ผลของพลาสติไซเซอร์ต่อการปลดปล่อยยาจากระบบเมทริกซ์ของโพลีเมทราไครเลทและโพลีไวนิล อะซิเตดเตรียมโดยการทำแกรนูลแบบหลอมด้วยความร้อน

นายธนานพ จิตต์อารี

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต

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EFFECT OF PLASTICIZERS ON DRUG RELEASE FROM POLYMETHRACRYLATE AND POLYVINYL ACETATE MATRICES PREPARED BY THERMAL GRANULATION

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งานวิจัยนี้เป็นการศึกษาผลของพลาสติไซเซอร์ต่อการปลดปล่อยยาธีโอฟิลลินจากระบบเมทริกซ์ของโพลีเมทราไคเลท (ยูดราจิทอาร์เอส) และโพลีไวนิลอะซิเตท (คอลลิดอนเอสอาร์) ซึ่งเตรียมโดยทำแกรนูลแบบหลอมด้วยความร้อนที่อุณหภูมิ 60 องศาเซลเซียสและ 80 องศาเซลเซียส ทำการผสมพลาสติไซเซอร์ 2 ชนิดได้แก่ ไดรเอธิลซิเตรทและไดบิวธิลพทาเลทเข้ากับพอลิเมอร์โดยวิธีที่แตกต่างกัน ค่าอุณหภูมิกลาสแทรนสิชันของยูดราจิทอาร์เอสและคอลลิดอนเอสอาร์มีค่า 64.2 องศาเซลเซียสและ 40.1 องศาเซลเซียสตามลำดับ พบว่าพลาสติไซเซอร์ทั้ง 2 ชนิดมีประสิทธิภาพเท่ากันในการลดค่าอุณหภูมิกลาสแทรนสิชัน วิธีการพ่นแห้งของพลาสติไซเซอร์ร่วมกับพอลิเมอร์เป็นวิธีที่มีประสิทธิภาพมากที่สุดในการผสมพลาสติไซเซอร์กับพอลิเมอร์ พบว่าอุณหภูมิกลาสแทรนสิชันของยูดราจิทอาร์เอส 100 จะลดลง 2.26 และ 2.36 องศาเซลเซียสต่อหนึ่งเปอร์เซนต์ของปริมาณไดรเอธิลซิเตรท และ ไดบิวธิลพทาเลทตามลำดับ และค่าอุณหภูมิกลาสแทรนสิชันของคอลลิดอนเอสอาร์ ลดลง 1.55 องศาเซลเซียส ต่อหนึ่งเปอร์เซนต์ของปริมาณพลาสติไซเซอร์ทั้งสองชนิด อุณหภูมิมีผลน้อยต่ออัตราการปลดปล่อยยาของระบบคอลลิดอนเอสอาร์เมทริกซ์ เมื่อใช้ความร้อนของกระบวนการเตรียมแกรนูลเป็น 80 องศาเซลเซียสทำให้อัตราการปลดปล่อยยาของระบบยูดราจิทอาร์เอสเมทริกซ์มีค่าลดลงอย่างมีนัยสำคัญ แรงตอกและความเป็นกรด-ด่างของสารละลายที่ใช้ในการทดสอบการปลดปล่อยยาไม่มีผลต่ออัตราการปลดปล่อยยา

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ปีการศึกษา 2548 ลายมือชื่ออาจารย์ที่ปรึกษาร่วม

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KEY WORD: PLASTICIZERS /DRUG RELEASE /POLYMETHRACRYLATE /POLYVINYL ACETATE /MATRICES /THERMAL GRANULATION

THANANOP CHITAREE: EFFECT OF PLASTICIZERS ON DRUG RELEASE FROM POLYMETHRACRYLATE AND POLYVINYL ACETATE MATRICES PREPARED BY THERMAL GRANULATION. THESIS ADVISOR : ASSOC. PROF. POJ KULVANICH, Ph.D., 162 pp. ISBN 974-53-1915-5

The effect of plasticizers on the release rate of theophylline matrices prepared by thermal granulation using ammonio methacrylate copolymer type B (Eudragit®RS 100) and polyvinyl acetate/polyvinyl pyrrolidone (Kollidon®SR) as matrix forming agent was investigated. The thermal granulation was conducted at the temperature of 60°C and 80°C. Various methods were employed to incorporate the plasticizers, triethyl citrate (TEC) and dibutyl phthalate (DBP) into the polymer. The glass transition temperature (Tg) of Eudragit®RS and Kollidon®SR before plasticization was 64.2 °C and 40.1°C, respectively. The plasticization efficiency of TEC and DBP in reduction of Tg of both polymers were comparable. Co-spray drying of polymer with plasticizer was found to be the effective incorporation method to produce the plasticizer polymer powder prior to thermal granulation with the drug powder. For each percentage amount of TEC and DBP incorporated, Tg of Eudragit®RS 100 decreased for 2.26 °C and 2.36 °C, respectively and Tg of Kollidon®SR decreased for 1.55°C for each percentage of both plasticizer. Granulation process temperature slightly affected drug release rate of Kollidon®SR system. An increase of granulation process temperature to 80°C significantly decreased in drug release rate of Eudragit®RS system both with and without plasticizer. Compression force employed to prepare the matrices and pH of dissolution medium had no significant effect on drug release rate of these two systems.

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LIST OF ABBREVIATIONS

°C	degree celsius
cm	centimeter
DBP	dibutyl phthalate
e.g.	exampli gratia (for example)
et al.	et alli and orthers
Fig.	Figure
g	gram
hr	hour
kg	kilogram
mcg	microgram
mg	milligram
ml	milliliter
mm	millimeter
Mpa	mega pascal
N	normality
nm	nanometer
No.	number
pH	the negative logarithm of the hydrogen ion concentration
®	Registered
r^2	coefficient of determination
rpm	revolutions per minute
sec	second
SD	standard deviation
TEC	triethyl citrate
UV	ultraviolet
μl	microliterμ m
w/v	weight by volume

CHAPTER I

INTRODUCTION

The production of sustained release oral dosage forms has been achieved by a number of methods including; coated pellets, osmotic pumps and matrix devices. Matrix devices are relatively cheap and easy to manufacture. Matrix systems prepared by thermal processing are gaining attention in the pharmaceutical field. Hot melt granulation and hot melt extrusions are two processes utilizing heat that can overcome the disadvantage of traditional processing technologies, including stability issues associated with wet granulation, as well as flowability and content uniformity problems associated with direct compression. Furthermore, the process offers several advantages over alcoholic granulation, namely cost and safety. Solvents and the associated flameproof facilities, and solvent recovery equipment are not required. A heat jacket and heat of friction from the impeller blades generates the heat required for the granulation process (Flanders et al., 1987). Materials for melt granulation are different kinds of low melting point excipient as binder: polyethylene glycols 3000, 6000, and 8000, various types of waxes and stearic acid. (Mctaggart et al., 1984; Royce et al., 1996)

Plasticizers are incorporated into pharmaceutical polymer to facilitated thermal processing, to modify drug release from polymeric system and to enhance mechanical and physiochemical properties. But most pharmaceutical plasticizers are in a liquid state and a homogeneous blend of the plasticizer with the powder blend containing active ingredient must be result an incomplete mixing of a polymer powder with a liquid additive. Which has been shown to result in an unstable due to the evaporation and loss of plasticizer, during a high temperature operation, thus causing stability problems in the finished dosage forms. Most recently, solid state plasticizers for acrylic polymer including ibuprofen chlorpheniramine and methylparaben were reported for both coating and hot melt processing.

Plasticizer functions by weakening the intermolecular attractions between polymeric chain. Result in drug release from polymeric system was modifying which reported for film and matrix system. Wu and McGinity (1999) investigated the influence of methylparaben, ibuprofen, chlorpheniramine maleate on the thermal and

mechanical properties of polymeric films of Eudragit® RS 30D. The dissolution data demonstrated that increasing the amount of ibuprofen and methylparaben decreased the rate of release of the ibuprofen from coated beads. Zhu et al.(2002) found that the effect of triethyl citrate on drug release from Eudragit® RSPO was dependent on the tablet preparation method. The drug releases decreased in tablet prepared by direct compression and hot melt granulation. While, drug release rate increases from hot melt extrusion.

Eudragit® RS and Kollidon® SR were suitable to prepared sustained release dosage form by hot melt extrusion and granulation. Due to their glass transition temperature is relatively low so that the temperature of the process could be conducted at 60°C for Eudragit® RS and Kollidon® SR. The plasticizer was sprayed into the powder blend of polymer and drug during thermal processing (Zhu et al., 2002). In this study, plasticizer was incorporated into the polymer before thermal processing by different methods, which lowered the glass transition temperature of polymer and softened polymer functioned as a thermal binder in the granulation. The efficiency of the granulation process obtained from this experiment exhibited a well blend between drug and polymer than the traditional method, which could modify the drug release rate.

The Objectives of the study

1. Investigate the effect of plasticizer on the drug release from matrices containing ammonio methacrylate copolymer type B (Eudragit® RS100) and polyvinylacetate/povidone (Kollidon®SR) prepared by thermal granulation.
2. Investigate the effect of plasticizer incorporation methods into the polymer on the drug release.
3. Investigate the effect of processing parameter i.e. processing temperature, compaction force and pH of dissolution medium.

Literature reviews

1.Melt granulation

Melt granulation or thermoplastic granulation, is based on agglomeration by use of a binder material that is solid at room temperature and softens and melts at higher temperature (i.e. 50-90°C). When melted, the action of the binder liquid is similar to that of wet granulation process.

The water-soluble binders used for melt granulation are polyethylene glycol. Solid dispersion can be prepared by dissolving a drug in the molten PEG binder. By selecting a binder that is insoluble in water, melt granulation is a way of producing sustained release granules. The binder is added either in powder form to the starting material at ambient temperature, followed by heating above the melting point of a binder, or in molten form to the heated material. The temperature of the mixture is increased by heating jacket and by heat of friction caused by agitation. (Parikh,1997; Matsunaga et al, 1997)

The advantages of this process compared with wet granulation are as follow.

1. The amount of liquid binder can be controlled precisely, resulting in highly reproducible granule properties
2. The liquid addition and drying phases are eliminated.
3. For water sensitive material, melt granulation is an alternative to the use of organic solvents.
4. The production labor and equipment costs are reduced

The disadvantages are

1. The risk of chemical degradation of thermolabile substances (i.e. loss of water of crystallization).
2. The granules must be cooled before further handling.
3. The only water soluble melt binders for immediate release granules are the polyethylene glycol types.

2.Theophylline

Theophylline has been used as a bronchodilator in the treatment of asthma. The relatively narrow safety margin of drug range is commonly stated to be either 5 to 20 ug/ml or 10 to 20 ug/ml that created many problems and its remained limited. The first problem of theophylline if the dosage interval is too long, each single dose must be higher. This implies that the upper border of therapeutic concentration is easily exceeded, increasing the risk of toxic manifestation. A second problem with frequent medications, is that the patient forgets or decides not to take the drug at the prescribed times of the day, especially if the asthma does not cause must discomfort at that time. The most significant factor in increasing medical awareness of theophylline is the development of controlled release preparations of drug. Indeed, one of the main purposes of the controlled release is to improve safety and minimize side effects of drug by reducing fluctuations in drug levels. (Gennaro et al., 1990).

Matrix type tablet as well as coated tablets and particles has been reported as a useful controlled release dosage form with coating polymers. It can be prepared by several methods. For example, it can be compressed directly from the powder mixture of drug and polymer or tableting microcapsules or solid dispersed particles prepared with polymers. The latter method imparts the more precisely controlled and predictable drug release rated to the resultant tablet. Because the active ingredients are coated or embedded

Theophylline is a dimethyllated xanthine. Its structure is similar to the other xanthine derivatives, i.e., caffeine and theobromine, which are commonly found in coffee, tea, cola beverages and chocolate. Although it is present in natural sources, theophylline is available commercially by total synthesis.

2.1 Physio-chemical properties (Cohen,1975)

Chemical name: 1-purine-2, 6-dione, 3,7-dihydro-1, 3-dimrthyl, mono or anhydrous; 1,3-dimethylxanthine

Empirical formula: $C_7H_8N_4O_2$

Structure formula:

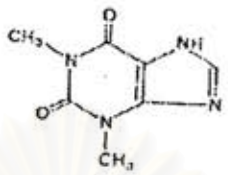


Figure 1. Chemical structure of theophylline

Molecular weight:	Theophylline monohydrate 198.18 Theophylline anhydrous 180.17
Description	white, odorless, crystalline powder with a bitter taste. Its saturated aqueous solution is neutral or slightly acid to limus.
Solubility:	8.3 mg/ml in water, 12.5 mg/ml in ethanol, 11.6mg /ml in chloroform, and freely soluble in solution of alkali hydroxides and ammonia.
Melting point:	269°C-274°C
Stability:	theophylline is stable in air. Its solutions are generally quite stable over the entire pH range. Strongly alkali solution showed decomposition after several weeks Theophylline will precipitate from aqueous solutions if pH drops below 9 unless presents in concentration less than the water solubility

3. Matrix devices.

The literature about the matrix system was well documented by Baker (1987). A matrix system as the name implies consists of drug distributed homogeneously throughout a polymer matrix as represented in Figure2.

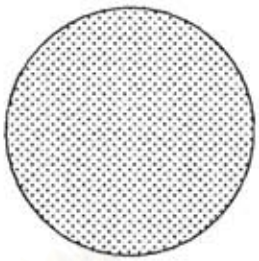


Figure 2 Matrix device

When the term " matrix device " is used without qualification, all typically means that the polymer it contained does not chemically disintegrate. If the polymer does erode, the device although actually a type of matrix device is referred to as an erodible, biodegradable or biodegradable system.

There are two principal categories of matrix device. The active agent is dissolved in the polymer medium, the device called a matrix solution. A device of this is often used the active agent is a liquid; some polymers can easily dissolve up to 20 % or more of these liquids. If the active agent has a more limited solubility in the polymer medium, then only a portion of agent is dissolved in the polymer medium and the remainder is dispersed as small particles throughout the polymer. A device of this type is called matrix dispersion.

3.1 matrix solution

One method of preparing a matrix devices containing dissolved active material is to equilibrate it with the material: for example, the device may be soaked in heat liquid or a concentrated solution. If the active constituent is dissolved homogeneously in the polymer matrix and it is assumed, for simplicity, that one planar surface was available for release, the amount of drug delivered will be obtained by solving Fick's second law of diffusion.

3.2 Matrix dispersion

The second type of matrix system consists of a dispersion of solid active agent in a rate-limiting polymer matrix. The characteristics of matrix dispersion

are listed in Table1 (Grass IV and Robinson, 1990). Matrix dispersion systems are of three types; which would be described latter, depending on the volume fraction of agent in matrix.

Table1 characteristics of matrix diffusion systems

Description	Homogenous dispersion of solid drug in a polymer
Advantages	Easier to produce than reservoir devices Can deliver high molecular weight compounds
Disadvantages	Cannot obtain zero order release Removal of remaining matrix is necessary for implanted system

At low loading levels of agent (0-5 volume percent), the release of the compound involves dissolution of the agent in the polymer medium followed by diffusion to the surface of the device. We will call these devices simple matrix dispersion.

At slightly higher loading levels (5-10 volume percent), the release mechanism is more complex since the cavities remaining from the loss of material near the surface are filled with fluid imbibed from the external environment. And these cavities provide preferred pathways for the escape of material remaining within the device. At those loading levels, the cavities are not connect to form continuous pathways to the surface, but they may increase the overall apparent permeability of the agent in the device. We will call these devices complex matrix dispersions.

When the loading of dispersed agent exceed 20 volume percent, the cavities left by the lost of material are sufficiently numerous to form a continuous channel to the surface of the matrix. In this case, the majority of the entire active agent is released by diffusion through these channels. We will call these types of device monolithic matrix systems or simply matrix system. The solubility and diffusivity of the dispersed agent in the fluid filling the channels determines its rate of release.

Release from these matrix dispersion systems can be described by percolation theory. The concept behind percolation theory can be conveniently illustrated in a two-dimensional grid in which some of the sites are randomly occupied, as shown in

Figure 3 (Baker, 1987) the empty sites represent the polymer matrix while the filled sites are the active agent particles. At low loading, as in the simple dispersion case, the active agents are well separated. At higher loading, as in the complex dispersion case, some small islands of interconnected particles grow, while at even higher loading these islands grow in size and form connected to form extended pathway. At loading above a certain critical value, continuous channels permeate the grid, and almost all the agent particles are connected to the channels. This is the matrix system. For the two dimension grid illustrated in Figure 3, the critical value at which almost all the agent particles are contact with one another is an agent volume fraction of 0.45, but in three dimensional matrix the critical loading value above which a continuous network formed in only 0.15 (Zaller, 1977).

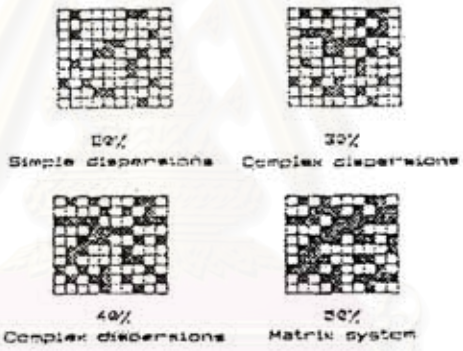


Figure 3 A two dimentional representation of a random distribution of agent particles (filled squares) in a polymer matrix. Agent loading of 20,30,40 and 50 % are shown.

The two types of matrix dispersion are

1. Simple matrix dispersion

When the active agent concentration is in the range of 0-5 volume percent, a simple Higuchi model[14] can describe the release rate from these systems. This model assumed that solid agent in the surface layer of the device dissolves in the polymer matrix and diffuses from the device first. When the surface layer becomes exhausted of agent, the next layer begins to be depleted. The interfaces between the region containing dispersed agent and the region containing only dissolved agent thus move

into the interior as a front. The release kinetics for such system has been solved and the appropriate equation is as follows.

$$\frac{dM_t}{dt} = \frac{A}{2}\left(\frac{2DC_{g(m)}C_o}{t}\right)^{1/2} \quad \text{for } Co >> C_{g(m)} \qquad \text{.....(1)}$$

Where M_t = the mass of drug released at time t

A = the total area of slab (both sides)

D = agent diffusion coefficient

t = time

$C_{g(m)}$ = the solubility of the agent in the polymer matrix

C_o = the total concentration of agent (dissolved plus dispersed) initially present

The release is proportional to the square root of time

2.Complex matrix dispersion

The Higuchi model is generally a good predicator of regent release for matrix polymer dispersion containing low levels (5 %) of active material. However, at higher loading, deviation from the expected release profile occurs. The rate release is still is proportional to the square root of time but has a higher value than the model predicts. As described earlier, this is due to the presence of the fluid filling cavities created by dissolution of the particle near the surface, which increase the system permeability to substance. At high loading dose, the drug can form a continuous capillary network throughout the polymer and release is governed by drug leaching through this region. Thus equation 2 may be modified for the complex dispersion matrix to

$$\frac{dM_t}{dt} = \frac{A}{2}\left(\frac{2DC_{s(m)}}{t} \cdot \frac{1+\frac{2C_o}{\rho}}{1-\frac{C_o}{\rho}}\right)^{\frac{1}{2}} \qquad \text{.....(2)}$$

where ρ is the density of permeate

4.Polymer

4.1 Eudragit® RS

Eudragit acrylic resins have been widely used in the pharmaceutical industry as a film coating for bitter taste prevention and controlled drug delivery by direct compression. Since Eudragit acrylic resins have specific dissolution and permeability properties under physiological condition and have been used to produce the desired drug release pattern during the process of pharmaceutical research.

Eudragit® RS is copolymers of acrylic acid and methacylic ester with a low content ion quaternary ammonium groups usually used for the preparation of controlled released product. Eudragit® RS is referred to as ammonio-methacrylate copolymer in the USP/NF monograph, and are prepared by copolymerization of ethyl acrylate, methyl methacrylate and trimethyl-ammonioethyl methacrylate chloride with a mole ratio of1: 2:0.1. It is report that Eudragit® RS is a water insoluble polymer and the drug delivery system prepared from it shows the pH independent drug released attributed to the quaternary ammonium groups (Lehmann1989). The average molecular weight is approximately 150,000.

Eudragit® RS dissolves in 7g aqueous methanol, ethanol and isopropyl alcohol, as well as in acetone, ethyl acetate and methylene chloride to give clear to cloudy solutions

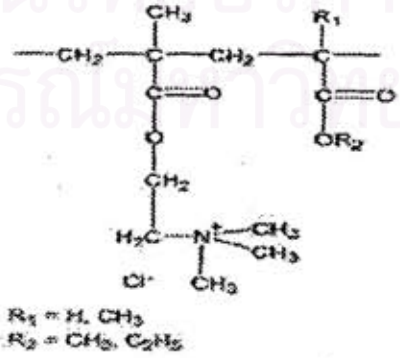


Figure 4 Chemical structure of Eudragit® RS

Although sustained release tablet containing acrylic resin polymers as a film coating are widely developed, matrix system appear to be quite attractive and an interesting approach from the economic and the process development point of view. Cameron et al. (1997) have studied the application of acrylic resins in controlled-release theophylline tablets. Tablets containing the four different acrylic resins (Eudragit® RS, Eudragit® RL Eudragit® S100, Eudragit® L100) were easily prepared by direct compression of the drug and excipient blend. No problems were experienced with flow, weight uniformity and compression characteristics of the granulation. Dissolution properties of Theodur® in acid and simulated intestinal media showed a similarity in release properties to those of theophylline in tablet containing the Eudragit® RL. The combination of cationic and anionic Eudragit®resins as a retardant matrix in a theophylline tablet formulation was demonstrated to have good potential in a controlled-release dosage form. The retardant effects in acidic medium were dependent upon the levels of acrylic resin polymer in the dosage form. The rapid release at pH 7.4 was due to the high solubility of the Eudragit® L100. The release rate at pH 7.4 was similar for tablets containing from 5-15 percent resin. Compatibility studies showed good compaction properties for theophylline in combination with the Eudragit resins(Cameron and McGinity. 1987).

Sustained release of indomethacin was prepared using Eudragit® RS Two types of formulation were considered, one was directly compressed powder mixture that produced a matrix system, and the other was prepared by wet granulation, such that the drug was to some extent scaled within a cast film of the polymer. The drug release from the matrix was directly proportional to the concentration of the polymer that was used. Drug release from the granulated system was much slower than from the directly compressed matrix. (Efentakis and Buckton, 1990)

4.2 Kollidon®SR

Polyvinylacetate /Povidone based polymer (Kollidon® SR) is a relatively new excipient in the development of oral controlled-release product. It consists of 80 % polyvinylacetate and 19 % povidone in a physical mixture, stabilized with 0.8 %

sodium lauryl sulfate and 0.2 % collidal silica. Although water insoluble, it is slightly hydrophilic and able to absorb water to a slight extent.(Fussnegger,2000)

Polyvinylacetate is a homopolymer of vinylacetate. It is obtained by emulsion polymerization.Description water white, clear solid resin, soluble in benzene and acetone, insoluble in water or emulsion readily diluted with water. Polyvinylacetate is a very plastic material that produces a coherent matrix even under low compression forces.

Povidone (polyvinylpyrrolidone) is a white amorphous hygroscopic powder, soluble in water. It has good binding properties both under dry or wet conditions. Due to its hygroscopicity, povidone promotes water uptake and facilitates diffusion and drug release.

The manufacture procedure for the polyvinylacetate /povidone redispersible polymer powders and their application as binder at 0.5-20 %, when the active ingredients are released within a time of 0.1-1.0 hour.

Figure 5 Chemical structure of Kollidon® SR (Fussnegger,2000)

The use of Kollidon® SR as a plastic material in direct compression process to formulate sustained release dosage form has also been reported including theophylline, nifedipine and chlorpromazine hydrochloride (Schmidt et al., 1996; Niwa et al., 1994 ; Shao et al., 2001; Reza et al., 2003). Kollidon® SR is particularly suitable for the manufacture of pH independent sustained release matrix tablets (pH and salt/ion content medium). It contains no ionic group, which render the polymer inert to the drug molecule. (Fussnegger, 2000)

Zhang and McGinity(2000) have investigated the properties of polyvinylacetate as a retardant polymer processed by hot melt extrusion. Due to the low grass transition temperature of the polymer, the melt extrusion process could be conducted at temperature within the range 50°C to 70°C. During the processing, the extrudates was subjected to minimal thermal and mechanical stress. The extrudates had to be ground into fine powder and compressed into tablets with directly compressible. Theophylline was present in the extrudate in its crystalline form and was released from the tablet by diffusion. The Higuchi diffusion model and percolation theories were applied to the dissolution data to explain the drug release of the matrix system.

Kollidon® SR gave an intermediate release profile between carnauba wax and HPMC. Fickian (case I) transport was predominant mechanism of drug release from Kollidon® SR matrix system. (Reza at al., 2003)

5.Plasticizer

Plasticizers are usually high boiling organic solvents used to impart flexibility to otherwise hard or brittle polymeric materials under normal ambient temperatures and humidity conditions. Plasticizers generally cause a reduction in the cohesive intermolecular forces along the polymer chains resulting in various changes in the polymer properties

Plasticizers are an important component in a polymeric film coating formulation since pharmaceutical polymers are brittle rather than ductile materials. Plasticizer may be classified as internal and external. The internal plasticizer modify the chemical nature of the basic polymer, thereby altering the physical properties i.e. copolymerization with softening monomers of greater chain length. The external plasticizers change the mechanical and adhesive properties of the film i.e. adding suitable substances to the coating formulations. (Sears, and Darby 1982)

The basic requirements of plasticizer are permanence and compatibility. Permanence dictates that plasticizer has a low vapor pressure and low diffusion rate within the polymeric film, a requirement that favors high molecular weight plasticizers. Compatibility, on the other hand, demands that the plasticizer be miscible with the polymer and exhibit similar intermolecular forces to those present within the polymer. (Wheatley and Steuernagel, Sears and Darby 1982).

The plasticization of a polymer is generally attributed to the intermolecular secondary valence forces between the plasticizer and the polymer. Different plasticizers at the same concentration will affect the glass transition temperature and hence the mechanical properties to a different extent. The degree of plasticization of the polymer is dependent to a large extent on the amount of plasticization in the film and the interaction between the plasticizer and the polymer. For a plasticizer to be effective, it must be able to diffuse into and interact with the polymer and have minimal or no tendency to migration or exudation from the polymer. The decrease in the *Tg* of a polymeric film as the plasticizer concentration increase is a common measure of plasticizer effectiveness. (Lin et al., 2000)

This result allowing the polymer molecular to move more readily which increasing in free film elongation, reduction in elastic modules, tensile strength, polymer melt viscosity, glass transition temperature or softening temperature of the polymer. The polymer toughness and flexibility is improved and lower thermal processing temperature can be employed. For instance, pharmaceutical polymers used in film coating typically require a plasticizer in order to reduce brittleness and enhance polymer coalescence and film formation. The plasticizer reduces both the glass transition temperature and the minimum film formation temperature (MFT) as a result, the temperature requires for film coating is reduced. (Wheatley and Steuernagel,

The solubility and miscibility of the plasticizer with the retardant polymer are important criteria to consider since, for example, acetyl triethyl citrate will plasticizer HPMC during process but it is immisible with Eudragit L100. Tributyl citrate seems to be the first choice for plasticizing the Eudragit E film. (Lin et al., 2000) The efficiency of a plasticizer was related to its functional groups with those of the polymer.(Gutierrez- Rocca and McGinity, 1997) A strong interaction between a drug

and a polymer has been reported to significant influence drug release through a polymeric film. (Bodmeier and Paeratakul, 1989). The physical-mechanical properties of polymers will be influenced by both environment factors and the chemical composition of the polymer. structural properties of the polymer will include molecular weight, crosslinging and branching, crystallinity and crystal morphology, type and amount of plasticizer, and presence of additives or fillers. Environmental factors influencing polymer properties will include temperature, time and rate of stressing the polymer, pressure, stress and strain amplitude, type of deformation, and the nature-surrounding atmosphere.

With the addition of a plasticizer, hot melt extrusion process can be conducted at lower temperature and with less torque. (Repka et al., 1992) A high plasticizer amount was necessary to achieve complete film formation in dry powder coating. (Pearnchob, Bodmeier, 2003) to enhance the mechanical properties (Wang. et al., 1997; Wu and McGinity, 1999)

Plasticizers are incorporated into pharmaceutical polymers to modify drug released from polymeric system and to enhance the mechanical properties and surface appearance of dosage form. Saettone et al. (1995) demonstrated the type and amount of plasticizer influence the drug release rate of pellet coated with latex aqueous dispersion of ethylcellulose and acrylic polymer by altering the water permeability. Rey et al (2000) show the slightly lower dissolution rate from minitablet when Triethyl citrate was incorporated And many researches have demonstrated plasticizer modified drug release from polymeric system (Bodmeier and Paeratakul ,1990; Mulye and Turco, 1994 Frohoff-Hulsmann et al., 1999;Okarter and Singla, 2000)

However, most pharmaceutical grade plasticizers are in a liquid state and Homogeneous blend of plasticizer with the powder blend containing the active ingredient must be obtained after the process. An incomplete mixing for a polymer powder with a liquid additive has been show to result in an unstable mass flow when feeding mixture.(Tate et al, 1996). Several reports have focus on the evaporation and loss of plasticizer during a high temperature operation, thus causing stability problem in a finished dosage form. (Gutierrez- Rocca and McGinity, 1993; Skultety and Sims, 1987)

Recently, solid state plasticization for acrylic polymer was reported for both coating and hot melts process. Lidocain HCl and chlorpheniramine maleate was able to plasticize the acrylic polymer and hydroxypropylcelluluse films and that the drug completely dispersed at the molecular level in the extruded films.(Aitken-Nichol et al.,1996 ;Repka and McGinity, 2001) Wu C. and McGinity (2001) found that ibuprofen was able to plasticize Eudragit® RS 30D films. Higher concentration of ibuprofen in the film produced a relatively smooth surface. Ibuprofen interacted with the Eudragit® RS30D polymer through hydrogen bonding. Increasing the amount of ibuprofen in the polymeric film reduced the drug release rate. Zhu et al.(2002) shows the effect of triethyl citrate levels on drug release rates were dependent on the thermal processing method used to prepared the solid composite. As triethyl citrate levels increased the drug release rate decreased for tablet prepared by either direct compression or from granule made by high shear hot melt granulation. In contrast, drug release rates increased with increasing triethyl citrate levels for the hot melt extruded tablet. Methyl paraben has shown to be an effective plasticizer for Eudragit® RSPO when a hot melt extrusion technique was employed for developing sustained release tablets. X-ray diffraction studies demonstrated that methylparaben was dissolved in the polymer and the solid state NMR shows the interaction between the hydroxyl group of methyl paraben and the ester group of the Eudragit® RSPO. (Wu and McGinity, 2003) Fujimori et al (2002) were successfully developed the polymer materials having temperature-sensitive and high biological safety, Eudragit® RS and PEG400 blend polymers were prepared. The Eudragit® RS and PEG400 blend polymers that have the Tg around the body temperature were prepared by the addition of 5-13% PEG400 into Eudragit® RS. The acetaminophen release rate and release mechanism from the matrix tablet changed slightly below the Tg of the tablet and then changed markedly above the Tg.. Incorporation of Diethyl Phthalate or Triethyl citrate into solid dispersion system of the Propanolol and Eudragit® RS affected drug release profiles and increase in crushing strength of matrices and provided better control of drug release. The effect was more pronounced for higher concentrations of plasticizers, which helped matrices to retain their shape throughout the dissolution test. (Sadeghi et al., 2004) The plasticizer was used in this study are generally

classified as water-soluble and water insoluble. For the organic system, dibutyl phthalate was previously selected by many researchers to investigate effect of drug release. Triethyl citrate, water-soluble plasticizer is one of the most popular plasticizer that was used in organic system and hot melt process.

