เพาเดอร์เอ็นจิเนียริงเทคนิคของผลึกไอบูโพรเฟนที่ใช้การผสมผสานของการเกิดสารประกอบเชิงซ้อนและวิธีการเปลี่ยนวัฏภาค

นางสาวชวาลินี อัศวเหม

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาเภสัชอุตสาหกรรม
คณะเภสัชศาสตร์
จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2544

ISBN 974-17-0561-1

POWDER ENGINEERING TECHNIQUE OF IBUPROFEN CRYSTAL USING COMBINATION OF COMPLEXATION AND PHASE PARTITION METHOD

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy
Department of Manufacturing Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Academic Year 2001

ISBN 974-17-0561-1

Thesis Title	Powder engineering technique of ibuprofen crystal using combination of complexation and phase partition method
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ชวาลินี อัศวเหม : เพาเดอร์เอ็นจิเนียริงเทคนิคของผลึกไอบูโพรเฟนที่ใช้การผสมผสานของการเกิดสารประกอบเชิงซ้อนและวิธีการเปลี่ยนวัฏภาค (POWDER ENGINEERING TECHNIQUE OF IBUPROFEN CRYSTAL USING COMBINATION OF COMPLEXATION AND PHASE PARTITION METHOD) อ.ที่ปรึกษา : รศ.ดร. ไกรสีห์ อัมพรายน์ 174 หน้า ISBN 974-17-0561-1)

การผสมผสานวิธีการเปลี่ยนวัฏภาคและการใช้ตัวพาช่วยกระจายตัว พอลิไวนิลไพโรลิโดน (พีวีพี เค 30) และ พอลิเอทิลิน กลัยคอล (พีอีจี) ในการเตรียมเพลเลททรงกลมสามารถใช้ในการปรับปรุงคุณสมบัติค่าการละลายและคุณสมบัติทางกายภาพของตัวยาที่ละลายน้ำได้น้อยอย่างไอบูโพรเฟน ไอบูโพรเฟนเพลเลทที่ประกอบด้วย พีวีพี เค 30จะให้เพลเลทที่มีขนาดสม่ำเสมอและรูปร่างทรงกลม ในขณะที่ไอบูโพรเฟนเพลเลทที่ประกอบด้วย พีอีจีก่อให้เกิดเพลเลทที่มีพื้นผิวที่ขรุขระและขนาดที่ไม่สม่ำเสมอ

คุณสมบัติทางด้านเคมีฟิสิกส์ศึกษาได้จากการใช้การเลี้ยวเบนรังสีเอ็กซ์(พีเอ็กซ์อาร์ดี) ดิฟเฟอเรนเชียลสแกนนิงแคลอริเมทรี (ดีเอสซี), ฟูเรียร์แทรนส์ฟอร์มอินฟราเรด สเปกโตรเมทรี (เอฟทีไออาร์) และศึกษาการเปลี่ยนแปลงตำแหน่งคาร์บอนเนื่องจากการสั่นพ้องที่มาจากแม่เหล็กนิวเคลียร์ (13ซี เอ็นเอ็มอาร์) พบว่ามีการเกิดอันตรกิริยาทางเคมีระหว่างตัวยาและพอลิเมอร์ (พีวีพี เค 30) ในระยะขั้นตอนของการเกิดสารกระจายตัว โดยพบว่าอันตรกิริยาทางเคมีที่เกิดขึ้นเกี่ยวเนื่องกับการเกิดสารประกอบเชิงซ้อนระหว่างไอบูโพรเฟนและพีวีพี เค 30 โดยพันธะไฮโดรเจน ขณะที่ผลจากพีเอ็กซ์อาร์ดีและดีเอสซีของสารกระจายตัวระหว่างไอบูโพรเฟนและพีอีจีแสดงถึงการเกิดอินเทอร์สทิเชียล โซลิดโซลูชันระหว่างไอบูโพรเฟนและพีอีจีในสารกระจายตัวนั้น หรืออาจเกิดเนื่องจากการจัดเรียงตัวของโครงสร้างของไอบูโพรเฟนและพีอีจีที่เปลี่ยนแปลงไป ในกรณีของสารกระจายตัวระหว่างไอบูโพรเฟนกับพีวีพี เค 30 ร่วมกับพีอีจีในอัตราส่วนที่เหมาะสม พันธะไฮโดรเจนอย่างอ่อนอาจเกิดระหว่างไอบูโพรเฟนและพีวีพี เค 30 อย่างไรก็ตาม ในสูตรตำรับของไอบูโพรเฟนหลังจากการแบ่งส่วนวัฏภาคไปเป็นเพลเลทพบหลักฐานที่อาจแสดงการเกิดอันตรกิริยาทางเคมีจาก13 ซี เอ็นเอ็มอาร์ มีการเคลื่อนที่ของสัญญาณในตำแหน่งของคาร์บอกไซลิก คาร์บอนของตัวยา (ยกเว้นในสูตรตำรับของตัวยากับพีอีจีเดี่ยว) อาจเกิดเนื่องจากพันธะไฮโดรเจนอย่างอ่อนระหว่างไอบูโพรเฟนและพีวีพี เค 30 หรือจากการเปลี่ยนแปลงของลักษณะการจัดเรียงตัวในโครงสร้างตัวยา

สำหรับการศึกษาคุณสมบัติค่าการละลายพบว่า ไอบูโพรเฟนเพลเลทที่ประกอบด้วย พีวีพี เค 30 หรือสารผสมของพีวีพี เค 30และพีอีจี ในอัตราส่วนที่เหมาะสมมีการปลดปล่อยตัวยาที่สูงกว่าในสูตรตำรับของไอบูโพรเฟนเพลเลทที่ประกอบด้วยตัวยาอย่างเดียว หรือของไอบูโพรเฟนเพลเลทที่ประกอบด้วยพีอีจี ทั้งยังพบว่า ไอบูโพรเฟนเพลเลทที่มีอัตราส่วนระหว่างตัวยาและพอลิเมอร์ที่เหมาะสมมีคุณสมบัติทางกายภาพที่ดี

ภาควิชา.....เภสัชอุตสาหกรรม..... ลายมือชื่อนิสิต.....ชวาลินี อัศวเหม.....

สาขาวิชา.....เภสัชอุตสาหกรรม..... ลายมือชื่ออาจารย์ที่ปรึกษา.....ไกรสีห์ อัมพรายน์.....

ปีการศึกษา.....2544..... ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4376566933: MAJOR MANUFACTURING PHARMACY
KEY WORDS : IBUPROFEN / POLYVINYLPYRROLIDONE / POLYETHYLENE GLYCOL / PHASE PARTITION / COMPLEXATION
CHAWALINEE ASAWAHAME : POWDER ENGINEERING TECHNIQUE OF IBUPROFEN CRYSTAL USING COMBINATION OF COMPLEXATION AND PHASE PARTITION METHOD
THESIS ADVISOR : ASSOC. PROF. KAISRI UMPRAYN, Ph.D.
174 pp. ISBN 974-17-0561-1

By combinding phase partition technique and using dispersion carriers such as polyvinylpyrrolidone (PVP K 30) and polyethylene glycol (PEG) to produce the spherical pellets could improve the dissolution property including physical property of a poorly water soluble drug, ibuprofen. Ibuprofen pellets produced with PVP K 30 had uniform size and spherical in shape. Whereas, ibuprofen pellets with PEG had rough surface and size variation.

Physicochemical properties of pellets were characterized by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), fourier transform infrared (FTIR) spectrometry and ^{13}C nuclear magnetic resonance (^{13}C NMR). Chemical interaction between drug and polymer (PVP K 30) were found during the dispersion state of ibuprofen and PVP K 30. This chemical interaction was due to complex formation of ibuprofen with PVP K 30 by hydrogen bonding. Whereas, X-ray diffractogram and DSC thermogram of the dispersion of ibuprofen and PEG showed the evidence like the interstitial solid solution between ibuprofen and PEG had formed. The other reason, by disorientation of the structure between ibuprofen and PEG in this mixture. In the case of the dispersion of ibuprofen with both of PVP K 30 and PEG at suitable ratio, the weak hydrogen bonding may occur. However, an evidence of chemical interaction between drug and polymers in the formulations after phase partition of ibuprofen into pellets maybe found. As indicated by ^{13}C NMR, the signal of carboxylic acid carbon of drug had shifted (except in the case of the formulations of ibuprofen with PEG alone). It maybe caused by the weak hydrogen bonding between ibuprofen and PVP K 30 or by disorientation of the structure of drug.

For dissolution study, ibuprofen pellets with PVP K 30 or the mixture of PVP K 30 and PEG in suitable ratio had faster release than the formulation of ibuprofen pellets with drug alone or ibuprofen pellets with PEG. Furthermore, ibuprofen pellets from a suitable ratio of drug: polymers had good physical properties.

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my thesis advisor, Associate Professor Kaisri Umprayn, Ph.D. for his helpful advice, guidance, attention, encouragement and understanding. His kindness and helpfulness are also deeply appreciated.

My special thanks send to the National Metal and Material Technology Center (MTEC) for supporting the evaluations on X-ray diffractometry.

A special thankfulness is also to my friends and all staff members in the Department of Manufacturing Pharmacy for their assistance and great encouragement.

And most importantly to my family, I would like to give extra special gratitude for their continuous support, care and encouragement.

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LIST OF ABBREVIATIONS

° C	=	degree Celsius
^{13} C NMR	=	carbon nuclear magnetic resonance spectroscopy
DSC	=	differential scanning calorimetry
IB	=	ibuprofen
i.e.	=	id est (that is)
IPs	=	ibuprofen pellets
IR	=	infrared spectroscopy
e.g.	=	exampli gratia (for example)
et al.	=	et alii (and others)
FTIR	=	Fourier Transform Infrared Spectroscopy
mcg	=	microgram(s)
mg	=	milligram(s)
ml	=	milliliter(s)
mm	=	millimeter(s)
NMR	=	nuclear magnetic resonance
No.	=	number of sample
PEG	=	polyethylene glycol
pH	=	the negative logarithym of the hydrogen ion concentration
PVP	=	polyvinylpyrrolidone
PXRD	=	powder x-ray diffractometry
rpm	=	revolution(s) per minute
SEM	=	scanning electron microscopy
SD	=	standard deviation
w/w	=	weight by weight
%	=	percentage
α	=	alpha
θ	=	theta

CHAPTER I

INTRODUCTION

The concept of the powder engineering technique using the phase partition method to obtain spherical crystals will have an impact in the field of pharmaceutical technology. This technique can cut down the cost of an expensive equipment and labor, and is capable of minimizing the complications of the manufacturing process of various solid dosage forms.

Aim of development of spherical crystallization is to obtain suitable property of drug substances for manufacturing processes and modified the released property of spherical agglomerated crystals. These including to provide an increased, prolonged or sustained release by using modification about method of preparations or by using various specific properties of some materials that can be add into the preparations.

There were many techniques that used for enhancing drug dissolution. Solid dispersion is the one of the useful technique. Several of carrier systems have been used in the preparation of solid dispersion, sometimes the active drug interact with carrier in the system. There are six types of drug-carrier interaction in solid state dispersion, they are simple eutectic mixtures, solid solution, glass solution, glass suspension, amorphous precipitate in a crystalline carrier and another of the interaction is complex formation of drug-carrier *(Chiou and Riegelman, 1971)*.

Ibuprofen is one of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of a wide range of indications, including pain, inflammation, arthritis, fever and dysmenorrhea. The properties of ibuprofen showed poor water solubility and poor dissolution properties. In addition, ibuprofen also had the problem about micromeritic properties such as flowability and compressibility as well.

Using the concept of powder engineering technique by phase partition method to produce ibuprofen pellets is one of the methods to defeat these problems of ibuprofen raw material (*Umprayn et al., 2001).* Nevertheless, this technique is not enough to completely defeat the problem of dissolution properties. So combination of ibuprofen with a suitable carrier to make solid dispersion in combination of spherical crystallization technique is the interesting method to introduce for leading to an increase in drug dissolution. The increasing in dissolution of ibuprofen was translated into better bioavailability. This, resulting from less time to reach maximum blood concentration may cause less gastric irritation because it spends less time in the gastrointestinal tract. All of these advantages could improve the performance of ibuprofen.

The present work was aimed to study on the preparations of ibuprofen pellets which contained a polymer as the dispersion carrier by using spherical crystallization technique in combining with solid interaction method. Interaction between drug and polymer, such as complexation or another interactions which affected the physicochemical properties in solid state would be elucidated. Freely soluble, inert and nontoxic substances: polyvinylpyrrolidone and polyethylene glycol were selected as carriers used for this study. In addition, an evaluation in physical characteristics and polymorphic transition of the prepared pellets were included. Finally, the dissolution profiles were examined.

Objective of this study

On the basis of the rationale mentioned above, the objectives of this study were;

1. Using powder engineering approach by phase partition technique of spherical crystallization, to prepare ibuprofen pellets which contained suitable dispersion carriers.

2. To elucidate interaction between ibuprofen and dispersion carriers, that effected physicochemical properties in solid state.

3. To study the dissolution of ibuprofen pellets and compare the release profiles which drug pellets contained various types and amounts of dispersion carriers.

4. To develop the formulation for manufacturing process and can employed this technique for other poorly water soluble drugs.

Literature Review

Concept of the powder engineering technique using the phase partition method for spherical crystallization

Spherical crystallization is a method for the concept of powder engineering technique that can be used for modifying the properties of various drug substances. Crystal morphology of many drug substances causes them to have extremely poor flowability and poor compressibility, in accordance with the problem about their poor solubility. Spherical crystallization is a novel particle designing technique, which could possibly solve about these problems.

Definition of spherical crystallization

The definition of "Spherical crystallization" is the process of the crystallization of drug in solution phase to give the micro-crystals that will be held together to form the agglomeration of these micro-crystals to spherical shape during crystallization, by which crystallization and agglomeration can be carried out simultaneously in one step (*Paradkar et al., 1993).*

Important parts for spherical crystallization

Commonly, they are four parts for spherical crystallization technique:

1. Solid phase (S): Mostly is the drug substance that is not soluble in continuous liquid phase; L_1.

2. Continuous liquid phase (L_1): It is the medium or liquid dispersion for drug substances so this solvent has to be undissoluble for drug substances.

3. Discontinuous liquid phase (L_2): This phase maybe used in the term of agglomeration liquid, bonding agent, binding solvent or bridging solvent; L_2 and L_1 have to be immisible to each other.

4. Solvent liquid phase (L_3): It is the good solvent for dissolving drug substances and this solvent have to dissolve in continuous liquid phase (L_1) too.

Process in the spherical crystallization technique

Two processes to produce spherical crystals:

1. Crystallization: From the property of the drug substance that can not dissolve in continuous liquid phase (L_1) so crystallization process has occur to produce micro-crystals of drug substance from the solution.

2. Agglomeration: Micro-crystals held together by bridging liquid to form spherical crystals, the agglomerates are formed by agitating the crystals in a liquid suspension.

There are the study about the growth of agglomerates (*Bemer et al.)* proposed four regions as follows;

1. Floculation Zone: Where loose opens flocs of particles are formed by pendular bridges.

2. Zero-Growth Zone: Loose flocs get transformed into tightly packed pellets, during which the entrapped suspension fluid is squeezed out followed by squeezing of bridging liquid onto the surface of small flocs causing pore space in the pellet to be completely filled with the bridging liquid.

The driving force for this transformation is provided by the agitation of the slurry causing liquid turbulance, pellet – pellet and pellet – stirrer collision.

3. Fast- Growth Zone: The fast growth of the agglomerate takes place when sufficient bridging liquid has squeezed out to the surface of small agglomerates.

4. Constant-Size Zone: In this zone the agglomerate cease to grow, or even shows slight decrease in size. For this stage, the frequency of coalescence is balanced by the breaking frequency of agglomerates.

There are two theories to specify the rate-determining step. Firstly, the rate determining step in the agglomeration growth occurs in zero – growth zone when the bridging liquid is squeezed out of the pores as an initial flocs are transformed into small agglomerates. Another assumption point of view proposed that the rate determining step is the collision of particles with the bridging liquid droplets prior to the formation of liquid bridges, this rate is governed by the rate of agitation.

Methods of spherical crystallization *(A.R. Paradkar et al., 1993)*

1. Simple spherical crystallization method or the spherical agglomeration method

Crystallization is generally achieved by changing of solvent or salting out. The solution of drug in a "soluble solvent" is poured in an "insoluble solvent" under controlled conditions to produce the formation of fine crystals. The agglomerates are formed by agitating the crystals in a liquid suspension and adding a "bridging liquid" which preferentially wets the crystal surface to cause binding. Several studies can be found in the literature for numerous drug such as salicylic acid *(Kawashima et al., 1982),* naproxen *(Gordon and Chowhan. 1990).*

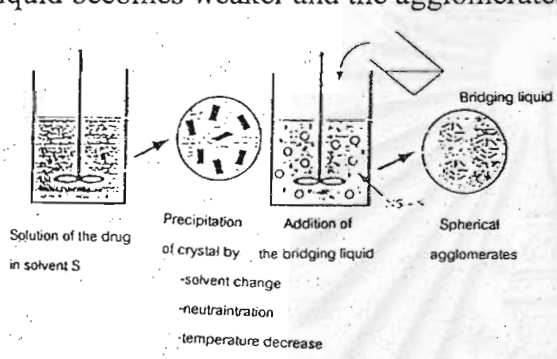
2. Emulsion solvent diffusion method or quasi- emulsion solvent diffusion (QESD) method also known as the transient emulsion (TE) method

By this method spherical crystallization can be carried out using a mixed system of two or three partially miscible solvents. When bridging liquid (or plus good solvent) solution of the drug was poured into poor solvent (dispersing medium) under agitation, quasi emulsion droplets of bridging liquid or good solvent from the emulsion droplet into the dispersing medium induced the crystallization of the drug, followed by agglomeration. Many drugs such as acebutolol hydrochloride *(Kawashima et al., 1994)* and chlorpromazine hydrochloride *(Niwa et al., 1994)* have been spherically crystallized by the QESD. In some cases, they have to stabilize the initial emulsion, which is an essential intermediate for forming spherical agglomerates by adding some of additive *(Morishima and Kawashima, 1993).*

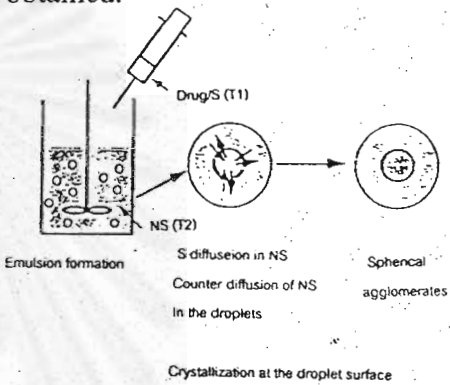
3. Ammonia diffusion system method (ADS)

Ueda et al., 1990 studied a novel method for spherical crystallization of amphoteric drug substances. This technique is useful in agglomeration of drugs which are soluble only in an acidic or an alkaline solution. For this study, they carried out spherical crystallization of enoxacin, which is slightly soluble in water but soluble in acidic and alkaline solution. A mixture of three partially immiscible solvent i.e. acetone – ammonia water – dichloromethane was used as a crystallization system. The mechanism of the modified system is as follows: ammonia water acted as both a bridging liquid and a good solvent for enoxacin.

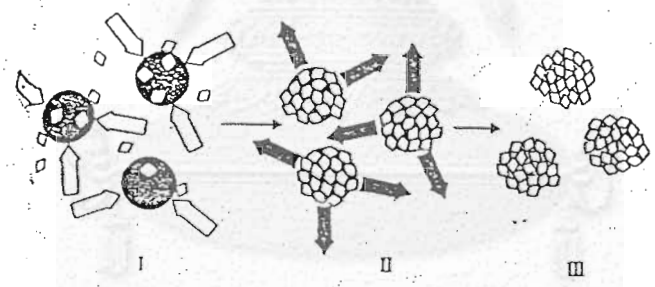
Acetone is a water miscible but act as a poor solvent, thus enoxacin gets agglomerated by solvent change without forming an ammonia salt. Water immiscible solvents such as hydrocarbon or halogenated hydrocarbons e.g. dichloromethane induced liberation of the ammonia water. Thus acetone in the solvent, outer into droplets of ammonia water which are liberated from the acetone – ammonia water – dichloromethane systems and consequently, enoxacin dissolved in ammonia water is precipitated into droplets of the crystals. At the same time, ammonia in the agglomerates diffuses to the outer organic solvent phase and it is ability as a bridging liquid becomes weaker and the agglomerates are obtained.



A. Simple spherical crystallization



B. Quasi-emulsion solvent diffusion method



Mechanism for Spherical Crystallization Using ADS (I) Invasion of Acetone into Ammonia Water Droplets; (II) Diffusion of Ammonia in Agglomerates to the Outer Solvent; (III) Ending of Agglomeration ○, invasion of acetone; ☞, diffusion of ammonia; ◇, crystals of enoxacin; ●, ammonia water.

C. Ammonia diffusion system method

Figure 1 Illustration of 3 methods of spherical crystallization : (A) Simple spherical crystallization method , (B) Quasi- emulsion solvent diffusion (QESD) and (C) Ammonia diffusion system method (ADS)

Applications and advantages of spherical crystallization technique

1. Modification of physical properties of drug substances

The crystal morphology of many drug substances causes them to have extremely poor flow ability and in some cases, crystal morphology can also significantly impact a material's compression characteristics, and many formulas which a high percentage of drug substance do not lend themselves to direct compression due to poor compressibility and poor flowability.*Kawashima et* al's work (*1984 , 1994 , 1995)* indicate that the spherical crystallization technique has the potential of improving the flowability and compressibilty.

Poorly compressible crystal of acebutolol hydrochloride was agglomerated by the spherical crystallization technique can improve compressilbility properties for direct compression. When comparing compression of the agglomerated crystals with an initial crystal, it was found that, the higher relaxation pressure and the lower elastic recovery of the agglomerated crystals than of the original crystals under the same conditions. These results suggested that the agglomerated crystals exhibit greater plasticity during compression, and the greater tensile strength of the tablet of agglomerated crystals. Furthermore it also confirmed the fact that a stronger bonding occurred due to plastic deformation during compression of agglomerated crystals than in the case of original crystals. The main factor in an improvement of flow properties was a significant reduction in interparticle friction, due to their spherical shape and the lower static charge of the agglomerated crystals. *Gordon and Chowhan , 1990* modified crystal morphology of naproxen which have plate shaped crystals by the spherical crystallization technique. The resulting agglomerates were compact spherical aggregates of plate shape crystals. The data indicated that the spherical crystallization technique increases drug compressibility to the degree that can directly compressed. Further, *Despande et al., 1997* recommended that spherical crystallizayion can be an alternative granulation technique for moisture sensitive drugs, such as aspirin that use as a model drug sensitive to moisture. This study has been showed that the spherical agglomeration of aspirin using water – methanol – chloroform blend is an inexpensive and satisfactory method for its particle size enlargement, and can significantly improve the flow properties of aspirin. The result showed that, this process would be a better alternative to slugging of moisture sensitive drugs.

In addition, spherical crystallization technique can gave the new crystalline form of drug substance that different from the original crystals such as the study of a poorly water – soluble antiallergic agent, tranilast (*Kawashima et al., 1991).* The agglomerates from the crystallization process were composed of new polymorphic or amorphous form that could enhance the solubility and the dissolution rate of drug substance.

2. Modification of dissolution of drug substance

- Increased aqueous drug solubility

It is well recognized that the dissolution property of drug substance is somewhat important to bioavailability of the drug. Spherical crystallization has been described as an effective technique in improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile. *Martino et al., 1999* studied about fenbufen, an anti-inflammatory and antipyretic agent. The very poor solubility of fenbufen at low pH value is a limiting factor for good absorption in the upper part of the gastrointestinal tract. This is the reason to improve the fenbufen dissolution rate to obtain rapid analgesic and antipyretic effects. For the experimental data showed that, the dissolution profile of fenbufen exhibit better dissolution behavior for spherical crystals than upstream raw material. The reason for this faster dissolution could be due to better wettability or increasing about surface area of drug substance in the form of micro – crystals. Tolbutamine, another example of a poorly soluble drug was prepared for agglomerated crystal from spherical crystallization technique (*Sano et al., 1992),* the data showed the increase in dissolution rate and gave better bioavailability from agglomerated crystals product.

Otherwise, preparations of agglomerated crystal from spherical crystallization technique by incorporation of some substances for increasing water solubility or enhancing bioavailability or sustaining the release of drug were investigated. Incorporated of water – soluble polymers resulted an improved in wettability with water and increase in solubility (*Sano et al., 1987). Kachrimanis et al., 2000* suggested that the physicochemical properties of the agglomerates, such as size, sphericity, surface roughness, porosity as well as flowability and compression behavier during tabletting were affected by polymer nature and drug/polymer ratios.

- Design a controlled or sustained action dosage form

Since controlled release dosage forms have been designed to reduce its side effect and to improve the bioavailability, *Kawashima et al., 1989* modified spherical crystallization technique by coprecipitating the drug with acrylate polymers to prepared the controlled release microsphere of ibuprofen. The drug release rate could be controlled by the type and the concentration of polymer in the formula. In some cases, spherical crystallization can employ to produce sustained release dosage form for the drug substances to prolong its pharmacological effect. *Niwa et al., 1994* used chlopromazine hydrochloride as a model drug. After agglomeration of the drug crystals, microencapsulation was continually performed, and encapsulating polymer was added to the crystallization system to prepare microcapsules that can retard release.

3. Reduce the complicated process in the manufacturing process

Spherical crystallization technique can produce an agglomerated crystals of drug substance and give the good physicochemical properties of these drug crystals that suitable for direct compression. This difference from, wet granulation or dry granulation that required the complicated process. So, using this technique to modify the properties of upstream raw material of various drug substances for directly compressible can eliminate many complication steps of granulation process.

4. Dust elimination and reduce cross contamination effect

Spherical crystallization technique is an alternative choice to prevent and eliminate dust generating during manufacturing process of pharmaceutical solid dosage forms, such as; size reduction, mixing and dry granulation. In addition, it is safety and health protection for the operator in workplace area.

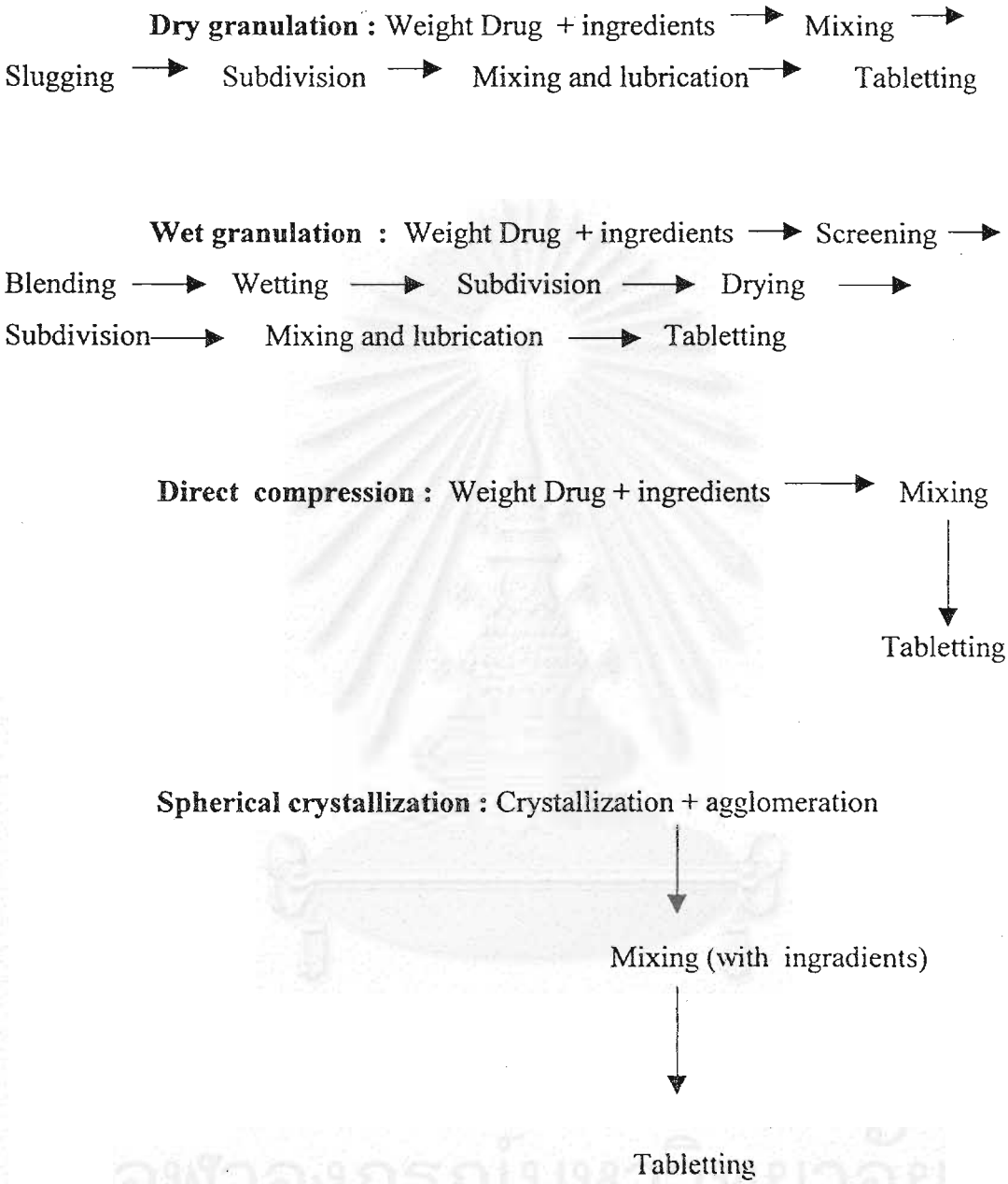


Figure 2 Comparing various processes involved in wet granulation, dry granulation, direct compression and spherical crystallization

Concept of using dispersion carrier in solid dispersion technique

The bioavailabilities of various poorly water-soluble drugs are limited by their dissolution rates. (*Ford, 1986)* For drug whose GI absorption is rate limited by dissolution, in enhancement of dissolution rate should improve its absorption efficiency (*Shin et al., 1979)*. Several methods can be utilized to improve the dissolution properties of poorly soluble drug (*Hoener et al., 1979; McGinity, 1978)*, these include particle size reduction, reduction in hydrophobicity such as coating and granulation with a hydrophilic material or surfactant, formation of polymorphs and salt, complexation, surface adsorption and solid dispersion.

Solid dispersion is one of the methods for changing pattern of dissolution behavior (*Chiou and Riegelman, 1971)*. This method can be used for increasing dissolution, absorption and therapeutic efficacy of drugs by using the water-soluble carrier in combination with a poorly water-soluble drug. From the above method the results showed a fast release of the drug from the matrix. On the other hand, using poorly soluble or insoluble carrier combined with a good water-soluble drug leads to the formulation of sustained release or prolonged release from the matrix.

The concept of solid dispersion was first introduced in 1961 (*Sekiguchi and Obi, 1961)* as a method for reduce the particle size, and increase rates of dissolution and absorption by the formation of a eutectic mixture of poorly soluble drug, sulfathiazole, mix with a physiologically inert, easily soluble carriers such as urea.

Definition of solid dispersion

Solid dispersion was defined by *Chiou and Riegelman (Chiou and Riegelman, 1971)* as " a dispersion of one or more active ingredients in an inert carrier or matrix at a molecular level in a solid state prepared by the melting or fusion, solvent or melting solvent method "

Method of preparation for solid dispersion

1. Melting or Fusion method

This method was first introduced by *Sekiguchi and Obi* (*Sekiguchi and Obi, 1961)* to prepare fast release solid dispersion dosage forms and was subsequently modified by a lot of investigators *(Despande et al., 1982; Chiou and Riegelman, 1969; Geneidi et al., 1980).*

Procedure:

The physical mixture of a drug and a water-soluble carrier was heated directly until it melts. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized to a powder and sieved.

A supersaturation of the drug can be obtained by quenching the melt rapidly. Then, solidified on stainless steel plates to favor rapid heat loss. A modification of the process involves spray – congealing from a modify spray drier onto cold metal surfaces to gave pellets of the dispersion to eliminated grinding process and without altering the crystalline modification of the drug.

Advantages:

- Simplicity and economy
- No toxic solvents required
- Possible to obtain a supersaturating of a drug in the system by quenching the melt rapidly from high temperature

Disadvantages:

- Immiscibility between drug and carrier may occur
- Thermal degradation, sublimation and polymorph transformation
- The solidified melts maybe tacky and unhandable
- Only low melting point carriers can be used

2. Solvent method

Procedure:

This method used organic solvent to dissolve the drug and carrier, evaporate the solvent (with or without aids of heat or vacuum), and pulverize the solid product (which maybe called coprecipitate or coevaporate). The choice of solvent and its removal rate are critical to the quality of the dispersion. Otherwise, the choice of solvent maybe effects to polymorphic form of the drug substance.

Advantages:

- Preventing from the thermal decomposition of drugs or carriers due to the low temperature required for the evaporation of organic solvent
- High melting point carriers can be used

Disadvantages:

- Higher cost of operations.
- Difficulty in selection of a common volatile solvent since carriers are generally hydrophilic and the drugs are hydrophobic
- Trace of liquid solvent still presented which may cause toxicity problem
- Costly process due to the large volume of the solvents required and recovery of solvent is not feasible
- Effect on chemical stability of drugs
- Difficulty to reproducing crystal forms of drug

3. Melting – Solvent method

This method developed because of the problem of the previous two methods that mentioned above, this method has the advantages of both melting and solvent method

Procedure:

Dissolving a drug in a small quantity using suitable organic solvent and then incorporating the solution directly into the melt of carrier, and the resultant solution was evaporated to dryness

Physicochemical structure of solid dispersion (*Ford, 1986)*

The physicochemical structure of these dispersions plays an important role in controlling their drug substance. Representative of interaction between drug and carrier can be divided into six structures.

1. Simple eutectic mixtures
2. Solid solutions
3. Glass solution and Glass suspension
4. Amorphous precipitation in a crystalline carrier
5. Compound or complex formation
6. Combination

To investigate about an interaction between drug and carrier maybe examined by using thermal analysis, X-ray diffraction, microscopic, spectroscopic or thermodynamic techniques and by dissolution rate data.

1. Simple eutectic mixture

Usually prepared from the rapid solidfication of the fused liquid of two components, which show complete liquid miscibility, which the materials are not able to form solid solution. This property can be illustrated in a phase diagram in Figure 3. Except beside a phase diagram, the eutectic mixture can be evaluated by X-ray diffraction and thermal analysis (*Sekiguchi et al., 1964).*

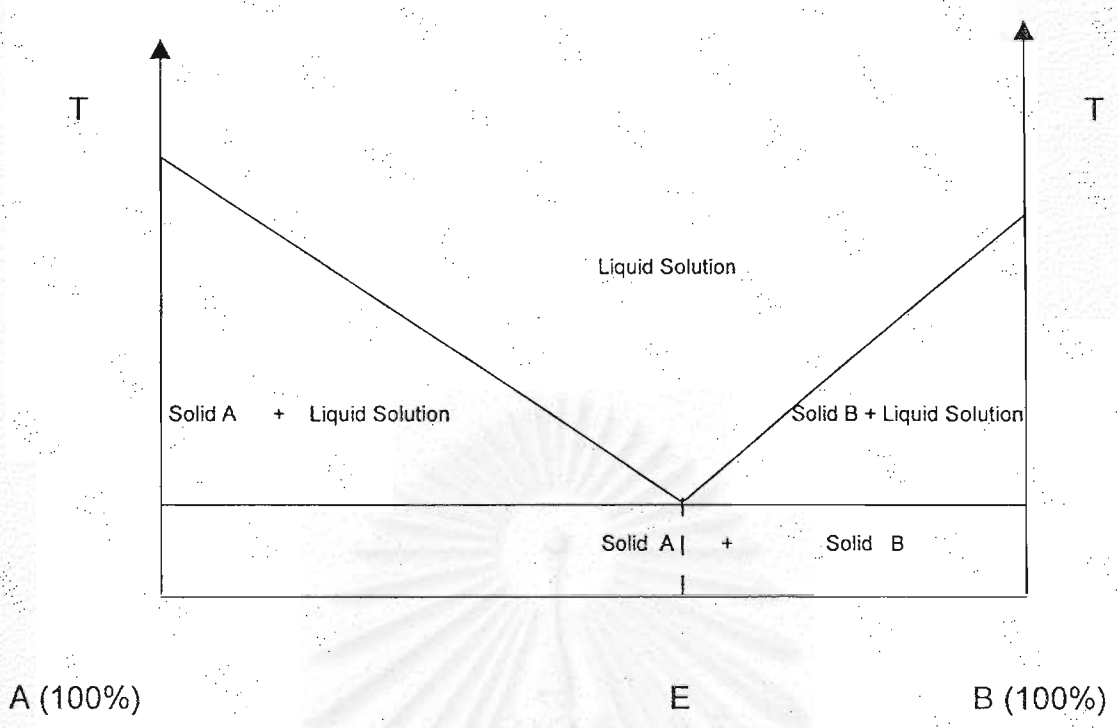


Figure 3 Phase diagram of a simple eutectic mixture

When a eutectic composed of a poorly soluble drug is exposed to water or GI fluids, the carrier maybe released into aqueous medium in fine crystalline form *(Goldberg et al., 1965)*, based on an assumption that both components may simutaneously crystallized out in very small particulate size. From reduction of particle size cause an increase in the specific area so effected to increase dissolution and absorption of poorly soluble drug. The faster dissolution may cause by the effect from carrier that operate in the diffusion layer surrounding the drug particles in an early state of dissolution since the carrier completely dissolve in a short period time; as demonstrated by the faster dissolution rate of acetaminophen from its physical mixture with urea than the pure drug substance. (*Goldberg et al., 1966).*

2. Solid solution

A solid solution as compared with liquid solution, is made up of solid solute dissolved in a solid solvent. It is often called a mixed crystal because the two components, crystallize together in homogeneous one phase system. *Goldberg et al., 1966* studied and suggested that a solid solution of poorly soluble drug in a rapidly soluble carrier achieved a faster dissolution rate than a eutectic mixture because the particle size of the drug in the solid solution was reduced to a minimum state to its molecular size.

The classification of solid solution can be divided into two categories. The first classification depending on their solid miscibility (*Chiou and Riegelman, 1971)* which separated into two groups;

1. The continuous solid solution: two components are miscible or soluble at solid state in all proportions. The bond strength between the different components is greater than the bond strength between the same species of molecules. Up to now, no solid dispersion fall into this category.

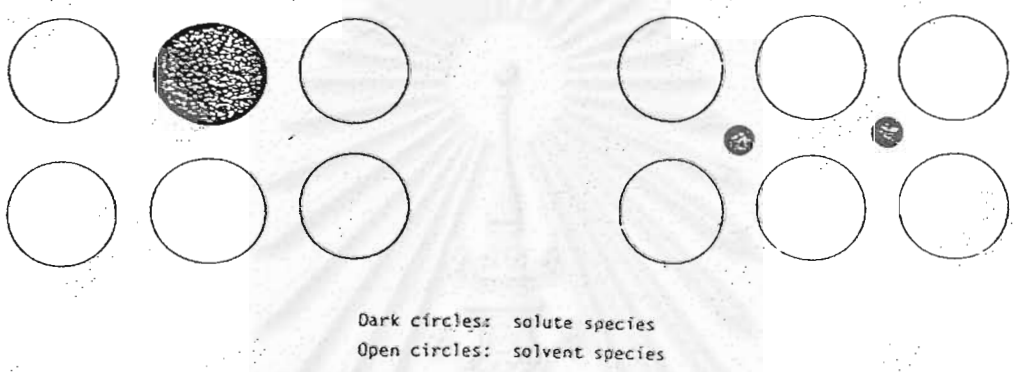
2. The discontinuous solid solution: in contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent in this group of solid solution. Each component showed it capable of dissolving the other components to a certain degree above the eutectic temperature.

The second classification is based on the molecular size of the two components as divided as follows;

1. Substitutional solid solution: the solute molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent. The size of the solute and the solvent molecule should be as close as possible. The molecular size of the two components should not differ by more than 15 %.

2. Interstitial solid solution: the solute molecule occupies the interstitial space between the solvent molecule, solute molecule diameter should be less than 0.59 of the solvent molecule, and that the volume of the solute molecule should be

less than 20 % of the solvent. Large crystalline polymer e.g. polyethylene glycols favors this type of solid solution formation; other factors such as high viscosity, supercooling and physical-chemical interaction between the drugs and the polymers may contribute to the formation of metastable solid solution if the drug – polyethylene glycol melt is solidified rapidly *(Craig, 1990)*. When the temperature was increased, the viscosity increases rapidly so, when quickly solidified of drug – polyethylene glycol was occurred; the crystallization of the drug is retarded due to reduced solute migration and the difficulty in nucleation of the drug in the viscous media.



A. Substitutional solid solution B. Interstitial solid solution

Figure 4 Illustration the structure of (A) substitutional solid solution (B) interstitial solid solution

3. Glassy solution or dispersion

A glass solution is a homogeneous, system in which a solute dissolves in a glassy solvent. It is characterized by transparency and brittleness below the glass – transforming temperature, Tg. During heating, it softens progressively and continuously without a sharp melting point due to the facts that bonding of chemical moieties in the glassy state differ in length therefore, in strength and there is no one temperature at which all the bonds become loosened simultaneously. Liquid or

supercooled liquid whose viscosity is greater than 10^{13} pulses is generally called a glass. This can be differentiated easily by X- ray diffraction methods, a glass is also amorphous to X – ray diffraction so only produce weak and diffuse diffraction effects, while crystallites can give strong and sharp diffraction effect.

Pure polyvinylpyrrolidone and some other polymers dissolved in the organic solvent may become glassy after an evaporation of the solvents. It is possible that the precipitation of drugs introduced into the system is inhibited due to an increase in viscosity while the solvent evaporates. Such inhibition may also be facilitated by possible complexation between the drug and the polymer.The particle size of crystallization of the solute is much smaller in the glass solution due to the difference growth of the crystal in its viscous medium. There is another important advantage of glass solution about the dissolution rate of drug should be faster than in the solid solution.

4. Amorphous precipitation in a crystalline carrier

In the case of drug and carrier crystallize simultaneously from melting process or a solvent method of preparation, the drug may precipitate out in an amorphous form in the crystalline carrier. This, because of an amorphous form is the highest energy form of pure drug so it will produce faster dissolution and absorption rates than the crystalline form. For example, amorphous norubiocin has 10 – fold higher solubility than it crystalline form (*Mullins et al., 1960).*

5. Compound or complex formation

Complex is defined as a species formed by an association of two or more interactant molecules or ions *(Repta, 1981).*

The definition of a complex leads to a classification into two groups based on the type of chemical bonding (*Gennaro et al., 1990).*

1. Coordination complexes: These complexes are formed by covalent bonds in which a pair of electron is, in some degree, transferred from an interactant to the others. The most important examples are the metal ion coordination, complexes between metal ions and bases. Such complex can be classified as products of Lewis acid – base interaction. Protonation of an acid species then constitute a special case of this type.

2. Molecular complexes: These species are formed by noncovalent bonding between the substrate and ligand. The noncovalent forces obviously come from electrostatic, induction and dispersion interaction. These phenomena can give rise to, hydrogen bonding, and charge – transfer and hydrophobic effect. Usually, the kinds of complex species that are included in this class are small – molecule compounds, small molecule – macro molecule species, ion pairs, dimers and other self – associated species, inclusion complexes, intramolecule interaction and clathrate complexes, in which a crystal structure of one interactant encloses molecules of the second interaction. It can be classified molecular complex in term of the kind of an interaction involved in their formation, the kinds of interactants involved or the kinds of complex formed are shown in the Table 1.

Table 1 Classification of molecular complexes

1. Types of bonding or interaction - Charge – transfer - Hydrogen bonding - Hydrophobic interaction - Stacking interaction	3. Type of structure of complex - Self – associated aggregate - Micelle - Inclusion complex - Clathrate
2. Type of structure of interactants - Small molecule – small molecule complex - Small molecule – macro molecule binding - Drug – protein binding	4. Type of structure of interacrants - Enzyme – substrate complex - Antigen – Antibody complex

The dissolution and absorption of a drug into body from a complex is shown in Figure 5

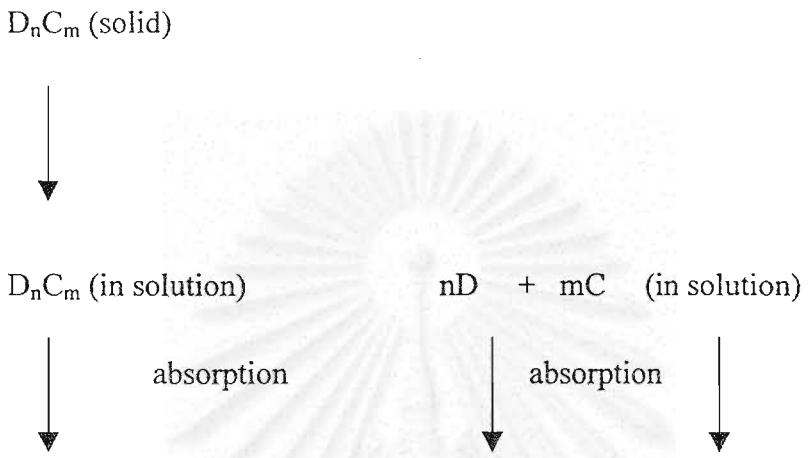


Figure 5 Illustration of the dissolution and absorption of a drug into the body from a complex

The availability of drugs depending on its solubility, the dissolution constant, and the intrinsic absorption rate of the complex *(Chiou and Reigelman, 1971).* Polyvinylpyrrolidone was shown to retard the pharmacological action of numerous compounds such as penicillin, prostigmine, hexobarbital and quinine.The formation of an insoluble complex between phenobarbital and polyethylene glycol 4000 or 6000 appeared to reduce rates of dissolution and permeation of phenobarbital through everted guts of rats *(Kono et al., 1971).*The complexation between griseofulvin and polyethylene glycol 6000 may be thought to occur on the basic of traditional solubility study. Methods that have been used to studying complexes include calorimeter, refractive index, optical rotary dispersion, nuclear magnetic resonance spectrometer, spectrophotometry, kinetics and solubility technique.

