การใช้พอลิไวนิลอะซีเทต ชนิดกระจายตัวในน้ำ ในการเตรียมเมทริกซ์ชนิดออกฤทธิ์นาน โดยกระบวนการพ่นแห้ง

นางสาว ศิริมา สังคพัฒน์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาเภสัชอุตสาหกรรม
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2547

ISBN 974-17-5691-7

APPLICATION OF POLYVINYL ACETATE AQUEOUS DISPERSION IN PREPARATION OF SUSTAINED RELEASE MATRICES BY SPRAY DRYING PROCESS

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy

Department of Manufacturing Pharmacy
Faculty of Pharmaceutical Science
Chulalongkorn University

Academic Year 2004

ISBN 974-17-5691-7

Thesis Title	APPLICATION OF POLYVINYL ACETATE AQUEOUS DISPERSION IN PREPARATION OF SUSTAINED RELEASE MATRICES BY SPRAY DRYING PROCESS
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ศิริมา สังคพัฒน์ : การใช้พอลิไวนิลอะซีเทต ชนิดกระจายตัวในน้ำ ในการเตรียมเมทริกซ์ชนิดออกฤทธิ์นาน โดยกระบวนการพ่นแห้ง (APPLICATION OF POLYVINYL ACETATE AQUEOUS DISPERSION IN PREPARATION OF SUSTAINED RELEASE MATRICES BY SPRAY DRYING PROCESS) อ.ที่ปรึกษา : รศ.ดร. พจน์ กุลวานิช. 186 หน้า. ISBN 974-17-5691-7

งานวิจัยนี้ศึกษาการใช้พอลิไวนิลอะซีเทต (พีวีเอซี) ชนิดกระจายตัวในน้ำ ในการเตรียมเมทริกซ์ชนิดออกฤทธิ์นาน โดยกระบวนการพ่นแห้ง โดยศึกษาเปรียบเทียบตัวยาจำลองที่มีค่าการละลายแตกต่างกัน 3 ชนิด คือ ดิลไทอะเซม ไฮโดรคลอไรด์, ทีโอฟิลินและฟูโรซีมายด์ การศึกษาคุณสมบัติทางกายภาพของผงพ่นแห้งร่วมระหว่างตัวยากับพีวีเอซี พบว่าอนุภาคพ่นแห้งร่วมระหว่างทีโอฟิลินกับพีวีเอซีมีความกลมมากกว่าอนุภาคพ่นแห้งร่วมระหว่างฟูโรซีมายด์กับพีวีเอซีและดิลไทอะเซม ไฮโดรคลอไรด์กับพีวีเอซี ตามลำดับ ทำให้อนุภาคพ่นแห้งร่วมระหว่างทีโอฟิลินกับพีวีเอซีมีการไหลที่ดี อนุภาคพ่นแห้งของตัวยาทั้งสามชนิดมีการกระจายขนาดของอนุภาคแคบ การศึกษาคุณสมบัติทางเอกซ์เรย์ดิฟแฟรคโทรเมทรี พบว่า หลังจากผ่านกระบวนการพ่นแห้งกับพีวีเอซี ดิลไทอะเซม ไฮโดรคลอไรด์และฟูโรซีมายด์กระจายตัวอยู่ในรูปอสัณฐาน สำหรับทีโอฟิลินกระจายตัวอยู่ทั้งในรูปผลึกและ อสัณฐาน นอกจากนี้ลักษณะทางเอกซ์เรย์ของผงพ่นแห้งร่วมระหว่างทีโอฟิลินกับพีวีเอซีแสดงให้เห็นว่า เกิดการเปลี่ยนแปลงผลึกจากทีโอฟิลิน แอนไฮดรัส form II เป็น ทีโอฟิลิน แอนไฮดรัส form I การวิเคราะห์ทางดิฟเฟอเรนเชียลสแกนนิงแคลอริเมทรีและอินฟราเรดสเปกโตรสโคปี แสดงให้เห็นว่าไม่เกิดปฏิกิริยาระหว่างตัวยาและพีวีเอซีหรือส่วนประกอบอื่นในตำรับ ยกเว้นผงพ่นแห้งของตัวยาฟูโรซีมายด์ที่แสดงให้เห็นว่าเกิดการเปลี่ยนแปลงสเปกตรัม เมื่อนำผงพ่นแห้งของตัวยาทั้งสามชนิดไปตอกอัดเป็นยาเม็ดชนิดเมทริกซ์ พบว่าปัจจัยสำคัญที่มีผลต่อการปลดปล่อยตัวยา คือ ค่าการละลายของตัวยา, ปริมาณของพอลิเมอร์ และความเป็นกรดด่างของตัวกลางการละลาย ขณะที่แรงตอกที่ใช้ไม่มีผลต่อการปลดปล่อยตัวยา จลนศาสตร์ของการปลดปล่อยยาเป็นไปตามรากที่สองของเวลา ดังนั้นกลไกหลักในการควบคุมปลดปล่อยตัวยาคือการแพร่ของยาในตัวกลางการละลาย แต่ที่ปริมาณพอลิเมอร์ต่ำอาจมีกลไกของการกร่อนร่วมด้วย ซึ่งสรุปได้ว่าพีวีเอซี ชนิดกระจายตัวในน้ำสามารถใช้ร่วมกับกระบวนการพ่นแห้งเพื่อผลิตเมทริกซ์ชนิดออกฤทธิ์นานได้

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

สาขาวิชา…… เภสัชอุตสาหกรรม…….. ลายมือชื่ออาจารย์ที่ปรึกษา……

ปีการศึกษา……..2547……..…….. ลายมือชื่ออาจารย์ที่ปรึกษาร่วม……-……

4476621833: MAJOR MANUFACTURING PHARMACY
KEY WORD: SPRAY DRYING / POLYVINYL ACETATE DISPERSION / SUSTAINED RELEASE
SIRIMA SANGKAPAT: THESIS TITLE. APPLICATION OF POLYVINYL ACETATE AQUEOUS DISPERSION IN PREPARATION OF SUSTAINED RELEASE MATRICES BY SPRAY DRYING PROCESS THESIS ADVISOR: ASSOC. PROF. POJ KULVANICH, Ph.D. 186 pp. ISBN 974-17-5691-7

An application of polyvinyl acetate (PVAc) aqueous dispersion in preparation of sustained release matrices via spray drying technique was investigated. Three different water soluble drugs, diltiazem hydrochloride, theophylline and furosemide, were employed as model drugs. The physical properties of spray dried drug-PVAc powders were evaluated. Spray dried theophylline-PVAc powders (T-PVAc) was more spherical than furosemide-PVAc (F-PVAc) and diltiazem hydrochloride-PVAc powders (D-PVAc). Therefore, the T-PVAc powders possessed better flow characteristics than the others. All spray dried drug-PVAc powders had narrow size distribution. In addition, X-ray diffractogram revealed that diltiazem hydrochloride and furosemide existed in an amorphous state after spray drying with PVAc, while theophylline anhydrous seemed to be in both crystalline and amorphous state. In addition, the X-ray patterns of T-PVAc powders displayed the polymorphic change of theophylline from a theophylline anhydrous form II to a theophylline anhydrous form I. Thermal analysis and infrared spectroscopy studies revealed that theophylline and diltiazem hydrochloride did not react chemically with PVAc and additives. However, F-PVAc powders showed some change in spectrum. Spray dried drug-PVAc powders were easily compressed directly into the matrices. The release profile studies indicated that diltiazem hydrochloride matrix tablet had a faster release rate than theophylline and furosemide matrix tablet, respectively. Water solubility of drugs, amount of polymer and pH of the dissolution medium were important factors in the controlling the release of matrix tablet. However, the different compression force did not play an effect on drug release. The drug release kinetic of the PVAc matrices could be explained by Higuchi's equation, but at low polymer content, both diffusion and erosion controlled the drug release from the PVAc matrices. In conclusion, polyvinyl acetate aqueous dispersion was applied well in conjunction with spray drying technique to produce sustained release matrix.

Department Manufacturing Pharmacy Student's signature.....
Field of study Industrial Pharmacy Advisor's signature.....
Academic year 2004 Co-advisor's signature.....

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to my thesis advisor, Associated Professor Poj Kulvanich, Ph.D. for his invaluable advice, guidance, encouragement, hearten and understanding. His kindness and cheerfulness are also deeply appreciated.

I also wish to express deep appreciation to thesis committee for spending their valuable times to be on my thesis and for their discussion and invaluable comments

Special thanks are also extended to Chulalongkorn University for partial financial support to my thesis work.

The other special thanks were giving to staff, my friends and my senior graduate student of the Department of Manufacturing Pharmacy for their assistance and great helpful support.

Furthermore, I would like to express my honest thanks to everyone in my family especially my parents for their help, cheerful, endless love, understanding and encouragement.

Eventually, I also express my thanks to others that concerned in this thesis whose names have not been mentioned which help and made my thesis a reality.

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LISTS OF ABBREVIATIONS

%	percentage
%CV	percent of coefficient of variation
>	more than
<	less than
=	as same as
˚C	degree Celsius (centigrade)
DSC	differential scanning calorimetry
D-PVAc	diltiazem hydrochloride-PVAc spray dried powder
e.g.	for example, exempli gratia
et.al.	Et alli, and others
F-PVAc	furosemide-PVAc spray dried powder
g	gram(s)
HCl	hydrochloric acid or hydrochloride salt
hr	hour(s)
IR	infrared
kg	kilogram(s)
lb.	pound(s)
mcg	microgram(s)
MDT	mean dissolution time
mg	milligram(s)
min	minute(s)
ml	milliliter(s)
mp	melting point
MW	molecular weight
N	normality
NaOH	sodium hydroxide
nm	nanometer(s)
No.	number

LISTS OF ABBREVIATIONS(cont.)

PBS pH 6.8	phosphate buffer pH 6.8
pH	the negative logarithm of the hydrogen ion concentration
pKa	the negative logarithm of the dissolution constant
PVAc	polyvinyl acetate
q.s.	make to
r^2	correlation of determination
RDT	relative dissolution time
rpm	revolution per minute
SD	standard deviation
SEM	scanning electron microscope
T-PVAc	theophylline-PVAc spray dried powder
USP	The United State Pharmacopoeia
UV	ultraviolet
UV-vis	ultraviolet and visible
w/w	weight by weight
w/v	weight by volume
µg	microgram(s)
µm	micrometer(s)

CHAPTER I

INTRODUCTION

An aqueous-based polymeric dispersion has been developed and applied successfully in pharmaceutical system. Several water dispersing polymers have been become commercially available for controlled release formulation such as Surelease® (ethyl cellulose aqueous dispersion), commercial Eudragit® (acrylate aqueous dispersion). A new polyvinyl acetate-based coating dispersion, PVAc: Kollicoat® SR 30D (BASF AG, Ludwigshafen, Germany), was an alternative agent for tablet coating or matrix forms. Polyvinyl acetate dispersion is hydrophobic polymer stabilized with povidone and sodium lauryl sulfate. The dispersion is suitable for the manufacture of pH – independent sustained release formulation.

Recently, polyvinyl acetate powders (Kollicoat® SR) have been used in the formulation of dosage form, most commonly in preparation of matrices for oral sustained release by direct compression, wet granulation or hot melt extrusion method.

From a manufacturing viewpoint, spray drying offers the advantage of being a single-step process in a spray dryer. This can both simplify the process and shorten the processing time. By modifying the spray drying process, it is possible to alter and control many properties of spray dried product. Spray drying techniques have been widely used in the pharmaceutical system with different applications. An application in the pharmaceutical industries include with the drying of heat sensitive material, preparing granulations for tabletting and coating drug with suitable polymers to produce dust-free powders. Spray drying techniques have improved flow properties and compressibility, thus increasing the ease of tabletting into matrices. In addition, spray drying has been used successfully in the preparation of sustained release systems made from various polymers such as cellulose derivative polymers, methacrylic polymers (commercial Eudragit®) and polylactic acid etc. However, there is no study of application of PVAc using spray drying process.

It is of interest to investigate the application of PVAc aqueous dispersion in preparation of sustained release matrices via spray drying technique. Three different drug solubility, diltiazem hydrochloride, theophylline and furosemide were employed as model drugs. The influencing variables on the physical, physicochemical properties of spray dried powders and release characteristics of matrices were evaluated. The formulation variables included in this study were the drug solubility and the concentration of polymer in matrices. In addition, the tabletting properties of spray dried powders were also studied.

The objectives of this investigation are followed

1. To study the spray drying technique in the preparation of spray dried matrices of diltiazem hydrochloride – PVAc, theophylline –PVAc and furosemide – PVAc.
2. To study the effect of drug solubility on its release profiles from the matrices prepared with PVAc.
3. To study the effect of the amount of PVAc in matrices on drug release profiles.
4. To study the effect of compression forces during tabletting on the drug release from matrices.
5. To determine the physicochemical properties of drug-PVAc powders.
6. To examine the drug release characteristics from matrices.

CHAPTER II

LITERATURE REVIEW

1. Spray Drying Process

Spray drying process has been widely used in the pharmaceutical, chemical and food industries mainly for the drying of substances. However, other applications in the pharmaceutical industries include the drying of heat sensitive materials (Newton, 1966), preparing granulations for tabletting (Sugimori et al., 1990), improving the solubility of poorly water-soluble substances (Takeuchi et al., 1987), coating drugs with suitable polymers to produce dust-free powders and other more recent application like microencapsulation and microsphere for controlled release preparations. Spray drying technique may prove to be more useful for the preparation of microcapsules because the coated particles can be produced directly from droplets in a single process (Takenaka et al., 1981).

1.1 The General Principles of Spray Drying

Spray drying is the transformation of feed from a fluid state into a dried particulate form by spraying the feed into a hot drying medium. It is a one-step, continuous particle-processing operation involving drying. The feed can either be a solution, suspension or paste. The resulting dried product conforms to powders, granules or agglomerates, the form of which depends upon the physical and chemical properties of the feed and the dryer design and operation (Master, 1985).

2. Effect of processing formulation variables on the properties of spray dried powders

Spray dried powders are usually approximately spherical with a narrow size distribution and are usually hollow. The hollow nature imparts a low bulk density to the powders, but despite this, their spherical shape means that they are usually free-flowing (Newton, 1966). By modifying the spray drying process, it is possible to alter and control the following properties of spray dried powders ; appearance, particle size and size distribution, bulk density, particle density, porosity, moisture content, flowability, stability, dispersability, friability and retention of activity, aroma and flavor (Master, 1979 ; Newton, 1966). Obviously, the design of the nozzle and drying chamber will affect particle properties, and the desired powder characteristics should be borne in mind when a spray dryer design in selected.

3. Application of spray drying for sustained release system in pharmaceutical technology

Spray drying technique has received considerable interest as a microencapsulation process to obtain a controlled delivery systems, involved dispersing a solid or liquid core material in a coating solution and then atomizing the mixture into an airstream. Microcapsules can be either an individually coated solid particle or liquid droplet, or a matrix of wall material containing many small, fine core particles. The former type of microcapsules can be prepared by numerous methods including coacervation, coating, and interfacial reaction techniques. Matrix microcapsules are usually prepared by spray drying or spray congealing. Spray drying can be used simply to separate previously prepared microcapsules from the vehicle, or for the preparation of microcapsules in a single operation. In the spray congealing process, no solvent is used. The feed, which consists of the coating and core material, is fed to the atomizer in the molten state. Microcapsules form when the droplets meet the cool air in the drying chamber and congeal.

Kulvanich et al. (2004) studied the release characteristics of the matices prepared from Co-spray dried powders of theophylline and ethylcellulose. The Co-spray dried powders were prepared using aqueous ethylcellulose dispersion. Co-spray dried powders were directly compressed into the matrices. The Co-spray dried powders exhibited good matrix formations with high hardness at rather low compression force. The concentration of ethylcellulose in the matrices was, as expected, the rate-determining factor in controlling the release rate of drug. Increasing the weight fractions of ethylcellulose resulted in a corresponding decrease in the drug release rates in both 0.1 N HCl and phosphate buffer pH 6.8. However, at the same level of ethylcellulose content, the drug release in acidic conditions was higher than in alkaline medium. To modify release characteristics of the matrices, PVP K30 and lactose were employed as channeling agent. At concentrations of 5 and 10% PVP K30 was found to slow the drug release when incorporated into the co-spray dried powder formulations containing 5% ethylcellulose. Lactose at a concentration of 15% provided an increasing effect on drug release when added in the formulations. But an increase in lactose quantity from 15 to 25% did not exert much more influence on release characteristics. Higuchi plots were found to be best applicable to all release data.

Theophylline particle design using chitosan by the spray drying was investigated (Asada et al., 2004). Solid dispersions of theophylline with chitosan as a carrier were prepared. In this study, they aimed to apply this ability to sustained release pharmaceutics. The physicochemical properties of the solid dispersions obtained were investigated by powder X-ray diffraction, differential scanning calorimetry, and dissolution rates analyses, with a view to clarify the effect of crystallinity on the dissolution rate. Futhermore, the interaction between the drug and the carrier was investigated by FT-IR analysis. The powder X-ray diffraction intensity of the drug in the spray dried samples decreased with an increase in chitosan contents, which also caused changes from crystalline to amorphous forms. These results indicated that the system formed a solid dispersion. The dissolution profiles of the drug from the physical mixtures and solid dispersions were almost the same at pH 1.2. However, at pH 6.8, the release from the solid dispersion was sustained more than that from the physical mixtures. The FT-IR spectroscopy for the theophylline solid

dispersions suggested that the carbonyl group of theophylline and the amino group of chitosan formed a hydrogen bond.

Palmieri et al. (1994) evaluated the possibility to obtain microcapsules or microspheres for controlled release by spray drying technique. Drugs of different solubilities like theophylline and sodium sulfamethazine were used. Eudragit® RS was used as coating polymer, either dissolved in a hydroalcoholic solution or suspended (pseudolatex) in water, in different weight ratios with the drug. The obtained solution or suspension was spray-dried. They found that no microencapsulation occurred by spray drying a drug and polymer solution; the spray-dried particles were simple minimatrices, that was, a fine drug dispersion in the polymer network. Even if these microparticles were not able to reduce the rate of drug release, tablets derived from their compression, were very effective as controlled release system and offer a real advantage compared with the matrix-tablets obtained by direct compression of the polymer powder or by compression of the solid dispersion powders realized by evaporation under vacuum. So, spray drying was a useful step in the formulation of controlled release matrix tablets.

Wan et al. (1992) prepared microcapsule of theophylline by a spray drying technique using an aqueous system. Comparison was made between the use of a solution and a suspension feed. The results showed that a suspension-feed produced microcapsules with better flow properties and slower drug dissolution than the products from a solution-feed. Most of the products from the solution-feed contain drug particles on the polymer surface, resulting in a rapid drug release. The dissolution profiles of spray dried product were dependent on the type of polymer and its hydrophilicity.

The productions of biodegradable microparticles by spray drying method appear to be an attractive alternative of conventional microencapsulation method. Co-poly (dl-lactic/glycolic acid) microparticles for injectable sustained release of a water soluble drug (thyrotropin releasing hormone: TRH) were prepared by a spray drying method (Takada et al., 1994 and 1995). It was seen that a higher entrapment ratio was achieved with the spray drying method than with the in-water drying method. In order

to avoid agglomeration of the microparticles, a double-nozzle spray drying method was designed using mannitol, and the extent of agglomeration was decreased.

Poly (lactide-co-glycolide) powders with good compaction properties can be prepared by spray drying (Avgoustakis and Nixon, 1993). The important factor for the successful spray powdering of poly (lactide-co-glyolide) polymers appeared to be the molecular weight of the polymer and not the viscosity of the sprayed solution.

Bovine serum albumin was microencapsulated into poly (D, L-lactic acid) by spray drying using single solvents and binary solvent mixtures (Gander et al., 1996). Microencapsulation was studied by a thermodynamic approach taking quantitatively into account the molecular interactions between polymer, solvent and the aqueous protein phase. Entrapment efficiency is increased and burst release is reduced if polymer-drug interaction is dominant and polymer-solvent, drug-solvent interactions are reduced.

Sutinen et al. (1995) described a new type of microspheres that control drug release with changing inner core pH. In the microspheres, micronized model drug, timolol maleate and pH adjusting agent (mono, di, and trisodium phosphate or Tris buffer) were either dry blended by mixing or co-precipitated by spray drying, and encapsulated in X7-3012 silicone microspheres using emulsion vulcanization technique. Spray drying of the drug and buffer together was the most effective in controlling the drug release since, in this case, buffer was in the same microcompartment inside silicone and thus buffering effect was maximal.

Pavanetto et al. (1992) compared three different techniques used for the preparation of polylactide microspheres loaded with a lipophilic drug. The three methods were emulsification by solvent evaporation, emulsification by solvent extraction and spray drying. They found that spray drying achieved a highest encapsulation efficiency and shortest duration for the process of preparation. Moreover, the dissolution profile of microspheres prepared by spray drying demonstrated that more gradual release of drug was promoted.

Takenaka et al. (1981) prepared enteric coated microcapsules of sulphamethoxazole by spray drying an aqueous solution of drug and cellulose acetate phthalate (CAP) 5%, with or without various additives, such as monmorillonite clay and colloidal silica. Particles with diameters ranging from 3.6 to 22.0 μm were obtained. Formulation containing additives yielded smaller particles than those without additives. The addition of additives also improved the surface texture of the spray dried products, as compared to particle prepared from non-additive formulations, which tended to have flaky surfaces. Non-additive formulations also exhibited poor flow properties and thus were not easily tabletted. Formulation containing CAP exhibited some conversion of the drug from crystalline form I to form II and an amorphous form during spray drying. Form II was also obtained by freeze drying or vacuum drying sulphamethoxazole. When microcapsules were prepared by a coacervation technique the drug remained in form I. CAP was presumed to interact with the sulphamethoxazole since the degree of amorphism increased with an increase in the concentration of CAP in the formulation.

Further studies examined the effect of spray drying sulphamethoxazole with xanthan gum or guar gum with and without colloidal silica or cellulose acetate phthalate (Kawashima et al., 1983). It was found that the film forming capacity of xanthan gum alone was superior to that of guar gum, but inclusion of colloidal silica or cellulose acetate phthalate made the resultant product smoother. X-ray diffraction data showed that the presence of cellulose acetate phthalate actually caused a polymorphic change resulting in a mixture of form I, II and III (form III had been indistinguishable in the previous study which used IR analysis). When the formulation contained colloidal silica, however, the sulphamethoxazole was always present in form I, irrespective of the gum type. When neither CAP or colloidal silica was included in the formulation, the product was usually a mixture of all three forms.

A spray drying method has been described for the manufacture of a drug matrix which possesses sustained action when compressed into tablets (Kornblum, 1969). The method possesses the advantages of uniformity of drug distribution and reproducibility of drug release pattern for consecutive batches. He reported that

significantly less binder is required to achieve a given sustaining effect when compared with conventional granulation methods.

Asker and Becker (1966) used spray drying technology to produce prolonged release sulfaethythiadiazole (SETD) granulations. A follow-up series of papers investigated the production of slow release sulfaethythiadiazole-wax granulations by spray congealing (Cusimano and Becker, 1968 ; John and Becker, 1968 ; Hamid and Becker, 1970). This technique had previously been used for the production of 35 μm SETD-hydrogenated castor oil granules, which were used in the formulation of a slow release suspension. A decrease in particle size was observed with a decrease in nozzle diameter, as would be expected. The type of wax used also had a significant effect on particle size. Interestingly, these authors observed larger particle diameters with the least viscous feed solutions. This corresponding with the data of Scott et al. (1964), who observed an inverse relationship between particle size and the viscosity of the feed medium, but contrasts with most other observations of the spray drying process which indicate an increase in particle size with increasing feed viscosity.

Controlled release theophylline tablets were prepared by compressing spray dried microspheres with Eudragit® L30D, L100-55 and E30D (Takeuchi et al., 1989). Depending on the amount of polymer present, the spray dried powder consisted of either agglomerated, polymer coated theophylline crystals or spherical particles of a solid dispersion of amorphous drug in a polymer base. Completely enteric function was observed with drug-to-polymer ratio of 1: 3 using Eudragit® L30D or L100-55. Tablet with Eudragit® E30D formulated at the 2-40% level showed good sustained drug release which was thoroughly independent of the pH of dissolution media. In each tablet, the controlled drug release was attributed to continuous and well-dispersed polymer matrix formed by spray drying and subsequent compressing process.

4. Advantage of spray drying techniques (Masters, 1985)

1. Spray drying is a single-step operation from liquid feed to dry product. Frequently this eliminates such steps as precipitating or crystallizing, centrifuging or filtering, grinding, classifying, and perhaps the additional pumping, storage, and dust collecting operations associated with them.

2. The process is continuous, although it can operate with feed from a prior batch process.

3. Adaptable to full automatic control.

4. Dried product specifications meet through dryer design and operational flexibility:

    4.1 Required product form (particle as spheres, fines, agglomerates)

    4.2 Required properties (dusty or dustless, degree of flowability, wettability, etc.)

5. Applicable to both heat sensitive and heat-resistance materials.

6. Feedstocks in solution, slurry, thixotropic paste or melt form can be handled.

7. Corrosive and abrasive fed stocks can be readily handled.

8. Corrosion is reduced or prevented because the material does not contact the equipment surfaces until it is dry. This permits selection of lower-cost materials of construction.

9. Maintenance costs are low because there are few moving parts.

10. Labor costs are low because only one operator is required, even on large installations. Because the evaporation usually is done under slight vacuum, it is easy to keep to equipment and area clean.

11. Operator requirements are the same for both small and large dryers, hence spray drying is basically a high-volume system with low labor cost.

12. In co-current designs, surface temperatures are low (except at the hot gas inlet) because the extremely rapid: evaporation cools the inlet gas nearly to its outlet temperature a few inches from the points of atomization. This feature further restrains corrosion of the equipment.

13. Spray drying is an airborne process; hence there is very low material holdup in the equipment.

14. Designs are available to handle:

    14.1 Evaporation of organic solvents without explosion/fire risks.

    14.2 Powders that form potentially explosive mixtures in air.

14.3 Products that create odor during drying.

14.4 Toxic products.

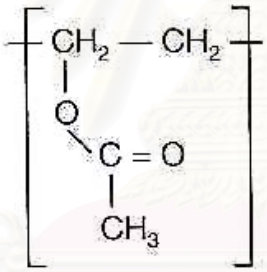
14.5 Products requiring aseptic/hygienic drying conditions.

5. Use of vinyl acetate polymer

5.1 General

Kollicoat SR 30 D is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate. The dispersion is suitable for the manufacture of pH-independent sustained-release formulations. The dispersion can also be used for taste masking.

5.2 Chemical structure



5.3 Commercial formulation

Kollicoat SR 30 D is an aqueous dispersion with solids content of 30%. The low viscosity product has a weak characteristic odor and a milky white or slightly yellowish appearance.

5.4 Specifications and properties

5.4.1 Description The dispersion consists of about 27% polyvinyl acetate, 2.5% povidone and 0.3% sodium lauryl sulfate.

5.4.2 Physical and chemical properties

Identification:	Conforms
Film formation:	Conforms
Solubility:	Conforms
pH:	3.5-5.5
Relative density:	1.045-1.065
Viscosity	<100 mPas
Coagulate content:	<0.5%
Solids content:	28.5-31.5%
Sulfated ash:	<0.5%
Heavy metals:	<20 ppm
Monomers:	<100ppm
Microbiological status:	Conforms

5.4.3 Film formation

10 g of Kollicoat® SR30 D are mixed with 0.3g of propylene glycol. When poured onto a glass plate, a colorless or faintly yellowish film forms after the liquid has evaporated.

5.4.4 Viscosity

Viscosity is determined in accordance with DIN EN ISO 3219 at a shear gradient of 250 sec^{-1} and 23 °C

5.4.5 Coagulate content

100 g of the substance is filtered through a 90 um sieve. The residue is dried to constant weight at 105 °C in a drying oven.

5.4.6 Microbiologcal status

Kollicoat® SR 30 D is not susceptible to microbial contamination. Microbiological testing is carried out in accordance with Ph.Eur. VIII. 15. Category 3. Unless otherwise stated, the methods of determination are taken from European Pharmacopoeia 1997.

5.4.7 Pharmacopoeia

No monograph is currently available for Kollicoat® SR 30 D.

5.4.8 Marketing authorization

Polyvinyl acetate is described with reference to oral administration in Japanese Pharmaceutical Excipients (JPE) 1993. Polyvinyl acetate is used in a variety of medicinal products for oral administration in numerous countries including Germany, France and the USA.

Polyvinyl acetate is also used in the food industry such as a chewing gum base or for coating fruits and vegetables. It is listed, for example, in Germany in the Regulations for Marketing Authorization of Food Additives for Technological Purposes, in the USA in the Code of Federal Regulations, Section 172.615, in South Korea in the Public Code on Food Additives 1995 and in Japan in the Japanese Standard for Food Additives 1997.

5.5 Application and Processing

5.5.1 Application

5.5.1.1 Sustained-release coated formulations

Kollicoat® SR 30 D is used mainly for the manufacture of sustained-release dosage forms. Very effective control of drug release is achieved by coating pellets, granules and crystals.

5.5.1.2 Protective coats

Applied in small quantities or with hydrophilic additives, Kollicoat® SR 30 D provides good protection against odor or taste. It can also be used, for example as a subcoating, for isolating active ingredients to prevent interactions.

5.5.1.3 Sustained-release matrix formulations

Matrix tablets can be produced by granulating active ingredients, for example in the fluidized bed process, followed by compression.

Flick and Kolter (2003) developed the sustained release pharmaceutical dosage forms by granulation and tableting using polyvinyl acetate dispersion. The objectives of this study were to develop various formulations (actives) using the wet granulation technique with sustained release excipient, to investigate the processing characteristics during granulation and tableting, and to determine the influence of various formulation components (e.g., readily and poorly soluble actives and excipient and various particle sizes). The compression forces used to tablet the individual trial series were varied between 10, 18 and 25 kN, with the 18 kN value as the main parameter for assessing the formulations. The tableting speed was 30 tablets/min on the single punch and 30 rpm on the rotary press. The true density, depending on the composition of the tablet, was calculated from the percentage proportions of the true densities of the individual components. The porosity decreased with increasing compression force and indicated the proportion of the void volume in the total volume. Although hardness values were highly dependent on compression force, this parameter was not found to have any influence on the release profile which was particularly surprising because the porosities of the tablets differ greatly depending on the compression force. The matrix of a propranolol HCl tablet release over 24 h. The scanning electronic microscopic image of a broken tablet clearly reveals the pores and channels that formed. Similar to the effects of the fillers, the solubility of the active also had a strong effect on the dissolution rate. A much higher content of polymer was required to manufacture sustained release propranolol granule because of the better solubility of propranolol hydrochloride (~ 100 mg /ml compared

with ~ 7 mg/ml of theophylline). A higher solubility of the active caused a higher diffusion gradient and therefore a quicker release rate. The particle size of the active was also confirmed to be an other important criterion that influenced drug release. Figure 11 show that the dissolution rate is markly increased if the particle size of the active is too coarse or too fine. Fluid-bed processing is also difficult when extreme particle sizes are used. The optimal mean particle size for this manufacturing process was therefore between 100 and 200 μm. Processing the theophylline powder 200 with a polymer content of only 7.5 % in the fluid bed was not effective. The amount of dispersion to be sprayed onto the fine powder was too low to wet the high surface area and to achieve a proper granulation effect. Therefore, a large amount of fine remained. Large active particles generated large pore in the matrix, which resulted in a quicker release profile. The tableting of granules that were produced using Kollicoay SR 30D thus yielded tablets that exhibited excellent properties and had a release rate that was not dependent on the compression force.

Kondaiah and Parkash (2002) formulated and evaluated theophylline polymeric matrix tablets for controlled release using sintering technique. The powder of ethylene vinyl acetate copolymer 1802 was prepared by a novel spray technique. The micrometrics of powdered vinyl acetate copolymer were studied. Matrix tablets of theophylline in vinyl acetate copolymer were prepared in different drug and polymer ratios using direct compression and subsequent sintering technique at various temperatures. The sintered tablets were evaluated for various tablet characteristics including dissolution rate. A comparative dissolution rate study was conducted with the optimized formula against three commercial theophylline sustained release product. A simple process for powdering of vinyl acetate copolymer was developed. The sintering technique produced nonerodible matrix tablets. The in vitro dissolution studies have shown a considerable sustained release of theophylline from the matrix tablets of different drug polymer ratio. The controls of release of theophylline from the sintering tablets depend on the polymer-drug ratio, temperature of sintering and time of sintering.

Zhang et al. (2000) studied the properties of PVAC as a retardant polymer and to study the drug release mechanism of theophylline from matrix tablets prepared by hot melt extrution. The author reported that polyvinyl acetate is a homopolymer

synthesized from a vinyl acetate monomer via a free-radical polymerization technique. It is amorphous due to the presence of an acetate ester side chain in the backbone structure. The glass transition temperature of PVAc is relatively low due to its highly flexible backbone structure. Although water insoluble, it is slightly hydrophilic and able to absorb water to a slight extent. The polymer has been used in the preparation of matrix pellets, sustained release coating, and buccal drug delivery systems. PVAc was demonstrated to be an excellent carrier for the preparation of controlled release granules processed by hot melt extrusion. During processing, the extrudate was subjected to minimal thermal and mechanical stresses. Theophylline was released from the melt-extrided systems by diffusion mechanism. Drug release data fro the PVAc matrix tablets were in good agreement with the Higuchi model.

El-Shattawy et al. (1992) prepared microcapsules of phenylpropanolamine HCl by three techniques, viz. coacervation-phase separation, air suspension, and pan coating, using different polymers and/or waxes as wall-forming materials. Formulations showed reasonable dissolution behavior, viz. microcapsules prepared by air suspension with polymer level of 20% polyvinyl acetate copolymer (PVAc) associated with 40% carnauba wax and microcapsules prepared by pan coating with polymer level of 25% Rodopace® .

Sa (1991) studied polyvinyl acetate microspheres containing theophylline were prepared by emulsification and solvent removal method. The release pattern of theophylline from the microspheres was to be explained by diffusion process. The rates of release were found to be influenced by drug-polymer ratio, size of microsphere, concentration of surfactant used for the preparation of microsphere, and pH of dissolution media.

5.5.2 Processing information

The minimum film-forming temperature (MFT) or the pure dispersion is 18 °C. It can be lowered by adding plasticizers. The dispersion can theoretically also be used without plasticizers, but these additives enhance film formation and the flexibility of the films. The following are suitable as plasticizers or gloss enhancers: 1,2-propylene glycol, triethyl citrate, polyethylene glycols and triacetin.

The recommended plasticizer content is 0-10% with reference to the dried polymer substance 1,2-Propylene glycol offers advantages for processing the dispersion and for film properties.

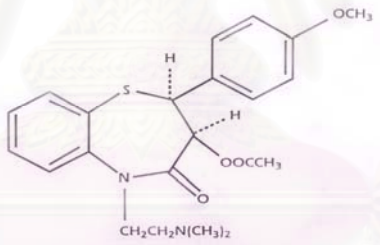
6. Active ingredients

6.1 Diltiazem hydrochloride

6.1.1 Description

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

6.1.2 Structure formular and Molecular weight:



$C_{22}H_{26}N_2O_4S_2.HCl = 450.98$

6.1.3 Physical properties

Diltiazem hydrochloride is a white to off-white crystalline powder, odorless and bitter taste. Find needle crystals are obtained from crystallization with ethanol-isopropanol 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 is show in Table 1.

Diltiazem hydrochloride has not been observed on polymorphic transition from. The saturated solution in aqueous system has a pH value about 3.0. The 1 % w/w solution of diltiazem hydrochloride in purified water has approximately pH at 4.2 while 1% w/v solution has higher pH value about 4.7.

Dissociation constant (pKa) of diltiazem hydrochloride is equal to 7.7. In addition, liquid-liquid partitioning value 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.

Table 1 Solubility's parameter of diltiazem hydrochloride 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

Diltiazem hydrochloride 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.

Diltiazem hydrochloride in aqueous system is stable over a pH range of 3-6, especially, optimal point is indicated at pH 5.0. Degradation kinetics of

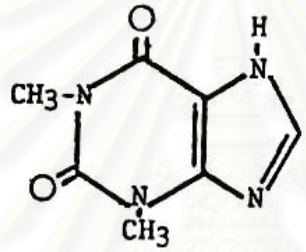
diltiazem hychloride in various pH was values follow pseudo-first order kinetics and undergoes with hydrolysis reaction (Suliemam et al., 1990).

6.2 Theophylline

6.2.1 Description

Name: Theophylline is designated by Chemical Abstracts as 1, 3-dimethylxanthine. It is also known as theocin.

6.2.2 Structural formula and molecular weight



Molecular weight: $C_7H_8N_4O_2$ = 180.17

6.2.3 Appearance

Theophylline occurs as a white, odorless, crystalline powder with a bitter taste.

6.2.4 Physical Properties

6.2.4.1 Melting Range

The original synthetic literature reported a melting point of 264 ° C for theophylline subsequently the melting range has been reported to be between 271 °C and 247 °C.

6.2.4.2 Solubility

The reported solubility of theophylline is 8.3 mg/ml in water; 12.5 mg/ml in ethanol; 11.6 mg/ml in chloroform; and sparingly soluble in ether. Several basic salts have been prepared which enhance the water solubility of theophylline and have been utilized therapeutically intended for oral, rectal and parenteral administration. In addition, there are numerous literature reports of altered theophylline solubility due to specific interactions with a variety of chemical substances. A British patent reports a six-fold increase in theophylline water solubility in the presence of guiacol. Several other papers have reported specific interactions of theophylline with a multitude of planer organic molecules in aqueous solution usually resulting in an increase in the solubility of both interacting species.

6.2.4.3 Thophylline Stability and Compatibility

Theophylline solutions are generally quite stable over the entire pH range. Strongly alkaline solutions (pH> 12) show decomposition and apparent ring opening after several week. Solutions of theophylline have been shown to be susceptible to oxidation at position 8 forming 1, 3-dimethyluric acid in the presence of methylene blue which acts as a photosensitizing dye. Because of its low solubility and relatively high pKa theophylline will precipitate from aqueous solutions if the pH drops below 9 unless present in concentrations less than the water solubility. All acidic salts, therefore, are potentially incompatible with theophylline forms generally soluble complexes with a variety of other compounds. In the solid state however, these complexes may lead to formation of eutectic mixtures as in the cases of theophylline, phenobarbital and papaverine hydrochloride and theophylline riboflavin interactions which have been reported.

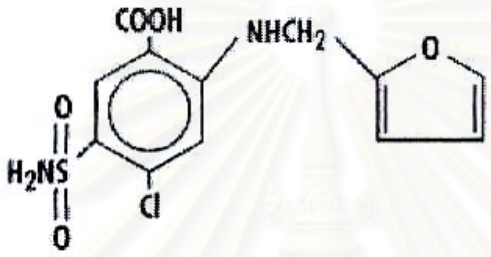
Theophylline ethylenediame (aminophylline) , which is commonly employed in alkaline parenteral solutions in concentrations considerably greater than the solubility of theophylline, has many incompatibilities associated with it. Since the solutions are alkaline, but essentially unbuffered, all acidic substances

produce precipitation of the free theophylline when mixed together with aminophylline solutions.

6.3 Furosemide

6.3.1 Description

Structural formula and molecular weight



Molecular weight: $C_{12}H_{11}Cl\ N_2O_5S$ = 330.77

6.3.2 Elemental Composition

C = 43.57 %, H = 3.35 %, Cl = 10.72 %, N = 8.47 %, O = 24.19 %, S = 9.70 %

6.3.3 Appearance, Color, Odor and Taste

A white to slightly yellow, odorless, almost tasteless crystalline powder.

6.3.4 Physical Properties

6.3.4.1 Melting Range

m.p. : 206 °C

6.3.4.2 Solubility

It is slightly soluble in water and chloroform and ether. Soluble in acetone, methanol, dimethyl formamide and in solutions of alkali hydroxides.

6.3.4.3 pH

pH of aqueous solution is in between 8.9 to 9.3.

6.3.4.4 Stability

Furosemide injection should be stored at temperature of 15-30 ˚C and protected from light, injections having yellow color should not be used. Exposure of furosemide tablets to light may cause discoloration, discolored tablets should not be dispensed. Tablets should be stored and dispensed in well closed, light resistant containers. Commercially available furosemide tablets have an expiration date of 5 years and commercially available injections has an expiration date of 42 months following the date of manufacture. Furosemide oral solution should be stored at 15-30 ˚C and protected from light and freezing ; once opened unused portion should be discarded after 60 days.

Furosemide injections can usually be mixed with weakly alkaline and neutral solutions having pH of 7-10, such as 0.9% sodium chloride injection or Ringer's injection and some weakly acidic solutions (i.e. pH less than 5.5) such as those containing ascorbic acid, tetracycline, epinephrine, norepinephrine, because furosemide may be precipitated. Other drugs which should not be mixed with furosemide injections include most salts of organic bases including local anesthetics, alkaloid, antihistamines, hypnotics, and morphine.

7. The analysis of dissolution data of controlled release system

7.1 The release mechanism of control release system

In order to analyze the mechanism of the drug from the matrices, the dissolution data may be analyzed using the semiempirical equation of Peppas (1985) given below

$$\frac{Mt}{M\alpha} = kt^n \qquad (1)$$

Where Mt/ Mα is the fraction of drug released up to time t

t is the release time

k is a constant incorporating structural and geometric characteristics of the controlled device

n is the diffusional release exponent indicative of the mechanism of release

The determination of the exponent n is valid for the first 60% of the total release drug ($Mt/ M\alpha \leq 0.6$), which also applied only to the early times of release

Clearly, a desiable mechanism for many applications is that which leaded to n equal 1, which characterized zero order release behavior. Table 2 summarized the general dependence of n on the diffusional mechanism (Peppas, 1985)

Table 2 Interpretation of diffusional release mechanisms of drug release data from thin polymer film.

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1	Anomalous (non-Fickian) transport	t^{n-1}
1.0	Case-II transport	Zero-order (time-independent) release
n>1.0	Super-Case-II transport	t^{n-1}

The empirical Equation 1 could be modified for application to non-planar geometries. The relationship between the diffusional exponent n and the corresponding release mechanism is clearly dependent upon the geometry employed as shown in table 4 (Ritger and Peppas, 1987a).

In non-swellable matrices, the values of n are 0.45 and 1.00 for Fickian and Case-II transport, respectively. Case II transport is a special case readily identified and characterized by the constant velocity of the moving solvent front and the resulting linear weight gain with time. However, its characteristics are not as well understood, nor are they as fundamental in origin as those of Fickian diffusion (Tyle, 1990). When the value of n is > 0.45 and < 1.00, the release was said to be non-Fickian (Ritger and Peppas, 1987a). A value of n=1, however, mean that the drug release is independent of time, regardless of the geometry. Thus, zero order release can exist for any geometry.

Table 3 Diffusional exponent and mechanism of drug from various non-swellable controlled release systems.

Diffusional Exponent, n			Drug release mechanism
Thin Film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
0.5<n<1.00	0.45<n<1.00	0.43<n<1.00	Anomalous (non-Fickian) transport
1.00	1.00	1.00	Zero order release

In swellable controlled release systems, Case-I (Fickain diffusion) and Case II solute release behaviors are unique in that each can be described in terms of a single parameter. Case-I transport is described by a diffusion coefficient, while Case-II transport was described by a characteristic relaxation constant. Non-Fickian behavior, by comparison, required two or more parameters to described the coupling of diffusion and relaxation phenomena.