5.1 Properties of plasticizer in experiment

5.1.1.Triethyl citrate

USP/NF: Triethyl citrate

: Formular: $C_{12}H_{20}O_7$

: Molecular weight: 276 29

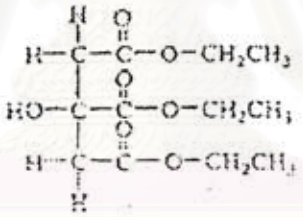


Figure 6 Chemical structure of triethyl citrate

Appreance: clear, odorless, practically colorless, oily liquid

Boiling point: 288 °C

Solubility: soluble 1 in 125 of peanut, 1 in 15 of water, miscible with ethanol(95%), acetone and isopropanol.

5.1.2 Dibutyl phthalate

USP/NF: Dibutyl phthalate

Formular: $C_6H_4(COOC_4H_9)_2$

Molecular weight: 278.35

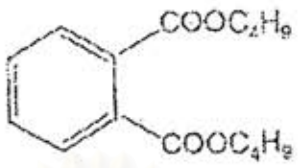


Figure 7 Chemical structure of dibutyl phthalate

Appearance : a clear, colorless, or faintly colored oily liquid

Boiling point : 340°C

Solubility : very soluble in acetone, benzene, ethanol (95 %) and ether, soluble 1 in 2500 of water

6. The analysis of dissolution data of controlled release system

6.1 The-release mechanism of controlled release system

In order to analyze the mechanism of the drug from the matrices, the dissolution data may be analyzed using the semi-empirical equation of Peppas given below

$$\frac{M_t}{M_\infty} = kt^n \qquad \text{.....(3)}$$

Where $\frac{M_t}{M_\infty}$ 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 released drug ($M_t/M_\infty < 0.6$), which also applied only to the early times of release.

Clearly, a desirable mechanism for many applications is that which leaded to n equal to 1, which characterized zero-order release behavior.

In non-swelling metrices, the value of n are 0.45 and 1.00 for Fickian and case II transport, respectively. Case II transport is 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 characteristic 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 (Riger and Peppas, 1987) 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 2 Diffusion exponential and mechanism of diffusional release from various non-swellable controlled release systems

Diffusion 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

6.2 The release pattern of controlled release system

The pattern of delivery achieves by a controlled release system can vary over a wide range, but most release profiles categorized into three types

1. Zero order release pattern
2. Square root time release pattern
3. First order release pattern

1 Zero order 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

$$\frac{dM_t}{dt} = k \quad \text{.....(4)}$$

Where k is a constant, t is time and the mass of active agent released was Mt. This pattern of release is called zero order release models

2 Square root of time model (Higuchi model)

The second common release pattern, frequently referred to as square root of time, provided compound release that was linear with the reciprocal of the square root of time The release rate then given as

$$\frac{dM_t}{dt} = \frac{k}{t^{1/2}} \quad \text{.....(5)}$$

In contrast to first order release, the release rate here remained finite as the device approach exhaustion

The release pattern of this type can be described by Higuchi equation

$$\frac{Q=[De(2A-\varepsilon Cs)Cst]^{1/2}}{\tau} \quad \text{.....(6)}$$

Where Q = weight in grams of drug released per unit surface area

D = diffusion coefficient of drug in the release medium

ε = porosity of matrix

τ = tortuosity of matrix

Cs = solubility of drug in the release medium

A = concentration of drug in the tablet, expressed as g/ml

The assumptions made deriving equation 6 are as follows

1 A pseudo-steady state is maintained during release

2. A >> Cs, i.e., excess solute is present

3. The system is in perfectly sinking condition in which C is approximately to zero at all time.

4. Drugs particles are much smaller than those in the matrix are

5. The diffusion coefficient remains constant.

6. No interaction between the drug and the matrix occurs.

for purposes of data treatment, equation 6 is usually reduced to

$$Q = k_H t^{1/2} \quad \text{.....(7)}$$

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

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

$$\text{Log } Q\ k_H = \log k_H + 1/2 \log t \quad \text{.....(8)}$$

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

3.First order release model

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

$$\frac{dM_t}{dt} = k(M_o - M_t) \quad \text{.....(9)}$$

Where M_o is the mass of agent in the device at t=0. On rearrangement, this gave

$$\frac{dM_t}{dt} = kM_o \exp^{-kt} \quad \text{.....(10)}$$

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, Wanger (1969) suggested that drug release from most controlled release matrices could be described by apparent first order kinetics, thus:

$$A_t = A_0 e^{-kt} \quad \text{.....(11)}$$

Where k is first order release constant

A_0 is initail amount of drug

A_t is amount of drug remaining in the matrix at time t

Simplifying and taking the logarithm of equation11yielded

$$\log A_t = k A_0 - k Q' \quad \text{.....(12)}$$

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

The plot of rates of release versus 1/Q' is linear, indicating that the release is fitted with Higuchi model. If the plots of the 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 8 (Baker, 1987), the release model of zero order, square root time and first order depicted (equation2, 3and7) respectively.

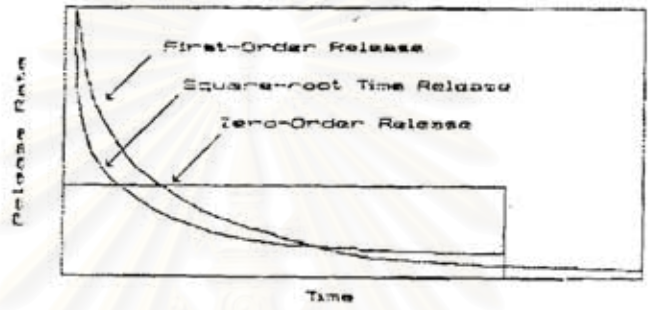


Figure 8 Zero order, square root time and first order release models from devices containing the same initial active agent content

Chapter II

Experimental

1. Materials

1.1 Model drug

-Theophylline anhydrous BP

(BL. Hua &Co., Ltd. Thailand, Lot.No.SE2002005)

1.2 Additives

-Ammoio methacrylate copolymer, type B

(Eudragit® RS100, Rohm GMBH, Germany, Lot.No.8321108218)

-Polyvinylacetate/ Povidone

(Kollidon® SR, BASF, Germany, Lot.No. 91663956 PO)

-Lactose monohydrate

(Wyndale, New Zealand, Lot. No. 00087527)

-Magnesium stearate

-Dibutyl phthalate

(Merck, Germany Lot.No.61279343)

-Trietyl citrate

(Fluka AG, Switzerland Lot.No 445571/1)

1.3 dissolution medium

-Potassium dihydrogen phosphate

(Ajax Finechem, Australia Lot.No. 3A2822631)

-Sodium hydroxide, AR grade

(Mallinckrodt, USA Lot.No.B231098 243)

-Hydrochloric acid 37% AR grade

(Mallinckrodt, USA Lot. No.3B45789)

-Potassium chloride

(Ajax Finechem, Australia Lot.No. 51005275N)

-Ammonium hydroxide

(J.T. Baker, U.S.A. Lot.No. 51005275N)

1.4 other chemicals

-Ethyl alcohol

-Acetone

2.Equipment

-Analytical balance (Modela200S, Satorious GmBh, Germany and Model PB3002, Mettler, Switzerland)

-Differential scanning calorimeter (DSC-TA instrument, Mettler Star^e)

-Dissolution Aparatus (Model DT-6R, Erweka GmBh, Germany)

-Fourier transformed infrared spectrometer (Model SP2000, Perkin-Elmer Ltd., England)

-Friabilator (Erweka TAR 20, Germany)

-Hot air oven (Model UL80, Memmert, Germany)

-Hydraulic press equipment

-Sieve shaker (Josef Deckehnann Aschaflenberg, Germany)

-pH meter (Model 292, Pye Unicham, England)

-Scanning electron microscope (Model JSM5410LV, Jeol Ltd., Japan and Model JSM 5800 LV Jeol Ltd. Japan)

-Sieve shaker (Josef Deckehnann Aschaflenberg, Germany)

-Spray dryer (Mobile Minor Spray, Type" Hi-Tec" Serial 2648 Nitro atomizer Denmark)

-Tablet hardness tester (Model TBH 30, Erweka GmBh, Germany)

-Tablet thickness tester (Teclock Corp., Japan)

-Ultravilolet-visible Spectrophotometer (Model UV, Shimadzu corp., Japan)

-Ultrasound transonic digital sonicator (Model D-78224, Elma, Germany)

-X-ray powder diffractometer (Model JDX-3530, Rigaku Denki Jeol Ltd., Japan)

3. Methods

3.1 Preparation of granules by thermal granulation

Granules containing 50 % w/w of theophylline were prepared by thermal granulation using planetary mixture. The processing temperature was maintained at 60°C and 80°C by circulating water in the jacket surrounding the chamber. The temperature inside the chamber was monitored using thermometer. Fraction of drug, polymer, and diluent were mixed for 5 minutes at a speed of 150 rpm. After mixing, the granules were sieved through 16-mesh screen and cooled at room temperature .The granules were stored in the desiccator for further evaluation. The granulation composition is presented in Table 3.

Table 3 The formulation of theophylline matrices

Theophylline anhydrous	150g
Polymer*	90g
Plasticizer**	10-20% of polymer
Magnesium stearate	1.5g
Lactose monohydrate	qs. 300g

*Eudragit® RS100 or Kollidon® SR, ** triethyl citrate or dibutyl phthalate

3.2 Plasticizer Incorporation methods.

Plasticizer was incorporated into the polymer by 4 methods.

3.2.1 Method I (wet granulation)

The polymer was dissolved in organic solvent (acetone: ethanol =1:1) then the plasticizer was incorporated to the polymer solution. The polymer solution was added into the powder mixture containing theophylline and lactose in planetary mixture. As shown in the chart below

Eudragit® RS100 or Kollidon® SR dissolved in Ethanol: acetone=1:1

⇩ + Plasticizer

Polymer solution

⇩ + Theophylline + Lactose

Thermal granulation

⇩

Granules

⇩ Compress

Tablets

3.2.2 Method II (ground polymer)

Plasticizer was incorporated into the polymer solution and put on the petridish. The petridish was placed to the hot air oven to dry at 50°C for 48-72 hrs. The dried polymer with plasticizer was ground to powder by grinder (De Longhi® KG 39) and the size fraction below 250 μm were collected and stored in the refrigerator prior to thermal processing. As shown in chart below.

Eudragit® RS100/ Kollidon® SR dissolved in Ethanol: acetone=1:1

⇩ + Plasticizer

Polymer solution

⇩ Drying at 50°C and ground

Powder

⇩ + theophylline + lactose

Thermal granulation

⇩

Granules

⇩ Compress

Tablets

3.2.3 Method III (spray plasticizer into polymer)

Plasticizer was sprayed into the powder mixture of theophylline, polymer and lactose during the thermal processing. As show in chart below.

Theophylline + Lactose + Eudragit® RS100/ Kollidon ® SR

⇩

Thermal granulation

⇩

Spray plasticizer into polymer mixing

⇩

Granules

⇩ Compress

Tablets

3.2.4 Method IV(spray dried)

Plasticizer was incorporated into the polymer by co spray drying of polymer and plasticizer. As show in chart below.

Eudragit® RS100/ Kollidon ® SR dissolved in Ethanol: acetone=1:1

⇩ + Plasticizer

Polymer solution

⇩

Spray drying

⇩

Spray dried powder

⇩ + theophylline + lactose

Thermal granulation

⇩

Granules

⇩ Compress

Tablets

Polymer are water insoluble, the nonaqueous solvent system had to be used, to avoid the explosion problem, acetone was not used. Ethanol was found to be suitable for spray drying. Instrument conditions, for example inlet air temperature, outlet air temperature, pump setting and spray flow, were optimized to obtain a good product.

Table4 The experimental setting for spray drying

Inlet air temperature	45°C
Outlet air temperature	40°C
Pump setting	2 bar
Spray flow	15 ml/min.
Concentration of spray solution	1.25 % w/v

Table 5 The compositions of spray dry solution

Polymer	1.25 % w/v
Plasticizer	10-20 % of polymer
Ethanol qs.	100 %

A rotary atomization was used throughout the experiment. The spray drying parameters were kept constant. The spray-dried powders from the process were collected from the chamber and collector of the apparatus. The spray-dried powder was mixed with theophylline and lactose for thermal granulation processing.

3.3 Tablet preparation

Prior to compression, The granules were blended with magnesium stearate for 5 minutes. Granules (400 mg.) were compressed into tablet with 8 mm flat face punch using a hydraulic press with a compression force of 500, 1000 and 1500 psi. Tablet hardness was controlled about 5 kg. Tablet hardness was measured using a tablet hardness tester.

4. Evaluation of polymer with plasticizer

The powder of polymer with plasticizer, which obtained from plasticizer incorporation method II and IV were examined as followed.

4.1 Determination of glass transition temperature

A differential scanning calorimeter (Mettler Model 822) was used to determine the effect of plasticizer on the polymer. Approximately 5-10 mg of sample was accurately weighed and hermetically sealed in an aluminum pan. The sample was equilibrated at -20°C for 10 min. The temperature of the sample was then ramped from -10 to 150 °C at a rate 5.0 °C / min. The sample were cycled triple to remove thermal history. The glass transition temperature was determined in the third cycle as the step transition in the plot of reversible heat flow versus temperature. The DSC was calibrated using an abbreviated calibration method with an indium standard prior to sample analysis.

4.2 Determination of particle size distribution

Particle size was measured using laser light scattering size distribution measurement equipment (Mastersizer 2000)). The relative frequency of the diameter of the particles was shown with the calculation based on volume distribution. The particle size at 50% of total fraction was used as average particle size. The particle was the average of three measurements.

5. Evaluation of granules

5.1 Morphology of granules

The granules with and without plasticizer were examined under a scanning electron microscope (SEM) for morphological evaluation. Shape and surface of granules were determined. The samples were prepared by gold sputtering technique before SEM examinations.

5.2 Bulk, Tapped density and Carr's index

The bulk and tapped densities were determined by pouring 30 g. of the granules into a 100 ml. Graduate cylinder. The bulk volume was recorded and bulk density was calculated dropping graduate cylinder on a hard surface from height 5 cm until a constant volume was obtained performed tapped density. Then, tapped volume was divided by weight to attain tapped density. Both densities were averaged from three determinations. the Carr's compressibility was calculated from the following equation.

$$\text{Carr's index} = \frac{(T-B)*100}{T}$$

Where T and B are tapped and bulk density, respectively.

5.3 Determination of angle of repose

Each angle of repose was determined by the cylinder method. An appropriate amount of powder was carefully filled into a cylinder, which was place on the graph paper until it was filled at the top of the cylinder. Then the cylinder was slowly lifted in the vertical direction, thus producing around heap of powder. the result was calculated from the following equation.

$$\alpha = \tan^{-1} \frac{H}{R}$$

Where α, H and R are the angle of repose, height and radius of the heap, respectively.

5.4 Determination of flow rate

Accurate weight of about 30 g of granules was filled in a glass funnel with 8-mm internal stem diameter fixed on a clamp. The time was recorded when the granules started to flow until finished. The flow rate averaged from three determinations was reported in term of g/second.

6. Evaluation of matrix

6.1 weight variation

The weight of tablet after compression was measured by analytical balance. The mean and standard deviation were calculated from twenty tablets.

6.2 Matrix hardness and thickness

The hardness and thickness was measured using the Schleuniger-2E hardness tester and tablet thickness tester. The mean and standard deviation of ten determinations were calculated.

6.3 Tensile strength

The hardness of the tablets was determined using the tablet hardness tester and the tensile strength were then calculated using the relationship (Fell and Newton, 1971)

$$T = 2P/HD\pi$$

Where T is the tensile strength (N/m^2)
H is the thickness of the tablet (mm)
D is diameter of the tablet (mm)
P is the applied force to fracture the tablet (N)

6.4 Dissolution studies of matrices tablet.

Dissolution of theophylline from tablet was studied by using USP 24 paddle method with 900 ml of hydrochloric acid buffer pH 1.2 and phosphate buffer pH 6.8 as a dissolution medium maintained at 37 ± 0.5 °C. The paddle was set to rotate at 50 rpm. Ten milliliters aliquots of the dissolution medium were pipetted out at the

predetermined interval of 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours. The equivalent volume of fresh dissolution medium was immediately replaced at each time interval of withdrawal.

Each sample was diluted to suitable concentration, which gave the absorbance between 0.2-0.8. The absorbance was determined spectrophotometrically at 270 nm. Each of the dissolution values reported was based on an average of three determinations of each formulation. The amount of theophylline released at any time interval was calculated from the calibration absorbance –concentration curve.

6.4.1 Calibration curve of theophylline

Theophylline anhydrous of 200mg was accurately weighed and dissolved in hydrochloric acid buffer pH 1.2 and phosphate buffer pH 6.8. The solution was then adjusted to 2000 ml in a volumetric flask with the same medium and used as a stock solution to obtain the solution of known concentration between 0-14 mcg/ml.

The UV absorbance of each concentration was determined by using a single beam UV-VIS spectrophotometer in a 1-cm cell at 270 nm. The hydrochloric acid buffer pH 1.2 and phosphate buffer pH 6.8 were used as a blank solution Each concentration was determined in triplicate.

The concentration versus absorbance of theophylline in hydrochloric acid buffer pH 1.2 and phosphate buffer pH 6.8 at 270 nm are presented in **tables 34-35** (appendix A) shown a linear relationship. The standard curve of theophylline after regression analysis are illustrated in **figures 68-69** (appendix A)

6.5 Drug content Determination

Ten tablets were randomly selected to determine the drug content. One tablet of theophylline was placed into a 100-ml volumetric flask. Add 20 ml of water and 25 ml of 6N ammonium hydroxide, sonicated for about 45 mins, and cooled to room temperature. Diluted with water to volume. Filter the portion of mixture, discarding the first 20-ml of filtrate. Dilute a portion of the filtrate quantitatively and stepwise if

necessary, with water to obtain a solution containing about 10 mcg of theophylline per ml.

UV absorbance of each concentration was determined by using a single beam spectrophotometer in a 1-cm cell at 270 nm. Water was used as a blank solution. Each concentration was determined in triplicate.

The tablets were considered uniform in their drug contents only if they met the USP uniformity of dosage unit acceptance criteria (USP & NF 25th Ed). The criteria specify that the percent drug content in each sample must be within 85-110 % of the theoretical label claim and the relative standard deviation (RSD) is less than 6 %.

7 Physiochemical properties

7.1 Wide angle powder X-ray diffraction (XRD)

Scanning powder X-ray diffractometer (type JDX-3530, Jeol ltd., Japan and Rigaku Denki) was used to characterize the crystalline properties of the drugs and Eudragit® RS100 and Kollidon® SR were exposed to Cu-Kα radiation under 40 Kv and 30 mA over the 2-theta range from 5.0-90.0 deg.

8 Statistics

To compare the means of drug release rate and to assess statistical significance between them, single-factor analysis of variance (ANOVA) was carried out at 5 % significance level.

CHAPTER III

RESULTS AND DISCUSSION

1. Evaluation of polymer with plasticizer

1.2 The Glass transition temperature of polymer

The glass transition temperature (Tg) is found in all amorphous polymers and in amorphous regions of partially crystalline polymers. The Tg of the latter is independent of the degree of crystallization but the magnitude of the transition decreases with an increase in crystallinity with the result that the transition becomes difficult to detect in high polymers. (Ford and Timmins, 1989)

At low enough temperatures, all amorphous polymers exist in a glassy state where no large-scale molecular motion can take place, and while in glassy state, polymers are characterized by their hardness, stiffness, and brittleness. As the temperature is raised, polymers undergo a transition, known as the glass transition temperature, Tg, where their change from a glass to a rubbery elastomer or flexible plastic. This transition take place over narrow temperature range and corresponds to the onset of segmental motion of long segments of the polymer chain, which is brought about by the availability of sufficient thermal energy to overcome intermolecular interactions.

As a consequence of this transition, the polymer undergoes an abrupt change in properties. Among these is coefficient of expansion, permeability, heat content, refractive index and hardness. Thus, in designing a controlled-release device, it must be known whether at use, the polymer will be above or below its glass transition temperature.

The glass transition temperature, also known as the second-order transition, is a characteristic of a particular polymer structure, and its value is closely related to intermolecular forces and chain stiffness. Thus, because above the Tg segmental motions of polymer chains take place, it follows that very flexible polymers, where free rotation about bonds along the polymer chains is possible, will in general have low Tg values.

Changes in the Tg of one polymer usually affect different film properties. Adding plasticizer can generally lower Tg because plasticizer enhances segmental mobility of polymer. In another way, adding pigment can generally reduce polymer chain mobility that manifests as an increase in Tg. Moreover, modification to the polymer that increase the presence of polar groups, hydrogen bond, and other factors that enhance the intermolecular forces tend to raise Tg.

1.2.1 The Glass transition temperature of Eudragit® RS and Kollidon® SR without plasticizer

The glass transition temperature of Eudragit® RS and Kollidon® SR without plasticizer was determine by a differential scanning calorimeter (Mettler® 822) with the heating rate of 5 °C/min. The Tg of Eudragit® RS and Kollidon® SR was determined to be 64.24°C, 40.09°C, respectively, as shown in Figures 76-83(Appendix D). A value of 67.4°C and 61.5°C has been reported by other researchers. (Okhamafe and York, 1987; Zhu et al., 2002). The difference between the Tg values may be due to the different condition used to experimentally determine this property.

1.2.2 The Glass transition temperature of Eudragit® RS and Kollidon® SR with plasticizer

When 10 % and 20 % TEC or DBP was incorporated into Eudragit® RS, the glass transition temperature was determined to be 37.14°C, 13.19°C and 32.78°C, 18.79°C prepared by method II (ground polymer) and to be 34.14°C, 12.63°C and 33.55°C, 17.35 °C prepared by method IV (spray dried), respectively, as shown in Figures 76-79(Appendix D).

When 10 % TEC or DBP was incorporated into Kollidon® SR, the glass transition temperatures were determined to be 22.65°C, 21.74 °C prepared by method II(ground polymer) and to be 21.74°C, 23.59°C prepared by method IV (spray dried). The glass transition temperature of Kollidon® SR with 20 % TEC or DBP prepared by method IV (spray dried) was 9.08°C, 9.11°C as shown in Figures 80-83(Appendix D).

Table 6 Glass transition temperature of Eudragit® RS and Kollidon® SR without plasticizer and with 10% and 20% plasticizer prepared by method II

Formulation	Glass transition temperature(°C)
Eudragit® RS	
0 %	62.12
10 % TEC	37.14
20 % TEC	13.19
10 % DBP	32.78
20 % DBP	18.79
Kollidon® SR	
0 %	40.09
10 % TEC	22.65
20 % TEC	*
10 % DBP	21.74
20 % DBP	*

*Could not be processed

Table 7 Glass transition temperature of Eudragit® RS and Kollidon® SR without plasticizer and with 10% and 20% plasticizer prepared by method IV

Formulation	Glass transition temperature(°C)
Eudragit® RS	
0 %	62.45
10 % TEC	34.14
20 % TEC	12.63
10 % DBP	33.55
20 % DBP	17.35
Kollidon® SR	
0%	40.09
10 % TEC	21.74
20 % TEC	9.08
10 % DBP	23.59
20 % DBP	9.11

An absence of data in amount of 20 % plasticizer in the Kollidon® SR prepared by method II was due to the polymer agglomeration and stickiness could not be processed.

Figures 21-24 demonstrate that the glass transition temperature of Eudragit® RS with 10 % and 20 % TEC or DBP decreased as a function of percentage of TEC or DBP level. A linear relationship between the glass transition temperature and percent of TEC or DBP with high correlation was observed. The glass transition temperature decreased 2.55°C for each percentage of TEC and 2.27°C of DBP in method II. A value of 2.26°C for TEC and 2.36°C for DBP were observed for polymer in method IV. The glass transition temperature of Kollidon® SR system prepared by method IV decreased 1.55°C for each percentage of TEC and DBP.

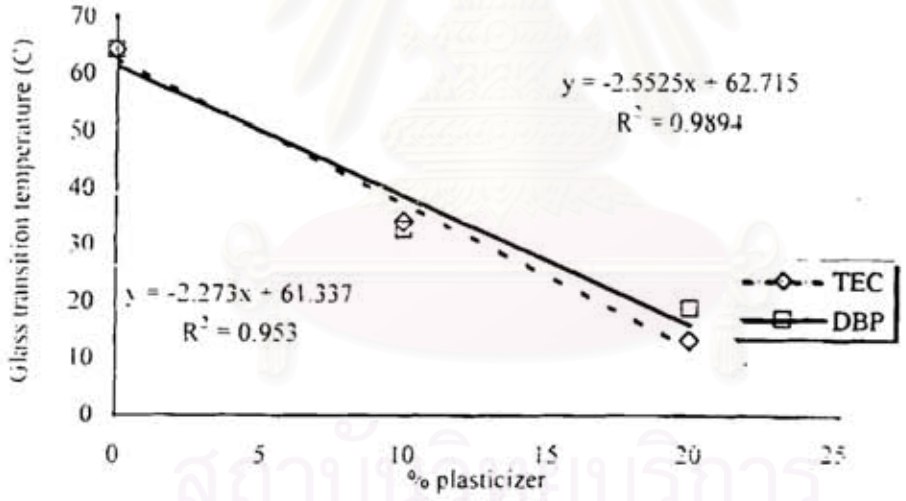


Figure 21 Glass transition temperature of Eudragit® RS as a function of TEC and DBP prepared by method II(ground polymer)

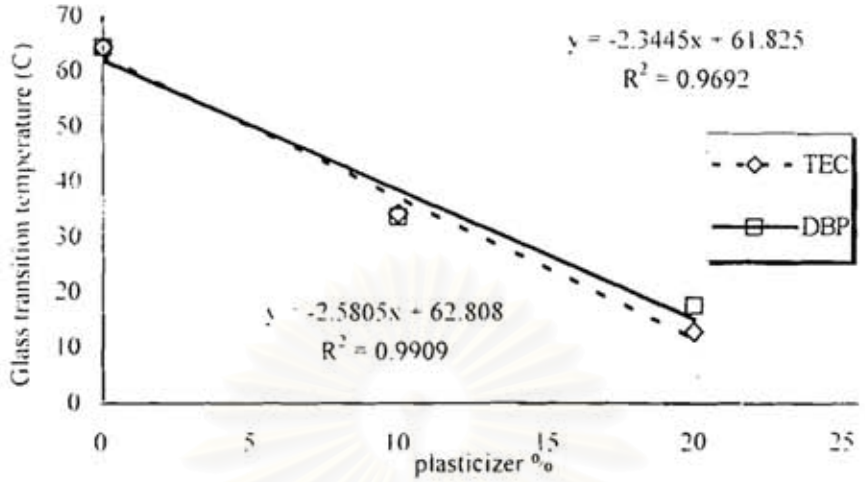


Figure 22 Glass transition temperature of Eudragit® RS as a function of TEC and DBP prepared by method IV(spray dried)

Figure 23 Glass transition temperature of Kollidon® SR as a function of TEC and DBP prepared by method II (ground polymer)

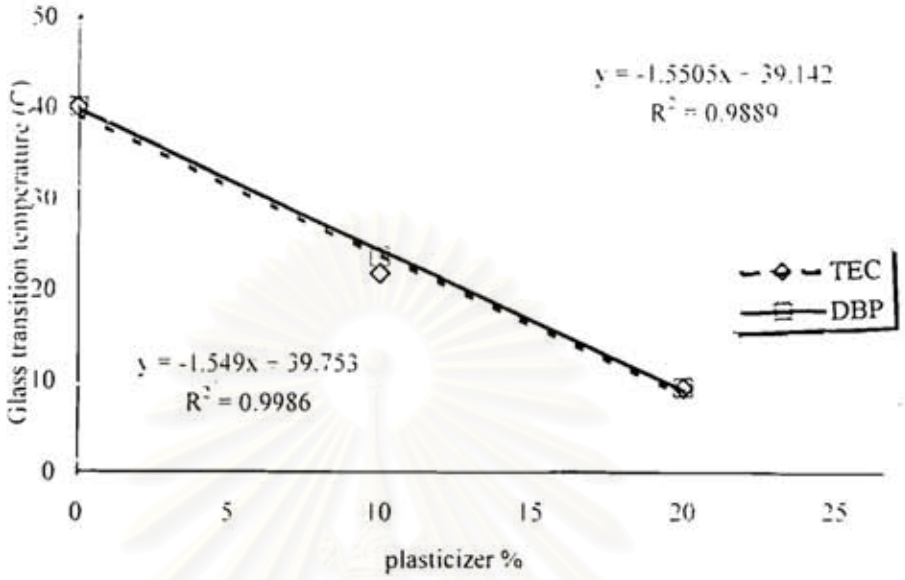


Figure 24 Glass transition temperature of Kollidon® SR as a function of TEC and DBP prepared by method IV (spray dried)

From the DSC thermograms and the relationship between the glass transition temperature and percent of plasticizer demonstrated that TEC or DBP could plasticized Eudragit® RS and Kollidon® SR in the same efficiency.

1.2 Particle size analysis of polymer with and without plasticizer

Particle size analysis of polymer before thermal granulation was necessary to be determined due to its influenced the drug release rate. Particle size obtained from the plasticizer incorporation by method II (ground polymer) were different from method IV (spray dried). Plasticizer incorporation by method II, TEC or DBP was added into the polymer solution then ground to the powder by the grinder. Whereas, plasticizer incorporation by method IV, TEC or DBP was co-spray dried with the polymer. The particle size analysis was evaluated by laser light scattering method.

The particle size of Eudragit® RS and Kollidon® SR prepared by method II (ground polymer) significantly increased when the level of plasticizer increased for both TEC and DBP. It gave the mean particle size diameter in the range from 100 to

Table 8. The problem of this process was the sticky of polymer, which adhere to the container (plate) after drying by hot air oven due to the nature of polymer. Kollidon® SR with 20 % plasticizer could not be processed due to the product exhibited sticky and soft mass.

The particle size of Eudragit® RS and Kollidon® SR prepared by method IV (spray dried) significantly increased in the formulation with 20 % plasticizer. In contrast to the method II (ground polymer), the particle size of formulation with 10 % did not significantly increase compared to the formulation without plasticizer for both TEC and DBP. It gave the mean particle diameter 40 to70 μm from Eudragit® RS and 10 to30 μm from Kollidon® SR as show in Table 9. The problem of this process was found in the formulation with 20 % plasticizer. The adhesions of spray dried polymer to the spray dry chamber was observed. Consequently the percent yield obtained from the formulation 20 % plasticizer was lower than 10 % plasticizer.

Table 8 Mean diameter, percent recovery and characteristic of Eudragit® RS and Kollidon® SR prepared by method II(ground polymer) .

Formulation	Mean diameter (μm)(span)	Recovery(%)	Remark
Eudragit® RS			
0 %	81.80(1.52)	81.24	Not adhere to the container
10 % TEC	107.30(2.03)	76.5	Few adhere the container
20 % TEC	190.35(1.33)	65.75	More adhere the container
10 % DBP	105.45(1.76)	83.34	Few adhere the container
20 % DBP	192.17(1.44)	62.85	More adhere the container
Kollidon® SR			
0 %	94.04(1.76)	87.75	Few adhere the container
10 % TEC	198.58(1.34)	65.73	More adhere the container
20% TEC	*	*	*
10% DBP	246.75(1.02)	58.31	More adhere the container
20% DBP	*	*	*

* Could not be processed.

Table 9 Mean diameter, percent recovery and characteristic of Eudragit® RS and Kollidon® SR prepared by method IV .

