ดิลไทอะเซม ไฮโดรคลอไรด์ ออกฤทธิ์นาน โดยใช้สารพื้นชนิดเทอร์โมซอฟเทนนิงเป็นเมทริกซ์กึ่งแข็งบรรจุในแคปซูลแข็ง

นายวันชัย จงเจริญ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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SUSTAINED RELEASE OF DILTIAZEM HYDROCHLORIDE USING THERMOSOFTENING BASES AS SEMISOLID MATRIX FILLED IN HARD CAPSULE

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วันชัย จงเจริญ : ดิลไทอะเซม ไฮโดรคลอไรด์ ออกฤทธิ์นาน โดยใช้สารพื้นชนิดเทอร์โมซอฟเทนนิงเป็นเมทริกซ์กึ่งแข็งบรรจุในแคปซูลแข็ง(SUSTAINED RELEASE OF DILTIAZEM HYDROCHLORIDE USING THERMOSOFTENING BASES AS SEMISOLID MATRIX FILLED IN HARD CAPSULE) อาจารย์ที่ปรึกษา: รศ. ดร. ไกรสีห์ อัมพรายน์, 235 หน้า. ISBN 974-346-388-7

ดิลไทอะเซม ไฮโดรคลอไรด์ ชนิดออกฤทธิ์นานในรูปแบบแคปซูลที่เตรียมจากสารพื้นชนิดเทอร์โมซอฟเทนนิงเป็นระบบเมทริกซ์กึ่งแข็งซึ่งมีขนาดของตัวยาสำคัญ 90 มิลลิกรัม ที่มีคุณสมบัติการละลายผ่านตามเกณฑ์ยูเอสพี 23 ซัพพลีเมนท์ 5 การทดสอบที่ 1 สำหรับผลิตภัณฑ์ที่ระบุว่าใช้ทุก ๆ 12 ชั่วโมง มีส่วนประกอบดังนี้ คือ ดิลไทอะเซม ไฮโดรคลอไรด์ 90 มิลลิกรัม และ สารพื้นเทอร์โมซอฟเทนนิง (เกลูเซอร์ 50/02) ปริมาณ 180 มิลลิกรัมต่อแคปซูล น้ำหนักสุดท้ายของแคปซูลเท่ากับ 270 มิลลิกรัมและเหมาะกับขนาดแคปซูลหมายเลข 2 ทั้งเกลูเซอร์ 50/02 บริสุทธิ์และส่วนผสมของมันกับเกลูเซอร์ชนิดอื่น ได้แก่ 46/07, 53/10 และ 50/13 ในอัตราส่วนโดยน้ำหนักเท่ากับ 144 ต่อ 36, 169 ต่อ 11.2 และ 172 ต่อ 8 มิลลิกรัม ตามลำดับ มีความเพียงพอสำหรับควบคุมการปลดปล่อยตามเกณฑ์ที่กำหนดดังกล่าวเบื้องต้น

ความสัมพันธ์เชิงเส้นตรงระหว่างค่าเฉลี่ยของเวลาในการละลาย (เอ็ม ดี ที) กับค่าเอช แอล บี ที่ได้จากการคำนวณของสารพื้นผสมเกลูเซอร์สามารถพบได้ในกรณีของการผสมเกลูเซอร์ 50/02 ร่วมกับ เกลูเซอร์ 46/07, เกลูเซอร์ 44/14 และ เกลูเซอร์ 42/12 ในขณะที่ไม่พบความสัมพันธ์ดังกล่าวกับสารผสมเกลูเซอร์ 50/02 ร่วมกับ เกลูเซอร์ 50/13 และ เกลูเซอร์ 53/10

การวิเคราะห์ทางอุณหภูมิ และอินฟราเรดสเปกโตรสโคปี แสดงให้เห็นว่าการผสมเกลูเซอร์สองชนิดเข้าด้วยกันด้วยกระบวนการหลอมร่วมกันไม่ก่อให้เกิดอันตรกิริยาทางเคมีระหว่างสารทั้งสอง เพียงแต่เกิดการผสมกันทางกายภาพใหม่เท่านั้น นอกจากนี้เกลูเซอร์เมทริกซ์ที่เตรียมจากสารพื้นชนิดเดียวหรือสารพื้นผสม แสดงให้เห็นว่าดิลไทอะเซม ไฮโดรคลอไรด์ ยังคงมีลักษณะเป็นรูปผลึกของแข็งกระจายตัวอยู่ในสารพื้นในรูปแบบของแข็งกระจายตัวเท่านั้น

ภายใต้การทดลองการเปลี่ยนแปลงภาวะของความเป็นกรดด่าง ในการศึกษาการทดสอบการละลายของดิลไทอะเซม ไฮโดรคลอไรด์ แคปซูลแบบเมทริกซ์กึ่งแข็งที่ได้กล่าวข้างต้น ซึ่งผ่านเกณฑ์การทดสอบการละลายเบื้องต้น แสดงให้เห็นว่าการปลดปล่อยตัวยาสำคัญจากเมทริกซ์กึ่งแข็งของแคปซูลในช่วงความเป็นกรดด่างที่ค่า พี เอช 1.2 และ 4.5 ไม่แตกต่างกันอย่างมีนัยสำคัญ ในขณะที่ในตัวกลางที่ค่า พี เอช 7 การปลดปล่อยตัวยาลดต่ำลงอย่างมีนัยสำคัญเมื่อเทียบกับน้ำบริสุทธิ์

ภาควิชา.....เภสัชอุตสาหกรรม.....ลายมือชื่อนิสิต.....

สาขาวิชา.....เภสัชอุตสาหกรรม.....ลายมือชื่ออาจารย์ที่ปรึกษา.....

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KEY WORD: DILTIAZEM HYDROCHLORIDE/ SEMISOLID MATRIX / SUSTAINED RELEASE / GELUCIRES /THERMOSOFTENING BASES

WANCHAI CHONGCHAROEN : SUSTAINED RELEASE OF DILTIAZEM HYDROCHLORIDE USING THERMOSOFTENING BASES AS SEMISOLID MATRIX FILLED IN HARD CAPSULE. THESIS ADVISOR : ASSOC. PROF. KAISRI UMPRAYN, Ph.D. 235 pp. ISBN 974-346-388-7

Sustained release diltiazem hydrochloride capsules using thermosoftening vehicle as semisolid matrix with 90 mg dosing level which had a dissolution properties following tolerance according to USP 23 supplement 5, Test 1, for product labeled for every 12 hours could be prepared. They were composed of diltazem hydrochloride 90 mg and thermosoftening bases for 180 mg per capsule. Final weight of capsule was equal to 270 mg and the suitable hard gelatin capsule size was #2 capsule. Both pure Gelucire 50/02 and combination with other Gelucires were sufficient enough for controlling drug release as following above criterion. Combination weight ratios among Gelucire 50/02 and Gelucire 46/07, Gelucire 53/10 and Gelucire 50/13 as 144:36, 169:11.2 and 172:8, respectively, were preferred for the preparation and desirable property.

Linear relationship between means dissolution time (MDT) and calculated HLB of Gelucire® mixture could be explored from the combination of Gelucire 50/02 with Gelucire 46/07, Gelucire 44/14 and Gelucire 42/12. Meanwhile, the relationship as mentioned above were not founded with combination among Gelucire 50/02 with Gelucire 50/13 and Gelucire 53/10.

Thermal analysis and infrared spectroscopy study revealed that combining of two types of Gelucires® by co-melting process upon preparation did not provide chemical interaction between both compounds. Physical combination was the appropriate answer for stage of co-melting Gelucire® mixture. Moreover, solid crystals of diltiazem hydrochloride in single or combination Gelucire® matrix were also presented and solid dispersion of particle was obtained.

The pH change method in the dissolution study of desirable diltiazem hydrochloride semisolid matrix capsule formulations described above showed different dissolution profiles when compared with reference medium (purified water). The initial and intermediate pH region, 1.2 and 4.5 gave nearly similar profile with the references while the dissolution in higher pH range (pH 7.0) gave lower values than the references medium with significant difference.

Department……Manufacturing Pharmacy….Student's signature …….
Field of study……Industrial Pharmacy……..Advisor's signature……..
Academic year.……2000……....Co-advisor's signature……

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LISTS OF ABBREVIATIONS

%	percentage
%CV	percent of coefficient of variation
%RH	percent of relative humidity
%RSD	percent of relative standard deviation
>	more than
<	less than
≅	as same as
°C	degree celcius (centigrade)
DSC	differential scanning calorimetry
DTZ	diltiazem
e.g.	for example, exempli gratia
et. al.	Et alli, and others
f_1	dissimilarity factor
f_2	similarity factor
g	gram(s)
G	Gelucire(s)
HCl	hydrochloric acid or hydrochloride salt
HGC	hard gelatin capsule
HLB	hydrophile lipophile balance
hr	hour(s)
IR	infrared
kg	kilogram(s)
M	molarity
mcg	microgram(s)
MDT	mean dissolution time
Meq	milliequivalent(s)
mg	milligram(s)
min	minute(s)
ml	milliliter(s)
mm^2	square millimeter(s)

LISTS OF ABBREVIATIONS (cont.)

mp.	melting point
mPa.s	millipascal per second(s)
MW	molecular weight
N	normality
nm	nanometer(s)
PEG	polyethylene glycol
pH	the negative logarithm of the hydrogen ion concentration
pKa	the negative logarithm of the dissolution constant
ppm	part per million(s)
Pu	liquid-liquid partitioning value
q.s.	make to
r^2	correlation of determination
rpm	revolution per minute
SD	standard deviation
SEM	scanning electron microscope
sp. gr.	specific gravity
SSM	semisolid matrix
USP	The United State Pharmacopoeia
UV	ultraviolet
UV-visultraviolet and visible	
w/w	weight by weight
w/v	weight by volume
v/v	volume by volume

CHAPTER I
GENERAL BACKGROUND

Traditionally, oral administration is one of the most convenient and acceptable route of drug delivery for the medical treatment. At early stage of drug development, new technology of the coating processes are used to modify the conventional immediate release dosage form to prolonged or sustained the release using specific properties of some materials such as polymer, wax etc. Coated bead, placed in hard gelatin capsule, was introduced in the market with a brand "Spansule®" and was classified as a prolonged release system. In 1960's, a main objective of new concept that preface the improvement of drug delivery systems were intended deliver the drug as a constant rate to blood stream and provide constant drug concentration in blood. Alternatively, they are called "controlled release system". Furthermore, the other objectives of controlled drug delivery are enhancing safety, extended duration of action and increase delivery efficiency.

Several drugs are categorized as chronic or extended basis medication (such as, cardiovascular, respiratory and analgesic, etc) have the most possibility to be designed as sustained or controlled release drug delivery system. For example, diltiazem hydrochloride, a calcium ion influx inhibitor (slow channel blocker), the indication is for the treatment of hypertension and management of chronic stable angina or coronary spasm induced angina. It is well absorbed from gastrointestinal tract and subjected to an extensive first pass metabolism or metabolized by the liver, giving an absolute bioavailability when compared to intravenous administration. Thus, it is a propable candidate for controlled release dosage form.

Potential challenge of controlled or sustained release preparations are as follows: drug delivery system itself and gastrointestinal transit time. Not only the two aspects mentioned above but hepatic first pass metabolism is also the important problem in formulation of this type of dosage form. To overcome the hepatic first pass effect, many physical and chemical approaches were used to solve this problem. It is not appropriate for a drug with hepatic first pass metabolism to be formulated into oral controlled or

sustained release dosage forms because a grater extent of hepatic first pass metabolism may occur over conventional oral immediate release (Chien, 1982 and 1993). Since diltiazem hydrochloride has this hepatic first pass problem, it may not be suitable to design it as a controlled or sustained release oral dosage form. It has, however, a short elimination half-life, which make it a good candidate which liberates with constant release rate. Therefore, diltiazem hydrochloride in various sustained drug delivery systems are designed (Shyamala et al., 1999).

Fabrication of oral sustained or controlled release drug delivery system will be contemplate with limited data of the active ingredient such as dose, rate constants for absorption and elimination, metabolism which one can calculate an optimal release rate (Vasant, 1995). Many approaches are introduced to help the formulation of sustained release dosage form. Among the innumerable approaches, matrix system is one of the most widely used for sustained release formulation. It has various benefits such as ease of preparation, wide varieties of matrix forming agents available and ability to control the drug liberation with the intended rate of release. In spite of the various advantages of the matrix system, it has many disadvantages too. After the matrix system is in contact with the liquid medium, the entrapped drug on the matrix surface is rapidly dissolved. This phenomenon is called “burst effect”. The burst effect is a disadvantage of matrix system that will influence the release kinetics and extent of drug in the blood stream.

Waxy substances are one of several choices of matrix forming agents that can provide retardation effect. In material sciences, wax is generally defined as a substance, which has a physical state as solid at a room or an ambient temperature and become fluid at elevated temperature above its melting point. Chemically, it is an ester of monohydric long chain fatty alcohol and a long chain fatty acid. Wax components usually consist of a wide variety of substances such as glycerides, fatty alcohol, including free fatty acid and their esters. Normally, these materials have common physical and chemical properties, e.g., high lipophilic or low hydrophilic characteristics, water insolubility but high capacity to dissolved or solubilized in non polar solvents.

Waxes are mainly used in pharmaceutical industry for a long time. Especially in semisolid dosage form such as ointments, creams, lotions and suppositories, its major

roles is to regulate the consistency and controlled physical character of products. Furthermore, it can be used as vehicle for new technique called “Liquid filling technologies”. The previous data had shown that wax have many advantages in various dosage forms. Due to some chemical properties such as hydrophobicity or lipophilicity, waxes are interesting to many researcher and have many benefits to be developed into a sustained or prolong release dosage forms for water soluble drugs. It is intended to be used as retardant for drug release from several dosage form devices (Bodmeier and Hermann, 1997).

Until 20 years ago, many substances were developed with the desired properties, which is a solid form at ambient temperature and changes to fluid at elevated temperature as same as waxy material. On a contrary, it has a good hydrophilicity which differ from waxy solid or semisolid. These substances have a potential to increase the solubility of water insoluble drugs or improved bioavailabity. Examples of these substances are polyethylene glycol with various molecular weights or polyglycolyzed glycerides. Furthermore, these semi synthetic materials can be synthesized with various hydrophilicities depending on its components and expressed in terms of Hydrophile Lipophile Balance (HLB). High HLB materials are appropriate for improving solubility. On the other hand, sustained release action is selected from low HLB materials.

Without any doubt, the interests in liquid filling techniques mentioned above has grown continuously. There is still expansion for seeking further application or production scale-up technique in order to contribute these knowledge to industrial scale in the future. Especially in hard capsule filling technologies, this method is adapted for filling various physical states of active ingredients in hard gelatin capsule (HGC) rather than soft gelatin capsule (SGC). Traditionally HGC has been used as a container for solid particles such as powder, granule or pellets. It is known that liquid form which consisted of water or hygroscopic substances are not suitable for filling in HGC because of water migration and leaking problems can occur. Consequently, HGC shell will be brittle, weak and affected the dosage form stability and leading to an unacceptable product. But several developments put effort to change both nature of the filling substances and a type of capsule shell to overcome that problem.

Until the past decades, sealing technique of HGC is discovered by using the gelatin band to reduce the junction between cap and body portion and provide a tamper-proof capsule. However, this technique is not enough to defeat overall problem particularly water desorption problem. Semisolid matrix (SSM) filling technique is an alternative choice to conquer these problems. This technique converts the nature of solid active material into another form, i.e., semisolid or solid form and fill in hard capsule that can prevent leakage. According to the semisolid matrix vehicle properties, which frequently absence of water component and hygroscopic substances, desorption phenomena probably does not happen.

A highly water soluble drug is more difficult to formulate in a controlled or sustained release dosage form due to its high water solubility. It is prompt to diffuse throughout in gastrointestinal tract after ingestion. Subsequently, huge amount of drug concentration may reach the blood toxic level and act as poison substance. The best drug release regulation by suitable formulation design approach is essential.

The main reason that promote semisolid matrix, using the liquid filling technology, in sustained release design is because its ease of preparation. In addition, matrix bases in semisolid type has a wide variety to choose from and could modify desired physical, chemical properties relating to drug release pattern. Thereby, the above reason leads to the preparation of diltiazem hydrochloride at 90-mg dosage level with semisolid matrix filled in HGC by liquid filling technique.

Objective of this study

1. Formulate the suitable sustained release capsule preparation of 90 mg diltiazem hydrochloride dosing level with semisolid system which are in accordance with the tolerance of Diltiazem Hydrochloride Extended-release capsule mentioned in USP 23 Supplement 5 (for products labeled for dosing every 12 hours, Test 1).
2. Investigate the relationship between calculated HLB of base mixture over drug release pattern.
3. Study the release characteristics of Gelucire® semisolid matrix.
4. Observe and evaluate the mechanism and kinetic of drug release on drug loading level of highly water-soluble drug in thermosoftening bases especially in sustained formulation base.
5. Observe a pH sensitivity effect of diltiazem hydrochloride semi-solid capsule formulation that followed Diltiazem Hydrochloride Extended-release capsule USP 23 Supplement 5 (for products labeled for dosing every 12 hours, Test 1).

Literature Review

A recent attempt to control the drug release with suitable clinical efficacy and patient compliance has lead to the development of several approaches and modification of dosage forms. These have been inferred to delay release, extended action, prolong release or sustained release, etc (Lisbeth and Stanley, 1987). Various methods and types of preparation are introduced to satisfy the desirable dosage form.

Since 1950's, the field encompasses a multitude of systems, one of which was the "Polymer Matrix System". Matrix is the system which consists of active ingredients, matrix forming agent and other additives. It is a solid dispersion dosage form. If a main active material is solid form, it becomes solid dispersion or solid solution. On the other hand, liquids active materials might be oriented as liquid droplets among resistant support to disintegration materials.

Classification of matrix systems can utilize several criteria such as matrix structure, release kinetics, release mechanism and chemical nature of support materials. If the last criterion is the desirable standard, matrix system can be classified in according to Table 1 (Salsa et al., 1997).

Table 1 Matrix type or system classification.

Mineral Matrices	Hydrophilic Matrices	Inert Matrices	Lipidic Matrices	Biodegradable Matrices
*Drug retained in the support *Drug adsorbed on the support	*Unlimited swelling, delivery by diffusion *Limited swelling, controlled delivery through swelling	*Controlled delivery by diffusion	*Delivery by diffusion *Delivery by surface erosion	*Non-lipidic

The major important type of matrix system can be separated into three major groups.

Hydrophilic Matrices

This type interestes many researchers and has many reports on study of drug-hydrophilic polymer matrix for controlled drug delivery. Perhaps it can be called swellable controlled systems due to high gelling efficiency and high water absorption of matrix base. The polymers or matrix-forming agent in this case are classified for three major groups - cellulose ether derivatives, natural or semi-synthetic gum and synthetic polymer (acrylic copolymer) (Salsa et al., 1997). The formulation was prepared by mixing all ingredients and direct compression into tablet. Most of studies revealed that swellable controlled systems provide zero-order drug release kinetics but depended on physicochemical properties of all ingredients in the formulation.

Embedding in Plastic Matrices

This approach is similar to the hydrophilic matrices but a plastic skeleton material is use as a matrix forming agent.

Embedment in Slowly Eroding Matrices

Slowly eroding matrices mean that the vehicle or bases sustained the release of active portion and slowly erode when immersed in liquid environment. Examples of slowly eroding material are fat and wax e.g. beeswax, carnuaba wax, semi-synthetic glycerides. The active materials in slowly eroding matrices can be formulate in granule form and compressed to tablet or fill in HGC.

Liquid filling technologies

Liquid filled or molten filled is the new technologies that conducted into hard gelatin capsule formulations. Normally, liquid substances appropriate to transfer in only soft gelatin shell so called “soft gelatin capsule”. In contrary, recently, liquid substances can be fill in not only soft-shell but also hard gelatin container by modifying or converting method which given the final stage of mixture to solid or semisolid stage. Liquid filling consisted of active substances that dispersed or dissolved in molten matrix (thermosoftening type) or liquid stage of some matrix bases (thixotropic type). Sometimes molten filling technologies is called semisolid matrix (SSM) due to the thermal properties of bases.

SSM can be classified by the nature of matrix forming material into three main major groups (Jones, 1985 and Baykara et al., 1991).

1. Thermosoftening system

This system is conposed of material bases which have thermosoftening properties. The property is determined by physical stage of materials when temperature changing has occurred. Thermosoftening vehicles appear to be solid stage at lower temperature (lower than its melting temperature) but change to fluid at elevated temperature (much more than its melting temperature) and still present as fluid stage until temperature decreasing immediately. Sometimes this process is called “hot melt process”. This system is not suitable for heat labile substance because heat is necessary for this process. For instance, thermosofetening vehicles are polyethylene glycol (PEG) derivatives, glycerides, modified glycerides, wax or fatty alcohol.

Modified glycerides or chemical glyceriedes are semi-synthesized from natural hydrogenated vegetable oil with polyalcohol by esterification process. Sometimes, they are called “saturate polyglycolyzed glycerides”. The brand name of modified glycerides is “Gelucires®”. A cluster of Gelucire® family consist of two major constituents between total or partial of mono-, di- or triglycerides(triacylglycerol) and mono-, di PEG ester of fatty acids. Their complexities are obtained from different components and lead to the resulted in wide range of overall amphiphilicity. They have

a wide variety range of properties which can defined by two set of number. First two digit numbers are indicated to their melting point or thermal properties and the second set are referred to HLB or hydrophilic/lipophilic properties. Starting fatty materials of Gelucire® are separated in two type of natural oily substance as hydrogenated palm kernel and hydrogenated palm oil which as the results of hydrophobicity. The palm kernel oil derivative show low melting point product while palm oil give the higher thermal property product. The intermediate melting point base is obtained by the blending among both oily materials at satisfied proportion. On the other hand, hydrophilicity property is influenced by polyester of fatty acid under alcoholysis reactions at high temperature and cover with inert gas condition. In this stage, triglyceride in fatty acid becomes mobile and undergoes a molecular arrangement and attachs to the free moving hydroxyls in polyalcohol at the heart of reacting mixture. The chain length of polyalcohol is the directly control factor to hydrophilicity. Gelucires® family have the melting point varies from 33 to 70°C and amphiphilicity defined by HLB value on the scale of 1 to 18 and categorized in thermosoftening vehicles. The diversity of Gelucire® grades are lead to a specific characteristic after oral ingestion and influence to hydrodispersibility, melting and floatability properties. They are practically pharmaceutical inert and non-toxic. Toxicological study data indicated that G44/14 and G50/13 were non-toxic after acute oral administration. G 44/14 oral sub chronic toxicity study with 90 day on dogs showed that the total absence of toxic effects for doses up to 1000 mg/kg/days. In addition, genotoxic study was revealed that G44/14 gave negative results of various genetotoxic testing procedures. All Gelucires® grade meet the requirement of French and European Pharmacopoeias.

In particular, almost all Gelucires® have a physical stage as semisolid or solid materials at room temperature and suitable for utilized in two major applications. Increased water solubility or enhanced bioavailability and sustained release formulation are the application of the materials.

Bowtle (1999) suggested about the criterion selection of various types of thermosoftening for each desirable formulation. According to various benefits of SSM, simplified scheme for selection is exhibited in Figure 1.

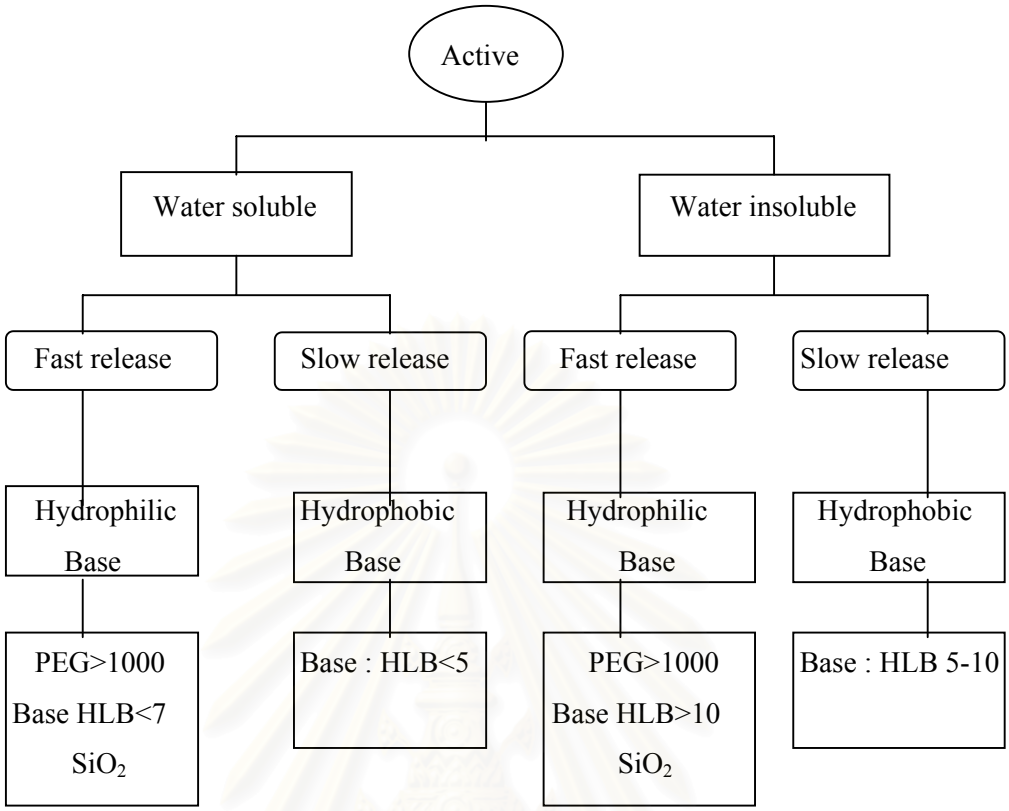


Figure 1 Schematic demonstrations of thermosoftening base formulations.

Further, Ortigosa et al. (1991) recommend that Gelucire® with high melting point (>50°C) and low HLB was suitable for sustained action while the lower melting point and high HLB (>10) could be employed as solubility enhancer. The selection of Gelucire® grade for sustained intention is applied by multiple combinations but focusing on dominant release mechanism shall be consider for providing the suitable bases material proportion. Lists of Gelucires® product in commercially materials supply are presented in Figure 2.

Stearyl alcohol derivatives or Simulsol® are poly(oxyethylene) stearyl alcohol with varying 2-200 units of ethylene oxide and various HLB values between 5 to 15. It limited in oral pharmaceutical dosage form especially for prolong release preparation due to low melting temperature (Bowtle, 1999).

Melting point(°C)											
		70/02									
		64/02									
			62/05								
											55/18
		54/02									
							53/10				
		50/02							50/13		
						48/09					
					46/07						
										44/14	
	43/01										
								42/12			
	39/01										
		37/02		37/06							
							35/10				
	33/01										
HLB	1	2	5	6	7	9	10	12	13	14	18

Figure 2 Commercial Gelucire® product categorization with melting point and hydrophilicity (HLB).

Suppocire® is the modified glycerides as same as Gelucire®. It is designed and treated for suppository bases system but it can be possible to substituted for oral administration. Melting property of general suppository base is playing the major role for ingestion designation. In gastrointestinal tract, suppository bases are melt and lose of rigidity so the drug liberation cannot be controlled. Thus, Suppocire® is not interesting to employ for various oral SSM.

Imwitor and softisan are medium chain partial glycerides with varying in melting point and HLB. Mono, di-glycerides of fatty acid are the main component of them.

Poloxamer is the alternative choice for use as thermosofetening base. Due to hydrophilic properties, it can improve drug solubility. Laxative effect of poloxamer, at high level, is the barrier to employ in formulation.

2. Thixotropic system

Thixotropic properties are observed with the above same manner. Thixotropy is one type of rheology in rheological sciences. It has been time-dependent non-newtonian flow. It can be expressed in liquid state by input an outer force without temperature changing. The shear stress is the main factor or force to convert thixotropic matrix substance from solid or semi solid to fluid stage. If the outer force is not supplied continuously or pulls out from the system, it becomes non-flowable appearance again. Thereby, the system will be produce stable and resistant to leakage by gelation. For example, thixotropic substances are a mixture of colloidal silicon dioxide and oil, cutina HR in liquid paraffin, etc.

3. Combination of thermosoftening and thixotropic system

Combinations of both phenomena are attractive to formulators because it show various benefits over single materials properties. However, they have a few studies deal with these dual-combinations system.

SSM has a several advantages over another dosage forms. However, they also have the disadvantages too as reported by many researchers (Mctaggart, 1984; Jones, 1985 and Bowtle, 1999).

Advantages

1. Taste and odor masking.

Clarithromycin is an oral antibiotic with non-desirable odor and bitter taste. Film coated tablet is the most suitable dosage form for used on its formulation due to taste masking properties of film former. Alternatively, Yajima et al. (1999) used spray congealing between clarithromycin and thermosoftening vehicles for taste and odor masking. The study revealed that wax matrix forming agent (glyceryl monostearate and aminoalkyl methacrylate copolymer E) had the excellent taste blinding properties for masking the bitter taste of clarithromycin antibiotic.

2. Dust elimination and reduce cross contamination effect

Extremely potent, potential toxic and low dose drug such as cytotoxic agent or hormone must be careful about the dust of drug particle, which may be cross contaminate to other production sections via airborne particles. Furthermore, it is directly affect to health and safety of the operators in workplace area. Air suit wearing is utilized for defeating the problem but it is most uncomfortable. SSM is an alternative choice to prevent and eliminate dust generating problem. When drug particles are dispersed in molten bases, they had a little chance to spill and spread like a powder in dust form. Even if drug dispersion is splitted during the filling process, material will not spread and contaminate to other capsules. Sometimes, it is called dust-free process.

3. Precise weight and content uniformity

In powder filling capsule or tableting process, content uniformity and weight variation are the main problems in process due to density, shape difference and flowability of powder. The segregation phenomena may occur during manufacturing process. A dispersion of drug in molten bases seemed to present a dispersion form that provide good homogeneity and lead to precise content uniformity. The delivery of fluid or liquid by volumetric fixing was more accurate than powder filling with weight determination. Thus, pumping of molten dispersion with volumetric fixing valve in automatic liquid filling machine give the low weight variation of capsule. Walker et al. (1980) was studies in content uniformity and weight variation of triamterene SSM with PEG compare with powder fill capsule of triameterene. The study was exhibited that percent relative standard deviation (%RSD) in content and capsule weight of liquid fill was lower than powder fill form. They concluded that the liquid fill technique achieved less problem in weight variation and content uniformity problem.

4. Applicable to various drugs

Ethereal extract, natural oil and some fluid vitamins are difficult to formulate in solid dosage form. Adsorption method seems to be a possible process to convert the liquid substance to solid state. Colloidal silicon dioxide is utilized as and adsorbent due to adsorbing ability and small surface area. After that, saturated colloidal silicon dioxide

with fluid substances are mixed with other excipients and prepared in solid dosage form. Limitation of adsorption activity has become a consideration. Large amount of liquid consumes high adsorbent and leads to the huge dosage form. SSM can conquer this problem because of its high limitation for liquid manipulation. Furthermore, it is possible to convert liquid to semisolid or solid form properties due to thermosoftening or thixotropic bases.

5. Simplification of production process

Production of SSM filling in HGC required a few processes. First, liquefying of dispersion by heat for thermosoftening system or shear thinning for thixotropic system and followed by pumping into container and allow to solidify at an ambient condition then close the cap to bodies of hard capsule. Thus, they comprise of few process parameters and easy to adjust process variable between processing time.

6. Good reproducibility

Due to both few components and simple process in SSM formulation, a variation is minimized when comparing with tableting or powder filling capsule process. Although several materials in SSM bases most obtained from nature and might have batch to batch variation, semi-synthetic process is the root for overcome and can be control variation problem. Hence, constant properties of matrix base will lead to consistency in production process and gained reproducibility.

7. Possible rework process

Rework process is the most problem that occur in the manufacturing process. In order to solve above problem from processing and personal error correction, several approaches must be done. Rework method of solid dosage form is difficult and complex. Whereas, in SSM, it can be rework with simple process and easy to adjust any parameters for desirable quality of products.

8. Increased aqueous drug solubility

Solid dispersion is employed for improved drug solubility especially poorly water-soluble drug. Several SSM bases can be utilized as solid dispersion bases with hydrophilic properties. Either enhance wettability or reduce drug particles size may be the main mechanism for multipling water solubility.

9. Design a sustained action dosage form

Many SSM bases have hydrophobicity properties and can be retard the drug liberation from device. So it shall be applied in sustained or prolong release dosage form.

10. Improved stability of oxygen or moisture sensitive drug

Oxidation and hydrolysis reactions are the most reasons of drug instability. Barrier substances, such as SSM bases, can be employed as the tool for preventing instability caused by above reactions. They are totally surrounding the drug particles and become shield for protect a sensitive substances.

11. Alternative choice in solid pharmaceutical dosage form

Disadvantages (Bowtle, 1999)

1. Limitation of capsule size is a main problem in designing formulation.

High dose drug cannot be filled in the biggest size HGC. Usually for human ingestion, maximum hard capsule size is No 0, which contained powder not exceeding average 600 mg per capsule. If the formulation's drug has a dose over 600 mg, tablet dosage form is more suitable than SSM in capsule.

2. High concentration of dispersion particles cannot be filled or transfered to hard capsule due to rheological properties.

3. Heat labile drugs are not appropriate for thermosoftening vehicles. On the other hand, thixotropic materials can be employed for SSM bases. If a thermosoftening

vehicle is the desirable for formulation, it is therefore extremely important to perform and investigate a thermal stability of active materials.

4. Scale up parameter should be considered.

Typically, laboratory scale experiment and process parameters of SSM are often simple. Whenever the scale of production is enlarged, these methods may be difficult to perform and control as same as on small scale. Trials preclude adjustment of process variables on production scale are the major consideration.

5. Bridging phenomena

Bridging effect is the phenomena that viscosity of molten mass is not optimal level. It can produce a connection solid between next capsule bodies in liquid filling process. Dispersion of lactose in PEG 20,000 at 70°C which fill in hard capsule with semiautomatic filling machine had bridging phenomena in filling process as reported by Rowley et al. (1998).

In liquid fill method, they have many consideration, which concern to the process and properties of product.

- Capsule container

HGC shell is made, generally, from gelatin substance which is possible to be softened and fused at high level of moisture environment. Furthermore, in recent year's, cellulose ether such as methylcellulose are introduced for instead of gelatin shell. Due to robustness and good stability on storage at high moisture conditions (35-65%RH), hard capsule was suitable for drug powder or mass for used in countries with climate ranging from arctic to tropical (Bowtle, 1999). Liquid filling in HGC container will be suitable utilized for a leakage-prevention capsule type. Thus, several companies are produce special self-locking design two-piece HGC container. For instance, Lokcap® and Posilok® of Eli Lilly, Snapfit® or Conisnap® or Licaps® from Parke Davis, Star -

lock® and Lox-It® of R.P.Scherer, are developed in recent centuries for defeat these problems.

- Mass filler.

SSM is the system that is composed of a few ingredients between active substances, matrix forming materials and other additives (if required). Thus, matrix properties could be influenced the process, stage of production, machine selection and over to the final product properties. Suitable semisolid or molten mass for fills in hard capsules should be as follows:

- Final weight and volume of SSM shall be correlated to void volume of capsule shell. According to standard size of HGC, in industrial market, the capsule has a wide range in size on scale number 000 to 4. Normally in human pharmaceutical dosage form, size 0 (largest) through size 4 (smallest) was populated in drug formulation. Generally, suitable fill volume in body capsule shell is about 90% of maximum volume of capsule body part although it can be contained at higher base level.

- Matrix or resistant supporting agent must have moderate melting point. If it is a high melting substance, high temperature in process can lead to a molten stage of matrix base meanwhile instability of active substances may occur. On the other hand, low melting point bases are not suitable because leakage phenomena may happen at storage temperature.

- A rheological property of molten mass is the important factor in formulation and production of SSM with automatic liquid filling machine.
  Rowley et al. (1998) was classified as liquid filling system in HGC along with rheological properties as

  a) Mobile newtonian liquid
  b) Thixotropic gels, both a) and b) could be filled at an ambient temperature.

c) Thermosoftened systems that were newtonian or non-newtonian at high temperature above its melting point.

At suitable viscosity of molten mass, suggested by Rowley is approximately about 0.01-25 Pa.s, it's prevent the drug particles sedimentation and lead to a homogeneous dispersion. While Walker et al (1980) and Shah et al (1996) recommended a proper viscosity of SSM that should be greater than 500 mPa.s (at 20°C) and 300-600 mPa.s, respectively. Further, Newtonian rheology is the most desirable semisolid bases properties for filling process. In addition, surface tension is the most popular parameter for optimized the SSM formulation and prevents the leaking effect. The higher value in surface tension is desired for achieving a better preparation.

- Hygroscopicity of matrix base is the most concerning factor and directly affected to the rigidity of gelatin container. Normally, gelatin shell has intrinsic moisture content of approximately 13-16 % by weight. Moisture content of capsule shell is raised depend upon atmospheric moisture level. At high moisture environment, capsule shell may absorb the water vapor then it will be softened and loss rigidity to protect the inner mass. On the other hand, during storage condition, moisture desorption from gelatin shell may be occurred by the component of inner mass in capsule. Water migration from soft gelatin capsule to inner mass was observed by Serajundin et al. (1986). The study revealed that pure PEG could be lead to water migration of SGC to fill material and alter drug solubility in that base. On contrary, G44/14 that most popular to used as SSM base did not cause this phenomena. In addition, alcohol and low molecular weight PEG could dehydrate the capsule shell very fast and lead to gross embrittlement with short period (Bowtle, 1999). Thus, SSM preformulation is interesting in matrix base selection. The combining of differ matrix base substance will overcome these problems.

- Most important consideration of material selection in formulation is safety. It must be non-toxic and pharmacologically inert. Almost all of SSM agents

are derived from nature so it may be a biodegradable and high safety for oral administration. Further, low cost of substance will be appreciable in formula designation.

- Equipment and process.

History of liquid filling machine development was started by Walker et al. (1980). They modified the automatic capsule-filling machine (Model Zanasi LZ64, ACM Machinery Ltd.) with Liquid filling pump instead of powder hopper and powder dosator tube head. A modified machine are presented in Figures 3 and 4. The volume of fill mass could be adjusted by microswitch that control the valve of dispenser shot into capsule shell. The evaluation study of filling system by modifying liquid filling machine shown that it provided a pleasure in weight uniformity and appearance of product. Although a desirable product could be achieved, the development of filling operation would be studied.

Few years later, Mctargrat et al. (1984) studied about innovative liquid filling machine as same as Walker et al. (1980). The modification utilized heat stainless steel reservoir and liquid metering pump (Hibar Model HBD-1A, Holfliger, West Germany) instead of powder hopper and dosator tubes. These reservoir and pump could control the wide range of temperature (from am ambient to 100°C) and transfer volume in the range of 0.05 to 1.5 ml. The presentation of mechanical part of modifying machine is shown in Figure 5. The investigation of this study exhibited that innovative machinery is versatile, excellent in fill weight variation and suitable for liquid fill or intermittent motion powder in bench scale.

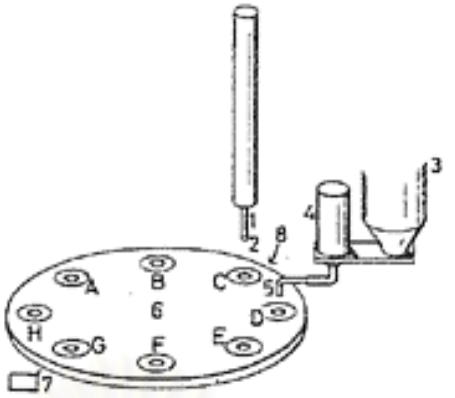


Figure 3 The components of modifying capsule filling machine. 1-Locating bar, 2-Light emitting diode, 3-Dispenser reservoir, 4-Dispenser valve, 5-Dispenser nozzle, 6-Turntable, 7-microswitch, 8-Light detector

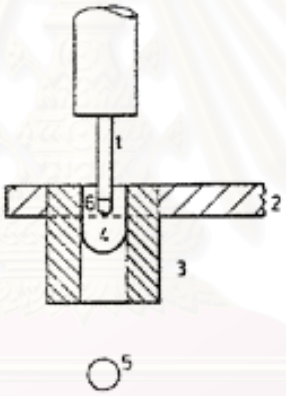


Figure 4 Diagram of turntable constituent for semisolid capsule filling machine. 1-Locating bar, 2-Turntable, 3-Capsule body holding bush, 4-Capsule body, 5-Detector, 6-Light emitting diode.

Nowadays, several companies reconstruct the capsule filling which specify and suitable in liquid fill process. For instance various GFK models of Robert Borsch GmbH, Nuova Zanasi or KFM model of Harro Holfiger GmbH etc.

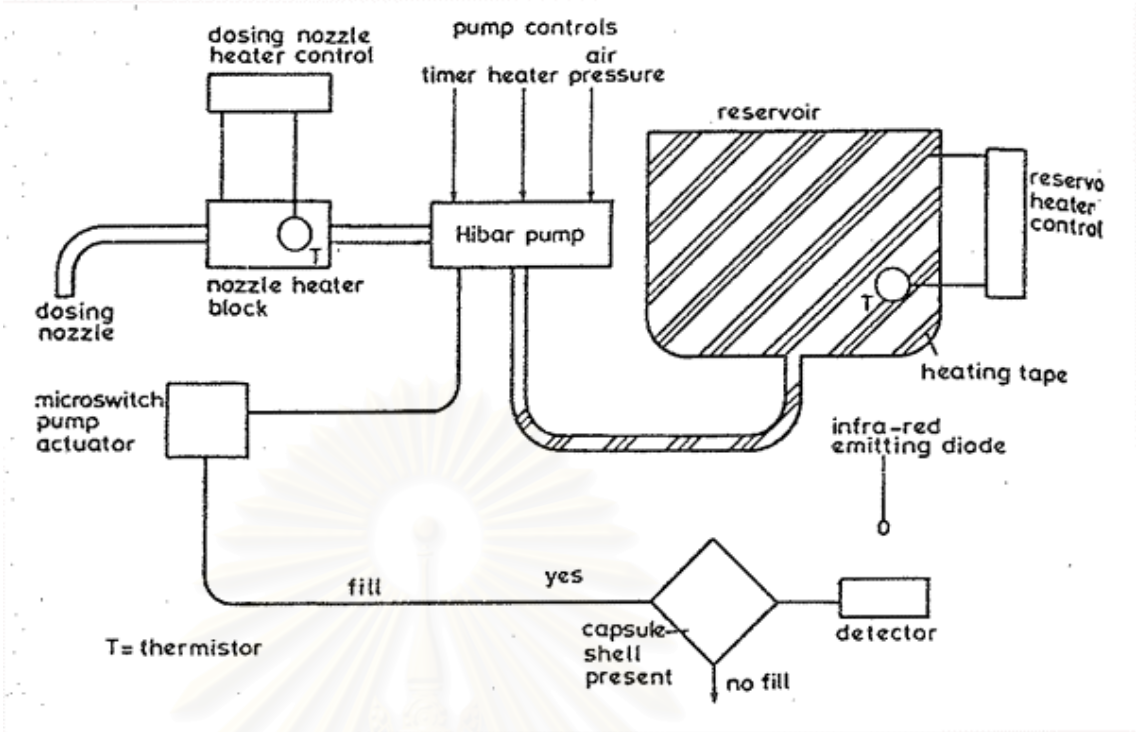


Figure 5 Diagrammatic of modify liquid filling machine for HGC (pump and control system)

Liquid filling machine must have several appropriate properties.

1. In thermosoftening system, the constant temperature of the reservoir or liquid fill hopper must be controlled with acceptable low variation throughout the processing run to regulate a viscosity of dispersion. It should have agitation or stirring blade for prevention of the sedimentation of active materials and obtain homogeneity.

2. High precision in transfer volume controller.

3. The synchronization of filling process and detection of empty capsule shell in stage cycle must be harmonized. They should have a detectable system by sensor. If a position on stage don't have any capsule body, the filling cycle must be interrupted and pass to fill in the next capsule stage position.

4. A further desirable property is ejection system of incomplete capsule from the machine.

Sutanata (1996) and Bowtle (1999) simplified the liquid fill in HGC process using the following three steps.

- Base liquefying (melting for thermosoftening system or stirring for thixotropic system)
- Drug dispersion in fluid bases by simple agitation
- Transferring of dispersion to the containers and closing the container as the final step.

Early three stages of production must be careful to monitor and adjust with the optimal parameters. In thermosoftening bases, narrow melting range of substances may affect the viscosity and the best filling control must be ensured. Temperature controlling during liquefying process is, thus, play the important role to regulate the viscosity of molten bases. On a contrary, shear force or stirring rates are the dominant factor to control liquidity of thixotropic bases.

Whereas, a controlling of filled volume is necessary to regulate in precision and accuracy of weight and content in capsule. Pumping system of head fill dosator in liquid filling machine will provide good precision and low deviations in fill volume.

- Process evaluations

Several effects of preparation conditions were studied by Sutanata (1995). These studies showed that theophylline from G50/13 or G55/18 matrices with different drug release pattern were occurred under different preparation conditions. Heating and cooling cycle of molten base played the major role to altered drug release, drug recrystallization and other several properties of matrix system. Thermal characteristics of molten base were monitored because they might affect the physical and chemical properties of bases. Further, the above study revealed that rapid cooling cycle resulted in low drug concentration of theophylline in G55/18. Meanwhile, at high drug loading level, it had negligible effect on drug release. Likewise, slow cooling cycle gave the

same result as the rapid cooling process. The difference in drug release could be expected from degree of crystallinity changing, lattice strength of polymer structure, structure complexity and crystal distribution of materials. Sutanata (1994) reported about thermal history and tensile properties of Gelucire® under various preparation conditions. It was suggested that faster cooling cycle might be lead to combined chemical component in homogeneous structure. While slower cycle might provide the fractionation of base component into different regions on microscopic scale.

Dordunoo et al. (1996) separated melt solidifications into three minor steps: I) supercooling formations, II) nucleation and III) crystal growth. The study showed that solidification rate was the critical factor for the degree of substances supercooling. While crystal growth rate of bases were influenced by fusion temperature, drug content, MW of polymer bases and cooling rate. Solidification enthalpies were major parameter for assessment the degree of crystallinity. The experiment data indicated that it was decreased when cooling rate was increased. Hence, it could be lead to incomplete matrix structure and liable to unstable after storage. The results further displayed that various MW of PEG, which were usually utilized as matrix forming agents provided a different polymorphic form under different cooling rate.

Once more, heating and cooling cycle directly influenced the physical and chemical properties of SSM with above-mentioned reason. Dordunoo et al. (1991) discovered the relationship between cooling cycle and particle size of active ingredients in dispersion. The aggregation or agglomeration of drug particle was direct variation depending upon drug loading level. To reduce particle size of drug powder, rapid cooling by liquid nitrogen would be an alternative method which provides a smaller drug particle size. For example, the studies of temazepam at 10% w/w in PEG bases indicated that in supercooling stage, drug particles became less than 2.5 micron. Whilst, an ambient cooling resulted in approximately about 40% of particle being less than 2.5 micron. A particle size and particle orientation in SSM bases might lead to the different release mechanisms (via water or pore forming) and alter the release pattern of drug liberation. These method were utilized for modification of the drug release formulation.

Viscosity and step processing time were the main parameters to regulate too. Sutanata et al. (1995) utilized rheology properties for chemical stability appraisal of Gelucires®. Continuous shear flow technique was employed to monitor a viscosity and rheological properties of molten base at temperature range of 15-90°C. The viscosity changing was assumed to indicate the chemical instability. The lower viscosity was expected as the result from degradation of polymer chain and produced the lower fragment of polymer. The increasing of short fragment portion was lead to the minimal energy requirement for bond breaking in polymer chain. So, at the specified temperatures, which lower than original melting point of bases, they could be fused as liquid stage.

Storage time and conditions influence to thermal behavior and mechanical properties and instability of active ingredients (Sutananta, 1994). The study of endothermic peak from differential scanning calorimeter (DSC) showed that different endothermic shape and peak temperature was obtained from various treat preparation conditions that altered the physical and chemical properties of bases. The study of theophylline in previous work exhibited that the release rate of theophylline in Gelucire® tablet would increase after 180 days storage time.

During aging conditions, structural changes of major constituent of waxy or SSM bases might occur. Laine et al. (1988) studied the polymorphic formation of triglycerides or fatty suppository bases. The results showed that after recent solidification of waxy substances, partially amorphous formations of the component in layered structure were obtained but these could be shifted to crystal form with gradually time. Furthermore, they confounded the relationship between melting temperature and crystallization process. During crystallization step, the suppository base was solidified and provided the new melting temperature, which higher than original melting point. Polymorphism formation has not been investigated among storage time but they have only various degrees of crystal arrangement.

Although in vitro dissolution profile of aging SSM could provide a different pattern (Sutananta, 1994) but Dennis et al. (1990) presented in vivo evaluation of

storage ketoprofen SSM (1 month after preparation), insignificance difference had been observed.

Applications

SSM has a wide range of applicability to formulate either sustained or fast drug release preparation. In addition, it can be utilized to overcome the stability problem of labile substances.

Improve drug stability

Vancomycin hydrochloride, an oral antibiotic, is used as the key in pseudomembranous colitis therapy. Because, it is highly hygroscopic substance, it must be prepared in lyophilized dosage form and reconstituted with water before parenteral administration. Bowtle et al. (1988) sought for optimal vancomycin oral dosage form with patient acceptability. Their study revealed that SSM of vancomycin hydrochloride 125 and 250 mg with polyethylene glycol filled in HGC could prevent the moisture sorption in order to exhibit elegant appearance. In vitro dissolution of both strength of vancomycin hydrochloride SSM occurred by surface erosion and exceed 75% of amount of drug was release after 60 min. In present drug market, vancomycin hydrochloride SSMs are introduced and sold in brand “Vancocin Matrigel”.

Improved or enhanced bioavailabity

For a long time, SSM in HGC are employed and developed in a field of bioavailabity enhancement. Several researchers modified this system for an attempt to produce an alternative approach for bioavailabity improvement.

For instance, nifedipine which is sparingly water soluble calcium channel blocker drug, has a low bioavailabilty. To overcome this problem, it is prepared as a solution in low molecular weight PEG (liquid form) and filled in soft capsule. In addition, Lahr had used SSM filling to change bioavailabity of nifedipine by using thermosoftening bases, a blending of mean molecular weight PEG between 200 and 35,000 were used as matrix bases. The preparation consisted of 10-mg nifedipine and

matrix bases make to target weight. It was filled in hard capsule and allowed to solidified at ambient temperature. From experiment data, they showed that either soft gelatin capsule or SSM formulations had similar bioequivalence and were not different from solution dosage form (Cole, 1989).

Triamterene a poorly water-soluble drug, was formulated using PEG MW>1500 in SSM form and powder filled in HGC. When comparing the in vitro dissolution data, it was found that 100% of triamterene release from SSM meanwhile in powder fill form only 10% release was obtained. Possible mechanisms for improvement of triamterene dissolution were rapid dissolution of water soluble matrix, increased surface area and improved wettability of drug particles (Dordunoo et al., 1991). New protease inhibitor, DMP 323- poorly water soluble drug, a good oral bioavailability at low dose (approximately 100 mg) in animal was developed to provide acceptable oral bioavailability at high dose as well as low doses. One of several methods that were used for enhanced bioavailability, SSM of G44/14 was chosen to observations. The study expressed that G44/14 vehicles increased oral bioavailability of high dose DMP 323 much more than other dispersion vehicles such as PEG 3350, PEG 400 or Labrasol®. Further from experimental data, F range also indicated that G44/14 had an advantage than other vehicles for reduction of interanimal variability. Hence, G44/14 solid dispersion was accomplished the goal of dose-proportional bioavailabity (Aungst et al., 1994).

Kinget and Greef (1994) reported the possibility of employment of various semisolid lipid matrices (SSLMs), such as G44/14 or Cremophor®RH 60, to enhanced bioavailabity of novel 8-methoxypsoralen (8-MOP). The study of 8-MOP with lipid material from several researchers demonstrated that they were more effectively absorbed. However, the bioavailabilty of 8-MOP SSLM was found to be lower than solution form.

Ibuprofen, a low water solubility and low melting point drug, generally has a dissolution problem. Many ibuprofen preparations in the drug market have an in vitro drug liberation problem. Hawley et al. (1992) formulated ibuprofen with PEG, Dynasan® or Lutrol® F-68 as the potential bases for the preparation of fusion formed

solid dispersion and fill in hard capsule. It was shown that ibuprofen in SSM form had a desirable in vitro dissolution. Recently, ibuprofen SSM with G44/14 was distributed in Europe in the name “Solufen”.

A dispersion of α-pentyl-3 - (2-quinolinylmethoxy) benzenemethanol, REV 5901-poorly hydrosoluble material, was prepared in the form of semisolid dispersion in G44/14 and various molecular weight of PEG bases and encapsulating hot solutions or dispersion in HGC. In vitro dissolution data depicted that REV5901 solid dispersion with G44/14 was completely dissolute while only partial section of drug dispersion occurred with PEG alone (Serajundin et al., 1988). Further study was conducted with the same group researcher (Serajundin et al., 1991). The in vivo study showed that plasma level of REV 5901 in healthy volunteer which was given dispersion of REV 5901 soft capsule formulation compared with tablet form had significant different. The soft capsule form gave statistically significant superior bioavailability over tablet form.

Solid dispersion of cinnarizine, a poorly water-soluble drug, had been prepared in SSM with G53/10 (Genis et al., 1995). These authors found that at low drug concentration (<10% w/w), it became a solid solution. The reason might be due to absent of cinnarizine endothermic peak in dispersion endotherm, which might inferred that a solid solution was closely formed. Whilst, at higher drug content (>20%), the appearance of cinnarizine in base was observed in solid dispersion form because they could be seen cinnarizine particle in dispersion on hot stage study. They concluded that G53/10 has a powerful to solubilized drug particles on the basis of its surfactant properties.

Cephalexin, an oral cephalosporinic antibiotic drug, is supplied in dry powder fill in HGC and dry syrup form. Eli Lilly researcher by Thakkar et al. (1987) prepared its in SSMs form with G50/13, G48/09 and G46/07 fill in HGC. In vitro dissolution studies showed that the drug release ranking in order of G50/13>G 48/09>G46/07. In addition, in vivo evaluation revealed that both 50/13 and 48/09 had the same plasma level in time and concentration (C_{max} and t_{max}) and closely correlated to conventional capsule.

Comparative in vitro dissolution study of ketoprofen 100 mg between reference sample (Orudis®100) and ketoprofen SSM using G44/14 (Dennis et al., 1990) was investigated. The result showed that ketoprofen in SSM form released higher and faster than reference. This might be attributed to both improved wettability and increased contacted surface area of molecular dispersion in vehicles. In vivo evaluation indicated the correlated result with in vitro study. Ketoprofen-G44/14 codispersion provided rapid absorption time (t_{max}) and the extent of absorption was slightly higher than references. It could be concluded that possibility of SSM to apply for increased drug bioavailabity become reality.

Sustained release formulation

Various substances can be used as sustained matrix bases, for instance, water-insoluble polymer, wax, fat, resin and acrylic copolymer. Although modified waxy substances (polyglycolyzed glycerides) which one type of SSM bases can be used for increase dissolution properties or improved bioavailability of poorly water-soluble but some type has a powerful to be applied as retardant of drug liberation from device depend upon its constituents.

The prevalence study has expressed the potential of polymer matrix as retardant in oral drug delivery system. A blending of polyvinyl acetate and PEG 1500 was investigated for matrix base of nomifensine hydrogen maleate liquid filling capsule. The experiment indicated that mixtures of polymer decrease in vitro dissolution release rate of nomifesine capsule (Walker et al., 1980).

After several studies about various SSM that applied for sustained release preparation. Oily semisolid matrix (OSSM) was interesting to many researchers. It was inferred to one type of SSM that was composed of oily substances as the main component in matrix system. The study of potential of some waxy materials as sustainable substance had revealed by Seta et al. Captopril, ACE inhibitor, was prepared in the dispersion form of active materials in mixture between soybean oil and glyceryl monostearate and fill the molten mass into HGC. The experiment data displayed that in vitro dissolution could be delayed by OSSM system (Seta et al., 1988 (a) and (b)).

Whilst, in vivo test indicated that this system could be utilized for prolong captopril activity throughout 6-8 hours after ingestion although they had a low plasma concentration when comparing with conventional tablet. Moreover, OSSM of captopril improved the stability during foodstuff contact in gastrointestinal tract.

Treatment of hypertension and angina pectoris, nifedipine is the most calcium channel blocker for use in medication therapy. Due to low water solubility, several studies tried to increase the solubility and bioavailability. In previous section, nifedipine was formulated with SSM base as increasing or improving bioavailabiltiy agent. Whilst, many studies were prepared sustained action of nifedipine due to very short biological half-life (approximately 2-3 hours). Wax matrices in tablet form of nifedipine with G53/10 were prepared by Remunan et al. (1992). With reference preparation, Adalat retard®, the statistical moment study in rabbits revealed that nifedipine wax matrix tablet were slightly slower absorption rate than references but not significantly different in the extent of absorption.

In order to compare in vivo and in vitro correlation data, ketoprofen was selected as a model drug for study (Dennis et al., 1990). Ketoprofen sustained release consisted of G50/13 or dual component of G50/02 and G50/13. In vitro dissolution studies indicated that G50/13 dispersion was faster than standard preparation (Oruvial® 200mg). Meanwhile combination of Gelucire® provided similar dissolution release to standard reference. In vivo evaluation of both experimental formulations showed that the relative bioavailability was lower than the predicted value from in vitro experiment section. These explained that employment of slow hydrating and erodible wax matrix formulation could produce sustained release for in vivo evaluation.

Prolong action drug release dosage form is the one in various types of attractive dosage form to overcome patient compliance. Oxprenolol hydrochloride, beta-blocker, which was most popular for hypertension treatment was selected for preparation of various types of SSM system filled in HGC (Baykara and Yuksel et al., 1992). Thermosoftening class or thermocap could be sepearted into two subgroups: I) Gelucire® family with various thermal and amphiphilicity properties and II) mixture of hard fat or waxy materials. In addition, thixotropic formulation or thixocap was choose

to represent another prolong action SSM formulation. Both studies indicated that, in the case of thermosoftening, sustained actions were derived from low hydrophilicity or low HLB bases while higher HLB was provided a rapid or fast release. In the case of thixotropic, hydrophilicity played the major role for regulated drug release. The modification of hydrophilicity of bases might become the alternative way to change the drug release pattern. Blending combination of each Gelucire® type by heating process was succeeded to alter drug release control. There was, further, another choice to produce desirable drug release rate via channeling or pore-forming agent, such as PEG, embedded into hydrophobic bases. From the above studies, incorporation of PEG into both thixo and thermocap achieved faster drug release rate.

Sparingly water and acid soluble drug, indomethacin, was formulated with monolithic lipid matrix systems and filled into HGC for extended zero order release. The clusters of Gelucire® family were used as matrix forming agent. Combination of G46/07 and G33/01was satisfied for 75-mg sustained release dosage form. As used Indocid-R® 75 mg for reference, in vitro dissolution of indomethacin SSM showed the release nearly zero order pattern over the reference. Comparatively, in vivo evaluation, mean plasma profiles of both references and test preparation were typical although there were minor different shift of t_{max}. Due to intersubject variability and poor in vitro-in vivo correlation, they could not be assumed that the test formulation had a bioequivalence as same as the reference. They only concluded that indomethacin in combination of experimental Gelucire® dispersion displayed zero order characteristics under in vitro dissolution observations and had a potential to develop for sustained release preparation. Thereby, poorly water and acid solubility should be possible employed particular Gelucire® family, especially in experiment type Gelucire®, to achieve erosion-controlled and constant release rate dosage form.

SSM in sustained or rapid release is typical prepared by direct filling of molten drug dispersion in the mould or container with different shape devices. Another special technique, fluidization by fluid bed dryer can be applied for helping in-situ semi solid matrices forming in HGC. Bodmeier et al. (1990) prepared SSM or wax matrix in HGC in fluid bed chamber. Initially, homogeneous powder blend of active material and solid particle of wax matrix bases were transferred into HGC. Next step, powder fill capsules

were suspended in hot air stream during air suspension of fluidization process. The elevated temperature induced the fusion of waxy or matrix forming agent and leaded to formation of drug wax matrices. Due to the rotational and movement of the capsule in fluidization, the appearance of matrices differed from general liquid fill in HGC. It was a complete capsule shape plug with embedded large void-air space at the center of capsule and at each end portion was connected with thin sheet of matrices as illustrated in Figure 6.

The irregular formation matrices were lack of rigidity for hydrodynamic stress resistant under dissolution conditions or motility of gastrointestinal tract in human digestion and non-consistency in drug release pattern. Propranolol and theophylline were introduced for investigation studies. The combination of wax, which had differed HLB or amphiphilicity, could be regulate over both drug release as sustained release.

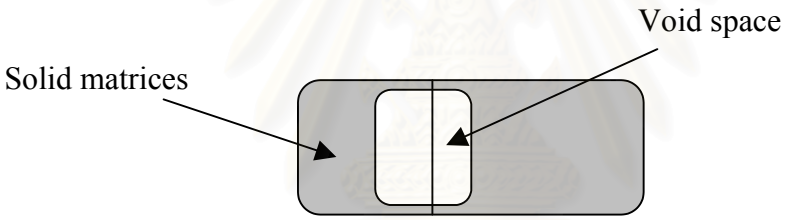


Figure 6 Diagrammatic of the orientation of drug wax matrices within hard gelatin capsule after solidified in fluidization.

Additional of other substances, channeling agent, was discovered by Bidah and Vergnard (1991). Sumikagel, an acrylic acid vinyl copolymer, was introduced with SSM (G46/07) for modifying drug release pattern. With high swelling capacity in lower pH medium, in gastric or acid medium it could control drug release via swelling-control mechanism. Expansion of particle dimension of sumikagel, at lower pH, provoked a faster erosional of G46/07 and leaded faster release of sodium salicylate. This system was succeeded for sustained release formulation.

Drug release mechanism from matrix system

Predication and realization of drug release mechanism from original device is the most importance and play the significant guide in drug formulation design. Mechanism of drug release is generally studied and concluded with the various mathematical treatment models on each basis of experiment. The rate of release is, further, obtained after mechanism definition is set up. It is a main parameter for comparison among various preparations for indication of the significant difference of each formulation. Although, at present, many developments introduced other release parameters (Mean dissolution time (MDT), similarity factor (f_2)) for substitute and represent the drug release pattern, release rate constant is also popular to used by many experiments. Matrix is the most interesting system for finding the flexible model with closely related to drug release prediction.

Dissolution or release of active compounds from device may be expressed agreed with various kinetics. Briefly, in general concept, there are three kinetics patterns which are most popular in drug release expectation. They are zero; first and square root of time model, respectively.

The simplest mathematical model is zero order type. It is the most desirable mechanism due to time independent on drug release. The relationship between extent of drug release versus release time was linear. Consequently, release rate of this kinetic remains constant until the device is exhaust of active compound. Hence, it can be inferred to time independent release mechanism. In this model, contacting time of device does not affect the amount of drug liberation. Thus, it will be assumed that, in human body, the phenomena will be take place and provide the constant drug amount in blood level. Zero order relationship scheme is displayed in Figure 7. The mathematical formula of zero order kinetic is presented below.

$$Q = kt \qquad \ldots(1)$$

Where Q is cumulative amount or extent of drug release, k is drug release constant and t is time.

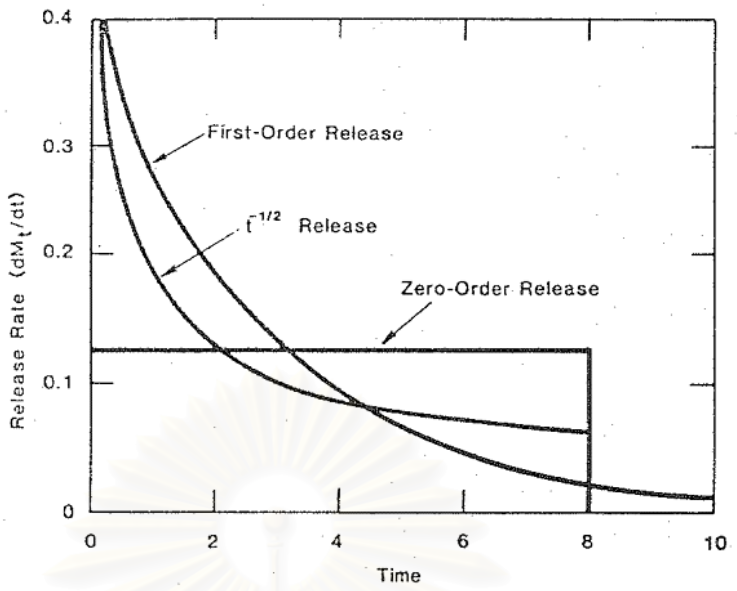


Figure 7 Typical drug release pattern from system which containing the same initial active content.

Hydrophilic matrix forming agent, such as cellulosic ether polymer, gelatin and natural gum, can be express the possible of zero order kinetic. Nevertheless, other parameters will be concern, for instance, loading dose, matrix type, swelling power (Golomb and Fischer, 1990) and so on. These factors can be influence to the hydrocolloid matrix release (Mockel et al., 1993). In addition, polymer relaxation is become the main factor for elucidating drug release from hydrophilic matrices.

First order drug release behavior is indicated in equation (2) (Benita et al., 1982 and Pillay et al., 1999)

$$B = Q_0 e^{-kt}$$

or $$\ln B = \ln Q_0 - kt \qquad \ldots(2)$$

Where B is quantity of drug remaining in device at time t, Q_0 is initial drug content, k and t is mean as previously described.

The relationship of this model is exhibited as a monoexponential declination of drug release and presented in Figure 7.

Higuchi (1963) and Schwartz (1963) discovered square root of time model. Graphical representation of this model is showed in Figure 7. The model equation was derived from drug release throughout continuous ointment base experiment. Occasionally, it was called in "Higuchi's model". It was summarized and presented below:

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2C_0 - \varepsilon C_s) C_s t} \qquad \ldots(3)$$

Where Q is amount of drug release per unit area, D is diffusion coefficient , ε is porosity of device, τ is tortuosity of device, C_0 is initial concentration of active in device, C_s = saturated solubility of drug in device material and t is time.

From the above equation, the relationship of Q and √ t has been established. Main mechanism, which regulated in square root of time model is diffusion controlled. Linear relation of Q as a function of √ t is almost obtained from non-erodible matrix system. Matrices with plastic polymer are dominated with diffusion controlled. Generally, wax matrices is elucidated with Higuchi's model at certain condition but at different condition, it may be expressed another model for regulate drug release. Although many experiments showed that the initial period of drug release pattern from matrix system is deviated from straight line of Q versus √ t plot. This effect is called "Burst effect". It can be explained that drug crystal must be embedded on the surface of device and rapidly dissolved when touching dissolution medium. Burst effect becomes a coupling process with diffusion control in drug dispersed matrix type. Some studies indicated that burst effect is a minor influence and can be ignored.

Some experimental data showed that nearly linear relation with both first order and square root of time kinetic are discovered. Accuracy justifying of best-correlated model is introduced for indication. Plotted curve between release rate (dQ/dt) and Q′ were utilized as distinguish parameter whereas Q′ is amount of drug release calculated by multiplied surface area of device with amount of drug release. If the linear tendency from rate and Q′ is achieve, it can be assumed that diffusion controlled or square root of

time model is the major regulator. Controversy, linear straight line from rate and inversely proportional of Q′ profile is expressed first order kinetic behavior. (Schwartz et al., 1968; Goodhart et al., 1974 and Benila et al., 1982).

Another model can be employed for analyzed the various drug delivery systems. Hixson and Crowell or cube root model is the one of most popular for uses as the test model. This model describes the release form systems showing dissolution rate limitation and does not dramatically change in spherical shape as release process. The represented equation is depicted below.

$$(1-Q)^{1/3} = 1-kt \qquad \ldots(4)$$

Where Q, k and t are the same as above.

Bidah and Vergnaud (1990) developed similar equation in the studies of pellets containing sodium salicylate dispersed in polyglycolyzed glycerides. On the assumption, sphere shape of pellet, homogeneous drug distribution in matrix, erosion is the main mechanism and rate of erosion is related to external surface area of bead. The mathematical approach is shown as:

$$[1-M_t/M_\infty]^{1/3} = 1-kt \qquad \ldots(5)$$

Where M_t/M_∞ is fraction of drug release.