In swellable matrices, when the system did not swell more than 25% of its original volume, the value of n are 0.45 and 0.89 for Fickian and Case-II transport, respectively. When the value of n is >0.45 and 0.89, the release was said to be non-Fickian (Ritger and Peppas, 1987b). When the value of n was greater than that of the Case-II transport, the release was said to be Super Case-II transport. Table 4 summarized the range of values of diffusional exponent n, and the related transport mechanism for each geometry (Ritger and Peppas, 1987b). A value of n=1, mean that the drug release was indepentdent of time, regardless of geometry. Thus, zero order release can exist for any geometry; only for slabs did this release coincide with Case-II transport.

Table 4 Diffusional exponent and mechanism of drug from various swellable controlled release systems.

Diffusional Exponent, n			Drug release mechanism
Thin Film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
0.5<n<1.00	0.45<n<0.89	0.43<n<0.85	Anomalous (non-Fickian) transport
1.00	0.89	0.85	Case-II transport

7.2 The release pattern of controlled release system

Controlled release of drugs can be achieved by incorporating solutes either in dissolved or in dispersed form in polymers. From a mathematical modeling point of view, controlled release systems may be classified according to the physical mechanisms of release of the incorporated solute. Mathematical modeling of the release kinetics of specific classes of controlled release systems may be used to: (1) predict solute release rates from and solute diffusion behavior through polymer, and (2) to elucidate the physical mechanisms of solute transport by simply comparing the release data to mathematical models (Ranade and Hollinger, 1996)

Mathematical models can be categorized into three types :zero-order release model, square-root-time release model and first-order release model

7.2.1 Zero-order release model

An ideal controlled release device is one which can deliver the drug at a constant rate until the device is exhausted of active agent. Mathematically, the release rate from this device is given as :

$$\frac{dM_t}{dt} = k \qquad (2)$$

where k is a constant, t is time, and M_t is the mass of active agent released. This model of release is called zero-order release model.

7.2.2 Square-root-of-time release model (Higuchi model)

The second common release model is frequently referred to as square-root-of-time or $t^{1/2}$ release, providing compound release that is linear with the reciprocal of the square root of time. The release rate is then given as:

$$\frac{dM_t}{dt} = \frac{k}{\sqrt{t}} \qquad (3)$$

In contrast to first-order release, the release rate here remained finite as the device approached exhaustion.

The release model of this type can be described by Higuchi equation (Higuchi, 1963)

$$Q = \left[\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s t \right]^{1/2} \qquad (4)$$

Where Q is weight is grams of drug released per unit surface area
D is diffusion coefficient of drug in the release medium
ε is porosity of the matrix
τ is tortuosity of matrix
C_s is solubility of drug in the release medium
A is concentration of drug in the tablet, expressed as g/ml

These assumption made deriving Equation are as follows :

1. A pseudo-steady state is maintained during release
2. $A >> C_s$, i.e., excess solute is present
3. The system is in perfectly sink condition in which C, is approximately to zero at all time
4. Drug particles are much smaller than those in the matrix

5. The diffusion coefficient remains constant
6. No interaction between the drug and the matrix occurs

For purposes of data treatment, Equation (4) is usually reduced to

$$Q = k_H t^{1/2} \quad (5)$$

Where k_H is Higuchi constant. Therefore, the plot of amount of drug released from matrix versus the square root of time should be increased linearity if drug release from the matrix is diffusion controlled. Although the above equation was based on release from a single face, it may used to describe diffusion-controlled release from all surface matrixes.

In order to further verify that the release followed Higuchi model, Higuchi equation is converted into logarithmic form as :

$$\text{Log } Q = \log k_H + 1/2 \log t \quad (6)$$

The plot of log Q versus log t must not only yield a straight line, but must have a slope of 0.5.

7.2.3 First-order release model

The first-order release model is the third common type of the release model. The release rate in this case in proportional to the mass of active agent contained within the device. The rate is then given as:

$$\frac{dM_t}{dt} = k (M_0 - M_t) \quad (7)$$

where M_0 is the mass of agent in the device at $t = 0$. On rearrangement, this gave

$$\frac{dM_t}{dt} = kM_0 \exp^{-kt} \quad (8)$$

In first-order model, therefore, the rate declined exponentially with time, approaching a release rate of zero as the device approached exhaustion.

On the assumption that the exposed surface area of matrix decreased exponential with time, Wagner (1969) suggested that drug release from most controlled-release matrices could be described by apparent first order kinetics, thus :

$$A_t = A_0 e^{-k} 1^t \quad (9)$$

where k_1 is first order release constant
A_0 is initial amount of drug
A_t is amount of drug remaining in the matrix at time t

Simplifying and taking the logarithm of Equation (9) yielded

$$\log A_t = \log A_0 - \frac{k_1 t}{2.303} \quad (10)$$

First order model can be predicted by plotting the logarithm of the percentage of drug remaining against time. If the release pattern follows first order model, linear relationship is obtained. Sa, Bandyopadhyay and Gupta (1990) reported that the initial curvature of the plot may be obtained because of the presence of surface drugs and they suggested to be ignored.

Since both the square root of time release and first order release plots are linear, as indicated by correlation coefficient, it is necessary to distinguish between the model. The treatment has been based upon use the differential forms of the first order and square root of time equations (Schwartz, Simonelli, and Higuchi, 1968)

For Higuchi model, the rate will be inversely proportional to the total amount of drug release in accordance with equation (Sa, Bandyopadhyay and Gupta, 1990)

$$\frac{dQ'}{dt} = \frac{k_H^2 S^2}{2Q'} \qquad (11)$$

where $Q' = Q*S$ (S is the surface area of matrix). The rate predicted by first-order model was given by :

$$dQ' = k A_0 - kQ' \qquad (12)$$

where $A = A_0 - Q'$. This indicated that rate will be proportional to Q'. The rates of release are determined by measuring the slopes at different points on the percentage of drug release versus times curves.

The plots of rates of release versus 1/Q' are linear, indicating that the release is fitted with Higuchi model. If the plots of rates of release versus Q' were linear, indicating that first order model is operative.

The release model for each classes of device is illustrated in Figure 1 (Baker, 1987), the release models of Zero-Order, Square-root time, and First-Order are depicted (Equation 2, 3 and 7) respectively.

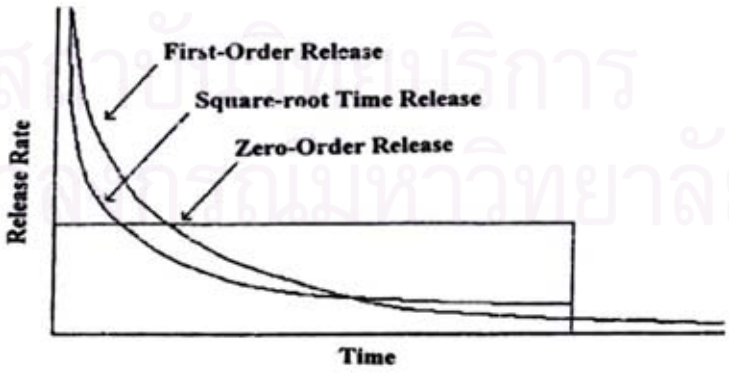


Figure 1. Zero-order, first-order, and square-root time release models from devices containing the same initial active agent content

CHAPTER III

EXPERIMENTAL

1. Materials

1.1 Active Drug

- Diltiazem hydrochloride
  (Lot No. DIL/M-01502, supplied by Siam Pharmaceutical Co., Ltd, Thailand)
- Theophylline anhydrous
  (Lot No. 4789, China)
- Furosemide
  (Lot No. F-0201097, China)

1.2 Additives

- Polyvinyl acetate dispersion : Kollicoat® SR 30D (Lot No. 11452, BASF Ltd, Germany)
- Aerosil®200 (supplied by Pharmaceutical Science, Thailand)
- Maltodextrin (supplied by Pharmaceutical Science, Thailand)
- Magnesium stearate (Lot No. F1G253, Asia Pacific Pte Ltd., Australia)

1.3 Other chemicals

- Potassium dihydrogen orthophosphate, AR grade
  (Lot No.F1F125, Asia Pacific Specialty Chemicals Ltd., Australia)
- Sodium hydroxide pellets, AR grade
  (Lot No.B 131198 241, Merck, Germany)
- Hydrochloric acid solution 37%, AR grade
  (Lot No.03 02 0186, Lab-scan Analytical Sciences , Ireland)

- 25% Ammonium hydroxide, AR grade
  (Lot No. 02 08 0415, Lab-scan Analytical Sciences, Ireland)
- Methanol, HPLC grade
  (Lot No.02 09 0153, Lab-scan Analytical Sciences, Ireland)
- Ethanol, Analytical grade
  (Lot No.03 10 0189, Lab-scan Analytical Sciences, Ireland)

2. Methods

2.1 Solubility determination

The solubility of diltiazem hydrochloride, theophylline and furosemide in deionized water, 0.1 N HCl sollution and phosphate buffer pH 6.8 solution (PBS pH 6.8) at 37± 0.5 º C were determined by flask shaking method (Shaker bath, Polyscience®, U.S.A.). The excess amount of drug was dissolved and sample of 2 ml was withdrawn at the time interval of 12, 24, 48, 72, 120 and 168 hrs. Each sample was filtered through 0.45-μm membrane filter. The filtrate was diluted to a suitable concentration and the drug dissolved was determined using UV/VIS spectrophotometry at the maximum wavelength of each medium.

2.2 Preparation of spray dried powders

2.2.1 Formulation of spray dried dispersion

The composition of spray dried powders are presented in Table 5.

Table 5 Formulation of spray dried dispersion

Ingredient	Parts
Active ingredient*	1
30% polyvinyl acetate dispersion (Kollicoat® SR 30D)**	0.5, 1, 1.5
Maltodextrin	0.5
Aerosil® 200	1% of above solid
Solvent***	qs. to 2,000 ml

* diltiazem hydrochloride or theophylline anhydrous or furosemide

** 30% polyvinyl acetate dispersion (PVAc dispersion, Kollicoat SR 30D)

*** deionized water for diltiazem hydrochloride, 2% ammonia solution for theophylline anhydrous and 12.5% ammonia solution for furosemide

2.2.2 Preparation of spray dried dispersion

2.2.2.1 Preparation of spray dried diltiazem hydrochloride-PVAc dispersion

Diltiazem hydrochloride and maltodextrin were weighed and dissolved in deionized water, whereas Aerosil®200 was dispersed in deionized water and then mixed together. 30% polyvinyl acetate dispersion (PVAc dispersion, Kollicoat® SR 30D) was mixed in this dispersion and then adjusted to 2,000 ml with deionized water. The dispersion contained 200 g total solid.

2.2.2.2 Preparation of spray dried theophylline-PVAc dispersion

Theophylline and maltodextrin were weighed and dissolved in 2% ammonia solution. Aerosil® 200 was then dispersed in 2% ammonia solution and adjusted to 2,000 ml with 2% ammonia solution. 30% polyvinyl acetate dispersion (PVAc dispersion, Kollicoat® SR 30D) was mixed in this dispersion and then adjusted to 2,000 ml with 2% ammonia solution. The dispersion contained 200 g total solid.

2.2.2.3 Preparation of spray dried furosemide-PVAc dispersion

Furosemide and maltodextrin were weighed and dissolved in 12.5% ammonia solution. Aerosil® 200 was dispersed in 12.5% ammonia solution and adjusted to 4,000 ml with 12.5% ammonia solution. The dispersion contained 200 g total solid.

2.2.3 Spray drying process

The spray drying apparatus was a laboratory type (NIRO ATOMIZER Mobile Minor Unit, Denmark), the specification of which is a drying chamber of 80 cm. in diameter, 60 cm. in cylindrical height and conical base with the angle of 60°. The dispersion was atomized into a drying chamber by rotating centrifugal wheel atomizer. The spray drying conditions were as follows:

A. Condition of spray drying process of D-PVAc dispersion

Inlet air temperature	:	118-119 º C
Outlet air temperature	:	80-83 º C
Atomizing air pressure	:	4 bars
Feed rate	:	20 ml/min

B. Condition of spray drying process of T-PVAc dispersion

Inlet air temperature	:	118-119 º C
Outlet air temperature	:	70-73 º C
Atomizing air pressure	:	4 bars
Feed rate	:	20 ml/min

C. Condition of spray drying process of F-PVAc dispersion

Inlet air temperature	:	118-119 º C
Outlet air temperature	:	69-72 º C
Atomizing air pressure	:	4 bars
Feed rate	:	20 ml/min

3. Evaluation of physical properties of spray dried powders

3.1 Moisture determination

The moisture content of powder was determined using the moisture analyzer (Model MA30, Sartorius, Germany). About 1 gram of sample was exposed to an IR Lamp until constant weight was obtained. The percent of moisture content was calculated automatically. The results were obtained from an average of three determinations.

3.2 Powder morphology

Morphology of powder samples was determined using scanning electron microscopy (JSM-5800LV, Jeol LTD, Tokyo, Japan). The samples were coated with gold prior to the microscopic examination using ion sputtering. Size, shape and surface topography of spray-dried powders were observed.

3.3 Particle size distribution

Particle size distribution was determined using light scattering method (laser particle size distribution analyzer, Model Mastersizer-S, Malvern Instrument Ltd., UK). Haft of the dispensing spoon sample was dispersed in 200 ml of deionized water which was used as a dispersion medium.

3.4 Bulk, tapped densities and compressibility

The bulk volumes for bulk density determination was recorded by weighing the 2 grams of spray dried powder, and transferred to 10 ml graduated cylinder and then tapped 3 times. For continuous tapping until a constant volume was obtained, a tapped volume was performed. Division of weight by this volume showed tapped density. Both densities were average of three determinations. The compressibility was calculated from the following equation.

$$\text{Percent Compressibility} = \frac{(T - B)}{T} \times 100$$

T and B are tapped and bulk densities, respectively.

3.5 Angle of repose

Angle of repose was determined by powder characteristics tester (Model PTN, Hosokawa Micron Corporation, Japan). The angle of repose was measured from a heap carefully built up by dropping the samples through a glass funnel to the horizontal plate. When the angle of repose came to the desired condition. Then, the angle measuring arm was moved by fingers to the position at which the angle of repose could be measured in accordance with the display. The angle of repose was averaged from three determinations.

4. Physicochemical properties of spray dried powders

4.1 Infrared spectroscopy

Infrared spectroscopy was used to confirm the change in the functional groups of the pure drug, physical mixture, spray dried PVAc, spray dried maltodextrin and spray dried drugs-PVAc powder by observing the positions and intensities of IR peaks.

The IR spectra of diltiazem hydrochloride, theophylline, furosemide and excipient in the matrices were examined using the potassium bromide disk (KBr) method with an infrared spectroscopy in the range of 4000-400 cm^{-1} (Infrared spectrometer Model FT-IR 1760X, Perkin Elmer, Germany).

4.2 Powder X-ray diffraction analysis

An X-ray diffractometry, which shows crystallinity and interplanar spacing of the crystal planes and determines the interaction between each component in spray dried powder, was used to determine the diffraction angle of the substance. The crystallinity of pure drug, physical mixture, spray dried PVAc, spray dried

maltodextrin and spray dried drugs-PVAc powder were examined by X-ray diffractometer (X-ray diffractometer Model JDX-8030, Jeol, Japan)

The powder were ground in the mortar and firmly packed in the cavity of a thin rectangular quartz slide by the other glass slide. The glass slide was taken off and the prepared sample was exposed to the X-ray beam in the X-ray diffraction chamber. The X-ray diffraction patterns were recorded at the speed of 0.04° per minute from 5° - 60° in the term of 2θ angle.

4.3 Differential scanning calorimetry (DSC)

DSC thermograms were determined by differential scanning calorimeter (Differntial scanning calorimeter Model DSC7, Perkin-Elmer, USA). The differences in thermal energy pattern between the original substances and their products were evaluated after spray drying. The DSC runs were conducted at the temperature range of 0 – 300 ºC with a scanning rate of 5 ºC/min.

5. Preparation of matrices

5.1 Preparation of drugs-PVAc matrices

The spray dried drugs-PVAc powder was compressed into matrix to have hardness of about 15 kp by hydraulic press using a 10 mm diameter round flat faced punch. The compression pressure was maintained for 10 second and quickly released. The compositions of each matrix are shown in Table 6.

Table 6 Composition of each matrix

Ingredient	Amount per matrix (mg)		
Active ingredient*	90	90	90
Polyvinyl acetate	45	90	135
Maltodextrin	45	45	45
Aerosil	1%	1%	1%
Magnesium stearate	1%	1%	1%

* diltiazem hydrochloride or theophylline anhydrous or furosemide

5.2 Preparation of placebo tablets

5.2.1 Formulation of placebo tablets

Under the condition selected for drug release studies, the peaks of non-active ingredients in the matrices must not interfere with the peak of the drugs. The placebo tablets of similar composition without the drugs were also prepared. The compositions of placebo tablet formulations are shown in Table 7.

Table 7 Formulation of placebo tablets

Ingredients	Amount per matrix (mg)
Polyvinyl acetate	135
Maltodextrin	45
Aerosil	1%
Magnesium stearate	1%

5.2.2 Preparation of placebo tablets

The procedure for preparation of placebo tablets was the same as that of drug-PVAc matrices. The 10–cm. diameter round flat faced punch and die were used to compress the placebo tablet. The tablet weight and hardness were adjusted to 183.6 mg and 7-9 kp, respectively.

6. Matrix evaluation

The following evaluation procedures were used for drugs-PVAc matrices.

6.1 Determination of weight variation

Weight variation test was carried out by weighing 20 tablets individually. The mean and standard deviation were calculated.

6.2 Determination of thickness

The thickness of matrix was determined using the Erweka tester and expressed in mm. The thickness was an average of ten determinations.

6.3 Determination of hardness

The hardness of matrix was determined using the Erweka tester. The mean and Standard deviation of ten determinations were calculated and expressed in kilopound (kp).

6.4 Determiantion of tablet friability

The friability was performed on 20 tablets using the Roche type friabilator. The drum was rotated at 25 rpm for 4 minutes. Loss of tablet weight with respect to the initial value was calculated as percent friability.

6.5 Disintegration Time

Disintegration time was determined according to the USP XXV method (Disintegration apparatus: Hanson Research Corporation, Model QC-21, USA). The average of disintegration time was evaluated in water at 37 $\pm$ 2 º C with disk.

6.6 Determination of diltiazem hydrochloride, theophylline anhydrous and furosemide content in matrices

6.6.1 Calibration curve for diltiazem hydrochloride, theophylline anhydrous and furosemide assay

A. Calibration curve of diltiazem hydrochloride assay

In order to make a standard curve, 250 mg of diltiazem hydrochloride was accurately weighed into a 100 ml volumetric flask through the aid of a glass funnel. The powder was dissolved and adjusted to volume with absolute methanol. The solution was used as the first stock solution. Four milliliters of the first stock solution was pipetted into the 100 ml volumetric flask and adjusted to volume as the second stock solution.

The 2, 3, 4, 5, 6 and 8 ml, respectively, of second stock solution were individually pipetted into 50 ml volumetric flasks. All solutions were adjusted to volume with absolute methanol. The final concentrations of each solution were 4, 6, 8, 10, 12 and 16 µg/ml, respectively.

The final solution was assayed spectrophotometrically at 235 nm (Ultraviolet/ visible recording spectrophotometer, Model V-530, Jasco, Japan). The absorbances and the calibration curves of diltiazem hydrochloride in absolute methanol are presented in Table 1A and Figure 1A, respectively, in Appendix A. Each concentration was determined in triplicate.

B. Calibration curve of theophylline anhydrous assay

In order to make a standard curve, 200 mg of theophylline was accurately weighed into a 100 ml volumetric flask through the aid of a glass funnel. The powder was dissolved and adjusted to volume with 6 N ammonium hydroxide. The solution was used as the first stock solution. Five milliliters of the first stock solution was pipetted into the 100 ml volumetric flask and adjusted to volume as the second stock solution.

The 2, 3, 4, 5, 6 and 8 ml, respectively, of second stock solution were individually pipetted into 50 ml volumetric flasks. All solutions were adjusted to volume with 6 N ammonium hydroxide. The final concentration of each solution were 4, 6, 8, 10, 12, 16 μg/ml, respectively.

The final solution was assayed spectrophotometrically at 272 nm. The absorbances and the calibration curves of theophylline anhydrous in 6 N ammonium hydroxide are presented in Table 5A and Figure 5A, respectively, in Appendix A. Each concentration was determined in triplicate.

C. Calibration curve of furosemide assay

In order to make a standard curve, 100 mg of furosemide was accurately weighed into a 100 ml volumetric flask through the aid of a glass funnel. The powder was dissolved and adjusted to volume with ethanol. The solution was used as the first stock solution. Five milliliters of the first stock solution was pipetted into the 100 ml volumetric flask and adjusted to volume as the second stock solution.

The 2, 3, 4, 5 ml, respectively, of second stock solution were individually pipetted into 50 ml volumetric flasks and 5 ml of second stock solution were individually pipetted into 100 ml volumetric flask. All solution were adjusted to volume with ethanol. The final concentrations of each solution were 4, 5, 6, 8, 10 μg/ml, respectively.

The final solution was assayed spectrophotometrically at 277 nm. The absorbances and the calibration curves of furosemide in ethanol are presented in Table 9A and Figure 9A, respectively, in Appendix A. Each concentration was determined in triplicate.

6.6.2 Assay of diltiazem hydrochloride, theophylline anhydrous and furosemide in matrices

D-PVAc, T-PVAc and F-PVAc matrix tablets were ground with mortar and pestle and were accurately weighed into a 100 ml volumetric flask. The powders were extracted with suitable solvent by the aid of a sonicator for 1 hour, then adjusted to volume with solvent and mixed thoroughly. The solution was filtered through filter paper and used as stock solution. One ml of the stock solution was individually pipetted into a 100 ml volumetric flask, then adjusted to volume with solvent and mixed.

The absorbance of diltiazem hydrochloride, theophylline and furosemide was determined by UV/VIS spectrophotometry at 235, 272 and 277 nm, respectively. Amount of drug content was calculated from the calibration curve in Tables 1A, 5A, 7A and Figures 1A, 5A, 7A, respectively, in Appendix A. Each sample was determined in triplicate.

6.7 Dissolution Studies

6.7.1 Calibration curve of diltiazem hydrochloride, theophylline anhydrous and furosemide

6.7.1.1 Calibration curve of diltiazem hydrochloride in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution

In order to make a standard curve, 250 mg of diltiazem hydrochloride was accurately weighed into a 100 ml volumetric flask through the aid of a glass funnel. The powder was dissolved and adjusted to volume with deionized water or 0.1 N HCl solution or PBS pH 6.8. The solution was used as the first stock solution. Four milliliters of the first stock solution was pipetted into the 100 ml volumetric flask and adjusted to volume as the second stock solution.

The 2, 3, 4, 5, 6 and 8 ml, respectively, of second stock solution were individually pipetted into 50 ml volumetric flasks. All solutions were adjusted to volume with each medium. The final concentrations of each solution were 4, 6, 8, 10, 12, 16 μg/ml, respectively.

The absorbance was assayed spectrophotometrically at 236 nm. The absorbances and the calibration curves of diltiazem hydrochloride in each medium are presented in Tables 2A-4A and Figures 2A-4A, respectively, in Appendix A. Each concentration was determined in triplicate.

6.7.1.2 Calibration curve of theophylline anhydrous in deionized water, 0.1 N HCl and solution and PBS pH 6.8 solution

In order to make a standard curve, 200 mg of theophylline was accurately weighed into a 100 ml volumetric flask through the aid of a glass funnel. The powder was dissolved and adjusted to volume with deionized water or 0.1 N HCl solution or PBS pH 6.8.. The solution was used as the first stock solution. Five milliliters of the first stock solution was pipetted into a 100 ml volumetric flask and adjusted to volume as the second stock solution.

The 2, 3, 4, 5, 6 and 8 ml, respectively, of second stock solution were individually pipetted into 50 ml volumetric flasks. All solutions were adjusted to volume with each medium. The final concentrations of each solution were 4, 6, 8, 10, 12, 16 μg/ml, respectively.

The final solution was assayed spectrophotometrically at 272 nm. The absorbance and the calibration curve of theophylline anhydrous in deionized water are presented in Tables 5A-7A and Figures 5A-7A, respectively, in Appendix A. Each concentration was determined in triplicate.

6.7.1.3 Calibration curve of furosemide in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution

In order to make a standard curve, 100 mg of furosemide was accurately weighed into a 100 ml volumetric flask through the aid of a glass funnel. The powder was dissolved and adjusted to volume with deionized water or 0.1 N HCl solution or PBS pH 6.8. The solution was used as the first stock solution. Five milliliter of the first stock solution was pipetted into the 100 ml volumetric flask and adjusted to volume as the second stock solution.

The 2, 3, 4, 5 ml, respectively, of second stock solution were individually pipetted into 50 ml volumetric flasks and 5 ml of second stock solution were individually pipetted into 100 ml volumetric flask All solutions were adjusted to volume with each medium. The final concentrations of each solution were 4, 5, 6, 8, 10 µg/ml, respectively.

The final solution was assayed spectrophotometrically at 272 nm. The absorbances and the calibration curves of furosemide in deionized water are presented in Tables 10A-12A and Figures 10A-12A, respectively, in Appendix A. Each concentration was determined in triplicate.

6.7.2 Dissolution Studies

The Dissolution tests of matrix tablets were performed using USP XXIV dissolution test apparatus 2 (paddle method). Nine hundred milliliters of deionized water, 0.1 N HCl solution, PBS pH 6.8 solution and pH-changed solution were used as dissolution medium. Stirring rate was maintained at 100 rpm at temperature of 37$\pm$ 0.5 º C. The dissolution test of each formulation was done in tripicate.

The sample of 10 ml was withdrawn at the time intervals of 0.08, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hrs. The same volume of the medium at that time was added immediately after each sampling to keep the constant volume of the medium in the vessel throughout the experiment.

Each sample was filtered through filter paper. The filtrate was diluted to a suitable concentration assayed by spectrophotometrically at the maximum wavelength in each dissolution medium.

The amount of diltiazem hydrochloride, theophylline anhydrous and furosemide release at any times were calculated from the calibration curve for each dissolution medium. A cumulative correction was achieved for the previously removed sample to determine the total amount of the drug release. Each of the dissolution values reported was based on an average of three determinations of each formulation.

6.7.3 Study on the effect of compression force

The spray dried powders (D-PVAc 1:1, Theophylline anhydrous-PVAc 1:0.5, F-PVAc 1:0.5) were compressed into matrices at three compressional pressures of 300, 500 and 1,000 lbs by the hydraulic press, and the relationships of compression force and release behaviors were evaluated.

6.7.4 Dissolution studies of placebo tablets

The objective of the dissolution studies of placebo tablets was to verify specificity of the method for quantitative analysis of drug release. Dissolution test of high polymer containing formulation was performed in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution. The samples were withdrawn at the time intervals of 1, 6 and 12 hours. The concentrations of sample were determined without further dilution. The results obtained from the dissolution studies of placebo tablets are shown in Appendix B.

6.7.5 Data analysis

The dissolution data were fitted according to the following well-known exponential equation given below, which is often used to describe the drug release behavior from polymeric systems:

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t / M_∞ is the fraction of drug released, t is the release time, k is a kinetic constant (with units of t^{-n}) incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release. This equation can be used to analyze the first 60% of a release profile where the release profile is linearly related to t^{-n}, regardless of geometric shape (Ritger and Peppas, 1987). Values for n and k for each matrix formulation were obtained by plotting the logarithm of the fractional release against the logarithm of time. The slope

of the line is n while log k is the intercept. The drug release data were plotted using values of M_t / M_∞ within the range of 0-0.60.

Many studies attempted to use flexible parameter as framework to correlate the most suitable relationship of drug release profile. For example, $t_{x\%}$ is a most popular variable to employ as forecasting parameter which mean the time at fix % drug release such as $t_{50\%}$ (time to 50% drug release). Although $t_{x\%}$ is a well known approach but they are not probably appropriate as description parameter. Several researches usually employ rate constant value of individual dissolution profile to find out the relationship among them. The disadvantage of this approach was the unidentical drug release mechanism of each profile. Thereby, it will lead to deficiency comparison. Futhermore, the constant k is one of the measures of the drug release rate, it should not be used for comparison because different kinetics are usually involved in different test conditions (Talukdar et al., 1996). Therefore, relative dissolution time (RDT) is introduced to overcome the previous problem. RDT is the parameter that all part of dissolution profile is governed in the calculation and value. Trapezoidal of area between curve (ABC) is one of the most widely used as computing procedures of RDT determination.

The computation of RDT was performed and ascribed by using following equation

$$RDT = \frac{ABC}{M_\alpha}$$

This equation was calculated based on that for determining mean dissolution time MDT (Brockmeier and Hattingberg, 1982).

The diagrammatic of dissolution profile for explaining RDT calculation is illustrated in Figure 2

Figure 2 Diagrammatic of dissolution profile for explaining RDT calculation. ABC is area between upper line (M_α) and dissolution curve, M_α is maximum drug release at infinite time and M_t is amount of drug release at any time t.

ABC was calculated indirectly by substracting total area (M_α multiplied with time function) with area under dissolution curve (AUC). The trapezoidal method was used to calculate AUC

In this study, relative dissolution time (RDT) was calculated from dissolution data for 12 hours and was used for comparing the release profile under different test conditions.

6.8 Surface morphology of PVAc matrices

All formulation of drugs-PVAc matrices were investigated for their surface morphology by scanning electron microscopy. The matrices were investigated both before and after dissolution test. In preparation of scanning electron microscopy, tablet of each formulation was hydrated in deionized water, 0.1 N HCl solution , PBS pH 6.8 solution using the same condition of dissolution test. Afterwards, these matrix tablets at 12 hours were dried in a desiccator at room temperature. The dried matrices with constant weight were used to investigate for their surface morphology. The sample was positioned on the sample holder and then observed after it had been coated with gold.

CHAPTER IV

RESULTS AND DISCUSSION

1. Solubility determination

The solubility of diltiazem hydrochloride, theophylline and furosemide in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution are presented in Table 8.

Table 8 Solubility of diltiazem hydrochloride, theophylline and furosemide in various mediums.

Medium	Solubility (mg/ml)		
	Diltiazem hydrocloride	Theophylline	Furosemide
deionized water	544.16 $\pm$ 13.22	11.51 $\pm$ 0.11	0.08 $\pm$ 0.001
0.1 N HCl	562.78 $\pm$ 13.54	13.26 $\pm$ 0.08	0.03 $\pm$ 0.001
PBS pH 6.8	527.68 $\pm$ 26.44	10.68 $\pm$ 0.14	5.24 $\pm$ 0.14

The results found that solubility of diltiazem hydrochloride in 0.1 N HCl solution was higher than its solubility in deionized water and PBS pH 6.8 solution, respectively. This result could be explained by the pKa of diltiazem hydrochloride, which is 7.7 thus a decreasing in pH resulted in an increasing in the ionized form of diltiazem hydrochloride. Therefore, its solubility was higher solubility in the acid medium. The solubility of theophylline in 0.1 N HCl solution, deionized water and PBS pH 6.8 solution was comparable. The pH-solubility profile of theophylline is shown in Figure 1H (Appendix H), the solubility of thephylline was similar between the pH of 2-8.5 (Strafford et al.). The solubility of furosemide in PBS pH 6.8 solution was higher than these in deionized water and 0.1 N HCl solution, respectively. According to the results in Table 8, it is evident that the solubility of furosemide

depends on pH of the medium. Furosemide is a weak acid, therefore, the solubility strongly depends on the pH of the medium.

According to USP 25, the number of parts of water required for dissolving 1 part of the drug are lower than 1 for very soluble (> 1000 mg/ml), 1-10 for freely soluble (1000-100 mg/ml), 10-30 for soluble (100-33.33 mg/ml), 30-100 for sparingly soluble (33.33-10 mg/ml), and 100-1000 for slightly soluble drugs (10-1 mg/ml). The solubility of diltiazem hydrochloride, theophylline and furosemide in deionized water were 544.16 $\pm$ 13.22, 11.51 $\pm$ 0.11 and 0.08 $\pm$ 0.001mg/ml, respectively. Their solubilities in 0.1 N HCl solution were 562.78 $\pm$ 13.54, 13.26 $\pm$ 0.08 and 0.03 $\pm$ 0.001mg/ml, respectively. Their solubilities in PBS pH 6.8 solution were 527.68 $\pm$ 26.44, 10.68 $\pm$ 0.14 and 5.24 $\pm$ 0.14, respectively. Therefore, their solubilities confirmed that diltiazem hydrochloride was a freely soluble model drug, theophylline was a sparing soluble drug and furosemide was a slightly soluble drug.

2. Drug content

The percent drug content of spray dried drugs – PVAc powders prepared from different drug to polymer ratios are presented in Table 9. The small standard deviation shown implied the uniformity of drug distribution in spray dried powders. The data revealed that the amount of PVAc did not influence the drug distribution. In addition, the good uniformity of drug distribution in spray dried drug – PVAc powder was obtained. These findings were attributed to the fact that the spray dispersion offered excellent homogeneity of drug, polymer and excipient, since they were dissolved in the solvent system.

Table 9 The percent of drug content of spray dried product.

Formulation	Drug to polymer ratio	% Drug content	
		Collector	Chamber
D-PVAc	1:0.5	101.83 ± 1.49	101.83 ± 1.49
	1:1	102.00 ± 1.35	100.98 ± 0.49
	1:1.5	99.99± 1.15	98.74 ± 0.36
T-PVAc	1:0.5	102.98± 0.62	101.72 ± 0.64
	1:1	102.53 ± 0.21	101.73 ± 0.46
	1:1.5	102.31± 0.41	101.68 ± 0.29
F-PVAc	1:0.5	97.75 ± 0.20	96.77 ± 0.48
	1:1	96.64 ± 0.32	95.26 ± 0.26
	1:1.5	95.93 ± 0.32	94.40 ± 0.23

3. Evaluation of physical properties of spray dried drugs– PVAc powder

3.1 Moisture Determination

The moisture content of spray dried drug – PVAc powders prepared from various formulations are shown in Table 10. The drug to polymer ratio had no significant effect on the moisture content of the powders. The percentage of moisture content of spray dried powders ranged from 2.15 – 3.15 %. The product of F-PVAc provided the higher moisture content. This result might be explained in Section 3.2.3

Table 10 The percentage moisture content of spray dried products at various formulations.

Formulation	Drug to polymer ratio	% Moisture content
D-PVAc	1:0.5	2.50 ± 0.04
	1:1	2.45 ± 0.02
	1:1.5	2.52 ± 0.02
T-PVAc	1:0.5	2.10 ± 0.53
	1:1	2.29 ± 0.03
	1:1.5	2.15 ± 0.02
F-PVAc	1:0.5	3.10 ± 0.04
	1:1	2.98 ± 0.05
	1:1.5	3.15 ± 0.03

3.2 Morphology of drugs-PVAc prepared by different drug to polymer ratio.

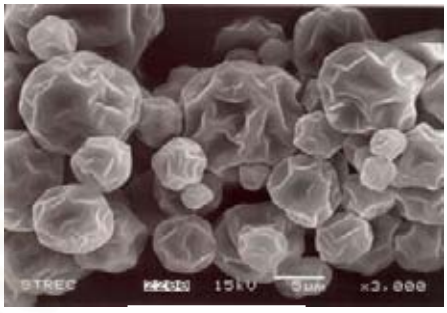
3.2.1 Diltiazem hydrochloride

Figure 3A shows a scanning electron photomicrograph of diltiazem hydrochloride drug powder. Diltiazem hydrochloride appeared in rhombic crystals form of various sizes.

Scanning electron photomicrographs of diltiazem hydrochloride-PVAc spray dried powders (D-PVAc) are shown in Figures 3B-3D. The shape and surface topography of D-PVAc powders prepared at different drug to polymer ratios were found to be affected by the drug to polymer ratio in the formulation. A higher number of agglomerates were formed when the drug to polymer ratio was increased. Because of some of the small particles were attached to each other and/or attached to the large particles.

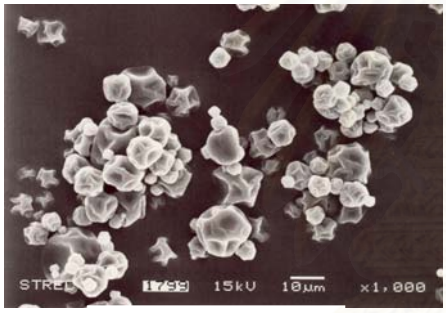
A (x100)

(x1000)

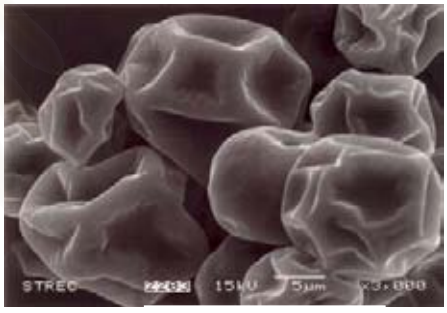


(x 3000)

(B) drug to polymer ratio of 1:0.5

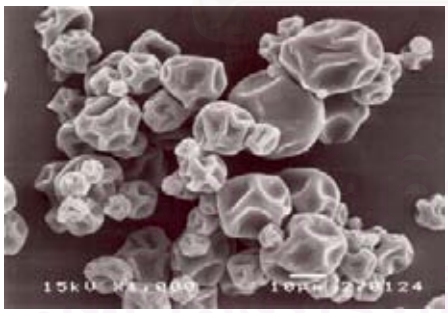


(x1000)

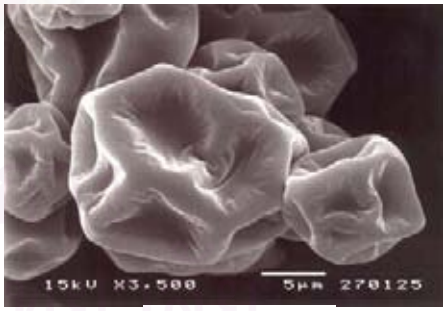


(x3000)

(C) drug to polymer ratio of 1:1



(x1000)

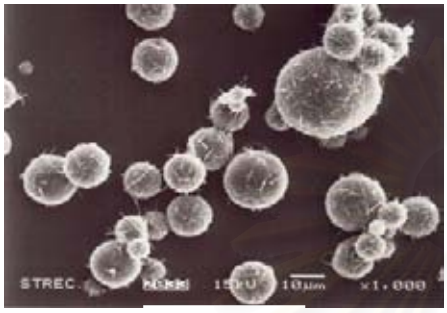


(x3000)

(D) drug to polymer ratio of 1:1.5

Figure 3 Photomicrographs of original diltiazem hydrochloride powder and D-PVAc powder prepared at different drug to polymer ratio (A) pure diltiazem hydrochloride, (B) drug to polymer ratio of 1:0.5, (C) drug to polymer ratio of 1:1 and (D) drug to polymer ratio of 1:1.5.

A (x100)



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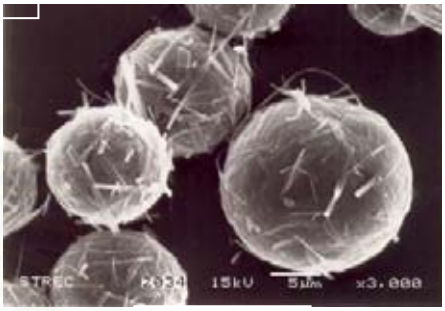

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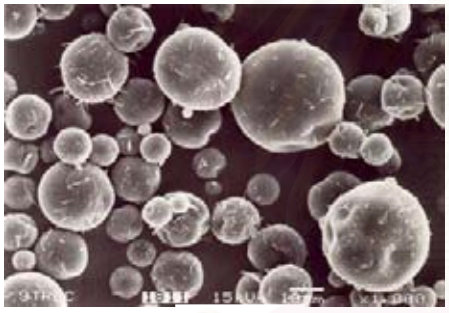
(B) drug to polymer ratio of 1:0.5



(x1000)

(x3000)

(C) drug to polymer ratio of 1:1

(x1000)

(x3000)

(D) drug to polymer ratio of 1:1.5

Figure 4 Photomicrographs of original theophylline powder and T-PVAc powder prepared at different drug to polymer ratio (A) pure theophylline, (B) drug to polymer ratio of 1:0.5, (C) drug to polymer ratio of 1:1 and (D) drug to polymer ratio of 1:1.5.

The D-PVAc powder particles were partly shrunk. Lin et al. (1991) suggested that the shrinkages of the surface wall were due to the entrapped air bubbles expanding considerably at higher drying temperature, a process that was offset partially by the loss of water. Deep indentations in the microcapsules were also found occasionally, which was probably the result of water loss from the drying droplets during the early stage of processing. This result was similar to previous studied from spray dried sulbutamol sulphate with APG-surfactant (Columbano et al., 2003). Futhermore, the partial shunkage of D-PVAc particles might suggest that the incompleted water evaporation from the particles during the spray drying process and then the particles was kept in the collector. In this step, the loss of water from particles might be occurred.

The surface of spray dried D-PVAc particle was smooth and no drug crystal was observed on the surface. The D-PVAc powders appeared homogenous, with no drug crystals. The results indicated that diltiazem hydrochloride and PVAc were presented as solid dispersion within the structure of the drug and/or on the surface of the particles. This behavior was similar to previous study of diltiazem hydrochloride spray drying with Eudragit® RS and Eudragit® RL (Kristmundsdottir, 1996). They reported that the drug crystal or irregularities was not observed on the surface of microparticle.

3.2.2 Theophylline

Scanning electron photomicrographs of theophylline drug powder are shown in Figure 4A. Theophylline crystals appeared in different size.

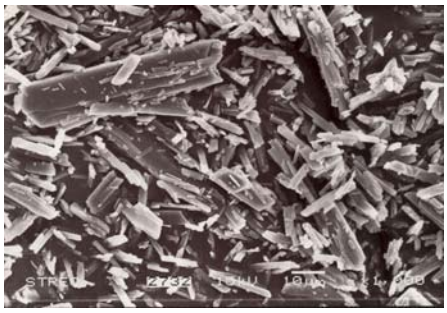
The shape and surface topography of theophylline-PVAc spray dried powders (T-PVAc) prepared at various drug to polymer ratio are displayed in Figure 4B-4D. The size of T-PVAc powder having different PVAc content was comparable. The scanning electron photomicrograph shows that some of the very small spheres were found attached to the large particles. The surface of T-PVAc was covered with microcrystals that presented a rough surface but some of them had rather smooth surfaces. The T-PVAc produced at drug to polymer ratio 1:1.5 gave smoother surfaces than those produced using drug to polymer ratio of 1:0.5 and 1:1. The similar

characteristics of particles and the formation of these particles were observed and explained by Wan et al. (1990). They suggested that on drying a droplet atomized from a solution feed, there was formation of a polymeric solid crust. Subsequently, water within the crust evaporated, carrying dissolved and undissolved drug particle to the surface of the crust. This was evident by the deposition of rod-like particles on the surface of the microspheres. Furthermore, the similar observations of SEM of theophylline were reported. Several researchers (Palmieri et al., 1994; Kulvanich et al., 2002 and Asada et al., 2004) found that the surface of theophylline-polymer spray dried powder was covered with microcrystal of the drug.

3.2.3 Furosemide

The shape and surface topography of original furosemide powder is presented in Figure 5A. Furosemide crystals were irregular shapes of various sizes.