6. Combinations and miscellaneous mechanism

Increasing in dissolution and absorption rates maybe the contribution of different mechanisms.

Mechanism of increasing dissolution rates from solid dispersion

The increase in dissolution rates from solid dispersion are attributed to:

1. The reduction of particle size of the drug within the dispersion, this can increase of specific area due to particle size reduction and generally increase rates of dissolution.

2. The amorphous form of the drug precipitate in the crystalline carrier.

3. The absence of aggregation and agglomeration between hydrophobic drug particles.

4. Many carriers increase an aqueous solubility of drugs and may be led to induce microenvironmental solubilization of drug in the static fluid layer surrounding the dissolving dispersion.

The possible solubilization effect by the carrier may operate in the microenvironment immediately surrounding the drug particle in an early stage of dissolution studies. Micellar solubilization and/or lowering surface tension of liquid layer by carrier can lead to decrease in diffusion layer thickness and increase in dissolution rate of drug (*Yalkosky, 1981)*. Some carriers, such as urea (*Feldman and Gibbaldi, 1967)*, can solubilize drugs by effectively breaking up the clusters of hydrogen bond of water molecules in an aqueous solution. This, resulting in an increase in the enthalpy of the system and an increase in water solubility of the drug molecule. Probably the most important solution effect caused by hydrophyllic macromolecules is the solution viscosity. The microenvironment viscosity is a true reflection of resistance of flow by substrate molecules in the solution.

5. An increase in wettability and dispersibility of a drug. This is due to the fact that each single crystalline of drug is very intimately surrounded by the soluble carrier which can readily dissolved, and induce the water to contact and wets the drug particle. In the preparation of dispersion, surfactants are often employed to aid in the wetting of insoluble powder (*Chiou et al., 1976; Andererg et al., 1988).*

6. Formation of soluble compound or complex between drug and carrier

Advantages and disadvantages of solid dispersion

Advantages:

Many advantages according to their rapid dissolution and absorption rates *(Takayama et al., 1982; Stupak et al., 1972; Anastasiadou et al., 1983).* Moreover, this method can be use to obtain a homogeneous distribution of small amount of drugs in solid state, to increase stability of unstable drugs, to formulate a fast initial release priming dose in a sustained release dosage form, and to formulate sustained release or prolonged release dosage form of soluble drugs by using various poorly soluble or insoluble carriers *(Schroeder et al., 1978; Dakkuri et al., 1978).*

Disadvantages:

Solid dispersion resulted in decreasing rate of dissolution of many drugs *(Chang and Jarowski, 1980; Geneidi et al., 1978).* Formulation problem, such as tackyness and unhandable characteristic of some dispersions made it difficult for size reduction. In addition, wet granulation techniques are also unacceptable for tableting the solid dispersion. Stability of the dispersion is an important problem to be concerned.

Criteria of selection the suitable carrier for solid dispersion (*Ford, 1986)*

1.Should be freely water soluble with rapid intrinsic dissolution behavior

2. Non – toxic substance

3. Used for fusion processes, the carriers should be chemically, physically and thermally stable, low melting point is required to avoid the use of excessive heat

4. For solvent processes, the carriers should be soluble in a variety of organic solvents

5. Carrier should increase an aqueous solubility of the drug

6. Carrier should be chemically compatible with the drug

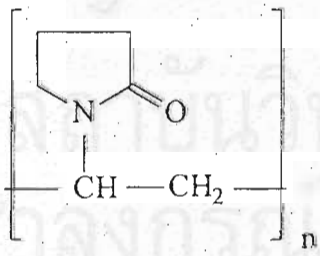
7. Carrier should be pharmacologically inert

In this present study, we are interesting to peruse only two carriers that can be used for dispersion of drug. These carriers are polyvinylpyrrolidone and polyethylene glycol.

Polyvinylpyrrolidone

(American Pharmaceutical Association, 1986)

For this study polyvinylpyrrolidone K 30 (PVP K 30) was used, the molecular structure is shown below.



It molecular weight is 40,000. PVP K 30 is a white to creamy, white odorless or almost odorless, hygroscopic powder. Its melting range is over 275°C with decomposition. PVP K 30 is soluble in water up to 60 % and freely soluble in many organic solvents, including monohydric (ethanol, methanol) and polyhydric alcohol, acid, esters, ketone, methylene chloride and chloroform. In addition, it is

essentially insoluble in ether, hydrocarbon, carbon tetrachloride, ethyl acetate and mineral oil.

From the melting temperature that excess 275 °C, it is suitable for solvent prepare dispersions. PVP of various grade may be use to solubilize many drugs. These, result in an increasing in drug solubility which maybe effect from wetting and hydration of the polymer surface that leads to swelling. When the molecular weight of PVP was increased, the dissolution rates of drugs from dispersion decreased. This maybe explained that when molecular weight increase, the viscosity of the polymer solution increase and the solubility of the polymer decrease.

PVP can be utilized in preparing solid dispersion as a carrier such as furosemide (*Anastasidou et al., 1983)* and griseofulvin*(Kaur and Eaves , 1980)*, etc.

Polyethyleneglycol

(American Pharmaceutical Association, 1986)

For this study, we use Polyethylene glycol 1450 , 4000 and 6000

The molecular structure is shown below,

$$H(OCH_2CH_2)_nOH$$

For the empirical formula is shown : $OHCH_2(CH_2OCH_2)_mCH_2OH$

Where m represents the average number of oxylene groups.

Table 2 Structural formula and molecular weight of typical polyethylene glycol polymers

Grade	m	Average molecular weight
PEG 200	4.2	190-210
PEG 300	6.4	285-315
PEG 400	8.7	380-420
PEG 540 (blend)	-	500-600
PEG 600	13.2	570-613
PEG 900	15.3	855-900
PEG 1000	22.3	950-1050
PEG 1450	32.5	1300-1600
PEG 1540	28-36	1300-1600
PEG 2000	40-50	1800-2200
PEG 3000	60-75	2700-3300
PEG 3350	75.7	3000-3700
PEG 4000	69-84	3000-4800
PEG 4600	104.1	4400-4800
PEG 8000	181.4	7000-9000

Where m represents the average number of oxylene groups.

Polyethylene glycol composed of ethylene oxide and water, PEG grades 200-600 is liquids, while grade 1000 and above are solids at an ambient temperatures. Solid grades are white to off-white color and range from pastes to waxy flakes. The odor or faint and sweet. All grades of PEG are soluble in water and miscible in all

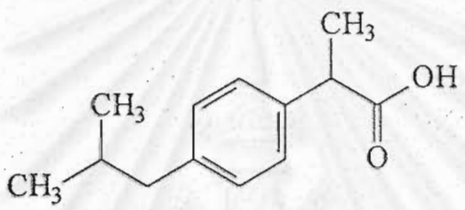
proportions with the other PEG grades. Solid PEGs are soluble in acetone, dichloromethane, ethanol and methanol. They are slightly soluble in aliphatic hydrocarbons and ethers but insoluble in fats, fixed oils and mineral oil. The molecular weight fractions used for solid dispersion vary from 1000 (soft unctuous solids) to 20000 (hard brittle crystals). Their molecular size of the polymer favors the formation of interstitial solid solution with drugs. In addition their viscous properties at temperature just above their freezing points retard crystallization and favor supercooling of the drug substrate. The high viscosity of the solid PEG may also lead to precipitation of metastable product. Their low melting point (< 65 °C) provide an economic basis for preparing dispersion by the melt method, and their solubility in a wide range of organic solvent favors solvent method since highly concentrated PEG solution are viscous and retard crystallization of drugs.

There are many studies about properties of PEG – drug systems (*Ford, 1986)*, during dissolution test PEG may also wet the disperses drug and promote dissolution rate. PEG can increase an aqueous solubility of many drugs such as aspirin, indomethacin, griseofulvin probably by weak complexation and restructuring the arrangement of water molecules. The ability to form solid solution enables PEG to solidify liquid drug, which are immisible with water and increase their solution rates. On the other hands, they are evidences indicated the problem of using PEG in solid dispersion techniques. For example the problem about chemical instability with drug e.g. digitoxin in PEG 6000 is unstable and fusion of aspirin with PEG 6000 lead to transesterification of drug by forming salicylic acid. In some cases such as, phenobarbitone, may form poorly soluble complexes with PEG. This reducing the bioavailability of the drug.Studied about the effect of molecular weight on dissolution behavior. The dissolution rates of the pure polymers, without drugs, decrease as the molecular weight increase and were inversely related to the molecular weight and showed the similar results when some drugs were dispersed with PEG, dissolution rate of drugs decreased as the molecular weight of the polymer increased. These were found for hydroflumethiazine, indomethacin, sulphadimadine and tolbutamide. However, for the other drugs such as papaverine, frusemide and hydrochlorothiazine showed the reverse trend that dissolution rate decrease which decreasing molecular

weight of PEG. The reason maybe the higher molecular weight of PEGs caused more viscous solutions, thereby further reducing crystallization of the drug or increasing for incorporation of drugs as solid solution and maybe flake materials more readily during dissolution.

Ibuprofen: A model drug

Ibuprofen is an anti – inflammatory drug in the group of NSAIDs.



2-(4- Iso – butylphenyl) propionic acid

Description A white or almost white powder or crystals with a characteristic odour and a slight taste.

Melting point 75 – 78 ° C

Apparent pKa 5.2

Solubility Ibuprofen is practically insoluble in water; soluble 1 in 1.5 of ethanol, 1 in 2 of ether , 1 in 1 of chloroform , and 1 in 1.5 of acetone. Ibuprofen is readily soluble in most organic solvents, and is soluble in aqueous solutions and in aqueous solutions of alkali hydroxides and carbonates. It is freely soluble in dichloromethane.

Use Analgesic, antipyretic, anti-inflammatory. In low doses, it is effective in the management of mild to moderate pain and fever. In higher doses, it is anti – inflammatory, used in treatment of rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders.

Dose 600 – 1200 mg daily in divided doses.

Maximum total daily dosage was 2400 mg.

Adverse Effect The most common adverse effects were gastrointestinal disturbances. Others were allergic reaction, dizziness and nervousness, etc.

CHAPTER II

MATERIALS AND METHODS

MATERIALS :

1. MODEL DRUG

Ibuprofen (Lot no. 4050-0041, Albemarle corporation, South Carolina U.S.A.; Distributed by Acdon Co.,th Thailand)

2. DISPERSION CARRIERS

Polyvinylpyrrolidone K30 (Distributed by Samchai chemical, Thailand)

Polyethylene glycol grade 1450 (Distributed by Pharmaceutical trades Co.,Ltd., Bangkok Thailand)

Polyethylene glycol grade 4000 (Distributed by Srichand United dispensary Co.,Ltd., Bangkok Thailand,Lot no. 0702BSO319)

Polyethylene glycol grade 6000 (Lot no. 427124/1 33901, Fluka chemie, steinheim Switzerland)

3.CHEMICALS

Absolute ethanol AR grade (Lot no. L 113207 BDH Laboratory supplies;England)

Methanol AR grade (Lot no. 01 04 1072, Labscan Asia Co.,Ltd., Bangkok Thailand)

Chloroform AR grade(Lot no. 01 03 1125, Labscan Asia Co.,Ltd., Bangkok Thailand)

Potassium dihydrogen orthophosphate (KH_2PO_4) (Lot no. 0071508, Fisher scientific UK Limitted, Leics UK)

Sodium hydroxide pellets (Mallinckrodt Baker, Xalostoc Mexico)

4. EQUIPMENT

Stirrer(RW 10 R, JANKE&KUNKEL, IKA® Labortechnik)

Analytical balance (Model A200S, Satorious, Germany)

Dissolution Apparatus (Model DT-6R, Erweka®, USA.)

Differential Scanning Calorimeter with Thermal Analysis Controller (NETZCH DSC 200, Germany)

Fourier Transform Infrared Spectrophotometer (FT-IR, Model 1760X, Perkin Elmer.Ltd, USA.)

Scanning Electron Microscope (Model JSM-5410 LV, Jeol Ltd., Japan.)

Powder X- rays diffractometer (Model JDX-3530 Diffraction System, JEOL, Japan)

^{13}C Nuclear Magnetic Resonance (Model Bruker AVANCE Dex-300)

Powder flow meter equipped with the following:

an analog-to-digital convector (MacLab™)

a personel computer (Macintosh) and printer

a MacLab™ front-ends and a isotronic transducer

pH meter (Model 292, Pye Unicam Ltd., England.)

Water bath (Model DT 2 CB22-20e DT Hetotherm, Switerland))

Ultraviolet/visible (UV/Vis) spectrophotometer (Shimadzu UV 1601. Shimadzu Co.,Ltd., Japan)

Sieve Shaker (Josef Deckelmann, type EMK4, Western Germany)

Size measurement by computor program; SemAfore version 2.0

METHODS:

1. Preparations of solid dispersion of ibuprofen with dispersion carriers; Polyvinylpyrrolidone and Polyethylene glycol

Ibuprofen (IB) was weighed accurately (10.67 g) and transferred into 10 ml beaker. We added 16 ml of absolute ethanol and mix together until a saturated and clear solution was obtained. Accurately weighed quantity of polymer that was used as dispersion carrier, PVP K 30 and PEG grades; 1450, 4000 and 6000, into saturated solution of IB in ethanol; in various weight proportions of drug: polymer 1:0.5, 1:0.75, 1:1 as shown in Table 3. The mixtures were then stirred until viscous or and clear solutions was obtained. In the case of using PEG, have to increase by using waterbath to control the temperature to 55 ± 1 °C to produce the complete solubility of PEG. The solvent was removed by evaporation under reduce pressure at approximately 40 °C and stored in a desiccator for further studies.

2. Preparations of ibuprofen pellets (IPs) by phase partition technique

From the preliminary study, chloroform was dispersed in water (which was contained in the reactor) in a ratio as indicated in Table 4.These experiments designed for the determination of suitable quantity of bridging agent (chloroform) for phase partition technique of IB.

Table 3 The amount of IB and dispersion carriers in given preparations

Ingredient(s)	Weight (g)											
Ibuprofen	10.67	10.67	10.67	10.67	10.67	10.67	10.67	10.67	10.67	10.67	10.67	10.67
PVP K 30	5.335	8.003	10.67	-	-	-	-	-	-	-	-	-
PEG 1450	-	-	-	5.335	8.003	10.67	-	-	-	-	-	-
PEG 4000	-	-	-	-	-	-	5.335	8.003	10.67	-	-	-
PEG 6000	-	-	-	-	-	-	-	-	-	5.335	8.003	10.67
Ratio	1:0.5 PVP K 30	1:0.75 PVP K 30	1:1 PVP K 30	1:0.5 PEG 1450	1:0.75 PEG 1450	1:1 PEG 1450	1:0.5 PEG 4000	1:0.75 PEG 4000	1:1 PEG 4000	1:0.5 PEG 6000	1:0.75 PEG 6000	1:1 PEG 6000

Table 4 Amount of solvents selected from phase diagram used to prepare IPs

Chloroform (%)	Chloroform (ml)	Ethanol (ml)	Water (ml)
1%	2	16	182
1.5%	3	16	181
2%	4	16	180

* from phase diagram of cholroform , ethanol , water

The agitator was turned on and adjusted to 1500 rpm at 25 ± 2 ° C for 20 minutes to disperse bridging solvent into small droplets. Then, a clear solution of pure drug or dispersion mixture of drug and carriers in ethanol was added to the reactor, and the phase partition of drug (plus carrier) in ethanol to bridging solvent started to occur. The appropriate time for stirring after phase partition started was 15 minutes. After that, the IPs were separated from solvent by filtering with vacuum and dried in a desiccator for a week then kept in a closed container for further studies.

3. Physicochemical studies of ibuprofen and drug carriers

3.1 Powder X-ray diffraction

Powder X-ray diffractogram can indicate about the crystal structure and atomic arrangement of drug molecule. The diffractograms will be presented in specific fingerprint for each molecule with diffracting and scattering at specific angle 2θ. Degree of crystallinity of sample is show in tracing. Moreover, it can be employed for observing the interaction of each component in the samples as well.

In our studies, the samples were evaluated with X-ray powder diffraction, diffraction patterns were obtained on X-rays diffractrometer (Model JDX-3530 Diffraction System, JEOL, Japan). The pattern was collected with 30 kV of tube voltage and 30 mA of tube current in an angular range $5 < 2\theta < 40$, in a stepwise scan mode (step width 0.04 ° , counting time 1 sec/step).

3.2 Infrared spectroscopy study

Infrared (IR) spectroscopy was used to confirm the interaction between IB and carriers in the formulations. If the change in the IR spectra were observed, it could be infer that chemical interaction between substance was occurred.

Fourier transform IR spectroscopy (FT-IR) is a new generation instrument of IR spectroscopy. It has advantages to record the signal with high sensitivity and modifying the noise of experiments.(Model 1760X,Perkin Elmer. Ltd.,USA).

Samples were weighed about 1 mg and co-grinding with potassium bromide (KBr) and press into disc. Using the scanning range was 400 – 4000 cm^{-1}. FT-IR spectra of IB (with carrier) before and after phase partition were obtained. It was noticed that rigorous grinding should be avoided to prevent false interpretation of the data obtained.

3.3 Thermal analysis

Differential scanning calorimeter was widely used to determine an interaction of materials, using differential scanning calorimeter with thermal analysis controller (Model NETZCH DSC 200, Germany).

Samples (3 – 5 g) were weighed in an closed aluminum sample pan and placed in the equipment beside the reference pan made by the same method except without sample. Nitrogen was use as carrier gas for preventing sample oxidation. The rate of temperature increment in heating cycle was 10 ° C per minute. Pure water and indium were used to calibrate the DSC temperature scale and enthalpic response. Thermogram of endothermic peak of each sample was collected and compared with the heat flow pattern, and otherwise, can give the data in the term of fusion or enthalpy changing values.

3.4 ^{13} Carbon Nuclear magnetic resonance (^{13}C–NMR) spectroscopy

^{13}C-NMR spectra were obtained from a Bruker AVANCE Dex–300 FT-NMR Spectrometer, operating at 75 MHz for carbon NMR and chemical shifts (ppm) of the residual undeuterated solvent ($CDCl_3$) were used as reference.

4. Physical properties of IPs after phase partition technique

4.1 Scanning electron microscopy (SEM)

Studying about powder morphology of the raw materials as compared with IPs from the formulation by the scanning electron microscopy (SEM).

The samples were coated with gold prior to the microscopic examination with ion sputtering. Size, shape, surface topography of IPs were observed.

4.2 Bulk, tapped density and percent Compressibility

Five grams of the samples were accurately weighed and carefully transferred into a 25 ml cylinder, The bulk volume was recorded and the bulk density was calculated according to equation 1.

$$\text{Bulk density (g/ml)} = \frac{\text{weight of the powder}}{\text{Bulk volume}} \quad \ldots\ldots (1)$$

Tapped density is an extension of bulk density measurements. It was performed by dropping graduate cylinder filled with sample on a hard surface from 5 cm height, until the volume was stable or at lease 500 times (*Carr, R.L., 1970).* Division of the weight by this constant volume presented as tapped density.

$$\text{Tapped density (g/ml)} = \frac{\text{weight of the powder}}{\text{volume after tapped}} \quad \text{..... (2)}$$

The percent compressibility (% Carr's compressibility or index) of the powder was calculated from the tapped and bulk density measurements from the following equation *(Carr, R.L., 1970)*.

$$\text{Percent compressibility} = \frac{(Td - Bd) \times 100}{Td} \quad \text{..... (3)}$$

Where Td and Bd are tapped and bulk density, respectively. The results were average from three determinations.

4.3 Determination of flowability

The rate of flow of IPs was adapted from MacLab™ program. Adequate amount of sample was weighed and filled into the funnel which was placed on the holder. There was a plastic bottle on the sensor. The isotronic transducer was placed on the other holders and below the funnel. Then the powder was allowed to pass through the funnel into the plastic bottle. The graph showed the changing weight of the sample when time passed. Slope of this graph showed the rate of flow of the samples.

Calculation of angle of repose is one of the method to determined about flow property of the sample. The amount of the sample was weighed and filled in the funnel that fixed on the stable height with the clamp. Angle of repose was calculated from the following equation.

$$\propto = \tan^{-1} \frac{H}{R} \quad \text{.....(4)}$$

Where $\propto$ is the angle of repose: H and R are the height and radius of pellet pile, respectively. The results were average from three determinations.

4.4 Particle size and Particle size distribution determination

Using microscope equipment and by computer program; SemAfore, the mean particle size and particle size distribution of the samples can be determined, using 200 IPs for the measurement in each formulation.

5. Dissolution studies of IPs

5.1 Determination of ibuprofen content

Calibration curve of ibuprofen in methanol

Ibuprofen of 400 mg was accurately weighed into a 100 ml volumetric flask through the aid of a glass funnel. The powder was rinsed off the funnel by absolute methanol, then dissolved and adjusted to volume with absolute methanol. Precisely pipetted 10 ml of this solution into 25 ml volumetric flask, and used as stock solution.

Different amounts of the standard stock solution, 1, 2, 3, 4, 5 ml was individually pipetted into the 10 ml volumetric flask and dilute to volume with absolute methanol. The final concentrations of the obtained standard solutions were 160, 320, 480, 640, 800 mcg/ml, respectively.

The absorbances of the standard solutions were determined by a UV/Visible spectrophotometer at 265 nm with absolute methanol as a blank reference. The absorbance and the calibration curves of IB are presented in Table 1 A and Figure 1 A , (Appendix A) , respectively. The result of each concentration of the standard solution was averaged from three determinations.

IPs from the formulations were determined about their drug content by weighing accurately 500 mg of IPs into 100 ml volumetric flask, dissolved and

adjusted to volume with absolute methanol. Pipetted 10 ml of this solution and transferred into 25 ml volumetric flask, and diluted to volume with absolute methanol. Pipetted 3 ml of the solution into 10 ml volumetric flask diluted and adjusted to volume. Then analyzed this solution with UV/Vis spectrophotometer at the same wavelength of 265 nm. The content of IPs was calculated by comparing with the standard curve of IB in methanol. The result was averaged from three determinations.

Calibration curve of ibuprofen in phosphate buffer pH 7.2

The 150 mg of IB was weighed accurately and transferred to 100 ml volumnmetric flask, then adjusted the volume with phosphate buffer pH 7.2. This solution was used as stock solution. Different amounts of stock solution, 1, 2, 3, 4, 5 ml was pipetted accuratlty into 10 ml volumemetric flask and adjusted to volume with phosphate buffer pH 7.2 to obtained standard solution in final concentrations of; 150, 300, 450, 600, 750 mcg/ml, respectively.

Absorbance was determined by a UV/Visible spectrophotometer at the same wavelength, 265 nm with phosphate buffer as a blank reference. The absorbance and the calibration curves of IB were presented in Table 2 A and Figure 2 A, in Appendix A, respectively. The result was averaged from three determinations. This calibration curve for dissolution study of IPs from the formulations.

5.2 The release of ibuprofen from IPs

5.2.1 Preparation of dissolution medium

In this study, phosphate buffer pH 7.2 was used in the dissolution testing. It was prepared by following the direction according to phosphate buffer solution pH 7.2 as appeared in USP 23.

5.2.2 Dissolution study of IPs

Dissolution studies were performed using USP 24, apparatus # 2. Samples of pure drug, pellets of pure IB and pellets of mixture between IB and dispersion carriers (PVP and PEG) equivalent to 400 mg of the drug (except in the case of finished product that filled the pellets into capsules, samples were equivalent to 200 mg of the drug) were added into dissolution medium (900 ml of pH 7.2 phosphate buffer at a temperature of 37 ± 0.5°C), which was stirred with a rotating paddle at 50 rpm. At suitable time intervals, 10 ml samples were withdrawn filtered and analyzed with UV/Vis spectophotometer at 265 nm. The same volume of fresh medium was replaced and the correction for the cumulative dilution was calculated. Each test was performed in tripicate.

6. Preparation of IPs filled in capsule

To observe and compare the dissolution profiles between the capsule of IB powder and the capsules that contained IPs, weighed IB powder and IPs from the selected formulation of this study equivalent to 200 mg of the drug filled in the gelatin capsule No.0 were studied. The dissolution was performed in the same condition that we used in dissolution study of IPs.

7. Statistical analysis

The indication of different dissolution profiles was tough to justify by using only visual observation from dissolution pattern comparison. One of the parameters for measuring the difference between dissolution curves was dissimilarity "f_1" and similarity factor "f_2". At early stage, either dissimilarity or similarity factor was developed to specified for immediate release dosage form (*Shah et al., 1998*) but for sustained release dosage form, this was applicable to utilize both parameters (*Pillay and Fassihi,* 1998). Both parameters were calculated from the following equations (*Shah et al., 1998*).

$$f_1 = \left\{ \left[\sum_{i=1}^{p} |\mu_{ti} - \mu_{ri}| \right] \Big/ \left[\sum_{i=1}^{p} \mu_{ri} \right] \right\} \times 100 \qquad \text{.....(5)}$$

$$f_2 = 50 \log \left\{ \left[1 + (1/P) \sum_{i=1}^{p} (\mu_{ti} - \mu_{ri})^2 \right]^{-1/2} \times 100 \right\} \qquad \text{.....(6)}$$

Where μ_{ti} and μ_{ri} represent mean cumulative dissolution measurement at P time of test and references preparations, respectively, while P is time point of dissolution observations.

Conceptually, f_1 is a function of average absolute difference and could be referred as a difference factor. On the other hand, f_2 is a function of the reciprocal of mean square transform of the sum square distances at all point and could be implied as similarity factor. If the two dissolution profiles are identical then f_1 is equal to 0 whereas f_2 is close to 100. Thus, similarity of dissolution pattern is indication of the lowest values in f_1 and highest values in f_2 variable. By the way, unequality between dissolution profile was determined as values for displaying the magnitude of difference. Average percentage of difference which calculated from equation 7 was very useful parameter for the above proposal. The example of various average percentages difference and limit of similarity factor are given in Table 5. If the data of similarity factor could be obtained then the average percentage difference was calculated from equation 7. The higher average percentage difference indicate the numerous unlikable.

$$f_2 = 50 \log \left\{ \left[1 + \left(\textit{percent average difference} \right)^2 \right]^{-1/2} \times 100 \right\} \qquad \text{.....(7)}$$

Table 5 Relationship between average percentage difference and similarity factor "f_2" of two dissolution profiles

Average percentage difference	Limit of similarity factor *
1	92.47
2	82.53
3	75.00
4	69.24
5	64.63
6	60.80
7	57.53
8	54.68
9	52.15
10	50.00

* Limit of similarity factor "f_2" is computed according to the equation 7.

Empirically from the experience in dissolution data analysis, many researchers agree that an average difference of not more than 10 % at any sample time point, of the batches of the same formulation may be acceptable that mean f_2 become approach to 50 for simplicity. So, we considered that the test batch dissolution similar to the reference batch , if the $f\,2$ value of the two true profiles is not less than 50. We use this criteria for studied and determined about dissolution profile in this research work.

CHAPTER III

RESULTS

Part I Preparation and evaluation of ibuprofen pellets without drug carrier

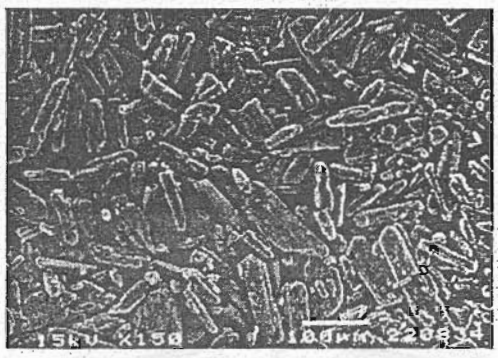
Preparation of IPs (drug alone) with phase partition technique

1. Preliminary studies for determining suitable quantity of bridging solvent in phase partition

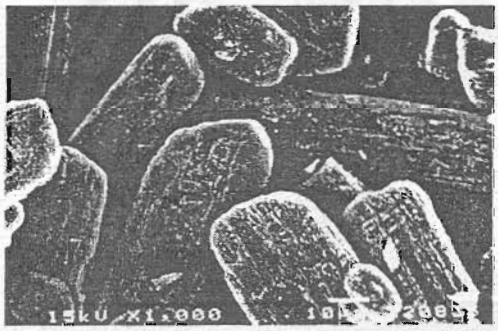
A suitable amount of bridging solvent was selected from a ternary diagram that representing the solubility of bridging solvent (chloroform) in mixtures of ethanol and water as indicated from previous reported (Umprayn et al., 2001) . For this study, the quantities of chloroform were varied (1%, 1.5%, 2 % , respectively) and used for phase partition technique.

1.1 Morphology of IPs by SEM

Scanning electron photomicrographs of ibuprofen (IB) raw material and ibuprofen pellets (IPs) from phase partition technique with different percentages of bridging solvent are given in Figures 6 and 7. The microscopic appearance of the original IB crystals showed many short rods and some needle shaped crystals (Figures 6A and 6B). All the ratios of bridging solvent used in this study (1%, 1.5%, 2% chloroform) can be used to prepare the spherical pellets that showed in Figures 7A, 7C and 7E, respectively. However, at 1.5 % bridging solvent, the IPs seem to be rounder. From surface investigation indicated that, the surface of IPs were composed of small IB crystals. We found that, at 2 % bridging solvent, the surface of the pellets that composed of small crystals were tightly packing when compare with IPs from 1 and 1.5 % bridging solvent (Figures 7B, 7D and 7F). The results of microscopic examination indicated the crystal habit of IB microcrystals were combination of rod and plate shapes. From these results, 1.5 % chloroform in the phase partition technique found to be suitable for further studies.

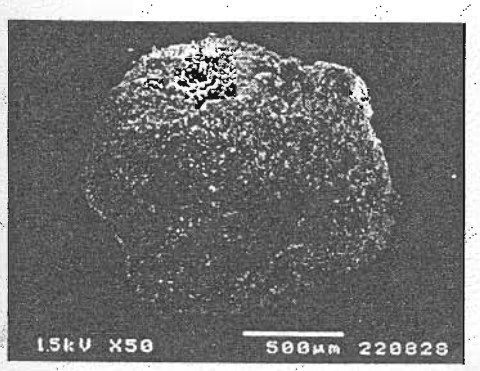


A



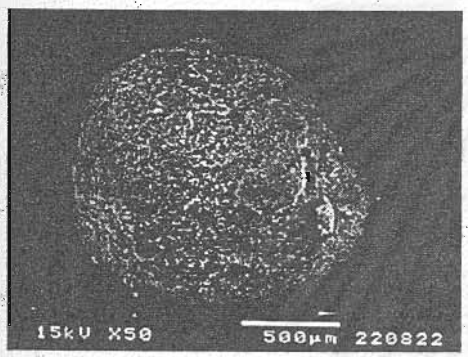
B

Figure 6 Scanning electron photomicrographs of IB original crystals
(6A: x 150, 6 B: x 1000)

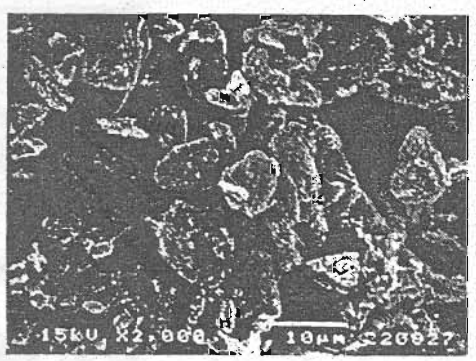


A

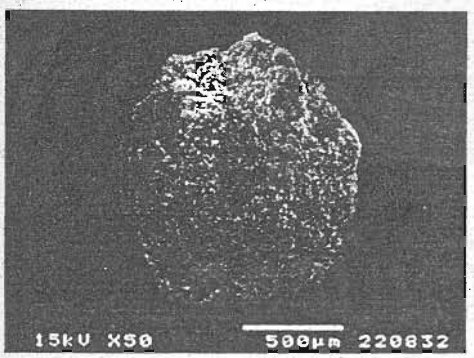
B



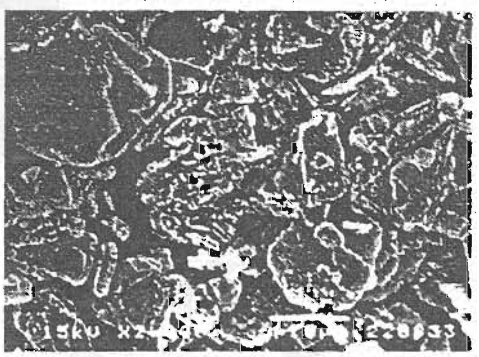
C



D



E



F

Figure 7 Scanning electron photomicrographs of IPs using various ratios of bridging solvent (7 A , B are IPs with 1% chloroform, x 50, x 2000 ; 7C , D are IPs with 1.5% chloroform, x 50, x 2000 ; 7E , F are IPs with 2% chloroform, x 50, x 2000, respectively)

1.2 Powder X-ray diffraction study of IPs of drug alone

Powder X-ray diffractometry is a useful tool for the detection of crystallinity of solid phases. The X-ray powder pattern of each crystalline form of a compound is an unique pattern. The X- ray diffractograms of IB is shown in Figure 8. Major X-ray diffraction peaks of IB were at 6.05°(2θ), 12.18°(2θ), 16.54°(2θ), 17.58° (2θ), 18.70 °(2θ), 19.02°(2θ), 19.42°(2θ), 20.10°(2θ), 22.30°(2θ), 22.74°(2θ)and 24.54°(2θ) respectively. All of the X- ray diffractrograms of IPs from different ratios of bridging solvent (1%, 1.5%, 2 % chloroform) were not different from each other as shown in Figure 9. When compared the X- ray diffractrograms of IPs with the X-ray diffractograms of IB, their diffractograms appeared similar to major X-ray diffractograms of IB original crystals, but found some changes in intensities, as shown in Figure 10.

1.3 Differential scanning calorimetry (DSC) of IPs of drug alone

The DSC thermograms of IB, pure drug exhibited a single endothermic response coresponding to the melting point of the drug, the melting point was observed at 78.3 °C as showed in Figure 11. Figure 12 shows the DSC thermograms of IPs at different ratios of bridging solvent (1%, 1.5%, 2 % chloroform). All of these formulations gave the same characteristic of melting endothermic peak and closed to the endothermic peak of ibuprofen, original crystals.

1.4 Infrared spectroscopy of IPs of drug alone

The IR spectrum of IB raw material is given in Figure 13. As focused in an important region of 4000 – 2000 cm^{-1}, the drug showed aliphatic stretching frequency at 2960 cm^{-1}. This band had a broad baseline due to the presence of carboxylic OH group. In the carbonyl frequency region, IB showed a strong band at 1700 cm^{-1} due to C = O stretching in carboxylic group. All of the IPs, from the different formulations that varied in an amount of bridging agent, showed the same IR spectra when compared with each other and were not different from the IR spectrum of IB raw material. These spectra are given in Figure 14.

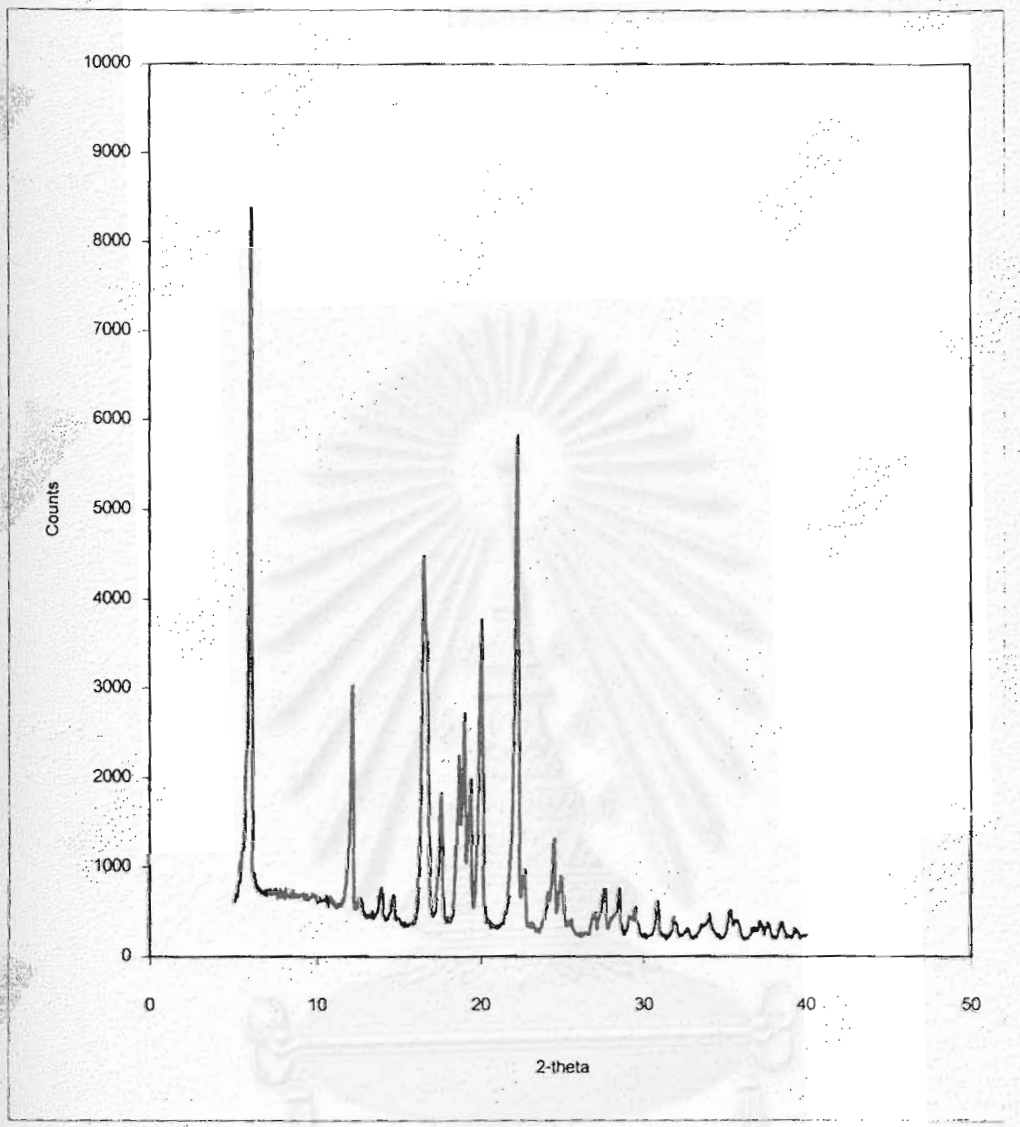


Figure 8 X-ray powder diffractogram of IB raw material

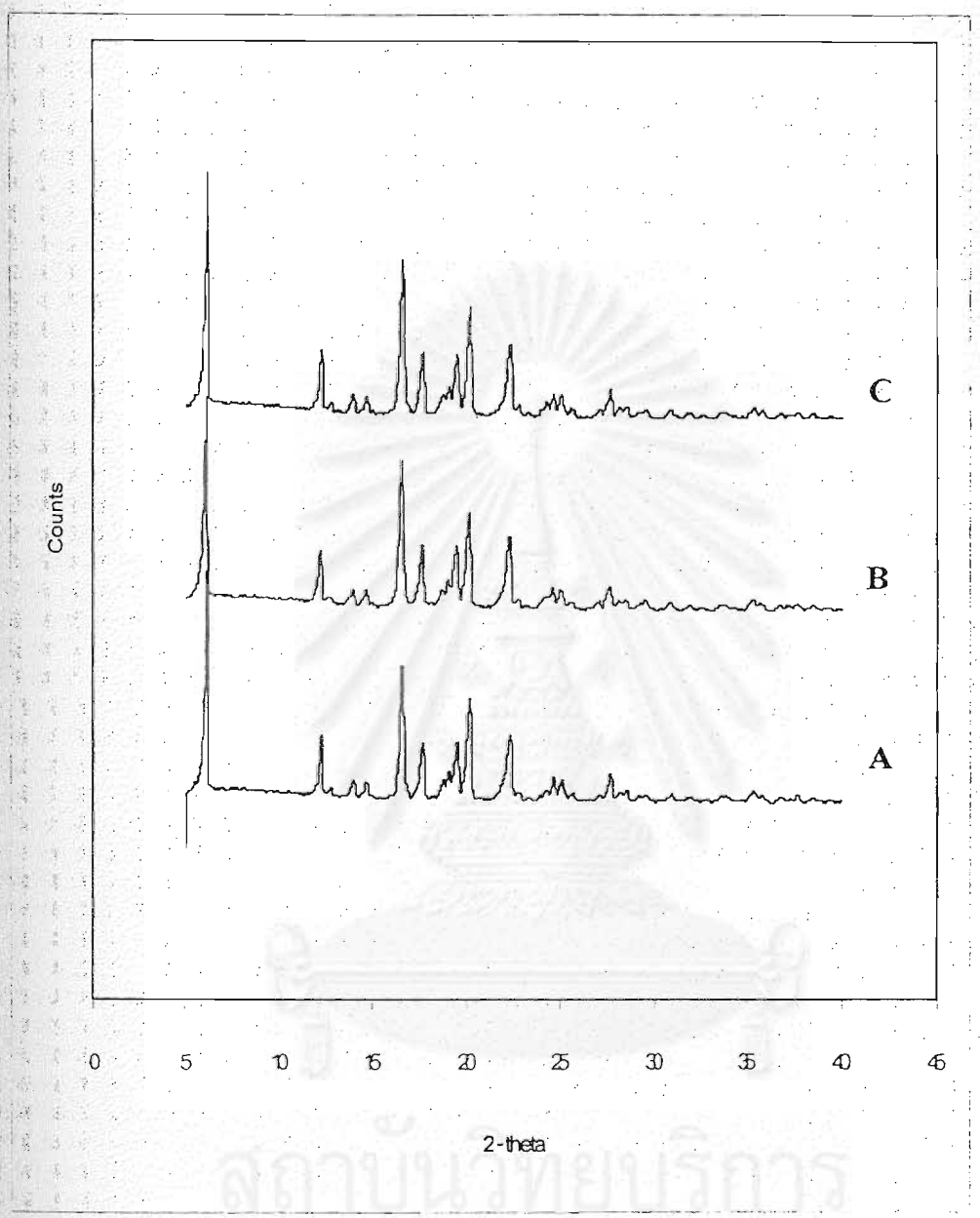


Figure 9 X-ray powder diffractograms of IPs at various percentages of bridging solvent (A) 1% $CHCl_3$, (B) 1.5 % $CHCl_3$ and (C) 2% $CHCl_3$

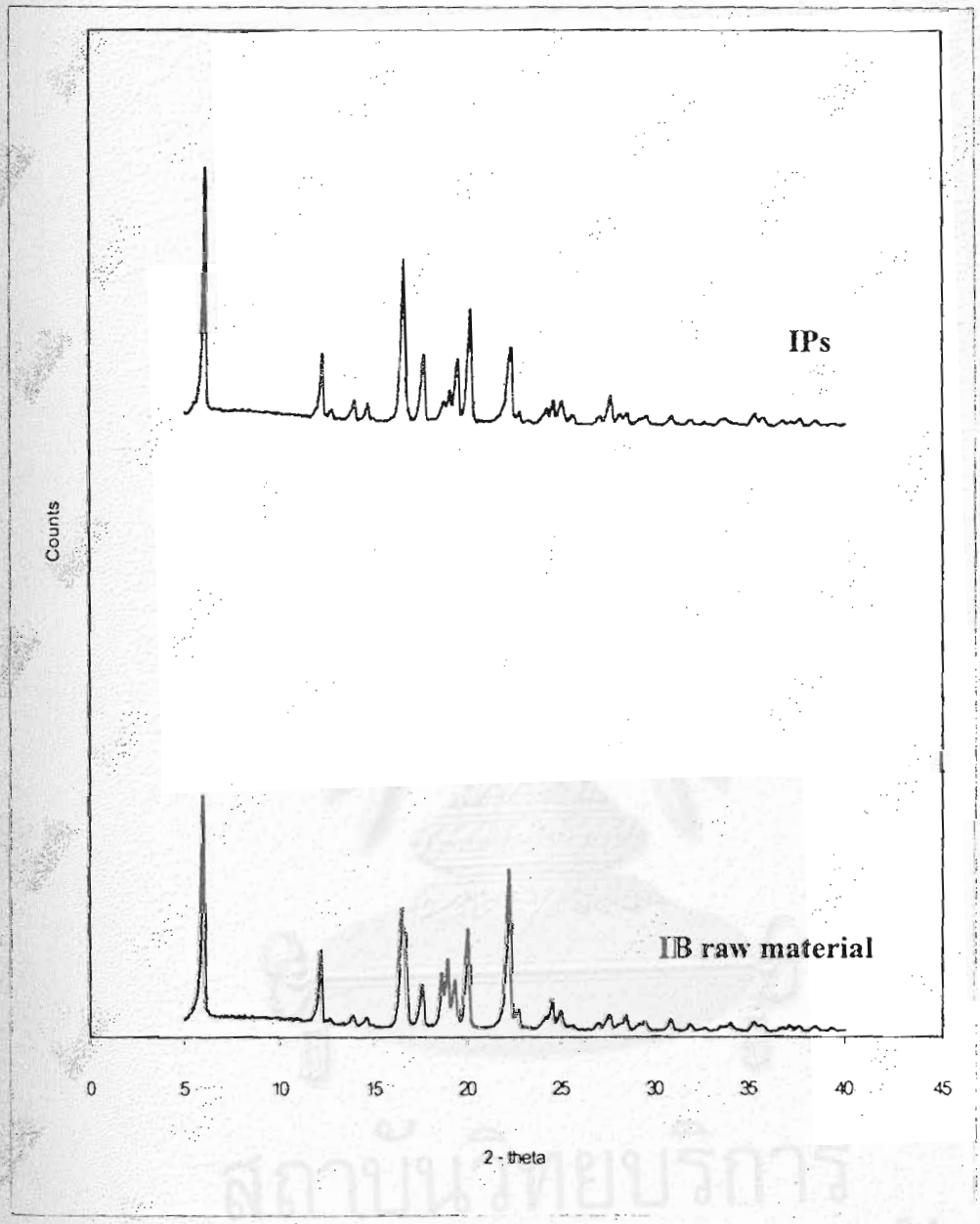


Figure 10 Comparison of the X –ray powder diffractograms of IB raw material with IPs (after phase partition)