Formulation	Mean diameter (μm)(span)	Recovery(%)	Remark
Eudragit® RS			
0 %	42.93(1.51)	81.50	Not adhere to the chamber
10 % TEC	40.47(1.82))	61.84	Few adhere the chamber
20 % TEC	71.28(2.53)	46.31	More adhere the chamber
10 % DBP	39.04(1.76)	63.16	Few adhere the chamber
20 % DBP	63.06(2.20)	45.29	More adhere the chamber
Kollidon® SR			
0 %	14.47(1.51)	87.31	Not adhere to the chamber
10 % TEC	17.52(2.12)	65.45	Few adhere the chamber
20 % TEC	24.69(1.52)	48.15	More adhere the chamber
10 % DBP	14.31(2.16)	68.33	Few adhere the chamber
20 % DBP	32.69(1.74)	45.5	More adhere the chamber

As shown in Figures 25-28, it was found that the particle size of spray dried polymer (method IV) was smaller than the polymer prepared by method II (ground polymer) In addition, this varies somewhat, depending on the process and amount of plasticizer. An increasing amount of plasticizer consequently increased in particle size. When plasticizer was incorporated, the particles agglomerated were observed as seen in SEM examination. The presence of particle agglomerates led to incorrectly detect by particle size analyzer. The particle size from this experiment increased when the level of plasticizer increased. In SEM examination, the true particle size was smaller than particle examined by particle size analyzer. The agglomerate phenomena occurred by different experimental parameter (i.e.solvent, feed rate, airflow rate, and air drying temperature) which should be investigated in the future.

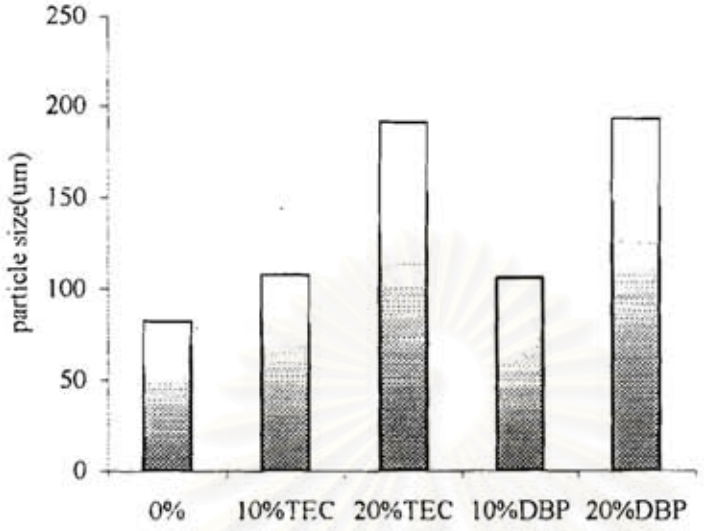


Figure 25 Particle size of Eudragit® RS containing 10 % and 20 % plasticizer prepared by method II (ground polymer)

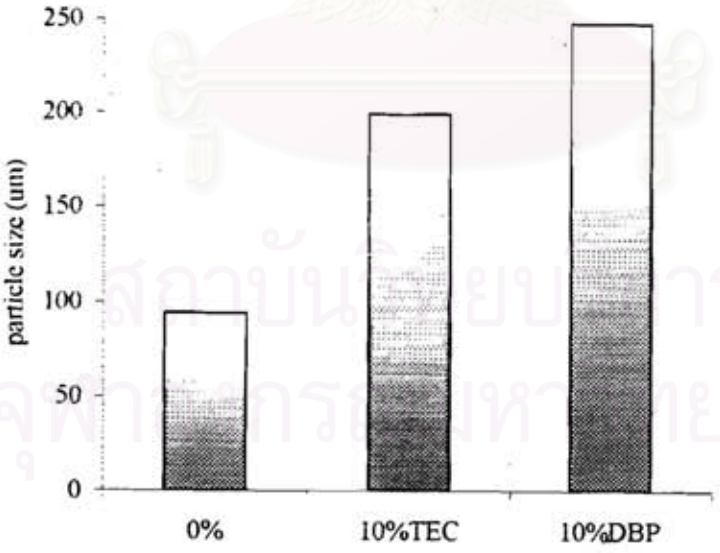


Figure 26 Particle size of Kollidon® SR containing 10 % plasticizer prepared by method II (ground polymer)

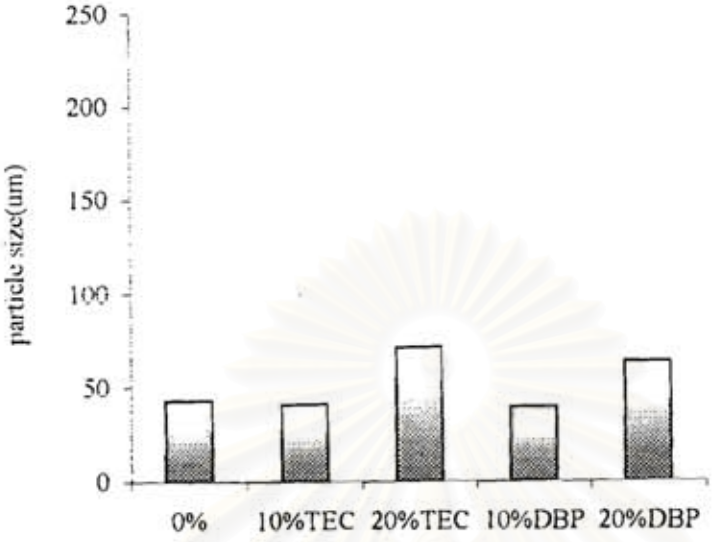


Figure 27 Particle size of Eudragit® RS containing 10 % and 20 % plasticizer prepared by method IV (spray dried)

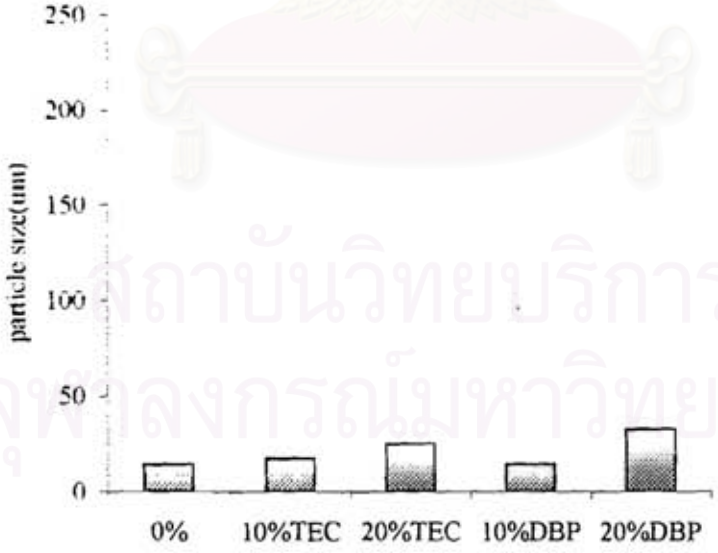


Figure 28 Particle size of Kollidon® SR containing 10 % and 20 % plasticizer prepared by method IV(spray dried)

2 Evaluation of theophylline granules

The theophylline granules were prepared by thermal processing at 60°C. The plasticizer was incorporated into polymer by 4 methods. In method I (wet granulation), the plasticizer was incorporated into polymer solution before thermal processing. For method III (spray plasticizer into polymer), the plasticizer was sprayed into powder blend of drug and polymer during thermal processing. For method II (ground polymer), plasticizer was incorporated into plasticizer solution and dried in hot air oven. And method IV (spray dried), spray dried method was used to eliminate the problem of process and particle size in method II. Only method III the plasticizer was incorporated into the polymer during thermal process, while the other was incorporated before thermal processing. The temperature of the processing were 60°C, the selected formulation was used to study the effect of temperature by granulation at 80°C and compared with the granulation process at room temperature. The granules obtained by these methods were evaluated as follows.

2.1 Morphology of theophylline granules.

The theophylline granules of Eudragit® RS or Kollidon® SR were examined using scanning electron microscope (SEM) at different magnifications. The 100x and 1000x magnifications were used to investigate the surface of granules. Two model of scanning electron microscope were used to investigate. The granules of Eudragit® RS or Kollidon® SR with 20 % plasticizer prepared at 80°C were used model JSM 5800 LV to examine. The others used model JSM 5410 LV to examine.

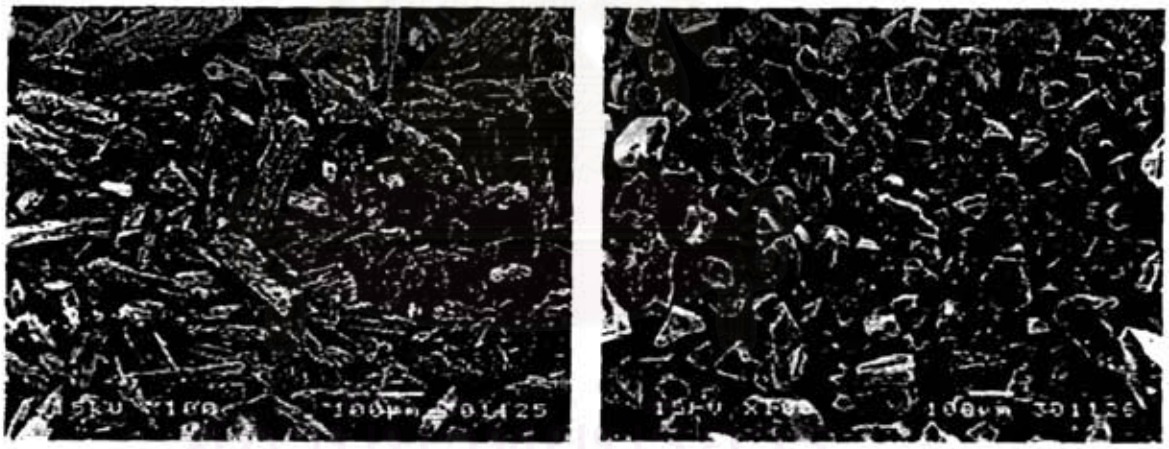
2.1.1 Morphology of drug and excipients

The photomicrographs of theophylline, Eudragit® RS, Kollidon® SR, spray dried Eudragit® RS or Kollidon® SR without plasticizer, with 10 and 20 % plasticizer are shown in Figure 17-19. The photomicrographs of theophylline powder were

irregular rod shapes, rough surface, various size and seem adhering together. Eudragit® RS showed a rough surface filled with irregular flakes with different sizes.

The photomicrographs of spray dried Eudragit® RS and Kollidon® SR with out plasticizer are shown in Figures 18-19(A,B). The powder was round shape to microball with smooth surface and found the particle were adhered to each other and attached to the large particles.

The photomicrographs of spray dried Eudragit® RS or Kollidon® SR with 10-20 % plasticizer are shown in Figures 18-19(C-F). The small particle of spray dried polymer more adhered to each other as seen in the spray dried powder with 10 % plasticizer. The adhesion of the spray-dried particle due to the temperature of the process (inlet and outlet temperature) was higher than the Tg of the polymer. The adhesion of the small spray dried particles to form the large particles resulted in the increasing of particle size when determinated by particle size analyzer.



Theophylline Eudragit®RS

Figure 17 Photomicrographs of Theophylline and Eudragit® RS (×100)

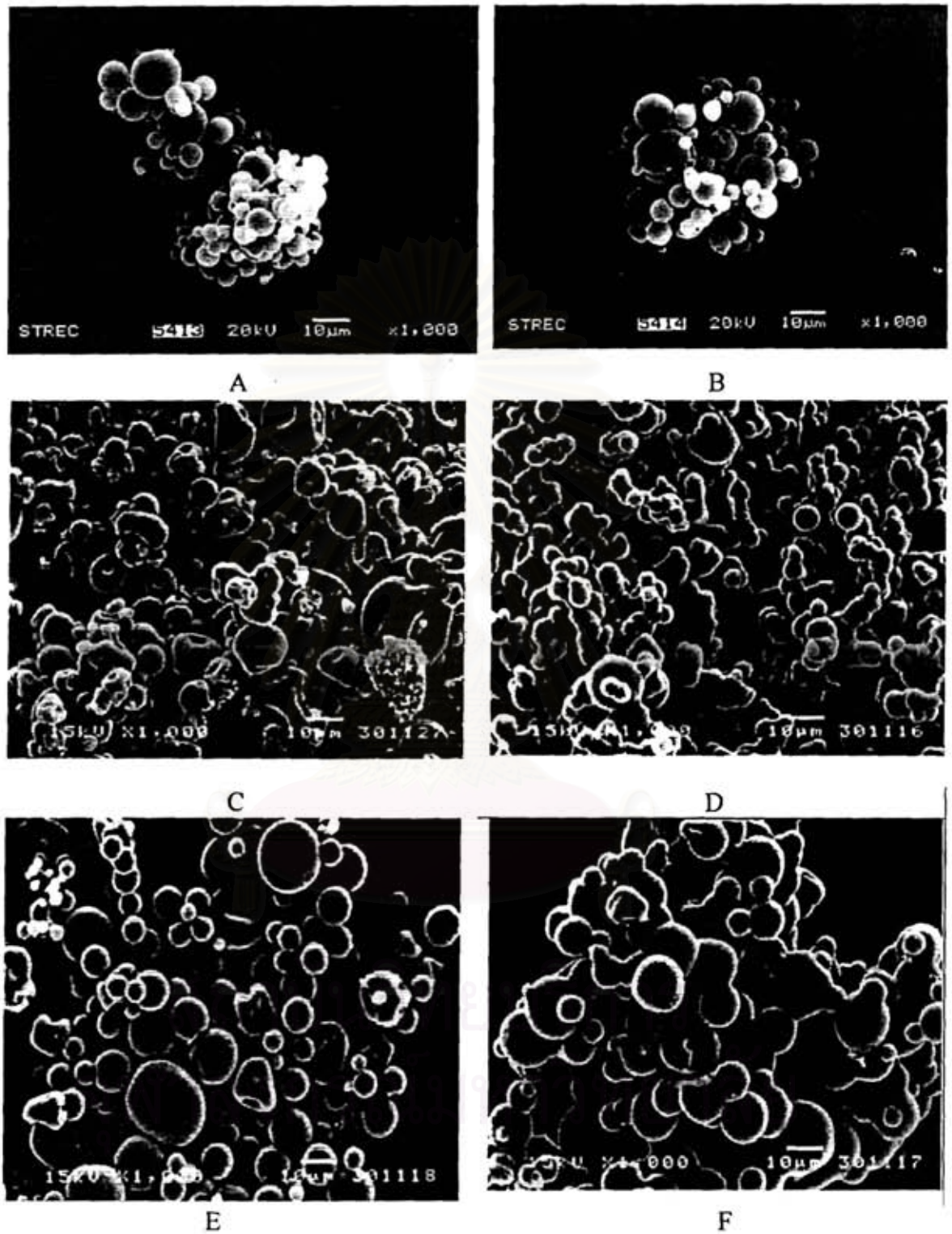


Figure18 Photomicrographs of spray dried Eudragit® RS without plasticizer (A,B), spray dried Eudragit® RS with 10 % TEC (C) and 20 % TEC (E), spray dried Eudragit® with 10 % DBP(D) and 20 % DBP (F) (×1000)

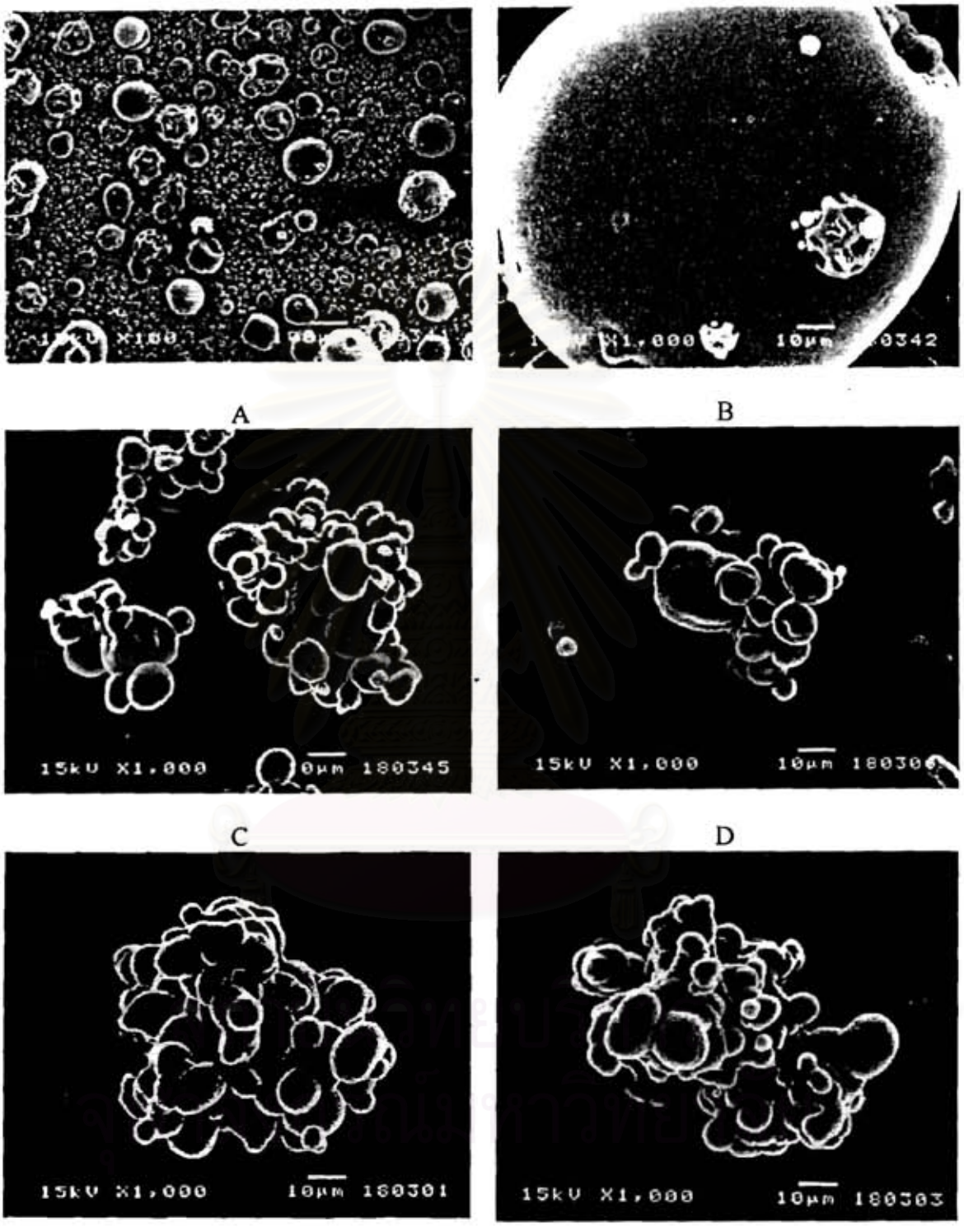


Figure 19 Photomicrographs of spray dried Kollidon® SR without plasticizer (A,B), spray dried Kollidon® SR with 10 % TEC (C) and 20 % TEC (E), spray dried Kollidon® SR with 10 % DBP(D) and 20 % DBP (F) (×1000)

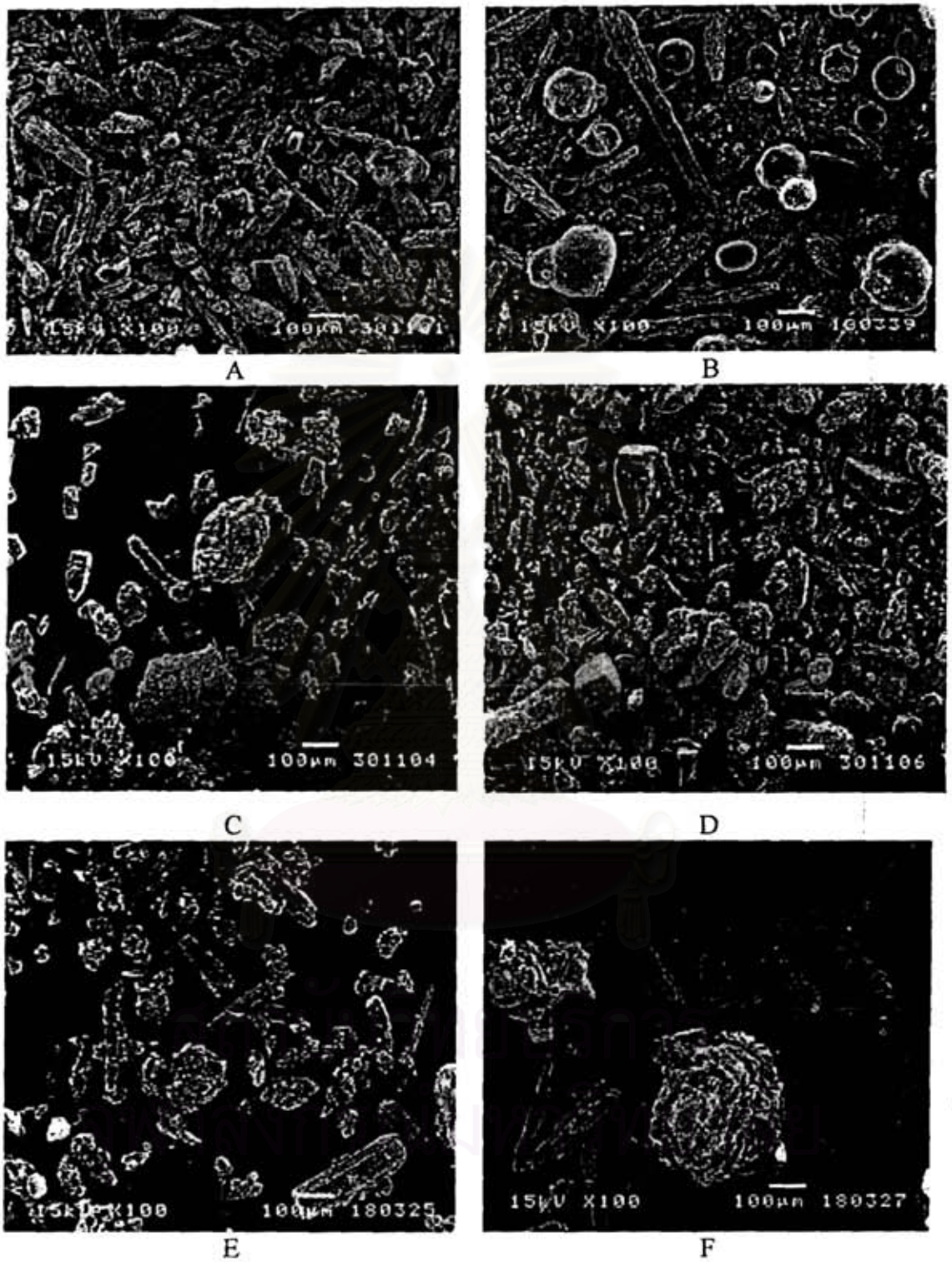
2.1.2 Morphology of polymer without plasticizer

The surfaces of theophylline granules of Eudragit® RS and Kollidon® SR without plasticizer prepared by direct compression at room temperature (physical mixture) and thermal granulation at 60°C and 80°C are shown in Figure 20-28(A,B). Due to the processing conducted without heating, the photograph of the physical mixture showed that theophylline, polymer and lactose exhibited scatter. When the temperature of the processing was at 60°C and 80°C, the powder mixing still scatter due to an inadequate of heating of the processing. No powder agglomerated into granule was observed.

2.1.3Morphology of polymer with 10 % and 20 % plasticizer

The surface of theophylline granules prepared by thermal granulation using Eudragit® RS and Kollidon® SR with 10 % TEC and DBP at 60°C are shown in Figures 20 (C-F). The granules prepared by method I(wet granulation) are shown in Figures 21-22. It was shown that the powder mixing was in the most agglomerate. Whereas, the other methods gave less powder agglomerates than method I. In method II (ground polymer) and method IV (spray dried), the granule was small and found that some theophylline particles still separated from polymer. When 10 % TEC and DBP were incorporated into polymer, which became soften. Theophylline particles partly were adsorbed on the surface of Eudragit® RS and Kollidon® SR to form granules. No difference between the morphology of granule with 10 % TEC and DBP were observe.

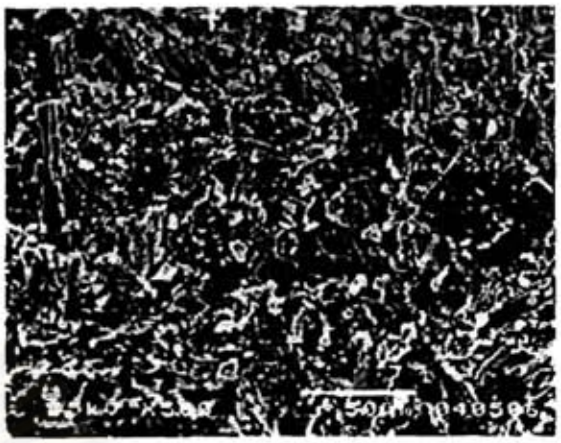
The morphology of theophylline granules prepared by thermal granulation of Eudragit® RS and Kollidon® SR with 20 % TEC and DBP at 60°C using method 1-4 are shown in (Figures 21-26) The photographs show that all formulations powder mixing was more aggregate than 10 % plasticizer. The 20 % plasticizer and thermal processing influenced the powder mixing to form the large granules than 10% plasticizer. At the higher amount of plasticizer, both TEC and DBP gave the large granules and smoother surface.



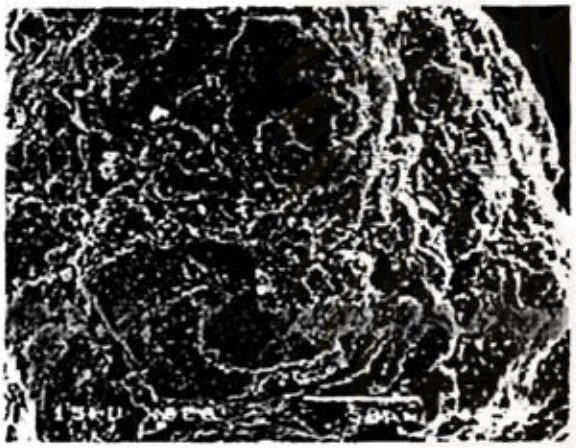
A B C D E F

Figure 20 Photomicrographs of physical mixture of Eudragit® RS (A),Kollidon® SR (B), Eudragit® RS granules with 10 % TEC (C), Eudragit® RS granules with 10 % DBP (D), Kollidon® SR granules with 10 % TEC (E), Kollidon® SR granules with 10 % DBP (F), (× 100)

A×100

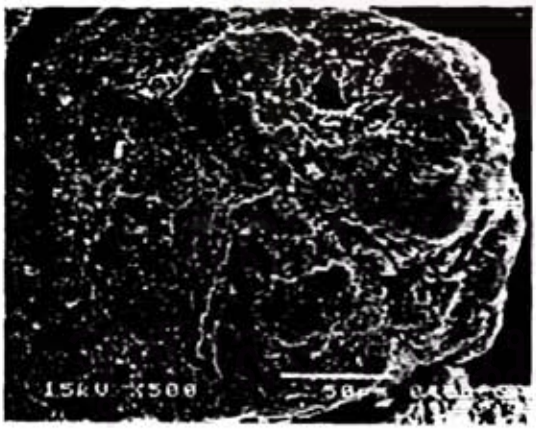


B×1000

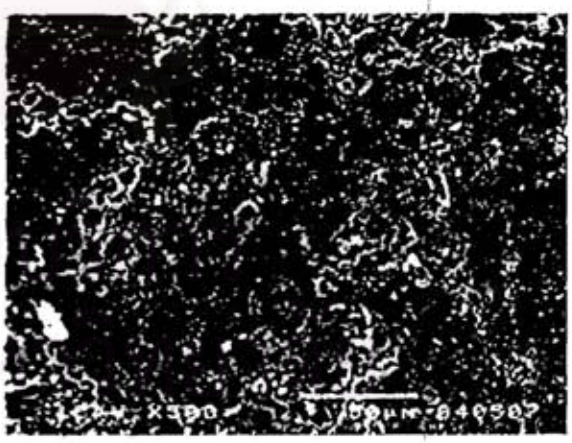


C×100

D×1000

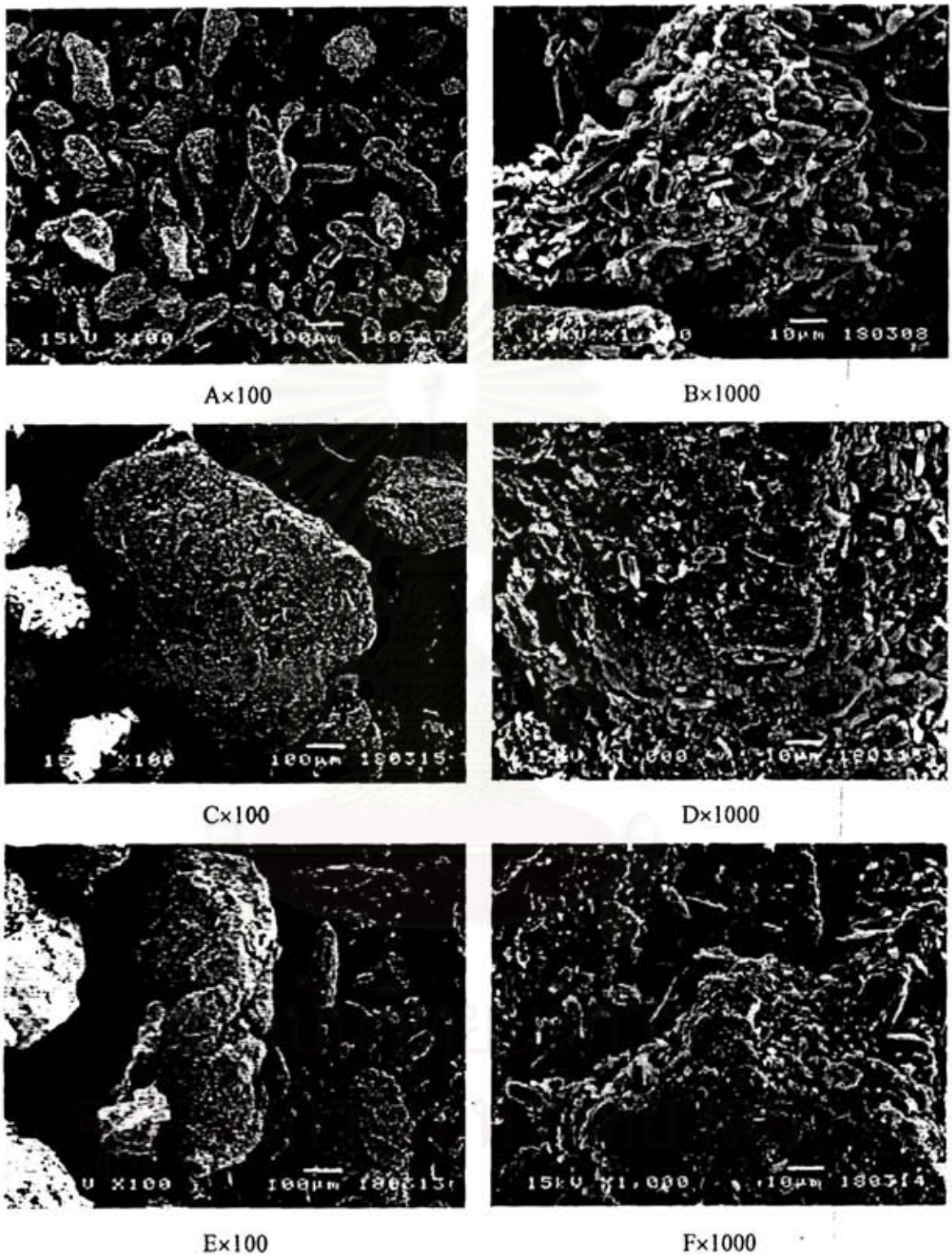


E×100



F×1000

Figure 21 Photomicrographs of Eudragit® RS granules without plasticizer(A,B), with 20 % TEC (C,D) and 20 % DBP(E,F) prepared by method I (wet granulation) at 60 °C.