The shape and surface topography of furosemide-PVAc spray dried powders (F-PVAc) when changing the drug to polymer ratios are shown in Figures 5B-5D. The shape of F-PVAc powder was spherical. The surface of some particles was shrunk and some of them had an orange peel texture. The agglomeration of particle was increased when the content of PVAc was increased. Some small particles were attached to the large particles. The products obtained from F-PVAc powder had a smaller particle size than those obtained from D-PVAc and T-PVAc powder. Thus, the F-PVAc powder gave the higher moisture content. This result might be explained by the smaller paticle size resulted in a higher surface area of particle, which could adsorb the moisture and made the powder more cohesive. Moreover, the higher moisture content affected the flow properties of the powder. This result will be discussed in Section 3.4. The surface of F-PVAc powder was smooth and the drug crystal on the surface was not obsevrved. Thus, the F-PVAc powder might be in the form of solid dispersion or solid solution. This characteristic could be confirmed by the physicochemical properties of F-PVAc powder in Section 4.1-4.3



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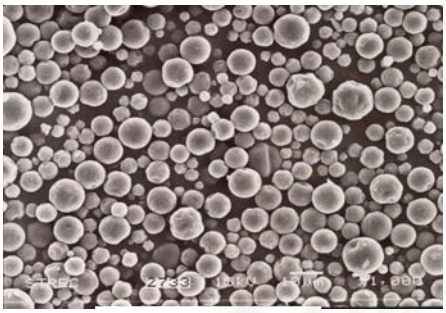

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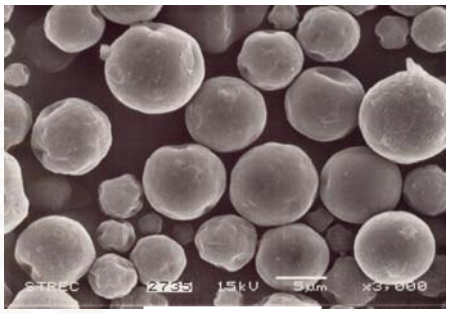

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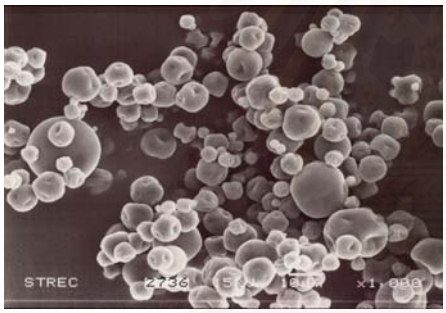
(B) drug to polymer ratio of 1:0.5



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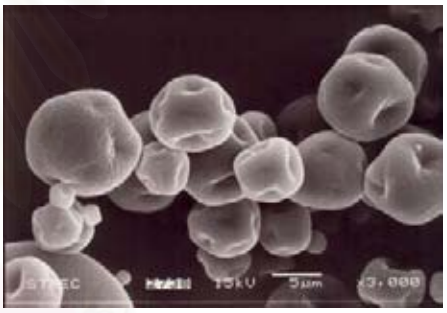

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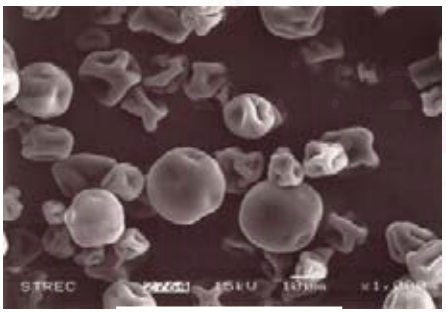
(C) drug to polymer ratio of 1:1



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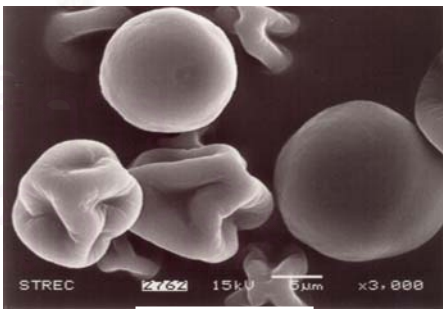


(x 3000)

(D) drug to polymer ratio of 1:1.5

Figure 5 Photomicrographs of original furosemide powder and F-PVAc powder prepared at different drug to polymer ratio (A) pure furosemide, (B) drug to polymer ratio of 1:0.5, (C) drug to polymer ratio of 1:1 and (D) drug to polymer ratio of 1:1.5.

3.3 Particle size distribution

The particle size distributions of the powders are shown in Table 11.

Table 11 The particle size distributions of spray dried drugs– PVAc powders.

Formulation	Drug to polymer ratio	Average D10	Average D50	Average D90	Span
D-PVAc	1:0.5	3.03 ± 0.15	14.15 ± 0.22	29.02 ± 1.35	1.84 ± 0.07
	1:1	7.79 ± 0.04	23.02 ± 0.45	52.73 ± 1.81	1.95 ± 0.0.6
	1:1.5	7.49 ± 0.37	26.77 ± 1.57	109.28 ± 9.52	3.80 ± 0.14
T-PVAc	1:0.5	5.24 ±0.25	13.02 ± 0.38	29.33 ± 2.65	1.85 ± 0.16
	1:1	5.58 ± 0.15	20.04 ± 0.56	40.74 ± 2.10	1.75 ± 0.05
	1:1.5	8.84 ± 0.25	32.11 ± 0.61	77.57 ± 2.73	2.14 ± 0.04
F-PVAc	1:0.5	5.18 ± 0.14	25.77 ± 0.18	74.30 ± 0.49	2.68 ± 0.05
	1:1	4.88 ± 0.03	24.24 ± 0.25	84.12 ± 3.33	3.27 ± 0.11
	1:1.5	2.84 ± 0.03	13.46 ± 0.34	34.75 ± 2.22	2.37 ± 0.06

Spray drying is one step process transforming liquid into a dried particulate form. Qualitative and quantitative composition of liquid feed and drying conditions strongly affects properties of the spray dried particles such as size, morphology, density, shape, porosity and flowability (Sacchetti et al., 2001). Usaully, spray dried powders are resulting in almost spherical and amorphous microparticle (Vidgren et al., 1987), with a range of median diameter between 2 and 50 micron and a narrow size distribution (Broadhead et al., 1992).

In this study, the geometric mean diameter (D_{50}), the size at 50% cumulative frequency plotted on probability scale, was determined and compared between different formulations of spray dried powders. Frequency distribution plot of spray dried drug –PVAc powders were shown in Appendix D.

The mean particle size of spray dried powders were 14.15, 23.02 and 26.77 mm. for D-PVAc powders. The mean particle sizes of T-PVAc powders were 13.02, 20.04 and 32.11 mm. and 25.77, 24.24 and 13.46 for F-PVAc. The increasing proportion of PVAc in spray dried drug – PVAc powders resulted in larger particle sizes. This effect could be observed in D-PVAc and T-PVAc powders. This might be attributed to the effect of appeared viscosity of spray dispertion. It was found that the dispersion with higher PVAc concentration had higher viscosity. Increasing viscosity of the feed solution could increase the dried particle size by increasing the size of the wet droplet formed during spraying. This observation was similar to that observed by Master (1985) and Clarke (1998), who reported that an increase in particle size was the result of an increase in the concentration and viscosity of spray drying solution. However, the particle size of F-PVAc mean by particle size analyzer showed a decreasing in D_{50} when increasing polymer concentration. This result was contradictory to the results obtained for the other spray dried drugs – PVAc powder. However, by observation on SEM photograph, It was observed that particle size of F-PVAc at an increasing polymer content was larger than low polymer content powder.

The SEM observation showed that the size of the microsphere ranged from 8 to 10 micron. However, the analysis of particle size using the light scattering method shows that the mean diameter of the drugs-PVAc powder was lager than 15 micron (Table 11). The operation temperature of spray dring (120º C) was higher the the glass transition temperature (Tg) of PVAc (35-40º C), resulting in the aggregated microspheres during the analysis of particle size distribution. Thus, a larger mean of diameter was detected compared to the actual particle size. From the result of this study, it might be suggested that SEM observation method gave the closer actual particle size than than light scattering method.

3.4 Angle of repose, bulk, tapped density and %compressibility

Angle of repose, bulk density, tapped density and compressibility of spray dried drug – PVAc powders prepared at different drug to polymer ratio are shown in Table 12. Angle of repose, density and %compressibility indicated the flowability of powders.

Table 12 Angle of Repose, bulk density, tapped density and %compressibility of spray dried drugs – PVAc powder.

Formulation	Drug to Polymer	Angle of Repose	Bulk Density (g/ml)	Tapped Density(g/ml)	Compressibility (%)
D-PVAc	1:0.5	52.30 ± 0.55	0.272 ± 0.002	0.370 ± 0.000	26.69
	1:1	55.56 ± 0.47	0.267 ± 0.000	0.375 ± 0.004	28.89
	1:1.5	55.06 ± 0.41	0.234 ± 0.002	0.366 ± 0.010	35.97
T-PVAc	1:0.5	34.90 ± 0.26	0.289 ± 0.05	0.380 ± 0.004	24.03
	1:1	47.43 ± 0.20	0.214 ± 0.001	0.311 ± 0.003	31.32
	1:1.5	47.33 ± 0.15	0.201 ± 0.001	0.309 ± 0.003	35.12
F-PVAc	1:0.5	53.26 ± 0.11	0.268 ± 0.002	0.405 ± 0.005	33.93
	1:1	57.43 ± 0.25	0.246 ± 0.002	0.373 ± 0.008	34.03
	1:1.5	65.33 ± 0.20	0.251 ± 0.002	0.382 ± 0.004	34.31

In this study, the angle of repose of spray dried products was determined by a powder characteristics tester. The angle of repose value tended to increase when content of polymer increased. It was found that the amount of polymer seemed to have slight effect on the angle of repose of spray dried drug - PVAc powders. In addition, T-PVAc exhibited a lower angle of repose than D-PVAc powders due to T-

PVAc particles were more spherical than the D-PVAc powders. This result could be supported by the particle shape of spray dried powder due to the particle shape is an important factor in powder flow. Powders consisting of spherical shape reduce interparticle friction (Oneda et al, 2003) and decreased the cohesiveness or the bridges between the particles.

In contrary, F-PVAc powders showed a higher angle of repose than D-PVAc powders although particles of F-PVAc were spherical than D-PVAC powders. This result could be explained by the F-PVAc powders had the higher moisture content (Table 10) lead to flow problems because of the formation of liquid bridges between the particle (Pather et al., 1998).

All the spray dried products of D-PVAc and F-PVAc had angle of repose of approximately higher than 50°. The T-PVAc powders had angle of repose of 34.9°, 47.43° and 47.33° depending on the polymer ratios. It has been concluded that values of angle of repose are lower than 40° generally indicates a free-flowing material and angle of repose values are higher than 40° suggests a poor flowing material (Todd, 1995). From the above data (Table 12), the D-PVAc, T-PVAc (ratio 1:1 and 1:1.5) and F-PVAc powders exhibited poor flowability. The reason for the poor flow included the presence of electrostatic charge, some nonspherical particles due to collapsing of the spray dried partcles (Foster and Leatherman, 1995). Lin and Kao (1991) also reported that the spray dried products exhibited very poor flowability due to the formation of many small particles.

Table 12 shows that an increase in PVAc content resulted in a decrease in both bulk density and tapped density. Generally, the particles with high density and low internal porosity tended to posses free-flowing characteristics (Nagel and Peck, 2003). The spray drying process produces approximately spherical with narrow size range and generally hollow particles. The hollow nature imparts a low bulk density to the powders (Broadhead et al., 1992). A difference in the density of the drugs-PVAc powder might be influenced by the concentration of the PVAc (See Table 12). In addition, among the three level of PVAc, the lowest PVAc content provided the most

bulky powder. It might be said that the lower PVAc content showed the better flow property than the higher PVAc content.

Compressibility of powder is also related to the flowability of a powder. The higher flowability of powder, the lower value of compressibility was obtained. Compressibility Index value smaller than 20% was suggested excellent flowability of powder (Carr, 1965). Table 12 shows that the compressibility of spray dried product were in the range 24.03 – 35.97. The highest compressibility of D-PVAc, T-PVAc and F-PVAc powders were obtained from ratio of PVAc at 1.5. This result could be suggested that the spray-dried powder had poor flowability.

However, the flow property of spray dried drugs-PVAc powder was contradictory to the result of SEM observation. The SEM observation showed that a increase in PVAc content resulted in a increase in agglomerated powder which caused the larger particle size. The larger particles size should led to the better flowability. Nevertheless, the flow characteristics (angle of repose, bulk density, tapped density and %compressibility) provide that an increase in particle size (corresponding to increase in PVAc content) exhibited a decrease in flowability. This result might be caused by the stickiness of polymer. When increasing in PVAc content resulted in a increase in stickiness of drugs-PVAc powder. It was found that the stickiness of PVAc caused poor flowability of drugs-PVAc powder. This might be concluded that the stickiness of PVAc was the important factor to predict the flow property.

4. Physicochemical properties of spray dried powder

4.1 Powder X-ray diffractometry

4.1.1 Powder X-ray diffractograms of spray dried PVAc and spray dried maltodextrin.

The powder X-ray diffractograms of spray dried PVAc and spray dried maltodextrin are displayed in Figure 6F and 6G. The diffraction patterns of spray drying PVAc and maltodextrin showed halo pattern of amorphous characteristics.

4.1.2 Powder X-ray diffratograms of the drugs, the physical mixture of drugs with spray dried PVAc, maltodextrin and the drugs-PVAc powder.

The X-ray diffractograms of diltiazem hydrochloride, the physical mixture of diltiazem hydrochloride with spray dried PVAc; spray dried maltodextrin and the D-PVAc powder at various polymer ratios are shown in Figure 6A-6E.

The diffractograms of diltiazem hydrochloride exhibited a series of intense peak, which indicative of their crystalline characteristic. Furthermore, the physical mixture of thses drug with PVAc exhibited crystalline form. But the x-ray diffracttion patterns of diltiazem hydrochloride are shown to have halo pattern of amorphous characteristics after spray drying with PVAc. According to the fact that powders obtained from spray drying technique usually shows broader peaks of amorphous forms. These were no difference between the diffraction patterns of their samples with difference in polymer ratio. This reduction in crystallinity was complete in the D-PVAc powders, showing a diffraction pattern completely diffuse, which revealed its amorphousness. These results might be attribute to a solid dispersion between diltiazem hydrochloride and PVAc in spray dried product, suggesting the presence of a new solid phase with lower crystallinity than the pure drug (Hassan et al., 1990), where a possible solid dispersion of diltiazem hydrochloride was contemplated (Moyano et al., 1995). Similar results have been reported from Eudragit microsphere containing nicardippine hydrochloride (Yuksel et al., 1996) and Eudragit microcapsule of nifedipine (Chowdary and Sankar, 1997).

The X-ray diffractograms of theophylline, the physical mixture of theophylline with spray dried PVAc; spray dried maltodextrin and the T-PVAc powders are shown in Figure 7A-7E. The X-ray diffraction of theophylline alone showed that drug was crystalline in nature as indicated by numerous distinctive diffraction peaks. This result confirmed that theophylline was in crystalline characteristic. X-ray diffraction patterns of the physical mixtures were similar to the pure theophylline. The characteristic crystalline peak of theophylline was also observed for the polymer-

theophylline physical mixtures but the peak size was reduced. The X-ray pattern of T-PVAc seemed to be partial crystalline. It was observed that the intensities of the diffration peaks of T-PVAc were weakening than that of theophylline. The degree of crystallinity was reduced due to some crystalline characteristics of these products converted to an amorphous form. This revealed that the major part of the drug transformed to the amorphous state, whereas a small part was in crystalline form. This was in agreement with the SEM observation of the T-PVAc powder because the surface of T-PVAc powder was covered with drug microcrystal (Figure 4B-4D). This similar result have been studied from Eudragit L100-55 microsphere containing theophylline (Takeuchi et al., 1989), ethyl cellulose co-spray dried powder containing theophylline (Leesawat, 1991) and theophylline-chitosan solid dispersion. They found that theophylline in spray dried particle of theophylline-Eudragit L100-55 theophylline- ethyl cellulose and theophylline-chitosan was not perfectly transformed into amorphous state.

In comparison of the peak of pure theophylline and T-PVAc powder, the X-ray diffraction peak of those was different. The peak of T-PVAc powder was shifted to the lower degree of diffraction pattern. This result might be caused by the polymorphic change of theophylline. From the previous study, Suzuki et al., (1989) reported that anhydrous theophylline exhibited polymorphism and two modifications, which were named as form I and form II. In this work, the polymorphism of theophylline was found. The pure theophylline displayed a theophylline anhydrous form II whereas the T-PVAc powder showed a theophylline anhydrous form I.

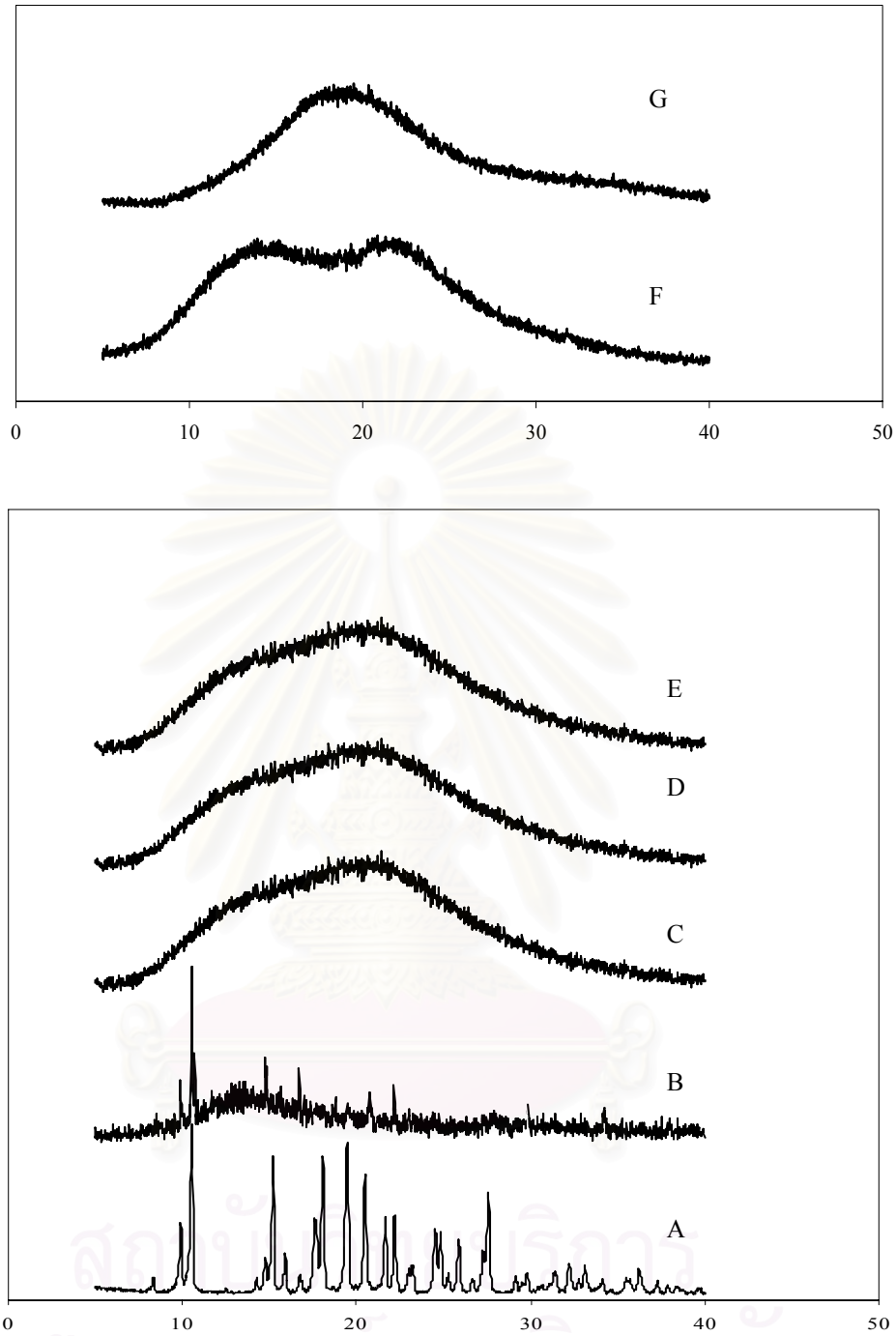


Figure 6 X-ray diffratogram of diltiazem hydrochloride, D-PVAc systems spray dried PVAc and spray dried maltodextrin. (A) Diltiazem hydrochloride, (B) Physical mixture at drug to polymer ratio 1:1, (C) D-PVAc at drug to polymer ratio of 1:0.5, (D) D-PVAc at drug to polymer ratio of 1:1, (E) D-PVAc at drug to polymer ratio of 1:1.5, (F) Spray dried PVAc and (G) Spray dried maltodextrin.

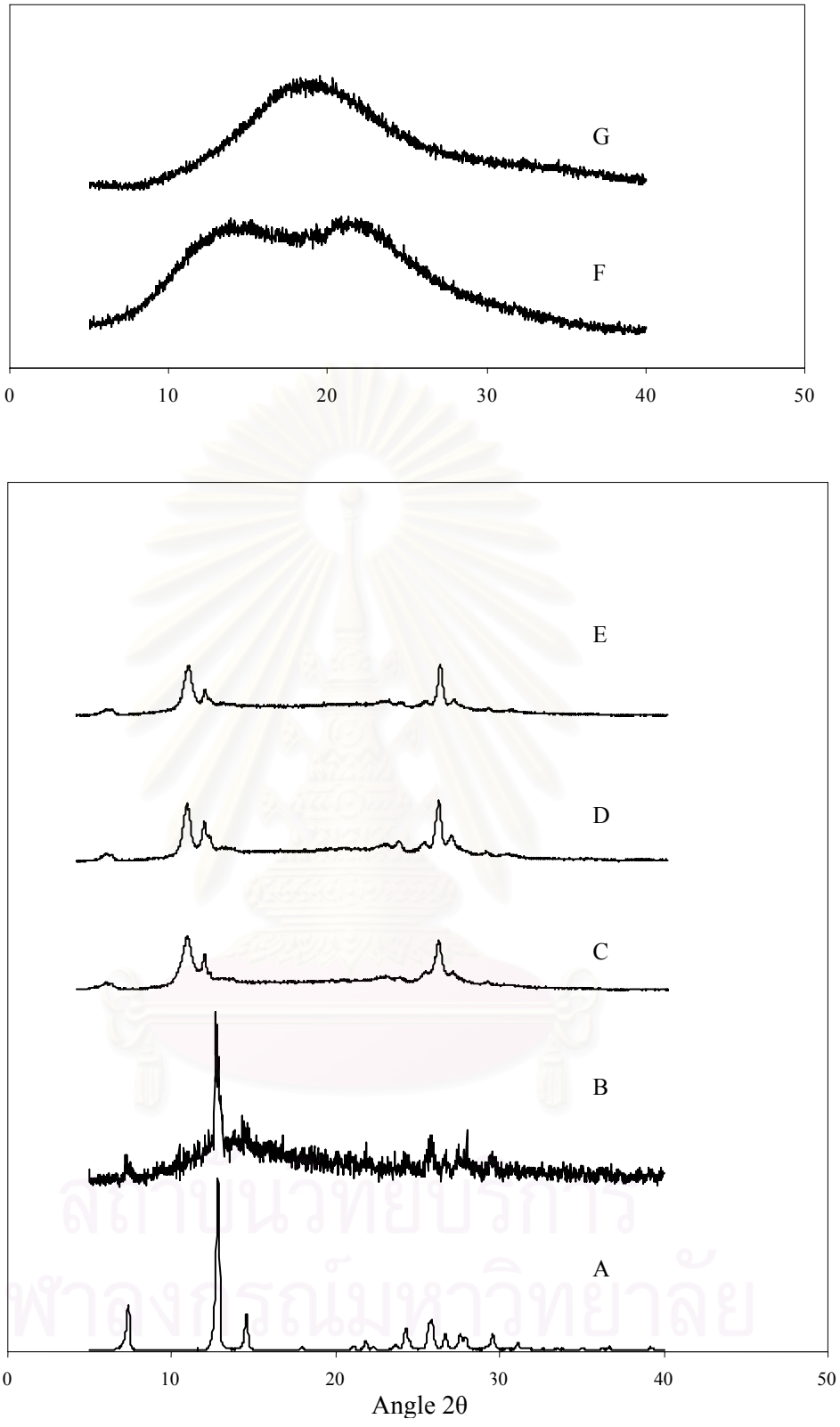


Figure 7 X-ray diffratogram of theophylline, T-PVAc systems spray dried PVAc and spray dried maltodextrin. (A) Theophylline, (B) Physical mixture at drug to polymer ratio 1:1, (C) T-PVAc at drug to polymer ratio of 1:0.5, (D) T-PVAc at drug to polymer ratio of 1:1, (E) T-PVAc at drug to polymer ratio of 1:1.5, (F) Spray dried PVAc and (G) Spray dried maltodextrin.

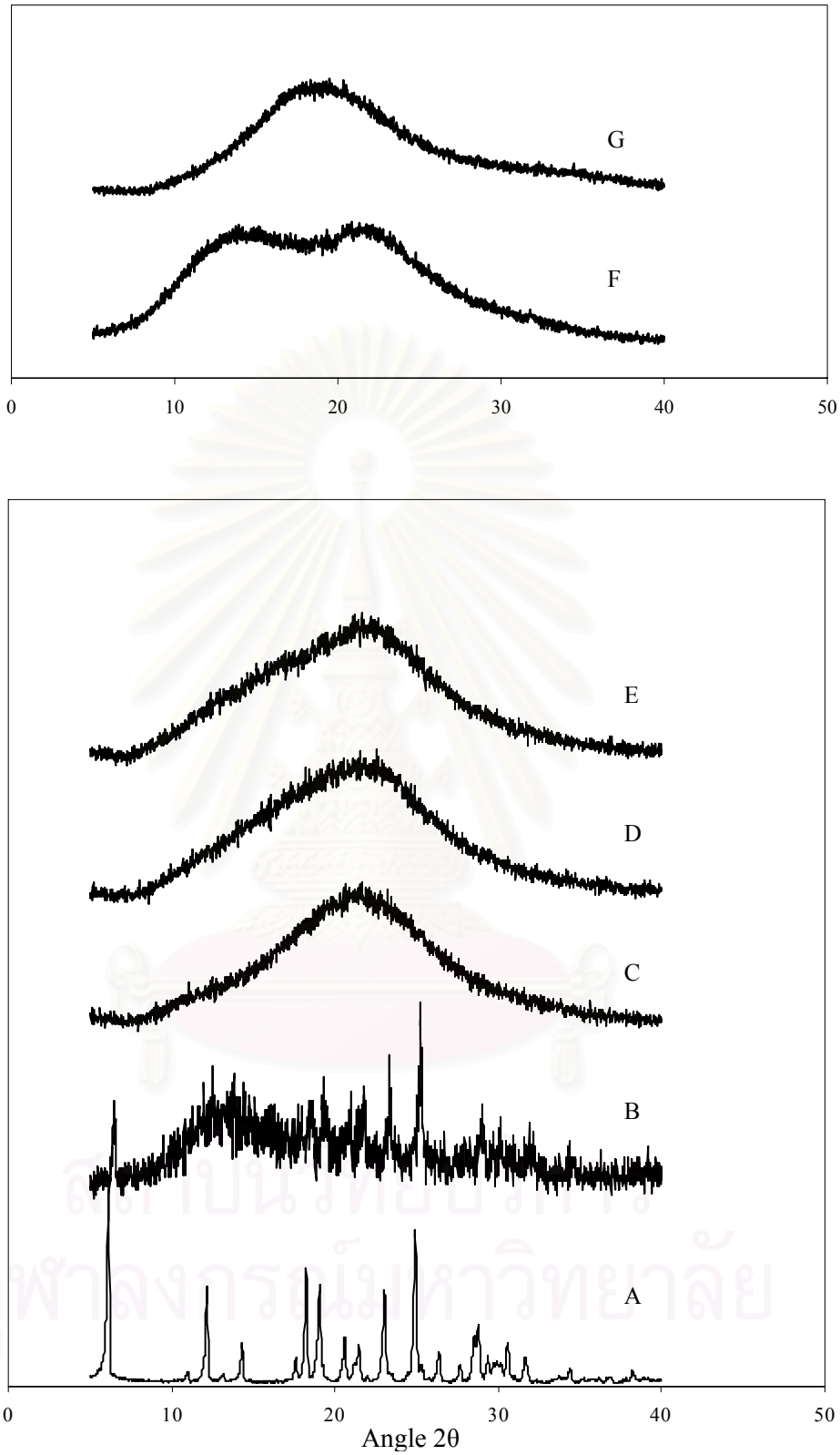


Figure 8 X-ray diffratogram of furosemide, F-PVAc systems spray dried PVAc and spray dried maltodextrin. (A) Furosemide, (B) Physical mixture at drug to polymer ratio 1:1, (C) F-PVAc at drug to polymer ratio of 1:0.5, (D) F-PVAc at drug to polymer ratio of 1:1, (E) F-PVAc at drug to polymer ratio of 1:1.5, (F) Spray dried PVAc and (G) Spray dried maltodextrin.

Figures 8A-8E showed the X-ray diffratogram of furosemide, the physical mixture of furosemide with spray dried PVAc, maltodextrin and the F-PVAc powders. The pure furosemide showed the high intensity of diffraction peaks, which indicated that, the presence of crystalline property of furosemide. But the F-PVAc powders showed amorphous form. Similar results have been reported from spray dried D-α-tocophenyl polyethylene glycol 1000 succinate (TPGS) containing furosemide (Shin et al., 2003).

Generally, spray drying is one step process transforming liquid into a dried particulate form. Usaully, spray dried powders are made of almost spherical and amorphous microparticle (Vidgren et al., 1987). Futhermore, Martino et al. (2001) suggested that an amorphous form or a form with a low crystallinity could be obtained for example by grinding or by rapid solvent evaporation (spray drying, freeze drying). This corresponds to a mechanical activated state, which is charcaterised by higher crystal disorder and higher energy content, and by better compression properties.

In this study, the result of X-ray pattern demonstrated that diltiazem hydrochloride and furosemide exhibited the amorphous state after spray drying with PVAc whereas thephylline seemed to be in both crystalline and amorphous state.

4.2 Infrared spectroscopy

4.2.1 IR pattern of spray dried PVAc and spray dried maltodextrin

The IR pattern of spray dried PVAc and spray dried maltodextrin are displayed in Figures 9B-9C. The FTIR spectra of spray dried PVAc showed characteristic peak of C-H aliphatic stretching vibration at 2978 cm^{-1}. The peak at 1745 cm^{-1} indicated carbonyl C=O stretching and the peak of C-O ester stretching showed at 1239 cm^{-1}. The FTIR spectra of maltodextrin showed characteristic peak of O-H

stretching vibration from 3500-3200 cm^{-1} and the peak of C-H aliphatic stretching at 2929 cm^{-1} whereas the characteristic vibration band of C-O stretching was shown at 1238-1270 cm^{-1}.

4.2.2 IR pattern of drugs, physical mixture of drugs with spray dried PVAc, maltodextrin and drugs-PVAc powders.

The IR spectra of diltiazem hydrochloride, the physical mixture of diltiazem hydrochloride with spray dried PVAc, maltodextrin and the D-PVAc powders at various polymer ratios are shown in Figures 9D-9H. The infrared spectrums of pure diltiazem hydrochloride, a sharp band were observed at 1743 and 1680 cm^{-1} in the region of 1700-1550 cm^{-1}. The band at 1743 cm^{-1} was assigned to acetate C=O stretching and 1680 cm^{-1} was assigned to lactam C=O stretching.

The IR spectra of the physical mixture and D-PVAc showed the combination of diltiazem hydrochloride peaks with other excipients, whereas the principal peaks of diltiazem hydrochloride were observed. Some positions of the peak were slightly shifted from the original material. But they have no noticeable difference. Therefore the interaction between drug, polymer and other excipients was unlikely to occur.

The IR spectra of theophylline, the physical mixture of theophylline with spray dried PVAc, maltodextrin and the T-PVAc powders are shown in Figures 10D-10H. The peak of theophylline at 3400-3100 cm^{-1} resulted from N-H stretching. The IR absorption bands at 1720-1715 cm^{-1} and 1677 cm^{-1} were resulted from C=O stretching. The peaks at 1568 cm^{-1} and 1665 cm^{-1} were resulted from C=C and C=N stretching, respectively. The slightly shifted of IR spectra was observed in spray dried product. This would be assumed that the interaction between theophylline and PVAc was not occurred. Similar result was revealed that the co-spray dried powder from theophylline and ethylcellulose had a stable characteristic and the drug interaction was not observed which confirmed by unchanged of peaks from IR study (Leesawat, 1991). However, the pattern of IR spectra of theophylline after spray drying with PVAc in the region of 1720-1715 cm^{-1} was changed. This result might be explained by the change of polymorphic form of theophylline. Suzuki et al. (1989) suggested that the polymorphism of anhydrous theophylline was observed. From IR spectra of

theophylline and T-PVAc systems (Figure 10), pure theophylline exhibited the theophylline anhydrous form II whereas T-PVAc powder displayed the theophylline anhydrous form I. This result agreed with the result from X-ray diffractogram of theophylline and T-PVAc systems.

Figures 11D-11H showed the IR spectra of furosemide, the physical mixture of furosemide with spray dried PVAc, maltodextrin and the F-PVAc powders. From infrared spectrum of pure furosemide, an absorption band was observed at 3352 and 3285 cm^{-1} in the region of 3500-3200 cm^{-1} and a sharp band was observed at 1673 and 1565 cm^{-1} in the region of 1700-1500 cm^{-1} (Figure 11D). The 3340 cm^{-1} band was assigned to the NH_2 stretching vibration of Ar-NH-CH_2 and the 3285 cm^{-1} band was assigned to stretching vibration of SO_2NH_2 and the 1673 cm^{-1} band, which appeared at such high frequency region, was assigned to the bending vibration of carboxyl group. The 1565 cm^{-1} band was due to the asymmetric stretching vibration of the amino group and the 1324 cm^{-1} and was assigned to the asymmetric stretching vibration of the sulfonyl group in the furosemide structure (Shin et al., 2003). The IR spectra of F-PVAc spray dried powder showed the different main characteristic peaks from all of furosemide, PVAc and maltodextrin. The carboxylic peak at around 1600-1550 cm^{-1} was disappeared. This was due to the fact that acid–base interaction. The ammonia molecule might interact with the carboxyl group of furosemide which resulted ammonium carboxylate salt formation.

4.3 Differential scanning calorimetry

The DSC thermograms of PVAc (Figure 12G) showed no sharp melting peak resulting that it is amorphous in nature and the glass transition temperatures (Tg) of the spray dried PVAc was approximately 43.39° C. In our study, the Tg was higher than these in previous study (Zhang et al., 2000). The previous study found that the Tg of PVAc was 35-37° C. This finding might be caused by the different composition of PVAc. According to this study, PVAc dispersion composed of PVP and SLS, whereas in previous experiment used PVAc powder alone. Hence, the higher of Tg of PVAc dispersion (spray dried) might be caused by the additives in the dispersion.

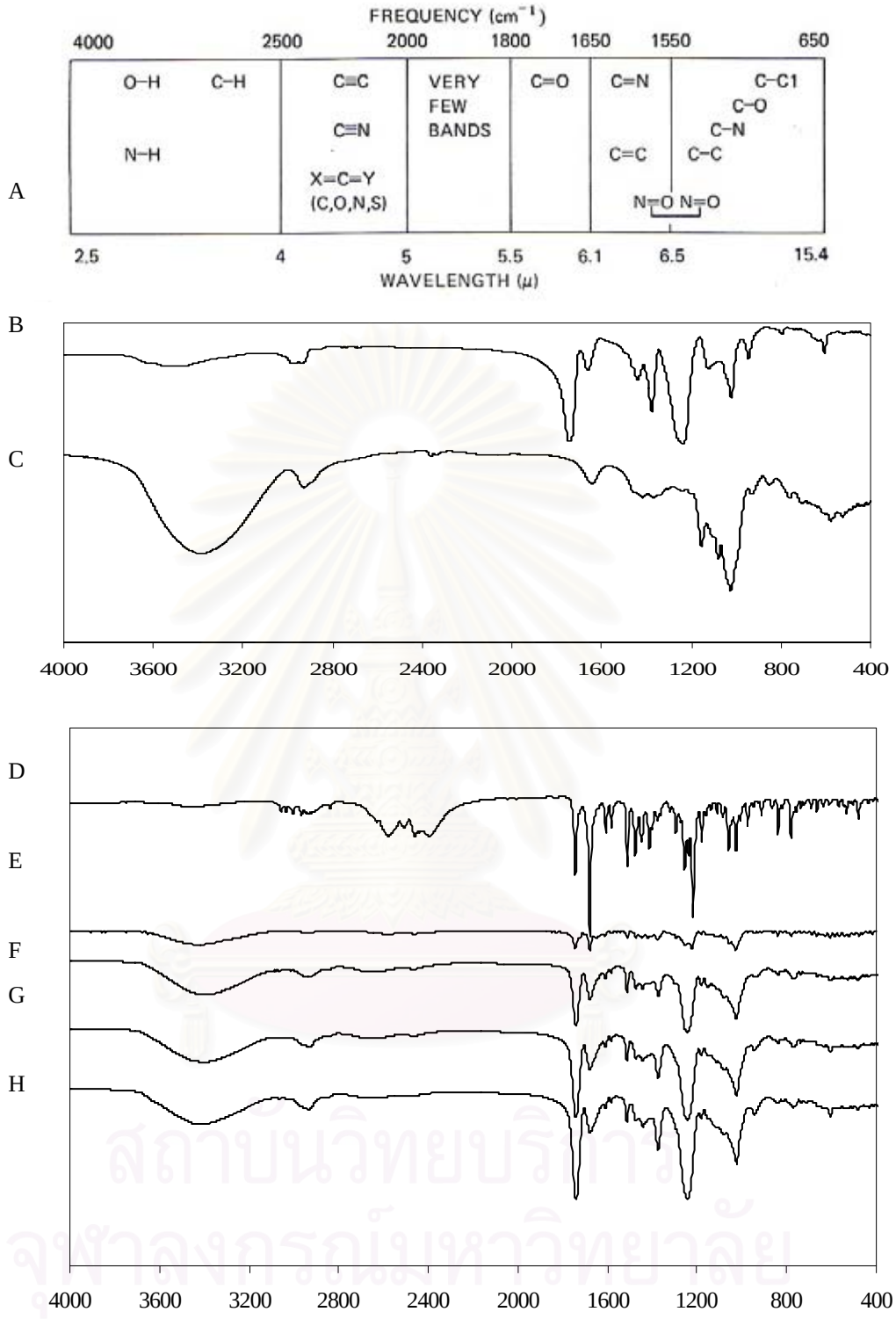


Figure 9 Infrared absorption spectrum of Spray dried PVAc, spray dried maltodextrin, diltiazem hydrochloride and D-PVAc systems. (A) The approximate regions that indicate various common types of bonds, (B) Spray dried PVAc, (C) Spray dried maltodextrin, (D) pure diltiazem hydrochloride, (E) physical mixture at drug to polymer ratio of 1:1, (F) D-PVAc at drug to polymer ratio of 1:0.5, (G) D-PVAc at drug to polymer ratio of 1:1, (H) D-PVAc at drug : polymer ratio of 1:1.5.

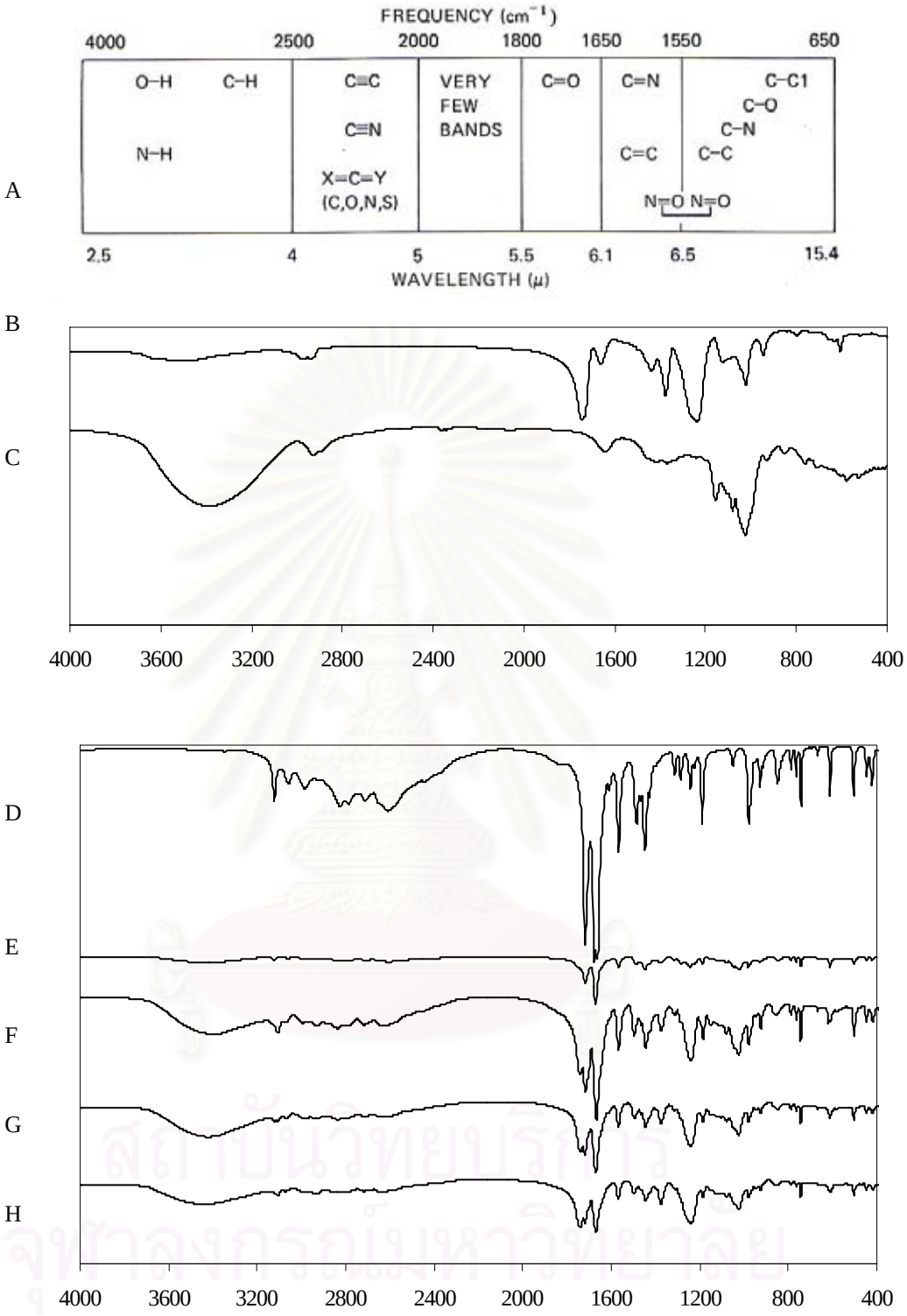


Figure 10 Infrared absorption spectrum of Spray dried PVAc, spray dried maltodextrin, theophylline and T-PVAc systems. (A) The approximate regions that indicate various common types of bonds, (B) Spray dried PVAc, (C) Spray dried maltodextrin, (D) pure theophylline, (E) physical mixture at drug to polymer ratio of 1:1, (F) T-PVAc at drug to polymer ratio of 1:0.5, (G) T-PVAc at drug to polymer ratio of 1:1, (H) T-PVAc at drug : polymer ratio of 1:1.5.

