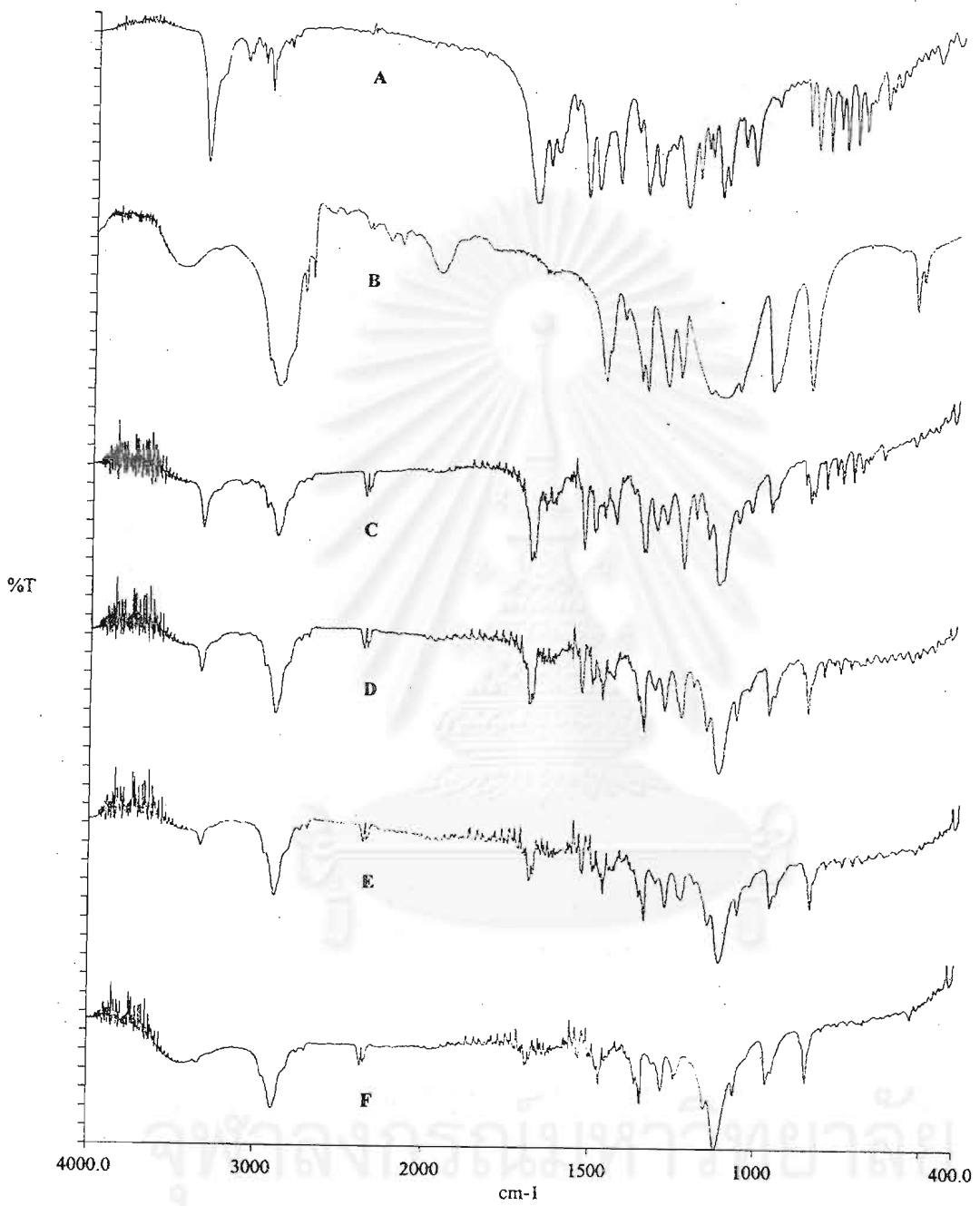


Figure 131 IR spectra of nifedipine-PEG6000 prepared by melting method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

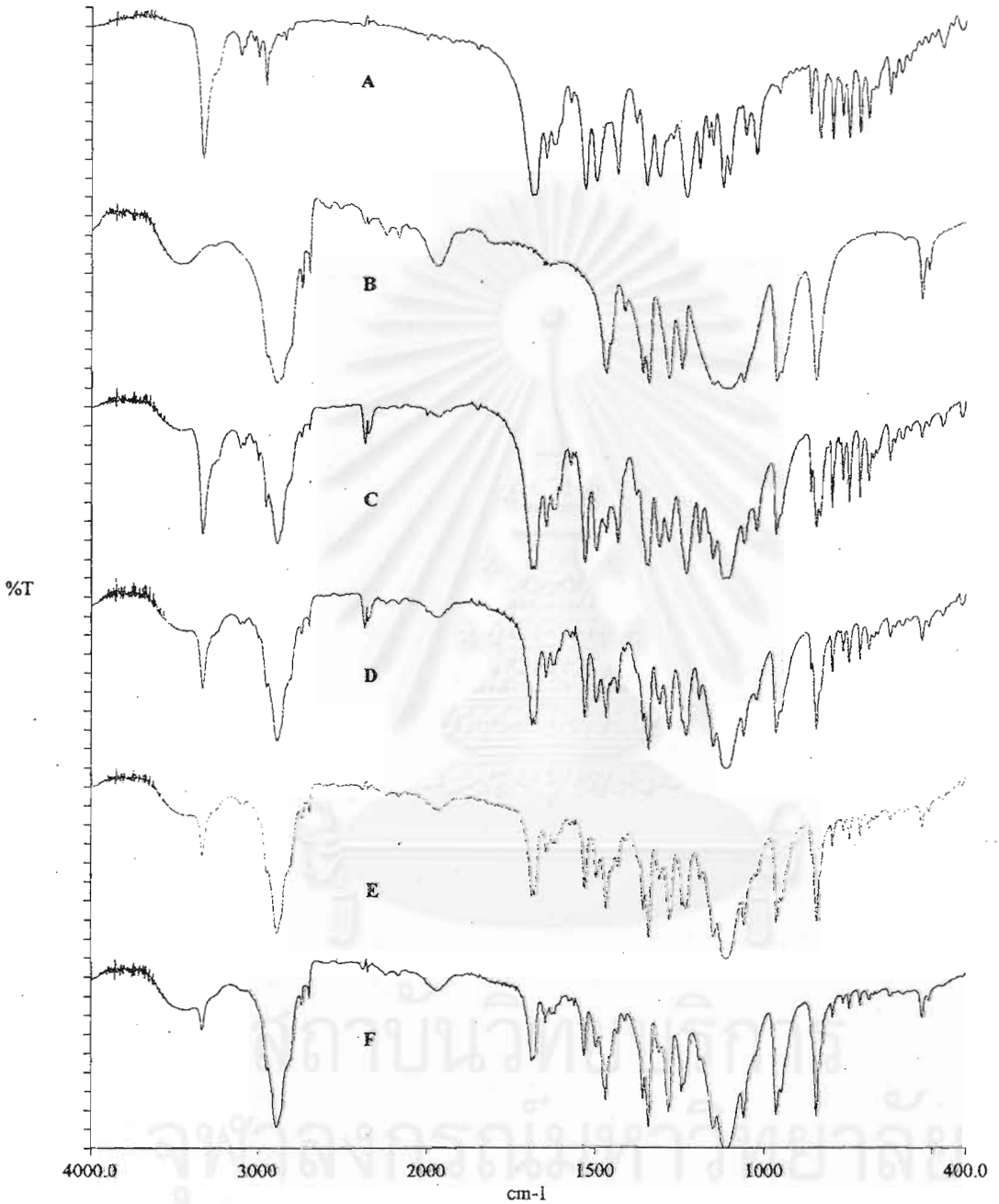


Figure 132 IR spectra of nifedipine-PEG6000 prepared by solvent method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

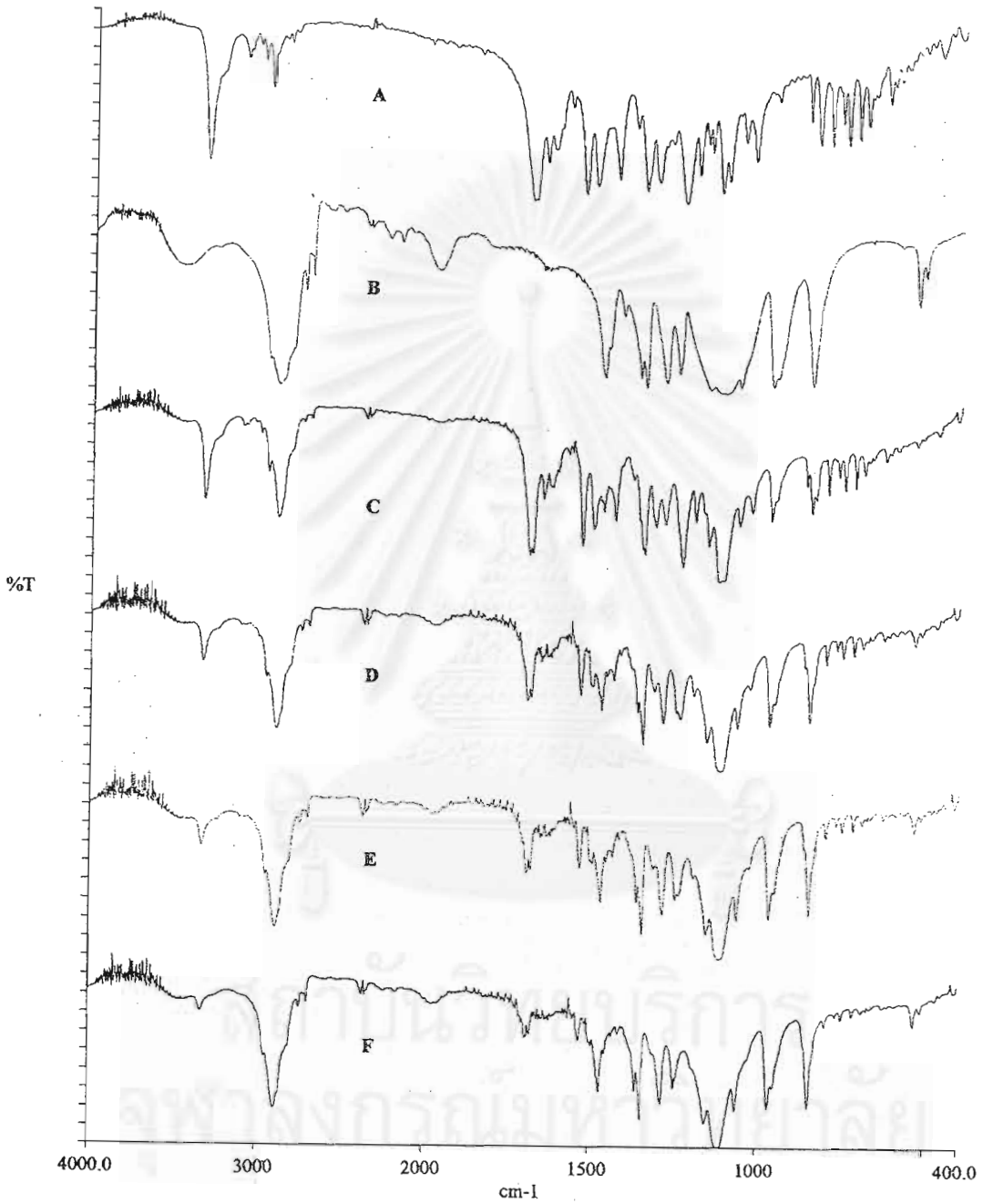


Figure 133 IR spectra of nifedipine-PEG6000 prepared by kneading method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

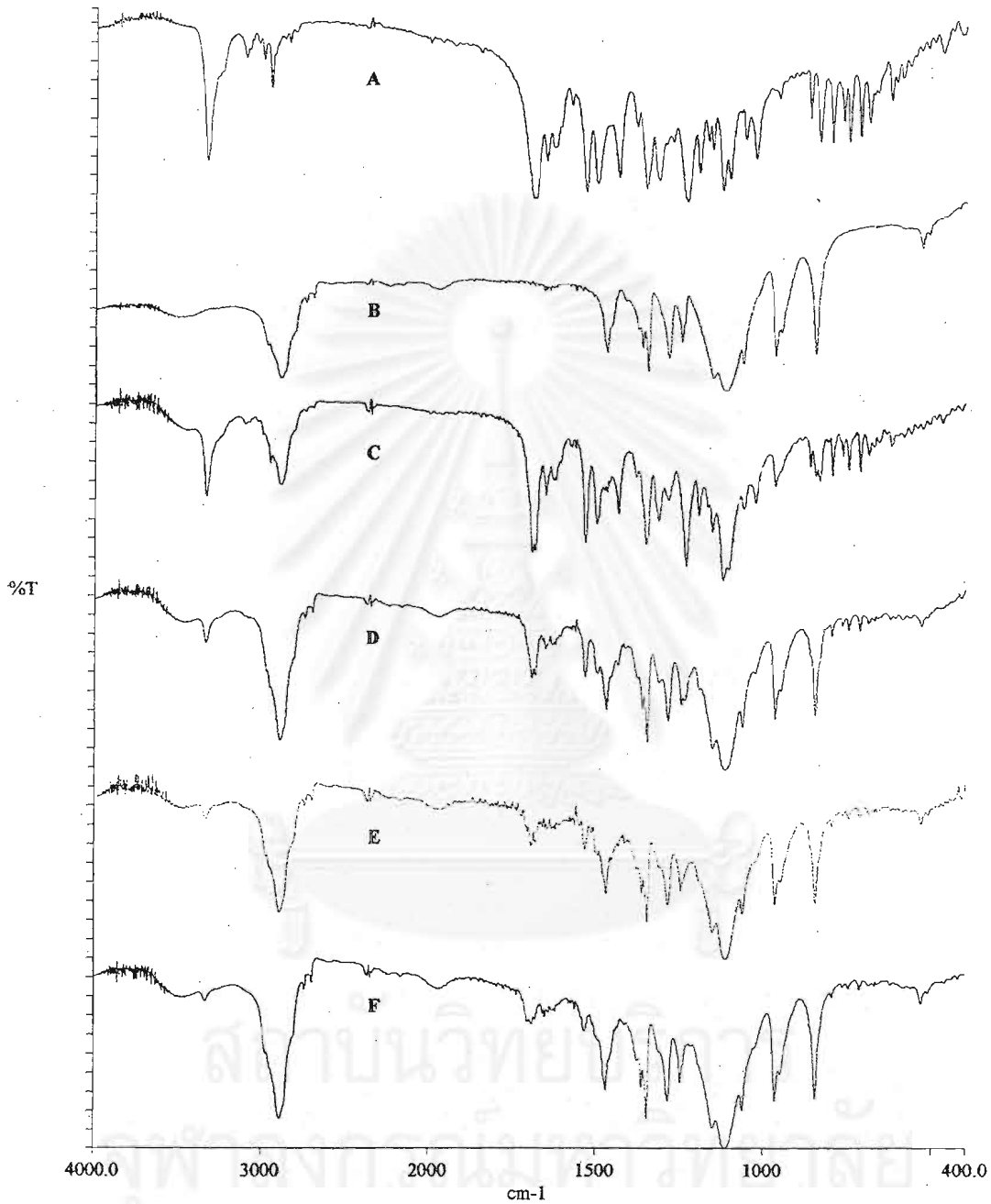


Figure 134 IR spectra of nifedipine-poloxamer188 prepared by physical mixture

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

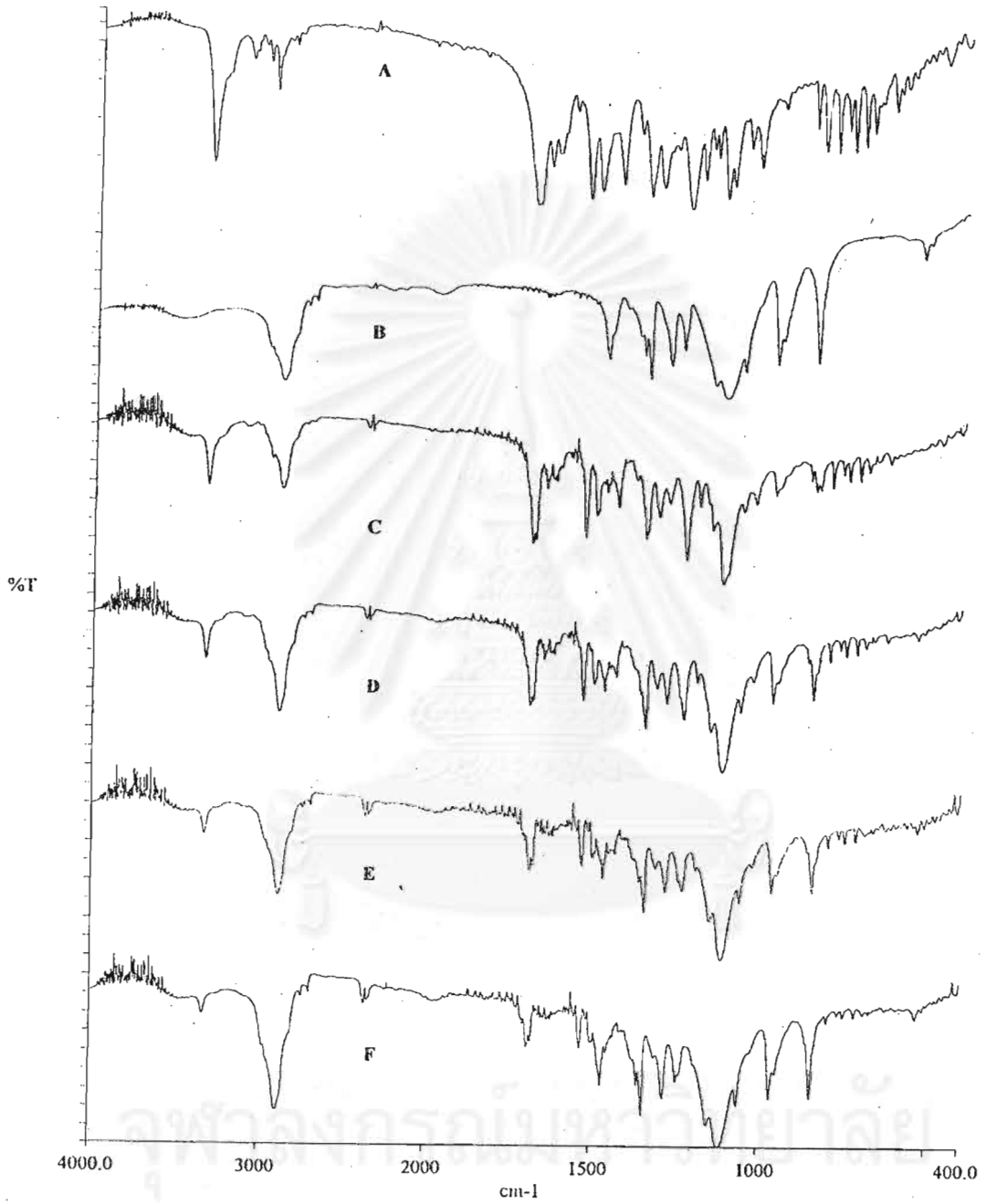


Figure 135 IR spectra of nifedipine-poloxamer188 prepared by melting method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

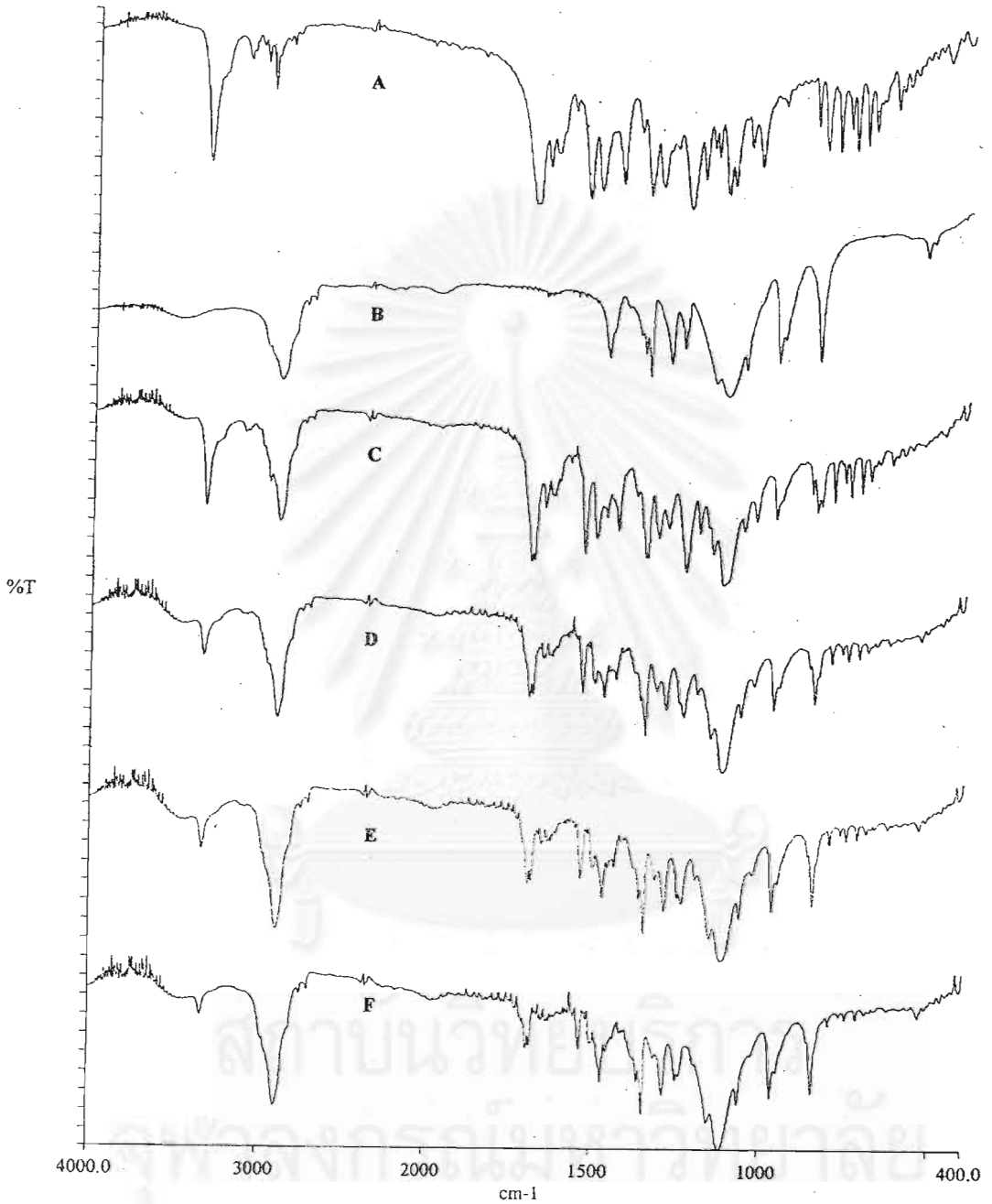


Figure 136 IR spectra of nifedipine-poloxamer188 prepared by solvent method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

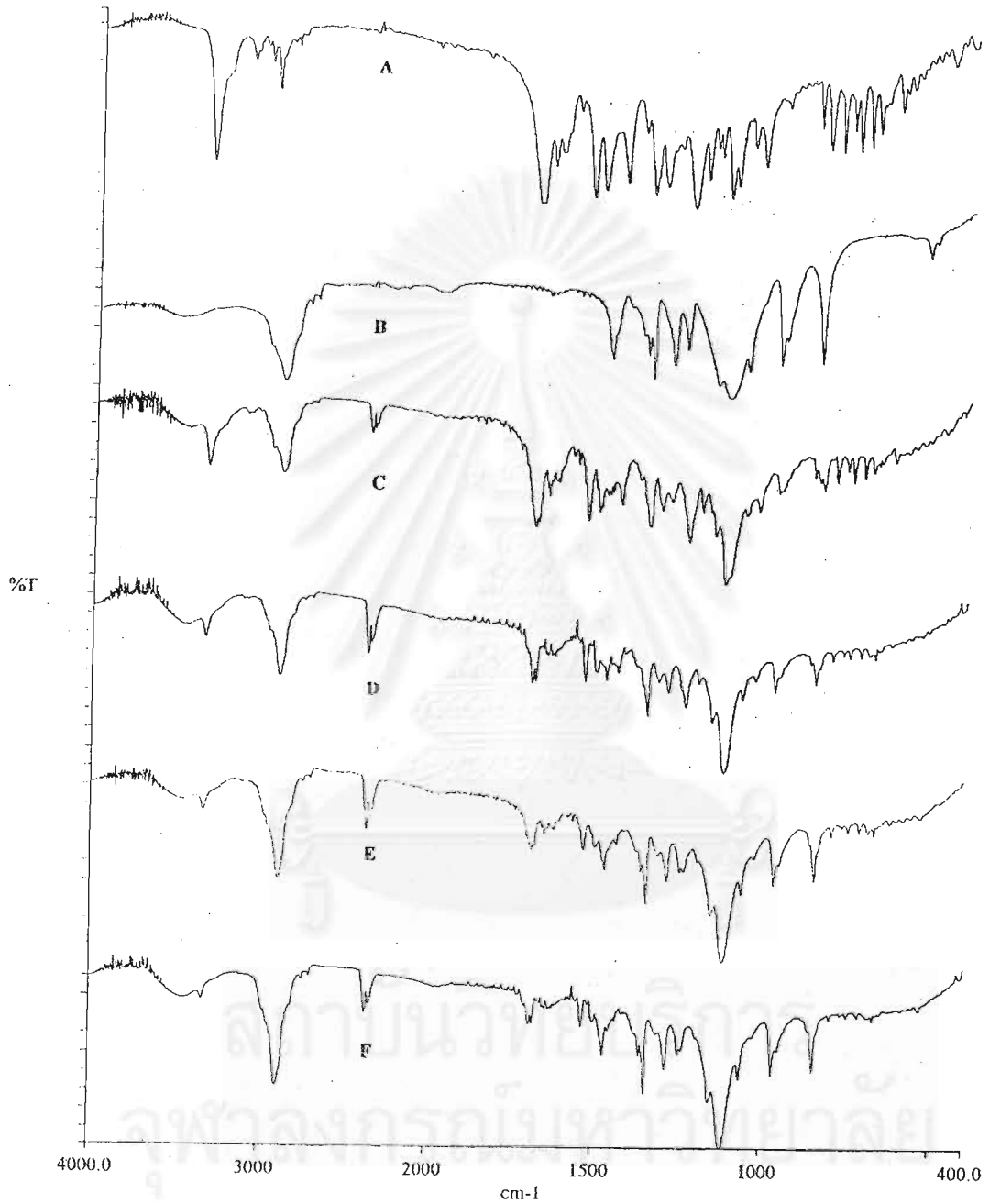


Figure 137 IR spectra of nifedipine-poloxamer188 prepared by kneading method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

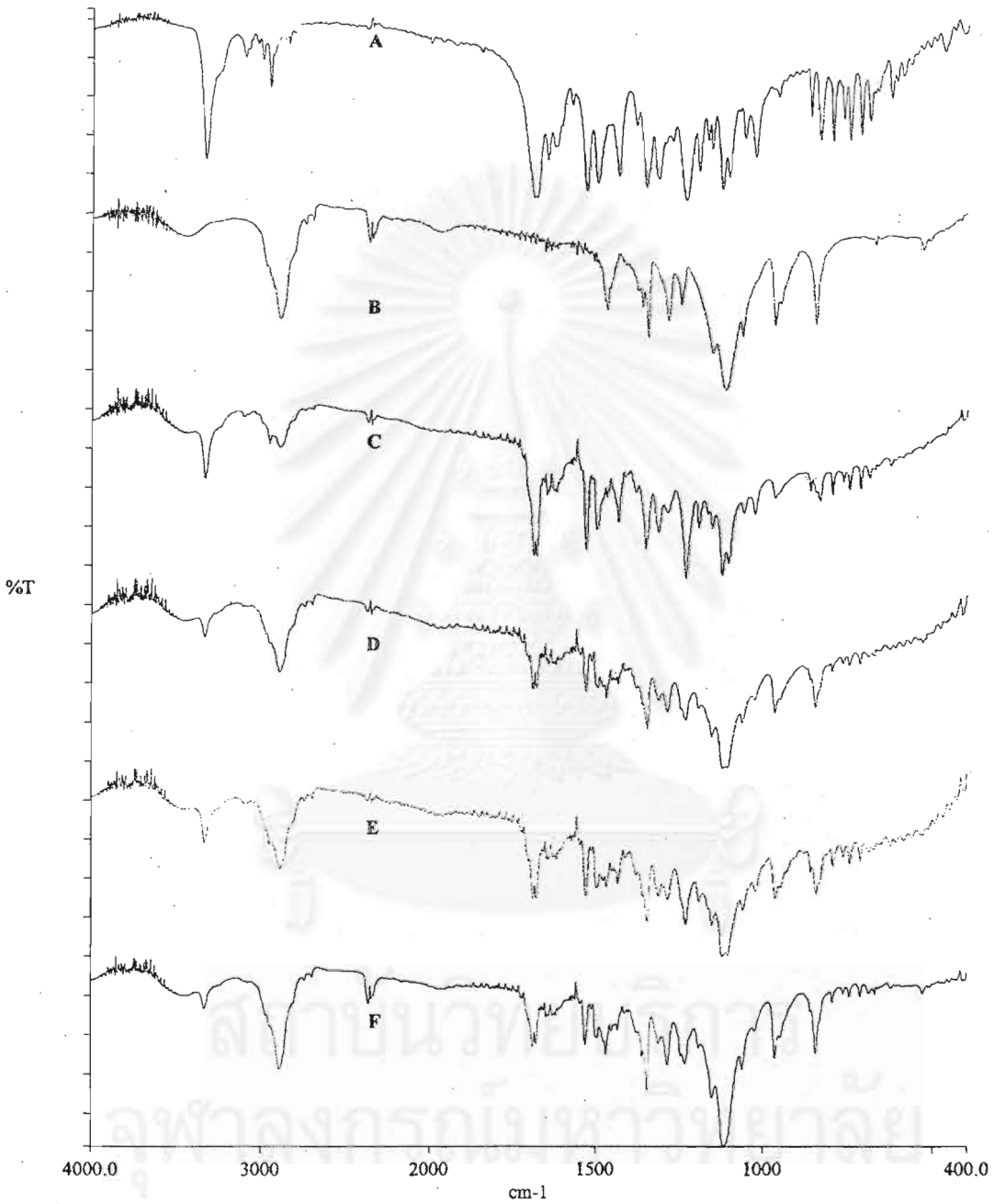


Figure 138 IR spectra of nifedipine-poloxamer288 prepared by physical mixture.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

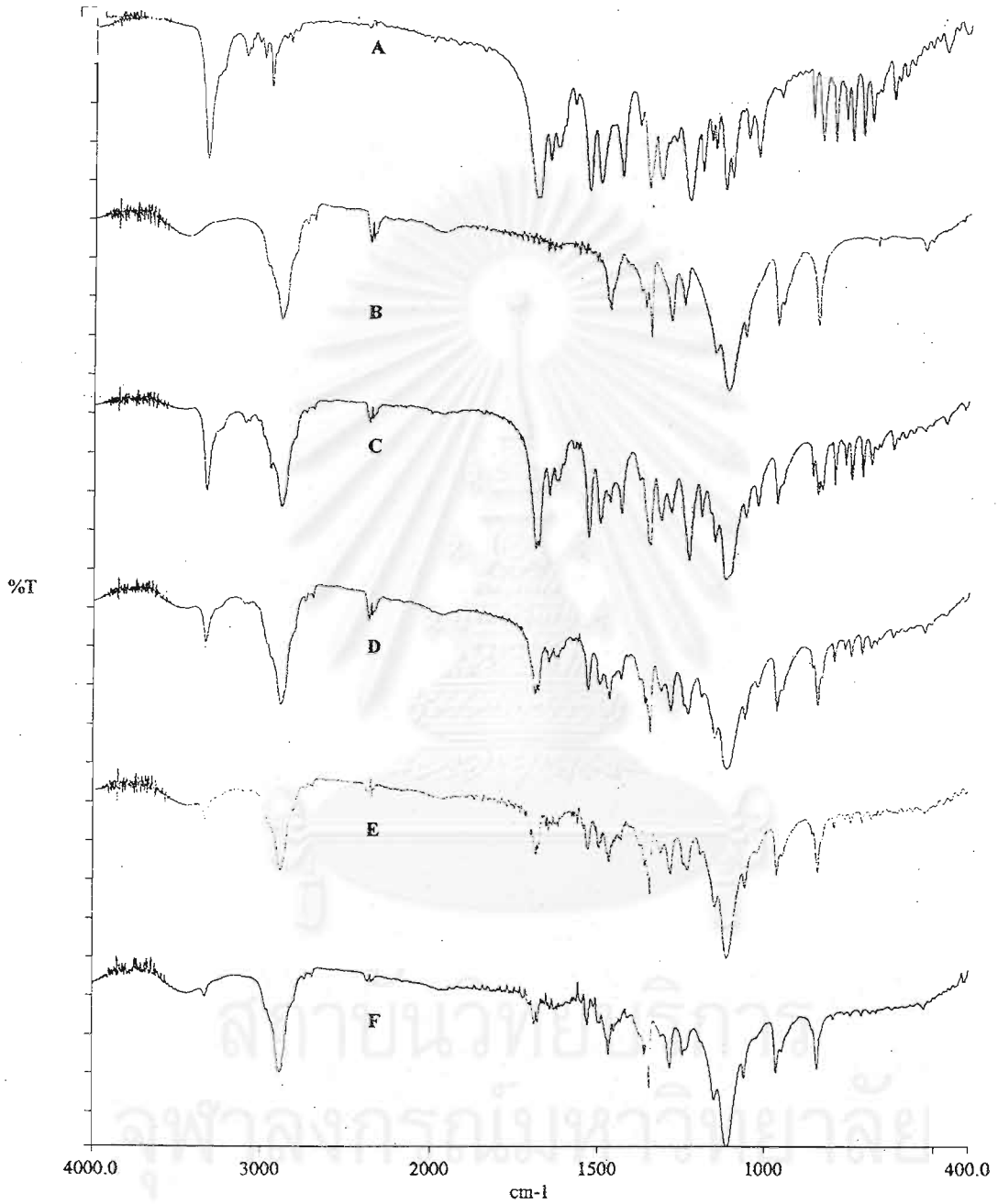


Figure 139 IR spectra of nifedipine-poloxamer288 prepared by melting method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

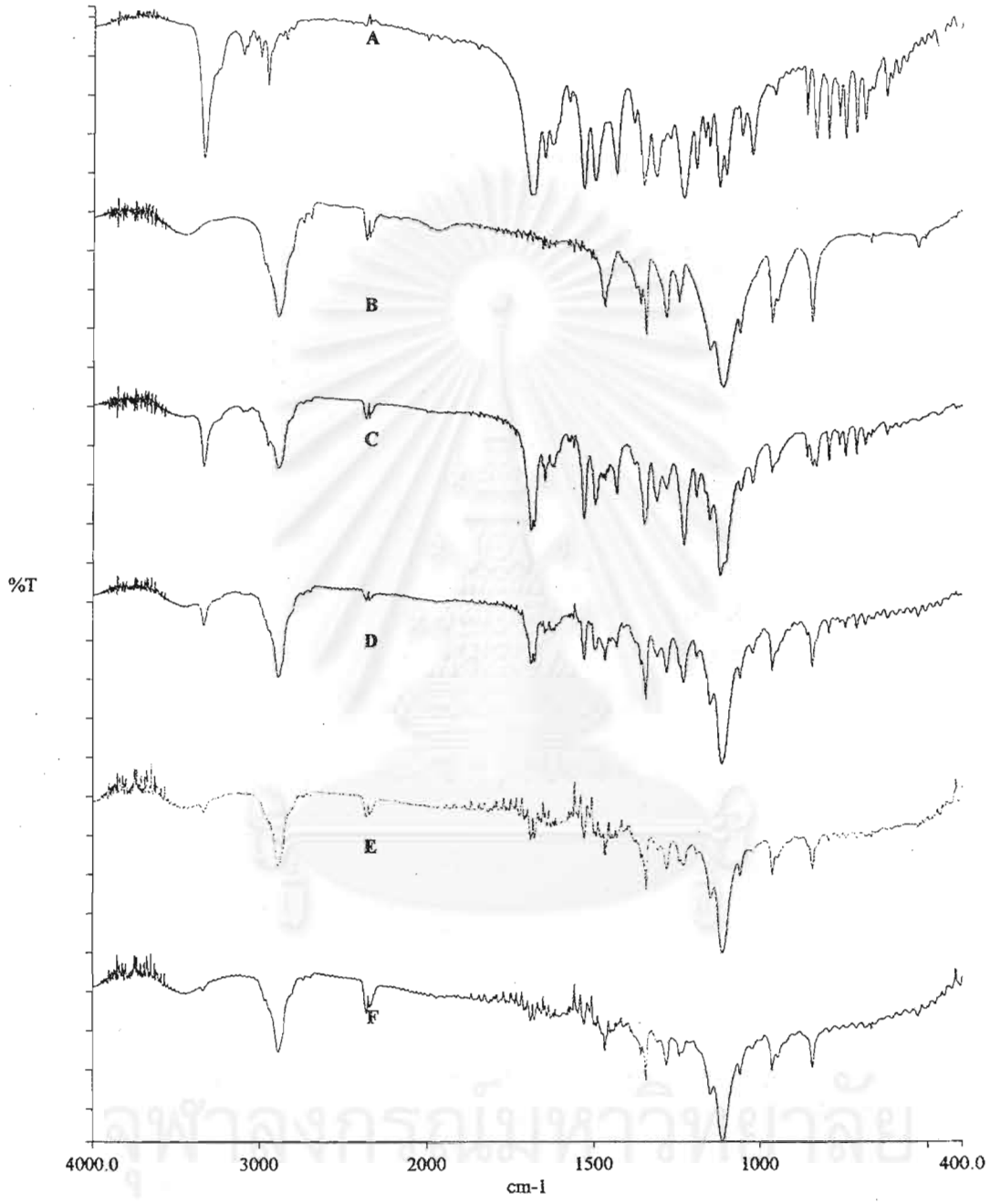


Figure 140 IR spectra of nifedipine-poloxamer288 prepared by solvent method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

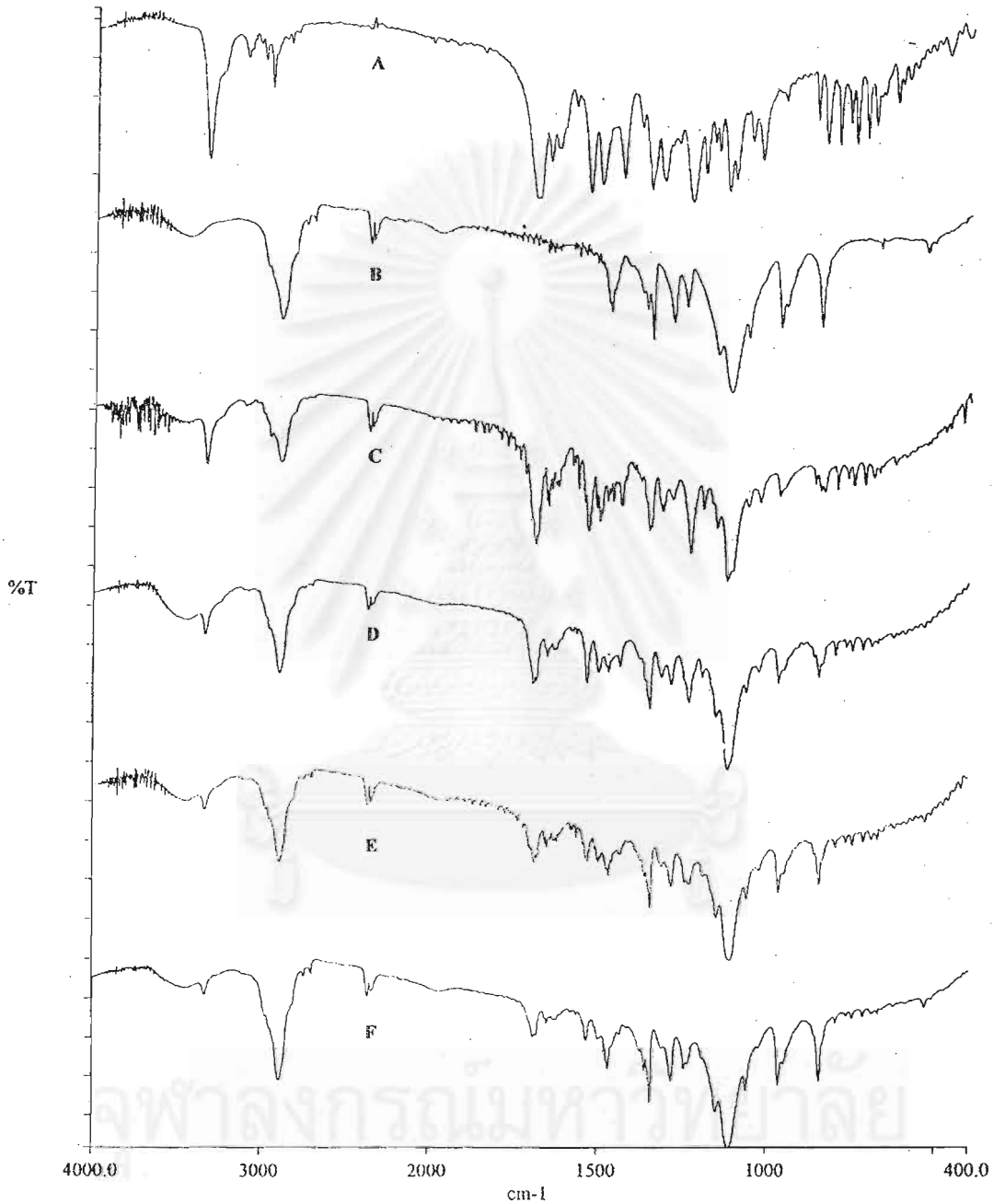


Figure 141 IR spectra of nifedipine-poloxamer288 prepared by kneading method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

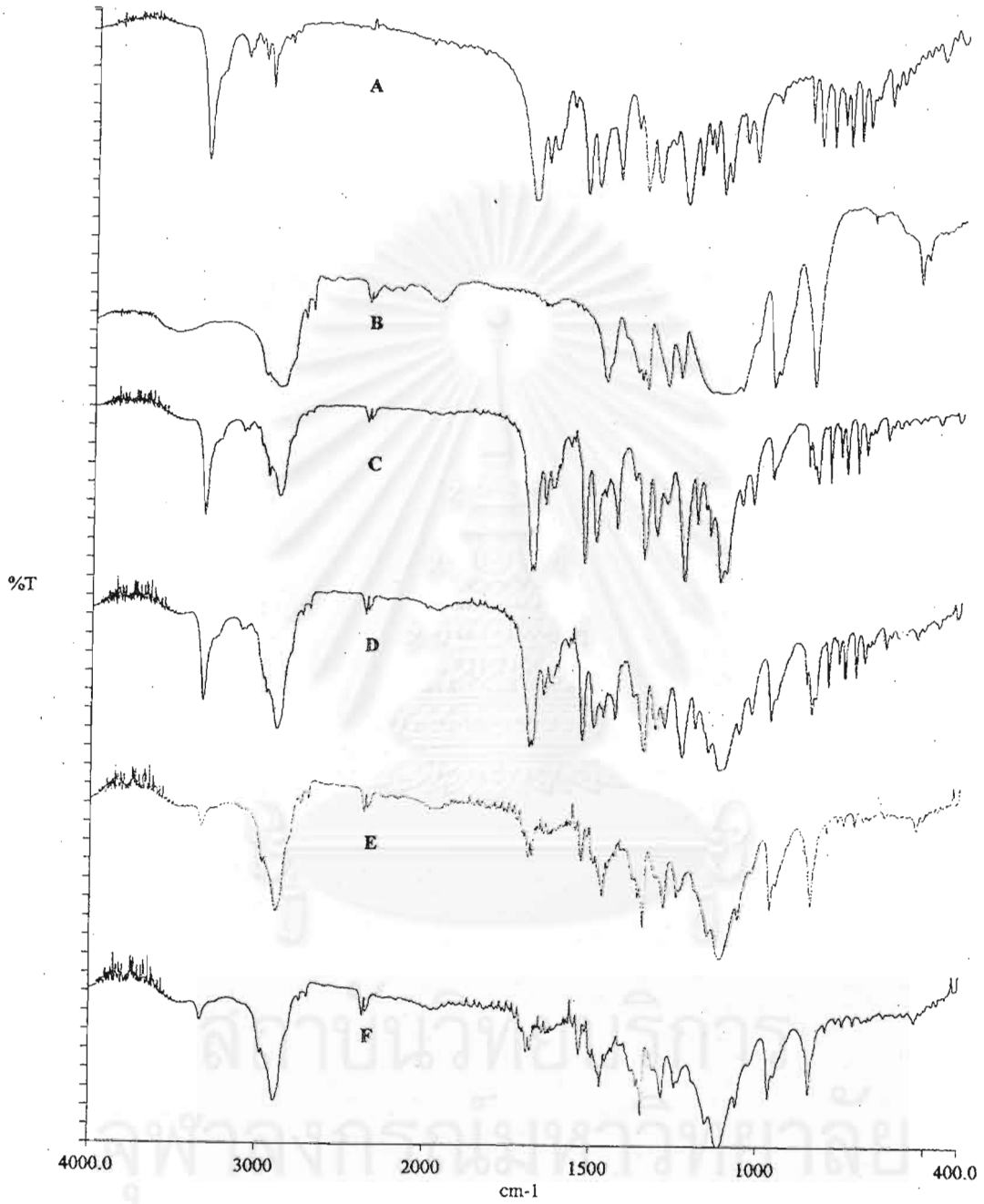


Figure 142 IR spectra of nifedipine-poloxamer407 prepared by physical mixture.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