A×100 B×1000

C×100 D×1000

E×100 F×1000

Figure 22 Photomicrographs of Kollidon® SR granules without plasticizer(A,B), with 20 % TEC (C,D)and 20 % DBP(E,F) prepared by method I(wet granulation) at 60 °C

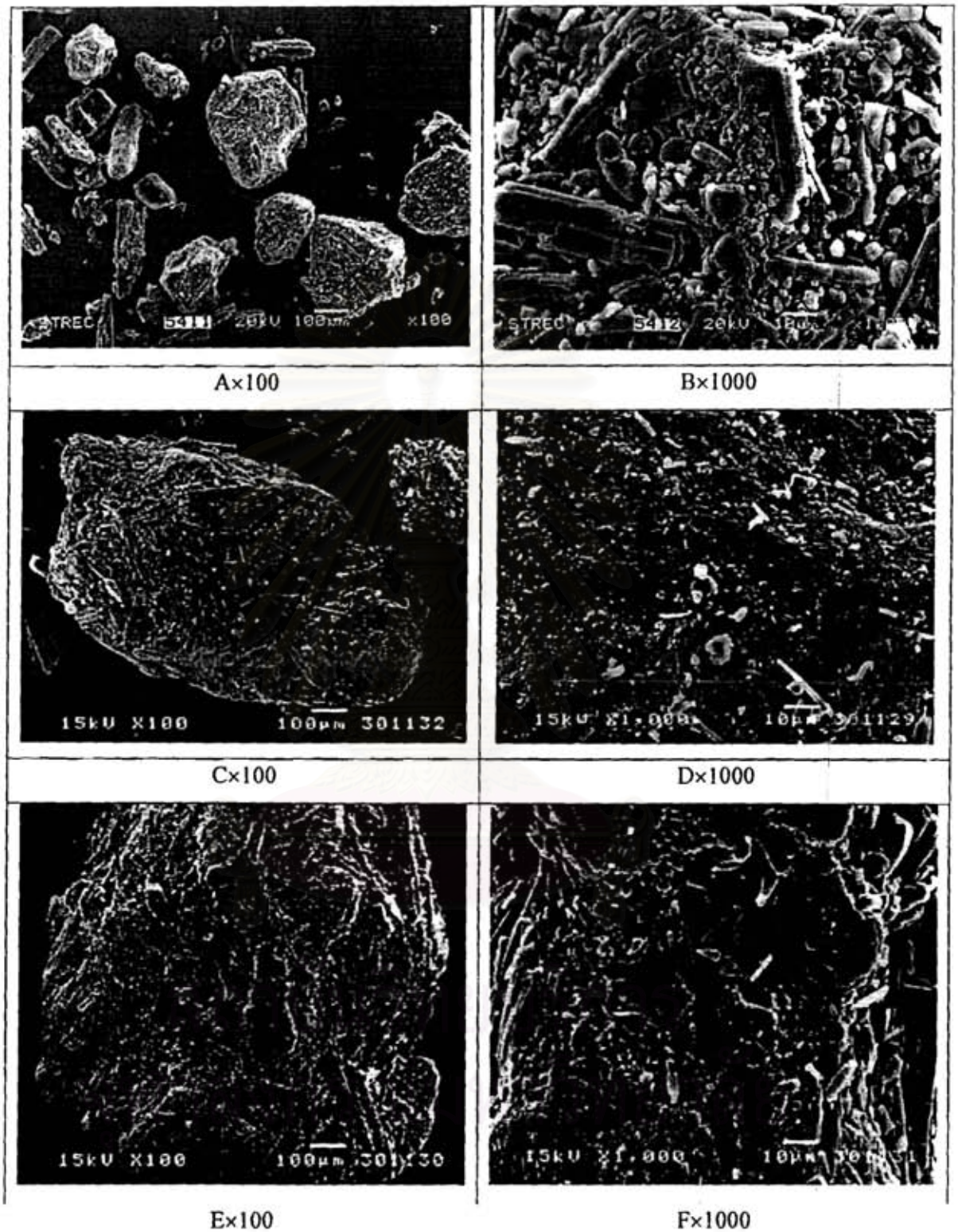
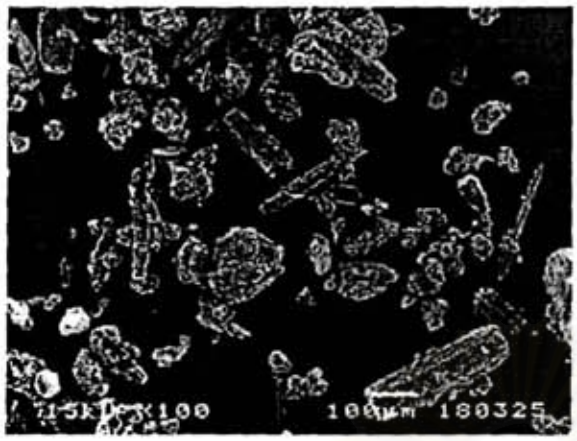
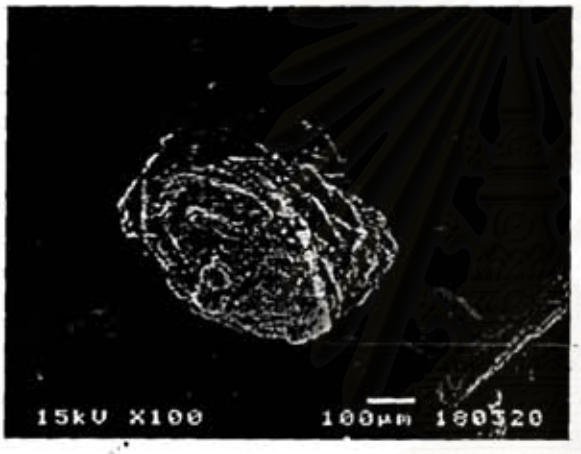


Figure 23 Photomicrographs of Eudragit® RS granules without plasticizer(A,B), with 20 % TEC(C,D)and 20 % DBP (E,F)prepared by method II(ground polymer) at 60 °C



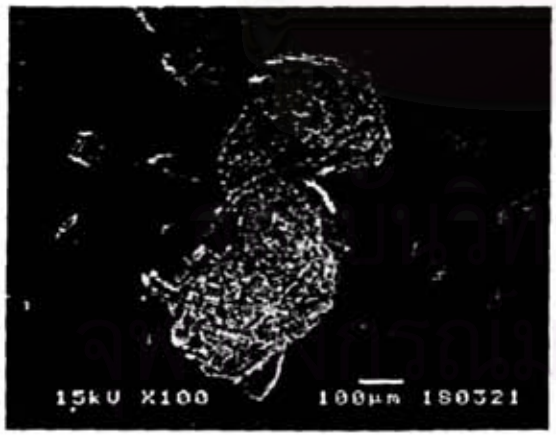
A×100

B×1000



C×100

D×1000

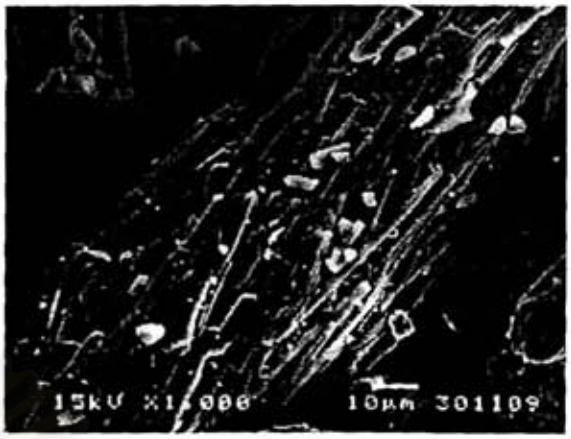


E×100

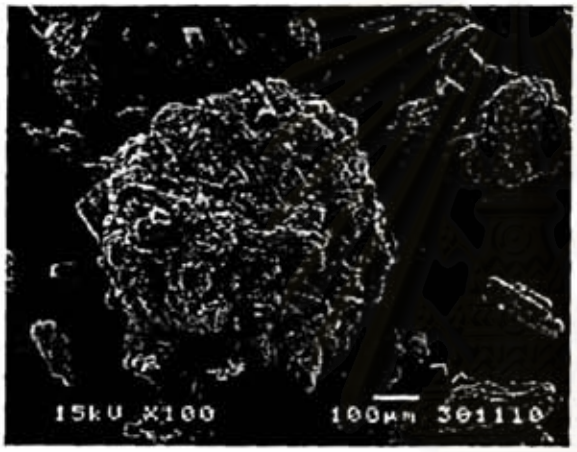
F×1000

Figure24 Photomicrographs of Kollidon® SR granules without plasticizer(A,B), with 20 % TEC(C,D) and 20 % DBP(E,F) prepared by method II(ground polymer)

A×100



B×1000



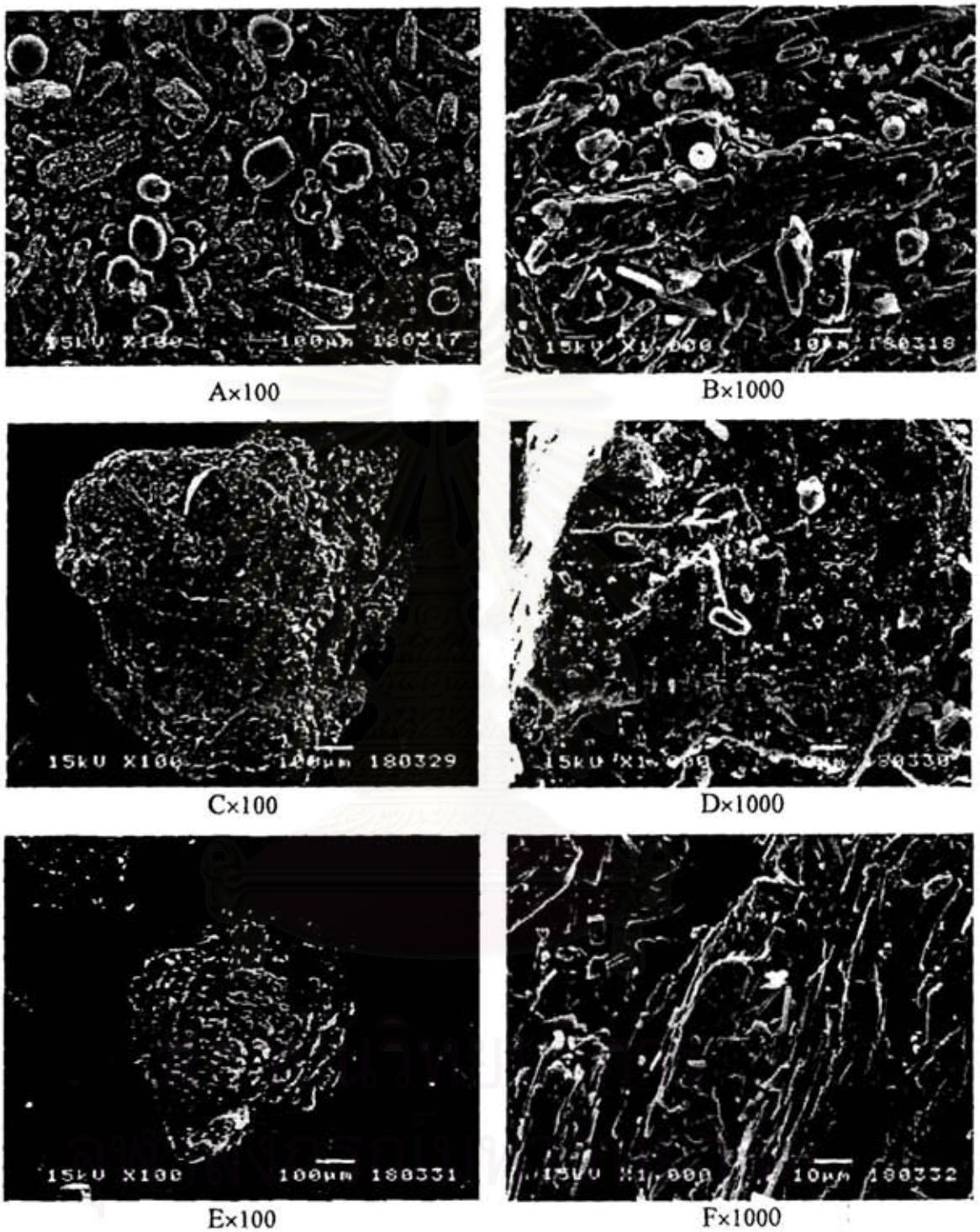
C×100

D×1000

E×100

F×1000

Figure 25 Photomicrographs of Eudragit® RS granules without plasticizer(A,B), with 20 % TEC (C,D) and 20 % DBP (E,F) prepared by method IV(spray dried) at 60 °C



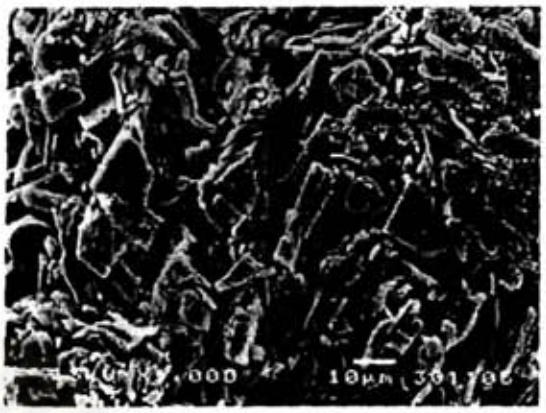
A×100 B×1000

C×100 D×1000

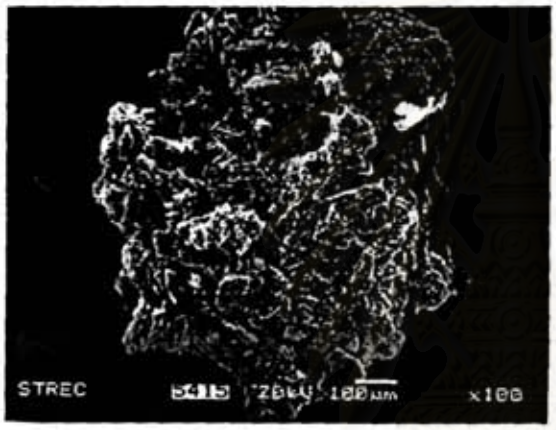
E×100 F×1000

Figure 26 Photomicrographs of Kollidon® SR granules without plasticizer (A,B), with 20 % TEC (C,D) and 20 % DBP (E,F) prepared by method IV(spray dried) at 60 °C

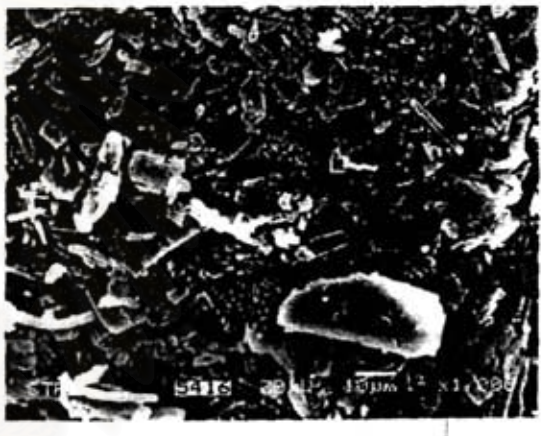
A×100



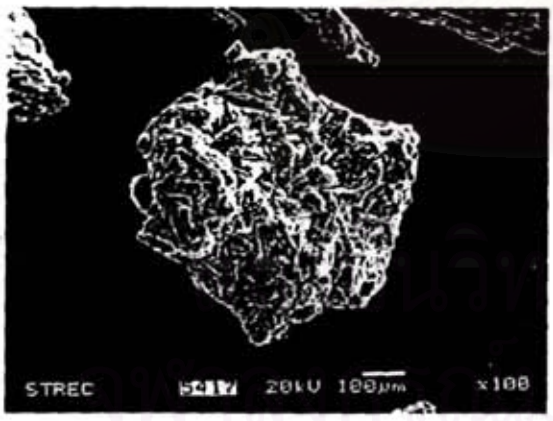
B×1000



C×100



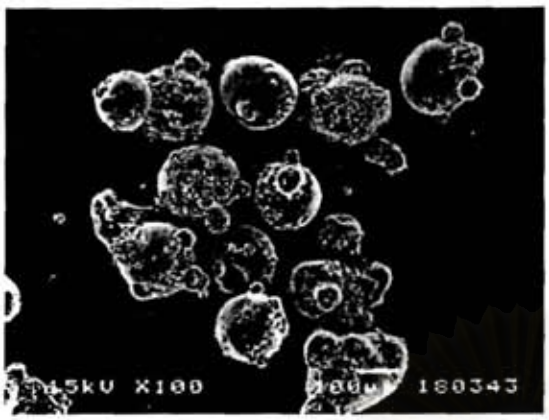
D×1000



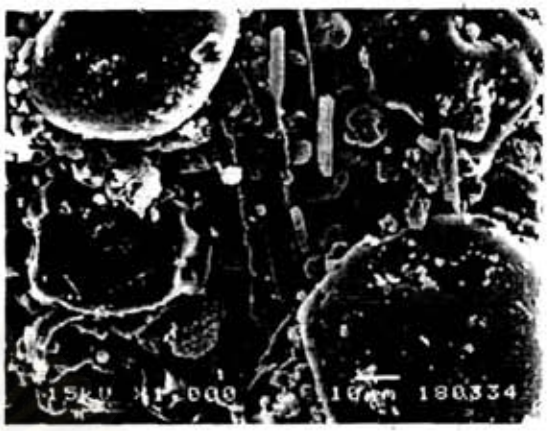
E×100

F×1000

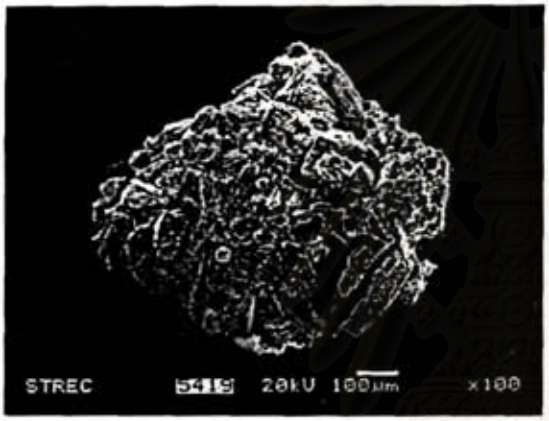
Figure 27 Photomicrographs of Eudragit® RS granules without plasticizer (A,B), with 20 % TEC (C,D) and 20 % DBP (E,F) prepared by method IV (spray dried) at 80°C



A×100

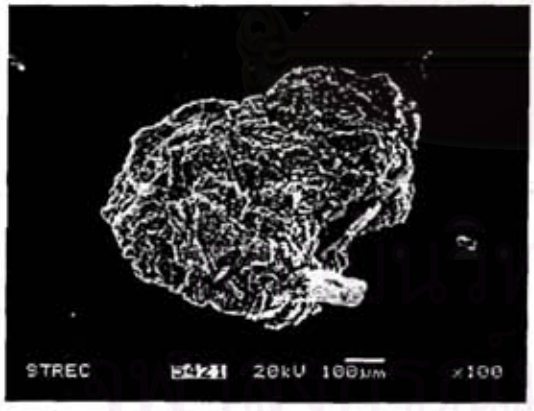


B×1000



C×100

D×1000



E×100

F×1000

Figure 28 Photomicrographs of Kollidon® SR granules without plasticizer(A,B) , with 20 % TEC (C,D) and 20 % DBP (E,F) prepared by method IV(spray dried) at 80°C

The photomicrographs of formulation with 10-20% plasticizer were notable that granules prepared by method I (wet granulation) were more agglomerate than the others due to the penetration of the polymer solution into theophylline particles. The polymer solution facilitates the formation of granules as the same in wet granulation. When the temperature of processing was at 80°C, the photomicrographs are shown in Figures 27-28. They demonstrated that theophylline particle adhered to the swollen surface of the spray-dried polymer with plasticizer, in particulate to which 20 % plasticizer was incorporated into polymer by method IV. The surface of the granules exhibited smoother than the granules without plasticizer. The lower magnification photograph shows the typical porous granule. At higher magnification, the porous structure of granule formed by the fusing of theophylline particles and polymer after thermal processing. The homogenous distribution of the theophylline in the polymer was not observed in this study.

2.2 Bulk densities, tapped densities and Carr's index of theophylline granules

The bulk densities, tapped densities and Carr's index of theophylline granules containing Eudragit® RS and Kollidon® SR for all formulation prepared by thermal granulation at 60°C are presented in Tables 10-11.

Comparison of the bulk density and tapped density of granules for all formulations demonstrated that when the amount of plasticizer increased, the bulk density and tapped density slightly increased. The tapped densities were much higher than bulk densities indicated that loose agglomerates were formed. Higher percentage of Carr's index was obtained from all formulations. The values of Carr's index from the granules prepared by method I were lower than the other methods. This finding corresponded to the result of flow rate belonging to the granules prepared by Eudragit® RS method I could flow but the other method failed to be measure

Table 10 Bulk densities, tapped densities and Carr's index of theophylline granules containing Eudragit® RS

Method	Formulations	Bulk density (g/ml)(SD)	Tapped density (g/ml) (SD)	Carr's index(%)
I (wet granulation)	0%	0.60(0.01)	0.70(0.01)	14.00
	10%TEC	0.63(0.01)	0.71(0.01)	12.50
	10%DBP	0.65(0.02)	0.71(0.01)	8.70
	20%TEC	0.63(0.02)	0.71(0.01)	12.50
	20%DBP	0.65(0.01)	0.75(0.02)	13.04
II (ground polymer)	0%	0.48(0.01)	0.63(0.02)	22.58
	10%TEC	0.50(0.02)	0.64(0.01)	22.52
	10%DBP	0.52(0.02)	0.67(0.01)	22.41
	20%TEC	0.50(0.03)	0.64(0.01)	22.44
	20%DBP	0.51(0.02)	0.67(0.01)	23.63
III (spray plasticizer into polymer)	0%	0.53(0.02)	0.65(0.01)	19.30
	10%TEC	0.55(0.01)	0.66(0.02)	17.45
	10%DBP	0.56(0.02)	0.68(0.01)	18.52
	20%TEC	0.54(0.02)	0.67(0.02)	18.92
	20%DBP	0.56(0.01)	0.69(0.01)	19.26
IV (spray dried)	0%	0.50(0.03)	0.63(0.01)	20.67
	10%TEC	0.50(0.02)	0.66(0.02)	24.00
	10%DBP	0.52(0.02)	0.68(0.02)	23.45
	20%TEC	0.50(0.01)	0.66(0.01)	24.67
	20%DBP	0.54(0.02)	0.70(0.01)	23.21

Table 11 Bulk densities, tapped densities and Carr's index of theophylline granules containing Kollidon® SR

Method	Formulations	Bulk density (g/ml) (SD)	Tapped density (g/ml) (SD)	Carr's index(%)
I (wet granulation)	0%	0.52(0.02)	0.67(0.01)	22.41
	10%TEC	0.52(0.01)	0.65(0.01)	20.69
	10%DBP	0.50(0.01)	0.67(0.01)	25.00
	20%TEC	0.52(0.02)	0.65(0.01)	20.69
	20%DBP	0.58(0.02)	0.65(0.01)	17.86
II (ground polymer)	0%	0.33(0.01)	0.42(0.01)	21.74
	10%TEC	0.38(0.01)	0.50(0.01)	25.00
	10%DBP	0.36(0.02)	0.47(0.02)	23.81
	20%TEC	*	*	*
	20%DBP	*	*	*
III (spray plasticizer into polymer)	0%	0.45(0.01)	0.60(0.01)	24.24
	10%TEC	0.46(0.01)	0.62(0.01)	25.23
	10%DBP	0.47(0.02)	0.63(0.01)	25.23
	20%TEC	0.46(0.01)	0.62(0.01)	25.54
	20%DBP	0.47(0.01)	0.63(0.01)	25.31
IV (spray dried)	0%	0.42(0.02)	0.52(0.01)	19.44
	10%TEC	0.43(0.02)	0.51(0.01)	16.57
	10%DBP	0.44(0.01)	0.52(0.01)	15.29
	20%TEC	0.43(0.02)	0.52(0.01)	17.61
	20%DBP	0.44(0.02)	0.52(0.01)	16.33

- could not be processed

2.3 Flow rates and angles of repose of theophylline granules

Only the theophylline granules prepared by Eudragit® RS method I (wet granulation) at 60°C could flow but the other which prepared by method II, III and IV could not be measured. There are many parameters that affect the flow rate of the granules; various forces such as frictional forces, surface tension forces, mechanical forces caused by inter locking of particle of irregular shape, electrostatic forces, cohesive force or Van der Waals forces. As the result from tapped density, the

granules could not flow due to more irregular shaped particles with agglomerates was observed.

The flow rate of granules prepared by Eudragit® RS method I was 5.5 g/sec. which obtained from formulation with 20 % plasticizer and the value of 5.0g/sec. from the formulation with 10 % plasticizer and without plasticizer. This can be attributed to their bulk density were greater than their density obtained by the other formulation.

The angles of repose of granules prepared by Eudragit® RS method I was 32.01° indicating that the granules was good flow. The granules, which had the repose angle of 30 or below indicated that it was free flow, angle of 40 or above the flow was broken and the phenomenon of balling might occurred. The angles of repose could not be measured because of the nonflowable of the granules. The repose angle that could be measured was the formulation prepared by method I

3 Evaluation of matrices

3.1 Weight variation

The weight of theophylline tablets was in the range of 399.86-400.21 mg.

3.2 *Hardness and thickness of matrices.*

The mechanical strength of pharmaceutical tablets is frequently assessed as an in-process control during manufacturing and a means to understand the compaction behavior of a material. The force necessary to break the tablet can characterize the mechanical strength of a tablet. There are several methods to measuring the mechanical strength of tablets. The most common strength test in pharmaceutical applications is the diameter compression test, which is used to calculate the radial tensile strength of a tablet. During radial tensile strength measurements, the fracture occurs through a predetermined diametral cross section of the tablet. Therefore, the radial tensile strength is likely to reflect the average strength of tablet rather than the strength of the weakest plane in the tablet. The mean and standard deviation of tablet hardness and thickness of theophylline matrices prepare by thermal granulation at 60°C was displayed in Table12-13.

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Table 10 Hardness and thickness profile of Eudragit® RS matrices prepared by method I, II, III and IV

Formulation	0 % plasticizer		10 % TEC		20 % TEC		10 % DBP		20 % DBP	
Compression force(psi)	Hardness (kg)(SD)	Thickness (mm)(SD)	Hardness (kg)(SD)	Thickness (mm)(SD)	Hardness (kg)(SD)	Thickness (mm)(SD)	Hardness (kg)(SD)	Thickness (mm)(SD)	Hardness (kg)(SD)	Thickness (mm)(SD)
Method I										
500	15.8(0.016)	4.09(0.018)	13.4(0.020)	3.99(0.021)	10(0.018)	3.80.(0.009)	12.6(0.012)	4.05(0.015)	10.8(0.010)	3.98(0.016)
1000	>20	3.98(0.015)	19.8(0.009)	3.95(0.016)	19.4(0.015)	3.76(0.010)	19.5(0.016)	4.01(0.008)	19.6(0.012)	3.85(0.012)
1500	>20	3.88(0.016)	>20	3.85(0.020)	>20	3.71(0.018)	>20	3.94(0.012)	>20	3.78(0.010)
Method II										
500	8.4(0.009)	4.16(0.0089)	6.4(0.014)	4.12(0.015)	4.4(0.020)	4.03(0.012)	6.2(0.017)	4.14(0.019)	4.0(0.012)	3.98(0.016)
1000	14.8(0.015)	4.05(0.010)	10(0.017)	4.06(0.014)	7.8(0.018)	3.95(0.024)	9.6(0.021)	4.06(0.024)	8.4(0.015)	3.94(0.015)
1500	>20	3.98(0.005)	12.4(0.015)	4.02(0.019)	10.2(0.014)	3.88(0.015)	12.8(0.019)	3.96(0.010)	11.4(0.018)	3.88(0.010)
Method III										
500	6.8(0.005)	4.04(0.017)	4.4(0.012)	3.87(0.015)	4.4(0.015)	3.96(0.027)	4.2(0.007)	4.02(0.017)	2.8(0.015)	3.96(0.024)
1000	9.0(0.008)	3.94(0.013)	9.0(0.010)	3.81(0.017)	7.2(0.010)	3.90(0.013)	8.6(0.012)	3.95(0.018)	5.2(0.008)	3.88(0.018)
1500	10.4(0.008)	3.88(0.021)	11.4(0.010)	3.77(0.019)	8.0(0.008)	3.82(0.015)	9.6(0.009)	3.87(0.014)	6.2(0.010)	3.85(0.016)
Method IV										
500	8.0(0.014)	4.16(0.015)	8.0(0.011)	4.10(0.012)	8.6(0.014)	3.95(0.015)	8.4(0.017)	4.08(0.010)	5.0(0.008)	3.96(0.017)
1000	15.4(0.018)	4.14(0.012)	11.0(0.012)	4.06(0.015)	10.2(0.015)	3.95(0.018)	12.6(0.014)	4.02(0.009)	8.2(0.012)	3.92(0.010)
1500	15.6(0.015)	4.13(0.019)	11.8(0.009)	3.98(0.016)	10.2(0.014)	3.88(0.015)	13.5(0.013)	3.97(0.010)	11.2(0.015)	3.91(0.021)

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Table 11 Hardness and thickness profile of Kollidon® SRmatrices prepared by method I, II, III and IV

Formulation	0 % plasticizer		10 % TEC		20 % TEC		10 % DBP		20 % DBP	
Compression force(psi)	Hardness (kg)(SD)	Thickness (mm)(SD)	Hardness (kg)(SD)	Thickness (mm)(SD)	Hardness (kg)(SD)	Thickness (mm)(SD)	Hardness (kg)(SD)	Thickness (mm)(SD)	Hardness (kg)(SD)	Thickness (mm)(SD)
Method I										
500	16(0.017)	3.95(0.012)	11.0(0.013)	3.92(0.018)	8.0(0.018)	3.78(0.015)	10.4(0.019)	3.88(0.015)	9.2(0.016)	3.86(0.016)
1000	>20	3.78(0.014)	15.8(0.015)	3.76(0.019)	14.2(0.014)	3.70(0.018)	14.6(0.012)	3.74(0.014)	12.4(0.012)	3.76(0.017)
1500	>20	3.67(0.015)	18.8(0.017)	3.72(0.017)	17.0(0.024)	3.68(0.017)	15.5(0.015)	3.70(0.019)	14.1(0.015)	3.70(0.012)
Method II										
500	14.2(0.020)	4.11(0.084)	5.60.017)	4.08(0.014)	*	*	5.2(0.024)	4.12(0.010)	*	*
1000	18.6(0.017)	3.91(0.012)	7.2(0.018)	4.01(0.015)	*	*	6.8(0.021)	3.98(0.018)	*	*
1500	>20	3.81(0.010)	9.1(0.015)	3.96(0.014)	*	*	9.2(0.025)	3.91(0.016)	*	*
Method III										
500	6.8(0.005)	7.8(0.016)	4.10(0.021)	5.4(0.020)	4.8(0.008)	3.96(0.015)	5.2(0.012)	4.00(0.013)	5.8(0.015)	3.94(0.017)
1000	9.0(0.008)	10.4(0.021)	4.06(0.020)	10(0.009)	8.2(0.012)	3.90(0.016)	9.6(0.01)	3.96(0.015)	6.8(0.014)	3.90(0.014)
1500	10.4(0.008)	16.4(0.016)	4.01(0.019)	12.6(0.010)	10.4(0.016)	3.85(0.018)	12.6(0.012)	3.92(0.015)	9.2(0.019)	3.84(0.015)
Method IV										
500	7.8(0.012)	4.15(0.021)	6.5(0.019)	4.12(0.018)	8.6(0.014)	5.2(0.016)	6.4(0.017)	4.04(0.025)	5.0(0.015)	4.06(0.018)
1000	13.8(0.024)	4.02(0.018)	10.6(0.024)	3.96(0.019)	10.2(0.015)	6.5(0.015)	11.6(0.013)	3.92(0.015)	8.2(0.017)	3.98(0.015)
1500	15.4(0.015)	3.86(0.024)	13.0(0.010)	3.85(0.015)	10.2(0.014)	7.5(0.010)	13.8(0.021)	3.86(0.017)	9.0(0.019)	3.86(0.017)