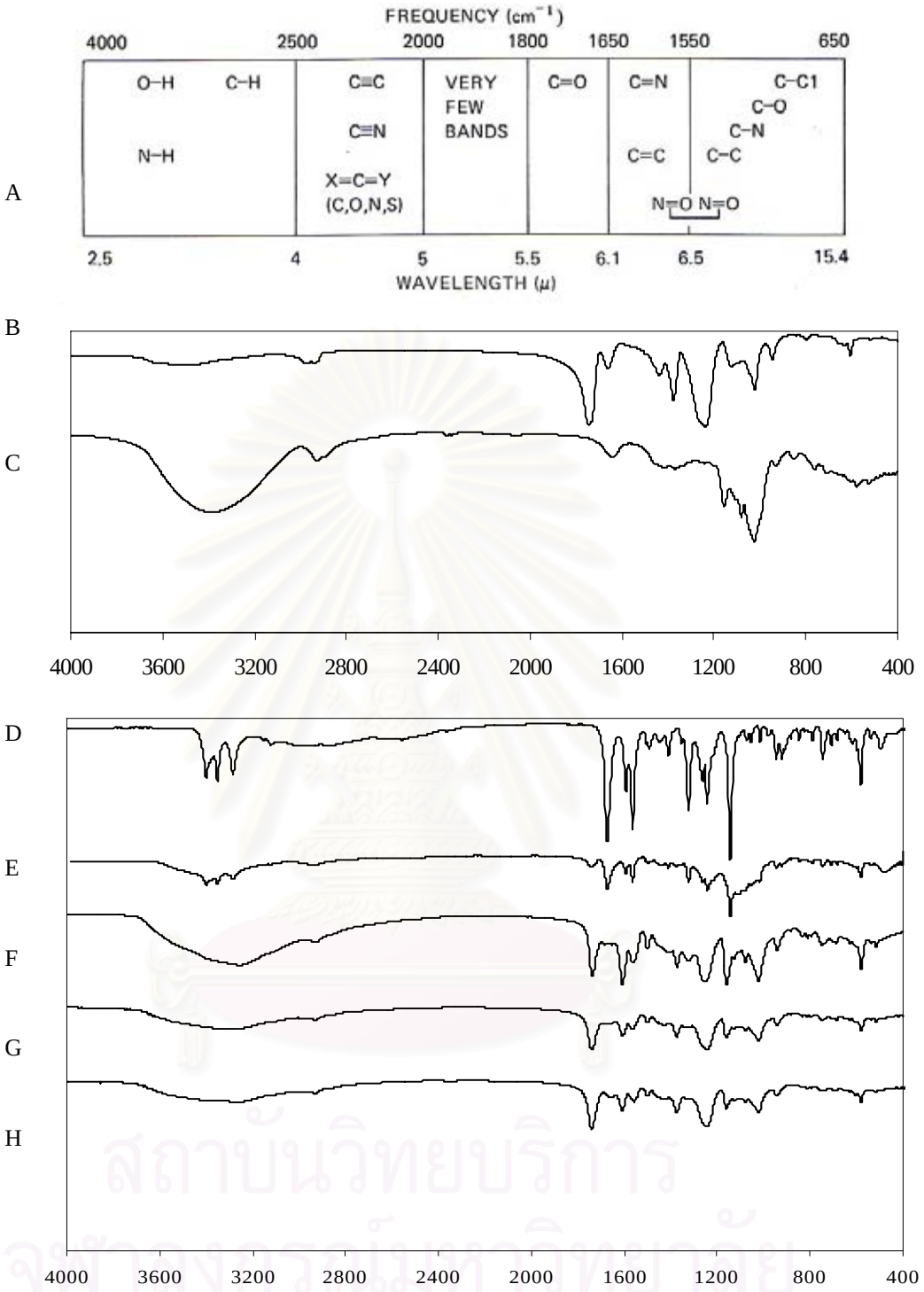


Figure 11 Infrared absorption spectrum of Spray dried PVAc, spray dried maltodextrin, furosemide and F-PVAc systems. (A) The approximate regions that indictae various common types of bonds, (B) Spray dried PVAc, (C) Spray dried maltodextrin, (D) pure furosemide, (E) physical mixture at drug to polymer ratio of 1:1, (F) F-PVAc at drug to polymer ratio of 1:0.5, (G) F-PVAc at drug to polymer ratio of 1:1, (H) F-PVAc at drug : polymer ratio of 1:1.5.

Figure 12F shows the DSC pattern of spray dried maltodextrin. The broadening endothermic peaks were found around 100 °C and 70 °C, respectively. The peak might be played by the moisture in the spray dried maltodextrin.

The DSC thermograms of diltiazem hydrochloride, the physical mixture of diltiazem hydrochloride with spray dried PVAc, maltodextrin and the D-PVAc powders at various polymer ratios are shown in Figure 12.

The melting point of pure diltiazem hydrochloride was found to be about at 215.5°C, whereas spray dried D-PVAc displayed broad band that was enlarged and shifted to lower melting temperatures of diltiazem hydrochloride (approximately193-194 °C). The lower in melting point indicated the presence of amorphous from of these samples. This showed that the polymer and most likely the drug are (partly or completely) amorphous in the microphere. This result was similar to the DSC thermogram from diltaizem hydrochloride-Eudrgit® RS and diltiazem hydrochloride-Eudragit® RL spray dried microcapsule (Kristmundsdottit, 1996). They found that the melting point of diltaizem hydrochloride-Eudragit® RS/RL micropraticle was 195 °C, which lower than that of diltiazem hydrochloride alone. In addition, they suggested that the diltaizem hydrochloride-Eudragit® RS/RL micropraticle was in amorphous state. Furthermore, the DSC thermograms of D-PVAc powder showed that the endothermic peak at approximately 250 °C. It might be the degradation peak of maltodextrin. Concerning the physical mixture of diltiazem hydrochloride with PVAc, the drug endothermic peak was observed at 213.5 °C.

The DSC thermograms of theophylline, physical mixture of theophylline with spray dried PVAc, maltodextrin and T-PVAc powders at various polymer ratios are shown in Figure 13. The thermogram of pure theophylline gave the characteristic melting endotherm at 273.4 °C. The physical mixtures of theophylline and PVAc showed an apparent endothermic peak of theophylline at 272.5 °C. Similar observations have been reported for theophylline-ethylcellulose and theophylline-chitosan (Leesawat, 1991; Asada et al., 2004). While in T-PVAc at 0.5 ratio of polymer had endothermic

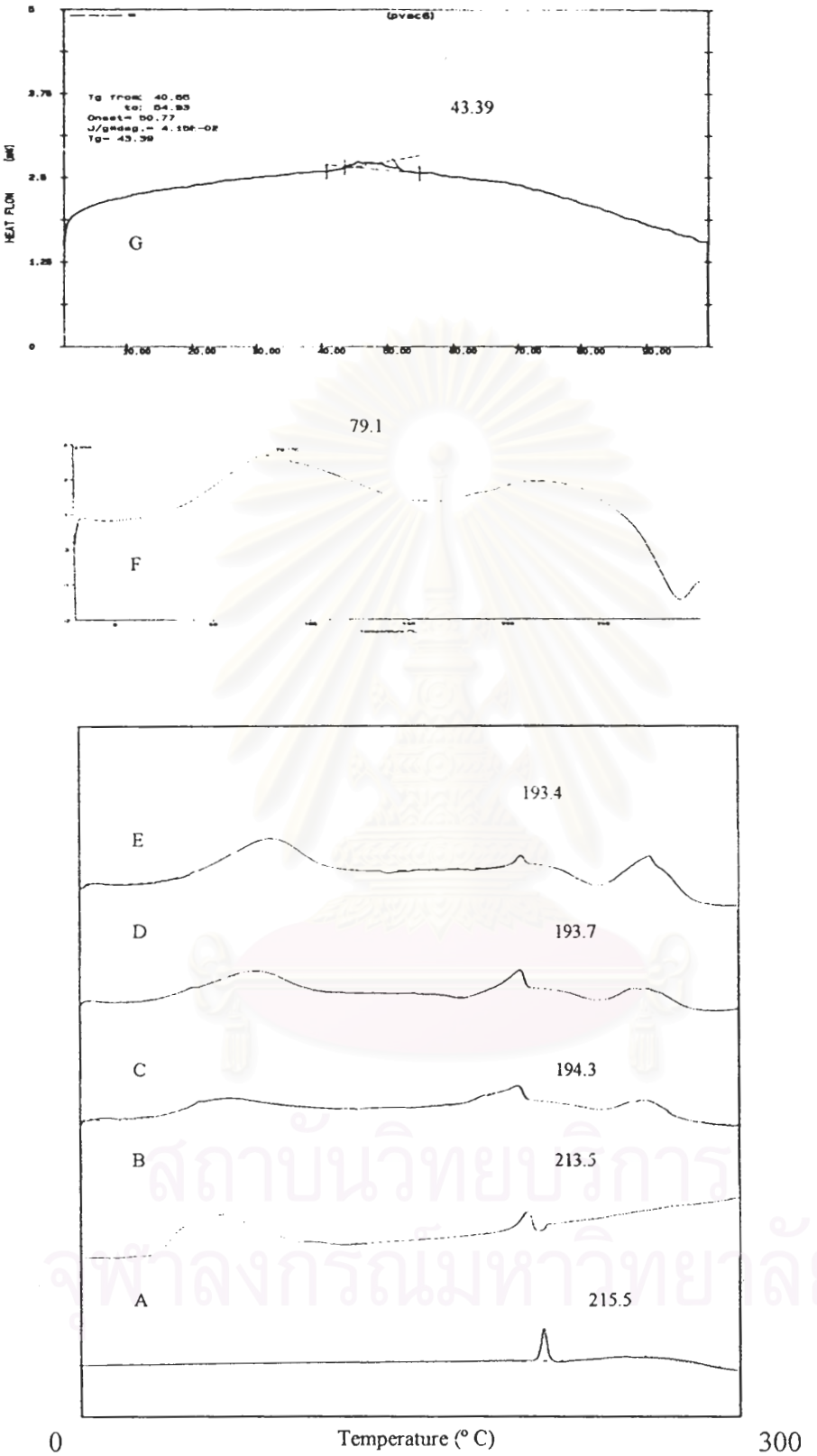


Figure 12 DSC thermograms of diltiazem hydrochloride and D-PVAc systems

A : diltiazem hydrochloride
B : physical mixture at drug to polymer ratio of 1:1
C : D-PVAc at drug to polymer ratio of 1:0.5
D : D-PVAc at drug to polymer ratio of 1:1
E : D-PVAc at drug to polymer ratio of 1:1.5
F : Spray dried maltodextrin
G : Spray dried PVAc

peak at 262.7 °C, at 1:1 ratio of polymer had endothermic peak at 259.2 °C and 1:1.5 ratio of polymer exhibited the characteristic melting endothermic of theophylline with shifted to 257 °C. These results might be due to the formation of solid dispersion between the components in spray dried powders. Furthermore, this property led to the melting point of theophylline was slightly shifted to lower temperature than that of pure theophylline.

The thermograms for the furosemide test systems are shown in Figure 14. The pure furosemide was melted at 206 °C. The furosemide exhibited a single, sharp endothermic peak, whereas the single endothermic peak of furosemide was not shown in the F-PVAc. The DSC curves of F-PVAc showed the disappeared endothermic peak of furusemide. In order to analyze the curve, the derivative method was used. The endothermic peak of furosemide was observed at 195-196°C and the crystallinity of furosemide was decreased. This result might be caused by the mixture of the component in F-PVAc powder. It could be said that the F-PVAc was a solid dispersion or solid solution. The spray dried powder might be the solid solution which was not a simple mixture of drug and additives. The solid solution was a molecular solid dispersion between the components in powder. However, it was not clear for of F-PVAc powder. This result might be confirmed by the further physicochemical study. For the physical mixture of furosemide-PVAc system, the endothermic peak was observed at 204.5°C. This result might be due to the furosemide in physical mixture existed in crystalline state.

There were no clearly differences between the DSC thermograms pattern of pure drug and spray dried products in different ratios of polymer but the difference in peak temperature were visible. The melting point of diltiazem hydrochloride, theophylline and furosemide in spray dried powder was found to be slightly shifted. The lower in melting point indicated the presence of amorphous from in these samples or polymorphic change of furosemide products. These results might be explained by the fact that the denser or more closely packed crystal has the smaller free energy. This means that the heat of sublimation (melting point) increases as the packing density increases. These could be explained the lower melting temperature of active ingredient in this method that spray dried product (amorphous form) had to

have the lower packing density in the structure, hence, the melting point temperature of this products should be decreased. Furthermore, due to crystalline forms had the various forces to hold molecules in the solid (hydrogen bonding or non-covalent attractive forces); on the other hand, the nature of amorphous forms had less force holding the molecule. Therefore, the lower energy used in amorphous resulted in the lower melting temperature. These could be explained by the lower melting temperature in the spray dried products (amorphous form) in this experiment. In addition, the drug-excipient compatibility (DSC method), it should be noted that the DSC thermograms of mixtures showed some changes simply from eutectic formation; thus, a change in DSC melting point for a drug and excipient might not indicative of a stability problem by itself.

From D-PVAc and T-PVAc spray dried powder, the IR study no extra bonds or chemical shifts were observed, indicated that there were no strong chemical interaction between drugs and polymer, and the changes in drugs-polymer thermal behavior from DSC data might be due to the physical interactions between drugs and polymer. In conclusion, the relative enthalpy change may be considered to correspond to the disappearance of crystallinity. It may be said that the drug molecules are dispersed in the polymer matrix of the solid dispersion and that the thermal property was changed. However, the result of the IR spectrum of F-PVAc powder showed the disappeared carboxyl peak. Thus both DSC thermogram and IR spectra indiacted that the chemical interaction between furosemide and ammonia solution (solvent of spray drying dispersion) was occurred.

4.4 Solid state stability

4.4.1 Physical appearance

The physical appearance of diltiazem hydrochloride, theophylline and furosemide standard were not changed under storage condition. The color of D-PVAc and T-PVAc powders, initially white, were apparently constant within 4 month, whereas the color of F-PVAc powders became a yellow powder within 3 month. Other ingredient powders samples stored under same conditions remained in the white color and free-flowing state.

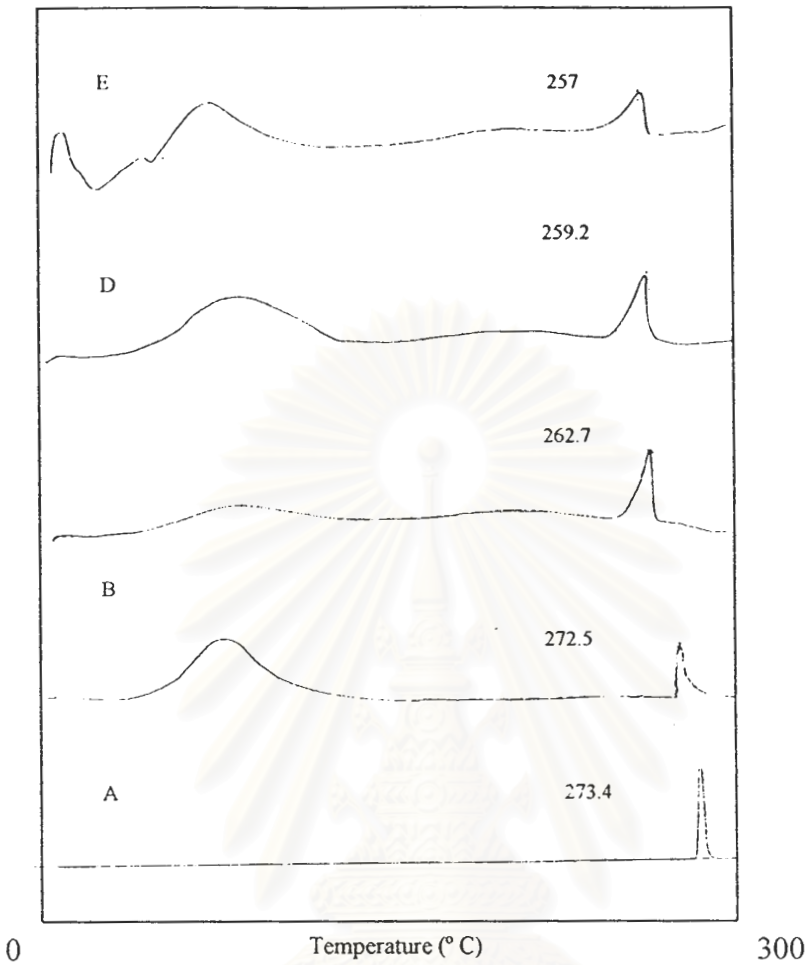


Figure 13 DSC thermograms of theophylline and T-PVAc systems

A : theophylline
B : physical mixture at drug to polymer ratio of 1:1
C : T-PVAc at drug to polymer ratio of 1:0.5
D : T-PVAc at drug to polymer ratio of 1:1
E : T-PVAc at drug to polymer ratio of 1:1.5

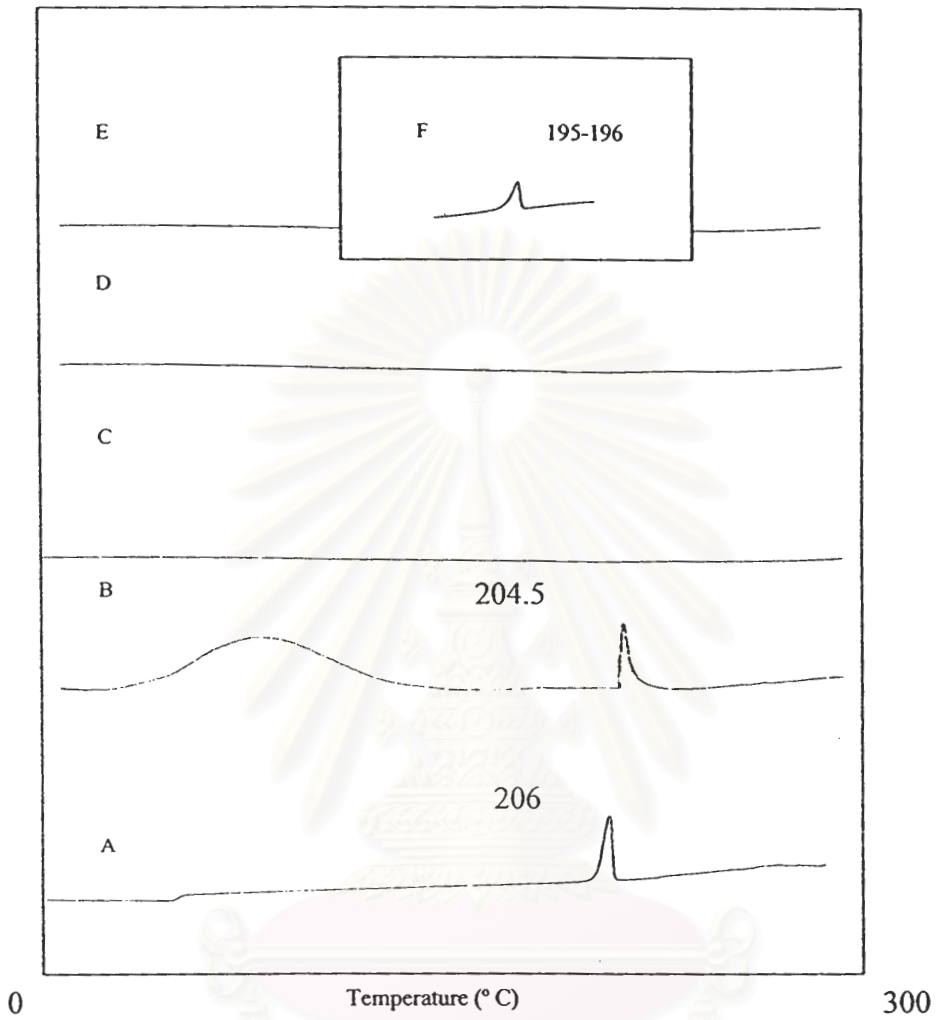


Figure 14 DSC thermograms of furosemide and F-PVAc systems

A : furosemide
B : physical mixture
C : F-PVAc at drug : polymer ratio of 1:0.5
D : F-PVAc at drug : polymer ratio of 1:1
E : F-PVAc at drug : polymer ratio of 1:1.5
F : Secondary derivative of F-PVAc

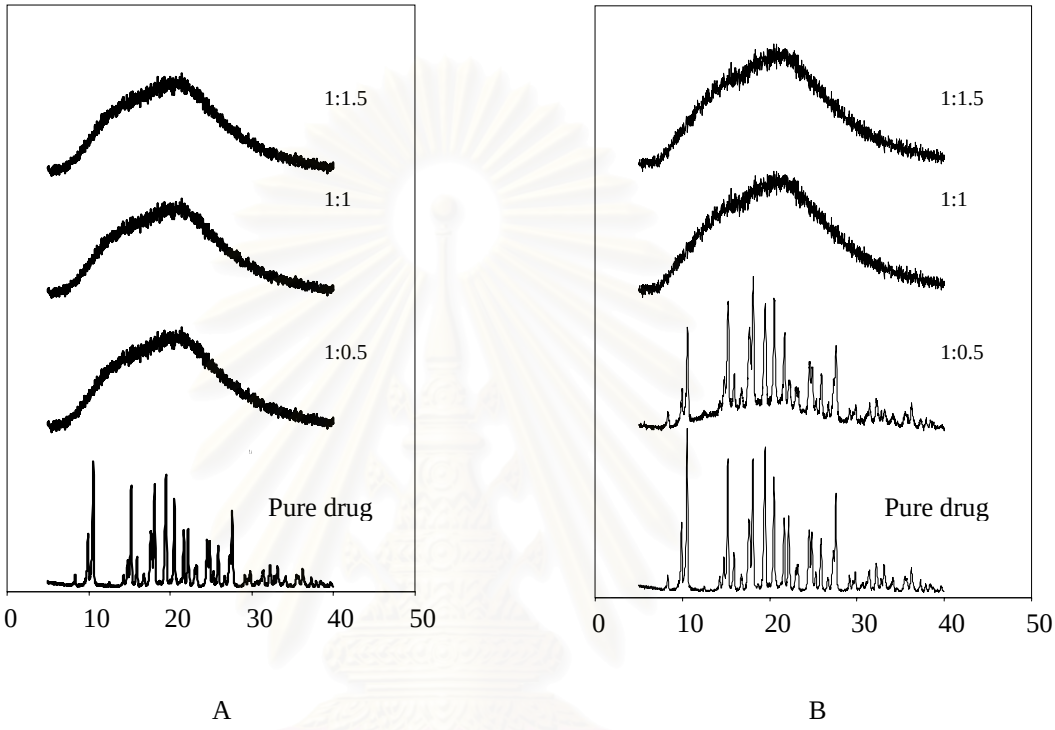


Figure 15 X-ray diffractograms of diltaizem hydrochloride and D-PVAc system. (A) before stability testing and (B) after stability testing at different drug to polymer ratio.

4.4.2 Physicochemical stability

The physicochemical studies were included x-ray diffractometry, differential scanning calorimetry and infrared spectroscopy. The different properties of D-PVAc, T-PVAc, F-PVAc powders were not occurred (See Figures 1E-5E, Appendix E), except the D-PVAc powders at drug to polymer ratio of 1:0.5 (Figure 15). It was changed from amorphous state to semicrystalline state under storage condition for 4 month. This result could be explained by the low amount of PVAc in spray dried powder did not inhibit the recrystallisation of diltiazem hydrochloride.

5. Physical properties of drugs-PVAc matrices

The physical properties of drug-PVAc matrices are summarized in Table 13.

5.1 Weight variation

The average weight of the matrices prepared at drug to polymer ratio 1:0.5, 1:1 and 1:1.5 ranged from 181.58 to 183.88, 227.66 to 231.99 and 273.34 to 275.59 mg, respectively. The weight variations of all formulations conformed to USP 24 specification. The higher polymer content exhibited the higher average weight since the ratio of active ingredient, polymer and additives kept constant.

5.2 Hardness

All spray dried powders showed good tablet formation. The hardness of the matrices was between 13.05 – 19.08 kp. The hardness increased when amount of polymer increased.

5.3 Thickness

The drugs-PVAc powder prepared at drug to polymer ratio of 1:0.5 showed the least thickness of matrices and the highest thickness of matrices were taken from product prepared at drug to polymer ratio of 1:1.5. The thickness of matrices was increased when increasing the PVAc content because of the higher amount of powder per matrix.

5.4 Friability

The average friability of the matrices was undetectable due to very low friable. Since the acceptable limit of friability conforming to USP 24 is not more than 1%, the percent friability of the prepared matrices passed the specifications. The friability data demonstrated that matrices from all formulations were non-friable.

5.5 Disintegration time

The disintegration time of all matrices was more than 120 minutes. This result confirmed that the matrices were non-disintegrated.

Table 13 Physical properties of D-PVAc, T-PVAC and F-PVAc matrices containing various amounts of PVAc.

Formulation	Drug to polymer ratio	Weight variation (mg) (mean (SD))[a]	Hardness (kp) (mean (SD)) [b]	Thickness (mm) (mean (SD)) [b]	Friability (%)[a]	Disintegration time (min) [c]
D-PVAc	1:0.5	183.68 (1.48)	13.94 (0.40)	1.88 (0.02)	Not detecable	>120
	1:1	231.99 (2.43)	18.16 (0.27)	2.56 (0.03)	Not detecable	>120
	1:1.5	274.93 (2.58)	18.95 (0.34)	3.08 (0.02)	Not detecable	>120
T-PVAc	1:0.5	181.58 (0.87)	13.05 (0.24)	1.82 (0.02)	Not detecable	>120
	1:1	227.66 (1.98)	16.55 (0.46)	2.50 (0.01)	Not detecable	>120
	1:1.5	273.34 (2.03)	18.95 (0.20)	3.17 (0.01)	Not detecable	>120
F-PVAc	1:0.5	183.50 (1.53)	15.35 (0.66)	1.89 (0.02)	Not detecable	>120
	1:1	230.89 (2.43)	18.04 (0.41)	2.71 (0.02)	Not detecable	>120
	1:1.5	275.59 (1.78)	19.08 (0.24)	3.20 (0.02)	Not detecable	>120

[a] Average of twenty determinations [b] Average of ten determinationS [c] Average of six determinationS

6. Dissolution study

6.1 Effect of drug to polymer ratio

From the experimental data, the drug release profiles could be plotted between percentages of drug release against time. Then, the change of release rate profile was constructed from the dissolution profile to elucidate the release rate at various time intervals during the drug dissolution from the matrices. The dissolution and release rate data of each formulation were described in Tables 1F-3F (Appendix F).

The dissolution profiles of D-PVAc, T-PVAc and F-PVAc matrices with various PVAc contents in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution are shown in Figures 16-18. Each point represents the average value which was obtained from three determinations at the given sampling time.

The D-PVAc matrices were not disintegrated into particles during dissolution studies in these mediums. This observation was similar to T-PVAc and F-PVAc matrices. This observation could be confirmed that the matrices prepared from PVAc were non-swelled and non-disintegrated tablets.

The dissolution profiles of D-PVAc and T-PVAc matrices showed that the lower content of PVAc gave the higher burst release effect. The release rates of these matrices were relatively fast at the initial stage, followed by the decreasing of release rate. Furthermore, the release rate was decreased with the time due to an increasing in diffusional path length for the drugs when the dissolution time was longer. The effect of polymer content on drug release from D-PVAc and T-PVAc was observed. The increasing in the weight fraction of PVAc resulted in a corresponding decrease of the dissolution rate. In addition, the higher PVAc ratios of the D-PVAc and T-PVAc matrices affected the slower release rate of those drugs. As the concentration of PVAc was increased in matrices, the higher hydrophobic property was obtained. This result could be explained by the decreasing of dissolution medium penetration into the matrices dueing to a decrease in porosity and an increase in tortuosity of the matrices.

Figures 16D and 17D shows the relationship between the relative dissolution time (RDT value) and the polymer ratios of D-PVAc and T-PVAc matrices in various dissolution medium. The lower RDT value of those matrices at low content of PVAc than that of these at high content of PVAc were observed. Moreover, when increasing the polymer content in the matrices, the RDT value was increased. In conclusion, the concentration of the polymer in the formulation was the determining factor in controlling release rate of the drug.

In this work, the retardation of drug release might be explained by the hydrophobic property, the wettability and the minimum film formation temperature property of PVAc polymer. In the case of D-PVAc and T-PVAc matrices, the effect of PVAc concentration was obtained. Diltiazem hydrochloride and theophylline were released slower from matrices with higher PVAc content. Since, PVAc was hydrophobic polymer which had known to be able to retard the drug dissolution of a dosage form. Thus, the ability of PVAc to retard the rate of drug release from the matrices might be attributed to its hydrophobic property. Incorporation of PVAc caused an increasing the hydrophobicity of matrices led to a decreasing in effective interfacial wettability. Consequently, there was a slower rate of water penetration and dissolution of the drug within matrices causing a slower rate of drug release.

Furthermore, the retardation of drug release profile could be the result from the continuous polymer network within the spray dried particles when compressed into the matrix. By the visual observation of the matrices after dissolution testing; the matrices was covered with polymeric film network of PVAc in the dissolution medium. Moreover, the matrices remained visually intact during dissolution testing. Therefore, the mechanism of drug release from PVAc matrices might be described according to Higuchi equation (diffusion process).

Higuchi (1963) showed that in the matrix type delivery system, the porosity and degree of tortuosity in the capillaries influenced drug release rate and reported that the amount of drug per unit of matrix volume decreased with the time as dissolution occurred. From PVAc matrices, drug release from a porous hydrophobic polymeric drug delivery system occurs when the drug comes into contact with the

release media, subsequently dissolves and diffuses through media filled pores. Thus, the geometry and structure of the pore network are important in this process.

In addition, an increase in polymer content led to a decreasing porosity and increasing the tortuosity of polymer network. The lowest release rate was seen with tablets containing high level of PVAc. PVAc was insoluble, non-swelling, and the tablets remained intact throughout the dissolution process. Drug release was by diffusion through the small inter- and intra-microparticle spaces. The matrices were soften and exhibited a flexible property of tablets during the dissolution process. Drug diffusion was promoted due to the pores and channels that were created following the solubilization of the soluble ingredient.

Futhermore, the mechanism of drug release from PVAc matrices could be explained by Percolation theory. According to percolation theory (Crowley et al., 2004), when a matrix is composed of a water soluble drug and a water insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network. As drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse. The total tortuosity of matrices increased when the PVAc content increased. This result might be due to the pore network becomes less extensive and more tortuous caused a slower drug release.

From the F-PVAc matrices, the percentage of furosemide release from matrix in 0.1 N HCl was less than 10%. This result was corresponding in the solubility of furosemide which depended on pH of dissolution medium. The release of furosemide in deionized water and PBS pH 6.8 solution was decreased when the drug to polymer ratio in matrices was changed from 0.5 to 1. The experiment confirmed that the important factor affecting the drug release from PVAc matrices was drug to polymer ratio (See Figures 18A-18B).

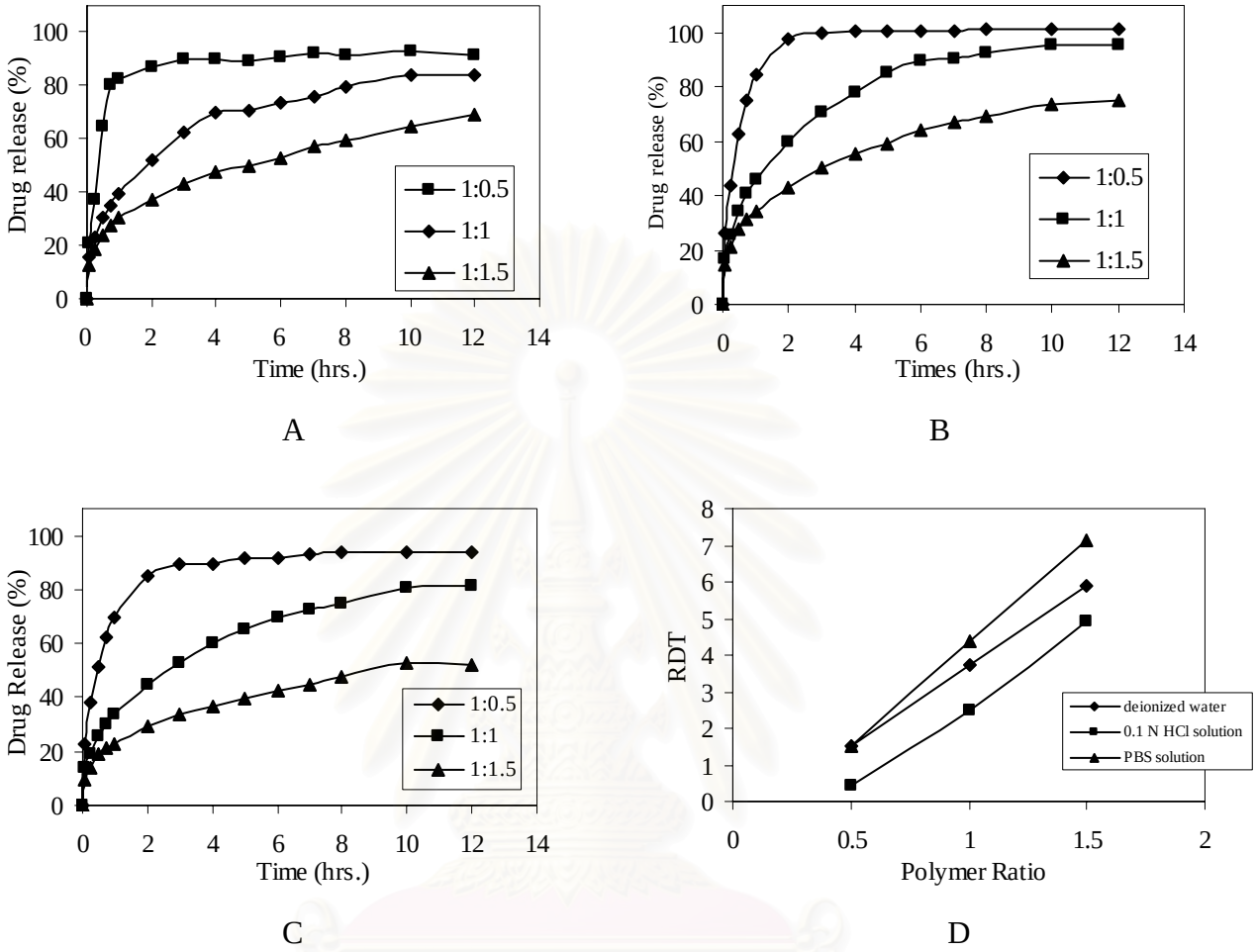


Figure 16 The release profile of D-PVAc matrices prepared from PVAc dispersion at drug to polymer ratio of 1:0.5, 1:1, 1:1.5 and the relationship between the relative dissolution time (RDT value) and the polymer ratios of D-PVAc matrices in various dissolution medium. (A) D-PVAc matrices in deionized water, (B) D-PVAc matrices in 0.1 N HCl solution, (C) D-PVAc matrices in PBS solution and (D) the RDT value of D-PVAc matrices in various dissolution medium.

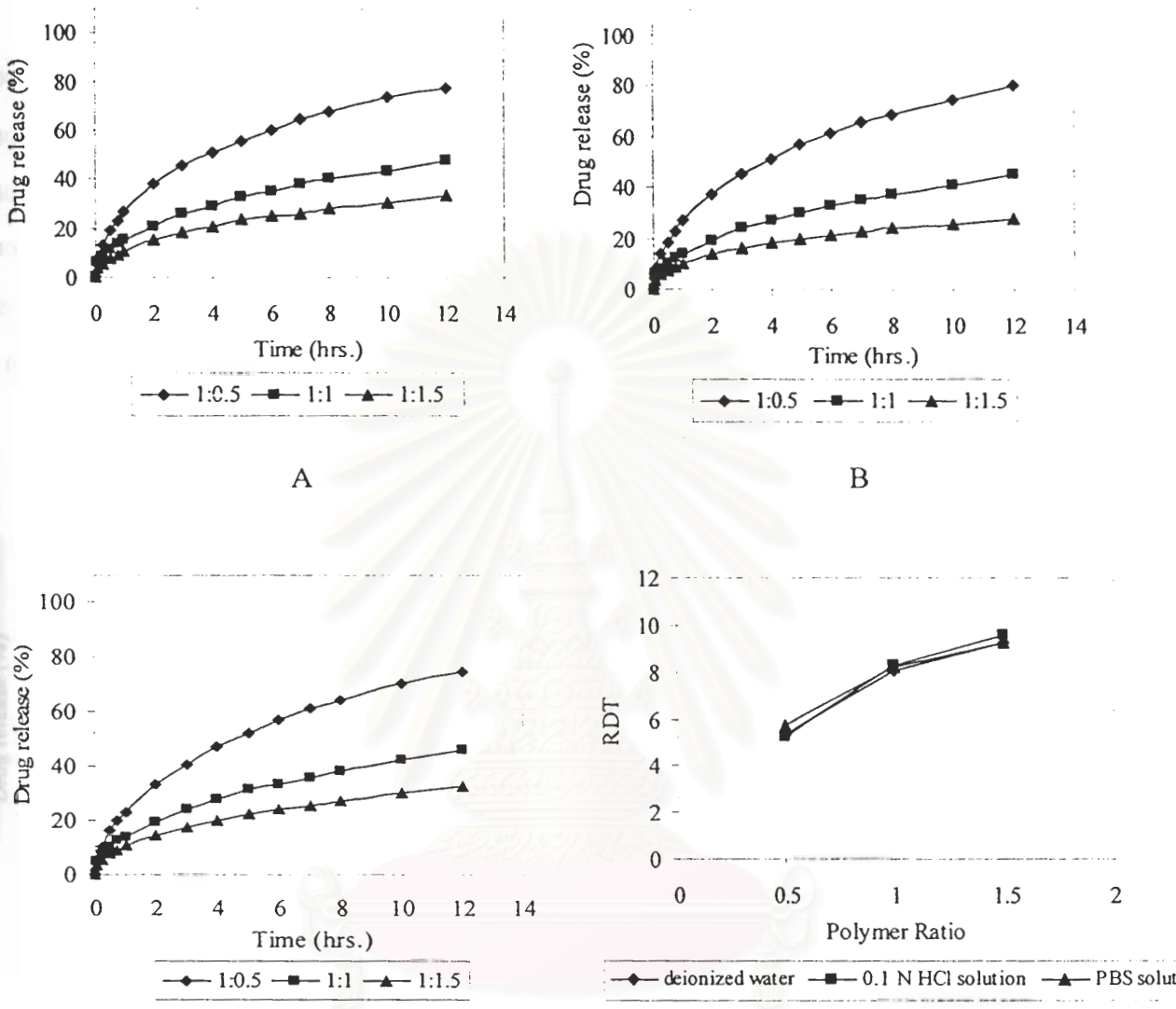


Figure 17 The release profile of T-PVAc matrices prepared from PVAc dispersion at drug to polymer ratio of 1:0.5, 1:1, 1:1.5 and the relationship between the relative dissolution time (RDT value) and the polymer ratios of T-PVAc matrices in various dissolution medium. (A) T-PVAc matrices in deionized water, (B) T-PVAc matrices in 0.1 N HCl solution, (C) T-PVAc matrices in PBS solution and (D) the RDT value of T-PVAc matrices in various dissolution medium.

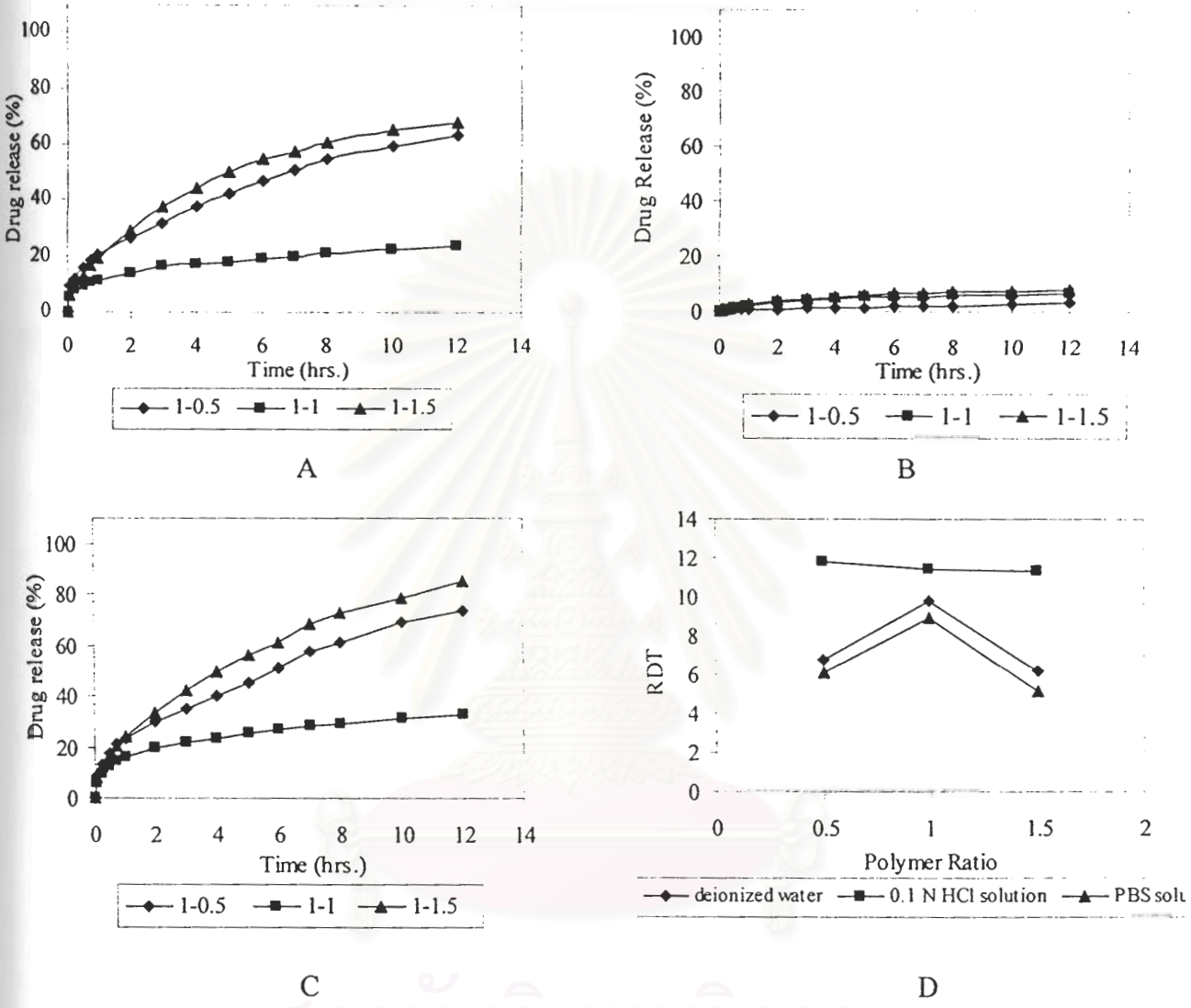


Figure 18 The release profile of F-PVAc matrices prepared from PVAc dispersion at drug to polymer ratio of 1:0.5, 1:1, 1:1.5 and the relationship between the relative dissolution time (RDT value) and the polymer ratios of F-PVAc matrices in various dissolution medium. (A) F-PVAc matrices in deionized water, (B) F-PVAc matrices in 0.1 N HCl solution, (C) F-PVAc matrices in PBS solution and (D) the RDT value of F-PVAc matrices in various dissolution medium.