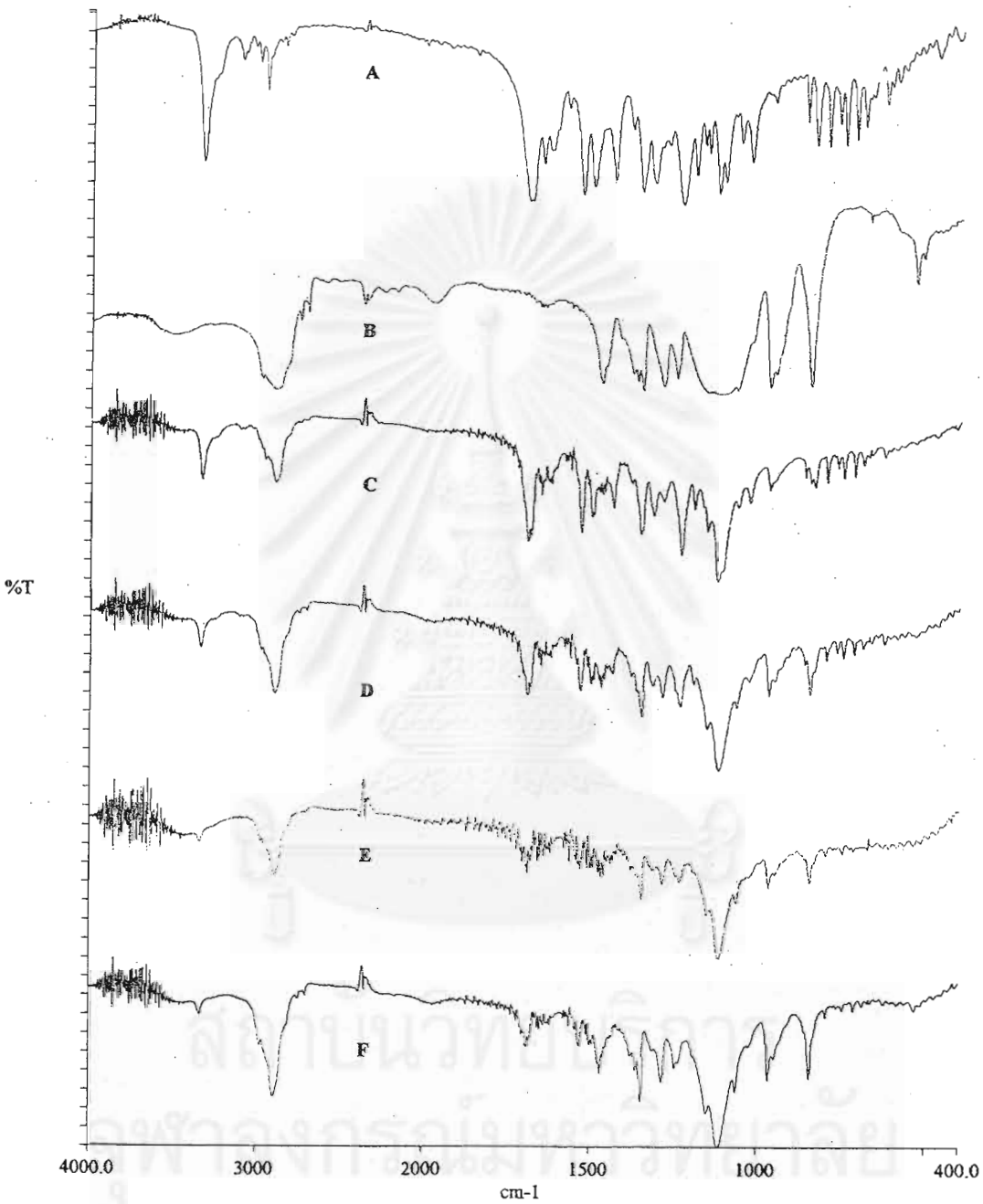


Figure 143 IR spectra of nifedipine-poloxamer407 prepared by melting method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

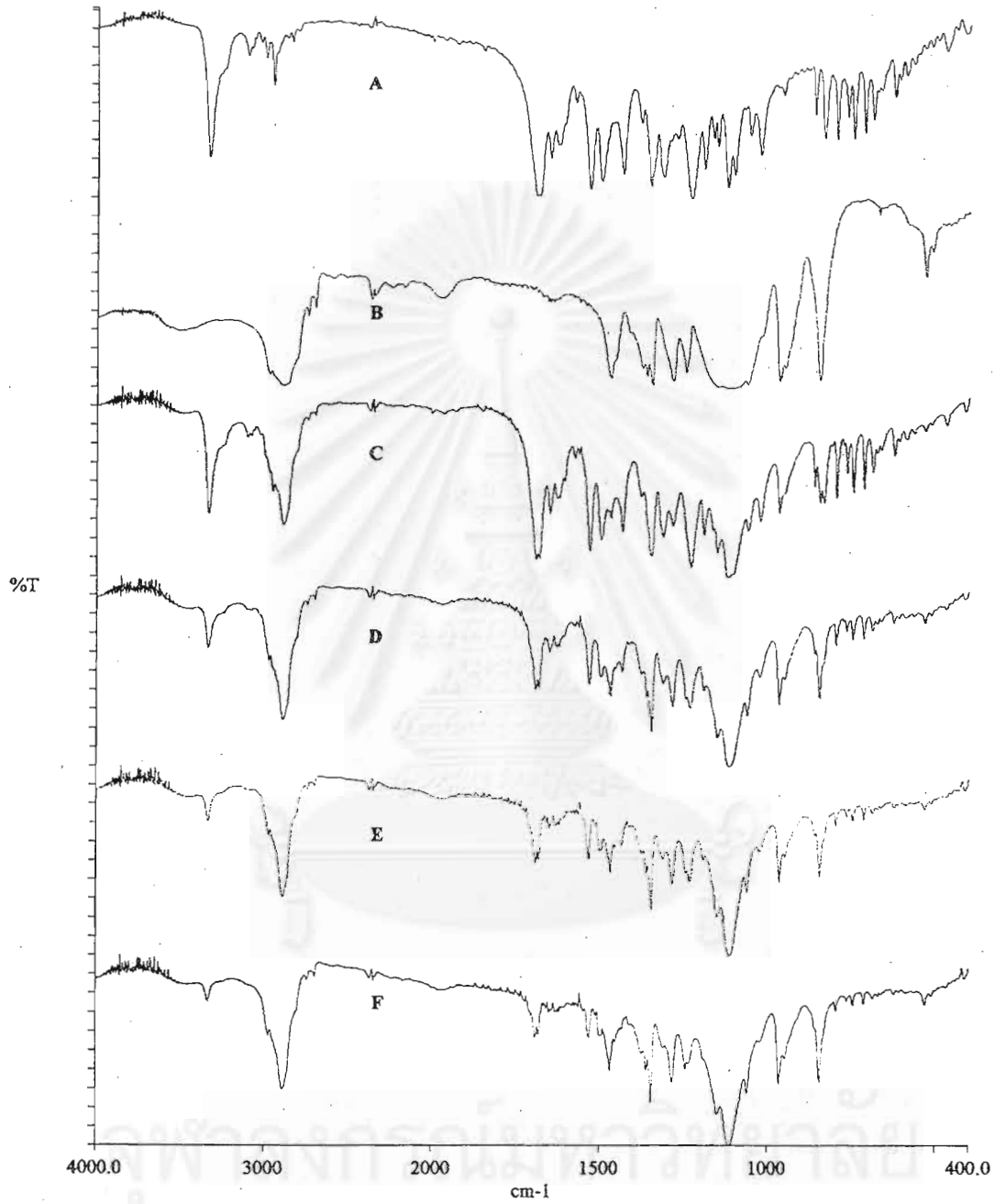


Figure 144 IR spectra of nifedipine-poloxamer407 prepared by solvent method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

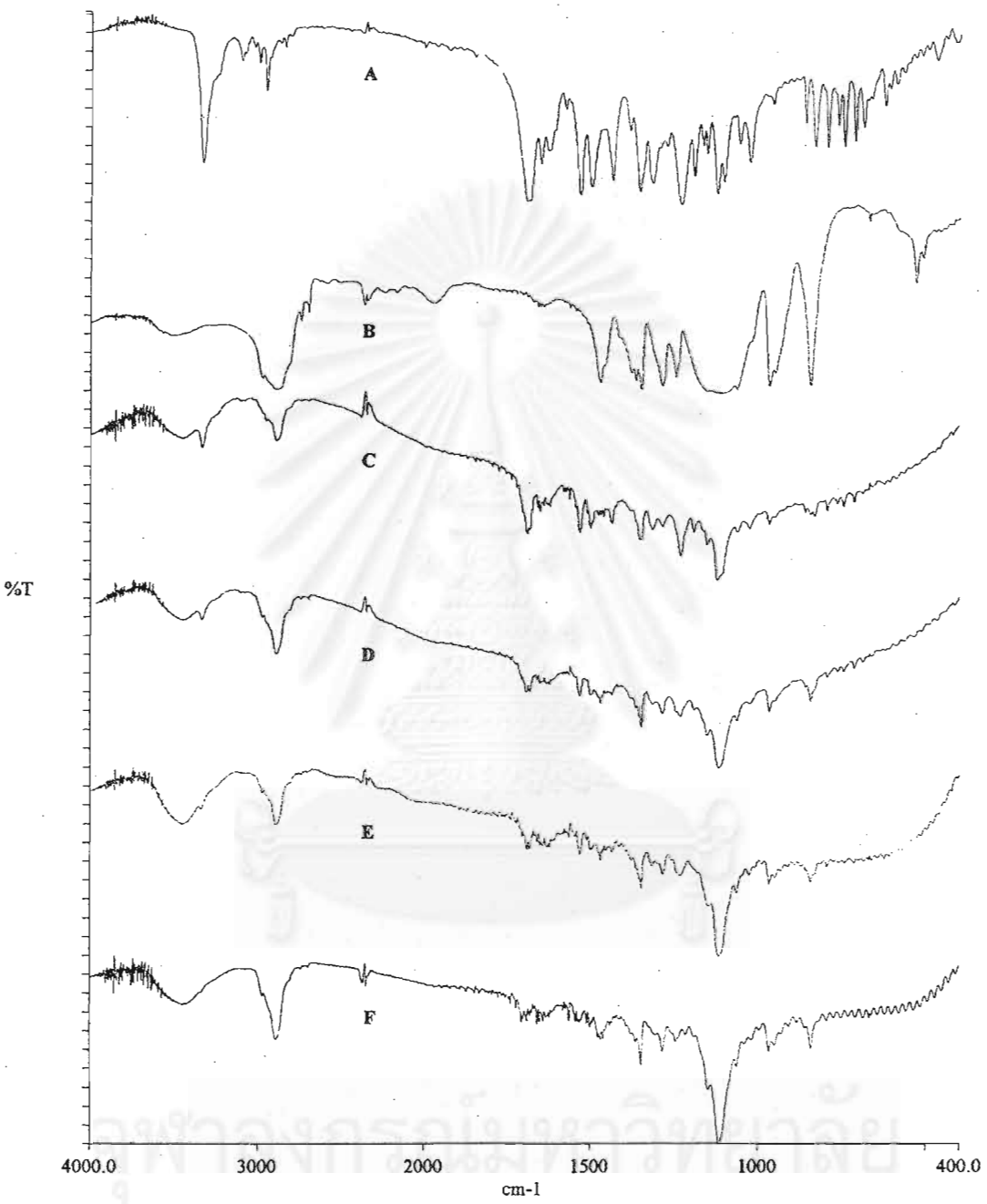


Figure 145 IR spectra of nifedipine-poloxamer407 prepared by kneading method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

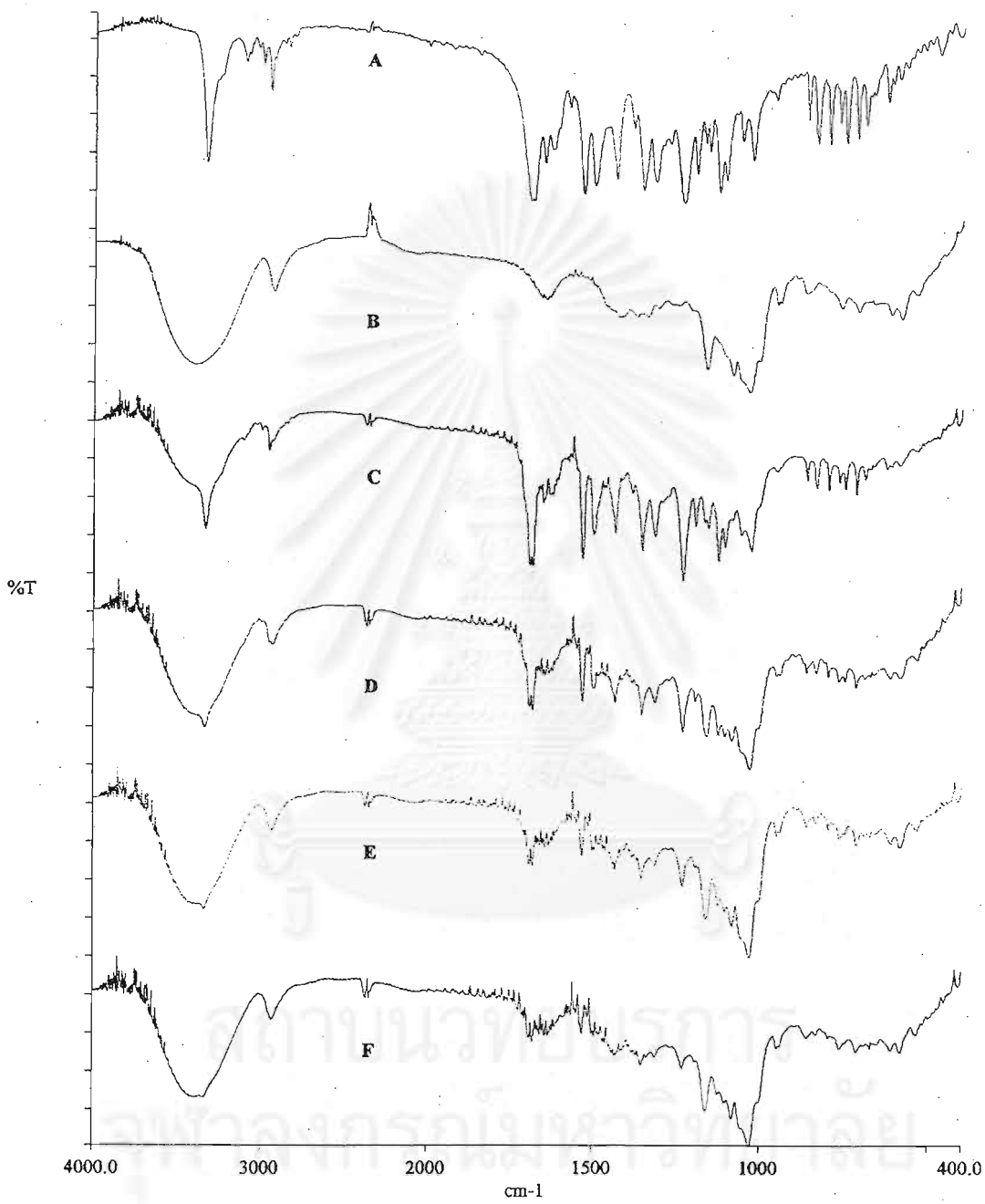


Figure 146 IR spectra of nifedipine-β-cyclodextrin prepared by physical mixture.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

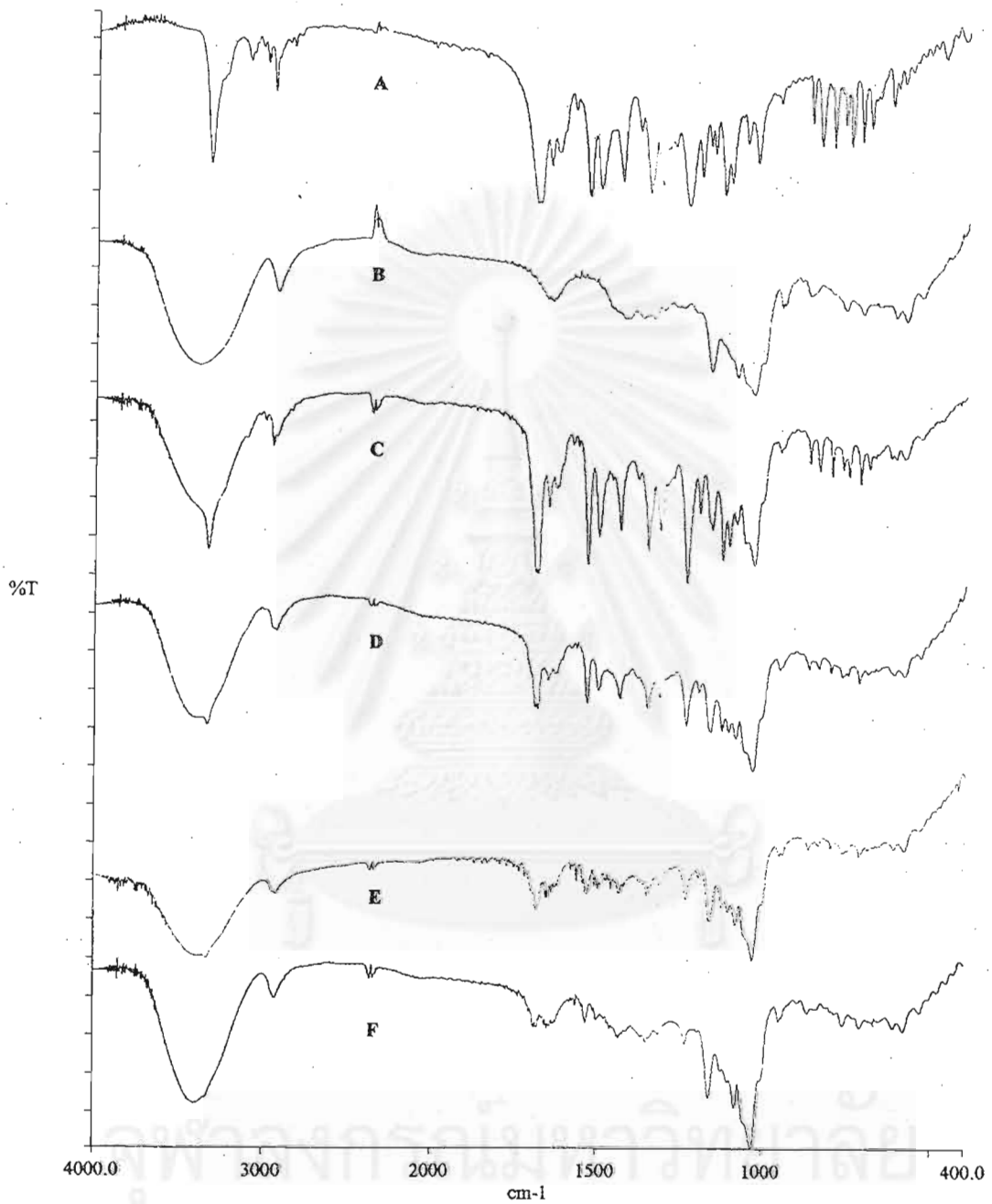


Figure 147 IR spectra of nifedipine-β-cyclodextrin prepared by kneading method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

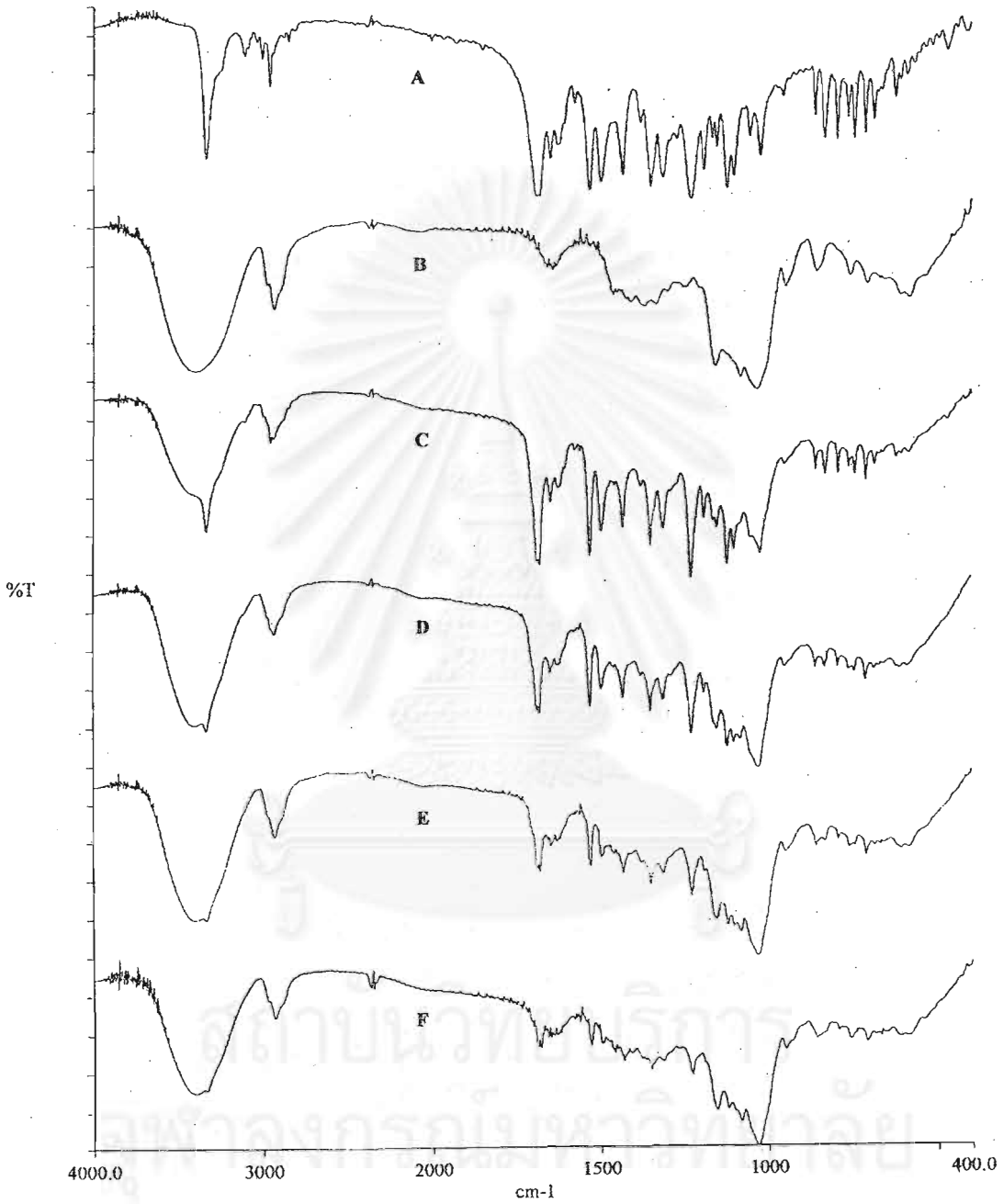


Figure 148 IR spectra of nifedipine-2-hydroxypropyl-β-cyclodextrin prepared by physical mixture .

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

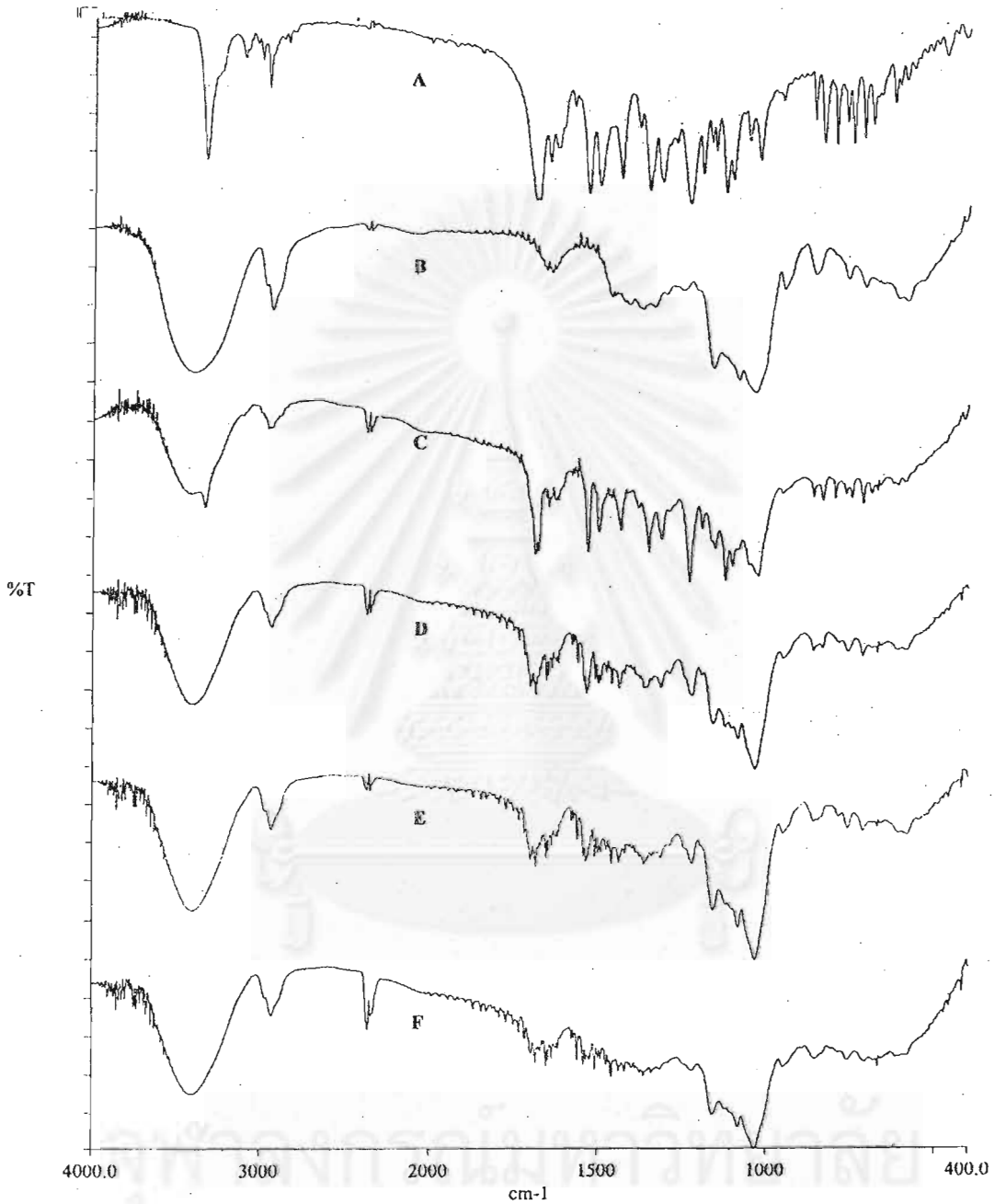


Figure 149 IR spectra of nifedipine-2-hydroxypropyl-β-cyclodextrin prepared by solvent method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

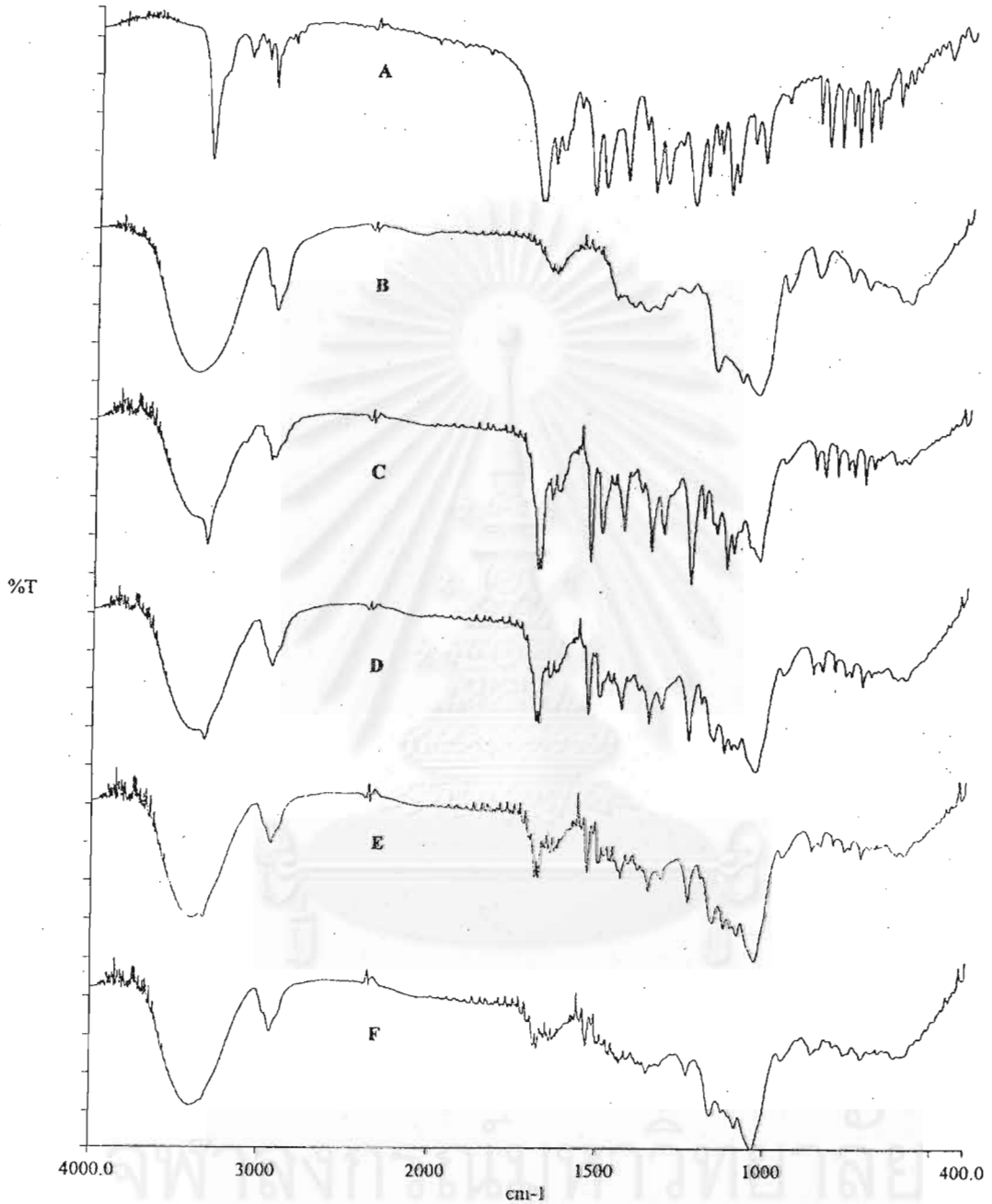


Figure 150 IR spectra of nifedipine-2-hydroxypropyl-β-cyclodextrin prepared by kneading method.

A: nifedipine B: carrier

C: drug to carrier ratio of 1:1 D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5 F: drug to carrier ratio of 1:10

stretching of OC_2H_5 groups from 2800 to 2990 cm^{-1} and C-O stretching band of other from 1000 to 1200 cm^{-1}. The noticeable peak also showed at 1960 cm-1.

The nifedipine-PEG4000 physical mixtures, especially at the 1:1 mixing ratio showed the superimposed spectra of both compounds **(Figure 126C)** . At higher drug : carrier mixing ratios, according to the dilution effect, the intensity of some vibration bands of nifedipine markedly reduced.

The solid dispersions of nifedipine-PEG4000 prepared by melting, solvent and kneading method **(Figure127-129)** showed similar IR spectra patterns to their corresponding physical mixture **(Figure126).** The IR spectra of both nifedipine and PEG4000 superimposed. However, the IR spectra of the solid dispersion prepared by melting method at 1:5 and 1:10 ratios **(Figure127E,F)** showed noticeable changes of C=O stretching bands at 1690 and 1680 cm^{-1}. The C=O ester peaks of nifedipine at 1690 cm^{-1} shifted to the lowering frequency at 1686cm^{-1} and at 1680 cm^{-1} could not be detected. In addition, the spectra of PEG4000 at 1960 cm^{-1} in all solid dispersions showed certain changes in their peak intensity.

7.3 The IR spectra of nifedipine–PEG6000 solid dispersions

The IR spectra of PEG6000 as shown from **Figure 130B-133B** showed similar patterns to PEG4000, due to their similarity in their molecular structure. The characteristic broad peaks of O-H stretching bands showed from 3300 to 3600 cm^{-1}, C-H stretching from 2800 to 2990 cm^{-1} and C-O stretching from 1000 to 1200 cm^{-1}. The medium intensity peak at 1960 cm^{-1} were also detected.

The IR spectra of nifedipine-PEG6000 solid dispersion **(Figure130-133)** showed no difference from their corresponding physical mixtures. The spectra showed the superimposition of characteristic peaks of both nifedipine and PEG6000. Certainly, at the higher mixing ratios, the intensity of nifedipine peaks reduced due to the dilution by PEG6000.

7.4 The IR spectra of nifedipine-poloxamer188 solid dispersion

The IR spectra of poloxamer188 **(Figure134B-137B)** showed the characteristics broad peaks of O-H stretching from 3300 to 3600 cm^{-1}, C-H stretching from 2800 to 2990 cm^{-1} and C-O stretching of ether linkage from 1000-1200 cm^{-1}.

The physical mixtures of nifedipine and poloxamer188 showed superimposed characteristic peaks of both compounds. However, the intensity of nifedipine peaks were reduced at higher mixing ratios.

The solid dispersions of nifedipine-poloxamer188 prepared by melting, solvent and kneading method showed similar IR spectral patterns to their corresponding physical mixtures **(Figure135-137).** It was interesting that all solid dispersions showed some changes of the O-H stretching band of poloxamer188. The intensity of the broad O-H stretching band of intermolecular hydrogen bonding was more than poloxamer itself and also shift to lower frequency.

7.5 The IR spectra of nifedipine-poloxamer288 solid dispersions

The IR spectra of poloxamer288 were very similar to those of the other two poloxamers **(Figure138B-141B).** The broad peak of O-H stretching were detected from 3300 to 3600 cm^{-1}, C-H stretching from 2800 to 2990 cm^{-1} and C-O stretching from 1000-1200 cm^{-1}.

The physical mixtures of nifedipine and poloxamer288 showed superimposed IR spectra of both compounds (Figure138). However, at the higher mixing ratio, many peaks of nifedipine showed reduced intensity. The solid dispersions prepared by melting, solvent and kneading method showed IR spectra not different from their corresponding physical mixtures **(Figure 139-141).** The shift of O-H stretching to lowering frequency that observed in the poloxamer188 and 407 could not be clearly detected in poloxamer288 systems.

7.6 The IR spectra of nifedipine-poloxamer407 solid dispersions

The IR spectra of poloxamer407 **(Figure142-145)** showed no difference from those of poloxamer188, due to their similarity in the molecular structure. They showed broad O-H stretching from 3300 to 3600 cm^{-1}, C-H stretching from 2800 to 2990 cm^{-1} and C-O stretching of ether linkage from 1000 to 1200 cm^{-1}, however this latter bond was more intense than that of poloxamer188.

The IR spectra of nifedipine-poloxamer407 physical mixtures **(Figure142)** showed the superimposition of those of nifedipine and poloxamer407.

The solid dispersions prepared by melting method and kneading method at 1:5 and 1:10 mixing ratios **(Figure143 and 145)** showed some changes of C=O stretching at 1690 cm^{-1} that lowered to 1686 cm^{-1}.

All solid dispersions showed the slight shift to lower frequency of O-H stretching of poloxamer407 and changes in C-O stretching band appearances at 1000-1200 cm^{-1} of poloxamer407.

7.7 The IR spectra of nifedipine-β-cyclodextrin solid dispersion

β-Cyclodextrin in **Figure 146B-147B** showed characteristic broad O-H stretching peak from 3000 to 3600 cm^{-1}. The C-H stretching could be detected at 2927 cm^{-1}. The C-O stretching of primary O-H groups and secondary O-H groups could be observed at 1029 and 1158 cm^{-1}, respectively.

The physical mixtures showed showed superimposed IR spectral patterns of nifedipine and β-cyclodextrin.

The solid dispersions prepared from kneading method showed similar IR spectra to their corresponding physical mixtures. However, both systems at higher mixing ratios at 1:5 and 1:10 showed slightly changes of aromatic C-H stretching of nifedipine at 3102 cm^{-1} and aliphatic C-H stretching at 2954 cm^{-1}. The aromatic C=C stretching of phenyl nucleus at 1600 cm^{-1} showed some changes in their patterns.

7.8 The IR spectra of nifedipine –2-hydroxypropyl-β-cyclodextrin solid dispersions

The IR spectra of 2-hydroxypropyl-β-cyclodextrin showed very intense O-H stretching vibration from 3000 to 3600 cm^{-1}. The C-H stretching vibration showed at 2930 cm^{-1}. The primary O-H stretching and secondary O-H stretching could be detected at 1033 and 1156 cm^{-1}, respectively **(Figures148-150).**

The IR spectra of physical mixtures showed superimposition of those of nifedipine and 2-hydroxypropyl-β-cyclodextrin. Certainly many peaks of nifedipine disappeared due to dilution by the carrier. However, at higher mixing ratios, some changes could be observed at the C-H stretching of nifedipine at 3102 and 2954 cm^{-1}.

The solid dispersions prepared by kneading methods showed similar IR spectra to their corresponding physical mixtures **(Figure150).**

It was interesting that the IR spectra of the solid dispersions prepared by solvent method **(Figure149)** showed remarkable changes at the mixing ratio 1:1 to 1:10. Besides the change of C-H stretching of nifedipine at 3102 and 2954 cm^{-1}, the change to C=O stretching of nifedipine at 1689 cm^{-1} could be observed. In addition, the aromatic C=C stretching of phenyl nucleus at 1600 cm^{-1} showed noticeable changes in their patterns.

8. Solubility study

The solubility of nifedipine in water and in solutions containing various carriers at various concentrations were shown in **Table 9-11** and **Figure 151-153**.

The solubility phase diagram of nifedipine in PEGs were illustrated in **Table 9** and **Figure 151**. The solubility of nifedipine in purified water at 24 hours was about 8.0 μg/ml. From the solubility study of the 1-4% of the carrier system, it was revealed that PEG4000 had solubilizing effect in the solubility range of 9.3-14.8 μg/ml, almost as the same solubilizing effect as PEG6000 which gave the solubility range of 9.0-14.3 μg/ml.

From **Table 10** and **Figure 152** in the group of poloxamers, poloxamer407 obviously affected solubility of nifedipine more than the other two poloxamers which have solubilizing effect of 9.5-19.3 μg/ml for poloxamer188 and 11.25-29.31 μg/ml for poloxamer288 respectively. The solubility effect of poloxamer407 was of the solubility range 32.5-214.4 μg/ml which was about 4 to 27-fold of the pure drug solubility.

From **Table 11** and **Figure 153**, β-cyclodextrin was differently studied in the range of 0.1-0.8%. The concentration range ot ite carrier studied was lower due to its limited solubility. It showed slight increased solubility of nifedipine. In contrary,2-hydroxypropyl-β-cyclodextrin itself has better water solubility and also had better solubilizing effect to nifedipine in the range of 9.5-17.8 μg/ml.