* Could not be process

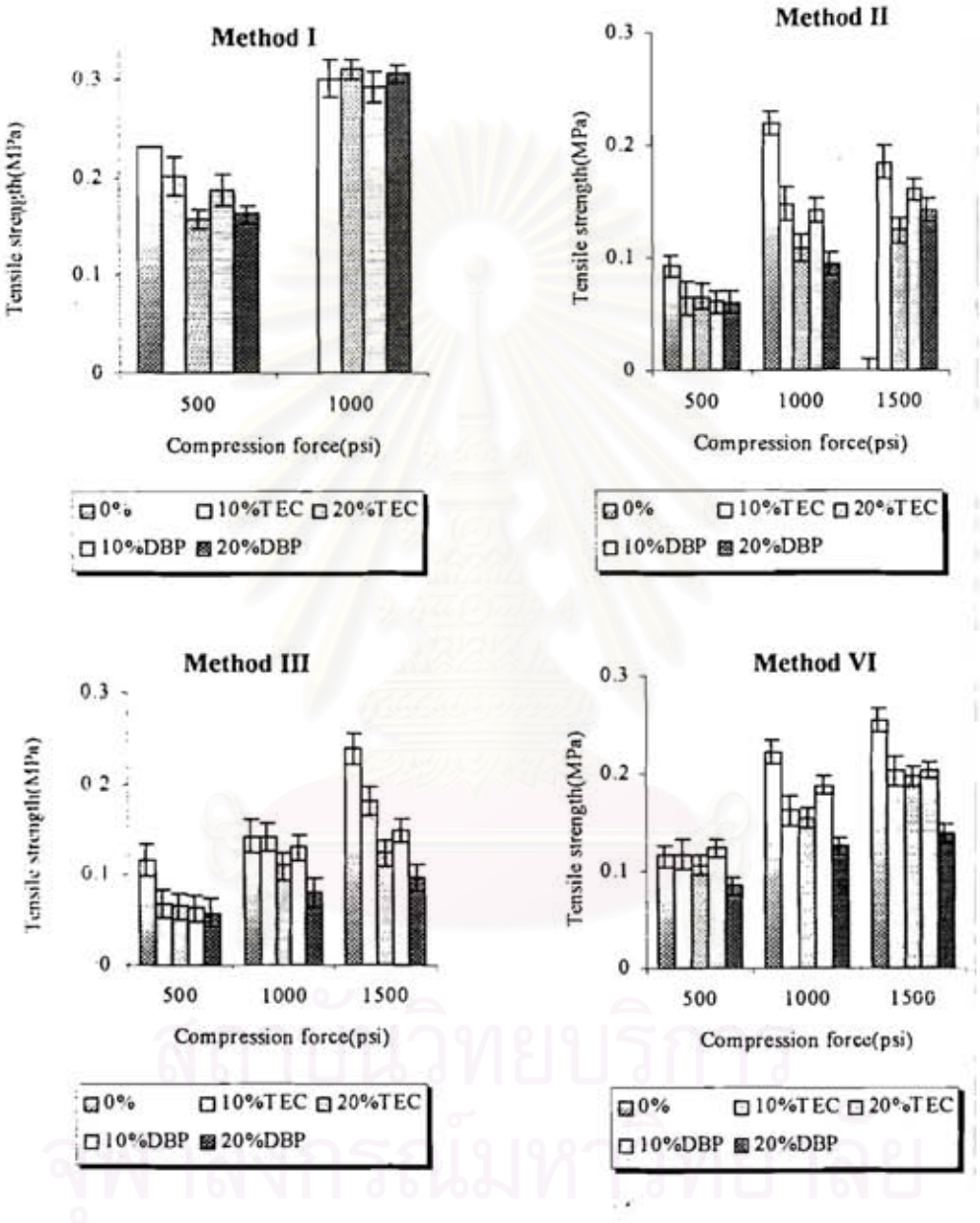

Figure 29 Tablet tensile strength of Eudragit® RS matrices prepared by method I, II, III and IV at 60 °C

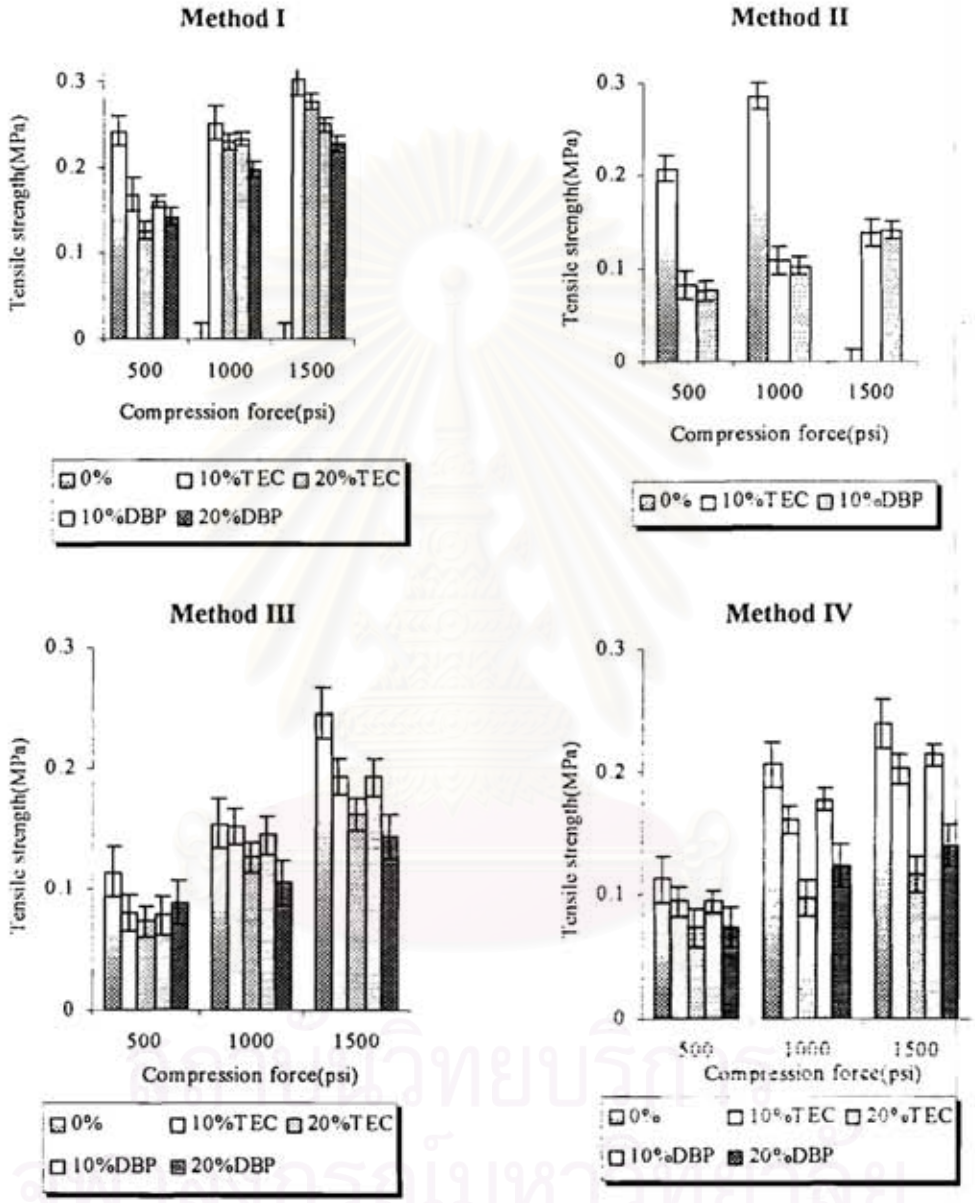

Figure 30 Tablet tensile strength of Kollidon® SR matrices prepared by method I, II, III, IV at 60 °C

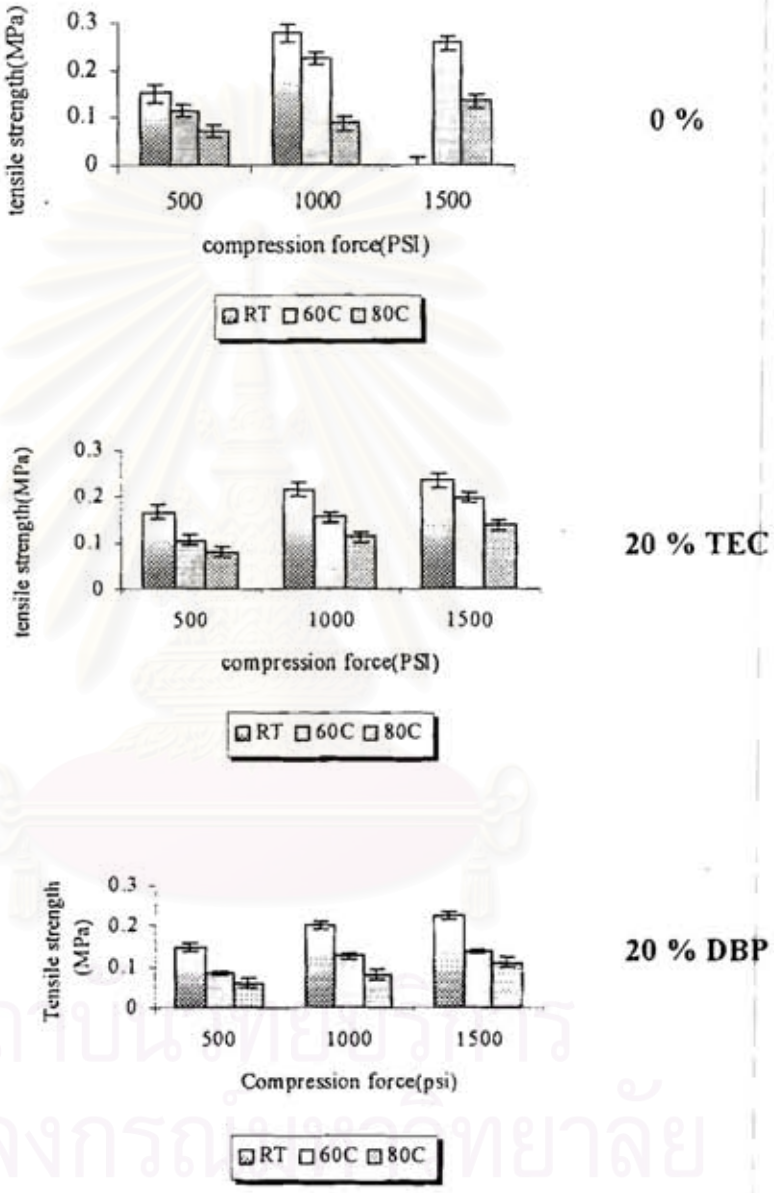

Figure 31 Effect of the processing temperature on the tablet tensile strength of Eudragit® RS matrices without plasticizer (0 %), 20%TEC, 20%DBP prepared by method IV at room temp.,60 °C, and 80 °C.

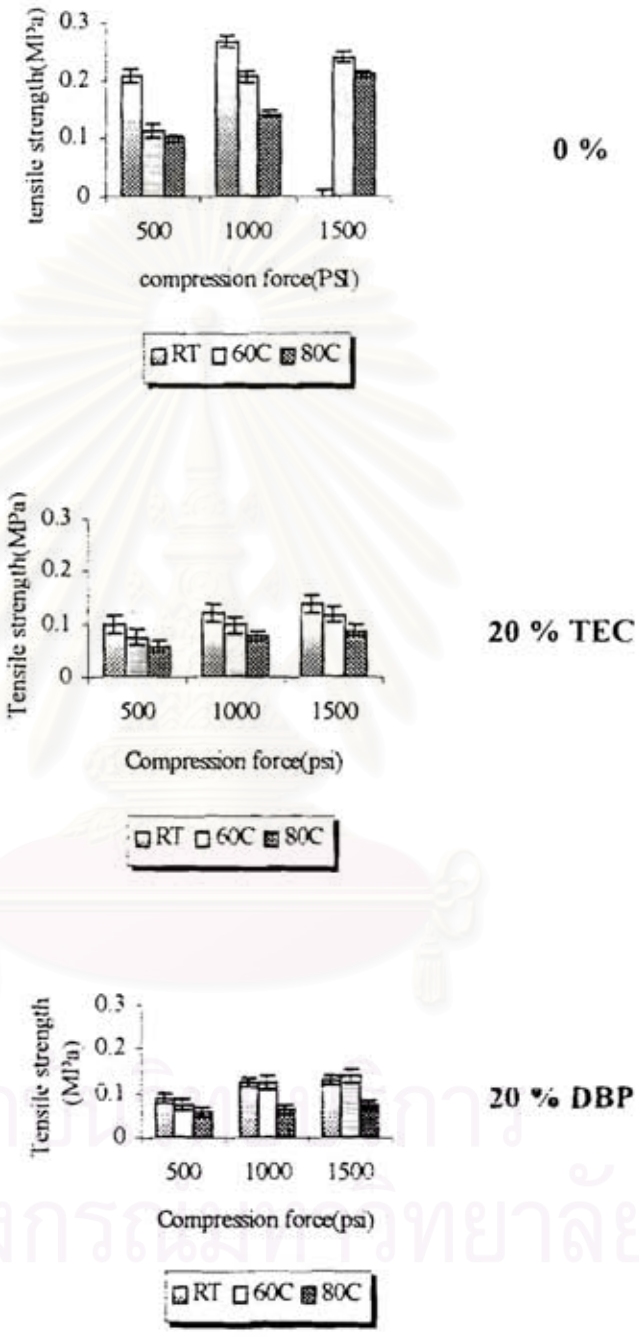

Figure 32 Effect of the processing temperature on the tablet tensile strength of Kollidon® SR matrices without plasticizer(0%) ,20% TEC ,20%DBP prepared by method IV at room temp.,60 °C, and 80 °C.

3.4 Disintegration studies

All of the formulations had disintegration time that was longer than 2 hours due to its was plastic polymer which insignificant swelling and diffusion was the mechanism of drug release in this experiment.

3.5 % Friability

% Friability of matrices tablet not more than 1 % for allformulations.

3.6 drug content

The tablet weight can not be used as a potency indicator, except where the active ingredient is 90 to 95 % of the total tablet weight. It is advisable to determine the drug content of tablets especially with new production runs of a product with which there is a little experience or in tableting system. The percent drug contents are shown in Table 12-13.

The values of the percent drug contents of theophylline matrices were within the USP limit of 85-115 % for all formulations.

Table 12 The percent drug contents of Eudragit® RS matrices

Method	Formulations	Drug content(SD)	Method	Formulation	Drug content(SD)
I	0 %	102.40(1.48)	IV at room temp.	0%	98.34(1.71)
	10 % TEC	101..85(1.34)		10 % TEC	97.84(1.16)
	10 % DBP	102.10(1.50)		10 % DBP	97.78(1.13)
	20 % TEC	100.70(2.07)		20 % TEC	98.16(1.10)
	20 % DBP	100.481.56)		20 % DBP	98.70(1.29)
II	0 %	99.89(1.84)	IV at 80°C	0 %	99.75(1.63)
	10 % TEC	100.05(1.65)		10 % TEC	99.92(1.34)
	10 % DBP	99.73(0.86)		10 % DBP	98.99(1.60)
	20 % TEC	98.97(1.14)		20 % TEC	98.65(1.39)
	20 % DBP	98.49(0.96)		20 % DBP	99.99(1.30)
III	0 %	101.89(1.41)			
	10 % TEC	101.43(1.47)			
	10 % DBP	102.67(1.45)			
	20 % TEC	101.67(1.36)			
	20 % DBP	100.89(1.65)			
IV	0 %	98.43(1.52)			
	10 % TEC	99.43(1.15)			
	10 % DBP	98.58(1.13)			
	20 % TEC	98.23(1.47)			
	20 % DBP	98.01(1.01)			

Table 7 the percent drug content of Kollidon® SR matrices

Method	Formulations	Drug content(SD)	Method	Formulations	Drug content(SD)
I	0 %	101.43(1.52)	IV at room temp.	0%	99.00(1.24)
	10 % TEC	101.431(.15)		10 % TEC	98.09(1.15)
	10 % DBP	100.58(1.13)		10 % DBP	99.41(1.51)
	20 % TEC	101.23(1.47)		20 % TEC	99.89(1.20)
	20 % DBP	101.01(1.01)		20 % DBP	99.65(1.70)
II	0 %	99.38(1.45)	IV at 80 °C	0 %	99.77(1.48)
	10 % TEC	99.40(1.34)		10 % TEC	99.61(1.40)
	10 % DBP	98.43(1.54)		10 % DBP	99.57(1.11)
	20 % TEC	*		20 % TEC	98.65(1.43)
	20 % DBP	*		20 % DBP	99.10(1.15)
III	0 %	102.14(1.42)			
	10 % TEC	102.23(1.98)			
	10 % DBP	101.95(1.58)			
	20 % TEC	101.68(1.48)			
	20 % DBP	100.90(1.35)			
IV	0 %	98.84(1.74)			
	10 % TEC	98.91(1.07)			
	10 % DBP	99.23(1.61)			
	20 % TEC	99.48(1.22)			
	20 % DBP	99.73(1.35)			

* Could not be processed

3.4 Dissolution studies

The dissolution data of all formulations were studied by paddle method in phosphate buffer pH 6.8 were shown in Table 39-96 (Appendix B). From these data, the released profile could be plotted between the percentage of amount of drug release against time.

The release rate constants were fitted to Higuchi model, which calculated as the percentage of drug released versus square root of time. A double logarithmic plot of drug release as a function of time for the drug release from all formulations, resulted in a good fit to a straight line for each case (Appendix D).

Eudragit® RS or Kollidon® SR forms a non-disintegrating matrix, which will only slightly swell to a limited amount. When placed in an aqueous environment, drug release from Eudragit® RS or Kollidon® SR matrices will be governed by diffusion of liquid into a matrix, dissolution of the theophylline and then diffusion of dissolved drug out of the tablet.

3.4.1 Polymer without plasticizer

The dissolution data of theophylline from matrices of Eudragit® RS or Kollidon® SR without plasticizer prepared by thermal granulation at 60°C and at room temperature are listed in Tables 39-42(Appendix B) and are shown graphically in Figure 33-34 the released rate profile is tabulated in Table16 These results demonstrate that the dissolution of theophylline matrices prepared by direct compression almost released 100 % in 12 hour and the erosion on matrix tablets was seen whereas the dissolution of theophylline was about 68 % in 12 hour from wet granulation, the Higuchi constant was 27.06 % $hr^{-1/2}$ and 18.47 % $hr^{-1/2}$, respectively. For the Kollidon® SR matrices, the dissolution of theophylline almost 74 % in 12 hour by direct compression and 62 % by wet granulation. The erosion of matrix tablet was not found. The Higuchi constant was 24.27 % $hr^{-1/2}$ and 17.79 % $hr^{-1/2}$, respectively.

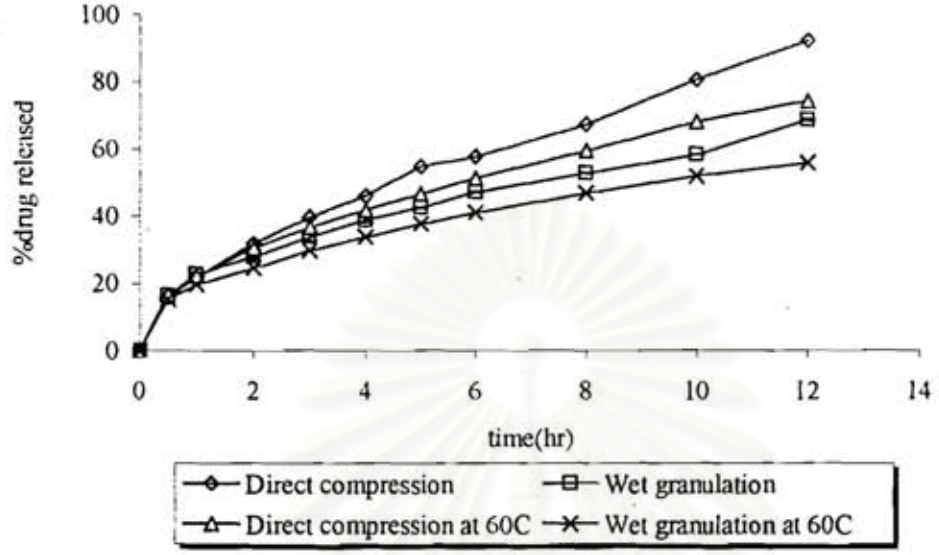

Figure 33 Release profiles of Eudragit® RS matrices prepared by wet granulation and direct compression at room temp and 60°C

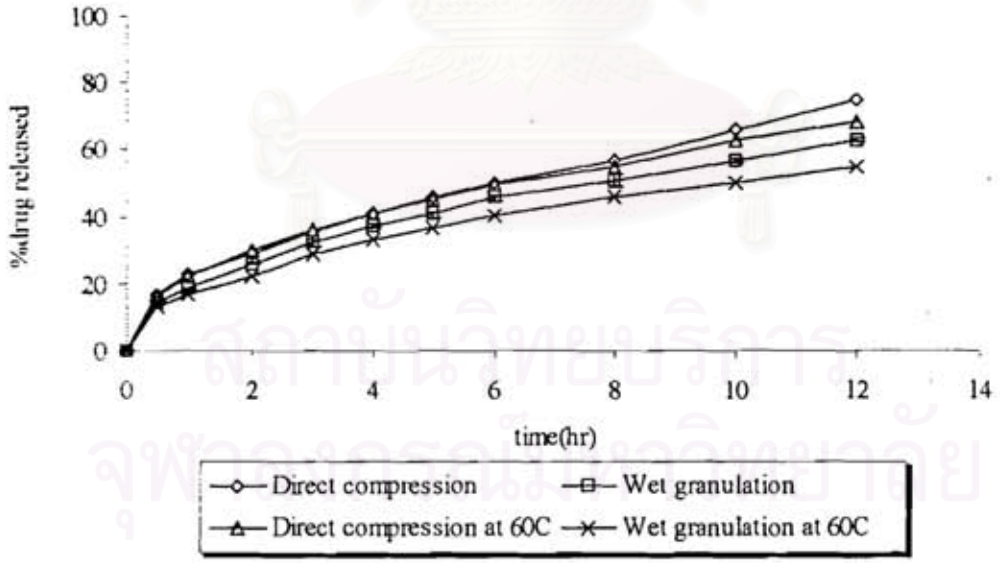

Figure 34 The release profiles of Kollidon® SR matrices prepared by wet granulation and direct compression at room temp and 60°C

Table16 The effect of thermal processing on Higuchi constant (k) and diffusion exponent (n) of theophylline matrices prepared by direct compression and wet granulation at room temperature and 60°C

Method	Formulation	k(% $h^{-1/2}$)	r^2	(n)	r^2
Direct compression	Eudragit® RS	27.06	0.9905	0.5302	0.9965
	Eudragit® RS at 60°C	24.17	0.9969	0.4799	0.9970
	Kollidon® SR	24.27	0.9952	0.4307	0.9960
	Kollidon® SR at 60°C	20.49	0.9967	0.4543	0.9941
Wet Granulation	Eudragit® RS	18.47	0.9937	0.4202	0.9968
	Eudragit® RS at 60°C	15.51	0.9958	0.4138	0.9943
	Kollidon® SR	17.79	0.9985	0.4739	0.9957
	Kollidon® SR at 60°C	15.80	0.9981	0.4677	0.9964

When thermal granulation process at 60°C was used to prepared matrices tablet. These results show that the dissolution profile and Higuchi constant significantly decreased compared to direct compression and wet granulation at room temperature($p < 0.05$). The Higuchi constant was 24.17 % $h^{-1/2}$ by direct compression and 15.51 % $h^{-1/2}$ by wet granulation for Eudragit® RS at 60°C.The Higuchi constant for Kollidon® SR with thermal process at 60°C was 20.49 % $h^{-1/2}$ by direct compression and 15.80 % $h^{-1/2}$ by wet granulation, which slower than the process without heat due to the effect of thermal treatment over the Tg of polymer. By fitting drug release profiles to the Higuchi equation, the best fit with good correlation($r^2 > 0.99$) was found with the Higuchi equation for all the formulations. The results suggested that the mechanism of drug release from these tablets occurred by a diffusion-controlled process. To confirm the diffusion mechanism, the data were fit to Peppas's equation and found that all formulations showed a good linearity and slope (n) values ranging from 0.41 to 0.53, indicating that diffusion is the dominant mechanism of drug release with these formulations.

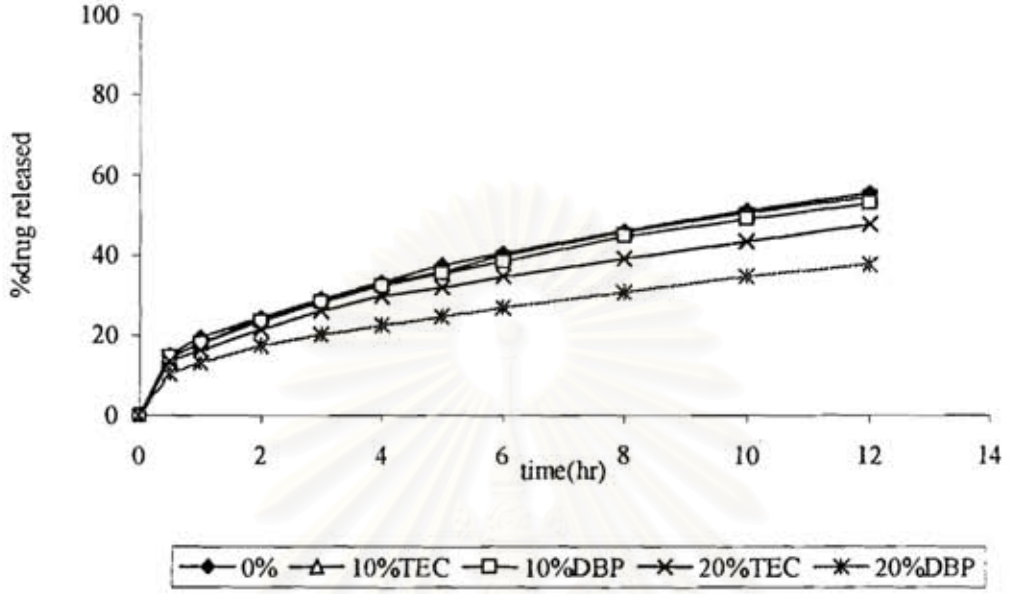

Figure 35 The release profiles of theophylline from Eudragit® RS with 10 % and 20 % plasticizer prepared by method I at 60°C(wet granulation)

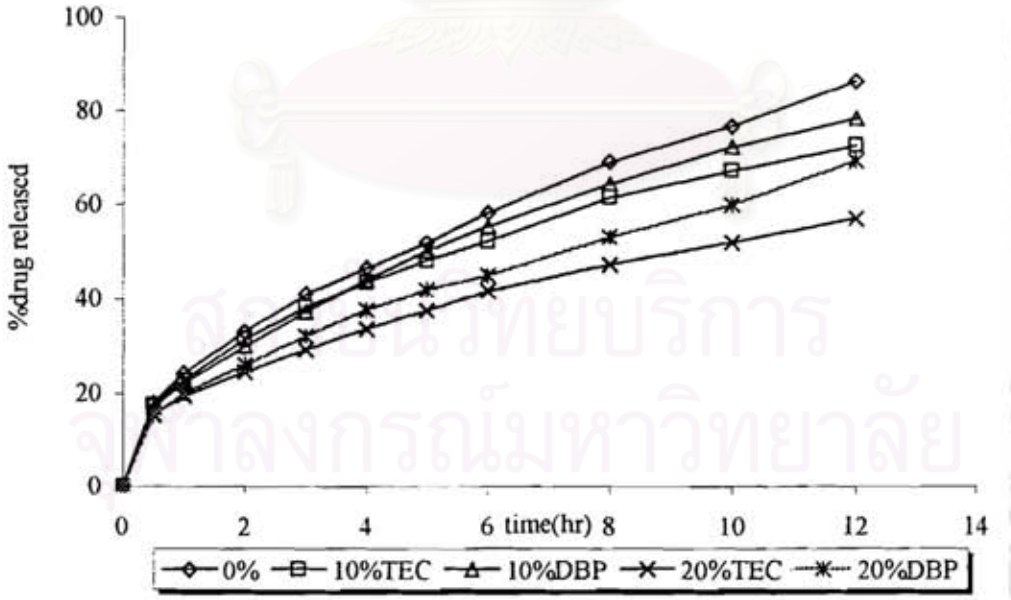

Figure 36 The release profiles of theophylline from Eudragit® RS with 10 % and 20 % plasticizer prepared by method II at 60°C (ground polymer)

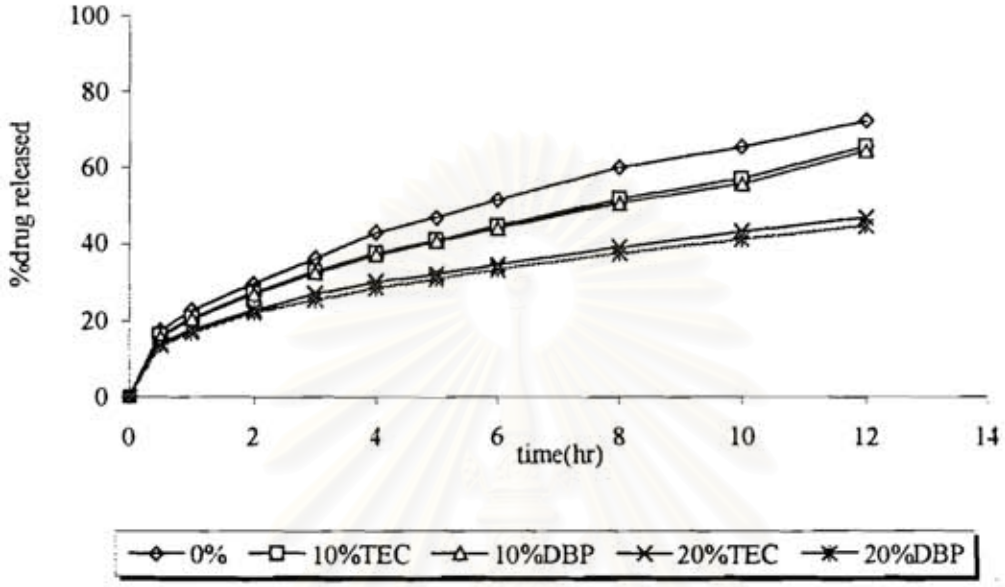

Figure 37 The release profiles of theophylline from Eudragit® RS with 10 % and 20 % plasticizer prepared by method III (spray plasticizer)

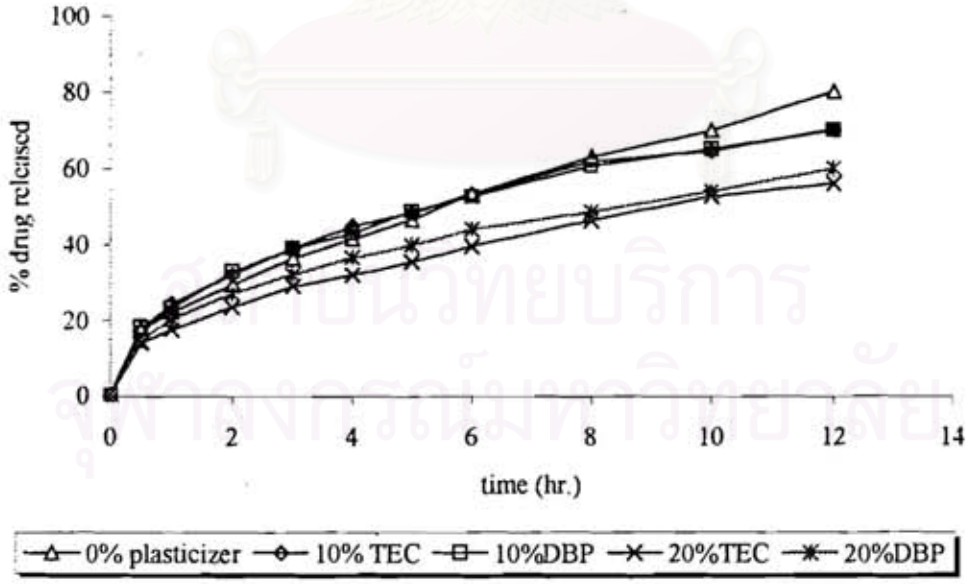

Figure 38 The release profiles of theophylline from Eudragit® RS with 10 % and 20 % plasticizer prepared by method IV at 60°C (spray dried)