The results indicated that the release of furosemide at drug to polymer ratio of 1:1.5 was faster than other ratios. The drug release rate was inversely correlated to the polymer concentration. This might be explained by the floatation of the matrices near the distal paddle, which was observed visually during the dissolution test at the first 15 minutes of dissolution test. Considering the agitation force during the paddle rotation, the force at the position near the distal paddle might be more than that at the bottom of dissolution vessel. Consequently, the agitation forces at the position near the distal paddle could eliminate the stagnant layer around the floatable matrices, resulted in faster drug release rate. As the dissolution progressed, the floatable matrices were rapidly eroded. Futhermore, this result could be confirmed by the SEM observation of F-PVAc matrices (drug to polymer ratio of 1:1.5) after dissolution testing. The lagre pore and the erosion of PVAc were observed (See Figure 1G, Appendix G). This result implied that the release of furosemide at drug to polymer ratio of 1:1.5 was faster than other ratios.

6.2 Effect of drug solubility

6.2.1 The dissolution studies in deionized water

The dissolution profiles of D-PVAc, T-PVAc and F –PVAc matrices at drug to polymer ratios of 1:0.5, 1:1 and 1:1.5 in deionized water are presented in Figures 19-21

The dissolution profiles of D-PVAc, T-PVAc, and F-PVAc matrices at drug to polymer ratios of 1:0.5 and 1:1 in deionized water are shown in Figures 19A-19B. The influence of the drug solubility on drug release rate was observed. The drug release rate of D-PVAc matrices was faster than T-PVAc and F-PVAc matrices, respectively.

The dissolution profiles of drug to polymer ratio of 1:0.5 and 1:1 showed that the drug release rates were increased when the drug solubility increased. Moreover, the relationship between the RDT value and the logarithm drug solubility in different drug to polymer ratios when using deionized water as dissolution medium are shown in Figure 19D. These results indicated that the higher drug solubility led to a

decreasing in RDT values. These results might be explained by the mechanism of drug release from the PVAc matrices. First, the water dissolved the drug at the surface and then the water penetrated the matrices via pore which brought about a rubbery stage of polymer induced the flexibility of the polymer. The dissolved drug was released by diffusion through the network of polymer. Finally the drug release rate began to fall and the water reached the center of the matrix. The drug release rate at these steps depended on the drug solubility. According to several authors (Rao et al., 1990; Kurahashi et al., 1996 Tahara et al., 1996; Chebli et al., 2000; Skinner et al., 2001; Sadeghi et al., 2003; Zhang et al., 2003; Mehuys et al., 2004), the most important factor affecting the rate of drug release from matrices system was the drug solubility. They found that lower drug solubility yield slower release profiles.

The dissolution profiles of D-PVAc, T-PVAc and F-PVAc matrices at drug to polymer ratio of 1:1.5 in deionized water are displayed in Figure 19C. The effect of drug solubility on drug release rate was reported. The first 5-hour dissolution profile of D-PVAc matrices was higher than F-PVAc and T-PVAc, respectively. This result could be explained in section 5.2.3.

5.2.2. The dissolution studies in 0.1 N HCl solution

For the dissolution studies in 0.1 N HCl, the release profiles of D-PVAc, T-PVAc and F-PVAc matrices are displayed in Figure 20.

The dependence of the drug solubility on the drug release rate was observed. The dissolution profile of D-PVAc matrices was faster than T-PVAc and F-PVAc matrices, respectively. This result confirmed that the drug solubility played an important role on drug release rate. An increase in drug solubility resulted in increasing the drug release rate.

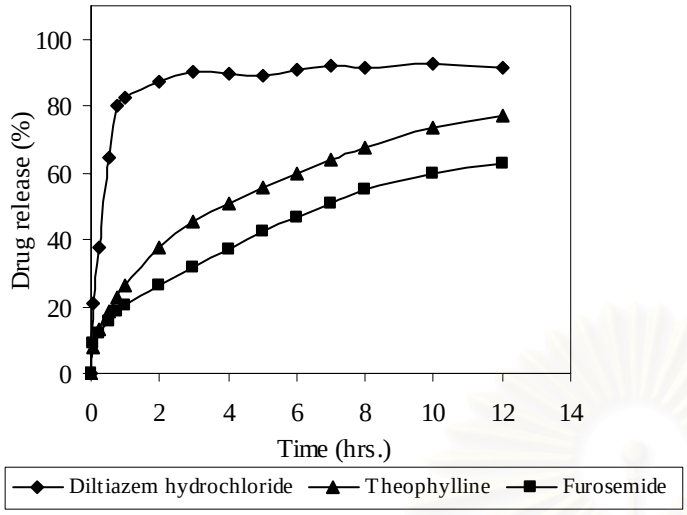
5.2.3 The dissolution studies in PBS pH 6.8 solution

The dissolution profile of D-PVAc, T-PVAc and F-PVAc matrices at drug to polymer ratio of 1:0.5, 1:1 and 1:1.5 in PBS pH 6.8 solution are shown in Figures 21.

The dissolution profiles of those matrices at drug to polymer ratio of 1:0.5 and 1:1 in PBS pH 6.8 solution are presented in Figure 21A-21B. The effect of drug solubility on drug release rate of those matrices was observed. The release profile of D-PVAc matrices was higher than T-PVAc and F-PVAc matrices, respectively. This could result from the different solubility of drug in dissolution medium. Therefore, the influence of freely soluble drug on release profile was attributed to the facilitation of dissolution medium could penetrate by increasing porosity of matrices.

As shown in Figure 21D, the relationship between the RDT value and the logarithm drug solubility in different drug to polymer ratios when using PBS pH 6.8 solution as dissolution medium. It was confirmed that higher drug solubility had lower RDT value.

However, the drug release from those matrices at drug to polymer ratio of 1:1.5 (see Figure 21C) showed that the drug released from F-PVAc matrices were the fastest and the drug released from T-PVAc matrices were the slowest. Generally, the lower drug solubility gave a slower drug release rate. However, this study found that the drug release rate of matrices at drug to polymer ratio of 1:1.5 was inversely correlated to the drug solubility. The reason for this finding might be due to the floatation of the matrices near the distal paddle, as previously mentioned in 5.1.3. Moreover, other worker (Pillay and Fassihi, 1998) studied the dissolution profiles of theophylline and diltiazem hydrochloride matrices. They found that the release profile from theophylline matrices was sensitive to its positioning in the dissolution vessel whereas diltiazem hydrochloride matrices did not show position sensitivity. This result was attributed to the different solubility of these drugs. This may supported the obtained result in this study since furosemide had lower solubility than other drugs. Therefore, furosemide matrices showed the position sensitivity.



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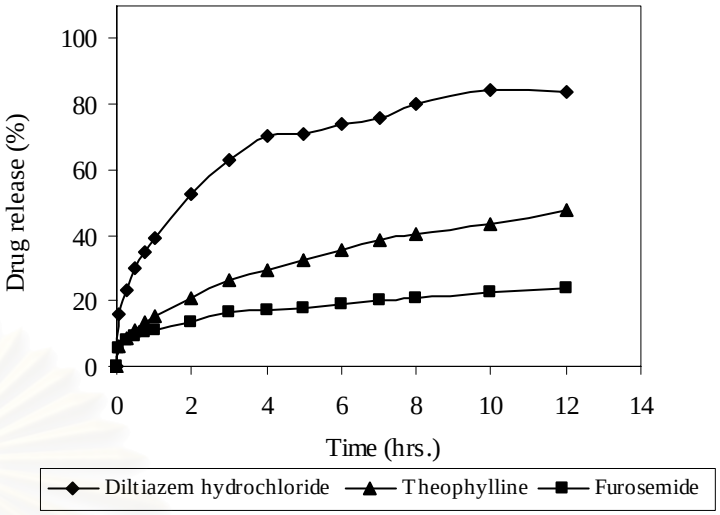

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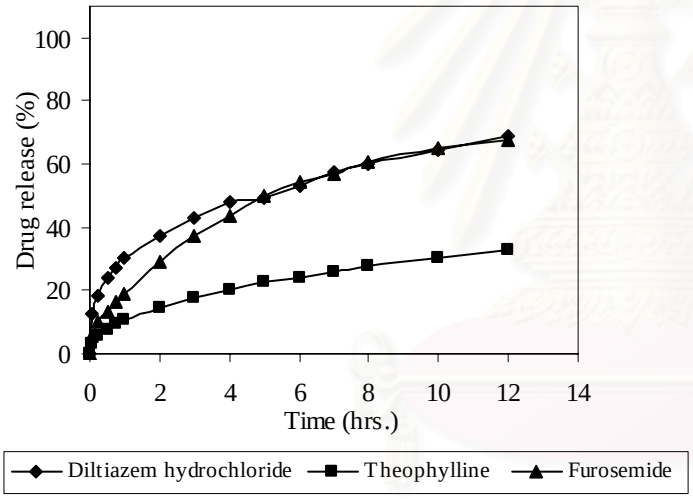

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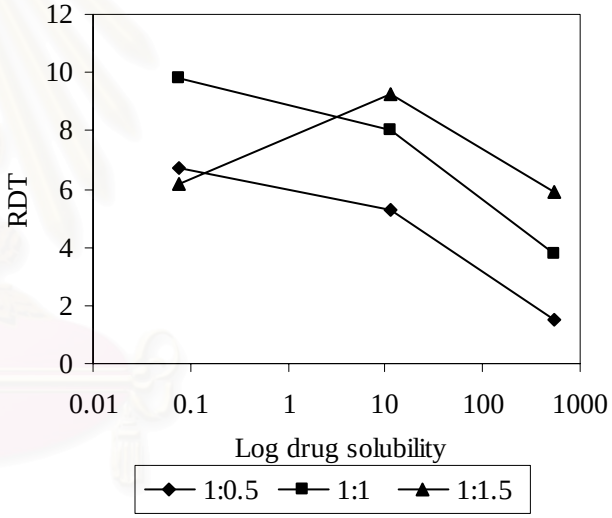

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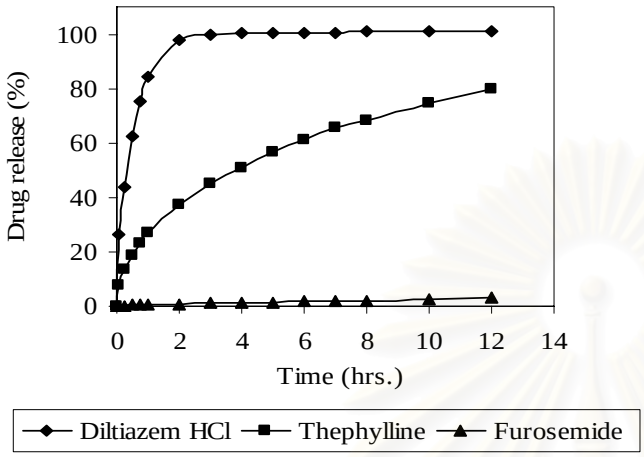
Figure 19 Effect of drug solubility on drug release profiles of matrix tablets prepared from polyvinyl acetate dispersion at different drug to polymer ratio, the relationship between the relative dissolution time (RDT value) and the log drug solubility when using deionized water as dissolution medium. (A) drug to polymer ratio of 1:0.5, (B) drug to polymer ratio of 1:1, (C) drug to polymer ratio of 1:1.5 and (D) the RDT value.



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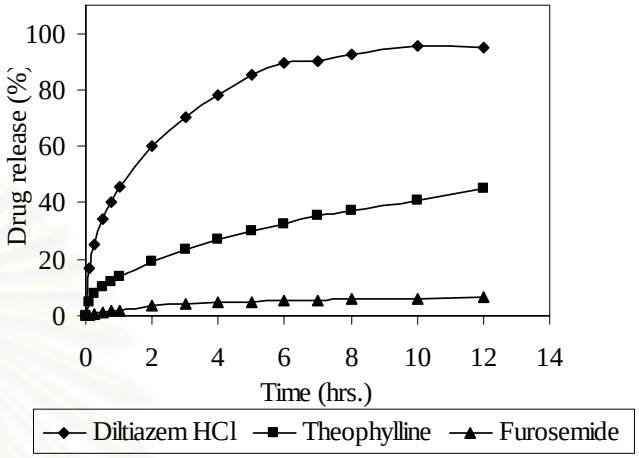

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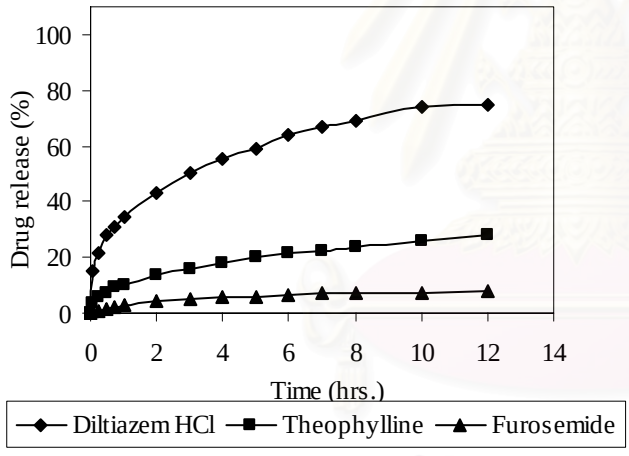

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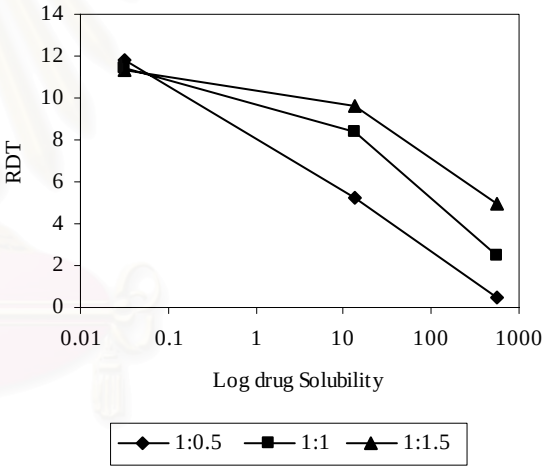

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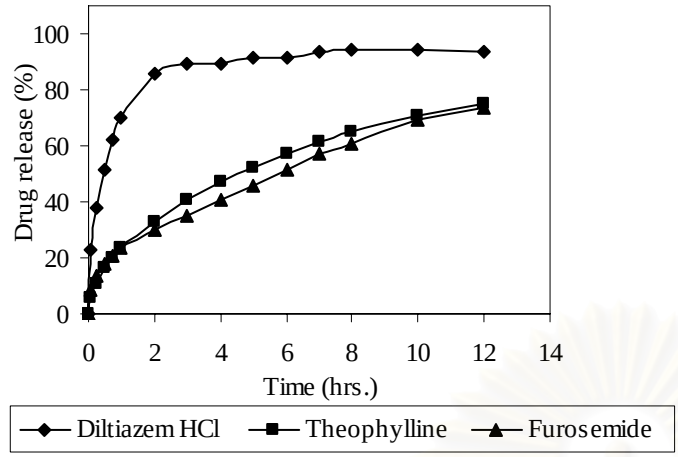
Figure 20 Effect of drug solubility on drug release profiles of matrix tablets prepared from polyvinyl acetate dispersion at different drug to polymer ratio, the relationship between the relative dissolution time (RDT value) and the log drug solubility when using 0.1 N HCl solution as dissolution medium. (A) drug to polymer ratio of 1:0.5, (B) drug to polymer ratio of 1:1, (C) drug to polymer ratio of 1:1.5 and (D) the RDT value.



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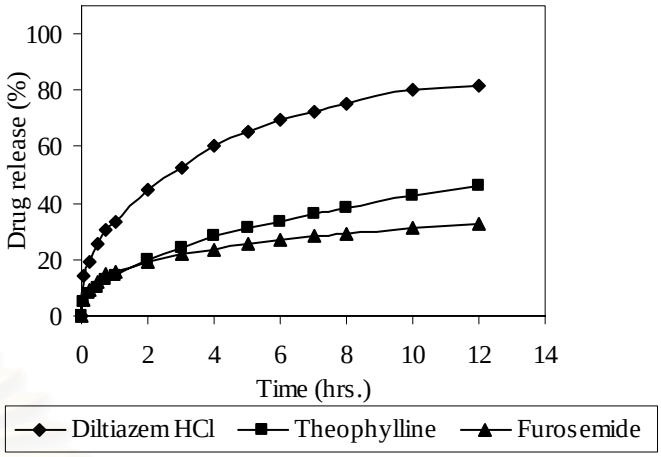

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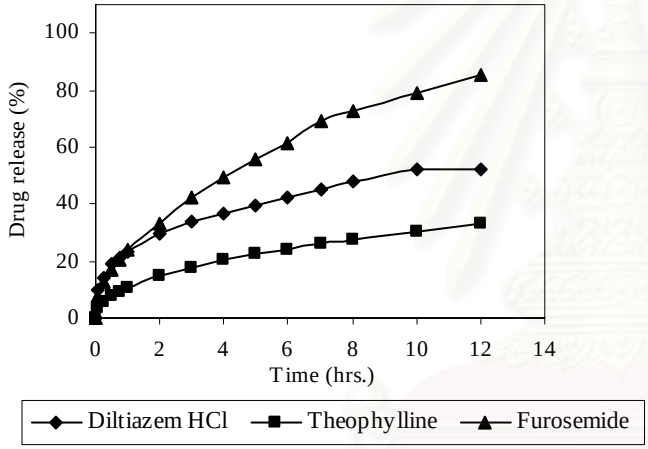

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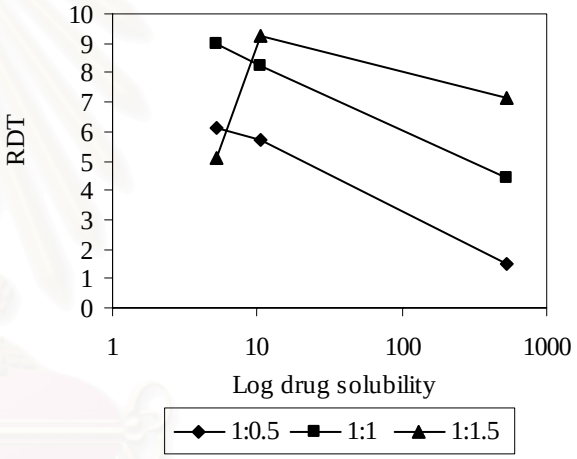

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Figure 21 Effect of drug solubility on drug release profiles of matrix tablets prepared from polyvinyl acetate dispersion at different drug to polymer ratio, the relationship between the relative dissolution time (RDT value) and the log drug solubility when using PBS solution as dissolution medium. (A) drug to polymer ratio of 1:0.5, (B) drug to polymer ratio of 1:1, (C) drug to polymer ratio of 1:1.5 and (D) the RDT value.

5.3 Effect of pH of the dissolution medium on drug release

The influence of pH of dissolution medium on drug release from D-PVAc, T-PVAc and F-PVAc matrices at drug to polymer ratio 1:0.5, 1:1 and 1:1.5 were investigated. The dissolution mediums were 0.1 N HCl solution, deionized water and PBS pH 6.8 solution, which were corresponding to the pH of 1.2, 4.5 and 6.8, respectively.

Serveral researcher reported that the drug release rate was affected by the pH of dissolution medium (Chang et al., 1997; Cox et al., 1999; Ramos et al., 1999; Ebube et al., 2004; Kinel et al., 2004 Pallagi et al., 2004). This result could be explained by the different solubilties of drugs in each dissolution media. According to the chemical property of the drug, weak acidic drug exhibited the slightly soluble in acidic medium whereas the weak basic drug was less soluble in basic medium.

The influence of pH of dissolution medium on RDT value of D-PVAc matrices are shown in Figure 22A. The dissolution profile of D-PVAc matrices depended on the pH of dissolution medium. The drug release rates in 0.1 N HCl solution was faster than those in deionized water and PBS pH 6.8 solution, respectively. This result was supported by the different solubility of diltiazem hydrochloride in various mediums. The lowest solubility of diltiazem hydrochloride in PBS pH 6.8 solution caused a slower drug release rate. Diltiazem hydrochloride was a weak basic drug that could be accounted for the conversion of drug to the less soluble free base in PBS pH 6.8 solution. The effect of pH of dissolution medium in diltiazem hydrochloride solubility resulted in decreasing of the diffusion rate of drug through the polymer barrier. This result could be supported by the RDT value. An increase in pH of dissolution medium caused an increase in RDT value.

The influence of pH of dissolution medium on RDT value of T-PVAc matrices are shown in Figure 22B. The drug release rate of T-PVAc matrices in 0.1 N HCl solution, deionized water and PBS pH 6.8 solution were not different. The RDT values of those matrices were similar. This finding indicated that the solubility of theophylline in various pH of dissolution medium were comparable. Moreover, this result was consistent with the pH-solubility profile of theophylline. This profile

showed the constant solubility of theophylline in the pH range of 2-8.5 (see Figure 1H, Appendix H).

The influence of pH of dissolution medium on RDT value of F-PVAc matrices are shown in Figure 22C. The RDT value of acidic dissolution medium was highest and lowest in basic dissolution medium. The effect of pH of dissolution medium on drug release was noted. The drug release rates in 0.1 N HCl solution were almost negligible (< 10% after 12 hrs.) and those PBS pH 6.8 solution were faster than those in deionized water. This result might be caused by the different solubility of furosemide in various media. Considering the solubility in each dissolution medium, furosemide was very slightly soluble in 0.1 N HCl solution (pH 1.2) and slightly soluble in deionized water (pH 4.5). The increasing pH of dissolution medium at pH 6.8, the solubility of drug was better. The drug release rate increased greatly in basic pH. These results indicated that the drug release rate depended greatly on the pH of dissolution medium.

In conclusion, this result found that the pH of the dissolution medium was a critical factor in determining the dissolution rate of drug from PVAc matices.

5.4 Effect of compression forces

The spray dried powders were compressed into matrices with the following compression pressure: 300, 500 and 1000 lbs by hydraulic laboratory press. The amount of drug release at any time interval of D-PVAc, T-PVAc and F-PVAc matrices at three-level compression were illustrated in Figure 23 (Table 7F-9F, Appendix F).

Several authors (Dabbagh, et al., 1996; Chebli et al., 2000; Liu et al., 2000) state that although compression force is a statistically significant factor in tablet hardness, its effect on drug release from tablet matrix was minimal. It could be assumed that the variation in compression forces should be closely related to a change in the porosity of tablets. However, as the porosity of the hydrated matrix was

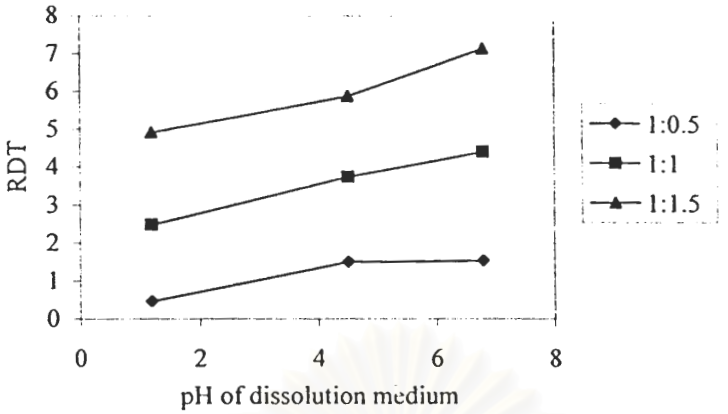
independent of the initial porosity, the compression force seems to have little influence on drug release.

The dissolution profiles of D-PVAc matrices at three-level compression were not different. The compression forces had no significant effect on the release of diltiazem hydrochloride matrices containing PVAc. Consequently, the applied compression force did not influence the RDT value for diltiazem hydrochloride.

The dissolution profiles of T-PVAc matrices prepared using the compression forces between 300-1000 lbs were slightly affected. When compression force was increased from 300 lb to 1000 lb., the obtained RDT value was similar.

The dissolution profiles of F-PVAc matrices would be discussed into two parts according to the characteristic in the dissolution medium. Furosemide had an extremely low solubility in acidic media, whereas it is soluble in basic media. In phosphate buffer pH 6.8, the effect of change in compression force on the drug release rate of furosemide was observed. Increasing of the compression forces from 300 lb to 1000 lb were similar. The results of the influence of compression force on the RDT value were not different. These results were agreed with previous reported. Rey et al. (2000) reported that the compression pressure from 200 to 250 MPa had no effect on theophylline release from microtablets.

A



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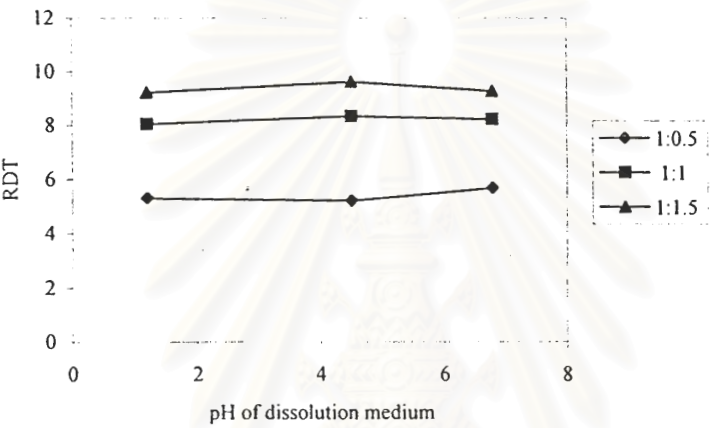

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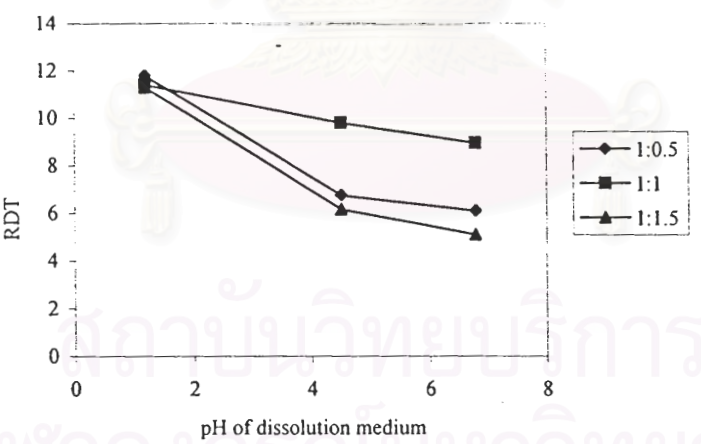
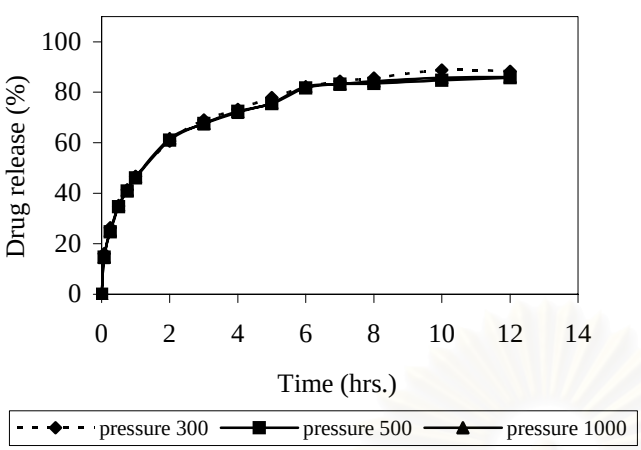


Figure 22 The relationship between the relative dissolution time (RDT value) of drugs-PVAc matrices and the pH of dissolution medium in different PVAc content. (A) D-PVAc matrices, (B) T-PVAc matrices and (C) F-PVAc matrices.



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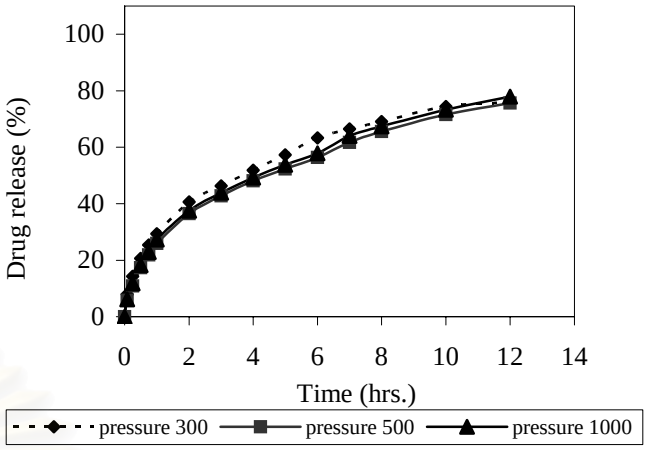

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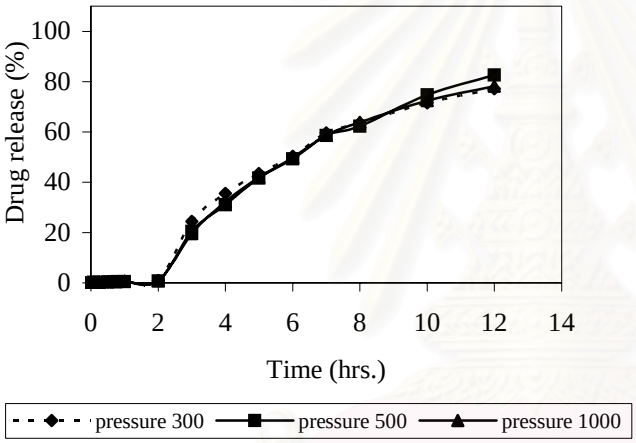

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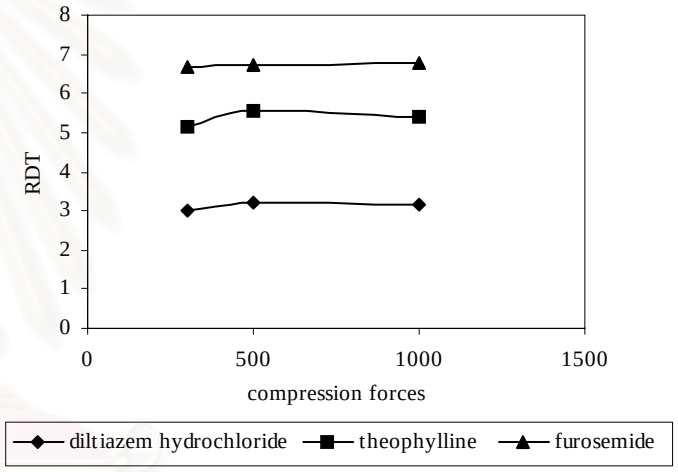

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Figure 23 Effect of compression force on drug release profile of D-PVAC matrices, T-PVAc matrices, F-PVAc matrices, the relationship between the relative dissolution time (RDT value) and the compression forces. (A) D-PVAc matrices prepared from polyvinyl acetate dispersion at drug to polymer ratio 1: 1 in pH changed medium. (B) T-PVAc matrices prepared from polyvinyl acetate dispersion at drug to polymer ratio 1: 0.5 in pH changed medium. (C) F-PVAc matrices prepared from polyvinyl acetate dispersion at drug to polymer ratio 1: 0.5 in pH changed medium. (D) the relationship between the relative dissolution time (RDT value) and the compression forces.

6. The evaluation of drug release kinetics

The drug release kinetic of PVAc matrices was investigated according to the zero-order, first-order and Higuchi's square root equation which were analyzed during the first 60% of drug release (see Table 1I, Appendix I). In all cases, the most suitable mathematical model for describing the experimental data was Higuchi's square root equation. Therefore, the release pattern was explained by Higuchi model. A plot of the percentage of drug release versus the square root time for matrices were shown in Figures 24-26. A linear relationship between the release percentage and the square root of time indicated that the drug release properties of the matrices were in good agreement with the diffusion model, as described by the Higuchi equation (Higuchi, 1963).

The Higuchi plots of release of D-PVAc, T-PVAc and F-PVAc in deionized water, 0.1 N HCl solution and PBS pH 6.8 were also depicted in Figures 24-26. It could be seen that a relatively linear relationship was obtained. The coefficients of determination (r^2) are presented in Table 14.

According to the Higuchi equation, the drug release from matrices system is proportional to the square root of time. In this study, the dissolution results were fitted to the Higuchi model (Higuchi, 1963). Pather et al. (1998) suggested the reason for the attenuation of the drug release rate in the Higuchi profile. When a matrix tablet was placed in the dissolution medium, the initial drug release occurs from the tablet's superficial layers and, consequently, the release rate is relatively fast. As time passes, the external layers of the tablet become depleted of the drug and water molecules must travel through long, tortuous channels to reach the drug remaining in the deeper layers of the tablet. Similarly, the drug solution that is formed within the tablet must diffuse through long capillaries to reach the external dissolution medium.

Table 14 The coefficient of determination (r^2) between percent of drug release versus square root time of D-PVAc, TPVAc and F-PVAc matrices in various dissolution medium.

Formulation	Drug to polymer ratio	Dissolution medium		
		Deionized water	0.1 N HCl	PBS pH 6.8
D-PVAc	1:0.5	0.9785	0.9995	0.9980
	1:1	0.9892	0.9899	0.9907
	1:1.5	0.9724	0.9714	0.9759
T-PVAc	1:0.5	0.9969	0.9989	0.9995
	1:1	0.9974	0.9992	0.9991
	1:1.5	0.9979	0.9918	0.9979
F-PVAc	1:0.5	0.9963	0.9823	0.9946
	1:1	0.9571	0.9677	0.9582
	1:1.5	0.9971	0.9774	0.9987

7. The Evaluation of release mechanism

The drug release mechanism of polymerc matrix was investigated by fiiting the dissolution data in to the exponential equation given below:

$$\frac{Mt}{M\alpha} = kt^n \qquad \text{(equation 1)}$$

where Mt / Mα is the fraction of drug release (0-0.60), t is the release time, k is a kinetic constant incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of druh release. In case of non-swelled tablet, n = 0.45 for Case I or Fickian diffusion, n = 1 for Case II transport, $0.45 < n < 1$ for anomalous or non-Fickian tramsport and $n > 0.89$ for super Case II transport (Ritger and Peppas, 1987).

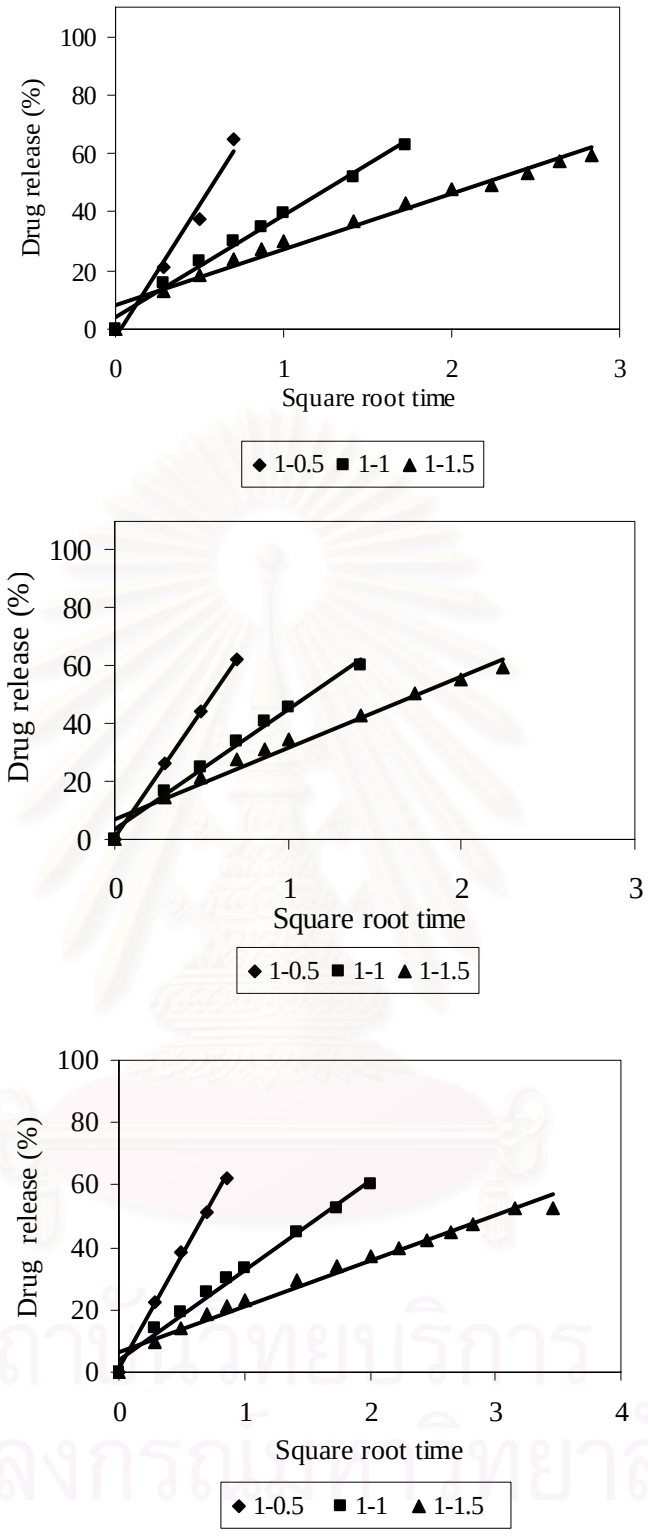


Figure 24 The Higuchi plot of D-PVAc matrices prepared from PVAc dispersion at drug to polymer ratio of 1:0.5, 1:1 and 1:1.5 (A) in deionized water, (B) in 0.1 N HClsolution and (C) in PBS pH 6.8 solution.

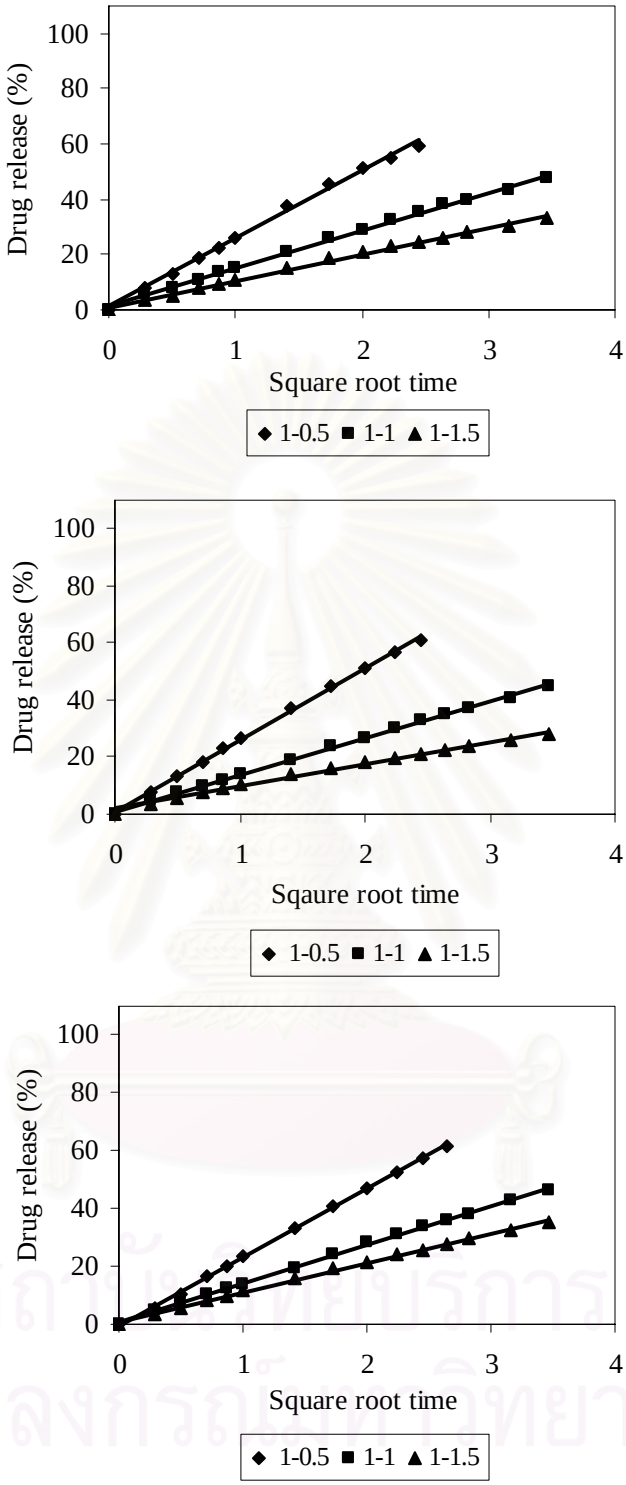


Figure 25 The Higuchi plot of T-PVAc matrices prepared from PVAc dispersion at drug to polymer ratio of 1:0.5, 1:1 and 1:1.5 (A) in deionized water, (B) in 0.1 N HClsolution and (C) in PBS pH 6.8 solution.

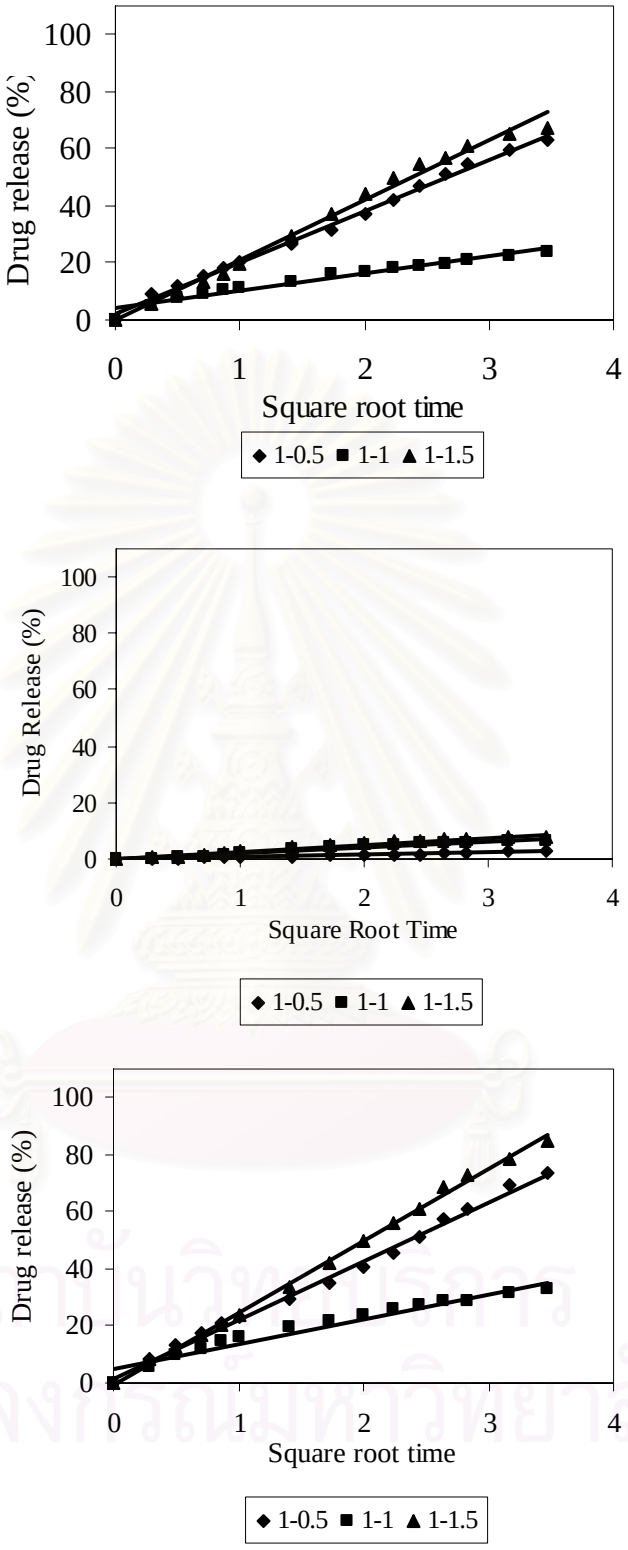


Figure 26 The Higuchi plot of F-PVAc matrices prepared from PVAc dispersion at drug to polymer ratio of 1:0.5, 1:1 and 1:1.5 (A) in deionized water, (B) in 0.1 N HClsolution and (C) in PBS pH 6.8 solution.