There has been other innovative attempts to proposed new concept in creating the simple and versatile mathematical equation for fortunate the drug liberation in various systems (Peppas, 1985). A simple and semiempirical equation could be established on the basis of fraction of drug release was related to time along with exponential relationship whereas the system was under perfect sink condition. It was known in “Power law expression”. The general equation is:

$$M_t/M_\infty = kt^n \qquad \ldots(6)$$

Where M_t/M_∞ is fraction of drug release, k is releases rate constant, t is time and n is power exponent, which indicates the mechanism of drug release.

Denoted that the power law expression equation was, further, derived under the other assumption. The geometry of device was the one assumption that concerned on equation derivatization. Based on the slab shape device, which had aspect ratio (length/thickness) at least 10 and required that diffusion would be one dimensional, equation 6 was obtained.

The equation could be transformed to the generalized relationship and presented below

$$\ln M_t/M_\infty = n \ln t + \ln k \qquad \ldots(7)$$

So, the straight line on ln of fraction drug release versus ln of time plot was obtained. The slope and intercept values were inferred to n exponent and rate constant, respectively. The release exponent (n) value would be demonstrated the main mechanism for regulate the drug liberation of device. In polymeric film device, n exponent was equal or greater than 0.5. If it lower than 0.5, it might assume that statistical analysis error might become take place. The interpretations among n value and release mechanism behavior are summarized in Table 2. In addition, power law expression would be applied for 60% of initial fractional drug release.

Table 2 Interpretation of n value correlated with predominant drug release mechanism

Release exponent (n)	Drug transport mechanism	Rate (dM_t/dt) as a function of time
= 0.5	Fickian diffusion	$t^{0.5}$
0.5 < n < 1	Anomalous(non-fickian diffusion)	t^{n-1}
= 1.0	Case II transport or Polymer relaxation	t^1 (zero order or time independent)
> 1.0	Super case II transport	t^{n-1}

The power (n) at 0.5 was correlated to Higuchi's model which diffusion behavior was the important mechanism in drug liberation. On the other hand, n=1, it meaned that the system was controlled by case II transport mechanism and become to zero order or time independence kinetics due to polymer relaxation principle. While, n value is among 0.5 to 1, Anomalous or non-fickian diffusion was occurred.

Nevertheless, geometry of device was also one of the most important parameter to affluent the analysis and indicates the proper power exponent (n) with power law equation. Utilizing the geometric knowledge, Peppas and Sahlin (1989) defined the n value for various shape of devices as shown in Table 3.

Table 3 Diffusion exponent for different device geometry.

Diffusion exponent(n)			Mechanism
Film	Cylinder	Sphere	
0.50	0.45	0.43	Fickian diffusion
0.50<n<1.00	0.45<n<0.89	0.43<n<0.85	Anomalous transport
1.00	0.89	0.85	Case II transport

Anomalous case was determined that they have complex mechanism for drug release regulation. Two or more mechanisms were composed in anomalous diffusion. Coupling of both main mechanism which major influence to its were fickian diffusion and relaxation with unequal strength depend upon differ parameter of system. Peppas and Sahlin (1989) proposed the equation for clarifing the influence release mechanism in anomalous transport case. When the solvent influxes to polymer matrix, the two phenomena that controlling the drug release were drug diffusion and polymer relaxation. Hence, the equation consist of two terms of diffusion and relaxation control and might be expressed as:

$$M_t/M_\infty = k_1 t^n + k_2 t^{2n} \qquad \ldots(8)$$

Where k_1 is diffusion rate controlling constant, k_2 is relaxation rate controlling constant and n is geometrical power exponent.

Furthermore, from their study, they also observed that n exponent could be separated into two constant values, by cubic spline method, depending upon aspect ratio of device. Aspect ratio was calculated from the ratio between diameter (2a) to length (l) of device. For 2a/l or aspect ratio value, if it < 0.1 then n value was 0.45, while aspect ratio > 100, 0.5 of n value could be utilized.

The ratio of k_1 to k_2 could express the strength of main mechanism over supporting mechanism for controlling drug release in anomalous system. If k_1 that was related to diffusion control was higher than k_2 (relaxation), it possible to implied that diffusion control was the major drug release regulation.

The development of equation for represent the release mechanism in combined dissolution and diffusion controlled transport is exhibited. Chandrasekaran and Paul (1982) solved the relation of matrix system which was composed of both dissolute or polymer relaxation and diffusion control. The final results are given by the following equations that are separated into two conditions:

I) Solute dissolution was offering the rate limiting step :

$$M_t/M_\infty = 2C_s/C_0 * \sqrt{Dk/t} * [\ 1/2k+t\ ] \quad \ldots(9)$$

II) Solute diffusion was limiting control behavior :

$$M_t/M_\infty = 4C_s/C_0 * \sqrt{Dt/\pi l^2} \quad \ldots(10)$$

Where M_t/M_∞ is drug release fraction, C_s and C_0 are solute solubility and total solute loading, respectively, D is solute diffusivity in matrix, k is solute dissolution rate constant, l is thickness of finite slab shape device and t is time.

From equation 9, It seem to be zero order kinetic with amount of drug release and time was linear relation, while equation 8 was identical to Higuchi's model which linear tendency were obtained from amount and square root of time. Hence, both simple models were benefits to analyze the kinetic model.

Both power law equation and anomalous equation are popular to employed for expect the release mechanism. Wax matrix granules of diclofenac sodium was evaluated by both equations (Sato et al., 1997). From the experiment, it could be seen that n exponent from power law equation was in the range of anomalous type. After that they utilized the anomalous equation and analyzed both diffusion and relaxation constant to correlate the mechanism and additive effect in matrix. In swellable polymer and blending, such HPMC and pectin, were studied by Kim and Fassihi (1997). They utilized the power law for clarified the drug release mechanism.

Modified equation with suitable surface erosion of matrix system is presented by Hofenberg et al. This model is also be applied with any matrix geometries (slab, cylinder or sphere) as shown by equation 11.

$$M_t/M_\infty = 1-(1-kt^n) \qquad \ldots(11)$$

Where k is equal to k_o/C_0r_0 which k_0 is the erosion rate constant, C_0 is homogeneous initial drug concentration in device and r_0 is the initial radius for device.

From above equation, if n equal to 1, 2 and 3, they could be refer to geometry of device with slab, cylinder and sphere, respectively. The disadvantages of this model were presented. On the basic assumption, time dependent diffusional resistance internal or external to eroding matrix did not influence the release kinetics and further contribution of secondary surface between release process was not considered. So, this approach was lack of versatile to apply for different system.

Gelucire®, one type of lipid matrix, the polyglycolyzed glycerides are studied in drug release mechanism based on various mathematical models. Due to the different

properties in family of it, complexities of drug release mechanism are observed. Almost early studies in Gelucire® matrix system with high melting point and low HLB(<7), the result showed that diffusion control was the main release mechanism in regulation control (Dennis and Kellaway, 1987; Howard and Gould, 1987; Naidoo, 1989; Baykara and Yuksel, 1991 and Prapaitrakul et al., 1991). On the next time, Kopcha et al. (1990 and 1991) studied other Gelucire® types, especially high HLB values, by follow equation 8 and discovered that both polymer relaxation and diffusion control influenced drug release mechanism. Further, Sutananta et al. (1994) explained the possibility of swelling and erosion of Gelucires® including to diffusion control by studies in matrix erosion and water uptake parameter. The Power law's equation and anomalous equation is possible to utilize for elucidation of the release mechanism. They found that, further diffusion, swelling or polymer relaxation may be play the major role for controlling the release of active compound.

Active component

Diltiazem hydrochloride (DTZ HCl) is a calcium ion influx inhibitor (slow calcium channel blocker).

Empirical formula and molecular structure are presented below. This chemical name is (2S-cis)-3-(acetyloxy-5- [2-(dimethylamino) ehtyl]-2,3-dihydro-2- (4-methoxy-phenyl)-1,5-benzothiazepin-4 (5H)-one monohydrochloride or (+)-cis-3- (acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-1,5-benzothiazepin-4 (5H)-one monohydrochloride and (+)-5-[2-(dimethylamino)ehtyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride.

Empirical formula is $C_{22}H_{26}N_2O_4S_2$.HCl and MW is equal to 450.98.

DTZ HCl is a white to off-white crystalline powder, odorless and bitter taste. Fine needle crystals are obtained from crystallization with ethanol-isoporpanol solvent. It has a high melting temperature and melt at approximately 210°C (207.5-212°C) with the decomposition at higher temperature. It is highly solubility in various solvents at 25° C. The solubility are shown in Table 4.

DTZ HCl hasn't been observed on polymorphic transition form. Saturated solution in aqueous system has a pH value about 3.0. The 1-% w/w solution of DTZ HCL in purified water has approximately pH at 4.2 while 1-% w/v solution has higher pH value about 4.7.

Dissociation constant (pK_a) of DTZ HCl is equal to 7.7. In addition, liquid-liquid partitioning value (log P_u) or apparent partition coefficient between varying organic solvents to aqueous buffer of n-hexane, dichloromethane, carbon tetrachloride and octanol are 1.0, 4.63, 3.52 and 2.7, respectively (Illum et al, 1983).

Table 4 Solubility's parameter of DTZ HCl in various solvents.

Solvent	Solubility
Chloroform	Freely soluble
Formic acid	Freely soluble
Methanol	Freely soluble
Water	Freely soluble
Dehydrated alcohol	Sparingly soluble
Benzene	Practically insoluble
Ether	Insoluble

DTZ HCl is highly stable in solid state. At ambient temperature and 33%RH or 79%RH solid powder is stable in both physical and chemical properties. In elevated temperature (44°C) and high moisture environment (75%RH), it is stable after three weeks on storage. UV light exposure may be a caused to developed powder color changing.

DTZ HCl in aqueous system is stable over pH range 3-6, especially, optimal point is indicated at pH 5.0. Degradation kinetics of DTZ HCl in various pH was values follow pseudo-first order kinetics and undergoes with hydrolysis reaction which produce desacetyldiltiazem (Sulieman et al, 1990).

Gelucire®

In this experiment families of Gelucire®, saturated polyglycolyzed glycerides, were employed as the semisolid matrix base. The six different types in HLB and melting characteristics of Gelucires® are introduced. (Specification data sheet by Gattefosse)

Gelucire 42/12 (G42/12).

Chemical definition: saturated polyglycolyzed glycerides obtained with hydrogenated vegetable oils consisted of glycerides and polyethylene glycol esters.

Physical characteristics:

HLB value : 12
Appearance : waxy solid
Odour : faint
Drop point (Mettler method): 41.55-46.5 °C
Colour (Gardner scale) : < 5
Solubilities (at 20°C):

Solvent	Soluble
96 % Ethanol	Soluble
Chloroform	Freely soluble
Methylene chloride	Freely soluble
Purified water	Dispersible

Chemical characteristics:

Acid value (mgKOH/g) : <2.00
Saponification value (mgKOH/g) : 95-115
Iodine value (gI_2/g) : <2

Hydroxyl value	(mgKOH/g)	:	30-50
Peroxide value	(meqO_2/g)	:	<6.0
Alkaline impurities	(ppm NaOH)	:	<80
Water content	(%)	:	<0.5
Free glycerol content	(%)	:	<3.0
Sulphated ashes content	(%)	:	<0.10
Heavy metals	(ppm Pb)	:	<10

Fatty acids compositions (%)

Caprylic acid (C_8)	:	4-14
Capric acid (C_{10})	:	2-12
Lauric acid (C_{12})	:	40-50
Myristic acid (C_{14})	:	14-24
Palmitic acid (C_{16})	:	4-14
Stearic acid (C_{18})	:	5-15

Storage conditions **:** It should avoid from air, light, heat and moisture and keep in tight, light resistant and well closed container.

Toxicity **:** Oral ingestion (rat) > 20g/Kg

Applications **:** It could be utilized as excipient in HGC , especially, as bioavailability regulator.
- Increase absorption and bioavailabilty improvement.
- Protective action against oxidation and hydrolysis.
- Handling of low dose and highly toxic drug.
- Converting liquid nature substance to solid form.

Gelucire 44/14 (G44/14).

Chemical definition: saturated polyglycolyzed glycerides specific mixture of mono, di and triglycerides and polyethylene glycol mono and diesters.

Physical characteristics:

HLB value : 14
Appearance : waxy solid
Odour : faint
Drop point (Mettler method): 42.5-47.5 °C
Colour (Gardner scale) : < 5
Solubilities (at 20°C):

Solvent	Soluble
96 % Ethanol	Soluble
Chloroform	Freely soluble
Methylene chloride	Freely soluble
Purified water	Dispersible
Mineral oils	Insoluble

Chemical characteristics:

Acid value (mgKOH/g) : <2.00
Saponification value (mgKOH/g) : 79-93
Iodine value (gI_2/g) : <2
Hydroxyl value (mgKOH/g) : 36-56
Peroxide value ($meqO_2/g$) : <6.0
Alkaline impurities (ppm NaOH) : <80
Water content (%) : <0.5
Free glycerol content (%) : <3.0

1 Monoglycerides content	(%)	:	3.0-80
Sulphated ashes content	(%)	:	<0.10
Heavy metals	(ppm Pb)	:	<10

Fatty acids compositions (%)

Caprylic acid (C_8)	:	4-10
Capric acid (C_{10})	:	3-9
Lauric acid (C_{12})	:	40-50
Myristic acid (C_{14})	:	14-24
Palmitic acid (C_{16})	:	4-14
Stearic acid (C_{18})	:	5-15

Storage conditions **:** It should avoid from air, light, heat and moisture and keep in tight, light resistant and well closed container.

Toxicity **:** Oral ingestion (rat) > 20g/Kg

Applications **:** It could be utilized as excipient in HGC especially, as bioavailability regulator.

- Increase absorption and bioavailabilty improvement.
- Protective action against oxidation and hydrolysis.
- Handling of low dose and highly toxic drug.
- Converting liquid nature substance to solid form.

Gelucire 46/07 (G46/07).

Chemical definition: saturated polyglycolyzed glycerides obtained with hydrogenated vegetable oils consisted of glycerides and polyethylene glycol esters.

Physical characteristics:

HLB value : 7
Appearance : waxy solid
Odour : faint
Drop point (Mettler method): 47.0-52.0 °C
Colour (Gardner scale) : < 5
Solubilities (at 20°C):

Solvent	Soluble
96 % Ethanol	Soluble
Chloroform	Freely soluble
Methylene chloride	Freely soluble
Purified water	Dispersible
Vegetable oils	Form emulsion at50°C
Mineral oils	Insoluble

Chemical characteristics:

Acid value (mgKOH/g) : <2.00
Saponification value (mgKOH/g) : 126-140
Iodine value (gI_2/g) : <2
Hydroxyl value (mgKOH/g) : 65-85
Peroxide value ($meqO_2/g$) : <6.0
Alkaline impurities (ppm NaOH) : <80
Water content (%) : <0.5

Free glycerol content	(%)	:	<3.0
Sulphated ashes content	(%)	:	<0.10

Fatty acids compositions (%)

Caprylic acid (C_8)	:	<3
Capric acid (C_{10})	:	<3
Lauric acid (C_{12})	:	<5
Myristic acid (C_{14})	:	<5
Palmitic acid (C_{16})	:	40-50
Stearic acid (C_{18})	:	48-58

Storage conditions **:** It should avoid from air, light, heat and moisture and keep in tight, light resistant and well closed container.

Toxicity **:** Oral ingestion (rat) > 20g/Kg

Applications **:** It could be utilized as excipient in HGC , especially, as bioavailability regulator.
- Increase absorption and bioavailabilty improvement.
- Protective action against oxidation and hydrolysis.
- Handling of low dose and highly toxic drug.
- Converting liquid nature substance to solid form.
- Sustained drug release formulation.

Gelucire 50/02 (G50/02).

Chemical definition: saturated polyglycolyzed glycerides : specific mixture of mono, di and triglycerides and polyethylene glycol mono and diesters.

Physical characteristics:

HLB value : 2
Appearance : waxy solid
Odour : faint
Drop point (Mettler method): 46.5-51.5 °C
Colour (Gardner scale) : < 5
Solubilities (at 20°C):

Solvent	Soluble
96 % Ethanol	Insoluble
Chloroform	Freely soluble
Methylene chloride	Freely soluble
Purified water	Dispersible
Mineral oils	insoluble

Chemical characteristics:

Acid value (mgKOH/g) : <2.00
Saponification value (mgKOH/g) : 181-195
Iodine value (gI_2/g) : <2
Hydroxyl value (mgKOH/g) : 25-45
Peroxide value ($meqO_2/g$) : <6.0
Alkaline impurities (ppm NaOH) : <80
Water content (%) : <0.5
Free glycerol content (%) : <3.0

Sulphated ashes content	(%)	:	<0.10
Heavy metals	(ppm Pb)	:	<10

Fatty acids compositions (%)

Caprylic acid (C_8)	:	<3
Capric acid (C_{10})	:	<3
Lauric acid (C_{12})	:	4-14
Myristic acid (C_{14})	:	2-12
Palmitic acid (C_{16})	:	32-42
Stearic acid (C_{18})	:	37-47

Storage conditions : It should avoid from air, light, heat and moisture and keep in tight, light resistant and well closed container.

Toxicity : Oral ingestion (rat) > 18g/Kg

Applications : It could be utilized as excipient in HGC, especially, as bioavailability regulator.
- Increase absorption and bioavailabilty improvement.
- Protective action against oxidation and hydrolysis.
- Handling of low dose and highly toxic drug.
- Converting liquid nature substance to solid form.
- Sustained release formulation.

Gelucire 50/13 (G50/13).

Chemical definition: saturated polyglycolyzed glycerides: specific mono, di and triglycerides and polyethylene glycol mono and diesters.

Physical characteristics:

HLB value : 13
Appearance : waxy solid
Odour : faint
Drop point (Mettler method): 46.0-51.0 °C
Colour (Gardner scale) : < 5
Solubilities (at 20°C):

Solvent	Soluble
96 % Ethanol	Insoluble
Chloroform	Soluble
Methylene chloride	Soluble
Purified water	Dispersible
Mineral oils	Insoluble

Chemical characteristics:

Acid value (mgKOH/g) : <2.00
Saponification value (mgKOH/g) : 67-81
Iodine value (gI_2/g) : <2
Hydroxyl value (mgKOH/g) : 36-56
Peroxide value ($meqO_2/g$) : <6.0
Alkaline impurities (ppm NaOH) : <80
Water content (%) : <0.5
Free glycerol content (%) : <3.0

Sulphated ashes content	(%)	:	<0.10
Heavy metals	(ppm Pb)	:	<10

Fatty acids compositions (%)

Caprylic acid (C_8)	:	<3
Capric acid (C_{10})	:	<3
Lauric acid (C_{12})	:	<5
Myristic acid (C_{14})	:	<5
Palmitic acid (C_{16})	:	40-50
Stearic acid (C_{18})	:	48-58

Storage conditions : It should avoid from air, light, heat and moisture and keep in tight, light resistant and well closed container.

Toxicity : Oral ingestion (rat) > 20g/Kg

Applications : It could be utilized as excipient in HGC, especially, as bioavailability regulator.
- Increase absorption and bioavailabilty improvement.
- Protective action against oxidation and hydrolysis.
- Handling of low dose and highly toxic drug.
- Converting liquid nature substance to solid form.

Gelucire 53/10 (G53/10).

Chemical definition: saturated polyglycolyzed glycerides obtained with hydrogenated vegetable oils consisted of glycerides and polyethylene glycol esters.

Physical characteristics:

HLB value : 10
Appearance : waxy solid
Odour : faint
Drop point (Mettler method): 49.0-54.0 °C
Colour (Gardner scale) : < 5
Solubilities (at 20°C):

Solvent	Soluble
96 % Ethanol	Sparingly soluble
Chloroform	Soluble
Methylene chloride	Soluble
Purified water	Dispersible
Mineral oils	Insoluble

Chemical characteristics:

Acid value (mgKOH/g) : <2.00
Saponification value (mgKOH/g) : 98-112
Iodine value (gI_2/g) : <2
Hydroxyl value (mgKOH/g) : 25-45
Peroxide value ($meqO_2/g$) : <6.0
Alkaline impurities (ppm NaOH) : <80
Water content (%) : <0.5
Free glycerol content (%) : <3.0

Sulphated ashes content	(%)	:	<0.10
Heavy metals	(ppm Pb)	:	<10

Fatty acids compositions (%)

Caprylic acid (C_8)	:	<3
Capric acid (C_{10})	:	<3
Lauric acid (C_{12})	:	<5
Myristic acid (C_{14})	:	<5
Palmitic acid (C_{16})	:	40-50
Stearic acid (C_{18})	:	48-58

Storage conditions : It should avoid from air, light, heat and moisture and keep in tight, light resistant and well closed container.

Toxicity : Oral ingestion (rat) > 20g/Kg

Applications : It could be utilized as excipient in HGC,
Especially, as bioavailability regulator.
- Increase absorption and bioavailabilty improvement.
- Protective action against oxidation and hydrolysis.
- Handling of low dose and highly toxic drug.
- Converting liquid nature substance to solid form.

CHAPTER II

EXPERIMENTAL

Materials

1) Model drug

- Diltiazem hydrochloride (Lot no. R2039901, Distributed by Siam Pharmaceutical Industry Co., Ltd., Thailand)

2) Additive

- C12-18 glycerides fatty acid (Gelucire®50/02, Lot 21289, Gattefose, France.)
- C16-18 glycerides fatty acid (Gelucire®46/07, Lot 13460, Gattefose, France.)
- C16-18 glycerides fatty acid (Gelucire®53/10, Lot 20906, Gattefose, France.)
- C16-18 glycerides fatty acid (Gelucire®50/13, Lot 20529, Gattefose, France.)
- C8-18 glycerides fatty acid (Gelucire®42/12, Lot 14242, Gattefose, France.)
- C8-18 glycerides fatty acid (Gelucire®44/14, Lot 22009, Gattefose, France.)

* All Gelucire® types are described by two suffix number, the first two digit referred to melting point and the last referred to Hydrophile Lipophile Balance (HLB) of each type, respectively.

3) Chemicals

- Hydrochloric acid 37%, sp. gr. 1.18, AR grades (Malinckrodt, USA.)
- Sodium hydroxide pellets (E. Merck, Germany.)
- Ortho-Phosphoric acid 85 %w/w, density about 1.69 g/ml, AR grade (Univar, Ajax Chemicals, Australia.)
- Sodium acetate, AR grades (Farmitalia Carlo Erba, Italy.)
- Dichloromethane (Stabilized) (Malinckrodt, USA.)
- Chloroform (Malinckrodt, USA.)

4) Equipment

- Analytical Balance (Model A200S, Sartorius GmbH, Germany)
- Autopipette and disposable pipettes tip (Pipetman®, Gilson Medical Electronics, France.)
- Dissolution Apparatus (Model DT-6R, Erweka®, USA.)
- Differential Scanning Calorimeter with Thermal Analysis Controller (DSC 7 with TAC 7/DX, Perkin Elmer, USA.)
- Fourier Transform Infrared Spectrophotometer (FT-IR, Model 1760X, Perkin Elmer.Ltd, USA.) with potassium bromide window cell.
- Magnetic Stirrer (Model Nuova 7, Sybron Thermolyne, USA.)
- pH meter (Model 292, Pye Unicam Ltd., England.)
- Scanning Electron Microscope with Cryoscopic Unit (Model JSM–6400 LV, Jeol Ltd., Japan.)
- Ultraviolet-Visible Recording Spectrophotometer (Model UV-160A, Shimadzu. Corp, Japan.)
- Microscope with polarized light filter (MTV 3 Model PM 10-AD) and Camera back 35 mm. (C-35AD4, Olympus Optical Co., Ltd., Japan)
- Glass double chamber apparatus with Water bath
- Shaking water bath (Model TBVS01, Hetomix® and DT Hetotherm®, Heto, Denmark)
- Powder X-rays diffraction (Model JDX-3530, Jeol Ltd., Japan)

Methods

1.Preparation of diltiazem hydrochloride (DTZ HCl) semisolid matrix (SSM) filled in HGC

1.1) Preliminary determination of suitable HGC size and SSM weight in HGC

By using G50/02 as model base, it was heated in the glass double jacket chamber and held at about 60°C (temperature above melting point of G50/02 of approximately about 10° C) and continuous stirring with a magnetic stirrer. The melted base was filled in various sizes of clear HGC (size 0, 1, 2 and 3) at maximum loading in the body part of the capsule and allowed to cool down at ambient temperature until it became solid plug. Each average maximum fill weight was calculated (n=10).

1.2) Determination of suitable active ingredient to thermosoftening base weight ratio

G50/02 was selected as representative thermosoftening vehicles to investigate an appropriate drug to base weight ratio. The target ratios that were observed were 1:1.5, 1:2, 1:2.5 and 1:3, respectively. The preparation of DTZ HCl SSM was followed in the next title below (1.3). Dissolution test was used for screening the optimal drug to base weight ratio to be further investigated in the next experimental section. Furthermore, possibility of liquid filling matrix preparation must be considered as well as drug liberation from semisolid matrix. The formulations of various drugs to vehicles weight ratio are depicted below in Table 5.

Table 5 The composition of DTZ HCl SSM capsule formulas with various drug to G50/02 weight ratios.

Ingredients	Content (mg)			
	R1	R2	R3	R4
DTZ HCl G50/02	90 135	90 180	90 225	90 270
Total fill weight(mg)	225	270	315	360
Capsule size	2	2	2	2
Calculated HLB	2	2	2	2
Ratio between drug : Gelucire 50/02	1:1.5	1:2	1:2.5	1:3

1.3) Preparation of DTZ HCl SSM filled in HGC

DTZ HCl powder was sieved through the screen at meshes number 80 two times before using. Semisolid filling process was done by dispersing DTZ HCl powder into melted Gelucire® in double jacket glass chamber at specified temperature above a melting point of each Gelucire® type approximately 10°C. Stirred to ensure homogeneous dispersion and held for a further 30 minutes at this condition. The mixture in the form of fluid dispersion was transferred to the body of a suitable HGC size by pipette method. The capsule was allowed to cool down at an ambient temperature until it solidified then close the capsule with cap completely and tightly. DTZ HCl SSM capsules were kept in a cool dry place and protect from light during storage. The capsule weights in the range of ± 5 % of initial fix weight were acceptable. Furthermore, any capsules with other defects were also rejected.

In the case of using combination of two Gelucire® type in the formula, the higher melting points base was melted until it became clear fluid and the lower one was incorporated and the liquid was kept clear again then followed the same process as described above.

Various DTZ HCl SSM capsule formulas in this study are described below. In the case of the investigations about the effect of various Gelucire® types on drug release control, the formulas are presented in Table 6.

Table 6 The compositions of various diltiazem hydrochloride SSM capsule formulas in single component bases with different type of Gelucires®.

Ingredients	Content (mg)					
	F1	F2	F3	F4	F5	F6
DTZ HCl	90	90	90	90	90	90
G42/12	180	-	-	-	-	-
G46/07	-	180	-	-	-	-
G44/14	-	-	180	-	-	-
G53/10	-	-	-	180	-	-
G50/13	-	-	-	-	180	-
G50/02	-	-	-	-	-	180
Total fill weight(mg)	270	270	270	270	270	270
Capsule size	2	2	2	2	2	2

Combination of various hydrophilicity (HLB) bases could provide different drug release property. Thus, desirable drug release pattern would be observed from this approach. A sustained or low HLB base was utilized for core material and high hydrophilicity was employed as adjuster in the formulations. Comparison on the effect of combination Gelucires® between fast-promoting and slow-release Gelucire® at various ratios or dual component system, which obtain different calculated HLB are shown in the Tables 7 - 10.

Table 7 The constituent of DTZ HCl SSM capsule formulas with combination of different Gelucires® type at diverse calculated HLB of Gelucire® mixture.

Ingredients	Content (mg)						
	A1	A2	B1	B2	B3	B4	B5
DTZ HCl	90	90	90	90	90	90	90
G50/02	144	72	169	157.5	112.5	67.5	22.5
G46/07	36	108	-	-	-	-	-
G53/10	-	-	11	22.5	67.5	112.5	157.5
Total fill weight (mg)	270	270	270	270	270	270	270
Capsule size	2	2	2	2	2	2	2
Calculated HLB	3	5	2.5	3	5	7	9
Ratio between slow release : fast release Gelucire	4:1	2:3	15:1	7:1	5:3	3:5	1:7

Table 8 The constituent of DTZ HCl SSM capsule formulas with combination of different Gelucires® type at diverse calculated HLB of Gelucire® mixture. (cont.)

Ingredients	Content (mg)						
	C1	C2	C3	C4	C5	C6	C7
DTZ HCl	90	90	90	90	90	90	90
G50/02	172.5	165	135	105	75	45	15
G44/14	7.5	15	45	75	105	135	165
Total fill weight (mg)	270	270	270	270	270	270	270
Capsule size	2	2	2	2	2	2	2
Calculated HLB	2.5	3	5	7	9	11	13
Ratio between slow release : fast release Gelucire	23:1	11:1	9:3	7:5	5:7	3:9	1:11

Table 9 The constituent of DTZ HCl SSM capsule formulas with combination of different Gelucires® type at diverse calculated HLB of Gelucire® mixture. (cont.)

Ingredients	Content (mg)					
	D1	D2	D3	D4	D5	D6
DTZ HCl	90	90	90	90	90	90
G50/02	171	162	126	90	54	18
G42/12	9	18	54	90	126	162
Total fill weight (mg)	270	270	270	270	270	270
Capsule size	2	2	2	2	2	2
Calculated HLB	2.5	3	5	7	9	11
Ratio between slow release : fast release Gelucire	19:1	9:1	7:3	5:5	3:7	1:9

Table 10 The constituent of DTZ HCl SSM capsule formulas with combination of different Gelucires® type at diverse calculated HLB of Gelucire® mixture. (cont.)

Ingredients	Content (mg)					
	E1	E2	E3	E4	E5	E6
DTZ HCl	90	90	90	90	90	90
G50/02	172	163.6	130.9	98.2	65.5	32.7
G50/13	8	16.4	49.1	81.8	114.5	147.3
Total fill weight (mg)	270	270	270	270	270	270
Capsule size	2	2	2	2	2	2
Calculated HLB	2.5	3	5	7	9	11
Ratio between slow release : fast release Gelucire	21.5:1	10:1	8:3	6:5	4:7	2:9

To investigate the effect of drug loading level in slow release Gelucire® (G50/02 as model), the ingredients in formulations are depicted in Table 11.

Table 11 The composition of DTZ HCl SSM capsule formulas with various drug loading levels in G50/02 as slow release thermosoftening base model.

Ingredients	Content (mg)			
	H1	H2	H3	H4
DTZ HCl	30	45	60	75
G50/02	240	225	210	195
Total fill weight (mg)	270	270	270	270
Capsule size	2	2	2	2
Calculated HLB	2	2	2	2
Ratio between drug : G50/02	1:8	1:5	1:3.5	1:2.6

2. Evaluations of DTZ HCl SSM capsule

2.1) Morphology

Organoleptic methods were used to evaluate the surface appearance of SSM capsule by microscope. If they had any defect such as hole, surface cracking then they should be rejected.

In addition microscopic morphology was required. Scanning Electron Microscope (SEM) was used as the investigational tool. Microscopic surface and cross section area of semisolid matrix before and after contact with the dissolution medium was examined. The heat, which was generated from electron beam in SEM apparatus, has an affect on semisolid matrix. Due to thermal sensitivity of semisolid matrix base, cryoscopic method was selected as optimal mode of observation. It consisted of cryoscopic unit attached with normal SEM. Liquid nitrogen was employed as temperature controller, which gave the temperature below 0°C. A sample was sectioned with blade to become a rod shape and

placed on the stub unit with the aid of carbon glue. After that the stub was dipped in liquid nitrogen until frozen and photomicrographed using SEM. For the cross section investigation, freeze fracture mode was choosing. Freeze-semisolid matrix samples was cut along the horizontal plane by cooling blade and take a photograph under SEM as previously described above.

2.2) Quantitative analysis of DTZ HCl contents in SSM capsule

Twenty capsules of DTZ HCl SSM were melted and kept at the constant melting temperature throughout the process. The process melting temperature was equal to a temperature of the preparation process of each formula. The sample preparation should be stirred continuously until it congealed and became solid mixture again at an ambient temperature. The SSM sample was accurately weigh that equivalent to DTZ HCl 45 mg in a 100-ml volumetric flask, then dissolved in dichloromethane by swirling until clear solution had occurred and adjusted to volume with dichloromethane again. One ml of the sample solution was individually pipetted into a 10-ml volumetric flask and make to volume with the same medium. Determination of DTZ HCl content was using UV-VIS spectrophotometer and determining the absorbance of the solution at maximum absorption wavelength of 241 nm with dichloromethane as reference medium and calculated the content from standard calibration curve of DTZ HCl in dichloromethane. Each sample was done in triplicate.

2.3) Dissolution Studies

The samples prepared as described above were examined on the dissolution property. Dissolution studies were performed according to **Diltiazem Hydrochloride Extended-Release Capsule USP 23 Supplement 5 (for products labeled for dosing every 12 hours, Test 1)** to measured a drug release and release characteristics of SSM capsule. Apparatus 2 (paddle) was used at 100 rpm and control the temperature of the medium at 37$\pm$0.5°C. To conform with test 1 in USP monograph as mentioned above, purified water was used as medium. For each test, the suitable capsules with weight variation not exceeding 5% and did not have any defect on the surface was chosen for the investigation.

In order to prevent the floating effect of the capsule which may have an effect on the drug release pattern of SSM capsule, the stainless steel coil was used to sink the capsule to the bottom of dissolution vessel. Sampling time was 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 9, 10 and 12 hours, respectively. At each time interval, the 10 ml of sample solution was withdrawn and filtered through nitrocellulose membrane pore size 0.45 micron to obtain clear solution and discard first 2-3 ml of filtrate and collected the rest. The equal volume of fresh medium was added immediately after each sampling to maintain the constant volume of dissolution medium throughout the experiment. The concentration and content of drug release were calculated from standard calibration curve by UV-VIS spectrophotometer either directly or after appropriate dilution with the fresh dissolution medium. The cumulative percent release of dissolved drug was subsequently determined and the release profiles were constructed from these data.

Tolerances for Test 1 is expressed as the percentage of the labeled amount of $C_{22}H_{26}N_2O_4S.HCl$ dissolved at the specified times that conform to acceptable criterion which are given below.

Time(hours)	Amount dissolved
3	between 10% and 25%
9	between 45% and 85%
12	not less than 70%

Further dissolution study was performed to determine the effect of continuous pH change as a function of time on the release of preparation. When the drug release study in purified water medium was completed some of DTZ HCl SSM formulas that follow a criteria in the **Diltiazem hydrochloride Extended-Release Capsule USP 23 Supplement 5 (for products labeled for dosing every 12 hours, Test 1)** was selected to examine in further pH change study.

The pH change systems were described below. The settings and parameters of dissolution were the same as the previous study but different in the type of medium used. Instead of purified water, 0.1 N hydrochloric acid with 0.05-M phosphoric acid and sodium acetate pH 1.2 was substituted. The initial volume of dissolution medium was set as 900 ml. A pH modification was made after 1 hr for the intermediate pH 4.5 and after 2 hrs for

the final pH of 7.0 and kept it throughout the experiment. 4 N sodium hydroxide solution was used to adjust the pH of medium in this study (Amighi and Moes, 1995).

Ten ml of samples were removed and equal volume of each fresh media were substituted immediately at each predetermine time interval of 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 9, 10 and 12 hrs, respectively. For determining the amount of drug release, the same method as previously describes was used. Standard calibration curve of DTZ HCl in each pH medium was utilized for calculation. Due to pH adjustment, cumulative correction factors of volume changing were concern to modify the cumulative drug release content.

2.4) Physical stage of active compound in SSM study

An observation of crystal habit of active ingredient in SSM after melt-processes were necessary to evaluated drug release mechanism and used to confirm possibility of substances interaction. The method that used in this study was modified from the basis of absorption properties of oil, melted wax or fat include another glyceride derivatives.

Indirect method, approximately 100 mg of milled preparations were weighed and placed on filter paper and incubated in hot air oven at 70°C for 1 hr. The remaining solid on the filter paper was collected and observed under microscope in the normal and polarized light condition. Photomicrograph of remained solid particles was taken and compared with various bases in the same light conditions.

2.5) Thermal analysis

Differential Scanning Calorimeter was widely used to determine an interaction of materials. In this study, DSC was main method to evaluate an interaction of base-base or drug-base of SSM.

DTZ HCl powder, pure Gelucire® base, mixture of Gelucire® base and milled preparations were weighed into aluminum pan in range of 2, 6 and 7 mg, respectively. DSC sample pans were sealed with aluminum piece by hermetically sealer and placed in sample holder of DSC 7 equipment and a reference pan was used for reference. Nitrogen gas was

used as carrier gas for preventing sample oxidation at flow rate 20 ml/min. Thermal increment cycle consist of two steps. Holding cycle, sample was equilibrated at 0°C for 1 min and starts the next cycle or heating cycle immediately. The rate of temperature increment in heating cycle was 10°C per min. The terminal temperature of sample and Gelucire® base was 240°C and 100°C, respectively. Thermogram of each sample was collected and compared the heat flow pattern including heat of fusion or enthalpy changing values.

2.6) Infrared spectroscopy analysis study

Infrared (IR) spectroscopy was used to confirm the interaction between drug and other excipients. The interaction of materials might observe from the IR-absorption spectra. If the change in the IR spectra were observed, it could be infer that chemical interaction between substance was occur.

Fourier transform IR spectroscopy (FT-IR) was the new generation instrument of IR spectroscopy. It had advantages to record the signal with high sensitivity and modifying the noise of experiment run.

According to physical properties of thermosoftening bases, which presented as semisolid stage; a co-grinding method, sample and potassium bromide (KBr), was not suitable for sample preparation since it was very sticky. Hence, the sample was prepared by alternative method as film technique. This technique was proper for semisolid materials. The sample was dissolved in volatile organic solvent at appropriate concentration and deposit on (KBr) window as thin film. Coated film on the window must be clear enough for IR beam transmission.

Samples were weighed about 50 mg and dissolved in approximately 2 ml of chloroform. The sample solutions (1-drop) were transferred on KBr window and allowed to become clear thin film coated on the window under vacuum. IR spectrum was investigated in the wave number range between 400 to 4,000.

2.7) Determination of DTZ HCl solubility

Solubility studies of DTZ HCl was performed in various dissolution media. The interesting media in this experiment were purified water and three types of buffer solution in various pH values (pH 1.2, 4.5 and 7.0). Excess amount of DTZ HCl, approximate about 2 g, was placed in 15-ml glass screw cap tube with desired medium (1.5 ml). The suspension was shaken in a shaker water bath at 60 rpm, 37±1°C for 12 hrs. Clear supernatant of saturated drug solution was withdrawn and filtered through 0.45-micron cellulose nitrate membrane. Suitable dilution of filter portion was done in each medium and assayed by UV-VIS spectroscopy as the same manner. The samples were done in triplicate.

2.8) Powder X-ray diffraction.

One of the most valuable analytical methods to determine crystal property was powder X-ray diffraction. It was an analytical tool for indicating crystal structure and atomic arrangement of drug molecule. The diffractogram was, furthermore, presented the specific fingerprint for each molecule which diffracting and scattering at specific angle 2θ. Degree of crystallinity of sample was shown in tracing. Moreover, it could be employed for observing the interaction of each component in sample.

X-ray diffractogram of DTZ HCl powder, G50/02 and SSM preparation with G50/02 were obtained. Specific scattering angle 2θ and interplanar spacing (d) were collected.

The sample were milled into smaller size and firmly packed in the sample holder in order to prevent the preferred orientation effect. Sample surface should be smooth after pressing for reproducible experimental run. The observation of X-rays diffraction pattern was in the range of 5 to 45° 2θ with scanning speed of 6° per minute at room temperature. X-ray source was nickle filter CuKα radiation generated at 45 kV and 35mA.

2.9) Data Analysis

In spite of general criterion to determine suitable drug to base weight ratio, in this research was monitored deal with relationship between percent cumulative drug release and time functions. According to uncontrollable constant surface area of matrix device in different drug to base weight ratios, another parameter was employed instead of percent cumulative drug release. Normalized parameter, flux (J), was a choice and obtained by calculating extent of drug release per unit area and time in $mg.cm^{-2}hr^{-1}$ unit. Flux-time curves were investigated at each drug to base weight ratios.

The use of mathematical equation to explain drug release mechanism had generated more interesting approach as a potential drug release predictor. The influence of drug loading level was performed with mathematical model for determining release-controlled mechanism over wide range of loading level. The profiles of percent drug release against time were performed and using multiple linear regression method with SPSS 7.0 computed-statistical program for describing constant value that imply to a term of each controlled mechanism. Simple equation model was based on combination of Fickian diffusion and case II transport or dissolution/erosion controlled mechanism (Peppas and Sahlin et al., 1989). This equation is treated as equation 8 in previous chapter.

$$M_t/M_\infty = A+k_1t^n+k_2t^{2n}$$

Where M_t and M_∞ is amount of drug release at time t and maximum amount of drug release at infinite time, respectively. k_1 and k_2 are rate constant of diffusion and case II transport mechanism or model coefficient, respectively. n is power component and A is constant value.

Moreover, indication for n value in above equation was dependent upon aspect ratio of matrix device. The calculation on aspect ratio matrix device is explained in Appendix B. Statistical analysis, ANOVA or F-test was represented as a part of statistical tool in multiple linear regression at 95% confidence interval ($\alpha = 0.05$). The statistical results were gain in k_1, k_2 and A value with significant indicating value of each variable (p value). Data

interpretation was implied with higher value on k_1 or k_2 as predominant mode of drug release mechanism.

Data treatments in the mixture between slow and fast release thermosoftening bases were established. Many studies attempted to use flexible parameter as framework for correlates the best relationship. For example, $t_{x\%}$ was a most popular variable to employ as forecasting parameter which mean to the time for fix % drug release such as $t_{50\%}$ (time to 50% drug release). Although $t_{x\%}$ was well known approach but they are not probably the appropriate description parameter. Another flexible parameter was rate constant of drug release. Several research usually employ rate constant value of individual dissolution profile to compare or find out the relationship. The disadvantage of this approach was the unidentical drug release mechanism of each profile. Thereby, it could lead to poor interpretation or comparison. Mean dissolution time (MDT) was introduced to overcome the previous problem as mentioned above. MDT was the parameter that all part of dissolution profile was governed in the calculation. Exactly MDT value was obtained from at least 7 to 8 calculating method. The advantage and disadvantage of each method was reviewed (Podczeck, 1993). Trapezoidal of area between curve (ABC) was one of the most widely used as computing procedures of MDT determination (Brockmeier and Hattingberg, 1982).

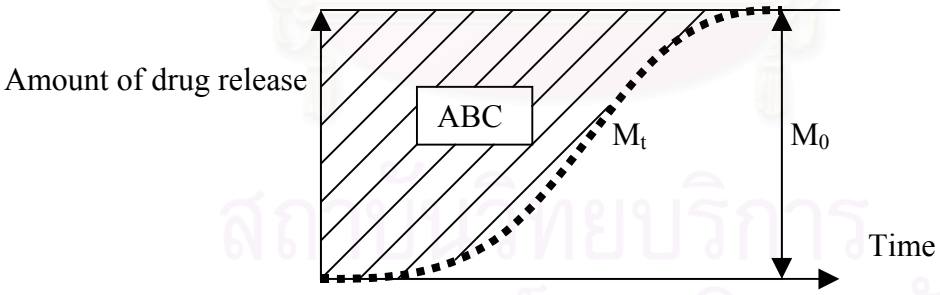


Figure 8 Diagrammatic of dissolution profile for explaining MDT calculation. ABC is area between upper line (M_0) and dissolution curve, M_0 is maximum drug release at infinite time and M_t is amount of drug release at any time t.

The computation of MDT was performed and ascribed in equation 12:

$$MDT = \frac{ABC}{M_0} \quad \ldots(12)$$

ABC was calculating indirectly way by subtracting total area (M_0 multiplied with time function) with area under dissolution curve (AUC). Area calculation was utilized trapezoidal method by integrating each time interval area.

The relationship between MDT value and calculated HLB of each mixture Gelucire® base were constructed. Linear regression, correlation of determination (r^2), was utilized for indicating the relation between both parameters.

In these studies, indication of different dissolution profiles was more important and essential. The indication of different dissolution profile was tough to justify by using only visual observation from dissolution pattern comparison. Clarification judgement for separated unidentical dissolution profiles were to used efficient parameter. In recent years, SUPAC-IR guideline was developed the parameter for measure the difference between dissolution curves as dissimilarity factor "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 sustained release dosage form was applicable to utilize both parameters (Pillay and Fasssihi, 1998). The success of an alternative method, dissimilarity and similarity factor, was finally accomplished. Both parameters are calculated from the following equations (Shah et al., 1998) .

$$f_1 = \{[\sum_{i=1}^{p} | \mu_{ti} - \mu_{ri} |] / [\sum_{i=1}^{p} \mu_{ri}]\} \times 100 \quad \ldots(13)$$

$$f_2 = 50 \log\{[1+(1/P)\sum_{i=1}^{p}(\mu_{ti} - \mu_{ri})^2]^{-1/2} \times 100\} \quad \ldots(14)$$

Where μ_{ti} and μ_{ri} represent mean cumulative dissolution measurement at P time of test and references preparations 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 could be implied to similar factor. If the two dissolution profiles are identical then f_1 is equal to 0 whereas f_2 is near to 100. Thus, similarity of dissolution pattern is indication of the lowest values in f_1 and highest values in f_2 variable.

Furthermore, unequality between dissolution profile was determined as values for displaying the magnitude of difference. Percent average difference which calculated from equation 15 is invaluable parameter for above proposed. The example of various percent averages difference and limit of similarity factor is shown in Table 12. If the result data of similarity factor could be obtained then percent average difference was calculated from equation 15. The higher percent average difference show about numerous unlikable.

$$f_2 = 50 \log\{[1+(\text{percent average difference})^2]^{-1/2} \times 100\} \quad \ldots(15)$$

Table 12 Average percentage difference and similarity factor "f_2" relationship between 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 15:

CHAPTER III
RESULTS

1.Preparation of DTZ HCl SSM filled in HGC

1.1) Preliminary determination of suitable HGC size and SSM weight in HGC

Various sizes of clear capsule container, body part, were filled with molten G50/02 at maximum level equal to the edge by using a pipette and record the weight. Maximum filled weight was represent as parameter for indicating the proper target fill weight of SSM capsule. Maximum fill weight values are presented in Table 13 and Figure 9.

Table 13 Maximum fill weight of matrix in diverse size of hard gelatin capsule shell.

Capsule size	Maximum fill weight (mg)*
0	658.6
1	483.15
2	367.35
3	280.15

* Data are shown as mean values (n=10)

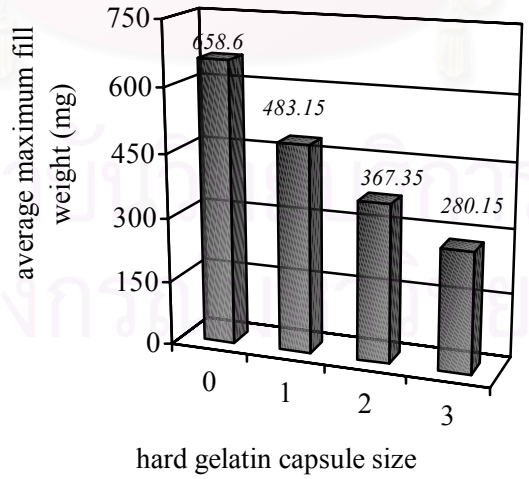


Figure 9 Maximum fill weight of SSM in various sizes of capsule shell.

In general, important factors in HGC formulation are the size of capsule shell and weight of the mass in capsule. Especially, semisolid matrix or liquid filling formula lacks the compressibility of inner mass in capsule when compare with solid powder. The density of the matrix is considered to be a “true density”. A weight and volume of formula are related and appropriate with the free space in the capsule shell.

Preliminary determination of HGC size and SSM weight study showed that capsule shell size 2 was suitable as a container since it was easy to swallow by oral administration. Moreover, pipette filled method used in this experiment applied as a transferring tool with a good precision to control the matrix weight in size 2 capsule. The maximum filled weight in empty capsule size 2 had approximately average weight about 367 mg (Figure 9). In later formulation design, the target weight of SSM should be less than the maximum filled weight because it has to be a free space or weight for other formula modifiers. Therefore, clear capsule shell size 2 was used throughout the experiment.

1.2) Determination of suitable active ingredient to thermosoftening base weight ratio

An attempt to find out the proportion of drug to base weight ratio was the most important goal to achieve a suitable drug release pattern. So the characterizations of in vitro dissolution-time curves were used to evaluate. The dissolution profiles of DTZ HCl SSM preparations with G50/02 at different drug to base ratios are shown in Figure 10. Normally, the dissolution rates of different drug to base ratios with constant initial drug loading level depend on the base content.

Interestingly, surface area of matrix device at each ratios was found to changed due to the change in the target fill weight which depends upon the formula ratio as well as affecting the drug release characteristics. Surface area of various drug to base weight ratios were calculated along with each geometry dimension (Appendix B). The data are shown in Table 14. Furthermore, aspect ratios are introduced. It is related to method of predicting drug release mechanism.

Aspect ratio = 2a/l

Whereas a is the radius of the cylinder or 2a is the diameter and l is the length of device.

Both surface area and aspect ratio values are displayed in Table 14.

Table 14 Surface area and aspect ratio of various drugs to thermosoftening base ratios.

Formula	Drug : bases ratio (DTZ HCl:G50/02)	Surface area (mm^2)	Aspect ratio
R1	1:1.5	*	*
R2	1:2	1.94	0.52
R3	1:2.5	2.26	0.45
R4	1:3	2.59	0.40

* The R1 formulation can not be prepared as SSM capsule.

The suitable ratios between DTZ HCl and thermosoftening base were necessary to act as a guide for the other SSM formulations. The study of drug to base ratios revealed that 1:2 ratio seemed to be the best proportion for controlling drug liberation at constant rate. Although cumulative drug release content and time profile was widely used to indicate drug release pattern (Figure 10). It was not effective enough to compare the differences in drug liberation among each formula. Variation of drug to base ratios study led to the change in surface area of device due to unequal target weight of each proportion which must be filled into fixed space of same size capsule shell. From above reason, it is related only to the height of the matrix plug. Thus, a normalized pattern was considered for drug release comparison. Modification of dissolution data (drug release value) was transformed to a unique standardization. Flux (J) was chosen as normalized parameter. Flux is amount of drug release through matrix per unit time and surface area. The relationship of J, time and drug to base weight ratios are constructed and presented

in Figure 11. It was utilized as selection criteria to find a suitable drug to base weight ratio and employed in the formulation design on the next study.

Dissolution data and flux relationship of 1:1.5 ratio (R1) was not displayed because it was suitable to be prepared in SSM capsule. In R1, a solid content was concentrated and solidified very fast. It could not be transferred into the capsule shell. Another reason was the rheological properties of SSM. The incorporation of particulate powder at high level would increase the viscosity and was impossible to fill in the capsule.

Focus on the flux and dissolution data of another drug to base weight ratios, they showed that flux of 1:2 ratio (R2) reached a steady state (flux constant) after forth hour of the experimental run. Meanwhile 1:2.5 and 1:3 levels provided the declining of flux after third hour. Initial phase or early stage of run (1^{st} to 3^{rd} hour), however, flux of all formulation would increase because the system was not at equilibrium. Further evaluation was the model-fitting test. Three types of drug release kinetics were selected. Zero-order, First order and Square root of time (Higichi diffusion model) are the most popular to predict the main mechanism of drug release. Correlation of determination (r^2) value is used to judge the predominant mechanisms of drug liberation. Zero order model is the most desirable pattern for drug formulation since it was time independent system and gave constant drug release rate. The study expressed that R2 formulation had closely related to zero order with $r^2 = 0.9977$ while 1:2.5 and 1:3 drug to base weight ratios were mainly correlated to first order kinetic with r^2 0.9981 and 0.9992, respectively (Table 15). Therefore, R2 formula was the best drug to base weight ratio that provided constant release rate. Finally, DTZ HCl SSM at 1:2 drug to base weight level was utilized as model on the next study. Furthermore, the filling weight was equal to 270 mg due to appropriate drug to base weight ratio (1:2).

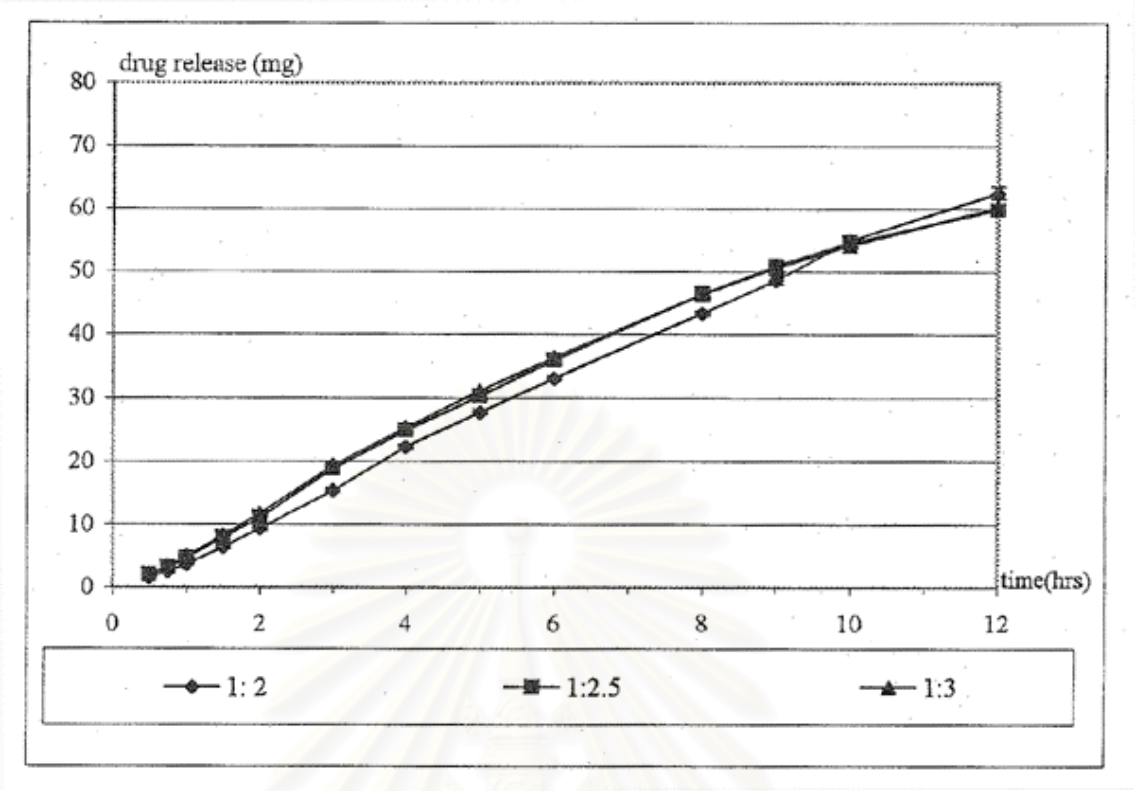


Figure 10 Dissolution time-release profiles of diltiazem hydrochloride semisolid matrix of G50/02 at various drug to base weight ratios.

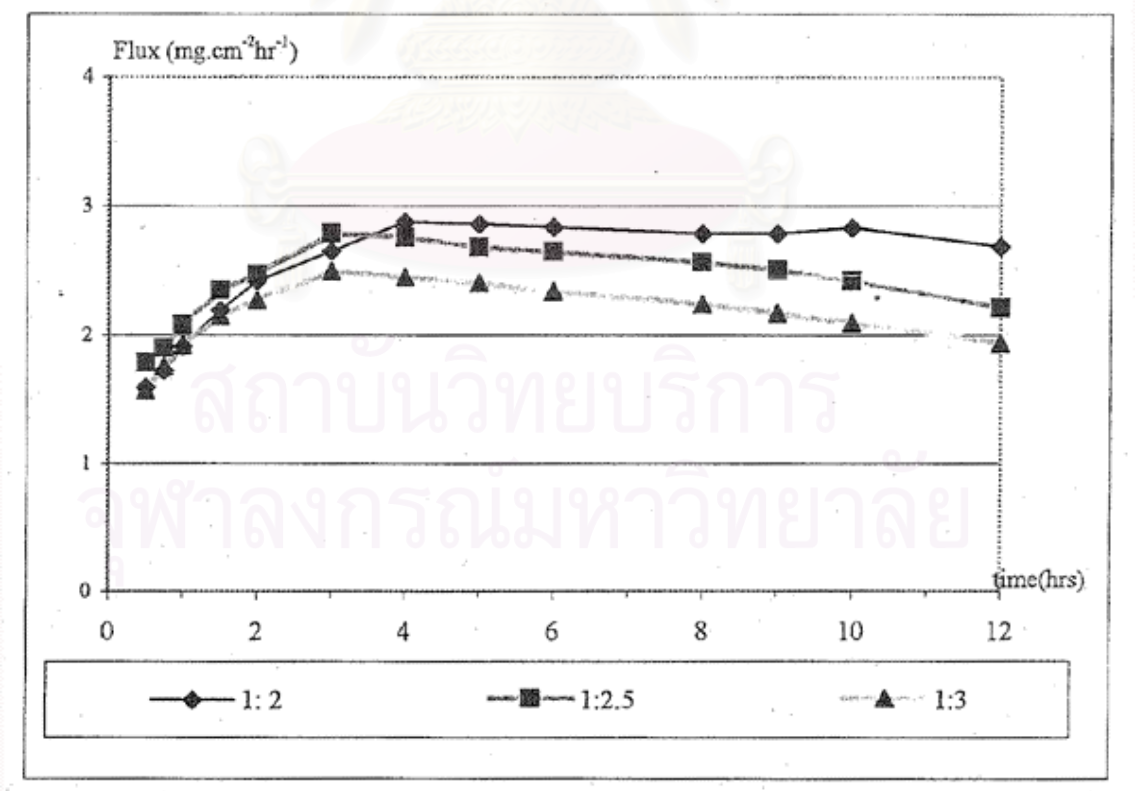


Figure 11 Relationship between flux and drug to base weight ratios of diltiazem hydrochloride to G50/02 semisolid matrix preparations.

Table 15 Correlation of determination values (r^2) of DTZ HCl SSM preparation with G50/02 at various drug to base ratios under assumption of three drug release mechanisms.

Drug to base ratio	Correlation of determination values (r^2)		
	Zero order	First order	Square root of time
1:2	0.9977	0.9865	0.9694
1:2.5	0.9874	0.9981	0.9839
1:3	0.9867	0.9992	0.9868

1.3) Dissolution study of 90-mg DTZ HCl SSM capsule with different thermosoftening bases

The observation of drug to base weight ratios were studied. The results indicated the proper ratio at fixed level of active material in the system. In addition, effect of drug loading level in G50/02 could be studied from drug release pattern of each investigation level. The dissolution-time profiles are expressed in Figure 12.

It was known that increasing in drug loading should directly affect the to percent of drug release. Rigid matrix of G50/02 SSM at different amounts of drug content exhibited nearly similar dissolution profiles. Additional evaluation method was employed to clarify this phenomenon. Combination of mathematical equation of dissolution and fickian diffusion phenomena was a valuable tool to indicate the key factor in release pattern.

Above mentioned equation was based on the simple and empirical mathematics equation which proposed by Peppas (1989) and explained by data analysis section in chapter II. In previous section, the importance of matrix surface area was described as the influential factor in predicting by this model. Assumption was made that the cylinder shape of the device could be used to define the power exponent although the real shape of the SSM fill in HGC were not cylindrical. The power (n) value for cylinder shape of SSM preparation at 1:2 drug to base weight ratio which had aspect ratio (2a/l) of approximately 0.52 was 0.44 (see further information in Peppas et al,

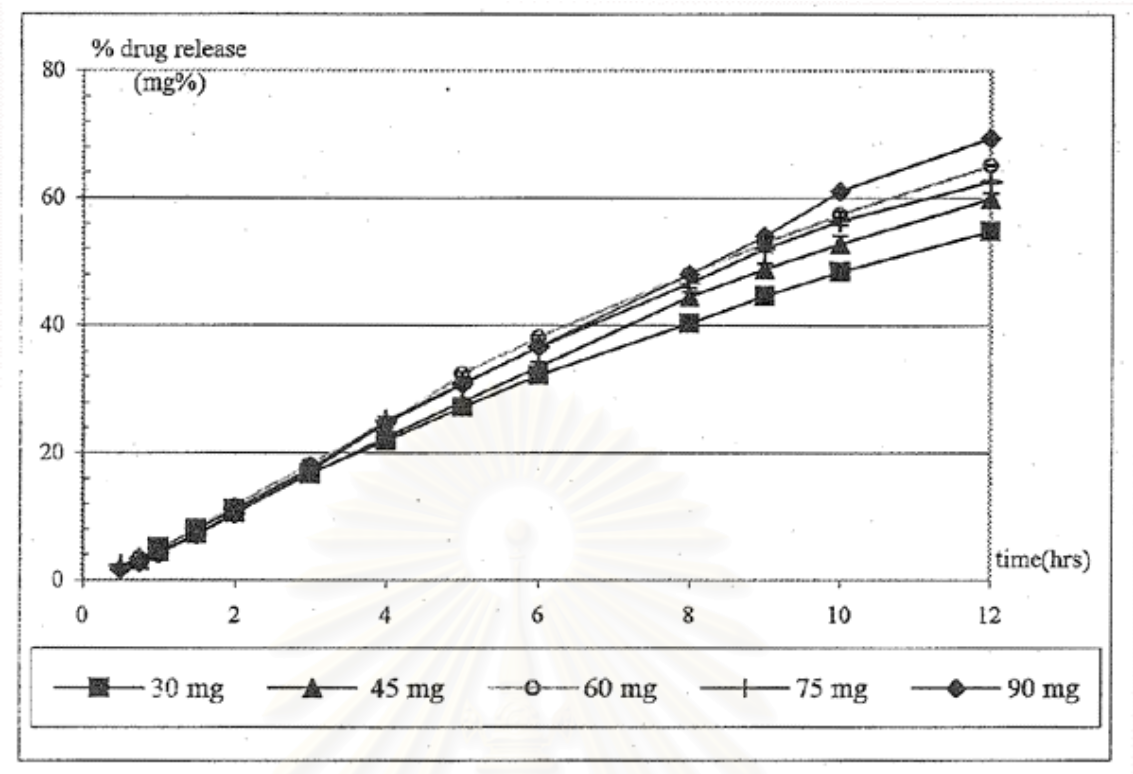


Figure 12 Dissolution profiles of diltiazem hydrochloride semisolid matrix with single G50/02 at different drug loading levels.

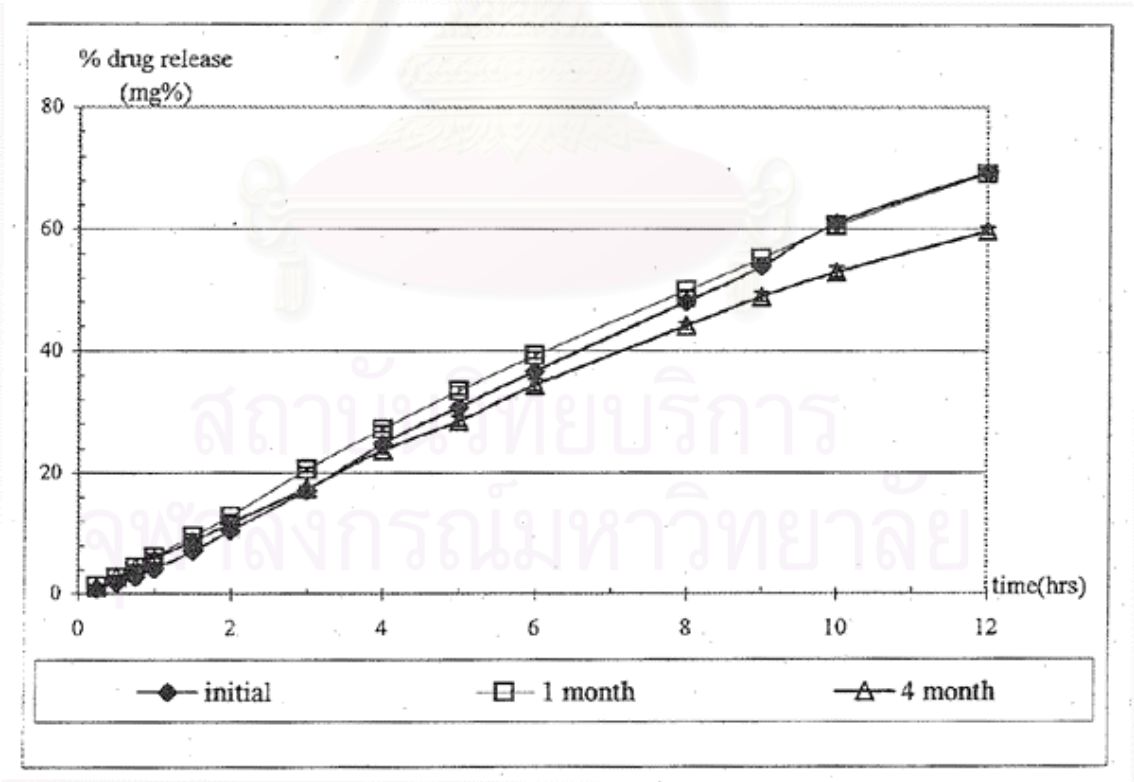


Figure 13 Dissolution profiles of diltiazem hydrochloride semisolid matrix with single G50/02 at 90 mg loading level with effect of storage time after preparation.

1989). Dissolution data of various drug loading levels should change according to this mathematical equation. Mathematical model fitting provides the release constant or model coefficient. Linear correlation of model dependent using multiple linear regression analysis was employed. The diffusion, case II transport or polymer relaxation rate constant (k_1 and k_2) and ratio k_2/k_1 of each loading level are exhibited in Table 16.

Table 16 Model coefficients calculated from dissolution data of DTZ HCl in G50/02 at various drug loading levels.

Formulation	Loading level (mg)	Model Coefficient			k_2/k_1 ratio
		A	k_1	k_2	
H 1	30	-0.0950	0.100	0.0393	0.3932
		(0.009)	(0.010)	(0.030)	
H 2	45	-0.0730	0.0580	0.0572	0.9855
		(0.017)	(0.019)	(0.005)	
H 3	60	-0.0680	0.0471	0.0684	1.4544
		(0.013)	(0.016)	(0.004)	
H 4	75	-0.0390	0.0160*	0.0684	-
		(0.010)	(0.013)	(0.004)	
H 5	90	-0.0310	0.0200*	0.0910	-
		(0.014)	(0.017)	(0.005)	

- * p value < 0.05 , The data are displayed as mean ± SEM (n=3)

The result from model fitting indicated that at low concentration (30 mg level) of drug in rigid mass demonstrated that diffusion was the main mechanism which k_1 was higher than k_2 and the k_2/k_1 ratio was lower than 1. Meanwhile intermediate drug concentration presented that dissolution/erosion or case II transport phenomena was a predominant release mechanism by observing the k_2/k_1 ratio as higher than 1. Furthermore, at 75 and 90 mg drug loading levels, diffusion constant (k_1) were lower than k_2 and also not significant at 95% confidence interval. In this case, the result indicated that dissolution/erosion mechanism seemed to be remarkable. Both diffusion

and dissolution/erosion mechanisms were playing an equal role for explaining the release profiles at intermediate drug loading level.

From the above reasons, it could be concluded that drug concentration in SSM mass played an important role to control drug release.

In addition, storage assayed at predetermine interval of aging condition of DTZ HCl SSM in G50/02 must be considered. At fixed drug loading level (90 mg), the results for the dissolution profiles indicated the optimal storage time at an ambient condition which could be used as the criteria for dissolution test of other preparations.

The dissolution profiles at different storage times were separated into two sets. The results are presented in Figure 13. In 1 week to 1 month of storage times, both profiles were closely similar while at 4 months the slower dissolution profile was obtained.

Determination of dissolution curve difference would be performed by using similarity factor. By using 1-week storage preparation as the reference, f_1 and f_2 of each storage times are computed and presented in Table 17. Furthermore, average percentage differences between the aging times are also provided in the same Table. Considerations of percent difference of dissolution profiles was used to compare with the standard value in Table 12 to indicate the difference between dissolution profiles.