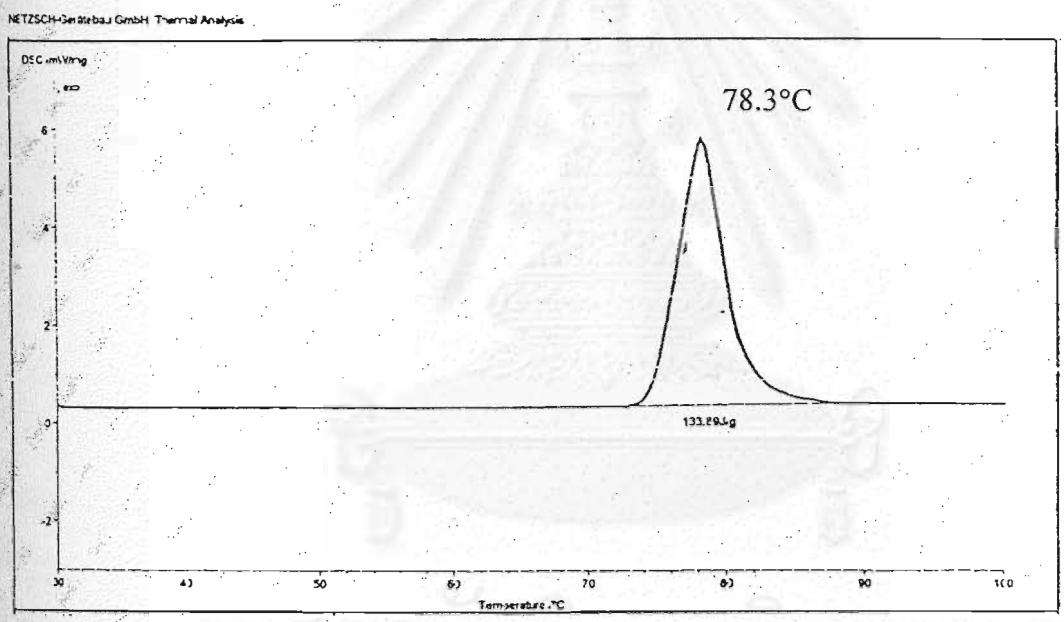


Figure 11 DSC thermogram of IB raw material

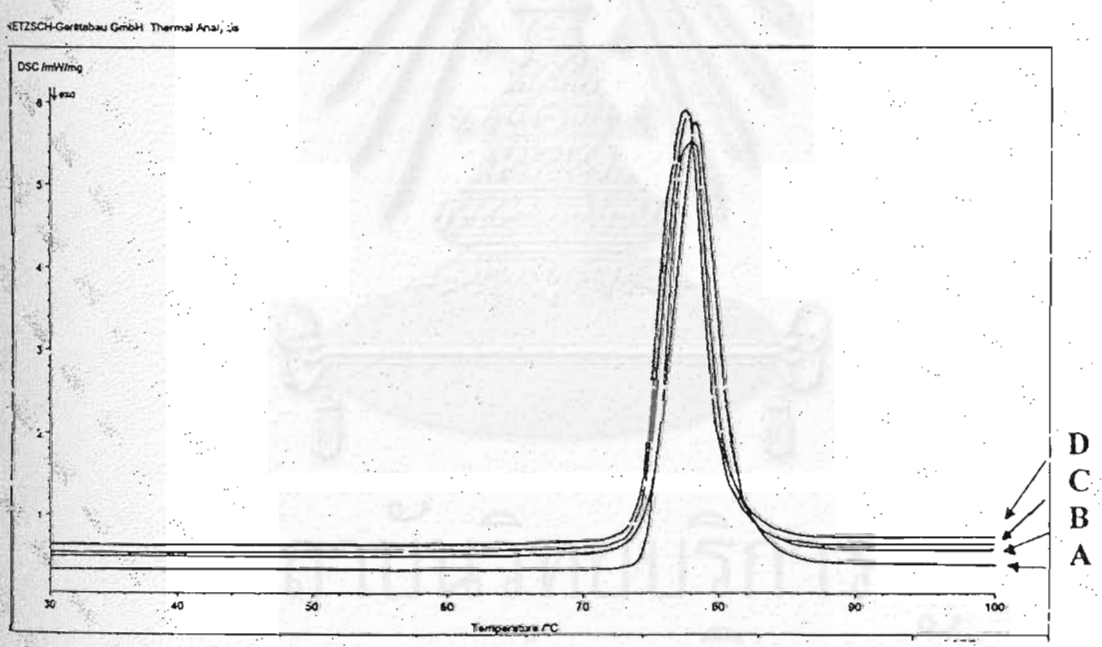


Figure 12 DSC thermograms of IPs at (A) 1 % $CHCl_3$, (B) 1.5 % $CHCl_3$ and (C) 2 % $CHCl_3$ as bridging solvent, as compared with (D) IB raw material

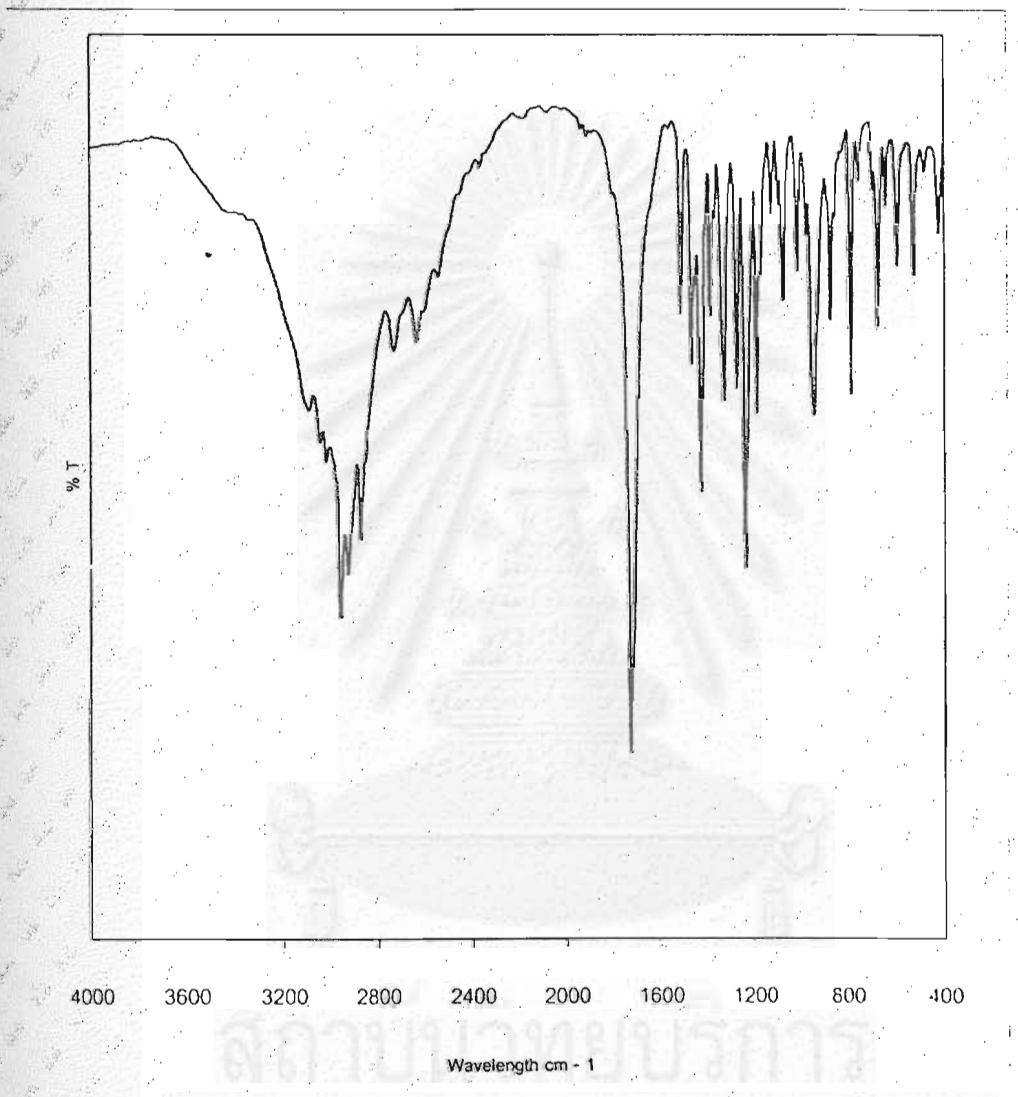


Figure 13 FTIR spectrum of IB raw material

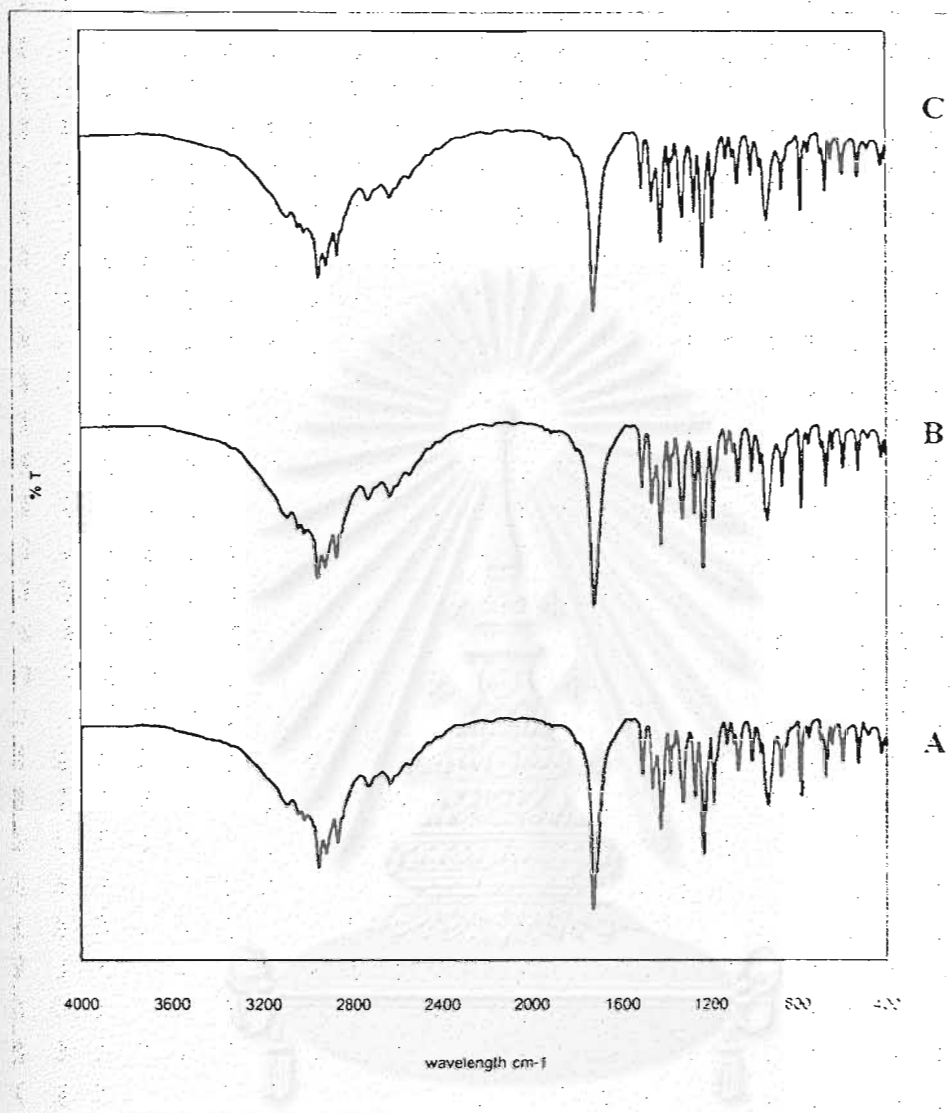


Figure 14 FTIR spectra of IPs at (A) 1 % $CHCl_3$, (B) 1.5 % $CHCl_3$ and (C) 2 % $CHCl_3$ as bridging solvent

2. Dissolution study of IPs with different percentage ratios of bridging solvent

The release profiles were plotted between the cumulative percentage amount of drug released as a function of time as indicated in Figures 15 and 16.

2.1 Dissolution profile of IB raw material

Dissolution data of IB raw material was studied in a dose of 400 mg with similarly to the commercial dose as shown in Table 1B (Appendix B).The dissolution profile of IB is presented in Figure 15. The profile exhibited that the powder of IB raw material was rapidly dissolved. We found an evidence that powder of the drug held together to form aggregates during the dissolution process. These aggregates could directly affect the percentage of drug release and may cause the problem about incomplete dissolution of the drug.

2.2 Dissolution profile of IPs with different ratios of percent bridging solvent

Quantity of IPs was weighed accurately from the calculated content to 400 mg of drug in IPs for dissolution testing. Dissolution data of IPs with different ratios of percent bridging solvent (1%, 1.5%, 2 % chloroform, respectevtly) are given in Tables 2 – 4B (Appendix B). The release profiles of IPs are presented in Figure 16. All of IPs from the formulations showed similar a percentage drug release when compared with each other and illustrated lower dissolution in an initial release period (f_2 analysis). The trend to give similar drug release profiles were observed after the time passed to 60 minutes when compared with the released profile of IB raw material.

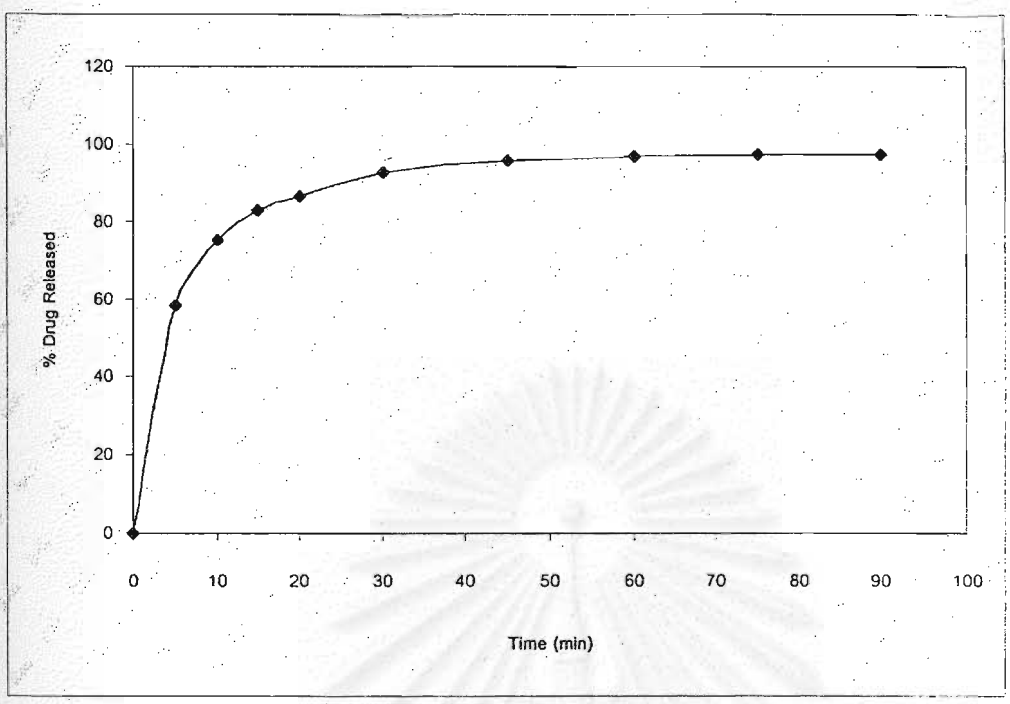


Figure 15 Dissolution profile of IB raw material

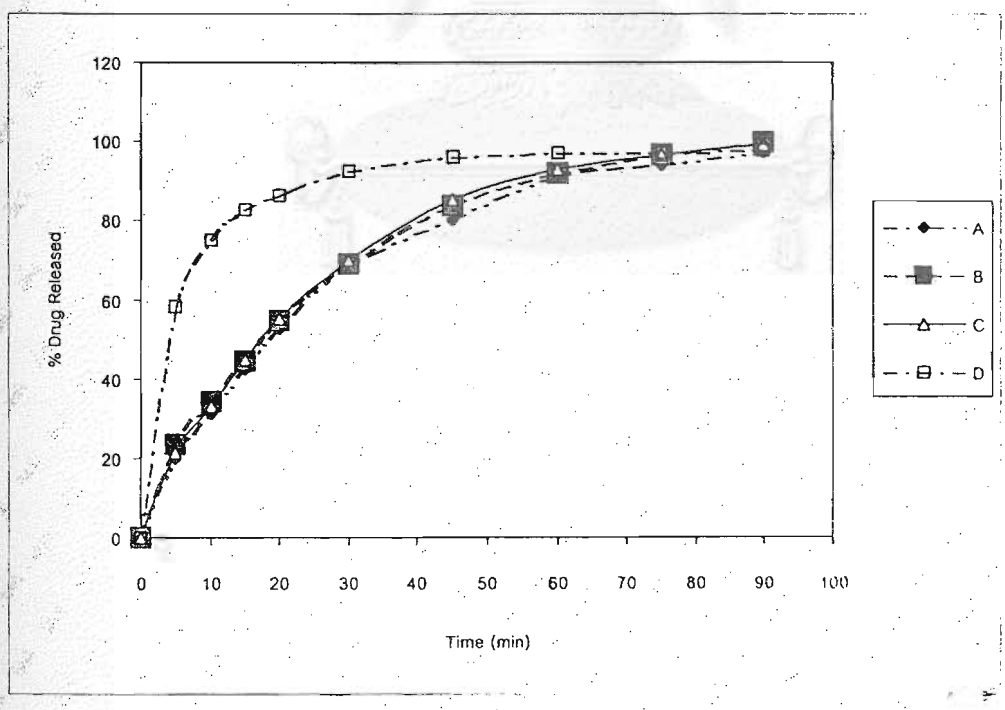


Figure 16 Dissolution profiles of IPs at various amount bridging solvents as compare with IB raw material (A, 1 % $CHCl_3$; B, 1.5 % $CHCl_3$; C, 2 % $CHCl_3$ and D, IB raw material)

Part 2 Preparation and evaluation of ibuprofen pellets with PVP K 30 as dispersion carrier

Preparation of IPs by using dispersion carrier: Polyvinylpyrrolidone K 30 in phase partition technique

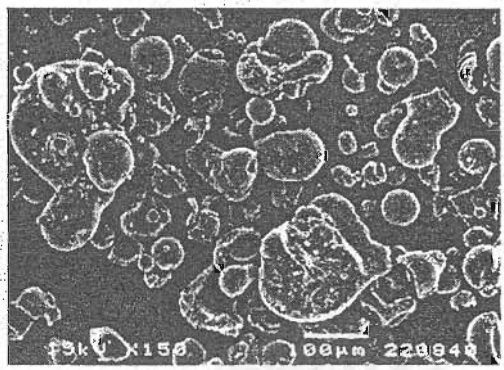
After studying about IPs from phase partition technique, we found that IPs of IB alone was not enough to overcome the dissolution problem. So, combination of IB with suitable carrier to make solid dispersion in the spherical crystallization process by phase partition method is interesting. Polyvinylpyrrolidone (PVP K 30) was a first dispersion carrier to be selected for this study.

1. Formulation of IPs at various ratios of PVP K 30

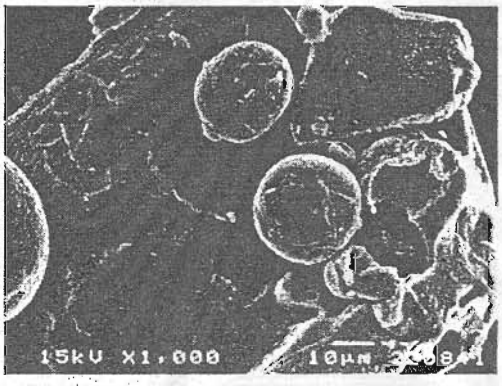
The various ratios of weight proportion of drug and PVP K 30 at 1:0.5, 1:0.75, 1: 1 were conducted as mentioned before.

Morphology of IPs by using different ratios of drug : PVP K 30

The photomicrographs from SEM showed that PVP K 30 powder was round shape with various sizes that can be seen in Figure 17.Figure 18, shows IPs with PVP K 30 at various ratios from this study. Misroscopic appearance revealed smaller in size and also gave very spherical shape of pellets (Figures 18 A, C and E) when compared with IPs using IB alone. Otherwise, after studied about the surface of these pellets, we found the network of polymer was adsorbed onto hydrophobic surface of drug microcrystals. At all of the ratios of IB: PVP K 30 studied, the crystal habit of IB in the pellet's surface had IB microcrystals in the shape of plate form with smaller size when compared with IPs from using drug alone, and all together the thin layer of the polymer adsorbed on the surface was also observed. In the case of increasing an amount of PVP K 30 to the proportion of IB : PVP K 30 at 1:0.75 and 1:1, were found to give thicker film of polymer, as the ratio increased, adsorbed onto the surface of the microcrystals of the IPs.(Figures 18 B,D and F).

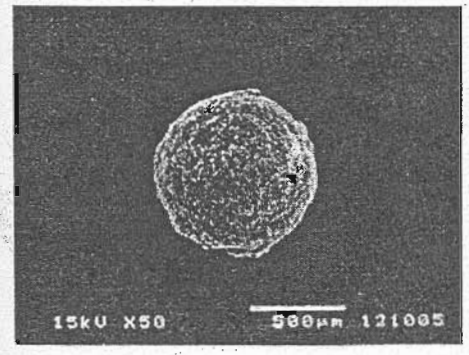


A

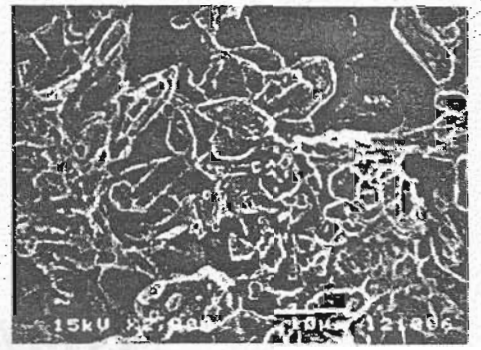


B

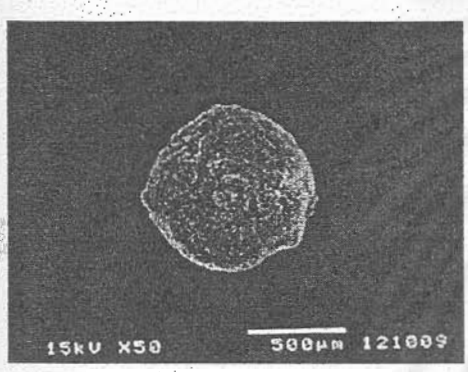
Figure 17 Scanning electron photomicrographs of PVP K 30 raw material at various magnifications (A x 150, B x 1000)



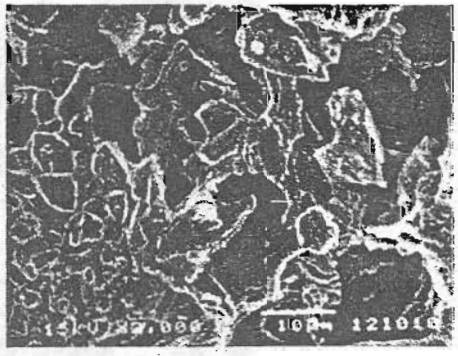
A



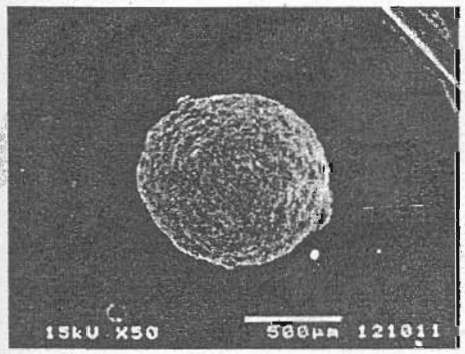
B



C



D



E

F

Figure 18 Scanning electron photomicrographs of IPs; IB: PVP K 30 at various ratios and various magnifications (A ,B: IPs of 1:0.5, x 50,x 2000; C, D: IPs of 1: 0.75, x 50, x 2000; E, F: IPs of 1:1,x 50, x 2000, respectively.)

2. Dissolution study of IPs with different ratios of PVP K 30

An amount of IB in the IB-PVP K30 pellets was assayed, and accurately weighed amount of IPs equivalent to 400 mg IB was used for dissolution study.

Dissolution data of IPs with different ratios of IB / PVP K 30 (1:0.5, 1:0.75 and 1:1, respectively) are provided in Tables 5B – 7B (Appendix B). The released profiles of IPs are presented in Figure 19. All of IPs from the formulations showed similar percentage drug release when compare with each other. Similarity factors "f_2" of 1:0.75 PVP and 1:1 PVP were calculated base on using the dissolution curve of the 1:0.5 PVP as reference, and had the similarity factor "f_2" values of 72.45 in the formulation of 1:0.75 PVP and 55.2 in the formulation 1:1 PVP, respectively. We found that, the formula containing PVP K 30 as the dispersion carrier had the faster release when compared with the IPs that contained drug alone in all of the point of time interval that we observed for dissolution studied. It was proved by calculating the similarity factors "f_2" of each preparation based on using the dissolution curve of IPs with drug alone at 1.5 % chloroform as a reference. The "f_2" values for the formulation of 1:0.5 PVP, 1:0.75 PVP, 1:1 PVP were 35.8, 33.15 and 28.4, respectively. The "f_2" values of these formulas that were less than 50 that mean the higher 10 % difference were remarkably significant.

3. Physicochemical properties of IPs containing PVP K 30

In this study, we evaluated the physicochemical properties that can revealed about the interaction between drug, IB with polymer, PVP K 30. The studies were conducted both before and after using phase partition technique to compare and investigated the interaction in the solid dispersion of IB with PVP K 30, and after the process of phase partition technique for producing IPs.

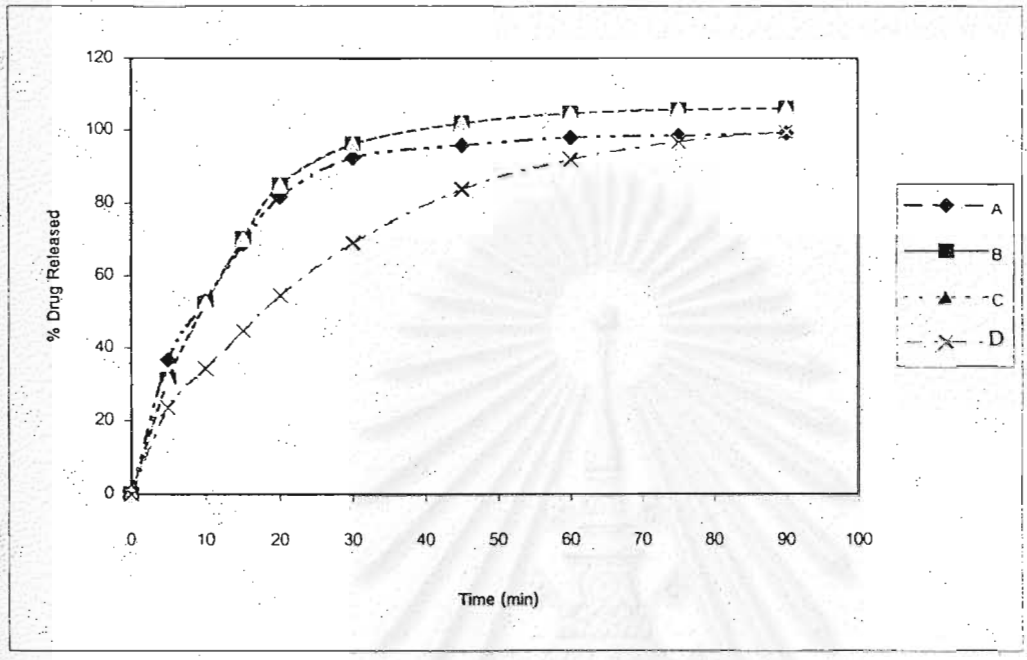


Figure 19 Dissolution profiles of IPs at various ratios of PVP K 30 (A) 1:0.5, (B) 1:0.75, (C) 1: 1 and (D) IPs with 1.5 % $CHCl_3$ (bridging solvent) as reference

3.1 Powder X–ray diffraction study of IPs containing PVP K 30

The X-ray diffractograms of solid dispersion between IB and PVP 30 at different ratios of 1:0.5, 1:0.75, and 1:1, and the X–ray diffractrograms of IPs containing PVP K 30 in their formulations with the same amount of IB and PVP K 30 are shown in Figures 20 – 22 , respectively.

Due to an amorphous property of PVP K 30, no sharp peaks were observed (Figure 20). In the case of solid dispersion between IB and PVP K 30, in the ratios between IB and PVP K 30; 1:0.5, 1:0.75 and 1:1 their X-ray diffractograms are provided in Figures 21A, B and C, respectively. The diffractograms exhibited a totally amorphous nature, and no spectrum peaks of IB was observed. Furthermore, we try to decrease the ratio between IB and PVP K 30 to 1:0.25, from the X-ray diffractogram in this ratio, a fingerprint of IB appeared (Figure 21D).

X-ray diffractograms of IPs with PVP K 30 in the ratios of 1:0.5, 1:0.75 and 1:1 are given in Figures 22A, B and C, respectively. By varying the ratio of drug and polymer like the ratios above, all of these X-ray diffractograms were not much different from each other but decreasing in the intensity of the diffractograms when compared with IB, original crystal were observed (Figure 22 D).

3.2 Infrared spectroscopy of IPs containing PVP K 30

Figure 23 shows IR spectra of PVP K 30 in the region of 4000 – 400 cm^{-1}, with the aliphatic C–H stretching frequency at 2940 cm^{-1} with a very broad band around 3500 cm^{-1} which could be attributed to the presence of trace of moisture in the PVP K 30. In the carbonyl frequency region, PVP K 30 gave a strong band at 1670 cm^{-1} due to the C=O stretching in the cyclic amide.

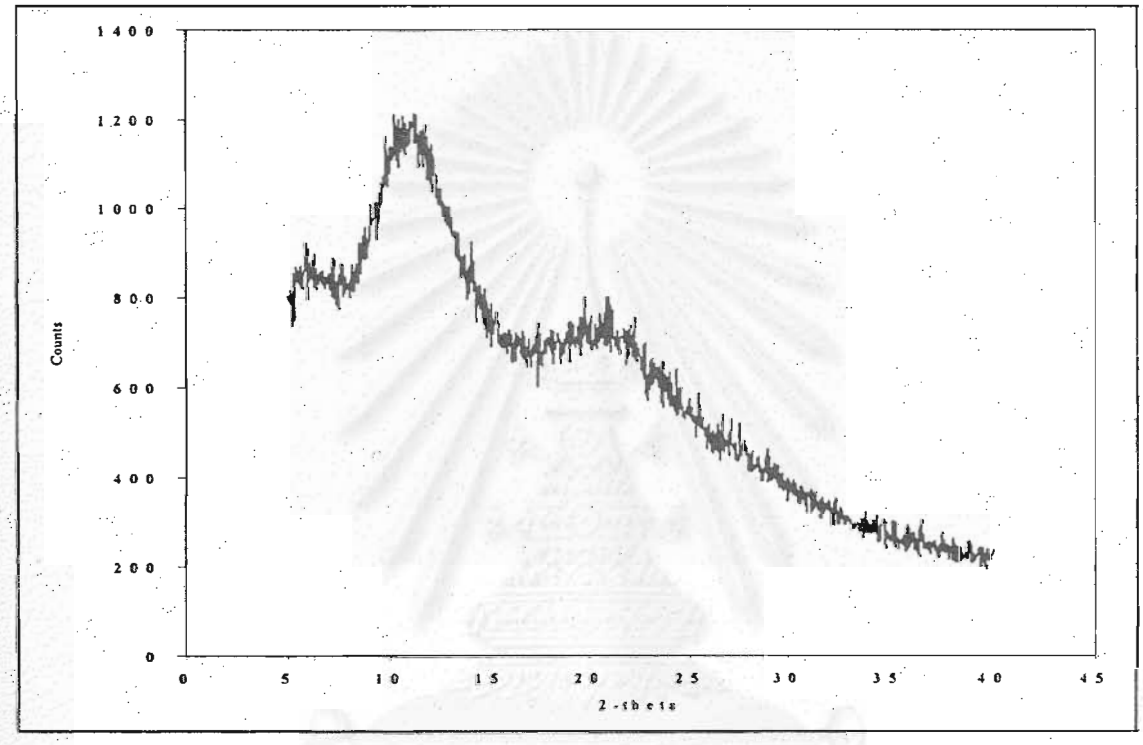


Figure 20 X-ray diffractogram of PVP K 30 raw material

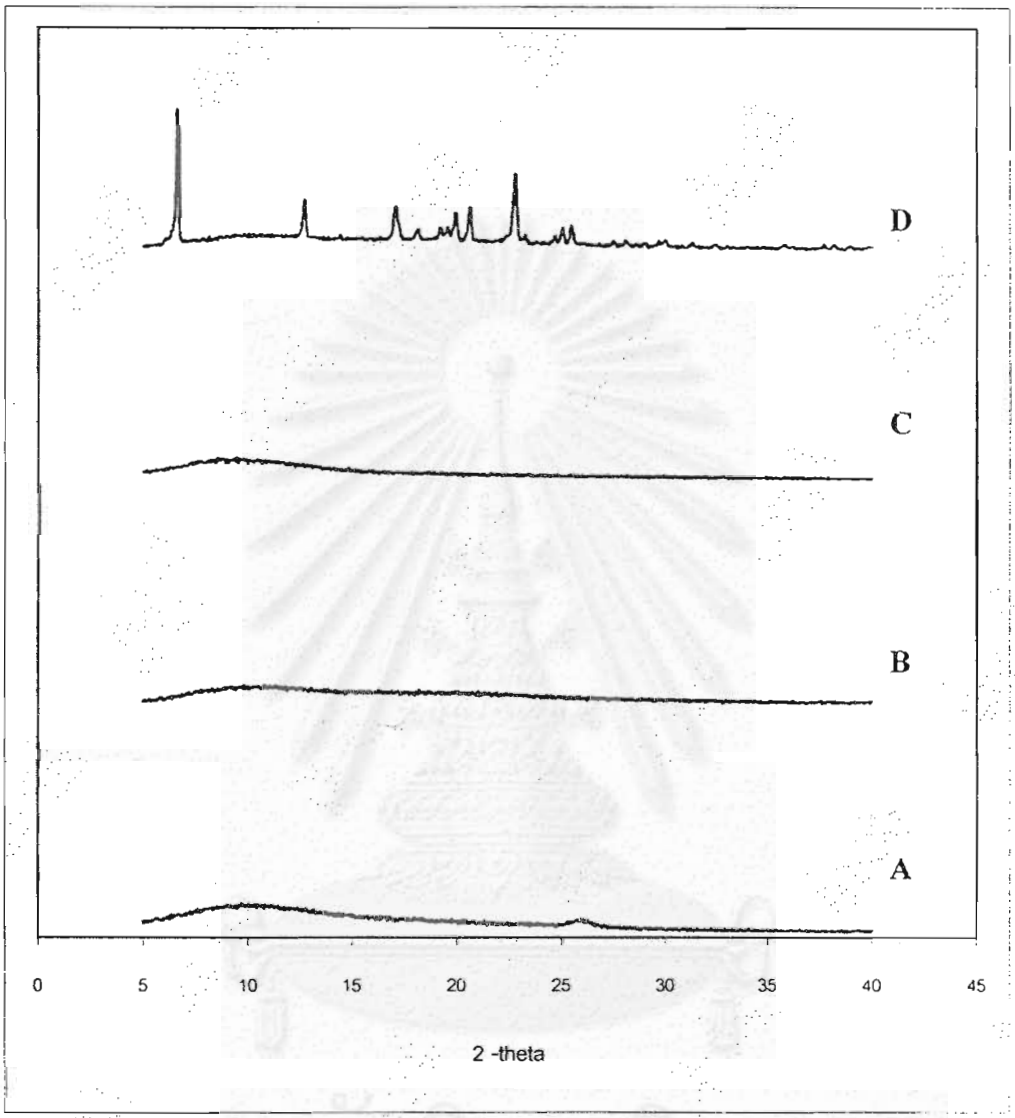


Figure 21 X -ray diffractograms of the solid dispersion of IB with PVP K 30 at various ratios ; (A) 1:0.5, (B) 1:0.75, (C) 1:1 and (D) 1:0.25

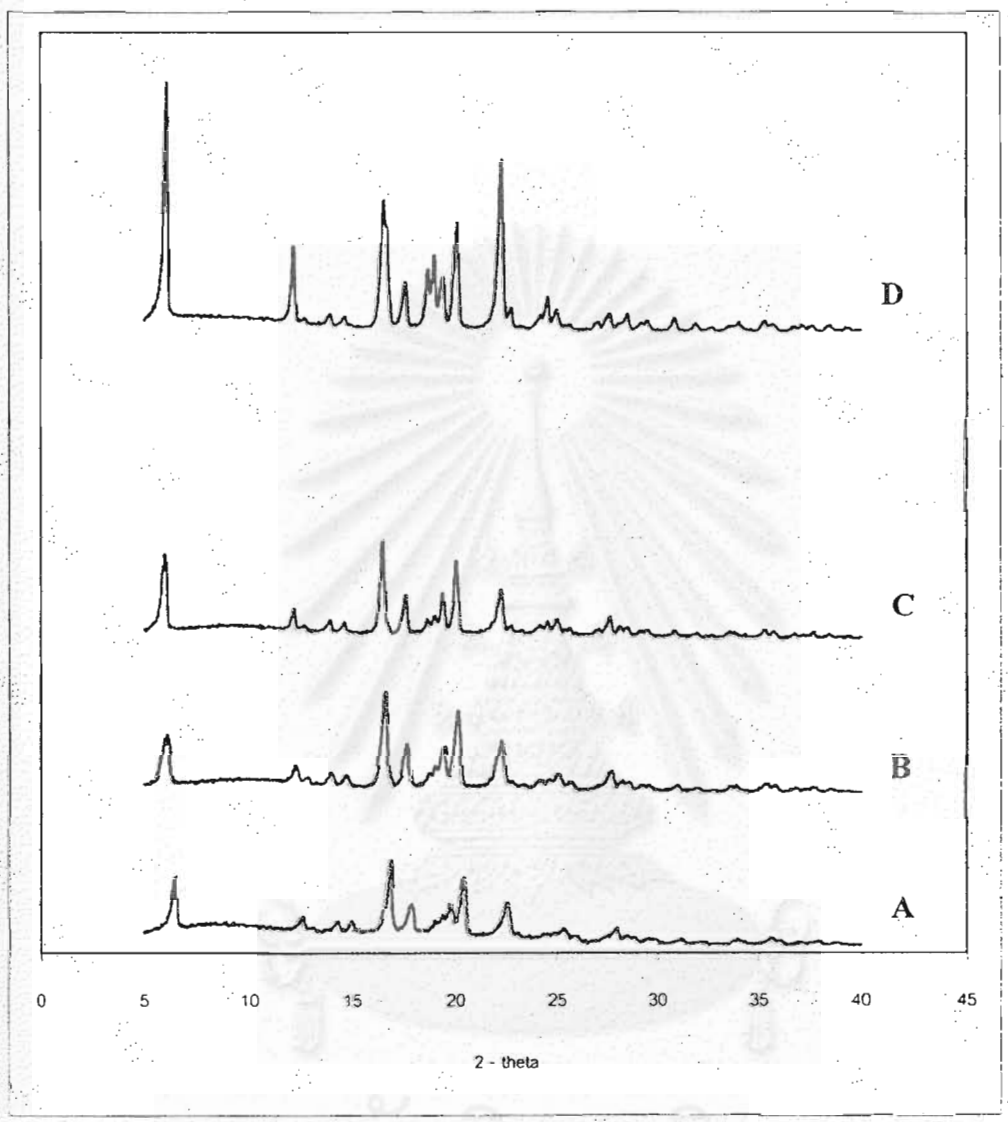


Figure 22 X- ray diffractograms of IPs with PVP K 30 at various ratios (A) 1:0.5, (B) 1:0.75, (C) 1:1 and (D) IB raw material

After prepared the solid dispersion between IB and PVP K 30 in all of the ratios for this study, the IR spectra showed similar results when compared to each other. Figure 24 shows the IR spectra of solid dispersion between IB and PVP K 30, we found the change in the IR spectra from these solid dispersions that showed that some interactions between two substances might occurr. At the carbonyl frequency region indicated the broad band coverd both C=O stretching of two substances and have the new spectrum at 1682cm^{-1} which can be seen. This may be due to the possible complex formation in this dispersion, and the spectra in the position of C=O stretching in carboxylic group of the IB at 1700 cm^{-1} still can be observed. Otherwise, the spectra of this solid dispersion still showed the same bands of C–H stretches for the IB and PVP K 30 at 2940 – 2960 cm^{-1} with a very broad baseline covering the range 2400 – 3500 cm^{-1}, indicating the presence of pronounced hydrogen bonding between IB and PVP K 30. In the low frequency region, 1600 – 600 cm^{-1} the bands were almost the same for both IB and PVP K 30. On the other hand, the IR spectra from IPs with PVP K 30 from these dispersions are given in Figure 25. This figure present interested results in the carbonyl frequency region and C–H stretching frequency that had some of evidences to shown about the interaction between IB and PVP K 30. We found that the broad region in their areas was decreased and in the carbonyl frequency region, had both of two C=O stretching bands from IB and PVP K 30 separated to 2 peaks.

3.3 Differential scanning calorimetry (DSC) of IPs containing PVP K 30

Scanning of PVP K 30, indicated amorphous in nature as indicated in Figure 26A. In the case of solid dispersion of IB with PVP K 30, all of these ratios had the same broad endothemic peaks as shown in Figures 26B-D. In the case of IPs with PVP K 30, their DSC thermograms represented the same endothermic peak about 74 °C in the small and decrease in intensity of endothermic peaks, these peaks are illustrated in Figure 27.