7.1 The evaluation of release mechanism of D-PVAc in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution

The D-PVAc matrices were not disintegrated and not swelled. The release exponent “n” was decreased when the PVAc concentration was increased in all of dissolution medium. This finding demonstrated that the release mechanism of D-PVAc matrices at drug to polymer ratio of 1:0.5 was controlled by a combination of both diffusion and polymer relaxation (anomalous transport). In higher PVAc, the release exponet “n” was approached to 0.45 that indicated that the main mechanism was Fickian transport. From this evaluation, it could be predicted that when the concentration of PVAc was increased until the critical concentration was reached, the mechanism would be Fickian transport.

7.2 The evaluation of release mechanism of T-PVAc in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution

The T-PVAc matrices were not disintegrated and not swelled. The increase in the PVAc concentration led to the release exponent “n” was closed to 0.45. The release exponent “n” of T-PVAc matrices at drug to polymer ratio of 1:0.5 was 0.4780. This result could be explained that the release mechanism of these in controlled by diffusion and minimal erosion. The high content of PVAc exhibited the release exponent was closed to 0.45. This finding indicated that the main mechanism was closed to Fickian transport and other mechanism was diminished.

7.3 The evaluation of release mechanism of F-PVAc in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution

The dissolution profiles of F-PVAc matrices in 0.1 N HCl solution were not evaluated because the drug release from these less than 10%.

The F-PVAc matrices at drug to polymer ratios of 1:0.5 and 1:1 in deionized water and those in PBS pH 6.8 solution were not disintegrated and not swelled. An increased in PVAc content caused a decreased in release exponent “n”. These results

confirmed that the release mechanism of F-PVAc matrices (ratio 0.5 and 1) was Fickian transport.

In contrast, the F-PVAc matrices at drug to polymer ratio 1:1.5 in deionized water and those in PBS pH 6.8 solution were not disintegrated but they were floated in the dissolution medium. Those matrices gave the highest release exponent "n". This result might be explained by the floatation of the matrices, as previously mentioned in 5.1.3.

Table 15 The values of release exponent (n) and coefficient of determination (r^2) of D-PVAc, TPVAc and F-PVAc matrices in various dissolution medium.

Formulation	Drug to polymer ratio	Dissolution medium					
		Deionized water		0.1 N HCl		PBS pH 6.8	
		n	r^2	n	r^2	n	r^2
D-PVAc	1:0.5	0.6078	0.9787	0.4802	0.9986	0.4569	0.9966
	1:1	0.3835	0.9964	0.3976	0.9982	0.3786	0.9935
	1:1.5	0.3325	0.9985	0.3361	0.9993	0.3418	0.9980
T-PVAc	1:0.5	0.4780	0.9981	0.4757	0.9991	0.5347	0.9976
	1:1	0.4573	0.9964	0.4500	0.9977	0.4615	0.9985
	1:1.5	0.4361	0.9983	0.4185	0.9992	0.4594	0.9993
F-PVAc	1:0.5	0.4180	0.9786	-	-	0.4174	0.9937
	1:1	0.2953	0.9930	-	-	0.3314	0.9922
	1:1.5	0.5326	0.9950	-	-	0.4786	0.9955

8. Morphology of D-PVAc, T-PVAc and F-PVAc matrices before and after release testing.

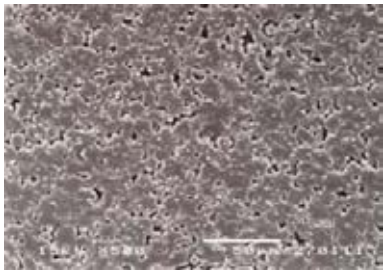
Scanning electron microscopy was used to investigate the surface structure of the matrices prior to and following the dissolution test in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution. The morphology of the surface of matrices after the dissolution test was the determining factor to support the release mechanism of drug from the matrices.

8.1 D-PVAC matrices

The photomicrographs of D-PVAc matrices before release testing in surface view are shown in Figure 27. The photomicrograph of D-PVAc matrices showed that the matrices were composed of compressed microspheres with smooth surface.

The photomicrographs of D-PVAc matrices at drug to polymer ratio of 1:0.5, 1:1 and 1:1.5 after release testing in various dissolution mediums in surface view are shown in Figures 28-30.

A smooth surface was observed for the matrices containing PVAc after release testing. PVAc might be in rubbery state at 37° C, and the smooth surface was the result of the hydrodynamic shearing force imposed on the surface of the matrices by the agitated dissolution medium (Zhang et al., 2000). The D-PVAc matrices at drug to polymer ratio of 1:0.5 gave a smooth surface with the pores on the tablet surface. The pores on the surface resulted from the diffusion of the diltiazem hydrochloride and maltodextrin in matrices. In addition, an increase in the polymer content caused a decrease in the pores. The D-PVAc matrices at drug to polymer ratio of 1:1 and 1:1.5 had a smooth surface without the pores. The correlation of surface morphology of D-PVAc matrices after release testing and the release mechanism was obtained. These results supported the result of drug release mechanism analysis in this study in that the release mechanism of D-PVAc closed to Fickian diffusion at high polymer content.



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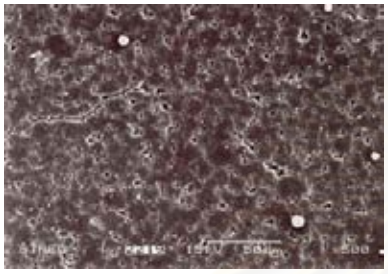

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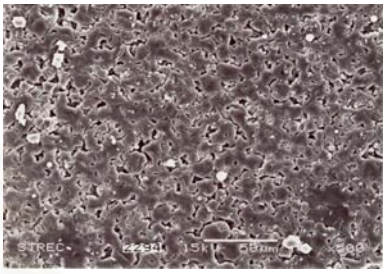
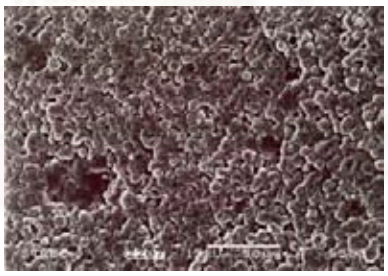


C

Figure 27 Photomicrograph of D-PVAc matrices before release testing (x 500 surface view) (A) D-PVAc matrices at drug to polymer ratio of 1:0.5, (B) D-PVAc matrices at drug to polymer ratio of 1:1, (C) D-PVAc matrices at drug to polymer ratio of 1:1.5.



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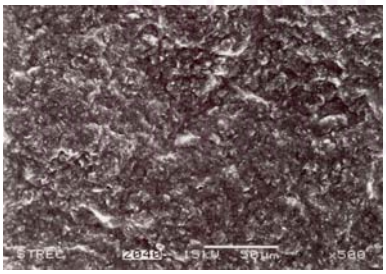

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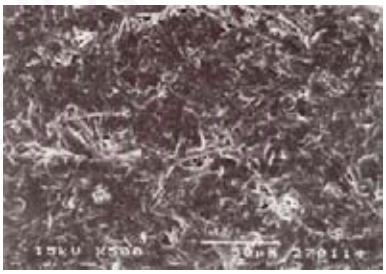
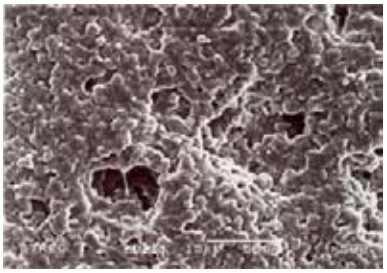


C

Figure 28 Photomicrograph of D-PVAc matrices after release testing in deionized water (x 500 surface view) (A) D-PVAc matrices at drug to polymer ratio of 1:0.5, (B) D-PVAc matrices at drug to polymer ratio of 1:1, (C) D-PVAc matrices at drug to polymer ratio of 1:1.5.



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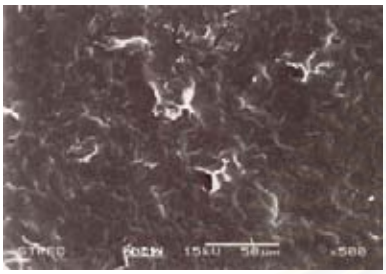

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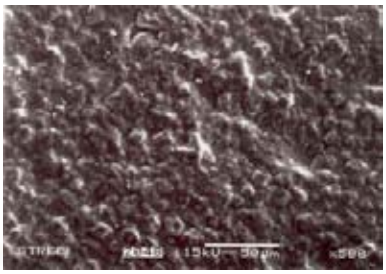
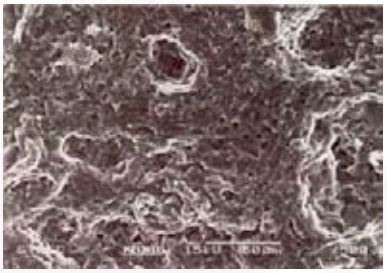
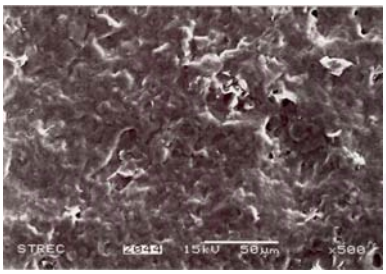


C

Figure 29 Photomicrograph of D-PVAc matrices after release testing in 0.1 N HCl solution (x 500 surface view) (A) D-PVAc matrices at drug to polymer ratio of 1:0.5, (B) D-PVAc matrices at drug to polymer ratio of 1:1, (C) D-PVAc matrices at drug to polymer ratio of 1:1.5.



A



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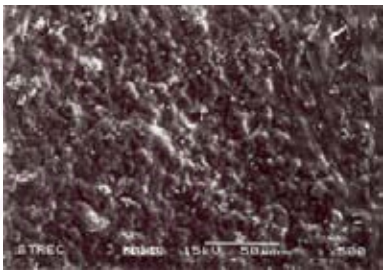


C

Figure 30 Photomicrograph of D-PVAc matrices after release testing in PBS solution (x 500 surface view) (A) D-PVAc matrices at drug to polymer ratio of 1:0.5, (B) D-PVAc matrices at drug to polymer ratio of 1:1, (C) D-PVAc matrices at drug to polymer ratio of 1:1.5.

8.2 T-PVAc matrices

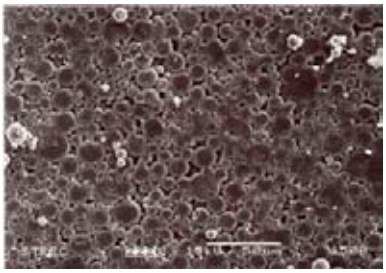
The photomicrographs of T-PVAc matrices before release testing in surface view are shown in Figure 31. The surface view of T-PVAc matrices showed that the matrices were composed of compressed microsheres. The microcrystal of theophylline could be found on them.

The photomicrographs of T-PVAc matrices at drug to polymer ratio of 1:0.5, 1:1 and 1:1.5 after release testing in various dissolution media in surface view are shown in Figures 32-34.

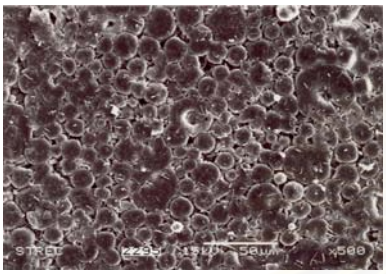
The photomicrographs of the immersed T-PVAc at drug to polymer ratio of 1:0.5 in deionized water and 0.1 N HCl solution showed the microcrystal of drug on the surface and these presented slightly rough surface. These results agreed with the result of drug release mechanism of T-PVAc (ratio 1:0.5). The release mechanism of these was anomalous transport (diffusion and polymer relaxation). However, the slightly rough surface indicated the minimal erosion of matrices.

The photomicrographs of the immersed T-PVAc matrices at drug to polymer ratio of 1:1 in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution showed the slightly rough surface without the pore and no the microcrystal of the drug. This obtained result was consistent with the drug release mechanism in this study. The release mechanism of T-PVAc (ratio 1:1) was anomalous transport. Whereas this might be closed to Fickian transport because the release exponent “n” was 0.4573.

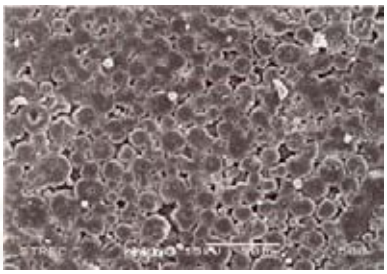
In addition, the photomicrographs of the immersed T-PVAc at highest PVAc content in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution showed the smoother surface than other PVAc content. This result agreed with the drug release mechanism of T-PVAc at highest PVAc content was Fickian transport.



A

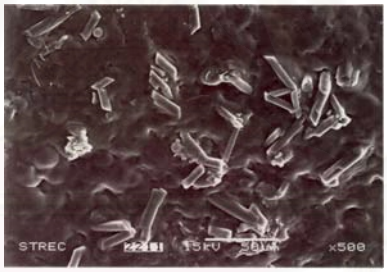


B



C

Figure 31 Photomicrograph of T-PVAc matrices before release testing (x 500 surface view) (A) T-PVAc matrices at drug to polymer ratio of 1:0.5, (B) T-PVAc matrices at drug to polymer ratio of 1:1, (C) T-PVAc matrices at drug to polymer ratio of 1:1.5.



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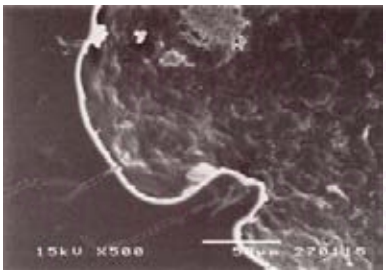

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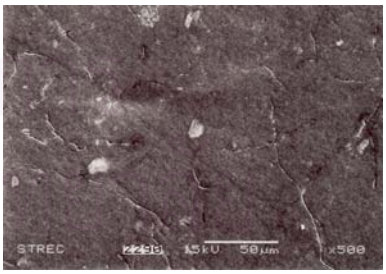
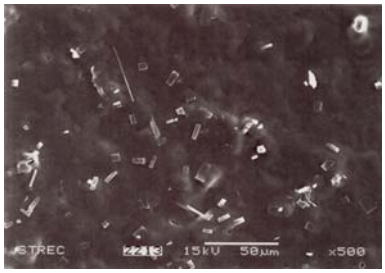


C

Figure 32 Photomicrograph of T-PVAc matrices after release testing in deionized water (x 500 surface view) (A) T-PVAc matrices at drug to polymer ratio of 1:0.5, (B) T-PVAc matrices at drug to polymer ratio of 1:1, (C) T-PVAc matrices at drug to polymer ratio of 1:1.5.



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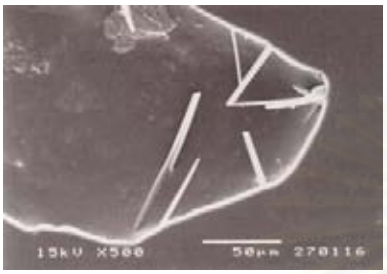

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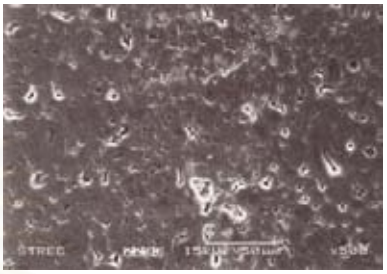
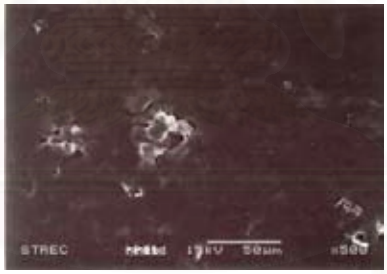


C

Figure 33 Photomicrograph of T-PVAc matrices after release testing in 0.1 N HCl solution (x 500 surface view) (A) T-PVAc matrices at drug to polymer ratio of 1:0.5, (B) T-PVAc matrices at drug to polymer ratio of 1:1, (C) T-PVAc matrices at drug to polymer ratio of 1:1.5.



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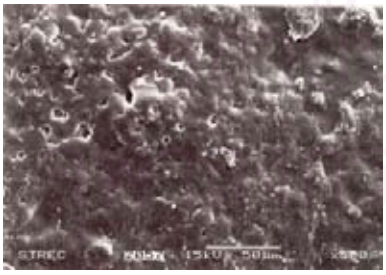

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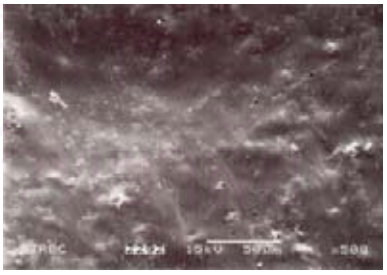


C

Figure 34 Photomicrograph of T-PVAc matrices after release testing in PBS solutin (x 500 surface view) (A) T-PVAc matrices at drug to polymer ratio of 1:0.5, (B) T-PVAc matrices at drug to polymer ratio of 1:1, (C) T-PVAc matrices at drug to polymer ratio of 1:1.5.

8.3 F-PVAC matrices

The photomicrographs of F-PVAc matrices before release testing in surface view are shown in Figure 35. The photomicrograph of F-PVAc matrices showed that the matrices were composed of compressed microspheres with smooth surface.

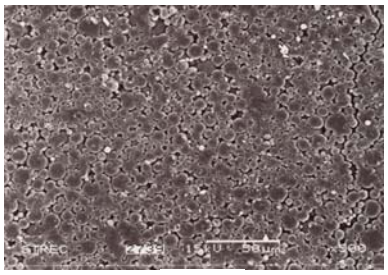
The photomicrographs of F-PVAc matrices at drug to polymer ratios of 1:0.5, 1:1 and 1:1.5 after release testing in various dissolution media in surface view are shown in Figures 36-38.

The photomicrograph of the immersed F-PVAc matrices at drug to polymer ratios of 1:0.5 and 1:1 in deionized water was observed. The surface of F-PVAc matrices (ratio 1:1) was smoother than that of ratio 1:0.5. This result correlated with the release mechanism. It was found that the release mechanism was Fickian transport.

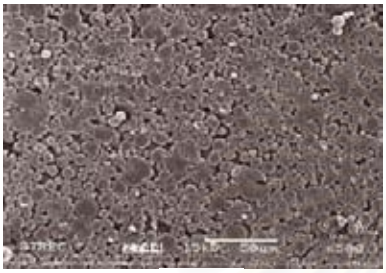
An unexpected, the surface of immersed F-PVAc matrices at highest polymer ratio (1:1.5) in deionized water gave a slightly rough surface. This result agrees with the release mechanism of these matrices, which was anomalous transport. This mechanism was both diffusion and erosion or polymer relaxation. Furthermore, the surface of immersed F-PVAc (ratio 1:1.5) in PBS pH 6.8 solution was similar.

Figures 37A-37B and 38A-38B show the surface of immersed F-PVAc matrices at drug polymer ratio 1:0.5 and 1:1 in PBS pH 6.8 solution.

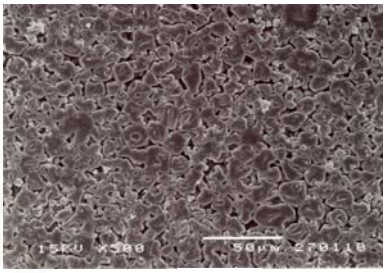
The immersed F-PVAc matrices at drug to polymer ratio of 1:0.5 were greater rough surface than that of ratio 1:1. Moreover, the small pores on the surface of matrices were also observed. The low PVAc content showed higher amount of pores than the high PVAc content.



A

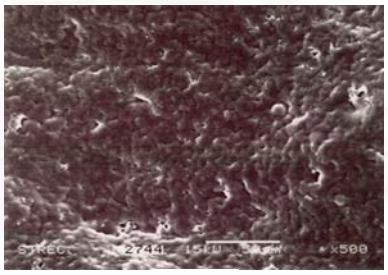


B

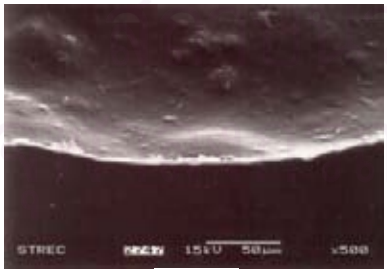


C

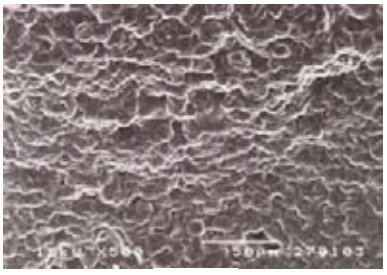
Figure 35 Photomicrograph of F-PVAc matrices before release testing (x 500 surface view) (A) F-PVAc matrices at drug to polymer ratio of 1:0.5, (B) F-PVAc matrices at drug to polymer ratio of 1:1, (C) F-PVAc matrices at drug to polymer ratio of 1:1.5.



A

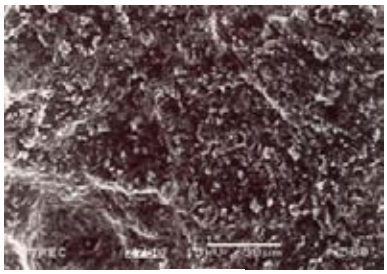


B

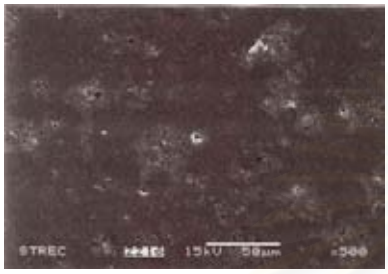


C

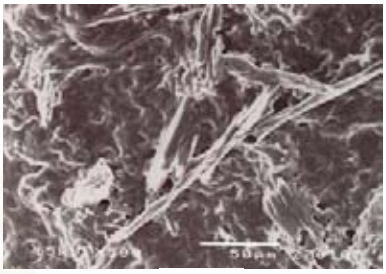
Figure 36 Photomicrograph of F-PVAc matrices after release testing in deionized water (x 500 surface view) (A) F-PVAc matrices at drug to polymer ratio of 1:0.5, (B) F-PVAc matrices at drug to polymer ratio of 1:1, (C) F-PVAc matrices at drug to polymer ratio of 1:1.5.



A

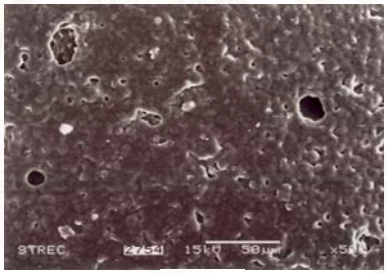


B

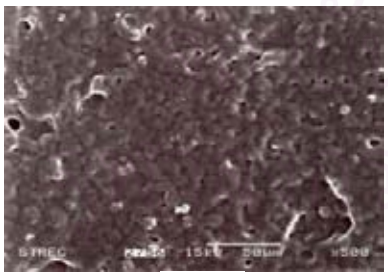


C

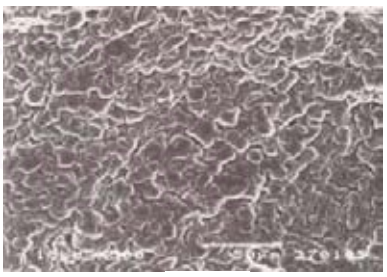
Figure 37 Photomicrograph of F-PVAc matrices after release testing in 0.1 N HCl solution (x 500 surface view) (A) F-PVAc matrices at drug to polymer ratio of 1:0.5, (B) F-PVAc matrices at drug to polymer ratio of 1:1, (C) F-PVAc matrices at drug to polymer ratio of 1:1.5.



A



B



C

Figure 38 Photomicrograph of F-PVAc matrices after release testing in PBS solution (x 500 surface view) (A) F-PVAc matrices at drug to polymer ratio of 1:0.5, (B) F-PVAc matrices at drug to polymer ratio of 1:1, (C) F-PVAc matrices at drug to polymer ratio of 1:1.5.

CHAPTER V

CONCLUSIONS

The homogeneous spray dried dispersions of three different type of drug with PVAc were obtained due to the uniformity of drug distribution throughout the spray drying process. They had a narrow particle size distribution and the mean particle size of spray dried was increased when increasing the polymer concentration. The shape of T-PVAc particle was spherical with microcrystal attached on the surface of each particle whereas the surface of F-PVAc particle had an orange peel texture. On the other hand, the shape and surface appearacne of D-PVAc were non spherical and partly shrunk which resulted from expansion of air bubbles. Thus, T-PVAc spray dried particles had better flow properties than the others.

The physicochemical properties studies show the following characteristics;

a. The X-ray pattern showed that D-PVAc and F-PVAc were amorphous state whereas T-PVAc exhibited both crystalline and amorphous state.

b. The change of thermal behaviors of D-PVAc, T-PVAc and F-PVAc were found, which could be the results from solubility or diffusibility of drug in polymer influenced on the changing in thermal properties

c. From the FTIR spectra, the major peak of intensity was not changed. This might be referred that the interaction of each component in both D-PVAc and T-PVAc was not occurred. However, the interaction between F-PVAc and ammonia solution were clearly take place via acid-base reaction.

The solid state stability study showed the physicochemically stable of the obtained spray dried powder except the spray dried of D-PVAc at low polymer concentration that shown the solid state transformation from amorphous to partial crystalline state.

The dissolution profiles of the compressed matrices from spray dried drugs-PVAc were influenced by the effect of drug to polymer ratio, drug solubility and pH of the dissolution medium. However, the compression force did not play an effect on the drug release. In the case of drug to polymer ratio, the higher the drug to polymer ratio, the slower the drug release was found. In addition, the relationship between drug solubility and the drug release profiles revealed that the higher drug release was obtained with the increasing drug solubility. However, the furosemide-PVAc system at the drug to polymer ratio of 1: 1.5 provided the controversial result which coming from the flotation effect of tablets by agitation force from paddle. The effect of pH of dissolution medium revealed that the release rate of dilatiazem from D-PVAc matrices in the basic medium was lower than the corresponding in acid medium due to the weak basic property. Meanwhile, the release rate of furosemide from F-PVAc matrices was lower in acid medium due to the weak acid property of furosemide. However, the release rates of theophylline in both basic and acid medium were nearly identical which resulted from similar pH solubility. Furthermore, the studied of the effect of compression force on the drug released revealed that the compression forces did not influence the release rate all of three different types of drug which represented a high soluble, sparingly soluble and slightly soluble drug.

The drug release kinetics of drugs-PVAc matrices were fitted with the Higuchi's equation. They can be concluded that the liberation of drugs was controlled by diffusion and polymer relaxation (Case I transport or anomalous transport). Moreover, the surface morphology of immersed drugs-PVAc matrices in dissolution medium was the further evidence that supported the main drug release mechanism as describe in previous section.

In conclusion, PVAc, normally used in controlled release tablet coating, could be employ in spray drying technique to fabricate the modified released matrices. The higher amount of polymer directly influence on the drug release from the matrices. In addition, the solubility of active ingredients is also the main crucial factor for the preparation of sustainable drugs- PVAc matrices.

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APPENDICES

Appendix A

Calibration Curve

The concentration versus absorbance Tables of diltiazem hydrochloride in methanol at 235 nm, deionized water, 0.1 N HCl and pH 6.8 phosphate buffer at 236 nm are presented in Table 1A - 4A, and the standard curve of diltiazem hydrochloride In each mediums are illustrated in figures 1A – 4A, respectively.

Table 1A Absorbance of diltiazem hydrochloride in methanol at 235 nm.

Concentration (µg/ml)	Abs(n1)	Abs(n2)	Abs(n3)	Abs(Average)	SD	%CV
4	0.2044	0.2045	0.2041	0.2043	0.0002	0.1019
6	0.2972	0.2979	0.2975	0.2975	0.0004	0.1180
8	0.3949	0.3953	0.3943	0.3948	0.0005	0.1275
10	0.4931	0.4938	0.4941	0.4937	0.0005	0.1039
12	0.5989	0.5994	0.5982	0.5988	0.0006	0.1007
16	0.7928	0.7931	0.7935	0.7931	0.0004	0.0443

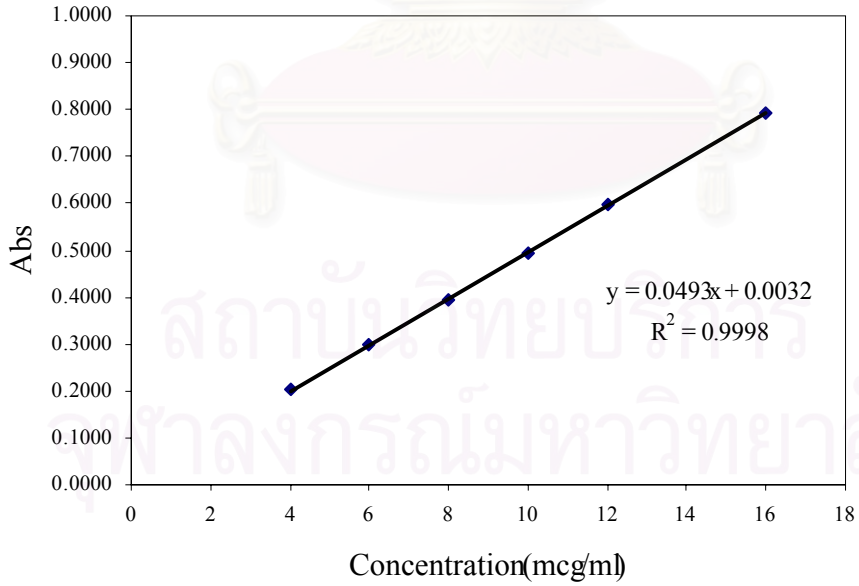


Figure 1A Calibration curve of diltiazem hydrochloride in methanol at 235 nm.

Table 2A Absorbance of diltiazem hydrochloride in deionized water at 236 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
3.9981	0.2136	0.2209	0.2137	0.2161	0.0041	1.9374
5.9971	0.3163	0.3273	0.3166	0.3201	0.0063	1.9577
7.9962	0.4214	0.4313	0.4226	0.4251	0.0054	1.2709
9.9952	0.5285	0.5362	0.5329	0.5325	0.0039	0.7254
11.9942	0.6261	0.6394	0.6314	0.6323	0.0067	1.0589
15.9923	0.837	0.856	0.8435	0.8455	0.0097	1.1421

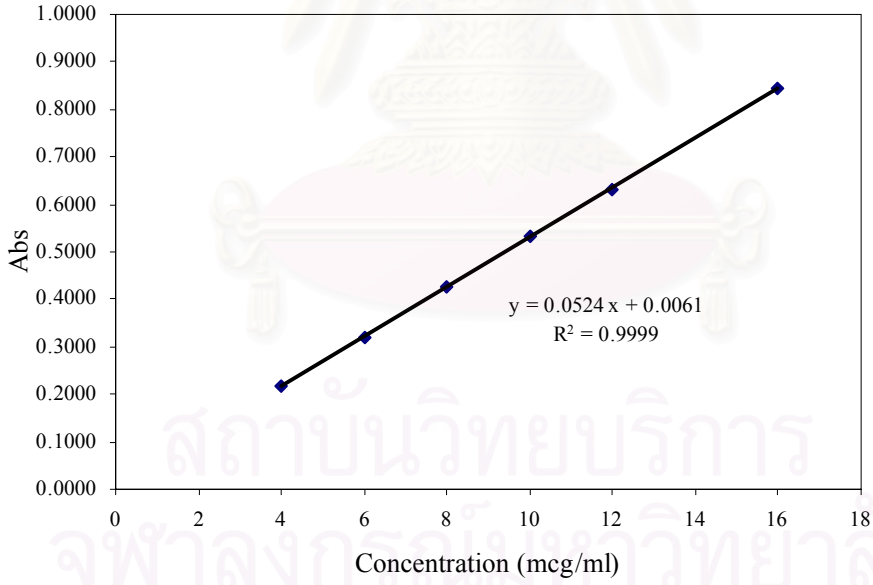


Figure 2A Calibration curve of diltiazem hydrochloride in deionized water at 236 nm.

Table 3A Absorbance of diltiazem hydrochloride in 0.1 N HCl at 236 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4.0160	0.2005	0.2090	0.2118	0.2071	0.0059	2.8415
6.0240	0.3160	0.3147	0.3178	0.3162	0.0016	0.4924
8.0320	0.4150	0.4191	0.4235	0.4192	0.0043	1.0140
10.0400	0.5278	0.5329	0.5348	0.5318	0.0036	0.6806
12.0480	0.6286	0.6345	0.6397	0.6343	0.0056	0.8756
16.0640	0.8383	0.8445	0.8508	0.8445	0.0063	0.7401

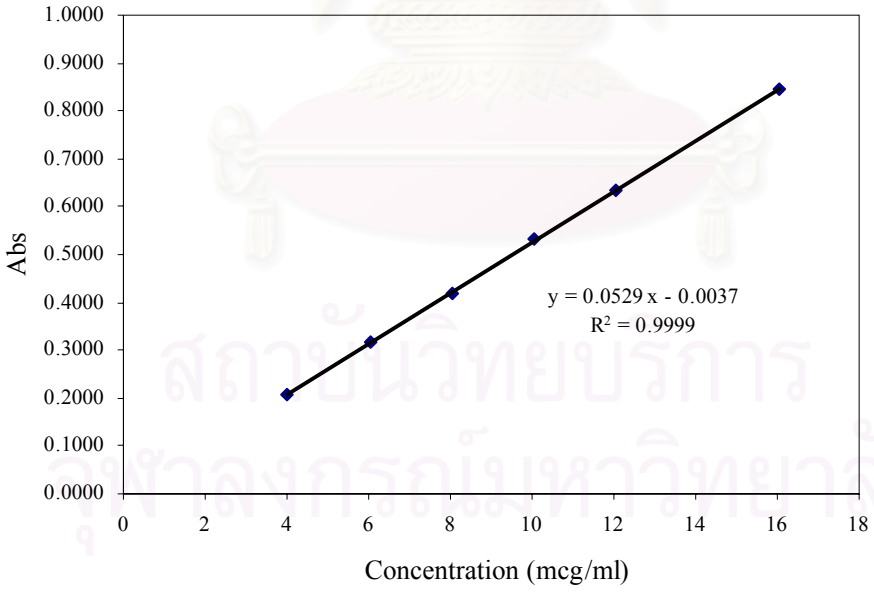


Figure 3A Calibration curve of diltiazem hydrochloride in 0.1 N HCl at 236 nm.

Table 4A Absorbance of diltiazem hydrochloride in pH 6.8 phosphate buffer at 236 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4	0.2268	0.21	0.2105	0.2158	0.0096	4.4300
6	0.317	0.3129	0.3177	0.3159	0.0026	0.8209
8	0.4219	0.4168	0.4222	0.4203	0.0030	0.7221
10	0.5215	0.527	0.5238	0.5241	0.0028	0.5270
12	0.6381	0.6331	0.6348	0.6353	0.0025	0.4002
16	0.8347	0.836	0.8447	0.8385	0.0054	0.6485

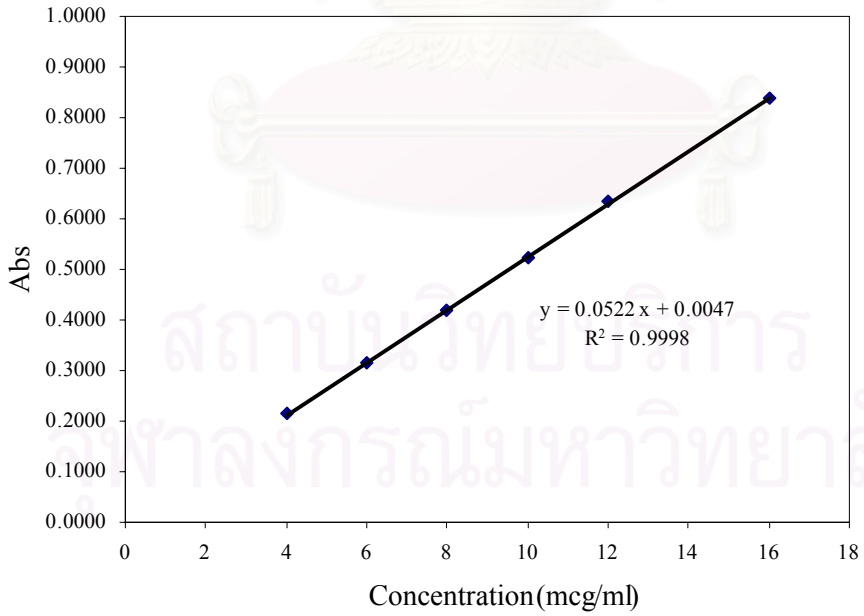


Figure 4A Calibration curve of diltiazem hydrochloride in pH 6.8 phosphate buffer at 236 nm.

The concentration versus absorbance Tables of theophylline in 6N ammonium hydroxide, deionized water, 0.1 N HCl and pH 6.8 phosphate buffer at 272 nm are presented in Table 5A - 8A, and the standard curve of theophylline in each mediums are illustrated in figures 5A – 8A, respectively.

Table 5A Absorbance of theophylline in 6N ammonium hydroxide at 272 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4	0.234	0.2338	0.2335	0.2338	0.0003	0.1077
6	0.346	0.3471	0.3459	0.3463	0.0007	0.1923
8	0.4632	0.464	0.4661	0.4644	0.0015	0.3225
10	0.5817	0.5829	0.5831	0.5826	0.0008	0.1300
12	0.6996	0.7001	0.7009	0.7002	0.0007	0.0937
16	0.924	0.9251	0.9233	0.9241	0.0009	0.0982

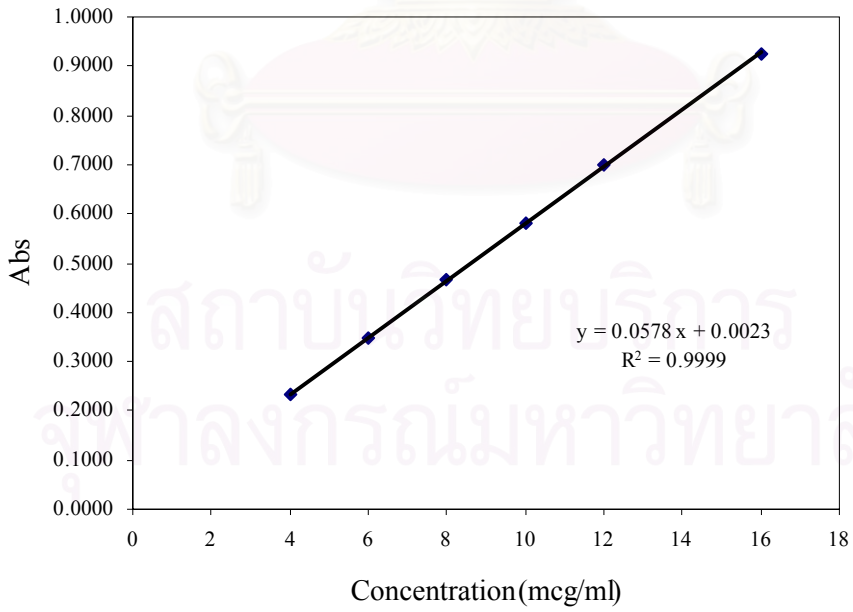


Figure 5A Calibration curve of theophylline in 6N ammonium hydroxide at 272 nm.

Table 6A Absorbance of theophylline in deionized water at 272 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4	0.2326	0.2363	0.2354	0.2348	0.0019	0.8219
6	0.3471	0.3495	0.3475	0.3480	0.0013	0.3695
8	0.463	0.4633	0.464	0.4634	0.0005	0.1107
10	0.5823	0.5808	0.5816	0.5816	0.0008	0.1291
12	0.7011	0.6966	0.7009	0.6995	0.0025	0.3634
16	0.9259	0.9233	0.925	0.9247	0.0013	0.1428

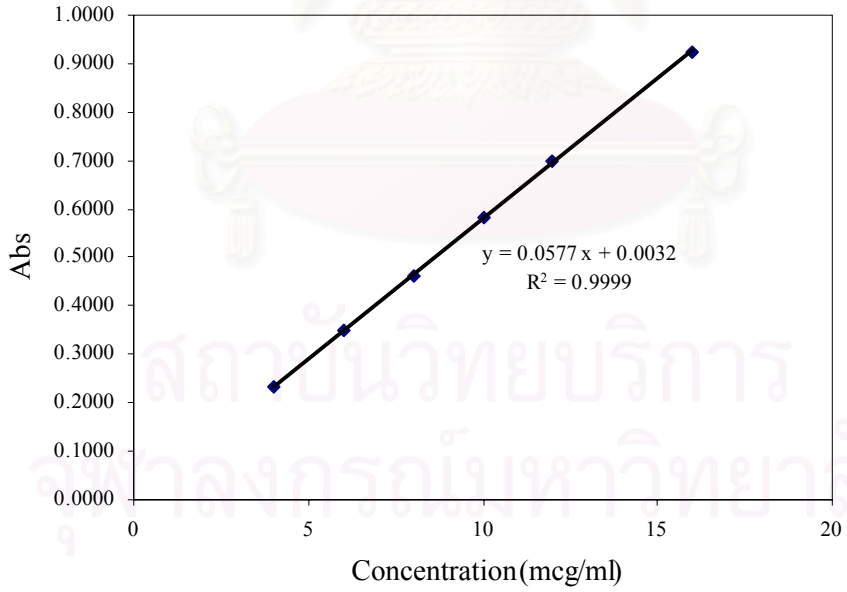


Figure 6A Calibration curve of theophylline in deionized water at 272 nm.

Table 7A Absorbance of theophylline in 0.1 N HCl at 272 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4	0.2174	0.2208	0.2198	0.2193	0.0017	0.7967
6	0.3272	0.3252	0.3266	0.3263	0.0010	0.3145
8	0.4337	0.4332	0.4341	0.4337	0.0005	0.1040
10	0.5457	0.5422	0.5429	0.5436	0.0019	0.3407
12	0.6584	0.6517	0.6513	0.6538	0.0040	0.6101
16	0.8753	0.8645	0.8658	0.8685	0.0059	0.6789

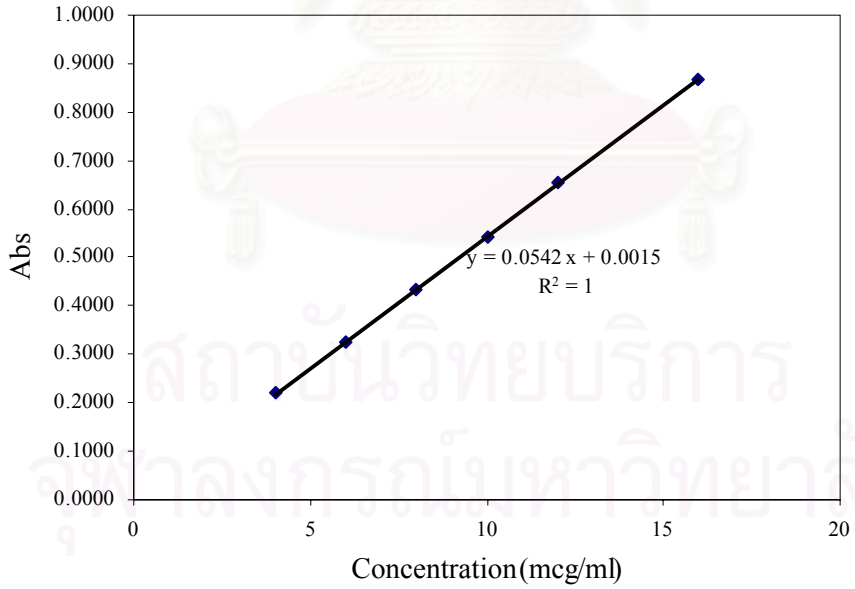


Figure 7A Calibration curve of theophylline in 0.1 N HCl at 272 nm.