Table 17 Dissimilarity factor, similarity factor and average percentage difference among DTZ HCl SSM with G50/02 dissolution profile under aging condition.

Aging condition (month)	Dissimilarity factor "f_1"	Similarity factor "f_2".	Average percentage difference*
1	6.36	83.04	1.94
4	11.70	68.33	4.18

* Calculated bases on 1-week storage preparation as reference.

Table 18 Model coefficients calculated from dissolution data of DTZ HCl in G50/02 in different storage time at an ambient condition.

Storage time	Model Coefficient			k_2/k_1 ratio
	A	k_1	k_2	
1 week	-0.0310	0.0200*	0.0910	-
	(0.014)	(0.017)	(0.005)	
1 month	-0.0270	0.0142*	0.0789	-
	(0.006)	(0.008)	(0.003)	
4 month	-0.0280	0.0265	0.0632	2.3848
	(0.008)	(0.010)	(0.003)	

- * p value < 0.05 , The data are displayed as mean ± SEM (n=3)

Aging times of G50/02 matrix demonstrated significant differences in drug release profiles. As a function of time, rigid matrix of G50/02 decreased the release of DTZ HCl from devices with longer storage time period. Interestingly, storage time at 1-month had not significantly affect the drug release as seen by a high similarity factor and only approximately 2 % average percentage difference. The longer storage period influenced the drug release with of about 4-5 % in average percentage difference. Proposed predominant drug release mechanisms at different storage time are shown in Table 18. It could be seen that 1 week and 1 month storage time, dissolution or erosion played the major role in drug release due to higher k_2 coefficient. On the contrary, 4-month storage time expressed that diffusion mechanism joined with case II transport but very slightly important (k_2 is significant but lower than k_1). Thus, it could be concluded that proper storage time for DTZ HCl SSM preparation prior to performing dissolution test was in the range of 1 week to 1 month at an ambient condition.

To investigate about polymorphic transformation of G50/02 matrix, X-rays powder diffraction was done. Powder X-ray diffractograms of DTZ HCl SSM with G50/02 at different storage times are presented in Figures 14-16. The diffractograms of DTZ HCl SSM with G50/02 was nearly similar to the combination of both fingerprints of each substances and without any chemical interaction.

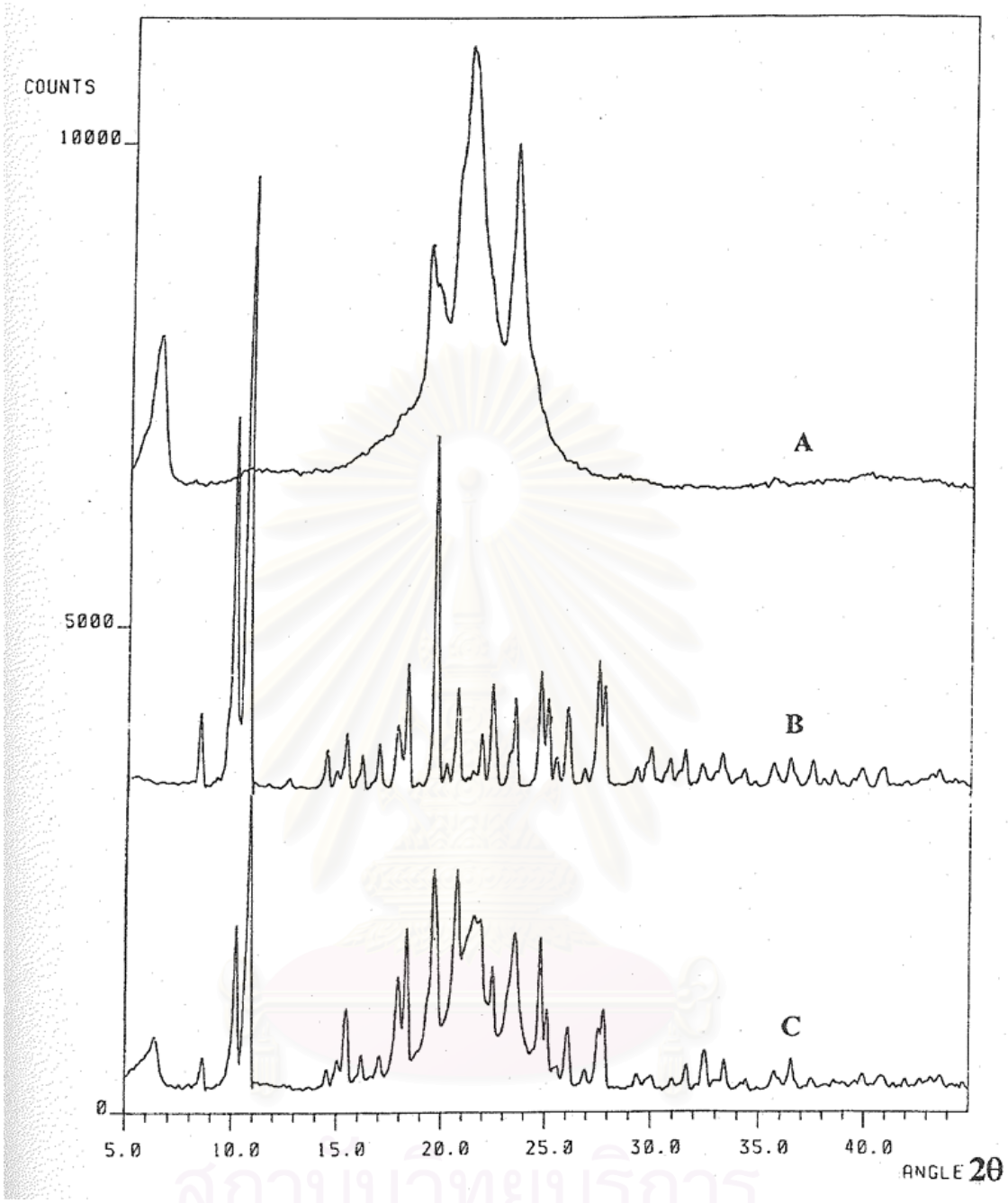


Figure 14 X-ray diffractograms of diltiazem hydrochloride SSM preparation. (A – initial G50/02, B – diltiazem hydrochloride powder and C – SSM preparation of diltiazem hydrochloride in G50/02 base and storage for 1 week after preparation)

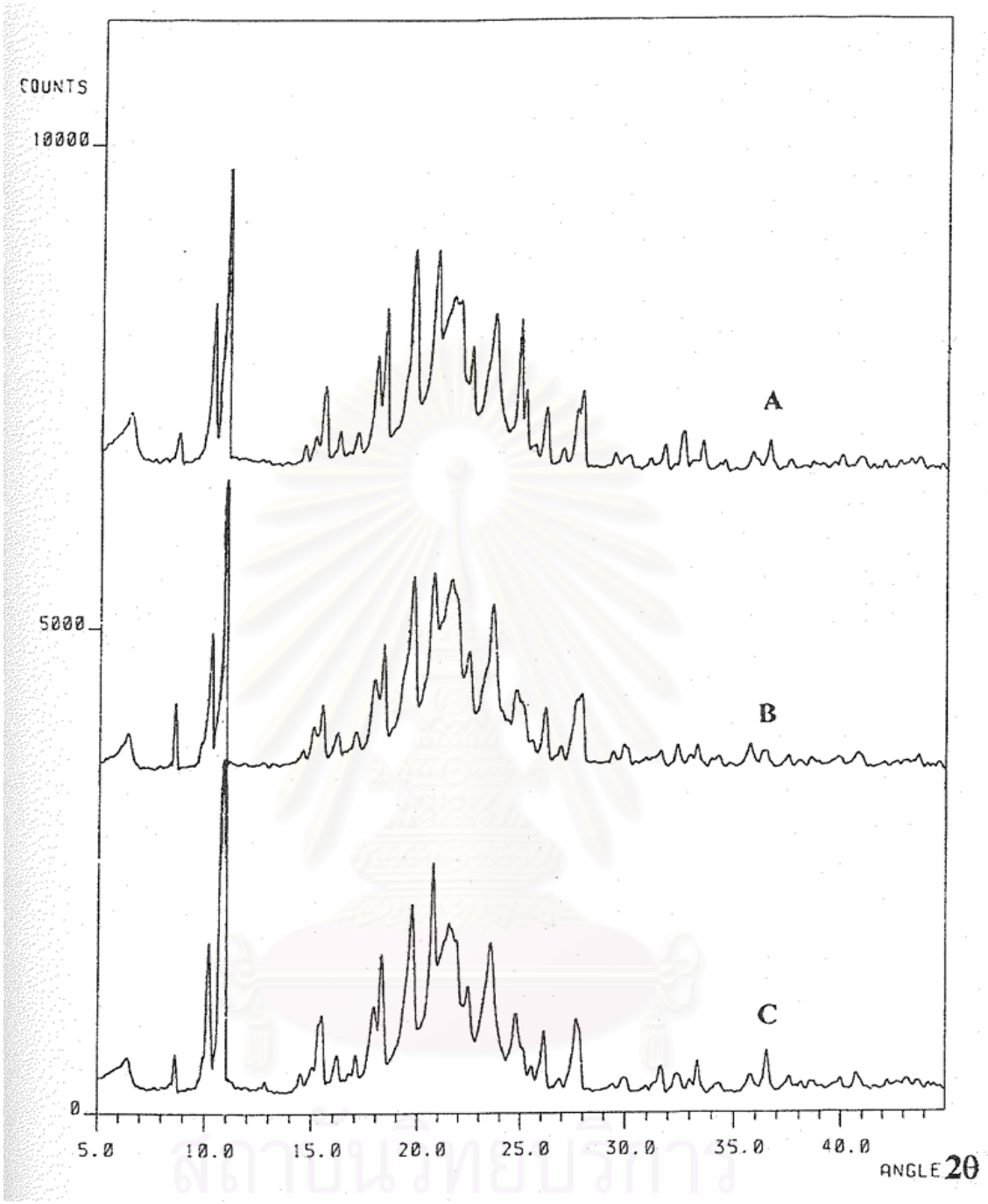


Figure 15 Comparative X-ray diffractograms of diltiazem hydrochloride SSM with G50/02 preparation in various storage times. (A – storage for 1 week after preparation, B – storage for 1 month after preparation and C – storage for 4 months after preparation)

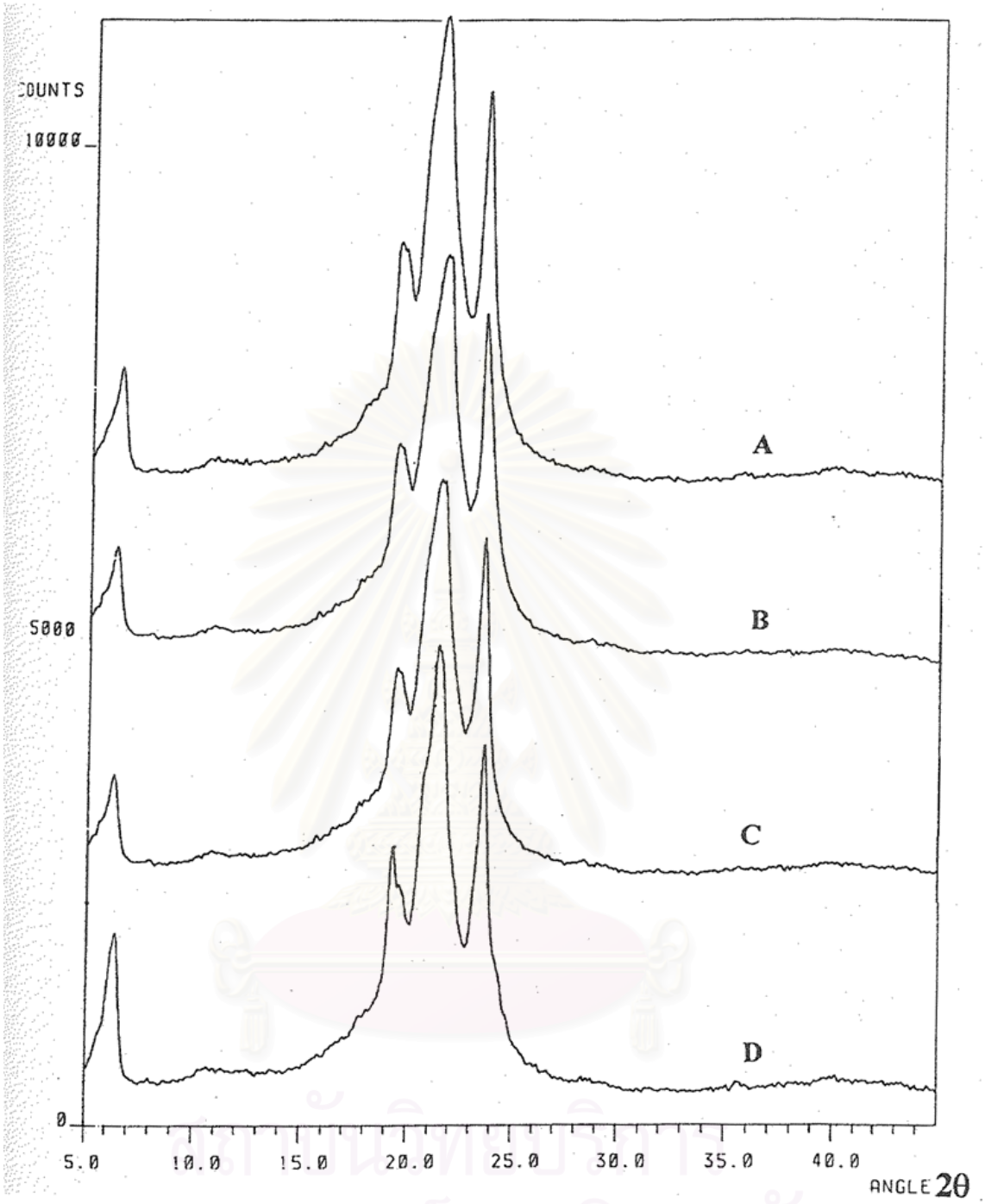


Figure 16 Comparative X-ray diffractograms of pure G50/02 base after passing the preparation process and storage in various times. (A – initial G50/02 without processing, B – storage for 1 week after preparation, C – storage for 1 month after preparation and D – storage for 4 months after preparation)

Comparative X-ray tracing of DTZ HCl SSM preparation after various storage times at an ambient condition are constructed and shown in Figure 15. In addition, pure G50/02 with the same processing as preparation process and storage in different storage times were observed and indicated the critical key factor in drug release (Figure16). Both results showed nearly identical tracing of both pure G50/02 base and DTZ HCl SSM preparations in different storage times.

The formulation of DTZ HCl with several type of thermosoftening bases instead of G50/02 were investigated and each dissolution profiles are shown in Figure 17.

Normally, categorization of thermosoftening bases or Gattefose® wax-like materials are separated as 2-groups depening on HLB value (hydrophile lipophile balance). The lower HLB substances provided sustained drug liberation. The higher HLB, on the contrary, expressed an ability to enhance or improve dissolution of drug particles. In this study, sustained action base was G50/02 whereas all of rest was defined as fast release materials (G42/12, G44/14, G46/07, G50/13 and G53/10).

The dissolution of DTZ HCl in single Gelucires® base with various HLB are presented in Figure 17. It could be seen that higher HLB base provided the fast dissolution while the lower ones gave the slow drug release pattern. The order of water solubility enhancement properties are as follow: G44/14>G42/12>G50/13>>G53/10> G46/07>>G50/02. Degree of hydrophilicity of base played a major role in controlling highly water soluble drug release such as DTZ HCl. Not only degree of hydrophilicity of the base but also melting range of the base must be simultaneously considered. Conclusively, HLB and melting point factors were an important factor in drug release regulation for single component DTZ HCl SSM preparation.

Based on the previous estimation that Gelucires® was able to separate in two different categories. The retardation group and the enhanced water solubility groups, they were combined and explored in the same manner as the pure base cases. Without any doubt, incorporation of faster group into a sustained base (G50/02), the dissolution rate might directly increased proportional to the weight ratio of a mixture base.

In experiment trials, the combination of the thermosoftening vehicles are divided into five groups. Each groups was indicated with desirable HLB that was calculated according to Appendix F. The appropriate amount of mixture could, however, be selected from dissolution assessment to ensure the best drug release pattern. The in-vitro dissolution patterns of various combination sets are depicted in Figures 18-22. Furthermore, comparative dissolution profile of each Gelucire®-mixture groups at the same calculated HLB values are constructed and shown in Figures 23-28.

Combination of different types of Gelucire® promoted the different drug release profiles compared to single Gelucire® matrix. Every mixture types of dual component Gelucires® expressed that increasing the amount of fast Gelucires® also raised the dissolution rate more than G50/02 single component matrix. The mixture bases which had calculated HLB equal to or lower than 7, could be set in rigid cylinder shape device except G46/07 while the higher calculated HLB (above 7) matrices were dispersed or disintegrated in small flake upon each type. From the exception above, G46/07 mixture occurred only at calculated HLB equal to 7 because it had only G 46/07.

In the case of G46/07 mixture, the matrix with calculated HLB 7 values that was composed of only pure G46/07 expressed specific phenomena under dissolution test. In early to middle period of dissolution profile, it was observed that erosion mechanism had taken place and followed with loose agglomeration of some swellable base flakes around the matrix surface in the later phase. Although G46/07 had specific sign, high amount of G46/07 combined with G50/02 did not exhibit the same occurance as mentioned above.

Disintegration effect of matrix base was the main factor for drug release due to surface change. The phenomena starting with peeling of surface matrix and followed by matrix brittleness. Surface area variation led to the uncontrollable fragile matrix pieces. In the high proportion of G53/10 mixture cases, surface alteration effect were still the same. The degree of disintegration directly proportional to the amount of G53/10 in the mixture bases. By observing the dissolution profile of G53/10 mixture and visual observation in dissolution test, it could be seen that above calculated HLB 7, dissolution

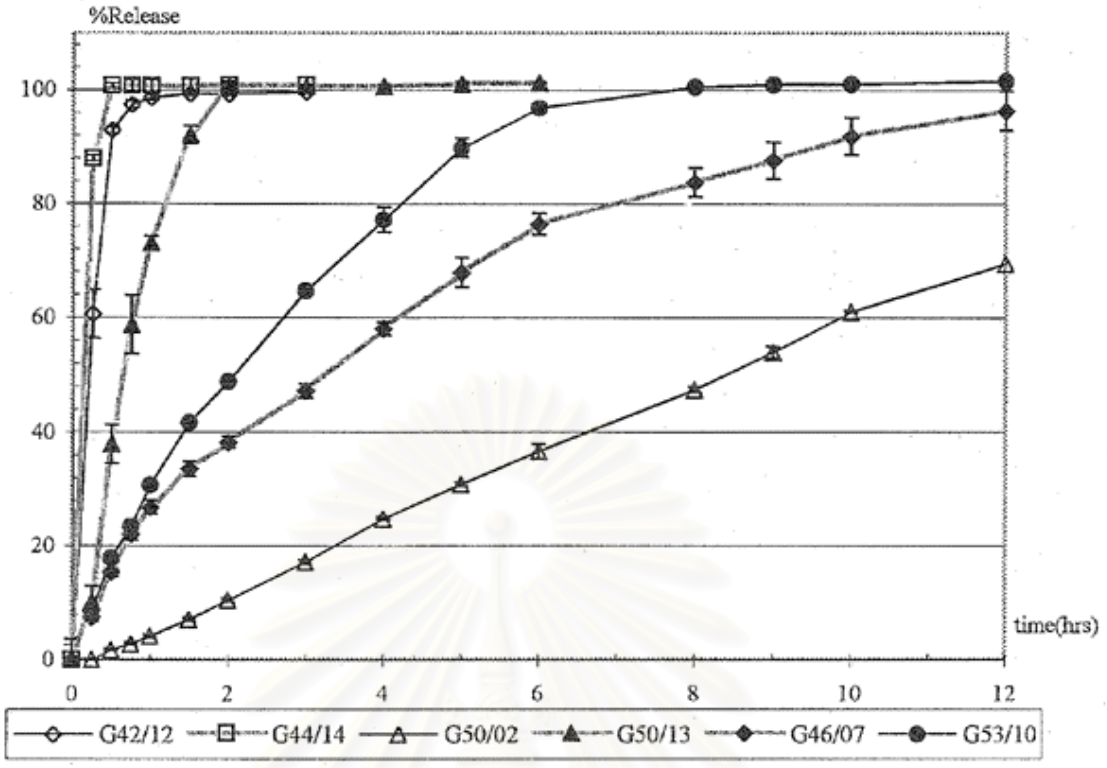


Figure 17 Dissolution profiles of diltiazem hydrochloride semisolid matrix in various Gelucire types.

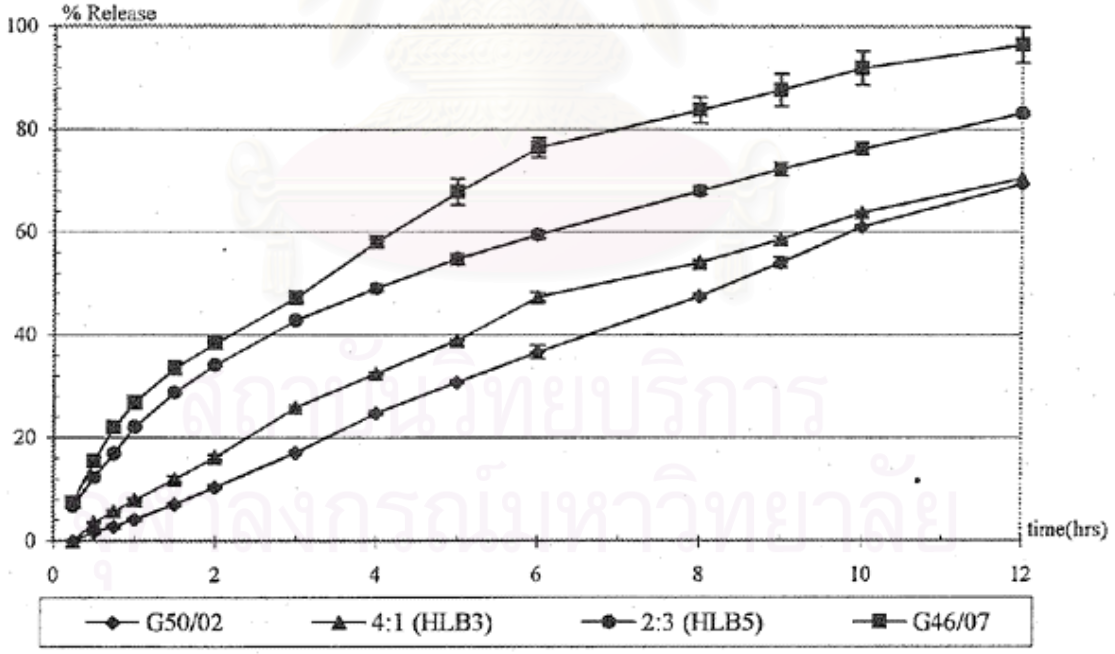


Figure 18 Dissolution profiles of diltiazem hydrochloride semisolid matrix in Gelucire blending between G50/02 and G46/07 at various calculated HLBs.

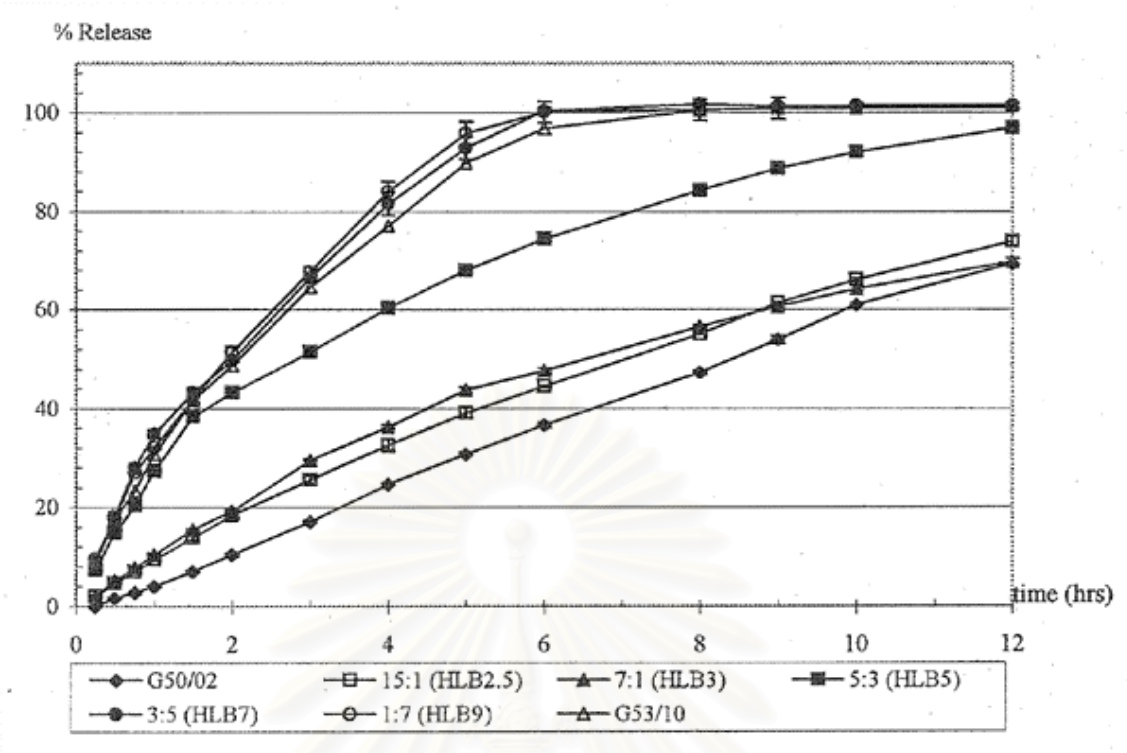


Figure 19 Dissolution profiles of diltiazem hydrochloride semisolid matrix in Gelucire blending between G50/02 and G53/10 at various calculated HLBs.

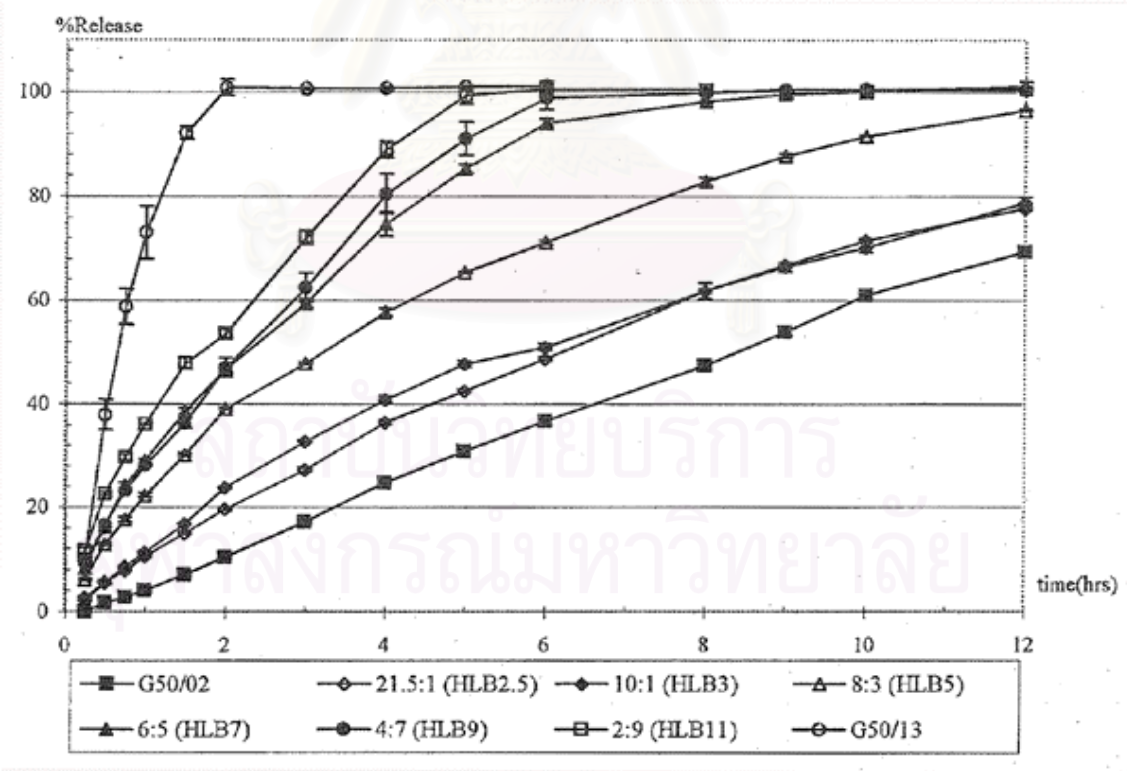


Figure 20 Dissolution profiles of diltiazem hydrochloride semisolid matrix in Gelucire blending between G50/02 and G50/13 at various calculated HLBs.

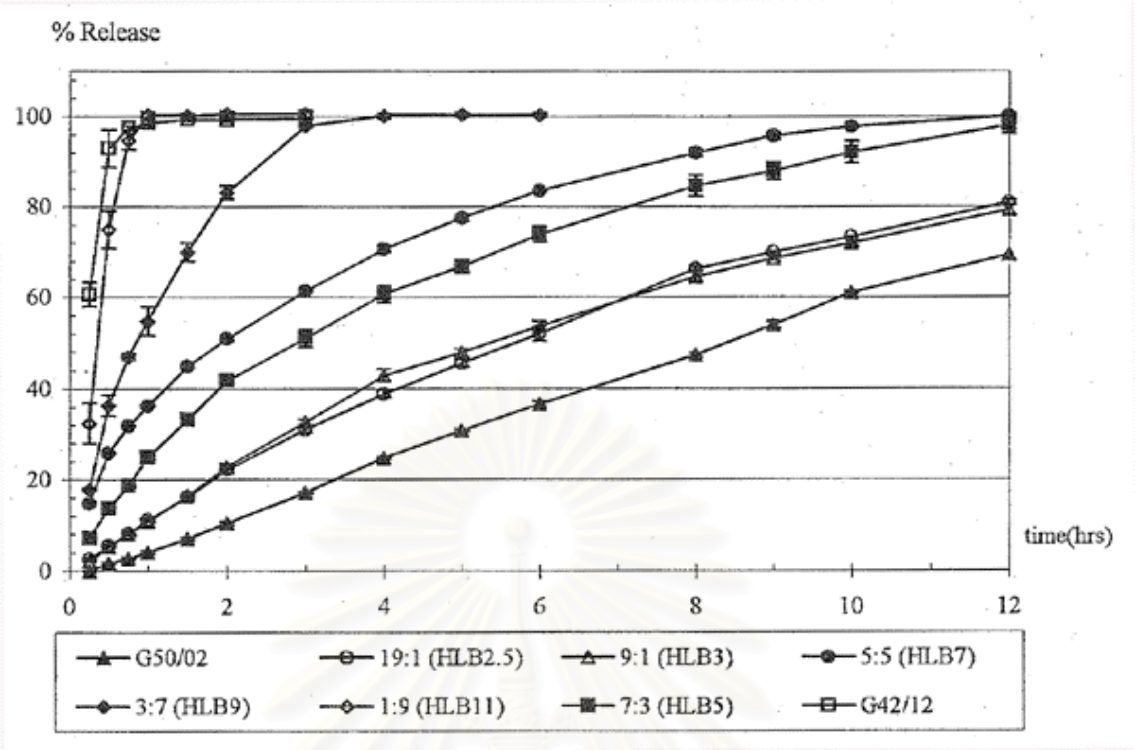


Figure 21 Dissolution profiles of diltiazem hydrochloride semisolid matrix in Gelucire blending between G50/02 and G42/12 at various calculated HLBs.

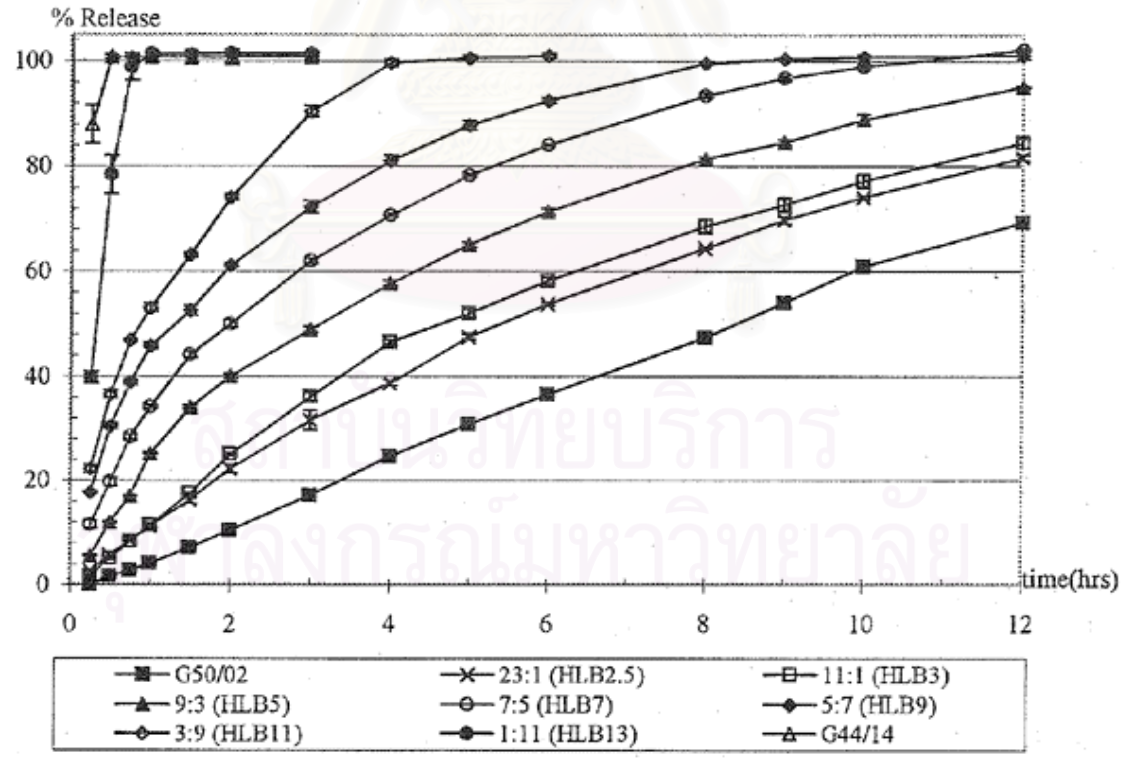


Figure 22 Dissolution profiles of diltiazem hydrochloride semisolid matrix in Gelucire blending between G50/02 and G44/14 at various calculated HLBs.

profiles were nearly identical because of uncontrollable matrix disintegration. The same characteristics of disintegration took place in G50/13 case too. At HLB higher than 7, production of small flakes base were an important factor in dissolution profile achieved.

For G42/12 and G44/14, which had the enhancement properties of single component base, also expressed complete dispersion in very short dissolution period. When blended with slow release Gelucire®, dispersions took place using longer period. In both cases, at calculated HLB above 9, the dispersion could possibly occurred. The relationship between amount of fast release portion and dissolution rate was compromised as mentioned above. Concerning the lower melting temperature of both bases, the softening of matrices were discovered after immerge in dissolution medium at final time of dissolution test.

The comparative dissolution profiles of various dual component of Gelucires® at constant calculated HLB are illustrated in Figures 23-28. The order of the influence of each Gelucire® type to drug release from fastest to lowest capability is given in Table 19.

The comparative results showed that G44/14 and G42/12 had the strongest power as driving force to enhance drug release while the weakest power was G46/07.

Table 19 Comparative and ordering the power of fast Gelucires® at constant calculated HLB.

Calculated HLB	Ordering of faster promotion property
2.5	44/14 > 42/12 ≥ 50/13 > 53/10
3	44/14 > 42/12 ≈ 50/13 > 53/10 > 46/07
5	44/14 ≈ 42/12 ≈ 50/13 ≈ 53/10 >> 46/07
7	53/10 > 50/13 > 44/14 ≈ 42/12
9	42/12 > 44/14 > 53/10 ≈ 50/13
11	42/12 > 44/14 > 50/13

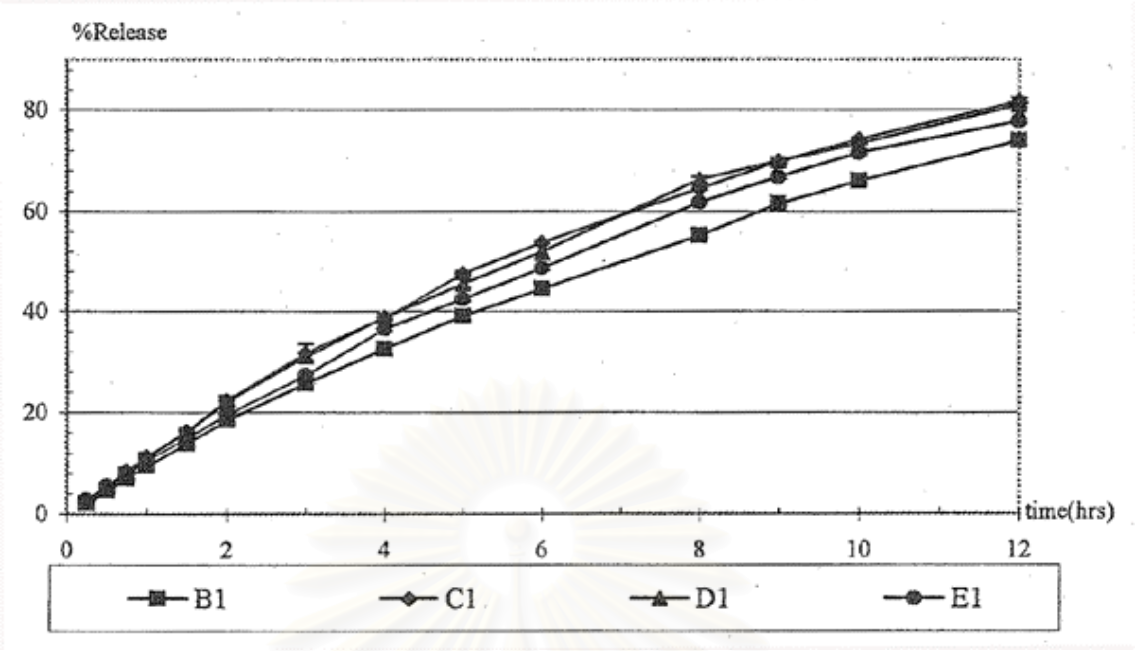


Figure 23 Comparative dissolution profiles of diltiazem hydrochloride semisolid matrix with various Gelucires combination at fix calculated LB of 2.5. (B1–G50/02: G53/10=15:1, C1-G50/02:G11/14=23:1, D1-G50/02:G42/12=19:1 and E1-G50/02:G50/13=21.5:1 in weight ratio unit)

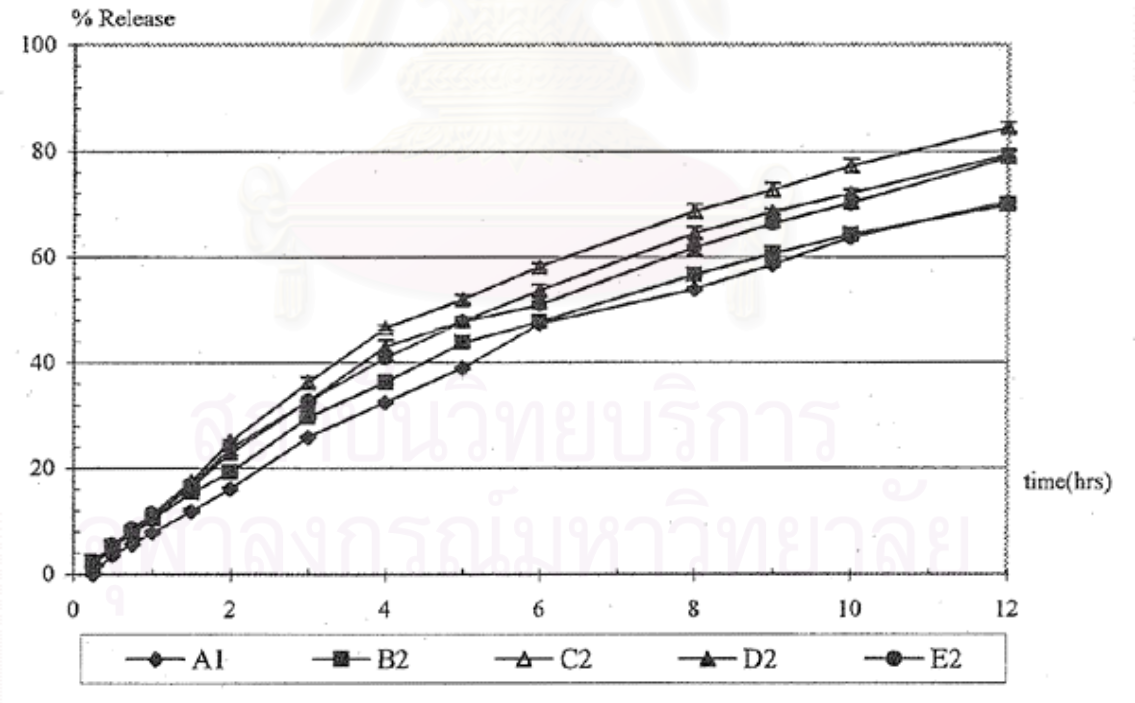


Figure 24 Comparative dissolution profiles of diltiazem hydrochloride semisolid matrix with various Gelucires combination at fix calculated LB of 3.(A1-G50/02:G46/07=4:1, B2-G50/02:G53/10=7:1, C2-G50/02:G44/14-11:1, D2-G50/02:G42/12=9:1 and E2-G50/02:G50/13=10:1 in weight ratio unit.)

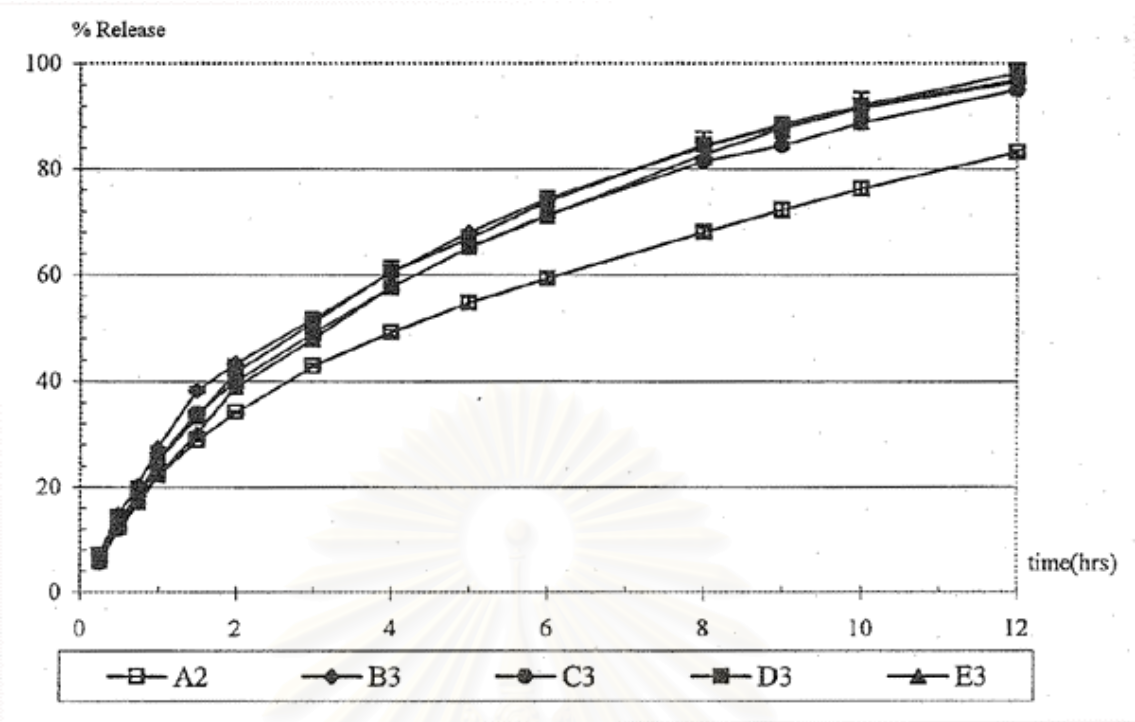


Figure 25 Comparative dissolution profiles of diltiazem hydrochloride semisolid matrix with various Gelucires combination at fix calculated HLB of 5.(A2-G50/02:G46/07=2:3, B3-G50/02:G53/10=5:3, C3-G50/02:G44/14=9:3, D3-G50/02:G42/12=7:3 and E3-G50/02:G50/13=8:3 in weight ratio unit.)

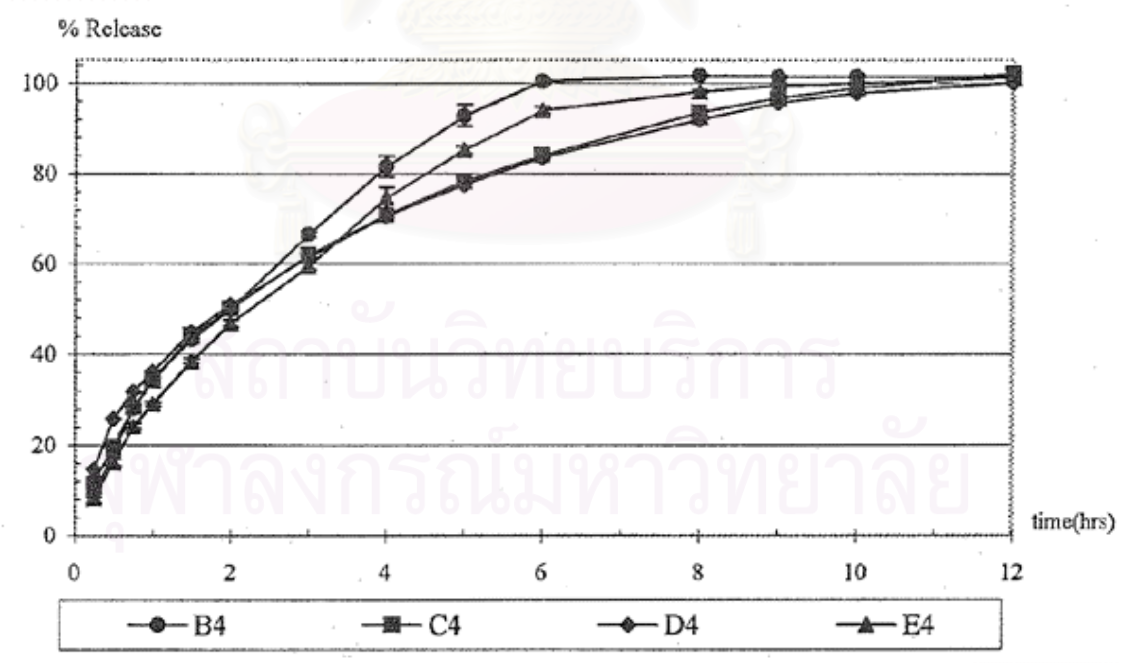


Figure 26 Comparative dissolution profiles of diltiazem hydrochloride semisolid matrix with various Gelucires combination at fix calculated HLB of 7.(B4-G50/02:G53/10=3:5, C4-G50/02:G44/14=7:5, D4-G50/02:G42/12=5:5 and E4-G50/02:G50/13=6:5 in weight ratio unit)

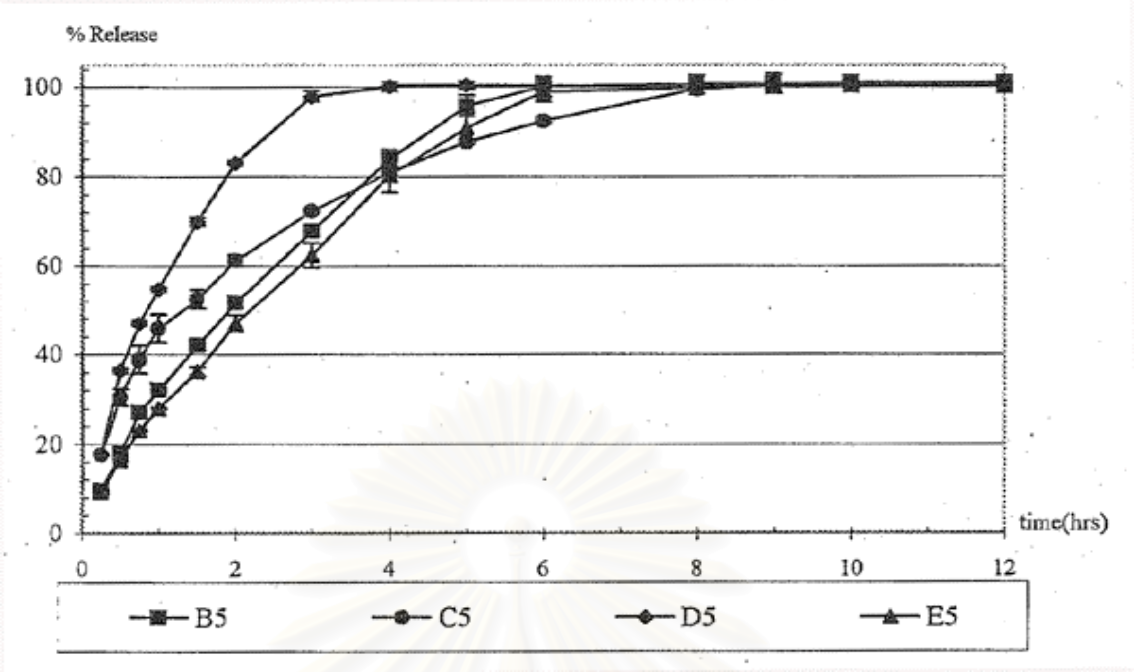


Figure 27 Comparative dissolution profiles of diltiazem hydrochloride semisolid matrix with various Gelucires combination at fix calculated HLB of 9.(B5-G50/02:G53/10=1:7, C5-G50/02:G44/14=5:7, D5-G50/02:G42/12=3:7 and E5-G50/02:G50/13=4:7 in weight ratio unit)

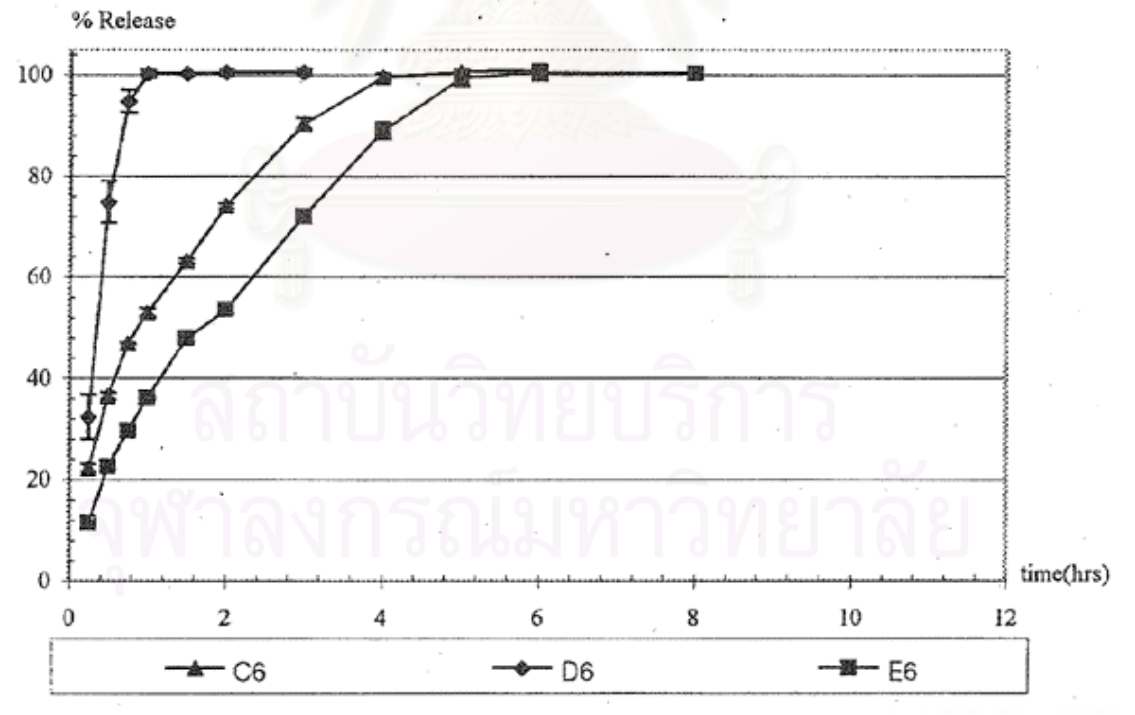


Figure 28 Comparative dissolution profiles of diltiazem hydrochloride semisolid matrix with various Gelucires combination at fix calculated HLB of 11.(C6-C50/02:G44/14=3:9, D6-G50/02:G42/12=1:9 and E6-G50/02:G50/13=2:9 in weight ratio unit)

Almost the entire dual component of thermosoftening base with slow and fast release exhibited the same results. They provided the faster release when calculated HLB was increased. Seeking the representable parameter to correlate calculated HLB and dissolution pattern was the most valuable tool for prediction in SSM product formulation. Many studies typically used time at fix percent drug release such as $t_{50\%}$ (time to 50% drug release) to search for the best correlation. Even if $t_{x\%}$ are widely used but they are not probably the best suitable parameter to represent of all points in dissolution-time curve. Mean dissolution time (MDT) represent all the time points on the dissolution profile. MDT of various SSM preparations are computed and presented in Table 20. Furthermore, relationship between MDT and calculated HLB of each mixture groups are constructed and displayed in Figures 29 and 30.

The relationship between MDT and calculated HLB declared that almost Gelucire® mixture groups exhibited linear relationship except G53/10 and G50/13. Correlations of determination (r2) of above relationship of G46/07, G42/12 and G44/14 mixture were 0.9963, 0.9824 and 0.9890, respectively. This relationship could be employed to forecast the approximate HLB of various mixture bases to formulate SSM with desirable MDT value.

The DTZ HCl SSM preparations that passed the criteria in Diltiazem hydrochloride Extended-release capsule USP 23 supplement 5(for products labeled for dosing every 12 hours, Test 1) are shown in Table 21. These were investigated on the pH-sensitive property under dissolution testing. Their dissolution profiles under different pH conditions are plotted as a function of time and depicted in Figures 31 and 32.

Table 20 MDT values of DTZ HCl SSM preparation with various single and dual Gelucire® bases at different HLB values.

Calculated HLB	MDT (hrs)				
	G50/02 & G42/12	G50/02 & G44/14	G50/02 & G46/07	G50/02 & G50/13	G50/02 & G53/10
2	7.688* (0.047)	7.688* (0.047)	7.688* (0.047)	7.688* (0.047)	7.688* (0.047)
2.5	6.131 (0.063)	6.087 (0.033)	-	6.460 (0.041)	6.908 (0.033)
3	6.152 (0.077)	5.723 (0.098)	7.138 (0.029)	6.350 (0.064)	6.782 (0.014)
5	3.988 (0.195)	4.276 (0.015)	5.424 (0.073)	4.198 (0.029)	3.915 (0.477)
7	3.008 (0.007)	3.104 (0.037)	4.047* (0.229)	2.790 (0.068)	2.329 (0.041)
9	1.123 (0.033)	2.218 (0.073)	-	2.508 (0.178)	2.329 (0.083)
10	-	-	-	-	2.561* (0.054)
11	0.394 (0.018)	1.335 (0.007)	-	2.084 (0.056)	-
12	0.235* (0.021)	-	-	-	-
13	-	0.374 (0.019)	-	0.790* (0.046)	-
14	-	×*	-	-	-

The data are presented in average ± SD (n=3)

× = MDT can not be calculated.

* is the MDT of DTZ HCl SSM with their slow or fast Gelucire® monocomponent in each blending group.

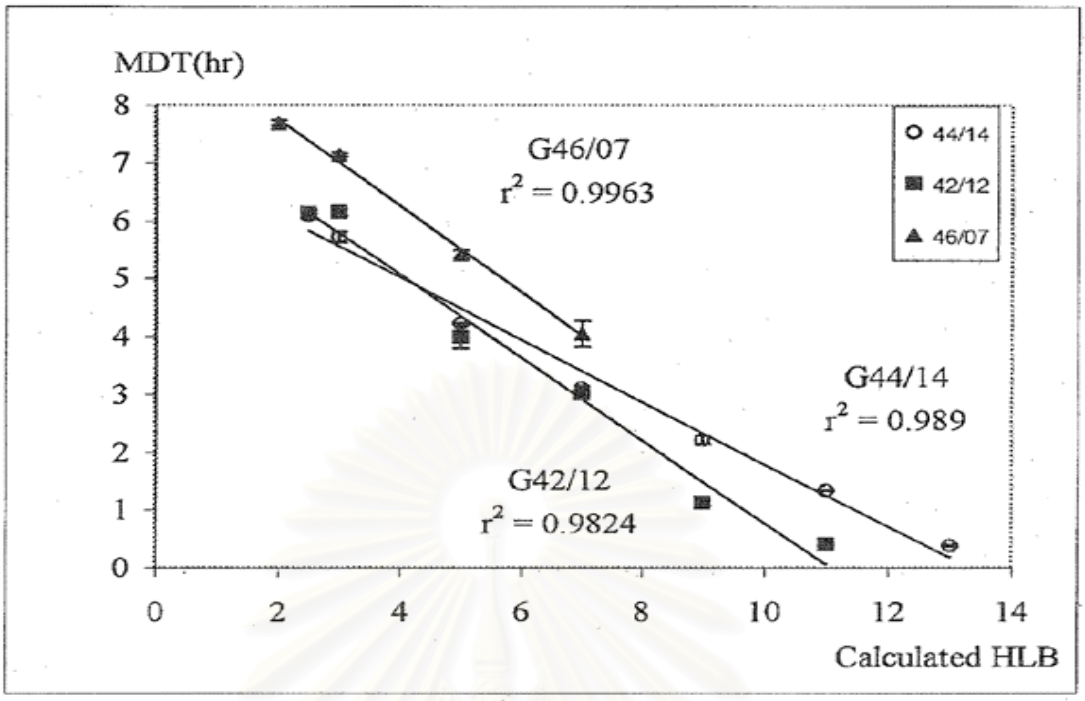


Figure 29 Relationship of MDT and calculated HLB of diltiazem hydrochloride semisolid matrix with various blending between G50/02 and other Gelucire types. Linear line are represent linear regression with correlation of determination (r^2).

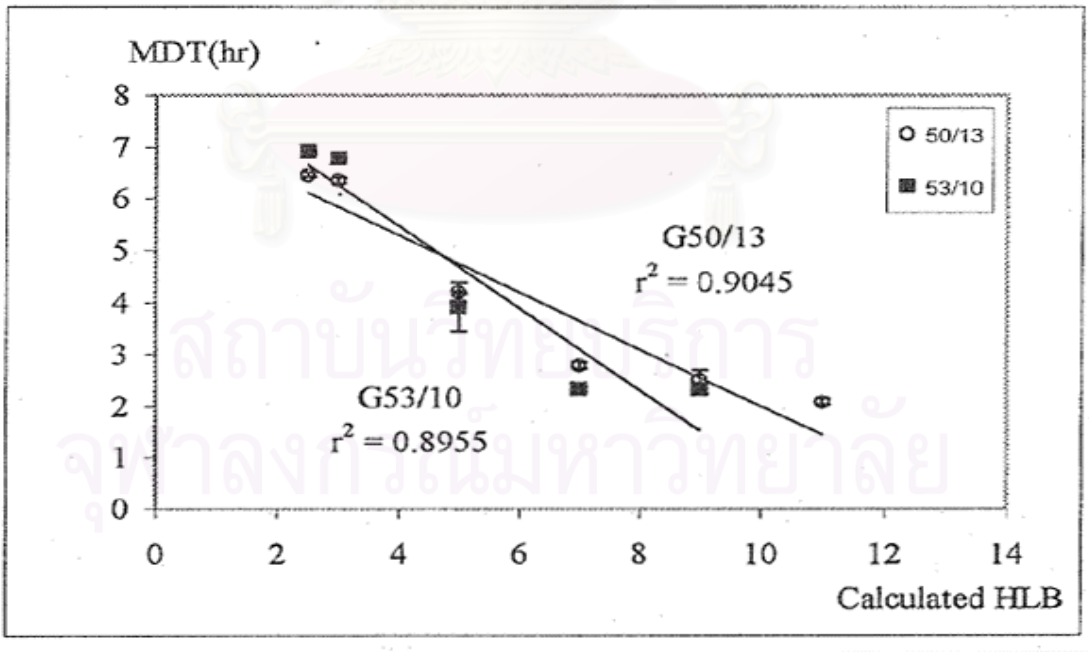


Figure 30 Relationship of MDT and calculated HLB of diltiazem hydrochloride semisolid matrix with various blending between G50/02 and other Gelucire types. Linear line are represent linear regression with correlation of determination (r^2).

Table 21 Percent cumulative drug release of DTZ HCl SSM preparations comparing with the tolerance under Test 1 of Diltiazem hydrochloride Extended-release capsule USP 23.

Time (hrs)	Acceptance criterion	% Cumulative drug release			
		F6	B1	A1	E1
3	10-25%	17.11	24.94	23.30	25.01
9	45-85%	54	61.39	58.46	66.81
12	Not less than 70%	70.42	73.91	70.36	77.77

pH sensitive dissolution study revealed that the acceptable formulas had both lower dissolution rate and amount of drug release compared with when using purified water as a dissolution medium. In early stage, pH 1.2 and 4.5, all preparations showed nearly similar release patterns corresponding to each the release pattern under purified water. Meanwhile, at later stage under pH 7.0, all preparations provided a significant difference from each original dissolution curves. Quantitative determination of dissolution profile difference under different dissolution conditions found to be significant. In this case, similarity factor was employed as mentioned previously. Similarity factors "f_2" of each preparation were calculated based on using the dissolution curves in purified water as reference and shown in Table 22.

Table 22 Similarity factor and average percentage difference among DTZ HCl SSM with G50/02 dissolution profile under pH sensitive dissolution study.

Formula	Similarity factor "f_2".	Average percentage difference
F6	45.98	11.99
A1	50.24	9.84
B1	51.67	9.21
E1	48.91	10.47

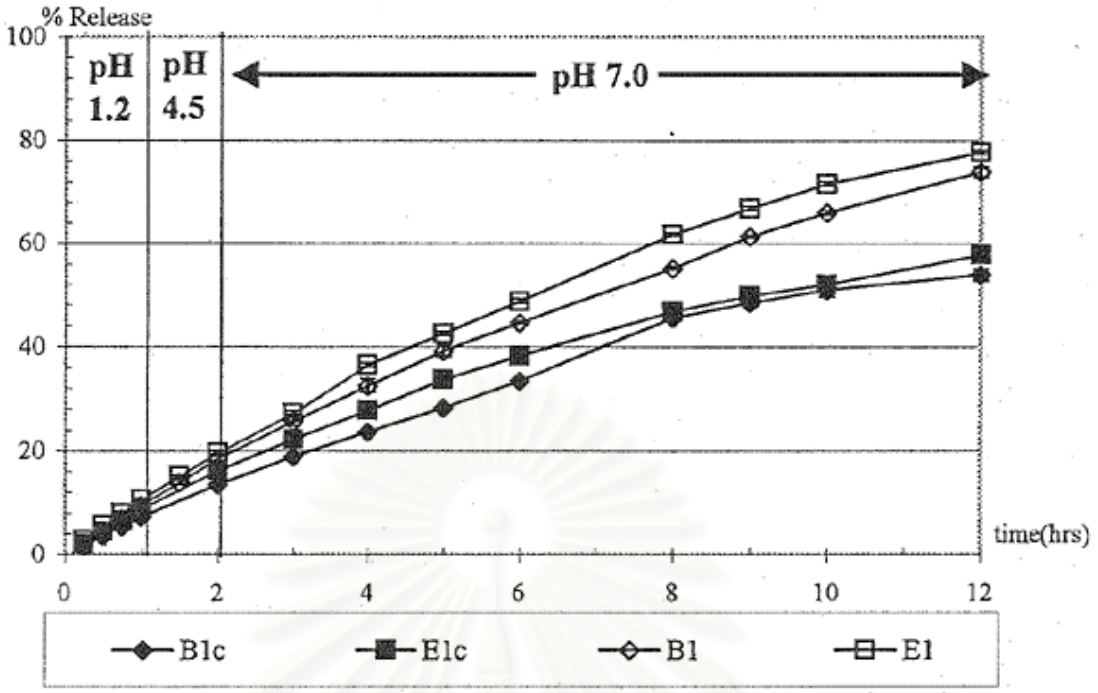


Figure 31 Comparative dissolution profiles of diltiazem hydrochloride semisolid matrix in pH change and purified water as dissolution media. (B1-G50/02:G53/10=15:1 weight ratio under purified water, B1c-B1 under pH change and E1-G50/02:G50/13=21.5:1 under purified water, E1c-E1 under pH change)

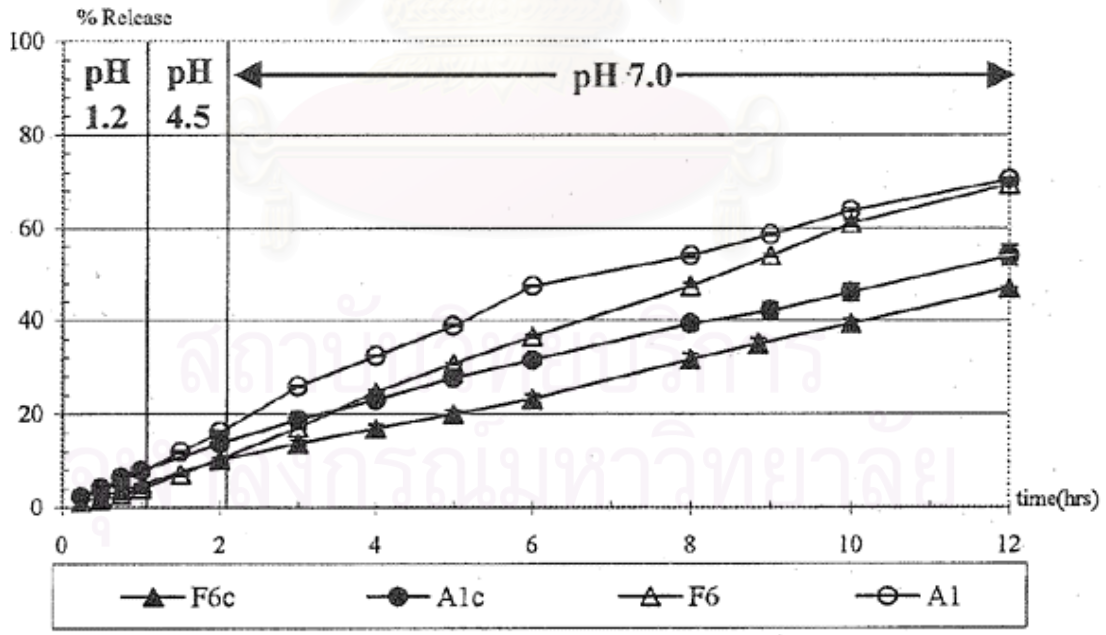


Figure 32 Comparative dissolution profiles of diltiazem hydrochloride semisolid matrix in pH change and purified water as dissolution media. (A1-G50/02:G46/07=4:1 weight ratio under purified water, A1c-A1 under pH change and F6-only G50/02 as present under purified water, F6c-F6 under pH change)

Similarity factor indicated that all preparations had a lower dissolution curves than original profile when purified water was used. This higher 10% difference was remarkably significant. It could be stated that in the acidic condition (pH lower than 4.5) dissolution profile was not altered. Contrary, neutral pH might affect the drug release profiles.

2.Evaluation of DTZ SSM capsule

2.1) Morphology of SSM preparations

The surface and inner section of matrix capsule were observed via scanning electron microscope (SEM) under freezing stage. The SSM formulas were investigated both before and after contacting with dissolution medium for 12 hours. The appearances of matrix after immersed in the medium were important clues to predict and determine the predominant mechanisms of drug release through matrix dosage form. On the other hand, the matrix of the dual component base were also investigated the same as above. The selected-preparations were the product that the shapes are still rigid and remained intact. Thus, the other matrices, which are soft or loose rigidity, were ignored. The SEM photomicrographs of all formulation are displayed in Figures 34-54.