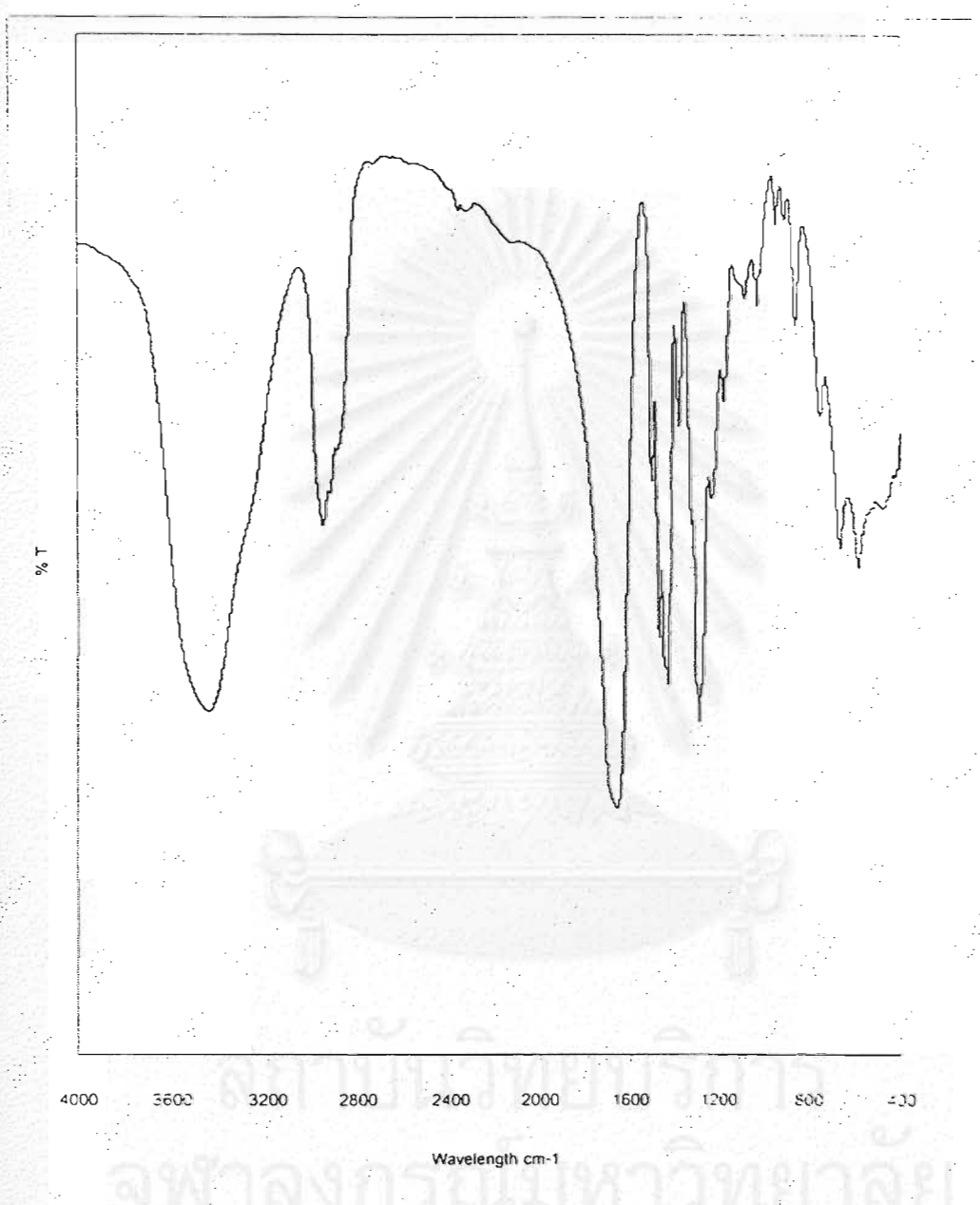


Figure 23 FTIR spectrum of PVP K 30, raw material

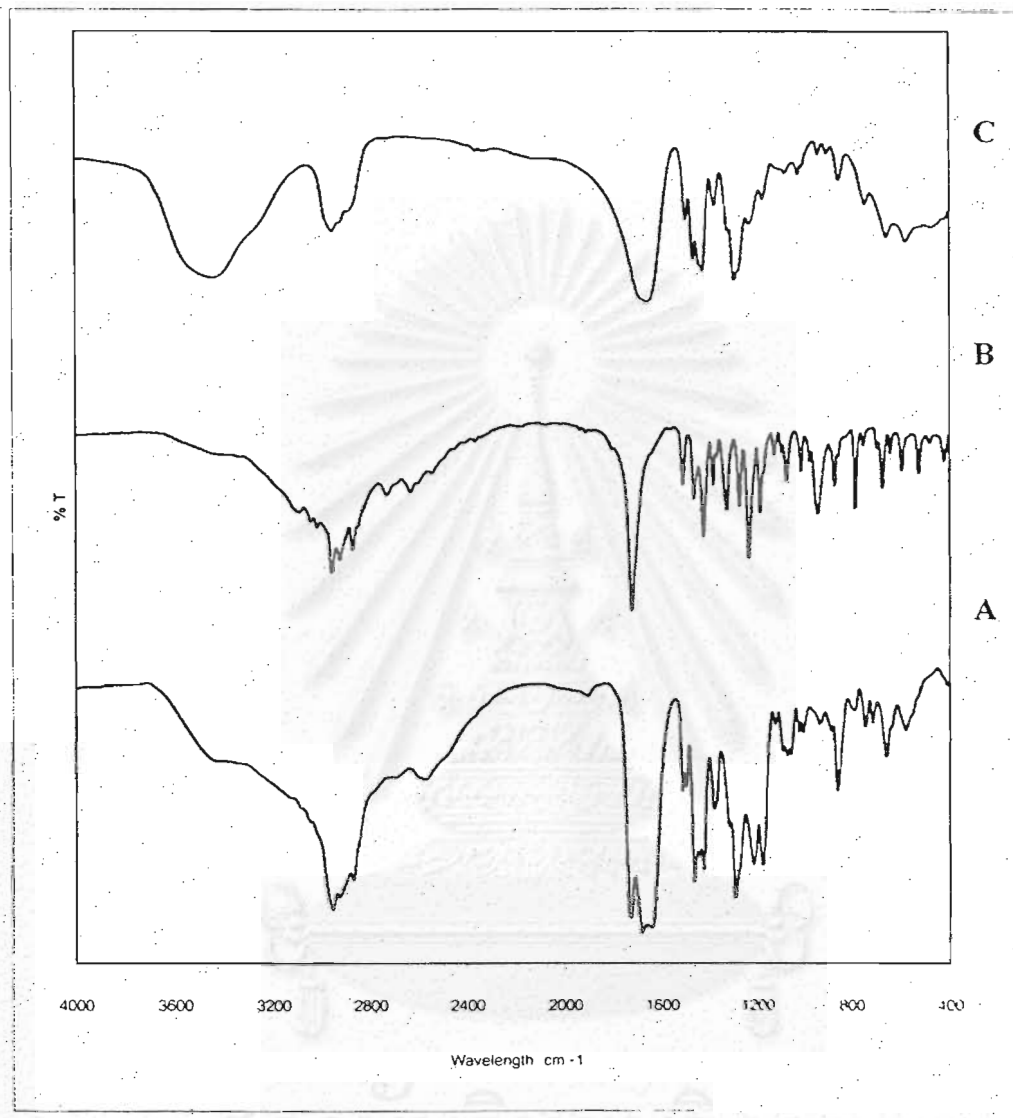


Figure 24 FTIR spectra of (A) solid dispesion of IB: PVP K 30 (B) IB raw material and (C) PVP K 30 raw material

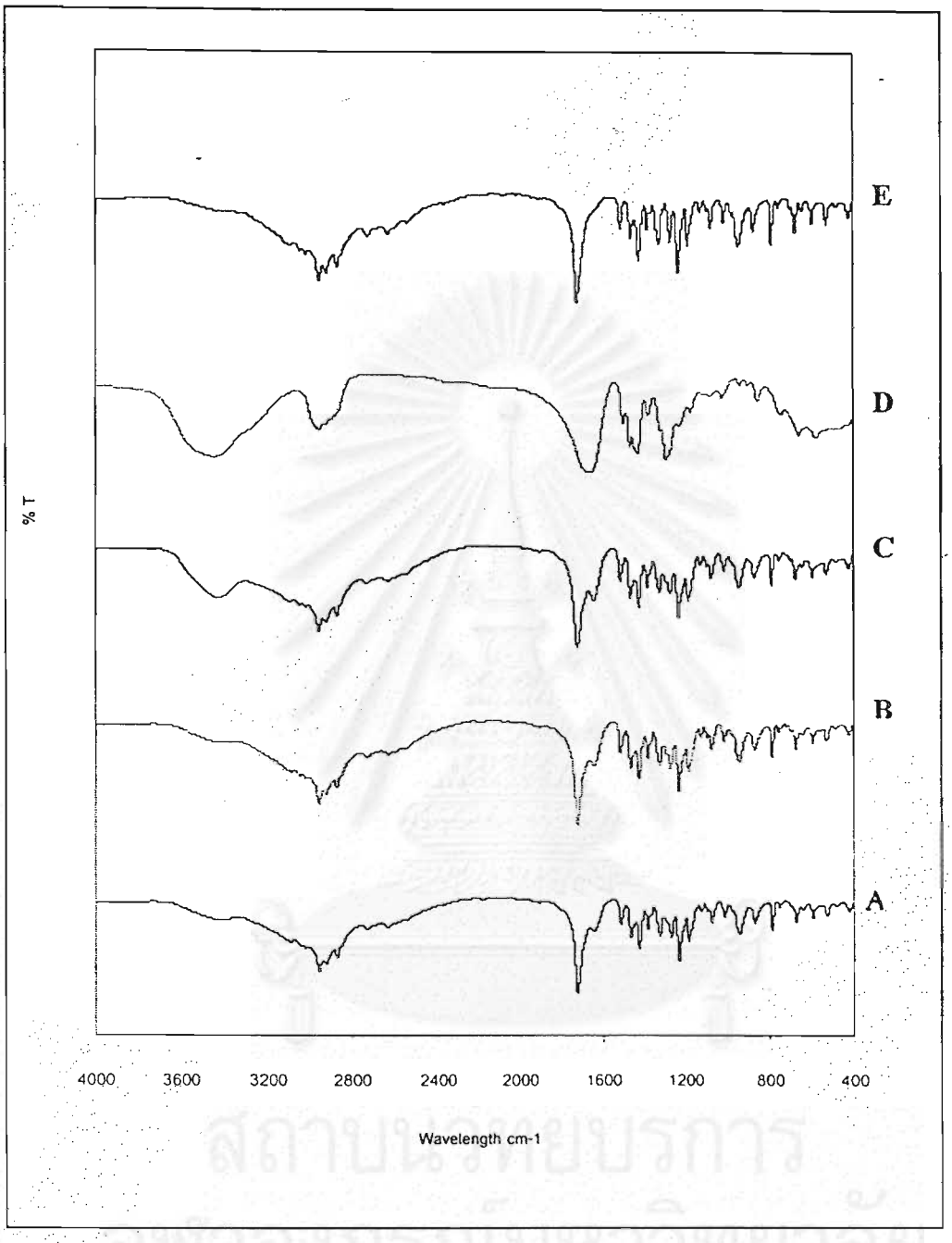


Figure 25 FTIR spectra of IPs prepared from various ratios of IB: PVP K 30; (A) 1:0.5, (B) 1:0.75, (C) 1:1 compared with (D)PVP K 30 raw material and (E) IB raw material

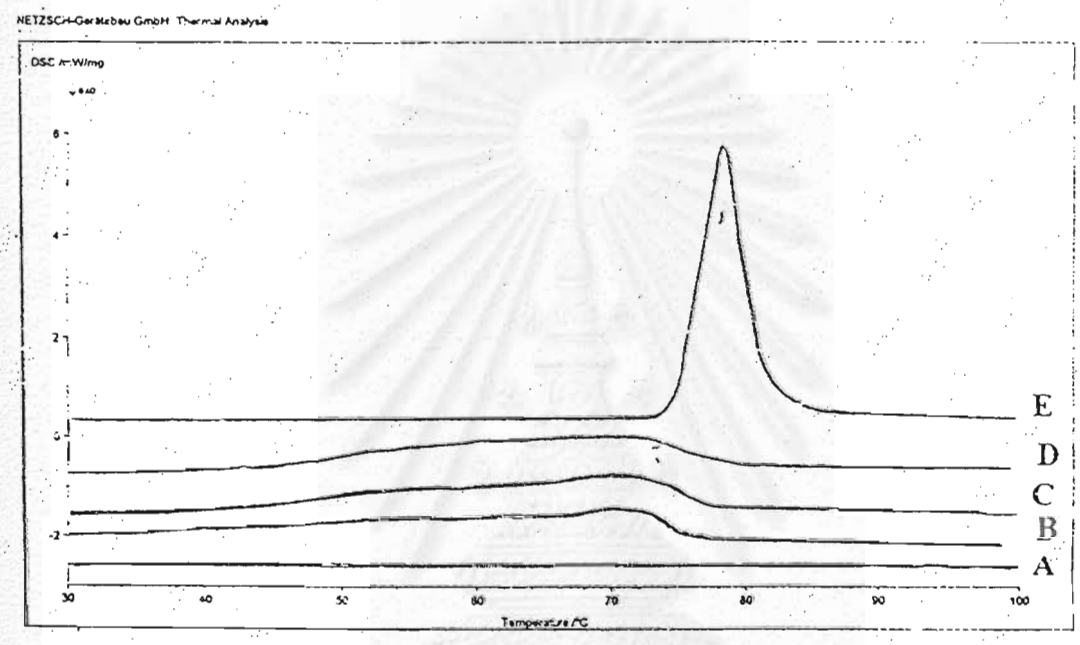


Figure 26 DSC thermograms of (A) PVP K 30 raw material and solid dispersion of IB with PVP K 30 at various ratios; (B) 1: 0.5, (C) 1: 0.75, (D) 1: 1, and (E) IB raw material

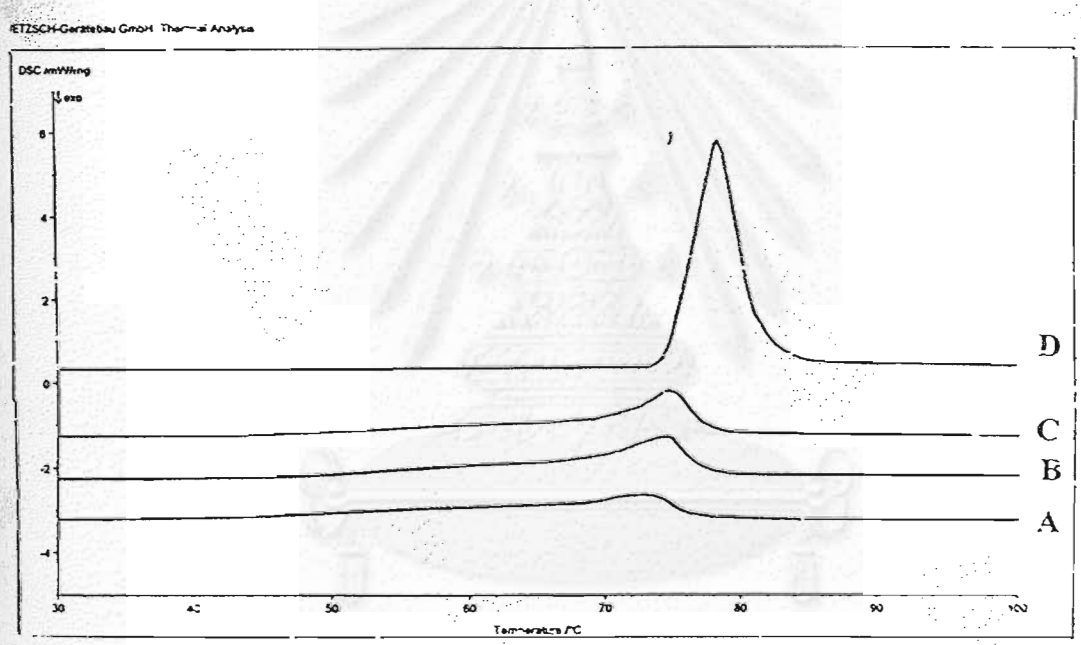


Figure 27 DSC thermograms of IPs at various ratios of IB with PVP K 30 (A) 1: 0.5, (B) 1:0.75, (C) 1:1,as compared with PVP K 30 raw material (D) and IB raw material (E)

3.4 ^{13}C Nuclear Magnetic Resonance of IPs containing PVP K 30

Figure 28 summarize the data about ^{13}C NMR spectra of IB, PVP K 30, solid dispersion of IB with PVP K 30 and IPs with PVP K 30.The signal of the carboxylic acid carbon in IB appeared at δ 180.715 ppm, which is typical of a free carboxylic acid. On the other hand, the signal of the carbonyl carbon in PVP appeared at δ 174.913 ppm. The spectrum of the solid dispersion between IB and PVP K 30 showed the carboxylic acid carbon signal appeared at 176.691 ppm and the carbonyl carbon signals at δ 175.467 ppm. After this dispersion was transferred though phase partition to gave IPs, the signal of carboxylic acid carbon and carbonyl carbon were shifted less than the signal from the solid dispersion alone. These shifts were appeared at 179.318 and 176.315 ppm, respectively.

Part 3 Preparation and evaluation of ibuprofen pellets with PEG as dispersion carrier

Preparation of IPs by using dispersion carrier: Polyethylene glycol in phase partition technique

As we know for a long time that, polyvinylpyrrolidone was hygroscopic substance and may cause some problems about aggregation and tackyness when used in the formulation. So, polyethylene glycol (PEG) was selected as another dispersion carrier in this study. We study three grades of PEG; 1450, 4000 and 6000, for determining the suitable grades of PEG and to employ as dispersion carrier with IB in phase partition technique to produce the IPs.

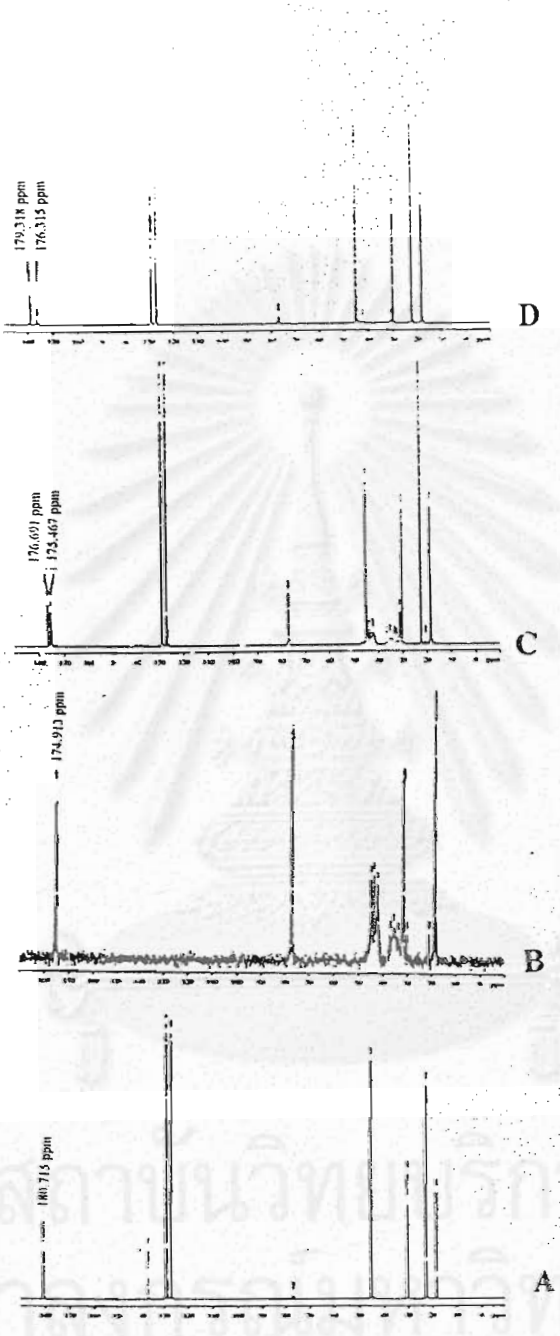


Figure 28 NMR Spectra of (A) IB raw material, (B) PVP K 30 raw material, (C) solid dispersion of IB with PVP K 30 and (D) IPs with PVP K 30

1 Formulation of IPs at various ratios of PEG 1450, 4000 and 6000, at various weight proportions of drug (1:0.5, 1:0.75, 1:1) at all grades of PEG as was mentioned before

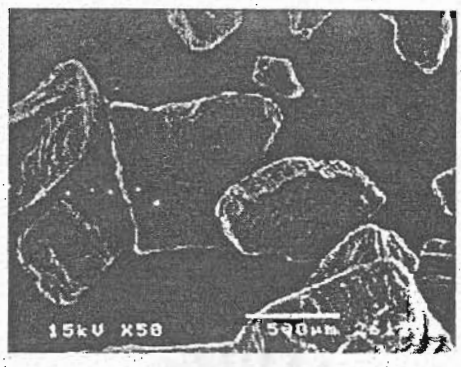
1.1. Morphology of IPs by using different ratios of drug:PEGs

1.1.1 Morphology of PEG raw material

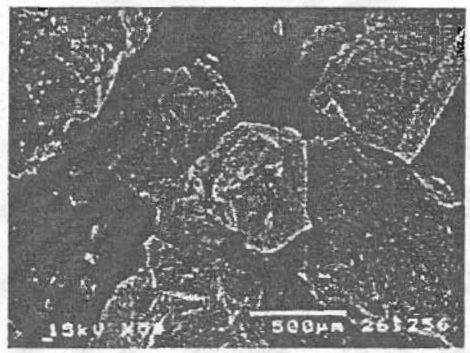
Various grades of PEG that we used in this study were the waxy flakes with various in sizes and have the smoother surface that can be seen in Figure 29.

1.1.1 IPs with PEG 1450,4000, 6000

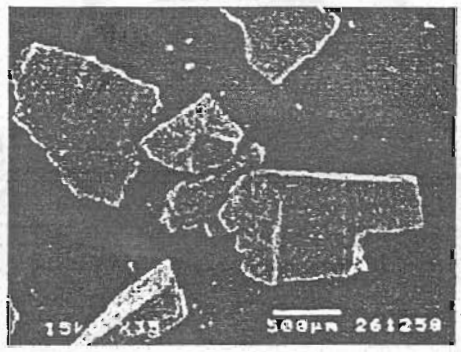
Figures 30 - 32 shows the photomicrographs from SEM of IPs with PEG 1450, 4000, 6000 at different ratios, respectively. All of the formulations showed less spherical in shape pellets, varied in size and gave the bigger pellets more than in the formulation that used PVP K 30 as dispersion carrier. Studying the surface of the pellets from these formulations, we observed their surface with much rougher than IPs with PVP K30, its composed of IB crystals rather loosely packed on the surface. In addition, the network of the PEG polymer adsorbed on the surface of IB microcrystals was not present as IPs with PVP K 30. PEG 6000 gave the most spherical pellets and less rougher surface when compared with others (Figures 30 – 32A, C and E). From the results of microscopic examination indicated that crystal habit of IB microcrystals, IPs with PEG 1450, 4000 and 6000 were the combination of rod and plate shape similarly to IPs with drug alone. (Figures 30 –32 B, D and E)



A

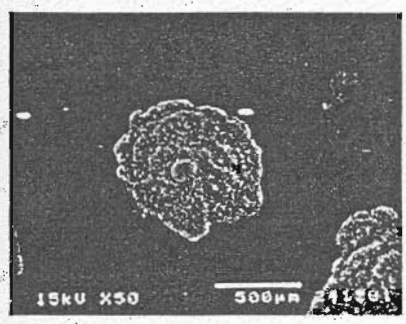


B



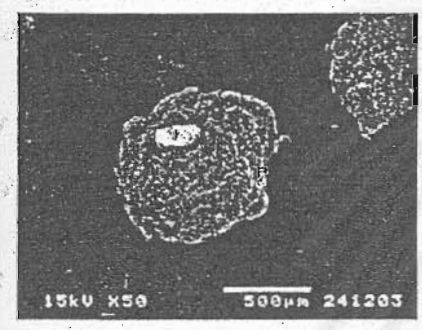
C

Figure 29 Scanning electron photomicrographs of PEG at various grades (A, PEG 1450 X 50; B, PEG 4000 X 50; C, PEG 6000 X 50)



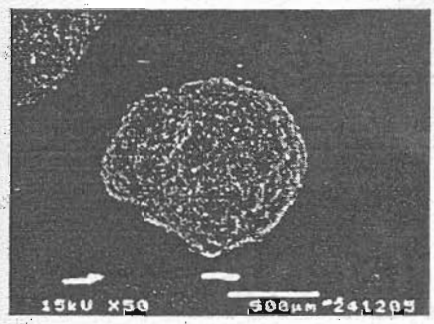
A

B

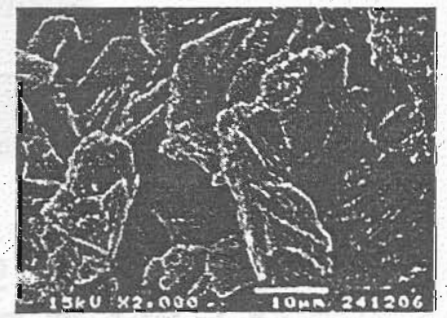


C

D

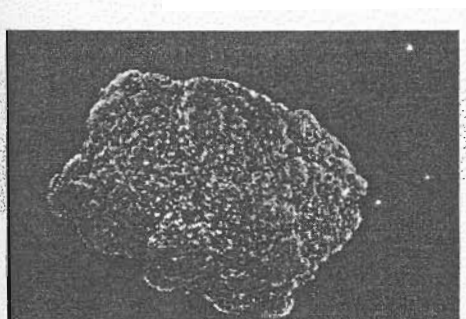


E



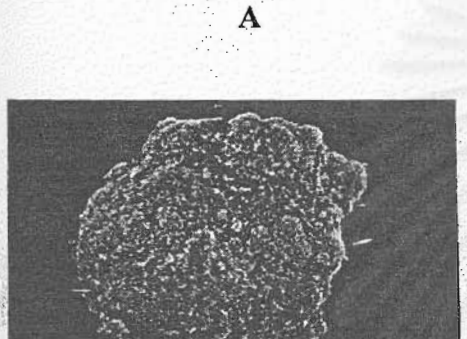
F

Figure 30 Scanning electron photomicrographs of IPs with PEG 1450 at various ratios of IB:PEG and at various magnifications (A,1:0.5 X 50; B, 1:0.5 X 2000; C, 1:0.75 X 50; D, 1:0.75 X 2000; E, 1:1 X 50; F,1:1 X 2000)

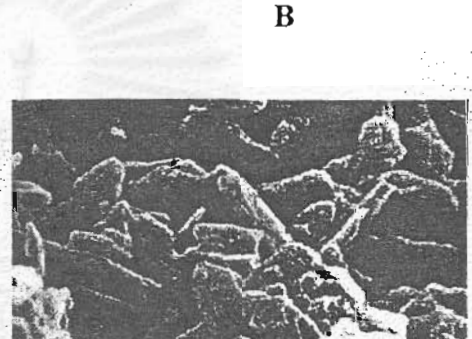


A

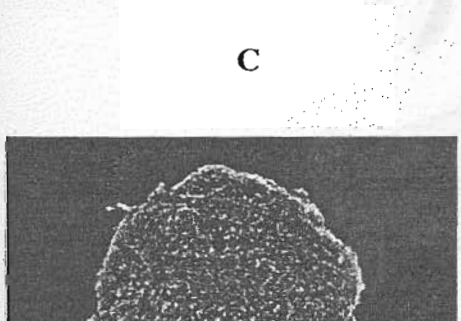
B



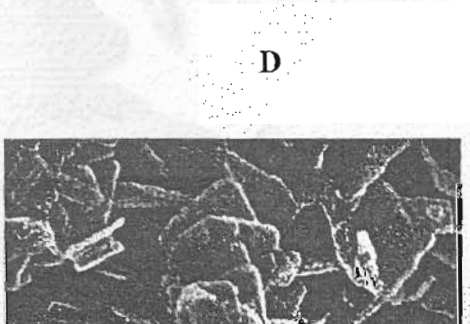
C



D

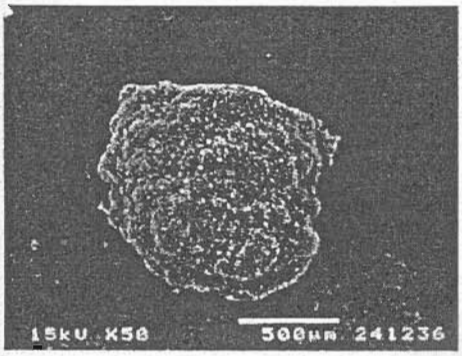


E

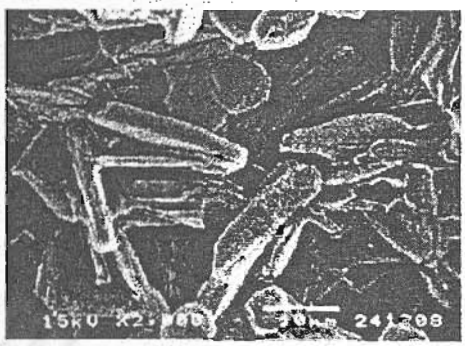


F

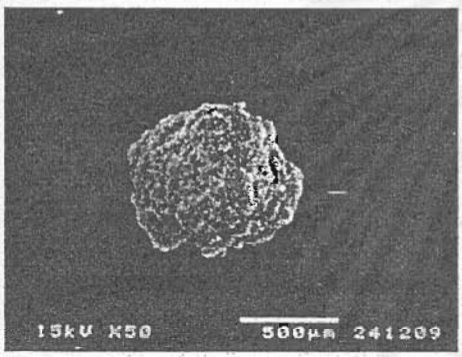
Figure 31 Scanning electron photomicrograph of IPs with PEG 4000 at various ratios of IB: PEG and at various magnifications (A, 1:0.5 X 50; B, 1:0.5 X 2000; C, 1:0.75 X 50; D, 1:0.75 X 2000; E, 1:1 X 50; F, 1:1 X 2000)



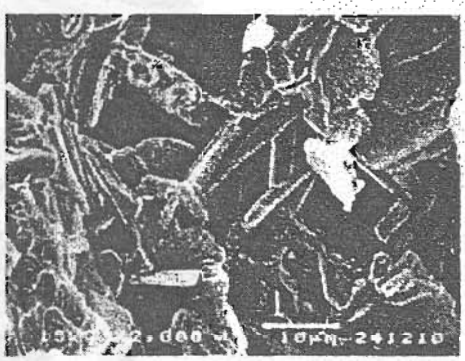
A



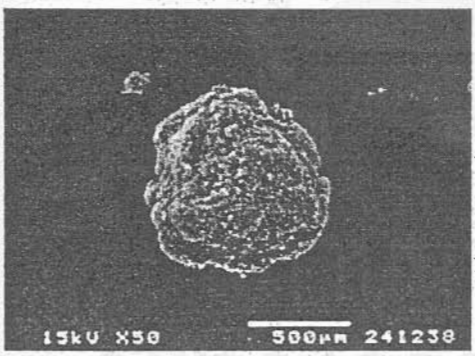
B



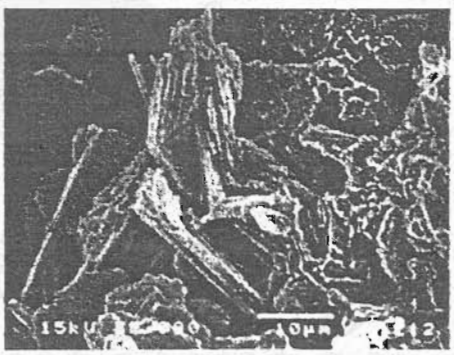
C



D



E



F

Figure 32 Scanning electron photomicrographs of IPs with PEG 6000 at various ratios of IB: PEG and at various magnifications (A, 1:0.5 X 50; B, 1:0.5 X 2000; C, 1:0.75 X 50; D, 1:0.75 X 2000; E, 1:1 X 50; F, 1:1 X 2000)

properties of IPs obtained after phase partition that produced by the used of IB with PEG were also included. The ratio we chose to study was IB: PEG 6000, at 1:1.

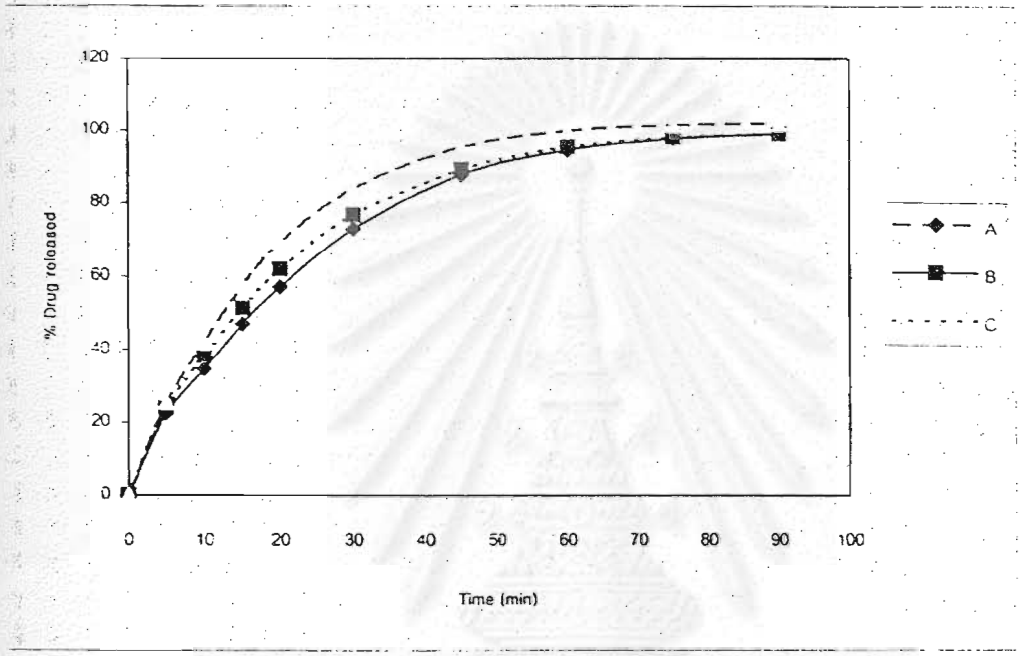


Figure 33 Dissolution profiles of IPs with PEG 1450 at various ratios of (A) 1:0.5, (B) 1:0.75 and (C) 1:1

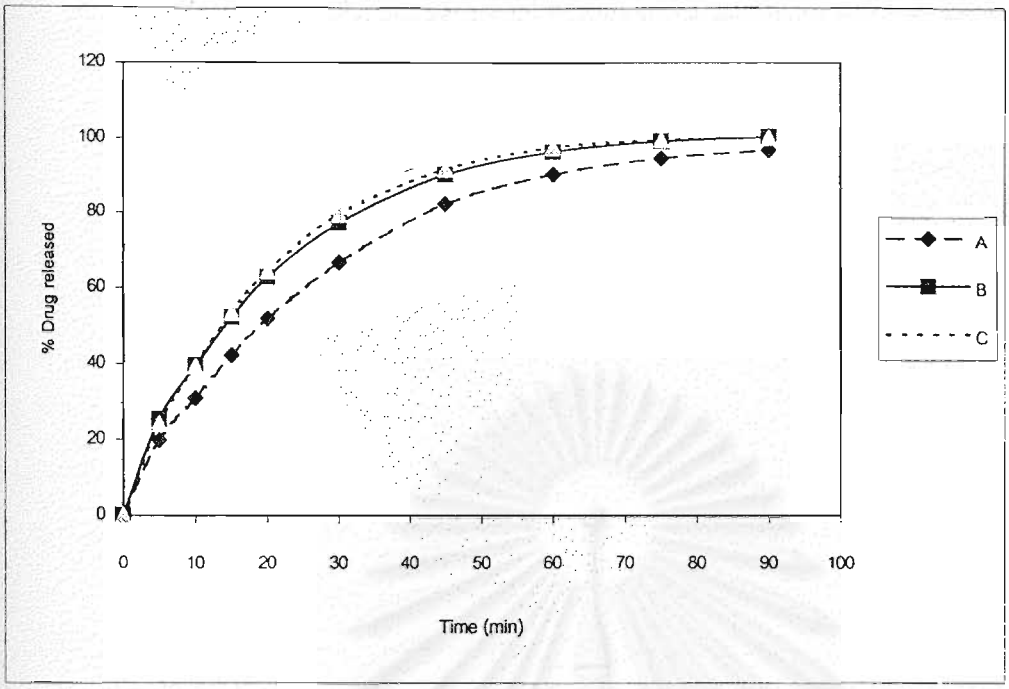


Figure 34 Dissolution profiles of IPs with PEG 4000 at various ratios of (A) 1:0.5, (B) 1:0.75 and (C) 1:1

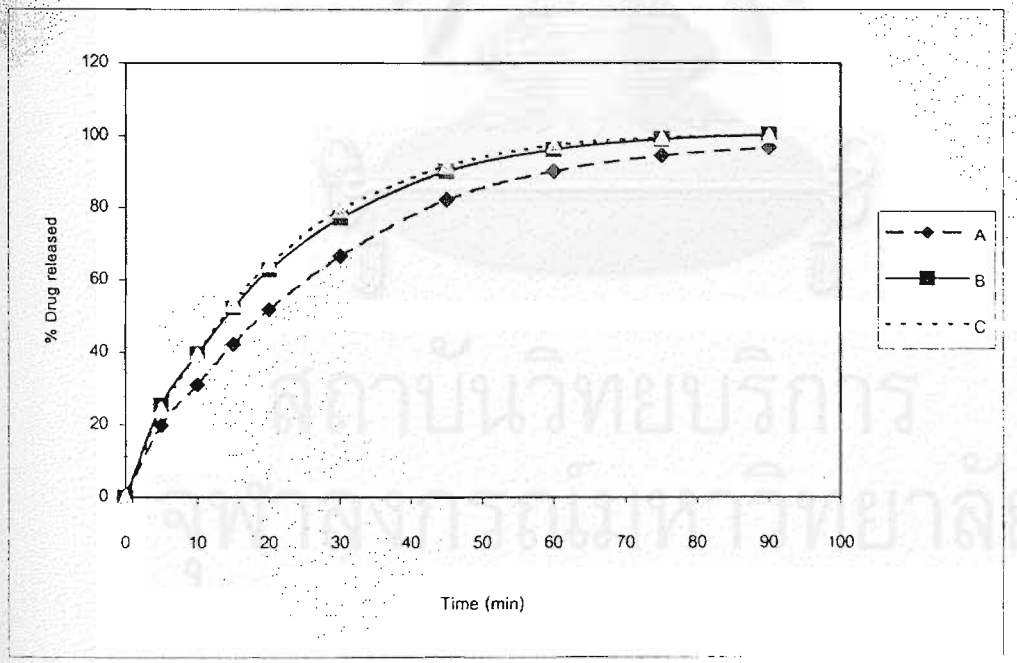


Figure 35 Dissolution profiles of IPs with PEG 6000 at various ratios of (A) 1:0.5, (B) 1:0.75 and (C) 1:1

3.1 Powder X–ray diffraction study

The X-ray diffractograms of PEG 1450, 4000 and 6000 are shown in Figure 36. All of these materials had the major X- ray diffraction peaks at about 19.3 °(2θ) and 23.4 °(2θ), respectively. Figure 37 displays the X- ray diffractograms of the solid dispersion between IB and PEG 6000 as compared with the X-ray diffractograms of IB, original crystal and raw material of PEG 6000. We found that several diffraction peaks of the drugs disappeared but some peaks such as at about 6.4 °(2θ), 12.5 °(2θ) and 24.8 °(2θ) could be detected in this dispersion, and the X-ray diffractograms of PEG still could observed as maybe seen at 23.4°(2θ). For the X-ray diffractograms of IPs with PEG which presented the peaks that corresponding to IB,original crystal. Similar results were observed in all of the grade of PEG that used for this study, as illustrated in Figure 38.

3.2 Infrared spectroscopy

Figure 39 shows IR spectra of PEG 1450, 4000 and 6000, an important spectra of PEG were the C–H stretching at 2900 cm^{-1} and the C–O (ether) stretching at 1110 cm^{-1}. Comparing the spectra of solid dispersion of IB and PEG 6000 with the IR spectra of IB original crystal, and raw material of PEG 6000, no difference was shown in every position of the IR spectra. The spectra can be simply regarded as the position of those IB and PEG 6000 as shown in Figure 40. IR spectra of IPs from the dispersion of IB with all grade of PEGs in all ratio that we used in this study showed the same wavenumber of all the spectra, and closely to the spectra of IB, original crystal, as given in Figures 41 - 43.

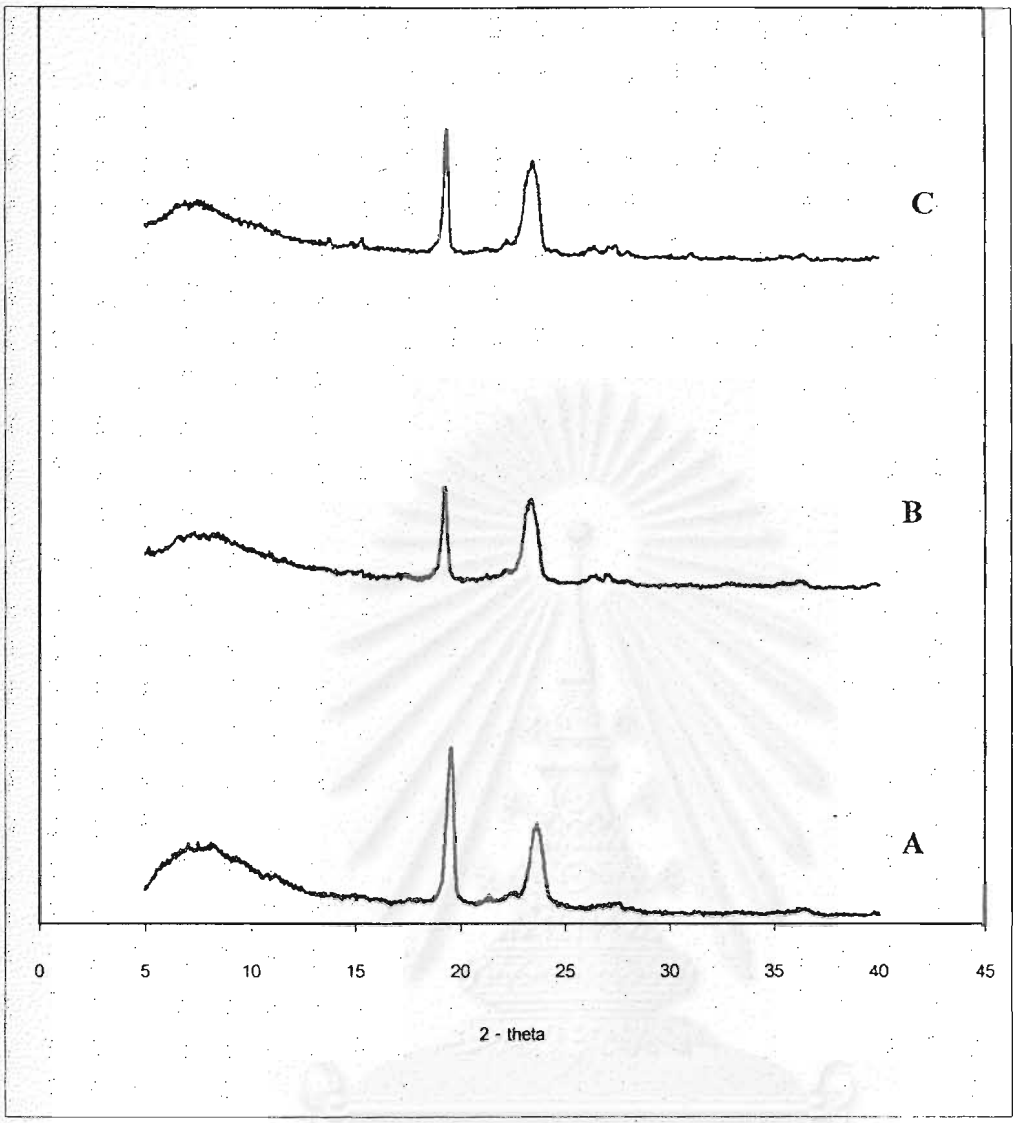


Figure 36 X- ray powder diffractograms of PEG; (A) PEG 1450, (B) PEG 4000, (C) PEG 6000

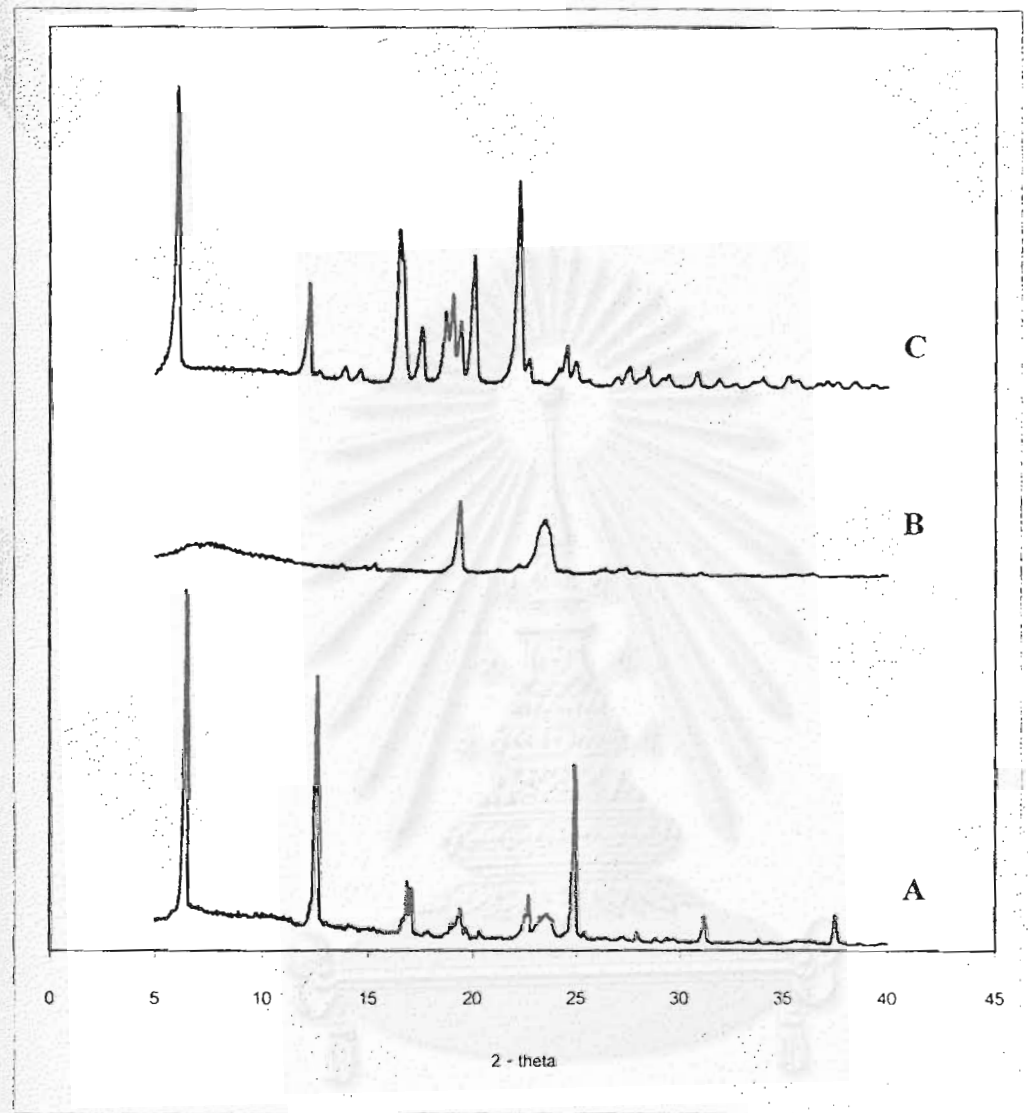


Figure 37 X - ray powder diffractograms of (A) the solid dispersion of IB with PEG 6000, (B) PEG 6000 raw material and (C) IB raw material

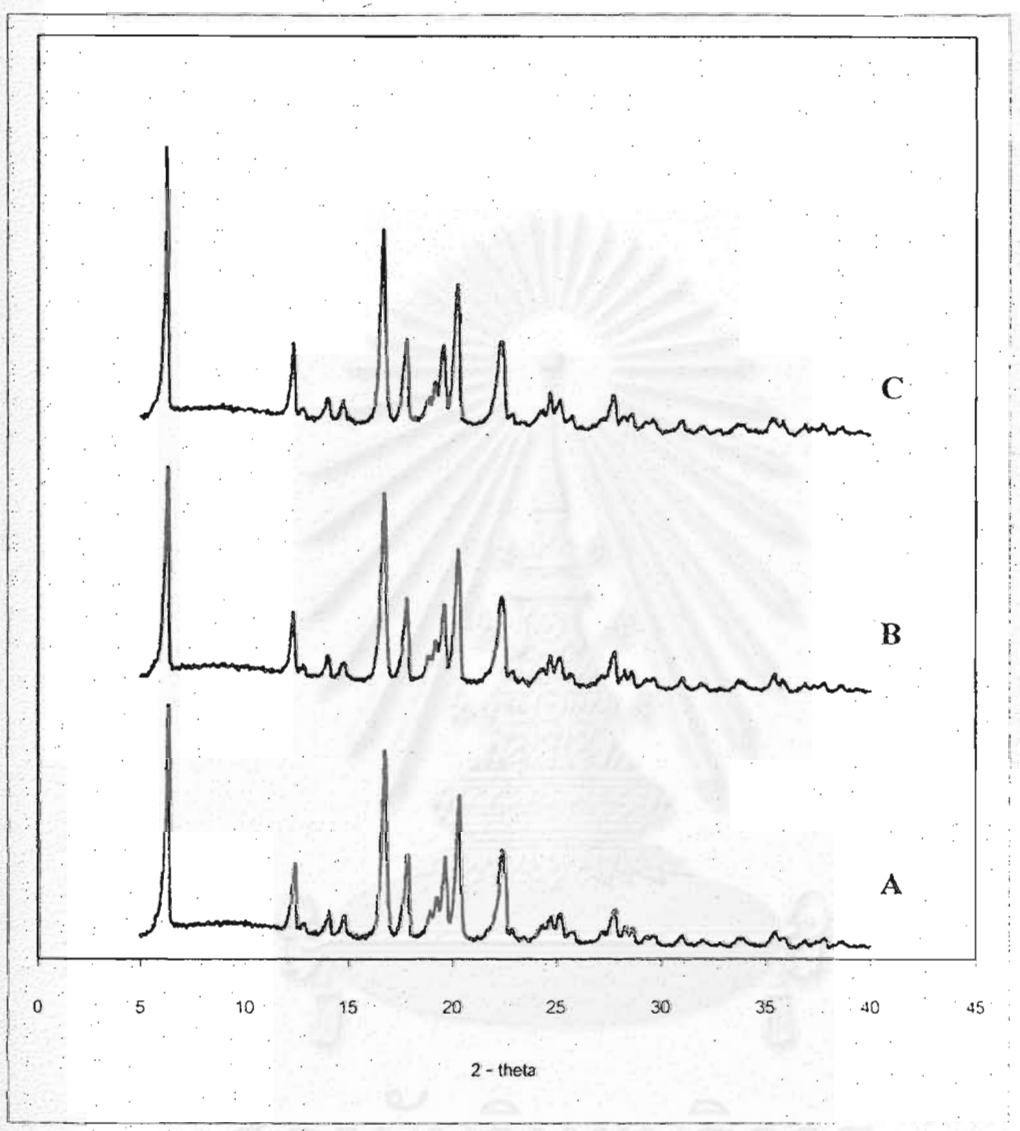


Figure 38 X- ray powder diffractograms of IPs with various grades of PEG at a ratio of 1:1 (A, PEG 1450; B, PEG 4000 and C, PEG 6000)