Table 8A Absorbance of theophylline in phosphate buffer pH 6.8 at 272 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4	0.2349	0.2355	0.235	0.2351	0.0003	0.1367
6	0.3507	0.3516	0.351	0.3511	0.0005	0.1305
8	0.4661	0.4658	0.4662	0.4660	0.0002	0.0447
10	0.5782	0.5779	0.5785	0.5782	0.0003	0.0519
12	0.6931	0.694	0.6944	0.6938	0.0007	0.0960
16	0.9248	0.9253	0.9268	0.9256	0.0010	0.1124

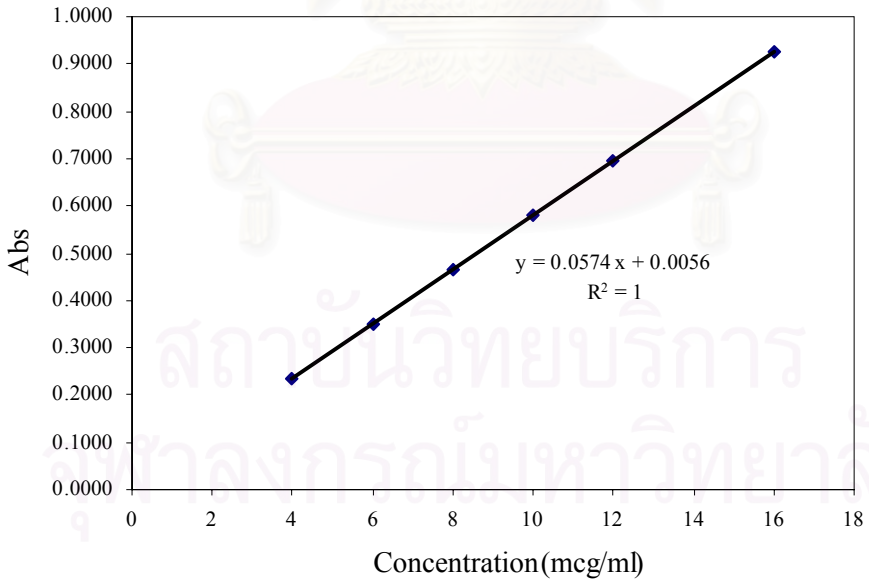


Figure 8A Calibration curve of theophylline in phosphate buffer pH 6.8 at 272 nm.

The concentration versus absorbance Tables of furosemide in ethanol, deionized water, phosphate buffer pH 6.8 at 277 nm and 0.1 N HCl at 275 nm are presented in Table 9A - 12A, and the standard curve of furosemide in each mediums are illustrated in figures 9A – 12A, respectively.

Table 9A Absorbance of furosemide in ethanol at 277 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
10	0.1716	0.1714	0.1718	0.1716	0.0002	0.1166
20	0.3388	0.3395	0.339	0.3391	0.0004	0.1063
30	0.5081	0.5087	0.5088	0.5085	0.0004	0.0744
40	0.6748	0.6756	0.6751	0.6752	0.0004	0.0599
50	0.8495	0.8499	0.8491	0.8495	0.0004	0.0471

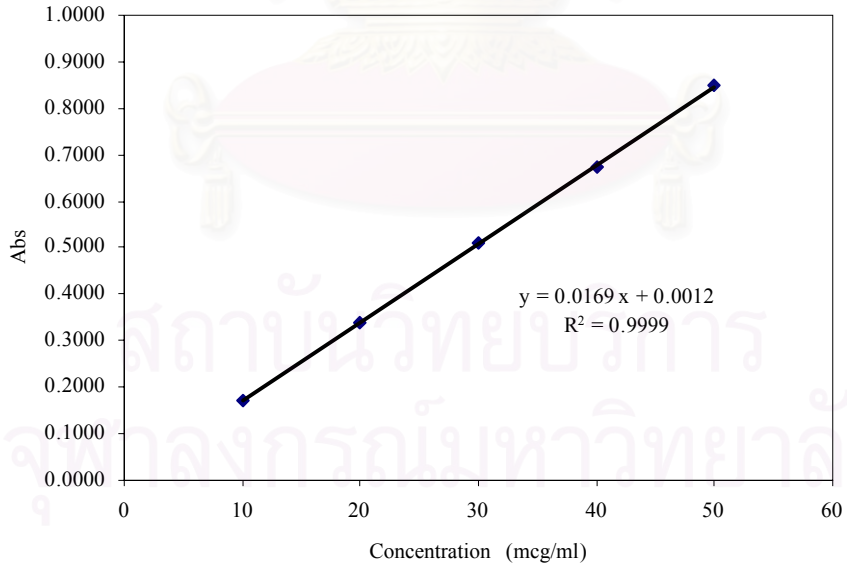


Figure 9A Calibration curve of furosemide in ethanol at 277 nm.

Table 10A Absorbance of furosemide in deionized water at 277 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4	0.2556	0.256	0.2558	0.2558	0.0002	0.0782
5	0.3253	0.3259	0.325	0.3254	0.0005	0.1408
6	0.3892	0.3903	0.3899	0.3898	0.0006	0.1428
8	0.5201	0.519	0.5199	0.5197	0.0006	0.1128
10	0.6625	0.6614	0.6618	0.6619	0.0006	0.0841
12	0.7876	0.788	0.7871	0.7876	0.0005	0.0573

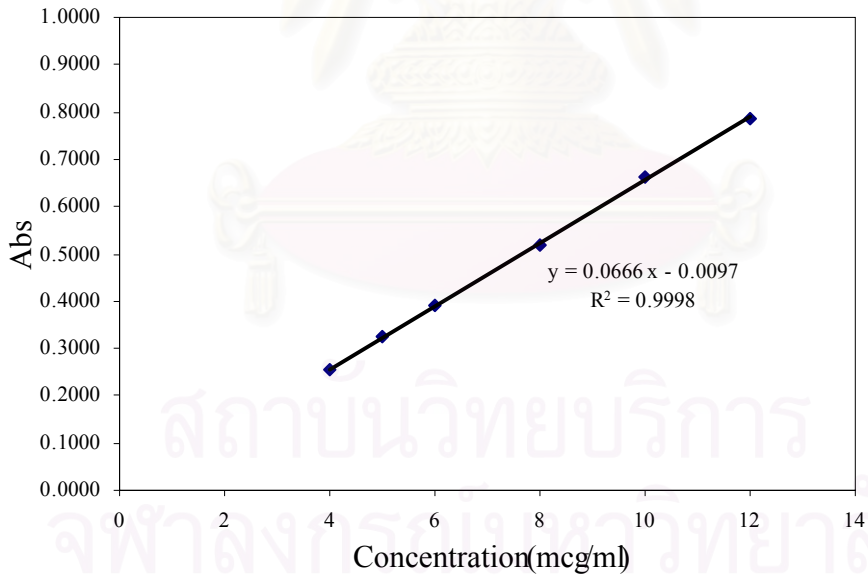


Figure 10A Calibration curve of furosemide in deionized water at 277 nm.

Table 11A Absorbance of furosemide in 0.1 N HCl at 275 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4	0.2552	0.2561	0.2559	0.2557	0.0005	0.1848
5	0.3191	0.3186	0.3199	0.3192	0.0007	0.2054
6	0.3888	0.3784	0.389	0.3854	0.0061	1.5732
8	0.5092	0.5045	0.5074	0.5070	0.0024	0.4677
10	0.6288	0.6294	0.6279	0.6287	0.0008	0.1201

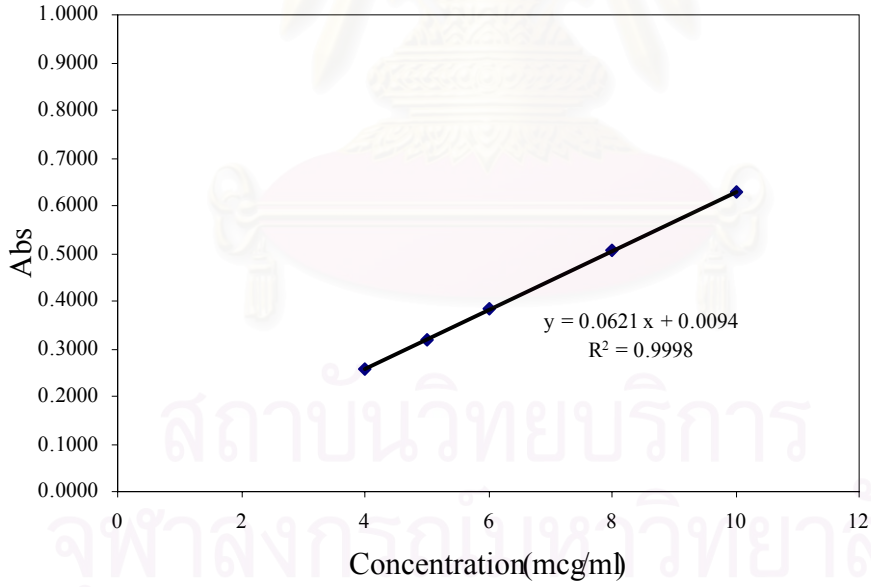


Figure 11A Calibration curve of furosemide in 0.1 N HCl at 277 nm.

Table 12A Absorbance of furosemide in phosphate buffer pH 6.8 at 277 nm.

Concentration (µg/ml)	Abs (n1)	Abs (n2)	Abs(n3)	Abs (Average)	SD	%CV
4	0.253	0.2545	0.2537	0.2537	0.0008	0.2958
5	0.3166	0.317	0.3144	0.3160	0.0014	0.4430
6	0.386	0.3841	0.3859	0.3853	0.0011	0.2775
8	0.5086	0.5097	0.5079	0.5087	0.0009	0.1784
10	0.6487	0.6421	0.649	0.6466	0.0039	0.6032
12	0.7745	0.7734	0.7751	0.7743	0.0009	0.1113

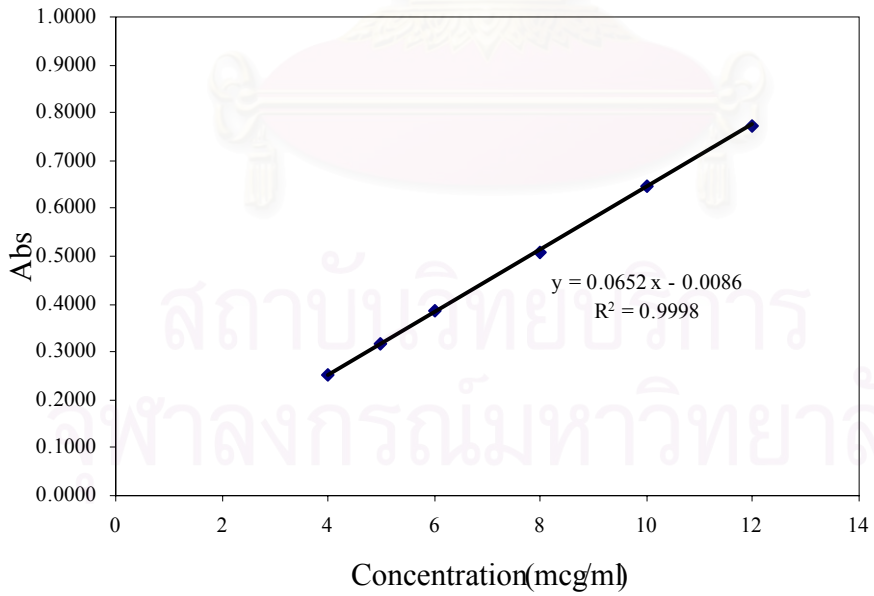


Figure 12A Calibration curve of furosemide in phosphate buffer pH 6.8 at 277 nm.

APPENDIX B

Validation for the quantitative determination of Diltiazem hydrochloride, Theophylline and Furosemide released from the matrices by UV spectroscopy.

The parameters evaluated to ensure the acceptability of the performance of the selected analytical method were accuracy, precision, specificity and linearity (USP XXI).

1. Accuracy

The standard solution were prepared at suitable concentration. Three sets of each concentrtion were prepared. Each individual sample was analyzed by UV spectrophotometry, and percent analytical recovery of each sample was calculated.

2. Precision

2.1 Within Run Precision

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

2.2 Between run Precision

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

3. Specificity

Under the condition selected for in vitro Diltiazem, Theophylline and Furosemide studies, the peaks of other components in the matrix systems must not interfere with the peak of these three drug. This validation was made by comparing the peak scan from UV spectrophotometer between the dissolution medium taken from the placebo system without drug with the one taken from the drug-containing system of the similar composition.

4. Linearity

Linear regression analysis of the absorbance versus the corresponding concentrations was performed, and the coefficient of determination was calculated. The results of validation process are as in the following tables:

1. Accuracy

Table 1B Accuracy data of Diltiazem

Expected concentration (μg/ml)	**Analytical Concentration** (μg/ml)	**% recovery**
4.00	4.08	101.98
	4.10	102.50
	3.98	99.50
8.00	7.94	99.24
	7.86	98.25
	7.98	99.75
16.00	16.00	100.01
	15.96	99.75
	16.10	100.63

Mean % recovery = 100.18, SD = 1.34, % CV=

Table 2B Accuracy data of Theophylline

Expected concentration (μg/ml)	**Analytical Concentration** (μg/ml)	**% recovery**
4.00	4.08	100.21
	4.18	104.50
	3.89	97.25
8.00	7.97	99.65
	7.85	98.13
	8.00	100.00
16.00	15.94	99.63
	16.20	101.25
	15.84	99.00

Mean % recovery = 99.96, SD = 2.07, % CV=

Table 3B Accuracy data of Furosemide

Expected concentration (μg/ml)	**Analytical Concentration** (μg/ml)	**% recovery**
4.00	4.01	100.32
	3.97	99.25
	4.15	103.75
8.00	7.93	99.09
	7.85	98.13
	8.08	101.00
12.00	12.01	100.12
	11.97	99.75
	11.89	99.08

Mean % recovery = 100.05, SD = 1.62, % CV=

2. Precision

Table 4B Within run precision data of Diltiazem

Concentration (mcg/ml)	Absorbance					
	n1	n2	n3	n4	n5	n6
4	0.2044	0.2045	0.2041	0.2041	0.2043	0.2044
6	0.2972	0.2979	0.2975	0.2976	0.2974	0.2973
8	0.3949	0.3953	0.3943	0.3949	0.3945	0.3944
10	0.4931	0.4938	0.4941	0.4936	0.4931	0.493
12	0.5989	0.5994	0.5982	0.5988	0.5984	0.599
16	0.7928	0.7931	0.7935	0.793	0.793	0.7933
Correlation	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999
R2	0.9998	0.9998	0.9998	0.9998	0.9998	0.9997

Concentration (mcg/ml)	Inverse Concentration						Mean	SD	%CV
	n1	n2	n3	n4	n5	n6			
4	4.079	4.081	4.073	4.073	4.077	4.079	4.077	0.003	0.083
6	5.959	5.974	5.965	5.968	5.963	5.961	5.965	0.005	0.084
8	7.939	7.947	7.927	7.939	7.931	7.929	7.935	0.008	0.097
10	9.929	9.943	9.949	9.939	9.929	9.927	9.936	0.009	0.092
12	12.072	12.082	12.058	12.070	12.062	12.074	12.070	0.009	0.072
16	16.001	16.007	16.015	16.005	16.005	16.011	16.007	0.005	0.031

Table 5B Within run precision data of Theophylline

Concentration (mcg/ml)	Absorbance					
	n1	n2	n3	n4	n5	n6
4	0.234	0.2338	0.2335	0.2341	0.2338	0.2337
6	0.346	0.3471	0.3459	0.3465	0.3464	0.3461
8	0.4632	0.464	0.4661	0.4638	0.4639	0.4638
10	0.5817	0.5829	0.5831	0.5834	0.583	0.5828
12	0.6996	0.7001	0.7009	0.7001	0.7008	0.6999
16	0.924	0.9251	0.9233	0.9245	0.9248	0.9242
Correlation	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999
R2	0.9999	0.9999	0.9998	0.9999	0.9999	0.9999

Concentration (mcg/ml)	Inverse Concentration						Mean	SD	%CV
	n1	n2	n3	n4	n5	n6			
4.000	4.008	4.005	4.000	4.010	4.005	4.003	4.005	0.004	0.092
6.000	5.945	5.964	5.944	5.954	5.952	5.947	5.951	0.008	0.128
8.000	7.972	7.986	8.022	7.983	7.984	7.983	7.988	0.017	0.217
10.000	10.022	10.042	10.046	10.051	10.044	10.041	10.041	0.010	0.101
12.000	12.061	12.069	12.083	12.069	12.081	12.066	12.072	0.009	0.073
16.000	15.941	15.960	15.929	15.950	15.955	15.945	15.947	0.011	0.069

Table 6B Within run precision data of Furosemide

Concentration (mcg/ml)	Absorbance					
	n1	n2	n3	n4	n5	n6
4	0.2535	0.2538	0.2537	0.253	0.253	0.2537
5	0.3166	0.317	0.316	0.3164	0.3171	0.317
6	0.3861	0.3855	0.3859	0.385	0.3854	0.3859
8	0.5085	0.509	0.5081	0.508	0.509	0.5085
10	0.645	0.6444	0.6462	0.6451	0.6442	0.645
12	0.7748	0.774	0.7751	0.7755	0.775	0.7745
Correlation	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999
R2	0.9998	0.9999	0.9998	0.9998	0.9999	0.9998

Concentration (mcg/ml)	Inverse Concentration						Mean	SD	%CV
	n1	n2	n3	n4	n5	n6			
4.000	4.013	4.017	4.016	4.005	4.005	4.016	4.012	0.006	0.138
5.000	4.981	4.987	4.972	4.978	4.989	4.987	4.983	0.007	0.133
6.000	6.048	6.039	6.045	6.031	6.037	6.045	6.041	0.006	0.104
8.000	7.927	7.935	7.921	7.919	7.935	7.927	7.927	0.007	0.083
10.000	10.022	10.013	10.041	10.024	10.010	10.022	10.022	0.011	0.107
12.000	12.015	12.002	12.019	12.026	12.018	12.010	12.015	0.008	0.066

Table 7B Between run precision data diltiazem

Conc (ug/ml)	Absorbance																	
	Day 1			Day 2			Day 3			Day 4			Day 5			Day 6		
	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3
4.000	0.204	0.205	0.204	0.204	0.205	0.204	0.204	0.205	0.204	0.204	0.205	0.205	0.204	0.205	0.205	0.204	0.204	0.205
6.000	0.297	0.298	0.298	0.298	0.298	0.298	0.298	0.298	0.298	0.297	0.298	0.298	0.298	0.298	0.298	0.298	0.298	0.299
8.000	0.395	0.395	0.394	0.395	0.395	0.395	0.395	0.395	0.395	0.395	0.395	0.395	0.395	0.395	0.394	0.395	0.395	0.395
10.000	0.493	0.494	0.494	0.495	0.495	0.495	0.495	0.496	0.496	0.493	0.494	0.494	0.495	0.495	0.495	0.495	0.495	0.496
12.000	0.599	0.599	0.598	0.599	0.599	0.599	0.599	0.599	0.599	0.599	0.599	0.598	0.599	0.599	0.599	0.599	0.599	0.599
16.000	0.793	0.793	0.794	0.793	0.793	0.793	0.793	0.793	0.793	0.793	0.793	0.794	0.793	0.793	0.793	0.793	0.793	0.793
Correlation	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
R2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Between run precision data (continue)

conc (ug/ml)	Inverse Concentration																		mean	SD	% CV
	Day 1			Day 2			Day 3			Day 4			Day 5			Day 6					
	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3			
4.00	4.08	4.08	4.07	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	4.08	0.00	0.06
6.00	5.96	5.97	5.97	5.97	5.97	5.98	5.98	5.98	5.98	5.96	5.97	5.97	5.97	5.97	5.97	5.98	5.98	6.00	5.97	0.01	0.15
8.00	7.94	7.95	7.93	7.93	7.93	7.93	7.93	7.93	7.94	7.94	7.95	7.93	7.93	7.94	7.93	7.93	7.93	7.94	7.94	0.01	0.08
10.00	9.93	9.94	9.95	9.97	9.97	9.97	9.97	9.98	9.98	9.93	9.94	9.95	9.97	9.97	9.97	9.97	9.97	9.98	9.96	0.02	0.17
12.00	12.07	12.08	12.06	12.07	12.08	12.08	12.08	12.08	12.07	12.08	12.08	12.06	12.07	12.08	12.07	12.08	12.08	12.07	12.08	0.01	0.06
16.00	16.00	16.01	16.01	16.00	16.01	16.01	16.01	16.01	16.01	16.00	16.01	16.01	16.00	16.01	16.00	16.01	16.01	16.00	16.01	0.00	0.03

Table 8B Between run precision data Theophylline

Conc (ug/ml)	Absorbance																	
	Day 1			Day 2			Day 3			Day 4			Day 5			Day 6		
	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3
4.000	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234	0.234
6.000	0.346	0.347	0.346	0.347	0.346	0.347	0.346	0.347	0.346	0.347	0.347	0.346	0.346	0.347	0.346	0.347	0.347	0.347
8.000	0.463	0.464	0.466	0.465	0.464	0.464	0.464	0.464	0.465	0.464	0.465	0.464	0.464	0.464	0.465	0.465	0.465	0.465
10.000	0.582	0.583	0.583	0.583	0.583	0.584	0.582	0.583	0.583	0.583	0.583	0.583	0.582	0.583	0.583	0.582	0.583	0.583
12.000	0.700	0.700	0.701	0.700	0.700	0.701	0.700	0.700	0.701	0.700	0.700	0.701	0.700	0.701	0.701	0.701	0.700	0.701
16.000	0.924	0.925	0.923	0.924	0.924	0.923	0.924	0.925	0.925	0.924	0.925	0.925	0.924	0.925	0.925	0.924	0.925	0.925
Correlation	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
R2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Between run precision data (continue)

conc (ug/ml)	Inverse Concentration																		mean	SD	% CV
	Day 1			Day 2			Day 3			Day 4			Day 5			Day 6					
	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3			
4.00	4.01	4.00	4.00	4.00	4.01	4.00	4.01	4.00	4.00	4.01	4.01	4.01	4.01	4.00	4.00	4.01	4.00	4.00	4.01	0.00	0.10
6.00	5.95	5.96	5.94	5.95	5.95	5.96	5.95	5.96	5.95	5.95	5.96	5.95	5.95	5.96	5.95	5.95	5.96	5.96	5.95	0.01	0.11
8.00	7.97	7.99	8.02	7.99	7.99	7.99	7.99	7.99	8.00	7.99	7.99	7.99	7.99	7.99	8.00	7.99	8.00	8.00	7.99	0.01	0.13
10.00	10.02	10.04	10.05	10.04	10.05	10.05	10.03	10.04	10.04	10.04	10.04	10.05	10.03	10.04	10.04	10.03	10.04	10.05	10.04	0.01	0.09
12.00	12.06	12.07	12.08	12.07	12.07	12.08	12.07	12.07	12.08	12.07	12.07	12.08	12.07	12.08	12.08	12.08	12.07	12.08	12.07	0.01	0.06
16.00	15.94	15.96	15.93	15.93	15.94	15.93	15.94	15.96	15.95	15.94	15.95	15.95	15.95	15.95	15.96	15.95	15.96	15.95	15.95	0.01	0.06

Table 9B Between run precision data furosemide

Conc (ug/ml)	Absorbance																	
	Day 1			Day 2			Day 3			Day 4			Day 5			Day 6		
	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3
4.0	0.254	0.254	0.254	0.254	0.254	0.254	0.253	0.253	0.253	0.254	0.254	0.254	0.253	0.253	0.253	0.253	0.253	0.254
5.0	0.317	0.317	0.316	0.317	0.317	0.317	0.317	0.318	0.317	0.317	0.316	0.317	0.317	0.318	0.317	0.318	0.317	0.317
6.0	0.386	0.386	0.386	0.385	0.386	0.386	0.386	0.386	0.387	0.385	0.386	0.387	0.387	0.387	0.387	0.387	0.387	0.388
8.0	0.509	0.509	0.508	0.508	0.508	0.508	0.508	0.509	0.508	0.509	0.508	0.510	0.509	0.508	0.508	0.510	0.509	0.510
10.0	0.645	0.644	0.646	0.646	0.646	0.645	0.646	0.646	0.645	0.644	0.646	0.646	0.645	0.645	0.646	0.646	0.645	0.645
12.0	0.775	0.774	0.775	0.775	0.775	0.775	0.775	0.775	0.775	0.775	0.776	0.775	0.775	0.775	0.775	0.775	0.774	0.775
Correlation	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
R2	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Between run precision data furosemide (continue)

conc (ug/ml)	Inverse Concentration																		mean	SD	% CV
	Day 1			Day 2			Day 3			Day 4			Day 5			Day 6					
	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3			
4.00	4.01	4.02	4.02	4.01	4.02	4.02	4.01	4.00	4.01	4.02	4.02	4.02	4.01	4.01	4.00	4.00	4.01	4.02	4.01	0.00	0.12
5.00	4.98	4.99	4.97	4.99	4.99	4.98	4.99	5.00	4.99	4.99	4.97	4.99	4.99	5.00	4.99	5.00	4.99	4.99	4.99	0.01	0.15
6.00	6.05	6.04	6.05	6.03	6.05	6.04	6.05	6.05	6.06	6.03	6.05	6.06	6.06	6.06	6.05	6.05	6.06	6.07	6.05	0.01	0.18
8.00	7.93	7.93	7.92	7.92	7.92	7.93	7.93	7.93	7.93	7.93	7.92	7.94	7.93	7.92	7.92	7.95	7.93	7.94	7.93	0.01	0.12
10.00	10.02	10.01	10.04	10.03	10.04	10.03	10.04	10.04	10.03	10.01	10.04	10.03	10.02	10.02	10.03	10.04	10.03	10.02	10.03	0.01	0.08
12.00	12.01	12.00	12.02	12.02	12.02	12.02	12.02	12.02	12.02	12.02	12.03	12.01	12.02	12.02	12.02	12.02	12.00	12.01	12.02	0.01	0.06

4. Specificity

The UV spectra from UV spectrophotometer of the dissolution medium taken from non-drug containing (placebo)

1. Placebo in deionized water at 236 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0008	0.0008	0.0008	0.0008	0	0
6	0.0008	0.0007	0.0008	0.000767	5.77E-05	7.530656
12	0.0008	0.0008	0.0007	0.000767	5.77E-05	7.530656

2. Placebo in deionized water at 272 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0008	0.0008	0.0008	0.0008	0	0
6	0.0008	0.0007	0.0008	0.000767	5.77E-05	7.530656
12	0.0008	0.0008	0.0007	0.000767	5.77E-05	7.530656

3. Placebo in deionized water at 275 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0007	0.0007	0.0007	0.0007	1.03E-11	1.47E-06
6	0.0007	0.0007	0.0007	0.0007	1.03E-11	1.47E-06
12	0.0007	0.0007	0.0007	0.0007	1.03E-11	1.47E-06

4. Placebo in 0.1 N HCl at 236 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.001	0.001	0.0011	0.001033	5.77E-05	5.587261
6	0.001	0.0011	0.0012	0.0011	0.0001	9.090909
12	0.001	0.001	0.0011	0.001033	5.77E-05	5.587261

5. Placebo in in 0.1 N HCl at 272 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0008	0.0008	0.0008	0.0008	0	0
6	0.0009	0.0008	0.0008	0.000833	5.77E-05	6.928203
12	0.0008	0.0008	0.0009	0.000833	5.77E-05	6.928203

6. Placebo in in 0.1 N HCl at 275 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0006	0.0006	0.0006	0.0006	0	0
6	0.0006	0.0006	0.0006	0.0006	0	0
12	0.0006	0.0006	0.0006	0.0006	0	0

7. Placebo in phosphate buffer pH 6.8 at 236 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0011	0.001	0.0011	0.001067	5.77E-05	5.412659
6	0.0011	0.001	0.0011	0.001067	5.77E-05	5.412659
12	0.0011	0.001	0.0011	0.001067	5.77E-05	5.412659

8. Placebo in phosphate buffer pH 6.8 at 272 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0008	0.0008	0.0008	0.0008	0	0
6	0.0008	0.0008	0.0008	0.0008	0	0
12	0.0008	0.0008	0.0008	0.0008	0	0

9. Placebo in phosphate buffer pH 6.8 at 275 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0006	0.0006	0.0006	0.0006	0	0
6	0.0006	0.0006	0.0006	0.0006	0	0
12	0.0006	0.0006	0.0006	0.0006	0	0

10. Placebo in methanol at 235 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0015	0.0015	0.0015	0.0015	0	0

11. Placebo in methanol at 272 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0008	0.0008	0.0008	0.0008	0	0

12. Placebo in methanol at 275 nm

Time	Abs1	Abs2	Abs3	Average	SD	%CV
1	0.0008	0.0008	0.0008	0.0008	0	0

Appendix C

Solubility of drugs

The drug solubility was experimentally determined since the type and temperature of medium can affect to solubility of them. The solubility of diltiazem hydrochloride, theophylline and furosemide in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution was determined by continuous shaking of excess amount of drugs in each medium at 37°C. The sample was removed at appropriate time intervals and was filtered to separate drug particle. The filtrate was appropriately diluted and analyzed by UV spectrophotometric method.

The results of the solubility of drugs are as follows :

The solubility Tables of diltiazem hydrochloride in deionized water, 0.1 N HCl solution and PBS solution pH 6.8 present in Table 1C – 3C, respectively.

Table 1C Solubility of Diltiazem hydrochloride in Deionized water at 37°C

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	200.9649	133.8407	105.2366	146.6807	49.1388	33.5005
24	368.0923	365.1127	361.5372	364.9141	3.2821	0.8994
48	403.8474	401.4637	391.6907	399.0006	6.4418	1.6145
72	488.8253	469.8751	500.9820	486.5608	15.6766	3.2219
168	497.4065	546.2718	539.3591	527.6791	26.4437	5.0113

Table 2C Solubility of Diltiazem hydrochloride in 0.1 N HCl solution at 37°C

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	507.1545	517.1924	521.4438	515.2636	7.3373	1.4240
24	506.5640	507.9812	521.7980	512.1144	8.4161	1.6434
48	540.8110	540.4567	543.2910	541.5196	1.5443	0.2852
72	559.5878	577.3017	551.4394	562.7763	13.2227	2.3496
168	560.4144	578.8370	558.8792	566.0435	11.1060	1.9620

Table 3C Solubility of Diltiazem hydrochloride PBS solution pH 6.8 at 37°C

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	146.6953	94.1126	116.5111	119.1063	26.3872	22.1543
24	367.0871	333.3097	340.0172	346.8047	17.8824	5.1563
48	364.4520	445.9012	446.9792	419.1108	47.3390	11.2951
72	558.8520	556.3367	553.5818	556.2568	2.6360	0.4739
168	557.8938	530.8239	543.7600	544.1592	13.5394	2.4881

The solubility Tables of theophylline in deionized water, 0.1 N HCl solutin and PBS pH 6.8 solution are present in Table 4C – 6C, respectively.

Table 4C Solubility of Theophylline in Deionized water at 37°C

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	11.7833	11.5344	11.9144	11.7440	0.1930	1.6437
24	11.6469	11.5040	11.8648	11.6719	0.1817	1.5567
48	11.5452	11.2615	11.6107	11.4725	0.1856	1.6176
72	11.6253	11.4521	11.6710	11.5828	0.1155	0.9970
168	11.6188	11.4109	11.4879	11.5059	0.1051	0.9134

Table 5C Solubility of Theophylline in 0.1 N HCl solution at 37°

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	13.3048	13.8351	13.9181	13.6860	0.3327	2.4310
24	13.8720	14.1094	13.9734	13.9849	0.1192	0.8520
48	13.1019	13.1296	13.7083	13.3133	0.3424	2.5716
72	13.1873	13.2656	13.3417	13.2649	0.0772	0.5823
168	13.2403	13.2449	13.3486	13.2779	0.0613	0.4615

Table 6C Solubility of Theophylline in PBS pH 6.8 solution at 37°C

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	10.9995	11.0844	10.9538	11.0126	0.0663	0.6017
24	10.4642	11.0169	10.7536	10.7449	0.2765	2.5732
48	10.4424	10.8994	10.7623	10.7014	0.2345	2.1915
72	10.7057	11.0039	10.7253	10.8116	0.1668	1.5425
168	10.5229	10.7732	10.7406	10.6789	0.1361	1.2740

The solubility Tables of furosemide in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution are present in Table 7C – 9C, respectively.

Table 7C Solubility of Furosemide in Deionized water at 37°C

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	0.0666	0.0733	0.0693	0.0697	0.0034	4.8178
24	0.0623	0.0666	0.0628	0.0639	0.0023	3.6646
48	0.0642	0.0687	0.0669	0.0666	0.0022	3.3786
72	0.0744	0.0763	0.0755	0.0754	0.0010	1.2962
168	0.0750	0.0760	0.0770	0.0760	0.0010	1.2837

Table 8C Solubility of Furosemide in 0.1 N HCl solution at 37°C

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	0.0132	0.0149	0.0123	0.0135	0.0014	10.0409
24	0.0228	0.0219	0.0215	0.0221	0.0007	3.0924
48	0.0242	0.0244	0.0237	0.0241	0.0004	1.4666
72	0.0305	0.0299	0.0329	0.0311	0.0016	5.0434
168	0.0309	0.0302	0.0325	0.0312	0.0012	3.7071

Table 9C Solubility of Furosemide in PBS pH 6.8 solution at 37°C

Times (hrs.)	Solubility 1 (mg/ml)	Solubility 2 (mg/ml)	Solubility 3 (mg/ml)	Average Solubility	SD	%CV
12	4.7576	5.3828	5.1146	4.7080	0.9460	20.0929
24	5.2142	5.9229	5.4709	5.5360	0.3588	6.4813
48	4.8539	5.3565	5.1297	5.1134	0.2517	4.9223
72	5.0117	5.5925	5.4453	5.3498	0.3019	5.6436
168	5.1128	5.3871	5.2109	5.2370	0.1390	2.6539