The microscopic examination of the matrix surface before and after immersed in dissolution medium were clearly shown that there are surface erosion and pores were formed or water channels were created. Cross-section pictures show how DTZ HCl particle oriented in the matrix. Focused on the rectangular particles in the cross-section field, it was drug particles, which corresponded to the crystal appearance of pure DTZ HCl under SEM photograph. Cross section pictures could not point out the new generating water pathway or the tortuosity of the inner matrix. From cross section of matrix before dissolution test, there are pores after cutting prior to scanning the texture. It might be due to drug particle orientation. Scanning electron microscope of pure DTZ HCl powder are shown in Figure 31. It is a rectangular shape crystal. If the drug particles were placed in the perpendicular against cutting plane, the crystal might be removed and generate a pore of the same size as the crystals in the inner mass. The possible scheme is predicted in Figure 33.

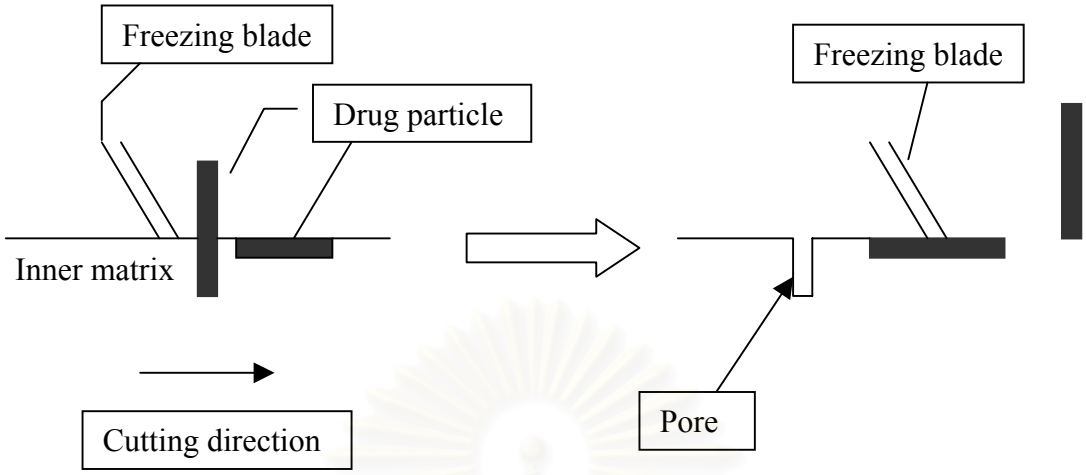


Figure 33 Possible schematic of inner matrix pore after cross section process.

The SEM photographs in various drug loading matrices showed that higher amount of drug particle replacing the base led to an increase in multiporous surface as seen in Figures 35-44. All of the mixture of G50/02 and the faster release Gelucire® matrix exhibited smooth surface matrix before dissolution. After immersing in the dissolution medium throughout the experimental run, the matrix's surface was clearly eroded as seen in Figures 45-54.

2.2) Differential scanning calorimetry

The DSC thermograms of active ingredient (DTZ HCl), the pure base, mixture of base and the preparations are shown in Figures 55-67. The summaries of main endothermic temperatures (Tm) are shown in Table 23.

The thermogram of various thermosoftening bases either single or dual component displayed broad peaks and all of the peaks were endothermic. While DTZ HCl powder exhibited sharp endothermic peak which indicates melting at 214.2°C. The system which was composed of DTZ HCl expressed the main distinct endothermic peak around 208-211°C and was lower than pure DTZ HCl powder. The results concluded that both Gelucire® and DTZ HCl were crystalline due to the presence of endothermic peaks in DSC tracing.

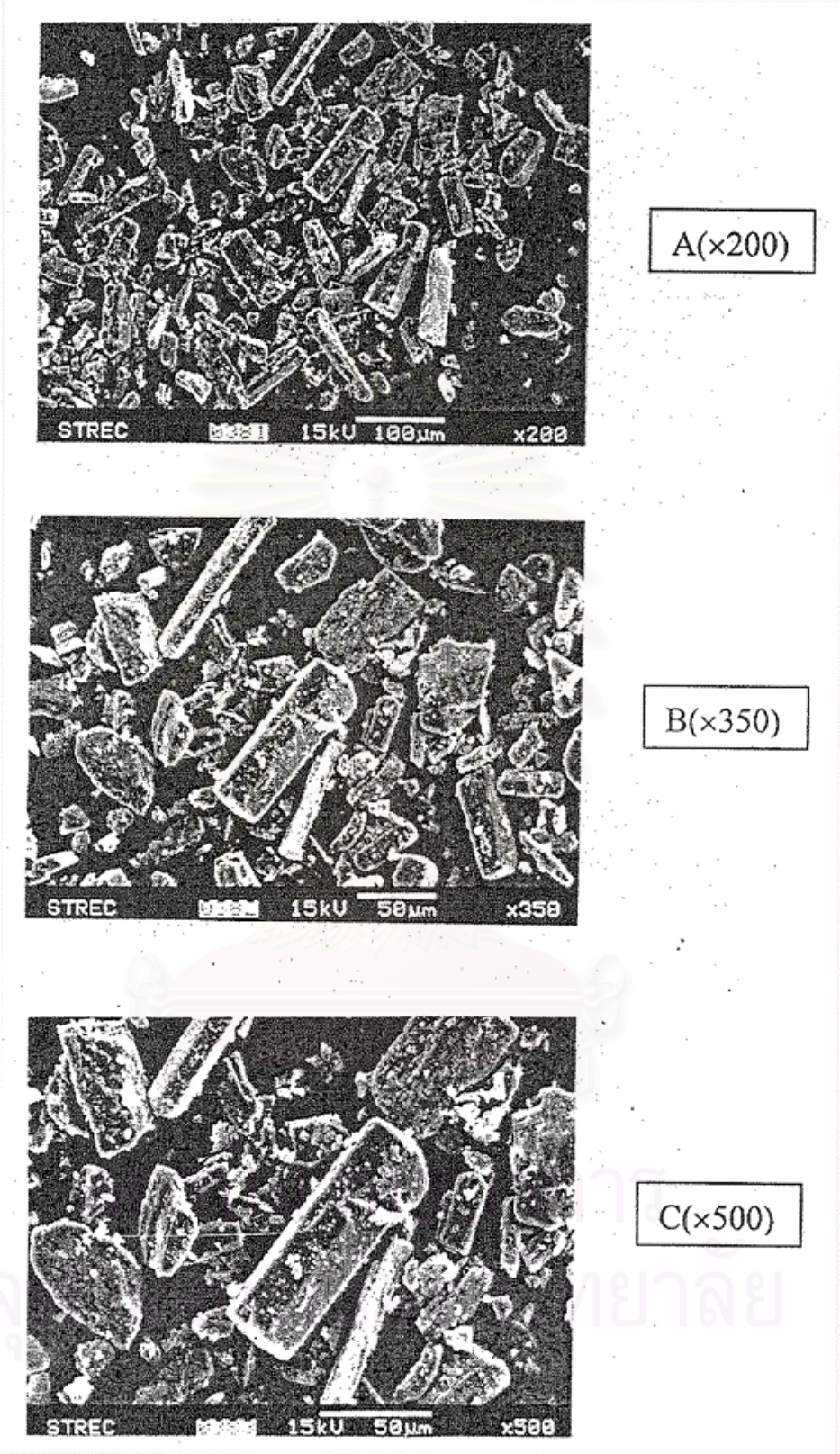


Figure 34 Scanning electron photomicrographs of diltiazem hydrochloride powder at various magnifications. [A(x200), B(x350) and C(x500)]

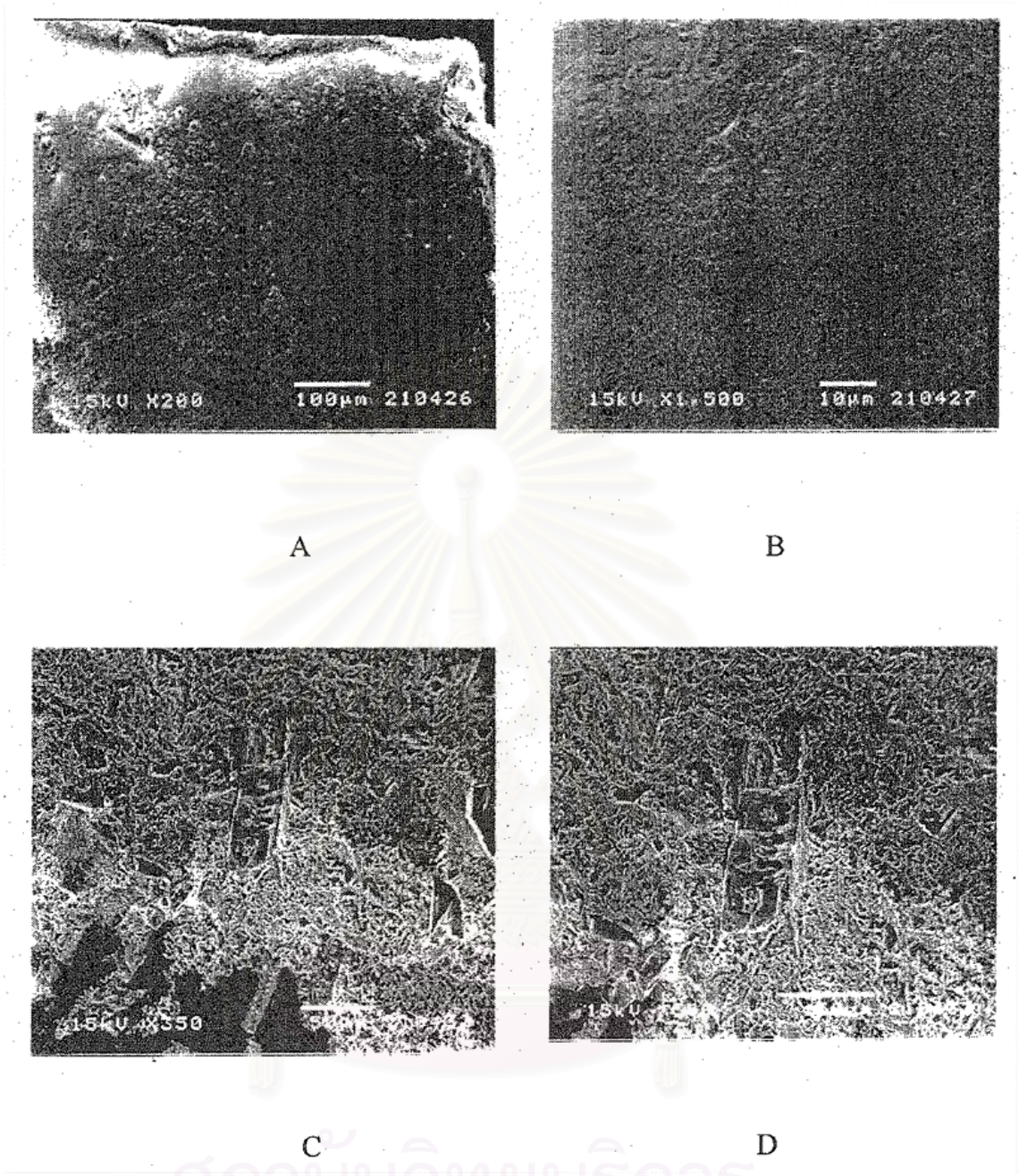


Figure 35 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 30 mg before dissolution test. (A-surface (x200), B-surface (x1,500)), C-cross section (x350) and D-cross section (x500))

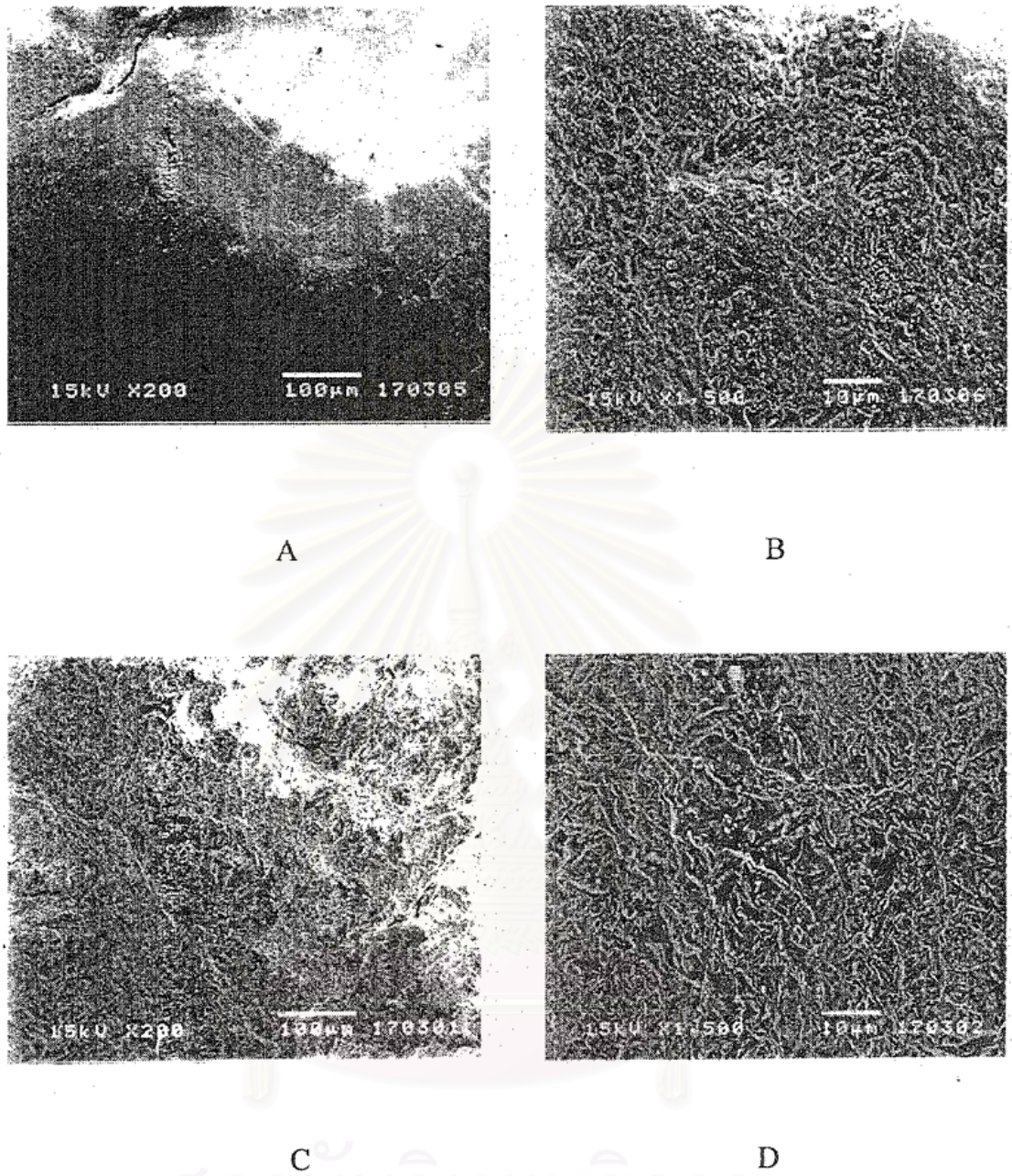


Figure 36 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 30 mg after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x200) and D-cross section (x1,500))

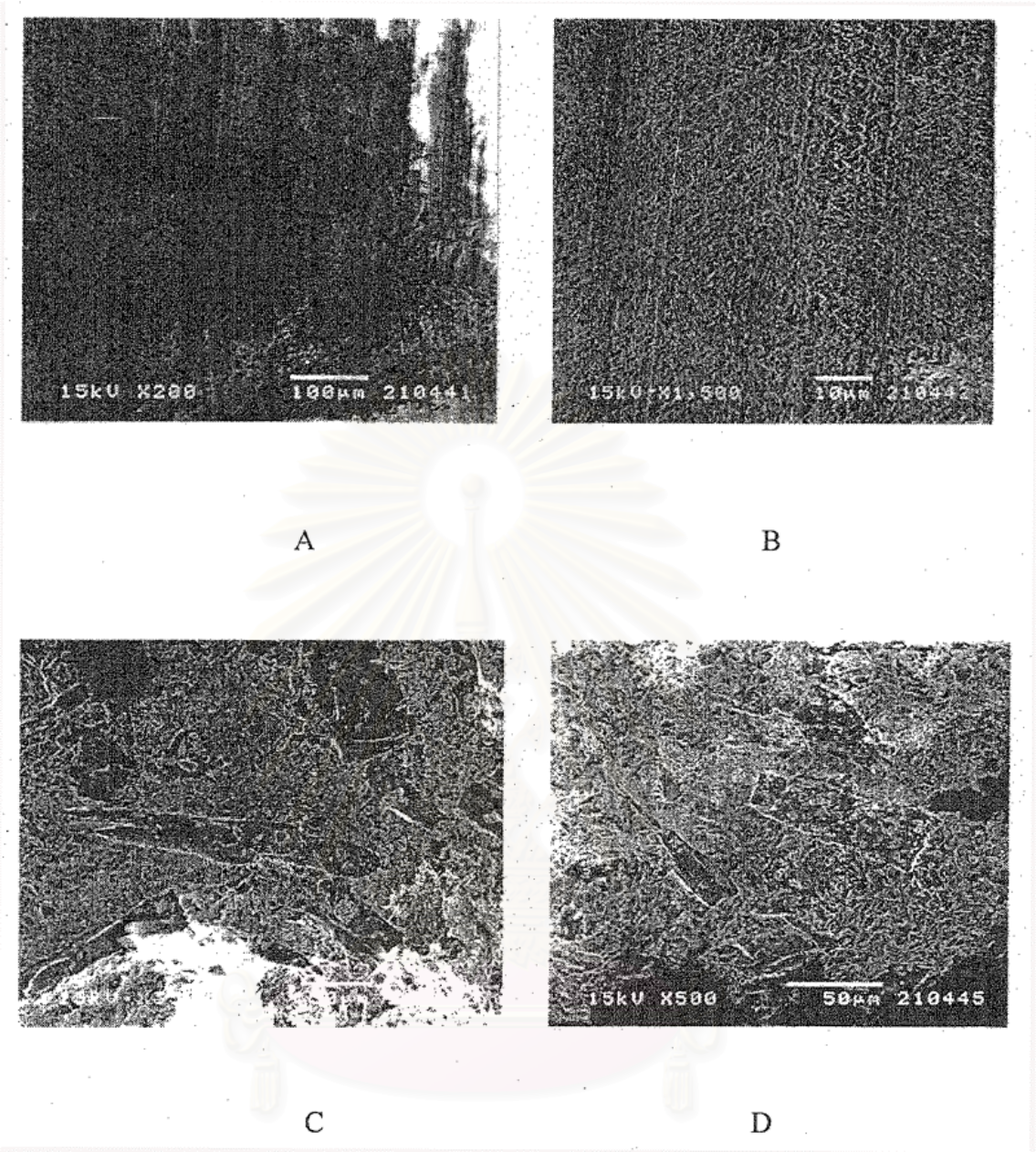


Figure 37 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 45 mg before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

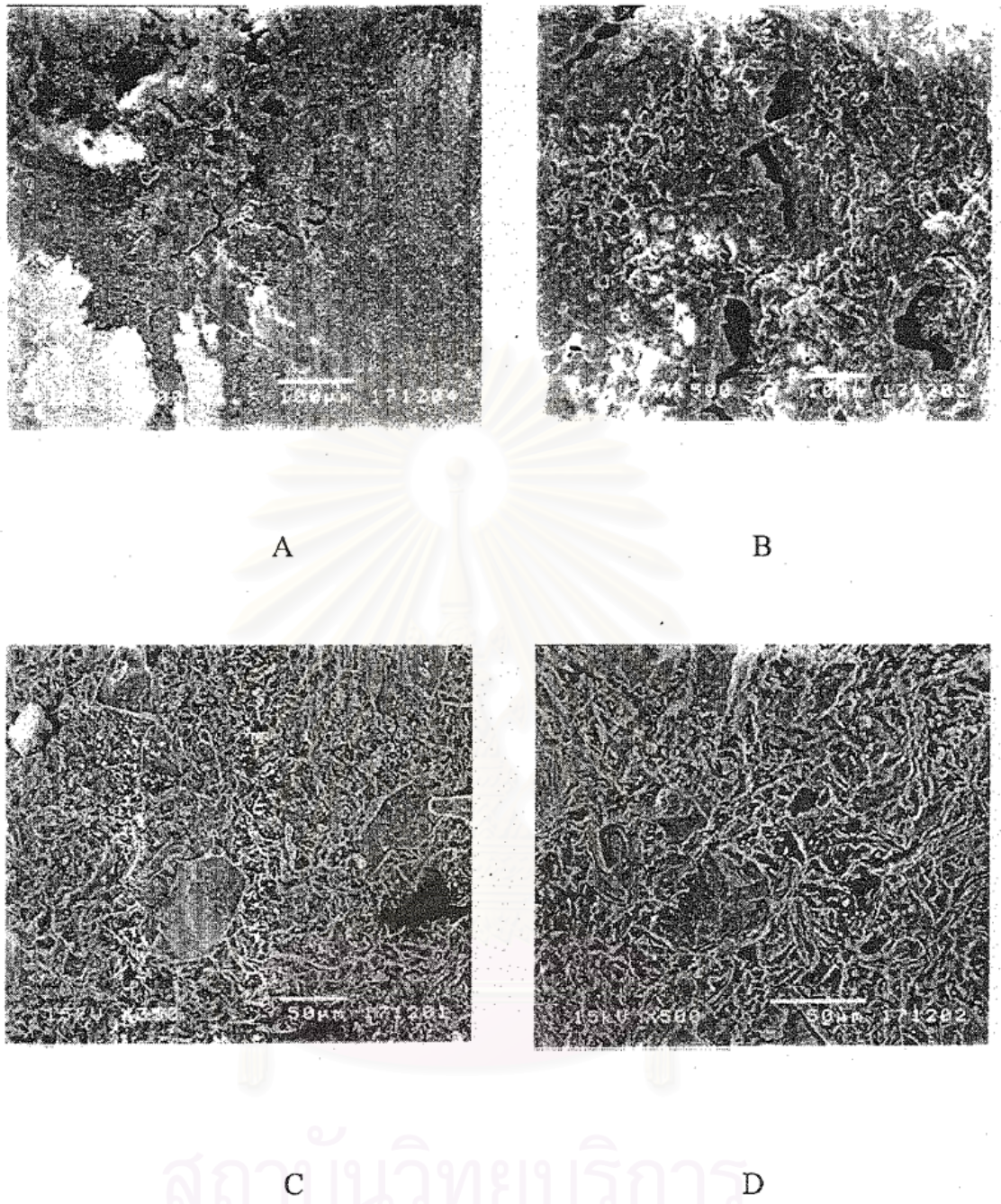


Figure 38 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 45 mg after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

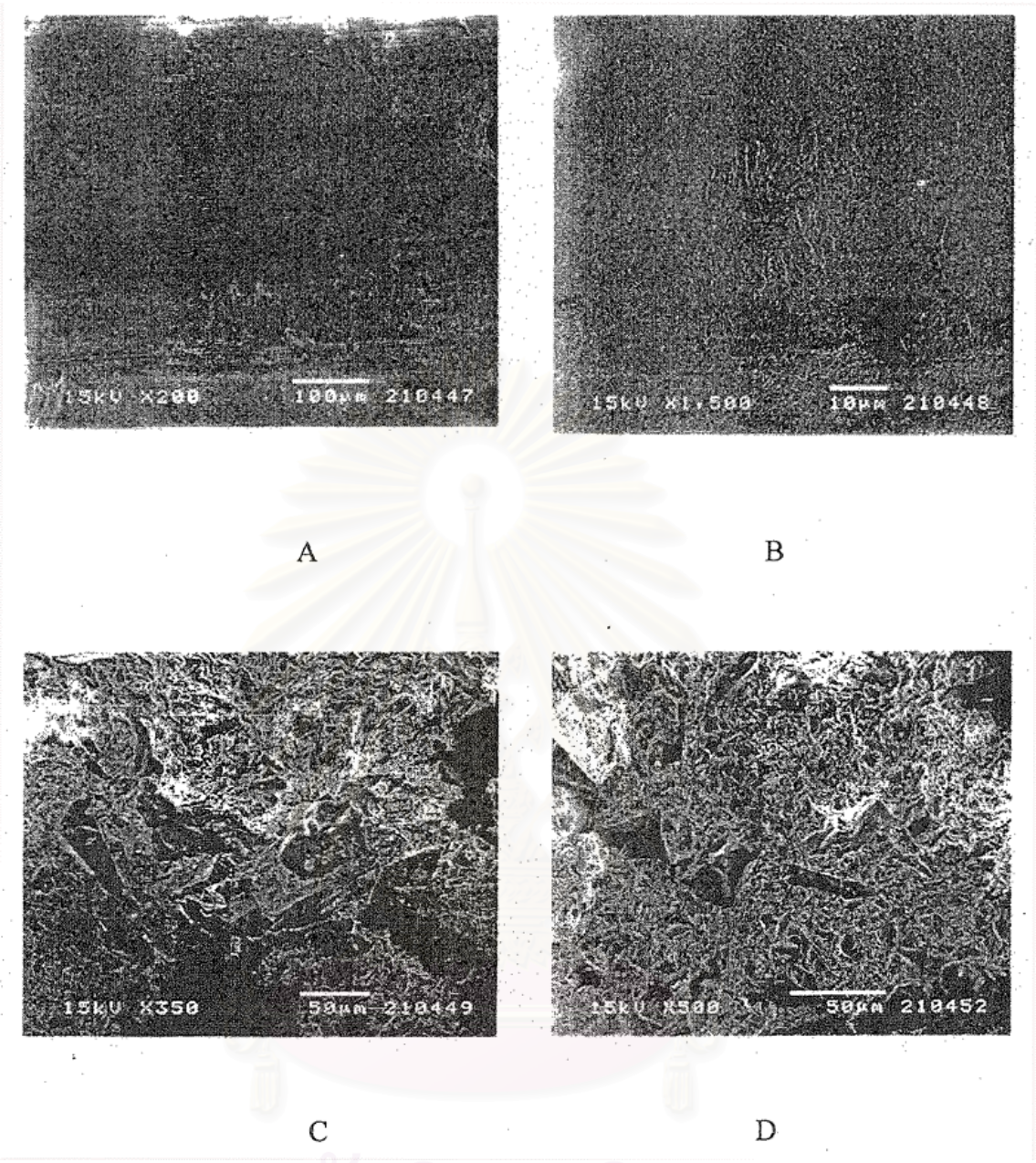


Figure 39 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 60 mg before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500)

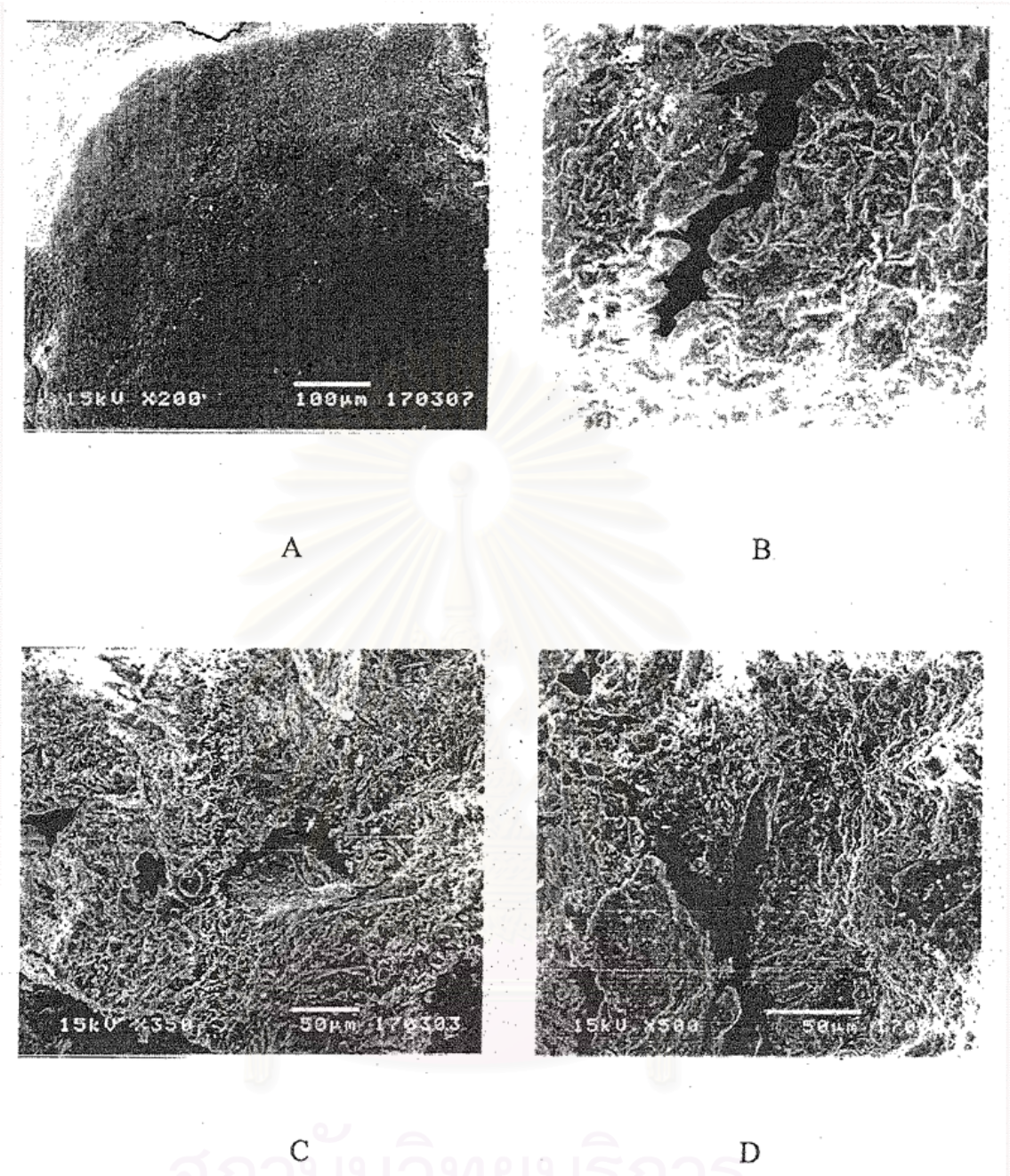


Figure 40 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 60 mg after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

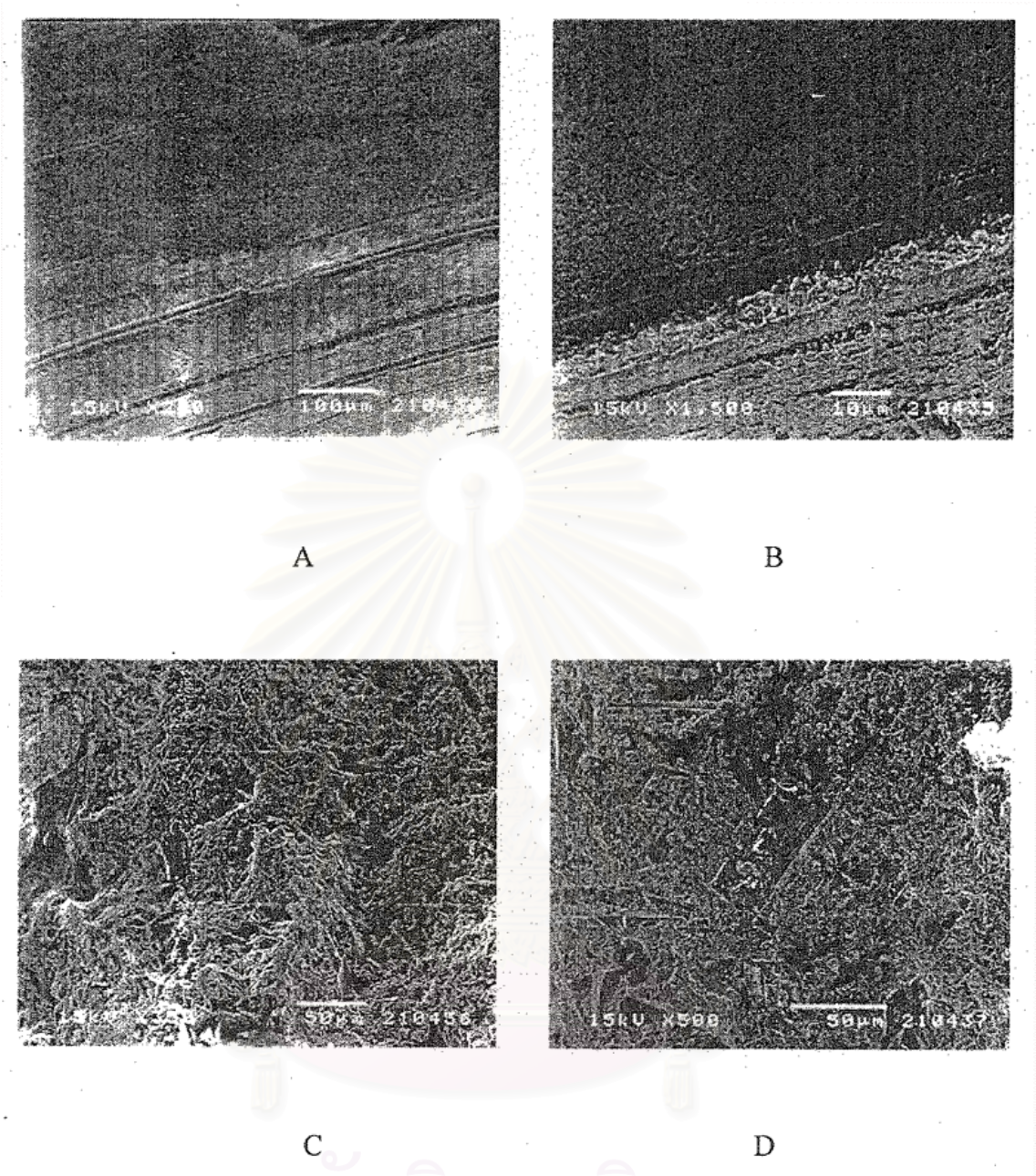


Figure 41 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 75 mg before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500)

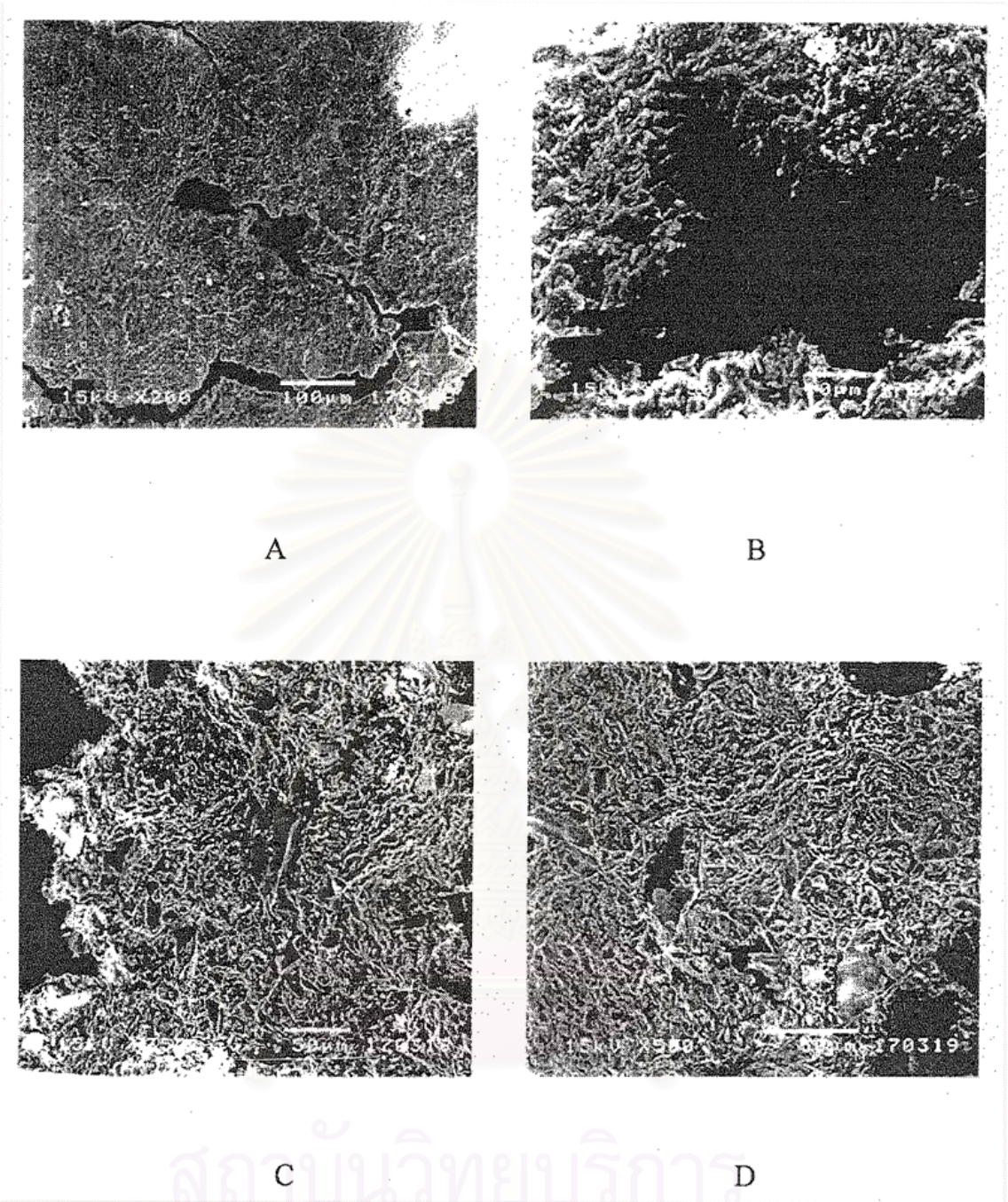


Figure 42 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 75 mg after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500)

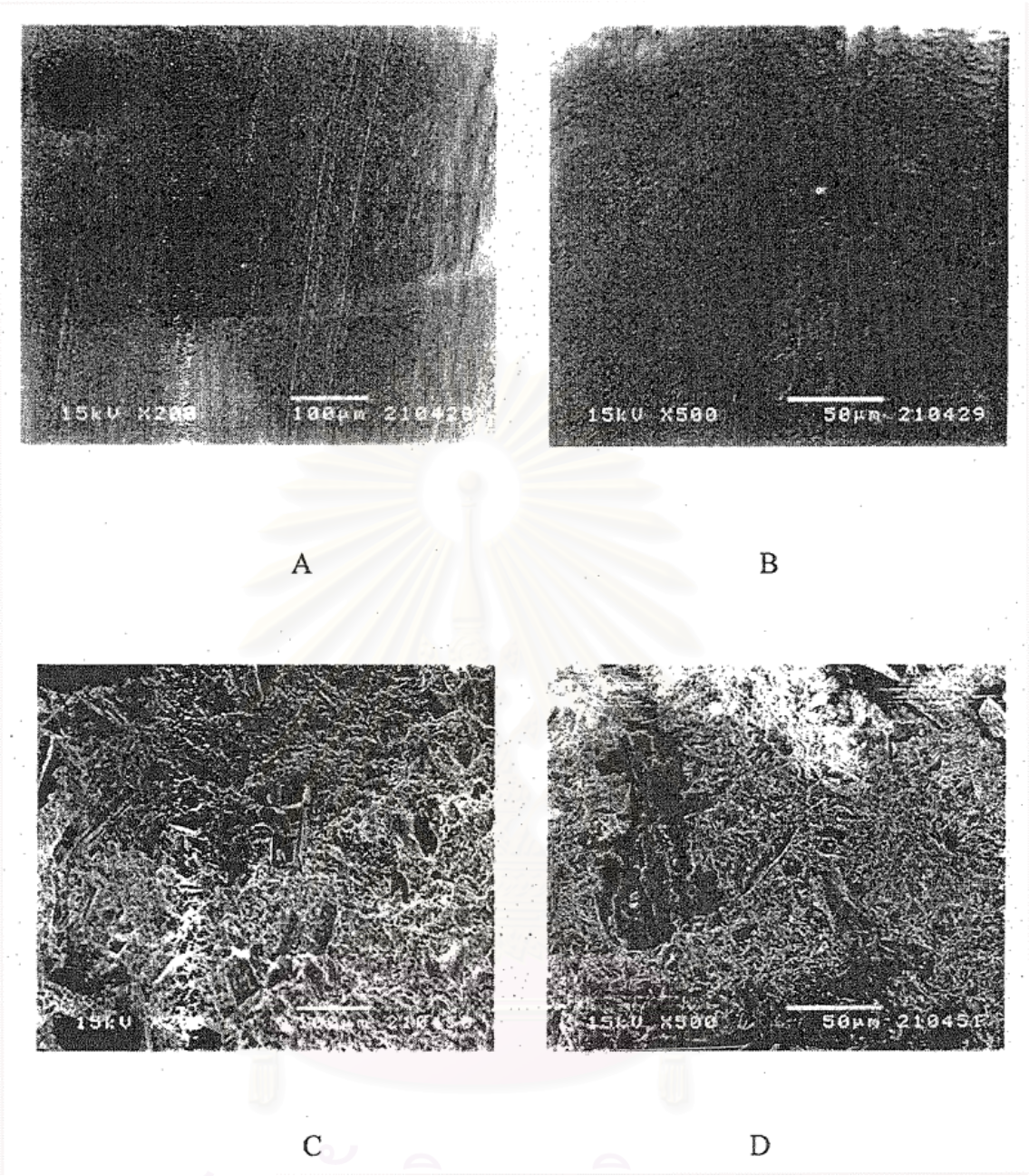


Figure 43 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 90 mg before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500)

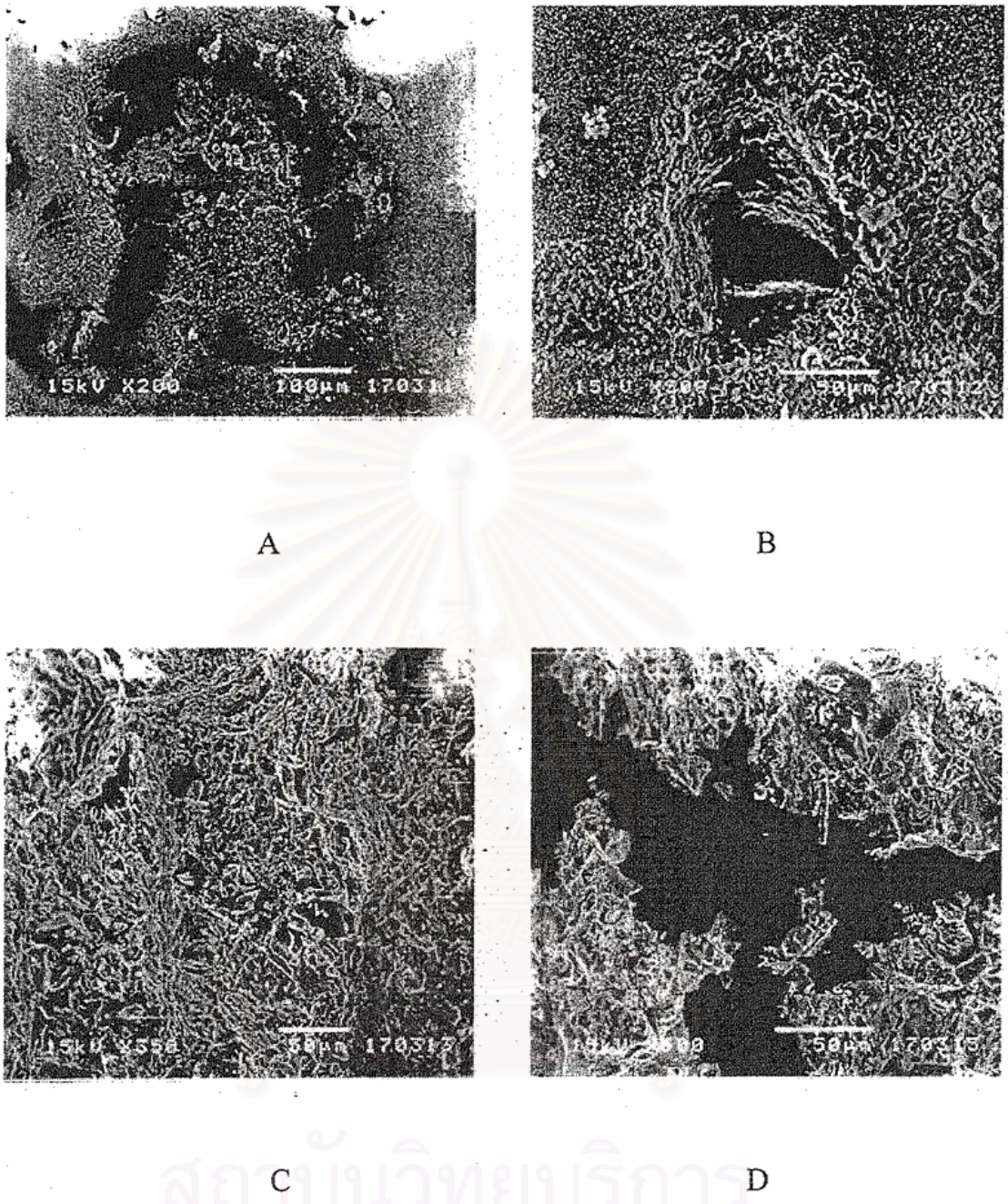


Figure 44 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 at drug loading level 90 mg after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

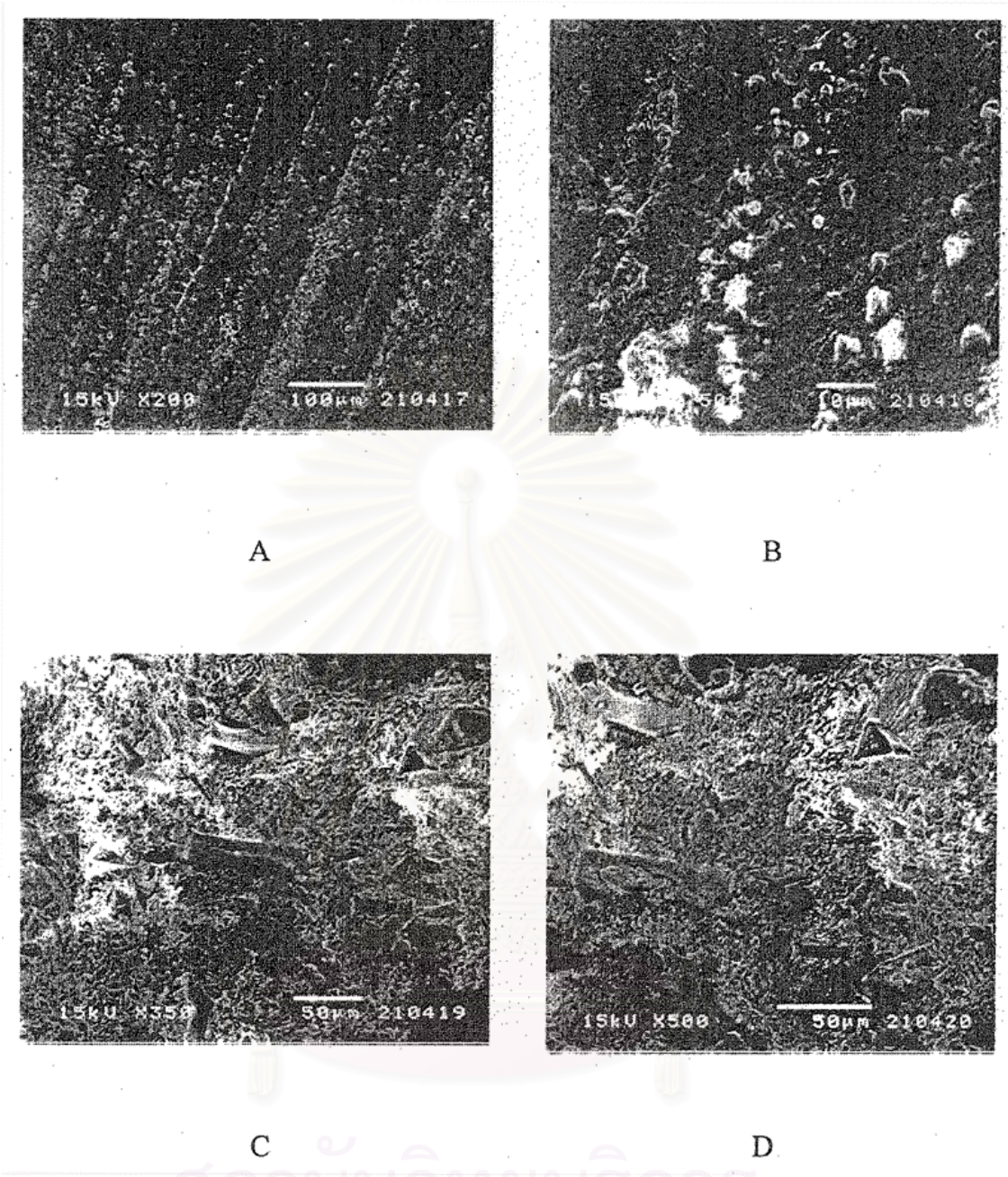


Figure 45 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix of G50/02 and G42/12 blending at 7:3 weight ratio and calculated HLB equal 5, before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

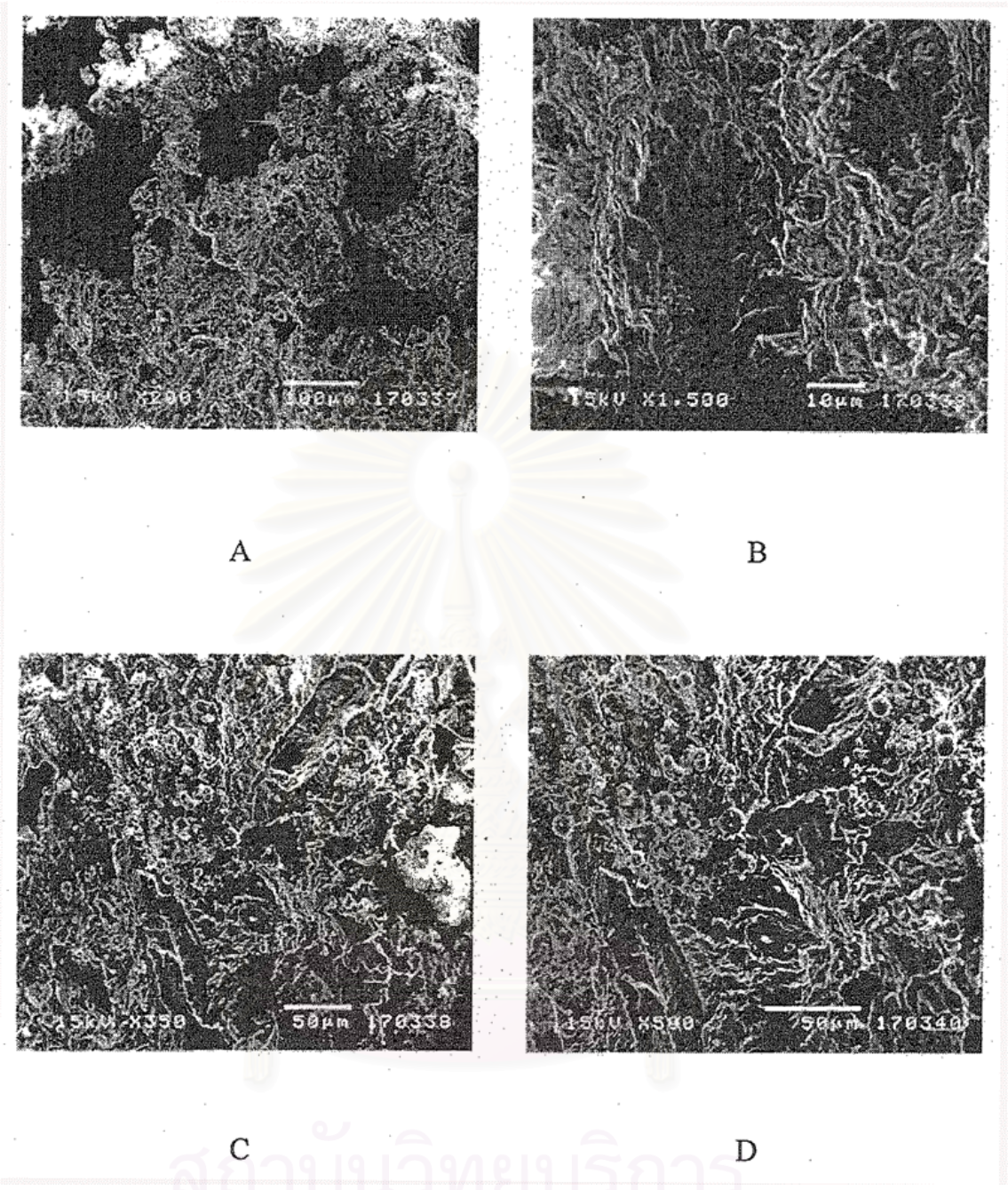


Figure 46 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G42/12 blending at 7:3 weight ratio and calculated HLB equal 5, after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

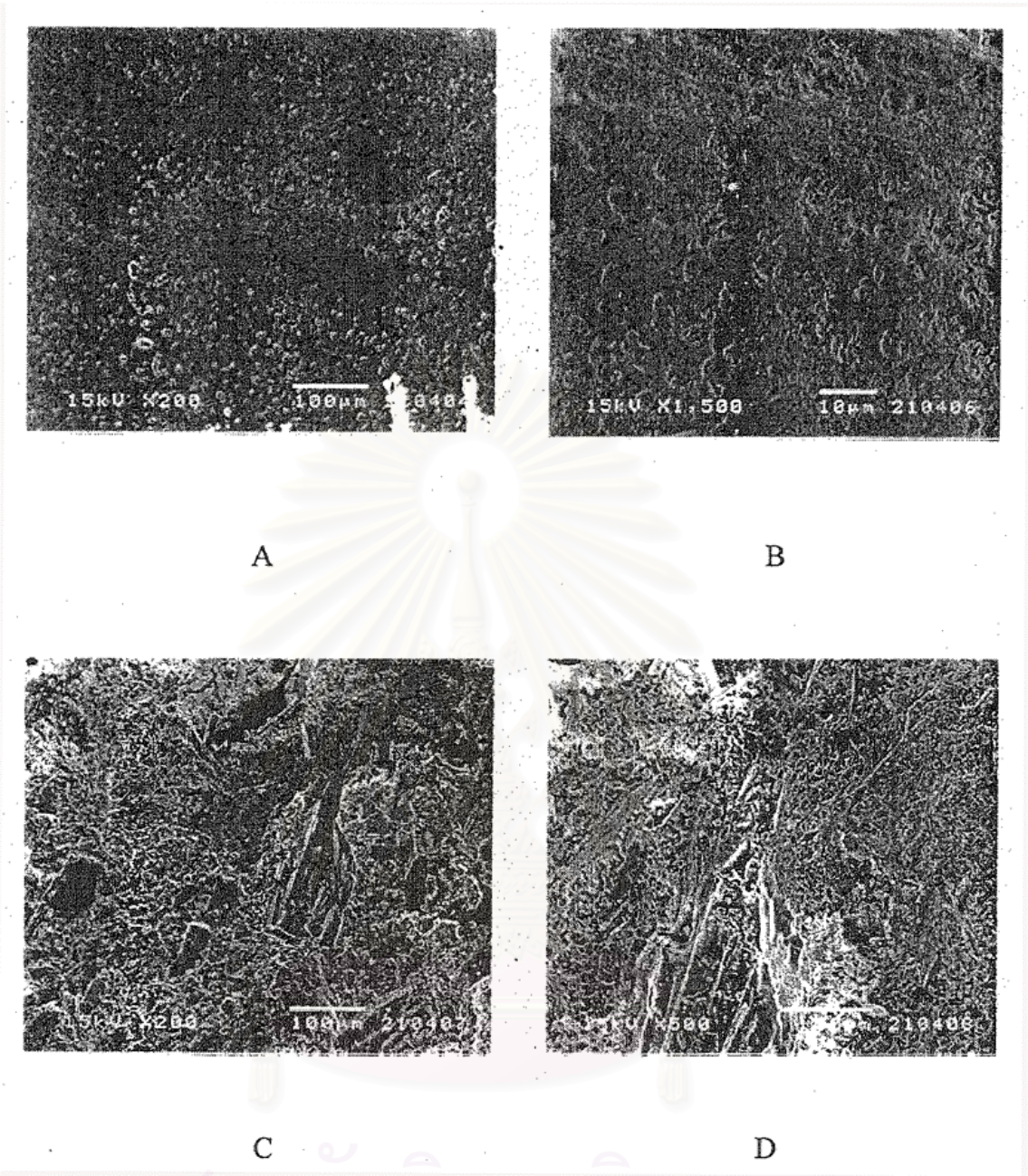


Figure 47 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G44/14 blending at 9:3 weight ratio and calculated HLB equal 5, before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

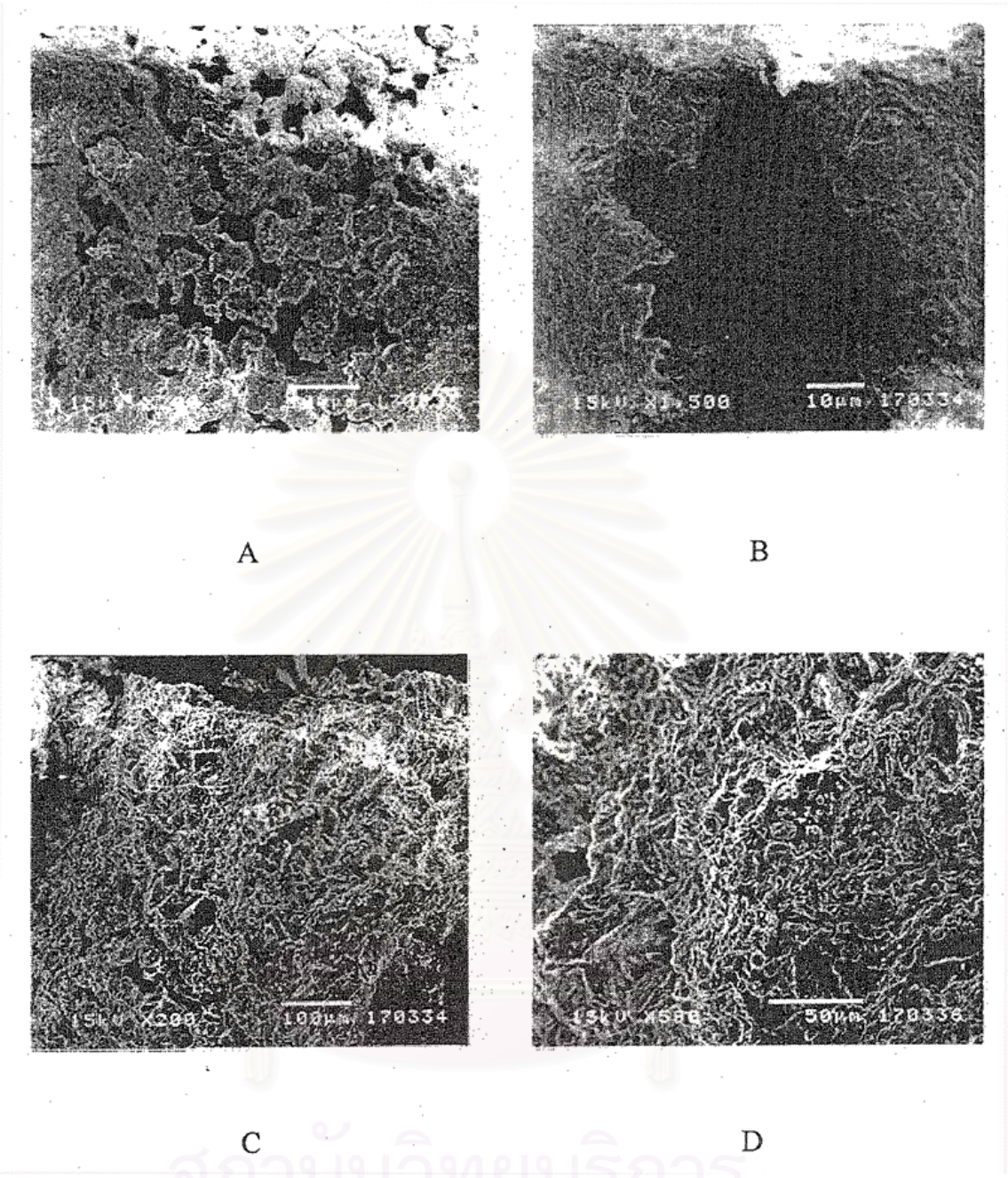


Figure 48 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G44/14 blending at 9:3 weight ratio and calculated HLB equal 5, after dissolution test. (A-surface (x200,) B-surface (x1,500), C-cross section (x200) and D-cross section (x500))

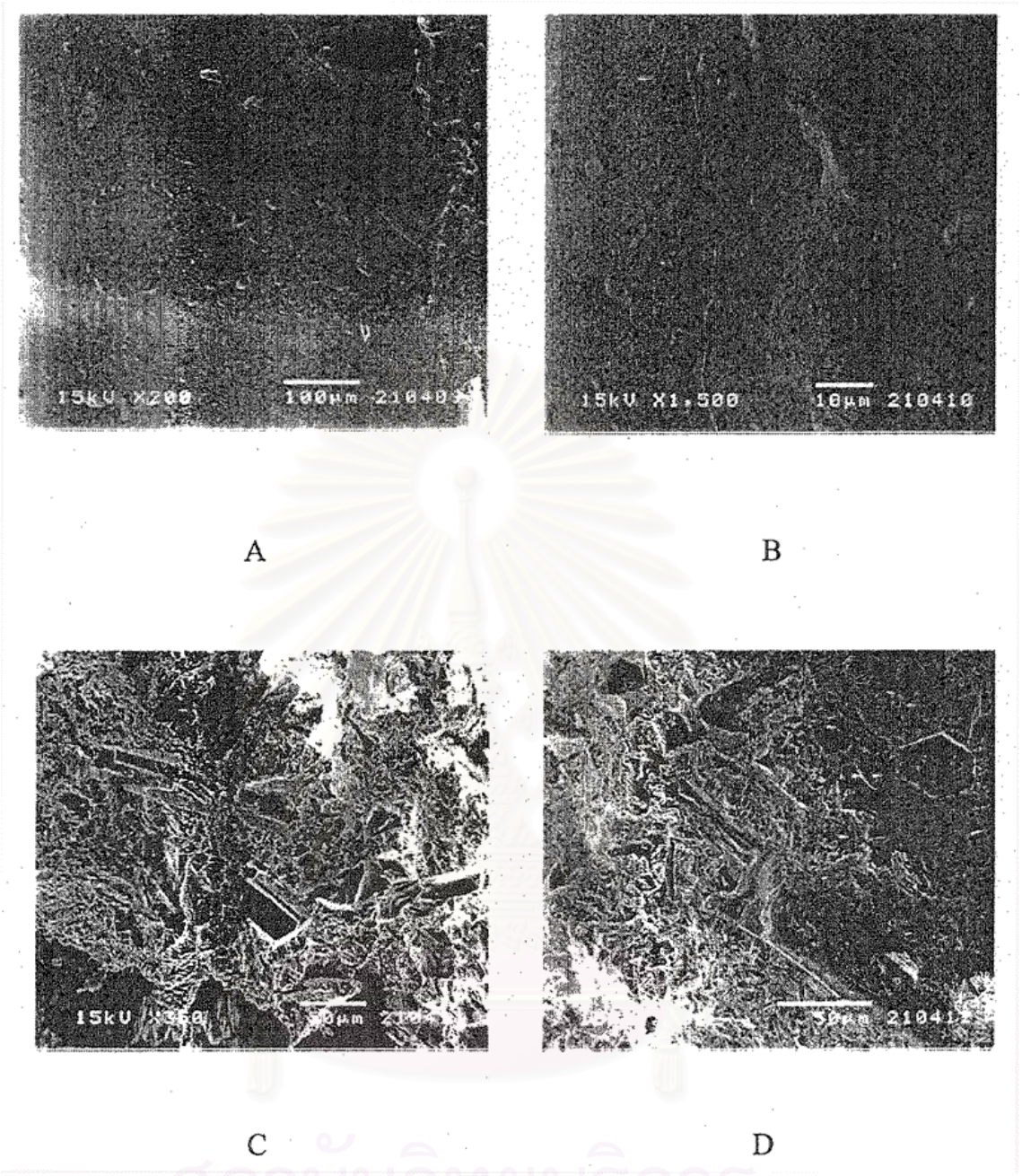


Figure 49 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G46/07 blending at 2:3 weight ratio and calculated HLB equal 5, before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

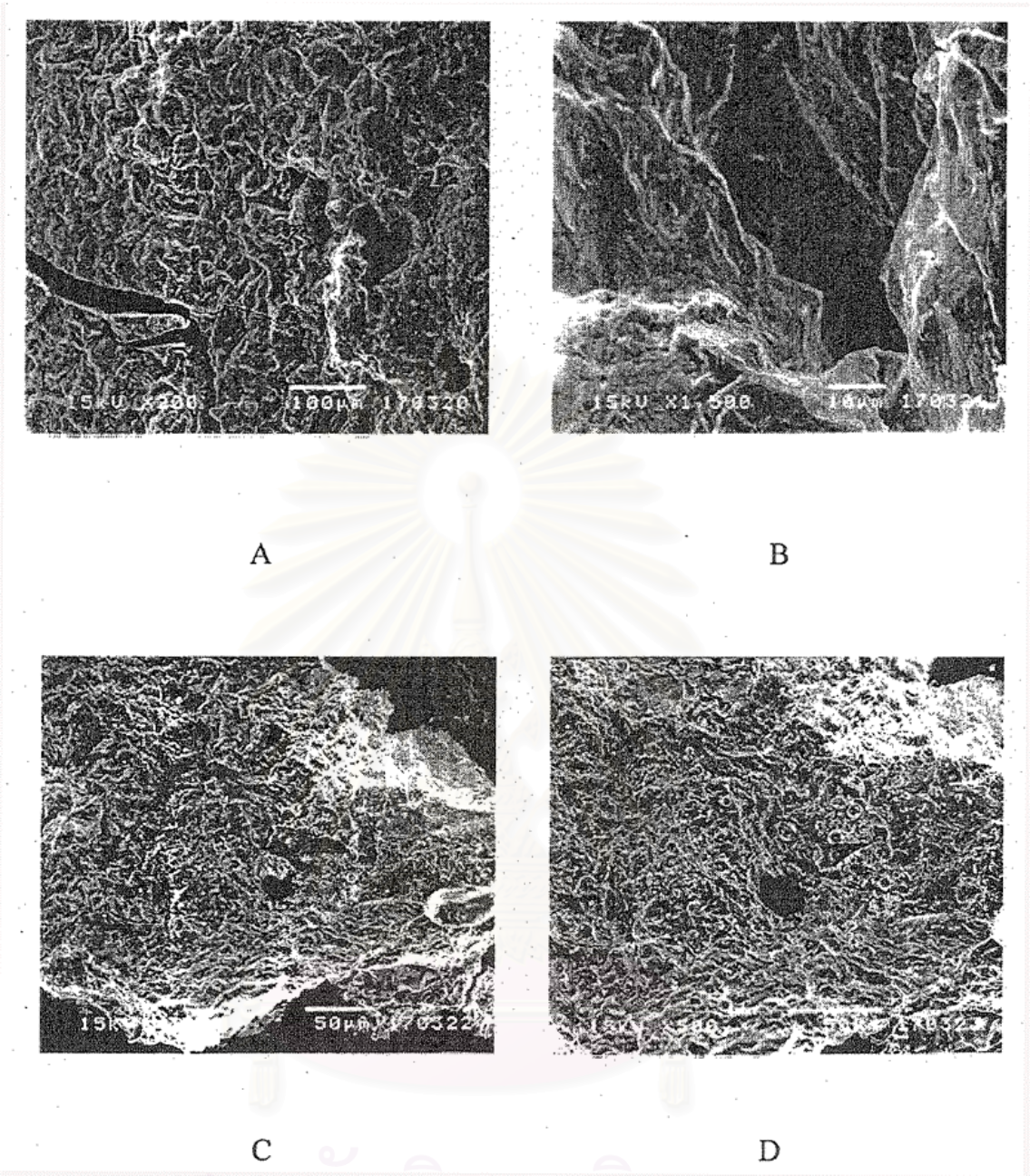


Figure 50 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G46/07 blending at 2:3 weight ratio and calculated HLB equal 5, after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