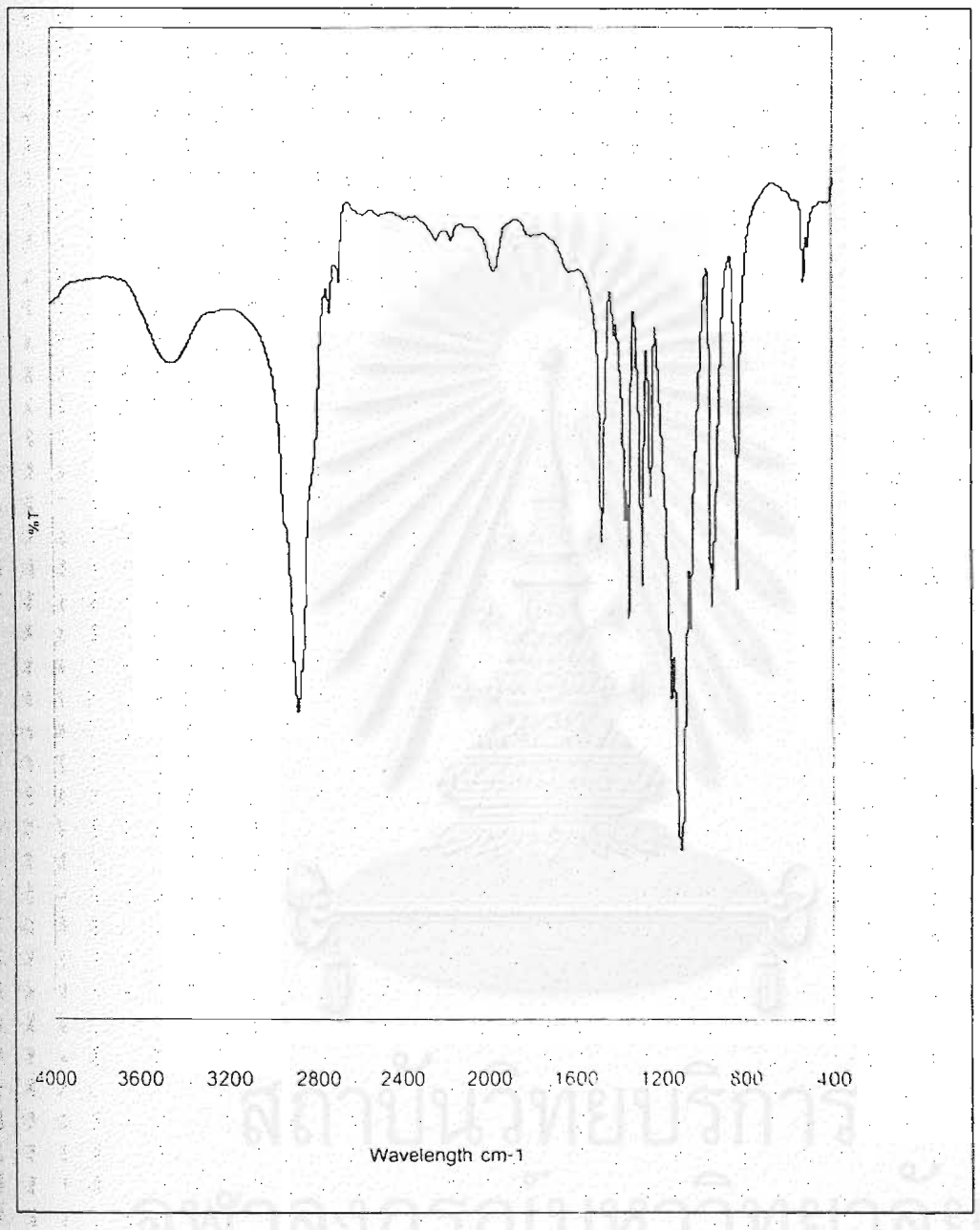


Figure 39 Typical FTIR spectrum of PEG raw material

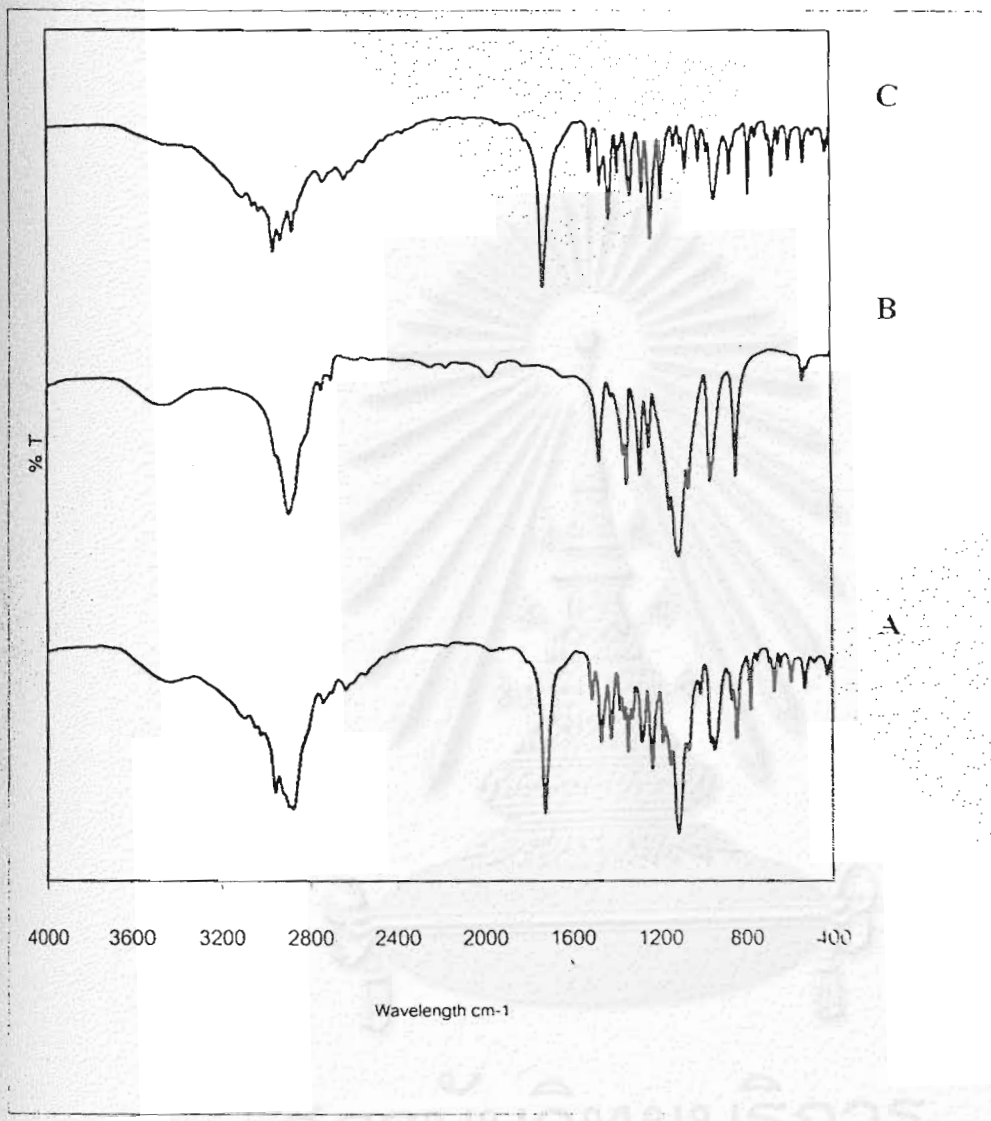


Figure 40 FTIR spectra of (A) solid dispersion of IB: PEG, (B) PEG 6000 raw material and (C) IB raw material

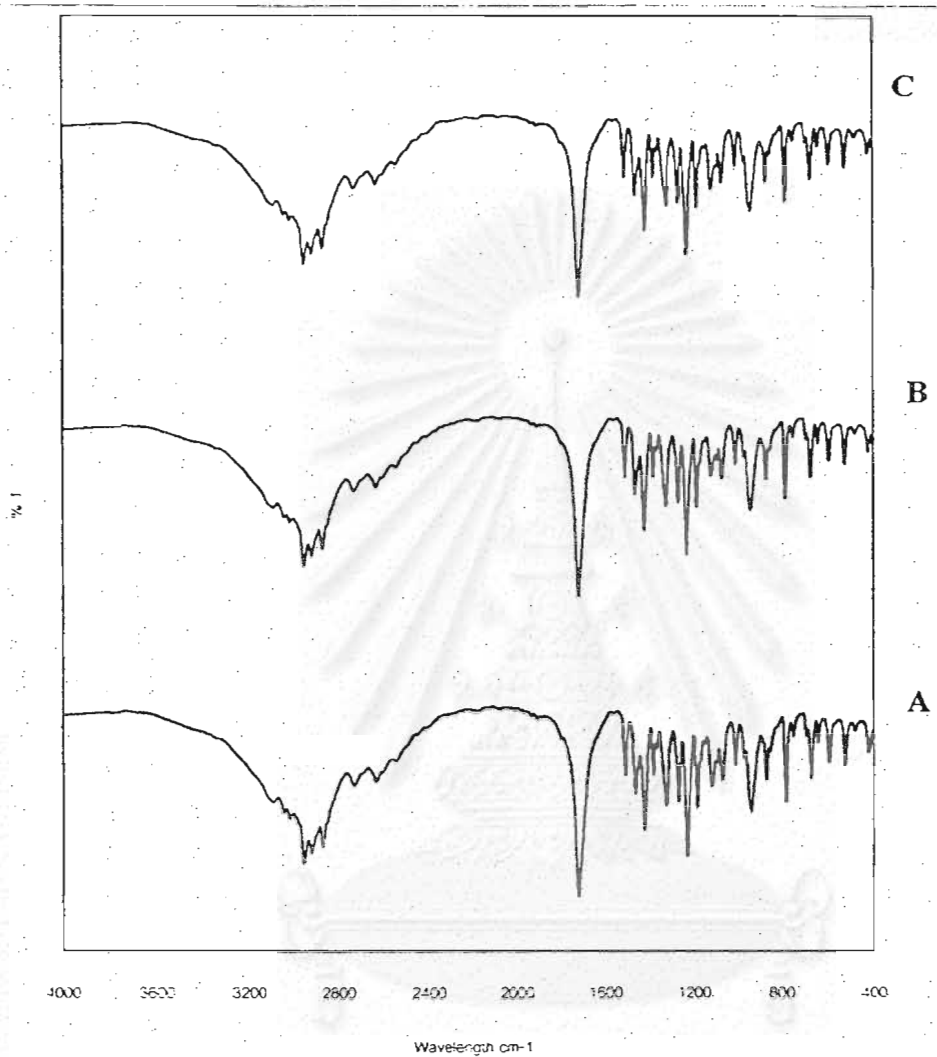


Figure 41 FTIR spectra of IPs at various ratios of PEG 1450 (A) 1: 0.5, (B) 1:0.75 and (C) 1:1

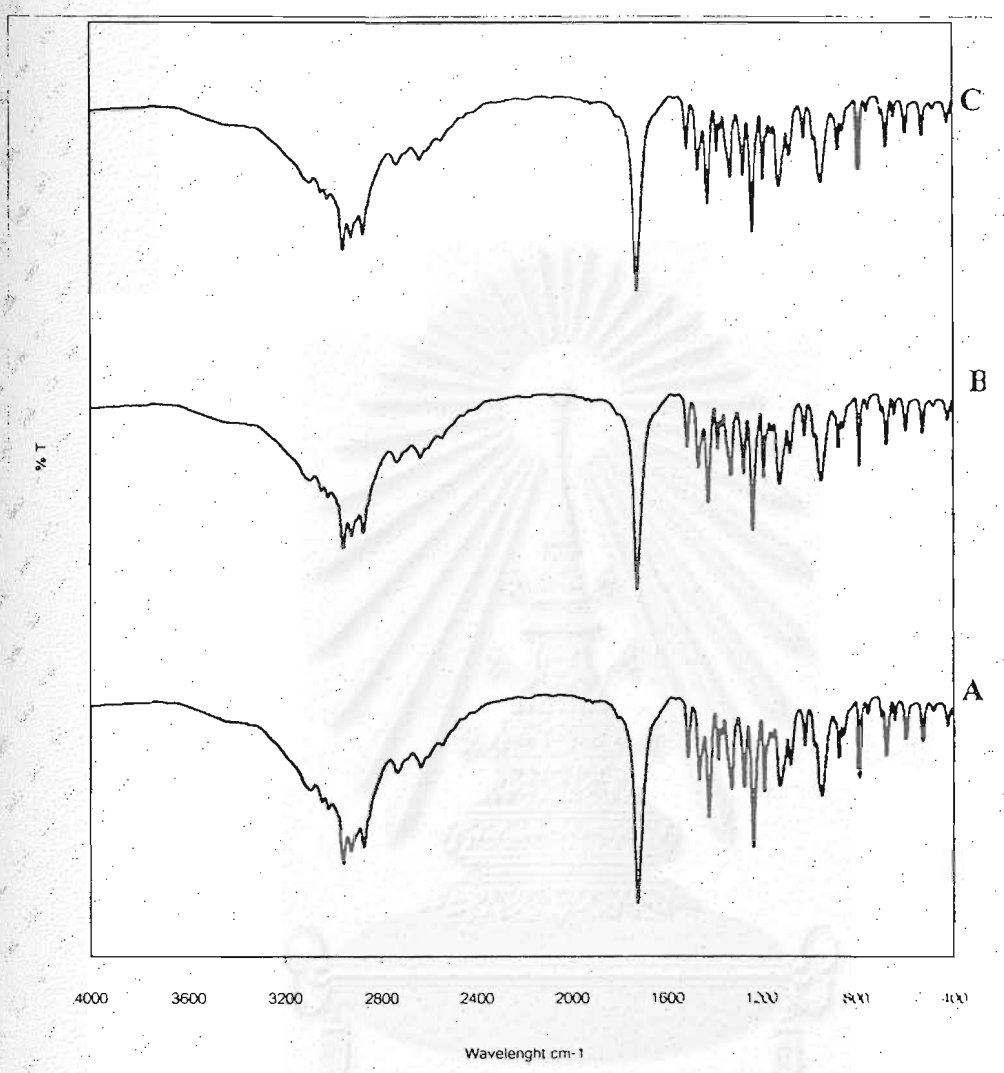


Figure 42 FTIR spectra of IPs at various ratios of PEG 4000 (A) 1:0.5, (B) 1: 0.75 and (C) 1:1

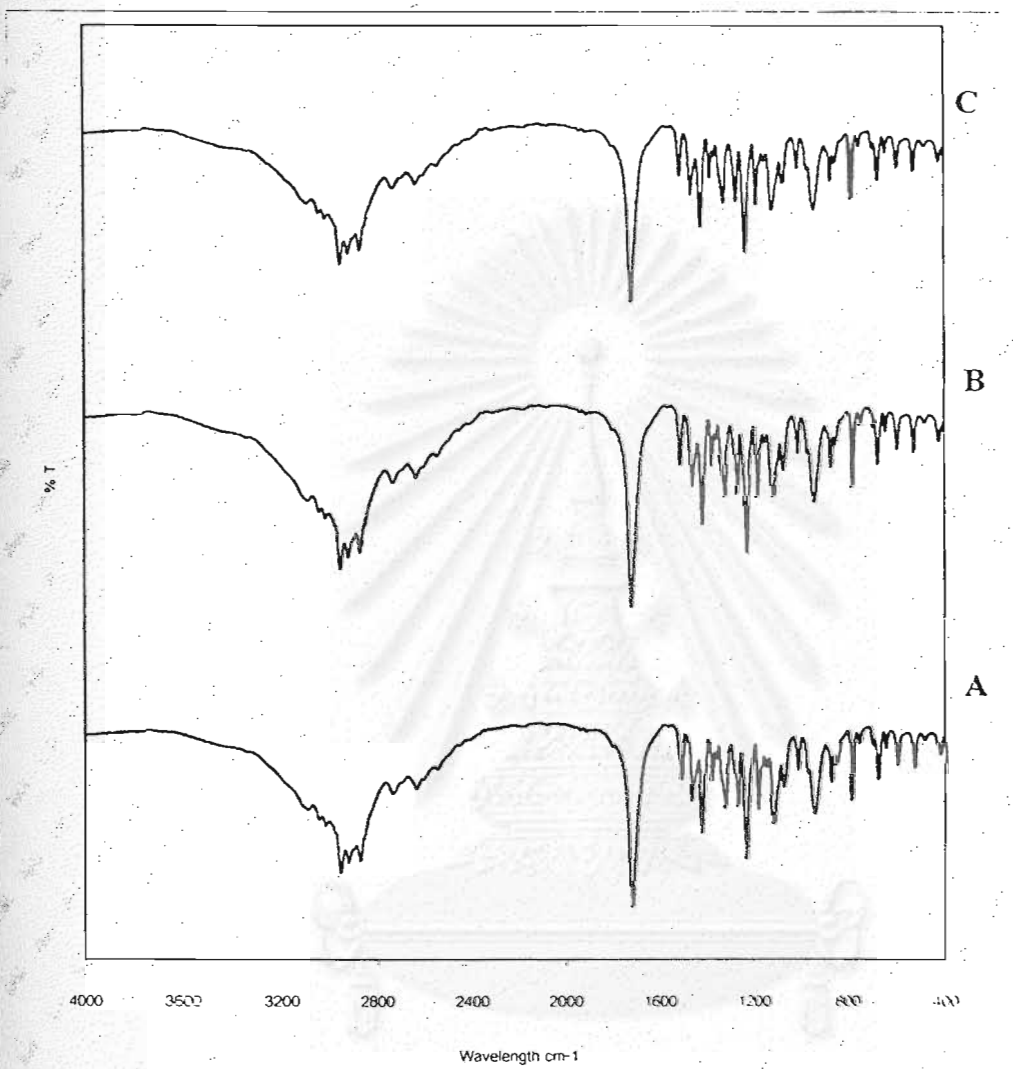


Figure 43 FTIR spectra of IPs at various ratios of PEG 6000 (A) 1: 0.5, (B) 1:0.75 and (C) 1:1

3.3 Differential scanning calorimetry (DSC) of formulas containing IB with PEG

The DSC curve of raw material of PEG at different grades; PEG 1450, 4000 and 6000, exhibited the single endothermic response which corresponded to the melting of each grade of PEG. Onset of melting was observed at 51 °C, 63 °C and 64.3 °C, for PEG 1450, 4000 and 6000, respectively as shown in Figure 44. The DSC thermograms of the mixtures containing IB with PEG 6000 are depicted in Figure 45. These thermograms demonstrated the endothermic peak coresponding to the melting at 55.8 °C and displayed a shoulder covered 65 °C - 78 °C. Whereas the thermograms of IPs at all grades of PEG shown the only endothermic peak in the same region around 72 °C, Figure 46.

3.4 ^{13}C Nuclear Magnetic Resonance of formulas containing IB with PEG

Figure 47 summarize the data about ^{13}C NMR spectra of IB, PEG 6000, solid dispersion of IB with PEG 6000 and IPs with PEG 6000. When compared the signals of solid dispersion and pellets of IB with PEG 6000 with the signal of the original crystal. It seems that all of the signals were closed to the original signal of their substances. There was only a little shift at the carboxylic carbon signal of the spectrum of the solid dispersion between IB and PEG 6000 which appeared at δ 178.748 ppm. This signal shifted from the signal of carboxylic acid carbon in IB original crystal that appeared at δ 180.715 ppm.

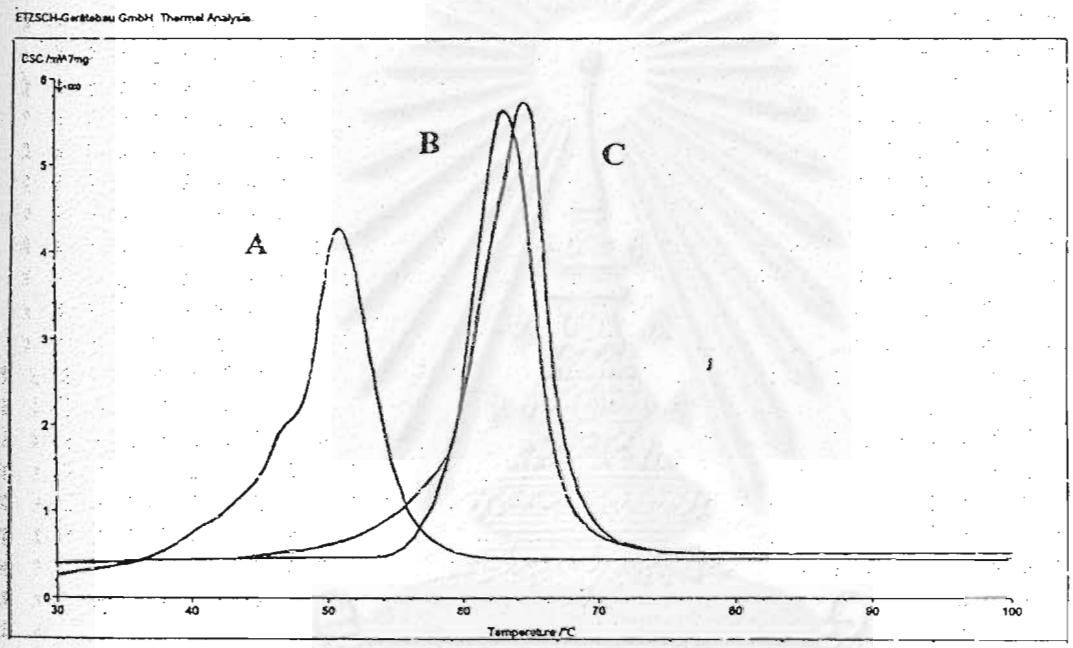


Figure 44 DSC thermograms of PEG at various grades (A) PEG 1450, (B) PEG 4000 and (C) PEG 6000

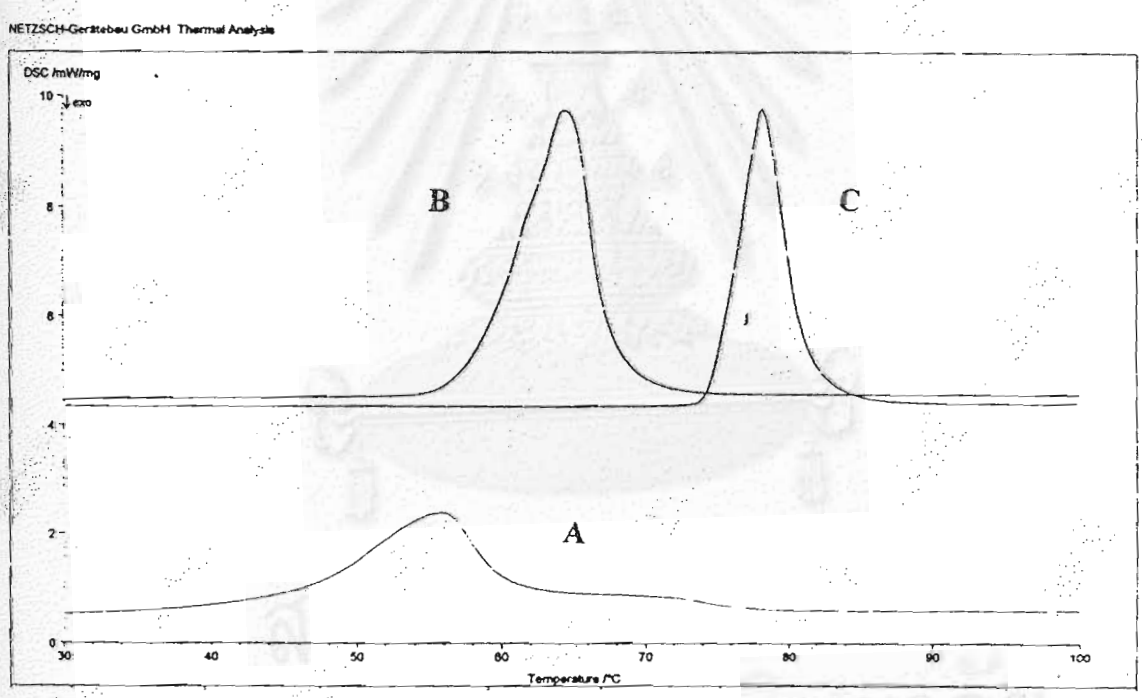


Figure 45 DSC thermograms of (A) solid dispersion of IB with PEG 6000 (B) PEG 6000 raw material and (C) IB raw material

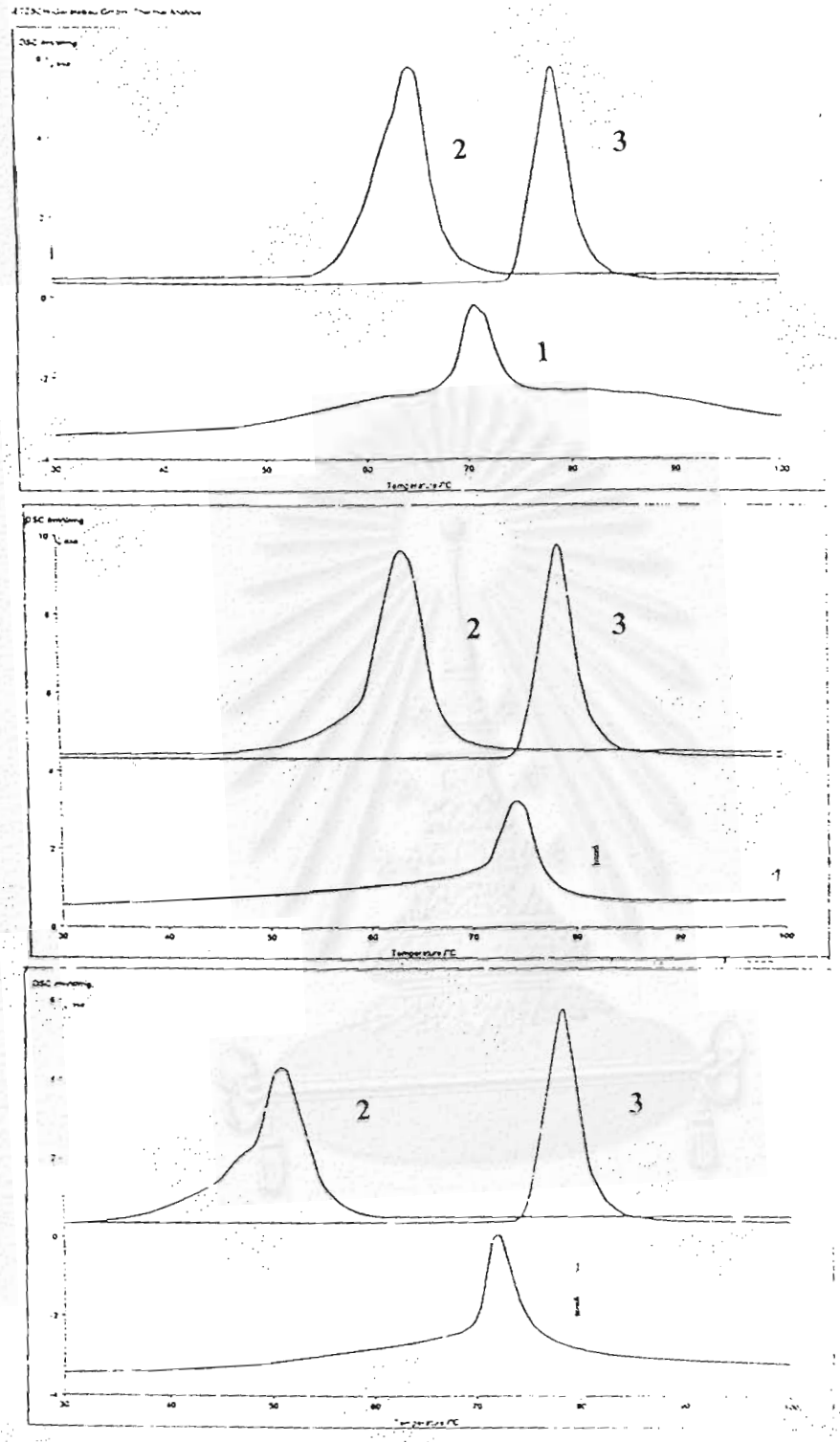


Figure 46 DSC thermograms of IPs in various grades of PEG, at a ratio of 1:1 (A) PEG 1450, (B) PEG 4000 and (C) PEG 6000, 1 = IPs at various grades of PEG, 2 = PEG raw material at various grades, 3 = IB raw material

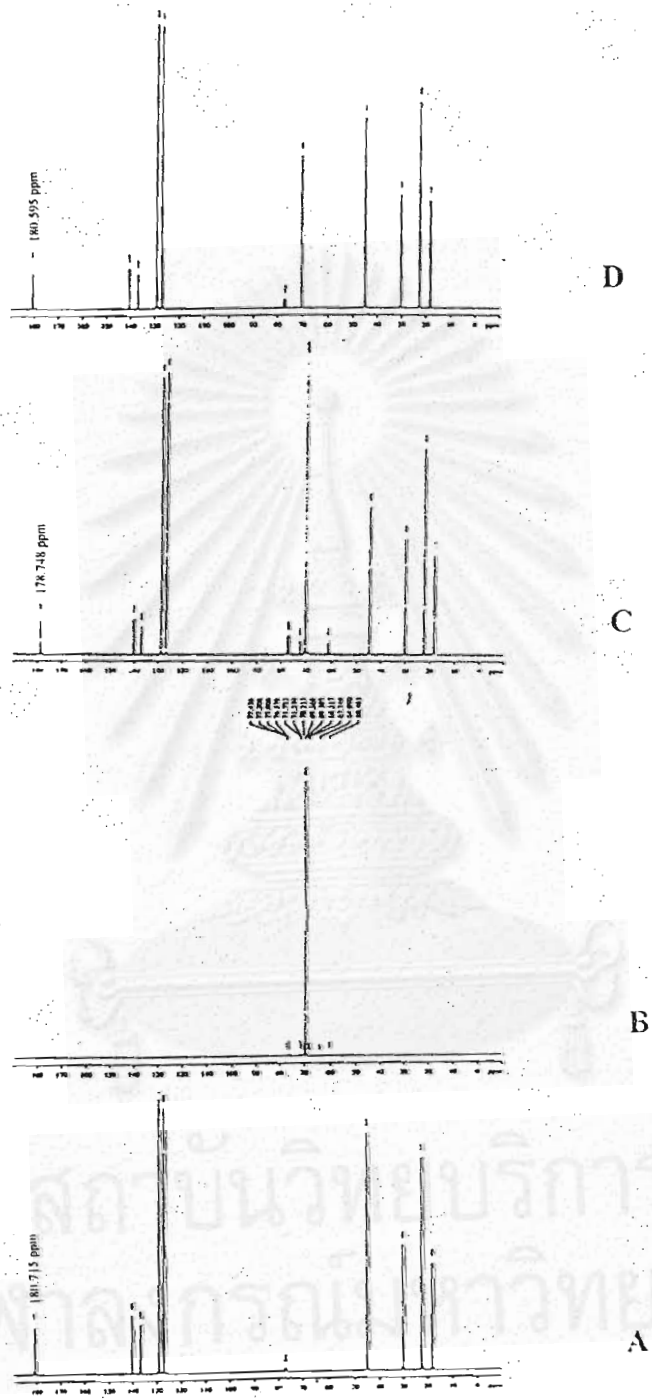


Figure 47 NMR Spectra of (A) IB raw material, (B) PEG 6000 raw material, (C) solid dispersion IB with PEG 6000 and (D) pellets of IB with PEG 6000

Part 4 Preparation and evaluation of ibuprofen pellets with PVP K 30 and PEG in suitable ratio

Preparation of IPs by using dispersion carrier: Combinding PVP and PEG in suitable ratio for phase partition technique

In this study, IPs from using solid dispersion that prepared from soluble carriers, PVP had the disadvantage of being tacky and hygroscopic properties, and therefore difficult to subdivide and handle. In the case of using PEG, we found the problems about physical properties, such as IPs from these substances had the less spherical in shape and had the rough surface. So in this study, combinations of PVP and PEG were used as dispersion carriers for IB that can produce the appropriate IPs from phase partition technique.

1. Formulation of IPs with combinding of PVP K 30 and PEG

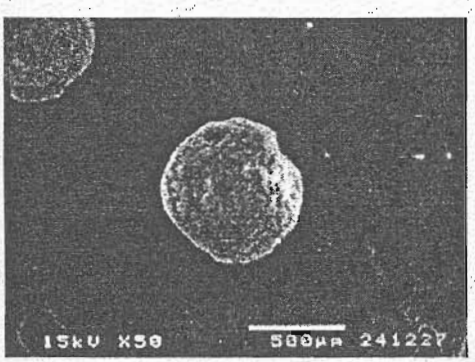
The preliminary formulations were conducted to find the suitable ratio of drug: PVP: PEG to form solid dispersion that can be used for phase partition technique to give IPs. We tried to reduce the ratio of PVP K 30 from the weight ratio of 0.5 because we found the problems as previously mentioned above, so added an amount of PEG to that formulation instead. In the case of using PEG 1450, we can not reduce an amount of PVP K 30 from the weight ratio of 0.5. If the quantity of PVP K 30 is less than this ratio, from phase partition technique we can not produce IPs. So, the formulation of mixing PVP K 30 with PEG 1450 that can gave spherical pellet was the ratio of drug: PVP K 30: PEG 1450; 1: 0.5: 0.25. On the other hand, using PEG 4000, it can be reduced an amount of PVP K 30 to the weight ratio of 0.35 and can added PEG 4000 in the weight ratio of 0.25 in the formulation. PEG 6000 was the best substance for the aim of decreasing an amount of PVP K 30 in these formulations because using PEG 6000 can reduce the weight ratio of PVP K 30 to 0.25 by adding PEG 6000 in the weight ratio of 0.35 into the formulation. PEG 6000 can also formulate IPs from the same ratio of PEG 4000 (IB: PVP K 30: PEG 4000 or 6000; 1: 0.35: 0.25) as well. In summary, the formulation of IPs by using dispersion carrier combinding PVP K 30 and PEG at the ratio are indicated in Table 6.

Table 6 Mixing ratio of IB : PVP K 30 : PEG solid dispersion

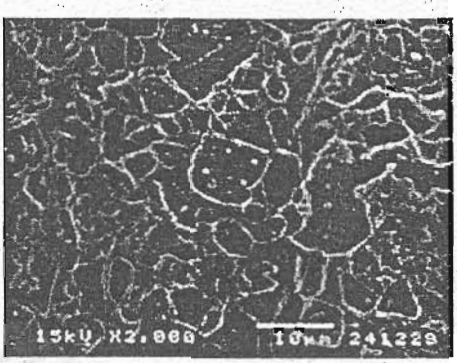
Type of PEG	Weight ratio of IB : PVP K 30 : PEG
PEG 1450	1: 0.5 : 0.25
PEG 4000	1: 0.35 : 0.25
PEG 6000	1: 0.35: 0.25 1: 0.25: 0.35

1.1 Morphology of IPs by using combination of PVP K 30 and PEG

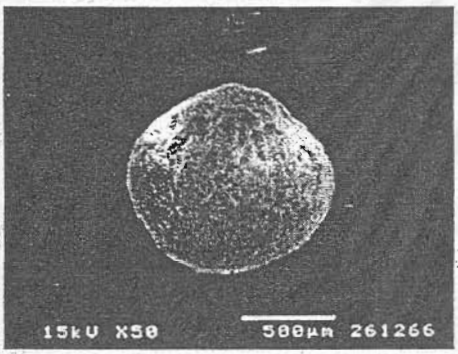
All of the IPs from these mixing ratios were spherical pellets and had smooth surface. When studied the crystal habit of IPs from these formulations, we found the small microcrystal in the shape of plate form which were smaller than the microcrystals of IB in IPs from the formulations that used PVP K 30 or PEG alone. We also found that, For the formulation contained the weight ratio of PVP K 30 up to 0.35, thin layer like the network of the polymer adsorbed on the surface of IPs were obvious. This was different from the formulation that used weight ratio of PVP K 30 ; 0.25 that had no network of the polymer adsorbed onto the surface. In the case of PEG 1450 that we can not decreased the weight ratio of PVP K 30. The result of crystal habit of the microcrystals was not different when compared with the formulation of IPs with PVP K 30, all of these results are illustrated in Figures 48 – 49.



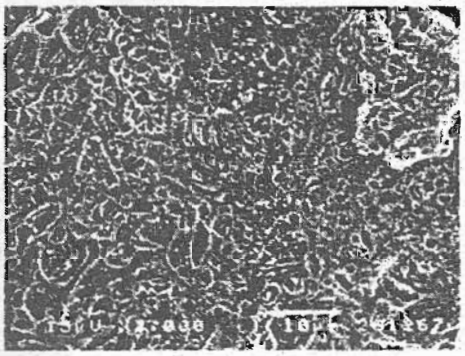
A



B

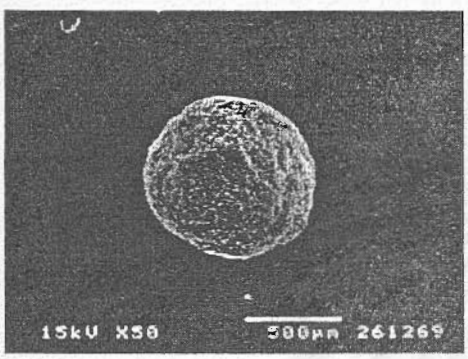


C

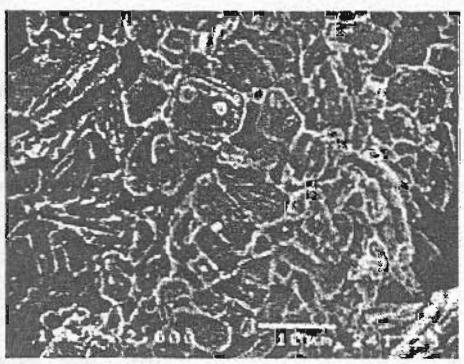


D

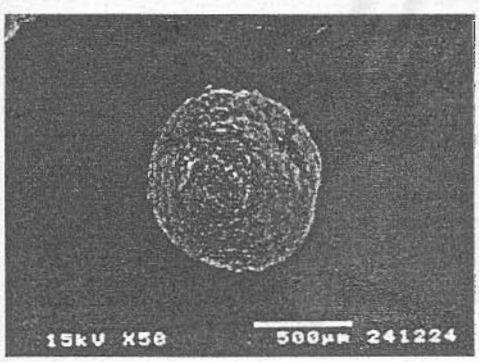
Figure 48 Scanning electron photomicrographs of IPs by using the weight ratio of (A),(B) IB:PVP K 30 : PEG 1450; 1:0.5:0.25 and (C), (D) IB:PVP K 30 : PEG 4000; 1:0.35:0.25, and at different magnifications (A, C X 50; B, D X 2000)



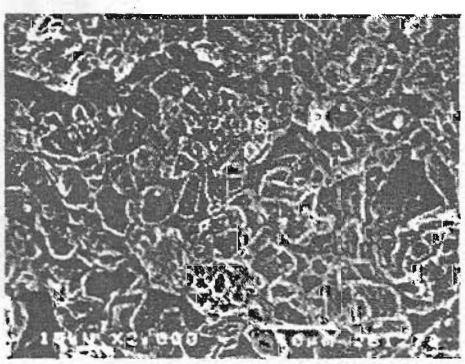
A



B



C



D

Figure 49 Scanning electron photomicrographs of IPs by using the weight ratio of (A),(B) IB:PVP K 30 : PEG 6000; 1:0.25:0.35 and (C), (D) IB:PVP K 30 : PEG 6000; 1:0.35:0.25, and at different magnifications (A, C X 50; B, D X 2000)

2. Dissolution study of IPs at different ratios of PVP K 30: PEG

We studied the drug content of IPs by analyzing an amount of IB in the pellets. Weighed the IPs acculately that contained 400 mg of drug for the studying on the dissolution property.

Dissolution data of IPs at different ratios of PVP K 30 with PEG as the dispersion carrier at the suitable ratio. Dissolution data from these formulations are shown in Tables 17B – 20B (Appendix B). The release profiles of IPs are presented in Figure 50. All of IPs from the formulations showed percentage drug release were not different when compared with others which had different weight ratios between PVP K 30 and PEG which were used in this study. When calculate the similarity factor "f_2" of these formulations and used the formulation; IB: PVP K 30:PEG 6000,1: 0.35: 0.25 as a reference, the data are given in Table 6D (Appendix D). We found all of the formulation had the "f_2" value more than 50 which indicated similary in the dissolution between these 4 formulations.

3. Physicochemical properties of IPs with PVP K 30 and PEG

The physicochemical properties was studied concerning the interaction between drug; IB with two polymers (PVP K 30 and PEG) that were used in the formulations. The studies were conducted in both before and after using phase partition technique to compared and investigated the interaction between these substances. In this case, we have selected to study on the interaction in solid dispersion between IB, PVP K 30 and PEG 6000 in the ratio 1:0.35:0.25 before using phase partition technique. The physicochemical properties of IPs was studied on mixing PVP K30 and PEG as the dispersion carriers in suitable ratio (see Table 6) after phase partition technique.

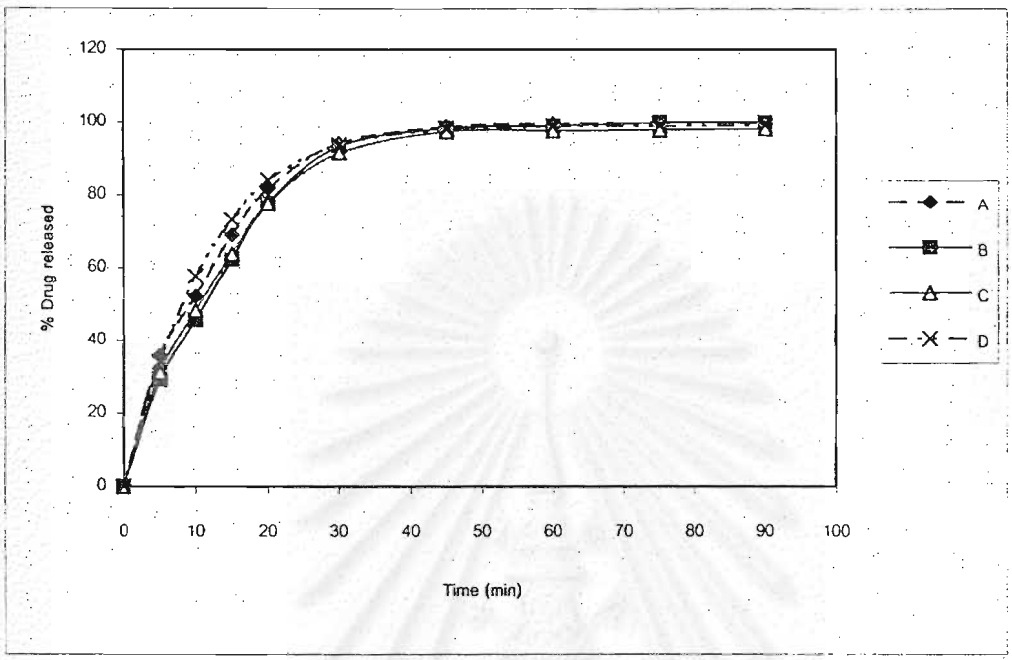


Figure 50 Dissolution profiles of IPs by using the weight ratio of (A) IB: PVP K 30: PEG 1450; 1: 0.5: 0.25, (B) IB: PVP K 30: PEG 4000; 1: 0.35: 0.25, (C) IB: PVP K 30: PEG 6000; 1: 0.25: 0.35 and (D) IB: PVP K 30: PEG 6000; 1: 0.35: 0.25

3.1 Powder X–ray diffraction study

Figure 51 displays the X-ray diffractograms of the dispersion between IB, PVP K 30 and PEG 6000 in the ratio, 1:0.35:0.25 as compared with the X- ray diffractograms of IB, original crystal and raw material of PVP K 30 and PEG 6000. We found that several diffraction peaks of the drugs were disappeared and some were decreased in intensity, and the X-ray diffractograms of PEG still could be observed as seen at 23.4°(2θ). For the X-ray diffractograms of IPs from 4 formulations of suitable ratio of PVP K 30 with PEG are illustrated in Figure 52. All of them presented the peaks that corresponding to IB, original crystal and the peaks of PEG were disappeared.