Appendix D

Particle size determination

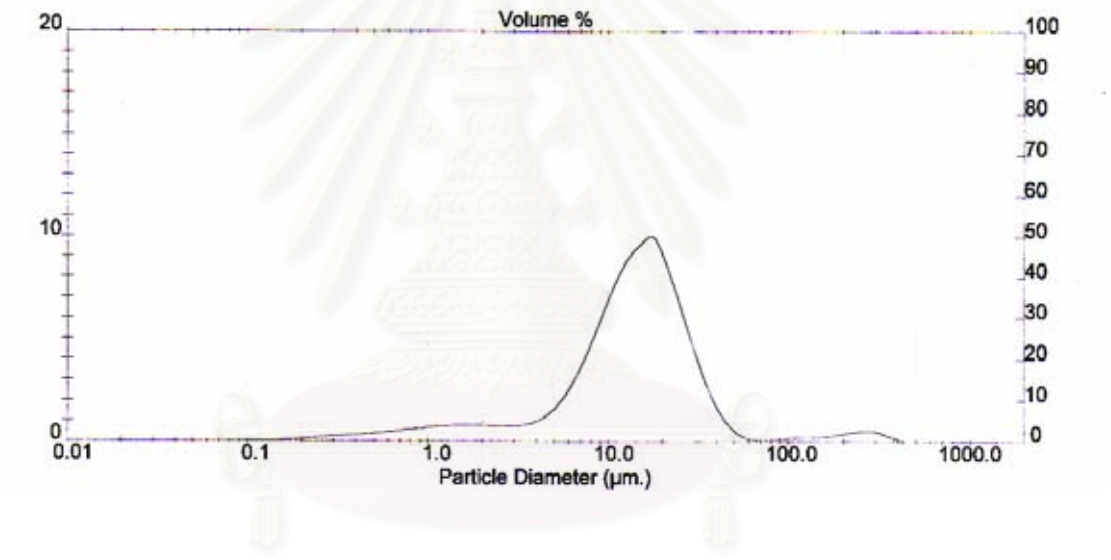


Figure 1D Particle size of D-PVAc at drug to polymer ratio 1:0.5

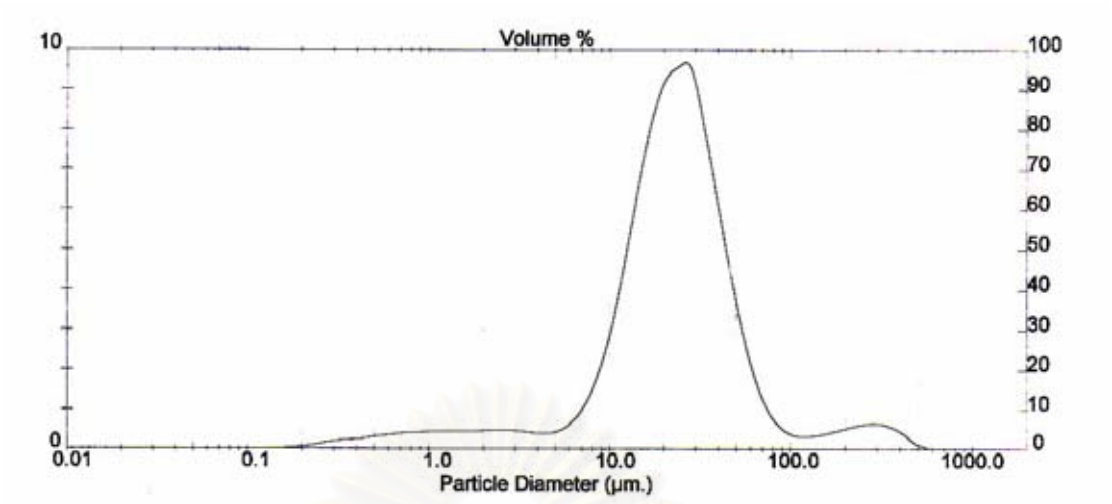


Figure 2D Particle size of D-PVAc at drug to polymer ratio 1:1

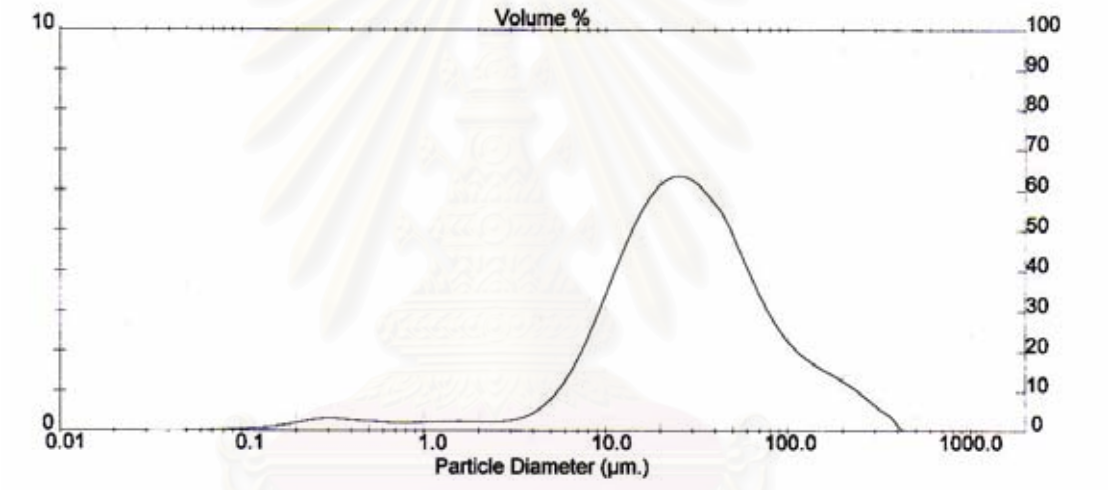


Figure 3D Particle size of D-PVAc at drug to polymer ratio 1:1.5

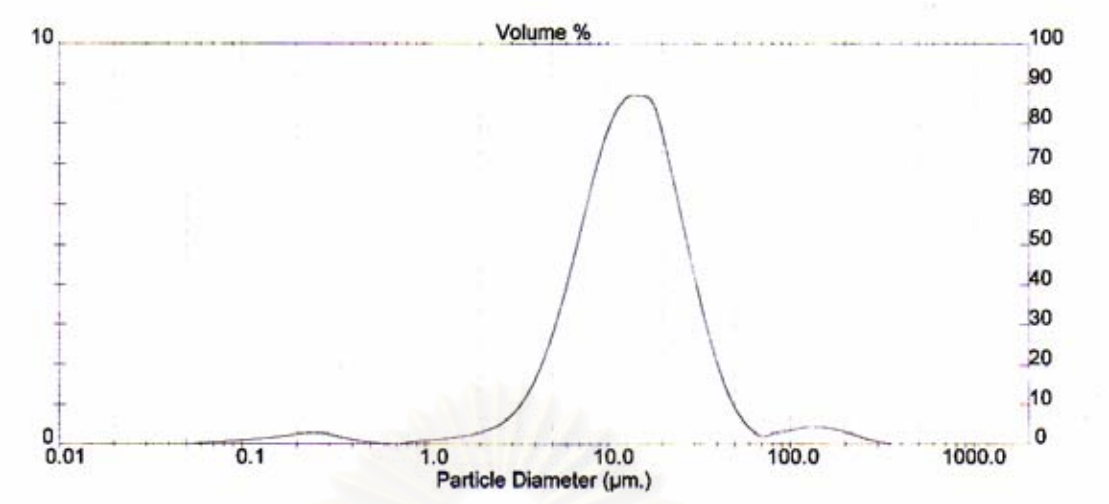


Figure 4D Particle size of T-PVAc at drug to polymer ratio 1:0.5

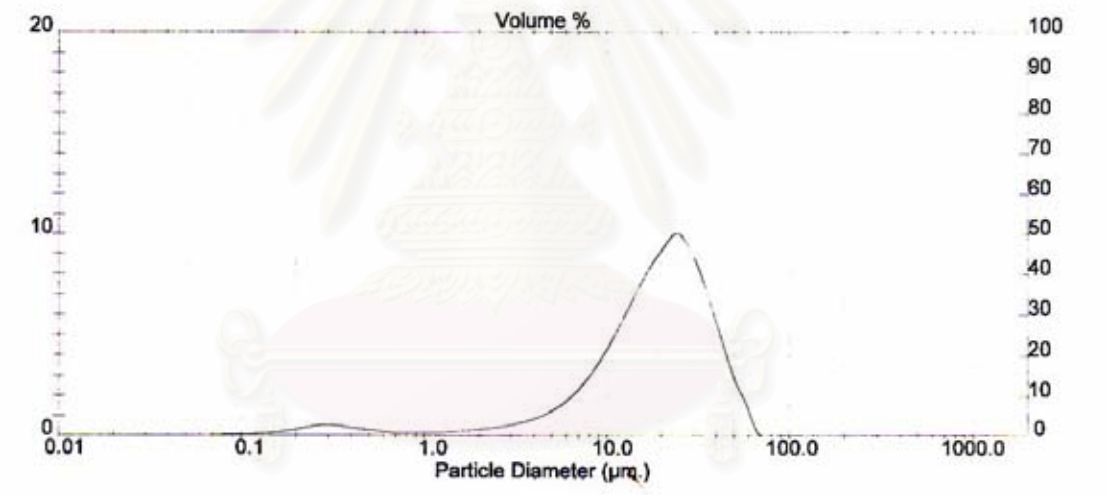


Figure 5D Particle size of T-PVAc at drug to polymer ratio 1:1

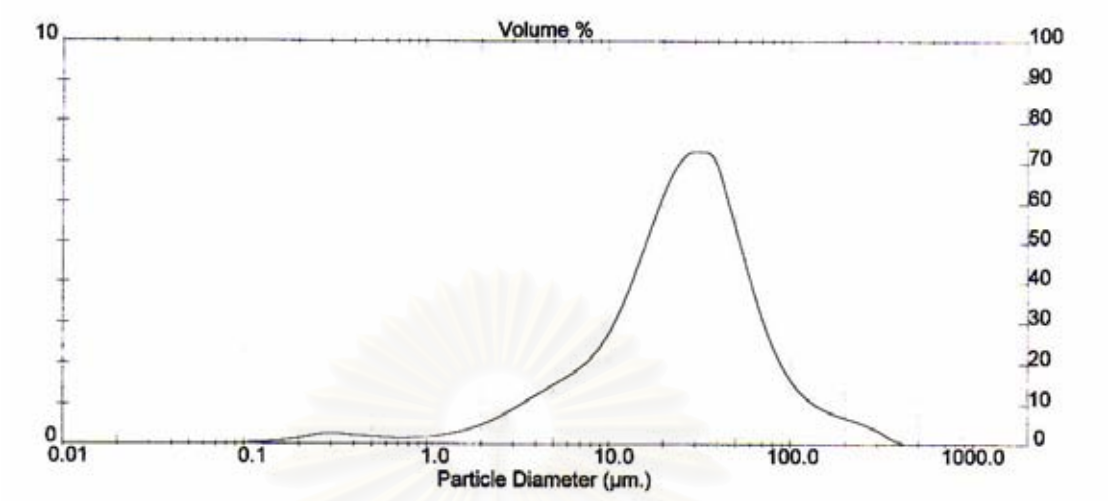


Figure 6D Particle size of T-PVAc at drug to polymer ratio 1:1.5

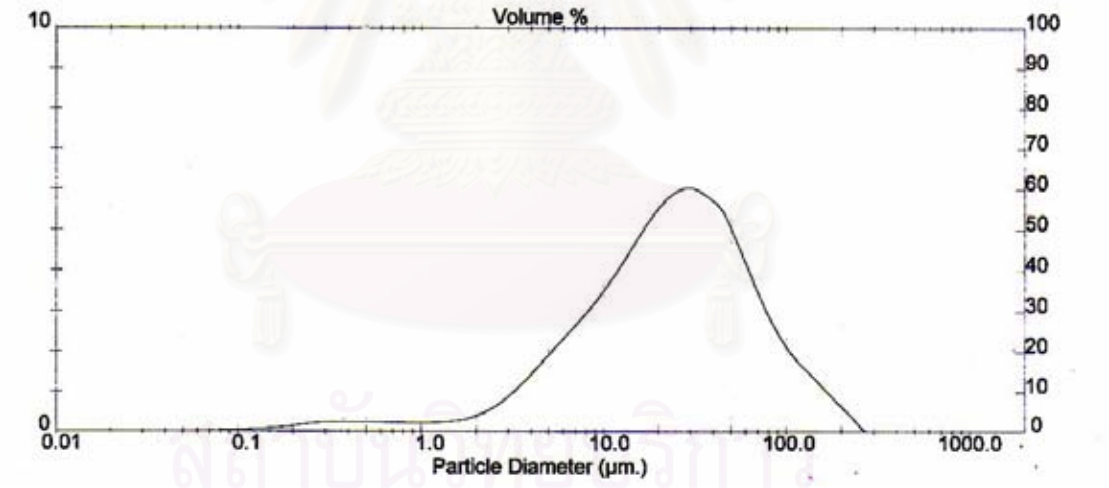


Figure 7D Particle size of F-PVAc at drug to polymer ratio 1:0.5

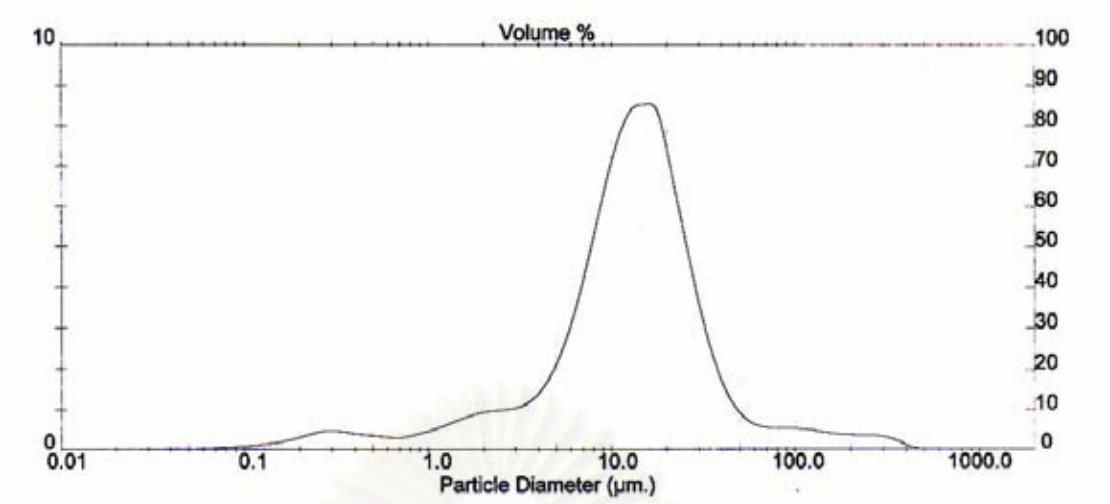


Figure 8D Particle size of F-PVAc at drug to polymer ratio 1:1

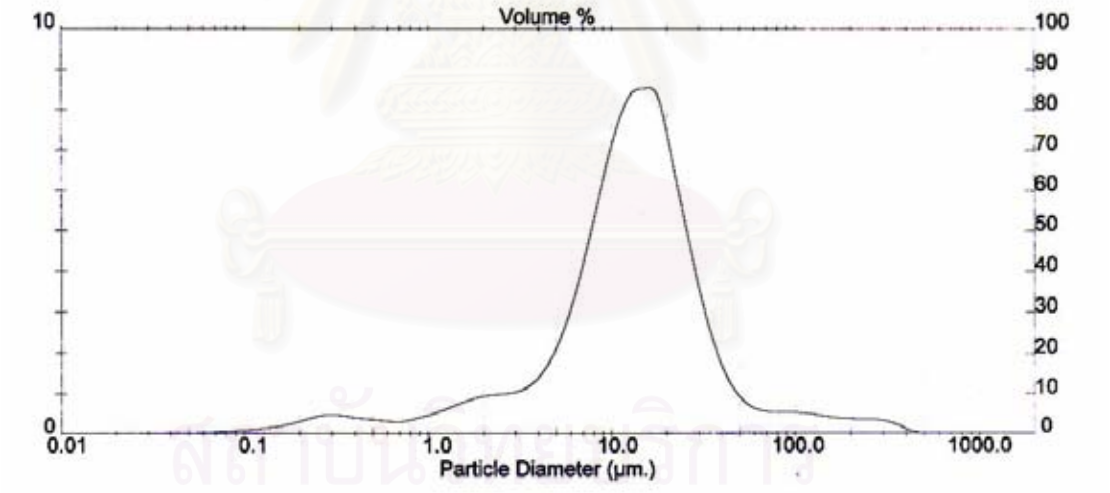


Figure 9D Particle size of F-PVAc at drug to polymer ratio 1:1.5

Appendix E

Physicochemical properties of spray dried drugs-PVAc powder after solid state stability testing

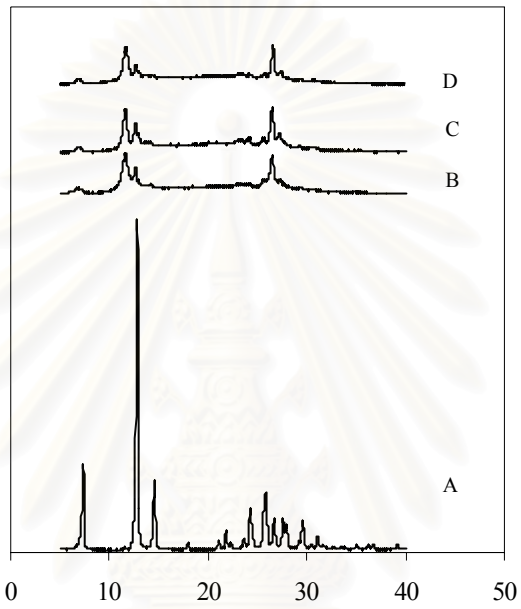


Figure 1E X-ray diffratograms of theophylline and T-PVAc systems after stability testing.

A : theophylline

B : T-PVAc at drug : polymer ratio of 1:0.5

C : T-PVAc at drug : polymer ratio of 1:1

D : T-PVAc at drug : polymer ratio of 1:1.5

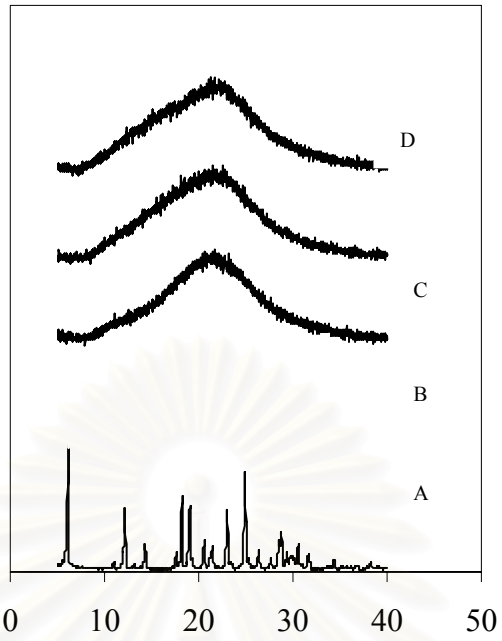


Figure 2E X-ray diffratograms of furosemide and F-PVAc systems after stability testing.

A : furosemide

B : F-PVAc at drug : polymer ratio of 1:0.5

C : F-PVAc at drug : polymer ratio of 1:1

D : F-PVAc at drug : polymer ratio of 1:1.5

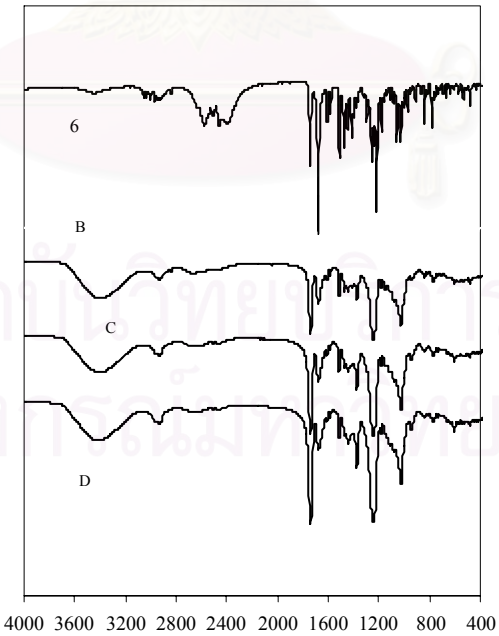


Figure 3E Infrared absorption spectrum of diltiazem hydrochloride and D-PVAc systems after stability testing.

A : Diltiazem hydrochloride

B : D-PVAc at drug : polymer ratio of 1:0.5

C : D-PVAc at drug : polymer ratio of 1:1

D : D-PVAc at drug : polymer ratio of 1:1.5

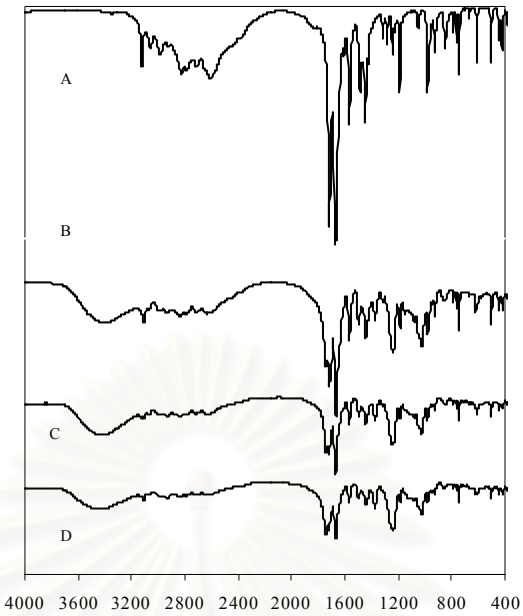


Figure 4E Infrared absorption spectrum of theophylline and T-PVAc systems after stability testing.

A : theophylline

B : T-PVAc at drug : polymer ratio of 1:0.5

C : T-PVAc at drug : polymer ratio of 1:1

D : T-PVAc at drug : polymer ratio of 1:1.5

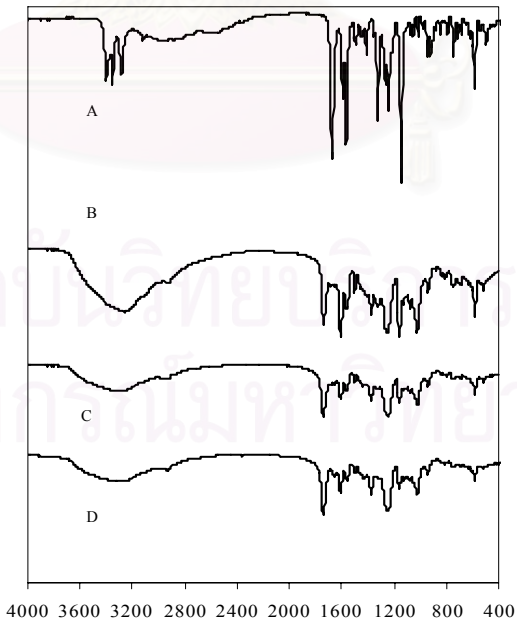


Figure 5E Infrared absorption spectrum of furosemide and F-PVAc systems after stability testing.

A : furosemide

B : F-PVAc at drug : polymer ratio of 1:0.5

C : F-PVAc at drug : polymer ratio of 1:1

D : F-PVAc at drug : polymer ratio of 1:1.5

Appendix F

Amount Percent of Drug Release, Release Rate

Table 1F Amount Percent of Diltiazem hydrochloride Release From D-PVAc matrices in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution.

Formulation	Time	√Time	Dissolution medium					
			Deionized water		0.1 N HCl		pH 6.8 phosphate buffer	
			%Release	SD	%Release	SD	%Release	SD
D-PVAc (1:0.5)	0	0	0	0	0	0	0	0
	0.08	0.2828	21.0515	2.0631	26.1688	4.7919	22.5745	4.0697
	0.25	0.5000	37.3864	4.9766	43.9688	3.2017	38.1537	1.0773
	0.5	0.7071	64.6760	10.5737	62.5531	1.8288	51.5412	0.6719
	0.75	0.8660	79.9579	1.2999	75.3889	0.1067	62.3340	0.5152
	1	1.0000	82.3695	0.9874	84.4785	0.9545	69.8101	0.1834
	2	1.4142	87.0420	2.0577	97.6691	0.4526	85.3792	0.2596
	3	1.7321	90.0594	0.6841	99.8777	0.5252	89.6328	0.4084
	4	2.0000	89.5785	0.2797	100.3293	0.5185	89.6114	2.3379
	5	2.2361	89.2977	1.3509	100.3899	0.8702	91.5787	0.7820
	6	2.4495	90.8086	1.6711	100.301	0.5280	91.6792	0.2581
	7	2.6458	91.8301	0.8635	100.5647	0.6252	93.4375	0.6227
	8	2.8284	91.4416	0.7893	101.2356	0.7942	94.1125	0.1596
	10	3.1623	92.8372	1.0296	101.3042	0.0500	93.9539	0.7002
	12	3.4641	91.5233	0.4458	100.9677	0.9188	93.6843	1.5525
D-PVAc (1:1)	0	0	0	0	0	0	0	0
	0.08	0.2828	15.9412	0.5711	16.9371	0.2825	14.0766	0.6333
	0.25	0.5000	23.1521	0.4275	25.1902	0.2653	19.3531	0.0958
	0.5	0.7071	30.2034	0.6249	34.1061	0.1934	25.3669	0.0478
	0.75	0.8660	34.8205	0.4184	40.4909	0.1173	30.1654	0.1168
	1	1.0000	39.3441	0.7084	45.5876	0.2726	33.4982	0.8021
	2	1.4142	52.2510	1.5609	60.0054	0.6196	44.8599	0.5734
	3	1.7321	62.7644	0.4992	70.4954	0.5427	52.6649	1.0658
	4	2.0000	70.1870	1.3618	78.0288	0.4113	60.0716	0.6499
	5	2.2361	70.9424	1.3662	85.3162	1.9798	65.4717	0.0863
	6	2.4495	73.7554	1.1912	89.6711	2.1267	69.4427	0.8001
	7	2.6458	76.0619	2.3574	90.0461	0.7224	72.7218	1.1695
	8	2.8284	79.8263	1.6032	92.3987	1.1091	74.9369	1.6209
	10	3.1623	84.3343	1.5900	95.2898	0.8280	80.3048	1.5685
	12	3.4641	83.6684	0.6975	95.0808	0.7251	81.3241	1.5261
D-PVAc (1:1.5)	0	0	0	0	0	0	0	0
	0.08	0.2828	12.8733	0.5362	14.8586	0.1211	9.7838	0.0264
	0.25	0.5000	18.5475	0.2603	21.4259	0.3295	14.0464	0.0548
	0.5	0.7071	23.9741	0.4950	27.9072	0.2932	18.8365	0.3197
	0.75	0.8660	27.2601	0.5777	31.0068	0.5740	20.9318	0.5888
	1	1.0000	30.3838	0.4331	34.3635	0.5647	22.9798	0.1743
	2	1.4142	37.0598	0.2745	43.0538	0.8542	29.6954	0.1997
	3	1.7321	43.2959	0.5976	50.4779	1.3554	33.8962	1.2898
	4	2.0000	47.8141	0.3316	55.4079	1.7438	36.9035	0.4855
	5	2.2361	49.4957	0.4963	59.2403	1.3170	39.8252	0.3543
	6	2.4495	53.1134	0.2498	63.9779	0.6040	42.3086	0.8295
	7	2.6458	57.2344	1.2551	67.1678	2.7344	44.8980	0.4069
	8	2.8284	59.7537	2.0352	69.1385	1.7356	47.7413	1.4160
	10	3.1623	64.5771	1.8804	73.8884	2.0121	52.5274	1.4750
	12	3.4641	68.7880	0.8102	75.1200	2.1177	52.4144	0.5249

Table 2F Amount Percent of theophylline Release From T-PVAc matrices in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution.

Formulation	Time	√Time	Dissolution medium					
			Deionized water		0.1 N HCl		pH 6.8 phosphate buffer	
			%Release	SD	%Release	SD	%Release	SD
T-PVAc (1:0.5)	0	0	0	0	0	0	0	0
	0.08	0.2828	7.9590	0.6717	8.0298	0.0669	5.4813	0.2539
	0.25	0.5000	12.9551	0.2722	13.5992	0.0918	10.5940	0.4107
	0.5	0.7071	18.6738	0.3266	18.3925	0.9283	16.6363	0.6754
	0.75	0.8660	22.6202	0.1524	22.8793	0.5103	19.8616	1.0315
	1	1.0000	26.2790	0.4537	26.8589	0.4318	23.2280	0.9314
	2	1.4142	37.5782	0.6708	37.2983	0.5857	33.1615	0.9170
	3	1.7321	45.6256	0.0877	45.0389	1.0153	40.8329	0.8301
	4	2.0000	51.1040	0.2925	50.8459	0.9594	47.2914	0.8039
	5	2.2361	55.3199	0.5097	56.9181	0.7406	52.3642	0.9509
	6	2.4495	59.5597	0.4978	61.0772	0.7696	57.2138	0.6250
	7	2.6458	64.1133	0.6050	65.4079	0.9266	61.4268	1.3246
	8	2.8284	67.8108	0.3859	68.3994	0.8204	64.6784	1.1172
	10	3.1623	73.5282	0.5497	74.5950	0.8845	70.5877	0.8350
	12	3.4641	77.3039	0.3036	80.0100	0.3327	74.9424	0.7727
T-PVAc (1:1)	0	0	0	0	0	0	0	0
	0.08	0.2828	5.8463	0.2551	5.0007	0.2082	4.8604	0.3224
	0.25	0.5000	8.3017	0.1046	7.6857	0.1838	7.5438	0.3059
	0.5	0.7071	11.2044	0.0544	10.0999	0.2873	10.2896	0.1738
	0.75	0.8660	13.6171	0.3001	12.1208	0.4333	12.5200	0.0779
	1	1.0000	15.4570	0.2465	13.8978	0.3577	14.2018	0.0376
	2	1.4142	20.8513	0.3136	19.0582	0.5052	19.6910	0.0542
	3	1.7321	26.1010	0.2868	23.7177	0.2216	24.0473	0.1100
	4	2.0000	29.0869	0.2494	26.9097	0.4416	28.1712	0.1323
	5	2.2361	32.6681	0.5837	30.0461	0.5539	31.3688	0.4495
	6	2.4495	35.2710	0.5142	32.5892	0.5984	33.6856	0.2760
	7	2.6458	38.2624	0.5019	35.1939	0.7336	36.1346	0.3445
	8	2.8284	40.1420	0.3627	37.0972	0.7102	38.3554	0.4769
	10	3.1623	43.1051	0.2472	40.8681	0.5761	42.7673	0.4838
	12	3.4641	47.6306	0.0845	45.1626	0.7018	46.0669	0.5064
T-PVAc (1:1.5)	0	0	0	0	0	0	0	0
	0.08	0.2828	3.5801	0.0044	3.3949	0.1106	3.3985	0.1491
	0.25	0.5000	5.3994	0.1069	5.6182	0.0284	5.3670	0.1259
	0.5	0.7071	7.7286	0.0399	7.4760	0.0852	7.6355	0.0385
	0.75	0.8660	9.4734	0.0140	9.0433	0.1082	9.3465	0.0656
	1	1.0000	10.8289	0.0540	10.2059	0.1974	10.7518	0.1065
	2	1.4142	15.0356	0.0299	13.7098	0.3126	14.8057	0.2012
	3	1.7321	18.5100	0.0288	16.1141	0.3439	17.9212	0.2342
	4	2.0000	20.7317	0.0490	18.3252	0.3809	20.3295	0.3048
	5	2.2361	23.3533	0.0553	19.8816	0.4244	22.4574	0.4492
	6	2.4495	24.7027	0.0443	21.2606	0.5012	24.0367	0.5620
	7	2.6458	26.0046	0.0681	22.5541	0.3834	25.8186	0.5920
	8	2.8284	28.0957	0.0533	23.7181	0.5687	27.5671	0.5162
	10	3.1623	30.4283	0.6567	25.7819	0.5491	30.1697	0.8388
	12	3.4641	33.4398	0.5004	27.7419	0.7207	32.9094	0.9219

Table 3F Amount Percent of Furosemide Release From F-PVAc matrices in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution.

Formulation	Time	√Time	Dissolution medium					
			Deionized water		0.1 N HCl		pH 6.8 phosphate buffer	
			%Release	SD	%Release	SD	%Release	SD
F-PVAc (1:0.5)	0	0	0	0	0	0	0	0
	0.08	0.2828	0.08	8.9427	0.1024	0.0802	8.6396	0.1312
	0.25	0.5000	0.25	11.8229	0.2288	0.0231	13.3103	0.0208
	0.5	0.7071	0.5	15.4925	0.4188	0.0262	17.7750	0.0244
	0.75	0.8660	0.75	18.3307	0.5573	0.0838	20.9238	0.2420
	1	1.0000	1	20.1324	0.6059	0.0416	23.3498	0.0653
	2	1.4142	2	26.4295	0.9206	0.0225	29.7075	0.3520
	3	1.7321	3	31.7460	1.1376	0.0110	34.9287	0.5556
	4	2.0000	4	37.2890	1.3650	0.0057	40.4016	0.6637
	5	2.2361	5	42.3467	1.5727	0.0113	45.3608	1.0238
	6	2.4495	6	46.8726	1.7686	0.0124	51.1343	1.6605
	7	2.6458	7	50.9814	1.9719	0.0262	57.2059	1.1283
	8	2.8284	8	54.8229	2.1982	0.0408	61.0426	1.1772
	10	3.1623	10	59.5556	2.5736	0.0784	69.1317	0.3692
	12	3.4641	12	62.9847	3.0396	0.2344	73.5882	0.5554
F-PVAc (1:1)	0	0	0	0	0	0	0	0
	0.08	0.2828	0.0800	5.2327	0.2065	0.0416	5.8701	0.6254
	0.25	0.5000	0.2500	7.8068	0.5377	0.0448	9.5635	0.4557
	0.5	0.7071	0.5000	9.4416	1.0455	0.0182	12.2561	0.3955
	0.75	0.8660	0.7500	10.5930	1.5486	0.0208	14.5739	0.2799
	1	1.0000	1.0000	11.2668	2.0646	0.0049	15.8249	0.3309
	2	1.4142	2.0000	13.5919	3.4159	0.0126	19.4516	0.2183
	3	1.7321	3.0000	16.4421	4.2491	0.0460	21.8226	0.1908
	4	2.0000	4.0000	16.8445	4.7835	0.0913	23.5957	0.2575
	5	2.2361	5.0000	17.9541	5.1083	0.1171	25.7221	0.1900
	6	2.4495	6.0000	19.0494	5.4189	0.1277	27.0358	0.3384
	7	2.6458	7.0000	19.9662	5.6543	0.1376	28.4198	0.2956
	8	2.8284	8.0000	20.9113	5.9095	0.1475	28.8445	0.5519
	10	3.1623	10.0000	22.5311	6.2324	0.1606	31.2623	0.2731
	12	3.4641	12.0000	23.9135	6.5191	0.1455	32.7354	0.3262
F-PVAc (1:1.5)	0	0	0	0	0	0	0	0
	0.08	0.2828	5.7370	0.7232	0.4683	0.0244	8.0897	0.0997
	0.25	0.5000	10.0676	1.5901	0.8467	0.0170	12.5084	0.1638
	0.5	0.7071	13.0520	2.1314	1.4412	0.0744	17.1097	0.1219
	0.75	0.8660	16.4068	2.0652	2.0717	0.1089	20.6218	0.0325
	1	1.0000	19.2744	2.3721	2.5321	0.1374	24.1712	0.2384
	2	1.4142	29.2730	1.3838	3.9605	0.1968	33.4515	0.4165
	3	1.7321	37.3785	1.2545	4.9442	0.2191	41.9802	0.6082
	4	2.0000	43.9343	1.4368	5.5930	0.2078	49.4776	0.7702
	5	2.2361	49.7550	1.4832	6.1060	0.2084	55.7477	0.9222
	6	2.4495	54.6094	1.2867	6.5724	0.2096	61.1131	0.8126
	7	2.6458	56.9916	1.2728	6.9443	0.2036	68.7767	0.8448
	8	2.8284	60.7710	1.0234	7.0232	0.2089	72.5942	0.9631
	10	3.1623	65.1688	0.6394	7.5157	0.1834	78.8123	1.3299
	12	3.4641	67.5977	0.6478	7.9229	0.0977	84.9763	1.2788

Table 4F The Release Rate D-PVAc matrices in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution.

Formulation	Mean Time	Dissolution medium		
		Deionized water	0.1 N HCl	pH 6.8 phosphate buffer
		Release Rate (% / hour)	Release Rate (% / hour)	Release Rate (% / hour)
D-PVAc (1:0.5)	0.04	263.1443	327.1098	282.1809
	0.165	96.0871	104.7060	91.6426
	0.375	109.1587	74.3372	53.5501
	0.625	61.1276	51.3433	43.1711
	0.875	9.6464	36.3584	29.9042
	1.5	4.6725	13.1906	15.5691
	2.5	3.0174	2.2086	4.2536
	3.5	-0.4809	0.4516	-0.0214
	4.5	-0.2808	0.0606	1.9673
	5.5	1.5109	-0.0890	0.1005
	6.5	1.0216	0.2637	1.7583
	7.5	-0.3886	0.6709	0.6750
	9	0.6978	0.0343	-0.0793
	11	-0.6570	-0.1682	-0.1348
D-PVAc (1:1)	0.04	199.2655	211.7133	175.9576
	0.165	42.4168	48.5480	31.0384
	0.375	28.2051	35.6636	24.0550
	0.625	18.4684	25.5391	19.1941
	0.875	18.0944	20.3868	13.3309
	1.5	12.9069	14.4178	11.3618
	2.5	10.5134	10.4900	7.8050
	3.5	7.4226	7.5334	7.4067
	4.5	0.7554	7.2874	5.4001
	5.5	2.8130	4.3549	3.9710
	6.5	2.3065	0.3749	3.2791
	7.5	3.7645	2.3526	2.2151
	9	2.2540	1.4455	2.6839
	11	-0.3329	-0.1045	0.5096
D-PVAc (1:1.5)	0.04	160.9161	185.7328	122.2970
	0.165	33.3776	38.6312	25.0742
	0.375	21.7066	25.9252	19.1604
	0.625	13.1439	12.3982	8.3813
	0.875	12.4950	13.4268	8.1919
	1.5	6.6759	8.6903	6.7156
	2.5	6.2361	7.4242	4.2008
	3.5	4.5182	4.9299	3.0073
	4.5	1.6816	3.8324	2.9217
	5.5	3.6177	4.7376	2.4834
	6.5	4.1210	3.1898	2.5894
	7.5	2.5192	1.9708	2.8432
	9	2.4117	2.3749	2.3931
	11	2.1055	0.6158	-0.0565

Table 5F The Release Rate T-PVAc matrices in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution.

Formulation	Mean Time	Dissolution medium		
		Deionized water	0.1 N HCl	pH 6.8 phosphate buffer
		Release Rate (% / hour)	Release Rate (% / hour)	Release Rate (% / hour)
T-PVAc (1:0.5)	0.04	99.4872	100.3721	68.5163
	0.165	29.3892	32.7616	30.0745
	0.375	22.8748	19.1732	24.1693
	0.625	15.7854	17.9472	12.9010
	0.875	14.6352	15.9182	13.4656
	1.5	11.2992	10.4394	9.9336
	2.5	8.0475	7.7405	7.6714
	3.5	5.4783	5.8071	6.4585
	4.5	4.2160	6.0721	5.0728
	5.5	4.2398	4.1591	4.8496
	6.5	4.5536	4.3307	4.2130
	7.5	3.6975	2.9915	3.2515
	9	2.8587	3.0978	2.9547
	11	1.8879	2.7075	2.1773
T-PVAc (1:1)	0.04	73.0793	62.5087	60.7544
	0.165	14.4430	15.7943	15.7851
	0.375	11.6111	9.6569	10.9831
	0.625	9.6506	8.0833	8.9217
	0.875	7.3597	7.1083	6.7270
	1.5	5.3943	5.1604	5.4892
	2.5	5.2497	4.6595	4.3563
	3.5	2.9859	3.1920	4.1239
	4.5	3.5812	3.1365	3.1976
	5.5	2.6029	2.5431	2.3167
	6.5	2.9914	2.6047	2.4490
	7.5	1.8796	1.9033	2.2208
	9	1.4815	1.8854	2.2059
	11	2.2628	2.1472	1.6498
T-PVAc (1:1.5)	0.04	44.7516	42.4357	42.4813
	0.165	10.7016	13.0783	11.5795
	0.375	9.3169	7.4312	9.0741
	0.625	6.9789	6.2692	6.8440
	0.875	5.4222	4.6507	5.6210
	1.5	4.2067	3.5039	4.0539
	2.5	3.4744	2.4043	3.1155
	3.5	2.2216	2.2111	2.4083
	4.5	2.6216	1.5564	2.1279
	5.5	1.3494	1.3789	1.5793
	6.5	1.3019	1.2935	1.7819
	7.5	2.0910	1.1640	1.7485
	9	1.1663	1.0319	1.3013
	11	1.5058	0.9800	1.3698

Table 6F The Release Rate F-PVAc matrices in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution.

Formulation	Mean Time	Dissolution medium		
		Deionized water	0.1 N HCl	pH 6.8 phosphate buffer
		Release Rate (% / hour)	Release Rate (% / hour)	Release Rate (% / hour)
F-PVAc (1:0.5)	0.04	111.7838	1.2804	107.9953
	0.165	16.9421	0.7431	27.4746
	0.375	14.6786	0.7600	17.8586
	0.625	11.3527	0.5541	12.5954
	0.875	7.2069	0.1943	9.7038
	1.5	6.2971	0.3147	6.3578
	2.5	5.3165	0.2170	5.2212
	3.5	5.5430	0.2274	5.4729
	4.5	5.0577	0.2077	4.9592
	5.5	4.5259	0.1959	5.7736
	6.5	4.1088	0.2033	6.0716
	7.5	3.8415	0.2263	3.8367
	9	2.3664	0.1877	4.0445
	11	1.7146	0.2330	2.2282
F-PVAc (1:1)	0.04	65.4091	2.5811	73.3760
	0.165	15.1418	1.9485	21.7258
	0.375	6.5389	2.0311	10.7705
	0.625	4.6057	2.0122	9.2713
	0.875	2.6952	2.0641	5.0039
	1.5	2.3251	1.3513	3.6267
	2.5	2.8501	0.8332	2.3710
	3.5	0.4024	0.5344	1.7732
	4.5	1.1096	0.3247	2.1264
	5.5	1.0953	0.3106	1.3137
	6.5	0.9168	0.2354	1.3840
	7.5	0.9450	0.2552	0.4247
	9	0.8099	0.1615	1.2089
	11	0.6912	0.1433	0.7365
F-PVAc (1:1.5)	0.04	71.7131	5.8541	101.1213
	0.165	25.4738	2.2259	25.9926
	0.375	11.9377	2.3777	18.4049
	0.625	13.4192	2.5220	14.0486
	0.875	11.4702	1.8417	14.1974
	1.5	9.9987	1.4284	9.2803
	2.5	8.1054	0.9837	8.5287
	3.5	6.5558	0.6489	7.4973
	4.5	5.8207	0.5130	6.2701
	5.5	4.8544	0.4664	5.3654
	6.5	2.3822	0.3719	7.6636
	7.5	3.7793	0.0789	3.8175
	9	2.1989	0.2463	3.1091
	11	1.2145	0.2036	3.0820

Table 7F Amount Percent of Diltiazem hydrochloride Release From D-PVAc matrices at drug to polymer ratio 1:1 with various compression forces in pH change medium.

Formulation	Time	√Time	Compression forces					
			300		500		1000	
			%Release	SD	%Release	SD	%Release	SD
D-PVAc (1:1)	0	0	0	0	0	0	0	0
	0.08	0.2828	16.1183	0.9186	14.7767	0.4895	14.6272	1.8303
	0.25	0.5000	26.4030	0.6227	24.7663	0.8661	25.0890	1.2547
	0.5	0.7071	34.9105	0.7303	34.6713	0.9263	35.1739	0.4770
	0.75	0.8660	41.3440	0.9255	40.8931	1.1823	41.0959	0.3033
	1	1.0000	46.7188	1.2166	46.0239	1.1961	46.3989	0.2575
	2	1.4142	60.6136	1.6023	60.9853	1.5857	61.7202	0.4714
	3	1.7321	68.9695	1.7044	67.5854	1.3681	67.4668	0.4440
	4	2.0000	73.1577	1.5505	72.4914	1.5637	72.0273	0.4480
	5	2.2361	77.8808	2.1898	75.4747	1.4742	75.7218	0.7349
	6	2.4495	81.9269	1.7635	81.6751	1.5401	82.2335	0.7982
	7	2.6458	84.4307	2.0939	83.1855	1.7484	83.2509	1.1937
	8	2.8284	85.6857	1.5903	83.4327	1.8792	84.3549	1.0225
	10	3.1623	88.7883	1.8606	84.7484	1.9888	85.7850	1.0951
	12	3.4641	88.3188	1.7866	85.7447	1.8466	85.9588	0.8406

Table 8F Amount Percent of Theophylline Release From T-PVAc matrices at drug to polymer ratio 1:0.5 with various compression forces in pH change medium.

Formulation	Time	√Time	Compression forces					
			300		500		1000	
			%Release	SD	%Release	SD	%Release	SD
T-PVAc (1:0.5)	0	0	0	0	0	0	0	0
	0.08	0.2828	7.9277	0.3525	5.8356	0.1152	6.0803	0.3874
	0.25	0.5000	14.2504	0.3222	10.8532	0.6806	11.7676	0.6219
	0.5	0.7071	20.6887	0.3520	17.3127	0.5839	18.2877	0.4744
	0.75	0.8660	25.4392	0.5113	21.9311	0.4384	22.9583	0.3055
	1	1.0000	29.3900	0.5790	25.9977	0.3817	27.2942	0.8055
	2	1.4142	40.6095	0.7278	36.5360	0.6655	37.5407	0.4328
	3	1.7321	46.2784	1.0313	42.7515	0.6050	43.8769	0.6605
	4	2.0000	51.7971	1.1860	48.0506	0.7476	49.2186	0.5806
	5	2.2361	57.2352	1.6642	52.2307	0.9240	53.7259	0.5781
	6	2.4495	63.2305	0.6745	56.3845	0.8127	57.8397	0.5685
	7	2.6458	66.4405	1.3728	61.6769	0.7852	63.9118	0.8891
	8	2.8284	69.0986	1.7308	65.5293	0.9599	67.3261	0.7281
	10	3.1623	74.4009	1.9479	71.5213	0.6984	73.2902	0.9462
	12	3.4641	75.9363	2.4510	75.6449	0.8770	77.9220	0.5170

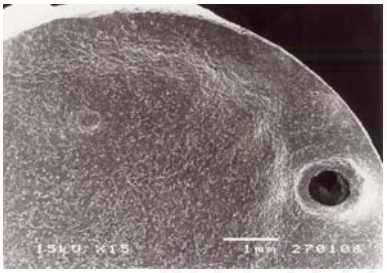
Table 9F Amount Percent of Furosemide Release From F-PVAc matrices at drug to polymer ratio 1:0.5 with various compression forces in pH change medium.

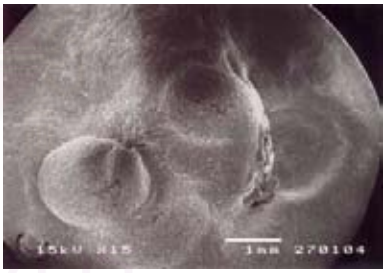
Formulation	Time	√Time	Compression forces					
			300		500		1000	
			%Release	SD	%Release	SD	%Release	SD
F-PVAc (1:0.5)	0	0	0	0	0	0	0	0
	0.08	0.2828	0.2484	0.0246	0.2409	0.0505	0.2564	0.0041
	0.25	0.5000	0.2667	0.0095	0.2258	0.0532	0.3061	0.0746
	0.5	0.7071	0.3740	0.0308	0.3573	0.0623	0.4971	0.0378
	0.75	0.8660	0.4959	0.0169	0.4570	0.0829	0.5397	0.1189
	1	1.0000	0.5975	0.0237	0.5146	0.0926	0.6332	0.1238
	2	1.4142	0.9358	0.0293	0.8052	0.1050	0.8777	0.1737
	3	1.7321	24.4098	0.2749	20.4682	0.6451	19.6489	1.2509
	4	2.0000	35.4795	0.3007	31.0271	0.7596	32.1488	0.1902
	5	2.2361	43.3728	0.8924	41.6049	1.2374	41.9400	0.4282
	6	2.4495	50.2313	0.8160	49.2502	0.5699	49.7646	0.6287
	7	2.6458	59.5239	1.5520	58.5369	0.3280	58.6446	0.9185
	8	2.8284	63.5791	0.8141	62.2028	0.4775	63.8162	0.9585
	10	3.1623	71.6099	1.2141	74.7470	0.6016	72.3786	1.0309
	12	3.4641	77.0985	0.4935	82.6595	0.6675	78.1943	1.5816

Appendix G

The surface morphology of F-PVAc matrices after release testing in deionized water, 0.1 N HCl solution and PBS pH 6.8 solution (x 15)

A





B C

Figure 1G Photomicrograph of F-PVAc matrices 1:1.5 after release testing (x 500 surface view)

A ; in deionized water
B ; in 0.1 N HCl
C ; in pH 6.8 phosphate buffer

Appendix H

The pH-solubility profile of theophylline

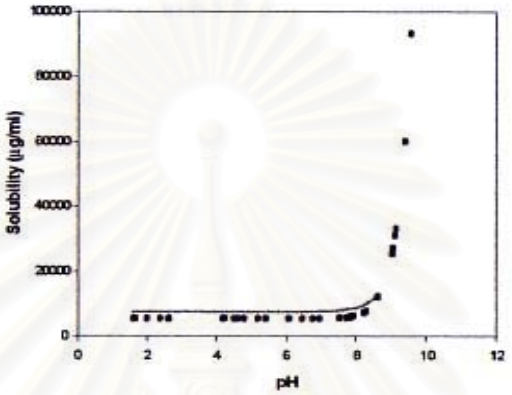


Figure 1H pH-solubility profile of theophylline

Appendix I

Table 1I Correlation of determination (r^2) of relationship between drug release versus time (zero order), log percentage drug remained versus time (first-order), percentage drug release versus square root time (Higuchi's equation)

Formulation	Drug to polymer ratio	Dissolution medium								
		Deionized water			0.1 N HCl			PBS pH 6.8		
		Zero-order	First-order	Higuchi	Zero-order	First-order	Higuchi	Zero-order	First-order	Higuchi
D-PVAc	1:0.5	0.9691	0.9780	0.9785	0.9068	0.9734	0.9995	0.8938	0.9646	0.9980
	1:1	0.8576	0.9478	0.9892	0.8372	0.9322	0.9899	0.8756	0.9505	0.9907
	1:1.5	0.8488	0.9265	0.9724	0.8299	0.9177	0.9714	0.8460	0.9109	0.9759
T-PVAc	1:0.5	0.9103	0.9645	0.9969	0.9204	0.9733	0.9989	0.9345	0.9807	0.9995
	1:1	0.9107	0.9519	0.9974	0.9231	0.9594	0.9992	0.9207	0.9585	0.9991
	1:1.5	0.9096	0.9373	0.9979	0.8825	0.9085	0.9918	0.9098	0.9375	0.9979
F-PVAc	1:0.5	0.9277	0.9778	0.9963	0.9803	0.9813	0.9823	0.9431	0.9902	0.9946
	1:1	0.8144	0.8438	0.9571	0.8385	0.8436	0.9677	0.8060	0.8469	0.9582
	1:1.5	0.9465	0.9845	0.9971	0.8552	0.8613	0.9774	0.9477	0.9867	0.9987

VITA

Miss Sirima Sangkapat was born on 23th December 1978, in Nakhonratchasima Thailand. She received her Bachelor Degree of Pharmaceutical Science in 2001 from Faculty of Pharmaceutical Sciences, Khonkean University, Khonkean, Thailand. She continue studies the Master's Degree Program in Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.