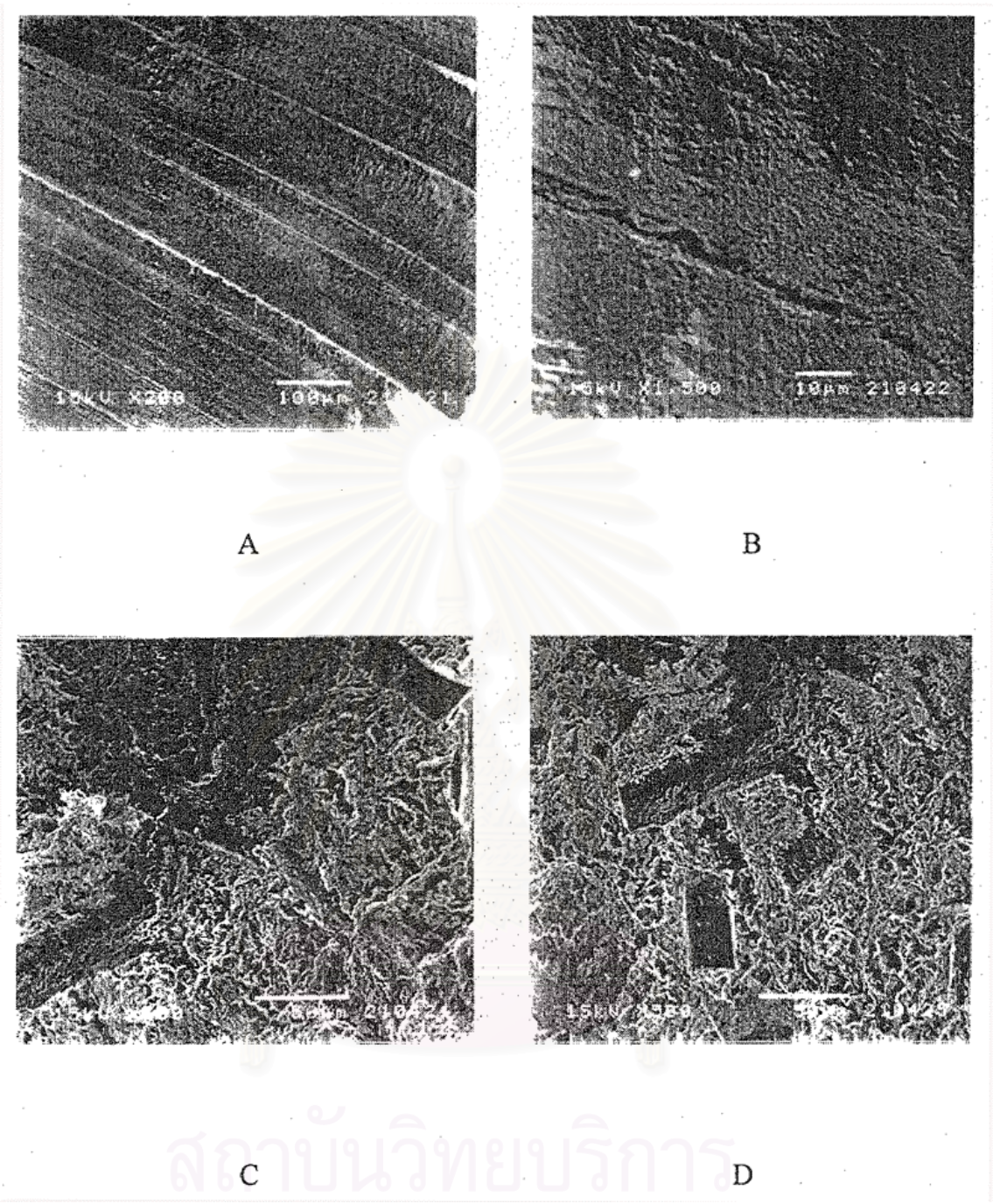


Figure 51 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G50/13 blending at 8:3 weight ratio and calculated HLB equal 5, before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500)

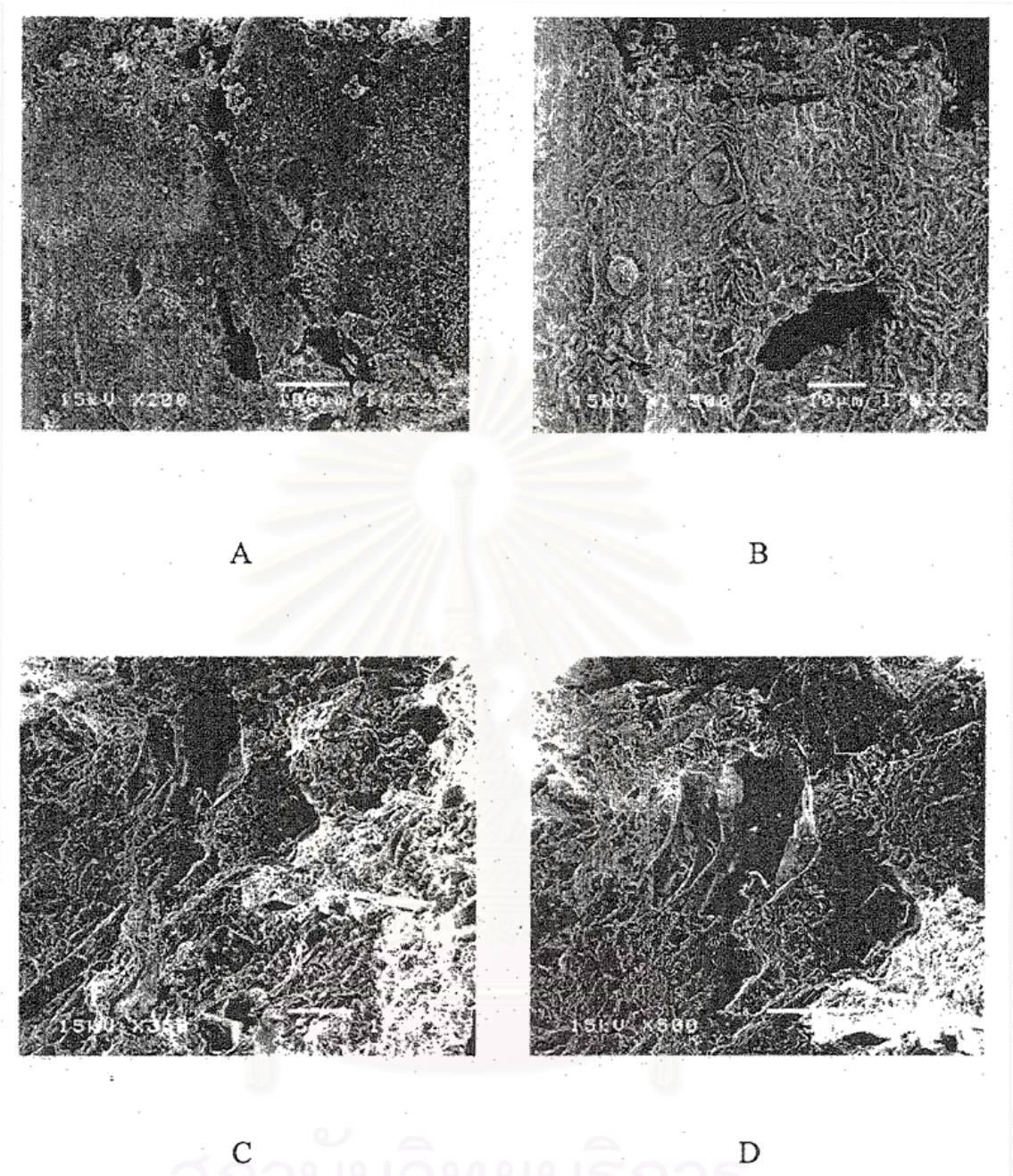


Figure 52 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G50/13 blending at 8:3 weight ratio and calculated HLB equal 5, after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

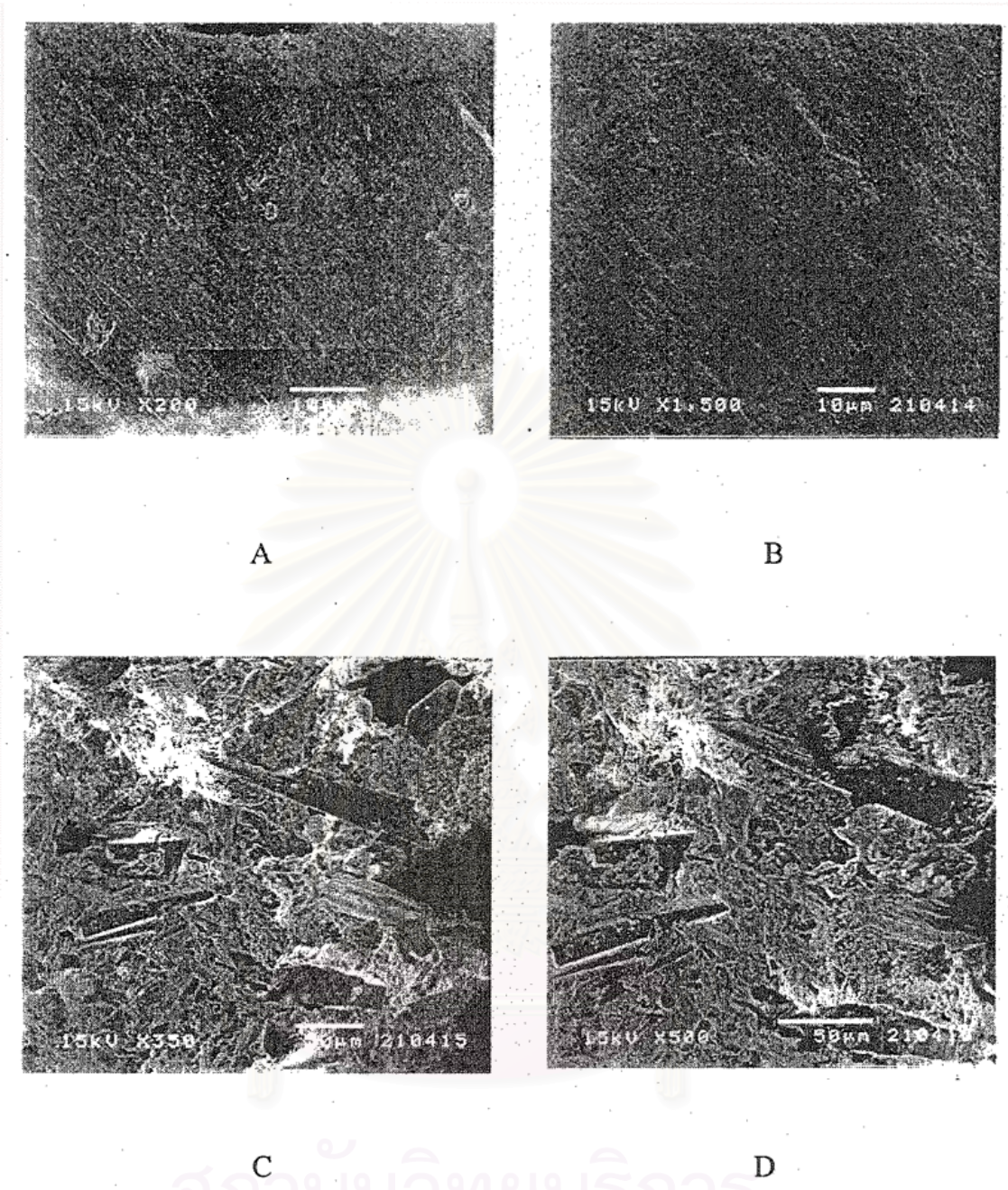


Figure 53 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G53/10 blending at 5:3 weight ratio and calculated HLB equal 5, before dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

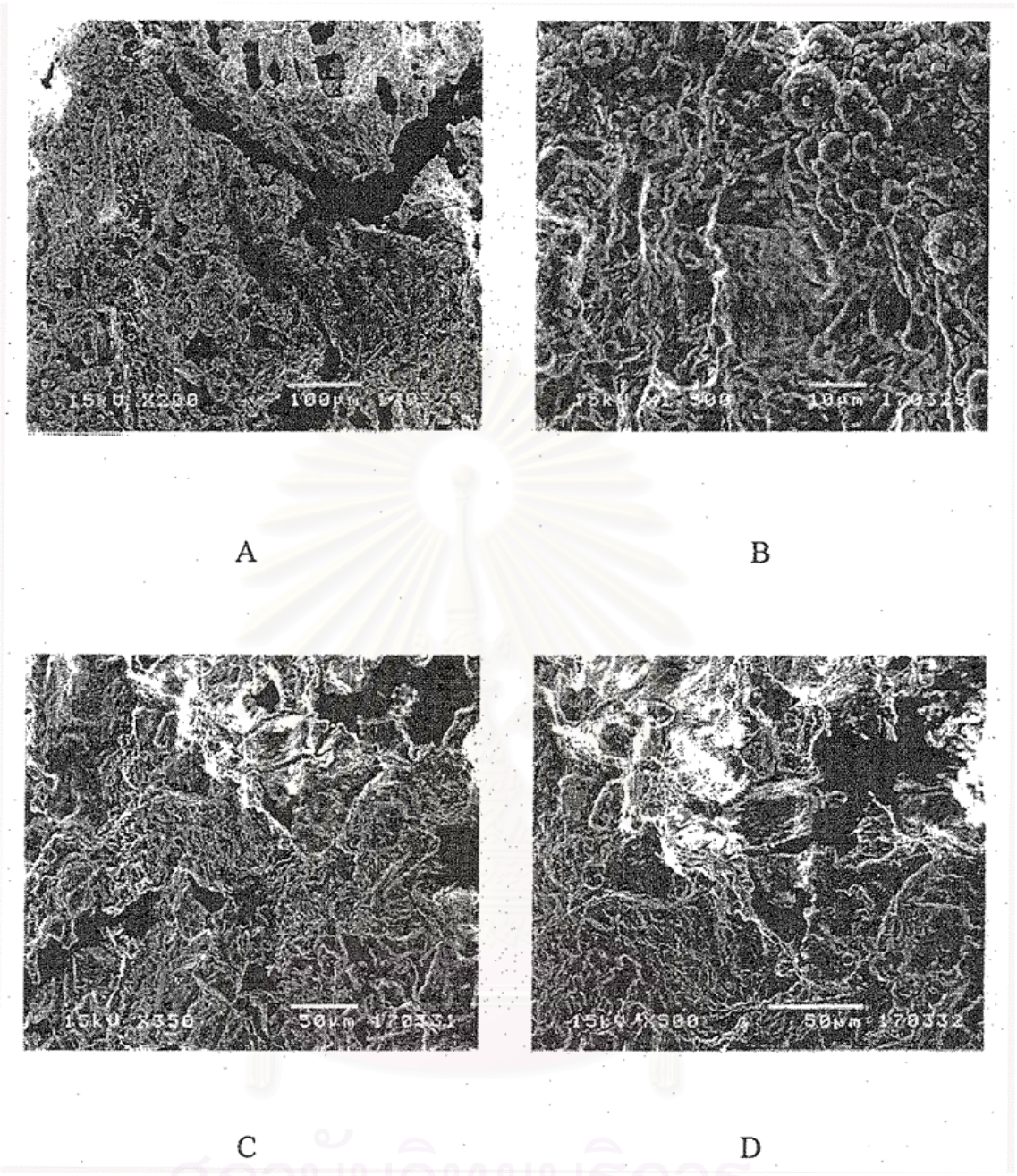


Figure 54 Scanning electron photomicrographs of diltiazem hydrochloride semisolid matrix with G50/02 and G53/10 blending at 5:3 weight ratio and calculated HLB equal 5, after dissolution test. (A-surface (x200), B-surface (x1,500), C-cross section (x350) and D-cross section (x500))

The major endothermic peak of Gelucires® might be used to forecast the melting point of each substance and correlated to first digit value of each Gelucire® type. Since melting point determination method of Supplier (Gattefose) used drop point method and was different than the process of thermal analysis, it might be suitable to be used for the indication of the true melting point. Thereby, main peak temperatures in degree celsius of base using DSC were employed as a representative thermal background. They are presented in Table 23.

The thermogram results of the mixture of bases showed that the mixtures exhibited two or more distinct endothermic peaks which corresponded to the major endothermic peak of each single pure component of the mixture (Tables 24-28). The results indicated that the intensities or the enthalpy (ΔH_f) of the endotherms directly dependent upon the proportion of each base in the mixture.

Similarly, incorporation of DTZ HCl powder in single or dual component of thermosoftening bases also revealed that DSC thermograms consisted of two-separated endothermic regions as the base region and the active compound region. The base region exhibited at lower temperature while the higher temperature was DTZ HCl powder. In single base preparations, the lower endothermic region of preparations was similar to the endothermic peak of the pure base and the higher endotherm was DTZ HCl peak which shifted from the pure DTZ HCl endotherm. The dual component base with DTZ HCl showed the lower endothermic region with minor shift from endothermic region of their mixture bases without DTZ HCl. The endothermic peak of DTZ HCl in dual bases component was still the same as described in single base component case. Thereby, the interaction between drug and base were minor or very negligible. The temperature shift might be due to the differences in the sample weight.

Heat of fusion (ΔH_f) or enthalpy of DTZ HCl endothermic peak are observed and summarized in Tables 23-28. They could be utilized for comparative studies among pure DTZ HCl powder, DTZ HCl in various single Gelucire® bases and different weight ratio of Gelucire® mixtures. The comparative results are presented in Figure 68.

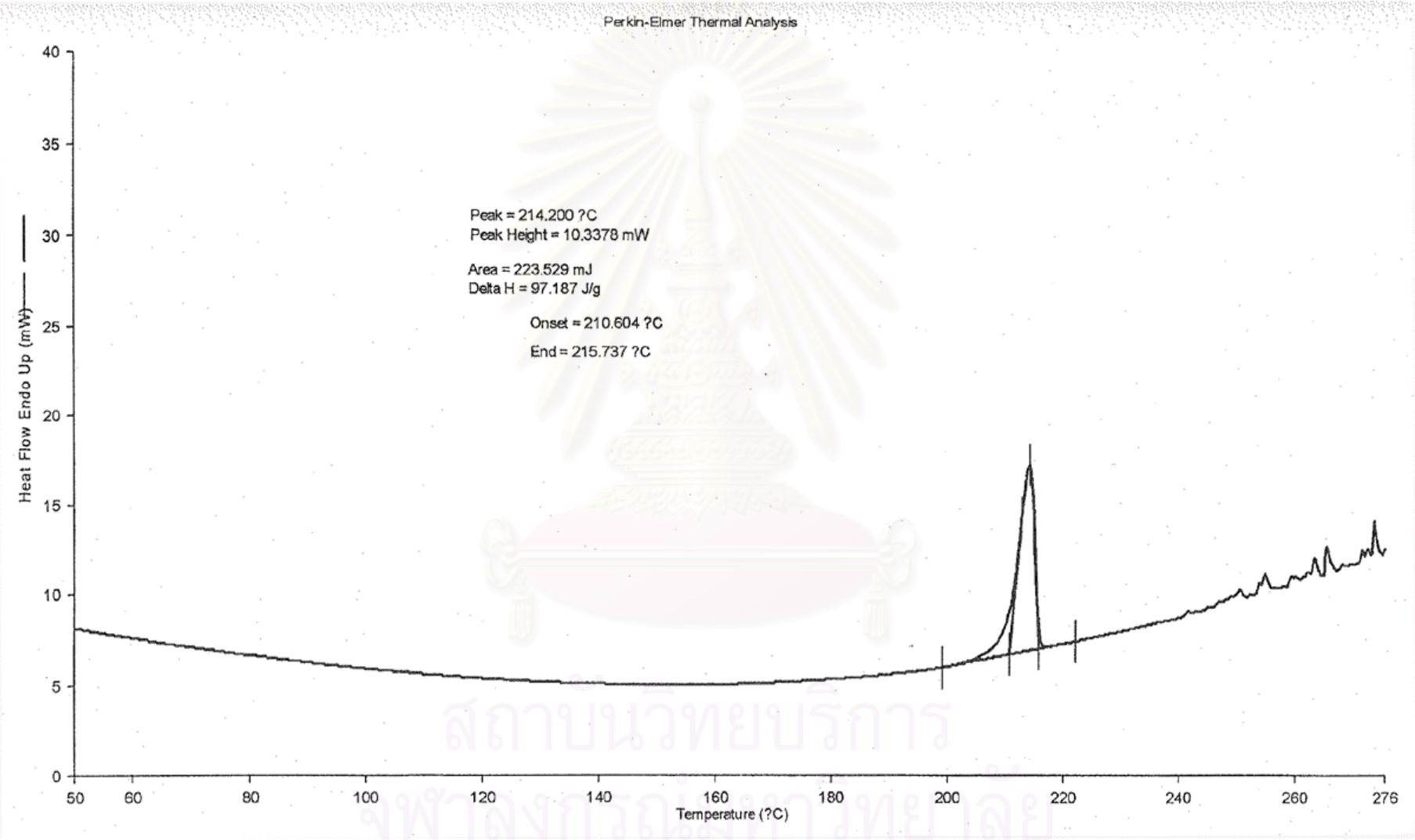


Figure 55 DSC thermogram of diltiazem hydrochloride powder with scanning rate 10°C/min

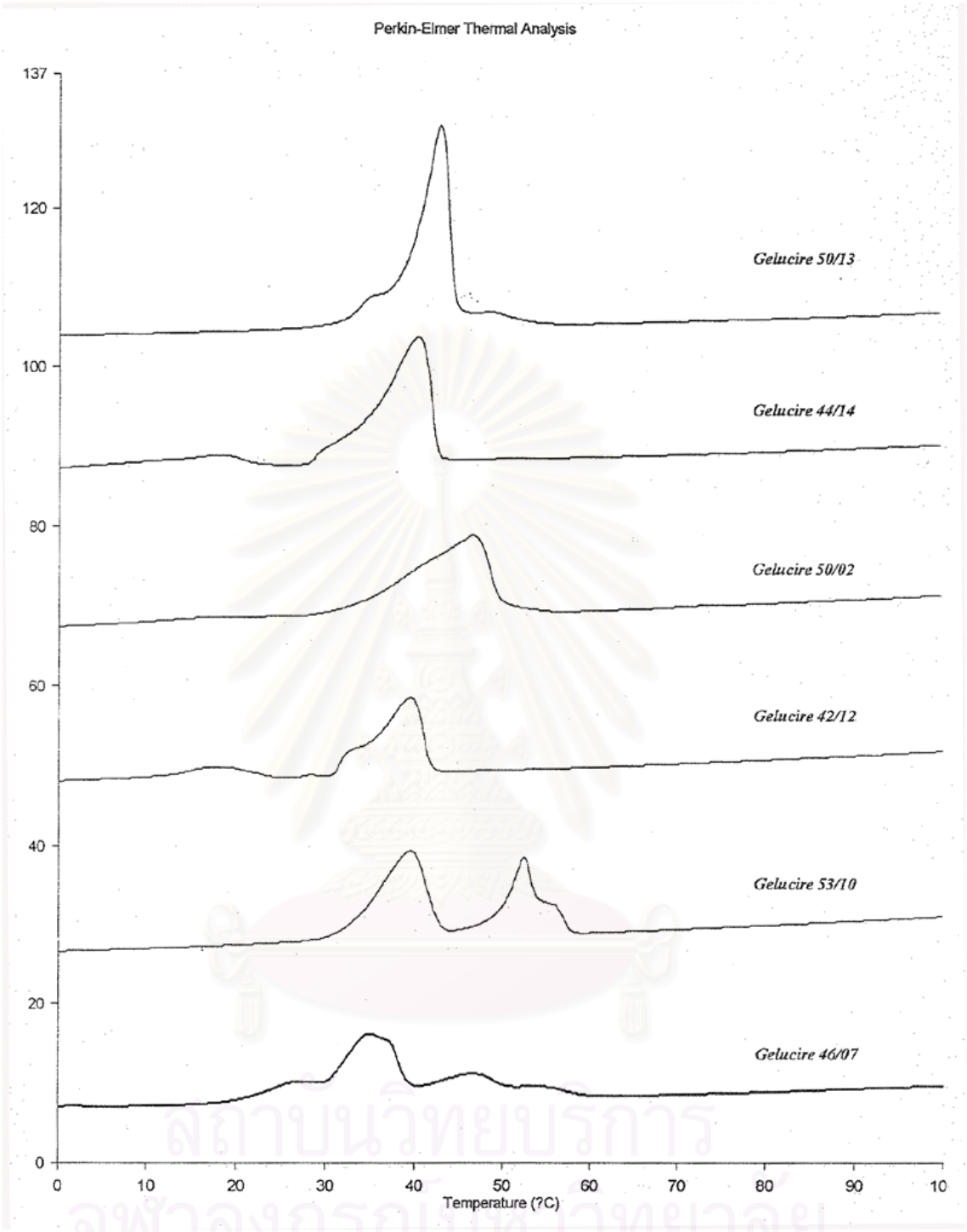


Figure 56 DSC thermograms of various thermosoftening bases.

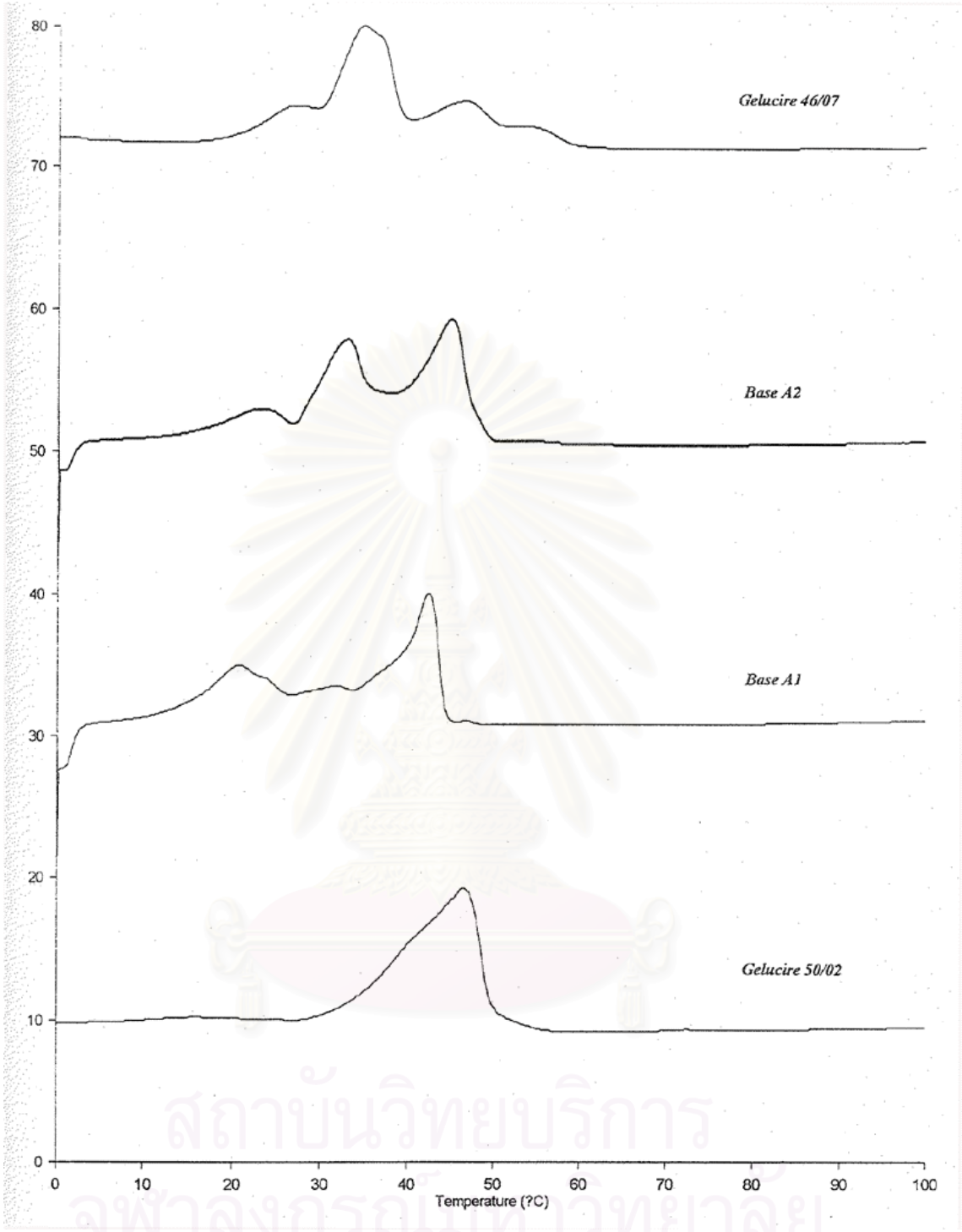


Figure 57 DSC thermograms of G50/02:G46/07 mixture bases. (The weight ratio of G50/02:G46/07 is 4:1 and 2:3 for A1 and A2, respectively.)

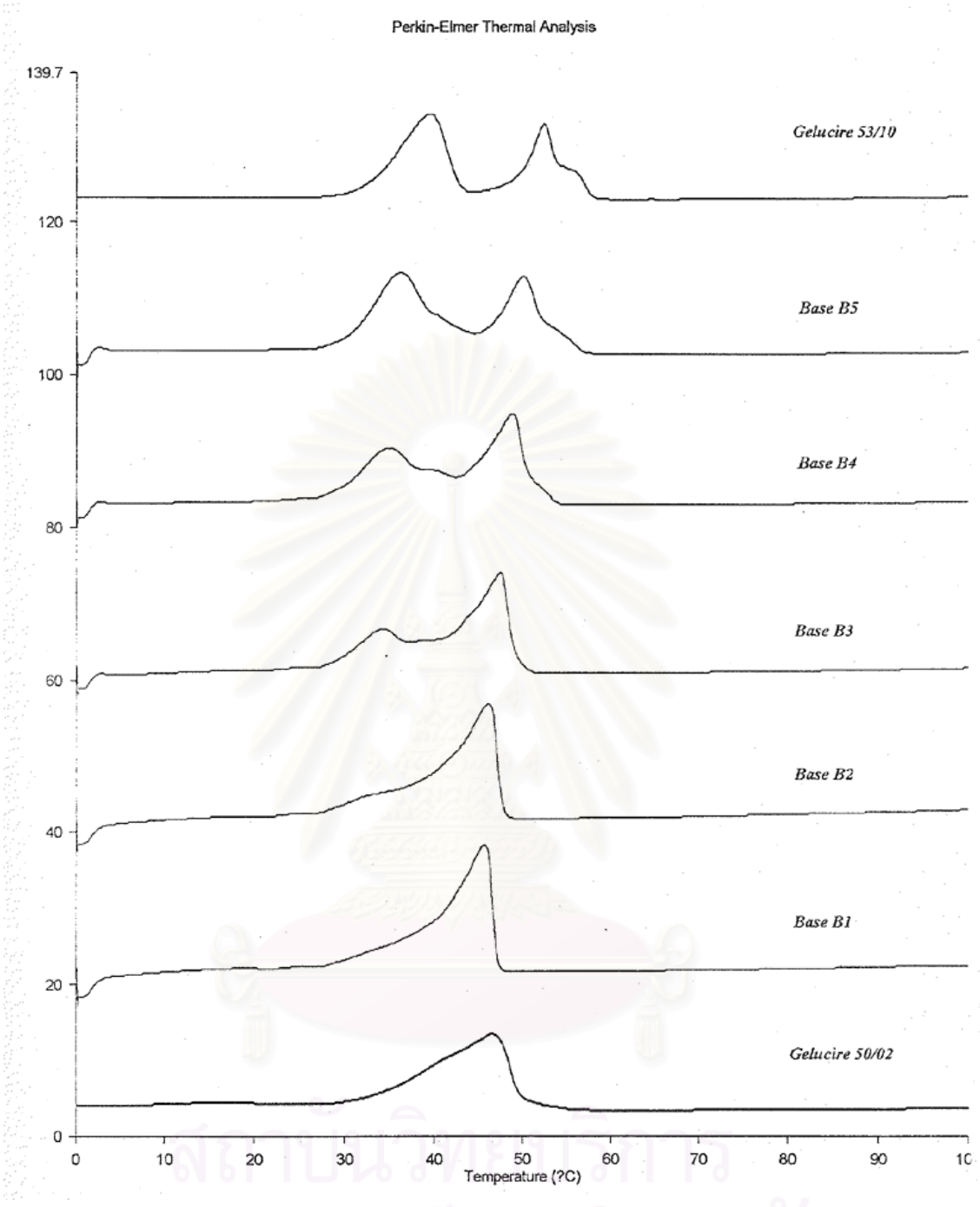


Figure 58 DSC thermograms of G50/02:G53/10 mixture bases. (The weight ratio of G50/02:G53/10 is 15:1, 7:1, 5:3, 3:5 and 1:7 for B1, B2, B3, B4 and B5, respectively.)

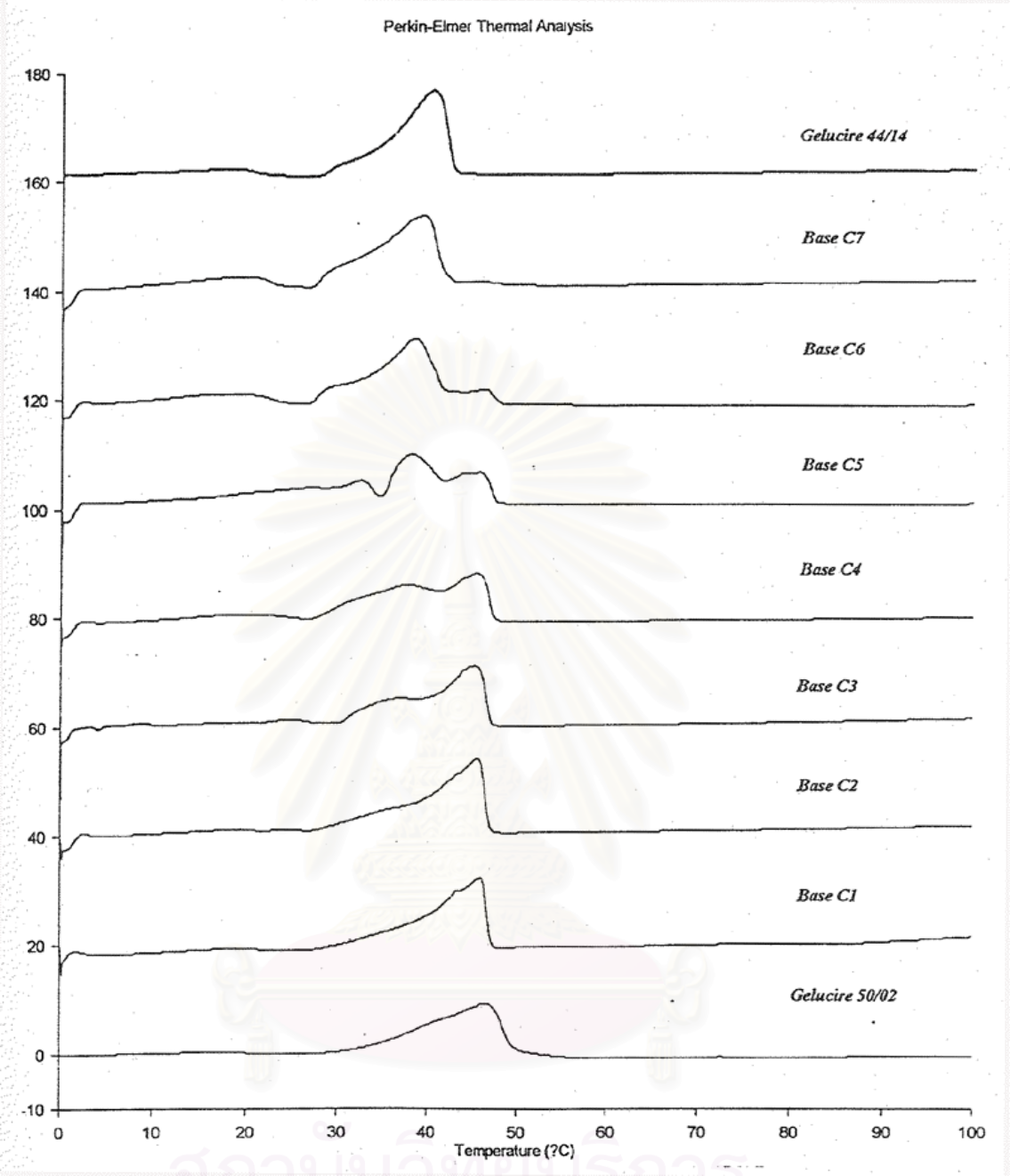
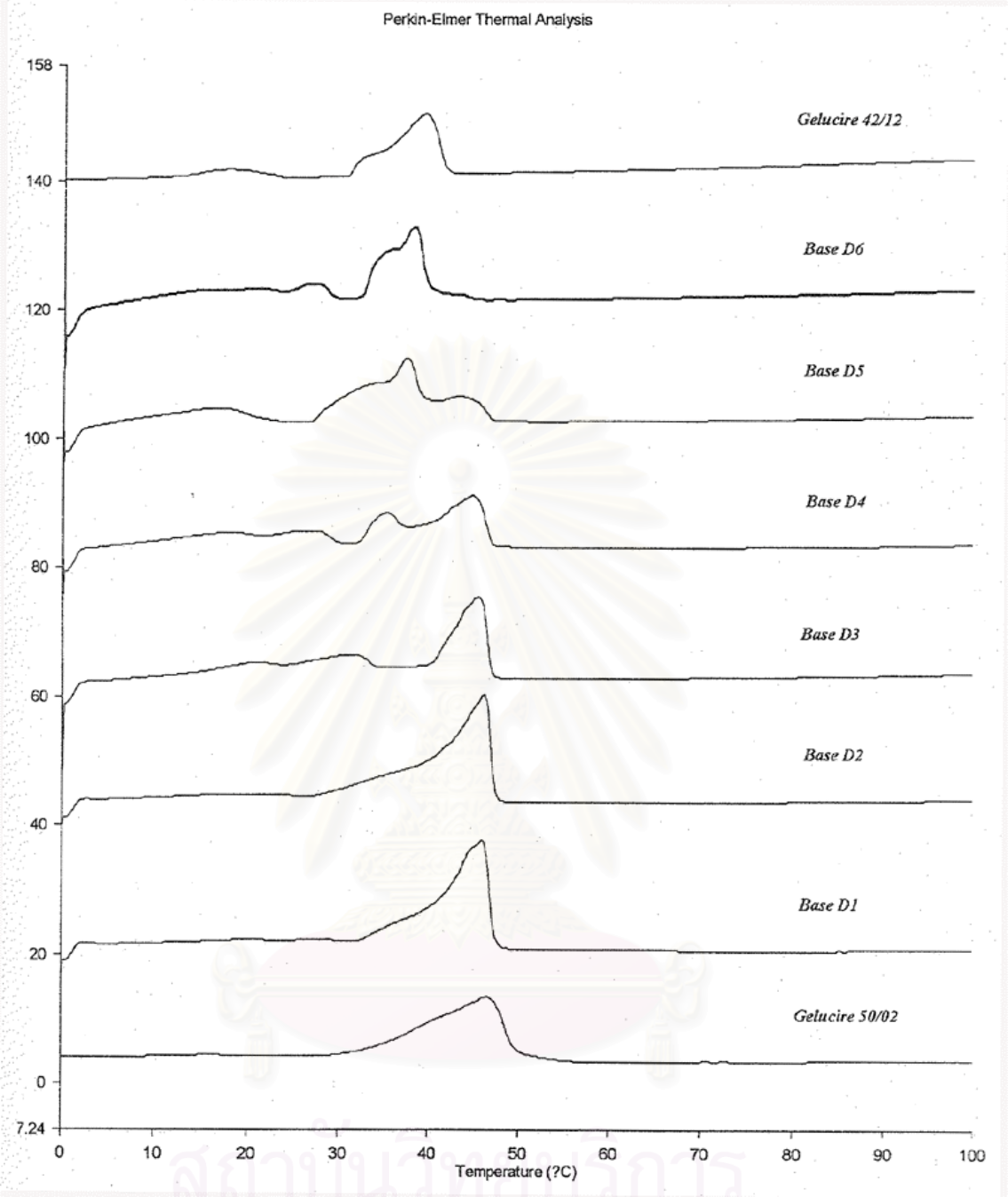


Figure 59 DSC thermograms of G50/02:G44/14 mixture bases. (The weight ratio of G50/02:G44/14 is 23:1, 11:1, 9:3, 7:5, 5:7, 3:9 and 1:11 for C1, C2, C3, C4, C5, C6 and C7, respectively.)



Figuer 60 DSC thermograms of G50/02:G42/12 mixture bases. (The weight ratio of G50/02:G42/12 is 19:1, 9:1, 7:3, 5:5, 3:7 and 1:9 for D1, D2, D3, D4, D5 and D6, respectively.)

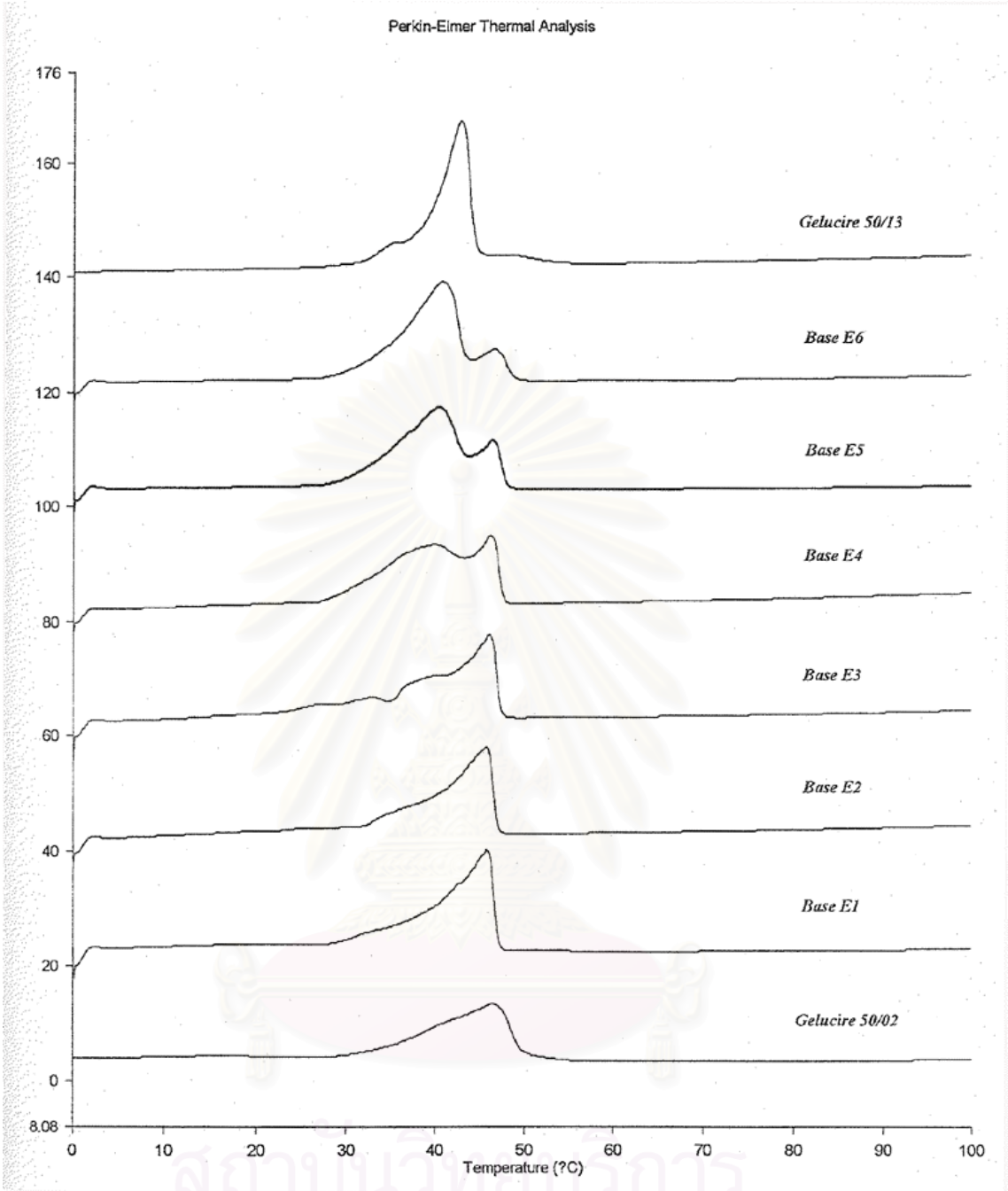


Figure 61 DSC thermograms of G50/02:G50/13 mixture bases. (The weight ratio of G50/02:G50/13 is 21.5:1, 10:1, 8:3, 6:5, 1:7 and 2:9 for E1, E2, E3, E4, E5 and E6, respectively.)

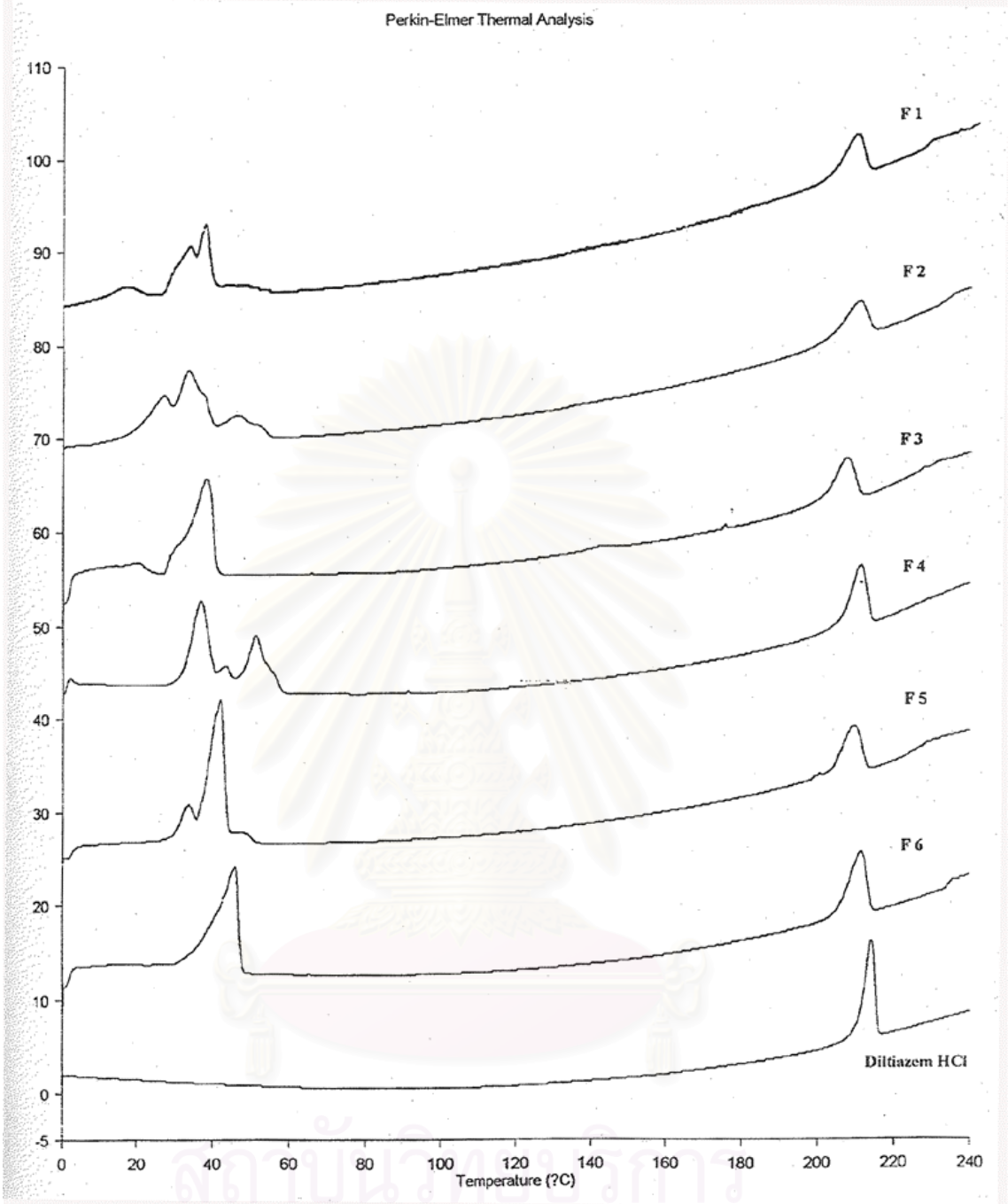


Figure 62 DSC thermograms of various preparations containing DTZ HCl at 90 mg level. (F1-DTZ HCl in G42/12, F2-DTZ HCl in G46/07, F3-DTZ HCl in G44/14, F4-DTZ HCl in G53/10, F5-DTZ HCl in G50/13 and F6-DTZ HCl in G50/02)

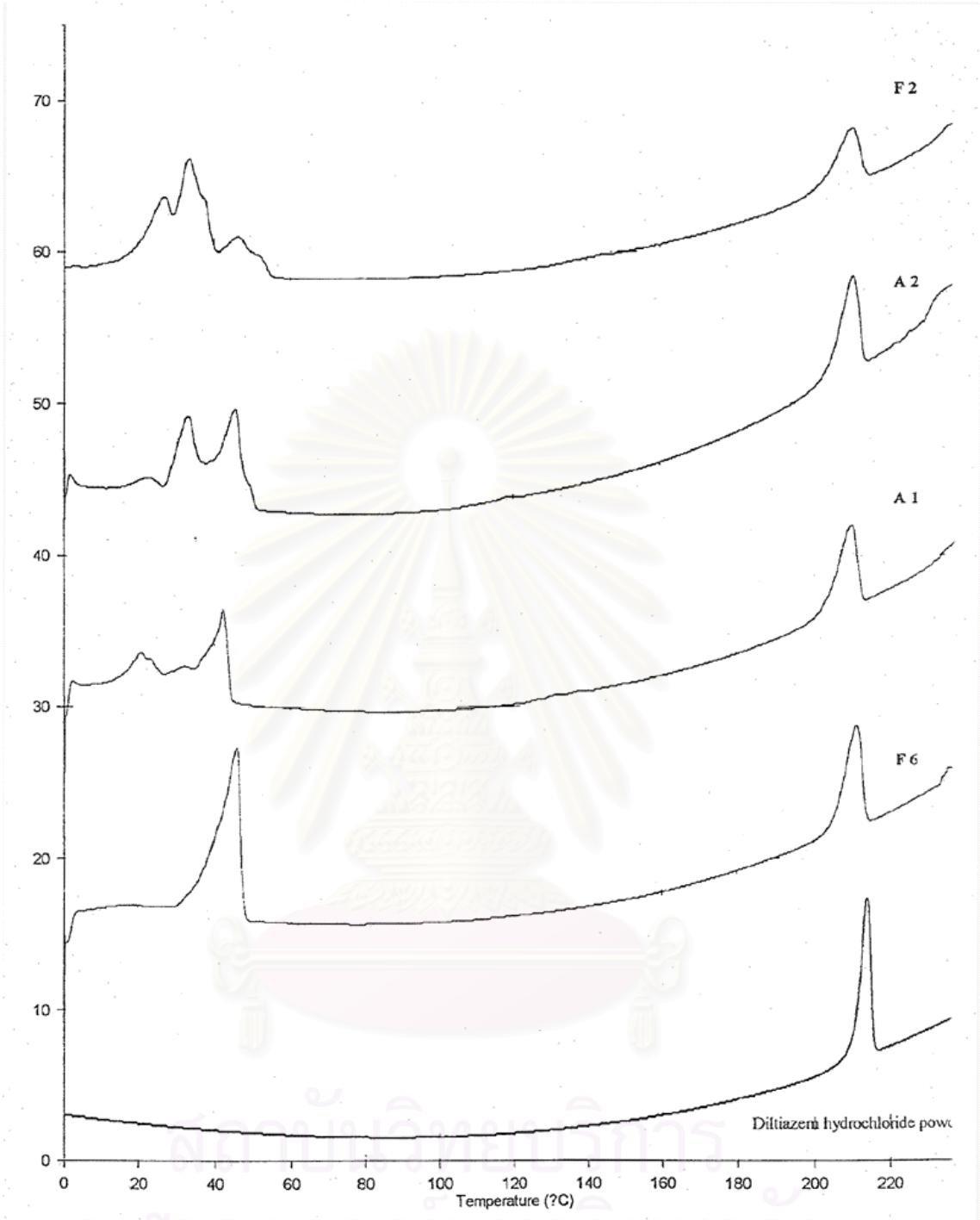


Figure 63 DSC thermograms of various preparations containing DTZ HCl at 90 mg level. (F2-DTZ HCl in G46/07, F6-DTZ HCl in G50/02, A1-DTZ HCl in mixed G50/02 and G46/07 and G46/07 as 4:1 weight ratio and A2-DTZ HCl in mixed G50/02 and G46/07 as 2:3 weight ratio)

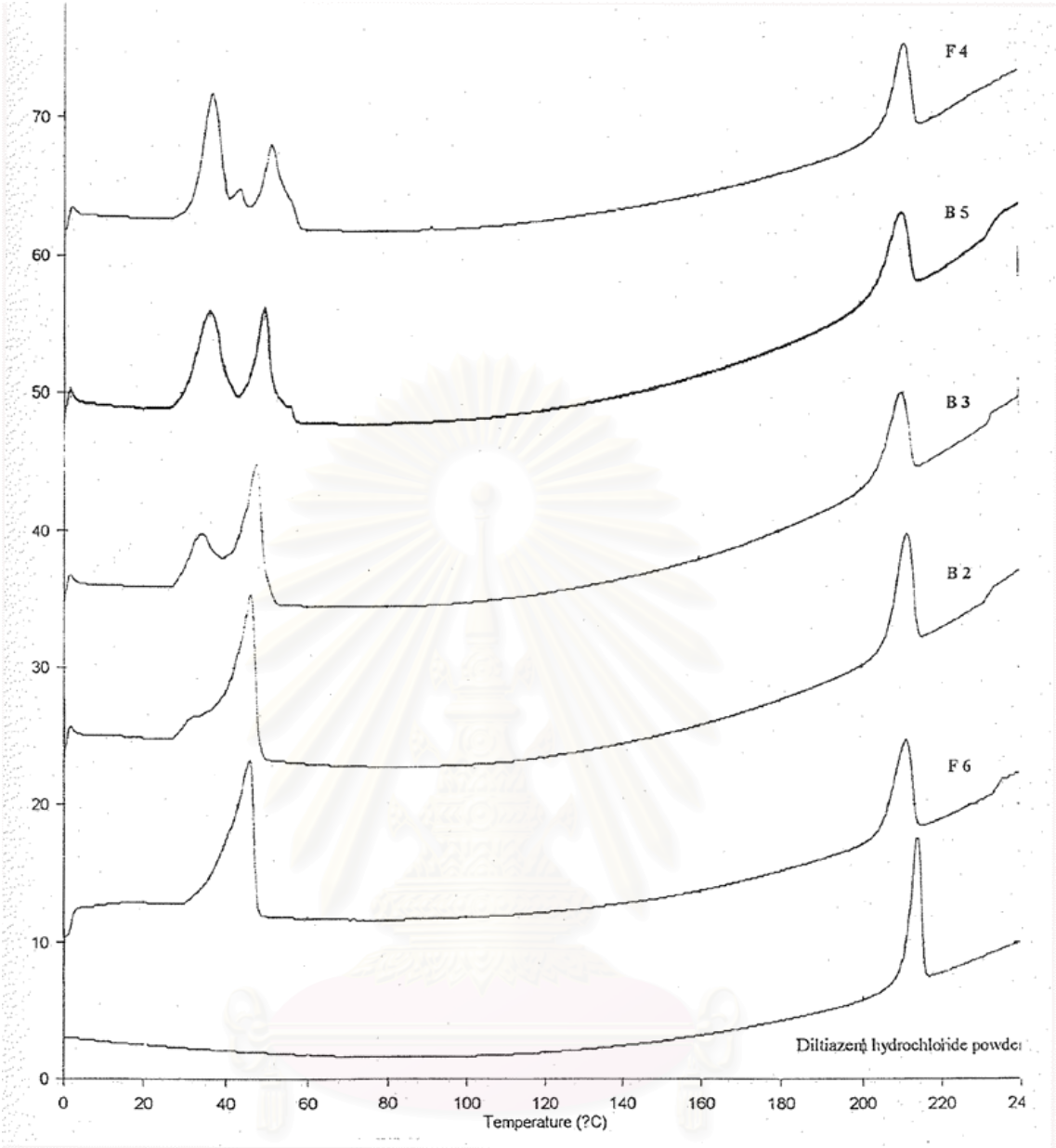


Figure 64 DSC thermograms of various preparations containing DTZ HCl at 90 mg level. (F4-DTZ HCl in G53/10, F6-DTZ HCl in G50/02, B2-DTZ HCl in mixed G50/02 and G53/10 as 7:1 weight ratio, B3-DTZ HCl in mixed G50/02 and G53/10 as 5:3 weight ratio and B5-DTZ HCl in mixed G50/02 and G53/10 as 1:7 weight ratio)

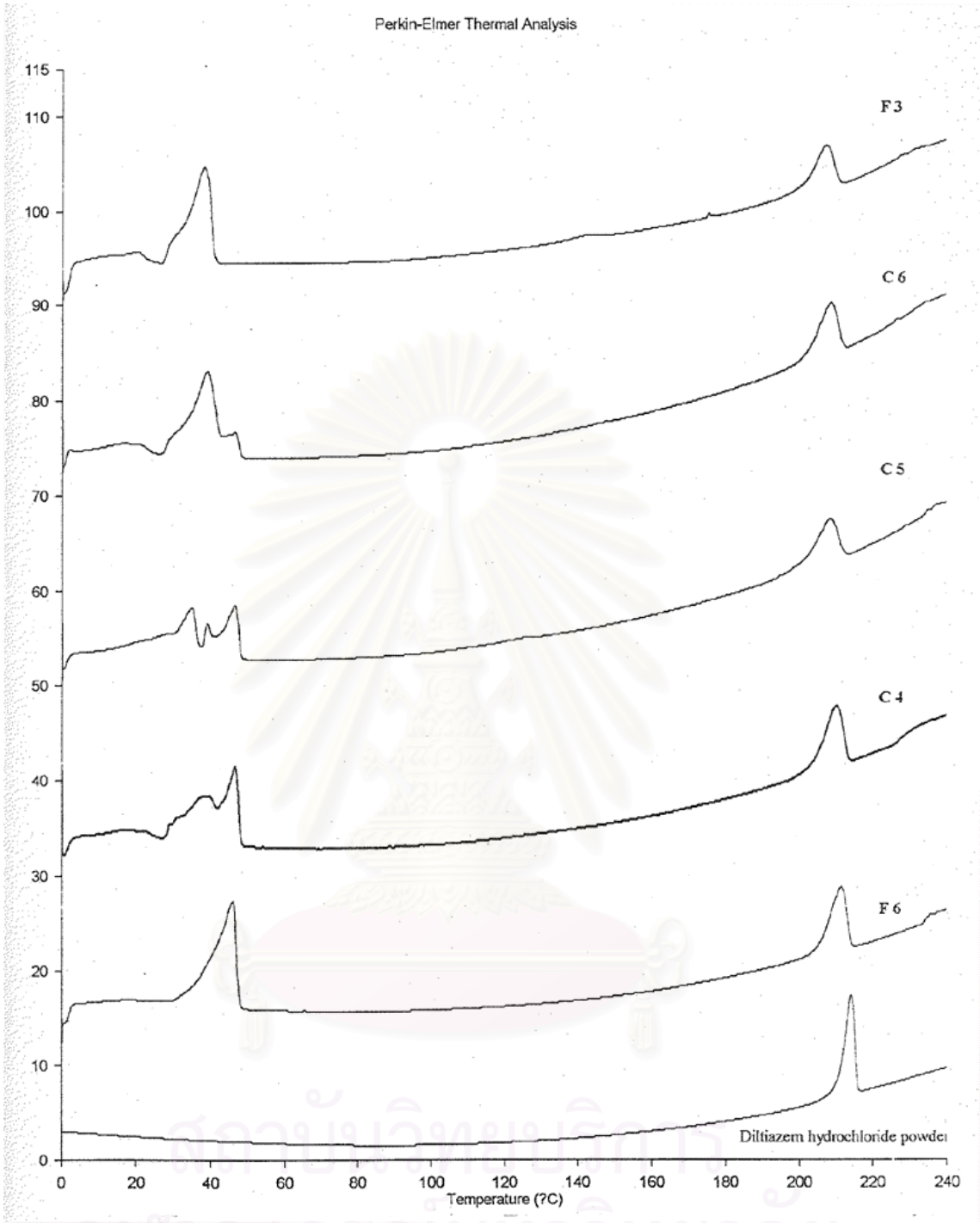


Figure 65 DSC thermograms of various preparations containing DTZ HCl at 90 mg level. (F3-DTZ HCl in G44/14, F6-DTZ HCl in G50/02, C4-DTZ HCl in mixed G50/02 and G44/14 as 7:5 weight ratio, C5-DTZ HCl in mixed G50/02 and G44/14 as 5:7 weight ratio and C6-DTZ HCl in mixed G50/02 and G44/14 as 3:9 weight ratio)

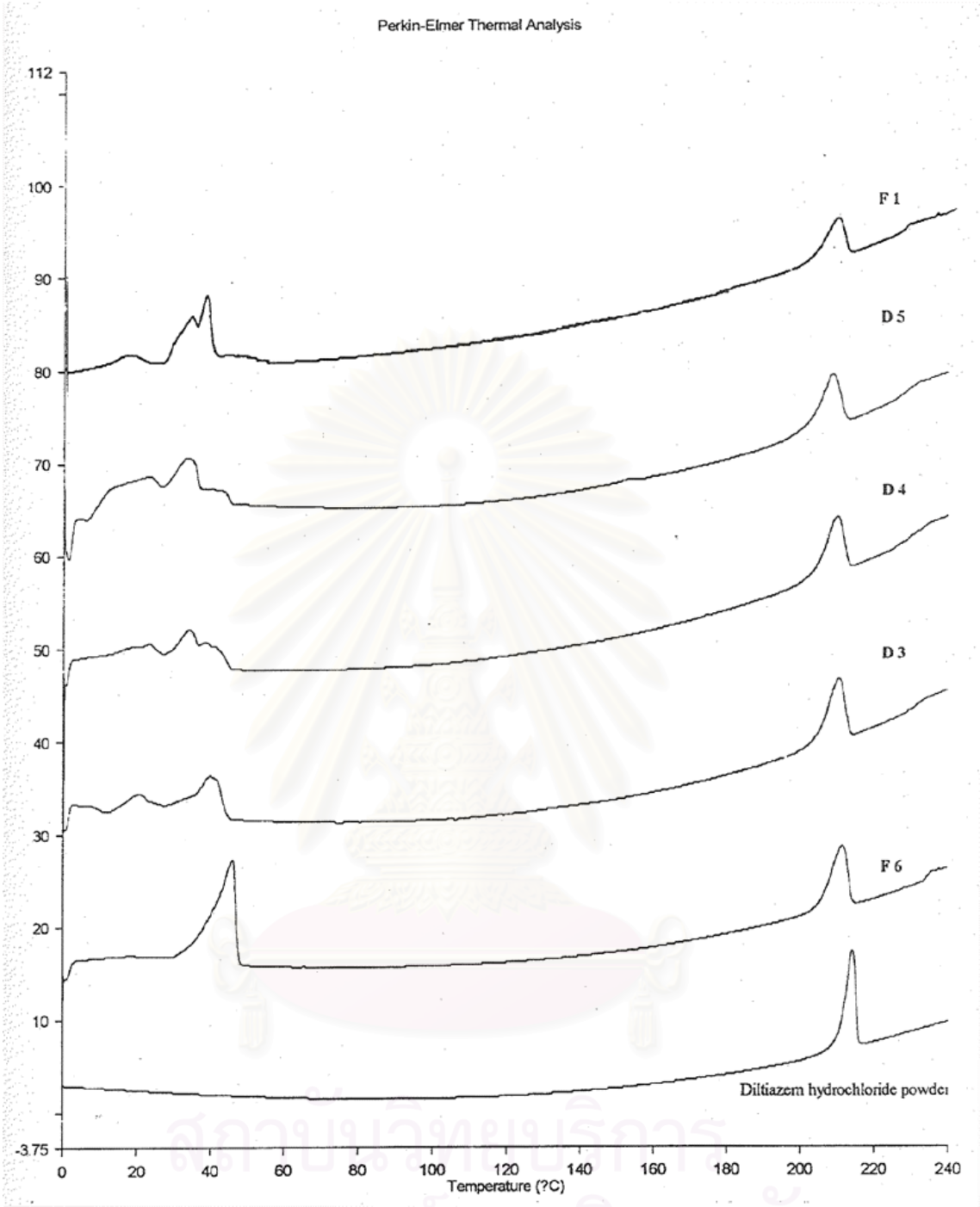


Figure 66 DSC thermograms of various preparations containing DTZ HCl at 90 mg level. (F1-DTZ HCl in G42/12, F6-DTZ HCl in G50/02, D3-DTZ HCl in mixed G50/02 and G42/12 as 7:3 weight ratio, D4-DTZ HCl in mixed G50/02 and G42/12 as 5:5 weight ratio and D5-DTZ HCl in mixed G50/02 and G42/12 as 3:7 weight ratio.)

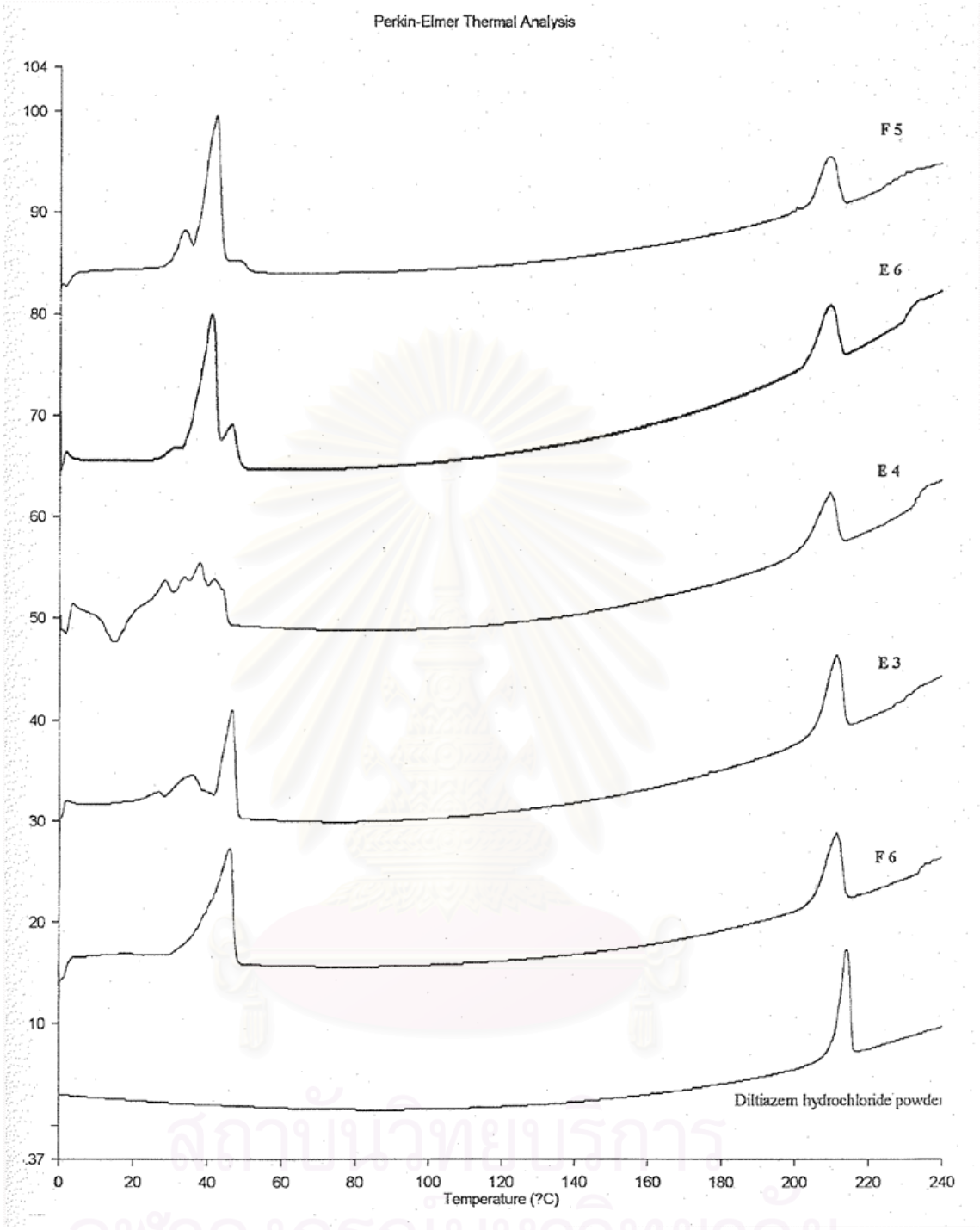


Figure 67 DSC thermogram of various preparations containing DTZ HCl at 90 mg level. (F5-DTZ HCl in G50/13, F6-DTZ HCl in G50/02, E3-DTZ HCl in mixed G50/02 and G50/13 as 8:3 weight ratio, E4-DTZ HCl in mixed G50/02 and G50/13 as 6:5 weight ratio and E6-DTZ HCl in mixed G50/02 and G50/13 as 2:9 weight ratio)

Table 23 Main endothermic peak temperature of pure DTZ HCl and other thermosoftening vehicles.