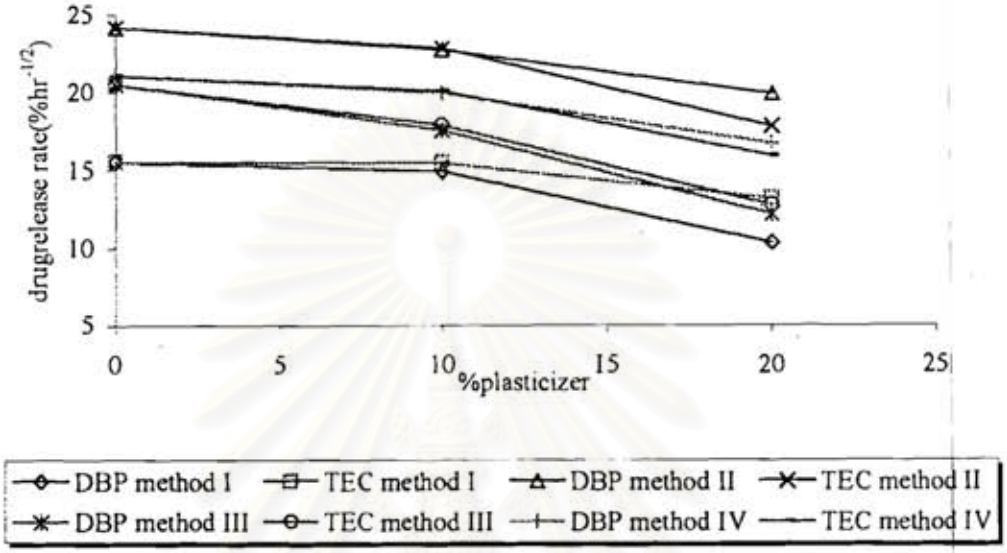

Figure 39 Higuchi constant of Eudragit® RS with 10 % and 20 % DBP or TEC prepared by method I-IV at 60°C

Table 17 The effect of 10 % and 20 % plasticizer on Higuchi constant (k) and diffusion exponents (n) of Eudragit® RS matrices prepared by method I at 60°C

Formulation	(k,% $hr^{-1/2}$)(SD)	r^2	n	r^2
0 % plasticizer	15.51(0.25)	0.9958	0.4138	0.9943
10 % DBP	14.91(0.10)	0.9962	0.4187	0.9948
20 % DBP	10.36(0.10)	0.9938	0.4015	0.9944
10 % TEC	15.46(0.10)	0.9973	0.4315	0.9960
20 % TEC	13.16(0.15)	0.9939	0.4039	0.9945

Table 18 The effect of 10 % and 20 % plasticizer on Higuchi constant (k) and diffusion exponents (n) of Eudragit® RS matrices prepared by method II at 60°C

Formulation	k (% $h^{-1/2}$)(SD)	r^2	n	r^2
0 % Plasticizer	24.17(0.18)	0.9969	0.4799	0.9970
10 % DBP	22.74(0.18)	0.9983	0.4828	0.9932
20 % DBP	19.90(0.20)	0.9938	0.4294	0.9982
10 % TEC	22.84(0.19)	0.9982	0.4505	0.9989
20 % TEC	17.79(0.18)	0.9931	0.3921	0.9989

Table19 The effect of 10 % and 20 % plasticizer on Higuchi constant (k) and diffusion exponents (n) from Eudragit® RS matrices prepared by method III at 60°C

Formulation	k (% $h^{-1/2}$)(SD)	r^2	n	r^2
0 % Plasticizer	20.49(0.19)	0.9985	0.4482	0.9949
10 % DBP	17.54(0.21)	0.9962	0.4272	0.9986
20 % DBP	12.18(0.17)	0.988	0.3689	0.9988
10 % TEC	17.87(0.20)	0.996	0.4226	0.9969
20 % TEC	12.75(0.22)	0.9881	0.3672	0.9984

Table20 The effect of 10 % and 20 % plasticizer on Higuchi constant (k) and diffusion exponents (n) from Eudragit® RS matrices prepared by method IV at 60°C

Formulation	k (% $h^{-1/2}$)(SD)	r^2	n	r^2
0 % Plasticizer	21.05(0.25)	0.9988	0.4605	0.9988
10 % DBP	19.95(0.10)	0.9938	0.4376	0.9977
20 % DBP	16.69(0.008)	0.9961	0.4372	0.9992
10 % TEC	20.05(0.14)	0.9937	0.4463	0.9989
20 % TEC	15.93(0.13)	0.997	0.4487	0.9963

At 20 % plasticizer, it was clearly demonstrated that the Higuchi constant of matrices prepared by method I and III (wet granulation and spray plasticizer into polymer) using TEC was faster than DBP compared with method II and IV (ground polymer and spray dried). This result indicated that there are two patterns of dissolution profiles. The matrices tablet containing TEC showed the faster release pattern than DBP which found in the matrices prepared by method I and III. Another one, which found in matrices prepared by method II and IV showed a convert release profiles. This could be due to the leaching of TEC to the dissolution medium so that, percentage amount of drug release was more than the matrices containing DBP.

Various factors influence the drug release rate, the additive is one factor to determine the release. Increasing amounts of plasticizer consequence decrease in amount of lactose in the formulation. This result may be caused by the water-soluble additive in the formulation causing a channel which drug could diffuse through this pore. Resulting in changing in drug release rate.

3.4.3 Kollidon® SR with plasticizer

The dissolution profiles of theophylline from Kollidon® SR matrices prepared by thermal granulation at 60°C using different methods to incorporate plasticizer into polymer are shown in Figures 40-43. Higuchi constant of Kollidon® SR matrices was shown in figure 44 and Tables 21-24. The Higuchi constant of Kollidon® SR matrices decreased in all formulations when 10 % TEC was incorporated into the system. The effect of 10 % TEC and DBP was also the same as in the case of Eudragit® RS which Higuchi constant at 10 % TEC was faster than 10 % DBP for method I and II while drug release rate of 10 % TEC were slightly slower than 10 % DBP for method IV.

A significantly decreased in Higuchi constant was found in matrices prepared by method II (ground polymer) and method IV (Figure 41 and 43). Higuchi constant prepared by method II with 10 % TEC significantly decreased from 24.27 % $hr^{-1/2}$ to 20.85 % $hr^{-1/2}$. This might be caused by the effect of particle size of polymer. The

particle size of ground Kollidon® SR with plasticizer (method II) showed the mean particle size of Kollidon® SR with TEC was 198.58 μm compared with the mean particle size of Kollidon® SR with DBP was 246.75 μm.This results demonstrated that the smaller particle of polymer have a well mix with the theophylline particle than the large particle during thermal granulation. For method IV (spray dried), the spray dried Kollidon® SR with plasticizer have a smaller particle size than the spray dried Eudragit® RS. Consequently, more drug and polymer with plasticizer were combined together to form the granule resulted in significantly decreased in drug release.

When 20 % plasticizer was incorporated into Kollidon® SR, the dissolution profiles and Higuchi constant significantly decreased from 10 % plasticizer ($p<0.05$) except in method IV .For method II, an absence of dissolution data due to the processing of preparation of Kollidon® SR with 20 % plasticizer was not accomplished as plasticized polymer could not be ground to the powder.

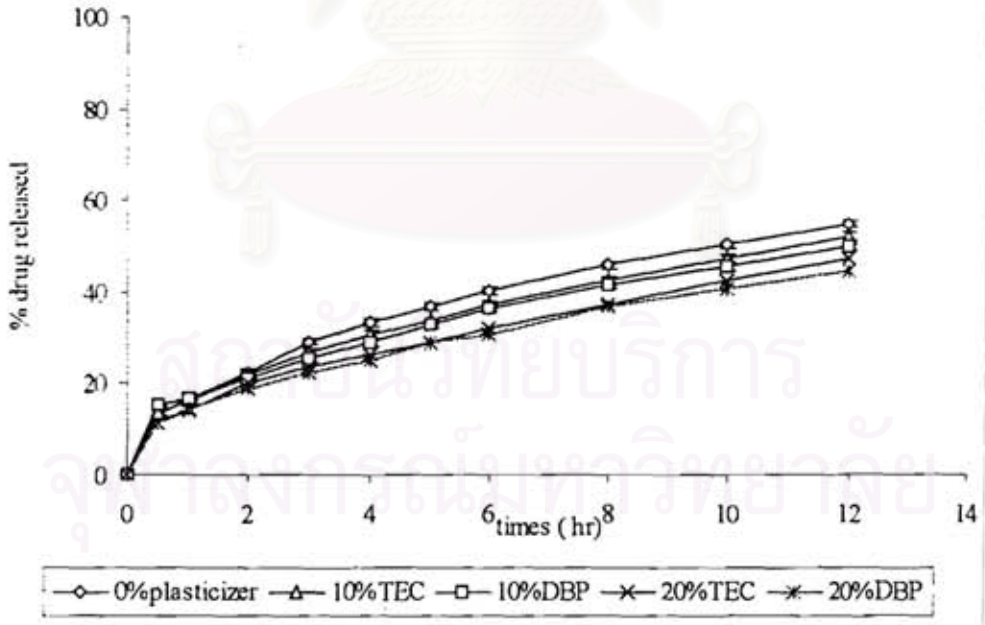

Figure 40 The release profiles of theophylline released from Kollidon® SR with 10 % and 20 % plasticizer prepared by method I(wet granulation)

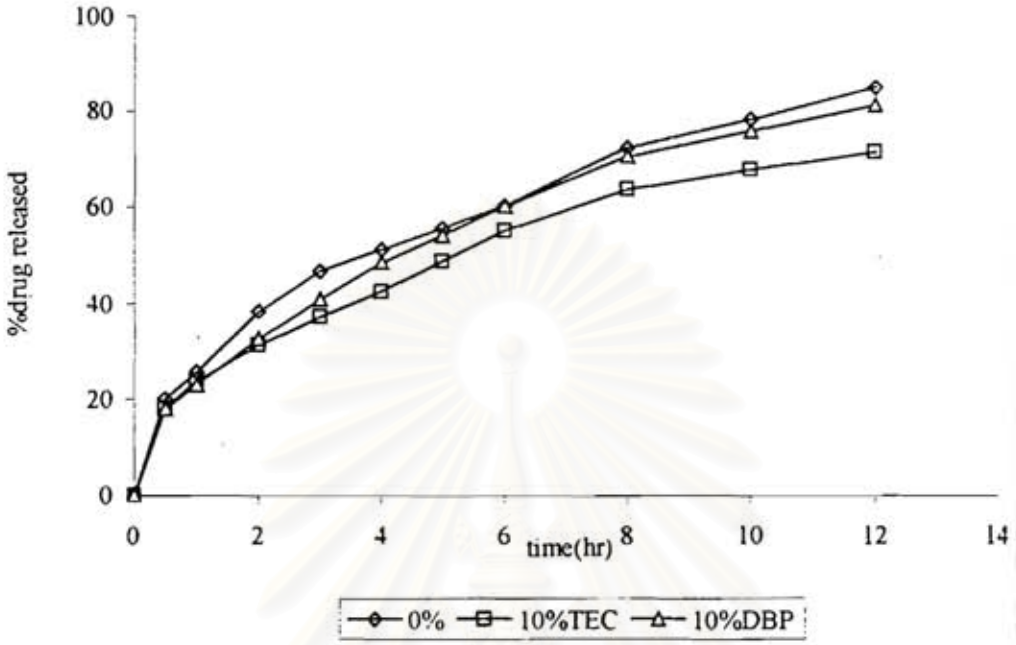

Figure 41 The release profiles of theophylline released from Kollidon® SR with 10 % plasticizer prepared by method II(ground polymer)

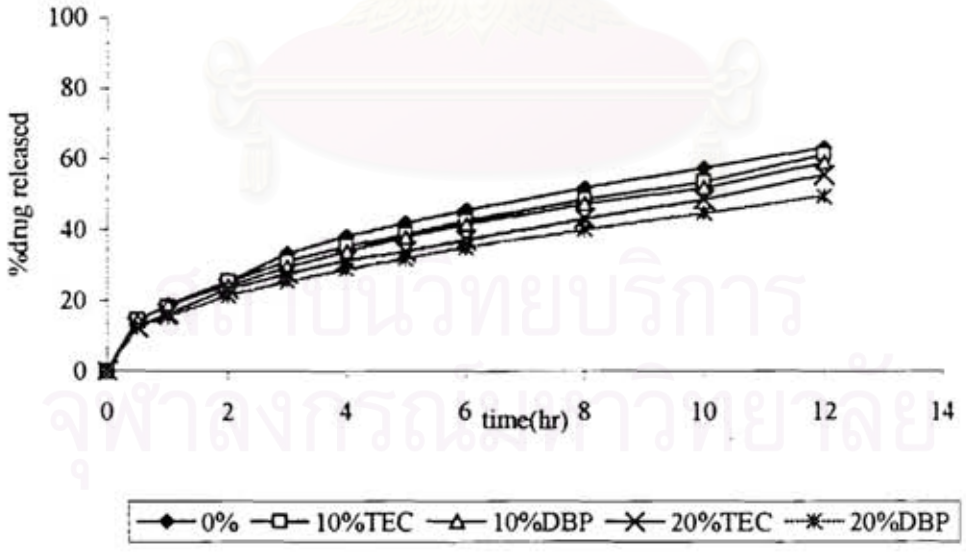

Figure 42 The release profiles of theophylline released from Kollidon® SR with 10 % and 20 % plasticizer prepared by method III(spray plasticizer into polymer)

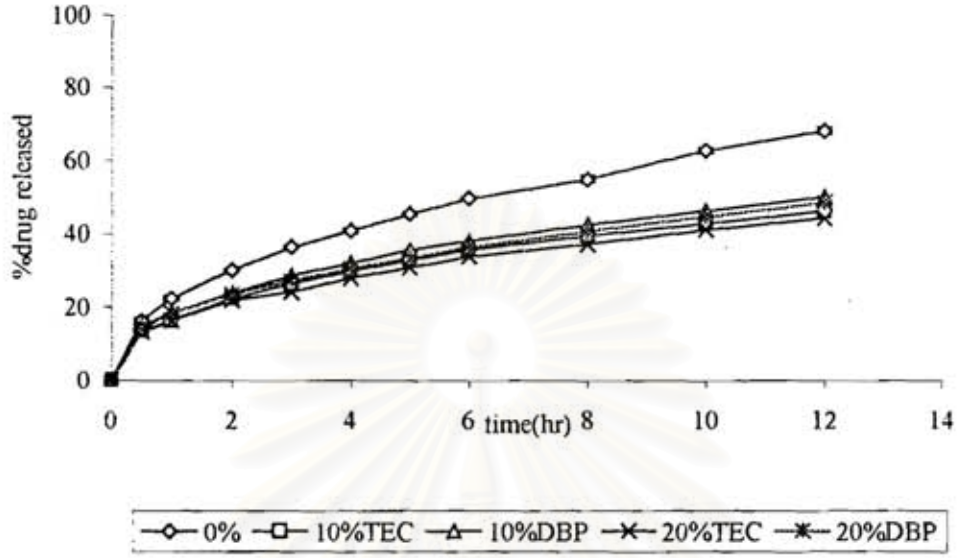

Figure 43 The release profiles of theophylline released from Kollidon® SR with 10 % and 20 % plasticizer prepared by method IV(spray dried)

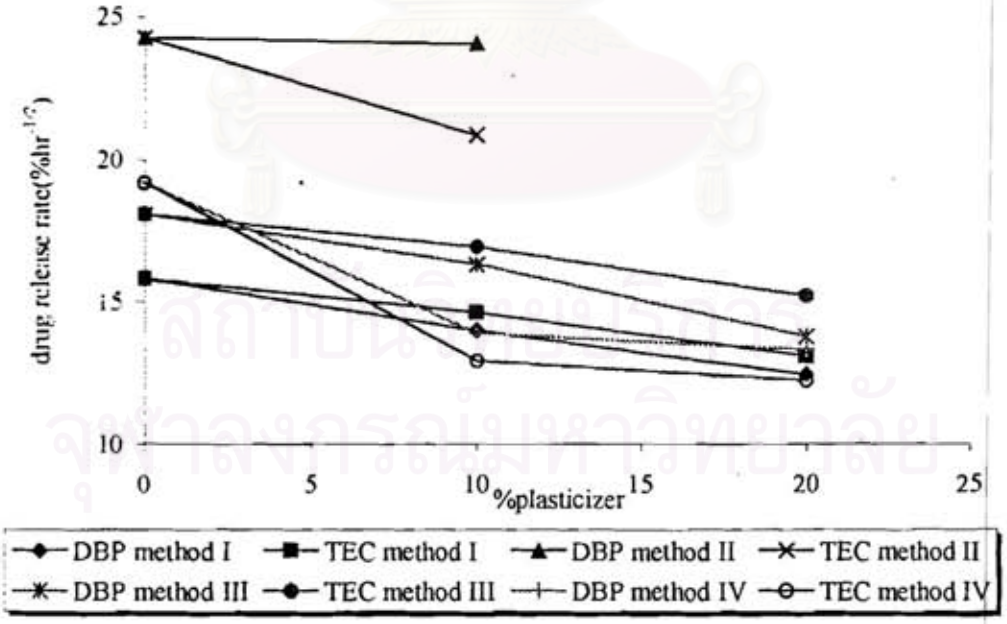

Figure 44 Higuchi constant of Kollidon® SR matrices with 10 % and 20 % TEC or DBP prepared by method I-IV at 60 °C

Table 21 The effect of plasticizer on Higuchi constant (k) and diffusion exponents (n)of Kollidon® SR matrices prepared by method I(wet granulation) at 60 °C

Formulation	K(% $hr^{-1/2}$)(SD)	r^2	n	r^2
0 % Plasticizer	15.80(0.008)	0.9981	0.4677	0.9964
10 % DBP	14.12(0.15)	0.9968	0.4295	0.9918
20 % DBP	12.45(0.12)	0.9960	0.4305	0.9902
10 % TEC	14.62(0.15)	0.9977	0.4374	0.9927
20 % TEC	13.09(0.15)	0.9954	0.4453	0.9917

Table 22 The effect of plasticizer on Higuchi constant (k) and diffusion exponents (n) of Kollidon® SR matrices prepared by method II(ground polymer) at 60 °C

Formulation	k(% $hr^{-1/2}$) (SD)	r^2	n	r^2
0 % Plasticizer	24.27(0.24)	0.9967	0.4543	0.9941
10 % DBP	24.05(0.24)	0.9974	0.4952	0.9938
10 % TEC	20.857(0.21)	0.9944	0.4337	0.9923

Table 23 The effect of plasticizer on Higuchi constant (k) and diffusion exponents (n) of Kollidon® SR matrices prepared by method III (spray plasticizer to polymer) at 60 °C

Formulation	k(%$hr^{-1/2}$) (SD)	r^2	n	r^2
0 % Plasticizer	18.08(0.11)	0.9986	0.4823	0.9969
10 % DBP	16.31(0.10)	0.9976	0.4367	0.9960
20 % DBP	13.79(0.15)	0.9983	0.4400	0.9969
10 % TEC	16.92(0.17)	0.9976	0.4434	0.9962
20 % TEC	15.20(0.15)	0.9966	0.4600	0.9961

Table 24 The effect of plasticizer on Higuchi constant (k) and diffusion exponents (n) of Kollidon® SR matrices prepared by method IV (spray dried) at 60 °C

Formulation	k(% $hr^{-1/2}$) (SD)	r^2	n	r^2
0 % Plasticizer	19.17(0.13)	0.9975	0.4438	0.9996
10 % DBP	13.91(0.12)	0.9902	0.3921	0.9978
20 % DBP	13.32(0.23)	0.9903	0.3874	0.9987
10 % TEC	12.93(0.15)	0.9912	0.4035	0.9975
20 % TEC	12.23(0.22)	0.9903	0.3884	0.9958

Thermal granulation at 60°C is expected to slow drug release rate for both Eudragit® RS and Kollidon® SR matrices with plasticizer compared to the formulation without plasticizer. These results due to the presence of plasticizer in the interstices of polymer enhance the drug and polymer intermolecular entanglement resulted in a decrease in the drug release rate. The influence of level plasticizer on the dissolution release rate from all formulations which seen in Figure 39 and 44(page 79 and 84), the drug release rate decreased when the amounts of plasticizer increased. When 10 % plasticizer was incorporated, the drug release rate slightly decreased. However a significant decrease in the dissolution rate was observed with 20 % plasticizer. An increase the binding of the drug to the polymer, facilitated the formation of a continuous matrix structure, which would decrease the diffusivity of the drug from the system.

The addition of plasticizer further enhanced drug and polymer binding during thermal processing, as a result, drug release rate from all formulations decreased. As observed by SEM examination, theophylline particles binding to the Eudragit® RS and Kollidon® SR to form the granules. The granules size increase following to 10 % and 20 % plasticizer was incorporated into polymer compared to the formulation without plasticizer. The binding of the theophylline and the polymer did not observe in the formulation without plasticizer resulted that the drug release rate was faster than the formulation with plasticizer. The plasticizers caused lower porosity, higher tortuosity and

enhance the formation of continuous matrix structure and also enhanced the adhesion of polymer particles in the granules.

Since the drug was released from the matrix by a diffusion mechanism, the decrease in the drug release rate from the tablet containing larger granules was a result of pore size. Increasing the plasticizer brought the particle close to each other which corresponding to a slow release rate.

Eudragit® RS contains ester groups that are shown in Figure 4 and chemical structure of DBP and TEC are depicted in Figure 6 and 7, respectively. The ester groups were capable of interacting with other molecules by hydrogen bonding, as well as electrostatic and dispersion forces. TEC had the ability to break up the polymer-polymer interaction, due to the accessibility of its free hydroxyl group to interact through hydrogen bonding with the ester groups of the copolymer. Although hindered by the presence of the side chains, they still had the ability to form hydrogen bond with the copolymer. (Gutierrez- Rocca and McGinity, 1997)

In the case of Kollidon® SR matrix tablet, an increase in the amount of plasticizer exhibited a decrease in the percent drug release especially from the formulation with 10 % plasticizer to 20 % plasticizer. However, as unexpected for the matrices prepared by spray dried Kollidon® SR (method IV)(see Figure 43), the percent drug release and drug release rate from matrices containing 10 % plasticizer was comparable to that from matrices containing 20 % plasticizer. Additionally, the dissolution profiles from the other methods which containing 20 % plasticizer slightly decreased from 10 % plasticizer which contrast to Eudragit® RS matrices system. Although the glass transition temperature of Kollidon® SR containing 10 % was greater than 20 % plasticizer (21.74°C, 9.08°C for TEC and 23.59°C, 9.11°C for DBP). These results might be caused by the Tg of Kollidon® SR without plasticizer was closed to room temperature (40.09°C), so that the addition of plasticizer from 10 % to 20 % did not play influence the dissolution profiles. On the other hand, the Tg of the Eudragit® RS without plasticizer was 64.24°C, which higher than the room temperature.When 10 % and 20 % plasticizer was incorporated, the Tg decreased to 34.14°C, 12.63°C and 33.55°C, 17.35 °C for TEC and

DBP, respectively. These results indicated that although the Tg of Kollidon® SR was decreased by the effect of plasticizer, the drug release rate displayed minimal change as the same way since limit of change of structure.

Engineer et al. (2004) found that tablet containing Kollidon® SR was influenced by temperature and humidity. When the matrix tablet exposed to the 40°C / 75 % RH condition caused change in the drug release rate and extent of drug release after at lease 1 hour of exposure time. In addition the dissolution profiles continuously decrease as a function times. Tablets were exposed to the temperature and moisture from 1 hr to 4 weeks resulted in decreased in drug release rate. However, exposure over this time resulted in steady decrease in the kinetic release constant.

The decreasing of lactose consequence an increasing of plasticizer in the formulation might influence the drug release. Lactose was added as the water soluble filler additives. An increasing 10 % and 20 % of plasticizer led to decrease of lactose from 19.5 % to 16.5 % and 13.5 % in the formulation. During the dissolution process, the lactose leached into the dissolution medium and created a porous matrix through which the theophylline diffused. However Zhang and Mc Ginity(2000) found that additional lactose lower than 25 % did not affect the drug release rate of hot melt extrude tablets.

3.3.4 The Effect of Processing Temperature

The influences of processing temperature on the dissolution profile and dissolution rate were investigated. In previous study, the processing temperature was 60°C, which closed to the Tg of Eudragit® RS (62.24°C) and above the Tg of Kollidon® SR(40.09°C) was investigated. The formulation used in this study were the preparation which 10-20 % plasticizer was incorporated by method IV(spray dried) and the processing temperature was at 80°C compared with at 60°C and physical mixture at room temperature(direct compression). The data are shown in Table 63-69 and 88-96 (Appendix B). The dissolution profiles are shown in Figure 45-48. The Higuchi constants are shown in Figure 49-50 and in Table 25-28.

For direct compression at room temperature, theophylline powder, polymer with plasticizer powder and lactose are mixed together in a planetary mixer without the use of heat. For Eudragit® RS matrices tablet, when 10 % TEC or DBP was incorporated into the system, the drug release rate slightly decreased from the Eudragit® RS matrices tablet without plasticizer. Further increase in amounts of plasticizer to 20 % exhibited a more decrease in Higuchi constants than 10 % plasticizer. However, at 10 and 20 % plasticizer, the Higuchi constants when using TEC was comparable to DBP (Figure 45). In contrast, in Kollidon® SR matrices tablet, the Higuchi constants of matrices containing 10 % plasticizer significantly decreased from matrices without plasticizer and found similar to that the matrices containing 20 % plasticizer ($p<0.05$) (figure 46)

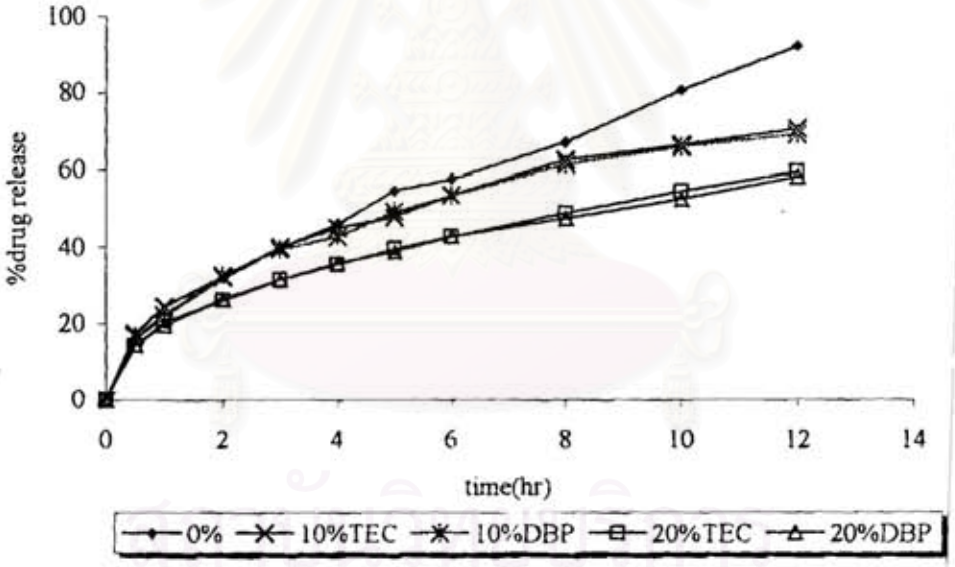

Figure 45 The release profiles of theophylline released from Eudragit® RS with 10 % and 20 % plasticizer prepared by method IV at room temperature(RT)

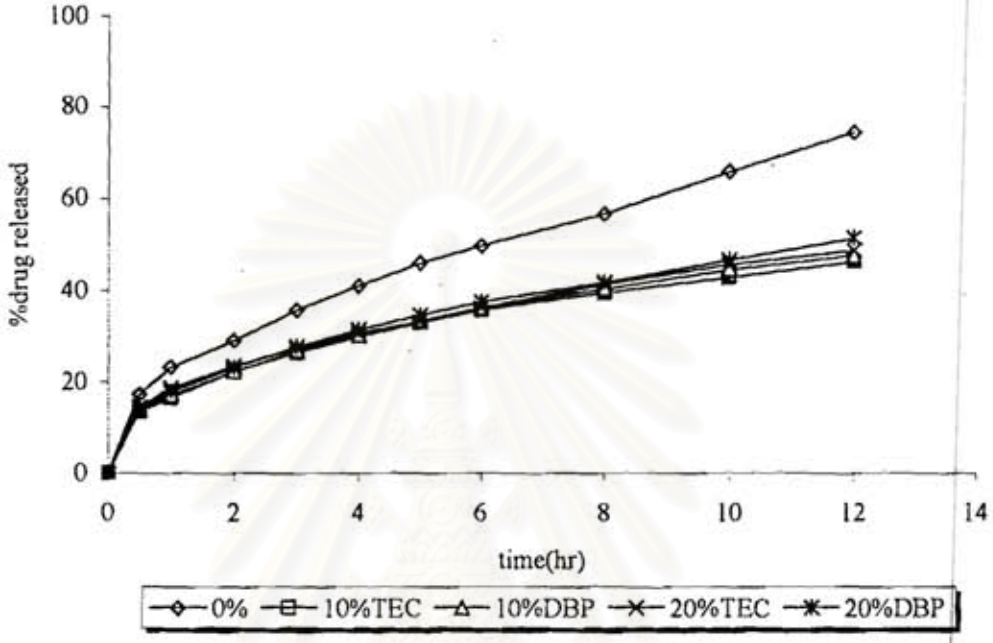

Figure 46 The release profiles of theophylline released from Kollidon® SR with 10% and 20% plasticizer prepared by method IV at room temperature (RT)

When the processing temperature was at 80°C, which much higher than the glass transition temperature of Eudragit® RS and Kollidon® SR, the theophylline particle was added to the polymer produced more agglomerated granules than the process temperature at 60°C (SEM Figures 27-28). Higuchi constants of matrix containing Eudragit® RS decreased as the amount of plasticizer increased. When 10 % TEC and 10 % DBP was incorporated into the system, the Higuchi constants significantly decreased compared to the Eudragit® RS matrices tablet without plasticizer. ($p<0.05$) Furthermore, an increase in amount of plasticizer to 20 % led to a significantly decreased in Higuchi constants from using 10 % plasticizer ($p<0.05$) (Figure 47). This result indicated that the thermal granulation at 80°C was sufficient to significantly decrease the Higuchi constants compared to the formulation without plasticizer.

For Kollidon® SR matrices tablet, at thermal granulation of 80°C, the Higuchi constants of matrices without plasticizer was higher than the matrices with 10 % plasticizer. The Higuchi constants of Kollidon® SR matrices with 10 % plasticizer significantly decrease compared to the formulation without plasticizer. In contrast to the Eudragit® RS matrices system, the effect of thermal processing at 80°C of Kollidon® SR with 20 % plasticizer did not further decrease compared to the formulation with 10 % plasticizer. The Higuchi constants of matrices containing 10 % plasticizer were similar to that from matrices containing 20 % plasticizer. (Figure 48 and 50). This result indicated that the thermal temperature at 80°C and the lower level of plasticizer at 10% were sufficient to significantly decrease the Higuchi constants of Kollidon® SR matrices system. An increasing plasticizer level to 20% slightly decreased the Higuchi constants from using 10 % plasticizer.