Table 9 Solubility of nifedipine at various concentrations of PEG 4000 and PEG 6000

	Nifedipine Solubility, ug/ml	
Carrier conc.	PEG 4000	PEG 6000
0	7.97	7.97
1	9.37	9.07
2	11.19	11.11
3	12.51	13.09
4	14.80	14.31

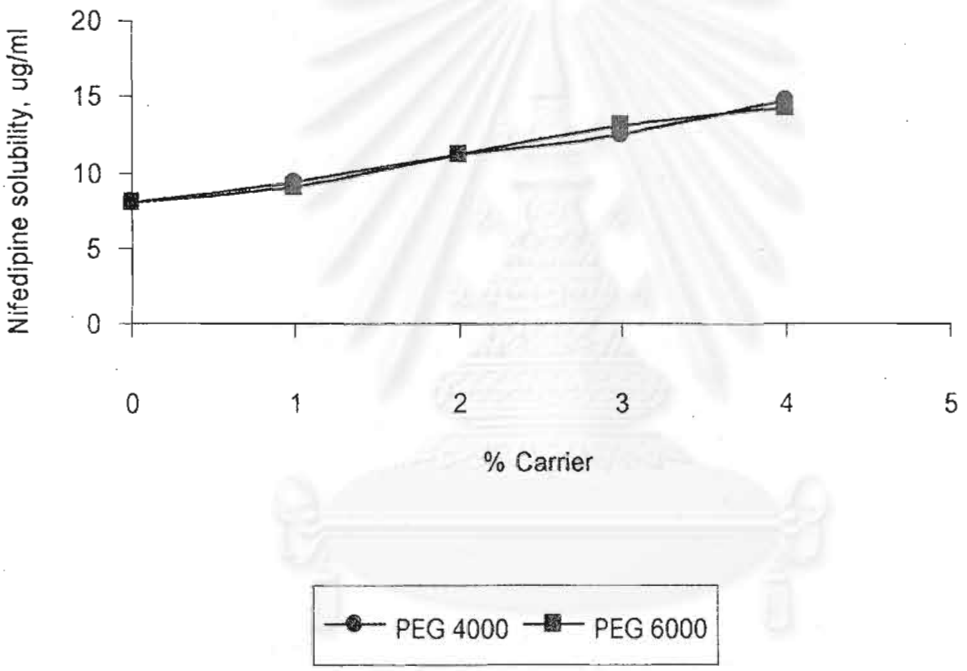


Figure 151 Solubility of nifedipine at various concentrations of PEG4000 and PEG 6000

Table 10 Solubility of nifedipine at various concentrations of poloxamer 188, poloxamer 288 and poloxamer 407

	Nifedipine Solubility, ug/ml		
Carrier conc.	Poloxamer188	Poloxamer288	Poloxamer407
0	7.974	7.974	7.974
1	9.587	11.251	32.538
2	12.689	17.422	88.069
3	15.849	25.351	149.711
4	19.324	29.318	214.475

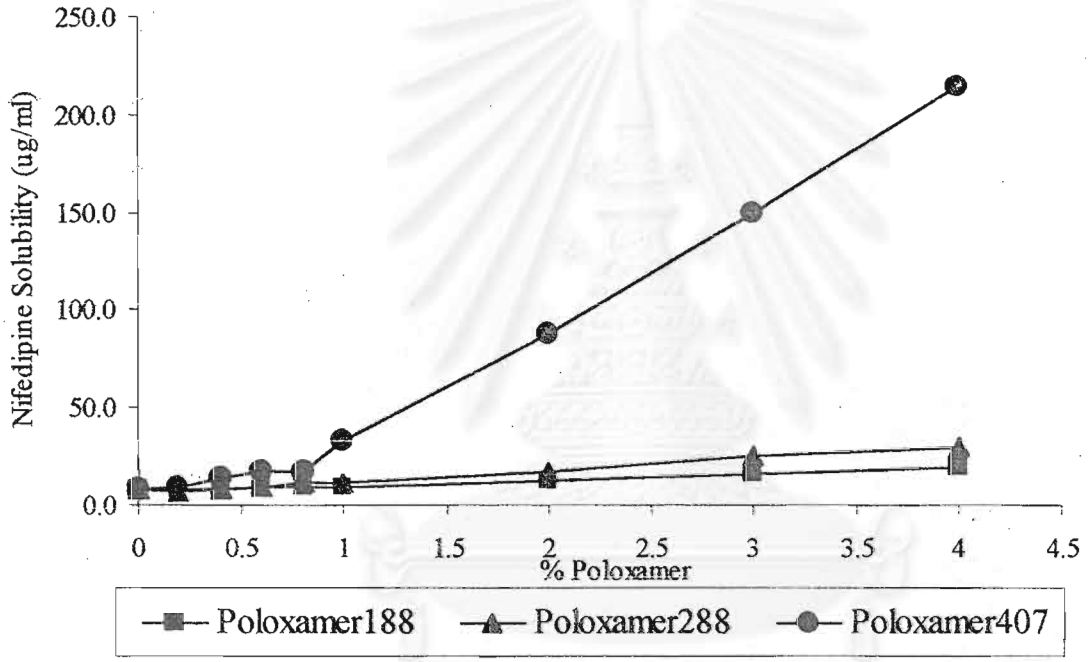


Figure 152 Solubility of nifedipine at various concentration of poloxamer 188, poloxamer 288 and poloxamer 407

Table 11 Solubility of nifedipine at various concentrations of β–cyclodextrin and hydroxypropyl-β-cyclodextrin

	Nifedipine Solubility, ug/ml	
Carrier Conc	BCD	HPBCD
0	7.97	7.97
0.2	7.29	7.81
0.4	8.16	7.99
0.6	8.15	8.32
0.8	9.21	9.04
1	-	9.59
2	-	12.49
4	-	17.85

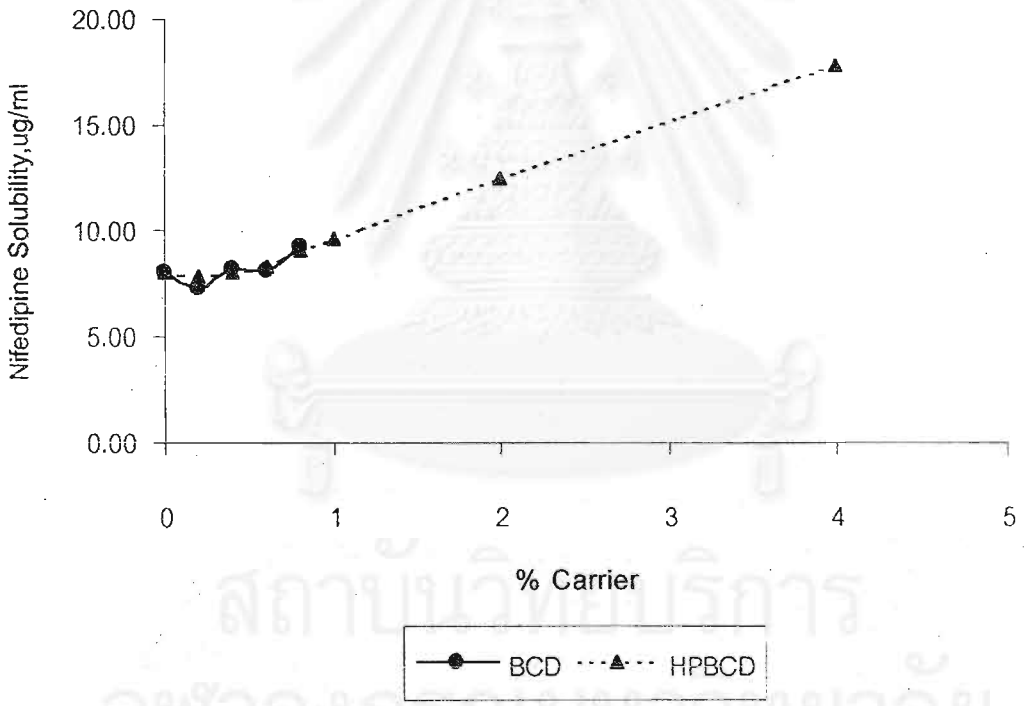


Figure 153 Solubility of nifedipine at various concentrations of β–cyclodextrin and hydroxypropyl- β–cyclodextrin

It can be said that the solubility of nifedipine was enhanced by all carriers studied. Poloxamers are the carrier group that have higher solubilizing effect than PEGs and β-cyclodextrin groups. Poloxamer407 shows interestingly highest solubilizing effect.

9. Wettability study

Wettability property of nifedipine, carriers and solid dispersion systems were studied by compressed disc method. the contact angles can be directly measured from the photographs of the experimented disc. The results are illustreated in **Table 12-20** and **Figure 154-162**.

From **Table 12** and **Figure 154**, it showed that pure drug gave very high contact angle of 85°. Treated drug by various methods showed different degrees of decrease in contact angles at about 52°-60°. The solid dispersions showed lower contact angle than pure nontreated and treated drug, however higher than those of pure carriers studied. The contact angles of all carriers in the study were shown in **Table 13** and **Figure 155.**

For PEGs system, in general, the contact angle was decreased with the amount of carrier increased. This indicated that the higher amount of carrier, the better wettability obtained.

For the system of PEG4000, comparing between different methods, at the ratio of 1:10, melting method exhibited the lowest contact angle. The ascending rank of

Table 12 Contact angle off nifedipine measured by compressed disc method

Contact angle	Mean	Measure1	Measure2	S.D.
Melting method	52	54	50	2.8
Solvent method	59	58	60	1.4
Kneading method	59.5	59	60	0.7
Physical mixture	59.5	60	59	0.7
Nontreated	85	86	84	1.4

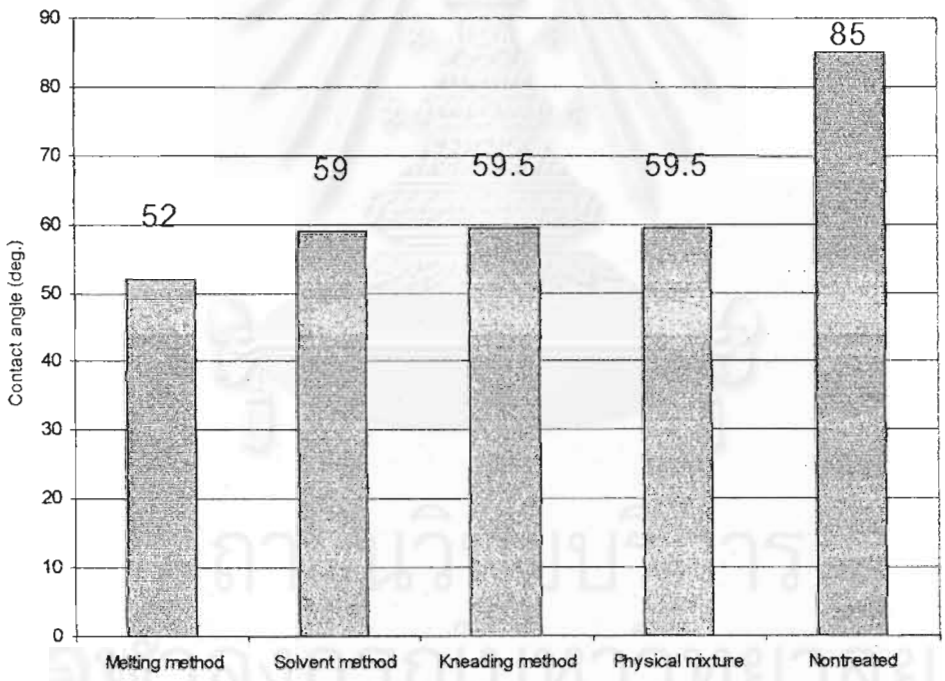


Figure 154 Contact angle of nifedipine measured by compressed disc method

Table 13 Contact angle of various carriers measured by compressed method

Carriers	Mean	Measure1	Measure2	S.D.
PEG4000	14.5	15	14	0.71
PEG6000	13.0	12	14	1.41
Poloxamer407	37.5	37	38	0.71
Poloxamer188	23.5	25	22	2.12
Poloxamer288	32.5	32	33	0.71
BCD	0.0	0	0	0.00
HBCD	24.0	24	24	0.00

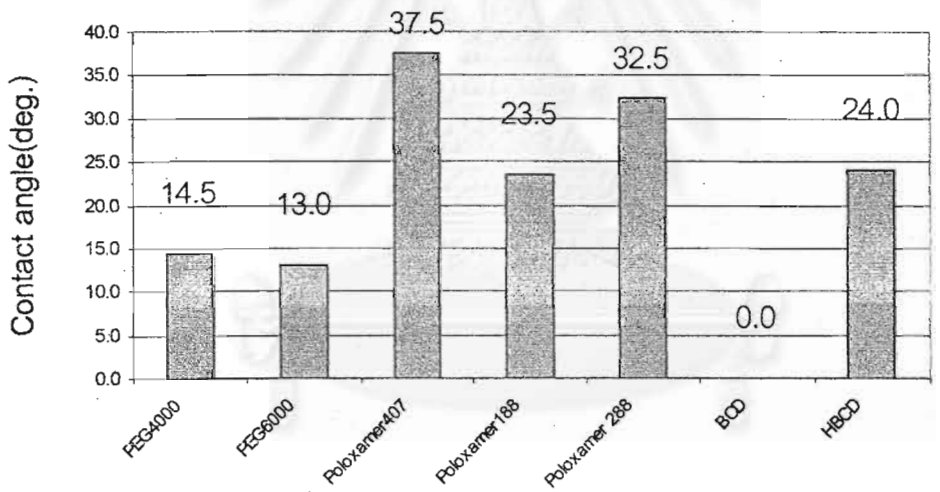


Figure 155 Contact angle of various carriers measured by compressed disc method

Table 14 Contact angle of nifedipine-PEG 4000 system at various drug: carrier ratios measured by compressed disc method

Ratio	Duplication	Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	25	21	28	32
	2	27	21	32	30
	Mean	**26**	**21**	**30**	**31**
	S.D.	**1.4**	**0.0**	**2.8**	**1.4**
1:3	1	21	19	26	22
	2	21	21	24	27
	Mean	**21**	**20**	**25**	**24.5**
	S.D.	**0.0**	**1.4**	**1.4**	**3.5**
1:5	1	17	17	20	22
	2	18	20	22	24
	Mean	**17.5**	**18.5**	**21**	**23**
	S.D.	**0.7**	**2.1**	**1.4**	**1.4**
1:10	1	16	14	16	25
	2	13	16	21	21
	Mean	**14.5**	**15**	**18.5**	**23**
	S.D.	**2.1**	**1.4**	**3.5**	**2.8**

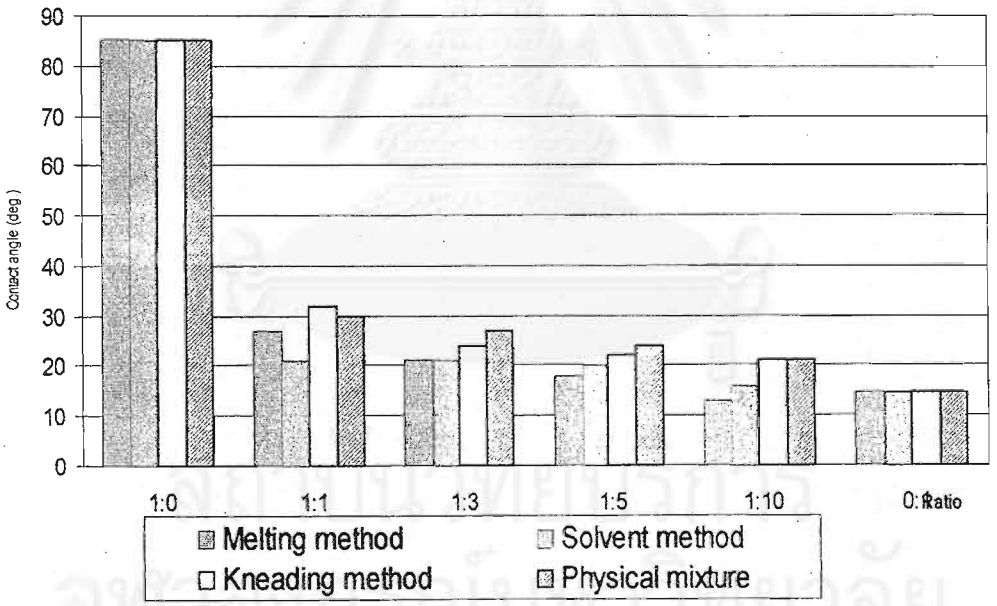


Figure 156 Contact angle of nifedipine-PEG 4000 system at various drug: carrier ratios measured by compressed disc method

Table 15 Contact angle of nifedipine-PEG 6000 system at various drug: carrier ratios measured by compressed disc method

Ratio		Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	27	29	24	35
	2	27	29	25	33
	Mean	**27**	**29**	**24.5**	**34**
	S.D.	**0.0**	**0.0**	**0.7**	**1.4**
1:3	1	21	24	21	26
	2	24	22	19	29
	Mean	**22.5**	**23**	**20**	**27.5**
	S.D.	**2.1**	**1.4**	**1.4**	**2.1**
1:5	1	20	19	19	23
	2	22	17	19	21
	Mean	**21**	**18**	**19**	**22**
	S.D.	**1.4**	**1.4**	**0.0**	**1.4**
1:10	1	17	16	16	20
	2	16	16	14	19
	Mean	**16.5**	**16**	**15**	**19.5**
	S.D.	**0.7**	**0.0**	**1.4**	**0.7**

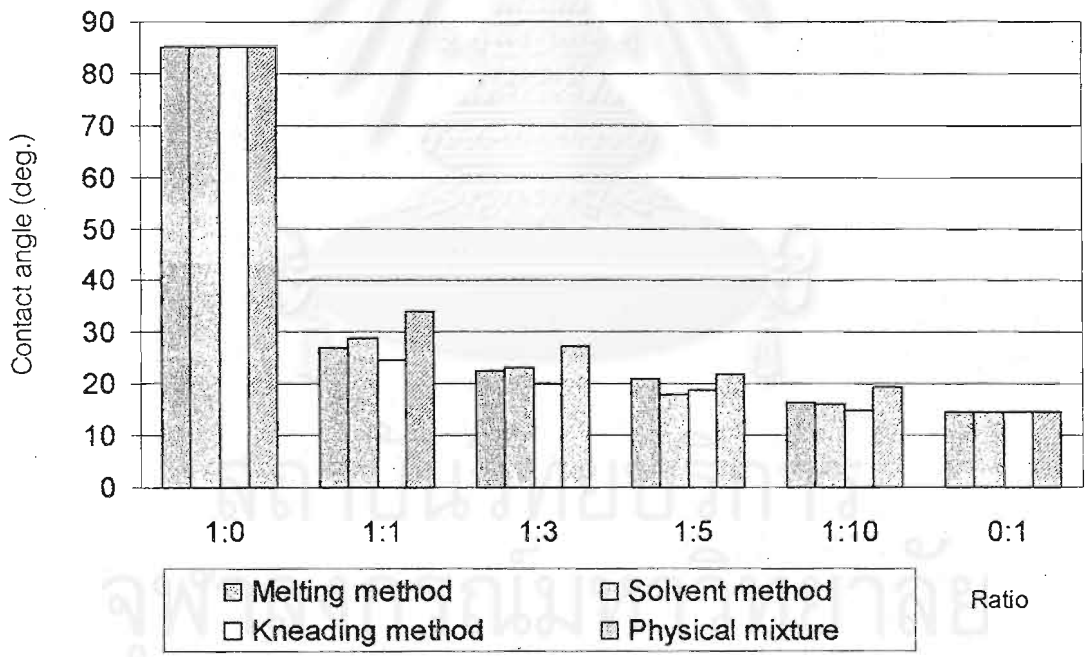


Figure 157 Contact angle of nifedipine-PEG 6000 system at various drug: carrier ratios measured by compressed disc method

Table 16 Contact angle of nifedipine-poloxamer 188 system at various drug: carrier ratios measured by compressed disc method

Ratio		Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	34	29	28	29
	2	29	31	27	31
	Mean	**31.5**	**30**	**27.5**	**30**
	S.D.	**3.5**	**1.4**	**0.7**	**1.4**
1:3	1	32	32	28	30
	2	33	29	27	30
	Mean	**32.5**	**30.5**	**27.5**	**30**
	S.D.	**0.7**	**2.1**	**0.7**	**0.0**
1:5	1	30	30	26	33
	2	30	32	28	30
	Mean	**30**	**31**	**27**	**31.5**
	S.D.	**0.0**	**1.4**	**1.4**	**2.1**
1:10	1	30	30	27	32
	2	29	30	28	31
	Mean	**29.5**	**30**	**27.5**	**31.5**
	S.D.	**0.7**	**0.0**	**0.7**	**0.7**

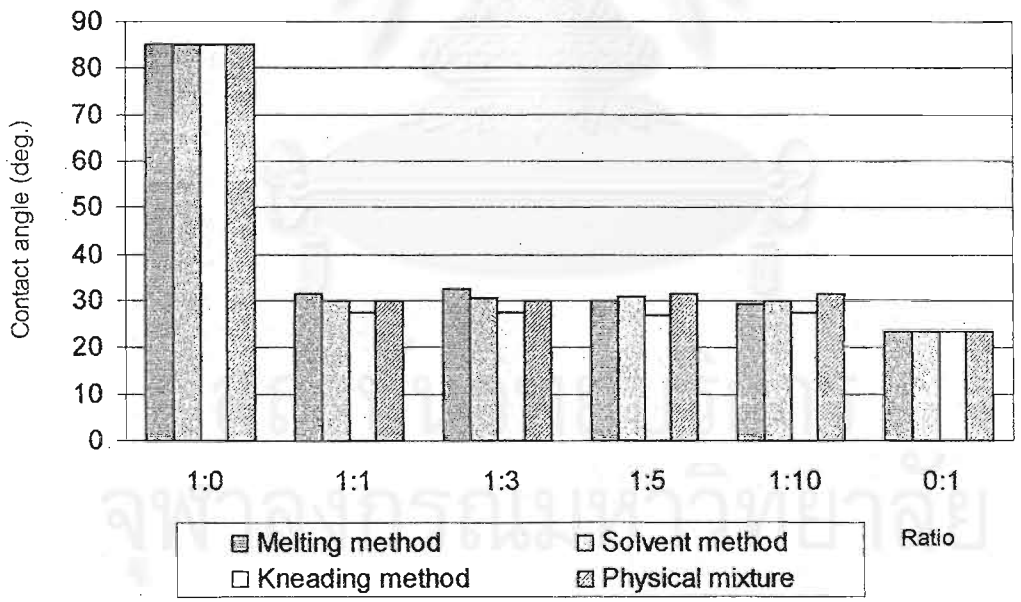


Figure 158 Contact angle of nifedipine-poloxamer 188 system at various drug: carrier ratios measured by compressed disc method

Table 17 Contact angle of nifedipine-poloxamer 288 system at various drug: carrier ratios measured by compressed disc method

Ratio		Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	36	44	40	46
	2	36	36	42	48
	Mean	36	40	41	47
	S.D.	0	5.7	1.4	1.4
1:3	1	35	38	36	47
	2	36	41	44	45
	Mean	35.5	39.5	40	46
	S.D.	0.7	2.1	5.7	1.4
1:5	1	35	38	42	44
	2	36	40	40	43
	Mean	35.5	39	41	43.5
	S.D.	0.7	1.4	1.4	0.7
1:10	1	35	31	40	40
	2	35	32	40	38
	Mean	35	31.5	40	39
	S.D.	0.0	0.7	0.0	1.4

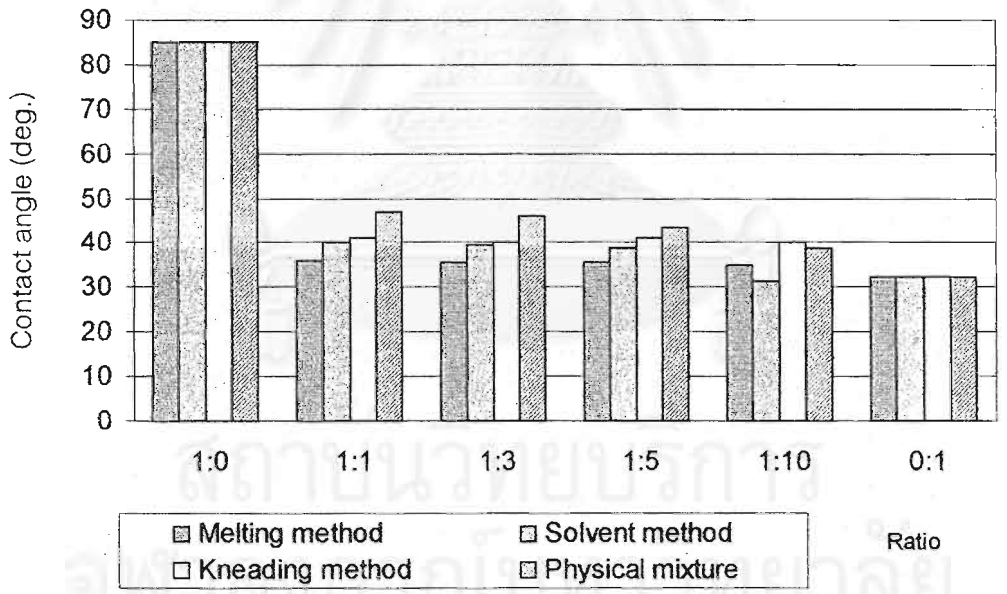


Figure 159 Contact angle of nifedipine-poloxamer 288 system at various drug: carrier ratios measured by compressed disc method

Table 18 Contact angle of nifedipine-poloxamer 407 system at various drug: carrier ratios measured by compressed disc method

Ratio		Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	55	55	39	38
	2	55	51	40	42
	Mean	**55**	**53**	**39.5**	**40**
	S.D.	**0.0**	**2.8**	**0.7**	**2.8**
1:3	1	50	53	38	44
	2	54	48	40	50
	Mean	**52**	**50.5**	**39**	**47**
	S.D.	**2.8**	**3.5**	**1.4**	**4.2**
1:5	1	40	50	37	45
	2	48	43	40	46
	Mean	**44**	**46.5**	**38.5**	**45.5**
	S.D.	**5.7**	**4.9**	**2.1**	**0.7**
1:10	1	44	42	40	42
	2	47	50	41	41
	Mean	**45.5**	**46**	**40.5**	**41.5**
	S.D.	**2.1**	**5.7**	**0.7**	**0.7**

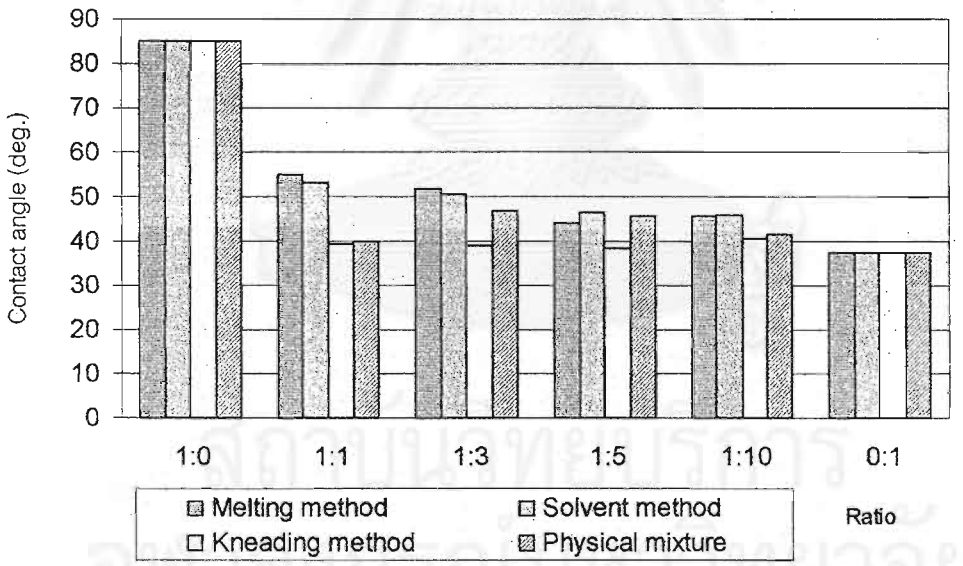


Figure 160 Contact angle of nifedipine-poloxamer 407 system at various drug: carrier ratios measured by compressed disc method

Table 19 Contact angle of nifedipine- β-cyclodextrin system at various drug: carrier ratios measured by compressed disc method

Ratio		Kneading method	Physical mixture
1:1	1	35	47
	2	38	48
	Mean	**36.5**	**47.5**
	S.D.	**2.1**	**0.7**
1:3	1	20	24
	2	20	25
	Mean	**20**	**24.5**
	S.D.	**0.0**	**0.7**
1:5	1	10	15
	2	8	9
	Mean	**9**	**12**
	S.D.	**1.4**	**4.2**
1:10	1	0	0
	2	0	0
	Mean	**0**	**0**
	S.D.	**0.0**	**0.0**

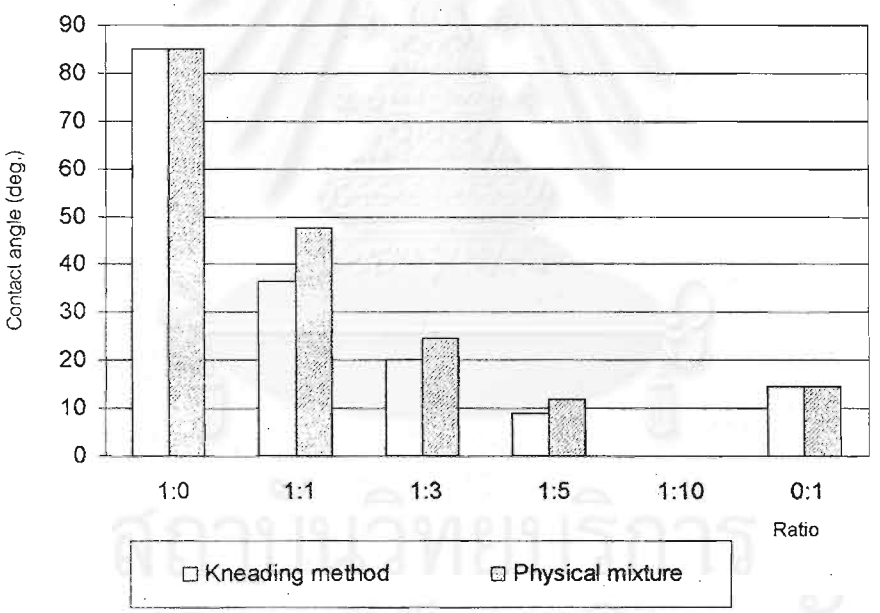


Figure 161 Contact angle of nifedipine-β-cyclodextrin system at various drug: carrier ratios measured by compressed disc method

Table 20 Contact angle of nifedipine-hydroxypropyl- β-cyclodextrin system at various drug: carrier ratios measured by compressed disc method

Ratio		Solvent method	Kneading method	Physical mixture
1:1	1	33	40	37
	2	27	40	37
	Mean	30	40	37
	S.D.	4.2	0.0	0.0
1:3	1	30	34	34
	2	27	32	35
	Mean	28.5	33	34.5
	S.D.	2.1	1.4	0.7
1:5	1	27	26	31
	2	27	25	29
	Mean	27	25.5	30
	S.D.	0.0	0.7	1.4
1:10	1	26	24	29
	2	24	25	30
	Mean	25	24.5	29.5
	S.D.	1.4	0.7	0.7

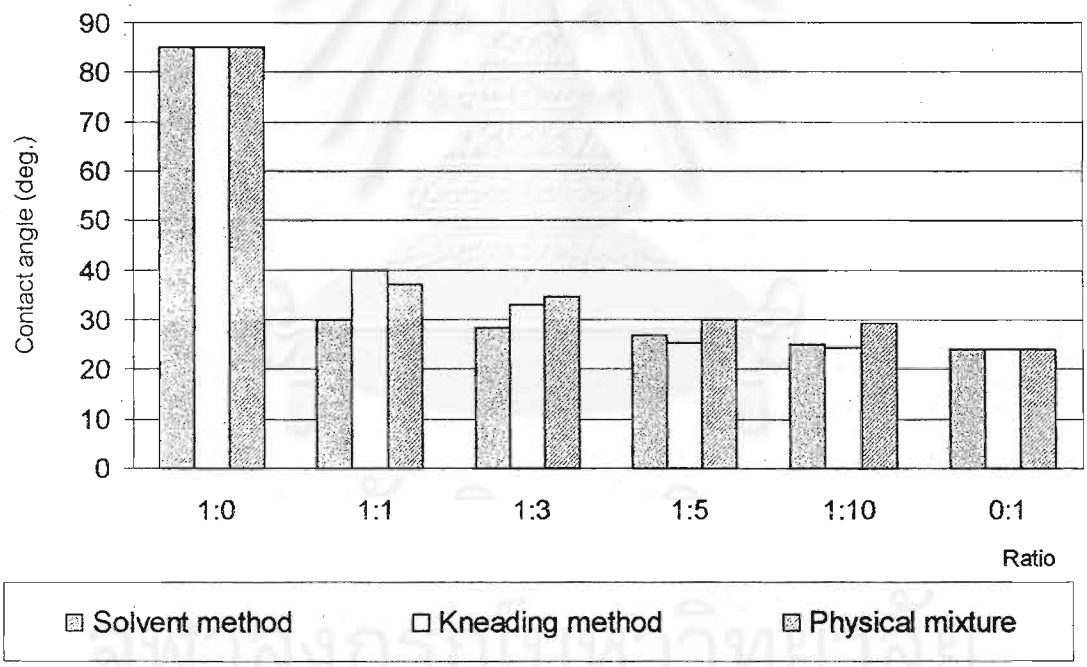


Figure 162 Contact angle of nifedipine-hydroxypropyl-β-cyclodextrin system at various drug: carrier ratios measured by compressed disc method

contact angle within the mixing ratio of 1:10 was from the method by melting < solvent < kneading < physical mixture. Very interestingly, at the ratio of 1:10 the contact angle is almost as good as PEG4000 itself (**Table 14** and **Figure 156**).

Differently from PEG4000, the lowest contact angle was found in PEG6000 at the ratio of 1:10 prepared by kneading method. No obvious difference was found between solvent, melting and physical mixing method (**Table 15** and **Figure 157**).

Most poloxamers exhibited high contact angles compared to those of PEGs. Unlike the PEGs system, the contact angles were not dramatically decreased with an increment of the poloxamers. It was found that the typical range of contact angles of poloxamer407 poloxamer288 and poloxamer188 were at about 50°, 40° and 30° respectively (**Table 16-18** and **Figure 158-160**).

For β-cyclodextrin, the contact angle was decreased dramatically when amount of carrier increased. At the ratio 1:10, the contact angle, surprisingly, became 0 ° giving the best wettability among all carriers (**Table19, Figure 161**). Whereas 2-hydroxypropyl- β-cyclodextrin gave the contact angle between 30-40 ° which found very similar to those of poloxamers group (**Table 20, Figure 162**).

CHAPTER V

DISCUSSION

The principal goal of this chapter is to understand the nifedipine solid dispersion system and the related factors affecting its dissolution rate, for instance, type of carriers used, drug to carrier ratio and preparation methods. The physicochemical characteristic studies together with the literature review provide the useful information to explain the obtained results.

Nontreated pure nifedipine and treated pure nifedipine

1. Dissolution behavior

The dissolution profiles revealed that treated pure nifedipine by various methods were apparently not different from its physical mixture. All treated pure nifedipine dissolution profiles were lower than that of nontreated pure nifedipine. The reason was possibly the agglomeration of nifedipine particles in treated drug from the processes caused a decrease of specific surface area, hence, poorer dissolution behavior.

2. Physicochemical characteristics

The melting endothermics of pure nontreated nifedipine show quite similar characteristics to those of treated nifedipine by physical mixing, melting, solvent, and kneading method in the range of 174.4-178.0 °C. This indicated that the experimental

condition in the four methods had no effect to nifedipine thermal property and stability.

From X-ray diffraction, there was no difference between nontreated and treated nifedipine pattern whereas the characteristic peaks at 7.9, 10.3 and 11.7° at 2 θ were existed in all methods.

The result from IR spectra also revealed that the pattern peaks were all the same as nifedipine itself. This suggested and confirmed that any changes later to X-ray diffraction peaks and IR patterns were caused by the studied factors not by any other influences.

Solid dispersion of nifedipine with various carriers

Solid dispersion of nifedipine with PEGs, poloxamers and β-cyclodextrin were studied in terms of dissolution rate and physicochemical characteristics. In general, dissolution rates obtained from nifedipine solid dispersed in poloxamers showed favorable results followed by those obtained from PEGs and β-cyclodextrin respectively.

1. Nifedipine-PEGs solid dispersion

1.1 Dissolution study of nifedipine-PEGs solid dispersions

The two way analysis of variance (ANOVA) showed statistically significant difference between methods, ratios and the interaction between methods and ratios for

both PEG4000 and PEG6000. This means that the mixing ratio, method and ratio-method interaction influenced the dissolution rates.

For PEG4000, the most favorable dissolution rate were found at the drug to carrier ratio of 1:10 in all methods. Melt method with the drug-carrier ratio 1:10 and solvent method also with the ratio of 1:10 yielded the highest dissolution rates. However they were not significantly different in terms of LSR test.

The most favorable mixing ratio, drug to carrier of 1:10, found in this study seemed to agree with Save and Vankitachalam (1992). For the nifedipine-PEG system, it was suspected that the drug-carrier ratio of 1:10 was a saturation point where PEG presented in a metastable form.

There was also a similar kind of report regarding the saturation level of carrier in nifedipine-PVP system. Nozawa, Mizumoto and Higashide (1986) reported that nifedipine crystals in the roll mixing with PVP 25% seemed to be converted to amorphous state easily.

For PEG6000, inspite of a slightly superior dissolution behavior, exhibited similar trend of dissolution results as those described in PEG4000.

1.2 Physicochemical characteristics of nifedipine-PEGs solid dispersions

The photomicrograph of nifedipine-PEGs systems mainly showed that nifedipine particles physically deposited on the surface of the carriers. The observation of

particle appearance of PEG4000 and PEG6000 suggested that PEGs may present in the crystalline state whereas nifedipine may not present in the crystalline state since the particles have already distorted from the pure drug. This phenomenon became clearer in the case of solid dispersions prepared by melting and solvent methods at higher ratios. The average particles size of nifedipine were found to be smaller than nontreated nifedipine.

The DSC results have confirmed that nifedipine did not present in the crystalline state because of the disappearance of nifedipine melting (Figure 160-161).

For the nifedipine-PEG4000 systems, only at lower proportion of PEG4000 (at 1:1) that a broad endothermic peak which referred to nifedipine melting point could be observed at the temperature range 145°-162°C. These lowering melting point of nifedipine, from initially 175°C, depended on the preparation methods. Nifedipine solid dispersions showed lower melting endotherms than that of physical mixture. The lowest temperature of endothermic peak was found in the solid dispersion by solvent method.

It was found that only at 1:1 ratio of the physical mixture of PEG4000 that a small endothermic peak at 230°C could be detected. This peak might indicate the decomposition of nifedipine at very high temperature.

Since it was obvious that nifedipine melting could not be observed in solid dispersions including physical mixtures when the ratio of drug to PEG4000 other than

1:1. The explanation of these finding may be in terms of amorphization of nifedipine in crystalline state of PEG4000 (Figure74-77).

Similar DSC thermograms were obtained in the nifedipine-PEG6000 systems that PEG6000 melting endotherms could be found in all systems slightly lower than that of pure PEG6000. Broadened melting endotherms of nifedipine could be detected at all ratios of physical mixture, only 1:1 ratio in melting method, 1:1 and 1:3 ratios in solvent method and 1:1, 1:3 and 1:5 in DSC thermograms.

The IR spectra of nifedipine-PEGs solid dispersions, in general, did not show significant difference from their corresponding physical mixtures. Also, solubility showed the similar result between PEG4000 and 6000. However in terms of wettability, PEG4000 had the lower contact angle, therefore higher wettability.

X-ray diffraction patterns of nifedipine-PEG4000 at the ratio of 1:10 prepared by melting and solvent methods showed nearly disappeared of nifedipine peak whereas the peak corresponding to PEG4000 still remained as depicted in Figure 131-132. This also reconfirmed that nifedipine was transformed into amorphous form and dispersed homogeneously as an amorphous state within the crystalline PEGs.

PEGs systems were also reported in other publications. McGinity, Maincent and Steinfink (1984) reported an improvement of tolbutamide dissolution rate from solid dispersion with PEG. It was found that the main mechanism was the transformation of tolbutamide into amorphous state in crystalline PEG.

This was also similar to the report of Chiou and Niazi (1971) where urea (carrier) was present in a crystalline form, while the sulphathiazole (drug) showed no diffraction peak referred to sulphathiazole crystals which meant that transformation of drug to amorphous form.

As far as the ratio concern, the drug-carrier ratio below 1:10 exhibited slight nifedipine peaks and intense PEG peaks. The combined explanations of Save and Venkitachalam (1992) and Chiou and Niazi (1971) can be applied to explain this phenomenon. At the drug-carrier ratio below 1:10, nifedipine might partly change to an amorphous form remaining some crystals. X-ray diffraction of solid dispersion with the ratio lower than 1:10 therefore still showed some intensity of nifedipine peak.

Comparison between nifedipine-PEG4000 and nifedipine-PEG6000, it was found that the dissolution rate constants from nifedipine-PEG6000 were just slightly higher than that of nifeipine-PEG4000. Ford (1986) reviewed the mechanisms for the system where the dissolution rates increase with increasing molecular weight of PEG. The positive factors that may enhance dissolution rate when the molecular weight is increased are higher viscosity hence reducing drug crystallization, increase tendency the incorporation of drug as solid dispersion and readily flake during dissolution.

2. Nifedipine-poloxamers solid dispersion

2.1 Dissolution behavior of nifedipine- poloxamers solid dispersions

The two way analysis of variance indicated statistically significant difference between method, ratio and the method-ratio interaction for all of poloxamer system. The most favorable dissolution rate was obtained from poloxamer188 by melting method at the ratio of drug to carrier 1:3 followed by 1:10 ratio of poloxamer407 by melting method and at 1:10 ratio of poloxamer288 by melting method.

In poloxamer188 system, the ranked order from the highest dissolution rate was melting 1:3, melting 1:5, kneading 1:10 and solvent 1:10; for poloxamer407 the ranking was melt 1:10, knead 1:10, solvent 1:10, melting 1:5 and for poloxamer288 the ranking was melting 1:10, melt 1:5, solvent 1:10 and kneading 1:10 respectively.

2.2 Physicochemical characteristics of nifedipine-poloxamers solid dispersions

The observation of photomicrographs showed very interesting features in the systems of poloxamers. Pure carriers showed very smooth surface liked melted wax. Fewer drug particles were found in this system compared with the other systems. Instead, it was found that the drug particles embedded into the surface of the carriers, not just physically deposited on it. SEM results were found to be closely related to dissolution rate. The more implantation of drug to the carrier, the better dissolution was found. Nifedipine-poloxamer188 at the ratio of 1:3 showed highest drug implantation followed closely by poloxamer288 at the ratio of 1:10.

DSC thermograms showed similar patterns to those of PEGs. A sharp endothermic peak of poloxamer melting was shown in every systems, interestingly at

the temperature lower than that of its pure corresponding poloxamers. It could be noticed that the lowering of melting points was different among the four preparation methods.

As the proportion of nifedipine decreased, at ratio 1:3, 1:5, 1:10, nifedipine melting could not be observed. This might be explained that the dispersion of nifedipine was greater with higher proportion of poloxamers, nifedipine appeared as very small particles of amorphous form dispersed in crystalline poloxamers. Certainly, this could be confirmed with the X-ray diffraction patterns (Figure 83,87 and 91).

From the X-ray diffraction of poloxamer systems, similarly to the dispersion with PEGs system, the crystallinity of nifedipine gradually decreased with the proportion of carriers increased and the peaks of both poloxamers and PEGs still existed in both systems in most methods. The endothermic peak of nifedipine from the DSC was disappeared in the solid dispersion. The SEM depicted the smooth surface and wax like particles. From these physicochemical properties, it was shown that the solid dispersion with poloxamers, nifedipine also possibly presented in an amorphous dispersing in crystalline carrier.

From the wettability and solubility studies, it was found that all solid dispersions with poloxamer were not easily wetted compared with PEGs and β-cyclodextrins. However all poloxamers showed higher solubility than that of PEGs and β-cyclodextrins. One can predict that dissolution rate of solid dispersion with

poloxamers, in general, would yield a higher dissolution rate than the solid dispersion with PEGs due to solubilizing effect.

Among poloxamers themselves, poloxamer188 gave the highest dissolution rate constant, of course among all carriers studied. The ranked dissolution rates from the highest is as poloxamer188 > poloxamer288 > Poloxamer407. The **Table 21** below shows some key properties that may play important role in dissolution mechanisms (extracted from (a) Nikitakis, 1988 (b) Miyazaki et al., 1986 (c) BASF, 1987 and (d) results from this experiment).

Table 21 Summarized physicochemical characteristics of poloxamers.

Poloxamers	188	288	407	Sources
Melting point (°C)	54.6	60.5	57.5	a, b
Molecular weight	8350	13,500	11,500	a, b
POE: POP ratio	80 : 20	80 : 20	70 : 30	a, b
Hydrophobe weight	1750	2750	3850	a, b
HLB	> 24	>24	18-23	c
Viscosity-Brookfield (cps)	1,000	2,700	3,100	c
Surface tension (dynes/cm)	50	43	41	c
Contact angle (θ)	30	40	50	d
Solubilizing effect	9.5-19.3	11.25-29.31	32.5-214.4	d

(a) Nikitakis, 1988 ; (b) Miyazaki et al., 1986 ; (c) BASF, 1987 ; and (d) results from this experiment.

From the results of dissolution study, it could be shown that poloxamer188 was superior, that showed highest dissolution rate constant and remarkably high $T_{80\%}$, followed by poloxamer407 and poloxamer288, respectively. It should be noted here

that poloxamer407 showed the highest solubilizing effect but yet not gave the highest dissolution rate. The dissolution rate constant obtained from solid dispersion with poloxamer407 was lower than that of poloxamer188. This may be due to the viscosity. It is ranked from the highest to the lowest as poloxamer407 > poloxamer288 > Poloxamer188. The viscosity from poloxamer407 was about 3 times higher than that of poloxamer188 but close to polxamer288. This may cause the thicker diffusional layer for the drug to transport to water.

Braun and Parrott (1972) and Morita and Hirota (1982) showed that viscosity, at certain level, might reduce the dissolution rate of the drug. This may be the key reason for explaining poloxamer systems. Poloxamer407 has the viscosity three time higher than that of poloxamer188. Even though the solubilizing effect of poloxamer407 was high, the viscosity seemed to be prevail in the systems studied. Viscosity may play an important role in inhibiting drug crystallization, in other words polymorphic transformation. However in the system of poloxamer407, the viscosity may be excessive for inhibiting nifedipine crystallization. Instead, the thicker diffusional layer was built.

3. Nifedipine-cyclodextrin solid dispersion

3.1 Dissolution behavior of nifedipine-cyclodextrins solid dispersion

The results from two way ANOVA revealed that β-cyclodextrin and 2-hydroxypropyl- β-cyclodextrin had significant difference between method of preparation and between ratio in preparation but there was no statistical difference between method - ratio interaction at 95% confidence interval.

It was shown that the dissolution rate constant of kneading method of β-cyclodextrin at 1:5 ratio was the highest dissolution value among the solid dispersion of β-cyclodextrin which could be prepared and at 1:10 ratio of kneading method gave the maximal dissolution rate constant of 2-hydroxypropyl- β-cyclodextrin.