	Main endothermic peak temperature (T_m = °C)				
	≤30	31-40	41-50	51-60	≥200
DTZ HCl					214.20 (97.19)*
G42/12		39.53			
G44/14		40.37			
G46/07		35.03	46.70		
G50/02			46.50		
G50/13			42.87		
G53/10		39.53		52.53	

* () is sample heat of transition in J/g unit.

Table 24 Comparison of main endothermic peak temperature of pure DTZ HCl, G50/02, G46/07, DTZ SSM of both pure bases and DTZ HCl SSM consisted of mixture of 2 types at various proportions.

	Main endothermic peak temperature (T_m = °C)				
	≤30	31-40	41-50	51-60	≥200
DTZ HCl					214.20 (97.19)*
G46/07		35.03	46.70		
G46/07+DTZ		33.53	46.53		211.03 (82.53)*
G50/02			46.50		
G50/02+DTZ			46.03		211.37 (98.57)*
A† 1:4	20.87	31.90	42.53		
A† 1:4+DTZ	20.87	32.77	42.53		210.53 (91.78)*
A† 3:2	23.20	33.03	45.03		
A† 3:2+DTZ	22.20	33.20	45.70		210.70 (94.02)*

* A is the abbreviation for mixture between G46/07 and G50/02

* () is sample heat of transition in J/g unit.

Table 25 Comparison of main endothermic peak temperature of pure DTZ HCl, G50/02, G53/10, DTZ SSM of both pure bases and DTZ HCl SSM consisted of mixture of 2 types at various proportions.

	Main endothermic peak temperature (T_m = °C)				
	≤30	31-40	41-50	51-60	≥200
DTZ HCl					214.20 (97.19)*
G53/10		39.53		52.53	
G53/10+DTZ		38.50	44.00	51.33	211.33 (90.14)*
G50/02			46.50		
G50/02+DTZ			46.03		211.37 (98.57)*
B† 1:7		34.00	46.20		
B† 1:7+DTZ			46.37		211.70 (103.40)*
B† 3:5		34.33	47.50		
B† 3:5+DTZ		34.39	47.70		210.53 (91.14)*
B† 1:7		36.20	50.03		
B† 1:7+DTZ		36.37	49.70		210.70 (95.39)*

† B is the abbreviation of mixture between G44/14 and G50/02.

* () is sample heat of transition in J/g unit.

Table 26 Comparison of main endothermic peak temperature of pure DTZ HCl, G50/02, G44/14, DTZ SSM of both pure bases and DTZ HCl SSM consisted of mixture of 2 types at various proportions.

	Main endothermic peak temperature (T_m = °C)				
	≤30	31-40	41-50	51-60	≥200
DTZ HCl					214.20 (97.19)*
G44/14		40.37			
G44/14+DTZ		38.37			207.53 (71.27)*
G50/02			46.50		
G50/02+DTZ			4603		211.37 (98.57)*
C† 5:7		37.87	45.37		
C† 5:7+DTZ		39.37	46.70		210.20 (99.98)*
C† 7:5		32.53 38.20	45.00		
C† 7:5+DTZ		35.03 39.20	46.70		208.53 (80.83)*
C† 9:3		38.37	42.00		
C† 9:3+DTZ		39.20	43.00		208.70 (83.99)*

† C is the abbreviation of mixture between G44/14 and G50/02.

* () is sample heat of transition in J/g unit.

Table 27 Comparison of main endothermic peak temperature of pure DTZ HCl, G50/02, G42/12, DTZ SSM of both pure bases and DTZ HCl SSM consisted of mixture of 2 types at various proportions.

	Main endothermic peak temperature (T_m = °C)				
	≤30	31-40	41-50	51-60	≥200
DTZ HCl					214.20 (97.19)*
G42/12		39.53			
G42/12+DTZ	23.37	38.20			208.20 (82.39)*
G50/02			46.50		
G50/02+DTZ			46.03		211.37 (98.57)*
D† 3:7	21.00	31.70	45.70		
D† 3:7+DTZ	20.00		40.00		210.33 (97.25)*
D† 5:5	18.50 26.00	35.67	44.87		
D† 5:5+DTZ		34.67			210.33 (91.57)*
D† 7:3	16.70	37.53	43.53		
D† 7:3+DTZ	23.50	33.67			208.67 (84.68)*

† D is the abbreviation of mixture between G42/12 and G50/02.

* () is sample heat of transition in J/g unit.

Table 28 Comparison of main endothermic peak temperature of pure DTZ HCl, G50/02, G50/13, DTZ SSM of both pure bases and DTZ HCl SSM consisted of mixture of 2 types at various proportions.

	Main endothermic peak temperature (T_m = °C)				
	≤30	31-40	41-50	51-60	≥200
DTZ HCl					214.20 (97.19)*
G50/13		35.00	42.87	48.00	
G50/13+DTZ		34.00	42.22	45.00-48.00	209.37 (80.48)*
G50/02			46.50		
G50/02+DTZ			46.03		211.37 (98.57)*
E† 3:8		34.70	46.20		
E† 3:8+DTZ		36.50	46.70		211.53 (103.97)*
E† 5:6			40.03 46.37		
E† 5:6+DTZ	28.53	33.70 38.03	41.87		209.70 (84.00)*
E† 9:2			40.87 46.70		
D† 9:2+DTZ		32.70	41.03 46.70		208.70 (84.01)*

† E is the abbreviation of mixture between G50/13 and G50/02.

* () is sample heat of transition in J/g unit.

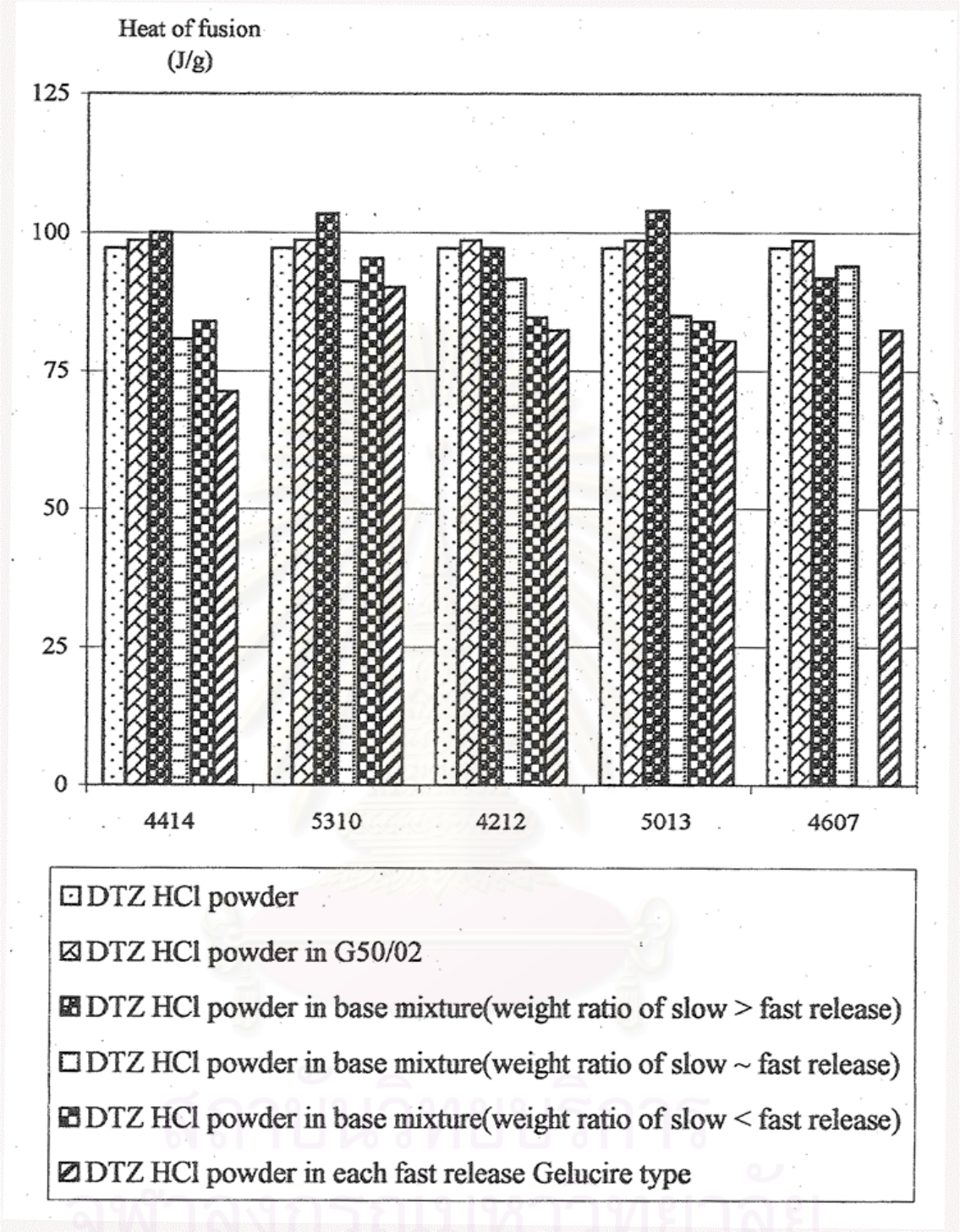


Figure 68 Comparative chart in heat of fusion of diltiazem hydrochloride substance in various single pure Gelucires and blending mixture of slow to fast release properties at different weight ratios.

Another reasons why endothermic peak of each component was shift will be discussed in the discussion chapter of this study.

2.3) Physical state of active ingredient in SSM

Indirect method to observe physical behavior of drug crystal in semisolid matrix remained on filter paper after heating process was used to understand about the distribution of drug particles in the matrix. Remain solid substances and thermosoftening substances were, hence, recorded in appearance, shape and optical properties as shown in Figures 69-74. The data of remain materials on the filter paper are summarized in Tables 29 and 30.

Entire thermosoftening bases were studied the same way as the remain solid particles and saved as the reference. The data was compared with either DTZ HCl powder or pure semisolid bases for the determination of the physical state orientation of drug particles in matrix system.

All thermosoftening bases were founded to be irregular in shape but they were stilled birefringent. The data concluded that they were crystalline which corresponded with the results from thermal analysis and X-ray powder diffraction. Pure DTZ HCl particles are rectangular in shape, translucent and birefringence under polarized light. The DTZ HCl crystal shape was correlated with SEM photograph (Figure 31). All of the remaining solid in the SSM formulas showed that they were similar to pure DTZ HCl particle in shape and birefringency. Vice versa, it was different from other wax-like materials in shape but birefringence properties was found to be the same as in Gelucire® materials.

Table 29 Physical appearance and optical properties of DTZ HCl powder and various thermosofening bases.

Formula	Physical Appearance under	
	Normal light	Polarized light
DTZ HCl Powder	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
G 42/12	Irregular shape and translucent	Irregular shape and birefringence
G 44/14	Irregular shape and translucent	Irregular shape and birefringence
G 46/07	Irregular shape and translucent	Irregular shape and birefringence
G 50/02	Irregular shape	Irregular shape and birefringence
G 50/13	Irregular shape and translucent	Irregular shape and birefringence
G 53/10	Irregular shape and translucent	Irregular shape and birefringence

2.4) The IR spectroscopy

IR spectra of samples were recorded for comparative study. The IR spectra of DTZ HCl powder, Gelucires® and DTZ HCl in single or dual mixture of Gelucires® are illustrated in Figures 75-87, respectively.

The major peaks of IR spectra were summarized and categorized to correlate the main functional group in the molecular structure (Tables 32-34). The principle peaks of pure DTZ HCl were exhibited at wave number (cm^{-1}) 782, 840, 1220, 1250, 1681, 1745, 2392, 2839, 2966 and 3036, respectively. The peaks at 782 and 840 cm^{-1} resulted from p-substituted and o-substituted aromatic C-H stretching. At 1220 cm^{-1} strong intensity peak referred to C=O stretching of the ester group. For 1250 cm^{-1} indicated O-CH_3 aromatic ether with asymmetric stretching. The strong peak responded at 1681, 1745 and 2392 cm^{-1}, showed lactam C=O stretching, acetate stretching and amine HCl NH stretching (tertiary amine salt group), respectively. Other peaks represented O-CH_3 stretching at 2839 cm^{-1}, aliphatic CH stretching at 2966 and aromatic CH stretching at 3036 cm^{-1}.

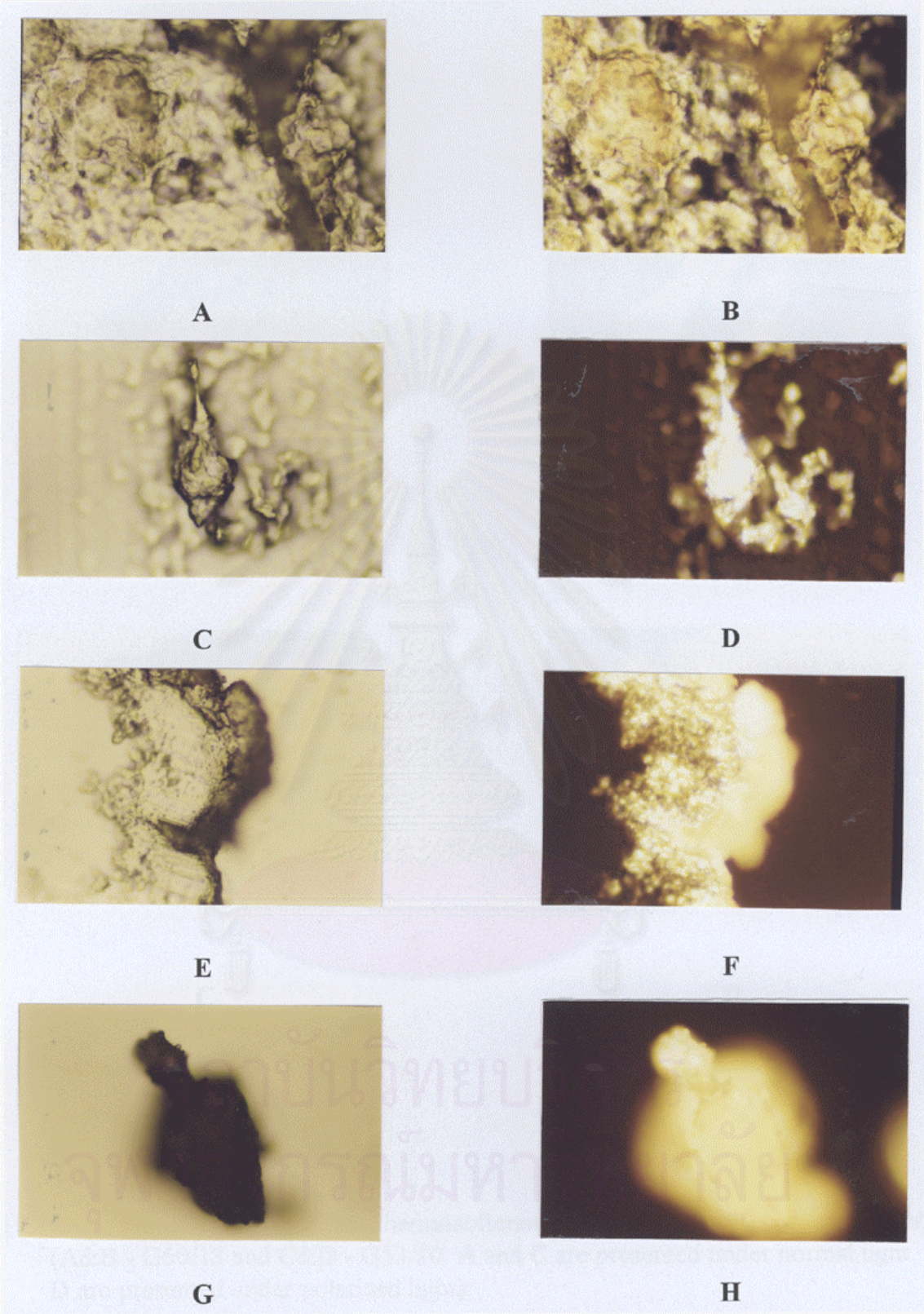


Figure 69 Photomicrographs of various thermosoftening bases under different light property. (A&B-G42/12, C&D-G44/14, E&F-G46/07 and G&H-G50/02. A, C, E and G are presented under normal light. B, D, F and H are presented under polarized light).

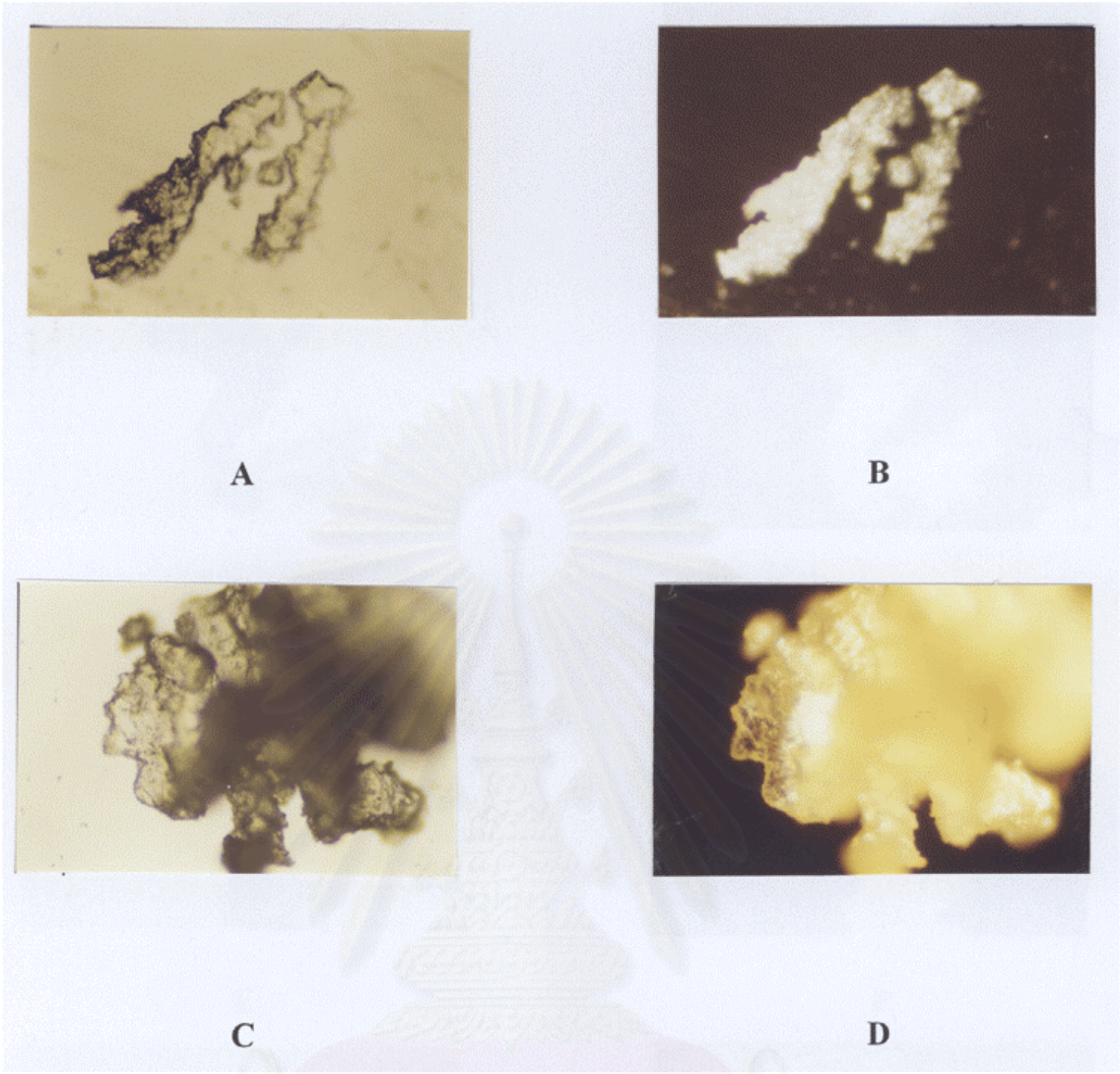


Figure 70 Photomicrographs of various thermosoftening basaes under different light property. (A&B-G50/13 and C&D-G53/10. A and C are presented under normal light. B and D are presented under polarized light).

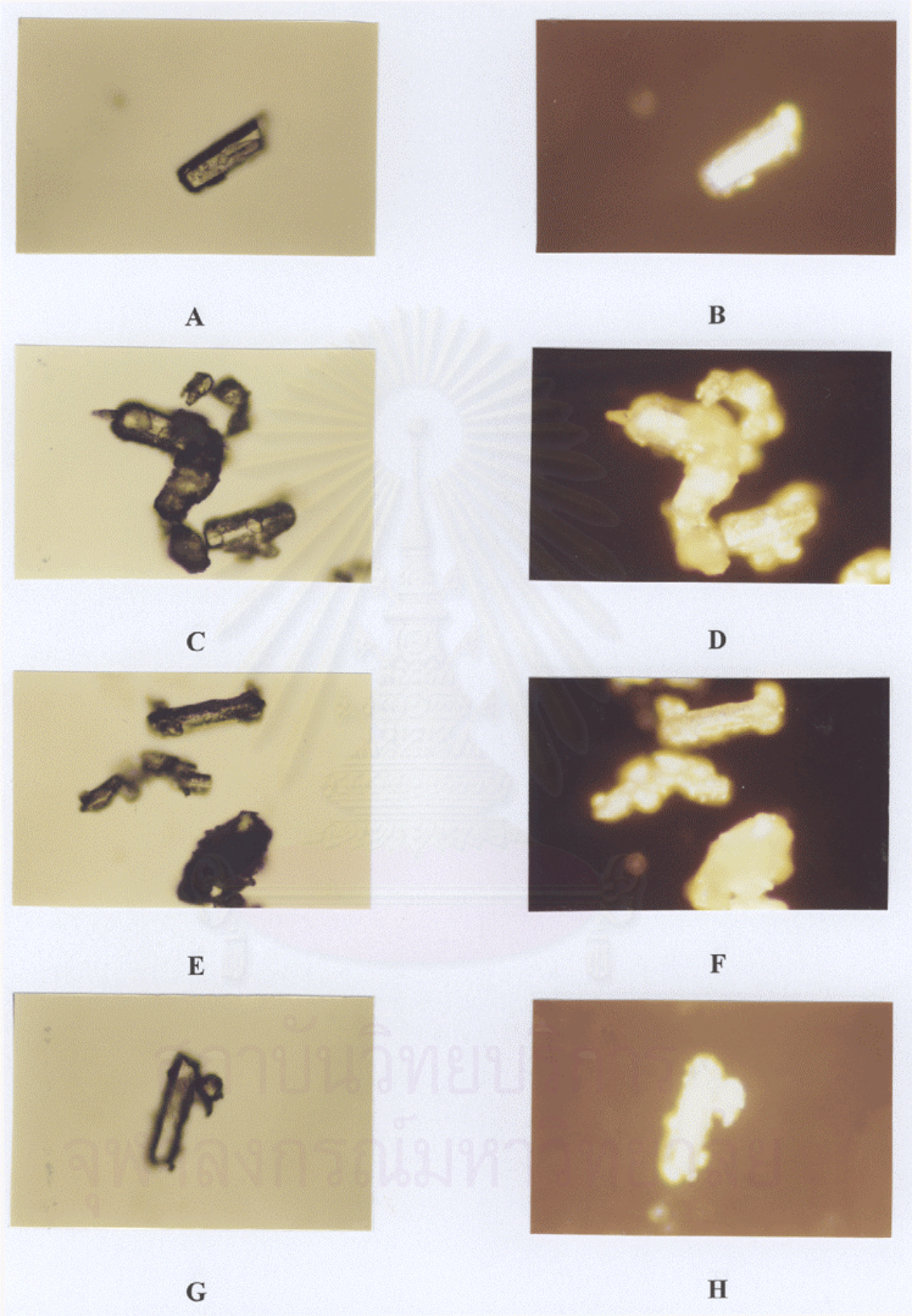


Figure 71 Photomicrographs of remained solid in physical state of active ingredients at various drug loading levels under different light property. (A&B-30 mg load, C&D-45 mg load, E&F-60 mg load and G&H-75 mg load. A, C, E and G are presented under normal light. B, D, F and H are presented under polarized light)

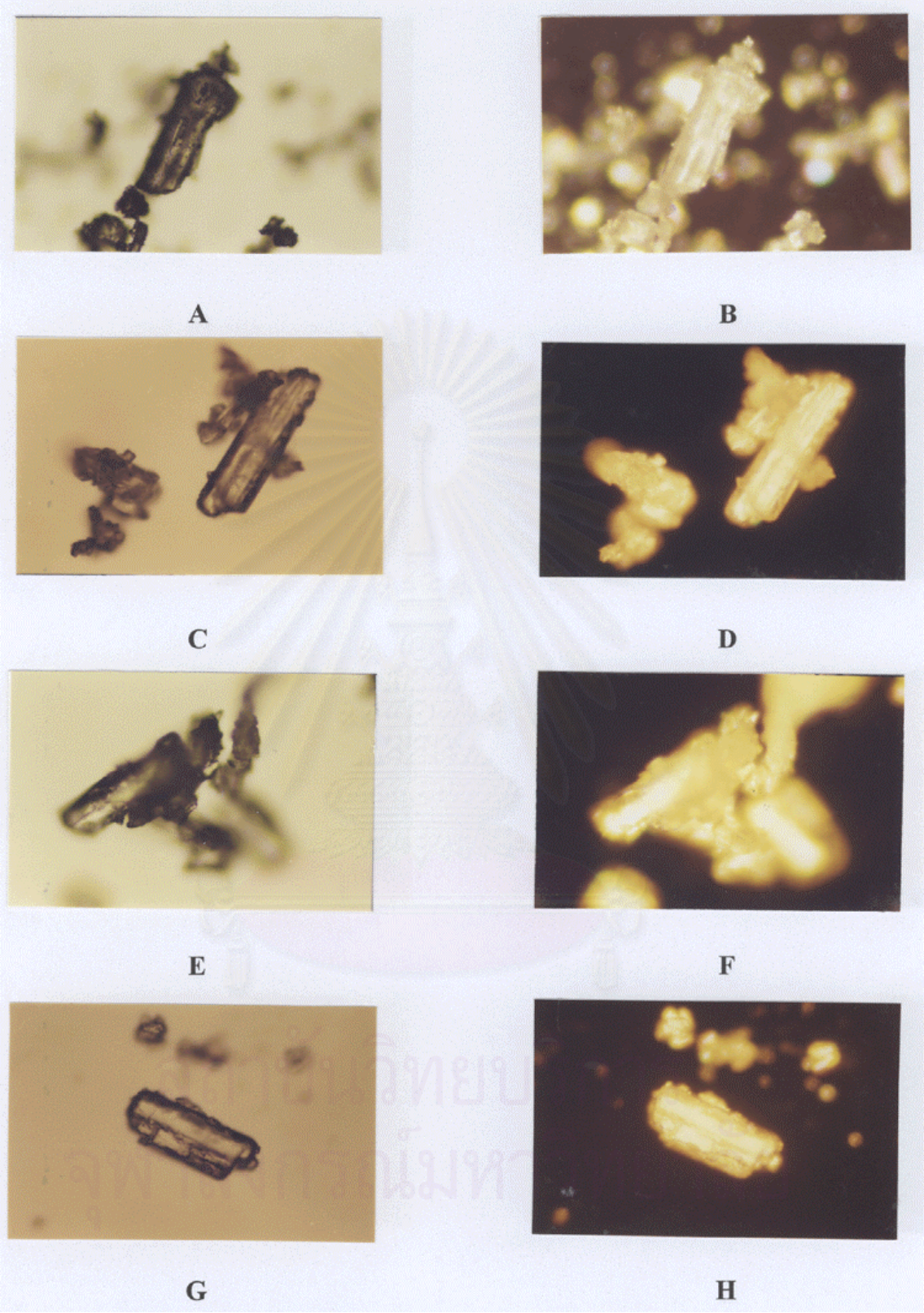


Figure 72 Photomicrographs of remained solid in physical state of active ingredients study under different light property. (A&B-DTZ HCl powder, C&D-in pure G42/12, E&F-in pure G44/14 and G&H-in pure G46/07. A, C, E and G are presented under normal light. B, D, F and H are presented under polarized light).

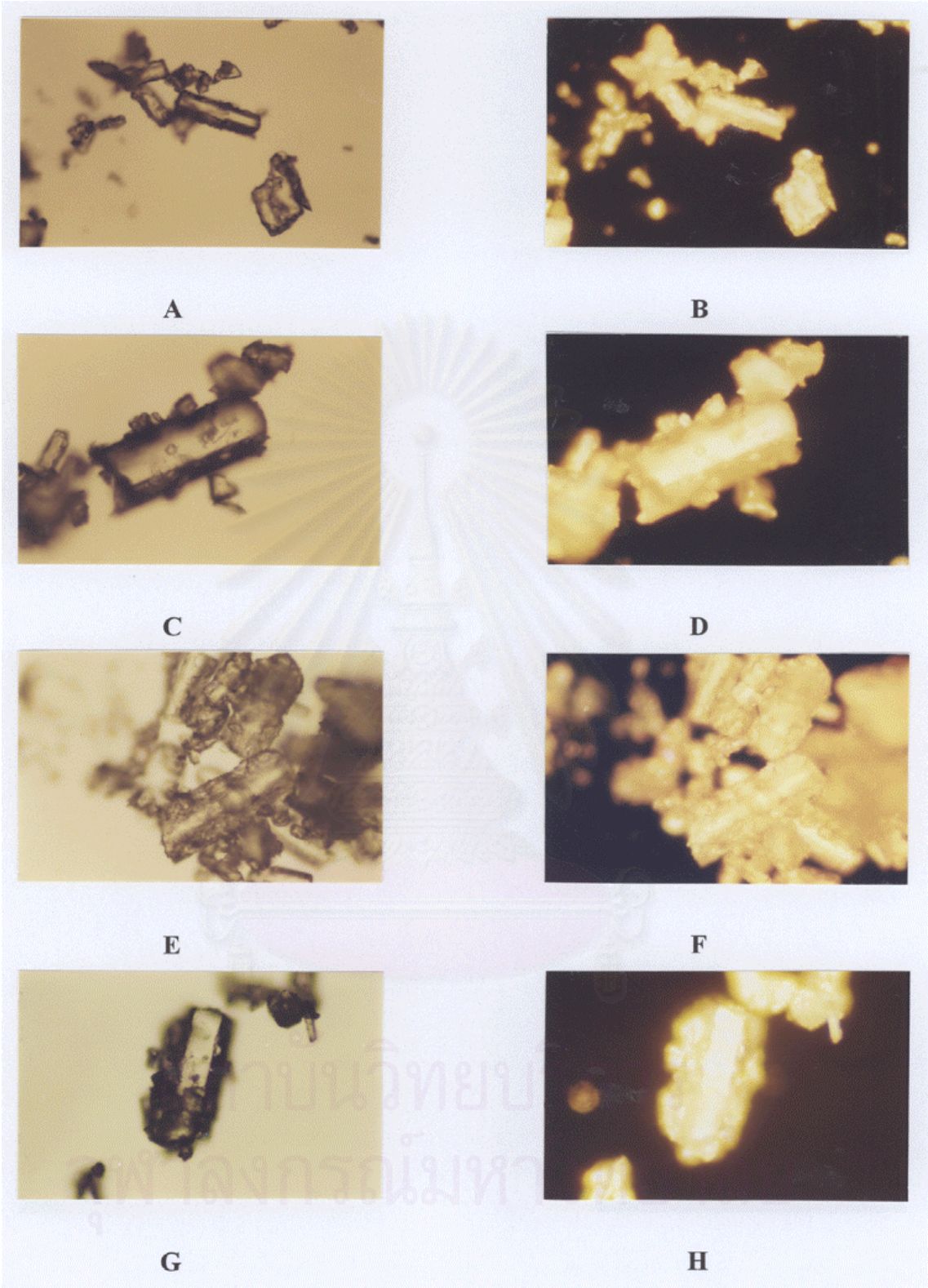


Figure 73 Photomicrographs of remained solid in physical state of active ingredients study under different light property. (A&B-in pure G50/02, C&D-in pure G50/13, E&F-in pure G53/10 and G&H-in combination of G50/02 and G46/07 (2:3). A, C, E and G are presented under normal light. B, D, F and H are presented under polarized light).

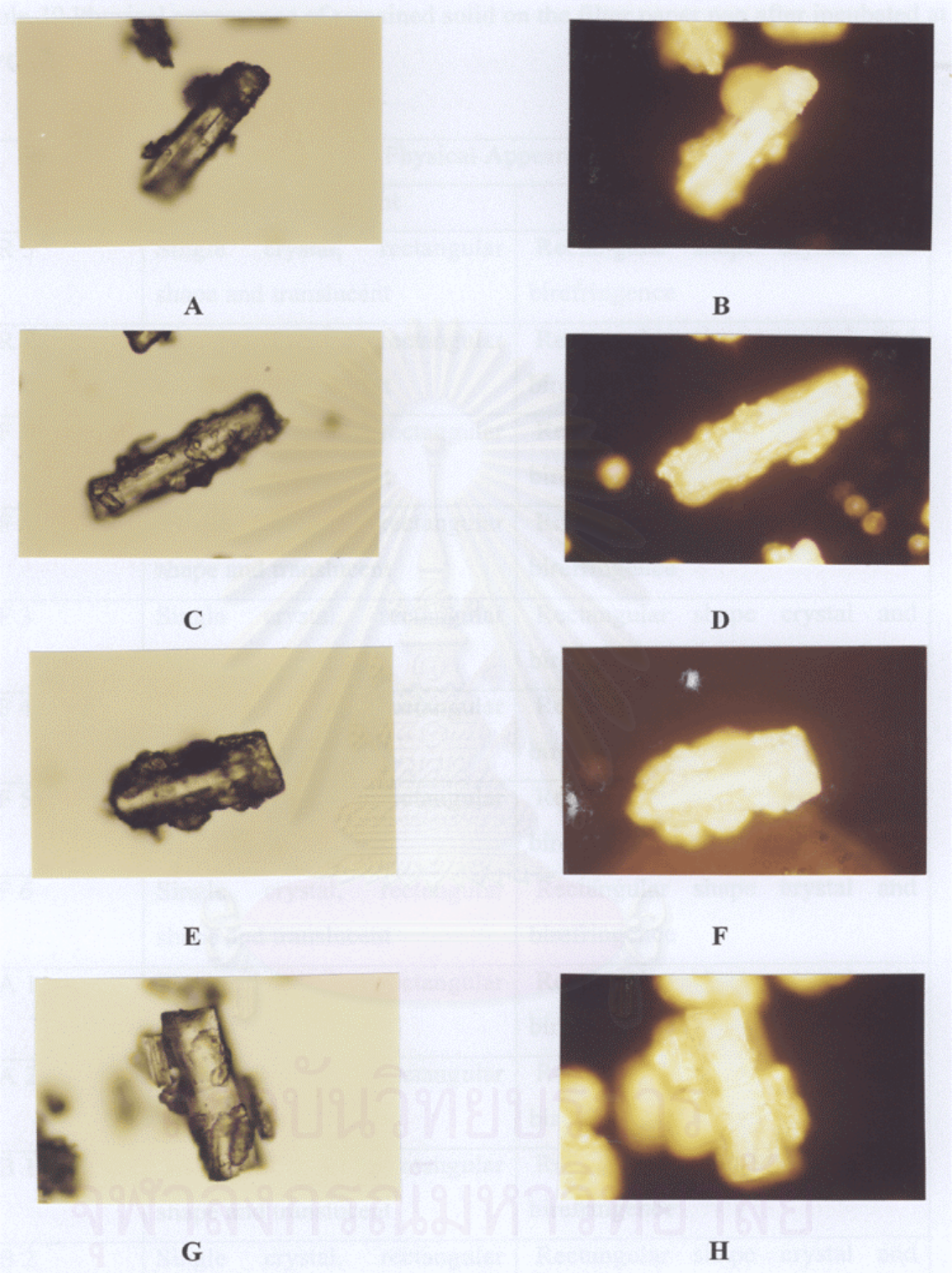


Figure 74 Photomicrographs of remained solid in physical state of active ingredients study under different light property. (A&B-in combination of G50/02 and 53/10 (5:3), C&D-in combination of G50/02 and G44/14 (5:7), E&F-in combination of G50/02 and G42/12 (5:5) and G&H-in combination of G50/02 and G50/13 (6:5). A, C, E and G are presented under normal light. B, D, F and H are presented under polarlized light).

Table 30 Physical appearance of remained solid on the filter paper pan after incubated at 70°C for 1 hour.

Formula	Physical Appearance under	
	Normal light	Polarized light
R 3	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
R 4	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
F 1	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
F 2	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
F 3	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
F 4	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
F 5	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
F 6	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
A 1	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
A 2	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
B 1	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
B 2	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
B 3	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
B 4	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence

Table 30 Physical appearance of remained solid on the filter paper pan after incubated at 70°C for 1 hour. (cont.)

Formula	Physical Appearance under	
	Normal light	Polarized light
B 5	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
C 1	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
C 2	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
C 3	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
C 4	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
C 5	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
C 6	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
C 7	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
D 1	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
D 2	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
D 3	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
D 4	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
D 5	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
D 6	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence

Table 30 Physical appearance of remained solid on the filter paper pan after incubated at 70°C for 1 hour. (cont.)

Formula	Physical Appearance under	
	Normal light	Polarized light
E 1	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
E 2	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
E 3	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
E 4	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
E 5	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
E 6	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
H 1	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
H 2	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
H 3	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence
H 4	Single crystal, rectangular shape and translucent	Rectangular shape crystal and birefringence

Gelucire® are polyglycolyzed glycerides that consist of specific mono, di or triglycerides and mono or di polyethylene glycol ester of fatty acid. Thus, the major functional groups of glycerides are carbonyl group and ester group. Meanwhile, polyethylene glycol has hydroxyl group at the end of the polymer chain and consisted of ether linkage within the repeating unit of the polymer. Furthermore, ester group can be seen in Gelucire® spectra due to mono or di- polyethylene glycol ester of fatty acid. The spectra of thermosoftenings base showed strong peak at 1113 cm^{-1} for -O- linkage, 1463 for aliphatic CH_2 bending, 1740 for carbonyl in ester group, 2858 and 2924 for aliphatic CH stretching and 3469 for primary alcohol of free hydroxyl group attached at the end of glycol moiety. In addition, 1251,1297 and 1352 cm^{-1} with mild to moderate peak intensities of primary alcohol were also presented.

Either single or dual mixture of thermosoftening bases exhibited the same spectra pattern. Due to the same principle peak with strong peak response at wave number (1113, 1740, 2858, 2924 and 3469 cm^{-1}). The result showed that every samples was composed of the same major constituents.

Although they had minor shifts in peak positions but they are negligible. The results revealed that the interaction between DTZ HCl and thermosoftening bases was toughly occur. These results strongly support DSC thermogram results that they were no chemical interaction between the drug and base. Furthermore, weight ratio and type of dual mixture Gelucires® did not affect the IR spectra because their spectra are the same as the reference.

2.6) Solubility of DTZ HCl

DTZ HCl is categorized as highly water-soluble drug. Thus, its solubility should be high in aqueous solvent. All media of interest provide a high solubility value of DTZ HCl. The solubility data of DTZ HCl in various dissolution media are shown in Table 31.

Table 31 Solubility of DTZ HCl in various dissolution media at 37±0.5°C.

Medium	Solubility(mg/ml)*
Purified water	606.67 ± 17.49
Dissolution media pH 1.2	578.60 ± 3.36
Dissolution media pH 4.5	591.20 ± 4.91
Dissolution media pH 7.0	574.89 ± 6.13

* Average ± S.D. and n=3.

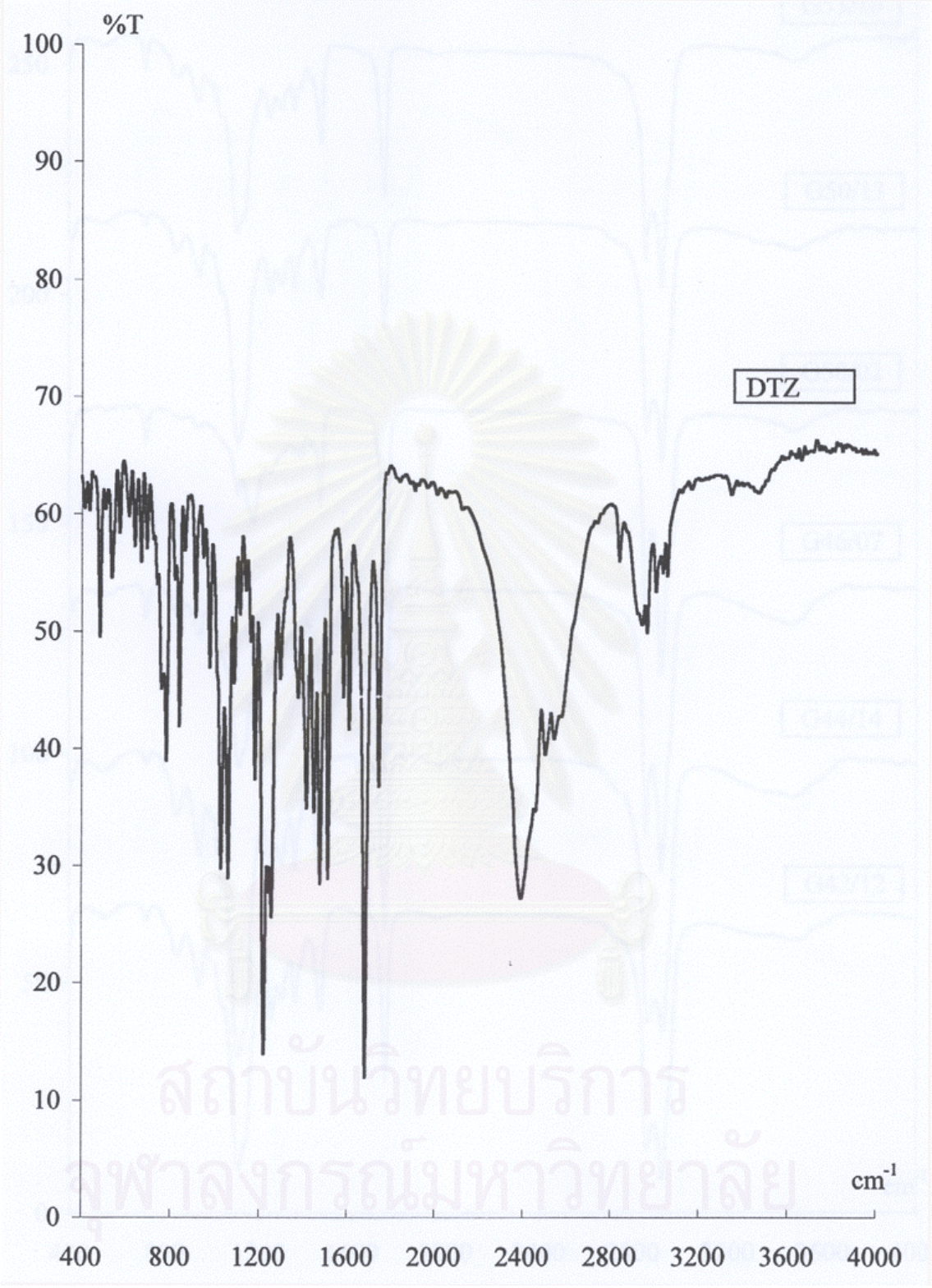


Figure 75 Typical IR spectrum of diltiazem hydrochloride powder.

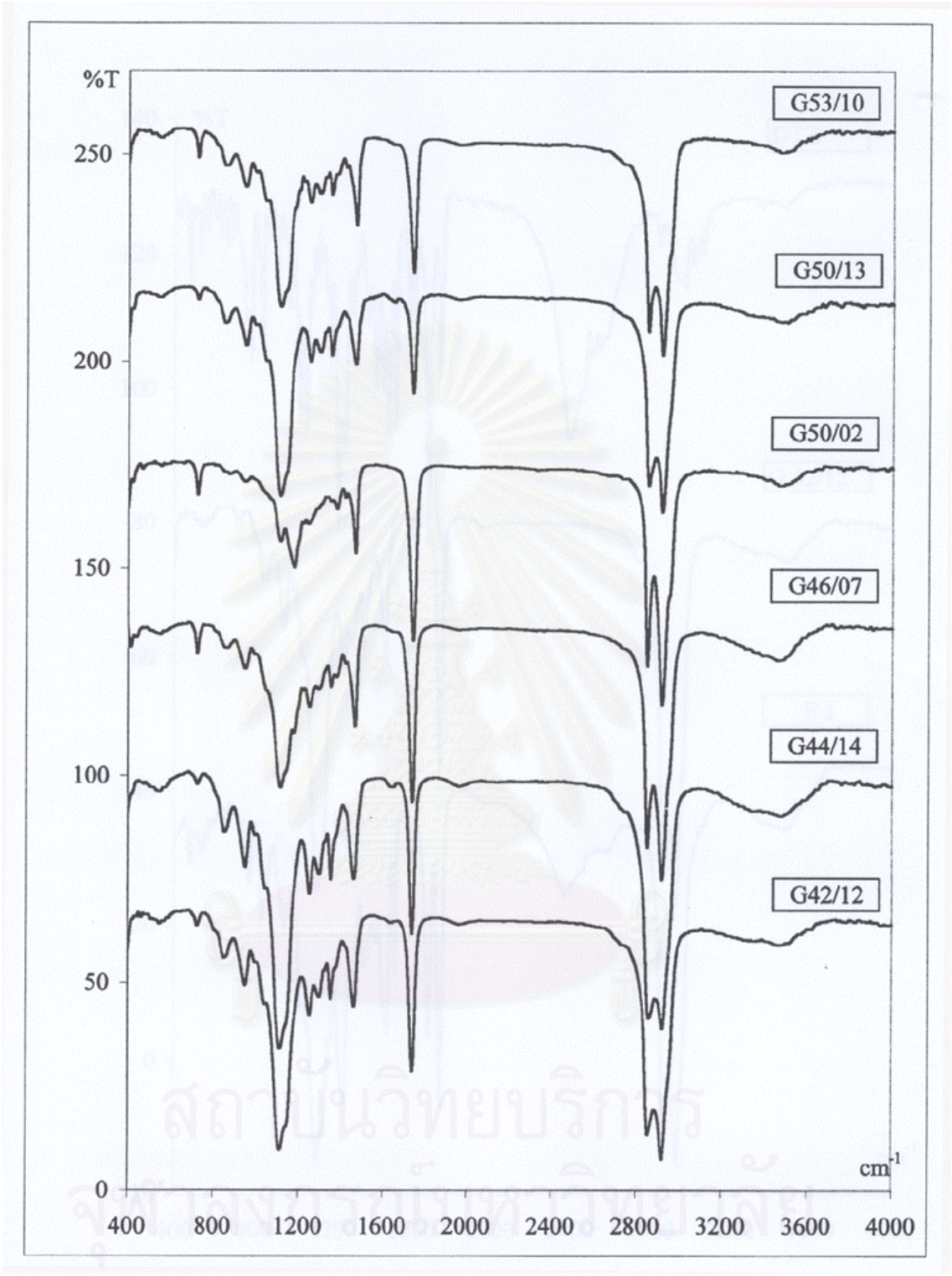


Figure 76 Comparative IR spectra of pure Gelucires family.

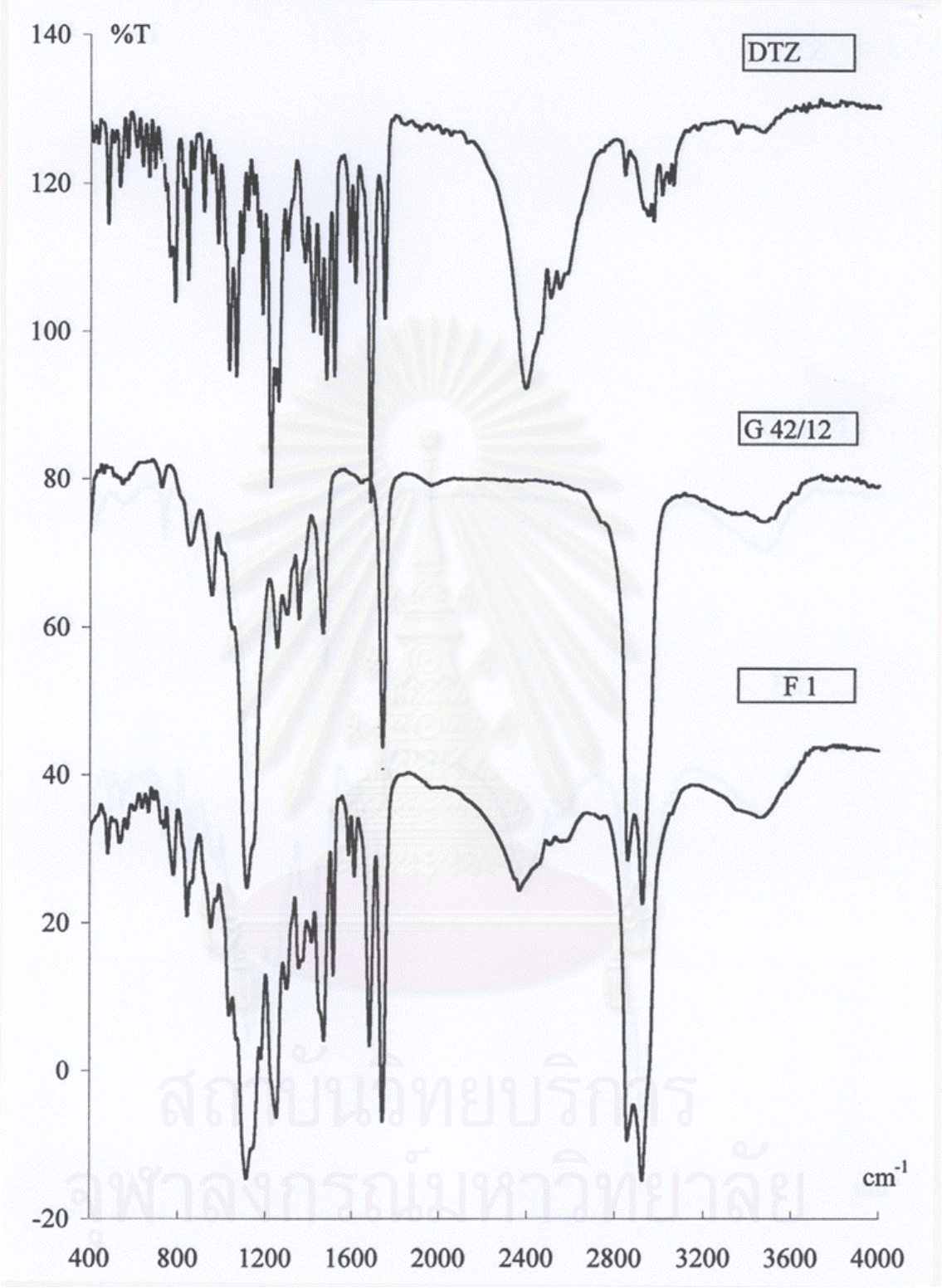


Figure 77 Comparative IR spectra of diltiazem hydrochloride, G42/12 and diltiazem hydrochloride in G42/12 semisolid matrix capsule.

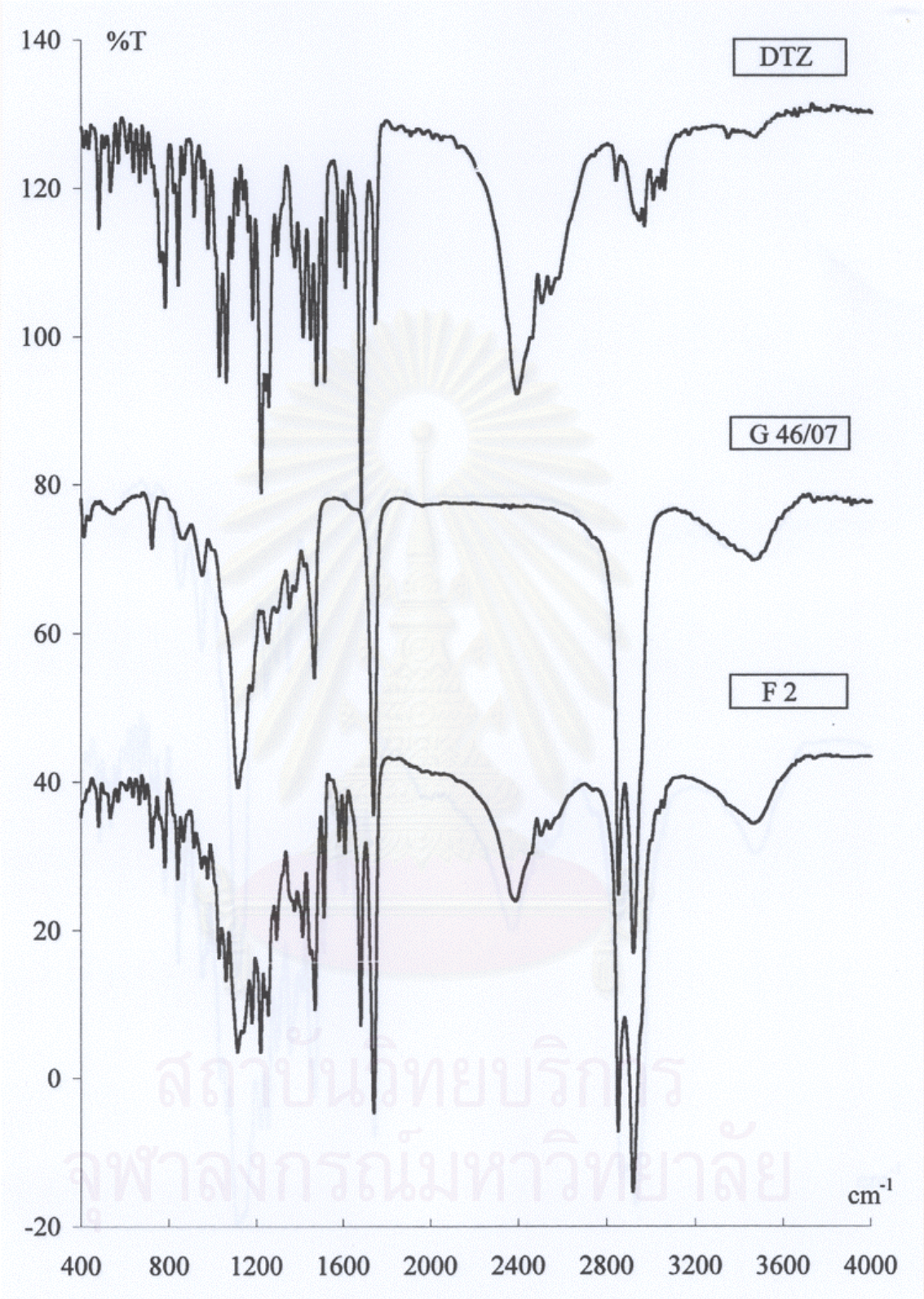


Figure 78 Comparative IR spectra of diltiazem hydrochloride, G46/07 and diltiazem hydrochloride in G46/07 semisolid matrix capsule.

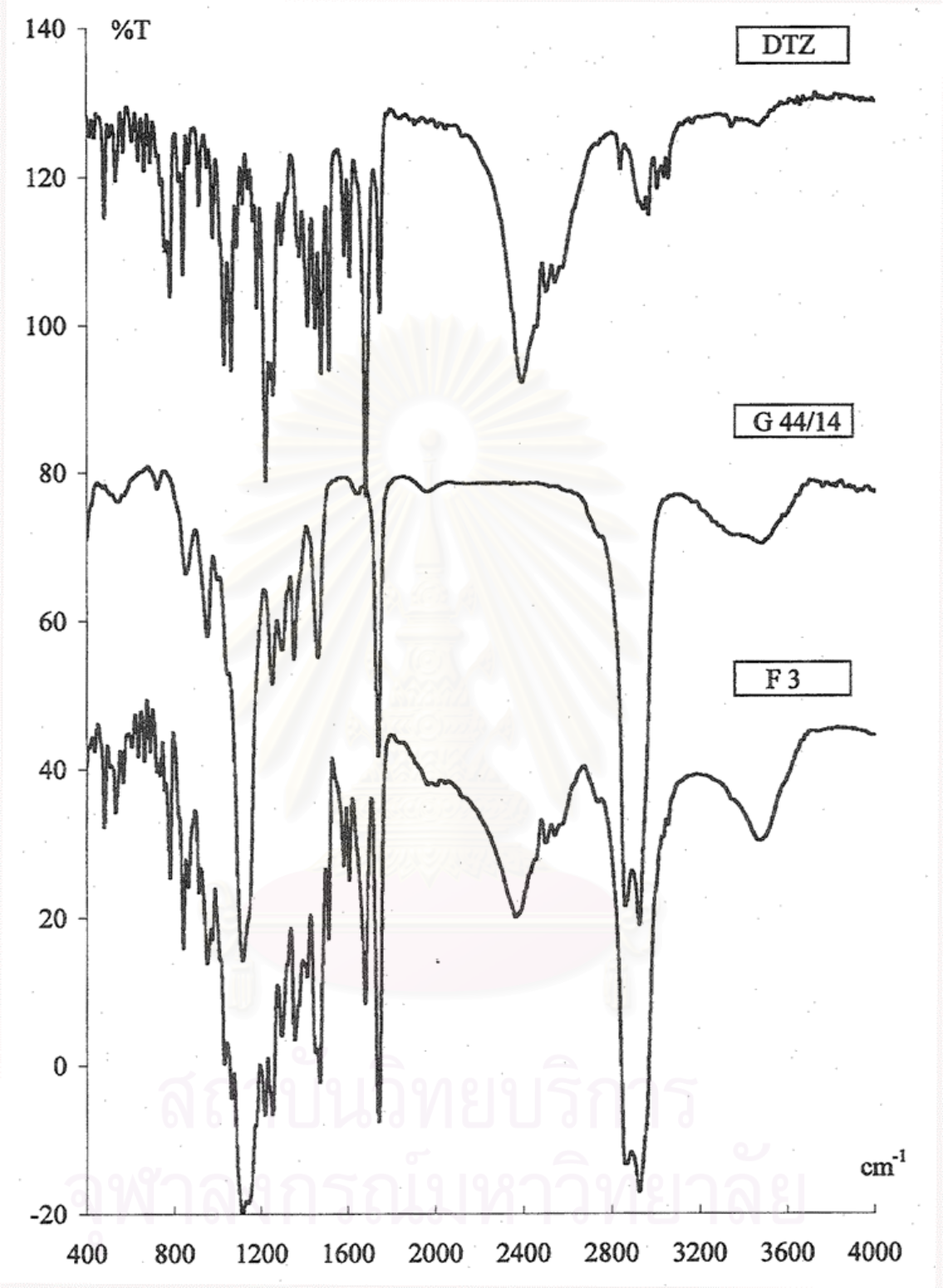


Figure 79 Comparative IR spectra of diltiazem hydrochloride, G44/14 and diltiazem hydrochloride in G44/14 semisolid matrix capsule.

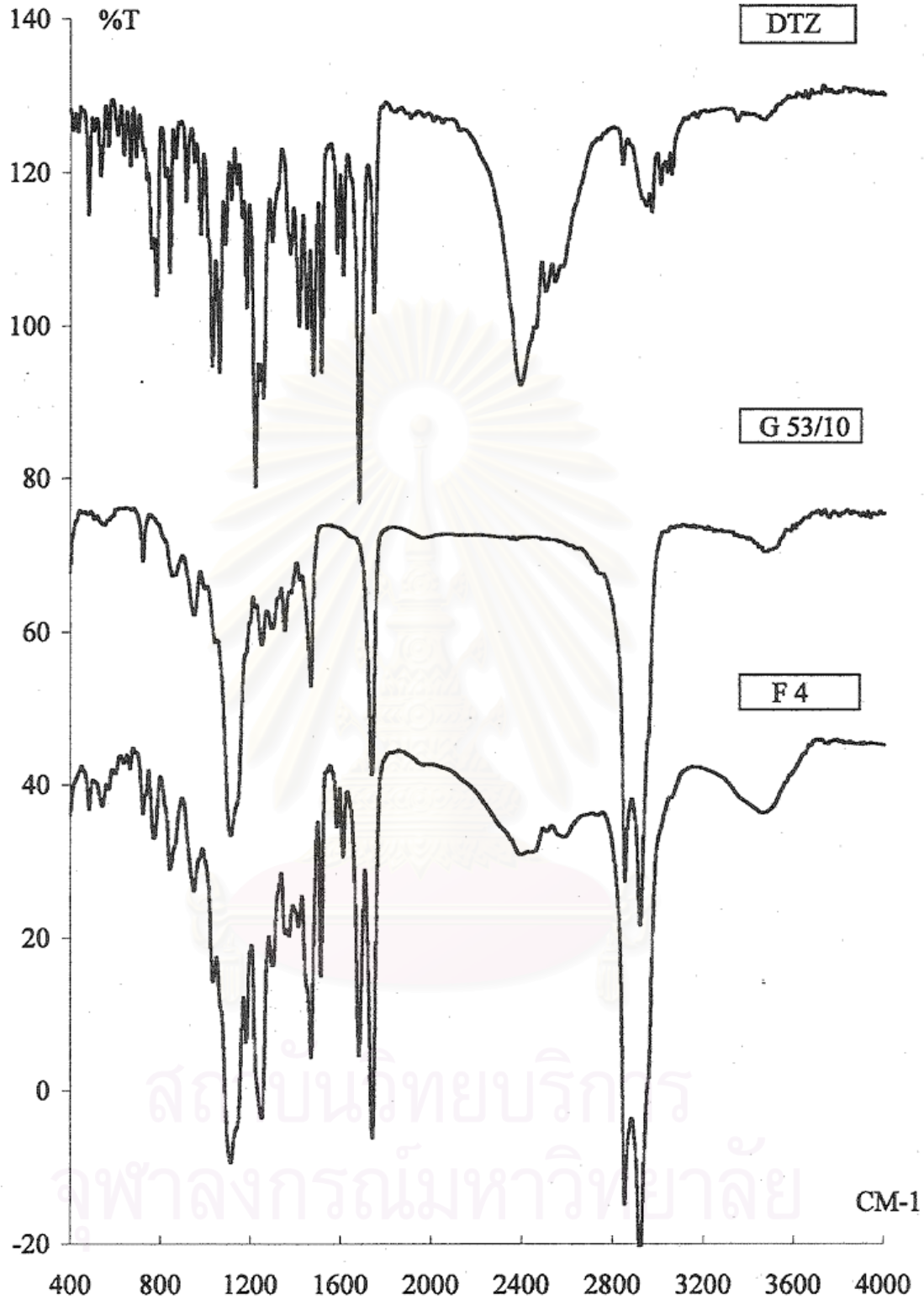


Figure 80 Comparative IR spectra of diltiazem hydrochloride, G53/10 and diltiazem hydrochloride in G53/10 semisolid matrix capsule.

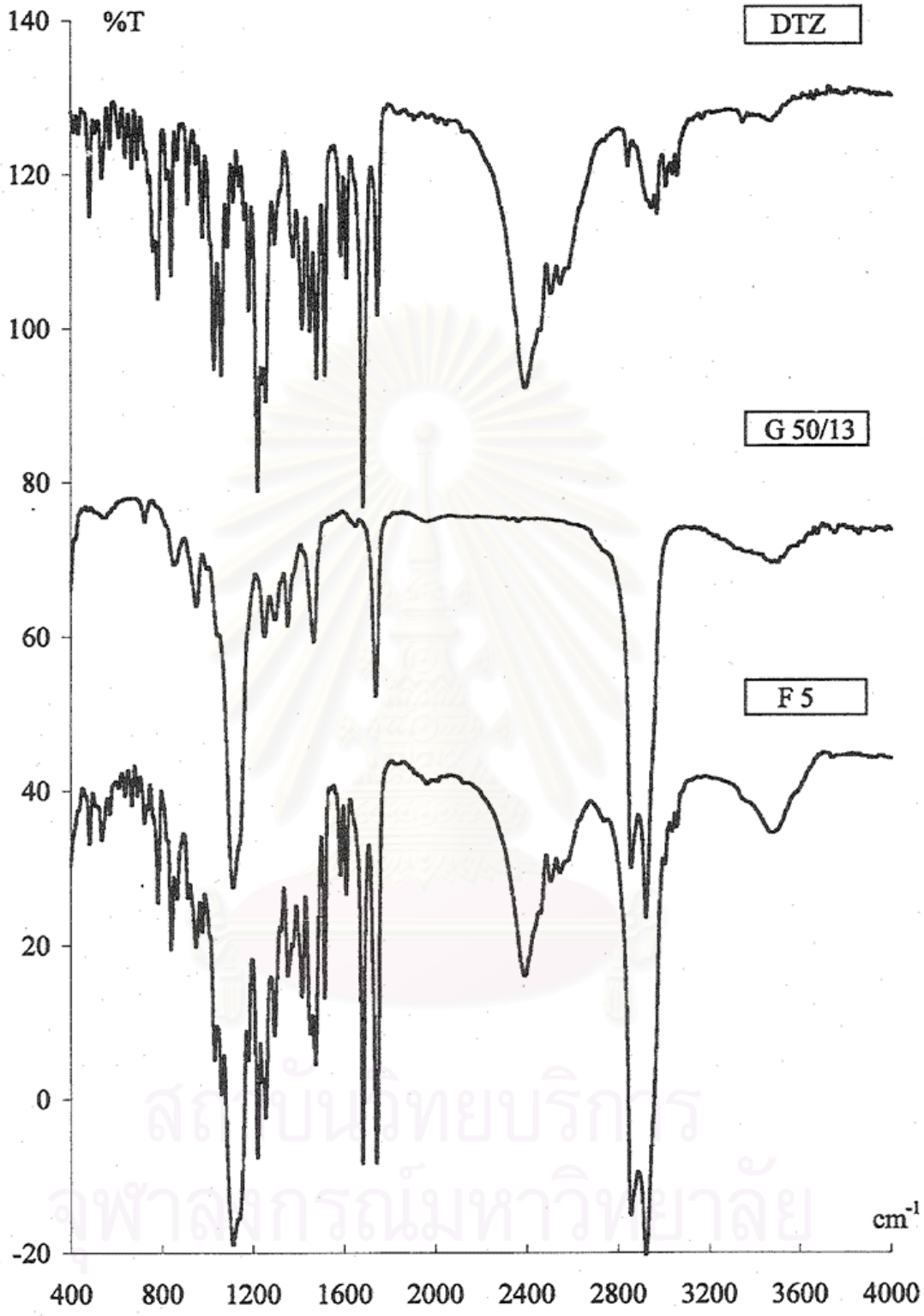


Figure 81 Comparative IR spectra of diltiazem hydrochloride, G50/13 and diltiazem hydrochloride in G50/13 semisolid matrix capsule.