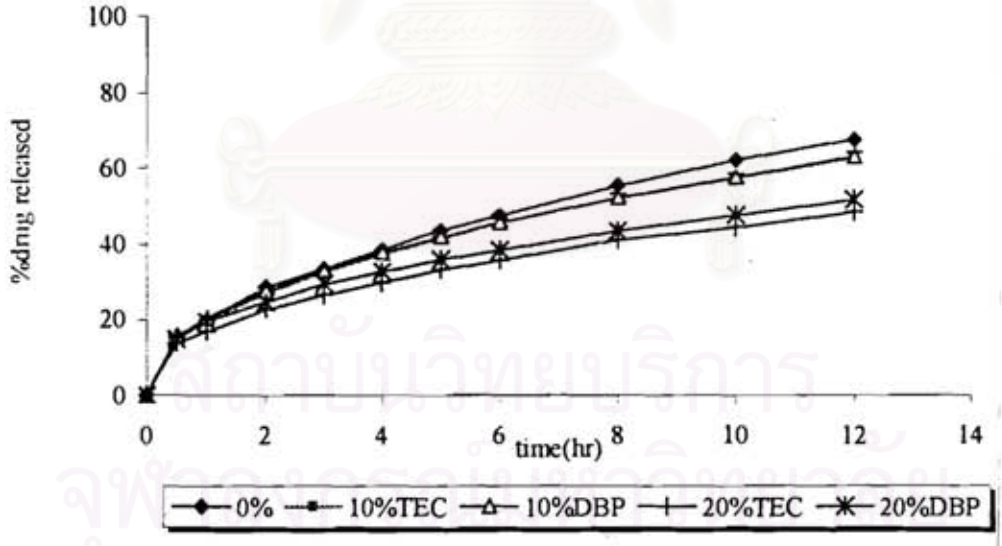

Figure 47 The release profiles of theophylline released from Eudragit® RS with 10 % and 20 % plasticizer prepared by method IV at 80°C

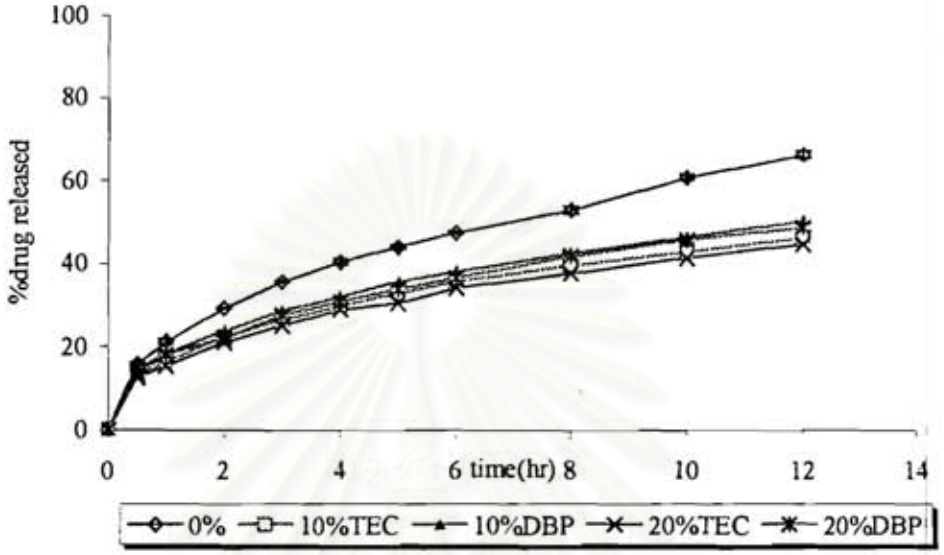

Figure 48 The release profiles of theophylline released from Kollidon® SR with 10 % and 20 % plasticizer prepared by method IV at 80°C

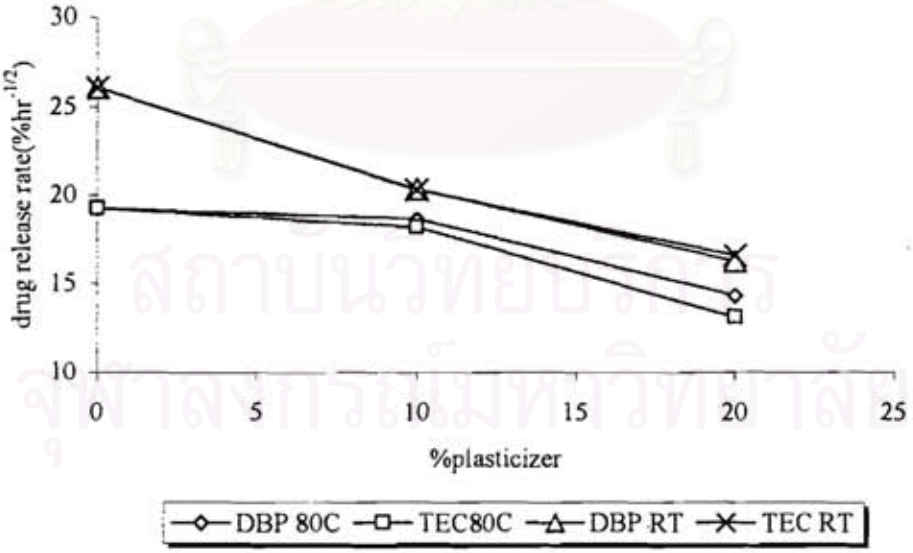

Figure 49 Higuchi constant of Eudragit® RS with 10-20 % DBP or TEC prepared by method IV at 80°C and room temperature (RT)

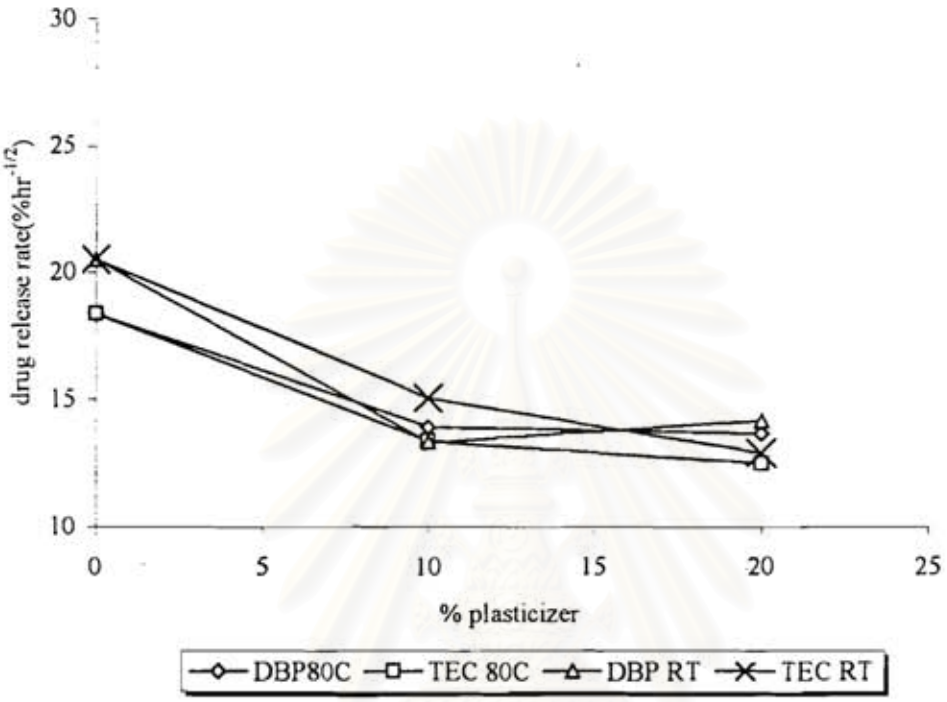

Figure 50 Higuchi constant of Kollidon® SR with 10- 20% DBP or TEC prepared by method IV at 80°C and room temperature (RT)

Table 25 The k (Higuchi constant) and n (diffusion exponents) value from Eudragit® RS with 10 % and 20 % plasticizer prepared by method IV at 80°C

Formulation	k(%hr$^{-1/2}$)(SD)	r^2	n	r^2
0 % plasticizer	19.25(0.008)	0.9991	0.4589	0.9968
10 % TEC	18.21(0.14)	0.9981	0.4300	0.9968
10 % DBP	18.65(0.14)	0.9986	0.4587	0.9977
20 % TEC	13.09(0.13)	0.9909	0.3956	0.9978
20 % DBP	14.31(0.11)	0.9914	0.3940	0.9989

Table 26 The k (Higuchi constant and n (diffusion exponents) of Kollidon® SR with 10 % and 20 % plasticizer prepared by method IV at 80°C

Formulation	k ($\%hr^{-1/2}$)(SD)	r^2	n	r^2
0 % plasticizer	18.35(0.009)	0.997	0.4440	0.999
10 % TEC	13.36(0.10)	0.9914	0.4035	0.9993
10 % DBP	13.91(0.008)	0.9902	0.4001	0.9966
20 % TEC	12.49(0.11)	0.9921	0.4003	0.9967
20 % DBP	13.67(0.12)	0.9926	0.4056	0.9969

Table 27 The k (Higuchi constant) and n (diffusion exponents) of Eudragit® RS with 10 % and 20 % plasticizer prepared by method IV at room temperature

Formulation	k ($\%hr^{-1/2}$)(SD)	r^2	n	r^2
0 % plasticizer	26.07(0.11)	0.9905	0.5321	0.9965
10 % TEC	20.30(0.15)	0.9939	0.4457	0.9982
10 % DBP	20.35(0.13)	0.9935	0.4765	0.9977
20 % TEC	16.59(0.20)	0.9975	0.4339	0.9973
20 % DBP	16.25(0.11)	0.9964	0.4281	0.9992

Table 28 The k (Higuchi constant) and n (diffusion exponents) value of Kollidon® SR with 10 % and 20 % plasticizer prepared by method IV at room temperature

Formulation	k ($\%hr^{-1/2}$)(SD)	r^2	n	r^2
0 % plasticizer	20.49(0.13)	0.9952	0.4307	0.9960
10 % TEC	15.04(0.12)	0.9968	0.4384	0.9989
10 % DBP	13.32(0.17)	0.9921	0.4001	0.9966
20 % TEC	12.91(0.12)	0.9908	0.4001	0.9966
20 % DBP	14.16(0.11)	0.9948	0.4102	0.9972

The comparison of drug release profiles of Eudragit® RS matrices at different processing temperature are shown in Figures 51-53. Higuchi constants are shown in Figure 57 and Table 29. The drug release profiles of Kollidon® SR matrices at different processing temperature are shown in Figures 54-56. Higuchi constants are shown in Figure 58 and Table 30.

Eudragit® RS and Kollidon® SR are the thermoplastic material, it will soften and become pliable when heated above its glass transition temperature. In the formulation without plasticizer, thermal granulation at 60°C was sufficient to significantly decrease in the Higuchi constants from the process at room temperature. Thermal granulation at 80°C subsequently decreases in drug release rate. When 20 % plasticizer was incorporated into Eudragit® RS system, the Higuchi constants at 60°C was slightly lower than the process at room temperature and significantly decrease at 80°C.On the other hand, the Higuchi constants of Kollidon® SR matrices tablet from thermal granulation at 60° C and at 80° C significantly decrease compared to the process at room temperature and exhibited comparative between both the processing temperature at 60° C and at 80°C

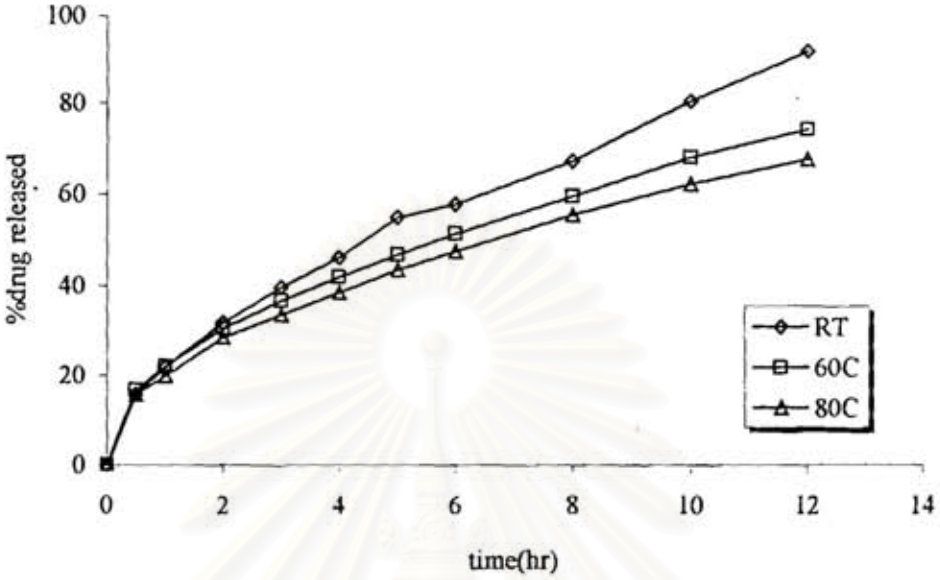

Figure 51 The release profiles of theophylline released from Eudragit® RS without plasticizer prepared by method IV at room temperature (RT), 60°C, 80°C

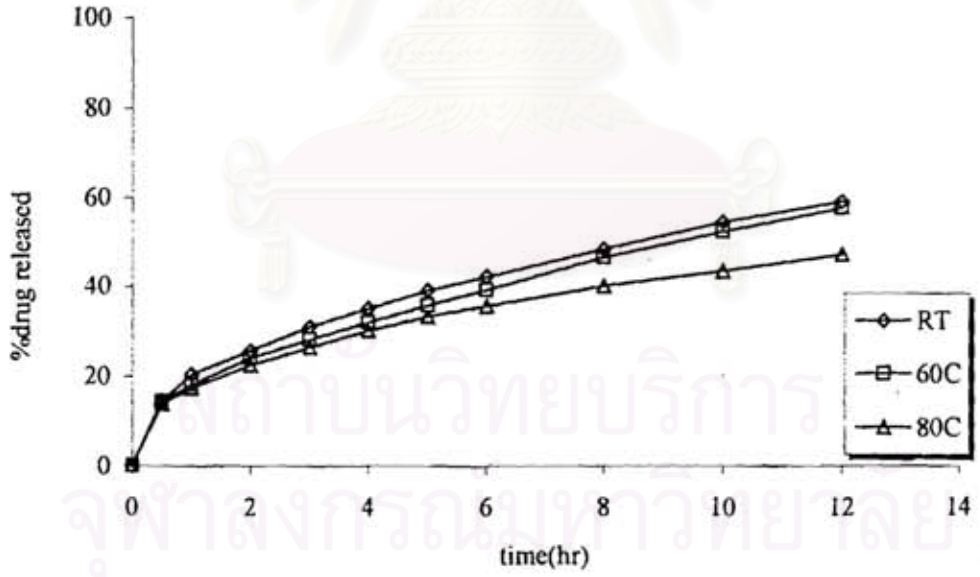

Figure 52 The release profiles of theophylline released from Eudragit® RS with 20 % TEC prepared by method IV at room temperature(RT), 60°C, 80°C

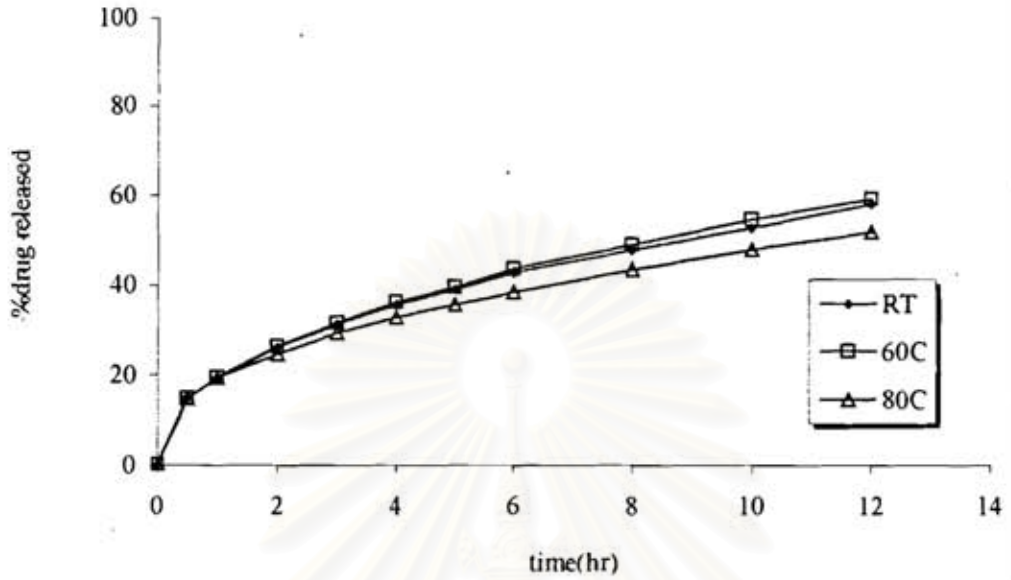

Figure 53 The release profiles of theophylline released from Eudragit® RS with 20 % DBP prepared by method IV at room temperature(RT)., 60°C, 80°C

Table 29 The effect of processing temperature on k (Higuchi constants) and n (diffusion exponents) value of Eudragit® RS with 20 % plasticizer prepared by method IV

Formulation	Processing temperature	k(%hr$^{-1/2}$)(SD)	r^2	n	r^2
0 % Plasticizer	RT	26.07(0.11)	0.9905	0.5314	0.9978
	60°C	21.05(0.25)	0.9988	0.4605	0.9988
	80°C	19.25(0.21)	0.9991	0.4589	0.9968
20 % TEC	RT	16.59(0.15)	0.9975	0.4377	0.9974
	60°C	15.93(0.13)	0.9970	0.4487	0.9963
	80°C	13.09(0.10)	0.9909	0.3956	0.9978
20 % DBP	RT	16.25(0.15)	0.9964	0.4281	0.9992
	60°C	16.69(0.008)	0.9961	0.4371	0.9992
	80°C	14.31(0.10)	0.9914	0.3942	0.9989

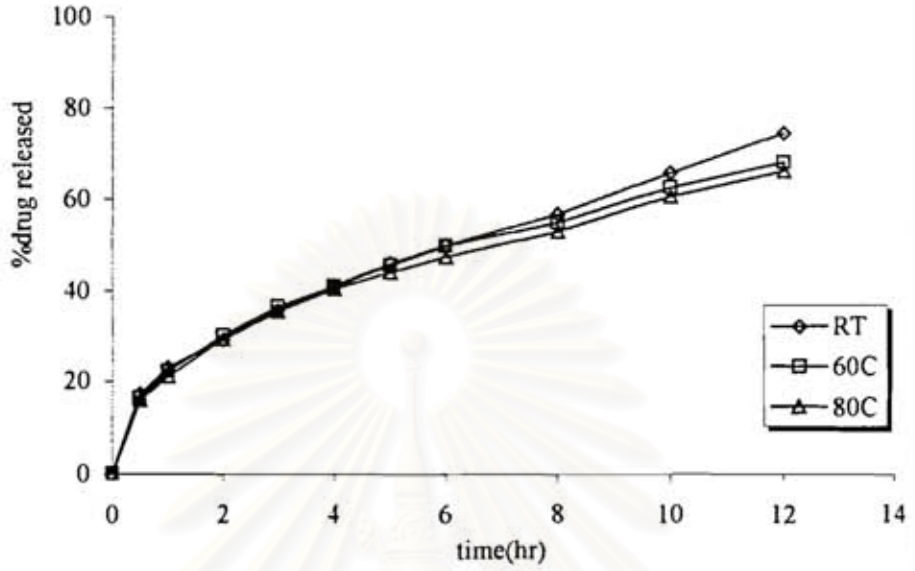

Figure 54 The release profiles of theophylline released from Kollidon® SR without plasticizer prepared by method IV at room temperature(RT), 60°C, 80°C

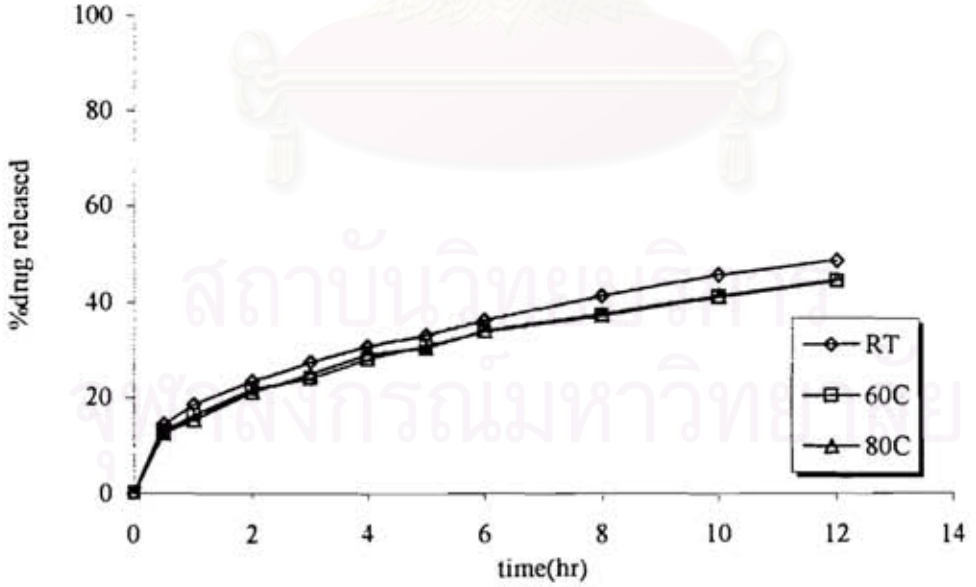

Figure.55 The release profiles of theophylline released from Kollidon® SR with 20 % TEC prepared by method IV at room temperature(RT), 60°C, 80°C

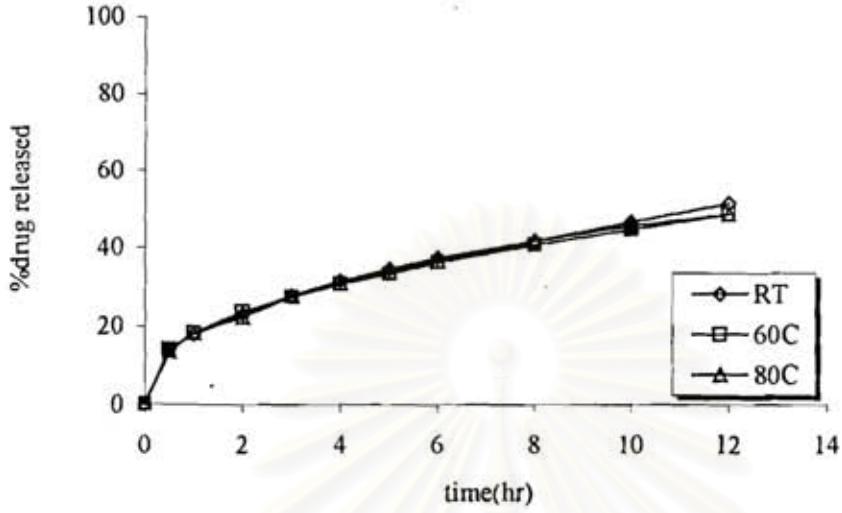

Figure 56 The release profiles of theophylline released from Kollidon® SR with 20 % DBP prepared by method IV at room temperature(RT) , 60°C, 80°C

Table 30 The effect of processing temperature on k (Higuchi constant) and n (diffusion exponent) value of Kollidon® SR with 20 % plasticizer prepared by method IV

Formulation	Processing ttemperature	k(%hr$^{-1/2}$)(SD)	r^2	n	r^2
0 %	RT	20.48(0.19)	0.9952	0.4417	0.9998
	60°C	19.18(0.13)	0.9975	0.4438	0.9996
	80°C	18.56(0.11)	0.997	0.4441	0.999
20 % TEC	RT	13.43(0.17)	0.9901	0.3827	0.9965
	60°C	12.24(0.22)	0.9903	0.3884	0.9958
	80°C	12.49(0.11)	0.9921	0.4000	0.9967
20 % DBP	RT	14.16(0.11)	0.9948	0.4102	0.9972
	60°C	13.32(0.23)	0.9903	0.3874	0.9987
	80°C	13.67(0.10)	0.9926	0.4056	0.9969

The Higuchi constants of matrices with plasticizer prepared by directly compressed matrices tablet at room temperature were similar to the Higuchi constants at 60°C except the formulation without plasticizer which the Higuchi constants of direct compression matrices at room temperature was faster than the thermal granulation at 60° C. The Higuchi constants of direct compression of theophylline and Eudragit® RS without plasticizer were 27 % $hr^{-1/2}$, which higher than the process at 60°C (21.05 % $hr^{-1/2}$) and decreased to 19.25 % $hr^{-1/2}$ in the processing at 80°C (Figure 57). The Higuchi constants of directly compressed of Kollidon® SR matrices at room temperature, 60°C and 80°C were 20.48 % $hr^{-1/2}$, 19.18 % $hr^{-1/2}$ and18.56 % $hr^{-1/2}$, respectively (Figure 58).

The diffusion exponent of the processing temperature at 80°C and at room temperature was below 0.5 for all formulation. These values indicated that diffusion was the mechanism of drug release for all formulations.

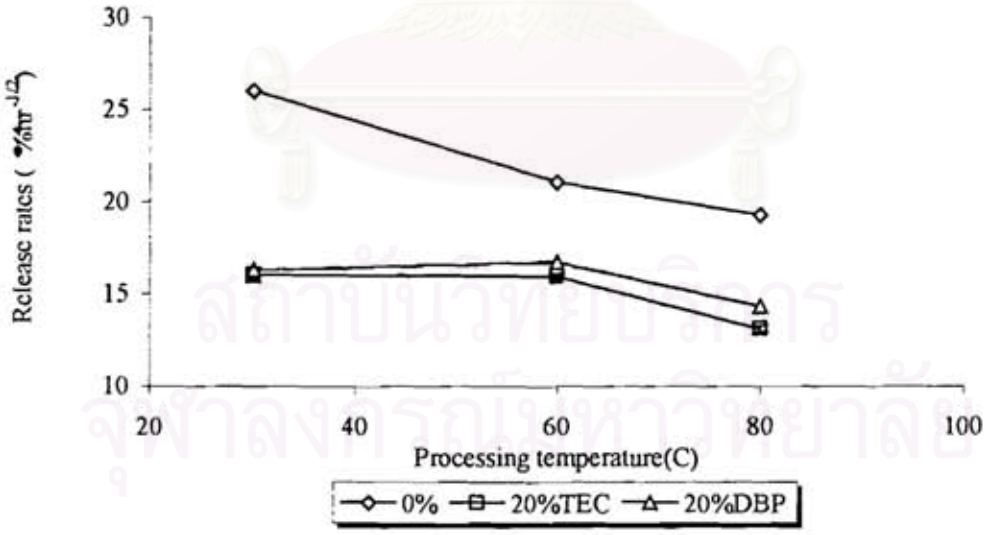

Figure 57 The effect of processing temperature on Higuchi constant from Eudragit® RS matrices

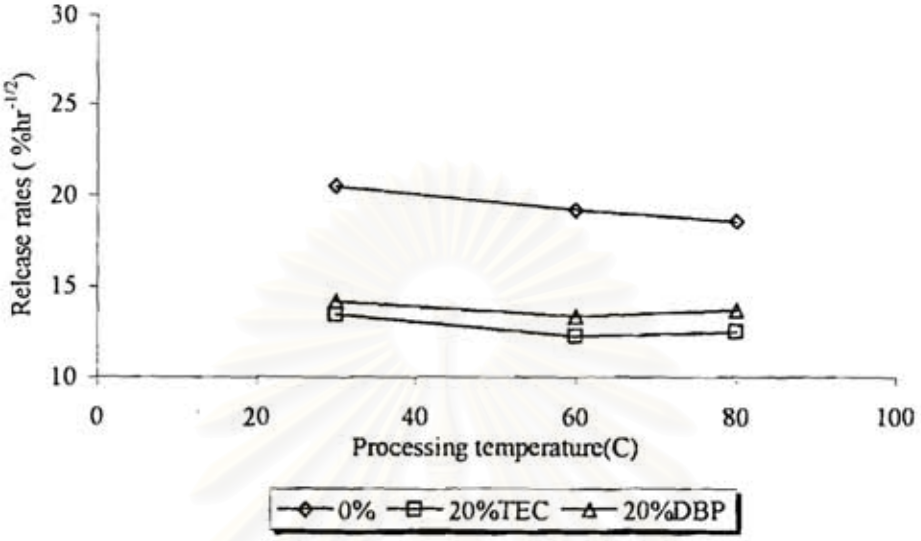

Figure 58 The effect of processing temperature on Higuchi constant from Kollidon® SR matrices

The Higuchi constants of Eudragit® RS matrices plasticized with 20 % TEC or 20 % DBP was significantly decreased when the thermal granulation was at 80°C. The influence of processing temperature and the amount of plasticizer on the drug release profiles from polymeric dosage form can be explained by the free volume theory, since the transport of materials in a closely packed system depend primarily on the degree of the entanglement, or the free volume of the system. The thermal processing of the polymer will increase the degree of entanglement and decrease the free volume of the system to cause a decrease in permeability of the polymer. The drug release rate decreased since the temperature of the process enhance polymer intermolecular entanglement inside the granules.

Kidokoro et al (2000) and Zhu et al (2002) reported the effect of thermal processing on drug release from Eudragit® RSPO with ibuprofen and chlorpheniramine maleate. Which the matrix tablets prepared by high shear hot melt granulation, the speed of blade was 1,000-1,500 rpm and the temperature of the process was 60°C and 70°C. In this study, although the processing temperature was 60°C, which higher than the Tg of

Eudragit® RS and Kollidon® SR with 10 % plasticizer, the drug release rate slightly decreased. This result might be caused by an insufficiency of process and heat from the jacket and blade agitation during granulation to introduce the thermal energy need to enhance the drug particle bound to polymer. The heat transfer from the circulation water and the blade rotation speed were the important factors that affected the formation of granules. In addition, it lacked of the shear force, which promoted a homogenous mixing of active substance and polymer. The hot melt extrusion, the material transfer through the barrel by movement of screw and require high temperature and pressure to process the powder blend into the extruded tablets. The polymer melt is formed in the barrel, the heat from the heating devices and the shear force is the important factor in determining the final product.

Azarmi et al (2002) and Yueon et al. (2002) found that the temperature at 60°C during high shear hot melt granulation was not insufficiency but the temperature at 60°C and 70°C with the following 24 hrs of thermal treatment reduction dramatically in drug release. This could be due to a specific time required for the penetration of heat into the granules. The effect of thermal treatment of the granules or tablet is similar to that of film formation during coating of dosage forms using aqueous polymer dispersions. The effect of thermal treatment on the drug release rate were attributed to the polymer chain movement and inter diffusion of the polymer chains in the matrix, which cause a better coalescence of the polymer particles to form a fine network and a matrix with lower porosity and high tortuosity. In this way, the drug surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug.

Zhu. et.al. (2002) also found that the influence of thermal treatment was enhanced as the time of post-processing thermal treatment time. After 24 hour of storage tablet containing 4 % TEC in the Eudragit® RS prepared by high shear hot melt granulation at 60°C, further decreased the drug release rate was observed. For Kollidon® SR matrix, a post- compression curing step also affected the release rate of tablets (Shao et al, 2001).

Plasticizer level was found to have a significant effect on the response of drug release from Eudragit® RS coated multiparticulate drug delivery system to curing

conditions. Lower plasticizer level of 10 % was not enough to complete the film formation process even after curing for 168 hr at 60°C. increasing the plasticizer level to 15 and 20 % facilitated the polymeric particle coalescence process and allowed complete film formation within shorter curing time (Hamed and Sakr, 2003).

When the matrix tablets were taken to dissolution medium, the temperature of the experiment was 37°C which above the glass transition temperature of Eudragit® RS and Kollidon® SR with 20 % plasticizer. Resulting the polymer exhibit in rubbery state during the dissolution test. The matrix tablets maintained their original shape throughout the dissolution process due to the sticky of Eudragit® RS and Kollidon®SR granules at 37 °C, hence the drug release rate from matrix tablet containing Eudragit® RS100 and Kollidon® SR with 20 % plasticizer from direct compression at room temperature and the process temperature at 60 °C were similarly. The drug release rate of direction compression of theophylline and Eudragit® RS100 at room temperature without plasticizer was higher than the formulation with thermal process and found erodable matrix.