3.2 Physicochemical characteristics of nifedipine-cyclodextrins solid dispersions

In the β-cyclodextrin systems, similar DSC thermograms were obtained in the physical mixtures and kneaded products. Two endotherms that one referred to nifedipine melting at 175 °C and the other to water dehydration of β-cyclodextrin at about 130-160 °C exhibited in all ratios. The latter endothermic peak was also found in Guyot et al. (1995) in the range of 120-150 °C whereas Kedzierewicz, Hoffman an Maincent (1990) reported the endothermic peak of β-cyclodextrin stretching between 50-125 °C and dehydration of tolbutamide- β-cyclodextrin complex between 50-163 °C. From the DSC thermogram conducted by Miazzi et al. (1988) also showed the dehydration of β-cyclodextrin began at about 55-160 °C.

The endothermic peaks of nifedipine became smaller and nearly fused to those of β-cyclodextrin at the ratio of 1:5 and 1:10 of kneaded mixtures. This might be due to nifedipine particles were dispersed more closely by β-cyclodextrin particles at higher proportion of β-cyclodextrin.

For the system of 2-hydroxypropyl- β-cyclodextrin, the solid dispersions prepared by solvent method exhibited different thermograms from its physical mixtures and kneaded mixtures. At the higher proportion of 2-hydroxypropyl- β-cyclodextrin, at the ratio of 1:3, 1:5. 1:10, nifedipine melting endotherm could not be detected. These were in agreement with their X-ray patterns (Figure 97) that nifedipine dispersed in amorphous form in the carrier.

Hirayama, Wang and Uekama (1994) explained the DSC thermogram of nifedipine in details. The glassy state of nifedipine was prepared in an absence and presence of 2-hydroxypropyl- β-cyclodextrin. The glassy nifedipine was reported at an endothermic peak at 48 °C, an exothermic peak at 105 °C was the crystallization to a metastable form of nifedipine (form B), an exothermic peak at 125 °C was the polymorphic transititon of form B to form A and an endothermic peak at 171 °C for the melting of form A. It was also found that in presence of 2-hydroxypropyl- β-cyclodextrin, the exothermic at 125 °C for the form B to A transition disappeared and a new endothermic peak appeared at 163 °C. However, in this study, only the endothermic peak responding to the melting point of form A was found. The appearance of exothermic peak at 125 °C and endothermic peak at 163 °C were not observed.

For the nifedipine- β-cyclodextrin system, X-ray diffraction revealed that dispersion of β-cyclodextrin still had crystallinity peak of the carrier itself and major peaks of nifedipine in kneaded products and physical mixtures. The results of DSC were in line with the X-ray diffraction pattern that still found the endothermic peaks of nifedipine at 167-174°C in each ratio of kneaded and physical mixed products.

These explained why the solid dispersion with β-cyclodextrin had lower dissolution rate than that of poloxamers and PEGs. Even though β-cyclodextrin gave the best wettability value (the contact angle was 0° at 1:10 ratio), the solubility effect of β-cyclodextrin was low in its solubility range.

In conclusion, β-cyclodextrin would have helped wetting of nifedipine in the first time of dissolution as it showed higher dissolution rate than the pure drug. However β-cyclodextrin did not form complex which seemed to be agree with the experiment of Acarturk, Kislal and Cebbi (1992) who explained that the enhanced dissolution rate of nifedipine - β-cyclodextrin may be due to the increase in solubility from β-cyclodextrin and its complex had not been completely formed in the solid state.

For 2-hydroxypropyl- β-cyclodextrin dispersion system, kneading method at the ratio of 1:10 gave the maximal dissolution rate constant among its group followed by solvent 1:10 which showed no statistical difference from kneading method. The DSC data exhibited the existence of sharp endothermics at the peak of nifedipine at 171-174°C which supported the evidence of the absence of complex formation in this system. If the complex formation had occurred, the endothermic peak of nifedipine would have been broadened as described by Nagarsenkar and Shenia (1996). Moreover the result of IR spectra revealed that scanned peaks of the dispersed products in each method were not different with those spectra obtained from physical mixtures.

Similarly to the study of Veiga and Espanol (1995) who found that oxodipine, a very similar drug to nifedipine, did not truley form inclusion complex with 2-hydroxypropyl- β-cyclodextrin. Instead, it was suspected that oxodipine particles was coated by 2-hydroxypropyl- β-cyclodextrin and help improve the dissolution rate.

Becirevic-Lacan et al. (1996) studied the formation of nifedipine complexes with β-cyclodextrin, 2-hydroxypropyl- β-cyclodextrin and heptakis (2,6-di-O-methyl)- β-cyclodextrin prepared by freeze drying, spray drying and physical mixing methods. It was found that drug in the freeze dried product was probably totally complexed while the spray dried product could contain a mixture of complexed and uncomplexed drug and physical mixed product, in contrast, did not form complex. Extrapolation made from their study to this study, it could be assumed that solvent method and kneading methods would hardly stimulate complex formation when compared to spray drying method. In this sense it is therefore sensible to find negligible complex formation occurred in solid dispersion prepared by solvent method and kneading methods in this experiment.

Moyano et al. (1997) studied solid complex between gliazide and β-cyclodextrin prepared by kneading, coprecipatation, neutralization, co-grinding and spray drying methods. Only neutralization and spray drying methods were found complex formation. The conclusion was then made as the extent of the enhancement of the dissolution rate, whether inclusion complex was formed, was somewhat dependent on the preparation methods. Palmieri et al. (1997) also reported similar result for the

drug of methoxybutropate which formed the soluble complex when prepared by spray drying method but not by kneading and solvent methods.

Not only the method used, drug to carrier ratio was also found to be another factor involving this mechanism. Palmieri, Wehrle and Martelli (1998) reported that the complexation percentages were acceptable only for the spray dried powders with 1:4 drug- β-cyclodextrin molar ratio specifically for lonidamine.

The wettability data showed that the contact angle of 2-hydroxypropyl- β-cyclodextrin were in the range of 25-40° and the contact angle decreased with an increase in carrier weight ratio. 2-Hydroxypropyl- β-cyclodextrin showed similar solubilizing effect to that of poloxamer188 in the range of 0-4% of carrier weight ratio. 2-Hydroxypropyl- β-cyclodextrin and nifedipine in kneaded product were vigorously contacted between molecules because of the compression force possibly causing a weak interaction.

Comparing between the system in PEGs and poloxamers with cyclodextrins, it was found that the system of cyclodextrins had lower dissolution rate than those systems. The main reason was possibly due to lesser amorphous transformation.

CHAPTER VI

CONCLUSIONS

The dissolution of nifedipine, a very slightly water-soluble drug, can be enhanced by incorporation of highly water soluble carriers via solid dispersion. The carriers in the scope of this study were polyethylene glycol 4000 and 6000, poloxamer 188, 288, 407, β-cyclodextrin and 2-hydroxypropyl- β-cyclodextrin. The investigation can be summarized as follows:

1. **Dissolution rate enhancement**: All carriers was found to enhance the dissolution rate of nifedipine via solid dispersions. The group of poloxamers showed the highest level of dissolution improvement, followed by PEGs and cyclodextrins respectively.

Among the poloxamer group, poloxamer188 exhibited highest dissolution rate followed by poloxamer288 and poloxamer407 respectively. Whereas PEG4000 and PEG6000 showed very similar dissolution rate improvement. β-Cyclodextrin and 2-hydroxypropyl- β-cyclodextrin also fell into the same manner with PEGs as β-cyclodextrin profile, in many cases, showed superimposed with 2-hydroxypropyl - β-cyclodextrin.

2. **$T_{80\%}$** : The shortest $T_{80\%}$ was found in the system of poloxamers at 15 minutes prepared by melting method whereas the pure drug showed $T_{80\%}$ of 225 minutes. Nifedipine-poloxamer188 melts at all ratios gave the $T_{80\%}$ of 15 minutes except the ratio of 1:1. These similar findings also were obtained in the system of poloxamer 407 that $T_{80\%}$ of 15 minutes were shown from the melts at 1:3, 1:5 and 1: 10 mixing ratio; and from the coevaporate at 1:10 ratio and the kneaded product at 1:10 ratio.

3. **The preparation method** : It was found that all carriers could be prepared by kneading method. Melting method was not applicable to cyclodextrin group whereas solvent method was suitable to prepare all carriers except β-cyclodextrin.

In terms of enhancement of dissolution rate, melting method seemed to be the most attractive technique followed by solvent method and kneading method respectively.

4. **Mechanism** : The main mechanisms in each groups were investigated by SEM, X-ray diffraction, DSC thermogram, IR spectra, solubility and wettability.

4.1 For the poloxamer systems, the main mechanisms were amorphous transformation and solubilizing effect.

4.2 For PEGs, amorphous transition was the main mechanism.

4.3 For cyclodextrins, amorphous transition, particle size reduction and enhanced wettability were the main mechanisms. In this case, amorphous transition was attained only some extent which was relatively less than that of the poloxamer and PEG systems. It was revealed that in this experiment nifedipine did not form inclusion complex with β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin.

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Appendix A

Determination of calibration curve

Method of determination of nifedipine concentration.

At t = 0 ; nifedipine is in the reduced form.

At 238 nm : $y = E^{R}_{238}\, C^{R} + I^{R}_{238}$

At 280 nm : $y = E^{R}_{280}\, C^{R} + I^{R}_{280}$

At t = α ; nifedipine is in the oxidized form.

At 238 nm : $y = E^{O}_{238}\, C^{O} + I^{O}_{238}$

At 280 nm : $y = E^{O}_{280}\, C^{O} + I^{O}_{280}$

At each wavelength,

$A238 = (E^{R}_{238}\, C^{R} + I^{R}_{238}) + (E^{O}_{238}\, C^{O} + I^{O}_{238})$ ..... (1)

$A280 = (E^{R}_{280}\, C^{R} + I^{R}_{280}) + (E^{O}_{280}\, C^{O} + I^{O}_{280})$ ..... (2)

Oxidized form of the drug will always be equal.

From equation 1

$C^{O} = [A_{238} - (E^{R}_{238} \times C^{R}) - I^{R}_{238} - I^{O}_{238}] / E^{O}_{238}$ .....(3)

From equation 2

$C^{O} = [A_{238} - (E^{R}_{238} \times C^{R}) - I^{R}_{238} - I^{O}_{238}] / E^{O}_{238}$ .....(4)

Solving equation (3) and (4)

$E^{O}_{238}A_{280} - (E^{O}_{238}E^{R}_{280}C^{R}) - E^{O}_{238}I^{R}_{280} - E^{O}_{238}I^{O}_{280} = E^{O}_{280}A_{238} - (E^{O}_{280}E^{R}_{238}C^{R}) - E^{O}_{280}I^{R}_{238} - E^{O}_{280}I^{O}_{238}$

$(E^{O}_{280}E^{R}_{238}C^{R}) - (E^{O}_{238}E^{R}_{280}C^{R}) = E^{O}_{280}A_{238} - E^{O}_{280}I^{R}_{238} - E^{O}_{280}I^{O}_{238} + E^{O}_{238}I^{R}_{280} + E^{O}_{238}I^{O}_{280} - E^{O}_{238}A_{280}$

$(E^{0}_{280}E^{R}_{238} - E^{O}_{238}E^{R}_{280})\, C^{R} = (E^{O}_{280}A_{238} - E^{O}_{238}A_{280}) - (E^{O}_{280}I^{R}_{238} + E^{O}_{280}I^{O}_{238}) + (E^{O}_{238}I^{R}_{280} + E^{O}_{238}I^{O}_{280})$

$= (E^{O}_{280}A_{238} - E^{O}_{238}A_{280}) - E^{O}_{280}(I^{R}_{238} + I^{O}_{238}) + E^{O}_{2}(I^{R}_{280} + I^{O}_{280})$

$$CR = \frac{(E^{O}_{280}A_{238} - E^{O}_{238}A_{280})}{(E^{0}_{280}E^{R}_{238} - E^{O}_{238}E^{R}_{280})} - \frac{E^{O}_{280}(I^{R}_{238} + I^{O}_{238}) + E^{O}_{238}(I^{R}_{280} + I^{O}_{280})}{(E^{0}_{280}E^{R}_{238} - E^{O}_{238}E^{R}_{280})}$$

$$CR = \frac{(E^{O}_{280}A_{238} - E^{O}_{238}A_{280})}{(E^{0}_{280}E^{R}_{238} - E^{O}_{238}E^{R}_{280})} - \frac{E^{O}_{280}(I^{R}_{238} + I^{O}_{238}) + E^{O}_{238}(I^{R}_{280} + I^{O}_{280})}{(E^{0}_{280}E^{R}_{238} - E^{O}_{238}E^{R}_{280})}$$

Validation of calibration curve

Validation for quantitative determination of nifedipine from dissolution test and percentage of content in various ratios was made by UV spectrophotometry. The parameters evaluated to ensure the validation of the selected analytical method were accuracy, precision and linearity (USPXXI)

1. Accuracy

Nifedipine solution were prepared at various concentrations. Three sets of each concentration were prepared. Each individual sample was analyzed by UV spectrophotometry, and percent recovery of each sample was calculated.

2. Precision

2.1 Within run precision

The within run precision was determined by analyzing of two sets of calibration curve in the same day. Inverse concentrations of nifedipine were compared, and the percent coefficient of variation (% CV) for each concentration was calculated.

2.2 Between run precision

The between run precision was determined by comparing each concentration of three sets of calibrationcurve prepared on different days for three days. Inverse concentration for the three standard curves on different days were determined and the percent coefficient of variation (% CV) for each concentration was calculated.

3. Linearity

Linear regression analysis of the absorbances versus the corresponding concentrations was performed and the coefficient of determination was calculated. The results of process are as following tables.

Table 22 Accuracy data of inversely estimated concentration.

Expected conc. (Molar x 10-5)	Inversely estimated conc (Molar x 10-5)	% Recovery
0.895	0.944	105,52
	0.903	100.84
	0.919	102.63
1.343	1.386	103.20
	1.382	102.89
	1.370	102.02
1.79	1.861	103.99
	1.853	103.55
	1.844	103.00
2.24	2.261	100.95
	2.277	101.67
	2.283	101.93
2.68	2.753	102.72
	2.751	102.65
	2.721	101.53
3.58	3.578	99.96
	3.585	100.13
	3.582	100.06
4.03	4.092	101.53
	4.092	101.53
	4.064	100.84
4.48	4.514	100.75
	4.506	100.57
	4.550	101.56
Mean		101.92
S.D		1.37
% CV		1.34

Table 23 Within run precision data

Expected conc. (Molar x 10-5)	Inversely estimated conc (Molar x 10-5)			Inversely estimated conc (Molar x 10-5)			Mean	S.D.	%CV
0.895	0.938	0.914	0.916	0.936	0.914	0.943	0.927	0.014	1.472
1.343	1.382	1.378	1.412	1.412	1.372	1.384	1.390	0.018	1.262
1.79	1.824	1.850	1.860	1.840	1.856	1.862	1.849	0.015	0.792
2.24	2.299	2.300	2.300	2.335	2.319	2.287	2.307	0.017	0.751
2.68	2.771	2.760	2.760	2.815	2.771	2.793	2.778	0.022	0.775
3.58	3.696	3.680	3.680	3.746	3.763	3.758	3.720	0.039	1.058
4.03	4.116	4.130	4.140	4.201	4.227	4.235	4.175	0.052	1.256
4.48	4.564	4.560	4.560	4.649	4.647	4.629	4.601	0.045	0.970

Table 24 Between run precision data

Expected conc. (Molar x 10-5)	Inversely estimated conc (Molar x 10-5)			Inversely estimated conc (Molar x 10-5)			Inversely estimated conc (Molar x 10-5)			Mean	S.D.	%CV
0.895	0.944	0.903	0.919	0.912	0.910	0.912	0.938	0.914	0.916	0.919	0.013	1.468
1.343	1.386	1.382	1.370	1.362	1.362	1.350	1.382	1.378	1.412	1.376	0.018	1.304
1.79	1.860	1.850	1.840	1.832	1.820	1.834	1.824	1.850	1.860	1.841	0.015	0.802
2.24	2.260	2.280	2.280	2.291	2.217	2.210	2.299	2.300	2.300	2.271	0.035	1.540
2.68	2.750	2.750	2.720	2.691	2.697	2.715	2.771	2.760	2.760	2.735	0.030	1.082
3.58	3.580	3.580	3.580	3.642	3.620	3.573	3.696	3.680	3.680	3.626	0.050	1.385
4.03	4.090	4.090	4.060	4.016	4.038	4.042	4.116	4.130	4.140	4.080	0.044	1.072
4.48	4.510	4.510	4.550	4.462	4.486	4.438	4.564	4.560	4.560	4.516	0.047	1.030

Standard curve plot : Absorbance λ 238 at t=0

Conc	Abs238 t=0
8.950E-06	0.180
1.343E-05	0.274
1.790E-05	0.362
2.240E-05	0.452
2.680E-05	0.547
3.580E-05	0.725
4.030E-05	0.811
4.480E-05	0.910

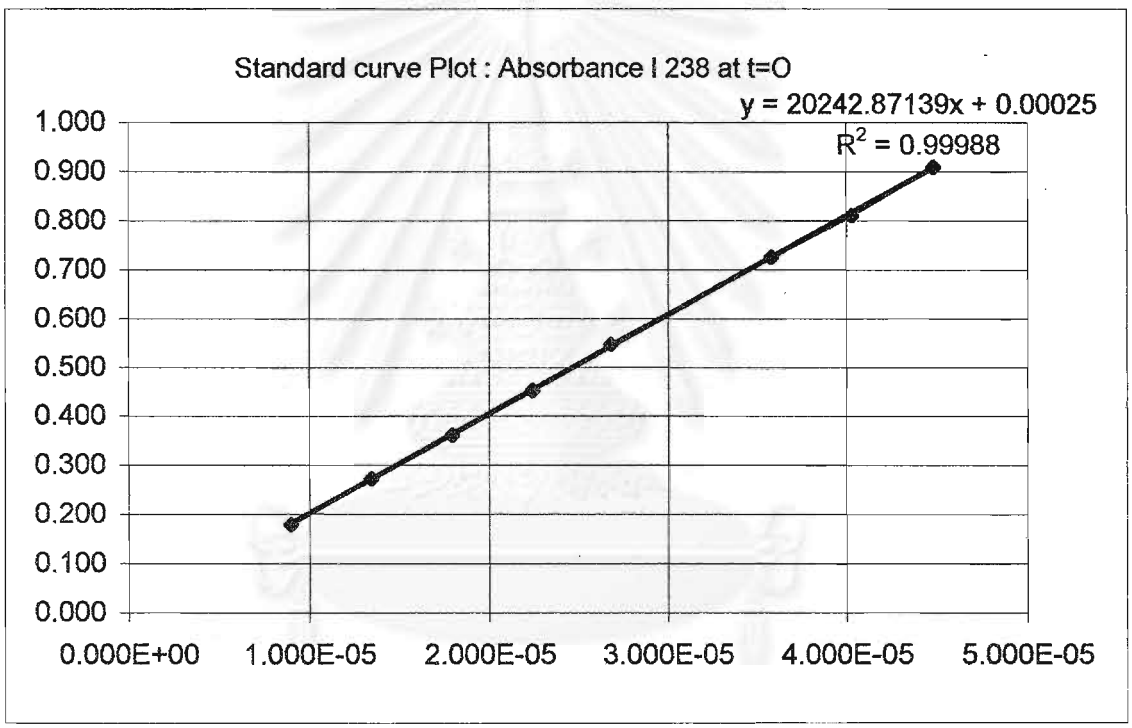


Figure 163 Calibration curve of standard solution of nifedipine at 238 nm, t=0

Standard curve plot : Absorbance λ 280 at t=0

Conc	Abs280 t=o
8.950E-06	0.032
1.343E-05	0.049
1.790E-05	0.061
2.240E-05	0.078
2.680E-05	0.093
3.580E-05	0.122
4.030E-05	0.136
4.480E-05	0.151

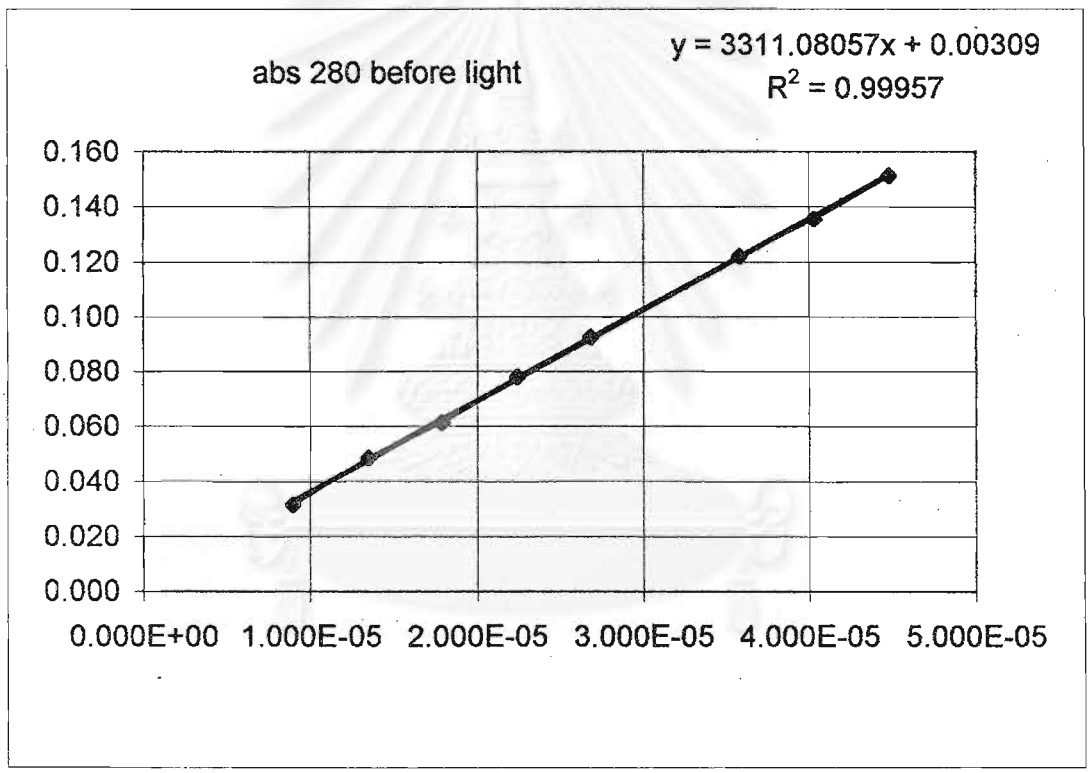


Figure 164 Calibration curve of standard solution of nifedipine at 280 nm, t=0

Standard curve plot : Absorbance λ 238 at t=a

Conc	Abs238 t=α
8.950E-06	0.107
1.343E-05	0.158
1.790E-05	0.206
2.240E-05	0.260
2.680E-05	0.309
3.580E-05	0.404
4.030E-05	0.454
4.480E-05	0.512

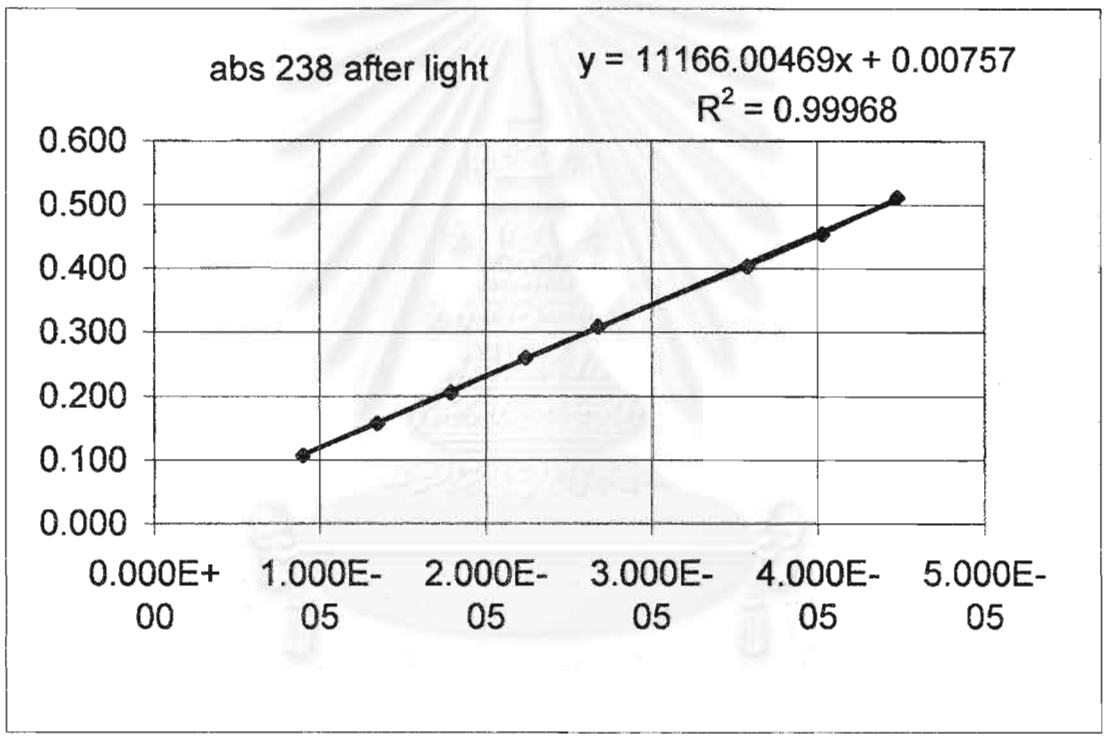


Figure 165 Calibration curve of standard solution of nifedipine at 238 nm, t=a

Standard curve plot : Absorbance λ 280 at t=a

Conc	Abs280 t=α
8.950E-06	0.072
1.343E-05	0.111
1.790E-05	0.145
2.240E-05	0.182
2.680E-05	0.224
3.580E-05	0.310
4.030E-05	0.351
4.480E-05	0.392

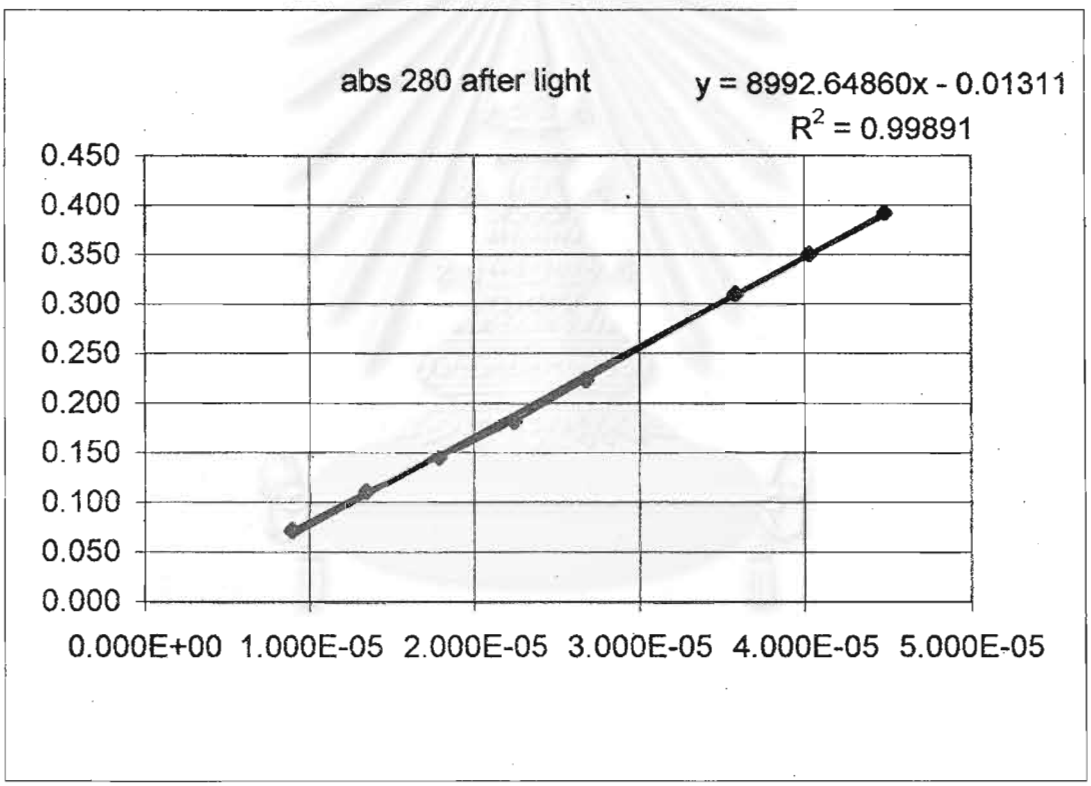


Figure 166 Calibration curve of standard solution of nifedipine at 280 nm, t=a

Appendix B

Percentage of content

Table 25 Percent content of nifedipine in nifedipine-PEG4000 solid dispersion.

Method		Nifedipine : Percentage of content.							
		Ratio 1:1		Ratio 1:3		Ratio 1:5		Ratio 1:10	
		mg	%	mg	%	mg	%	mg	%
Physical									
	# 1	10.0344	100.34	12.6246	126.25	11.2324	112.32	14.2911	142.91
	# 2	11.0273	110.27	12.8952	128.95	10.7937	107.94	15.5582	155.58
	# 3	10.9320	109.32	12.6938	126.94	12.0405	120.41	15.1291	151.29
	Average	10.6646	106.65	12.7379	127.38	11.3555	113.56	14.9928	149.93
	SD.	0.5478	5.48	0.1406	1.41	0.6325	6.32	0.6445	6.44
Melt									
	# 1	8.4704	84.70	8.9127	89.13	8.3155	83.15	8.4573	84.57
	# 2	8.6218	86.22	8.7804	87.80	8.4013	84.01	8.5002	85.00
	# 3	8.9127	89.13	8.8233	88.23	8.6421	86.42	8.7410	87.41
	Average	8.6683	86.68	8.8388	88.39	8.4529	84.53	8.5662	85.66
	SD.	0.2248	2.25	0.0675	0.68	0.1693	1.69	0.1529	1.53
Solvent									
	# 1	8.4573	84.57	8.6123	86.12	8.4013	84.01	8.5992	85.99
	# 2	7.8732	78.73	9.0509	90.51	8.6123	86.12	8.6254	86.25
	# 3	8.3846	83.85	8.9687	89.69	8.4275	84.28	8.7970	87.97
	Average	8.2384	82.38	8.8773	88.77	8.4804	84.80	8.6739	86.74
	SD.	0.3183	3.18	0.2332	2.33	0.1150	1.15	0.1075	1.07
Kneading									
	# 1	8.7935	87.93	8.2988	82.99	7.8899	78.90	7.2856	72.86
	# 2	8.8137	88.14	8.3846	83.85	8.1569	81.57	7.7779	77.78
	# 3	9.3513	93.51	8.5265	85.26	8.1009	81.01	8.1700	81.70
	Average	8.9862	89.86	8.4033	84.03	8.0492	80.49	7.7445	77.44
	SD.	0.3164	3.16	0.1150	1.15	0.1408	1.41	0.4432	4.43

Table 26 Percent content of nifedipine in nifedipine-PEG6000 solid dispersion.

Method		Nifedipine : Percentage of content.							
		Ratio 1:1		Ratio 1:3		Ratio 1:5		Ratio 1:10	
		mg	%	mg	%	mg	%	mg	%
Physical									
	# 1	8.8864	88.86	8.7148	87.15	9.1666	91.67	11.9547	119.55
	# 2	8.8531	88.53	8.9556	89.56	8.0842	80.84	9.9056	99.06
	# 3	8.8435	88.44	8.8531	88.53	9.9617	99.62	8.6647	86.65
	Average	8.8610	88.61	8.8411	88.41	9.0708	90.71	10.1750	101.75
	SD.	0.0225	0.23	0.1208	1.21	0.9424	9.42	1.6615	16.61
Melt									
	# 1	8.0151	80.15	8.9258	89.26	8.8268	88.27	8.4573	84.57
	# 2	8.8364	88.36	8.0318	80.32	8.8042	88.04	8.5002	85.00
	# 3	8.2427	82.43	8.7410	87.41	8.4740	84.74	8.7410	87.41
	Average	8.3647	83.65	8.5662	85.66	8.7017	87.02	8.5662	85.66
	SD.	0.4240	4.24	0.4720	4.72	0.1975	1.97	0.1529	1.53
Solvent									
	# 1	8.7148	87.15	8.9258	89.26	8.5229	85.23	8.8006	88.01
	# 2	8.9556	89.56	8.0318	80.32	9.0247	90.25	8.7112	87.11
	# 3	8.8531	88.53	8.7410	87.41	8.2857	82.86	8.0484	80.48
	Average	8.8411	88.41	8.5662	85.66	8.6111	86.11	8.5201	85.20
	SD.	0.1208	1.21	0.4720	4.72	0.3773	3.77	0.4109	4.11
Kneading									
	# 1	8.6981	86.98	8.2559	82.56	7.2629	72.63	8.2261	82.26
	# 2	8.2129	82.13	8.4406	84.41	7.8077	78.08	8.1009	81.01
	# 3	8.5265	85.26	8.5098	85.10	8.0616	80.62	8.1140	81.14
	Average	8.4792	84.79	8.4021	84.02	7.7107	77.11	8.1470	81.47
	SD.	0.2460	2.46	0.1313	1.31	0.4081	4.08	0.0688	0.69

Table 27 Percent content of nifedipine in nifedipine-poloxamer188 solid dispersion.

Method		Nifedipine : Percentage of content.							
		Ratio 1:1		Ratio 1:3		Ratio 1:5		Ratio 1:10	
		mg	%	mg	%	mg	%	mg	%
Physical									
	# 1	10.2096	102.10	9.3942	93.94	7.5633	75.63	8.5265	85.26
	# 2	10.2489	102.49	9.6219	96.22	5.3259	53.26	10.7341	107.34
	# 3	7.9328	79.33	10.0642	100.64	3.5664	35.66	9.1272	91.27
	Average	9.4638	94.64	9.6934	96.93	5.4852	54.85	9.4626	94.63
	SD.	1.3260	13.26	0.3406	3.41	2.0032	20.03	1.1414	11.41
Melt									
	# 1	9.2488	92.49	8.3906	83.91	8.7315	87.31	8.0508	80.51
	# 2	9.2226	92.23	8.4037	84.04	8.9687	89.69	7.7373	77.37
	# 3	9.5695	95.69	6.9387	69.39	8.8304	88.30	7.5001	75.00
	Average	9.3470	93.47	7.9110	79.11	8.8435	88.44	7.7628	77.63
	SD.	0.1931	1.93	0.8421	8.42	0.1192	1.19	0.2762	2.76
Solvent									
	# 1	9.1999	92.00	9.7209	97.21	8.7839	87.84	8.9782	89.78
	# 2	8.7839	87.84	9.2655	92.66	8.6850	86.85	9.1201	91.20
	# 3	8.8829	88.83	9.9354	99.35	9.3251	93.25	9.1201	91.20
	Average	8.9556	89.56	9.6406	96.41	8.9313	89.31	9.0728	90.73
	SD.	0.2173	2.17	0.3421	3.42	0.3446	3.45	0.0819	0.82
Kneading									
	# 1	8.1307	81.31	9.9021	99.02	9.2393	92.39	8.9222	89.22
	# 2	9.7340	97.34	9.3585	93.58	9.1535	91.53	9.2226	92.23
	# 3	9.2095	92.09	8.5300	85.30	9.2095	92.09	9.2226	92.23
	Average	9.0247	90.25	9.2635	92.64	9.2007	92.01	9.1225	91.22
	SD.	0.8175	8.17	0.6909	6.91	0.0436	0.44	0.1734	1.73

Table 28 Percent content of nifedipine in nifedipine-poloxamer288 solid dispersion.

Method		Nifedipine : Percentage of content.							
		Ratio 1:1		Ratio 1:3		Ratio 1:5		Ratio 1:10	
		mg	%	mg	%	mg	%	mg	%
Physical									
	# 1	7.3320	73.32	7.9924	79.92	8.3977	83.98	9.6052	96.05
	# 2	9.4670	94.67	10.3085	103.09	6.3617	63.62	9.5456	95.46
	# 3	9.6052	96.05	8.1009	81.01	10.4599	104.60	8.8268	88.27
	Average	8.8014	88.01	8.8006	88.01	8.4065	84.06	9.3259	93.26
	SD.	1.2744	12.74	1.3070	13.07	2.0491	20.49	0.4332	4.33
Melt									
	# 1	9.0843	90.84	8.8006	88.01	8.7708	87.71	8.7577	87.58
	# 2	9.0712	90.71	8.9854	89.85	8.9723	89.72	8.5431	85.43
	# 3	8.7708	87.71	9.2893	92.89	7.9590	79.59	8.4871	84.87
	Average	8.9754	89.75	9.0251	90.25	8.5674	85.67	8.5960	85.96
	SD.	0.1773	1.77	0.2468	2.47	0.5364	5.36	0.1428	1.43
Solvent									
	# 1	8.6588	86.59	8.8495	88.49	8.4800	84.80	8.5300	85.30
	# 2	9.0378	90.38	8.2690	82.69	8.2094	82.09	8.6361	86.36
	# 3	9.2226	92.23	9.0211	90.21	8.8233	88.23	8.5467	85.47
	Average	8.9731	89.73	8.7132	87.13	8.5042	85.04	8.5709	85.71
	SD.	0.2874	2.87	0.3942	3.94	0.3077	3.08	0.0570	0.57
Kneading									
	# 1	9.2691	92.69	8.9294	89.29	8.8400	88.40	8.7410	87.41
	# 2	9.2524	92.52	9.1010	91.01	8.6683	86.68	8.7017	87.02
	# 3	8.7875	87.88	8.5729	85.73	8.7374	87.37	8.6325	86.33
	Average	9.1030	91.03	8.8678	88.68	8.7486	87.49	8.6917	86.92
	SD.	0.2734	2.73	0.2694	2.69	0.0864	0.86	0.0549	0.55

Table 29 Percent content of nifedipine in nifedipine-poloxamer407 solid dispersion.

Method		Nifedipine : Percentage of content.							
		Ratio 1:1		Ratio 1:3		Ratio 1:5		Ratio 1:10	
		mg	%	mg	%	mg	%	mg	%
Physical									
	# 1	9.2095	92.09	11.5292	115.29	9.1666	91.67	7.6300	76.30
	# 2	9.7077	97.08	12.2253	122.25	10.5720	105.72	11.6150	116.15
	# 3	9.9617	99.62	10.4540	104.54	11.1763	111.76	8.1808	81.81
	Average	9.6263	96.26	11.4028	114.03	10.3050	103.05	9.1419	91.42
	SD.	0.3826	3.83	0.8924	8.92	1.0311	10.31	2.1594	21.59
Melt									
	# 1	8.8602	88.60	8.6612	86.61	9.0378	90.38	9.2417	92.42
	# 2	8.7219	87.22	8.4764	84.76	9.0211	90.21	8.6349	86.35
	# 3	9.2429	92.43	8.6743	86.74	8.8960	88.96	9.2953	92.95
	Average	8.9417	89.42	8.6039	86.04	8.9850	89.85	9.0573	90.57
	SD.	0.2698	2.70	0.1107	1.11	0.0775	0.78	0.3668	3.67
Solvent									
	# 1	9.4765	94.76	9.3942	93.94	8.4931	84.93	9.1272	91.27
	# 2	8.4967	84.97	8.7708	87.71	8.4704	84.70	9.2917	92.92
	# 3	8.8960	88.96	9.0545	90.55	8.9186	89.19	7.6885	76.88
	Average	8.9564	89.56	9.0732	90.73	8.6274	86.27	8.7025	87.02
	SD.	0.4927	4.93	0.3121	3.12	0.2525	2.52	0.8820	8.82
Kneading									
	# 1	9.2262	92.26	7.1008	71.01	8.7279	87.28	8.7279	87.28
	# 2	8.7017	87.02	6.7646	67.65	8.9425	89.42	8.9031	89.03
	# 3	9.6219	96.22	7.1902	71.90	8.6552	86.55	8.7410	87.41
	Average	9.1833	91.83	7.0185	70.19	8.7752	87.75	8.7907	87.91
	SD.	0.4616	4.62	0.2244	2.24	0.1494	1.49	0.0976	0.98

Table 30 Percent content of nifedipine in nifedipine-β-cyclodextrin solid dispersion.

Method		Nifedipine : Percentage of content.							
		Ratio 1:1		Ratio 1:3		Ratio 1:5		Ratio 1:10	
		mg	%	mg	%	mg	%	mg	%
Physical									
	# 1	8.2463	82.46	7.9650	79.65	8.6981	86.98	8.8304	88.30
	# 2	8.6123	86.12	8.5062	85.06	8.4311	84.31	8.4013	84.01
	# 3	8.4466	84.47	8.8888	88.89	8.4871	84.87	9.2262	92.26
	Average	8.4351	84.35	8.4533	84.53	8.5388	85.39	8.8193	88.19
	SD.	0.1832	1.83	0.4642	4.64	0.1408	1.41	0.4126	4.13
Melt									
	# 1	-	-	-	-	-	-	-	-
	# 2	-	-	-	-	-	-	-	-
	# 3	-	-	-	-	-	-	-	-
	Average	-	-	-	-	-	-	-	-
	SD.	-	-	-	-	-	-	-	-
Solvent									
	# 1	-	-	-	-	-	-	-	-
	# 2	-	-	-	-	-	-	-	-
	# 3	-	-	-	-	-	-	-	-
	Average	-	-	-	-	-	-	-	-
	SD.	-	-	-	-	-	-	-	-
Kneading									
	# 1	8.8137	88.14	8.5265	85.26	8.6850	86.85	8.8698	88.70
	# 2	9.1272	91.27	9.1403	91.40	8.8268	88.27	8.6290	86.29
	# 3	8.3882	83.88	9.1105	91.11	8.7541	87.54	8.6850	86.85
	Average	8.7764	87.76	8.9258	89.26	8.7553	87.55	8.7279	87.28
	SD.	0.3709	3.71	0.3461	3.46	0.0709	0.71	0.1260	1.26

Table 31 Percent content of nifedipine in nifedipine-2hydroxypropyl-β-cyclodextrin solid dispersion.

Method		Nifedipine : Percentage of content.							
		Ratio 1:1		Ratio 1:3		Ratio 1:5		Ratio 1:10	
		mg	%	mg	%	mg	%	mg	%
Physical									
	# 1	8.87	88.73	8.07	80.75	8.67	86.69	8.39	83.88
	# 2	7.69	76.88	8.45	84.54	8.66	86.55	8.30	82.99
	# 3	8.63	86.25	8.11	81.14	8.64	86.42	7.58	75.76
	Average	8.40	83.96	8.21	82.14	8.66	86.55	8.09	80.88
	SD.	0.62	6.25	0.21	2.08	0.01	0.13	0.45	4.45
Melt									
	# 1	-	-	-	-	-	-	-	-
	# 2	-	-	-	-	-	-	-	-
	# 3	-	-	-	-	-	-	-	-
	Average	-	-	-	-	-	-	-	-
	SD.	-	-	-	-	-	-	-	-
Solvent									
	# 1	8.08	80.84	8.41	84.14	8.39	83.92	7.80	78.04
	# 2	7.73	77.28	8.30	83.02	9.02	90.19	7.69	76.88
	# 3	7.56	75.60	8.46	84.61	8.76	87.64	8.40	84.01
	Average	7.79	77.91	8.39	83.93	8.72	87.25	7.96	79.65
	SD.	0.27	2.68	0.08	0.81	0.32	3.15	0.38	3.83
Kneading									
	# 1	9.10	90.97	8.83	88.27	8.77	87.74	8.75	87.54
	# 2	8.12	81.18	8.66	86.55	8.68	86.85	8.60	85.99
	# 3	9.13	91.31	8.60	86.03	8.35	83.45	8.64	86.42
	Average	8.78	87.82	8.69	86.95	8.60	86.02	8.67	86.65
	SD.	0.58	5.76	0.12	1.17	0.23	2.26	0.08	0.80

Appendix C

Percentage dissolved of nifedipine at various time in each chambers.