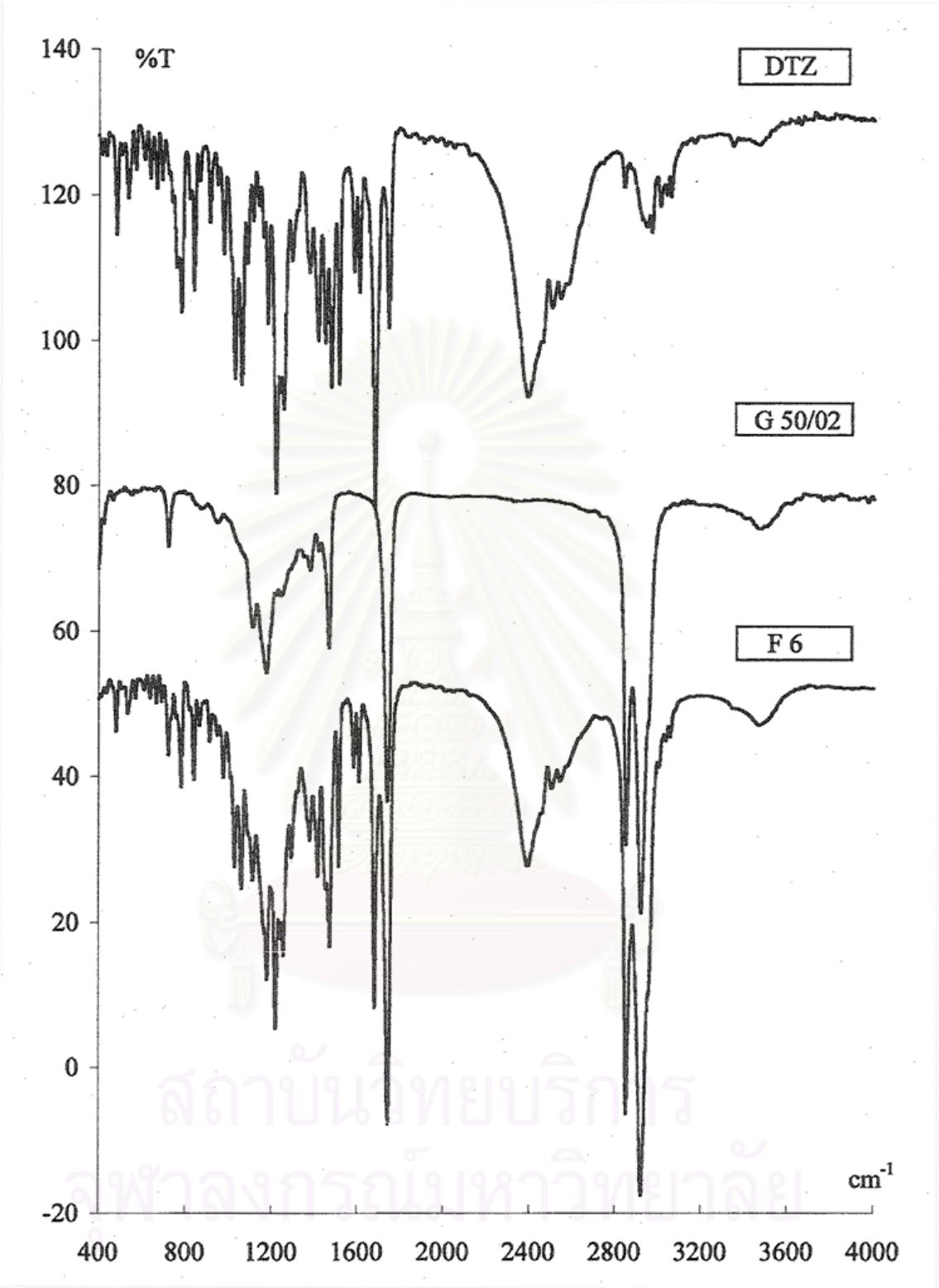


Figure 82 Comparative IR spectra of diltiazem hydrochloride, G50/02 and diltiazem hydrochloride in G50/02 semisolid matrix capsule.

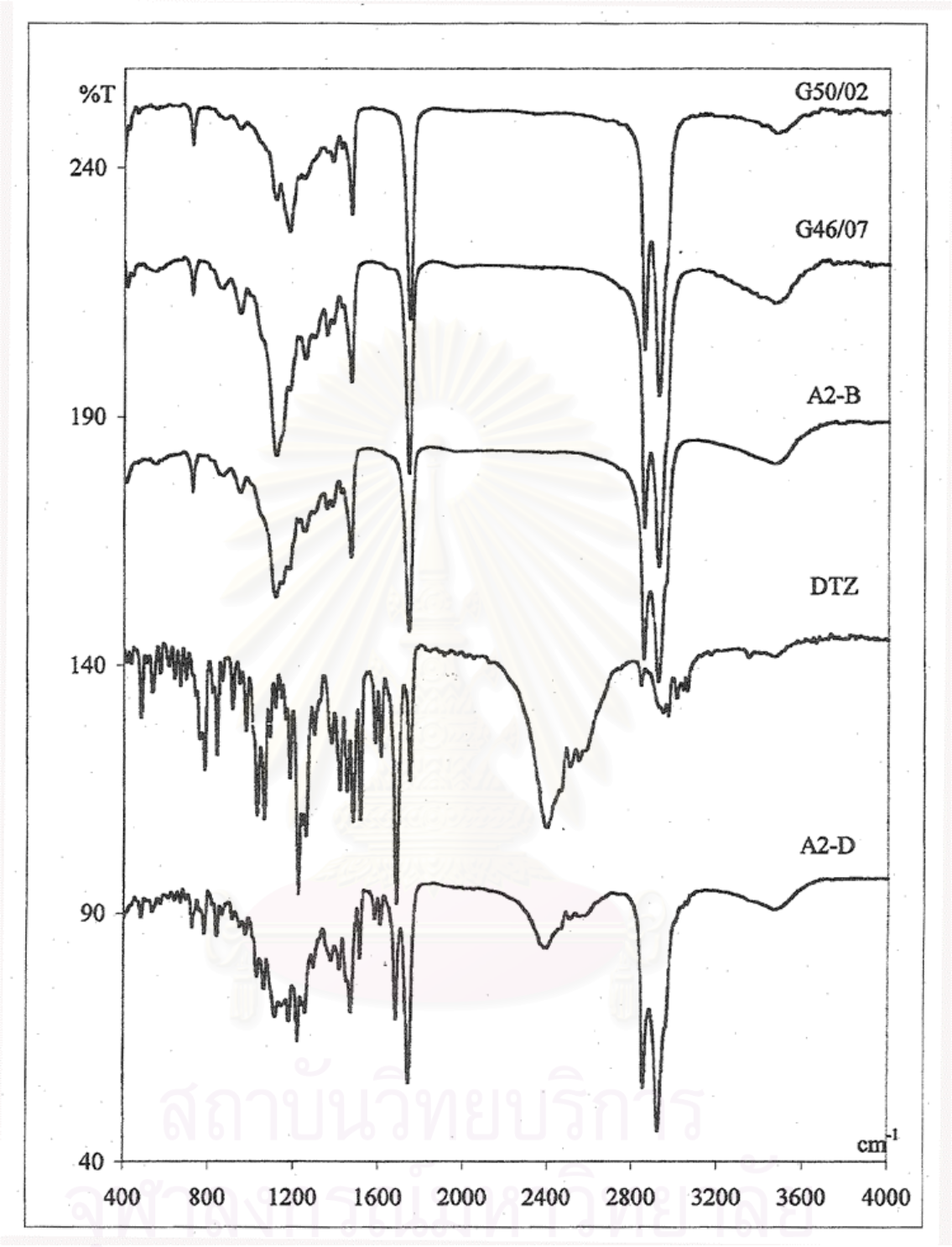


Figure 83 Comparative IR spectra of DTZ HCl, G50/02, G46/07, mixture of G50/02 and G46/07 and DTZ HCl in mixture of gelucires. (A2-B = mixture of G50/02 and G46/07 bases at 2:3 weight ratio, A2-D = DTZ HCl in mixture of G50/02 and G46/07 at 2:3 weight ratio)

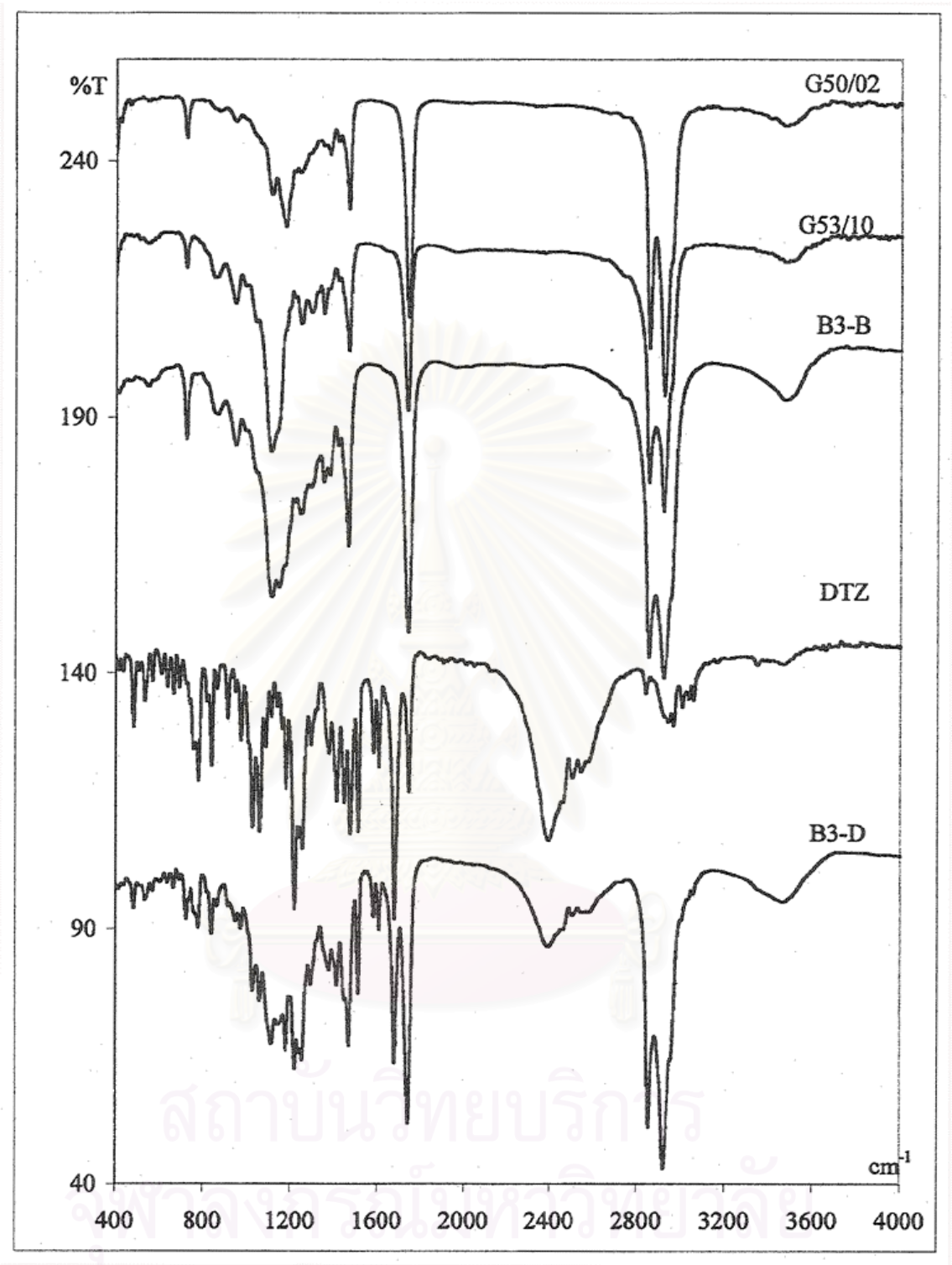


Figure 84 Comparative IR spectra of DTZ HCl, G50/02, G53/10, mixture of G50/02 and G53/10 and DTZ HCl in mixture of gelucires. (B3-B = mixture of G50/02 and G53/10 bases at 5:3 weight ratio, B3-D = DTZ HCl in mixture of G50/02 and G53/10 at 5:3 weight ratio)

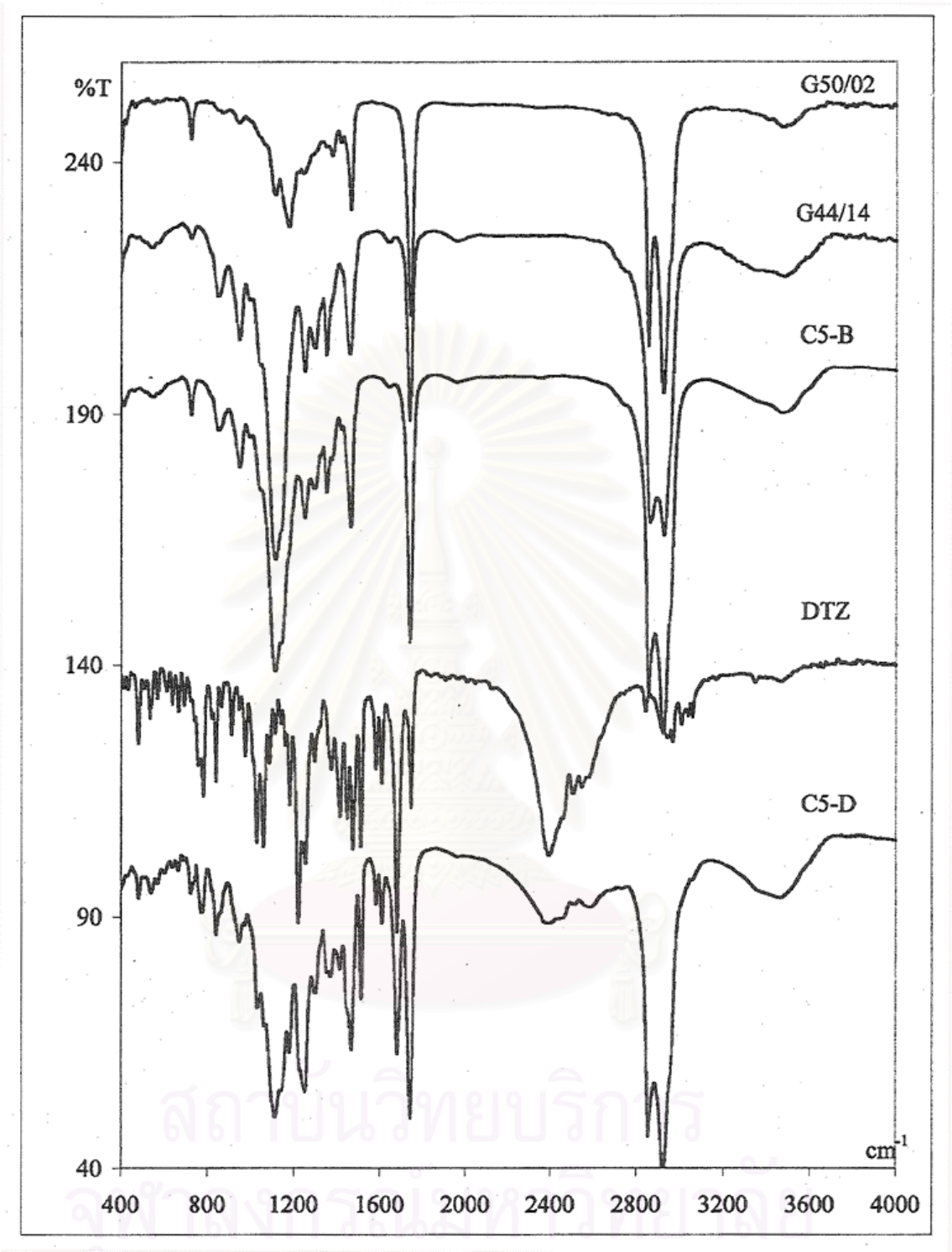


Figure 85 Comparative IR spectra of DTZ HCl, G50/02, G44/14, mixture of G50/02 and G44/14 and DTZ HCl in mixture of gelucires. (C5-B = mixture of G50/02 and G44/14 bases at 5:7 weight ratio, C5-D = DTZ HCl in mixture of G50/02 and G44/14 at 5:7 weight ratio)

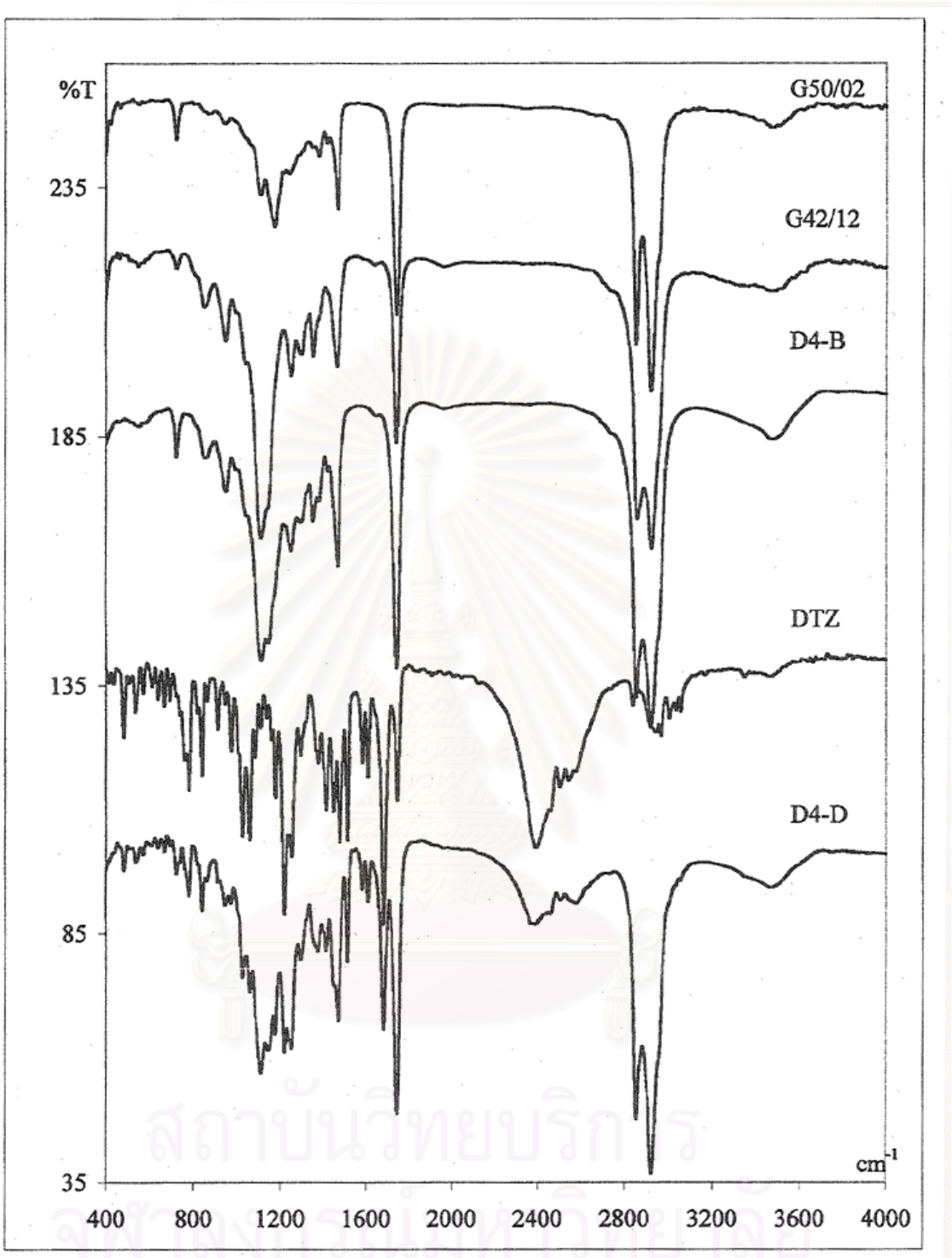


Figure 86 Comparative IR spectra of DTZ HCl, G50/02, G42/12, mixture of G50/02 and G42/12 and DTZ HCl in mixture of gelucires. (D4-B = mixture of G50/02 and G42/12 bases at 5:5 weight ratio, D4-D = DTZ HCl in mixture of G50/02 and G42/12 at 5:5 weight ratio)

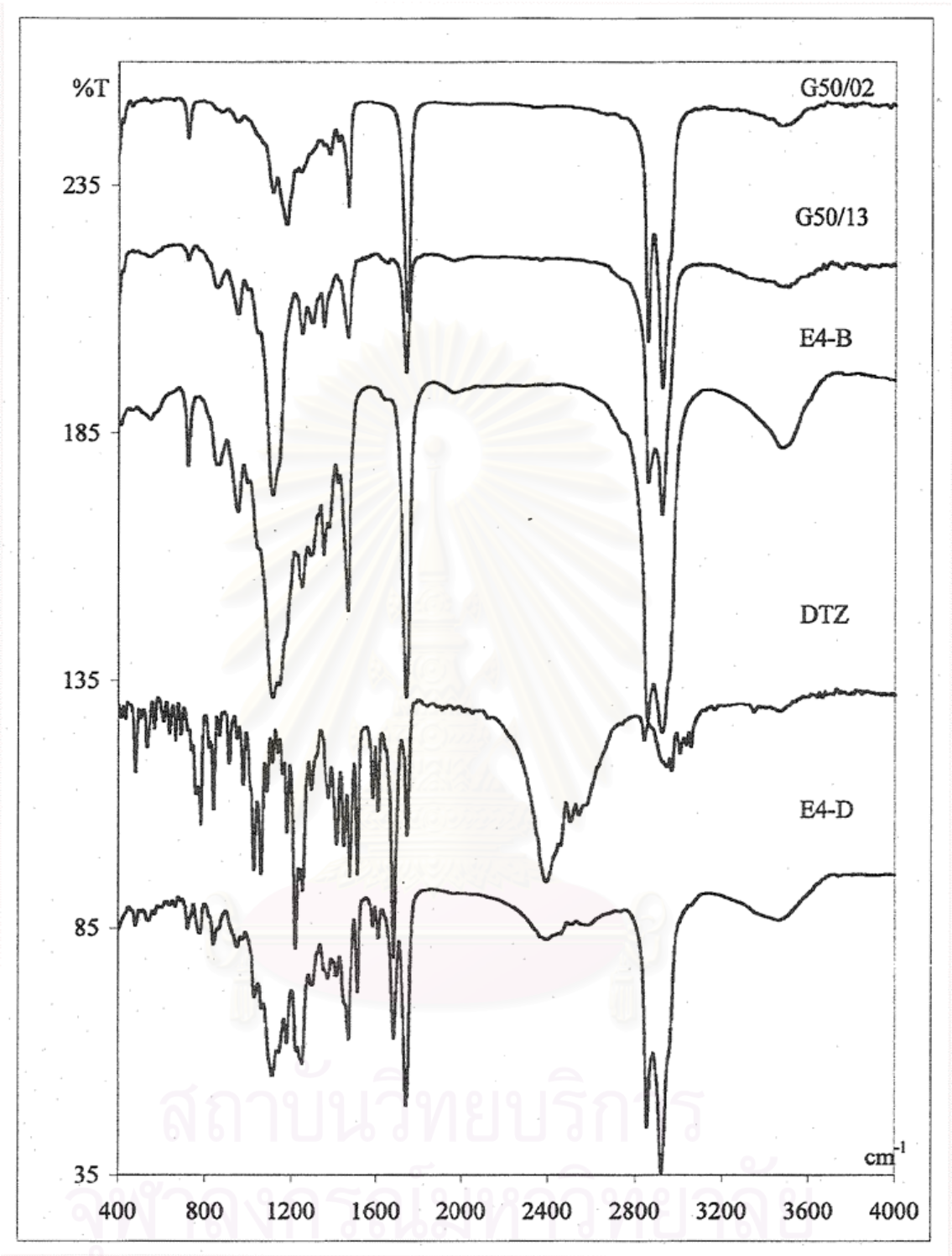


Figure 87 Comparative IR spectra of DTZ HCl, G50/02, G50/13, mixture of G50/02 and G50/13 and DTZ HCl in mixture of gelucires. (E4-B = mixture of G50/02 and G50/13 bases at 6:5 weight ratio, E4-D = DTZ HCl in mixture of G50/02 and G50/13 at 6:5 weight ratio)

Table 32 Summary of the principle IR peak of DTZ HCl powder, pure thermosoftening vehicles and DTZ HCl SSM with single component base.

	Peak respond (wave number = cm^{-1})				
	Fingerprint region		Group frequency region		
	400-1000	1001-1300	1301-2000	2001-3000	3001-4000
DTZ HCl	782 840	1220 1250	1476 1681 1745	2392 2839 2966	3036
G42/12		1113 1251 1297	1352 1463 1740	2858 2924	3469
G44/14		1113 1251 1297	1352 1462 1738	2861 2924	3479
G46/07		1115 1251	1352 1467 1739	2853 2921	3459
G50/02		1113	1379 1467 1741	2852 2921	3474
G50/13		1112 1251 1297	1352 1466 1738	2855 2921	3500
G53/10		1111 1250 1295	1351 1467 1738	2852 2919	3474

Table 33 Summary of the principle IR peak of DTZ HCl powder, pure thermosoftening vehicles and DTZ HCl SSM with single component base. (Cont.)

	Peak respond (wave number = cm^{-1})				
	Fingerprint region		Group frequency region		
	400-1000	1001-1300	1301-2000	2001-3000	3001-4000
F 1	779 841	1113 1252 1298	1354 1470 1682 1742	2366 2858 2926	3461
F 2	782 840	1113 1255 1293	1471 1681 1741	2387 2852 2920	3463
F 3	781 840	1113 1253 1293	1470 1679 1741	2364 2866 2926	3472
F 4	772 842	1112 1251 1299	1470 1682 1741	2395 2866 2920	3462
F 5	782 841	1113 1220 1255 1294	1353 1472 1681 1742	2391 2855 2921	3472
F 6	782 840	1113 1220 1294	1471 1682 1743	2393 2853 2922	3467

Table 34 Summary of the principle IR peak of dual component of thermosoftening vehicles and DTZ HCl SSM with dual component bases.

	Peak respond (wave number = cm^{-1})				
	Fingerprint region		Group frequency region		
	400-1000	1001-1300	1301-2000	2001-3000	3001-4000
DTZ HCl	782 840	1220 1250	1476 1681 1745	2392 2839 2966	3036
G50/02 & G42/12		1114 1250	1352 1466 1741	2854 2923	3473
G50/02 & G44/14		1113 1251	1352 1466 1740	2854 2922	3464
G50/02 & G46/07		1114 1249	1351 1467 1740	2852 2920	3463
G50/02 & G50/13		1115 1250	1352 1466 1741	2854 2922	3474
G50/02 & G53/10		1114 1248	1351 1467 1741	2853 2921	3471
A 2	782 840	1111 1219 1255	1470 1681 1742	2389 2853 2921	3464
B 3	781 840	1113 1221 1255	1470 1682 1742	2392 2852 2920	3462
C 5	776 841	1113 1252	1470 1682 1742	2392 2854 2922	3461
D 4	781 840	1113 1220 1254	1470 1681 1743	2385 2854 2923	3465
E 4	777 841	1112 1253	1470 1682 1742	2393 2853 2921	3462

CHAPTER IV
DISCUSSION AND CONCLUSIONS

Selection of hard capsule size and SSM weight

The use of liquid filling technique needed the appropriate initial evaluation prior experimental planning. Size of cappsule is the most commonly considered. Capsule No 2 was a typical candidate even the smaller capsule No.3 size was easily used to deliver to the gastrointestinal tract. It was very difficult to transfer SSM to capsule No. 3 due to the fact that it had a very small diameter which was narrower than the transferring pore of the pipette tip. Furthermore, the weight of inner mass in selected capsule was variable. The maximum drug to base ratio in this experiment was limited to 1:3. The maximum total weight of SSM would be equal to 360 mg per capsule which was impossible to fit the size of capsule No.3. Finally, capsule size 2 was selected as a model because it had all the qualifications needed.

Drug loading effect

The loading dose or initial amount of drug content in SSM performed a significant role in drug release pattern. As possibly seen in drug loading study results, it could be concluded that the predominant release mechanism depended on the drug content in the matrix. At low level of drug content, diffusion mechanism played the major role for controlling the release patterns more than dissolution/erosion mechanism (swelling, surface erosion or case II transport). Vice versa, high drug loading level had dominant dissolution/erosion mechanism with insignificant diffusion controlled mechanism.

Factors behind drug loading effect were complex. One of the most significant factors was rigidity of the matrix forming agents. Several studies indicated that G50/02 is a rigid matrix which had diffusion as predominant mechanism without erosion effect (Ainaoui and Vanguard, 1998; Bidah and Vergnaud, 1990; Kopcha et al., 1990 and 1991). Contrary, some researchers found that at some suitable drug content, polymer relaxation controls the release rather than diffusion mechanism in rigid matrix of

G50/02 (Sutananta et al., 1995). It implied that surface erosion or swelling had stronger influence than diffusion. Furthermore, it could be concluded that surface erosion was possibly occurred on G50/02 matrix. According to this experiment, G50/02 was used as a model SSM in drug loading studies. Surface appearance of G50/02 matrix with different drug content seen by SEM photomicrographs clearly indicated that surface erosion of low drug content matrix (lower than 45 mg) was not possible while at higher level, this phenomena often happened (Figures 35-44).

Additional reasons of the previous results were due to the solubility of the model drug. DTZ HCl is highly water soluble. After drug particles were embedded on the matrix surface, they were rapidly dissolved after came in contact with the surrounding medium and induced the medium towards adjacent inner portion of drug particle through channel or pore and disrupt the matrix structure. Sometimes drug particle with the above behavior is called “porosigen” (Baker, 1987).

Base on the probability of drug orientation in the matrix under solid dispersion stage, percolation theory or island model can be introduced to describe continuous pore or pinhole channel forming (Baker, 1987). The drug particles are suspensed in rate limiting polymer matrix as monolithic dispersion. The influencing factors in monolithic dispersion are both the geometry of device and drug loading. Normally, three types of monolithic are categorized depending on the volume fraction of active compound to matrix polymer. At low loading level, 0-5% v/v of active compound called simple monolithic dispersions. Drug release involves dissolution of drug embedded in the polymer and follow by diffusion to the surface of device. Slightly higher level, 5-10% v/v, is complex monolithic dispersions. According to the possibilities of creating water channel in the matrix structure and allowing the contacting medium to be filled in the cavities, the erosion of surface material of the matrix is the main exit for the remaining drug to escape by moving through water cavity pathway. In spite of increment of cavities in this dispersion structure took place but an appearance of cavities is another limiting factor on drug release. Continuous pathway of cavities to the surface of complex monolithic type are not provided due to insufficient amount of drug particles. Overall result of this type may be increase in total apparent permeability of the agent. The last type of dispersion is concerning with above 20% v/v of drug to polymer matrix was named as monolithic matrix system or simply matrix system. Tremendous amounts

of drug are enough to generate continuous channel throughout the device. In this cases, predominant release mechanism is the diffusion of active compound through these channels. Thus, diffusivity and solubility of drug in imbibed fluid filled in cavities indicate drug release.

Both length and number of water pore or channel are proportional to the amount of drug particles added. Furthermore, if the drug content was raised then the matrix base content decreased due to the adjustment of the constant final target weight. Large proportion of active content generates more small islands and interconnecting particles following percolation theory (Appendix E). The growth in size and connection of the extended pathway were formed. Thereby, matrix structure was disrupted (Sutananta et al., 1995). Finally, at high drug content, high solubility nature of drug and , porosity of matrix were increased and tends to reduce the surface and structure rigidity. The previous results concluded that G50/02 was rigid matrix but surface erosion occurred at high level of DTZ HCl content and also minor dissolution erosion mechanism.

As described above that the reasons were using the assumption that the system was a solid dispersion. At all drug content levels from the experiment, the remaining solids on the filter paper expressed the identical property of DTZ HCl particles which could prove that at every loading levels was solid dispersion stage. Additionally, There was no chemical interaction between DTZ HCl and G50/02 as seen by IR spectra. Ideally, the physical solid dispersion with unchangeable base properties was appropriate to interprete the phenomena without any interference. Partial interference of DTZ HCl in G50/02 might alter the actual drug particle orientation in matrix structure as well as amount of drug crystal in the matrix. If amount of crystals in the matrix device were less than actual amount of added crystals, it would mean that some of the crystals were solubilized into the matrix base. All of these would effect the length and numbers of new channels created through the matrix. Thermal interpretation, such as DSC, provide the initial sign of drug solubilization. The enthalpy change at main peak of solid compound indicated the base solubilizing power (Dordunoo et al,1996). Solubilization of drug particles in polymer base reduce the amount of crystal solutes present in the matrix. The absence of some drug crystals led to the lower energy consumption and lower enthalpy. Consequencely, area under endothermic curve of drug crystal region in the presence of base is lower than pure drug crystal. From the result, thermal analysis

of DTZ HCl SSM in G50/02 exhibited negligible difference in heat of fusion or ΔH_f of DTZ HCl endothermic peak compared with pure drug crystal. It can be concluded that there was a very minute or negligible chance that drug-base solubilization had occured.

DTZ HCl SSM with single and dual component of thermosoftening bases

Prior to go on further to the agreement reason in this topic, explanation of the basic DSC tracing was essential. DTZ HCl thermogram showed the single endothermic sharp peak without any interference of noise at around 214°C while almost all of the selected thermosoftening bases exhibited broadened endothermic peak at the particular temperature. Additionally, some types also displayed either two separated distinct peak or overlapped peak since either trace impurities or other components tend to broaden the melting range of a major component. In accordance to impurities of substances, thermal interpretation such as DSC reported the complexity and led to broad peak. Obviously, Gelucire® were the complex mixtures of at least two or more components (glycerides and PEG ester of fatty acid). Then, it acted as unpurified substance. So, broadening of the peaks were obtained. On the other hand, DTZ HCl crystal provided a thermogram as single and sharp peak due to the fact that it is pure. Sometimes it was called isothermal peak for sharp peak response.

Base mixtures were commonly used for drug-release adjustment. The observations in combining bases without active component were recorded as reference tracings. It was interesting that combining bases peak on tracing was the summation of each separate distinct peak of the individual base without any chemical interaction. As the function of base content, if the amount of one type of Gelucire® was much more than the other one, major peak was displayed along with the higher weight portion component while the minor peak of the lower weight portion component base content still existed. Peak of each component was shifted from the original peak. An agreement reason may concerned with the stage of mixtures and amount of samples used. Physical mixture of both non-interactive bases expressed the major distinct peaks at the temperature points exactly the same as their original properties. Conversly, base mixtures in this study had gone through the melting and resolidification processes prior to DSC studies. It might be possible that molecules of each base were loosely linked to

each other. The lower energy consumption was sufficient to break or change the physical state of both bases from solid to fluid state which caused minor shifts of those peaks. Thus, dual component of base showed the new physicochemical properties. According to IR detection, the result showed that no chemical interaction occurred in dual component bases because they had the same majority peaks as each pure bases. It could be summarized that chemical interaction of the functional group did not take place. Physicochemical property, melting appearance, of base mixture was the crucial point to predict and support the drug release data.

It is well understood that DSC peak temperature was affected by various factors such as sample preparation, temperature-scanning rate, holding time, sample size, etc. The result will be the peak temperature shift. The results in this study indicated that there were peak temperature shift. Almost all of DSC scanning patterns at 10°C scanning rate showed the shifts to lower temperature both the base and DTZ HCl peak. One reason for the shift is because of, in this case, the purity. Under scanning process, active component acted as impurity in base substance. In addition, the different in the sample size was also affect to the temperature shift.

Normally, progressive process of heating cycle in DSC was continuously increases until original endothermic DTZ HCl peak temperature, were present. In order to explain, why the active compound peak was shifted to lower temperature, we had to consider some reasonable factor. The concerned aspects were more complicated but at least there were 2 main reasons to support and explain this phenomena. In thermal analysis, pure crystal had an air cover around particles which provide low heat convection capacity. Focus on DSC determination of matrix system. At approximate temperature above 60°C, all types of thermosoftening base were completely melted as seen in the thermogram which returned to the base line again. Then, the melting bases in liquid state absolutely surrounded and contacted the entire active particles. The molten base were a good heat convectors than air. Consequently, lower energy was enough to break the structure of the active compound and peak temperature thus shown at the lower temperature. Another possible reason is the change in crystal morphology might occurred since high temperature of heating process and solubilizing power at high temperature of the thermosoftening bases. If the particles were smaller than the original

form and some base had enough solubilizing power, drug particles could dissolve much more easily and faster than at lower temperature condition. The results revealed that the decrease in the heat of fusion (ΔH_f) or enthalpy of DTZ HCl might be related to various factors such as chemical interaction between drug and base, complex formation between substances and solubilizing of crystal solute in the polymer base. In accordance with IR spectra, it clearly indicated that no chemical interaction among drug and base occurred. Hence, solubilization of drug crystal in base or polymer substances at higher temperature might be a crucial factor rather than other assumptions. Dordunoo (1996) introduced solubility determination of crystal solute in polymer base by thermal analysis. The change in heat of fusion of the active compound could be used as a parameter to measure solubilizing capacity of the base at higher temperature condition. The decline in heat of fusion of DTZ HCl showed that amount of the remain solid particles was decreased due to solubilization by the matrix base. So, a decrease in enthalpy were an indirect method to indicate solubility of the drug. This solubility was relative value. Nevertheless, it was commonly used as a relative comparison method since the observation of heat of fusion was collected at higher temperature than the actual preparation temperature. The result suggested that Gelucire® with higher HLB value had solubilizing power much more than lower HLB value (G50/02). According to the addition of slow release to fast release base, the base mixture tend to express minor solubilization effect (Figure 68). Moreover, the comparative result in each base mixture revealed that lower calculated HLB (higher portion of slow release) provide the negligible lowering in heat of fusion of DTZ HCl. It could be possible to estimate that high amount of slow release in mixture provide less solubilization at high temperature. Gelucire® which had high relative solubilities power such as G44/14, G42/12, G50/13 expressed the same results. In addition, they could be lower the peak temperature of the active component to about 5 to 7 °C and showed the power to solubilize drug particle at high temperature.

In DTZ HCl SSM thermogram, it could be observed that the baseline drifted after approximately above 100 °C. It was possibly due to decomposition or sublimation of low melting point wax. From the result, sublimation probably occurred and was more important than decomposition. If the decomposition of wax like material play the

important role, the rough portion between after melting range of thermosoftening bases region and higher scale of temperature before DTZ HCl melting peak should be seen.

Dissolution profiles of DTZ HCl SSM of single component base showed that significant different rate of drug release were obtained. IR spectra of DTZ HCl and all single Gelucires® in each preparation showed that there were no evidence of chemical interaction in the SSM. Especially in case of G50/02, X-ray diffractogram was used to confirm the evidence that there were no chemical interaction of drug and base in SSM. Therefore, differences in drug release of various preparations were not from the affect of chemical interaction. For the above reason, the important factor in controlling drug release might be the physicochemical properties of each thermosoftening bases itself. Specific characteristics of Gelucire® was divided into two properties either by its HLB or its melting range. The result revealed that HLB or hydrophilicity proved to be the most significant factor. The order of the rate and extent of drug release, observed at the same time point, from fastest to slowest are as follows: G44/14>G42/12>G50/13> G53/10>G46/07>>G50/02. Thus, it could be separated into two groups, fast and slow release matrix base. Fast release groups are G44/14, G42/12, G50/13 and G53/10 while the other were G46/07 and G50/02 as slow release group. According to the basic concept of indirect method of measuring the solubilizing power described above, heat of fusion of DTZ HCl decreased as the calculated HLB value increased. This meant that at higher HLB the relative solubilizing power was raised. These results correlate with the dissolution power. Additionally, one can also explain the release characteristics by observing the matrix appearance after dissolution testing. G44/14 and G42/12, both matrices completely and rapidly dispersed in the surrounding medium in 1 hour after immersing in purified water. Especially for G44/14, it was completely dispersed in first half an hour. The next group was G50/13 and G53/10, they became small flakes after 2 and 6 hours, respectively. The final group was the slow release group, G46/07 and G50/02, both base provide the validity in sustained release property due to its moderate to high hydrophobicity. The strange result was achieved with G46/07, tiny soften masses agglomerate around the inner core matrix.

Interpretation of thermosoftening base characteristics with melting points were considered along with hydrophilicity. Although Gelucire® melting range could not be

indicated as single point determination but for simplification, maximum peak temperature (T_m) was selected. From thermal analysis results, every single component bases had a melting temperature above 37°C except for G46/07 and G53/10. G46/07 displayed the main component peak at 33°C and the minor at 46°C. Since the experimental temperature in dissolution test was equal to 37°C, possible effect of lower melting point portion led to soft and molten base which influenced a faster drug release. This result was opposite from above reasons. It might be possible that larger portion of bases prompt to soften but minor portion with higher melting property was intact and remain as a solid core. Consequently, partially soften mass was produced and deposited around the surface matrix and led to agglomeration due to the viscosity. The swollen mass might act as drug release barrier while imbibed drugs in solid base were retarded by itself. Sustained action was improved with this reason. The base with highest melting point, G53/10, displayed three separate distinct endothermic peaks at 38, 44 and 51°C. Similar result was obtained with G46/07 and should also be obtained with G53/10. Conversely, the results were different in drug release. G53/10 matrix displayed the faster release than G46/07. Hydrophilicity of G53/10 was higher than G46/07 and led to faster drug release. Furthermore, the lower melting portion of G53/10 did not serve to protect the matrix rigidity. From matrix appearance in dissolution investigation, SSM that was made from G53/10 tend to erode slowly and completely disintegrate into small matrix pieces in 6 hours of dissolution study. Both high hydrophilicity and composition of lower melting portion were the main factor influencing disruption of the matrix structure.

Comparison between G44/14 and G42/12 that had the same T_m (approximately 39-40°C) and relative solubilization value were performed. Melting temperatures of both base were nearly identical to the contacting medium temperature. Thus, they were possible to disperse, melt or soften after immersion. Moreover, relative solubization or hydrophilicity also performed as the key parameter to define the differences. Decreasing in ΔH_f of active compound region of both base were significant. The reduction in ΔH_f value of G44/14 and G42/12 was 26 and 15 joule per gram, respectively. Hence, hydrophilic property was dominant in G44/14 much more than G42/12. Then, dispersing capacity was also higher and provided faster drug release pattern. In conclusion, G44/14 provided acceleration of drug release more than G42/12.

Dissolution from G50/13 which had higher melting point and HLB, was slower than G44/14 and G42/12. DSC endothermic peak represented T_m of G50/13 at 42 °C. The temperature was different from G44/14 and G42/12. The hydrophilicity of G50/13, basically depends on the relative value, was equal to G42/12 but lower than G44/14. So, it provided a slower dissolution rate than G44/14. Although the difference in melting point between G50/13 and G42/12 or G44/14 were only a few degrees celsius, it was used to support the reason for lower dissolution rate observed. Temperature of about 5 °C above surrounding dissolution medium temperature was sufficient to resist molten or soften stage. Despite the resistance to matrix softening of G50/13, matrix still could erode as small flakes after 2 hours, under hydrodynamic stress such as agitation force of paddle. If compared between G42/12 and G50/13 at same $\Delta H_{f,}$, peak temperature would be the dominant factor to explain about dissolution rate. In comparison with G53/10, although G53/10 had defect properties as previously described which influenced the rise in drug release, lower ΔH_f than G50/13 was observed and higher melting temperature portion also existed. From both reasons, G50/13 provide faster drug release profile.

Objective to combine slow and fast release base intended to adjust the physicochemical property of bases to conform with USP 23 supplement 5, for product labeled dosing every 12 hours, Test 1. The principle base was G50/02 according to high hydrophobicity and provided the suitable sustained release property. Other base, such as G44/14, G42/12, G50/13, G46/07 and G53/10, were incorporated to increase the hydrophilicity of pure G50/02. DSC thermograms of all base mixture revealed that their thermal property were the summation of each base property depending on the proportion of each components. Co-melting process seemed to provide a dispersion of both base types in homogeneous mixture and solid appearance. Chemical interaction among base under high temperature condition used in the preparation process was not discovered and negligible. IR spectra supported the evidence that there are no chemical interaction of each mixture bases. The depletion in T_m of DTZ HCl peak in all SSM preparation concluded that base mixture influenced the characteristics of active compound. Important factors that governed the release of active component from SSM were thermal property and dominant hydrophilicity of the base mixture.

In all conditions of blending the same results were established. The increment of amount for all fast release Gelucire® provided the faster and higher drug release than G50/02 SSM as reference. The results showed that improvement of hydrophilicity and thermal property of blending bases affected drug delivery from the matrix.

G42/12, G44/14, G50/13 and G46/07 mixture base provided the result for dual component preparation the same way as mentioned above. G53/10 was an outstading example, which provided a difference result from the basic estimation. Higher portion of G53/10 at calculated HLB value of over 7 displayed nearly identical dissolution profiles as G53/10 in single component form. The presents of G50/02 in G53/10 dual components provided lower hydrophilicity of the system than pure G53/10 and retarded the drug liberation. Controversial results could be explained from some phenomena under dissolution experiment. Combination of G50/02 and G53/10 at HLB 7, 9 and pure G53/10 (approximate HLB about 10) SSM device under dissolution testing process, disintegration of matrix device more influenced drug release and was clearly observed. Additionally, small flakes of matrix were generated after the disintegration occurrence. Major influencing factor was described from thermal analysis. DSC thermogram of higher T_m portion of G53/10 in dual component SSM preparations showed the large endothermic region with lower T_m which was lower than 37°C. Weakness of matrix structure was obtained after contacting with the 37°C surrounding dissolution medium and provide disintegration. Disintegration phenomena of matrix led to an increase in surface area and played the important factor in drug release pattern. Non-uniform disintegration was the main factor for uncontrollable drug release. Therefore, at calculated HLB above 7 of dual combination between G50/02 and G53/10 and pure G53/10 could not be estimated along with the early hypothesis.

HLB value was the advantage parameter as hydrophilicity indicator. The approximation of higher HLB value reflected higher hydrophilicity and provide faster drug release. Hence, dissolution profiles comparison of each base mixture at constant HLB are constructed and summarized. Normally, several SSM researchers suggested that the appropriate HLB for sustained release design should not be above 7 (Ortigosa, 1991).

In the range of calculated HLB less than 5, main component of SSM preparation was G50/02 and the minor varied from different degree of hydrophilicity by various thermosoftening base types. The result showed that the higher HLB bases, such as G42/12 and G44/14, had higher capacity for faster drug release. In calculated HLB 2.5 and 3, every preparation expressed nearly equal profiles since main composition of device was G50/02. In this case, the adjustment of the systems with various Gelucires® had negligible effect on drug release. However, higher portion of fast release Gelucire® (higher in calculated HLB) clearly indicated faster drug liberation. Calculated HLB 5 indicated that G46/07 blending group provided the lower and slower dissolution profile than the others due to low degree of hydrophilicity (Figures 23-25). Although the lower T_m portion of G46/07 base mixture (around 32°C) was equal to the higher T_m portion region (about 43°C) and might be possible that they partially softened the mass of matrix base, it might destroy the matrix rigidity and promote faster drug release. However, the lower hydrophiilic(G46/07) was still an important factor on drug release regulation.

The increase in calculated HLB over 7 for base mixture system gave a specific dissolution profiles. According to the proportion of base mixture, at higher calculated HLB, the main component converted from G50/02 to each fast release Gelucire® and affected the hydrophilicity of matrix device evenmore. High HLB SSM system (HLB> 7) was further focus on additional parameter as weight ratio of each components.

In HLB 7, G53/10 and 50/13 provided faster release profile than G44/14 and G42/12 base mixture. This result was opposite to the above conclusion. The critical factor that was under concern in this event was disintegration. The increase in lower T_m portion (<37°C) destroy the rigidity of matrix and altered surface area of the device. Increase in surface contact directly influenced the drug release. At this HLB, G42/12 and G44/14 device were still in capsule shape without complete disintegration although SEM of surface appearance indicated that there were erosion (Figures 45-48).

In HLB system equal to 9, interestingly, the results were quite different for from our estimation. Order of drug release improvement should be G44/14 > G42/12 > G50/13 and G53/10. The results showed that G42/12 > G44/14 > G53/10 ≅ 50/13

(Figure27). For G53/10, according to disintegration, played an important role for drug release on HLB above 7. Therefore, maximum profile of pure G53/10 was upper limit for base mixture of calculated HLB 9. Focus on dissolution pattern of only pure G53/10 which was lower than other base mixture groups. Clearly, the blending of G53/10 was also lower than other base mixture groups at identical HLB. Comparative studies for merely three base types were done. The estimation should be ranked as degree of hydrophilicity and thermal property. It was seen that pure G50/13 was the higher HLB, higher melting range but lower dissolution profile than pure G44/14 and G42/12. Making a decision between G44/14 and G42/12 base mixture was tough and contrast with the degree of hydrophilicity due to nearly similar property resulted. Consideration of the weight ratios of fast release Gelucire® to G50/02 became critical factor. G42/12: G50/02 weight ratio was equal to 2.3 while G44/14: G50/02 was only 1.4 value. It was clear to state that, at constant HLB of 9, G42/12 portion in mixture base was greater than G44/14 about 0.9 part. It became as the driving force of faster drug release evidence. In addition, thermal scanning profile displayed the lower T_m region G42/12 blending preparation was much more than G44/14 blending and led to softening or melting of the matrix device. It supported the evidence of the faster drug release result.

The maximum HLB for base mixture in this study was equivalent to 11. Three types of base, G44/14, G42/12 and G50/13 were sufficient in degree of hydrophilicity to obtained higher calculated HLB. The result at this HLB condition was similar to HLB 9 (Figure 28). As described above, upper limit of pure G50/13 was lower than G42/12 and G44/14 according to degree of hydrophilicity and thermal property. Slower dissolution profile of base mixture in G50/13 group was obtained. Between two types of most beneficial Gelucire® for fast release, contemplation on weight ratio of bases was the crucial parameter to clarify the differences in dissolution profiles. Constituent ratio of G42/12 and G44/14 to G50/02 were equal to 9 and 3, respectively and exhibited the higher portion of base mixture for about three folds. If there were large portion of fast release Gelucire® content then fast release matrix device was produced. It was confirmed that content was the possible reason for faster release from G42/12 base mixture over G44/14 base mixture.

Storage time effect

Aging condition and time were also an important factors to any dosage forms. In SSM dosage form, that base were especially composed of triglycerides, aging time and temperature were the critical variables effecting the crystal properties of thermosofetening base. Investigation of model base, G50/02, could be observed that all around 1 week to 1 month after freshly prepared, both dissolution profiles were nearly similar (with approximately 2 percent difference) while after 4 months at the same storage condition exhibited a few difference in dissolution patterns and expressed approximate 4 % difference.

Typically, the transformation of triglycerides polymorph or crystal structure was an important factor to drug release regulation due to crystallinity properties (Figure 88). Fat or waxes that were composed of major component as triglycerides, polymorphic transformation process usually occurs after resolidification. Triglycerides consist of the various polymorphs as β stable form, β′metastable form and α-unstable form, respectively. Normally, triglycerides in natural condition are present in the stable form. In melting process of triglyceride, converting of the β-stable form to α-unstable form may occur after resolidification. Around 3 to 6 hours after it solidified, the unstable polymorph is converted to β′ metastable form. After that at an ambient condition, β′-metastable eventually undergoes further transition to β-stable in several months of storage. Likewise, accelerate condition (about 40°C) can provide the polymorphic transformation within a few days.

Inhibitor and accelerator of polymorphic conversion are the interesting factor on the transformation process and involve drug release. The presence of mono and diglycerides content in SSM bases will inhibit polymorphic transformation (Eldem et al., 1991). Storage temperature is also the main accelerator to convert the polymorph of triglycerides. In addition, drug particles have the sophistical effect to the inhibitory conversion process.

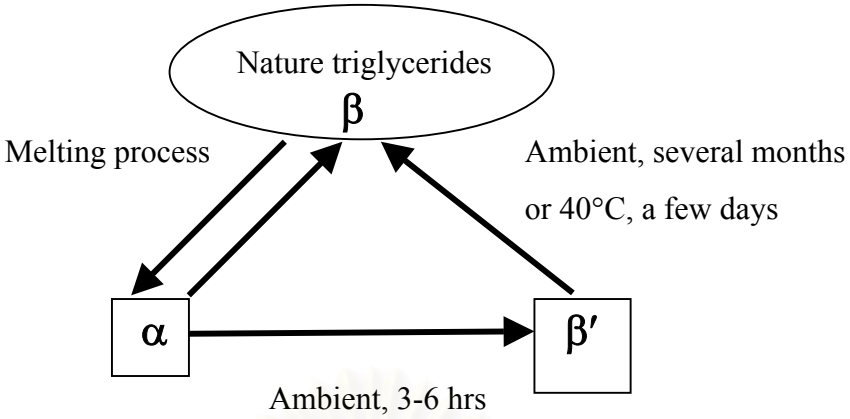


Figure 88 Schematic illustration of polymorphic transformation of glycerides.

Inhibitors such as mono or diglycerides can be stabilize and delay the polymorphic transformation of β′-stable form via restricting the molecular motion of the polymer chain and interlayer chain penetration. In the case of suspended drug particle, during solidification process, it may inhibit nucleation center of the base molecules and lead to disrupt the forming matrix structure. Decreasing the nucleation center of base reduced the solidification temperature. Possibility of microsegregation phenomena of base component will take place (Sutananta et al., 1994).

G50/02 was composed of the major component as triglycerides about 45 % and minor were diglycerides, diPEG esters and monoglycerides as 30 %, 20 % and 5 %, respectively (Sutananta et al., 1994). As possibly seen from chemical component of G50/02 thermosoftening base, the test hypothesis stated that the major component "triglyceride" had a possibility of polymorphic transformation.

The examination of structural and crystallinity change of pure G50/02 base by X-ray powder diffraction was performed. The diffractogram of original pure G50/02 (as reference of most stable structure) were nearly similar in °2θ and crystallinity to G50/02 which passed heating cycle prior to the preparation process and storage at different times. The result displayed that structural or polymorphic change of G50/02 did not occur under experimental storage condition and time. DTZ HCl SSM with G50/02 at various storage times were investigated and the results showed that long range storage time period was not enough to alter the structural form of G50/02. Alteration of X-ray

diffractogram of G50/02 with DTZ HCl at different storage times could not provide. It was confirmed that DTZ HCl did not involve in the changing of G50/02 polymorph. Finally, the slower and decrement of drug release from DTZ HCl SSM with G50/02 at long term storage was not due to polymorphic transformation of triglyceride component in G50/02. The proposed hypothesis would be rejected when X-ray evidence was used. Thereby, it had another complex factors which concerned about the decreasing of drug release. Further experiment would be studied and proved to be an important factors.

pH sensitive condition observation

Dissolution study of DTZ HCl SSM in pH change system revealed that lower dissolution profiles were obtained. Proposed factors that influence drug release were separated into two factors. One of them was the drug factor, as drug solubility in different dissolution medium and the other was the matrix or the base factor.

Conceptually, DTZ HCl is weak base with approximately 7.7 in pK_a value (Illum et al., 1983). The weak base or salt compound dissolved more or ionized in the low pH environment. In acidic condition which pH differ from pK_a value much more than 2 units will provide totally ionized drug molecules and was completely dissolved. Thus, on assumption, DTZ HCl solubility in acid medium should be higher than in intermediate to high pH conditions.

Comparative dissolution profiles of all preparation, which followed USP 23 suppement 5, Test 1 for product labeled every 12 hours, between purified water and pH change media were studied. The results revealed that pH influenced the drug release capacity of matrix device. They showed that initial period of studied in pH 1.2 and 4.5, drug release was the same as in purified water. Basically with above pH partition theory, solubility of DTZ HCl in water, pH 1.2 and 4.5 were nearly similar. It could be explained that purified water (pH about 5-5.5) pH 1.2 and 4.5 media had a pH lower than pK_a of DTZ HCl more than 2 units. Thus, entirely ionized drug species were generated. The final stage of pH change study (pH 7.0) expressed the lower drug release profile. Neutral pH such as 7.0 produced partially ionized DTZ HCl species as concerned with pH partition theory and the reduction in drug solubility. So, the primary

proposed hypothesis stated that drug solubilty in different pH environments was the main factor affecting drug release through thermosoftening matrix.

Determination of DTZ HCl solubility in various pH media are experimented and summarized in Table 31. The result harmonized with studies of other researchers such as Zenter et al.(1991), Bodmeier et al.(1996). The solubility expressed that DTZ HCl was really pH-independent molecule due to similar solubility in various pH conditions. They could be estimate that in purified water, pH 1.2, 4.5 and 7.0, drug release did not depend upon pH solubility of active compound due to nearly identical solubility. Hence, pH solubility was not the main factor controlling drug release in thermosoftening matrix. The hypothesis mentioned above was rejected. Thus, the matrix base factor became a crucial factor, although, it must undergo further study to clarify the real factor affecting drug release in neutral pH.

Conclusions

Sustained release of DTZ HCl (90mg) could be accomplished with SSM system and conformed to Diltiazem hydrochloride Extended release capsule in USP 23, for product labeled for every 12 hours, Test 1. In the study, suitable formulations for DTZ HCl SSM for 90-mg dosing level and consent drug release tolerance could be prepared with various formulas.

Geometrie form of SSM device was the first consideration prior to the formulation development. Furthermore, the change in matrix form was an important factor on the release mechanism of active component from rigid matrix system. In addition, drug concentration in matrix bases was the significant factor the same as geometry of device on drug release. In rigid SSM, G50/02, the main mechanism for controlling drug release were both diffusion and case I transport which depended on the concentration of drug in matrix and physicochemical property of active ingredients. So, the design of SSM formulation would concern about drug to bases weight ratio and it must be in accordance with the best suitable geometry. One of the best way for observing the appropriate drug to bases weight ratio was the flux or amount of drug release per unit area and time. The constant flux was the most desirable in controlled drug release.

Application of thermosoftening vehicle in sustained release dosage form of highly water soluble drug were achieved with desirable dissolution profiles by using low degree of hydrophilicity base as main component and combine with different HLB property of each bases. G50/02 was the most suitable base to retard drug liberation by itself. The other Gelucires® in the research were employed as adjustment additives for improvement of hydrophilicity and faster rate of drug release after mixed with G50/02. Generally research in SSM system recommended that the most proper HLB of SSM to utilized as sustainable property should be lower than 7. The result of this research was agreeable to previous suggestion that indicated suitable calculated HLB for sustained release property was lower than 7.

The relationship of MDT and calculated HLB were discovered. Linearization relationships of both parameters were obtained in some base mixture. The base mixture, which tend to express the above result, was a rigid structure device and without disintegration phenomenon. The relevant result was used for formulation development on SSM system. The advantage of this relationship helped to find out the proper type and weight ratios of base mixture to achieve desirable properties.

Without any doubt, in vitro dissolution testing was not enough to represent real situation as in vivo condition. In pH step change, at least mimic the real pH condition of the gastrointestinal tract, drug release from several formulas were delineated from purified water. Hence, there results potentiates the requirement for further study of SSM system by oral administration.

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APPENDICES

Appendix A
Standard calibration curve

A data and profile of relationship between drug concentration and absorbency at appropriate wavelength of DTZ HCl in various media were presented below in Tables 35-39 and Figures 89-93.

Suitable wavelength of DTZ HCl in purified water, dichloromethane, pH 1.2, pH 4.5 and pH 7.0 medium in pH change study were 237, 241, 237, 237 and 237 nm, respectively.

Table 35 Concentration and absorbency data for DTZ HCl in purified water.

Concentration(mcg/ml)	Absorbency
0	0
2.215	0.118
4.25	0.237
6.375	0.348
8.50	0.453
10.625	0.567
12.75	0.682
17.00	0.910
20.05	1.129

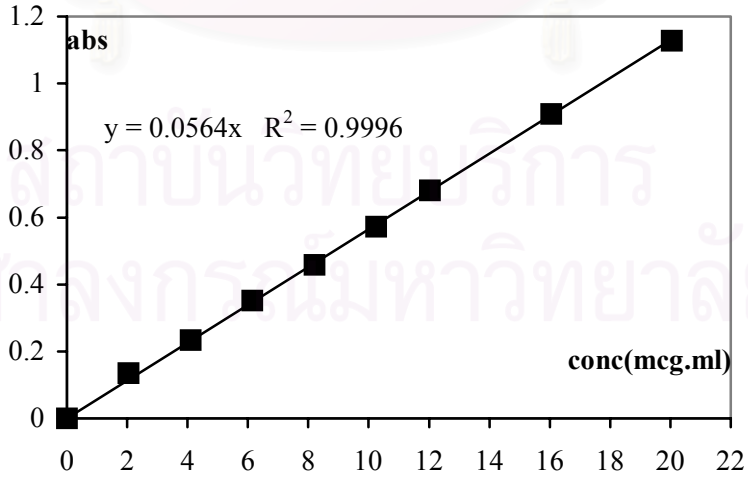


Figure 89 Standard calibration curve of diltiazem hydrochloride in purified water.

Table 36 Concentration and absorbency data for DTZ HCl in dichloromethane.

Concentration(mcg/ml)	Absorbency
0	0
3.93	0.222
4.91	0.297
7.86	0.460
9.82	0.572
11.78	0.690
14.73	0.860
19.64	1.144

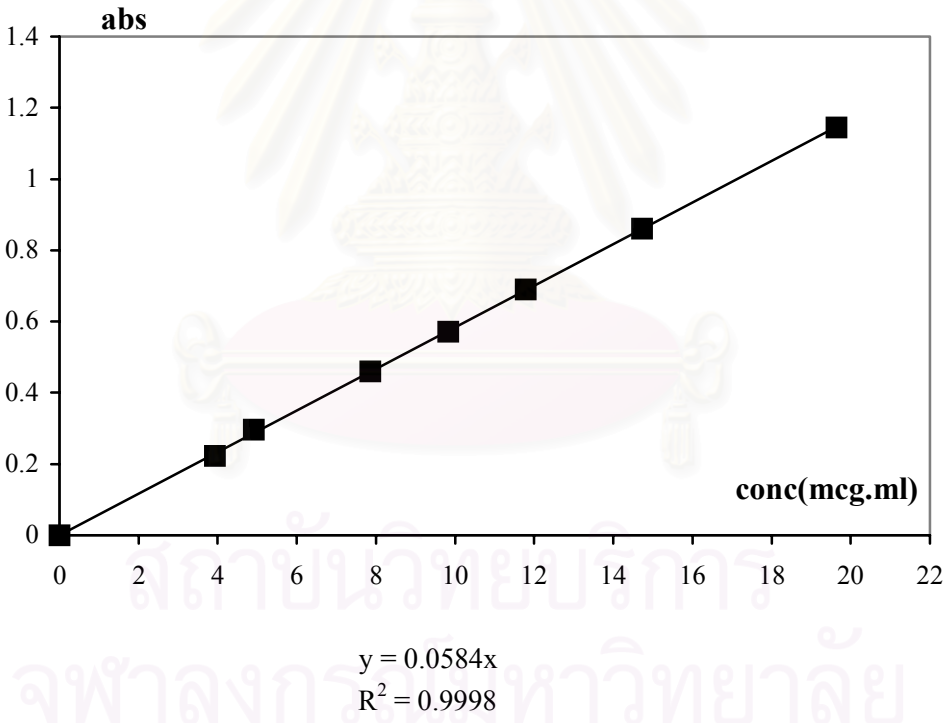


Figure 90 Standard calibration curve of diltiazem hydrochloride in dichloromethane.

Table 37 Concentration and absorbency data for DTZ HCl in pH 1.2 media of pH change system study.

Concentration(mcg/ml)	Absorbency
0	0
2.05	0.135
4.10	0.234
6.15	0.351
8.20	0.458
10.25	0.573
12.03	0.680
16.04	0.909
20.05	1.128

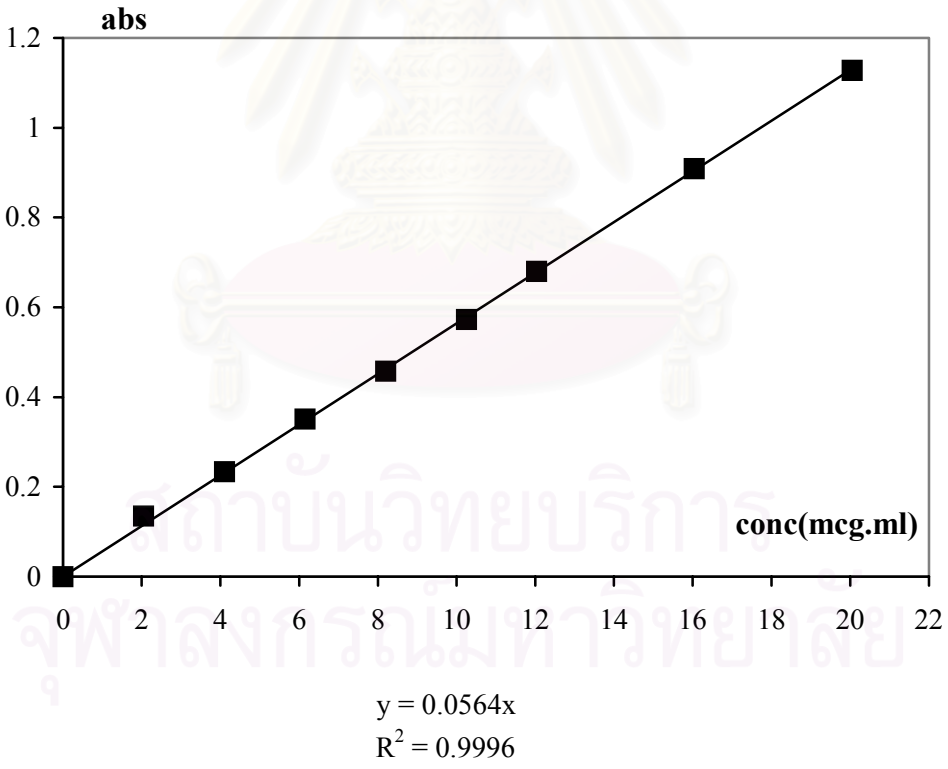
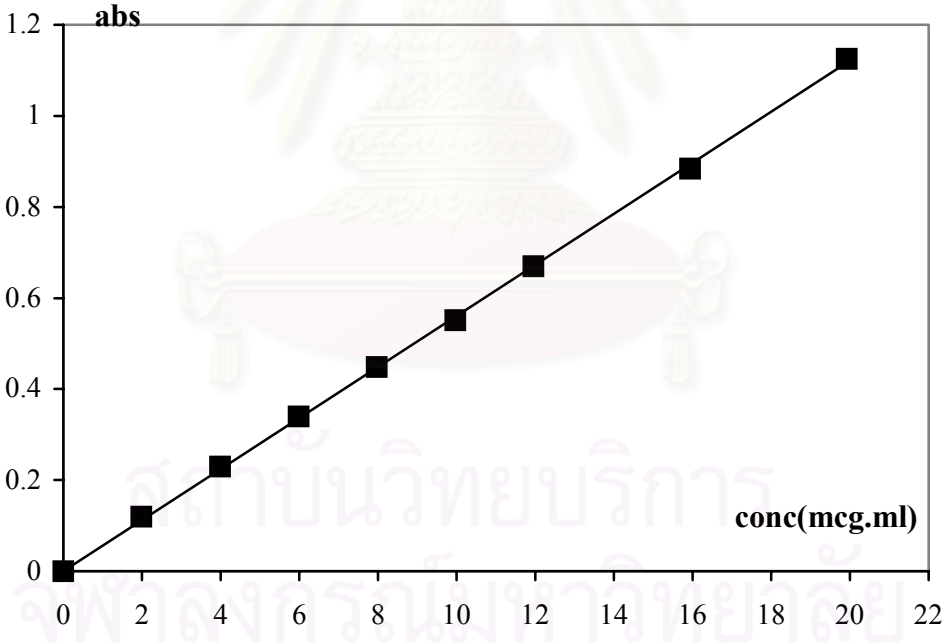


Figure 91 Standard calibration curve of diltiazem hydrochloride in pH 1.2 media of pH change system study.

Table 38 Concentration and absorbency data for DTZ HCl in intermediate pH 4.5 media of pH change system study.

Concentration(mcg/ml)	Absorbency
0	0
1.99	0.1205
3.98	0.23
5.98	0.3395
7.97	0.449
9.96	0.551
11.95	0.670
15.94	0.8835
19.92	1.125



$y = 0.0561x$

$R^2 = 0.9996$

Figure 92 Standard calibration curve of diltiazem hydrochloride in intermediate pH 4.5 media of pH change system study.

Table 39 Concentration and absorbency data for DTZ HCl in final pH 7.0 media of pH change system study.