3.2 Infrared spectroscopy

Figure 53 shows IR spectra of raw materials of IB, PVP K 30, PEG 6000 as compared with the dispersion of IB with PVP K 30 and PEG 6000 in the ratio of 1:0.35:0.25. The above dispersion of 1:0.35:0.25 showed the IR spectra that the positions of the bands were not different from the original substances that used in this formulation. It could be seen the strong bands in these spectra such as at 1700 cm^{-1} due to C=O stretching in carboxylic group of IB and still had the band at 1670 cm^{-1} due to the C=O stretching in the cyclic amide of PVP K 30.An another one of strong peak at 1110 cm-1 indicated the C–O (ether) stretching of PEG 6000 also can be seen in the IR spectra of these mixing substances. Studies in the IR spectra of IPs from the suitable weight ratio of the mixing between PVP K 30 and PEG in the grades of 1450, 4000 and 6000 that can produced the IPs after used phase partition technique. They are; IB: PVP K 30: PEG 6000, 1:0.25:0.35, IB: PVP K 30: PEG 6000, 1:0.35:0.25; IB: PVP K 30: PEG 4000, 1:0.35:0.25; IB: PVP K 30: PEG 1450, 1:0.5:0.25, respectively. All of these formulations had the same IR spectra as illustrated in Figure 54 .The spectra were not much different from the IR spectra of the dispersion of IB with PVP K 30 and PEG 6000 ; 1 : 0.35 :0.25 which we studied before, only had the decreasing in intensity of a peak at 1110 cm^{-1}, that was the PEG band as already mentioned previously.

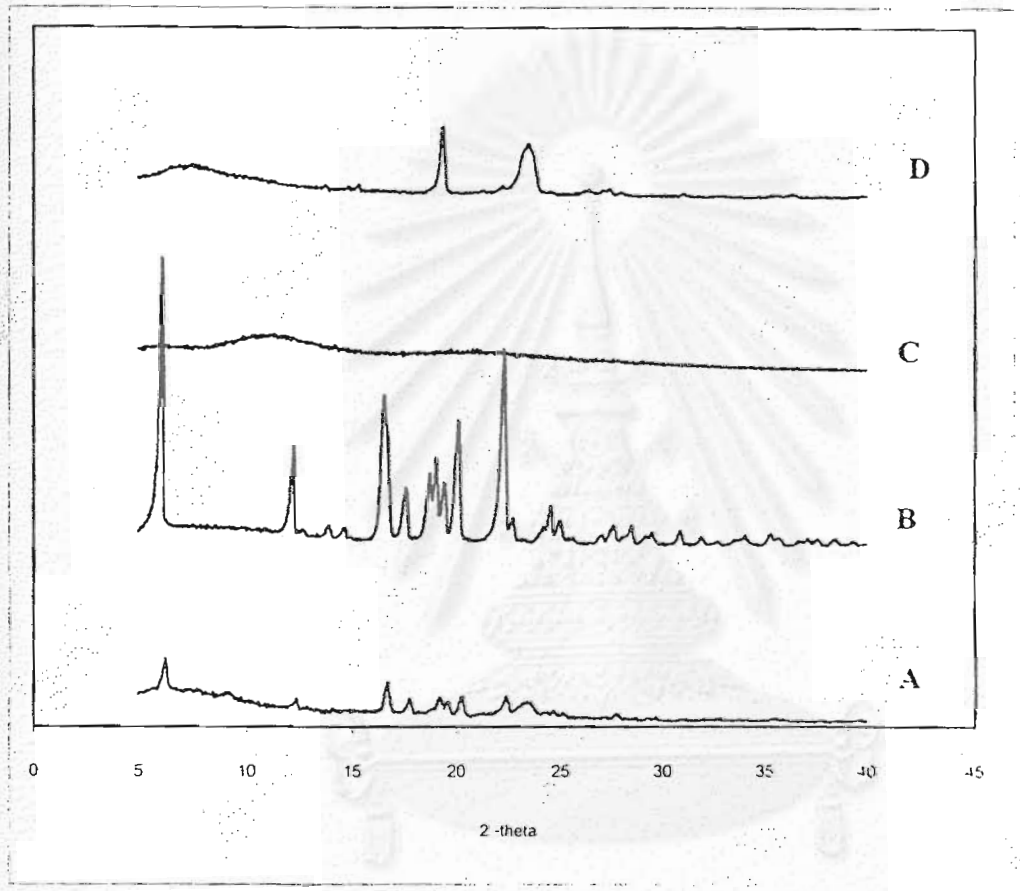
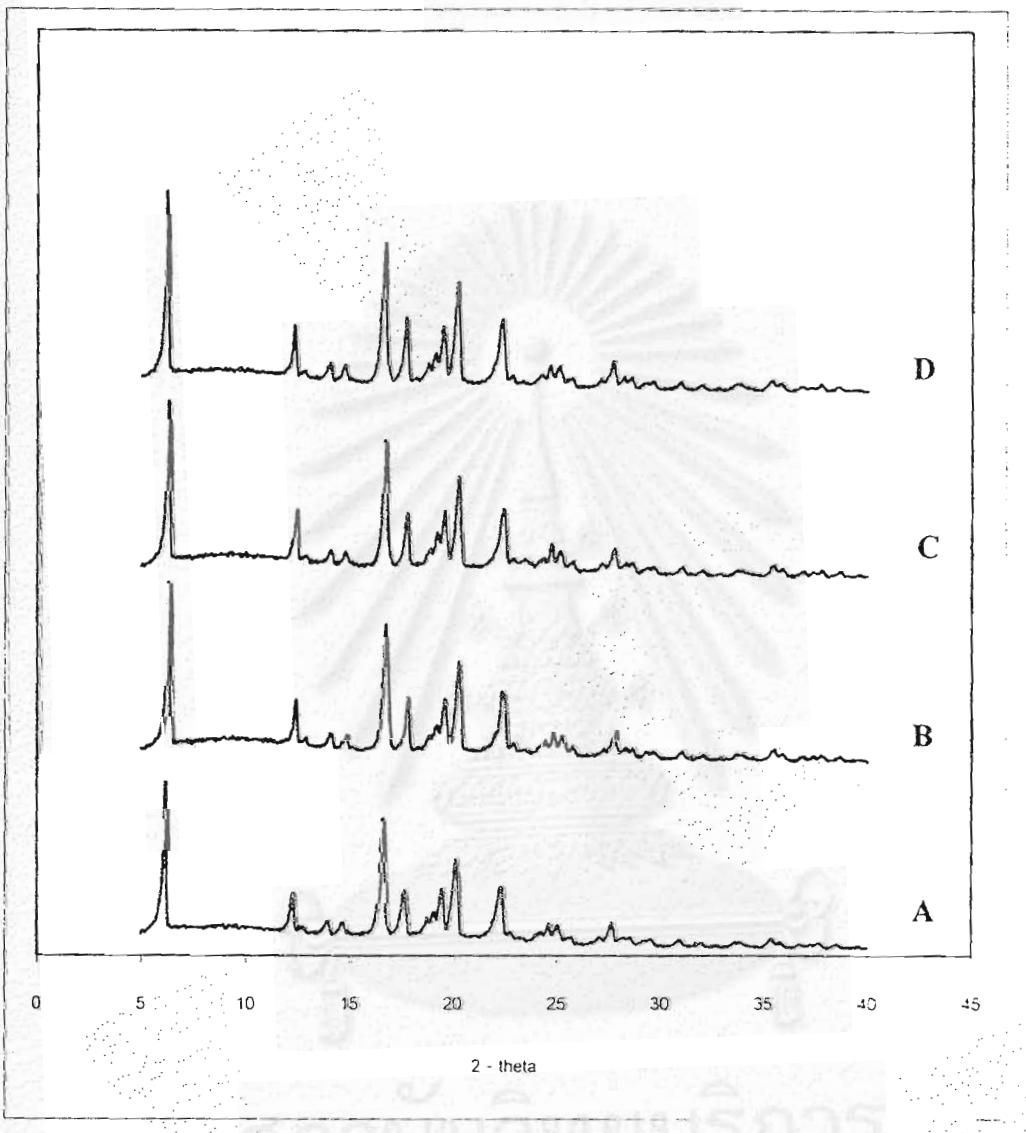


Figure 51 X- ray diffractograms of (A) the solid dispersion of IB: PVP K 30: PEG 6000; 1: 0.35: 0.25; (B) IB raw material; (C) PVP K 30 raw material and (D) PEG 6000 raw material



.Figure 52 X- ray diffractograms of IPs at various weight ratios of (A) IB: PVP K 30: PEG 1450; 1:0.5:0.25, (B) IB: PVP K 30: PEG 4000; 1:0.35:0.25, (C) IB: PVP K 30: PEG 6000; 1:0.25:0.35 and (D) IB: PVP K 30: PEG 6000; 1:0.35:0.25

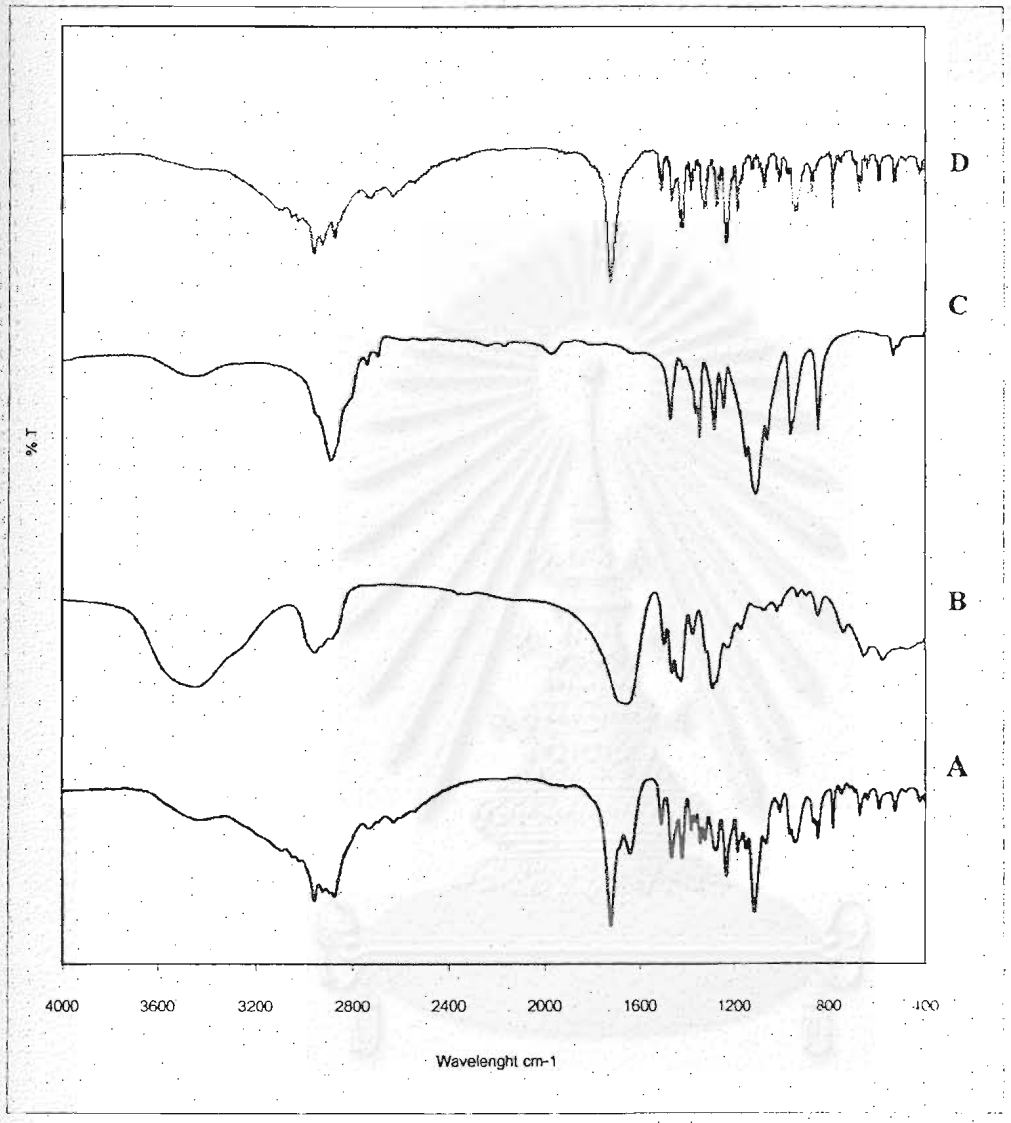


Figure 53 Infrared spectra of the solid dispersion of (A) IB: PVP K 30: PEG 6000; 1:0.35:0.25, (B) PVP K 30 raw material, (C) PEG 6000 raw material and (D) IB raw material

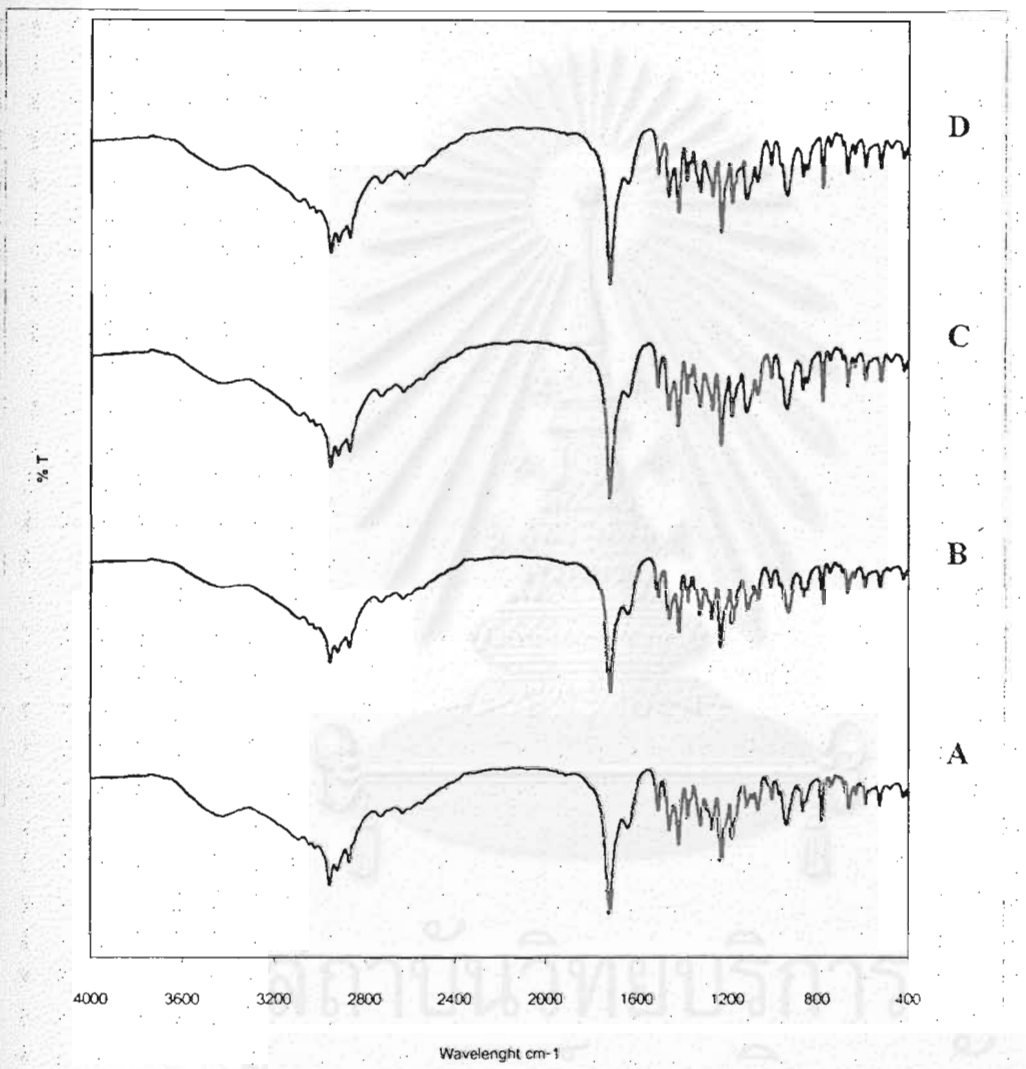


Figure 54 Infrared spectra of IPs at various weight ratios of (A) IB: PVP K 30: PEG 1450; 1:0.5:0.25, (B) IB: PVP K 30: PEG 4000; 1:0.35:0.25, (C) IB: PVP K 30: PEG 6000; 1:0.25:0.35 and (D) IB: PVP K 30: PEG 6000; 1:0.35:0.25

3.3 Differential scanning calorimetry (DSC) of formulas containing IB with PVP K 30 and PEG in suitable ratio

The DSC thermogram of the solid dispersion of IB, PVP K 30 and PEG 6000 that we used in a ratio of 1: 0.35: 0.25 for studying the interaction between these substances. The results exhibited the broad endotherm for the melting of IB, and the polymers were no longer appear as shown in Figure 55. Figure 56 illustrates the DSC thermograms of IPs from 4 suitable ratios as mentioned before, only a single broad endotherm was observed for all of these formulations. The melting points of these formulations were closed together about 67 – 70° C.

3.4 ^{13}C Nuclear Magnetic Resonance of formulas containing IB with PVP K 30 and PEG in suitable ratio

Figure 57 summarizes the data about ^{13}C NMR spectra of IB, PVP K 30 and PEG 6000, solid dispersion of IB with PVP K 30 and PEG 6000 in this ratio; 1: 0.35 : 0.25 and IPs from the same ratio after used phase partition technique. When compared the signals from the solid dispersion and IPs of this formulation with the signal from the original substances, it seems all of the signals were closed to the original signal of their substances. Only had a little shifte at the carboxylic carbon signal of the spectrum from the solid dispersion and IPs of this formulation. These signals appeared at δ 178.505 ppm and 179.412 ppm which shifted from the original signal of the carboxylic acid carbon of IB crystal that showed at δ 180.715 ppm.

Part 5 Physical properties study of IPs

Physical properties of IPs containing IB with PVP K 30 and PEG

1. Particle size & size distribution

Particle size and size distribution of IPs from the formulation are presented in Tables 1 C – 19 C (Appendix C). It was noticed that in the formulations of IPs with PVP K 30 alone at; 1: 0.5, 1: 0.75 and 1: 1 had the size of pellets less than 1 mm.

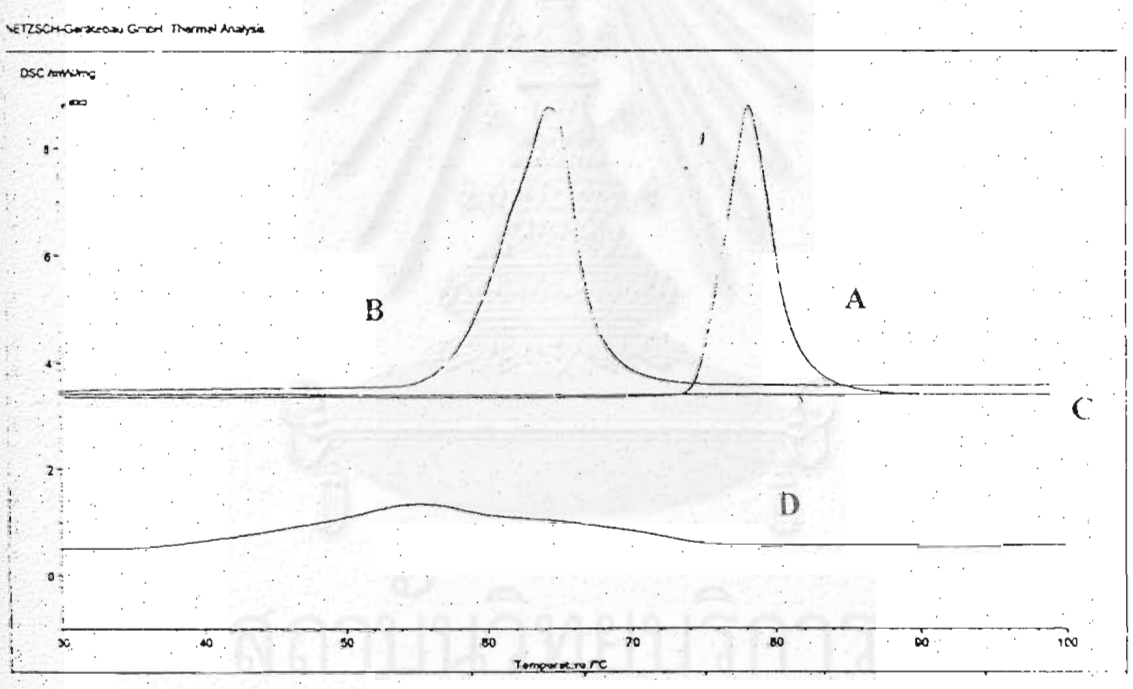


Figure 55 DSC thermograms of (A) IB raw material (B) PEG 6000 raw material, (C) PVP K 30 raw material (D) solid dispersion of IB: PVP K 30:PEG 6000; 1:0.35:0.25

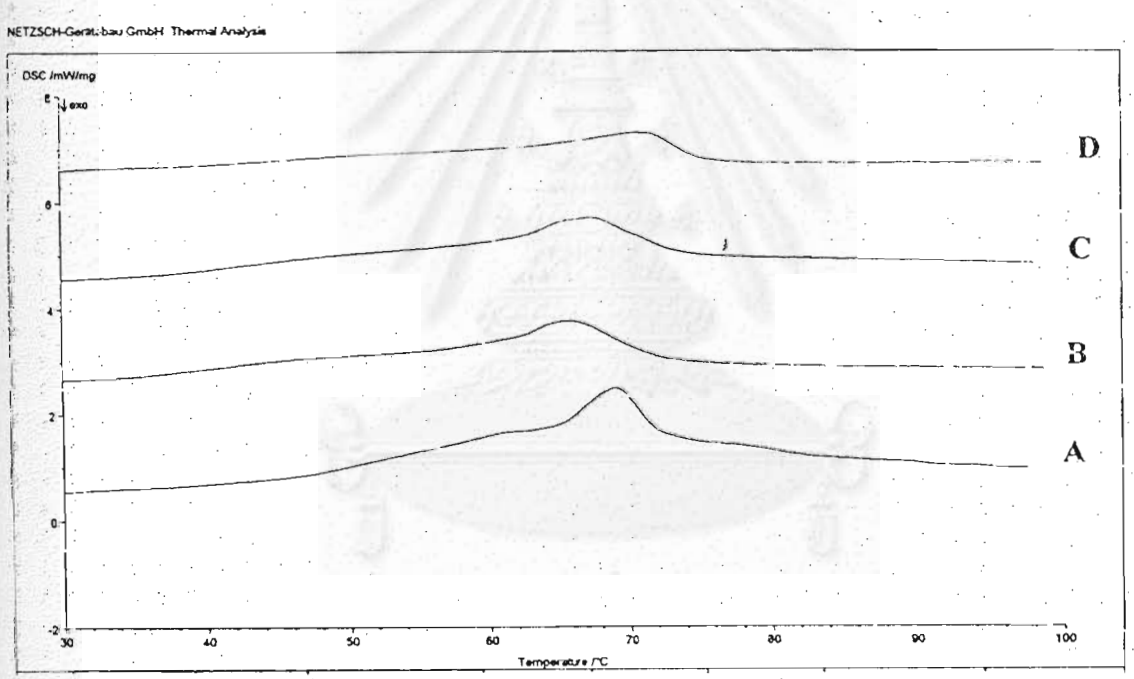


Figure 56 DSC thermograms of IPs in various ratios of IB: PVP K 30: PEG (A) 1: 0.5: 0.25 PEG 1450, (B) 1:0.35:0.25 PEG 4000, (C) 1:0.25:0.35 PEG 6000 and (D) 1:0.35:0.25 PEG 6000

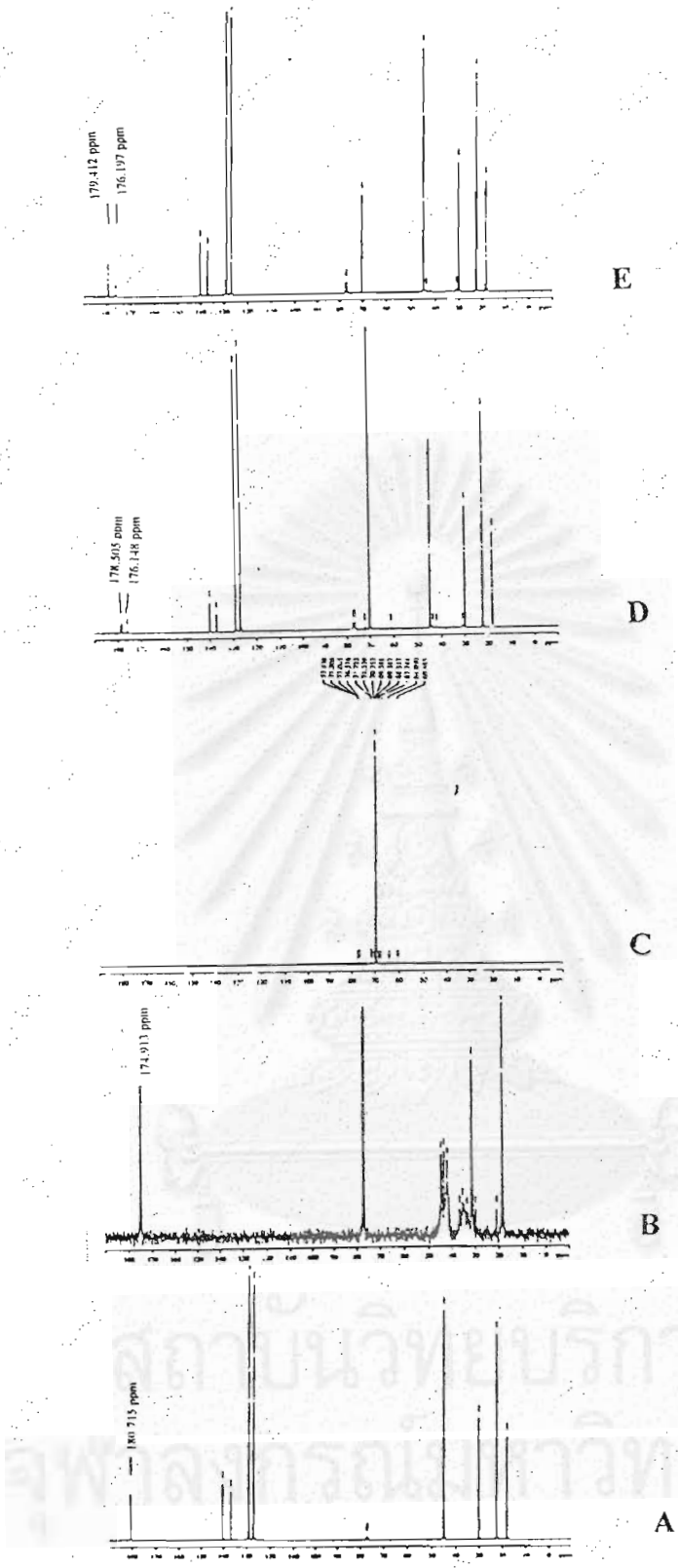


Figure 57 NMR spectra of (A) IB raw material, (B) PVP K 30 raw material, (C) PEG 6000 raw material, (D) solid dispersion of IB: PVP K 30: PEG 6000; 1:0.35:0.25 and (E) IPs of IB: PVP K 30: PEG 6000; 1:0.35:0.25

In addition, another formulations (IB: PEG 1450, 4000, 6000 at weight ratios; 1:0.5, 1:0.75 and 1:1,IB: PVP K 30: PEG 1450, 1: 0.5: 0.25, IB: PVP K 30: PEG 4000; 1:0.35:0.25, IB: PVP K 30: PEG 6000; 1:0.25:0.35 and IB: PVP K 30: PEG 6000; 1:0.35:0.25) had the bigger size that more than 1 mm. The results also showed that, in the formulation of IPs with PEG may cause variation in size of the pellets . In the case of IPs with PVP in the formulation of IB: PVP K 30 1:0.5, 1: 0.75, 1: 1 including in the formulation with IB: PVP K 30: PEG1450; 1:0.5:0.25, formulation with IB: PVP K 30: PEG 4000;1:0.35:0.25, formulation with IB: PVP K 30: PEG 6000;1:0.25:0.35 and 1: 0.35:0.25, we noticed the narrow size distribution of these pellets as indicated in Figures 1C – 19C (Appendix C).

2. Bulk density, Tapped density and Percent compressibility

Bulk volume and tapped volume of IPs in various formulations were recorded from the experiments. These data were calculated to bulk density, tapped density and percent compressibility. The results are shown in Table 7. The bulk densities and Tapped densities varied between 0.32 – 0.40 g/cm^3 and 0.33 – 0.42 g/cm^3, respectively. From the data, percent compressibility of IPs from various formulas had the range from 3.64 – 9.05 %.

3. Flow rate and angle of repose determination

We determined about flow property of IPs by using the data of flow rate and angle of repose that can be represented in each formulation. The results are presented in Table 8. When the angle of repose and flow rate of IPs from the formulation were compared, it was found that in the formulation of IB: PVP K 30: PEG 6000;1:0.25:0.35 had the highest flow rate of 747.60 g/min and the lowest angle of repose of 22.55 °. We found in the formulations that used the mixing ratio of PVP K 30 and PEG (excepted in the formulation of IB: PVP K 30: PEG 1450; 1:0.5:0.25) had better flow property when compared with another formulations of IPs.

Table 7 Bulk density, Tapped density and percent compressibility of IPs prepared from various conditions

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	% Compressibility
1 % $CHCl_3$ (1)	0.37	0.39	6.60
1.5 % $CHCl_3$ (1)	0.38	0.39	4.82
2 % $CHCl_3$ (1)	0.37	0.39	5.33
1:0.5 PVP K 30 (2)	0.37	0.39	5.63
1:0.75 PVP K 30 (2)	0.37	0.40	6.98
1:1 PVP K 30 (2)	0.37	0.40	7.27
1:0.5 PEG 1450 (3)	0.32	0.34	4.99
1:0.75 PEG 1450 (3)	0.34	0.37	8.38
1:1 PEG 1450 (3)	0.37	0.41	9.05
1:0.5 PEG 4000 (4)	0.32	0.34	5.34
1:0.75 PEG 4000 (4)	0.34	0.37	7.38
1:1 PEG 4000 (4)	0.36	0.38	5.32
1:0.5 PEG 6000 (5)	0.32	0.33	3.64
1:0.75 PEG 6000 (5)	0.35	0.37	3.84
1:1 PEG 6000 (5)	0.38	0.40	6.45
1:0.5:0.25 PEG 1450 (6)	0.34	0.37	6.27
1:0.35:0.25 PEG 4000 (7)	0.40	0.42	4.32
1:0.25:0.35 PEG 6000 (8)	0.40	0.41	3.89
1:0.35:0.25 PEG 6000 (8)	0.35	0.37	4.66

(1) = bridging solvent alone, (2) = IB with PVP K 30 in 1.5 % bridging solvent, (3) = IB with PEG 1450 in 1.5% bridging solvent, (4) = IB:PEG 4000 in 1.5% bridging solvent, (5) = IB: PEG 6000 in 1.5% bridging solvent, (6) = IB:PVP K 30 : PEG 1450 in 1.5% bridging solvent, (7) = IB:PVP K 30: PEG 4000 in 1.5% bridging solvent, (8) IB:PVP K 30: PEG 6000 in 1.5% bridging solvent

* Averaged from 3 determinations.

Table 8 Flow rate and Angle of repose of IPs

Formulation	Flow rate (g/min) *	Angle of repose (degree) *
1 % $CHCl_3$ (1)	528.60	27.49
1.5 % $CHCl_3$ (1)	574.20	27.52
2 % $CHCl_3$ (1)	578.40	27.19
1:0.5 PVP K 30 (2)	649.80	28.04
1:0.75 PVP K 30 (2)	579.60	28.92
1:1 PVP K 30 (2)	Not flow	Not flow
1:0.5 PEG 1450 (3)	486.00	26.09
1:0.75 PEG 1450 (3)	485.40	28.61
1:1 PEG 1450 (3)	592.80	25.81
1:0.5 PEG 4000 (4)	615.00	28.02
1:0.75 PEG 4000 (4)	589.20	28.49
1:1 PEG 4000 (4)	715.20	25.70
1:0.5 PEG 6000 (5)	490.80	27.57
1:0.75 PEG 6000 (5)	717.00	29.32
1:1 PEG 6000 (5)	701.40	29.66
1:0.5:0.25 PEG 1450 (6)	Not flow	Not flow
1:0.35:0.25 PEG 4000 (7)	678.00	24.42
1:0.25:0.35 PEG 6000 (8)	747.60	22.55
1:0.35:0.25 PEG 6000 (8)	686.40	23.54

(1) = bridging solvent alone, (2) = IB with PVP K 30 in 1.5 % bridging solvent, (3) = IB with PEG 1450 in 1.5% bridging solvent, (4) = IB:PEG 4000 in 1.5% bridging solvent, (5) = IB: PEG 6000 in 1.5% bridging solvent, (6) = IB:PVP K 30 : PEG 1450 in 1.5% bridging solvent, (7) = IB:PVP K 30: PEG 4000 in 1.5% bridging solvent, (8) IB:PVP K 30: PEG 6000 in 1.5% bridging solvent

* Averaged from 3 determinations.

Part 6 Formulation and evaluation of IB capsule

Using IPs prepared from mixed carriers for producing IB capsules

We selected a formulation of IB:PVP K 30:PEG 6000 at 1:0.35:0.25 that gave good dissolution and physical properties to produced the IB capsules. We studied the dissolution profile of IB capsules prepared from the IB powder and compared with IPs as previously mentioned in the dose of 200 mg per one capsule (capsule No. 0). Dissolution data of these formulations are given in Tables 21 – 22B (Appendix B). The release profiles of IPs are presented in Figures 58. We found the formulation of IPs capsules gave better dissolution profile when compared with the formulation of capsules with IB powder. Proved by calculating for "f_2" value and compared between these formulations, by using the dissolution curves of IB powder in the capsules as reference. For this case "f_2" value was 39.50 meaning that between this 2 formulations there was a significant different on the dissolution profiles.

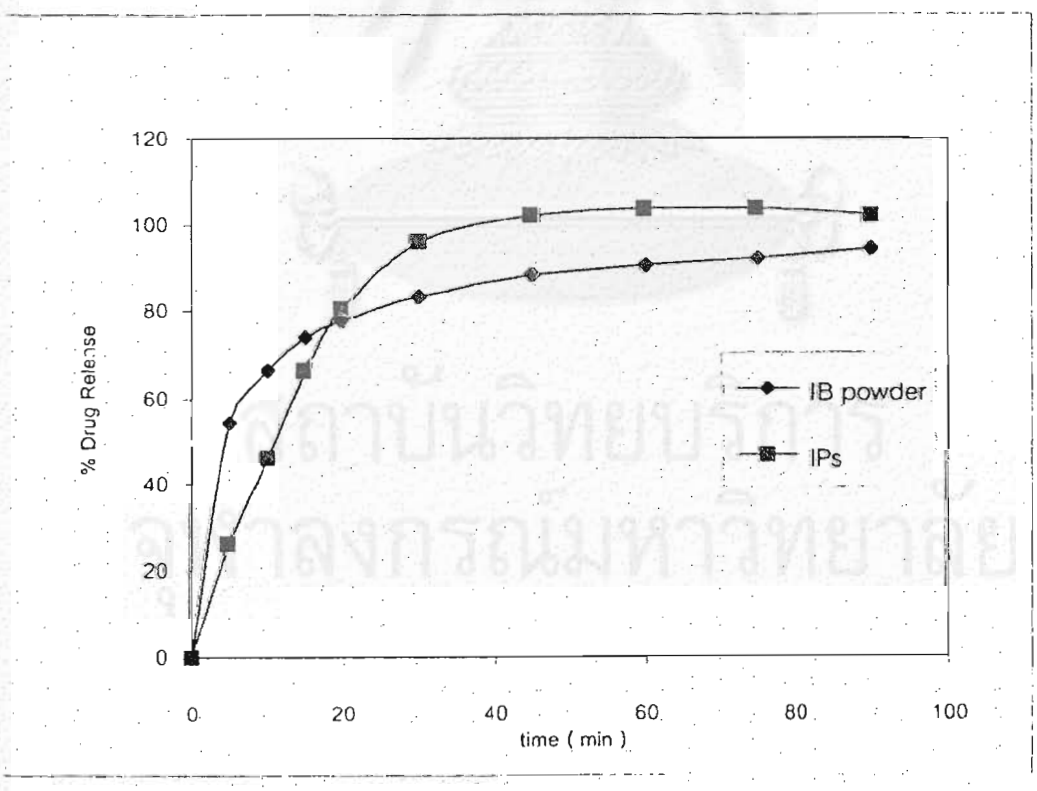


Figure 58 Dissolution profiles of capsule of IB powder and IPs prepared from IB: PVP K 30: PEG 6000 at a weight ratio of 1:0.35:0.25

CHAPTER IV

DISCUSSION AND CONCLUSIONS

Formulation and morphology of IPs

In this research work, we started to study the preliminary formulations that varied the amount of bridging solvent in phase partition technique at 1 %, 1.5 % and 2 % chloroform for producing IPs. From the scanning electron photomicrographs of these formulations revealed that IPs produced by using 3 ml of bridging solvent (1.5 % chloroform) was a suitable and gave rounder IPs (Figure 7). So we determined to use 1.5 % chloroform in the phase partition technique for future studies.

In the case of using PVP K 30 as the dispersion carrier in the preparation of IPs from phase partition technique that we studied in three ratios of IB:PVP K 30 at 1:0.5, 1:0.75 and 1:1, respectively. We found that, using the weight ratio of PVP K 30 less than 0.5, IPs could not be produced. IB microcrystals on the surface of the pellets from these formulations seemed to be composed of some aggregates of plate shape. Furthermore, we found the network of the polymer adsorbed onto the hydrophobic surface of drug microcrystals. The network of PVP K 30 seem to increased in thickness when the ratio of PVP K 30 in the drug was increased: i.e, polymer ratio from 1:0.5 to 1:0.75 or 1:1 (Figure 18).

PEG was another polymer that was used in this study, compared among the formulations containing various types (PEG 1450, 4000 and 6000) and amounts of PEG in three weight ratios of drug: PEG (1:0.5, 1:0.75 and 1:1). From this study, it was found all of the formulation had the same characteristic particle size, shape and the IB microcrystals that was deposited on the surface of IPs, and this characteristic was similar to IPs with drug alone. The microcrystals in the surface of the pellets of IB with PEG seemed to be larger in size when compared with IPs of drug alone (Figures 31-32). This might be explained that by using PEG in the formulation increased the viscosity of the system. It act like the barrier for phase partition of drug in ethanol: water to the bridging solvent.

When used both PVP K 30 and PEG in the formulation of IPs. It was found that using different in PEG chain lengths gave the different of suitable ratios that can produce IPs from phase partition technique. In addition, when using the high

molecular weight PEG, the result showed that we can reduced the amount of PVP K 30 in the formulation more than in the case of using low molecular weight PEG. From the results of this study that had four formulations of IPs from suitable ratio of drug : PVP K 30:PEG 1450 at the ratio;1:0.5:0.25, 1:0.35:0.35 PEG 4000, 1:0.25:0.35 PEG 6000 and1:0.35: 0.25 PEG 6000. However, the IPs of the formulation 1: 0.5:0.25 PEG 1450 had tackiness problem. *Leuner and Dressman, 2000* described that the influence of the PEG chain length, PEGs of molecular weight 4000 – 6000 are the most frequently used in the manufacture of solid dispersion, because in this molecular weight range the water solubility is still very high, but hygroscopicity is not a problem, and the melting points are already over 50 °C. However, when PEG with too low a molecular weight is used, this can lead to a product with a sticky consistency which is difficult to formulate into a pharmaceutically acceptable product. Surface investigation of IPs from these formulations indicated the surface of IPs composed of IB microcrystals and had the network of polymer adsorbed on the surface, and more dense when the weight ratio of PVP K 30 in the formulation increased (Figures 48-49).

In physicochemical properties studied, we used four methods for investigating on the molecular orientation of drug and interaction between drug with polymers that were used in the formulations; they are Powder X-ray diffraction , infrared spectroscopy, thermal analysis and ^{13}Carbon nuclear magnetic resonance (^{13}C – NMR) spectroscopy. For physicochemical properties of IPs with drug alone that was produced by phase partition technique to compare with IB raw material. The results can be explained that the process of phase partition and the solvent that was used in this process had no affect on the physicochemical properties of IB. We found that all of the three formulations which varied in amount of chloroform are no different in physicochemical properties. This previous results were also compared with IB raw material and all of the result can be explained that the property of IB from IPs did not change from IB original crystals. X- ray diffractograms that had the different in intensities of some peaks (Figures 9-10). In the process of phase partition technique, IB raw material was dissolved in ethanol had to recrystallized to produced the agglomerate of IB microcrystals and gave IPs. An arrangement of the drug molecule may be change from the original pattern so differences in the X- ray diffractograms can be found. The same pattern of DSC thermograms and IR spectra of

IPs with IB original crystal (Figure12 and Figure14, respectively) confirmed that , the process of phase partition technique and the solvent used in this method had no affect on the thermal and spectral properties of IB.

Chemical interaction between IB and PVP K 30 in solid dispersion state

PVP K 30 is a polymer that was used as a dispersion carrier to produce IPs. Comparing the X-ray diffractograms of IB, PVP K 30 and IB – PVP K 30 dispersion. From these diffractograms, it can be explained that IB was the crystalline drug which had very strong diffraction peaks and for PVP K 30 that showed an amorphous in nature as we mentioned before. For IB- PVP K 30 dispersion, it was observed that the X- ray diffractions of this dispersion exhibited a totally amorphous nature. In the case of decrease the ratio of IB: PVP K 30 from 1: 0.5 to 1:0.25, the peak of IB still appeared. This result indicated that the crystalline nature of free drug still remained even if a ratio of 1:0.25 PVP of the dispersion. While at the higher ratios of PVP K 30, we observed a totally amorphous in nature of IB (Figure 21). Similar results were reported for the nature of solid dispersion of IB with PVP 30 *(Najib et al., 1988).*

Studies in IR spectra of the dispersion of IB with PVP K 30 and compared with IB crystal and PVP K 30 raw material. Interesting result was observed for the spectra of solid dispersion of IB and PVP K 30, its presented a very broad band baseline covering the wavenumber of 2400 – 3500 cm^{-1}. This indicated the presence of pronounced hydrogen bonding between IB and PVP K 30 in this dispersion. For the carbonyl frequency region, the drug showed a narrow strong band at 1700 cm^{-1} due to carboxylic C=O stretching, and for PVP K 30 gave a broad strong band at 1670 cm^{-1} due to the cyclic amide C=O stretching. In this dispersion both C=O stretching were seen as a broad band at 1620 – 1740 cm^{-1}, presumably due to complex formation through hydrogen bonding. In the low frequency region of 600 –1600 cm^{-1}, the bands in these regions were almost the same for both IB and PVP (Figure 24). This might indicated that although the drug molecule was hydrogen bonded with PVP K 30 through the carboxylic acid OH group, the overall symmetry of the molecule was not significantly affected. *(Sekizaki et al., 1995)*

DSC studies were performed on IB, PVP K 30 and IB – PVP K 30 dispersion. The disappearance of the drug peak from the thermogram of IB – PVP K

30 dispersion indicated that all of the drug has interacted with the polymer and this excludes the presence of a crystalline drug in the dispersion (Figure 26). As a consequence of the evaporation of the solvent during the preparation of the solid dispersion, viscosity increased very rapidly leading to a decrease in drug mobility. When the solvent evaporated completely, drug molecule was frozen in the polymer matrix so a crystal lattice was not formed (*Mooter et al., 1998).*

In order to get further evidence on the possible interaction of IB with PVP K 30, ^{13}C – NMR spectra showed the changing in the orientation at molecular level of carbon atom of IB . The signal of the carboxylic acid carbon in IB and the carbonyl carbon in PVP K 30 that shifted from the original substances (Figure 28), suggested that the carboxylic acid group of IB interact with PVP through hydrogen bonding (*Sekizaki et al., 1995).*

From all of these results, it could be implied the formation of a IB – PVP 30 complexation in a type of H- bonding complexation was formed.

Chemical interaction between IB and PEG in solid dispersion state

The X- ray diffraction analysis of IB: PEG 6000 dispersion; at ratio 1:1 as compared with the diffractograms of IB and PEG 6000 original crystal demonstrated that the crystallinity of drug had been considerably less (Figure 37). The result like this revealed in another studies of IB: PEG dispersion *(Khan and Jiabi, 1998).* Their results showed that the dispersed system of IB with PEG 6000 were not a simple eutectic mixture but interstitial solid solution may have formed *(Betagari and Makrai,1996).* Furthermore, the lack of displacement of PEG peaks led to the conclusion of formation of an interstitial solid solution during preparation of solid dispersion. But from the X- ray diffractograms of this study, some diffractograms of IB still exists at high intensities, it was also implied that some parts of the structure of IB did not form an interstitial solid solution completely.

The DSC thermogram for this IB: PEG solid dispersion showed the single endotherm at 55.8 °C (Figure 45) which was close to the endothem of PEG 6000 at 64.3 °C. This supports an indicating of formation of solid solution.

IR spectra of IB: PEG dispersion also obviously showed the spectra of both IB and PEG 6000 that had not the new spectra or the changing from the original spectra of IB and PEG 6000 (Figure 40). So, it revealed that this dispersion had not a chemical interaction between drug and polymer in this system. The above result corresponding with the C –13 NMR data of this dispersion that only had a little shift at the carboxylic carbon signal of the drug from 180.715 ppm to 178.748 (Figure 47). The changing of the position of the carbon in this case maybe caused by small disorientation for the structure of the drug in the solid dispersion.