Table 32 Percent dissolved of nifedipine-PEG4000 prepared by physical mixing method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:1						
		5	14.65	14.79	16.05	15.16	0.77
		10	20.75	20.76	23.08	21.53	1.34
		15	28.15	27.31	31.40	28.96	2.16
		20	34.16	33.59	36.55	34.77	1.57
		30	43.95	44.72	45.57	44.75	0.81
		45	53.61	50.80	53.33	52.58	1.55
		60	55.22	57.09	59.91	57.41	2.36
		90	62.10	65.33	66.54	64.66	2.29
		120	66.49	70.91	71.76	69.72	2.83
		180	70.93	78.10	78.61	75.88	4.29
		240	76.58	82.64	82.92	80.71	3.58
		300	81.03	85.61	84.42	83.69	2.38
		360	88.00	88.59	86.60	87.73	1.02
		420	92.04	89.16	88.10	89.77	2.04
		540	99.72	94.36	92.75	95.61	3.65
		660	100.33	93.27	94.31	95.97	3.81
		1200	106.66	98.96	100.01	101.88	4.18
		1440	107.33	99.63	101.31	102.76	4.05
physical mixing	1:3						
		5	25.59	26.58	22.13	24.77	2.34
		10	23.51	24.16	23.77	23.81	0.33
		15	28.75	30.31	31.35	30.14	1.31
		20	34.20	36.10	37.15	35.82	1.49
		30	42.37	46.10	46.09	44.85	2.15
		45	52.37	56.74	56.80	55.31	2.54
		60	57.05	63.67	63.96	61.56	3.91
		90	64.17	72.56	72.13	69.62	4.72
		120	70.17	79.41	77.57	75.72	4.89
		180	77.23	86.96	84.27	82.82	5.03
		240	82.59	91.13	88.17	87.30	4.33
		300	87.13	93.34	90.72	90.40	3.12
		360	89.25	96.16	92.91	92.78	3.46
		420	91.09	98.57	93.98	94.55	3.77
		540	94.89	99.08	100.52	98.16	2.93
		660	96.03	100.91	97.61	98.18	2.49
		1200	101.96	105.08	101.96	103.00	1.80
		1440	101.86	105.31	103.18	103.45	1.74

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:5						
		5	14.89	14.25	14.67	14.60	0.33
		10	22.61	24.14	24.64	23.80	1.06
		15	29.17	30.45	31.64	30.42	1.24
		20	35.87	36.94	37.65	36.82	0.90
		30	45.60	47.99	47.58	47.05	1.28
		45	56.80	57.74	56.96	57.17	0.50
		60	62.49	64.87	63.75	63.70	1.19
		90	72.47	73.48	71.64	72.53	0.92
		120	77.65	77.59	76.53	77.26	0.63
		180	83.92	84.28	83.21	83.80	0.54
		240	88.66	88.24	86.13	87.68	1.36
		300	90.03	89.74	89.80	89.86	0.16
		360	91.16	91.58	89.47	90.73	1.12
		420	91.93	93.06	91.29	92.09	0.90
		540	94.89	96.02	94.18	95.03	0.93
		660	96.45	96.67	94.41	95.84	1.25
		1200	100.68	103.14	100.39	101.41	1.51
		1440	100.92	103.12	100.72	101.59	1.33
physical mixing	1:10						
		5	11.45	14.38	15.50	13.78	2.09
		10	27.36	29.18	29.12	28.55	1.04
		15	37.12	38.81	38.26	38.06	0.86
		20	43.06	45.74	45.82	44.88	1.57
		30	52.22	55.82	53.85	53.96	1.80
		45	61.32	64.92	61.75	62.66	1.96
		60	68.33	70.79	66.58	68.56	2.12
		90	74.37	78.47	71.87	74.90	3.33
		120	79.41	84.07	77.85	80.44	3.24
		180	83.99	87.05	82.53	84.52	2.31
		240	86.97	91.06	84.59	87.54	3.27
		300	88.60	92.55	86.84	89.33	2.93
		360	89.53	92.91	88.90	90.45	2.16
		420	91.08	95.10	88.89	91.69	3.15
		540	93.05	96.94	90.80	93.60	3.10
		660	95.79	98.56	92.15	95.50	3.21
		1200	97.74	104.04	95.78	99.19	4.31
		1440	96.36	102.15	94.67	97.73	3.92

Table 33 Percent dissolved of nifedipine-PEG4000 prepared by melting method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Melting	1:1						
		5	18.65	17.11	19.35	18.37	1.15
		10	20.79	22.68	25.63	23.03	2.44
		15	26.63	30.08	31.42	29.38	2.47
		20	31.71	34.74	36.85	34.43	2.59
		30	37.07	41.28	43.41	40.59	3.23
		45	43.77	48.34	50.40	47.50	3.39
		60	48.99	54.20	57.51	53.57	4.29
		90	55.49	61.46	63.24	60.06	4.06
		120	59.93	67.26	68.18	65.12	4.52
		180	67.12	74.10	75.51	72.24	4.49
		240	72.98	78.84	80.47	77.43	3.94
		300	76.10	81.68	82.87	80.22	3.62
		360	79.41	84.63	86.54	83.53	3.69
		420	84.28	86.14	86.71	85.71	1.27
		540	87.05	88.04	89.31	88.13	1.13
		660	88.61	88.97	90.94	89.51	1.26
		1200	97.47	98.10	101.97	99.18	2.44
		1440	94.79	97.05	99.45		
Melting	1:3						
		5	17.71	17.79	17.85	17.78	0.07
		10	23.55	26.58	25.80	25.31	1.57
		15	30.32	32.51	33.35	32.06	1.57
		20	36.04	37.80	42.13	38.66	3.13
		30	44.13	46.04	51.36	47.18	3.75
		45	51.69	53.94	54.67	53.43	1.56
		60	56.85	58.83	60.44	58.71	1.80
		90	62.49	65.16	69.46	65.71	3.52
		120	67.92	69.21	78.49	71.87	5.77
		180	73.99	74.84	82.04	76.96	4.42
		240	78.31	79.29	89.30	82.30	6.08
		300	81.14	81.49	93.15	85.26	6.84
		360	83.82	83.96	94.50	87.43	6.12
		420	85.32	85.30	97.39	89.34	6.98
		540	90.18	88.76	103.23	94.06	7.97
		660	88.38	86.88	103.33	92.86	9.10
		1200	95.19	94.06	107.64	98.97	7.54
		1440	93.55	94.11	107.74	98.47	8.04

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Melting	1:5						
		5	18.85	18.57	18.92	18.78	0.18
		10	31.37	33.47	33.83	32.89	1.33
		15	43.29	44.64	44.50	44.14	0.74
		20	50.17	51.72	52.63	51.50	1.24
		30	57.92	60.04	59.55	59.17	1.11
		45	64.83	65.41	66.25	65.50	0.71
		60	68.95	71.12	70.49	70.19	1.12
		90	75.07	77.40	76.41	76.30	1.17
		120	78.75	81.30	79.88	79.97	1.28
		180	83.76	87.14	83.97	84.96	1.89
		240	88.35	91.53	90.53	90.13	1.63
		300	90.48	93.44	92.66	92.19	1.54
		360	91.46	95.92	94.50	93.96	2.28
		420	92.75	96.35	95.98	95.03	1.99
		540	94.87	98.34	98.82	97.34	2.16
		660	97.97	101.03	101.85	100.28	2.04
		1200	98.22	102.53	104.48	101.74	3.20
		1440	99.06	102.53	105.41	102.33	3.18
Melting	1:10						
		5	8.52	8.65	12.72	9.96	2.39
		10	39.43	35.15	34.31	36.30	2.74
		15	51.73	49.10	48.76	49.86	1.62
		20	60.27	58.45	57.46	58.73	1.43
		30	69.17	66.99	67.26	67.81	1.19
		45	77.36	74.33	74.68	75.46	1.66
		60	81.61	78.23	78.94	79.59	1.78
		90	86.83	85.20	85.20	85.74	0.94
		120	89.37	87.62	88.18	88.39	0.90
		180	93.19	93.89	92.34	93.14	0.77
		240	93.77	94.62	94.41	94.27	0.44
		300	94.89	94.90	94.06	94.62	0.48
		360	93.93	96.00	93.67	94.53	1.27
		420	93.79	93.52	94.20	93.84	0.34
		540	92.74	91.61	93.09	92.48	0.77
		660	91.34	91.69	91.27	91.43	0.23

Table 34 Percent dissolved of nifedipine-PEG4000 prepared by solvent method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Solvent	1:1						
		5	15.02	14.31	19.30	16.21	2.70
		10	17.76	17.76	19.12	18.21	0.78
		15	23.11	24.58	29.99	25.89	3.62
		20	27.84	29.10	34.88	30.61	3.75
		30	35.16	36.29	41.44	37.63	3.35
		45	44.53	43.62	48.29	45.48	2.47
		60	54.14	49.27	53.17	52.19	2.57
		90	58.96	56.75	60.27	58.66	1.78
		120	62.90	61.21	65.79	63.30	2.32
		180	70.72	68.11	70.86	69.90	1.55
		240	74.62	72.78	76.09	74.50	1.66
		300	78.22	77.79	79.43	78.48	0.85
		360	81.04	79.85	81.62	80.84	0.90
		420	82.18	80.50	83.03	81.90	1.29
		540	83.11	81.63	84.17	82.97	1.27
		660	87.55	83.89	87.35	86.26	2.06
		1200	90.87	88.26	90.58	89.90	1.43
		1440	90.13	87.36	91.17	89.55	1.97
Solvent	1:3						
		5	19.28	18.79	20.18	19.42	0.71
		10	28.50	29.69	30.82	29.67	1.16
		15	38.30	38.80	40.07	39.06	0.91
		20	42.99	45.38	46.93	45.10	1.98
		30	49.96	53.13	55.25	52.78	2.66
		45	55.26	60.39	63.21	59.62	4.03
		60	58.87	64.15	68.74	63.92	4.94
		90	63.46	69.58	72.57	68.53	4.64
		120	66.42	73.20	77.50	72.37	5.58
		180	71.00	78.83	82.37	77.40	5.82
		240	76.56	82.45	86.19	81.73	4.85
		300	77.32	84.08	89.23	83.54	5.97
		360	78.01	87.19	90.93	85.38	6.65
		420	80.13	87.05	93.18	86.79	6.53
		540	85.28	89.38	94.47	89.71	4.61
		660	85.01	90.73	95.74	90.49	5.37
		1200	93.39	95.96	100.48	96.61	3.59
		1440	92.39	96.76	100.93	96.69	4.27

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Solvent	1:5						
		5	16.23	17.97	20.24	18.15	2.01
		10	36.60	33.29	34.92	34.94	1.66
		15	48.13	44.96	44.19	45.76	2.09
		20	53.73	52.52	51.05	52.43	1.34
		30	62.88	61.54	59.65	61.35	1.62
		45	70.85	69.87	66.99	69.24	2.01
		60	75.95	74.27	73.59	74.60	1.22
		90	81.03	80.38	76.25	79.22	2.59
		120	84.64	84.43	79.72	82.93	2.78
		180	88.03	88.94	84.01	86.99	2.63
		240	88.95	90.38	85.22	88.18	2.66
		300	89.73	93.20	86.85	89.93	3.18
		360	89.11	92.45	86.85	89.47	2.81
		420	90.17	92.29	87.85	90.10	2.22
		540	91.66	95.61	88.19	91.82	3.71
		660	90.06	94.43	90.18	91.55	2.49
		1200	88.82	92.56	93.74	91.70	2.57
		1440	0.11	0.13	0.14	0.12	0.01
Solvent	1:10						
		5	14.68	17.69	21.26	17.88	3.29
		10	40.57	45.35	46.14	44.02	3.01
		15	58.46	60.10	61.31	59.96	1.43
		20	66.20	67.62	68.04	67.29	0.96
		30	76.42	76.92	78.67	77.34	1.18
		45	83.00	82.37	86.17	83.84	2.04
		60	85.99	87.74	90.98	88.24	2.54
		90	89.79	92.27	93.25	91.77	1.78
		120	90.44	93.35	96.49	93.43	3.03
		180	91.23	94.76	98.40	94.80	3.59
		240	94.24	97.93	100.10	97.42	2.96
		300	95.32	99.37	100.11	98.27	2.58
		360	96.31	99.73	100.89	98.98	2.38
		420	96.10	100.30	103.42	99.94	3.67
		540	94.01	98.61	115.73	102.78	11.44
		660	94.35	98.67	116.29	103.10	11.62

Table 35 Percent dissolved of nifedipine-PEG4000 prepared by kneading method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Kneading	1:1						
		5	23.87	24.22	23.16	23.75	0.54
		10	30.80	30.95	30.66	30.80	0.15
		15	37.08	37.44	36.10	36.87	0.69
		20	41.76	43.16	40.34	41.75	1.41
		30	47.95	51.18	46.89	48.67	2.24
		45	56.60	58.60	54.77	56.66	1.91
		60	81.84	84.36	81.14	82.45	1.71
		90	69.21	71.98	70.03	70.87	1.46
		120	73.12	77.37	74.21	74.90	2.21
		180	78.84	82.94	80.88	80.89	2.05
		240	83.93	85.71	83.03	84.22	1.37
		300	92.25	88.74	87.67	89.55	2.39
		360	90.03	89.67	87.84	89.18	1.18
		420	93.33	90.66	89.11	91.03	2.13
		540	93.77	92.78	91.29	92.61	1.25
		660	94.61	94.27	92.00	93.63	1.42
		1200	99.28	98.50	95.68	97.82	1.89
		1440	99.17	97.47	95.91	97.51	1.63
Kneading	1:3						
		5	18.87	20.90	21.31	20.36	1.31
		10	29.20	31.59	32.52	31.10	1.71
		15	36.63	38.96	40.45	38.68	1.92
		20	42.37	44.47	46.09	44.31	1.87
		30	51.58	53.13	57.14	53.95	2.87
		45	60.19	62.23	64.23	62.22	2.02
		60	65.36	67.54	70.09	67.67	2.37
		90	72.34	74.73	76.79	74.62	2.23
		120	84.88	78.51	80.40	81.26	3.27
		180	81.99	82.93	84.92	83.28	1.49
		240	91.18	88.16	87.40	88.92	2.00
		300	94.95	89.58	87.89	90.81	3.69
		360	91.25	90.16	90.94	90.78	0.56
		420	98.58	90.09	90.88	93.18	4.69
		540	95.70	91.64	91.02	92.79	2.54
		660	102.42	92.91	91.79	95.71	5.84
		1200	101.35	94.00	93.71	96.35	4.33
		1440	100.09	93.86	93.58	95.84	3.68

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Kneading	1:5						
		5	18.95	19.15	20.26	19.45	0.71
		10	36.64	35.77	35.67	36.03	0.54
		15	44.81	43.98	43.83	44.21	0.53
		20	51.88	49.42	49.70	50.33	1.35
		30	58.51	58.22	57.09	57.94	0.75
		45	65.15	65.98	66.04	65.72	0.50
		60	68.77	70.30	69.25	69.44	0.78
		90	73.62	76.08	75.09	74.93	1.24
		120	78.22	78.36	78.00	78.19	0.18
		180	82.59	82.44	81.95	82.33	0.34
		240	90.15	83.58	83.73	85.82	3.75
		300	85.81	85.14	84.36	85.10	0.72
		360	87.33	85.65	84.93	85.97	1.23
		420	87.98	85.22	83.18	85.46	2.41
		540	87.06	86.06	85.06	86.06	1.00
		660	88.26	85.79	85.35	86.47	1.57
		1200	90.95	89.45	87.00	89.13	2.00
		1440	90.90	89.05	86.72	88.89	2.10
Kneading	1:10						
		5	28.90	32.84	32.48	31.41	2.18
		10	44.90	46.20	46.43	45.84	0.82
		15	53.57	54.07	55.33	54.32	0.91
		20	59.01	60.13	59.31	59.48	0.58
		30	65.49	65.93	66.56	65.99	0.54
		45	71.25	70.52	70.72	70.83	0.38
		60	75.24	73.85	75.69	74.93	0.96
		90	79.54	77.32	78.85	78.57	1.14
		120	82.65	78.58	81.83	81.02	2.15
		180	85.01	80.70	82.74	82.82	2.15
		240	85.78	81.55	84.10	83.81	2.13
		300	86.57	82.69	84.18	84.48	1.95
		360	86.14	82.83	84.45	84.48	1.65
		420	87.36	83.31	84.87	85.18	2.04
		540	86.51	83.13	85.31	84.98	1.72
		660	86.51	82.98	84.54	84.68	1.77
		1200	84.25	79.81	81.77	81.94	2.23
		1440	0.08	0.06	0.07	0.07	0.01

Table 36 Table Percent dissolved of nifedipine-PEG6000 prepared by physical mixing.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:1						
		5	13.94	15.98	15.76	15.23	1.12
		10	18.30	23.40	20.13	20.61	2.58
		15	24.30	26.27	24.99	25.19	1.00
		20	27.82	30.43	28.88	29.04	1.31
		30	36.11	39.57	37.25	37.65	1.76
		45	44.02	45.17	42.20	43.80	1.50
		60	47.16	50.25	46.30	47.90	2.08
		90	54.47	58.56	52.77	55.27	2.97
		120	60.68	64.49	57.44	60.87	3.53
		180	68.15	70.55	62.66	67.12	4.05
		240	74.72	74.24	66.34	71.77	4.71
		300	79.59	78.12	69.59	75.77	5.40
		360	78.51	80.18	73.90	77.53	3.26
		420	82.71	82.23	75.68	80.20	3.93
		540	84.08	86.94	75.19	82.07	6.13
		660	84.43	85.64	78.07	82.71	4.07
		1200	89.29	93.09	84.91	89.10	4.09
		1440	90.93	93.70	86.21	90.28	3.79
physical mixing	1:3						
		5	20.44	20.86	21.20	20.84	0.38
		10	25.10	26.79	27.97	26.62	1.45
		15	30.24	31.86	31.23	31.11	0.82
		20	34.90	37.15	37.64	36.56	1.46
		30	47.35	43.35	44.13	44.94	2.12
		45	58.73	50.89	50.26	53.29	4.71
		60	69.31	55.42	54.93	59.89	8.16
		90	74.27	64.64	60.91	66.61	6.89
		120	84.41	68.21	64.46	72.36	10.60
		180	85.93	74.11	70.23	76.76	8.18
		240	89.38	77.45	72.93	79.92	8.50
		300	93.97	80.42	75.12	83.17	9.72
		360	96.87	81.71	77.11	85.23	10.34
		420	98.93	82.84	78.38	86.71	10.81
		540	99.85	84.17	80.43	88.15	10.30
		660	100.77	86.22	82.26	89.75	9.75
		1200	105.29	90.89	86.71	94.30	9.75
		1380	105.47	92.18	88.21	95.29	9.04

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:5						
		5	15.85	15.99	17.55	16.46	0.95
		10	26.26	27.05	27.12	26.81	0.47
		15	33.68	33.34	34.25	33.76	0.46
		20	40.31	39.41	40.04	39.92	0.46
		30	48.78	47.17	49.06	48.33	1.02
		45	58.15	54.99	57.74	56.96	1.72
		60	64.17	59.39	63.61	62.39	2.61
		90	70.88	66.64	71.16	69.56	2.53
		120	75.47	70.60	74.34	73.47	2.55
		180	79.35	74.99	79.07	77.80	2.44
		240	82.61	77.46	82.26	80.77	2.88
		300	85.23	79.58	84.74	83.18	3.13
		360	86.22	80.86	85.65	84.24	2.95
		420	87.55	81.64	86.85	85.34	3.23
		540	90.65	83.68	90.87	88.40	4.09
		660	90.32	85.11	90.24	88.56	2.99
		1200	95.38	88.41	95.23	93.01	3.98
		1440	95.28	89.14	95.63	93.35	3.65
physical mixing	1:10						
		5	21.30	19.64	20.76	20.57	0.84
		10	27.50	27.34	28.41	27.75	0.57
		15	33.55	33.55	34.39	33.83	0.48
		20	39.27	39.35	40.12	39.58	0.47
		30	46.67	45.98	47.29	46.65	0.66
		45	52.53	51.89	54.15	52.86	1.16
		60	57.05	56.34	58.38	57.26	1.04
		90	62.70	60.63	63.16	62.16	1.35
		120	66.65	64.26	67.34	66.08	1.62
		180	70.82	67.16	72.70	70.23	2.82
		240	73.15	69.06	76.25	72.82	3.61
		300	74.63	71.49	78.86	74.99	3.70
		360	76.26	71.91	79.66	75.94	3.89
		420	77.61	72.39	86.81	78.93	7.30
		540	81.21	72.90	88.40	80.84	7.75
		660	83.61	74.31	91.00	82.98	8.37
		1200	85.34	74.05	96.40	85.27	11.17
		1440	85.28	72.28	96.29	84.61	12.02

Table 37 Percent dissolved of nifedipine-PEG6000 prepared by melting method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
melting	1:1						
		5	25.05	13.58	16.25	18.29	6.00
		10	33.39	24.47	24.21	27.36	5.22
		15	39.19	30.29	29.16	32.88	5.50
		20	42.51	33.98	33.54	36.67	5.06
		30	48.29	39.67	38.55	42.17	5.33
		45	53.93	44.96	43.90	47.60	5.51
		60	61.68	49.55	48.71	53.31	7.26
		90	69.66	55.34	53.78	59.59	8.75
		120	77.98	59.72	57.67	65.12	11.18
		180	88.19	66.27	63.52	72.66	13.52
		240	95.14	70.09	67.96	77.73	15.11
		300	104.37	73.20	71.43	83.00	18.53
		360	107.09	75.46	73.57	85.37	18.83
		420	110.34	75.84	73.16	86.44	20.73
		540	113.73	78.86	75.88	89.49	21.04
		660	114.59	81.12	77.09	90.94	20.59
		1200	121.81	90.90	85.95	99.56	19.44
		1440	121.19	89.76	84.61	98.52	19.80
melting	1:3						
		5	18.19	20.02	20.23	19.48	1.12
		10	27.47	29.32	28.89	28.56	0.97
		15	34.97	36.10	35.12	35.39	0.61
		20	40.41	41.96	39.92	40.76	1.06
		30	47.31	49.36	46.82	47.83	1.35
		45	53.59	56.41	54.02	54.67	1.52
		60	59.23	61.28	58.05	59.52	1.64
		90	65.23	67.00	64.88	65.70	1.14
		120	69.82	81.78	68.70	73.43	7.25
		180	75.32	87.96	75.46	79.58	7.25
		240	78.65	88.97	79.72	82.45	5.67
		300	81.68	91.30	82.63	85.20	5.30
		360	84.24	93.84	85.38	87.82	5.24
		420	86.72	97.37	86.88	90.32	6.10
		540	87.94	99.00	89.62	92.19	5.96
		660	90.53	99.15	91.04	93.58	4.84
		1200	95.96	104.31	96.62	98.96	4.64
		1440	95.73	104.91	95.94	98.86	5.24

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
melting	1:5						
		5	23.56	20.88	24.81	23.08	2.01
		10	38.20	38.68	37.85	38.24	0.41
		15	50.21	47.82	45.57	47.87	2.32
		20	57.64	54.40	50.95	54.33	3.35
		30	67.37	61.24	56.66	61.75	5.37
		45	71.62	65.97	62.37	66.66	4.66
		60	75.09	68.95	66.55	70.19	4.41
		90	81.22	75.21	72.25	76.23	4.57
		120	85.45	84.11	76.98	82.18	4.55
		180	86.89	86.94	82.34	85.39	2.64
		240	92.59	89.91	86.15	89.55	3.23
		300	95.97	92.24	88.42	92.21	3.77
		360	97.54	94.36	89.70	93.86	3.94
		420	98.25	95.35	91.67	95.09	3.30
		540	103.32	97.12	94.30	98.24	4.61
		660	104.97	100.72	96.36	100.68	4.30
		1200	106.88	102.37	96.59	101.95	5.16
		1440	106.12	102.11	95.82	101.35	5.19
melting	1:10						
		5	19.69	22.02	33.66	25.12	7.49
		10	44.42	47.94	59.73	50.70	8.02
		15	56.84	60.29	73.07	63.40	8.55
		20	65.82	66.74	81.07	71.21	8.55
		30	72.67	75.21	90.24	79.37	9.50
		45	80.99	83.74	97.37	87.37	8.77
		60	86.86	89.34	103.10	93.10	8.75
		90	93.06	95.27	108.47	98.93	8.33
		120	95.77	97.48	112.00	101.75	8.92
		180	100.06	101.49	117.22	106.26	9.52
		240	104.51	105.02	118.73	109.42	8.06
		300	105.73	106.09	119.36	110.39	7.77
		360	105.31	105.25	119.79	110.12	8.38
		420	105.53	105.33	120.56	110.47	8.74
		540	105.87	105.28	120.50	110.55	8.62
		660	105.73	105.54	120.63	110.64	8.66
		1200	105.39	105.47	120.42	110.43	8.66

Table 38 Percent dissolved of nifedipine-PEG6000 prepared by solvent method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
solvent	1:1						
		5	14.24	18.87	18.80	17.30	2.65
		10	24.56	19.46	24.15	22.72	2.83
		15	23.49	29.37	27.77	26.88	3.04
		20	27.48	32.01	31.57	30.35	2.50
		30	33.19	38.34	36.23	35.92	2.59
		45	39.33	44.00	40.95	41.43	2.37
		60	43.63	47.53	45.13	45.43	1.97
		90	49.27	53.72	48.87	50.62	2.69
		120	53.80	57.76	52.04	54.53	2.93
		180	60.07	63.32	57.60	60.33	2.87
		240	64.59	67.42	61.77	64.59	2.83
		300	68.41	70.54	65.52	68.16	2.52
		360	70.53	72.17	67.50	70.07	2.37
		420	73.36	75.27	69.69	72.77	2.83
		540	74.71	78.65	71.96	75.11	3.36
		660	79.00	81.78	75.84	78.87	2.97
		1200	83.44	89.23	81.74	84.80	3.92
		1440	85.23	90.46	83.32	86.34	3.70
solvent	1:3						
		5	21.94	24.54	24.53	23.67	1.50
		10	38.76	41.72	41.58	40.69	1.67
		15	50.36	53.67	51.49	51.84	1.68
		20	58.36	60.88	58.41	59.22	1.44
		30	67.30	68.22	65.76	67.09	1.24
		45	75.29	75.00	73.23	74.51	1.11
		60	77.29	78.20	75.94	77.14	1.14
		90	82.42	83.12	80.93	82.16	1.12
		120	86.24	86.38	84.26	85.63	1.18
		180	88.78	89.77	88.50	89.02	0.67
		240	91.96	91.69	91.05	91.57	0.47
		300	93.10	91.49	92.32	92.30	0.81
		360	93.74	93.39	92.90	93.34	0.42
		420	97.67	93.74	93.95	95.12	2.21
		540	101.63	94.45	93.05	96.38	4.61
		660	99.20	93.90	94.73	95.95	2.85
		1200	100.99	95.41	95.25	97.21	3.27
		1440	98.54	93.10	93.44	95.03	3.04

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
solvent	1:5						
		5	19.95	25.35	25.12	23.47	3.05
		10	43.40	44.14	45.54	44.36	1.08
		15	55.81	55.19	59.19	56.73	2.15
		20	62.82	61.15	66.28	63.42	2.62
		30	72.18	71.28	73.19	72.22	0.96
		45	79.05	78.62	80.88	79.52	1.20
		60	84.21	82.74	85.34	84.10	1.31
		90	89.24	86.31	89.08	88.21	1.65
		120	91.42	89.66	91.42	90.83	1.02
		180	95.00	91.42	95.36	93.93	2.18
		240	96.93	93.82	96.31	95.69	1.65
		300	97.56	95.60	97.56	96.91	1.13
		360	97.58	94.63	97.36	96.52	1.65
		420	98.35	95.32	98.21	97.30	1.71
		540	97.60	97.22	97.94	97.58	0.36
		660	97.31	96.70	96.62	96.87	0.38
		1200	92.07	92.79	92.85	92.57	0.44
solvent	1:10						
		5	15.91	14.00	15.04	14.99	0.96
		10	45.70	42.33	44.15	44.06	1.68
		15	63.61	59.37	60.87	61.28	2.15
		20	71.21	66.64	69.86	69.24	2.35
		30	80.94	77.96	77.00	78.63	2.06
		45	86.46	85.47	85.24	85.73	0.65
		60	90.51	88.80	89.14	89.48	0.91
		90	94.79	93.95	92.12	93.62	1.36
		120	96.09	96.22	94.16	95.49	1.15
		180	97.42	97.00	95.80	96.74	0.84
		240	97.37	97.30	96.24	96.97	0.63
		300	97.72	96.51	95.54	96.59	1.09
		360	96.52	97.23	94.19	95.98	1.59
		420	95.96	96.11	95.60	95.89	0.26
		540	94.91	94.64	92.52	94.02	1.31
		660	93.17	92.96	91.39	92.51	0.98

Table 39 Percent dissolved of nifedipine-PEG6000 prepared by kneading method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:1						
		5	24.50	25.48	26.26	25.41	0.88
		10	32.41	33.90	34.39	33.57	1.03
		15	39.90	40.05	41.32	40.42	0.78
		20	45.76	44.35	46.05	45.39	0.91
		30	55.55	53.36	53.09	54.00	1.35
		45	65.29	60.85	68.29	64.81	3.74
		60	68.35	66.08	65.92	66.78	1.36
		90	75.31	73.82	72.00	73.71	1.66
		120	80.75	78.57	75.89	78.40	2.43
		180	83.66	84.91	80.96	83.18	2.02
		240	86.91	85.65	82.47	85.01	2.29
		300	89.37	88.17	85.85	87.80	1.79
		360	89.05	89.45	84.74	87.75	2.61
		420	91.57	90.58	85.64	89.26	3.17
		540	91.59	93.41	87.20	90.74	3.19
		660	91.80	95.04	87.64	91.49	3.71
		1200	98.00	99.49	91.79	96.43	4.08
		1440	95.50	98.87	91.82	95.40	3.53
kneading	1:3						
		5	23.91	24.27	25.60	24.59	0.89
		10	34.42	35.41	34.51	34.78	0.55
		15	41.72	42.77	40.38	41.62	1.20
		20	48.21	48.29	45.67	47.39	1.49
		30	58.90	55.05	53.35	55.77	2.84
		45	70.47	63.22	60.92	64.87	4.98
		60	74.18	68.32	66.28	69.60	4.10
		90	82.77	74.31	70.73	75.94	6.19
		120	86.96	76.93	74.40	79.43	6.64
		180	92.52	81.31	78.00	83.94	7.61
		240	95.22	83.92	81.25	86.80	7.41
		300	97.83	86.34	82.18	88.78	8.11
		360	99.05	87.26	83.51	89.94	8.11
		420	98.85	86.57	82.90	89.44	8.35
		540	99.69	88.25	84.37	90.77	7.96
		660	100.68	88.89	85.36	91.64	8.02
		1200	101.41	90.25	86.08	92.58	7.92
		1440	101.27	90.40	86.94	92.87	7.48

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:5						
		5	28.37	28.54	28.55	28.48	0.10
		10	39.80	40.35	39.72	39.96	0.34
		15	47.92	49.12	47.29	48.11	0.93
		20	52.77	54.21	51.96	52.98	1.14
		30	58.83	60.63	57.74	59.07	1.46
		45	64.99	67.32	63.45	65.26	1.95
		60	68.67	71.30	67.42	69.13	1.98
		90	72.54	75.81	70.73	73.03	2.57
		120	76.24	79.83	74.18	76.75	2.86
		180	79.18	83.01	76.95	79.71	3.07
		240	81.76	85.20	79.97	82.31	2.65
		300	83.59	87.25	81.61	84.15	2.86
		360	84.85	88.67	82.74	85.42	3.00
		420	84.19	88.32	81.76	84.76	3.32
		540	86.24	90.35	83.86	86.82	3.29
		660	86.64	90.79	84.24	87.22	3.31
		1200	89.89	93.20	88.39	90.49	2.46
		1440	90.08	93.85	88.13	90.69	2.91
kneading	1:10						
		5	27.55	55.71	32.88	38.71	14.96
		10	43.98	70.05	46.60	53.54	14.35
		15	52.41	79.04	54.04	61.83	14.92
		20	58.07	84.64	59.14	67.28	15.04
		30	65.71	89.78	63.84	73.11	14.47
		45	70.14	95.99	70.77	78.96	14.74
		60	74.02	99.52	75.29	82.95	14.37
		90	79.94	105.37	80.64	88.65	14.49
		120	81.24	107.15	83.30	90.56	14.40
		180	84.62	110.19	84.28	93.03	14.86
		240	88.00	112.24	89.20	96.48	13.66
		300	89.29	112.81	90.14	97.42	13.34
		360	89.43	111.83	90.01	97.09	12.77
		420	90.49	114.29	90.07	98.28	13.86
		540	91.63	113.39	91.43	98.82	12.62
		660	0.12	0.24	0.12	0.16	0.07

Table 40 Percent dissolved of nifedipine-poloxamer188 prepared by physical mixing.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:1						
		5	18.80	18.66	20.31	19.26	0.92
		10	29.08	28.10	28.73	28.64	0.50
		15	35.66	33.77	35.12	34.85	0.98
		20	39.77	38.21	39.79	39.25	0.91
		30	47.86	45.54	46.56	46.65	1.17
		45	54.77	53.07	53.71	53.85	0.86
		60	60.64	58.39	60.12	59.72	1.18
		90	66.92	65.71	66.77	66.47	0.66
		120	71.64	71.09	69.60	70.78	1.05
		180	79.05	76.65	74.58	76.76	2.23
		240	83.50	80.96	77.86	80.78	2.83
		300	84.86	83.45	79.96	82.76	2.52
		360	86.76	86.13	81.31	84.74	2.98
		420	87.77	87.27	82.29	85.78	3.03
		540	90.00	89.09	83.47	87.52	3.54
		660	92.41	90.87	88.48	90.59	1.98
		1200	95.17	93.43	91.23	93.28	1.97
		1440	97.09	96.61	89.80	94.50	4.07
physical mixing	1:3						
		5	20.57	20.25	23.48	21.43	1.78
		10	32.20	30.40	32.86	31.82	1.27
		15	39.07	37.11	39.85	38.68	1.41
		20	44.45	42.34	44.44	43.74	1.21
		30	50.78	48.33	51.49	50.20	1.66
		45	58.96	54.68	57.50	57.04	2.18
		60	64.04	58.99	61.87	61.63	2.53
		90	72.70	65.39	69.18	69.09	3.66
		120	76.96	69.36	73.51	73.28	3.81
		180	83.24	74.36	78.52	78.71	4.44
		240	88.06	75.99	82.68	82.24	6.04
		300	89.18	78.04	84.60	83.94	5.60
		360	90.81	80.09	86.65	85.85	5.40
		420	92.78	81.37	87.85	87.33	5.72
		540	94.41	83.27	90.67	89.45	5.67
		660	96.25	85.40	91.75	91.13	5.45
		1200	99.17	87.41	94.73	93.77	5.94
		1440	100.02	88.67	96.15	94.95	5.77

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:5						
		5	21.69	22.47	24.14	22.77	1.25
		10	31.07	29.95	32.64	31.22	1.35
		15	36.31	35.33	37.51	36.38	1.10
		20	40.26	38.08	41.81	40.05	1.88
		30	44.85	42.17	46.19	44.40	2.05
		45	49.36	45.56	51.41	48.78	2.97
		60	52.13	47.68	54.46	51.42	3.44
		90	57.26	51.05	58.33	55.55	3.93
		120	58.69	53.04	61.44	57.72	4.28
		180	62.50	56.58	64.39	61.16	4.08
		240	65.39	58.21	67.44	63.68	4.85
		300	65.97	58.92	69.00	64.63	5.17
		360	66.89	59.75	70.13	65.59	5.31
		420	68.09	61.46	71.12	66.89	4.94
		540	68.67	61.47	72.47	67.54	5.59
		660	68.88	61.19	71.98	67.35	5.56
		1200	70.45	62.77	73.13	68.78	5.38
		1440	70.75	63.33	75.18	69.75	5.99
physical mixing	1:10						
		5	21.90	24.64	24.70	23.75	1.60
		10	31.20	35.37	36.35	34.31	2.73
		15	37.30	42.09	39.91	39.77	2.40
		20	41.82	46.82	43.48	44.04	2.55
		30	46.61	52.74	53.15	50.84	3.66
		45	52.11	59.59	56.91	56.20	3.79
		60	57.41	63.27	60.37	60.35	2.93
		90	61.36	68.91	64.87	65.05	3.78
		120	65.08	73.77	69.26	69.37	4.34
		180	71 03	80.62	73.44	75.03	4.99
		240	73.30	85.23	76.89	78.47	6.12
		300	75.35	86.08	77.82	79.75	5.62
		360	76.27	88.04	80.01	81.44	6.02
		420	73.44	91.02	80.52	81.66	8.85
		540	79.09	93.50	81.13	84.57	7.80
		660	78.06	93.31	82.70	84.69	7.82
		1200	80.53	99.16	86.25	88.65	9.54

Table 41 Percent dissolved of nifedipine-poloxamer188 by melting method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Melting	1:1						
		5	41.26	41.20	45.62	42.69	2.53
		10	62.19	61.49	61.16	61.61	0.53
		15	69.80	68.62	68.12	68.85	0.86
		20	73.77	72.86	70.38	72.34	1.75
		30	79.90	78.29	75.82	78.00	2.06
		45	85.27	82.16	79.84	82.42	2.72
		60	88.03	86.62	82.88	85.84	2.66
		90	92.41	91.49	84.51	89.47	4.32
		120	95.51	93.90	87.61	92.34	4.18
		180	97.55	96.02	89.80	94.46	4.11
		240	98.77	97.08	90.09	95.31	4.61
		300	99.42	97.93	92.14	96.49	3.85
		360	99.27	98.63	91.86	96.59	4.10
		420	99.00	99.14	92.29	96.81	3.91
		540	99.21	99.15	90.96	96.44	4.75
		660	98.73	98.32	89.84	95.63	5.02
		1200	99.39	98.12	89.64	95.72	5.30
		1440	97.14	96.99	88.10	94.07	5.18
Melting	1:3						
		5	55.22	58.11	61.31	58.21	3.05
		10	76.57	76.88	79.42	77.62	1.56
		15	85.10	83.79	83.16	84.02	0.99
		20	86.35	87.26	83.39	85.67	2.03
		30	87.54	87.91	84.58	86.68	1.82
		45	91.20	88.20	85.30	88.23	2.95
		60	93.47	91.22	87.97	90.89	2.76
		90	96.14	96.83	93.94	95.64	1.51
		120	99.53	98.41	97.20	98.38	1.16
		180	101.37	100.80	103.59	101.92	1.47
		240	101.87	101.93	101.66	101.82	0.14
		300	99.00	101.12	99.92	100.01	1.06
		360	98.01	99.50	99.35	98.95	0.82
		420	98.29	99.56	97.86	98.57	0.89
		540	98.01	99.85	99.42	99.09	0.96
		660	96.48	97.33	98.52	97.44	1.03
		1200	97.91	93.50	93.56	94.99	2.53

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Melting	1:5						
		5	27.27	45.08	48.50	40.28	11.40
		10	70.48	76.47	76.49	74.48	3.46
		15	84.76	81.27	80.43	82.15	2.30
		20	88.20	85.24	93.03	88.82	3.94
		30	90.81	87.36	100.58	92.92	6.86
		45	93.00	88.98	101.32	94.43	6.30
		60	93.79	92.86	102.04	96.23	5.06
		90	101.44	98.14	101.65	100.41	1.97
		120	105.61	102.23	102.98	103.61	1.78
		180	108.81	104.14	108.95	107.30	2.74
		240	108.12	104.17	110.10	107.46	3.02
		300	108.96	104.09	111.23	108.10	3.65
		360	112.49	103.42	112.58	109.50	5.26
		420	111.46	102.43	113.94	109.28	6.06
		540	108.99	100.96	116.54	108.83	7.79
		660	108.51	99.40	116.30	108.07	8.46
		1200	107.40	96.97	115.20	106.53	9.14
		1440	106.57	95.90	114.15	105.54	9.17
Melting	1:10						
		5	60.94	77.66	62.48	67.03	9.24
		10	71.03	84.87	72.24	76.05	7.66
		15	77.76	90.54	75.65	81.31	8.06
		20	80.24	95.35	82.40	86.00	8.17
		30	85.52	99.93	82.37	89.28	9.36
		45	85.61	99.39	85.74	90.25	7.92
		60	90.17	100.30	87.02	92.50	6.94
		90	89.86	103.18	88.79	93.94	8.02
		120	91.54	103.76	89.34	94.88	7.76
		180	93.72	105.72	91.89	97.11	7.51
		240	93.04	109.76	91.56	98.12	10.11
		300	91.09	108.16	90.44	96.57	10.05
		360	92.48	115.26	90.29	99.34	13.82
		420	91.85	112.68	89.52	98.02	12.75
		540	91.57	112.19	88.12	97.30	13.01
		660	89.33	110.99	87.14	95.82	13.18
		1200	88.20	109.41	85.95	94.52	12.94
		1440	88.06	109.68	85.10	94.28	13.42

Table 42 Percent dissolved of nifedipine-poloxamer188 prepared by solvent method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
solvent	1:1						
		5	20.26	20.89	45.62	28.92	14.46
		10	29.14	29.06	61.16	39.79	18.51
		15	35.57	35.57	68.12	46.42	18.79
		20	40.52	40.09	70.38	50.33	17.37
		30	47.34	46.99	75.82	56.72	16.54
		45	55.46	53.34	79.84	62.88	14.73
		60	61.89	59.91	82.88	68.23	12.73
		90	69.93	65.34	84.51	73.26	10.01
		120	73.26	67.75	87.61	76.21	10.25
		180	78.20	72.90	89.80	80.30	8.64
		240	81.94	75.80	90.09	82.61	7.17
		300	83.93	78.06	92.14	84.71	7.07
		360	85.61	79.12	91.86	85.53	6.37
		420	86.68	80.04	92.29	86.33	6.13
		540	88.01	81.09	90.96	86.69	5.06
		660	93.23	86.02	89.84	89.69	3.60
		1200	95.74	89.09	89.64	91.49	3.69
		1440	93.66	88.28	88.10	90.01	3.16
solvent	1:3						
		5	23.22	24.00	20.57	22.60	1.80
		10	32.15	32.98	29.31	31.48	1.93
		15	36.88	37.88	35.40	36.72	1.25
		20	39.87	40.64	40.06	40.19	0.40
		30	46.05	45.56	47.44	46.35	0.98
		45	49.45	50.01	54.93	51.46	3.01
		60	53.06	53.47	60.79	55.77	4.35
		90	57.13	57.76	68.20	61.03	6.22
		120	62.15	63.05	75.75	66.98	7.61
		180	65.88	67.84	82.24	71.99	8.93
		240	69.14	72.73	87.89	76.59	9.95
		300	71.54	74.22	91.93	79.23	11.08
		360	73.59	76.62	95.67	81.96	11.97
		420	77.32	79.72	99.75	85.60	12.32
		540	79.11	81.23	103.11	87.82	13.29
		660	80.79	84.11	104.58	89.83	12.88
		1200	86.80	90.53	105.16	94.16	9.71
		1440	82.67	85.65	106.65	91.66	13.07

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
solvent	1:5						
		5	55.43	55.52	55.16	55.37	0.18
		10	66.90	67.13	66.69	66.91	0.22
		15	73.97	73.71	74.12	73.93	0.21
		20	78.85	77.67	78.37	78.30	0.59
		30	83.24	81.96	82.67	82.62	0.64
		45	86.55	85.57	87.32	86.48	0.88
		60	90.35	87.98	89.89	89.41	1.26
		90	92.84	91.43	91.14	91.80	0.91
		120	94.19	92.69	93.97	93.61	0.81
		180	96.23	93.55	96.92	95.57	1.78
		240	96.96	94.47	97.44	96.29	1.59
		300	96.52	94.41	97.79	96.24	1.71
		360	96.03	94.83	97.86	96.24	1.53
		420	96.32	93.71	96.10	95.38	1.45
		540	95.68	93.23	96.32	95.07	1.63
		660	94.64	93.22	95.69	94.52	1.24
		1200	92.92	90.81	93.40	92.38	1.38
solvent	1:10						
		5	61.87	63.76	67.92	64.52	3.10
		10	75.81	77.47	75.09	76.12	1.22
		15	81.16	80.19	79.05	80.13	1.05
		20	83.15	82.59	81.74	82.50	0.71
		30	85.69	85.49	82.59	84.59	1.74
		45	87.02	87.94	85.41	86.79	1.28
		60	90.68	89.99	90.06	90.24	0.38
		90	97.58	97.58	91.13	95.43	3.72
		120	97.62	95.46	92.05	95.04	2.81
		180	99.44	99.56	97.59	98.86	1.10
		240	98.40	99.39	98.05	98.61	0.70
		300	100.65	100.30	99.04	100.00	0.85
		360	97.86	98.14	96.52	97.51	0.86
		420	96.17	97.50	96.30	96.66	0.73
		540	95.03	96.45	94.27	95.25	1.11
		660	93.69	94.28	92.79	93.59	0.75