Concentration(mcg/ml)	Absorbency
0	0
1.999	0.129
3.998	0.222
5.997	0.322
7.996	0.44
9.995	0.541
11.994	0.651
15.992	0.871
19.99	1.081

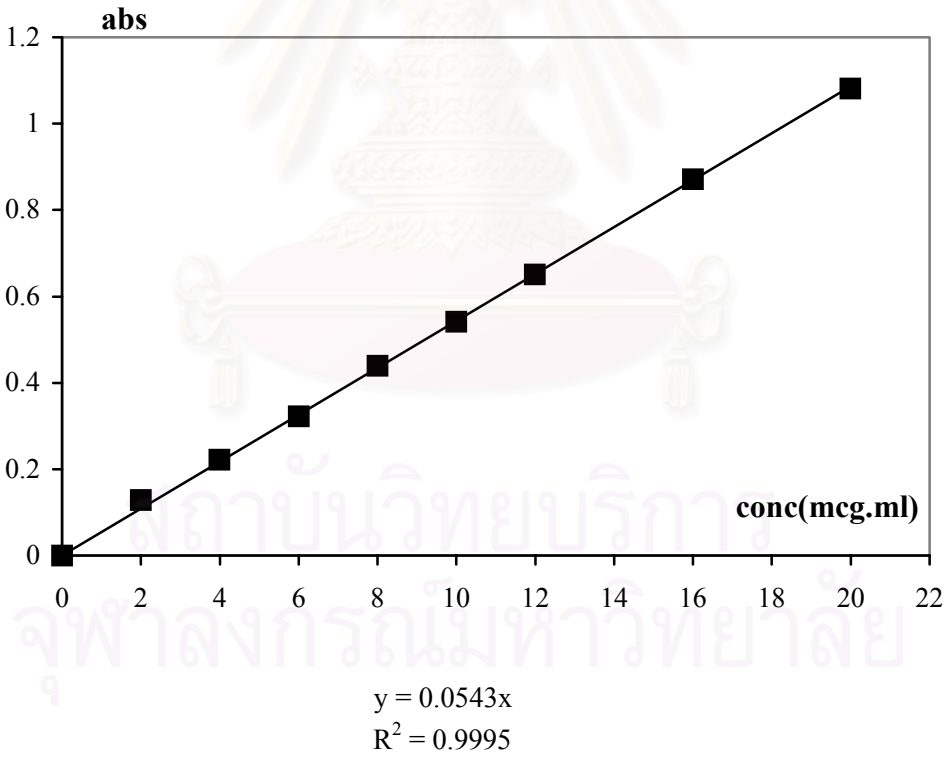


Figure 93 Standard calibration curve of diltiazem hydrochloride in final pH 7.0 media of pH change system study.

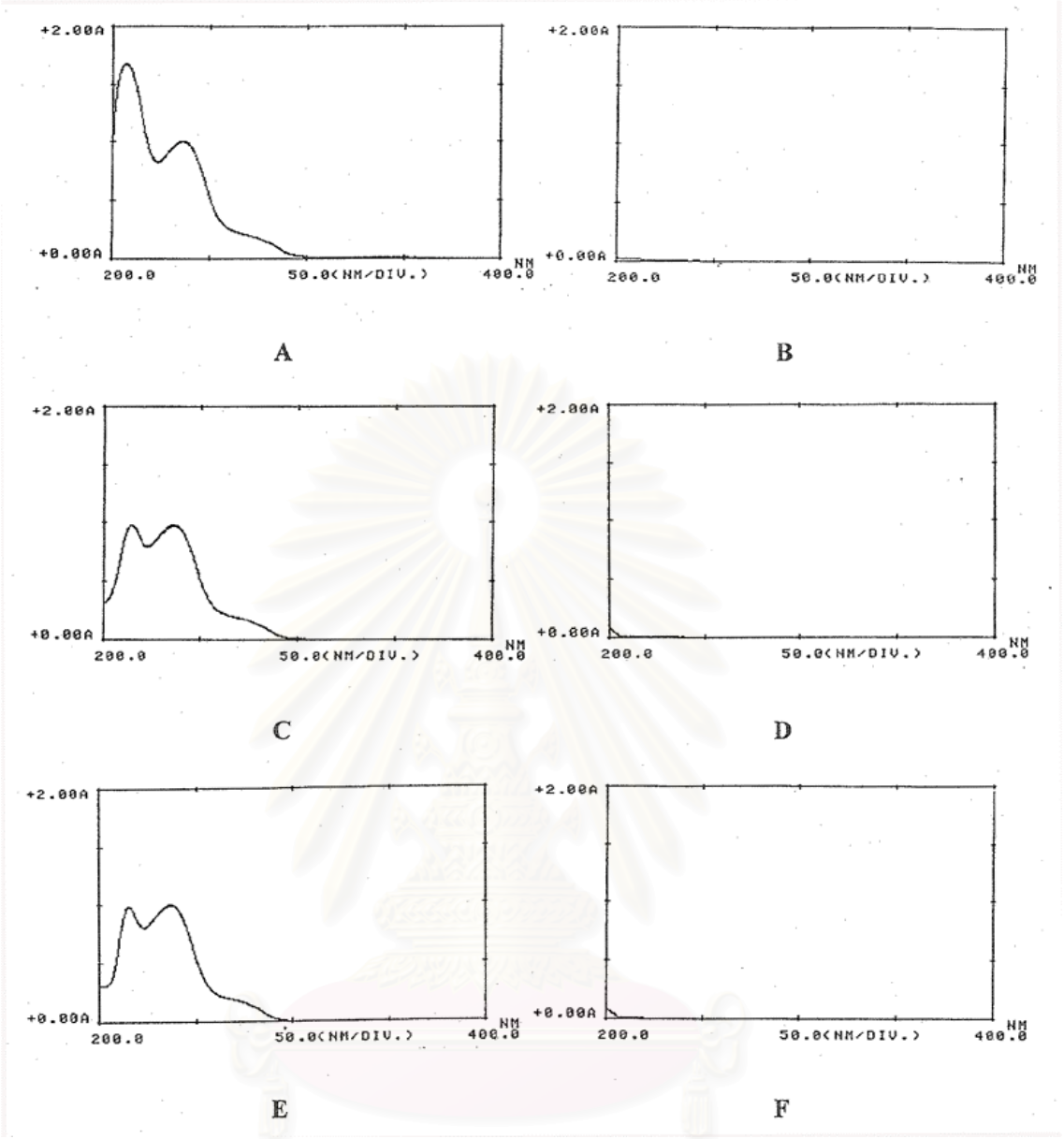


Figure 94 UV absorption spectrum of diltiazem hydrochloride in different media in pH change study. (A, C and E is diltiazem hydrochloride in pH 1.2, 4.5 and 7.0 media, respectively. B, D and F is pH 1.2, 4.5 and 7.0 media as references, respectively).

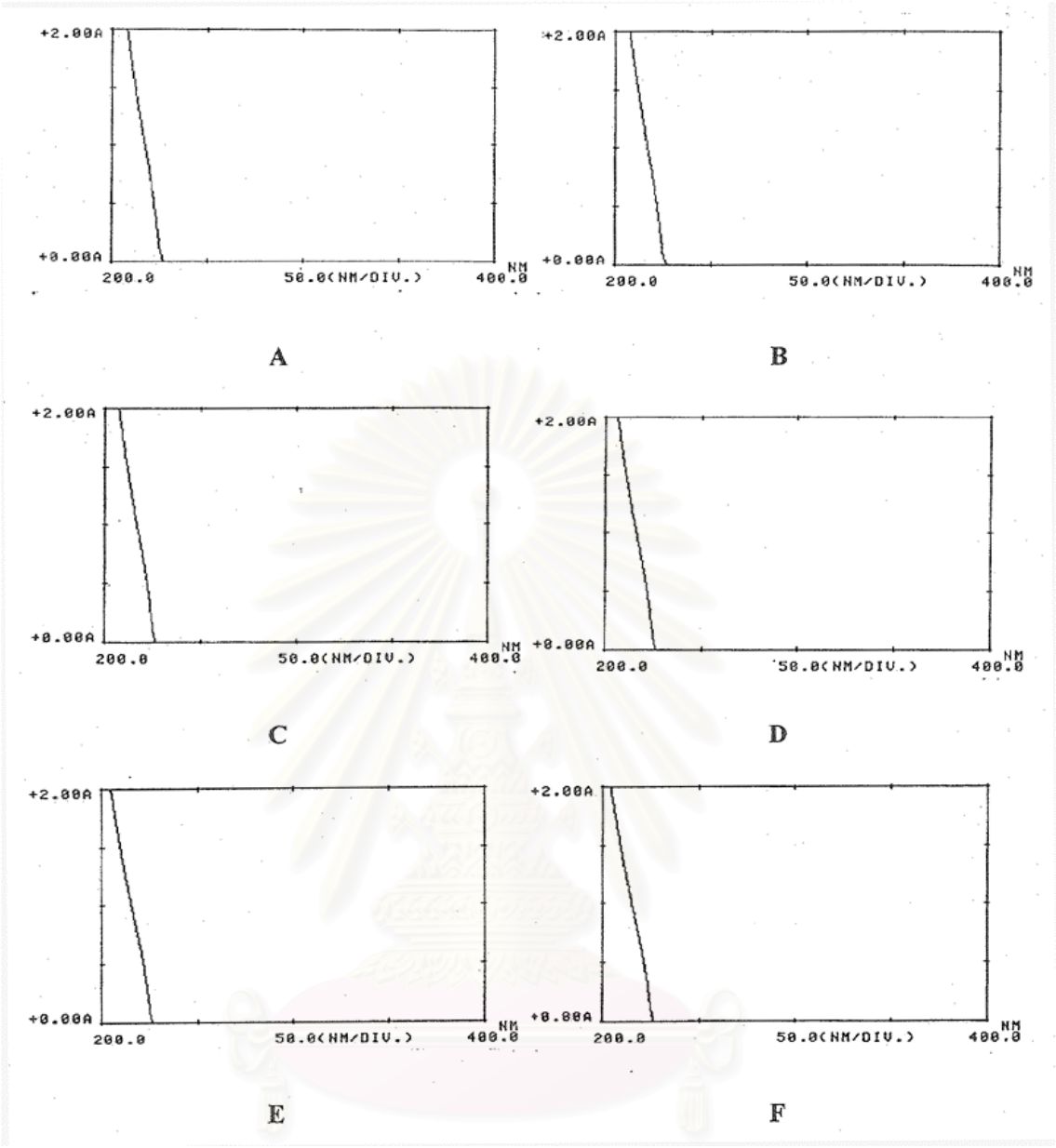


Figure 95 UV absorption spectrum of different thermosoftening bases in dichloromethane solvent (A – G42/12, B – G44/14, C – G46/07, D – G50/02, E – G50/13 and F – G53/10)

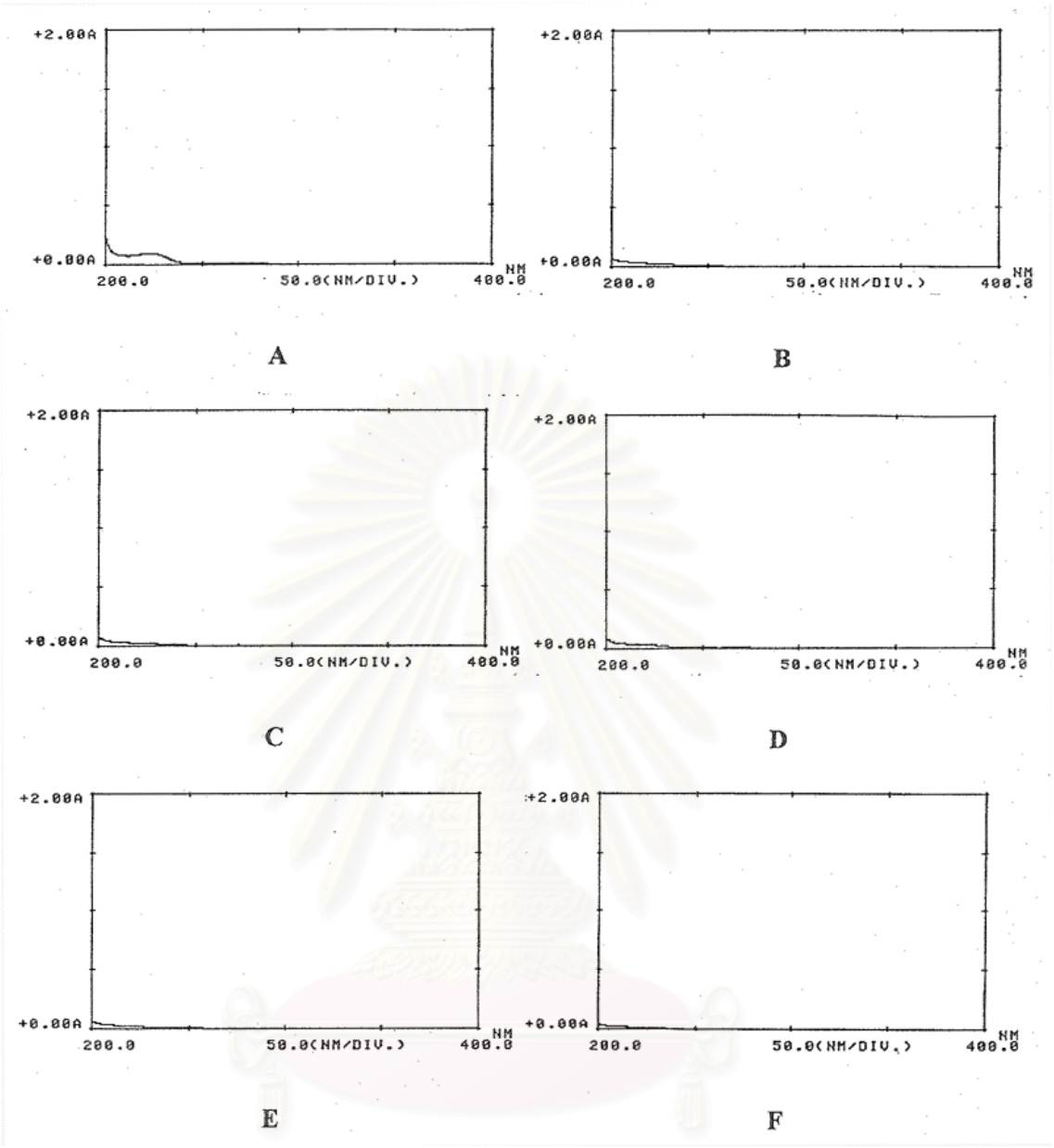


Figure 96 UV absorption spectrum of different thermosoftening bases in purified water as dissolution media. (A – G42/12, B – G44/14, C – G46/07, D – G50/02, E – G50/13 and F – G53/10)

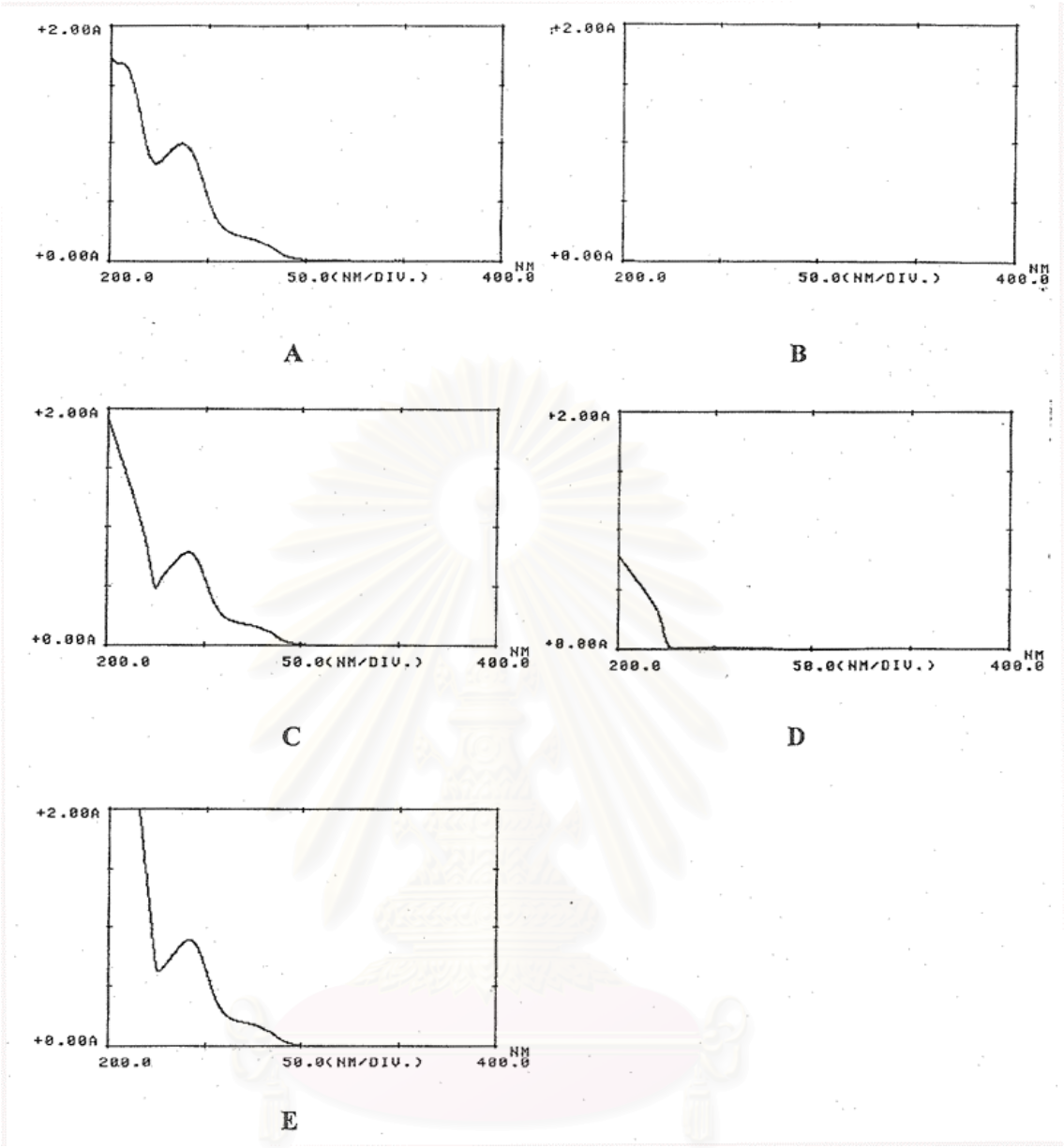
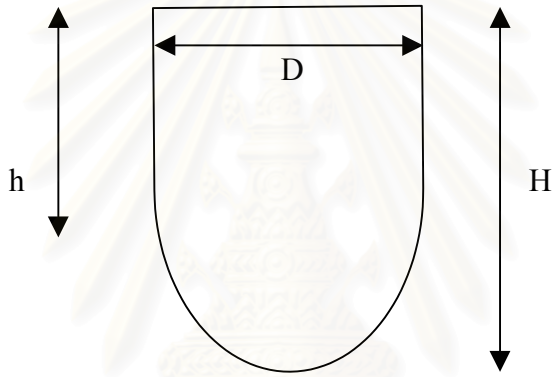


Figure 97 UV absorption spectrum of diltiazem hydrochloride in various media. (A – in purified water, C – in dichloromethane, E – diltiazem hydrochloride semisolid matrix preparation in dichloromethane, B – purified water as reference and D – dichloromethane as reference).

Appendix B

Surface calculation of SSM devices

Calculation of the whole surface area for the solute flux comparison was described. The dimensions of capsule shape wax matrix were measured by vernir caliper tool. The model of capsule shape wax matrix as presented below.



A radius (r) of plug shape wax matrix were describes as a half of inner diameter (D/2) of capsule-body shell. Total plug height (H) were recorded and used to determine a height of cylinder part (h) of plug shape. Mathematical equation to calculated total surface area of monoconvex capsule shape was summation of circle area on the top, right circular cylinder and a one segment of a sphere attached at the end. (David et al., 1988)

$$\text{Total surface area (SA)} = \pi r^2 + 2\pi rh + (r^2+(H-h)^2)$$

Table 40 The raw data of inner diameter of body part of capsule shell (centimeters unit.)

d *(cm)			
1	2	3	Average ± S.D.
0.590	0.600	0.588	0.593 ± 0.0064
0.590	0.592	0.586	0.589 ± 0.0031
0.584	0.608	0.602	0.598 ± 0.0125
0.586	0.590	0.586	0.587 ± 0.0023
0.592	0.592	0.592	0.592 ± < 0.0001
0.582	0.586	0.588	0.585 ± 0.0031
0.578	0.582	0.580	0.580 ± 0.0020
0.592	0.590	0.584	0.589 ± 0.0042
0.588	0.592	0.586	0.589 ± 0.0031
0.588	0.590	0.592	0.590 ± 0.0020
0.580	0.582	0.580	0.581 ± 0.0012
0.588	0.590	0.592	0.590 ± 0.0020
0.586	0.590	0.590	0.589 ± 0.0023
0.580	0.582	0.580	0.581 ± 0.0012
0.584	0.586	0.586	0.585 ± 0.0012
0.582	0.584	0.586	0.584 ± 0.0020
0.588	0.586	0.590	0.588 ± 0.0020
0.590	0.590	0.588	0.589 ± 0.0012
0.588	0.590	0.590	0.589 ± 0.0012
0.586	0.588	0.586	0.587 ± 0.0012
Average mean diameter (cm)			0.588

* The diameters of each empty hard gelatin capsule shell were measured triplicate and reported as mean diameter with standard deviation. Twenty capsules were investigated.

Table 41 The raw data in H of each drug-wax ratio formulas.

H *(cm)		
Formula Code : R2 Drug : wax ratio = 1: 2	Formula Code : R3 Drug : wax ratio = 1: 2.5	Formula Code : R4 Drug : wax ratio = 1: 3
1.180,1.180,1.120	1.320,1.322,1.320	1.440,1.450,1.452
1.190,1.190,1.190	1.292,1.290,1.286	1.482,1.480,1.478
1.140,1.140,1.130	1.300,1.290,1.292	1.480,1508,1.490
1.130,1.220,1.240	1.320,1.304,1.310	1.490,1.460,1.458
1.110,1.120,1.120	1.290,1.300,1.290	1.488,1.490,1.492
1.092,1.092,1.090	1.300,1.310,1.320	1.486,1.486,1.480
1.104,1.104,1.106	1.320,1.310,1.310	1.480,1.4822,1.480
1.130,1.120,1.118	1.290,1.298,1.310	1.500,1.510,1.502
1.114,1.118,1.120	1.288,1.310,1.310	1.472,1.470,1.472
1.118,1.132,1.120	1.310,1.310,1.300	1.478,1.474,1.476
1.108,1.109,1.108	1.292,1.284,1.290	1.470,1.470,1.472
1.112,1.118,1.112	1.288,1.292,1.290	1.500,1.490,1.486
1.110,1.104,1.112	1.300,1.294,1.294	1.488,1.484,1.490
1.112,1.116,1.106	1.316,1.310,1.322	1.472,1.474,1.480
1.101,1.098,1.100	1.282,1.288,1.278	1.488,1.484,1.488
1.112,1.116,1.114	1.310,1.300,1.290	1.472,1.472,1.474

Appendix C

Determination of DTZ HCl content in SSM preparation.

A raw data of percent labeled amount of DTZ HCl in each semisolid matrix formula were presented in Table 42. The data were reported as average percent labeled amount with standard deviation and percent coefficient of variation (%CV) in triplicate.

Generally, assay data were accepted with minimal %CV not exceeding 6 percent. %CV was calculated from two set of parameter both as average percent labeled amount and standard deviation with following equation.

$$\%\ CV = \frac{\text{Standard deviation} \times 100}{\text{Average percent labeled amount}}$$

Table 42 Percent labeled amount of DTZ HCl SSM formulas.

Formula Code	Run # 1	Run # 2	Run # 3	Average % labeled amount	SD	%CV
F 1	103.83	105.76	104.97	104.85	0.9693	0.9245
F 2	101.78	100.38	99.63	100.60	1.0900	1.0800
F 3	98.14	99.24	96.38	97.92	1.4422	1.4729
F 4	103.60	103.42	103.33	103.45	0.1300	0.1200
F 5	101.57	100.80	101.30	101.13	0.3950	0.3907
F 6	100.47	100.87	100.30	100.55	0.2900	0.2900
A 1	97.31	104.99	99.94	101.15	3.9000	3.8500
A2	98.36	96.35	96.49	97.07	1.1200	1.1500
B 1	101.61	101.69	101.65	101.65	0.0400	0.0300
B 2	101.84	102.99	103.38	102.74	0.8000	0.7700
B 3	97.53	99.42	100.46	99.14	1.4800	1.4900

B 4	101.86	102.31	102.14	102.10	0.2200	0.2200
B 5	99.70	98.78	98.47	98.98	0.6400	0.6400
C 1	102.42	101.18	101.85	101.82	0.6100	0.6000
C 2	101.91	100.83	101.66	101.47	0.5600	0.5500
C 3	102.08	103.79	101.06	102.31	1.3800	1.3400
C 4	100.34	99.66	101.03	100.35	0.6800	0.6800
C 5	100.21	99.92	99.98	100.04	0.1500	0.1500
C 6	97.67	98.90	98.53	98.37	0.6300	0.6300
C 7	101.12	99.36	99.62	100.03	0.9500	0.9500
D 1	102.10	101.77	101.73	101.87	0.2040	0.2000
D 2	103.55	105.76	103.59	104.30	1.2700	1.2100
D 3	101.46	100.81	101.12	101.13	0.3300	0.3200
D 4	100.27	100.53	100.39	100.40	0.1300	0.1200
D 5	100.24	98.50	99.96	99.57	0.9300	0.9300
D 6	102.77	101.01	102.39	102.06	0.9200	0.9100
E 1	102.35	101.95	102.06	102.12	0.2000	0.2000
E 2	102.59	102.21	103.45	102.75	0.6300	0.6100
E 3	101.18	101.59	101.73	101.50	0.2800	0.2800
E 4	105.67	101.82	103.60	103.70	1.9300	1.8600
E 5	101.58	99.93	99.34	100.28	1.1600	1.1500
E 6	104.06	102.15	101.38	102.53	1.3800	1.3400
R 1	99.59	97.08	98.38	98.35	1.2500	1.2700
R 3	102.65	102.47	102.62	102.58	0.0900	0.0900
R 4	102.56	102.18	102.55	102.43	0.2100	0.2000
H 1	102.46	102.32	100.58	101.79	1.0400	1.0300
H 2	103.60	103.98	103.16	103.42	0.2500	0.2400
H 3	101.61	101.83	101.76	101.73	0.1100	0.1000
H 4	102.83	102.64	101.91	102.46	0.4900	0.4700

Appendix D

Drug release data from dissolution study.

Formula R2-R4

Time	% cumulative release						Mean	SD
(hr)	1	2	3	4	5	6		
R2								
0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0
0.5	1.66	1.61	1.85	1.65	1.70	1.72	1.70	0.09
0.75	2.71	2.58	3.03	2.65	2.72	2.85	2.76	0.16
1	4.07	3.83	4.42	3.90	4.31	4.10	4.10	0.23
1.5	7.00	6.80	7.39	6.80	7.20	7.15	7.06	0.23
2	10.43	10.10	10.72	10.30	10.55	10.62	10.45	0.23
3	17.18	16.77	17.36	17.14	16.97	17.22	17.11	0.30
4	24.94	24.39	24.98	24.53	24.87	24.92	24.77	0.25
5	31.02	30.47	30.88	30.88	30.74	30.62	30.77	0.20
6	36.79	36.24	36.85	36.23	36.74	36.92	36.63	0.31
8	49.93	49.20	50.56	49.44	50.32	49.88	49.89	0.51
9	54.03	53.48	54.48	53.55	54.32	54.07	54.00	0.40
10	60.98	60.06	62.01	60.47	61.93	60.59	61.00	0.80
12	70.31	70.33	70.61	70.22	70.44	70.31	70.42	0.25

Time (hr)	% cumulative release			Mean	SD	Time (hr)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
R3						R4					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0.25	0	0	0	0	0
0.5	2.18	2.12	2.21	2.17	0.05	0.5	2.25	2.41	1.92	2.19	0.25
0.75	3.40	3.41	3.58	3.47	0.10	0.75	3.63	4.02	3.43	3.69	0.30
1	4.95	4.99	5.26	5.07	0.17	1	5.40	5.71	5.06	5.39	0.33
1.5	8.46	8.54	8.79	8.60	0.17	1.5	9.11	9.28	8.77	9.05	0.26
2	11.95	12.00	12.28	12.08	0.18	2	12.77	13.00	12.49	12.75	0.25
3	20.10	20.29	21.04	20.48	0.50	3	21.02	21.03	21.00	21.02	0.01
4	26.51	26.95	27.52	26.99	0.50	4	27.67	27.68	27.28	27.54	0.23
5	32.26	32.76	33.52	32.85	0.63	5	33.84	33.85	33.64	33.78	0.12
6	37.71	38.08	38.69	38.16	0.50	6	39.34	39.72	38.881	39.29	0.46
8	49.40	50.06	51.39	50.29	1.01	8	49.49	49.86	49.83	49.73	021
9	55.03	54.64	55.80	55.16	0.59	9	54.61	55.36	54.59	54.85	0.44
10	59.08	59.27	59.34	59.23	0.14	10	58.68	59.26	58.47	58.80	0.41
12	64.80	65.04	64.75	64.86	0.16	12	64.80	66.12	65.15	65.36	0.68

Formula F1-F5

Time (hr)	% cumulative release			Mean	SD	Time (hr)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
F1						F5					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	61.86	62.41	57.66	60.64	2.60	0.25	10.40	9.69	10.16	10.09	0.36
0.5	93.61	96.72	88.45	92.93	4.18	0.5	34.60	39.14	39.94	37.89	2.88
0.75	96.83	97.60	98.00	97.48	0.60	0.75	54.87	60.43	60.99	58.76	3.39
1	97.89	98.85	99.08	98.61	0.63	1	67.92	73.21	78.00	73.04	5.04
1.5	98.95	99.74	99.42	99.37	0.40	1.5	91.89	93.37	91.10	92.12	1.15
2	98.90	99.70	99.21	99.27	0.40	2	99.03	101.84	101.55	100.81	1.55
3	99.40	100.03	99.52	99.65	0.33	3	100.28	100.70	100.79	100.59	0.27
F3						4	100.42	100.66	100.94	100.68	0.26
0	0	0	0	0	0	5	100.93	101.35	100.89	101.06	0.25
0.25	91.27	84.10	88.42	87.98	3.61	6	101.05	101.66	101.01	101.24	0.36
0.5	100.35	101.22	100.66	100.74	0.44						
1	100.30	100.60	101.18	100.69	0.45						
1.5	99.66	101.69	100.93	100.76	1.02						
2	99.78	101.63	100.46	100.62	0.94						
3	100.45	102.33	99.59	100.79	1.40						
4	100.36	100.52	101.60	100.83	0.68						

Time (hr)	% cumulative release			Mean	SD	Time (hr)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
F2						F4					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	6.69	8.02	7.60	7.44	0.68	0.25	8.67	8.06	9.23	8.65	0.58
0.5	14.64	16.03	15.38	15.35	0.70	0.5	17.98	17.50	17.87	17.78	0.25
0.75	19.44	21.19	19.53	20.09	1.05	0.75	23.71	23.08	23.18	23.33	0.34
1	23.55	25.64	25.51	24.90	1.17	1	29.57	28.64	28.50	28.91	0.58
1.5	30.11	32.27	30.63	31.00	1.13	1.5	38.75	37.55	37.31	37.87	0.77
2	35.42	37.43	36.15	36.33	1.02	2	45.69	46.75	46.75	46.39	0.62
3	43.99	46.29	45.50	45.26	1.17	3	65.33	64.09	64.07	64.50	0.72
4	57.07	57.62	59.21	57.97	1.11	4	79.59	75.77	75.79	77.05	2.20
5	65.84	66.65	70.64	67.71	2.57	5	91.65	88.84	88.72	89.74	1.66
6	74.89	75.58	78.47	76.31	1.90	6	97.70	96.02	96.54	96.75	0.86
8	81.44	83.11	86.37	83.64	2.51	8	100.18	100.52	100.46	100.39	0.18
9	84.71	86.97	91.00	87.56	3.19	9	100.51	101.03	101.16	100.90	0.34
10	89.30	90.68	95.50	91.83	3.25	10	101.01	100.43	101.48	100.98	0.53
12	93.20	95.74	100.03	96.32	3.45	12	101.51	101.10	101.81	101.47	0.36

Formula A1-A2

Time (hr)	% cumulative release						Mean	SD
	1	2	3	4	5	6		
A1								
0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0
0.5	3.55	3.75	3.42	3.62	3.72	3.41	3.58	0.15
0.75	5.66	5.83	5.76	5.84	5.69	5.72	5.75	0.07
1	7.80	8.08	7.80	7.88	7.90	7.95	7.90	0.11
1.5	11.82	12.28	11.70	11.88	11.92	12.03	11.94	0.20
2	15.98	16.75	15.81	16.22	16.21	16.10	16.18	0.32
3	23.10	23.77	23.03	23.41	23.24	23.17	23.30	0.27
4	30.54	30.88	30.33	30.55	30.78	30.41	30.58	0.21
5	37.14	37.15	36.78	36.79	37.11	37.09	37.01	0.18
6	44.37	44.59	44.59	44.66	44.22	44.68	44.52	0.18
8	54.62	53.96	53.05	54.00	53.74	53.87	53.87	0.51
9	58.89	58.24	58.25	58.46	58.74	58.19	58.46	0.29
10	64.13	63.49	63.32	64.07	63.22	63.71	63.66	0.38
12	70.34	70.65	70.11	70.55	70.53	70.55	70.36	0.27

Time (hr)	% cumulative release			Mean	SD	Time (hr)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
A2						B2					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	6.69	6.84	6.85	6.79	0.09	0.25	2.25	2.16	2.17	2.19	0.05
0.5	12.04	12.57	12.43	12.35	0.27	0.5	5.17	5.14	5.02	5.11	0.08
0.75	16.75	17.22	17.03	17.00	0.24	0.75	8.07	7.75	7.62	7.81	0.23
1	19.98	20.26	20.02	20.09	0.15	1	10.47	20.54	10.24	10.42	0.16
1.5	26.37	26.87	26.81	26.68	0.27	1.5	15.60	15.48	15.27	15.45	0.17
2	31.48	32.00	31.93	31.80	0.28	2	19.38	19.44	19.13	19.32	0.17
3	39.73	40.09	40.38	40.07	0.33	3	29.66	29.66	29.37	29.57	0.17
4	49.22	48.27	49.32	48.94	058	4	36.64	35.86	36.32	36.28	0.39
5	53.61	54.59	55.64	54.62	1.02	5	41.96	42.79	42.91	42.56	0.51
6	59.00	58.66	60.10	59.26	0.75	6	47.47	48.27	47.48	47.74	0.46
8	67.73	67.41	68.85	68.00	0.76	8	56.83	56.66	56.44	56.64	0.20
9	71.12	71.81	73.64	72.19	1.30	9	60.14	60.49	61.38	60.67	0.64
10	75.16	75.85	77.50	76.17	1.20	10	63.81	64.14	64.86	64.27	0.53
12	82.57	83.22	83.52	83.10	0.49	12	69.69	69.25	70.53	69.82	0.65

Formula B1-B5

Time (hr)	% cumulative release						Mean	SD
	1	2	3	4	5	6		
B1								
0	0	0	0	0	0	0	0	0
0.25	1.99	1.98	2.15	1.94	2.20	1.97	2.04	0.11
0.5	4.76	4.60	4.55	4.52	4.69	4.73	4.64	0.10
0.75	6.49	6.71	7.09	6.78	6.87	6.62	6.76	0.21
1	8.74	9.29	9.55	9.22	9.01	9.27	9.18	0.28
1.5	12.68	13.71	13.86	13.72	12.87	13.55	13.40	0.50
2	17.04	18.32	18.63	18.37	17.84	17.89	18.02	0.56
3	23.49	25.57	25.67	25.11	24.79	25.00	24.94	0.78
4	28.98	32.90	31.68	31.22	31.19	31.09	31.18	1.27
5	36.06	38.82	39.42	38.10	38.22	37.99	38.10	1.13
6	44.67	44.25	44.84	44.70	44.67	44.98	44.68	0.25
8	55.50	55.30	54.75	55.12	55.49	54.86	55.17	0.32
9	61.65	61.20	61.35	61.66	61.39	61.11	61.39	0.27
10	66.68	65.63	65.78	65.78	66.32	66.10	66.05	0.40
12	74.85	74.68	72.21	73.41	74.35	73.98	73.91	0.98

Time	% cumulative release			Mean	SD	Time	% cumulative release			Mean	SD
(hr)	1	2	3			(hr)	1	2	3		
B3						B4					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	7.40	7.07	7.61	7.36	0.28	0.25	8.58	9.73	9.01	9.11	0.58
0.5	15.51	14.20	15.00	14.91	0.66	0.5	17.64	19.02	18.49	18.39	0.70
0.75	21.06	19.92	20.17	20.38	0.60	0.75	22.89	24.39	23.83	23.71	0.76
1	24.90	24.65	25.22	24.92	0.28	1	29.60	3130	30.73	30.54	0.87
1.5	35.44	34.522	34.63	34.86	0.50	1.5	39.69	40.83	41.39	40.65	0.87
2	40.38	39.23	39.73	39.78	0.58	2	49.53	49.60	50.14	49.76	0.33
3	51.26	51.32	51.85	51.48	0.33	3	65.93	66.18	67.09	66.40	0.61
4	60.17	60.35	60.53	60.35	0.18	4	80.65	79.62	84.05	81.44	2.31
5	67.65	6796	68.35	67.99	0.36	5	91.85	90.99	95.46	92.77	2.37
6	73.88	72.52	74.74	74.38	0.45	6	100.02	100.08	100.91	100.34	0.50
8	83.21	84.35	85.16	84.24	0.98	8	101.45	101.51	101.80	101.59	0.18
9	87.70	89.19	89.08	88.65	0.83	9	100.89	101.47	101.58	101.30	0.38
10	91.27	91.82	92.84	31.38	0.80	10	100.80	101.42	101.89	101.37	0.55
12	96.21	97.10	97.20	96.84	0.55	12	100.78	101.40	101.87	101.35	0.55

Formula C1-C7

Time	% cumulative release			Mean	SD	Time	% cumulative release			Mean	SD
(hr)	1	2	3			(hr)	1	2	3		
B5						C1					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	9.77	9.74	9.56	9.69	0.12	0.25	2.80	2.48	3.02	2.77	0.27
0.5	17.97	17.97	17.79	17.92	0.11	0.5	5.96	5.12	5.90	5.66	0.47
0.75	23.34	23.46	23.11	23.31	0.18	0.75	8.66	7.80	9.00	8.54	0.52
1	28.53	29.05	28.48	28.69	.32	1	11.25	10.67	11.89	11.27	0.61
1.5	37.17	38.70	37.87	37.92	0.77	1.5	16.18	15.69	16.92	16.27	0.62
2	45.35	47.12	46.80	46.42	0.95	2	21.74	21.97	23.30	22.34	0.84
3	66.68	68.39	68.12	67.73	0.92	3	30.62	30.52	33.78	31.64	1.86
4	81.80	84.56	85.69	84.02	2.00	4	38.49	38.42	39.36	38.76	0.52
5	93.30	97.86	96.46	95.87	2.34	5	47.37	47.15	48.15	47.55	0.53
6	100.36	102.52	98.25	100.38	2.14	6	53.39	53.92	53.87	53.73	0.29
8	100.29	102.66	98.34	100.43	2.16	8	64.27	64.47	64.68	64.47	0.21
9	101.34	103.74	99.38	101.49	2.19	9	70.56	69.68	69.17	69.81	0.70
10	-	-	-	-	-	10	74.56	74.02	73.91	74.16	0.35
12	-	-	-	-	-	12	82.03	81.99	81.01	81.68	0.58

Time (hrs)	% cumulative release			Mean	SD	Time (hrs)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
C2						C3					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	1.65	1.65	2.00	1.77	0.20	0.25	5.65	5.69	5.38	5.58	0.17
0.5	4.96	4.78	5.25	4.99	0.24	0.5	12.05	12.08	11.89	12.01	0.10
0.75	8.24	8.07	8.41	8.24	0.17	0.75	17.16	17.00	16.87	17.01	0.14
1	11.40	11.19	11.48	11.36	0.15	1	21.77	21.62	21.43	21.61	0.17
1.5	17.60	17.38	17.49	17.49	0.11	1.5	29.97	29.69	29.32	29.66	0.32
2	23.49	23.10	22.94	23.18	0.28	2	36.77	36.21	36.02	36.33	0.39
3	34.73	34.53	33.05	34.10	0.91	3	49.20	48.99	48.25	48.81	0.50
4	44.04	44.40	43.47	43.97	0.47	4	5032	58.27	57.33	57.64	0.54
5	52.15	52.51	51.01	51.89	0.78	5	64.78	65.45	64.69	64.98	0.42
6	58.11	58.66	57.52	58.10	0.57	6	71.58	71.62	70.67	71.29	0.54
8	69.35	69.35	67.07	68.59	1.31	8	81.04	81.31	81.62	81.32	0.29
9	73.06	73.62	71.14	72.61	1.30	9	83.93	84.36	85.04	84.44	0.56
10	77.74	78.138	75.61	77.16	1.35	10	88.33	87.97	89.94	88.75	1.05
12	84.89	84.90	83.29	84.36	0.93	12	94.79	95.08	95.07	94.98	0.16
C4						C5					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	11.36	10.88	12.46	11.571	0.81	0.25	17.71	17.70	17.89	17.76	0.11
0.5	19.62	19.03	20.62	19.76	0.81	0.5	27.74	28.21	28.84	28.27	0.55
0.75	25.80	25.20	26.32	25.77	0.56	0.75	34.96	35.50	35.96	35.47	0.50
1	30.93	30.87	31.33	31.04	0.25	1	41.32	42.11	42.21	41.88	0.47
1.5	40.02	40.52	41.10	40.55	0.64	1.5	51.47	52.56	53.26	52.43	0.90
2	49.40	49.71	50.79	49.97	0.73	2	61.18	60.67	61.58	61.14	0.46
3	61.68	61.60	62.47	61.92	0.48	3	72.85	70.94	72.83	72.21	1.10
4	70.73	70.46	71.07	70.75	0.31	4	81.10	80.00	81.92	81.01	0.97
5	78.20	78.10	78.62	78.31	0.28	5	87.94	86.88	88.46	87.76	0.81
6	84.06	83.77	84.17	84.00	0.21	6	92.04	92.33	92.99	92.45	0.49
8	93.15	93.22	93.93	93.43	0.43	8	99.35	99.71	99.45	99.50	0.18
9	96.55	96.43	97.18	96.72	0.41	9	100.58	100.18	100.29	100.35	0.20
10	98.67	98.55	99.32	98.85	0.41	10	100.31	101.03	100.76	100.70	0.36
12	101.74	102.18	102.24	102.05	0.27	12	100.21	101.87	101.03	101.04	0.83

Time (hrs)	% cumulative release			Mean	SD	Time (hrs)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
C6						C7					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	19.38	19.75	20.83	19.99	0.75	0.25	37.36	35.27	35.75	36.13	1.09
0.5	32.57	32.17	33.54	32.76	0.70	0.5	74.84	82.19	78.20	78.41	3.68
0.75	42.86	43.21	42.93	43.00	0.18	0.75	97.12	101.71	97.54	98.79	2.53
1	50.58	51.12	49.54	50.41	0.80	1	101.38	101.15	101.63	101.39	0.24
1.5	63.35	63.31	62.55	63.07	0.45	1.5	100.00	101.50	101.60	101.24	0.55
2	73.76	73.72	74.55	74.01	0.47	2	101.31	101.47	101.75	101.51	0.22
3	90.78	89.20	91.09	90.36	1.02	3	101.44	100.87	101.70	101.34	0.42
4	99.20	99.12	100.32	99.54	0.67	4	-	-	-	-	-
5	100.06	100.17	101.00	100.41	0.53	5	-	-	-	-	-
6	100.73	100.66	101.30	100.90	0.35	6	-	-	-	-	-
8	-	-	-	-	-	8	-	-	-	-	-
9	-	-	-	-	-	9	-	-	-	-	-
10	-	-	-	-	-	10	-	-	-	-	-
12	-	-	-	-	-	12	-	-	-	-	-

Formula D1-D6

Time (hr)	% cumulative release			Mean	SD	Time (hr)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
D1						D2					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	2.31	2.83	2.62	2.59	0.26	0.25	2.19	2.11	2.38	2.23	0.14
0.5	2.37	5.74	5.50	5.54	0.19	0.5	5.27	5.19	5.57	5.34	0.20
0.75	7.80	8.55	8.155	8.17	0.38	0.75	8.14	8.14	8.25	8.18	0.06
1	10.83	11.46	11.13	11.18	0.37	1	10.97	10.90	10.98	10.95	0.04
1.5	15.69	16.69	16.20	16.19	0.50	1.5	16.52	16.61	16.21	16.45	0.21
2	21.49	22.92	22.06	22.16	0.72	2	21.14	21.55	20.68	21.13	0.43
3	30.24	31.66	31.18	32.03	0.72	3	31.21	31.19	30.24	30.88	0.55
4	37.98	39.38	39.12	38.83	0.75	4	41.92	41.84	39.55	41.10	1.35
5	44.68	46.08	46.02	45.60	0.79	5	48.46	48.08	46.98	47.84	0.77
6	50.16	52.48	53.19	51.94	1.58	6	54.34	54.02	52.333	53.57	1.08
8	65.88	66.14	66.90	66.31	0.53	8	65.48	64.73	63.30	64.50	1.11
9	69.83	69.70	70.31	69.95	0.32	9	38.86	68.68	67.93	68.49	0.49
10	73.46	73.30	13.55	73.44	0.12	10	72.81	71.57	71.52	71.97	0.73
12	80.77	80.53	81.54	80.95	0.53	12	78.58	80.46	78.73	79.26	1.04

Time (hrs)	% cumulative release			Mean	SD	Time (hrs)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
D3						D4					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	6.87	7.32	7.41	7.20	0.29	0.25	14.87	14.86	14.82	14.85	0.03
0.5	13.52	13.83	13.5	13.77	0.22	0.5	23.31	22.95	23.11	23.09	0.13
0.75	18.75	18.38	18.87	18.67	0.26	0.75	28.69	28.46	28.60	28.58	0.12
1	22.34	21.78	22.64	22.25	0.44	1	33.10	32.89	33.03	33.01	0.11
1.5	30.663	29.72	31.13	30.50	0.72	1.5	40.55	40.18	40.69	40.48	0.36
2	7.57	36.43	37.46	37.15	0.63	2	48.45	47.93	48.81	48.40	0.44
3	50.95	49.04	52.65	50.88	1.81	3	61.09	61.00	61.050	61.20	0.26
4	61.27	58.40	62.02	60.56	1.91	4	69.95	70.29	71.33	70.53	0.72
5	67.75	65.04	67.37	66.72	1.47	5	77.04	76.85	78.27	77.39	0.77
6	73.92	71.94	75.57	73.81	1.82	6	83.64	83.47	83.22	83.45	0.21
8	85.04	82.10	86.67	84.61	2.32	8	91.05	91.85	92.71	91.87	0.83
9	88.38	85.78	89.46	87.88	1.89	9	94.80	96.00	96.12	95.64	0.73
10	91.94	89.69	94.52	92.05	2.42	10	97.28	97.94	97.86	97.70	0.36
12	98.16	96.07	99.80	98.01	1.87	12	99.59	100.07	100.56	100.07	0.48
D5						D6					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	17.67	17.66	18.09	17.81	0.25	0.25	27.50	36.11	33.60	32.41	4.43
0.5	33.66	30.50	33.55	32.57	1.80	0.5	70.19	77.46	77.24	74.69	4.13
0.75	47.42	41.90	47.19	45.50	3.12	0.75	92.44	95.31	96.68	94.81	2.16
1	56.42	50.99	56.49	54.36	3.15	1	100.12	99.65	101.06	100.28	0.72
1.5	72.30	68.80	68.69	69.93	2.05	1.5	100.28	100.00	100.50	100.26	0.25
2	84.58	83.05	81.58	83.07	1.20	2	100.99	99.79	100.84	100.54	0.65
3	98.12	98.02	97.59	97.91	0.28	3	101.14	99.76	100.81	100.57	0.72
4	100.3	100.57	99.38	100.09	0.62	4	-	-	-	-	-
5	100.80	100.52	99.88	100.40	0.47	5	-	-	-	-	-
6	100.73	100.45	99.81	100.33	0.47	6	-	-	-	-	-
8	-	-	-	-	-	8	-	-	-	-	-
9	-	-	-	-	-	9	-	-	-	-	-
10	-	-	-	-	-	10	-	-	-	-	-
12	-	-	-	-	-	12	-	-	-	-	-

Formula E1-E6

Time (hr)	% cumulative release						Mean	SD
	1	2	3	4	5	6		
E1								
0	0	0	0	0	0	0	0	0
0.25	2.55	2.81	2.83	2.75	2.67	2.60	2.70	0.11
0.5	5.29	5.71	5.65	5.22	5.66	5.75	5.55	0.23
0.75	7.59	8.04	8.11	8.10	7.64	7.97	7.91	0.23
1	10.21	10.69	10.76	10.77	10.18	10.71	10.55	0.28
1.5	14.72	15.22	15.13	15.07	15.19	14.80	15.02	0.21
2	19.09	19.85	19.89	19.77	19.83	19.28	19.62	0.34
3	25.08	25.48	24.49	24.97	25.28	24.77	25.01	0.35
4	36.09	37.05	36.23	36.05	36.48	36.84	36.46	0.41
5	42.23	43.02	42.14	42.24	42.74	42.35	42.45	0.35
6	48.43	49.41	48.30	48.55	49.05	48.55	48.72	0.43
8	61.18	61.99	62.07	62.05	61.56	61.62	61.75	0.35
9	67.47	66.83	66.14	57.02	66.71	66.68	66.81	0.44
10	71.83	71.89	70.98	71.74	71.45	71.55	71.57	0.34
12	77.45	78.77	77.07	76.97	78.51	77.85	77.77	0.34

Time (hr)	% cumulative release			Mean	SD
	1	2	3		
E2					
0	0	0	0	0	0
0.25	2.31	2.07	1.94	2.11	0.19
0.5	5.64	5.49	5.21	5.45	0.22
0.75	8.68	8.52	8.37	8.52	0.15
1	11.50	11.42	11.16	11.36	0.17
1.5	16.84	16.83	16.72	16.80	0.07
2	20.68	20.70	20.78	20.72	0.05
3	29.48	29.44	29.82	29.58	0.21
4	38.47	37.73	38.96	38.42	0.63
5	44.46	45.38	45.63	45.16	0.62
6	50.60	50.40	51.63	50.87	0.66
8	61.18	60.90	63.02	61.70	1.55
9	66.03	65.54	67.18	66.25	0.84
10	69.83	69.31	71.19	70.11	0.97
12	77.50	78.55	79.84	78.63	1.17

Time (hrs)	% cumulative release			Mean	SD	Time (hrs)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
E3						E4					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	6.24	6.23	5.77	6.08	0.27	0.25	8.10	7.31	9.50	8.31	1.11
0.5	13.22	12.56	12.95	12.91	0.33	0.5	16.23	15.42	16.89	16.18	0.74
0.75	18.04	17.122	17.69	17.62	0.46	0.75	21.50	20.68	21.76	21.31	0.56
1	21.29	20.50	21.14	20.97	0.42	1	26.84	26.13	26.92	26.63	0.44
1.5	28.50	27.94	28.43	28.29	0.30	1.5	36.61	35.94	37.08	36.54	0.57
2	34.88	34.36	34.87	34.70	0.30	2	44.66	44.25	45.070	44.87	0.75
3	47.57	47.69	48.07	47.78	0.26	3	59.53	58.10	60.07	59.33	0.85
4	57.27	57.28	58.44	57.66	0.67	4	72.38	74.50	76.97	74.62	2.30
5	65.06	65.30	65.39	65.26	0.17	5	86.09	84.84	84.73	85.222	0.76
6	71.08	70.81	71.48	71.12	0.33	6	93.57	94.93	93.49	94.00	0.81
8	82.13	82.67	83.57	82.79	0.73	8	98.21	98.28	97.77	98.09	0.28
9	87.23	87.99	87.80	87.68	0.40	9	100.16	99.31	98.98	99.48	0.61
10	91.63	91.33	91.51	91.49	0.16	10	101.02	99.80	99.28	100.04	0.89
12	96.63	96.35	96.55	96.51	0.15	12	102.06	100.84	100.49	101.13	0.83
E5						E6					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	8.73	9.83	9.61	9.39	0.58	0.25	10.93	11.77	12.08	11.59	0.60
0.5	16.13	16.88	16.58	16.53	0.38	0.5	19.79	20.11	19.41	19.77	0.35
0.75	20.83	21.08	20.95	20.95	0.13	0.75	26.58	26.35	25.52	26.15	0.56
1	25.89	25.60	25.90	25.80	0.17	1	32.73	33.02	32.43	32.73	0.29
1.5	33.98	34.07	35.61	34.55	0.92	1.5	44.60	43.95	42.55	43.71	1.05
2	46.80	43.39	46.37	45.52	1.86	2	54.23	53.55	52.61	53.46	0.82
3	64.04	59.13	63.85	62.34	2.78	3	73.10	72.55	70.50	72.05	1.37
4	82.02	76.00	83.02	80.34	3.81	4	89.24	90.29	87.11	88.88	1.62
5	92.95	87.23	92.78	90.99	3.25	5	100.81	99.65	97.45	99.30	1.71
6	100.82	96.36	99.4	98.87	2.28	6	101.70	100.90	98.68	100.43	1.57
8	99.85	99.81	99.74	99.80	0.06	8	101.13	100.32	98.98	100.15	1.09
9	100.34	100.30	100.41	100.35	0.05	9	-	-	-	-	-
10	100.08	101.35	99.94	100.46	0.78	10	-	-	-	-	-
12	99.63	101.10	100.03	100.25	0.76	12	-	-	-	-	-

In pH change study.

Time (hr)	% cumulative release			Mean	SD	Time (hr)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
F6						A1					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	1.22	1.16	1.17	1.19	0.03	0.25	2.53	2.35	1.96	2.28	0.29
0.5	2.50	2.16	2.09	2.25	0.22	0.5	3.85	4.42	3.86	4.05	0.33
0.75	3.93	3.51	3.52	3.65	0.24	0.75	5.86	7.04	6.08	6.33	0.63
1	4.86	4.93	5.05	4.95	0.10	1	7.77	8.31	7.53	7.87	0.40
2	10.33	9.66	10.61	10.17	0.45	2	13.84	14.67	13.54	14.02	0.58
3	14.45	13.57	13.56	13.86	0.51	3	18.97	19.31	17.98	18.75	0.69
4	17.89	16.64	16.49	17.01	0.77	4	23.67	24.05	22.31	23.34	0.92
5	21.24	20.03	19.70	20.32	0.81	5	27.75	28.19	28.10	28.01	0.23
6	24.56	23.17	22.81	23.52	0.92	6	32.25	32.76	30.68	31.90	1.08
8	32.37	30.64	32.95	31.99	1.20	8	40.63	39.70	38.28	39.54	1.18
9	35.96	34.25	35.97	35.39	0.99	9	43.09	43.34	40.33	42.25	1.67
10	40.25	38.55	39.87	39.56	0.89	10	47.80	46.77	44.26	46.28	1.82
12	47.05	46.96	47.27	47.09	0.16	12	55.95	54.83	51.79	54.19	2.15
B1						E1					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	1.55	1.62	1.52	1.57	0.05	0.25	2.04	1.87	2.29	2.07	0.21
0.5	3.58	3.76	3.51	3.62	0.13	0.5	4.61	4.20	4.47	4.53	0.29
0.75	5.39	5.62	5.37	5.46	0.14	0.75	6.84	6.20	6.99	6.68	0.42
1	7.26	7.41	7.32	7.33	0.07	1	8.92	8.26	9.15	8.78	0.46
2	13.51	13.65	13.79	13.65	0.14	2	16.59	15.74	17.09	16.48	0.68
3	18.70	18.85	19.04	18.86	0.17	3	22.82	21.69	23.11	22.54	0.75
4	23.97	23.79	24.17	23.98	0.19	4	28.39	27.31	28.51	28.07	0.66
5	28.85	28.47	28.47	28.60	0.22	5	34.40	33.38	34.35	34.04	0.58
6	34.16	33.59	33.39	33.71	0.40	6	37.62	38.54	39.49	38.55	0.94
8	46.47	45.69	45.30	45.82	0.59	8	47.91	46.25	46.78	46.98	0.85
9	49.20	48.61	48.02	48.61	0.59	9	51.00	49.16	49.66	49.94	0.95
10	52.07	51.67	49.73	51.16	1.25	10	53.49	51.65	51.58	52.24	1.08
12	54.72	54.89	52.93	54.18	1.09	12	59.17	56.60	58.22	58.00	1.30

Stability testing of R2 formula

Time (hr)	% cumulative release			Mean	SD	Time (hr)	% cumulative release			Mean	SD
	1	2	3				1	2	3		
1 M*						4M*					
0	0	0	0	0	0	0	0	0	0	0	0
0.25	1.41	1.04	1.23	1.23	0.19	0.25	1.07	1.18	1.16	1.14	0.06
0.5	2.83	2.48	2.66	2.66	0.17	0.5	2.77	2.99	2.69	2.81	0.16
0.75	3.75	4.11	4.18	4.29	0.26	0.75	4.25	4.59	4.36	4.40	0.18
1	5.37	5.96	5.97	6.12	0.26	1	5.72	6.06	5.81	5.86	0.8
1.5	8.35	9.29	9.30	9.47	0.31	1.5	8.57	9.02	8.67	8.75	0.24
2	11.49	12.64	12.79	12.79	0.23	2	11.40	11.99	11.65	11.67	0.31
3	20.90	20.23	20.46	20.53	0.34	3	17.02	17.81	17.32	17.38	0.40
4	27.66	27.16	26.71	27.18	0.48	4	23.11	24.13	23.96	23.73	0.55
5	34.13	33.22	32.84	33.40	0.67	5	27.63	28.74	29.03	28.46	0.74
6	39.74	39.17	38.65	39.19	0.54	6	33.31	34.91	34.88	34.37	0.92
8	49.88	49.83	49.80	49.84	0.04	8	43.31	44.35	44.32	43.99	0.59
9	55.28	55.40	54.86	55.18	0.28	9	48.04	48.99	49.60	48.88	0.78
10	60.35	61.20	60.34	60.63	0.50	10	52.08	52.91	53.83	52.94	0.87
12	69.03	69.11	69.07	69.07	0.04	12	59.13	59.71	60.31	59.72	0.59

M* = month storage

Drug loading effect

Rx	t (hr)	$t^{0.44}$ ($hr^{0.44}$)	$t^{0.88}$ ($hr^{0.88}$)	%cumulative drug release			Mean	SD	Mt/M∞		
				1	2	3			1	2	3
H1	0	0	0	0	0	0	0	0			
	0.25	0.543	0.295	0	0	0	0	0	-	-	-
	0.5	0.737	0.543	0	0	0	0	0	-	-	-
	0.75	0.881	0.776	0	0	0	0	0	-	-	-
	1	1	1	5.127	4.998	4.998	5.04	0.07	0.0513	0.0500	0.0500
	1.5	1.195	1.429	8.009	7.844	7.923	7.93	0.08	0.0801	0.0784	0.0792
	2	1.357	1.840	11.088	10.720	10.935	10.91	0.18	0.1109	0.1072	0.1094
	3	1.622	2.629	16.361	16.418	17.291	16.69	0.52	0.1636	0.1642	0.1729
	4	1.840	3.387	21.691	21.899	21.950	21.85	0.14	0.2169	0.2190	0.2195
	5	2.030	4.122	26.612	27.160	27.432	27.17	0.26	0.2691	0.2716	0.2743
	6	2.200	4.839	32.189	32.092	31.762	32.01	0.22	0.3219	0.3209	0.3176
	8	2.497	6.233	40.345	39.910	40.215	40.16	0.22	0.4035	0.3991	0.4021
	9	2.629	6.914	44.546	44.077	44.786	44.47	0.36	0.4455	0.4408	0.4479
	10	2.754	7.586	48.622	47.895	48.354	48.29	0.37	0.4862	0.4790	0.4835
	12	2.984	8.906	55.064	54.54	54.551	54.72	0.30	0.5506	0.5454	0.5455

Rx	t (hr)	$t^{0.44}$ ($hr^{0.44}$)	$t^{0.88}$ ($hr^{0.88}$)	%cumulative drug release			Mean	SD	Mt/M∞		
				1	2	3			1	2	3
H2	0	0	0	0	0	0	0	0			
	0.25	0.543	0.295	0	0	0	0	0	-	-	-
	0.5	0.737	0.543	0	0	0	0	0	-	-	-
	0.75	0.881	0.776	3.195	2.953	3.0848	3.80	0.12	0.0320	0.0295	0.0308
	1	1	1	4.421	4.290	4.505	4.41	0.11	0.0422	0.0429	0.0451
	1.5	1.195	1.429	7.212	7.306	7.473	7.33	0.130	0.0721	0.0731	0.0747
	2	1.357	1.840	10.429	10.718	10.693	10.61	.16	0.1043	0.1072	0.1069
	3	1.622	2.629	16.136	16.991	16.719	16.62	0.44	0.1614	0.1699	0.1672
	4	1.840	3.387	21.457	22.970	22.556	22.33	0.78	0.2146	0.2297	0.2256
	5	2.030	4.122	26.819	28.544	28.274	27.88	0.93	0.2682	0.2854	0.2827
	6	2.200	4.839	32.250	34.171	33.481	33.30	0.97	0.3225	0.3417	0.3348
	8	2.497	6.233	42.075	45.410	45.000	44.16	1.82	0.4208	0.4541	0.4500
	9	2.629	6.914	46.868	49.520	49.130	48.51	1.43	0.4687	0.4952	0.4913
	10	2.754	7.586	50.626	53.670	52.938	52.41	1.59	0.5063	0.5361	0.5294
	12	2.984	8.906	58.389	60.395	59.701	59.50	1.02	0.5839	0.6040	0.5970
H3	0	0	0	0	0	0	0	0			
	0.25	0.543	0.295	0	0	0	0	0	-	-	-
	0.5	0.737	0.543	0	0	0	0	0	-	-	-
	0.75	0.881	0.776	2.936	3.396	3.646	3.33	0.36	0.0294	0.0340	0.0365
	1	1	1	4.582	5.014	5.100	4.90	0.28	0.0458	0.0501	0.0510
	1.5	1.195	1.429	7.636	8.228	8.315	8.06	0.37	0.0764	0.0823	0.0831
	2	1.357	1.840	11.058	11.948	11.731	11.58	0.46	0.1106	0.1195	0.1173
	3	1.622	2.629	17.799	18.453	18.344	18.20	0.35	0.1780	0.1845	0.1834
	4	1.840	3.387	24.001	24.640	24.253	24.30	0.32	0.2400	0.2464	0.2425
	5	2.030	4.122	32.053	32.808	32.250	32.37	0.39	0.3205	0.3281	0.3225
	6	2.200	4.839	37.694	36.206	37.823	37.24	0.90	0.3769	0.3621	0.3782
	8	2.497	6.233	47.827	48.517	47.698	48.01	0.44	0.4748	0.4852	0.4770
	9	2.629	6.914	52.791	52.919	52.644	52.79	0.14	0.5279	0.5292	0.5264
	10	2.754	7.586	57.528	57.087	57.363	57.33	0.22	0.5753	0.5709	0.5736
	12	2.984	8.906	65.371	65.451	64.345	65.06	0.62	0.6537	0.6545	0.6435

Rx	t (hr)	$t^{0.44}$ ($hr^{0.44}$)	$t^{0.88}$ ($hr^{0.88}$)	%cumulative drug release			Mean	SD	Mt/M∞		
				1	2	3			1	2	3
H4	0	0	0	0	0	0	0	0			
	0.25	0.543	0.295	0	0	0	0	0	-	-	-
	0.5	0.737	0.543	2.244	2.133	2.328	2.24	0.10	0.0224	0.0213	0.0233
	0.75	0.881	0.776	3.484	3.173	3.665	3.44	0.25	0.0348	0.0317	0.0367
	1	1	1	5.069	4.600	5.257	4.98	0.34	0.0507	0.0460	0.0526
	1.5	1.195	1.429	8.019	7.545	8.242	7.94	0.36	0.0802	0.0754	0.0824
	2	1.357	1.840	11.023	10.808	11.500	11.11	0.35	0.1102	0.1081	0.1150
	3	1.622	2.629	17.130	17.444	18.028	17.53	0.46	0.1713	0.1744	0.1803
	4	1.840	3.387	24.498	25.369	25.567	25.14	0.57	0.2450	0.2537	0.2557
	5	2.030	4.122	30.288	31.168	31.308	30.92	0.55	0.3029	0.3117	0.3131
	6	2.200	4.839	35.707	37.255	36.581	36.51	0.78	0.3571	0.3725	0.3658
	8	2.497	6.233	46.023	47.51	46.683	46.62	0.57	0.4602	0.4715	0.4668
	9	2.629	6.914	52.262	52.519	51.335	52.04	0.62	0.5226	0.5252	0.5134
	10	2.754	7.586	56.356	56.615	56.034	56.34	0.29	0.5636	0.5661	0.5603
	12	2.984	8.906	62.698	62.738	61.872	62.44	0.49	0.6270	0.6274	0.6187

Rx	t (hr)	$t^{0.44}$ ($hr^{0.44}$)	$t^{0.88}$ ($hr^{0.88}$)	% cumulative release		Mt/M∞	
				Mean	SD	Mean	SD
R2	0	0	0	0	0	0	0
	0.25	0.543	0.295	0	0	0	0
	0.5	0.737	0.543	1.70	0.09	0.0170	0.0013
	0.75	0.881	0.776	2.76	0.16	0.0277	0.0023
	1	1	1	4.10	0.23	0.0411	0.0030
	1.5	1.195	1.429	7.06	0.23	0.0706	0.0030
	2	1.357	1.840	10.45	0.23	0.1042	0.0031
	3	1.622	2.629	17.11	0.30	0.1720	0.0016
	4	1.840	3.387	24.77	0.25	0.2481	0.0030
	5	2.030	4.122	30.77	0.20	0.3067	0.0051
	6	2.200	4.839	36.63	0.31	0.3646	0.0065
	8	2.497	6.233	49.89	0.51	0.4986	0.0078
	9	2.629	6.914	54.00	0.40	0.5366	0.0112
	10	2.754	7.586	61.00	0.80	0.6046	0.0139
	12	2.984	8.906	70.42	0.25	0.7044	0.0016

Appendix E

Percolation theory

Percolation theory demonstrated as two dimensional grid scheme that some sites were randomly occupied (Figure 98). As possible seen from scheme, white and black square were polymer and agent, respectively. At low drug loading level, the agent were well separated while the next higher level, small islands of interconnect particles grow in size and connected to form extended pathway. At high loading above a certain critical value, continuous cavity was obtained through total grid. There was a matrix system. Critical value in two-dimension model was given about 0.45 volume fraction. In fact, the consideration of device was concerning with three-dimensional. The value of 0.15 volume fraction was the critical value for three-dimension model for continuous network formation.

Figure 98 Two-dimensional grid of random distribution of drug particles in polymer in “island model” under percolation theory.

Appendix F

Calculation of calculated HLB

The hydrophile lipophile balance (HLB) value of blending thermosoftening base system was obtained from the summation of partial HLB of each bases component. The partial HLB was derived from the relationship between weight fraction of individual system and defining HLB of each thermosoftening vehicle types.

Total calculated HLB = ∑ of partial HLB of each components

Partial HLB of each component = weight fraction * originate HLB of each type

Example of calculated HLB value calculation was shown below:

The system, which composed of 36 mg of G46/07 and 144 mg of G50/02, had a total calculated HLB as 3.

According to partial HLB was equal to weight fraction multiply with originate HLB then partial HLB of G46/07 in this case was equal 36/(144+136)*7 or 1.4, while partial HLB of G50/02 was 144/(144+36)*2 or 1.6, the total calculated HLB was equivalent to 1.4 plus 1.6 or 3.0

VITAE

Mr. Wanchai Chongcharoen was born on December 4, 1973. He graduated from Chulalongkorn University, Bangkok, Thailand and received Bachelor degree of Science in Pharmacy with second class honor. In 1996-1998, He work in drug formulation development position of Local Manufacturing factory (M&H Manufacturing Co.,Ltd.) for two years after graduated.