Generally, PEG molecular structures are semi–crystalline, containing both ordered and amorphous components. In the crystalline state, the chains are presented as double helices. The helices are arranged as plate–like structure (lamellae), from which the hydroxyl end groups are rejected onto the surface. The PEG chains may be extended or folded within the lamellae (*Craig and Newton, 1991*). It was predicted that significant amounts of drug could be entrapped in this helical interstitial space. From this reason, it could be described this pattern to the presence of an interstitial dispersion of IB : PEG 6000, had the entrapment of IB molecule in the helical interstitial space when IB and PEG 6000 were coprecipitated in their dispersion. The PEG was expected to give an ultrafine or colloidal crystalline of the pure drug in the system. Because of, the system was melted and solidified immediately (*Chiou and Reigelman, 1969*). This was due to the difficulty for the crystalline to growth in a viscous medium and in a short time interval for completion of solidification

Chemical interaction between IB and mixing polymer of PVP K 30 and PEG in solid dispersion state

In the case of the dispersion of IB : PVP K 30 : PEG 6000 ; 1:0.35:0.25 that we studied about chemical interaction between these three substances. In this formulation, all of the results about physicochemical property were close to the result obtained from the dispersion of IB with PEG 6000 that we have studied before and explained in the previous part.

From X–ray thermograms, there were still evidence about the IB structure in the type of interstitial solid solution such as in the IB: PEG 6000 dispersion system (Figure 51). Moreover, the DSC thermograms of IB: PVP K 30: PEG 6000 at a

weight ratio of 1:0.35:0.25 revealed the pattern as the broad endothermic spectra (Figure 55). When studied about IR spectra, we also found that these solid dispersion gave the IR spectra that the position of the bands were not different from the three original substances, it could be seen in all of an important spectra such as C = O stretching in carboxylic group of IB at 1700 cm-1, C = O stretching in cyclic amide of PVP K 30 at 1670 cm^{-1} and C – O stretching of PEG 6000 at around 1110 cm-1. We could not find any new spectra for an evidence that can indicated about the interaction between substances, such as in IB , PVP K 30 and PEG 6000 (Figure53). From ^{13}C NMR spectra, only had shifted minutely at the signal of carboxylic carbon of the drug substance to δ 178.505 ppm from the original position at δ 180.715 ppm (Figure 57). We can implied that the arrangement which cause disorientation for molecular structure of IB in this dispersion system or maybe from weak hydrogen bond that occurred between IB and polymer.

Chemical interaction between drug and polymer in IPs

In all formulations that can produced IPs that were formulated in this study can be summarized as follow; 1:0.5 PVP K 30, 1:0.75 PVP K 30, 1:1 PVP K 30, 1:0.5 PEG 1450 , 1:0.75 PEG 1450 , 1:1 PEG 1450, 1:0.75 PEG 4000, 1:0.75 PEG 4000, 1:1 PEG 4000 , 1:0.5 PEG 6000 , 1:0.75 PEG 6000 , 1:1 PEG 6000, 1: 0.5:0.25 PEG 1450 , 1:0.35:0.25 PEG 4000 , 1:0.25:0.35 PEG 6000 and 1:0.35:0.25 PEG 6000 , It seem to be no interaction between substances in their formulations.

In the case of IPs with PVP K 30 that used IB: PVP K 30 dispersion to produce IPs with the process of phase partition technique. It seem to be no formation as the complexation structure between IB and PVP K 30 by hydrogen bonding. Proved with IR spectra of 1:0.5 PVP K 30, 1:0.75 PVP K 30 and 1:1 PVP K 30, these displayed like the combine peaks of IB and PVP K 30. The C = O stretching of the drug appeared as narrow and separated band from the C = O stretching of the polymer. In addition, broadening of the C = O band that we found in their dispersions might be due to the presence of hydrogen bonding did not exist in the IPs formulations (Figure 25).

From X – ray diffractograms of these above pellets formulations showed the diffraction pattern of IB in IPs that closed to the diffraction pattern of IB, raw

material. The above diffraction pattern of IB in IPs was different from the X – ray diffractogram of their solid dispersion that exhibited a totally amourphous glassy nature. About the DSC thermograms of IPs in these formulations, all of the formulation had the same pattern of small endothermic peak in a position that closed to an endothermic peak of IB, raw material (Figure 22). It was confirmed that there was no change in melting point of drug substance (Figure 27). ^{13}C NMR was the another method for investigating about physicochemical properties, we found the signal of carboxylic acid carbon in IB and the carbonyl carbon in PVP K 30 had little shife from 180.715 to 179.318 ppm and 174.913 to 176.315 ppm, respectively (Figure 28). In this case maybe caused by the weak bond of hydrogen bonding between IB and PVP K 30 that may still occur or by the disorientation of the structure of the drug.

In the case of IPs with PEG, all of the results from the X – ray diffractograms, the DSC thermogram, IR spectra and C -13 NMR spectra confirmed the evidence that there were no interaction between IB and PEG in IPs formulations. The thermograms of IPs formulations, which were different from the thermogram of the dispersion of IB with PEG that we studied before. In this case the endotherm peak from IPs formulation appeared at 72 °C that closed to the endotherm of IB raw material(Figure 46). From the X- ray diffractograms that was not different from the IB original crystal and had no trace of PEG peaks appeared (Figure 38). Fom all of this data, it was also evident that there was no structure of solid solution anymore but maybe composed with the microcrystals of IB that aggregated together. For the PEG substance, the structure appeared as an amorphous form that may penetrated in the system.

Additional studies in physicochemical property of IPs with PEG were also evident that there was no new compound produced and had no the chemical interaction between IB and PEG in the IPs formulations was seen.

For the case of IPs with both of PVP K 30 and PEG in the suitable ratio that had four formulations. Their results about physicochemical properties were not different from the case of the formulations of IPs with PVP K 30. It seem no chemical interaction occurred in these formulations when observed by X-ray diffractograms, IR spectra and DSC thermograms. From the data of ^{13}C NMR spectra that had a small shift in carboxylic acid carbon in IB indicated about changing in the structure of drug molecule, like we mentioned in the previous part, or maybe from the weak hydrogen bonding between drug and polymer.

Evaluation of physical properties

We compared the physical properties of the IPs that was produced from various formulations as mentioned before. The bulk density was an important parameter used to determine the space required for the storage of bulk drug. It can also influence flowability and may influence certain characteristics of the final product (*Foster and Leatherman, 1995)*. On the other hand, tapped density used to investigate the packing properties of material (*Grant and Brittain, 1995).*

The bulk density and tapped density of IPs formulations were also determined and computed for the percent compressibility. Compressibility value was a simple effective way of measuring flowability, the more flowable material had the smaller compressibility value. Angle of repose was one method to determine about flow properties. A compressibility value in the range of 5 to 10 % and the angle of repose varying from 25° to 30° indicated excellent flow *(Carr, R.L., 1970 ; Lin and Kao, 1989)*. In this study, from bulk density and tapped density showed that all of the formulations had the good flow property. By the way, calculated about percent compressibility was not the good method to compared and determined about these formulations so using the actual flow rate is the better way for that. The various values as mentioned above defined that the IPs obtained in this study had excellent flow property excepted in the case of 2 IPs at 1 : 1 PVP K 30 and 1:0.5 PVP K 30:0.25 PEG 1450 that had sticking problem and aggregated together. These problems caused by using large amount of the polymer in the formulation. PVP K 30 was hygroscopic substance, and large amount in IPs caused the reduction of flowability.

In fact, the variation of the compressibility values of IPs was due to the variation of particle size or about cohesiveness between the pellets. A better way to determine the flow of IPs should be evaluate the actual flow rate. The best flowing particles should have a rounder shape, since a rounder shape gave a minimum number of interparticle contacts (*Carr, 1970).* It was in an agreement with the results of sphericity of IPs obtained in this study, and IPs with mixing ratio between PVP K 30 and PEG gave the most spherical pellets. We found in the formulation of 1:0.25: 0.35 PEG 6000 had the highest flow rate. In the formulation of IPs with PVP K 30 (1:0.5 PVP K 30, 1:0.75 PVP K 30 and 1:1 PVP K 30), which were the most spherical shape when compared with another formulations. However the flow rate were decreased due to the sticky problem. It was found that when an amount of PVP K 30 was increased from the ratios of 1:0.5 PVP K 30 to 1: 0.75 PVP K 30 and 1:1 PVP K 30, the flow rate decrease in the descending order. As we mention before about the hygroscopicity of PVP K 30, high quantity of PVP K 30 caused IPs about poor flowablity in their formulations. Another formulations with less spherical in shape and also had wide range of size distribution also showed the decrease in flow rate.

We also determined the particle size of IPs from the formulations, the average particle size of IPs are given in Tables 1C- 19C (Appendix C) and were in the range of 0.89 – 1.47 mm. From the results, we found that type of the polymer affected the average particle size and size distribution of IPs. PVP K 30 was a suitable polymer (if not hygroscopic) that can produced IPs which had the smaller in size and narrow size distribution. On the other hand, PEG in all grade that were used for this study gave higher average particle size and size distribution that maybe due to IPs with PEG had large ,rough and vary in size of particles.

Dissolution profiles studies

We studied and compared the dissolution profiles of all formulation that produced IPs by phase partition technique. We found that IPs from using drug alone did not improve dissolution property of IB. Also, in the case of using PEG in all grade (PEG 1450 , 4000 and 6000) and all ratio of IB : PEG (1:0.5, 1:0.75 and 1:1) as the dispersion carrier for IB still can not increase the dissolution property of their IPs. On the other hand, we found the dissolution from the formulations of IPs that used PVP K 30 in their formulations with the suitable ratio and mentioned in the previous

part, had improved dissolution property. The dissolution of the IB from IPs showed the better drug release as compared with the formulation of IPs of drug alone and IPs with PEG. We also found that the dissolution profiles of IB from the IPs which contained PVP K 30 showed higher dissolution rate than the others (f_2 analysis).

Although, an evidence about chemical interaction or complexation of IB with PVP K 30 in the state of the dispersion before enter phase partition technique was observed. However, after phase partition technique to produced IPs, all of the data about physicochemical properties showed that there was a decrease in evidence of chemical interaction between substances such as complexation between IB and PVP K 30 in the formulation. Therefore, differences in drug release that gave the better dissolution profiles in these formulations might be resulted from another mechanism such as IB microcrystals of IPs were in a smaller size as we have already seen by SEM photomicrographs. So, increasing the surface area of drug to the solvent, the dissolution rate will increase as particle size decreased; owning to Noyes – Whitney equation *(Higuchi, 1967)*.

$$dc / dt = KA (C_s - C_t) \quad \ldots\ldots (8)$$

where dc / dt is an amount of solute dissolved per unit time, A is the surface area exposed to solvent, K is the dissolution rate constant, C_s and C_t are the saturated solubility of the solute in a medium and is its concentration at any given time, respectively.

In equation 8, the rate of dissolution varies directly to the surface area of the powder. The reduced particle size produced greater surface area. Thus, the smaller size of drug particle brought more dissolution of drug. Furthermore, we found the change in microenvironment of IB microcrystals due to the network of the polymer adsorbed on the surface of IB microcrystals. This behavior can be explained like had the hydrodynamic layer surrounding the drug particles.It is due to the fact that each single crystalline of drug is very intimately encircled by the soluble carrier which can readily dissolved and cause the water to contact and wet the drug particle. As we know, PVP K 30 was highly water soluble, it dissolves rapidly upon exposure to an aqueous medium thus can improve the wettability and hence dissolution of the drug *(Najib et al., 1986)*. Furthermore, we also studied the release of IB from the capsule

of IPs (1:0.35 PVP K 30:0.25 PEG 6000) and compared with the capsule of IB original powder. In the case of IB powder we found aggregation of powder, and floated on the surface of dissolution medium. These had not occur in the case of filled the capsule with IPs. The aggregation and agglomeration between fine crystallnity of the pure hydrophobic drug may play more important role in disturbing rate of dissolution and absorption (*Chiou and Riegelman, 1971).* The advantage of an increase in dissolution was translated into bioavailability when the IB dissolved faster, less time to maximum concentration, it might cause less gastric irritation.

CONCLUSIONS

IPs could be prepared by using phase partition technique by combining with three solvents in the system; ethanol as a dissolving solvent, water as a dispersion solvent and chloroform as a bridging solvent. The suitable ratio of bridging solvent was about 1.5 % chloroform to produced the good appearance pellets by this phase partition technique.

For modifying the dissolution property of IB, a poorly soluble drug substance that was used as a model drug in this study, by using PVP K 30 and PEG in the grade of 1450, 4000 and 6000. These carriers are water-soluble in order to produced the mixture of the dispersion between drug and polymer and can be used for phase partition technique to produced IPs, as well.

The results of the physicochemical study showed that the chemical interaction occurred between IB and PVP K 30 in the solid dispersion state like the complex formation with hydrogen bonding between drug and polymer. This complex formation was confirmed with the data from X–ray diffractograms, IR spectra, DSC thermograms and ^{13}C NMR spectra. However, this complexation maybe could not maintain after the phase partition to produce the IPs or still had the weak hydrogen bonding between IB and PVP K 30 in the pellets. IB and PEG may have the structure of interstitial solid solution in their solid dispersion. On the other hand, no interaction of IPs with PEG after phase partition technique. In the case of using the mixing of PVP K 30 and PEG with suitable ratio had the weak hydrogen bond between IB and PVP K 30 in the system.

The results of the dissolution data showed that IPs with PVP K 30 and IPs with the mixing of PVP K 30 and PEG in suitable ratio had the faster dissolution rate than the formulation of IPs with drug alone. In contrast to PEG, it seemed that the dissolution of IPs with PEG in all grade and all ratios that we used in this study were not faster than IPs with drug alone. The increase in dissolution of IPs for this study might be achieved by changing the microenvironment of drug crystals, by increasing wettability property including from deaggregation and deagglomeration of IB particles.

It could be concluded that combining two methods of powder engineering technique, one is the phase partition to produce the spherical pellets and the second one by using the dispersion carriers for enhancing drug dissolution. In term of using the carriers the suitable ratios of drug: polymer that still can use in phasc partition technique, were obtained. More specificly, the best combination that can be use for improving the dissolotion rate and physical properties of IB, a poorly solublte drug, was selected.

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APPENDICES

APPENDIX A

CALIBRATION CURVE DATA

The correlation between concentration versus absorbance of IB in various media at 265 nm are presented in the Tables 1A and 2A. The calibration curves of IB which show linear relationship between concentration and absorbance are illustrated in Figures 1 A and 2A.

Table 1 A Concentration and absorbance data for IB in methanol

Concentration (mcg/ml)	Absorbance
0	0
160	0.205
320	0.417
480	0.623
640	0.825
800	1.033

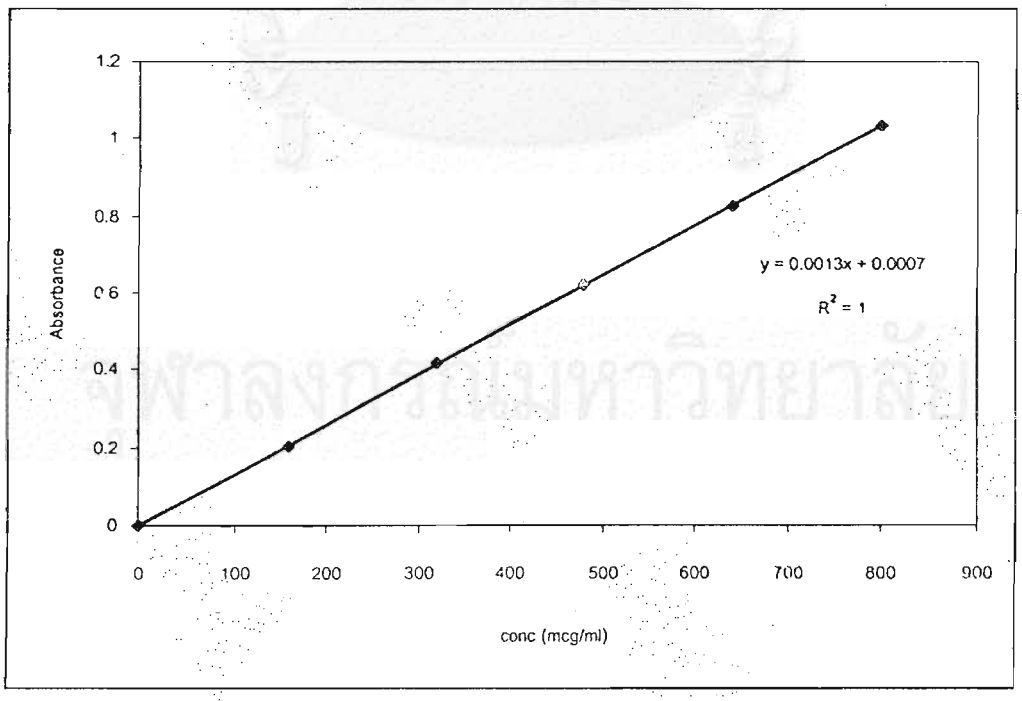

Figure 1A Calibration curve of IB in methanol

Table 2 A Concentration and absorbance data for IB in phosphate buffer pH 7.2

Concentration (mcg/ml)	Absorbance
0	0
150	0.268
300	0.525
450	0.797
600	1.058
750	1.319

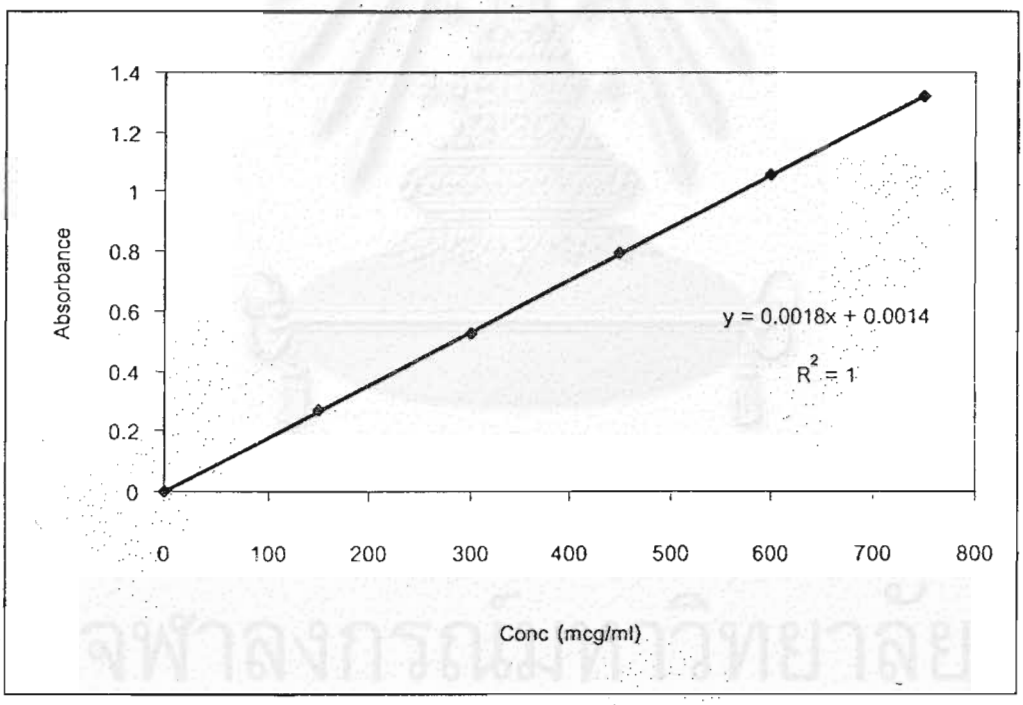

Figure 2 A Calibration curve of IB in phosphate buffer pH 7.2

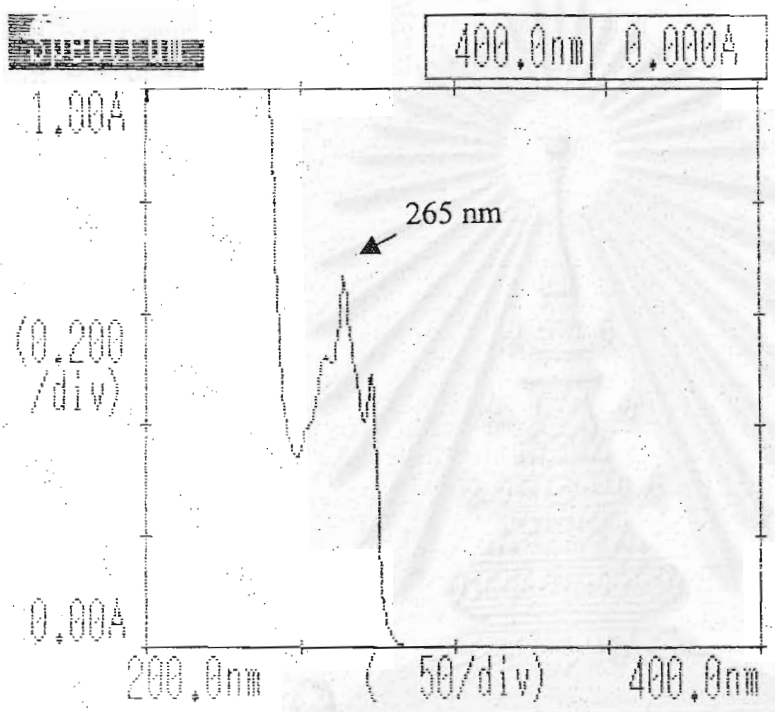

Figure 3 A The UV spectrum of IB

APPENDIX B

DISSOLUTION DATA

Table 1 B Dissolution data of IB raw material

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	56.70	62.08	56.45	58.41	3.18
10	79.51	79.51	72.45	75.18	3.79
15	80.77	88.39	79.50	82.89	4.81
20	85.65	89.39	84.62	86.54	2.49
30	92.82	93.82	90.91	92.52	1.48
45	96.32	96.32	95.38	96.01	0.54
60	97.22	97.09	96.65	96.99	0.30
75	97.61	97.11	96.79	97.17	0.42
90	98.13	97.24	96.79	97.39	0.68

Table 2 B Dissolution data of IPs at 1% $CHCl_3$ (binding solvent)

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	18.33	20.08	21.45	19.95	1.57
10	30.53	32.30	31.31	31.38	0.89
15	41.37	43.40	42.41	42.39	1.02
20	51.44	53.38	52.62	52.48	0.98
30	67.38	69.09	68.20	68.22	0.85
45	79.24	81.34	80.69	80.42	1.08
60	89.59	91.84	91.18	90.87	1.16
75	92.80	95.07	94.03	93.97	1.14
90	95.66	98.08	97.28	97.01	1.23

Table 3 B Dissolution data of IPs 1.5% $CHCl_3$ (binding solvent)

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	21.83	23.20	25.20	23.41	1.70
10	34.07	34.58	34.36	34.34	0.26
15	45.69	45.21	43.11	44.67	1.38
20	56.07	54.83	52.33	54.41	1.91
30	71.93	69.31	66.02	69.09	2.96
45	86.46	84.43	80.61	83.84	2.97
60	94.02	92.22	89.36	91.86	2.35
75	98.02	96.70	95.44	96.72	1.29
90	99.94	99.23	99.33	99.50	0.38

Table 4 B Dissolution data of IPs 2 % $CHCl_3$ (binding solvent)

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	19.45	22.08	23.08	21.53	1.87
10	32.29	33.45	34.33	33.36	1.02
15	43.40	44.94	46.09	44.81	1.35
20	54.62	54.81	55.97	55.13	0.73
30	69.72	69.28	71.32	70.11	1.08
45	84.48	85.40	86.60	85.49	1.06
60	91.64	92.70	93.78	92.71	1.07
75	95.37	96.44	97.54	96.45	1.08
90	98.13	99.22	99.57	98.97	0.75

Table 5 B Dissolution data of IPs at a ratio of IB:PVP K 30; 1 : 0.5

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	39.08	35.58	35.45	36.70	2.06
10	55.26	52.72	51.09	53.02	2.10
15	71.12	68.68	66.66	68.82	2.23
20	83.27	82.43	79.76	81.82	1.83
30	92.93	93.45	91.13	92.50	1.22
45	95.68	96.08	95.74	95.83	0.22
60	97.95	97.49	98.14	97.86	0.34
75	98.61	98.27	98.43	98.44	0.17
90	99.52	99.05	98.83	99.13	0.35

Table 6 B Dissolution data of IPs at a ratio of IB:PVP K 30; 1 : 0.75

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	29.70	30.7	32.83	31.08	1.60
10	50.78	51.92	54.19	52.30	1.74
15	68.84	71.11	70.66	70.21	1.20
20	83.85	85.52	85.69	85.02	1.02
30	94.88	96.83	97.00	96.23	1.17
45	100.91	101.75	103.04	101.90	1.07
60	104.12	104.09	105.52	104.57	0.82
75	105.35	105.07	106.02	105.48	0.49
90	106.2	105.54	106.13	105.96	0.36

Table 7 B Dissolution data of IPs at a ratio of IB:PVP K 30; 1 : 1

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	35.53	37.45	38.95	37.24	1.82
10	57.59	58.12	57.51	57.74	0.33
15	76.35	78.63	77.27	77.42	1.15
20	91.07	93.74	92.49	92.43	1.34
30	101.68	102.39	103.12	102.4	0.72
45	106.03	106.49	106.23	106.25	0.23
60	106.54	107.01	106.12	106.56	0.44
75	106.92	107.39	106.74	107.02	0.34
90	106.91	107.26	106.73	106.97	0.27

Table 8 B Dissolution data of IPs at a ratio of IB:PEG 1450; 1 : 0.5

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	21.95	22.08	23.45	22.49	0.83
10	33.82	34.20	36.34	34.78	1.36
15	46.07	46.95	48.24	47.08	1.09
20	55.7	57.59	58.39	57.22	1.38
30	70.68	74.21	73.78	72.89	1.93
45	85.94	89.39	88.20	87.85	1.75
60	93.00	95.48	95.03	94.50	1.32
75	96.74	98.26	98.29	97.76	0.88
90	98.14	99.67	99.58	99.13	0.86

Table 9 B Dissolution data of IPs at a ratio of IB:PEG 1450; 1 : 0.75

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	22.33	25.83	23.83	23.99	1.76
10	36.45	40.86	37.59	38.30	2.29
15	48.85	54.19	50.88	51.31	2.69
20	59.89	64.66	61.44	61.99	2.43
30	74.91	79.36	75.61	76.63	2.39
45	87.35	91.97	88.05	89.12	2.49
60	94.04	97.58	94.62	95.42	1.90
75	97.05	99.25	97.88	98.06	1.11
90	98.32	99.67	98.92	98.97	0.68

Table 10 B Dissolution data of IPs at a ratio of IB:PEG 1450; 1 : 1

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	25.08	25.58	26.08	25.58	0.50
10	42.35	41.48	42.11	41.98	0.45
15	60.32	55.94	56.83	57.70	2.32
20	71.61	67.18	68.83	69.21	2.24
30	85.39	82.66	84.20	84.08	1.37
45	95.56	94.18	96.49	95.41	1.16
60	99.59	99.20	100.90	99.90	0.89
75	101.40	101.00	102.10	101.5	0.56
90	101.72	101.57	102.68	101.99	0.60

Table 11 B Dissolution data of IPs at a ratio of IB:PEG 4000; 1 : 0.5

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	20.20	23.2	24.33	22.58	2.13
10	33.55	34.21	34.22	33.99	0.38
15	43.18	45.84	44.85	44.62	1.35
20	56.02	58.96	56.96	57.31	1.50
30	70.50	73.85	71.71	72.02	1.70
45	82.27	87.78	85.36	86.14	1.42
60	91.31	95.23	92.78	93.11	1.98
75	94.54	97.87	96.40	96.27	1.67
90	97.54	99.03	98.17	98.25	0.75

Table 12 B Dissolution data of IPs at a ratio of IB:PEG 4000; 1 : 0.75

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	23.20	25.83	25.45	24.83	1.42
10	33.83	37.99	37.48	36.43	2.27
15	46.71	50.66	49.15	48.84	1.99
20	57.34	61.21	61.81	60.12	2.24
30	71.09	76.00	73.98	73.69	2.47
45	86.99	89.70	87.28	87.99	1.49
60	94.05	95.92	94.47	94.81	0.98
75	97.93	98.94	97.36	98.08	0.30
90	98.97	100.24	99.14	99.45	0.69

Table 13 B Dissolution data of IPs at a ratio of IB:PEG 4000; 1 : 1

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	24.45	27.58	27.33	26.45	1.74
10	38.72	41.38	38.88	39.66	1.49
15	51.90	55.71	52.18	53.26	2.12
20	63.72	66.07	61.88	63.89	2.10
30	79.91	80.67	75.80	78.79	2.62
45	92.40	92.29	89.62	91.44	1.57
60	97.77	97.03	95.96	96.92	0.91
75	99.57	99.44	99.11	99.37	0.24
90	100.12	99.87	100.03	100.01	0.13

Table 14 B Dissolution data of IPs at a ratio of IB:PEG 6000; 1 : 0.5

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	20.45	19.08	20.08	19.87	0.71
10	31.68	30.16	31.17	31.00	0.77
15	43.03	41.24	42.27	42.18	0.89
20	52.62	51.07	51.61	51.77	0.79
30	67.32	66.50	66.04	66.62	0.65
45	83.18	82.48	81.26	82.30	0.97
60	90.95	89.99	89.39	90.11	0.79
75	94.67	94.46	94.47	94.53	0.12
90	97.18	96.46	96.72	96.79	0.36

Table 15 B Dissolution data of IPs at a ratio of IB:PEG 6000; 1 : 0.75

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	24.20	26.83	25.45	25.49	1.31
10	38.97	41.12	38.36	39.48	1.45
15	51.15	53.95	51.16	52.09	1.62
20	61.58	65.17	61.59	62.78	2.07
30	77.00	79.00	75.39	77.13	1.81
45	90.59	91.61	88.20	90.13	1.75
60	95.94	97.72	95.03	96.23	1.37
75	98.46	100.64	98.04	99.05	1.39
90	99.51	101.70	99.70	100.30	1.21

Table 16 B Dissolution data of IPs at a ratio of IB:PEG 6000; 1 : 1

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	24.95	23.58	23.83	24.12	0.73
10	41.1	38.46	38.46	39.34	1.52
15	56.68	51.26	52.26	53.40	2.88
20	67.55	62.2	63.34	64.36	2.82
30	81.66	77.63	78.78	79.36	2.08
45	92.92	89.97	91.88	91.59	1.50
60	97.8	96.44	97.87	97.37	0.81
75	99.84	98.59	99.92	99.45	0.74
90	100.64	99.51	100.6	100.25	0.64

Table 17 B Dissolution data of IPs at a ratio of IB:PVP K 30:PEG 1450; 1 : 0.5 : 0.25

Time (min)	% cumulative release			Mean	SD
	1	2	3		
0	0	0	0	0	0
5	32.83	35.70	38.2	35.58	2.69
10	49.31	52.97	54.25	52.18	2.56
15	65.86	70.56	70.72	69.05	2.76
20	78.83	82.95	83.50	81.76	2.55
30	93.31	95.11	94.28	94.23	0.90
45	98.95	98.76	98.8	98.83	0.10
60	99.63	99.31	99.73	99.56	0.22
75	99.69	99.62	100.16	99.82	0.29
90	99.86	99.53	99.96	99.78	0.22

Table 18 B Dissolution data of IPs at a ratio of IB:PVP K 30:PEG 4000; 1 : 0.35 : 0.25

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	27.83	30.08	29.83	29.24	1.23
10	43.76	47.41	45.78	45.65	1.83
15	60.24	62.68	64.04	62.32	1.92
20	76.78	78.87	77.74	77.80	1.05
30	94.24	93.23	92.84	93.43	0.72
45	97.01	98.99	99.09	98.36	1.17
60	97.80	99.67	99.40	98.96	1.01
75	99.72	100.48	99.33	99.84	0.58
90	99.89	100.16	99.63	99.89	0.27

Table 19 B Dissolution data of IPs at a ratio of IB:PVP K 30:PEG 6000; 1 : 0.25 : 0.35

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	30.45	31.83	31.08	31.12	0.69
10	47.16	49.30	48.17	48.21	1.07
15	62.56	65.22	63.70	63.83	1.34
20	75.87	80.19	77.27	77.78	2.20
30	90.45	93.06	91.12	91.54	1.36
45	98.92	96.82	96.48	97.41	1.33
60	97.86	97.48	97.64	97.66	0.19
75	97.90	97.64	97.92	97.82	0.16
90	98.30	97.91	98.20	98.14	0.20

Table 20 B Dissolution data of IPs at a ratio of IB:PVP K 30:PEG 6000; 1 : 0.35 : 0.25

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	32.45	33.83	36.2	34.16	1.90
10	56.69	55.95	60.48	57.70	2.43
15	73.44	71.44	74.89	73.26	1.73
20	84.87	83.60	83.72	84.06	0.70
30	95.54	93.64	92.37	93.85	1.59
45	98.32	98.52	97.37	98.07	0.62
60	98.87	99.45	98.03	98.79	0.71
75	99.04	99.38	98.19	98.87	0.61
90	99.08	99.79	98.35	99.07	0.72

Table 21 B Dissolution data of capsule filled with IB powder

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	56.65	50.90	55.15	54.23	2.98
10	70.53	64.72	63.26	66.17	3.85
15	76.56	73.18	72.21	73.98	2.28
20	81.14	76.98	76.50	78.21	2.55
30	84.52	83.06	82.32	83.30	1.12
45	88.67	90.45	85.96	88.36	2.26
60	92.86	92.91	86.62	90.80	3.62
75	92.59	96.39	88.53	92.50	3.93
90	93.30	97.15	93.70	94.72	2.12

Table 22 B Dissolution data of capsule filled with IPs at a ratio of IB:PVP K 30:PEG 6000;1 : 0.35 : 0.25

Time	% cumulative release			Mean	SD
(min)	1	2	3		
0	0	0	0	0	0
5	25.40	23.90	28.4	25.90	2.29
10	43.18	44.92	49.97	46.02	3.52
15	64.16	64.41	69.77	66.11	3.17
20	79.36	80.12	82.53	80.67	1.66
30	97.48	96.74	93.93	96.05	1.87
45	103.04	103.04	100.2	102.09	1.64
60	106.64	102.90	101.77	103.77	2.55
75	105.03	102.74	103.60	103.79	1.15
90	104.88	100.82	101.69	102.46	2.14

APPENDIX C

PARTICLE SIZE DETERMINATION

Table 1 C Particle size distribution of IPs at 1% $CHCl_3$ binding solvent

Distribution Type : Number	n = 200
Mean Diameter : 1.47 mm	SD = 0.39

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0	600	0
600	1.5	700	1.5
700	2.5	800	4
800	6.5	1000	10.5
1000	13	1200	23.5
1200	18	1400	41.5
1400	24	1600	65.5
1600	14.5	1800	80
1800	10	2000	90
2000	4.5	2200	94.5
2200	4	2400	98.5
2400	1	2500	99.5
2500	0	2600	100
2600	0.5	2700	100

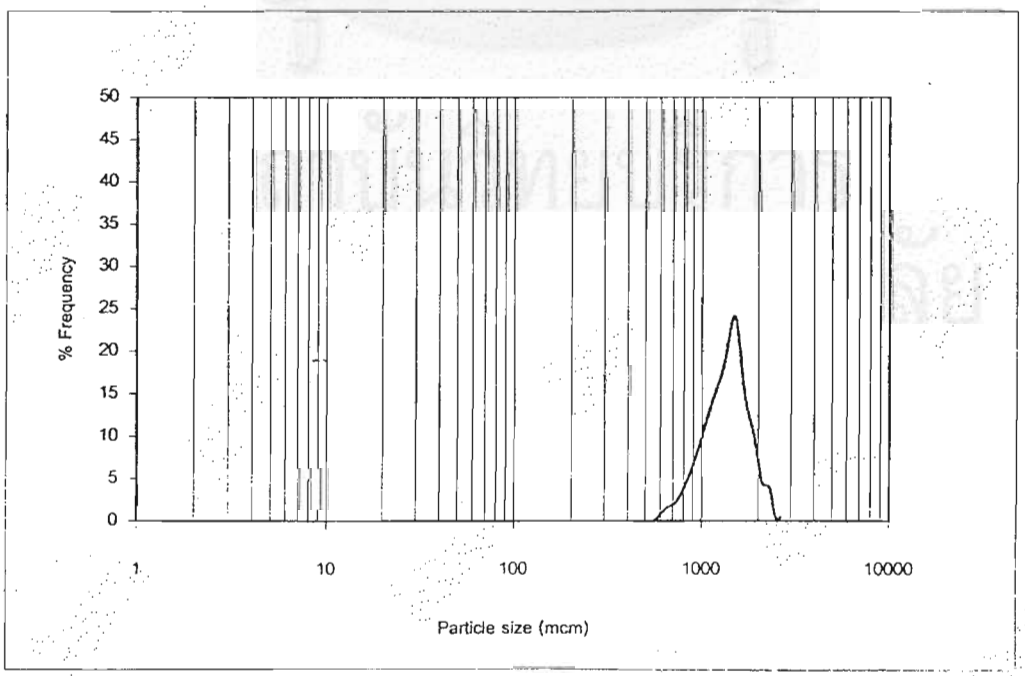

Figure 1 C Particle size distribution of IPs at 1% CHCl3 binding solvent

Table 2 C Particle size distribution of IPs at 1.5 % CHCl3 binding solvent

Distribution Type : Number	n = 200
Mean Diameter : 1.47 mm	SD = 0.38

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0	600	0
600	1	700	1
700	4	800	5
800	4.5	1000	9.5
1000	12.5	1200	22
1200	17.5	1400	39.5
1400	25.5	1600	65
1600	16	1800	81
1800	10	2000	91
2000	5	2200	96
2200	2.5	2400	98.5
2400	1	2500	99.5
2500	0.5	2600	100
2600	0	2700	100

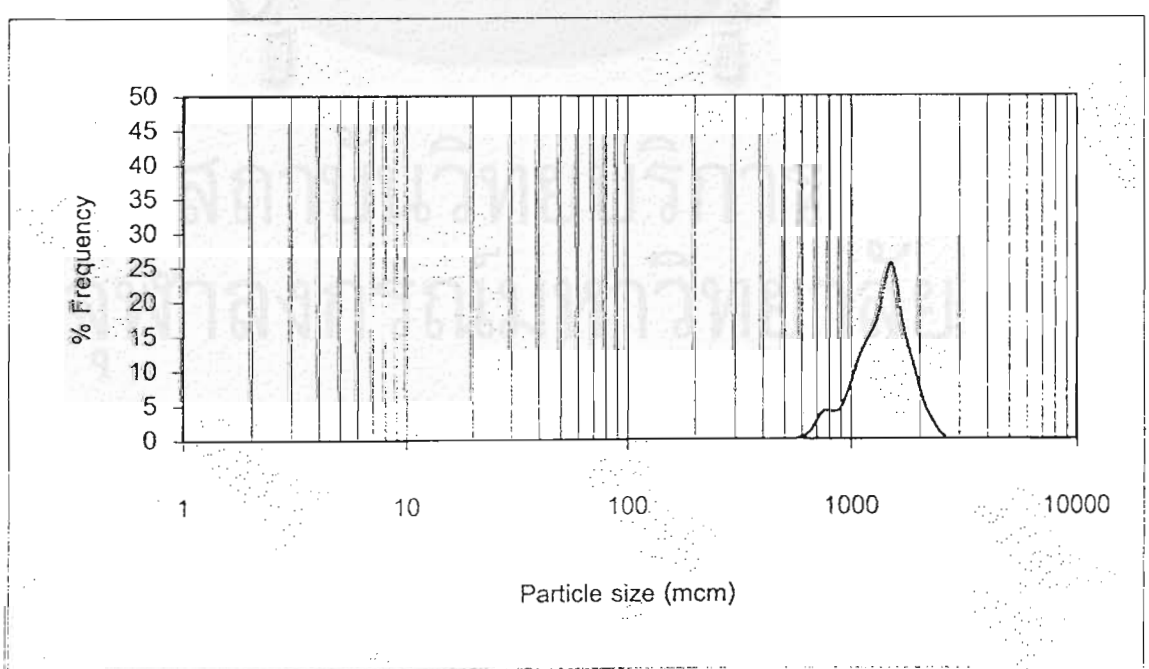

Figure 2 C Particle size distribution of IPs at 1.5 % CHCl3 binding solvent

Table 3 C Particle size distribution of IPs at 2 % CHCl3 binding solvent

Distribution Type : Number	n = 200
Mean Diameter : 1.43 mm	SD = 0.37

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0	600	0
600	2	700	2
700	4	800	6
800	6.5	1000	12.5
1000	13.5	1200	26
1200	15.5	1400	41.5
1400	24	1600	65.5
1600	16	1800	81.5
1800	12	2000	93.5
2000	4.5	2200	98
2200	1.5	2400	99.5
2400	0.5	2500	100
2500	0	2600	100
2600	0	2700	100

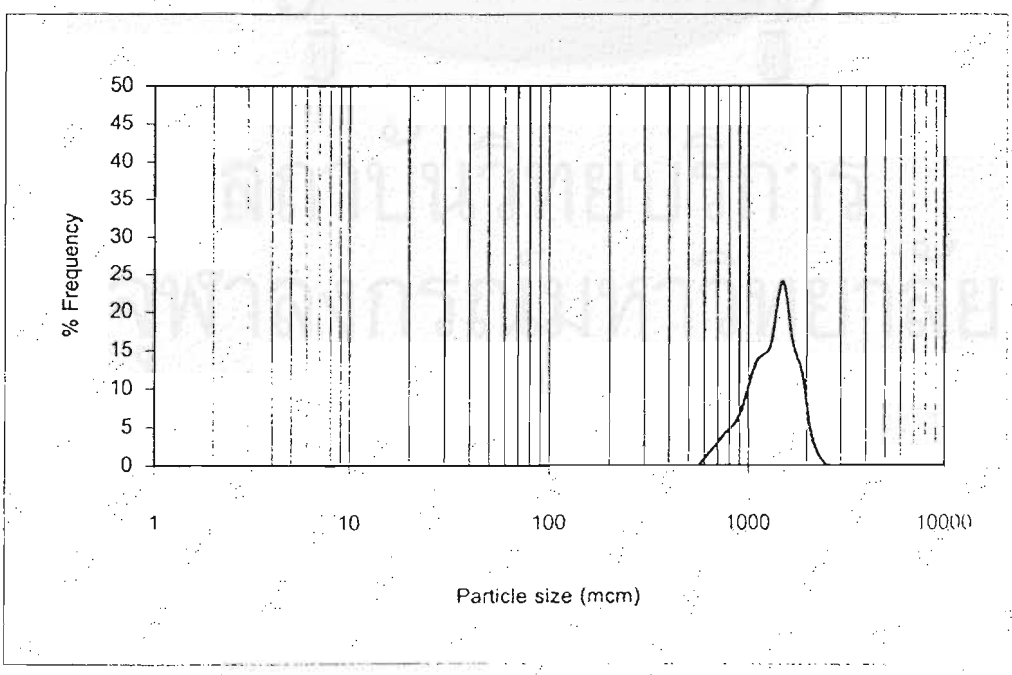

Figure 3 C Particle size distribution of IPs at 2 % CHCl3 binding solvent

Table 4 C Particle size distribution of IPs at a ratio of IB : PVP K 30 ; 1 : 0.5

Distribution Type : Number	n = 200
Mean Diameter : 0.94 mm	SD = 0.18

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	3.5	600	3.5
600	6.5	700	10
700	14	800	24
800	45	1000	69
1000	23.5	1200	92.5
1200	7	1400	99.5
1400	0.5	1600	100
1600	0	1800	100
1800	0	2000	100
2000	0	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

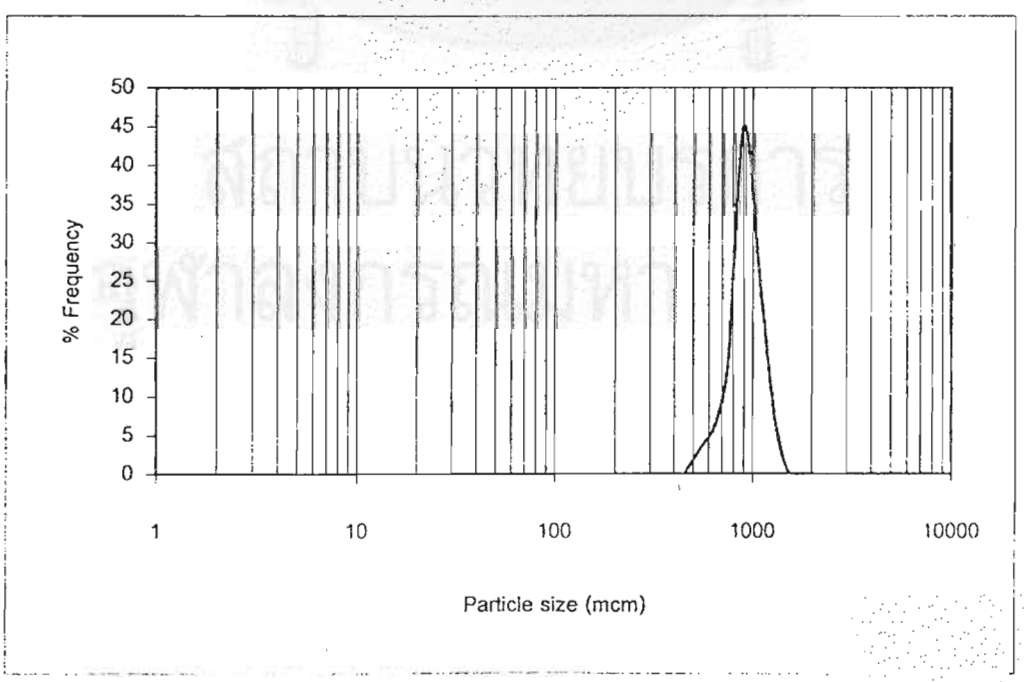

Figure 4 C Particle size distribution of IPs at a ratio of IB : PVP K 30 ; 1 : 0.5

Table 5 C Particle size distribution of IPs at a ratio of IB : PVP K 30 ; 1 : 0.75

Distribution Type : Number	n = 200
Mean Diameter : 0.94 mm	SD = 0.17

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	2	600	2
600	10	700	12
700	12	800	24
800	46.5	1000	70.5
1000	21.5	1200	92
1200	8	1400	100
1400	0	1600	100
1600	0	1800	100
1800	0	2000	100
2000	0	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