Table 43 Percent dissolved of nifedipine-poloxamer188 prepared by kneading method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:1						
		5	21.39	32.76	21.81	25.32	6.44
		10	33.01	42.75	31.69	35.82	6.04
		15	41.35	48.91	39.03	43.10	5.16
		20	46.37	53.15	44.54	48.02	4.53
		30	54.26	60.54	51.24	55.35	4.75
		45	61.25	67.53	58.23	62.34	4.74
		60	64.45	71.76	62.82	66.35	4.76
		90	72.40	77.70	69.02	73.04	4.38
		120	76.58	81.30	74.67	77.51	3.41
		180	81.59	86.59	79.61	82.60	3.60
		240	84.84	89.08	83.64	85.85	2.85
		300	87.24	89.79	85.91	87.64	1.97
		360	89.15	92.67	87.81	89.88	2.51
		420	89.72	92.63	88.24	90.20	2.23
		540	91.98	93.19	89.66	91.61	1.80
		660	93.25	94.53	90.65	92.81	1.98
		1200	97.20	95.07	93.70	95.32	1.76
		1440	96.18	96.34	95.04	95.85	0.71
kneading	1:3						
		5	34.44	32.76	34.08	33.76	0.89
		10	44.17	42.75	43.17	43.36	0.73
		15	50.39	48.91	49.19	49.50	0.79
		20	54.92	53.15	53.43	53.83	0.95
		30	61.41	60.54	59.20	60.38	1.11
		45	68.65	67.53	65.76	67.31	1.46
		60	72.98	71.76	70.08	71.61	1.46
		90	77.91	77.70	75.92	77.18	1.09
		120	80.88	81.30	79.18	80.45	1.12
		180	85.61	86.59	83.27	85.16	1.71
		240	88.17	89.08	85.54	87.59	1.84
		300	88.53	89.79	86.19	88.17	1.82
		360	91.69	92.67	87.87	90.74	2.54
		420	91.64	92.63	87.82	90.69	2.54
		540	96.48	93.19	89.15	92.94	3.67
		660	96.79	94.53	90.71	94.01	3.07
		1200	99.06	95.07	91.52	95.22	3.77
		1440	98.88	96.34	91.53	95.58	3.73

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:5						
		5	33.84	33.36	36.02	34.40	1.42
		10	47.42	46.59	46.94	46.99	0.42
		15	54.17	52.84	54.24	53.75	0.79
		20	58.19	58.14	57.78	58.04	0.22
		30	63.48	68.75	63.20	65.14	3.13
		45	69.60	76.46	67.23	71.10	4.79
		60	73.79	77.98	70.69	74.15	3.66
		90	78.23	84.93	76.25	79.80	4.55
		120	82.88	88.40	80.21	83.83	4.18
		180	86.91	95.32	84.88	89.03	5.53
		240	91.64	99.56	88.82	93.34	5.57
		300	93.14	101.47	90.25	94.96	5.83
		360	93.92	104.59	91.95	96.82	6.80
		420	95.34	107.63	91.96	98.31	8.25
		540	96.89	108.56	92.88	99.44	8.15
		660	96.97	108.21	93.66	99.61	7.63
		1200	100.79	117.95	96.28	105.01	11.43
		1440	100.75	117.44	96.79	104.99	10.96
kneading	1:10						
		5	61.48	68.91	68.69	66.36	4.22
		10	75.77	78.28	78.20	77.42	1.43
		15	81.25	84.50	81.47	82.41	1.81
		20	83.38	88.60	83.45	85.15	2.99
		30	87.82	87.85	84.16	86.61	2.12
		45	80.82	80.61	80.03	80.49	0.41
		60	83.38	82.96	80.22	82.19	1.71
		90	86.41	86.90	84.16	85.82	1.46
		120	90.99	90.43	88.02	89.81	1.58
		180	96.41	95.02	95.14	95.52	0.77
		240	99.40	97.64	98.19	98.41	0.90
		300	98.28	98.71	98.01	98.33	0.35
		360	100.19	98.43	98.14	98.92	1.11
		420	96.96	96.12	97.38	96.82	0.64
		540	96.18	95.91	95.34	95.81	0.43
		660	96.66	95.32	96.80	96.26	0.82

Table 44 Percent dissolved of nifedipine-poloxamer288 prepared by physical mixing.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:1						
		5	19.91	21.45	23.83	21.73	1.98
		10	35.80	33.99	35.69	35.16	1.01
		15	42.56	40.65	43.11	42.11	1.29
		20	47.64	45.89	48.58	47.37	1.37
		30	59.89	52.99	55.47	56.12	3.49
		45	63.18	61.11	62.60	62.29	1.07
		60	68.88	64.51	67.12	66.84	2.20
		90	74.10	74.79	72.13	73.68	1.38
		120	95.14	76.60	77.35	83.03	10.50
		180	87.03	84.26	81.87	84.39	2.58
		240	92.81	88.59	87.17	89.52	2.93
		300	95.71	92.47	89.71	92.63	3.00
		360	99.03	95.02	91.35	95.14	3.84
		420	101.16	94.96	92.19	96.10	4.59
		540	103.20	98.97	93.83	98.67	4.69
		660	110.23	99.69	95.09	101.67	7.76
		1200	110.14	106.21	103.05	106.47	3.55
		1440	99.57	98.86	95.69	98.04	2.07
physical mixing	1:3						
		5	16.98	24.75	20.20	20.64	3.90
		10	31.94	31.21	30.55	31.24	0.69
		15	39.60	39.25	37.00	38.61	1.41
		20	44.62	43.99	42.16	43.59	1.28
		30	52.37	51.39	50.25	51.34	1.06
		45	58.10	57.47	55.49	57.02	1.36
		60	62.41	61.85	59.80	61.35	1.37
		90	70.37	66.93	64.25	67.19	3.07
		120	74.27	71.17	67.42	70.95	3.43
		180	79.34	76.18	74.96	76.83	2.26
		240	83.09	79.78	79.08	80.65	2.14
		300	87.19	81.56	79.65	82.80	3.92
		360	90.50	83.89	82.19	85.53	4.39
		420	92.00	84.81	82.76	86.52	4.85
		540	94.19	87.13	85.00	88.77	4.81
		660	93.92	95.98	106.22	98.70	6.59
		1200	105.92	93.03	90.55	96.50	8.25
		1440	100.37	92.65	90.39	94.47	5.24

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:5						
		5	17.87	21.16	22.29	20.44	2.30
		10	32.63	35.10	33.91	33.88	1.24
		15	39.80	42.62	41.56	41.33	1.42
		20	44.12	47.43	45.04	45.53	1.71
		30	49.89	53.77	50.32	51.33	2.13
		45	59.89	62.44	58.56	60.29	1.97
		60	61.07	67.04	62.61	63.57	3.10
		90	65.28	71.49	66.77	67.85	3.24
		120	71.13	77.77	71.01	73.30	3.87
		180	75.37	83.41	74.53	77.77	4.90
		240	78.48	83.44	73.92	78.61	4.76
		300	79.55	85.69	76.45	80.56	4.70
		360	81.74	87.03	78.21	82.33	4.44
		420	84.13	88.09	78.66	83.63	4.74
		540	85.41	90.07	79.49	84.99	5.30
		660	85.99	89.88	81.11	85.66	4.39
		1200	92.24	94.86	86.11	91.07	4.49
		1440	92.42	94.05	86.29	90.92	4.10
physical mixing	1:10						
		5	21.47	24.28	24.90	23.55	1.83
		10	40.39	41.46	41.95	41.26	0.80
		15	47.64	48.56	49.34	48.51	0.85
		20	54.21	53.16	54.50	53.96	0.70
		30	59.44	59.85	64.72	61.34	2.94
		45	65.08	66.00	66.38	65.82	0.67
		60	68.90	69.55	70.17	69.54	0.64
		90	74.18	74.75	73.98	74.31	0.40
		120	77.73	78.99	78.42	78.38	0.63
		180	82.52	84.14	82.81	83.16	0.86
		240	85.20	86.35	85.57	85.71	0.58
		300	87.19	88.89	87.90	87.99	0.85
		360	88.04	89.60	90.06	89.24	1.06
		420	89.46	91.93	91.37	90.92	1.29
		540	90.52	92.08	91.66	91.42	0.80
		660	90.54	93.36	92.16	92.02	1.42
		1200	94.70	97.46	96.47	96.21	1.40
		1440	94.65	96.42	95.92	95.66	0.91

Table 45 Percent dissolved of nifedipine-poloxamer288 prepared by melting method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
melting	1:1						
		5	18.50	20.19	24.12	20.94	2.88
		10	31.65	31.53	33.44	32.21	1.07
		15	37.89	36.99	40.44	38.44	1.79
		20	42.29	41.30	44.26	42.62	1.51
		30	48.91	48.91	50.04	49.28	0.65
		45	54.06	55.26	58.14	55.82	2.09
		60	58.03	58.74	61.27	59.35	1.71
		90	68.16	65.21	67.74	67.04	1.59
		120	71.79	71.84	71.78	71.80	0.04
		180	76.79	75.95	77.34	76.69	0.70
		240	79.76	78.92	80.04	79.57	0.58
		300	82.30	81.74	82.44	82.16	0.37
		360	85.26	84.28	84.70	84.75	0.49
		420	85.20	85.98	85.48	85.55	0.39
		540	87.38	88.02	88.01	87.80	0.37
		660	89.93	91.27	91.68	90.96	0.92
		1200	93.05	93.13	94.32	93.50	0.72
		1440	90.68	90.96	93.56	91.73	1.59
melting	1:3						
		5	29.73	31.55	31.91	31.06	1.17
		10	41.96	43.16	41.83	42.32	0.73
		15	51.01	50.25	48.77	50.01	1.14
		20	54.28	54.49	52.87	53.88	0.88
		30	62.71	60.12	58.37	60.40	2.19
		45	68.17	65.56	63.66	65.79	2.27
		60	72.98	69.17	67.06	69.73	3.00
		90	75.95	75.01	71.70	74.22	2.23
		120	83.68	79.18	75.44	79.44	4.13
		180	87.66	82.64	78.34	82.88	4.66
		240	98.68	84.97	82.29	88.65	8.79
		300	98.20	80.43	83.65	87.42	9.47
		360	108.03	88.83	84.64	93.83	12.47
		420	106.95	89.37	85.77	94.03	11.34
		540	111.44	90.20	85.84	95.83	13.69
		660	112.88	93.80	89.49	98.72	12.45
		1200	116.27	96.43	92.90	101.87	12.60
		1440	112.15	95.04	88.84	98.68	12.07

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
melting	1:5						
		5	61.67	55.05	54.84	57.19	3.88
		10	76.74	67.71	67.21	70.55	5.36
		15	80.68	71.63	72.12	74.81	5.09
		20	82.67	73.97	74.05	76.90	5.00
		30	84.86	75.88	75.04	78.59	5.44
		45	86.06	78.07	78.13	80.75	4.59
		60	87.95	81.17	79.90	83.01	4.33
		90	92.18	85.32	84.89	87.46	4.09
		120	94.58	88.16	86.74	89.83	4.18
		180	100.36	94.20	89.63	94.73	5.38
		240	108.23	101.46	99.12	102.94	4.73
		300	105.06	97.30	94.76	99.04	5.37
		360	107.49	99.80	97.04	101.44	5.42
		420	108.99	101.51	98.81	103.10	5.27
		540	108.22	102.21	98.48	102.97	4.92
		660	104.43	98.43	94.12	98.99	5.18
melting	1:10						
		5	20.75	34.29	40.67	31.90	10.17
		10	65.63	67.18	66.29	66.36	0.78
		15	70.93	71.63	71.56	71.37	0.39
		20	74.89	71.80	72.91	73.20	1.56
		30	74.49	75.17	76.02	75.23	0.77
		45	76.59	79.20	79.40	78.40	1.57
		60	80.60	80.77	83.49	81.62	1.62
		90	85.75	85.68	87.02	86.15	0.75
		120	90.89	92.03	93.42	92.11	1.27
		180	91.00	92.55	95.99	93.18	2.55
		240	100.68	101.76	105.55	102.66	2.56
		300	99.47	100.04	103.36	100.96	2.10
		360	97.50	97.87	103.36	99.58	3.28
		420	99.66	100.52	103.76	101.32	2.16
		540	98.70	100.26	103.77	100.91	2.60
		660	94.20	96.90	98.85	96.65	2.34
		1200	0.14	0.15	0.16	0.15	0.01

Table 46 Percent dissolved of nifedipine-poloxamer288 prepared by solvent method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
solvent	1:1						
		5	18.36	19.63	20.81	19.60	1.23
		10	29.62	30.68	30.75	30.35	0.63
		15	36.41	37.54	38.87	37.61	1.23
		20	43.33	42.21	44.25	43.26	1.02
		30	49.27	49.46	52.13	50.29	1.60
		45	59.06	56.16	58.92	58.05	1.63
		60	61.00	60.91	63.44	61.78	1.43
		90	71.68	65.77	69.08	68.84	2.96
		120	70.18	69.66	73.96	71.26	2.35
		180	74.59	75.71	79.81	76.71	2.74
		240	76.79	79.11	83.63	79.84	3.47
		300	82.49	82.43	85.47	83.46	1.74
		360	82.03	83.27	87.72	84.34	2.99
		420	83.85	85.47	89.14	86.16	2.71
		540	86.54	87.94	91.11	88.53	2.34
		660	88.81	90.76	93.73	91.10	2.48
		1200	94.16	93.60	97.54	95.10	2.13
		1440	93.27	93.47	96.99	94.58	2.09
solvent	1:3						
		5	21.33	26.93	30.02	26.09	4.40
		10	55.81	55.35	57.05	56.07	0.88
		15	64.63	63.29	64.71	64.21	0.80
		20	70.57	65.03	70.15	68.58	3.09
		30	77.13	75.35	76.43	76.30	0.90
		45	83.20	81.58	84.40	83.06	1.42
		60	88.72	84.08	90.16	87.65	3.18
		90	91.69	89.00	94.12	91.60	2.56
		120	96.56	91.49	96.45	94.83	2.90
		180	98.62	93.53	99.13	97.10	3.10
		240	99.76	96.01	104.23	100.00	4.12
		300	100.32	94.75	103.25	99.44	4.32
		360	99.97	95.17	102.89	99.35	3.90
		420	99.41	97.29	103.66	100.12	3.25
		540	100.05	96.03	105.16	100.41	4.57
		660	101.46	97.37	105.02	101.28	3.83
		1200	98.88	97.12	106.17	100.72	4.80
		1440	98.88	95.71	105.12	99.90	4.79

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
solvent	1:5						
		5	37.17	41.37	44.32	40.95	3.59
		10	57.52	58.86	59.37	58.58	0.96
		15	64.71	66.32	65.49	65.51	0.80
		20	71.76	71.42	70.22	71.13	0.81
		30	77.56	77.97	75.87	77.14	1.12
		45	86.81	83.91	81.37	84.03	2.72
		60	87.62	87.45	84.55	86.54	1.72
		90	94.37	90.91	89.49	91.59	2.51
		120	96.02	94.10	91.97	94.03	2.03
		180	100.02	96.72	99.58	98.77	1.79
		240	101.15	100.80	98.42	100.12	1.49
		300	102.58	100.82	98.47	100.63	2.06
		360	101.54	101.11	97.78	100.14	2.06
		420	102.08	102.30	97.29	100.56	2.83
		540	102.94	101.19	97.57	100.57	2.74
		660	104.48	104.13	98.48	102.37	3.37
		1200	103.89	104.17	99.15	102.40	2.82
		1440	102.76	104.45	97.60	101.61	3.57
solvent	1:10						
		5	26.52	30.93	36.68	31.38	5.09
		10	64.12	66.46	68.51	66.36	2.20
		15	73.58	73.24	75.66	74.16	1.31
		20	74.83	76.86	77.50	76.40	1.39
		30	81.64	80.66	81.23	81.18	0.49
		45	88.68	89.24	84.34	87.42	2.69
		60	93.01	92.94	89.46	91.81	2.03
		90	90.08	89.95	103.41	94.48	7.73
		120	96.52	96.75	95.82	96.37	0.48
		180	98.88	100.30	98.38	99.18	0.99
		240	101.00	102.56	100.16	101.24	1.22
		300	101.15	102.57	100.66	101.46	1.00
		360	100.53	102.50	101.08	101.37	1.02
		420	101.02	102.08	100.38	101.16	0.86
		540	101.09	102.37	100.38	101.28	1.01

Table 47 Percent dissolved of nifedipine-poloxamer288 prepared by kneading method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:1						
		5	24.82	26.78	25.59	25.73	0.99
		10	37.65	37.38	35.62	36.88	1.10
		15	44.10	44.73	42.96	43.93	0.89
		20	52.14	50.25	47.50	49.96	2.33
		30	58.56	57.29	54.13	56.66	2.28
		45	64.98	64.21	60.32	63.17	2.50
		60	67.96	67.54	64.72	66.74	1.77
		90	73.45	73.17	69.29	71.97	2.32
		120	78.12	77.55	72.76	76.14	2.94
		180	82.00	82.98	77.69	80.89	2.81
		240	91.92	85.68	80.52	86.04	5.71
		300	96.12	87.72	84.49	89.44	6.00
		360	96.62	89.07	83.16	89.62	6.75
		420	98.24	90.48	84.77	91.16	6.76
		540	99.52	91.89	87.38	92.93	6.13
		660	106.06	94.72	91.18	97.32	7.77
		1200	107.65	97.47	93.51	99.54	7.29
		1440	106.67	98.90	97.40	100.99	4.98
kneading	1:3						
		5	23.85	24.96	24.54	24.45	0.56
		10	36.05	36.19	35.78	36.01	0.21
		15	43.13	43.55	42.50	43.06	0.53
		20	48.78	48.71	47.58	48.36	0.67
		30	55.27	55.83	54.21	55.10	0.82
		45	62.67	61.69	61.06	61.81	0.81
		60	68.05	67.63	69.60	68.42	1.04
		90	79.06	72.85	72.02	74.64	3.85
		120	78.53	76.73	76.10	77.12	1.26
		180	84.91	82.10	81.60	82.87	1.78
		240	90.70	85.56	83.73	86.67	3.61
		300	93.33	88.80	87.05	89.73	3.24
		360	98.05	89.59	88.53	92.06	5.22
		420	101.10	91.29	90.52	94.31	5.90
		540	102.23	93.19	91.17	95.53	5.89
		660	89.05	89.49	96.77	91.77	4.34
		1200	108.64	98.25	98.36	101.75	5.97
		1440	108.60	99.64	96.81	101.68	6.15

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:5						
		5	27.49	26.29	26.43	26.73	0.66
		10	39.21	36.53	37.52	37.75	1.35
		15	45.80	43.68	44.10	44.53	1.12
		20	51.03	48.91	49.26	49.73	1.14
		30	57.79	55.53	55.40	56.24	1.35
		45	67.30	65.25	64.70	65.75	1.37
		60	71.49	68.96	67.48	69.31	2.03
		90	74.18	71.57	72.97	72.91	1.31
		120	79.32	74.96	76.43	76.90	2.22
		180	82.01	79.33	78.63	79.99	1.78
		240	87.50	82.86	82.15	84.17	2.91
		300	88.24	85.13	83.78	85.71	2.28
		360	88.94	86.05	85.48	86.82	1.86
		420	99.75	87.53	85.42	90.90	7.74
		540	102.63	88.66	89.00	93.43	7.97
		660	105.28	89.59	88.18	94.35	9.49
		1200	102.75	93.67	92.81	96.41	5.50
		1440	99.01	94.05	93.41	95.49	3.07
kneading	1:10						
		5	65.74	43.20	46.91	51.95	12.09
		10	78.94	63.30	64.16	68.80	8.79
		15	85.75	71.41	71.12	76.09	8.36
		20	89.37	74.74	74.74	79.62	8.45
		30	93.17	79.53	79.53	84.08	7.87
		45	96.07	84.26	83.83	88.05	6.94
		60	101.62	89.06	86.65	92.45	8.04
		90	92.94	93.43	93.56	93.31	0.33
		120	105.41	92.26	91.56	96.41	7.80
		180	107.58	95.85	94.22	99.22	7.29
		240	108.99	96.20	95.15	100.11	7.70
		300	109.49	96.64	95.08	100.40	7.91
		360	109.21	97.36	94.59	100.38	7.76
		420	109.83	97.85	95.85	101.18	7.56
		540	110.20	97.85	95.93	101.32	7.75

Table 48 Percent dissolved of nifedipine-poloxamer407 prepared by physical mixing.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:1						
		5	15.93	17.75	18.95	17.54	1.52
		10	28.30	28.80	29.85	28.98	0.79
		15	35.59	35.16	37.28	36.01	1.12
		20	42.37	40.97	42.15	41.83	0.75
		30	48.93	48.85	50.89	49.56	1.16
		45	56.96	56.40	59.36	57.57	1.57
		60	62.34	62.55	64.74	63.21	1.33
		90	69.39	69.38	72.43	70.40	1.76
		120	74.06	75.41	78.02	75.83	2.01
		180	80.67	83.08	83.79	82.51	1.63
		240	84.57	86.14	87.19	85.97	1.32
		300	87.69	88.33	89.74	88.59	1.05
		360	93.04	91.37	91.59	92.00	0.91
		420	93.22	92.93	92.57	92.91	0.33
		540	99.10	96.52	94.54	96.72	2.29
		660	98.93	97.11	97.02	97.68	1.08
		1200	101.68	101.13	99.99	100.93	0.86
		1440	103.39	103.89	101.84	103.04	1.07
physical mixing	1:3						
		5	16.91	18.81	20.82	18.85	1.96
		10	32.55	33.12	33.96	33.21	0.71
		15	40.91	41.34	44.42	42.22	1.91
		20	46.64	47.84	53.18	49.22	3.48
		30	54.31	56.23	71.97	60.83	9.69
		45	62.14	63.50	72.56	66.07	5.66
		60	64.79	68.59	75.15	69.51	5.24
		90	73.56	77.11	87.86	79.51	7.45
		120	79.00	81.71	94.81	85.17	8.45
		180	84.79	87.99	100.60	91.13	8.36
		240	89.60	91.32	107.87	96.26	10.09
		300	92.29	93.02	110.08	98.46	10.07
		360	92.52	94.92	114.31	100.58	11.95
		420	93.86	95.36	118.55	102.59	13.84
		540	96.11	98.18	122.43	105.58	14.64
		660	97.26	99.74	123.15	106.72	14.29
		1200	99.68	101.61	126.15	109.15	14.76
		1440	100.46	102.74	127.01	110.07	14.71

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:5						
		5	17.80	23.86	26.52	22.73	4.47
		10	37.30	37.18	39.78	38.08	1.47
		15	44.26	45.67	48.41	46.11	2.11
		20	50.49	51.41	53.44	51.78	1.51
		30	57.96	58.86	60.49	59.10	1.28
		45	65.23	66.35	67.89	66.49	1.34
		60	67.30	70.74	72.43	70.16	2.62
		90	75.51	77.30	77.85	76.89	1.22
		120	79.49	79.56	83.08	80.71	2.05
		180	84.70	85.76	88.16	86.21	1.77
		240	88.18	88.19	91.63	89.33	1.99
		300	89.45	89.68	92.92	90.68	1.94
		360	90.67	91.22	95.23	92.37	2.49
		420	92.35	107.79	96.46	98.86	8.00
		540	94.20	94.78	99.42	96.13	2.86
		660	93.64	93.99	99.59	95.74	3.34
		1200	95.56	96.62	101.27	97.82	3.04
		1440	97.84	99.45	103.68	100.32	3.02
physical mixing	1:10						
		5	16.30	22.90	24.42	21.21	4.32
		10	34.91	34.66	33.74	34.44	0.62
		15	41.52	40.90	40.61	41.01	0.47
		20	46.40	46.12	45.77	46.10	0.31
		30	54.59	51.90	50.34	52.28	2.15
		45	59.58	58.19	57.18	58.32	1.20
		60	63.96	61.86	61.36	62.39	1.38
		90	70.09	70.08	67.22	69.13	1.66
		120	73.85	74.50	71.32	73.22	1.68
		180	79.41	79.71	75.75	78.29	2.20
		240	82.53	83.17	78.80	81.50	2.36
		300	84.36	87.07	80.56	84.00	3.27
		360	86.36	88.21	82.40	85.66	2.96
		420	86.16	88.37	83.68	86.07	2.34
		540	88.83	93.16	85.39	89.13	3.89
		660	88.99	91.26	86.59	88.95	2.34
		1200	94.56	94.79	91.32	93.56	1.94

Table 49. Percent dissolved of nifedipine-poloxamer407 prepared by melting method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Melting	1:1						
		5	20.58	20.64	27.23	22.82	3.82
		10	38.01	38.02	40.36	38.80	1.35
		15	44.98	44.64	46.25	45.29	0.85
		20	49.01	48.26	50.56	49.28	1.18
		30	53.81	53.40	55.78	54.33	1.27
		45	59.02	58.70	60.72	59.48	1.09
		60	63.48	62.60	64.67	63.58	1.04
		90	68.55	67.59	69.47	68.54	0.94
		120	72.59	71.20	73.85	72.55	1.32
		180	76.26	76.64	78.17	77.02	1.01
		240	80.56	79.12	81.69	80.46	1.29
		300	82.61	81.32	84.02	82.65	1.35
		360	85.43	83.31	86.01	84.92	1.42
		420	86.72	83.54	87.35	85.87	2.04
		540	87.29	85.24	88.62	87.05	1.70
		660	88.27	85.00	89.54	87.60	2.35
		1200	92.31	88.93	94.28	91.84	2.70
		1440	90.50	85.86	92.89	89.75	3.58
Melting	1:3						
		5	30.55	37.64	43.17	37.12	6.33
		10	68.79	69.47	69.77	69.35	0.50
		15	77.29	76.87	89.04	81.06	6.91
		20	82.18	80.91	83.57	82.22	1.33
		30	86.91	85.56	93.38	88.62	4.18
		45	91.42	88.55	95.45	91.81	3.47
		60	93.97	91.63	96.67	94.09	2.52
		90	91.46	94.74	101.86	96.02	5.31
		120	98.32	96.23	103.07	99.21	3.51
		180	102.79	99.89	106.24	102.97	3.18
		240	106.75	101.59	107.10	105.15	3.08
		300	101.26	99.99	106.55	102.60	3.48
		360	101.04	99.91	106.05	102.34	3.27
		420	100.06	99.28	104.94	101.43	3.06
		540	100.43	99.64	104.92	101.66	2.85
		660	99.16	98.60	104.94	100.90	3.51
		1200	92.89	92.53	101.04	95.49	4.82

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Melting	1:5						
		5	44.63	62.45	61.59	56.22	10.05
		10	77.50	77.88	79.06	78.15	0.82
		15	86.72	84.06	85.69	85.49	1.34
		20	89.51	87.81	89.37	88.90	0.94
		30	93.33	91.41	93.96	92.90	1.32
		45	98.39	95.44	98.68	97.50	1.80
		60	99.40	96.93	99.40	98.58	1.43
		90	104.39	97.43	101.02	100.95	3.48
		120	107.71	102.14	102.43	104.10	3.14
		180	109.34	106.17	106.02	107.18	1.88
		240	114.56	106.19	109.76	110.17	4.20
		300	114.79	105.99	111.33	110.70	4.44
		360	115.64	106.19	112.54	111.46	4.81
		420	115.02	106.55	113.74	111.77	4.57
		540	113.55	104.03	111.86	109.81	5.08
		660	111.80	103.33	113.60	109.58	5.48
		1200	110.89	102.14	119.34	110.79	8.60
		1440	107.66	98.50	107.71	104.62	5.30
Melting	1:10						
		5	44.10	44.39	44.02	44.17	0.19
		10	72.36	74.82	73.22	73.47	1.25
		15	81.14	82.50	81.41	81.68	0.72
		20	85.83	84.42	84.70	84.98	0.74
		30	91.18	86.53	88.41	88.71	2.34
		45	90.86	91.54	90.74	91.05	0.43
		60	93.87	93.95	93.44	93.75	0.27
		90	96.28	96.13	95.72	96.04	0.29
		120	96.78	98.48	97.14	97.47	0.89
		180	102.19	103.33	102.25	102.59	0.64
		240	101.88	105.14	102.99	103.33	1.66
		300	99.56	103.47	101.01	101.35	1.97
		360	99.12	104.88	101.49	101.83	2.89
		420	100.35	104.17	101.75	102.09	1.93
		540	101.75	101.77	101.25	101.59	0.29
		660	100.43	100.29	99.86	100.19	0.30

Table 50 Percent dissolved of nifedipine-poloxamer407 prepared by solvent method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Solvent	1:1						
		5	17.03	15.84	18.57	17.15	1.37
		10	26.73	25.75	30.27	27.58	2.38
		15	33.38	31.98	33.46	32.94	0.84
		20	37.98	36.99	38.62	37.86	0.82
		30	44.51	44.95	45.44	44.97	0.46
		45	53.05	52.77	53.69	53.17	0.47
		60	59.70	60.25	61.52	60.49	0.93
		90	66.05	66.33	69.15	67.17	1.71
		120	70.79	70.37	73.89	71.68	1.93
		180	76.08	76.77	79.68	77.51	1.91
		240	80.25	80.18	82.57	81.00	1.37
		300	83.21	82.86	85 82	83.96	1.62
		360	86.06	84.05	87.16	85.76	1.58
		420	85.64	85.20	88.73	86.52	1.92
		540	87.80	87.30	90.55	88.55	1.75
		660	91.62	92.32	95.84	93.26	2.26
		1200	82.37	94.89	97.57	91.61	8.12
		1440	94.49	93.65	96.68	94.94	1.56
Solvent	1:3						
		5	17.14	21.98	20.64	19.92	2.50
		10	33.50	34.86	33.45	33.94	0.80
		15	39.27	41.40	40.32	40.33	1.06
		20	44.43	45.28	44.43	44.71	0.49
		30	50.28	52.61	52.32	51.74	1.27
		45	56.01	57.48	59.08	57.52	1.54
		60	58.12	62.50	60.87	60.50	2.21
		90	63.19	65.89	70.93	66.67	3.93
		120	67.92	69.21	72.81	69.98	2.53
		180	72.51	73.93	78.44	74.96	3.09
		240	75.63	77.18	83.24	78.68	4.03
		300	79.51	80.09	84.33	81.31	2.63
		360	79.88	80.59	85.66	82.04	3.15
		420	82.12	82.64	88.42	84.40	3.50
		540	85.65	85.33	90.60	87.20	2.96
		660	87.16	87.16	92.58	88.97	3.13
		1200	95.25	92.95	98.44	95.55	2.76
		1440	89.87	88.48	94.26		

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Solvent	1:5						
		5	49.54	62.87	60.70	57.70	7.15
		10	62.11	66.60	66.45	65.05	2.55
		15	69.62	73.98	72.85	72.15	2.26
		20	75.75	78.16	76.61	76.84	1.22
		30	81.55	83.16	81.54	82.09	0.93
		45	86.00	87.68	86.41	86.70	0.88
		60	90.45	91.08	85.59	89.04	3.00
		90	92.28	91.58	91.20	91.69	0.55
		120	94.25	95.17	94.24	94.55	0.53
		180	97.01	97.79	96.23	97.01	0.78
		240	98.08	98.93	96.60	97.87	1.18
		300	98.36	99.22	96.68	98.09	1.29
		360	98.44	99.63	97.17	98.41	1.23
		420	97.39	98.46	95.69	97.18	1.40
		540	95.55	97.75	97.04	96.78	1.12
		660	95.84	96.49	94.44	95.59	1.04
		1200	92.71	93.71	91.37	92.60	1.17
Solvent	1:10						
		5.00	39.96	49.79	54.70	48.15	7.51
		10.00	70.05	75.18	71.04	72.09	2.72
		15.00	76.94	80.00	76.82	77.92	1.80
		20.00	81.90	83.25	79.29	81.48	2.01
		30.00	85.70	85.85	83.45	85.00	1.34
		45.00	89.66	89.44	87.11	88.74	1.41
		60.00	91.37	92.07	90.15	91.19	0.97
		90.00	94.03	95.79	93.97	94.60	1.04
		120.00	94.75	97.29	94.68	95.57	1.49
		180.00	96.53	100.18	95.46	97.39	2.48
		240.00	95.69	100.20	95.61	97.17	2.63
		300.00	94.63	98.50	94.71	95.95	2.21
		360.00	93.56	98.99	94.63	95.73	2.88

Table 51 Percent dissolved of nifedipine-poloxamer407 prepared by kneading method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Kneading	1:1						
		5	21.12	19.22	20.62	20.32	0.99
		10	32.60	31.25	33.50	32.45	1.13
		15	39.53	39.45	42.07	40.35	1.49
		20	45.11	45.46	46.74	45.77	0.86
		30	54.20	53.99	53.51	53.90	0.36
		45	59.85	61.05	61.54	60.81	0.87
		60	65.36	65.80	78.28	69.81	7.34
		90	73.32	73.32	86.87	77.84	7.82
		120	76.65	98.23	97.94	90.94	12.37
		180	82.64	96.37	108.17	95.73	12.78
		240	86.67	86.90	110.62	94.73	13.76
		300	89.72	88.19	112.39	96.77	13.55
		360	90.08	90.50	113.86	98.15	13.61
		420	90.93	91.49	114.15	98.86	13.25
		540	92.27	92.91	116.89	100.69	14.03
		660	94.03	93.48	116.98	101.50	13.41
		1200	98.05	97.78	120.58	105.47	13.09
		1440	97.25	97.32	120.33	104.97	13.30
Kneading	1:3						
		5	25.32	27.01	26.43	26.25	0.86
		10	34.02	33.81	34.26	34.03	0.23
		15	39.10	40.45	40.18	39.91	0.71
		20	43.63	46.65	45.60	45.29	1.54
		30	51.44	54.13	53.32	52.96	1.38
		45	58.98	61.96	61.09	60.68	1.53
		60	64.51	68.39	67.13	66.68	1.98
		90	71.55	74.81	73.92	73.43	1.68
		120	83.80	79.82	82.64	82.09	2.05
		180	83.80	85.61	85.56	84.99	1.03
		240	87.24	89.78	89.41	88.81	1.37
		300	90.56	90.02	91.21	90.60	0.59
		360	90.36	93.25	92.74	92.12	1.54
		420	91.56	93.97	93.71	93.08	1.32
		540	93.40	95.18	95.25	94.61	1.04
		660	95.80	96.87	97.31	96.66	0.78
		1200	97.25	98.45	98.84	98.18	0.83
		1440	97.05	98.13	98.58	97.92	0.79

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
Kneading	1:5						
		5.00	26.10	27.30	30.10	27.83	2.05
		10.00	35.64	35.02	36.94	35.87	0.98
		15.00	40.75	40.47	41.73	40.98	0.66
		20.00	44.56	45.76	46.68	45.67	1.06
		30.00	51.25	52.80	52.52	52.19	0.83
		45.00	58.58	59.50	58.45	58.84	0.57
		60.00	63.46	69.10	63.95	65.50	3.12
		90.00	70.84	76.23	69.46	72.18	3.58
		120.00	74.68	82.98	74.68	77.45	4.79
		180.00	81.79	91.26	81.94	85.00	5.42
		240.00	85.55	94.46	84.50	88.17	5.47
		300.00	88.24	97.28	88.59	91.37	5.12
		360.00	90.45	98.28	90.24	92.99	4.59
		420.00	90.93	99.34	91.94	94.07	4.59
		540.00	92.84	100.96	96.31	96.71	4.07
		660.00	94.97	105.39	95.34	98.57	5.91
		1200.00	98.23	105.10	100.69	101.34	3.48
		1440.00	116.09	96.87	98.95	103.97	10.55
Kneading	1:10						
		5.00	8.28	44.92	54.04	35.75	24.22
		10.00	66.71	71.27	73.43	70.47	3.43
		15.00	76.65	78.07	80.41	78.38	1.90
		20.00	81.19	82.19	83.60	82.32	1.21
		30.00	86.27	85.15	88.67	86.69	1.80
		45.00	90.34	85.65	87.43	87.81	2.37
		60.00	91.01	90.63	91.20	90.95	0.29
		90.00	95.72	94.32	95.93	95.32	0.88
		120.00	97.00	94.62	98.13	96.58	1.79
		180.00	98.20	96.79	100.45	98.48	1.85
		240.00	98.49	97.09	102.73	99.44	2.94
		300.00	99.05	97.01	102.59	99.55	2.82
		360.00	100.54	98.43	104.21	101.06	2.93
		420.00	98.94	96.12	104.65	99.90	4.35
		540.00	97.73	94.71	103.45	98.63	4.44
		660.00	99.63	96.81	105.20	100.55	4.27

Table 52 Percent dissolved of nifedipine-β-cyclodextrin prepared by physical mixing.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:1						
		5	16.32	18.31	17.50	17.38	1.00
		10	18.97	18.70	18.92	18.86	0.14
		15	20.09	20.39	20.24	20.24	0.15
		20	22.40	22.24	22.90	22.51	0.34
		30	27.04	26.00	27.56	26.86	0.79
		45	27.72	32.57	33.97	31.42	3.28
		60	36.43	37.90	40.92	38.42	2.29
		90	38.16	46.38	51.04	45.19	6.52
		120	46.03	53.27	59.03	52.78	6.52
		180	56.96	61.91	69.75	62.87	6.45
		240	64.88	67.40	74.57	68.95	5.03
		300	72.95	72.07	79.24	74.75	3.91
		360	74.83	74.30	82.50	77.21	4.59
		420	76.89	75.71	83.47	78.69	4.18
		540	82.06	80.21	87.23	83.16	3.64
		660	83.78	82.80	89.68	85.42	3.72
		1200	88.45	90.25	96.69	91.80	4.33
		1440	90.09	90.97	96.81	92.62	3.65
physical mixing	1:3						
		5	16.41	16.83	17.25	16.83	0.42
		10	19.80	20.99	21.42	20.74	0.84
		15	21.99	23.54	24.46	23.33	1.25
		20	24.25	25.60	26.44	25.43	1.10
		30	28.48	31.29	31.58	30.45	1.71
		45	33.90	38.40	36.10	36.13	2.25
		60	37.93	44.06	41.52	41.17	3.08
		90	44.97	53.70	49.98	49.55	4.38
		120	49.84	60.63	55.14	55.21	5.40
		180	58.79	69.78	62.81	63.80	5.56
		240	62.84	73.77	72.49	69.70	5.98
		300	66.22	76.94	76.81	73.33	6.15
		360	68.70	79.29	81.68	76.56	6.91
		420	71.03	80.98	84.23	78.75	6.88
		540	74.21	84.01	87.69	81.97	6.97
		660	75.20	84.88	90.38	83.48	7.68
		1200	80.48	91.20	96.50	89.40	8.16
		1440	78.77	88.64	94.65	87.35	8.02

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical muxing	1:5						
		5	11.65	13.13	12.98	12.59	0.81
		10	17.53	19.09	19.72	18.78	1.13
		15	21.92	21.98	25.79	23.23	2.22
		20	25.87	25.81	29.25	26.98	1.97
		30	30.11	30.03	34.89	31.68	2.78
		45	35.31	35.88	41.31	37.50	3.31
		60	39.06	40.04	45.76	41.62	3.62
		90	44.28	46.45	51.47	47.40	3.68
		120	49.92	49.64	55.55	51.71	3.33
		180	55.00	56.96	63.39	58.45	4.39
		240	59.81	61.92	64.96	62.23	2.59
		300	62.21	64.54	67.85	64.87	2.83
		360	63.69	67.36	70.32	67.12	3.32
		420	66.58	68.92	70.68	68.73	2.06
		540	71.16	71.10	73.99	72.08	1.65
		660	72.17	72.24	74.79	73.07	1.49
		1200	79.00	77.45	80.00	78.81	1.28
		1440	77.91	77.06	78.90	77.96	0.92
physical muxing	1:10						
		5	18.87	21.27	22.74	20.96	1.96
		10	27.89	30.92	32.13	30.31	2.19
		15	32.57	35.81	36.53	34.97	2.11
		20	37.32	39.48	39.56	38.79	1.27
		30	42.16	42.94	45.75	43.62	1.89
		45	48.00	49.34	51.54	49.63	1.79
		60	51.96	53.24	55.78	53.66	1.94
		90	59.14	58.24	61.27	59.55	1.56
		120	63.74	62.76	66.36	64.28	1.86
		180	69.45	69.48	70.17	69.70	0.41
		240	73.27	70.46	73.50	72.41	1.69
		300	74.84	74.35	75.26	74.81	0.45
		360	77.16	76.97	77.10	77.08	0.10
		420	79.00	78.17	78.17	78.45	0.48
		540	80.84	80.29	79.86	80.33	0.49
		660	83.58	82.41	82.32	82.77	0.70
		1200	87.50	85.05	86.44	86.33	1.23
		1440	88.51	85.77	88.36	87.55	1.54

Table 53 Percent dissolved of nifedipine-β-cyclodextrin prepared by kneading method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:1						
		5	17.38	16.18	16.39	16.65	0.64
		10	18.52	21.67	23.70	21.30	2.61
		15	24.28	26.68	29.43	26.80	2.58
		20	28.88	31.35	34.16	31.46	2.64
		30	36.21	37.69	41.84	38.58	2.92
		45	41.22	45.10	49.25	45.19	4.02
		60	47.22	49.34	55.61	50.72	4.36
		90	54.33	56.66	62.37	57.79	4.14
		120	60.13	63.51	67.46	63.70	3.67
		180	65.57	69.16	74.86	69.86	4.68
		240	69.31	74.52	78.20	74.01	4.46
		300	71.44	78.06	81.86	77.12	5.27
		360	74.40	80.40	83.43	79.41	4.60
		420	79.98	84.85	85.40	83.41	2.98
		540	78.32	85.37	87.52	83.74	4.81
		660	84.50	87.33	90.71	87.51	3.11
		1200	90.01	94.23	95.93	93.39	3.05
		1440	88.35	94.26	94.20	92.27	3.40
kneading	1:3						
		5	13.03	13.31	16.75	14.37	2.07
		10	23.83	25.45	27.08	25.46	1.62
		15	33.36	32.60	33.81	33.26	0.61
		20	37.07	38.33	40.01	38.47	1.47
		30	43.40	47.98	47.21	46.19	2.45
		45	49.05	55.11	53.70	52.62	3.17
		60	58.02	61.89	58.37	59.43	2.14
		90	58.54	67.04	63.79	63.13	4.29
		120	65.21	74.37	68.59	69.39	4.63
		180	66.86	78.13	72.83	72.61	5.64
		240	71.85	82.86	77.42	77.37	5.50
		300	73.14	84.15	78.15	78.48	5.51
		360	74.20	85.28	80.26	79.91	5.55
		420	76.31	87.67	81.81	81.93	5.68
		540	78.07	89.37	84.00	83.81	5.65
		660	79.15	89.66	84.09	84.30	5.26
		1200	84.15	91.92	88.43	88.17	3.89
		1440	83.34	91.66	89.46	88.15	4.31

Metho1	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:5						
		5	17.39	17.81	19.28	18.16	0.99
		10	30.32	31.52	35.32	32.39	2.61
		15	38.46	39.17	40.31	39.31	0.93
		20	43.77	44.05	44.97	44.26	0.63
		30	50.17	51.24	50.52	50.65	0.54
		45	56.38	57.45	57.08	56.97	0.55
		60	62.81	60.50	62.24	61.85	1.20
		90	68.32	66.35	67.33	67.33	0.99
		120	71.99	69.32	72.47	71.26	1.70
		180	76.02	73.89	76.85	75.59	1.52
		240	81.16	77.22	84.04	80.81	3.42
		300	82.32	78.57	81.63	80.84	2.00
		360	82.88	80.90	83.79	82.52	1.48
		420	84.57	83.58	85.62	84.59	1.02
		540	86.47	96.71	87.04	90.07	5.76
		660	87.19	86.34	88.11	87.21	0.88
		1200	92.21	92.61	92.91	92.58	0.35
		1440	91.74	94.41	94.89	93.68	1.70
kneading	1:10						
		5	22.94	22.67	23.04	22.88	0.19
		10	39.13	38.63	39.28	39.02	0.34
		15	47.39	47.82	48.09	47.77	0.35
		20	52.34	51.28	52.33	51.98	0.61
		30	60.19	60.04	60.73	60.32	0.36
		45	63.50	66.63	65.73	65.29	1.61
		60	66.93	72.29	70.31	69.84	2.71
		90	71.36	77.57	75.22	74.72	3.14
		120	73.80	81.08	78.23	77.70	3.67
		180	76.87	85.30	81.91	81.36	4.24
		240	78.87	88.38	84.47	83.91	4.78
		300	81.45	92.02	87.61	87.03	5.31
		360	81.75	92.54	88.03	87.44	5.42
		420	82.25	93.32	88.68	88.08	5.56
		540	83.34	94.70	89.92	89.32	5.70
		660	83.22	94.93	89.97	89.37	5.88

Table 54 Percent dissolved of nifedipine-2-hydroxypropyl-β-cyclodextrin prepared by physical mixing.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:1						
		5	18.45	18.45	18.38	18.43	0.04
		10	20.16	22.62	21.28	21.36	1.23
		15	21.79	24.04	23.76	23.20	1.23
		20	25.94	27.06	26.22	26.41	0.59
		30	29.75	32.97	30.95	31.22	1.63
		45	35.87	39.53	34.83	36.74	2.47
		60	44.75	44.97	38.63	42.79	3.60
		90	48.38	53.07	45.24	48.90	3.94
		120	56.11	59.15	50.62	55.30	4.32
		180	60.85	66.34	56.89	61.36	4.74
		240	65.16	70.58	62.27	66.00	4.22
		300	67.92	74.33	65.02	69.09	4.76
		360	72.36	76.88	67.77	72.34	4.55
		420	74.84	77.52	68.71	73.69	4.52
		540	78.78	80.33	72.01	77.04	4.43
		660	81.05	82.11	74.13	79.10	4.33
		1200	88.02	89.08	80.60	85.90	4.62
		1440	88.84	90.94	82.33	87.37	4.49
physical mixing	1:3						
		5	20.55	20.27	20.89	20.57	0.31
		10	25.37	24.32	27.26	25.65	1.49
		15	28.55	26.79	30.95	28.76	2.09
		20	32.92	29.68	34.19	32.26	2.33
		30	39.96	35.72	39.83	38.50	2.41
		45	46.73	41.80	45.68	44.73	2.60
		60	52.67	48.50	48.94	50.03	2.29
		90	59.37	58.00	54.92	57.43	2.28
		120	66.00	62.91	60.43	63.11	2.79
		180	71.79	70.30	64.60	68.90	3.79
		240	75.61	73.91	66.87	72.13	4.64
		300	78.08	76.24	69.62	74.65	4.45
		360	81.40	78.92	71.74	77.35	5.02
		420	83.81	81.19	72.87	79.29	5.71
		540	86.21	84.00	74.99	81.73	5.94
		660	86.99	85.64	76.12	82.92	5.92
		1200	93.81	89.87	82.23	88.64	5.89
		1440	91.24	89.20	79.62	86.69	6.20

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
physical mixing	1:5						
		5	27.67	20.98	19.72	22.79	4.27
		10	33.29	26.00	24.46	27.92	4.72
		15	43.49	30.46	28.41	34.12	8.18
		20	45.79	34.97	29.70	36.82	8.20
		30	56.33	41.03	33.56	43.64	11.61
		45	61.08	48.57	39.90	49.85	10.65
		60	70.52	53.67	43.45	55.88	13.67
		90	85.16	61.69	47.96	64.94	18.82
		120	100.40	66.58	50.85	72.61	25.32
		180	96.98	73.27	55.57	75.27	20.78
		240	101.87	79.76	59.24	80.29	21.32
		300	111.02	82.32	61.23	84.86	24.99
		360	108.76	85.63	64.18	86.19	22.29
		420	109.66	86.91	65.39	87.32	22.13
		540	113.45	90.58	67.86	90.63	22.80
		660	114.81	92.29	70.13	92.41	22.34
		1200	119.90	109.72	77.80	102.47	21.97
		1440	118.24	109.25	76.86	101.45	21.77
physical mixing	1:10						
		5	20.76	22.04	21.74	21.51	0.67
		10	28.51	28.75	28.46	28.57	0.16
		15	34.11	33.42	33.27	33.60	0.45
		20	37.57	35.41	36.32	36.43	1.09
		30	43.21	40.47	42.72	42.13	1.46
		45	49.33	45.90	48.15	47.79	1.74
		60	53.93	48.88	54.14	52.32	2.98
		90	60.42	63.56	61.34	61.77	1.62
		120	65.36	59.43	66.35	63.71	3.74
		180	70.93	66.07	72.42	69.81	3.32
		240	75.31	71.16	77.00	74.49	3.01
		300	77.09	73.37	79.71	76.72	3.19
		360	79.42	74.84	81.47	78.58	3.39
		420	80.41	89.53	82.76	84.23	4.74
		540	82.32	81.61	85.36	83.10	1.99
		660	83.53	85.07	86.85	85.15	1.66
		1200	87.75	89.04	92.63	89.81	2.53
		1440	87.42	88.64	92.59	89.55	2.70

Table 55 . Percent dissolved of nifedipine-2-hydroxypropyl-β-cyclodextrin prepared by solvent method.