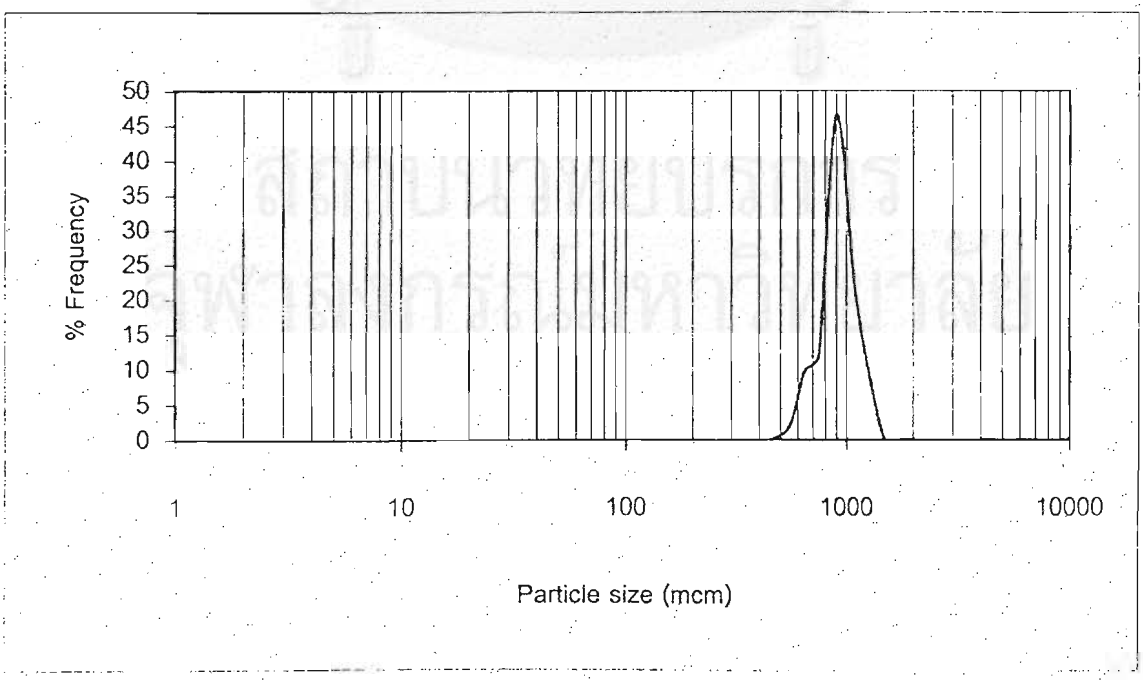

Figure 5 C Particle size distribution of IPs at a ratio of IB : PVP K 30 ; 1 : 0.75

Table 6 C Particle size distribution of IPs at a ratio of IB : PVP K 30 ; 1 : 1

Distribution Type : Number	n = 200
Mean Diameter : 0.89 mm	SD = 0.20

size low (mcm)	size in %	size high (mcm	under %
400	0.5	500	0.5
500	6.5	600	7
600	7.5	700	14.5
700	18.5	800	33
800	41.5	1000	74.5
1000	18.5	1200	93
1200	5.5	1400	98.5
1400	1.5	1600	100
1600	0	1800	100
1800	0	2000	100
2000	0	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

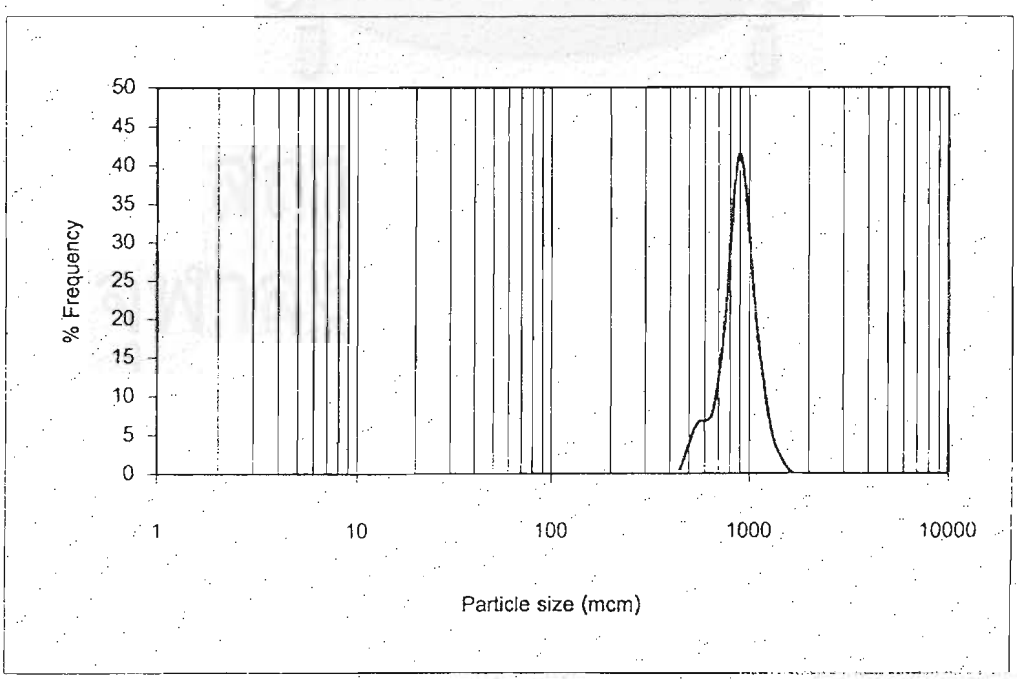

Figure 6 C Particle size distribution of IPs at a ratio of IB : PVP K 30 ; 1 : 1

Table 7 C Particle size distribution of IPs at a ratio of IB : PEG 1450; 1 : 0.5

Distribution Type : Number	n = 200
Mean Diameter : 1.34 mm	SD = 0.37

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	1	600	1
600	1.5	700	2.5
700	5	800	7.5
800	10	1000	17.5
1000	23	1200	40.5
1200	18.5	1400	59
1400	18.5	1600	77.5
1600	11.5	1800	89
1800	6.5	2000	95.5
2000	3	2200	98.5
2200	1	2400	99.5
2400	0	2500	99.5
2500	0.5	2600	100
2600	0	2700	100

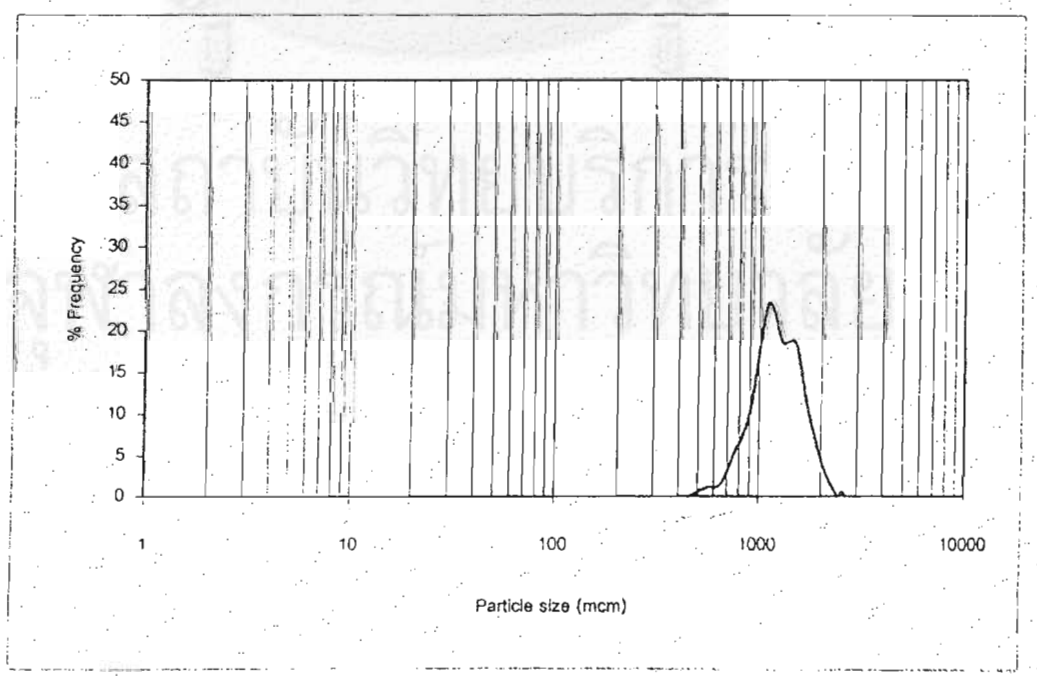

Figure 7 C Particle size distribution of IPs at a ratio of IB : PEG 1450; 1 : 0.5

Table 8 C Particle size distribution of IPs at a ratio of IB : PEG 1450 ; 1 : 0.75

Distribution Type : Number	n = 200
Mean Diameter : none	SD = none

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0	600	0
600	1	700	1
700	4.5	800	5.5
800	12	1000	17.5
1000	15	1200	32.5
1200	20	1400	52.5
1400	14.5	1600	67
1600	16.5	1800	83.5
1800	11	2000	97.5
2000	2	2200	99.5
2200	0.5	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

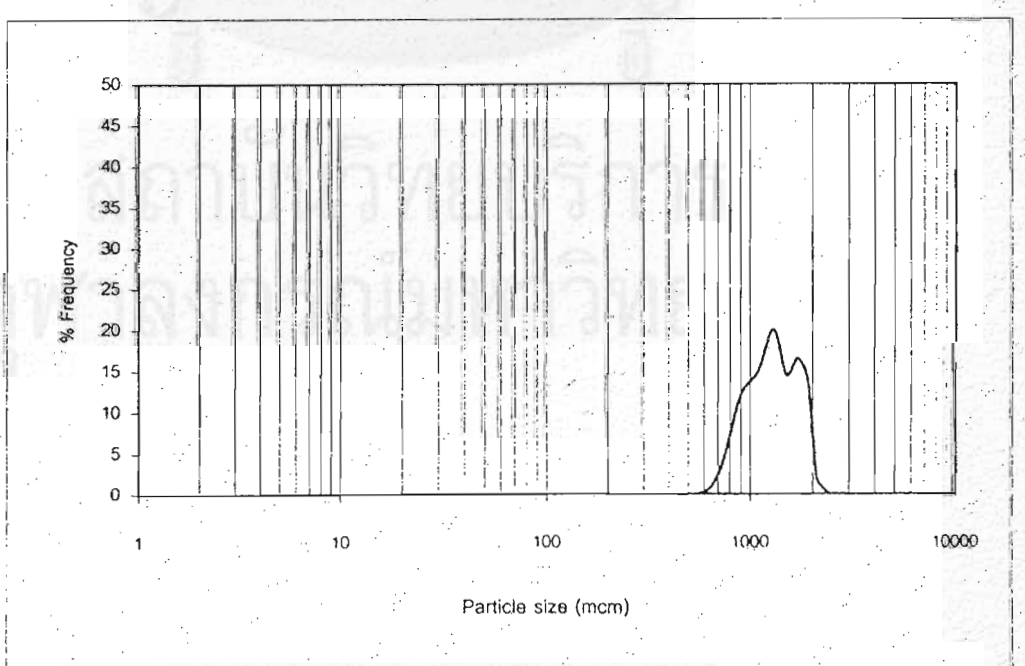

Figure 8 C Particle size distribution of IPs at a ratio of IB : PEG 1450 ; 1 : 0.75

Table 9 C Particle size distribution of IPs at a ratio of IB : PEG 1450 ; 1 : 1

Distribution Type : Number	n = 200
Mean Diameter : 1.19 mm	SD = 0.34

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0.5	600	0.5
600	3.5	700	4
700	6.5	800	10.5
800	17.5	1000	28
1000	28.5	1200	56.5
1200	20.5	1400	77
1400	11.5	1600	88.5
1600	6	1800	94.5
1800	3	2000	97.5
2000	1	2200	98.5
2200	0	2400	98.5
2400	1	2500	99.5
2500	0.5	2600	100
2600	0	2700	100

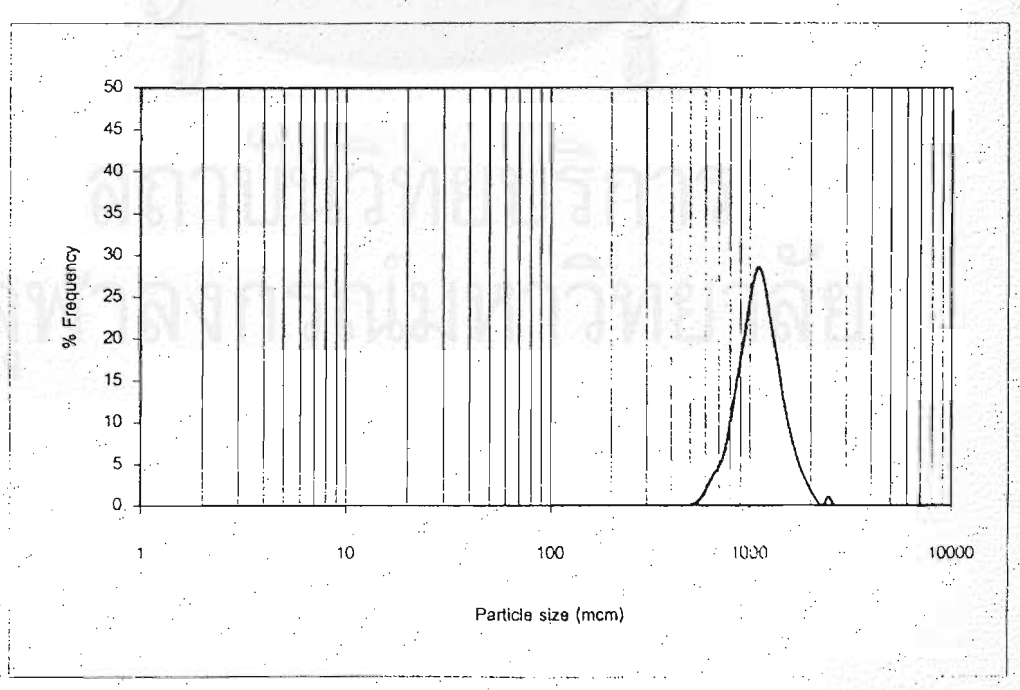

Figure 9 C Particle size distribution of IPs at a ratio of IB : PEG 1450 ; 1 : 1

Table 10 C Particle size distribution of IPs at a ratio of IB : PEG 4000 ; 1 : 0.5

Distribution Type : Number	n = 200
Mean Diameter : 1.09 mm	SD = 0.32

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	5.5	600	5.5
600	3	700	8.5
700	15.5	800	24
800	17.5	1000	41.5
1000	22	1200	63.5
1200	17	1400	80.5
1400	12	1600	92.5
1600	4.5	1800	97
1800	3	2000	100
2000	0	2200	100
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2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

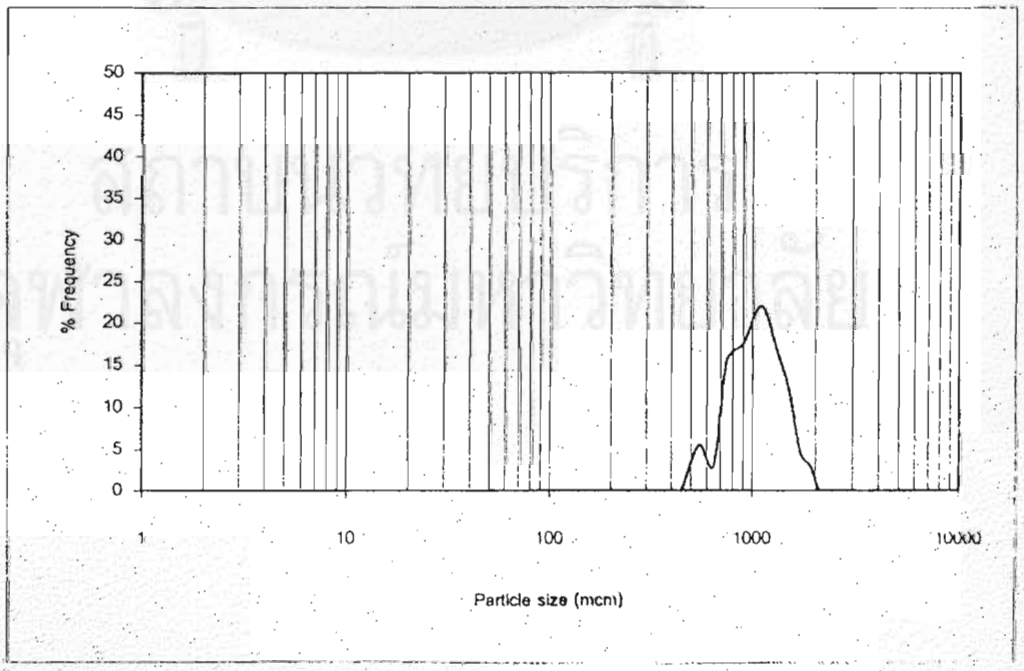

Figure 10 C Particle size distribution of IPs at a ratio of IB : PEG 4000 ; 1 : 0.5

Table 11 C Particle size distribution of IPs at a ratio of IB : PEG 4000 ; 1 : 0.75

Distribution Type : Number	n = 200
Mean Diameter : None	SD = None

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	2.5	600	2.5
600	0	700	2.5
700	6	800	8.5
800	15.5	1000	24
1000	16.5	1200	40.5
1200	19	1400	59.5
1400	16.5	1600	76
1600	18.5	1800	94.5
1800	4	2000	98.5
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2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

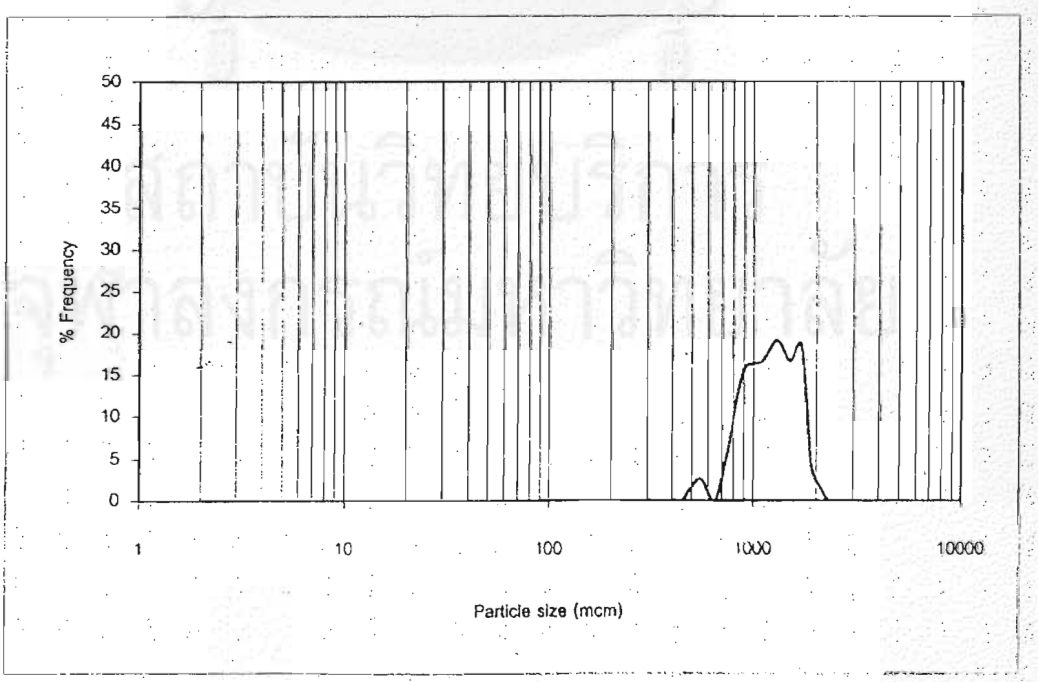

Figure 11 C Particle size distribution of IPs at a ratio of IB : PEG 4000 ; 1 : 0.75

Table 12 C Particle size distribution of IPs at a ratio of IB : PEG 4000 ; 1 : 1

Distribution Type : Number	n = 200
Mean Diameter : 1.14 mm	SD = 0.29

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	2	600	2
600	3	700	5
700	11.5	800	16.5
800	19.5	1000	36
1000	24	1200	60
1200	27	1400	87
1400	5.5	1600	92.5
1600	5	1800	97.5
1800	2.5	2000	100
2000	0	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

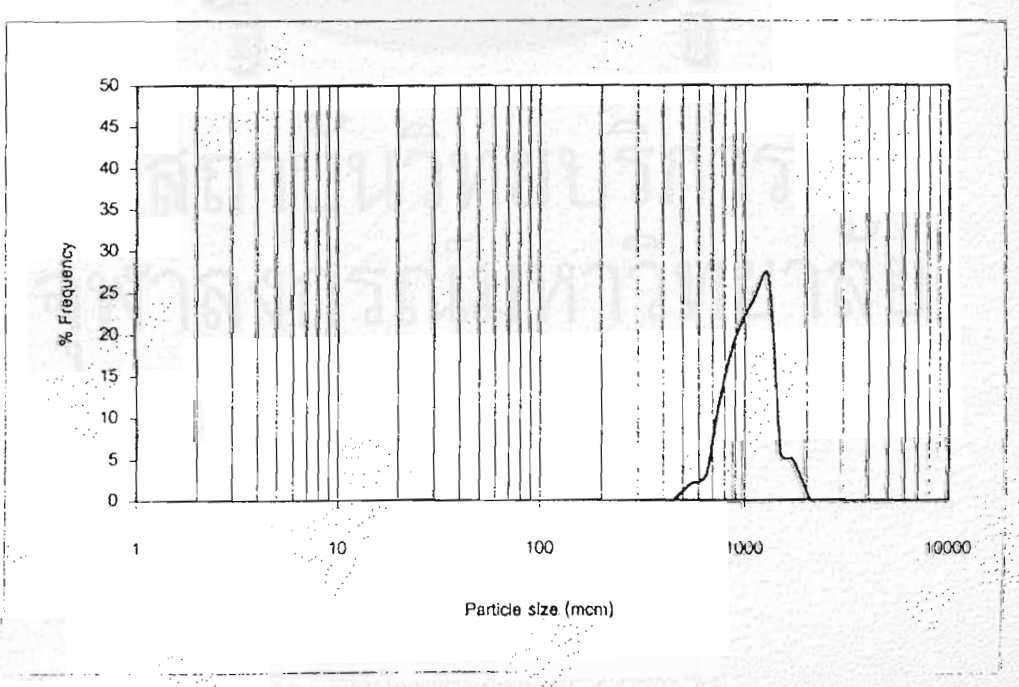

Figure 12 C Particle size distribution of IPs at a ratio of IB : PEG 4000 ; 1 : 1

Table 13 C Particle size distribution of IPs at a ratio of IB : PEG 6000 ; 1 : 0.5

Distribution Type : Number	n = 200
Mean Diameter : 1.37 mm	SD = 0.38

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	1.5	600	1.5
600	0.5	700	2
700	1.5	800	3.5
800	13.5	1000	17
1000	15.5	1200	32.5
1200	23.5	1400	56
1400	19	1600	75
1600	12.5	1800	87.5
1800	4.5	2000	92
2000	5	2200	97
2200	2.5	2400	99.5
2400	0.5	2500	100
2500	0	2600	100
2600	0	2700	100

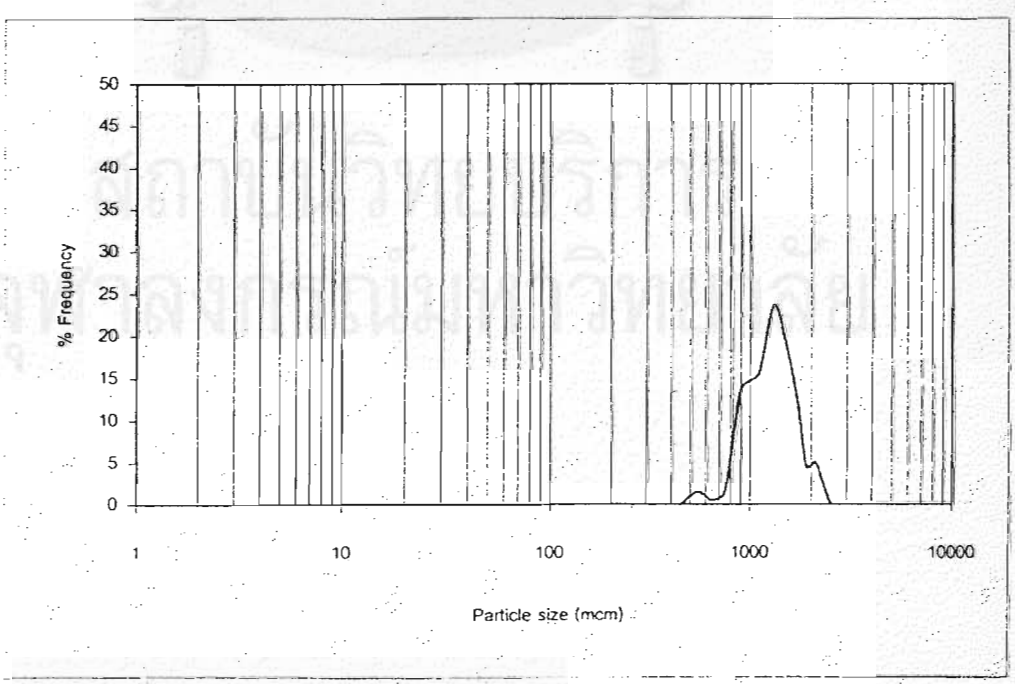

Figure 13 C Particle size distribution of IPs at a ratio of IB : PEG 6000 ; 1 : 0.5

Table 14 C Particle size distribution of IPs at a ratio of IB : PEG 6000 ; 1 : 0.75

Distribution Type : Number	n = 200
Mean Diameter : 1.31 mm	SD = 0.36

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0.5	600	0.5
600	1.5	700	2
700	5.5	800	7.5
800	16.5	1000	24
1000	22	1200	46
1200	21.5	1400	67.5
1400	14	1600	81.5
1600	10.5	1800	92
1800	4	2000	96
2000	1.5	2200	97.5
2200	2.5	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

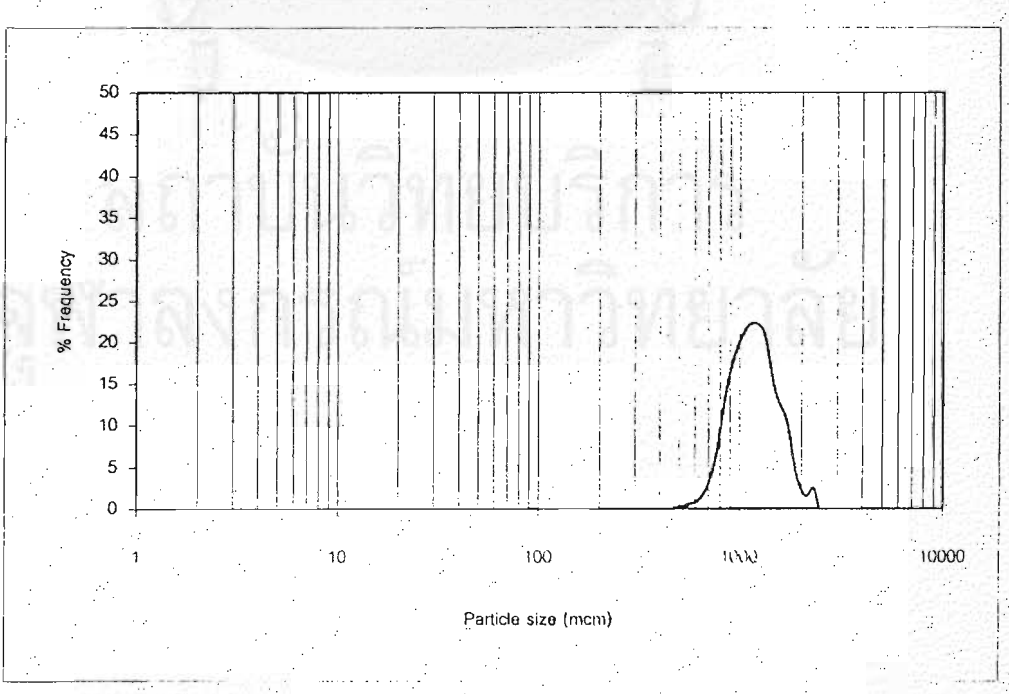

Figure 14 C Particle size distribution of IPs at a ratio of IB : PEG 6000 ; 1 : 0.75

Table 15 C Particle size distribution of IPs at a ratio of IB : PEG 6000 ; 1 : 1

Distribution Type : Number	n = 200
Mean Diameter : 1.33 mm	SD = 0.36

size low (mcm)	size in %	size high (mcm	under %
400	0.5	500	0.5
500	2	600	2.5
600	1	700	3.5
700	3	800	6.5
800	9.5	1000	16
1000	23	1200	39
1200	19.5	1400	58.5
1400	17	1600	75.5
1600	11.5	1800	87
1800	10.5	2000	97.5
2000	2.5	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

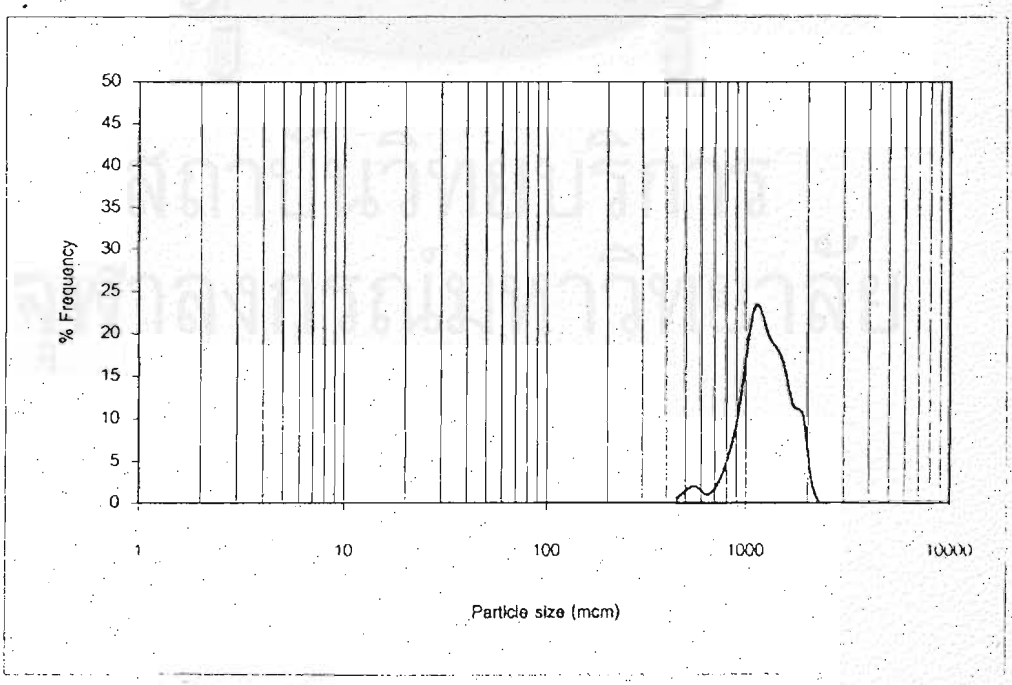

Figure 15 C Particle size distribution of IPs at a ratio of IB : PEG 6000 ; 1 : 1

Table 16 C Particle size distribution of IPs at a ratio of IB : PVP K 30 :PEG 1450; 1 : 0.5 : 0.25

Distribution Type : Number	n = 200
Mean Diameter : 1.03 mm	SD = 0.25

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0	600	0
600	3	700	3
700	20.5	800	23.5
800	26	1000	49.5
1000	28	1200	77.5
1200	13.5	1400	91
1400	5	1600	96
1600	4	1800	100
1800	0	2000	100
2000	0	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

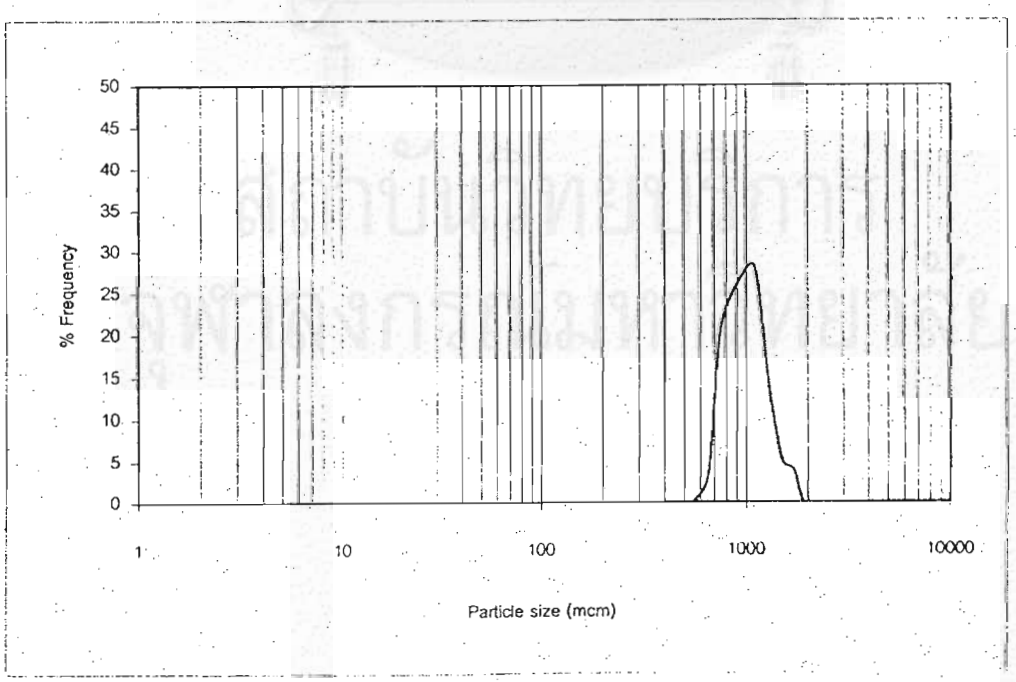

Figure 16 C Particle size distribution of IPs at a ratio of IB : PVP K 30 :PEG 1450; 1 : 0.5 : 0.25

Table 17 C Particle size distribution of IPs at a ratio of IB : PVP K 30 :PEG 4000; 1 : 0.35 : 0.25

Distribution Type : Number	n = 200
Mean Diameter : 1.17 mm	SD = 0.24

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0	600	0
600	1.5	700	1.5
700	7	800	8.5
800	16	1000	24.5
1000	34	1200	58.5
1200	28.5	1400	87
1400	8	1600	95
1600	4	1800	99
1800	1	2000	100
2000	0	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

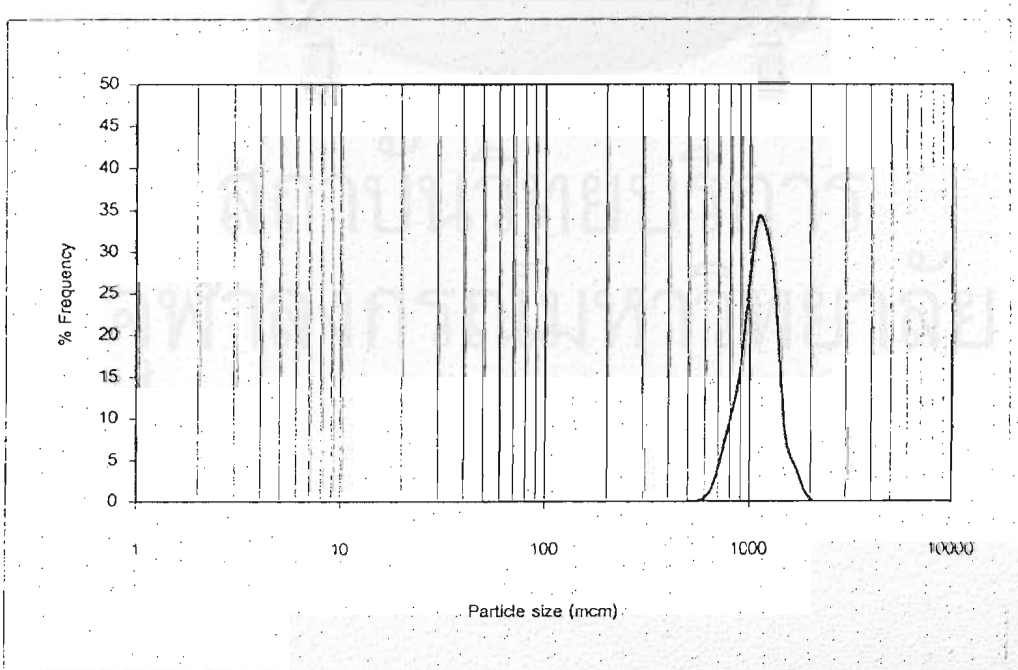

Figure 17 C Particle size distribution of IPs at a ratio of IB : PVP K 30 :PEG 4000; 1 : 0.35 : 0.25

Table 18 C Particle size distribution of IPs at a ratio of IB : PVP K 30 :PEG 6000; 1 : 0.25 : 0.35

Distribution Type : Number	n = 200
Mean Diameter : 1.16 mm	SD = 0.24

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0.5	600	0.5
600	0.5	700	1
700	4.5	800	5.5
800	14.5	1000	20
1000	28	1200	48
1200	34.5	1400	82.5
1400	14	1600	96.5
1600	3.5	1800	100
1800	0	2000	100
2000	0	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

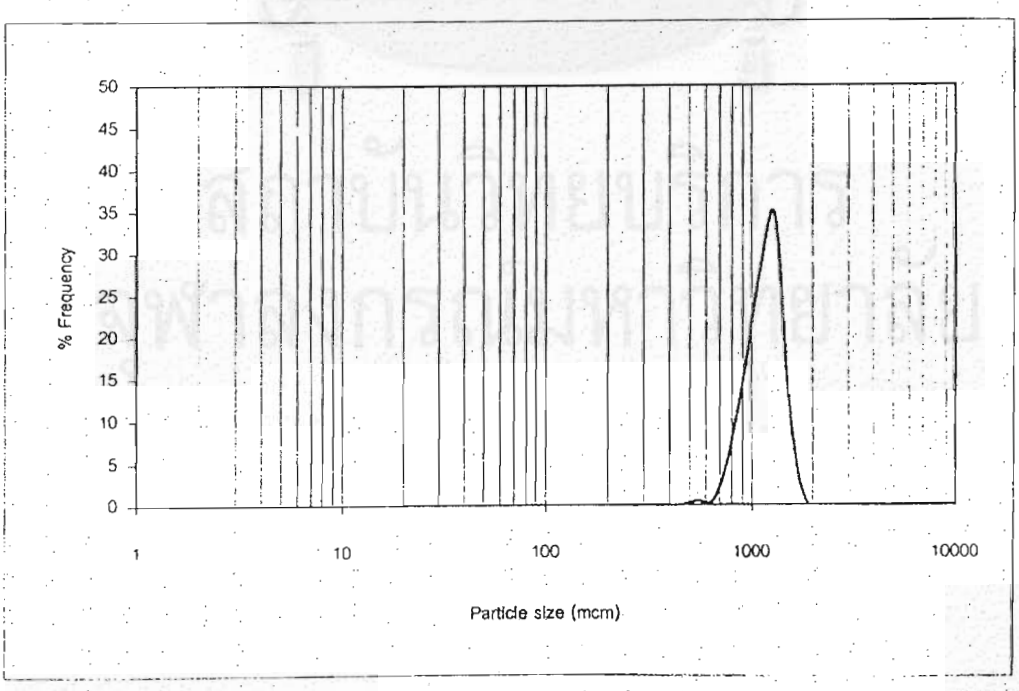

Figure 18 C Particle size distribution of IPs at a ratio of IB : PVP K 30 :PEG 6000; 1 : 0.25 : 0.35

Table 19 C Particle size distribution of IPs at a ratio of IB : PVP K 30 :PEG 6000; 1 : 0.35 : 0.25

Distribution Type : Number	n = 200
Mean Diameter : 1.19 mm	SD = 0.21

size low (mcm)	size in %	size high (mcm	under %
400	0	500	0
500	0.5	600	0.5
600	0	700	0.5
700	1	800	1.5
800	17	1000	18.5
1000	35.5	1200	54
1200	29.5	1400	83.5
1400	13.5	1600	97
1600	3	1800	100
1800	0	2000	100
2000	0	2200	100
2200	0	2400	100
2400	0	2500	100
2500	0	2600	100
2600	0	2700	100

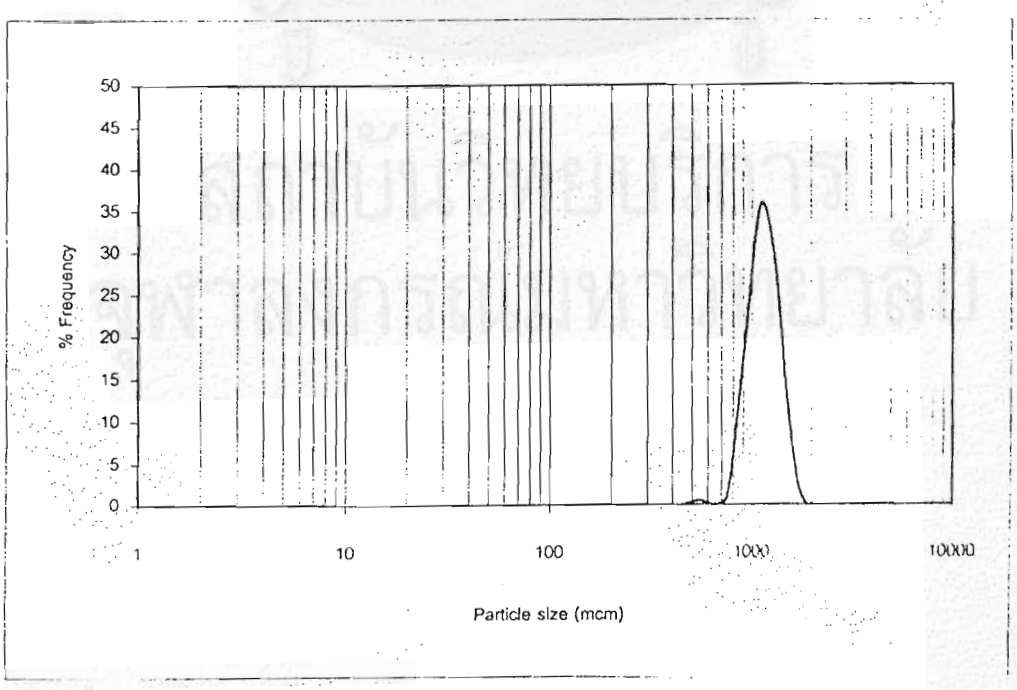

Figure 19 C Particle size distribution of IPs at a ratio of IB : PVP K 30 :PEG 6000; 1 : 0.35 : 0.25

APPENDIX D

SIMILARITY FACTOR DATA

Table 1 D Similarity factor between dissolution profiles of IPs at various ratios of PVP K 30; IB: PVP K 30

Formula	Similarity factor "f2"
1 : 0.75	72.45
1 : 1	55.20

* Using dissolution curve of the formulation of IPs at a ratio of IB : PVP K 30;1 : 0.5 as reference

Table 2 D Similarity factor between dissolution profiles of IPs at various grades and ratios of PEG ; IB : PEG

Formula	Similarity factor "f2"
1 : 0.5 PEG 1450	63.35
1 : 0.75 PEG 1450	82.25
1 : 1 PEG 1450	70.15
1 : 0.5 PEG 4000	59.65
1 : 0.75 PEG 4000	69.55
1 : 1 PEG 4000	92.40
1 : 0.5 PEG 6000	49.55
1 : 0.75 PEG 6000	87.55

* Using dissolution curve of the formulation of IPs at a ratio of IB : PEG 6000;1 : 1 as reference

Table 3 D Similarity factor between dissolution profile of IPs at various ratios of PEG 1450; IB : PEG 1450

Formula	Similarity factor "f2"
1 : 0.75	72.45
1 : 1	55.20

* Using dissolution curve of the formulation of IPs at a ratio of IB : PEG 1450;1 : 0.5 as reference

Table 4 D Similarity factor between dissolution profiles of IPs at various ratio of PEG 4000; IB : PEG 4000

Formula	Similarity factor "f2"
1 : 0.75	77.20
1 : 1	59.65

* Using dissolution curve of the formulation of IPs at a ratio of IB : PEG 4000;1 : 0.5 as reference

Table 5 D Similarity factor between dissolution profiles of IPs at various ratio of PEG 6000; IB : PEG 6000

Formula	Similarity factor "f2"
1 : 0.75	52.85
1 : 1	50.20

* Using dissolution curve of the formulation of IPs at a ratio of IB : PEG 6000;1 : 0.5 as reference

Table 6 D Similarity factor between dissolution profiles of IPs at various mixing ratio of PVP K 30 and PEG; IB : PVP K 30 : PEG

Formula	Similarity factor "f2"
1 : 0.5 : 0.25PEG1450	72.90
1 : 0.35 : 0.25 PEG4000	54.30
1 : 0.25 : 0.35PEG6000	58.05

* Using dissolution curve of the formulation of IPs at a ratio of IB : PVP K 30 : PEG 6000;1 : 0.35 : 0.25 as reference

Table 7 D Similarity factor between dissolution profiles of IPs at various grades and ratios of dispersion carriers

Formula	Similarity factor "f2"
1 : 0.5 PVP K 30	35.80
1 : 0.75 PVP K 30	33.15
1 : 1 PVP K 30	28.40
1 : 0.5 PEG 1450	76.85
1 : 0.75 PEG 1450	62.50
1 : 1 PEG 1450	47.45
1 : 0.5 PEG 4000	83.60
1 : 0.75 PEG 4000	70.05
1 :1 PEG 4000	56.50
1 : 0.5 PEG 6000	77.55
1 : 0.75 PEG 6000	59.65
1 : 1 PEG 6000	56.00
1 : 0.5PVP K 30 :0.25 PEG 1450	35.40
1 : 0.35PVP K 30: 0.25 PEG 4000	39.25
1 : 0.25PVP K 30 : 0.35PEG 6000	39.25
1 : 0.35PVP K 30: 0.25 PEG 6000	33.60

* Using dissolution curve of the formulation of IPs (drug alone) at 1.5 % $CHCl_3$ as reference

VITA

Miss Chawalinee Asawahame was born on August 23, 1975 in Bangkok, Thailand. She received her Bachelor of Pharmacy from The Faculty of Pharmaceutical Sciences, Chulalongkorn University in 1997.