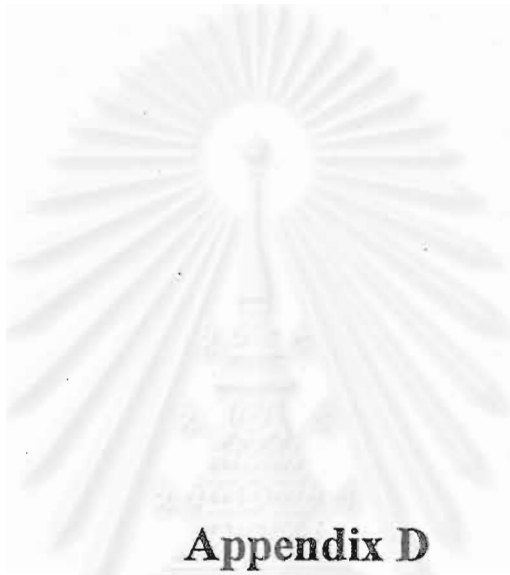
Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
solvent	1:1						
		5	16.84	17.82	17.89	17.51	0.59
		10	19.67	22.27	22.55	21.49	1.59
		15	25.09	27.34	27.69	26.71	1.41
		20	28.70	32.50	32.43	31.21	2.18
		30	37.43	40.96	39.33	39.24	1.76
		45	42.59	47.67	47.09	45.79	2.78
		60	47.18	59.10	54.93	53.74	6.05
		90	57.54	65.15	65.38	62.69	4.46
		120	62.94	69.47	72.67	68.36	4.96
		180	69.90	79.91	80.22	76.68	5.87
		240	79.73	85.51	84.76	83.33	3.15
		300	81.09	90.61	88.92	86.88	5.08
		360	84.13	92.10	91.20	89.14	4.37
		420	83.50	97.75	92.54	91.26	7.21
		540	88.86	94.12	98.17	93.72	4.67
		660	87.46	101.53	98.21	95.73	7.35
		1200	94.48	107.26	103.75	101.83	6.60
		1440	96.22	106.11	102.88	101.74	5.05
solvent	1:3						
		5	18.94	20.20	19.84	19.66	0.65
		10	24.16	27.11	25.28	25.52	1.49
		15	29.16	33.32	30.86	31.11	2.09
		20	33.55	38.62	34.82	35.66	2.64
		30	42.71	46.51	40.52	43.25	3.03
		45	55.46	54.48	47.71	52.55	4.22
		60	62.34	60.35	52.66	58.45	5.11
		90	70.73	70.56	61.18	67.49	5.47
		120	77.93	76.85	69.30	74.70	4.70
		180	88.64	85.32	76.58	83.51	6.23
		240	96.14	88.81	82.15	89.03	7.00
		300	102.43	93.60	85.90	93.98	8.27
		360	104.57	95.59	89.37	96.51	7.64
		420	107.81	96.72	91.42	98.65	8.37
		540	115.29	98.92	93.07	102.42	11.52
		660	117.57	100.62	97.58	105.26	10.77
		1200	122.92	104.98	105.89	111.27	10.10
		1440	121.70	104.52	105.53	110.58	9.64

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
solvent	1:5						
		5	14.72	15.57	15.99	19.91	1.32
		10	18.39	20.76	20.57	23.52	2.25
		15	21.07	25.51	23.96	26.88	2.59
		20	24.04	29.11	27.49	31.76	2.99
		30	28.48	34.32	32.49	37.41	2.93
		45	34.05	39.41	38.77	42.19	2.05
		60	39.84	43.58	43.15	48.01	1.08
		90	46.81	48.92	48.31	54.19	1.50
		120	52.61	54.37	55.58	62.69	1.83
		180	60.99	62.47	64.62	73.69	4.63
		240	74.03	68.90	78.14	77.02	4.48
		300	75.50	73.49	82.06	80.73	4.90
		360	78.52	77.32	86.35	84.28	4.54
		420	83.25	80.35	89.25	88.95	4.92
		540	87.41	84.99	94.46	93.92	5.54
		660	91.58	89.94	100.25	102.83	6.71
		1200	100.58	97.54	110.37	100.53	7.67
		1440	96.30	95.92	109.38	100.53	7.67
solvent	1:10						
		5	28.12	29.24	28.97	28.78	0.58
		10	44.42	42.59	42.53	43.18	1.07
		15	53.13	50.11	51.37	51.54	1.52
		20	57.88	57.09	58.22	57.73	0.58
		30	69.07	64.92	65.84	66.61	2.18
		45	76.36	72.12	72.27	73.58	2.41
		60	83.55	76.51	76.30	78.79	4.13
		90	97.32	82.64	80.74	86.90	9.08
		120	99.47	85.20	85.89	90.19	8.05
		180	104.96	90.97	89.36	95.10	8.58
		240	109.42	93.96	92.81	98.73	9.28
		300	115.78	96.49	93.88	102.05	11.96
		360	117.10	98.70	95.86	103.89	11.53
		420	117.43	99.20	96.08	104.24	11.53
		540	116.80	100.47	96.93	104.73	10.60
		660	119.47	101.69	100.72	107.36	10.50
		1200	117.66	100.51	100.48	106.21	9.91
		1440	115.70	99.44	97.61	104.25	9.96

Table 56 Percent dissolved of nifedipine-2-hydroxypropyl-β-cyclodextrin prepared by kneading method.

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:1						
		5	20.25	20.10	19.47	19.94	0.41
		10	30.89	30.45	29.39	30.24	0.77
		15	40.40	37.71	36.15	38.09	2.15
		20	45.11	43.06	40.85	43.01	2.13
		30	54.61	50.14	47.45	50.73	3.62
		45	64.55	57.11	53.49	58.38	5.64
		60	69.12	62.02	58.75	63.30	5.30
		90	79.54	69.11	63.23	70.63	8.26
		120	83.41	73.95	67.70	75.02	7.91
		180	87.32	78.29	72.39	79.33	7.52
		240	96.60	83.05	76.02	85.22	10.46
		300	97.92	86.83	78.15	87.63	9.91
		360	103.93	88.69	80.15	90.92	12.05
		420	107.87	91.54	81.01	93.47	13.53
		540	107.47	91.84	79.62	92.98	13.96
		660	108.74	92.91	82.16	94.60	13.37
		1320	117.39	99.77	86.48	101.21	15.51
		1440	115.88	97.34	85.09	99.43	15.50
kneading	1:3						
		5	19.53	21.24	21.60	20.79	1.11
		10	32.62	32.70	33.63	32.98	0.56
		15	42.89	41.25	41.97	42.04	0.82
		20	48.58	47.58	47.15	47.77	0.73
		30	60.89	55.03	54.67	56.86	3.49
		45	67.02	61.63	60.14	62.93	3.62
		60	69.76	66.52	63.88	66.72	2.95
		90	80.64	73.04	68.25	73.98	6.25
		120	83.04	78.15	72.56	77.91	5.25
		180	86.62	81.02	74.80	80.81	5.92
		240	90.99	86.04	79.51	85.51	5.76
		300	94.16	85.71	79.04	86.30	7.58
		360	98.90	87.49	80.54	88.98	9.27
		420	96.77	88.21	81.75	88.91	7.54
		540	97.48	88.65	83.04	89.72	7.28
		660	99.64	90.66	83.50	91.27	8.08
		1200	102.52	94.11	87.22	94.62	7.66
		1440	101.68	95.55	87.60	94.94	7.06

Method	Drug : Carrier ratio	Time (min)	% Drug dissolved			Mean	SD.
			# 1	# 2	# 3		
kneading	1:5						
		5	23.06	26.31	27.53	25.63	2.31
		10	37.75	39.71	39.29	38.92	1.03
		15	46.70	47.44	46.41	46.85	0.53
		20	53.82	54.69	52.37	53.63	1.17
		30	66.70	61.87	59.98	62.85	3.47
		45	71.97	70.70	65.06	69.24	3.68
		60	77.04	76.02	69.92	74.33	3.85
		90	82.33	81.96	76.01	80.10	3.55
		120	83.95	85.88	78.79	82.87	3.67
		180	89.94	90.81	82.04	87.60	4.83
		240	93.30	92.07	83.94	89.77	5.09
		300	93.46	94.02	85.39	90.96	4.83
		360	95.70	94.53	86.12	92.12	5.23
		420	96.43	97.50	87.28	93.74	5.62
		540	98.58	96.88	88.16	94.54	5.59
		660	97.32	98.60	88.17	94.70	5.69
		1200	99.00	101.37	90.50	96.96	5.72
		1440	100.01	101.96	88.56	96.84	7.24
kneading	1:10						
		5	18.49	31.92	32.77	27.73	8.01
		10	47.04	47.20	47.77	47.34	0.39
		15	55.29	54.65	54.93	54.96	0.32
		20	59.63	58.92	59.42	59.32	0.37
		30	67.10	65.23	67.74	66.69	1.30
		45	73.03	69.71	72.66	71.80	1.82
		60	77.62	72.67	76.26	75.52	2.56
		90	83.17	82.14	82.22	82.51	0.57
		120	86.20	84.85	86.91	85.98	1.05
		180	89.37	86.58	89.59	88.51	1.68
		240	92.10	90.39	91.68	91.39	0.89
		300	94.48	90.26	94.34	93.03	2.40
		360	95.43	91.86	96.23	94.51	2.33
		420	96.30	91.31	95.95	94.52	2.78
		540	96.83	92.44	95.53	94.93	2.26
		660	96.69	93.37	95.52	95.19	1.68
		1440	0.14	0.13	0.14	0.14	0.01



Appendix D

Two-way ANOVA of dissolution rate constant

Table 57 Two way analysis of variance for nifedipine-PEG4000 system.

Analysis of Variance (Two way)

PEG 4000

PEG 4000	Dissolution rate constant					
	Method (A)				Grand Total	Mean total
Ratio (B)	Melt	Solvent	Knead	Phys		
1:1						
Chamber 1	0.0829	0.0681	0.0906	0.0735	0.3151	0.0788
Chamber 2	0.0886	0.0763	0.0804	0.0658	0.3111	0.0778
Chamber 3	0.0859	0.0863	0.0854	0.0804	0.3380	0.0845
Total	0.2574	0.2307	0.2564	0.2197	0.9642	
Mean	0.0858	0.0769	0.0855	0.0732		0.0804
1:3						
Chamber 1	0.0790	0.1011	0.0841	0.0497	0.3139	0.0785
Chamber 2	0.0812	0.0991	0.0872	0.0467	0.3142	0.0786
Chamber 3	0.0843	0.0958	0.0784	0.0674	0.3259	0.0815
Total	0.2445	0.2960	0.2497	0.1638	0.9540	
Mean	0.0815	0.0987	0.0832	0.0546		0.0795
1:5						
Chamber 1	0.1089	0.1055	0.1166	0.0757	0.4067	0.1017
Chamber 2	0.1169	0.1052	0.0986	0.0731	0.3938	0.0985
Chamber 3	0.1073	0.1008	0.1059	0.0792	0.3932	0.0983
Total	0.3331	0.3115	0.3211	0.2280	1.1937	
Mean	0.1110	0.1038	0.1070	0.0760		0.0995
1:10						
Chamber 1	0.1259	0.1122	0.1140	0.0996	0.4517	0.1129
Chamber 2	0.1268	0.1237	0.1147	0.0938	0.4590	0.1148
Chamber 3	0.1145	0.1137	0.0871	0.1030	0.4183	0.1046
Total	0.3672	0.3496	0.3158	0.2964	1.3290	
Mean	0.1224	0.1165	0.1053	0.0988		0.1107
Grand total	1.2022	1.1878	1.1430	0.9079	4.4409	
Mean total	0.1002	0.0990	0.0953	0.0757		

ANOVA Table

Source	df	SS	Mean Square	F cal	F critical value	Significance
Between method	3	4.71E-03	1.57E-03	30.99	9.28	Yes
Between ratio	3	8.38E-03	2.79E-03	55.17	3.86	Yes
Method-ratio interaction	9	1.97E-03	2.19E-04	4.33	2.27	Yes
Error	32	1.62E-03	5.06E-05			
Total	47	0.0167	3.55E-04		$\alpha = 0.05$	

Table 58 LSR test of PEG4000

Test between method

Duncan's test

Dissolution rate constant

Melt	Solvent	Knead	Phys
0.1002	0.0990	0.0953	0.0757

Sorted;least to most value

Phys	Knead	Solvent	Melt
0.0757	0.0953	0.0990	0.1002

Difference with next values

Phys	0.0196	0.0233	0.0245
	Knead	0.0037	0.0049
		Solvent	0.0012

$LSR = SSR_{table} \times S_x$

LSR =	0.0058	0.0061	0.0063

Difference vs LSR test

Phys	Knead	Solvent	Melt
0.0757	0.0953	0.0990	0.1002

	0.0196	0.0233	0.0245
Phys	***0.0138***	***0.0172***	***0.0182***
		0.0037	0.0049
	Knead	**-0.0021**	**-0.0012**
			0.0012
		Solvent	-0.0046

Test between ratio

Duncan's test

1:1	1:3	1:5	1:10
0.0804	0.0795	0.0995	0.1107

Dissolution rate constant

Sorted;least to most value

1:3	1:1	1:5	1:10
0.0795	0.0804	0.0995	0.1107

Difference with next values

1:3	0.0009	0.0200	0.0312
	1:1	0.0191	0.0303
		1:5	0.0112

$LSR = SSR_{table} \times S_x$ LSR = 0.0058 0.0061 0.0063

Difference vs LSR test

1:3	1:1	1:5	1:10
0.0795	0.0804	0.0995	0.1107

	0.0009	0.0200	0.0312
1:3	-0.0049	***0.0139***	***0.0249***
		0.0191	0.0303
	1:1	***0.0133***	***0.0242***
			0.0112
		1:5	***0.0054***

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 59 LSR test of method-ratio interaction.

Test method-ratio interaction

Duncan's test

Dissoultion rate constant

Melt 1:1	Melt 1:3	Melt 1:5	Melt 1:10	Solvent 1:1	Solvent 1:3	Solvent 1:5	Solvent 1:10	Knead 1:1	Knead 1:3	Knead 1:5	Knead 1:10	Phys 1:1	Phys 1:3	Phys 1:5	Phys 1:10
0.0858	0.0815	0.1110	0.1224	0.0769	0.0987	0.1038	0.1197	0.0855	0.0832	0.1070	0.1053	0.0732	0.0546	0.0760	0.0988

Sorted;least to most value

Phys 1:3	Phys 1:1	Phys 1:5	Solvent 1:1	Melt 1:3	Knead 1:3	Knead 1:1	Melt 1:1	Solvent 1:3	Phys 1:10	Solvent 1:5	Knead 1:10	Knead 1:5	Melt 1:5	Solvent 1:10	Melt 1:10
0.0546	0.0732	0.0760	0.0769	0.0815	0.0832	0.0855	0.0858	0.0987	0.0988	0.1038	0.1053	0.1070	0.1110	0.1197	0.1224

$LSR = SSR_{table} \times S_x$

LSR =	0.0119	0.0125	0.0128	0.0131	0.0134	0.0135	0.0136	0.0138	0.0138	0.0140	0.0140	0.0140	0.0141	0.0141	0.0141

Difference vs LSR test

	Phys 1:3	Phys 1:1	Phys 1:5	Solvent 1:1	Melt 1:3	Knead 1:3	Knead 1:1	Melt 1:1	Solvent 1:3	Phys 1:10	Solvent 1:5	Knead 1:10	Knead 1:5	Melt 1:5	Solvent 1:10	Melt 1:10
Method	1:3	1:1	1:5	1:1	1:3	1:3	1:1	1:1	1:3	1:10	1:5	1:10	1:5	1:5	1:10	1:10
Mean	0.0546	0.0732	0.0760	0.0769	0.0815	0.0832	0.0855	0.0858	0.0987	0.0988	0.1038	0.1053	0.1070	0.1110	0.1197	0.1224
		0.0186	0.0214	0.0223	0.0269	0.0286	0.0309	0.0312	0.0441	0.0442	0.0492	0.0507	0.0524	0.0564	0.0651	0.0678
1:3		*0.0067*	*0.0089*	*0.0095*	*0.0138*	*0.0152*	*0.0174*	*0.0176*	*0.0303*	*0.0304*	*0.0352*	*0.0367*	*0.0384*	*0.0423*	*0.0510*	*0.0537*
			0.0028	0.0037	0.0083	0.0100	0.0123	0.0126	0.0255	0.0256	0.0306	0.0321	0.0338	0.0378	0.0465	0.0492
	1:1		-0.0091	-0.0088	-0.0045	-0.0031	-0.0011	-0.0009	*0.0119*	*0.0118*	*0.0168*	*0.0181*	*0.0198*	*0.0238*	*0.0324*	*0.0351*
				0.0009	0.0055	0.0072	0.0095	0.0098	0.0227	0.0228	0.0278	0.0293	0.0310	0.0350	0.0437	0.0464
		1:5		-0.0110	-0.0070	-0.0056	-0.0036	-0.0036	*0.0092*	*0.0092*	*0.0140*	*0.0155*	*0.0170*	*0.0210*	*0.0297*	*0.0323*
					0.0046	0.0063	0.0086	0.0089	0.0218	0.0219	0.0269	0.0284	0.0301	0.0341	0.0428	0.0455
			1:1		-0.0073	-0.0062	-0.0042	-0.0042	*0.0084*	*0.0084*	*0.0133*	*0.0148*	*0.0163*	*0.0201*	*0.0288*	*0.0315*
						0.0017	0.0040	0.0043	0.0172	0.0173	0.0223	0.0238	0.0255	0.0295	0.0382	0.0409
				1:3		-0.0102	-0.0085	-0.0085	*0.0041*	*0.0039*	*0.0088*	*0.0102*	*0.0117*	*0.0157*	*0.0242*	*0.0269*
							0.0023	0.0026	0.0155	0.0156	0.0206	0.0221	0.0238	0.0278	0.0365	0.0392
					1:3		-0.0096	-0.0099	*0.0027*	*0.0025*	*0.0073*	*0.0086*	*0.0102*	*0.0140*	*0.0227*	*0.0252*
								0.0003	0.0132	0.0133	0.0183	0.0198	0.0215	0.0255	0.0342	0.0369
							1:1	-0.0116	*0.0007*	*0.0005*	*0.0052*	*0.0064*	*0.0080*	*0.0119*	*0.0204*	*0.0231*
									0.0129	0.0130	0.0180	0.0195	0.0212	0.0252	0.0339	0.0366
								1:1	*0.0010*	*0.0005*	*0.0052*	*0.0064*	*0.0078*	*0.0117*	*0.0203*	*0.0228*
										0.0001	0.0051	0.0066	0.0083	0.0123	0.0210	0.0237
									1:3	-0.0118	-0.0074	-0.0062	-0.0048	-0.0011	*0.0075*	*0.0101*
											0.0050	0.0065	0.0082	0.0122	0.0209	0.0236
										1:10	-0.0069	-0.0060	-0.0046	-0.0009	*0.0075*	*0.0101*
												0.0015	0.0032	0.0072	0.0159	0.0186
											1:5	-0.0104	-0.0093	-0.0056	*0.0028*	*0.0062*
													0.0017	0.0057	0.0144	0.0171
												1:10	-0.0102	-0.0068	*0.0016*	*0.0040*
														0.0040	0.0127	0.0154
													1:5	-0.0079	*0.0002*	*0.0026*
															0.0087	0.0114
														1:5	-0.0032	-0.0011
																0.0027
															1:10	-0.0092
																1:10

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 60 Two way analysis of variance for nifedipine-PEG6000 system.

Analysis of Variance (Two way)
PEG 6000

PEG 6000	Dissolution rate constant					
	Method (A)				Grand Total	Mean total
Ratio (B)	Melt	Solvent	Knead	Phys		
1:1						
Chamber 1	0.0934	0.0697	0.0771	0.0672	0.3074	0.0769
Chamber 2	0.1010	0.0823	0.0754	0.0608	0.3195	0.0799
Chamber 3	0.0980	0.0863	0.0896	0.0633	0.3372	0.0843
Total	0.2924	0.2383	0.2421	0.1913	0.9641	
Mean	0.0975	0.0794	0.0807	0.0638		0.0803
1:3						
Chamber 1	0.0959	0.1079	0.0782	0.0844	0.3664	0.0916
Chamber 2	0.0909	0.1190	0.1003	0.0846	0.3948	0.0987
Chamber 3	0.0894	0.1141	0.0846	0.0843	0.3724	0.0931
Total	0.2762	0.3410	0.2631	0.2533	1.1336	
Mean	0.0921	0.1137	0.0877	0.0844		0.0945
1:5						
Chamber 1	0.1009	0.1145	0.1080	0.0895	0.4129	0.1032
Chamber 2	0.1169	0.1011	0.1079	0.0910	0.4169	0.1042
Chamber 3	0.1137	0.1300	0.1081	0.0829	0.4347	0.1087
Total	0.3315	0.3456	0.3240	0.2634	1.2645	
Mean	0.1105	0.1152	0.1080	0.0878		0.1054
1:10						
Chamber 1	0.1343	0.1282	0.1064	0.0816	0.4505	0.1126
Chamber 2	0.1224	0.1169	0.1256	0.0909	0.4558	0.1140
Chamber 3	0.1207	0.1439	0.1243	0.0861	0.4750	0.1188
Total	0.3774	0.3890	0.3563	0.2586	1.3813	
Mean	0.1258	0.1297	0.1188	0.0862		0.1151
Grand total	1.2775	1.3139	1.1855	0.9666	4.7435	
Mean total	0.1065	0.1095	0.0988	0.0806		

ANOVA table

Source	df	SS	Mean Square	F cal	F critical value	Significance
Between method	3	6.07E-03	2.02E-03	32.13	9.28	Yes
Between ratio	3	8.02E-03	2.67E-03	42.50	3.86	Yes
Method-ratio interaction	9	2.04E-03	2.27E-04	3.60	2.27	Yes
Error	32	2.01E-03	6.29E-05			
Total	47	0.0181	3.86E-04		$\alpha = 0.05$	

Table 61 LSR test of PEG6000

Test between method

Duncan's test

Dissolution rate constant

Melt	Solvent	Knead	Phys
0.1065	0.1096	0.0988	0.0806

Sorted; least to most value

Phys	Knead	Melt	Solvent
0.0806	0.0988	0.1065	0.1096

Difference with next values

Phys	0.0182	0.0259	0.0290
	Knead	0.0077	0.0108
		Melt	0.0031

$LSR = SSR_{table} \times S_x$

LSR =	0.0065	0.0068	0.0071

Difference vs LSR test

Phys	Knead	Melt	Solvent
0.0806	0.0988	0.1065	0.1096

	0.0182	0.0259	0.0290
Phys	***0.0117***	***0.0191***	***0.0219***
		0.0077	0.0108
	Knead	***0.0012***	***0.0040***
			0.0031
		Melt	-0.0034

Test between ratio

Duncan's test

Dissolution rate constant

1:1	1:3	1:5	1:10
0.0803	0.0945	0.1054	0.1151

Sorted;least to most values

1:1	1:3	1:5	1:10
0.0803	0.0945	0.1054	0.1151

Different with next values

1:1	0.0142	0.0251	0.0348
	1:3	0.0109	0.0206
		1:5	0.0097

$LSR = SSR_{table} \times S_x$

LSR =	0.0065	0.0068	0.0071

Difference vs LSR test

1:1	1:3	1:5	1:10
0.0803	0.0945	0.1054	0.1151

	0.0142	0.0251	0.0348
1:1	***0.0077***	***0.0183***	***0.0277***
		0.0109	0.0206
	1:3	***0.0044***	***0.0138***
			0.0097
		1:5	***0.0032***

Table 62 LSR test of method-ratio interaction (PEG6000)

Test method-ration interaction

Duncan's test

Dissolution rate constant	Melt	Melt	Melt	Melt	Solvent	Solvent	Solvent	Solvent	Knead	Knead	Knead	Knead	Phys	Phys	Phys	Phys
	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10
	0.0975	0.0921	0.1105	0.1258	0.0794	0.1137	0.1152	0.1297	0.0807	0.0877	0.1080	0.1188	0.0638	0.0735	0.0878	0.0862

Sorted; least to most value	Phys	Phys	Solvent	Knead	Phys	Knead	Phys	Melt	Melt	Knead	Melt	Solvent	Solvent	Knead	Melt	Solvent
	1:1	1:3	1:1	1:1	1:10	1:3	1:5	1:3	1:1	1:5	1:5	1:3	1:5	1:10	1:10	1:10
	0.0638	0.0735	0.0794	0.0807	0.0862	0.0877	0.0878	0.0921	0.0975	0.1080	0.1105	0.1137	0.1152	0.1188	0.1258	0.1297

$LSR = SSR_{table} \times S_x$	LSR =	0.0132	0.0139	0.0143	0.0147	0.0149	0.0151	0.0152	0.0153	0.0154	0.0156	0.0156	0.0157	0.0157	0.0157	0.0158

Difference vs LSR test

	Phys	Phys	Solvent	Knead	Phys	Knead	Phys	Melt	Melt	Knead	Melt	Solvent	Solvent	Knead	Melt	Solvent
Method	1:1	1:3	1:1	1:1	1:10	1:3	1:5	1:3	1:1	1:5	1:5	1:3	1:5	1:10	1:10	1:10
Mean	0.0638	0.0735	0.0794	0.0807	0.0862	0.0877	0.0878	0.0921	0.0975	0.1080	0.1105	0.1137	0.1152	0.1188	0.1258	0.1297

0	0.0097	0.0156	0.0169	0.0224	0.0239	0.0240	0.0283	0.0337	0.0442	0.0467	0.0499	0.0514	0.0550	0.0620	0.0659
1:1	-0.0035	*0.0017*	*0.0026*	*0.0077*	*0.0090*	*0.0089*	*0.0131*	*0.0184*	*0.0288*	*0.0311*	*0.0343*	*0.0357*	*0.0393*	*0.0463*	*0.0501*
	0	0.0059	0.0072	0.0127	0.0142	0.0143	0.0186	0.0240	0.0345	0.0370	0.0402	0.0417	0.0453	0.0523	0.0562
	1:3	-0.0073	-0.0067	-0.0016	-0.0005	-0.0006	*0.0035*	*0.0088*	*0.0192*	*0.0216*	*0.0246*	*0.0261*	*0.0296*	*0.0366*	*0.0405*
		0	0.0013	0.0068	0.0083	0.0084	0.0127	0.0181	0.0286	0.0311	0.0343	0.0358	0.0394	0.0464	0.0503
		1:1	-0.0119	-0.0071	-0.0060	-0.0063	-0.0022	*0.0030*	*0.0134*	*0.0158*	*0.0189*	*0.0202*	*0.0238*	*0.0307*	*0.0346*
			0	0.0055	0.0070	0.0071	0.0114	0.0168	0.0273	0.0298	0.0330	0.0345	0.0381	0.0451	0.0490
			1:1	-0.0077	-0.0069	-0.0072	-0.0033	*0.0019*	*0.0122*	*0.0146*	*0.0177*	*0.0191*	*0.0225*	*0.0295*	*0.0333*
				0	0.0015	0.0016	0.0059	0.0113	0.0218	0.0243	0.0275	0.0290	0.0326	0.0396	0.0435
				1:10	-0.0117	-0.0123	-0.0084	-0.0034	*0.0069*	*0.0092*	*0.0123*	*0.0137*	*0.0172*	*0.0240*	*0.0279*
					0	0.0001	0.0044	0.0098	0.0203	0.0228	0.0260	0.0275	0.0311	0.0381	0.0420
					1:3	-0.0131	-0.0095	-0.0045	*0.0056*	*0.0079*	*0.0109*	*0.0123*	*0.0158*	*0.0227*	*0.0264*
						0	0.0043	0.0097	0.0202	0.0227	0.0259	0.0274	0.0310	0.0380	0.0419
						1:5	-0.0089	-0.0042	*0.0059*	*0.0080*	*0.0110*	*0.0123*	*0.0158*	*0.0227*	*0.0265*
							)	0.0054	0.0159	0.0184	0.0216	0.0231	0.0267	0.0337	0.0376
							1:3	-0.0078	*0.0020*	*0.0041*	*0.0069*	*0.0082*	*0.0118*	*0.0185*	*0.0223*
								0	0.0105	0.0130	0.0162	0.0177	0.0213	0.0283	0.0322
								1:1	-0.0027	-0.0009	*0.0019*	*0.0030*	*0.0064*	*0.0132*	*0.0170*
									0	0.0025	0.0057	0.0072	0.0108	0.0178	0.0217
									1:5	-0.0107	-0.0082	-0.0071	-0.0039	*0.0029*	*0.0066*
										0	0.0032	0.0047	0.0083	0.0153	0.0192
										1:5	-0.0100	-0.0092	-0.0060	*0.0006*	*0.0043*
											0	0.0015	0.0051	0.0121	0.0160
											1:3	-0.0117	-0.0088	-0.0022	*0.0013*
												0	0.0036	0.0106	0.0145
												1:5	-0.0096	-0.0033	*0.0002*
													0	0.0070	0.0109
													1:10	-0.0062	-0.0030
														0	0.0039
														1:10	-0.0093
															0
															1:10

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 63 Two way analysis of varience for nifedipine-poloxamer188 system.

Analysis of Variance (Two way)

Poloxamer188

Poloxamer188	Dissolution rate constant					
	Method (A)				Grand Total	Mean total
Ratio (B)	Melt	Solvent	Knead	Phys		
1:1						
Chamber 1	0.1217	0.0914	0.0956	0.0853	0.3940	0.0985
Chamber 2	0.1264	0.0888	0.0959	0.0858	0.3969	0.0992
Chamber 3	0.1158	0.0938	0.0983	0.0939	0.4018	0.1005
Total	0.3639	0.2740	0.2898	0.2650	1.1927	
Mean	0.1213	0.0913	0.0966	0.0883		0.0994
1:3						
Chamber 1	0.2280	0.0867	0.0944	0.1029	0.5120	0.1280
Chamber 2	0.1974	0.0985	0.0878	0.1021	0.4858	0.1215
Chamber 3	0.2030	0.0857	0.0976	0.0922	0.4785	0.1196
Total	0.6284	0.2709	0.2798	0.2972	1.4763	
Mean	0.2095	0.0903	0.0933	0.0991		0.1230
1:5						
Chamber 1	0.2156	0.1221	0.1144	0.1068	0.5589	0.1397
Chamber 2	0.1911	0.1208	0.0789	0.1059	0.4967	0.1242
Chamber 3	0.1194	0.1239	0.1086	0.1060	0.4579	0.1145
Total	0.5261	0.3668	0.3019	0.3187	1.5135	
Mean	0.1754	0.1223	0.1006	0.1062		0.1261
1:10						
Chamber 1	0.1047	0.1499	0.1190	0.1004	0.4740	0.1185
Chamber 2	0.1044	0.1292	0.1732	0.1032	0.5100	0.1275
Chamber 3	0.1085	0.1658	0.1600	0.0695	0.5038	0.1260
Total	0.3176	0.4449	0.4522	0.2731	1.4878	
Mean	0.1059	0.1483	0.1507	0.0910		0.1240
Grand total	1.8360	1.3566	1.3237	1.1540	5.6703	
Mean total	0.1530	0.1131	0.1103	0.0962		

ANOVA table

Source	df	SS	Mean Square	F cal	F table	Significance
Between method	3	2.14E-02	7.14E-03	23.84	9.28	Yes
Between ratio	3	5.68E-03	1.89E-03	6.32	3.86	Yes
Method-ratio interaction	9	2.92E-02	3.25E-03	10.84	2.27	Yes
Error	32	9.58E-03	2.99E-04			
Total	47	0.0659	1.40E-03		$\alpha = 0.05$	

Table 64 LSR test of poloxamer188

Test between method

Duncan's test

Dissolution rate constant

Melt	Solvent	Knead	Phys
0.1530	0.1131	0.1103	0.0962

Sorted; least to most value

Phys	Knead	Solvent	Melt
0.0962	0.1103	0.1131	0.1530

$LSR = SSR_{table} \times S_x$

LSR =	0.0141	0.0149	0.0154

Difference vs LSR test

	Phys	Knead	Solvent	Melt
	0.0962	0.1103	0.1131	0.1530
		0.0141	0.0169	0.0568
Phys		-0.0000	***0.0020***	***0.0414***
			0.0028	0.0427
		Knead	-0.0113	***0.0278***
				0.0399
			Solvent	***0.0258***

Test between ratio

Duncan's test

Dissolution rate constant

1:1	1:3	1:5	1:10
0.0994	0.1230	0.1261	0.1240

Sorted; least to most value

1:1	1:3	1:10	1:5
0.0994	0.1230	0.1240	0.1261

Difference with next value

1:1	0.0236	0.0246	0.0267
	1:3	0.0010	0.0031
		1:10	0.0021

$LSR = SSR_{table} \times S_x$

LSR =	0.0141	0.0149	0.0154

Difference vs LSR test

	1:1	1:3	1:10	1:5
	0.0994	0.1230	0.1240	0.1261
		0.0236	0.0246	0.0267
	1:1	***0.0095***	***0.0097***	***0.0113***
			0.0010	0.0031
		1:3	-0.0131	-0.0118
				0.0021
			1:10	-0.0120

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 65 | Test of method-ratio interaction (poloxamer188)

Test method-ratio interaction

Duncan's test

Dissolution rate constant

Melt	Melt	Melt	Melt	Solvent	Solvent	Solvent	Solvent	Knead	Knead	Knead	Knead	Phys	Phys	Phys	Phys
1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10
0.1213	0.2095	0.1754	0.1059	0.0913	0.0903	0.1223	0.1483	0.0966	0.0933	0.1006	0.1507	0.0883	0.0991	0.1062	0.0910

Sorted; least to most value

Phys	Solvent	Phys	Solvent	Knead	Knead	Phys	Knead	Melt	Phys	Melt	Solvent	Solvent	Knead	Melt	Melt
1:1	1:3	1:10	1:1	1:3	1:1	1:3	1:5	1:10	1:5	1:1	1:5	1:10	1:10	1:5	1:3
0.0883	0.0903	0.0910	0.0913	0.0933	0.0966	0.0991	0.1006	0.1059	0.1062	0.1213	0.1223	0.1483	0.1507	0.1754	0.2095

$LSR = SSR_{table} \times S_r$ LSR = 0.0289 0.0304 0.0312 0.0320 0.0325 0.0329 0.0332 0.0335 0.0337 0.0340 0.0341 0.0342 0.0343 0.0343 0.0344

Difference vs LSR test

Method	Phys 1:1	Solvent 1:3	Phys 1:10	Solvent 1:1	Knead 1:3	Knead 1:1	Phys 1:3	Knead 1:5	Melt 1:10	Phys 1:5	Melt 1:1	Solvent 1:5	Solvent 1:10	Knead 1:10	Melt 1:5	Melt 1:3
Mean	0.0883	0.0903	0.0910	0.0913	0.0933	0.0966	0.0991	0.1006	0.1059	0.1062	0.1213	0.1223	0.1483	0.1507	0.1754	0.2095
		0.0020	0.0027	0.0030	0.0050	0.0083	0.0108	0.0123	0.0176	0.0179	0.0330	0.0340	0.0600	0.0624	0.0871	0.1212
1:1		-0.0269	-0.0277	-0.0282	-0.0270	-0.0242	-0.0221	-0.0209	-0.0159	-0.0158	-0.0010	-0.0001	*0.0258*	*0.0281*	*0.0528*	*0.0868*
			0.0007	0.0010	0.0030	0.0063	0.0088	0.0103	0.0156	0.0159	0.0310	0.0320	0.0580	0.0604	0.0851	0.1192
1:3			-0.0282	-0.0294	-0.0282	-0.0257	-0.0237	-0.0226	-0.0176	-0.0176	-0.0027	-0.0020	*0.0239*	*0.0262*	*0.0508*	*0.0849*
				0.0003	0.0023	0.0056	0.0081	0.0096	0.0149	0.0152	0.0303	0.0313	0.0573	0.0597	0.0844	0.1185
1:10				-0.0286	-0.0281	-0.0256	-0.0239	-0.0229	-0.0180	-0.0180	-0.0032	-0.0024	*0.0233*	*0.0256*	*0.0502*	*0.0842*
					0.0020	0.0053	0.0078	0.0093	0.0146	0.0149	0.0300	0.0310	0.0570	0.0594	0.0841	0.1182
1:1					-0.0269	-0.0251	-0.0234	-0.0227	-0.0179	-0.0180	-0.0032	-0.0025	*0.0233*	*0.0254*	*0.0500*	*0.0840*
						0.0033	0.0058	0.0073	0.0126	0.0129	0.0280	0.0290	0.0550	0.0574	0.0821	0.1162
1:3						-0.0258	-0.0246	-0.0239	-0.0194	-0.0196	-0.0049	-0.0042	*0.0126*	*0.0123*	*0.0335*	*0.0676*
							0.0025	0.0040	0.0093	0.0096	0.0247	0.0257	0.0517	0.0541	0.0788	0.1129
1:1							-0.0264	-0.0264	-0.0219	-0.0224	-0.0078	-0.0072	*0.0517*	*0.0541*	*0.0788*	*0.1129*
								0.0015	0.0068	0.0071	0.0222	0.0232	0.0492	0.0516	0.0763	0.1104
1:3								-0.0274	-0.0236	-0.0241	-0.0098	-0.0093	*0.0163*	*0.0184*	*0.0428*	*0.0767*
									0.0053	0.0056	0.0207	0.0217	0.0477	0.0501	0.0748	0.1089
1:5									-0.0236	-0.0248	-0.0105	-0.0103	*0.0152*	*0.0172*	*0.0416*	*0.0754*
										0.0003	0.0154	0.0164	0.0424	0.0448	0.0695	0.1036
1:10										-0.0286	-0.0150	-0.0148	*0.0104*	*0.0123*	*0.0366*	*0.0704*
											0.0151	0.0161	0.0421	0.0445	0.0692	0.1033
1:5											-0.0138	-0.0143	*0.0109*	*0.0125*	*0.0367*	*0.0704*
												0.0010	0.0270	0.0294	0.0541	0.0882
1:1												-0.0279	-0.0034	-0.0018	*0.0221*	*0.0557*
													0.0260	0.0284	0.0531	0.0872
1:5													-0.0029	-0.0020	*0.0219*	*0.0552*
														0.0024	0.0271	0.0612
1:10														-0.0265	-0.0033	*0.0300*
															0.0247	0.0588
1:10															-0.0042	*0.0284*
																0.0341
1:5																*0.0052*
1:3																

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 66 Two way analysis of varience for nifedipine-poloxamer288 system

Analysis of Variance (Two way)

Poloxamer288

Poloxamer288	Dissolution rate constant					
	Method (A)				Grand Total	Mean total
Ratio (B)	Melt	Solvent	Knead	Phys		
1:1						
Chamber 1	0.1004	0.1075	0.1069	0.0776	0.3924	0.0981
Chamber 2	0.0873	0.0939	0.0971	0.0980	0.3763	0.0941
Chamber 3	0.1010	0.0923	0.0977	0.1008	0.3918	0.0980
Total	0.2887	0.2937	0.3017	0.2764	1.1605	
Mean	0.0962	0.0979	0.1006	0.0921		0.0967
1:3						
Chamber 1	0.0933	0.1392	0.1038	0.1005	0.4368	0.1092
Chamber 2	0.1082	0.1029	0.0974	0.0871	0.3956	0.0989
Chamber 3	0.1051	0.1301	0.0990	0.0866	0.4208	0.1052
Total	0.3066	0.3722	0.3002	0.2742	1.2532	
Mean	0.1022	0.1241	0.1001	0.0914		0.1044
1:5						
Chamber 1	0.1551	0.1253	0.0988	0.1135	0.4927	0.1232
Chamber 2	0.1565	0.1131	0.0985	0.1086	0.4767	0.1192
Chamber 3	0.1998	0.1124	0.1024	0.1127	0.5273	0.1318
Total	0.5114	0.3508	0.2997	0.3348	1.4967	
Mean	0.1705	0.1169	0.0999	0.1116		0.1247
1:10						
Chamber 1	0.2714	0.1411	0.1316	0.1286	0.6727	0.1682
Chamber 2	0.1660	0.1673	0.1354	0.1100	0.5787	0.1447
Chamber 3	0.1614	0.1653	0.1272	0.0894	0.5433	0.1358
Total	0.5988	0.4737	0.3942	0.3280	1.7947	
Mean	0.1996	0.1579	0.1314	0.1093		0.1496
Grand total	1.7055	1.4904	1.2958	1.2134	5.7051	
Mean total	0.1421	0.1242	0.1080	0.1011		

ANOVA Table

Source	df	SS	Mean Square	F cal	F table	Significance
Between method	3	1.20E-02	4.01E-03	10.68	9.28	Yes
Between ratio	3	2.01E-02	6.70E-03	17.85	3.86	Yes
Method-ratio interaction	9	1.22E-02	1.36E-03	3.61	2.27	Yes
Error	32	1.20E-02	3.75E-04			
Total	47	0.0564	1.20E-03		$\alpha = 0.05$	

Table 67 LSR test of poloxamer288

Test between method

Duncan's test

Dissolution rate constant

Melt	Solvent	Knead	Phys
0.1421	0.1242	0.1080	0.1011

Sorte; Least to most value

Phys	Knead	Solvent	Melt
0.1011	0.1080	0.1242	0.1421

Difference with next values

Phys	0.0069	0.0231	0.0410
	Knead	0.0162	0.0341
		Solvent	0.0179

$LSR = SSR_{table} \times S_x$

LSR =	0.0158	0.0167	0.0172

Difference vs LSR test

Phys	Knead	Solvent	Melt
0.1011	0.1080	0.1242	0.1421

	0.0069	0.0231	0.0410
Phys	-0.0089	***0.0064***	***0.0238***
		0.0162	0.0341
	Knead	***0.0004***	***0.0174***
			0.0179
		Solvent	***0.0021***

Test between ratio

Duncan's test

Dissolution rate constant

1:1	1:3	1:5	1:10
0.0967	0.1044	0.1247	0.1496

Sorted; least to most value

1:1	1:3	1:5	1:10
0.0967	0.1044	0.1247	0.1496

Difference with next values

1:1	0.0077	0.0280	0.0529
	1:3	0.0203	0.0452
		1:5	0.0249

$LSR = SSR_{table} \times S_x$

LSR =	0.0158	0.0167	0.0172

Difference vs LSR test

1:1	1:3	1:5	1:10
0.0967	0.1044	0.1247	0.1496

	0.0077	0.0280	0.0529
1:1	-0.0081	***0.0113***	***0.0357***
		0.0203	0.0452
	1:3	***0.0045***	***0.0285***
			0.0249
		1:5	***0.0091***

Table 68 Test of method-ratio interaction (poloxamer288)

Test method-ratio interaction	

Duncan's test

Dissolution rate constant

Melt	Melt	Melt	Melt	Solvent	Solvent	Solvent	Solvent	Knead	Knead	Knead	Knead	Phys	Phys	Phys	Phys
1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10
0.0962	0.1022	0.1705	0.1996	0.0979	0.1241	0.1169	0.1579	0.1006	0.1001	0.0999	0.1314	0.0921	0.0914	0.1116	0.1093

Sorted: least to most value

Phys	Phys	Melt	Solvent	Knead	Knead	Knead	Melt	Phys	Phys	Solvent	Solvent	Knead	Solvent	Melt	Melt
1:3	1:1	1:1	1:1	1:5	1:3	1:1	1:3	1:10	1:5	1:5	1:3	1:10	1:10	1:5	1:10
0.0914	0.0921	0.0962	0.0979	0.0999	0.1001	0.1006	0.1022	0.1093	0.1116	0.1169	0.1241	0.1314	0.1579	0.1705	0.1996

LSR = SSR_{table} x S_x

LSR =	0.0323	0.0340	0.0349	0.0358	0.0364	0.0368	0.0371	0.0375	0.0377	0.0380	0.0381	0.0383	0.0384	0.0384	0.0385

Difference vs LSR test

	Phys	Phys	Melt	Solvent	Knead	Knead	Knead	Melt	Phys	Phys	Solvent	Solvent	Knead	Solvent	Melt	Melt
Method	1:3	1:1	1:1	1:1	1:5	1:3	1:1	1:3	1:10	1:5	1:5	1:3	1:10	1:10	1:5	1:10
Mean	0.0914	0.0921	0.0962	0.0979	0.0999	0.1001	0.1006	0.1022	0.1093	0.1116	0.1169	0.1241	0.1314	0.1579	0.1705	0.1996
0	0.0007	0.0048	0.0065	0.0085	0.0087	0.0092	0.0108	0.0179	0.0202	0.0255	0.0327	0.0400	0.0665	0.0791	0.1082
1:3	-0.0316	-0.0292	-0.0284	-0.0273	-0.0277	-0.0276	-0.0263	-0.0196	-0.0175	-0.0125	-0.0054	*0.0017*	*0.0281*	*0.0407*	*0.0697*
	0	0.0041	0.0058	0.0078	0.0080	0.0085	0.0101	0.0172	0.0195	0.0248	0.0320	0.0393	0.0658	0.0784	0.1075
	1:1	-0.0282	-0.0282	-0.0271	-0.0278	-0.0279	-0.0267	-0.0199	-0.0180	-0.0129	-0.0060	*0.0012*	*0.0275*	*0.0400*	*0.0691*
		0	0.0017	0.0037	0.0039	0.0044	0.0060	0.0131	0.0154	0.0207	0.0279	0.0352	0.0617	0.0743	0.1034
		1:1	-0.0306	-0.0303	-0.0310	-0.0314	-0.0304	-0.0237	-0.0217	-0.0168	-0.0098	-0.0028	*0.0236*	*0.0360*	*0.0650*
			0	0.0020	0.0022	0.0027	0.0043	0.0114	0.0137	0.0190	0.0262	0.0335	0.0600	0.0726	0.1017
			1:1	-0.0303	-0.0318	-0.0322	-0.0316	-0.0250	-0.0231	-0.0181	-0.0113	-0.0042	*0.0220*	*0.0345*	*0.0634*
				0	0.0002	0.0007	0.0023	0.0094	0.0117	0.0170	0.0242	0.0315	0.0580	0.0706	0.0997
				1:5	-0.0321	-0.0333	-0.0326	-0.0264	-0.0247	-0.0198	-0.0129	-0.0060	*0.0203*	*0.0326*	*0.0616*
					0	0.0005	0.0021	0.0092	0.0115	0.0168	0.0240	0.0313	0.0578	0.0704	0.0995
					1:3	-0.0318	-0.0319	-0.0257	-0.0243	-0.0196	-0.0128	-0.0058	*0.0203*	*0.0327*	*0.0615*
						0	0.0016	0.0087	0.0110	0.0163	0.0235	0.0308	0.0573	0.0699	0.0990
						1:1	-0.0307	-0.0253	-0.0239	-0.0195	-0.0129	-0.0060	*0.0202*	*0.0324*	*0.0613*
							0	0.0071	0.0094	0.0147	0.0219	0.0292	0.0557	0.0683	0.0974
							1:3	-0.0252	-0.0246	-0.0202	-0.0139	-0.0072	*0.0189*	*0.0312*	*0.0599*
								0	0.0023	0.0076	0.0148	0.0221	0.0486	0.0612	0.0903
								1:10	-0.0300	-0.0264	-0.0201	-0.0137	*0.0122*	*0.0244*	*0.0532*
									0	0.0053	0.0125	0.0198	0.0463	0.0589	0.0880
									1:5	-0.0270	-0.0215	-0.0151	*0.0105*	*0.0225*	*0.0512*
										0	0.0072	0.0145	0.0410	0.0536	0.0827
										1:5	-0.0251	-0.0195	*0.0061*	*0.0178*	*0.0463*
											0	0.0073	0.0338	0.0464	0.0755
											1:3	-0.0250	-0.0002	*0.0115*	*0.0397*
												0	0.0265	0.0391	0.0682
												1:10	-0.0058	*0.0051*	*0.0333*
													0	0.0126	0.0417
													1:10	-0.0197	*0.0077*
														0	0.0291
														1:5	-0.0032
															0
															1:10

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 69 Two way analysis of varience for nifedipine-poloxamer407 system.

Analysis of Variance (Two way)

Poloxamer407

Poloxamer407	Dissolution rate constant					
	Method (A)				Grand Total	Mean total
Ratio (B)	Melt	Solvent	Knead	Phys		
1:1						
Chamber 1	0.1270	0.0956	0.0853	0.1056	0.4135	0.1034
Chamber 2	0.1223	0.0857	0.0932	0.0900	0.3912	0.0978
Chamber 3	0.1116	0.0870	0.1061	0.0865	0.3912	0.0978
Total	0.3609	0.2683	0.2846	0.2821	1.1959	
Mean	0.1203	0.0894	0.0949	0.0940		0.0997
1:3						
Chamber 1	0.1614	0.1124	0.0793	0.1048	0.4579	0.1145
Chamber 2	0.1079	0.0950	0.0852	0.0985	0.3866	0.0967
Chamber 3	0.1641	0.0925	0.0803	0.0665	0.4034	0.1009
Total	0.4334	0.2999	0.2448	0.2698	1.2479	
Mean	0.1445	0.1000	0.0816	0.0899		0.1040
1:5						
Chamber 1	0.1703	0.1123	0.0874	0.1091	0.4791	0.1198
Chamber 2	0.1373	0.0958	0.0845	0.1028	0.4204	0.1051
Chamber 3	0.1290	0.0976	0.0880	0.1051	0.4197	0.1049
Total	0.4366	0.3057	0.2599	0.3170	1.3192	
Mean	0.1455	0.1019	0.0866	0.1057		0.1099
1:10						
Chamber 1	0.1430	0.1608	0.1781	0.1008	0.5827	0.1457
Chamber 2	0.2010	0.1699	0.1700	0.1058	0.6467	0.1617
Chamber 3	0.1644	0.1285	0.1275	0.1148	0.5352	0.1338
Total	0.5084	0.4592	0.4756	0.3214	1.7646	
Mean	0.1695	0.1531	0.1585	0.1071		0.1471
Grand total	1.7393	1.3331	1.2649	1.1903	5.5276	
Mean total	0.1449	0.1111	0.1054	0.0992		

ANOVA table

Source	df	SS	Mean Square	F cal	F table	Significance
Between method	3	1.50E-02	5.01E-03	17.62	9.28	Yes
Between ratio	3	1.69E-02	5.64E-03	19.80	3.86	Yes
Method-ratio interaction	9	6.24E-03	6.94E-04	2.44	2.27	Yes
Error	32	9.11E-03	2.85E-04			
Total	47	0.0473	1.01E-03		$\alpha = 0.05$	

Table 70 LSR test of poloxamer407

Test between method

Duncan's test

Dissolution rate constant

Melt	Solvent	Knead	Phys
0.1449	0.1111	0.1054	0.0992

Sorted; least to most values

Phys	Knead	Solvent	Melt
0.0992	0.1054	0.1111	0.1449

Difference with next value

Phys	0.0062	0.0119	0.0457
	Knead	0.0057	0.0395
		Solvent	0.0338

$LSR = SSR_{table} \times S_x$

LSR =	0.0138	0.0145	0.0150

Difference vs LSR test

	Phys	Knead	Solvent	Melt
	0.0992	0.1054	0.1111	0.1449
		0.0062	0.0119	0.0457
Phys		-0.0076	-0.0026	***0.0307***
			0.0057	0.0395
	Knead		-0.0081	***0.0250***
				0.0338
		Solvent		***0.0200***

Test between ratio

Duncan's test

Disssolution rate constant

1:1	1:3	1:5	1:10
0.0997	0.1040	0.1099	0.1471

Sorted; least to most value

1:1	1:3	1:5	1:10
0.0997	0.1040	0.1099	0.1471

Difference with next values

1:1	0.0043	0.0102	0.0474
	1:3	0.0059	0.0431
		1:5	0.0372

$LSR = SSR_{table} \times S_x$

LSR =	0.0138	0.0145	0.0150

Difference vs LSR test

	1:1	1:3	1:5	1:10
	0.0997	0.1040	0.1099	0.1471
		0.0043	0.0102	0.0474
	1:1	-0.0095	-0.0043	***0.0324***
			0.0059	0.0431
		1:3	-0.0079	***0.0286***
				0.0372
			1:5	***0.0234***

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 71 Test of method-ratio interaction (poloxamer407)

Test method-ratio interaction

Duncan's test

Dissolution rate constant

Melt	Melt	Melt	Melt	Solvent	Solvent	Solvent	Solvent	Knead	Knead	Knead	Knead	Phys	Phys	Phys	Phys
1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10	1:1	1:3	1:5	1:10
0.1203	0.1446	0.1455	0.1695	0.0894	0.1000	0.1019	0.1531	0.0949	0.0816	0.0866	0.1585	0.0940	0.0899	0.1057	0.1071

Sorted; least to most value

Knead	Knead	Solvent	Phys	Phys	Knead	Solvent	Solvent	Phys	Phys	Melt	Melt	Melt	Solvent	Knead	Melt
1:3	1:5	1:1	1:3	1:1	1:1	1:3	1:5	1:5	1:10	1:1	1:3	1:5	1:10	1:10	1:10
0.0816	0.0866	0.0894	0.0899	0.0940	0.0949	0.1000	0.1019	0.1057	0.1071	0.1203	0.1446	0.1455	0.1531	0.1585	0.1695

LSR = $SSR_{0.05}$ x S_x

LSR =	0.0282	0.0296	0.0304	0.0312	0.0317	0.0320	0.0323	0.0326	0.0328	0.0331	0.0332	0.0333	0.0334	0.0335	0.0335

Difference vs LSR test

	Knead	Knead	Solvent	Phys	Phys	Knead	Solvent	Solvent	Phys	Phys	Melt	Melt	Melt	Solvent	Knead	Melt
Method	1:3	1:5	1:1	1:3	1:1	1:1	1:3	1:5	1:5	1:10	1:1	1:3	1:5	1:10	1:10	1:10
Mean	0.0816	0.0866	0.0894	0.0899	0.0940	0.0949	0.1000	0.1019	0.1057	0.1071	0.1203	0.1446	0.1455	0.1531	0.1585	0.1695
		0.0050	0.0078	0.0083	0.0124	0.0133	0.0184	0.0203	0.0241	0.0255	0.0387	0.0629	0.0639	0.0715	0.0769	0.0879
	1:3	-0.0232	-0.0218	-0.0221	-0.0188	-0.0184	-0.0136	-0.0120	-0.0088	-0.0073	*0.0056*	*0.0297*	*0.0306*	*0.0381*	*0.0434*	*0.0544*
			0.0028	0.0033	0.0074	0.0083	0.0134	0.0153	0.0191	0.0205	0.0337	0.0579	0.0589	0.0665	0.0719	0.0829
		1:5	-0.0264	-0.0263	-0.0230	-0.0229	-0.0183	-0.0167	-0.0132	-0.0121	*0.0009*	*0.0248*	*0.0257*	*0.0332*	*0.0385*	*0.0494*
				0.0005	0.0046	0.0055	0.0106	0.0125	0.0163	0.0177	0.0309	0.0551	0.0561	0.0637	0.0691	0.0801
			1:1	-0.0277	-0.0250	-0.0249	-0.0206	-0.0192	-0.0157	-0.0146	-0.0017	*0.0223*	*0.0230*	*0.0305*	*0.0358*	*0.0467*
					0.0041	0.0050	0.0101	0.0120	0.0158	0.0172	0.0304	0.0546	0.0556	0.0632	0.0686	0.0796
				1:3	-0.0241	-0.0246	-0.0203	-0.0192	-0.0159	-0.0148	-0.0019	*0.0220*	*0.0228*	*0.0301*	*0.0354*	*0.0463*
						0.0009	0.0060	0.0079	0.0117	0.0131	0.0263	0.0505	0.0515	0.0591	0.0645	0.0755
					1:1	-0.0273	-0.0236	-0.0225	-0.0195	-0.0186	-0.0057	*0.0182*	*0.0189*	*0.0263*	*0.0314*	*0.0423*
							0.0051	0.0070	0.0108	0.0122	0.0254	0.0496	0.0506	0.0582	0.0636	0.0746
						1:1	-0.0231	-0.0226	-0.0196	-0.0190	-0.0063	*0.0176*	*0.0183*	*0.0256*	*0.0308*	*0.0415*
								0.0019	0.0057	0.0071	0.0203	0.0445	0.0455	0.0531	0.0585	0.0695
							1:3	-0.0263	-0.0239	-0.0233	-0.0109	*0.0128*	*0.0135*	*0.0208*	*0.0259*	*0.0367*
									0.0038	0.0052	0.0184	0.0426	0.0436	0.0512	0.0566	0.0676
								1:5	-0.0244	-0.0244	-0.0120	*0.0114*	*0.0119*	*0.0192*	*0.0243*	*0.0350*
										0.0014	0.0146	0.0388	0.0398	0.0474	0.0528	0.0638
									1:5	-0.0258	-0.0150	*0.0084*	*0.0086*	*0.0157*	*0.0208*	*0.0315*
											0.0132	0.0374	0.0384	0.0460	0.0514	0.0624
										1:10	-0.0160	*0.0078*	*0.0080*	*0.0148*	*0.0197*	*0.0304*
												0.0242	0.0252	0.0328	0.0382	0.0492
											1:1	-0.0040	-0.0044	*0.0024*	*0.0070*	*0.0175*
													0.0010	0.0086	0.0140	0.0250
												1:3	-0.0272	-0.0210	-0.0164	-0.0062
														0.0078	0.0130	0.0240
													1:5	-0.0206	-0.0166	-0.0064
															0.0054	0.0164
														1:10	-0.0228	-0.0132
																0.0110
															1:10	-0.0172
																1:10

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 72 Two way analysis of variance for nifedipine-β-cyclodextrin

Analysis of Variance (Two way)

Beta-CD

Beta-CD	Dissolution rate constant					
	Method (A)				Grand Total	Mean total
Ratio (B)	Melt	Solvent	Knead	Phys		
1:1						
Chamber 1	-	-	0.0645	0.0532	0.1177	0.0589
Chamber 2	-	-	0.0808	0.0482	0.1290	0.0645
Chamber 3	-	-	0.0795	0.0495	0.1290	0.0645
Total	-	-	0.2248	0.1509	0.3757	
Mean	-	-	0.0749	0.0503		0.0626
1:3	-	-				
Chamber 1	-	-	0.1075	0.0687	0.1762	0.0881
Chamber 2	-	-	0.0843	0.0617	0.1460	0.0730
Chamber 3	-	-	0.0947	0.0686	0.1633	0.0817
Total	-	-	0.2865	0.1990	0.4855	
Mean	-	-	0.0955	0.0663		0.0809
1:5	-	-				
Chamber 1	-	-	0.1029	0.0969	0.1998	0.0999
Chamber 2	-	-	0.1021	0.0893	0.1914	0.0957
Chamber 3	-	-	0.1116	0.0917	0.2033	0.1017
Total	-	-	0.3166	0.2779	0.5945	
Mean	-	-	0.1055	0.0926		0.0991
1:10	-	-				
Chamber 1	-	-	0.1034	0.1022	0.2056	0.1028
Chamber 2	-	-	0.0982	0.1205	0.2187	0.1094
Chamber 3	-	-	0.1097	0.0866	0.1963	0.0982
Total	-	-	0.3113	0.3093	0.6206	
Mean	-	-	0.1038	0.1031		0.1034
Grand total	-	-	1.1392	0.9371	2.0763	
Mean total	-	-	0.0949	0.0781		

ANOVA Table

Source	df	SS	Mean Square	F cal	F critical value	Significance
Between method	1	1.70E-03	1.70E-03	22.55	4.54	yes
Between ratio	3	6.28E-03	2.09E-03	27.73	3.29	yes
Method-ratio interaction	3	7.35E-04	2.45E-04	3.24	3.29	No
Error	16	1.21E-03	7.55E-05			
Total	23	0.0099	4.31E-04		$\alpha = 0.05$	

Table 73 LSR test of β-cyclodextrin

Test between method

Duncan's test

Dissolution rate constant

Melt	Solvent
0.0949	0.0781

Sorted;least to most value

Solvent	Melt
0.0781	0.0949

Difference with next values

Solvent	0.0168
	Melt

$LSR = SSR_{table} \times S_x$

LSR =	0.0073

Difference vs LSR test

Solvent	Melt
0.0781	0.0949

	0.0168
Solvent	***0.0095***
	Melt

Test between ratio

Duncan's test

Dissolution rate constant

1:1	1:3	1:5	1:10
0.0626	0.0809	0.0991	0.1013

Sorted;least to most value

1:1	1:3	1:5	1:10
0.0626	0.0809	0.0991	0.1013

Difference with next values

1:1	0.0183	0.0365	0.0387
	1:3	0.0182	0.0204
		1:5	0.0022

$LSR = SSR_{table} \times S_x$

LSR =	0.0105	0.0110	0.0113

Difference vs LSR test

1:1	1:3	1:5	1:10
0.0626	0.0809	0.0991	0.1013

	0.0183	*0.0365*	*0.0387*
1:1	***0.0078***	***0.0255***	***0.0274***
		0.0182	0.0204
	1:3	***0.0077***	***0.0094***
			0.0022
		1:5	**-0.0083**

* Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Table 74 Two way analysis of variance for nifedipine-2-hydroxypropyl-β-cyclodextrin system.

Analysis of Variance (Two way)

2-HBCD

2-HBCD	Dissolution rate constant					
	Method (A)				Total	Mean
Ratio (B)	Melt	Solvent	Knead	Phys		
1:1						
Chamber 1		0.0587	0.0874	0.0689	0.2150	0.0717
Chamber 2		0.0668	0.0959	0.0569	0.2196	0.0732
Chamber 3		0.0753	0.0961	0.0646	0.2360	0.0787
Total		0.2008	0.2794	0.1904	0.6706	
Mean		0.0669	0.0931	0.0635		0.0745
1:3						
Chamber 1		0.0635	0.0817	0.0657	0.2109	0.0703
Chamber 2		0.0800	0.1004	0.0612	0.2416	0.0805
Chamber 3		0.0865	0.0990	0.0796	0.2651	0.0884
Total		0.2300	0.2811	0.2065	0.7176	
Mean		0.0767	0.0937	0.0688		0.0797
1:5						
Chamber 1		0.0741	0.0806	0.0717	0.2264	0.0755
Chamber 2		0.0854	0.1046	0.0789	0.2689	0.0896
Chamber 3		0.0783	0.0955	0.0880	0.2618	0.0873
Total		0.2378	0.2807	0.2386	0.7571	
Mean		0.0793	0.0936	0.0795		0.0841
1:10						
Chamber 1		0.0866	0.1230	0.0925	0.3021	0.1007
Chamber 2		0.0992	0.1104	0.0877	0.2973	0.0991
Chamber 3		0.1042	0.0950	0.0794	0.2786	0.0929
Total		0.2900	0.3284	0.2596	0.8780	
Mean		0.0967	0.1095	0.0865		0.0976
Grand total		0.9586	1.1696	0.8951	3.0233	
Mean total		0.0799	0.0975	0.0746		

ANOVA Table

Source	df	SS	Mean Square	F cal	F critcal value	Significance
Between method	2	3.44E-03	1.72E-03	19.85	3.38	Yes
Between ratio	3	2.63E-03	8.76E-04	10.10	2.99	Yes
Method-ratio interaction	6	3.01E-04	5.01E-05	0.58	2.49	no
Error	24	2.08E-03	8.67E-05			
Total	35	0.0085	2.41E-04		$\alpha = 0.05$	

Table 75 LSR test of 2-hydroxypropyl-β-cyclodextrin.

Test between method

Duncan's test

Dissolution rate constant

Solvent	Knead	Phys
0.0799	0.0975	0.0746

Sorted; least to most value

Phys	Solvent	Knead
0.0746	0.0799	0.0975

Difference with next values

Phys	0.0053	0.0229
	Solvent	0.0176
		Knead

$LSR = SSR_{table} \times S_x$

LSR =	0.0077	0.0081

Difference vs LSR test

	Phys	Solvent	Knead
	0.0746	0.0799	0.0975
		0.0053	0.0229
Phys		-0.0024	***0.0148***
			0.0176
	Solvent		***0.0099***
			Knead

Test between ratio

Duncan's test

Dissolution rate constant

1:1	1:3	1:5	1:10
0.0745	0.0797	0.0841	0.0976

Sorted; least to most value

1:1	1:3	1:5	1:10
0.0745	0.0797	0.0841	0.0976

Difference with next values

1:1	0.0052	0.0096	0.0231
	1:3	0.0044	0.0179
		1:5	0.0135

$LSR = SSR_{table} \times S_x$

LSR =	0.0089	0.0093	0.0096

Difference vs LSR test

	1:1	1:3	1:5	1:10
	0.0745	0.0797	0.0841	0.0976
		0.0052	0.0096	0.0231
	1:1	-0.0037	***0.0003***	***0.0135***
			0.0044	0.0179
		1:3	-0.0045	***0.0086***
				0.0135
			1:5	***0.0046***

*Underlined positive values show statistical significance where the difference between its next value is greater than LSR

Appendix F

Fitness of dissolution plot

First order and Higuchi plots.

Determination of dissolution plot

In order to determine the fitness of dissolution plot,
first order and Higuchi plot was determined.

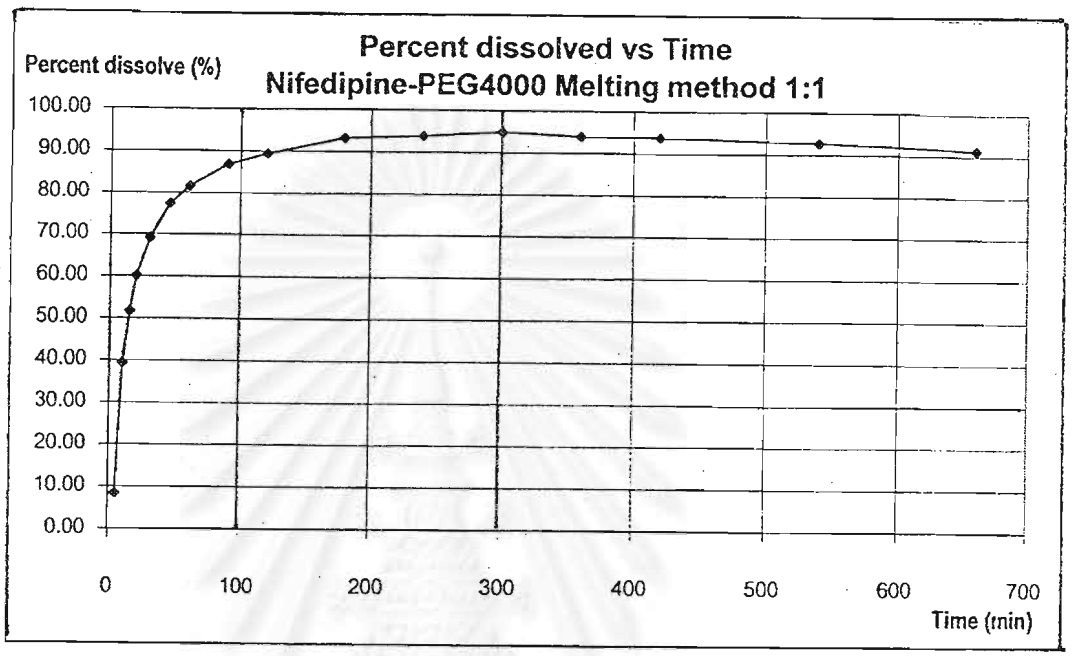


Figure 167 Percent dissolved plot of nifedipine from nifedipine-PEG4000 prepared by melting method ratio 1:10

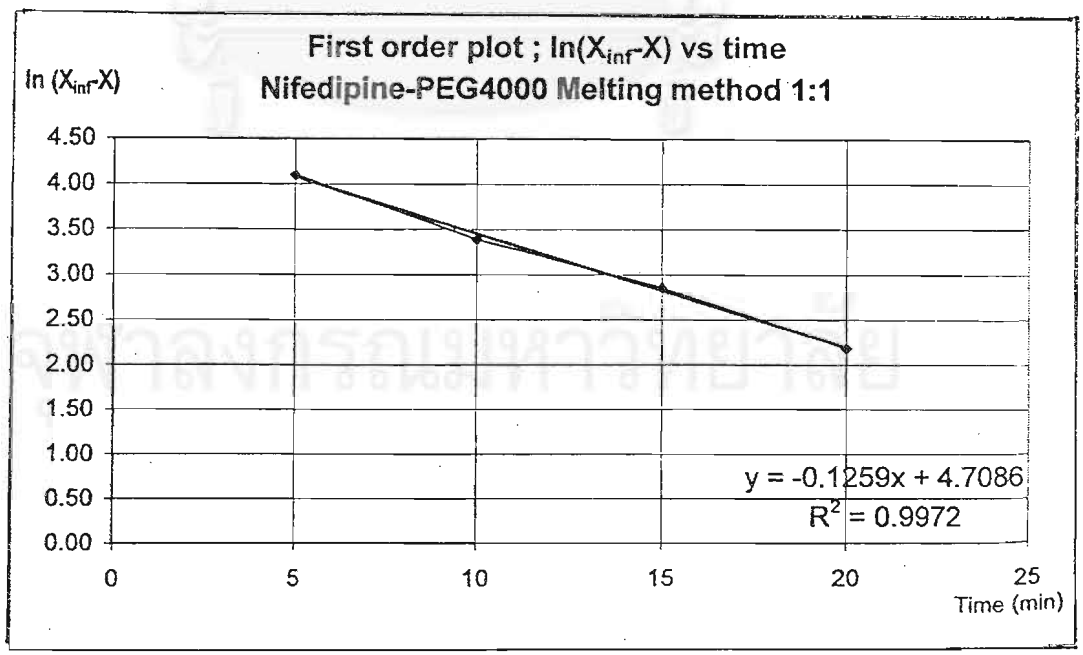


Figure 168 First order plot of nifedipine from nifedipine-PEG4000 prepared by melting method ratio 1:10

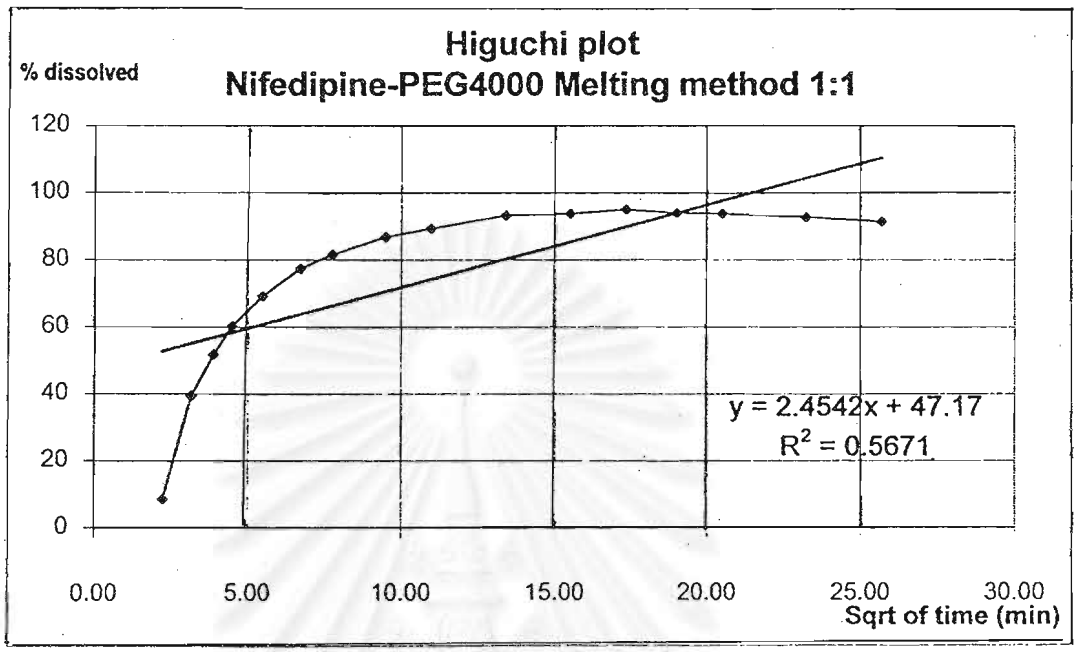


Figure 169 Higuchi plot of nifedipine from nifedipine-PEG4000 prepared by melting method ratio 1:10

Appendix G

Measurement of contact angle.

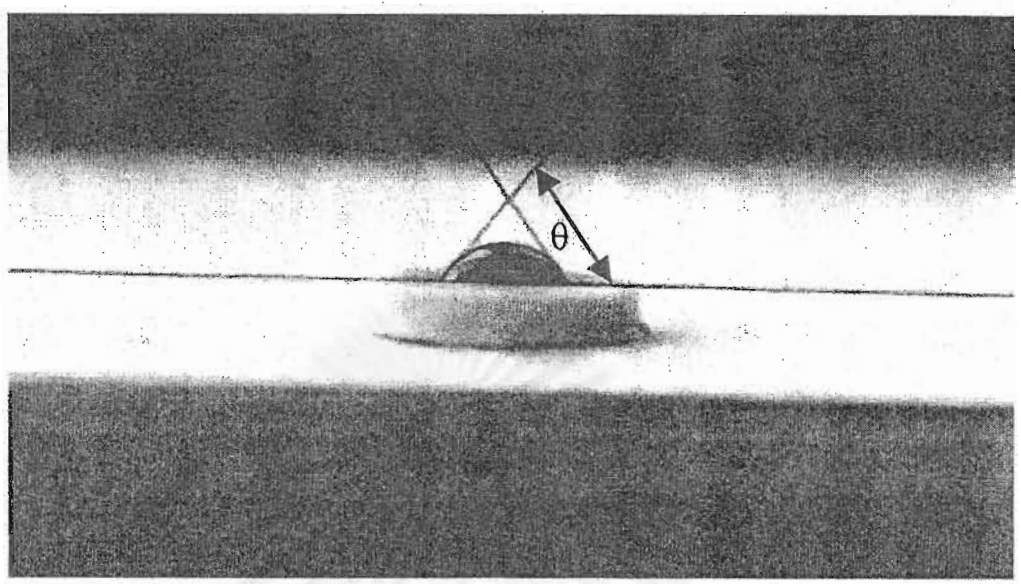


Figure170 Contact angle of nifedipine-poloxamer407 prepared by melting method, 1:3 ratio

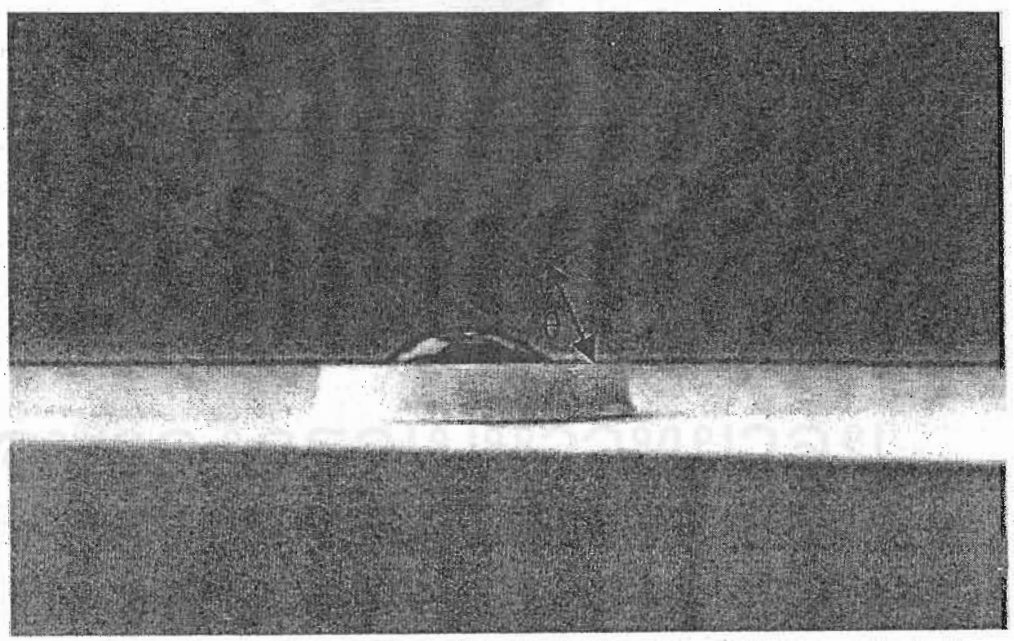


Figure171 Contact angle of nifedipine-poloxamer188 prepared by melting method, 1:5 ratio

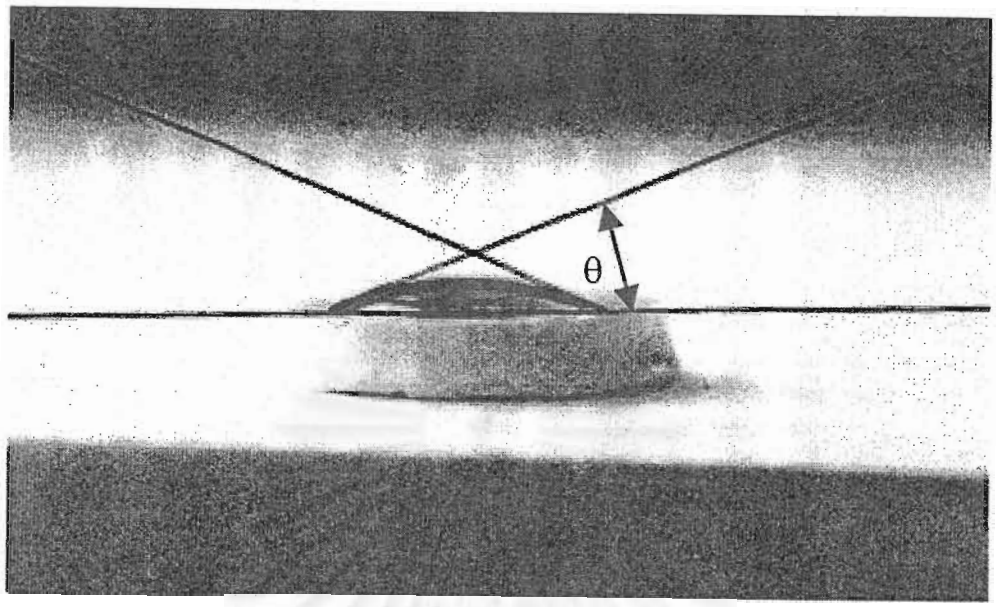


Figure172 Contact angle of nifedipine-PEG6000 prepared by melting method, 1:3 ratio

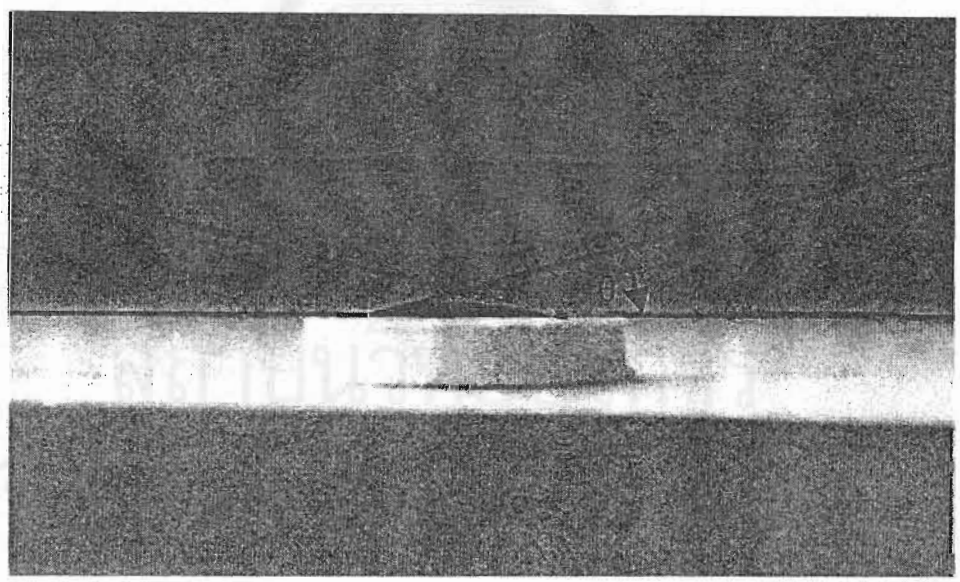


Figure173 Contact angle of nifedipine-β-cyclodextrin prepared by kneading method, 1:5 ratio

Appendix G

Properties of carriers used

Polyethylene glycols (PEGs)

PEGs are high-molecular-weight polymers, obtained by the reaction of ethylene oxide with ethylene glycol or water.

Their generalized structure may be written as:

$$HO(CH_2CH_2O)_nCH_2CH_2OH$$

-PEG4000, 6000 are white waxy solids that are supplied in flake or powder form.

-PEG4000, MW 2600-3800, freezing point 53-57°C, white flake appearance.

-PEG6000, MW 7300-9300, freezing point 56-61°C, white powder appearance.

-Highly soluble in water and soluble in many organic solvents except aliphatic hydrocarbons.

-Low toxicity and negligible skin irritation.

-The oral LD_{50} test for PEG4000, 6000 is 50g/kg (Wade, and Weller, 1990).

Poloxamers

The poloxamer polyols are a series of closely related block copolymer of ethylene oxide and propylene oxide conforming to the general formula

$$OH(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

Poloxamer	physical form	a	b	average moleculear weight
188	solid	80	27	7680-9516
288	solid	-	-	-
407	solid	101	56	9840-14600

-Poloxamers are nonionic polyoxyethylene-polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agent.

-The polyoxyethylene segment is hydrophilic, polyoxypropylene segment is hydrophobic.

-Generally occur as white-colored, waxy, freeflowing granules

-Melting point 52°C for poloxamer188, 56°C for poloxamer407

-Freely soluble in ethanol 95% and water.

-Poloxamer188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation.

-Poloxamer may also used therapeutically as wetting agents in eye-drop formulation, in the treatment of kidney stones and as wound cleansers.

-$LD_{50(rat,oral)}$ of poloxamer188 is 9.4g/kg (Wade, and Weller, 1990).

Cyclodextrins

Cyclodextrins are crystalline, nonhygroscopic, cyclic oligosaccharides derived from starch. β-Cyclodextrin has 7 glucose units. In shape, cyclodextrin are 'bucket-like' or 'cone-like', toroid molecules. They have a rigid structure with a central cavity whose size various according to the cyclodextrin type.

- β-Cyclodextrin is the most commonly used cyclodextrin although it is the least soluble. It should not be used in parenteral formulations since it is nephrotoxic but nontoxic when administered orally.

-Melting point of β-cyclodextrin is 255-265°C.

- β-Cylclodextrin: soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20°C, 1 in 20 at 50°C, practically insoluble in acetone and ethanol 95%.

-2-Hydroxypropyl-β-cyclodextrin soluble greater than 1 in 2 parts of water at 25°C.

-β-Cyclodextrins are stable in the solid state if protected from high humidity.

-Cyclodextrin administered orally is metabolized by microflora in yhe colon forming the metabolites maltodextrin, maltose and glucose, which are thenselves further metabolized before being finally excreted as carbon dioxide and water.

-Cyclodextrins are now approved for use in food products and orally administered pharmaceutical in a number of countries.

-Cyclodextrin are not irritatant to the skin and eyes, or upon inhalation and no evidence to suggest that cyclodextrins are mutagenic or teratogenic, $LD50_{(rat,oral)}$: 18.8 g/kg (Wede and Weller, 1990).