Van der voort Maarschalk et al(1998). found the relationship of tablet strength as a result of relaxation phenomena on the basis of the stress-deformation curve,which indicated that the tablet porosity is the final result of a relaxation propensity that creates a porous structure and a resistance against porosity creation. The amount of energy stored during densification is determined from the difference between the glass transition temperature and the tableting temperature. The energy is manifested as the stress relaxation propensity of material. Large stress relaxation yields porous and consequently weak tablets. At a low temperature difference (tableting temperature is much lower than the glass transition temperature), the amount of energy stored is large. A decreasing in glass transition temperature resulted in decrease in store energy. Consequently, production of less porous and stronger tablet is possible. From the data it is concluded that, compaction tablet at a temperature below the glass transition temperature resulted in amount of stored energy has minimum. Consequently, tablet porosity has a minimum and tablet strength has a maximum. In this study, Eudragit® RS and Kollidon® SR with

plasticizer presence the glass transition temperature below the tableting temperature caused create a minimum porosity, presenting in decrease in drug release rate.

3.3.5The Effect of plasticizer incorporation methods

The plasticizer was incorporated into Eudragit® RS and Kollidon® SR by 4 methods as described in Chapter II. The granulation method at 60°C can affect the granule characteristics and the dissolution of the final matrices tablet. A Higuchi constant, which was influenced by the differences in processing, are shown in Figures 59-60 and in Tables 31-32.

By dissolving polymer in the solvent (acetone/ethanol 1:1) then plasticizer was incorporated into the polymer solution which influenced the granules formation then affect percent drug release which found in plasticizer incorporation method I (wet granulation). For method III. (Spray plasticizer to polymer), plasticizer was diluted with ethanol then spray to powder mixing of drug, polymer and lactose. Thus the first 2 methods, drug was mixed with polymer and plasticizer by wet granulation. Whereas, by method II (ground polymer) and IV (spray dried), the solvent was evaporated by hot air oven and spray drying to obtained the polymer powder with plasticizer before mixing to the drug. From Figure 59 and Table 31 show the effect of plasticizer incorporation methods on Higuchi constants from Eudragit® RS matrix system, which demonstrate that the pattern of drug release profiles from method I and III was slower than method II and IV. The slowest drug release was found from method I for all formulations.

Figure 60 and Table 32 shown the effect of plasticizer incorporation methods on Higuchi constants from Kollidon® SR matrix system. The fastest drug release rate was found in method II. The difference behavior from Eudragit® RS system was observe in the plasticizer incorporation method IV. In the formulation without plasticizer, Higuchi constants from method I and III was slower than method IV, when 10 % and 20 % plasticizer was incorporated, the Higuchi constants from method IV was slower than method I and III.

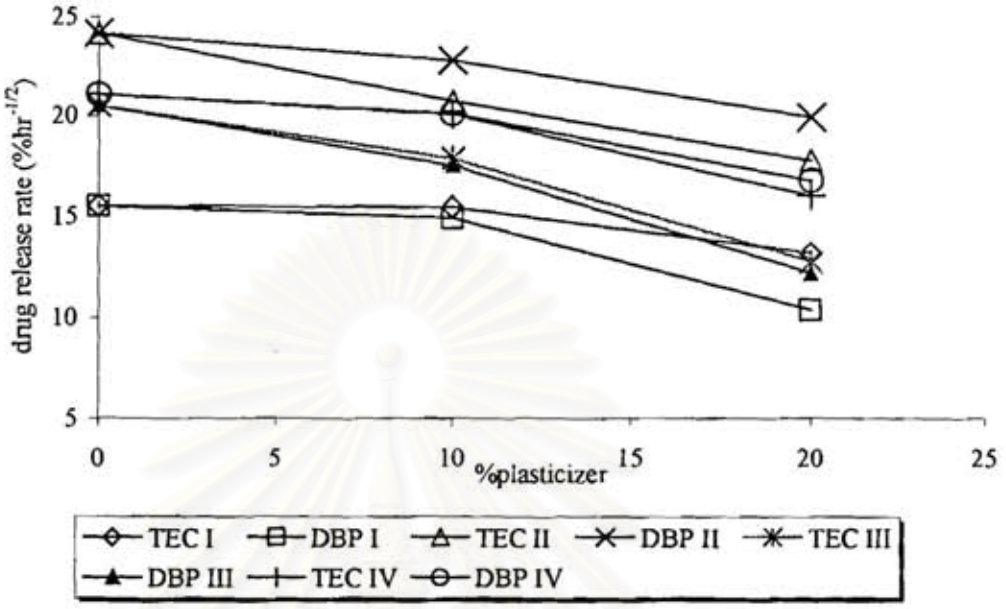

Figure 59 Effect of plasticizer incorporation method on Higuchi constant from Eudragit® RS matrices at 60°C

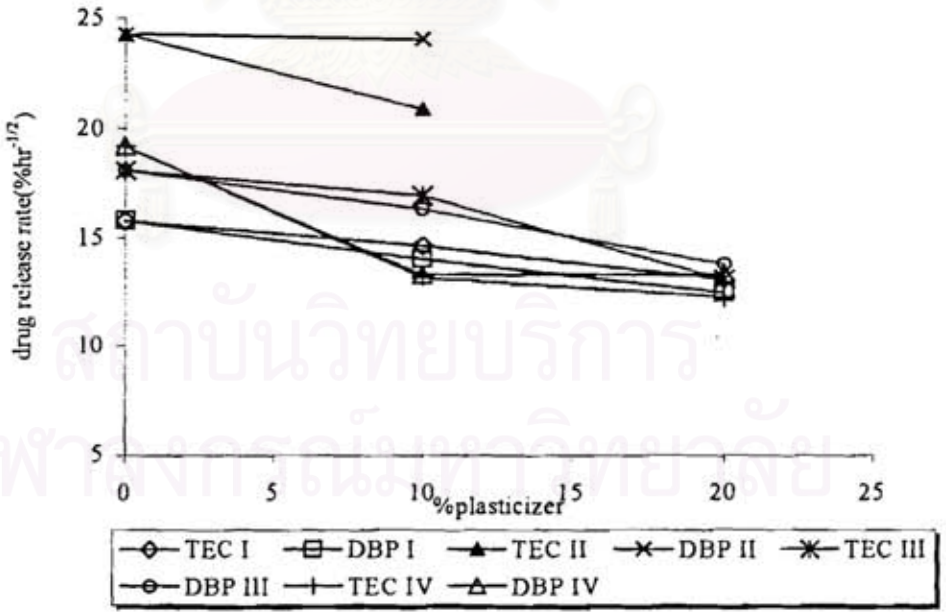

Figure 60 Effect of plasticizer incorporation methods on Higuchi constant from Kollidon® SR matrices at 60°C

Table 31 The effect of plasticizer incorporation methods into Eudragit®RS at 60°C

Formulation	Method	Higuchi constant (%$hr^{-1/2}$)(SD)	r^2
0 % Plasticizer	I	15.51 (0.21)	0.9956
	II	24.17 (0.29)	0.9969
	III	20.49 (0.23)	0.9985
	IV	21.06 (0.34)	0.9988
10 % TEC	I	15.46 (0.23)	0.9973
	II	20.74 (0.17)	0.9983
	III	17.88 (0.15)	0.9960
	IV	20.07 (0.24)	0.9936
10 % DBP	I	14.90 (0.18)	0.9962
	II	22.84 (0.16)	0.9982
	III	17.54 (0.20)	0.9962
	IV	20.13 (0.15)	0.9912
20 % TEC	I	13.17 (0.12)	0.9939
	II	17.79 (0.23)	0.9931
	III	12.76 (0.18)	0.9881
	IV	16.03 (0.16)	0.9962
20 % DBP	I	10.37 (0.14)	0.9938
	II	19.95 (0.16)	0.9936
	III	12.18 (0.19)	0.9000
	IV	16.79 (0.15)	0.9976

(I = wet granulation, II = ground polymer, III= spray plasticizer to polymer, IV= spray dried)

Table 32 The effect of plasticizer incorporation methods into Kollidon® SR at 60°C

Type and amount of plasticizer	Method	Higuchi constant ($\%hr^{-1/2}$)(SD)	r^2
0 %	I	15.80 (0.31)	0.9981
	II	24.27 (0.24)	0.9967
	III	18.08 (0.29)	0.9986
	IV	19.18 (0.38)	0.9975
10 % TEC	I	14.62 (0.18)	0.9977
	II	20.86 (0.14)	0.9944
	III	16.92 (0.25)	0.9976
	IV	13.17 (0.17)	0.9892
10 % DBP	I	14.01 (0.15)	0.9968
	II	24.05 (0.14)	0.9974
	III	16.31 (0.23)	0.9976
	IV	13.28 (0.15)	0.9922
20 % TEC	I	13.08 (0.14)	0.9966
	III	13.08 (0.17)	0.9954
	IV	12.23 (0.20)	0.9903
20 % DBP	I	12.46 (0.13)	0.9960
	III	13.78 (0.18)	0.9983
	IV	13.32 (0.17)	0.9903

(I = wet granulation, II = ground polymer, III= spray plasticizer to polymer, IV= spray dried)

The particle size of polymer powder with plasticizer was found to affect the drug release especially in Kollidon® SR matrix system. Zhang and McGinity (2000) reported the influence of granule size on the release rate of theophylline from the compressed tablet containing the hot melt extrudes theophylline/PVAc. As the size of granules was increase, there was a significant decrease in the release rate of theophylline. In this study, the spray dried Kollidon® SR with plasticizer gave mean diameter range from 20 μm to 30 μm which smaller than the spray dried Eudragit® RS 100(40 μm to 70 μm) have a tendency to bind with the theophylline which having mean diameter size of 45μm. This result indicated that why drug release rate when using Kollidon® SR with 10 % TEC or DBP and 20 % TEC prepared by method IV was slower than method I. However, the drug release rate from Eudragit® RS with 10 % and 20 % TEC or DBP prepared by method IV was faster than method I

Conflicting results have been reported in the literature regarding the effect of plasticizer incorporation process from Eudragit®RS system. Some investigators reported an increase in drug release when using triethyl citrate and others reported the different results. The difference of drug release rate between method I, III (wet granulation and spray plasticizer into polymer) and method II, IV (ground polymer and spray dried)in Eudragit® RS matrix system could be explained by the effect of processing. For method I and III polymer was binding to theophylline particle by solvent produced a film layer and found the water soluble plasticizer diffused from the tablet into the dissolution media, which, enhancing drug release rate. For the preparation prepared by method II and IV, plasticizer was incorporated into polymer and ground into powder by blending and spray drying before mixing with theophylline by thermal granulation process. The porous structures were formed by these methods.

Efentakis and Buckton(1990) studied the drug release from the indomethacin matrices which prepared using Eudragit® RS . Two type of formulation were considered, one was a directly compressed powder mixture which produced a matrix system, and the other was prepared by wet granulation, such that the drug was to some extent sealed within a cast film of the polymer. Drug release from the wet granulation system was

much slower than the directly compress matrix. The directly compressed system will inevitably have a more open porous structure than the cast film produced during granulation. The release of drug from the less porous system is expected to have a higher entropic hindrance as molecules will have to be ordered to pass through the membrane. Such entropic hindrance can be used to explain the greatly reduced rate of drug release from the granulated, as compared to the directly compressed product.

The plasticizer influenced the drug release rate significantly due to the solubility in water. The drug release rate of matrices with 20 % TEC was faster than 20 % DBP in method I of both Eudragit® RS and Kollidon® SR. Plasticizer, which dissolved in organic solvent before thermal granulation process (method I; wet granulation and III; spray plasticizer to polymer), was located in the cast film and leach during the dissolution test. Triethyl citrate, the water-soluble plasticizer, leaches from the matrix into the dissolution media and increase in drug release rate as a result of channel formation in the tablets. In contrast, dibutyl phthalate, the water insoluble plasticizer functions as a water insoluble additive decrease in the release rate of theophylline.

Previous research has demonstrated that triethyl citrate, the water-soluble plasticizer, diffused from the CPM-Eudragit RSPO hot melt extrudates.(Zhu et al,2002) dry polymer powder coating for Eudragit® RS (Pearnchob.and Bodmeier,2003) and polymeric films prepared from aqueous colloidal polymer dispersion. Bodmeier and Paeratakul(1992) had previously reported the diffusion of TEC into aqueous medium from cast films prepared from aqueous colloidal polymer dispersions. The leaching of plasticizer from cast film of Eudragit RS/RL can result in dramatic changes in drug release.

However, the effect of TEC for direct compressed tablets prepared by thermal granulation, the influence of plasticizer on the entanglement of theophylline in the Eudragit® RS was more dramatic than the effect of the leaching of plasticizer.(Zhu et al,2002 Wu and McGinity 2001, Kidokoro et al 2001,Sarisuta and Mahahpunt 2004, Rey et al 2000, Pearnchob.and Bodmeier,2003 (b), Maejima and McGinity, 2001) As seen in this study, The drug releases rate of matrices with water-soluble plasticizer, 20 % TEC,

was slower than water insoluble plasticizer, 20 % DBP in method II (ground polymer)and IV (spray dried) of both Eudragit® RS and Kollidon.®SR.

3.3.6 Effect of compression force

The effect of compression force on theophylline release was studied from the formulation of Eudragit® RS and Kollidon® SR with 20 % TEC and 20 % DBP prepared by method I and IV. The compression force in this study was 500, 1,000 and 1,500 psi. The Hydraulic press apparatus was used to compress the granules into tablets. Figures 61-64 and Tables 33-34 represents the effect of compression force on drug release rate.

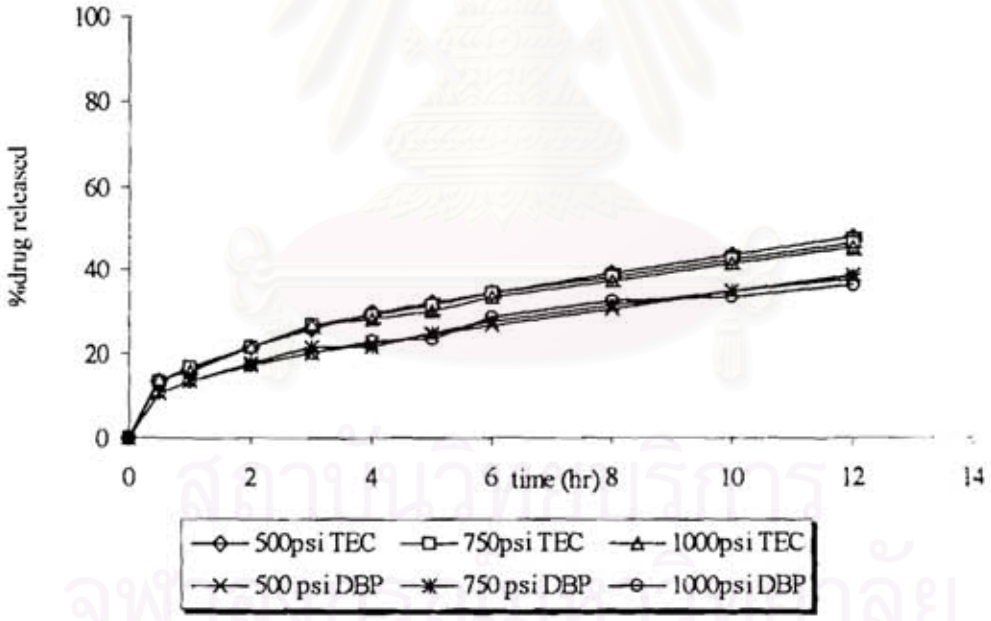

Figure 61 Effect of compression force on dissolution profiles of Eudragit® RS with 20 % TEC and 20 % DBP prepared by method I (wet granulation)

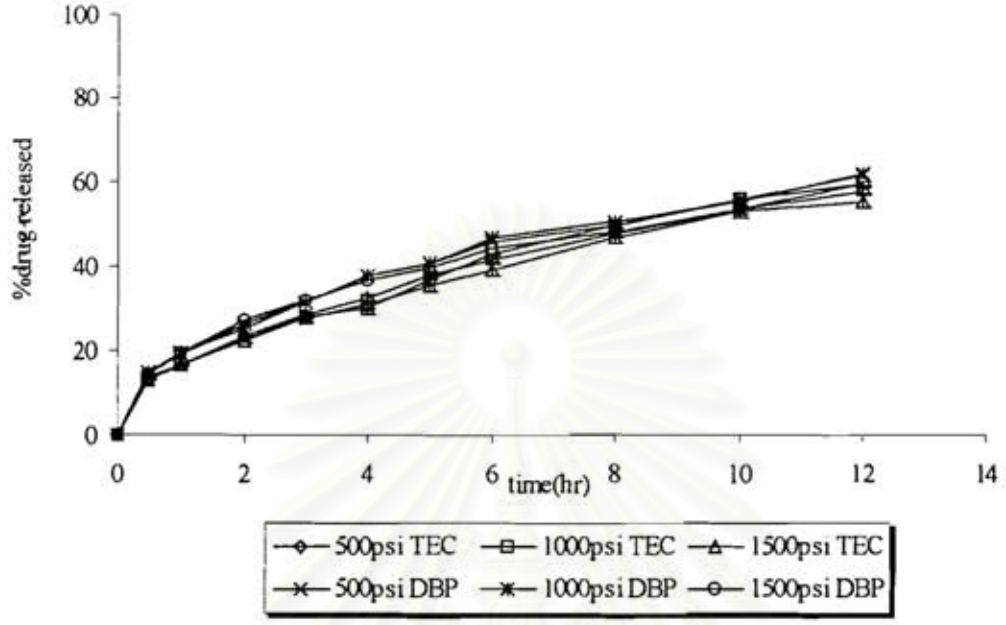

Figure 62 Effect of compression force on dissolution profiles of Eudragit® RS with 20 % TEC and 20 % DBP prepared by method IV (spray dried)

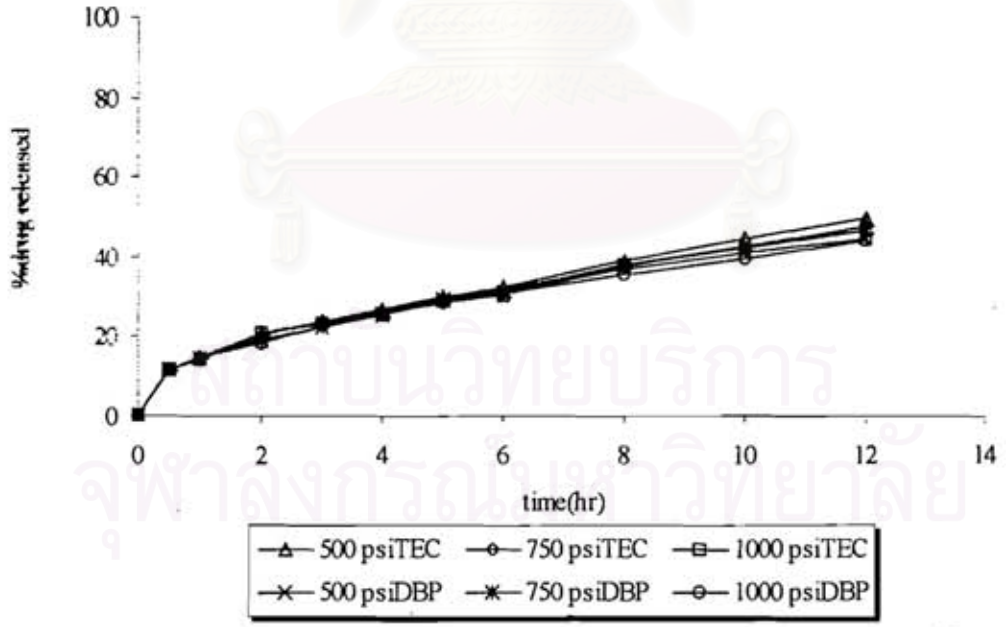

Figure 63 Effect of compression force on dissolution profiles of Kollidon® SR with 20 % TEC and 20 % DBP prepared by method I (wet granulation)

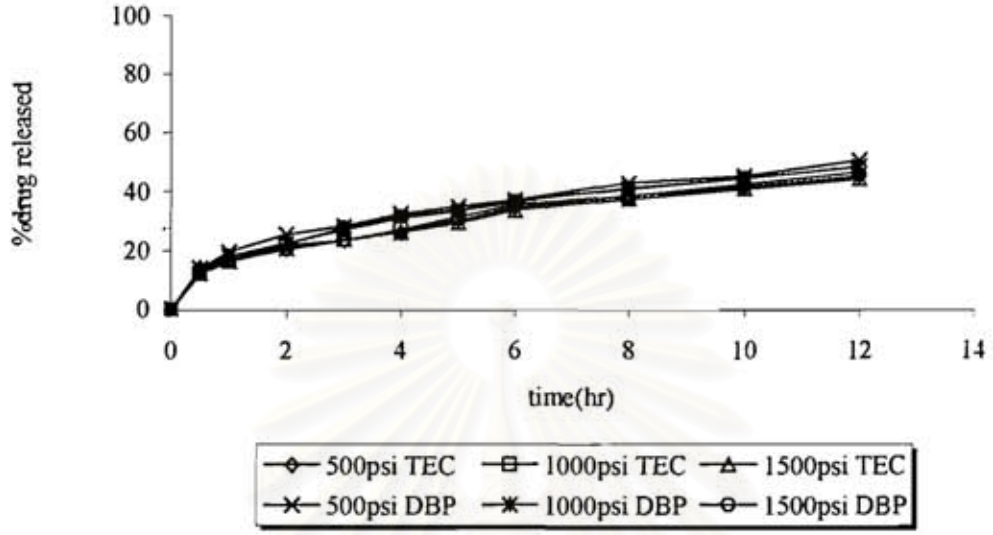

Figure 64 Effect of compression force on dissolution profiles of Kollidon® SR with 20 % TEC and 20 % DBP prepared by method IV (spray dried)

Table 33 Effect of compression force on Higuchi constant of Eudragit® RS prepared by method I and IV at 60°C

Method	Type and amount of plasticizer	Compression force (psi)	Higuchi constant ($\%hr^{-1}$)
I	20 % TEC	500	13.17
		750	12.72
		1000	12.44
I	20 % DBP	500	10.37
		750	10.52
		1000	9.87
IV	20 % TEC	500	16.64
		1000	17.01
		1500	16.06
IV	20 % DBP	500	17.31
		1000	17.54
		1500	16.66

Table 34 Effect of compression force on Higuchi constant of Kollidon® SR prepared by method I and IV at 60°C

Method	Type and amount of plasticizer	Compression force (psi)	Higuchi constant ($\%hr^{-1}$)
I	20 % TEC	500	13.68
		750	13.09
		1000	12.83
I	20 % DBP	500	12.98
		750	12.45
		1000	12.14
IV	20 % TEC	500	12.46
		1000	13.05
		1500	12.30
IV	20 % DBP	500	13.73
		1000	13.42
		1500	13.59

It was observed that when increased in compression force produced a significantly increased in tablets hardness and tablet tensile strength (Figure 29-30 page 71-72) Comparative release profile and Higuchi constants indicated that an increase in compression force slightly decrease in dissolution profile but did not influence the Higuchi constants significantly in both Eudragit® RS and Kollidon® SR matrix system($p > 0.05$). Although, the crushing strengths of matrices increased considerably when increase compression force from 500 to 1,500 psi. It has been previously shown that tablet hardness in the range of 7-15 kg had a minimal influence on the theophylline release profiles from Eudragit® RSPM and Eudragit® L100 matrices (Cameron and., McGinity,1987). Similarly, Sarisuta and Mahahpunt (1994) reported that compaction force as well as tablet crushing strength were not important factors in modifying the release pattern of diclofenac sodium from matrices containing Eudragit® RS, lactose, and Emcompress within the range of 300-600 kg force and 4-10 kg tablet crushing strength. It has been also reported that although increasing the compaction pressure from 56 to 492

MNm^{-2} resulted in a large reduction of pore volume and a shift of pore size distributions towards the small size, this did not influence the water penetration into the compacts and release profiles of aspirin from Eudragit® RS matrices. (Carli et al 1984)

However, according to the technical information by BASF, the compression force did not affect the drug release of Kollidon® SR matrix tablets. An increase in compression forces from 20 kN to 60kN causes a slight linear decrease in the release rate (Fussnegger, 2000)

3.3.7 Effect of dissolution media on drug releases

The theophylline matrices containing Eudragit® RS or Kollidon® SR with 20 % TEC or DBP prepared by method IV (spray dried) at 60°C were investigated for the release profiles in different dissolution media as displayed in Figures 65-68 and the Higuchi constants is show in Table 35. The dissolution media used in this study were phosphate buffer pH 6.8 and hydrochloric acid buffer pH 1.2.

The dissolution profiles of matrix containing 20 % TEC or DBP were similar in both media for the first 6 hours and the 6 hours later found that the dissolution profiles of hydrochloric acid buffer pH 1.2 was slightly faster than phosphate buffer pH 6.8 due to solubility of theophylline was 12.76 mg/ml in acidic medium while 9.03 mg/ml in basic medium (Nokhodchi et al ,1997). Except the formulation of Eudragit® RS with 20 % TEC, the dissolution profile in pH 1.2 was faster than pH 6.8 throughout the course of dissolution test.

However comparative dissolution rate in hydrochloric acid buffer pH 1.2 did not significantly different from phosphate buffer pH 6.8 for both Eudragit® RS and Kollidon® SR matrices ($p>0.05$). These results demonstrated that the dissolution media was not affecting the dissolution profiles and Higuchi constants. McGinity et al (1983) and Reza et al (2003) also reported a similar result that theophylline release from acrylic resin and Kollidon® SR was comparative since the pk_a of theophylline was 8.6. In

addition, two types of polymer are pH independent materials, which was not affected by acid and basic medium.

Table 35 Effect of dissolution media on Higuchi constant of Eudragit® RS or Kollidon® SR with 20 % TEC or DBP prepared by method IV at 60°C

Type of matrix	Type and amount of plasticizer		Higuchi constant (k)(% $hr^{-1/2}$)	r^2
Eudragit® RS	20 % TEC	pH1.2	16.61	0.9950
		pH6.8	15.94	0.9952
	20 % DBP	pH1.2	19.69	0.9951
		pH6.8	19.11	0.9953
Kollidon® SR	20 % TEC	pH1.2	13.41	0.9917
		pH6.8	12.86	0.9904
	20 % DBP	pH1.2	14.41	0.9954
		pH6.8	13.87	0.9945

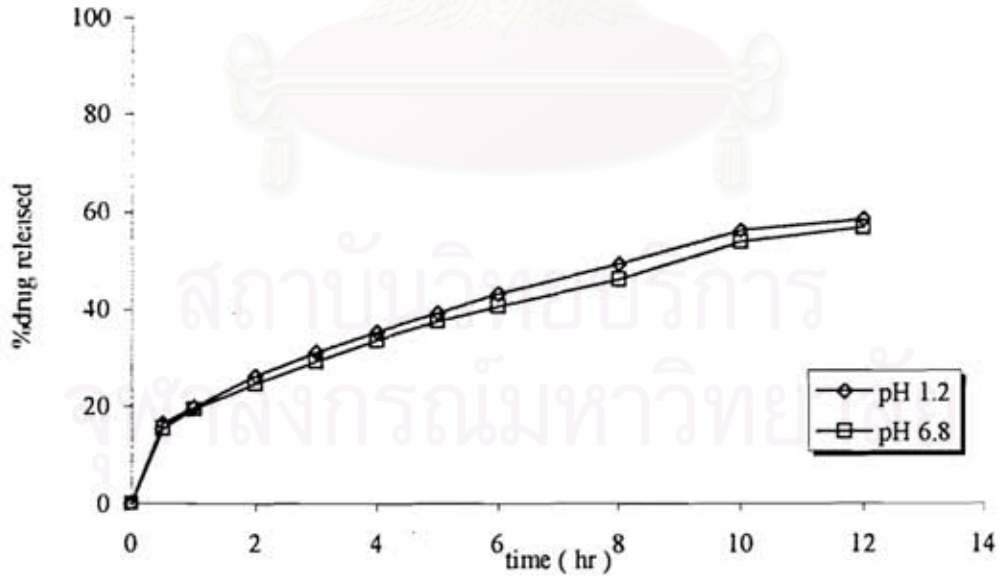

Figure 65 Effect of dissolution media on dissolution profiles of Eudragit® RS with with 20 % TEC prepared by method IV

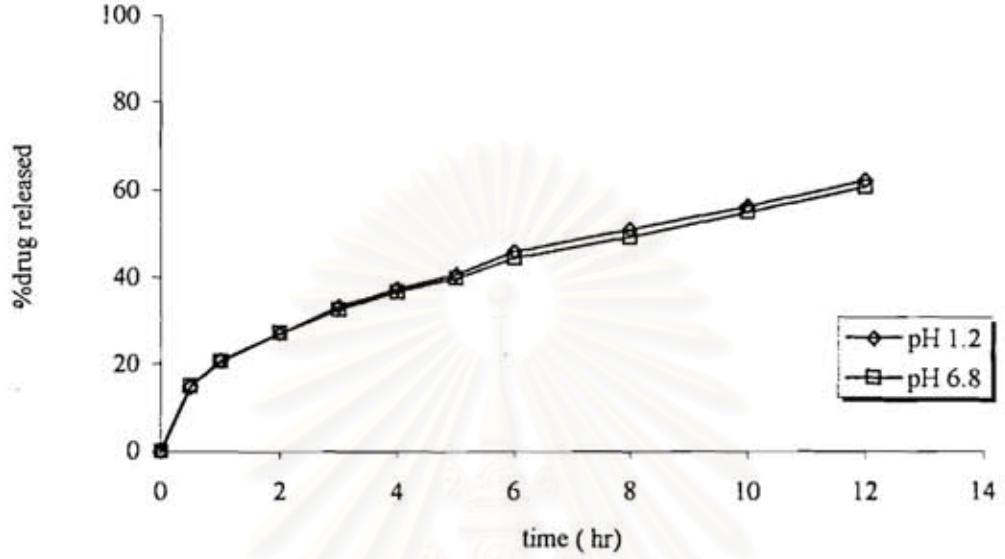

Figure 66 Effect of dissolution media on dissolution profiles of Eudragit® RS with 20 % DBP prepared by method IV

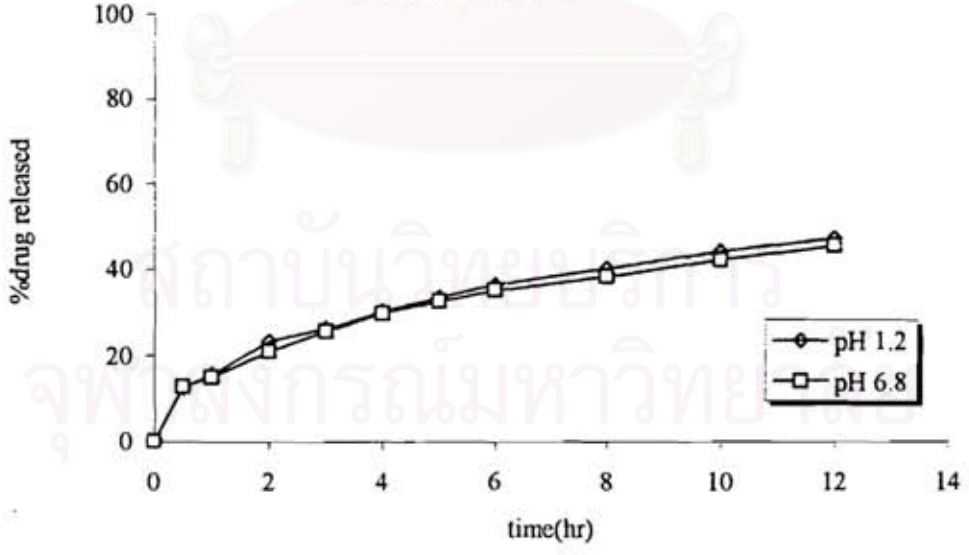

Figure 67 Effect of dissolution media on dissolution profiles of Kollidon® SR with 20 % TEC prepared by method IV

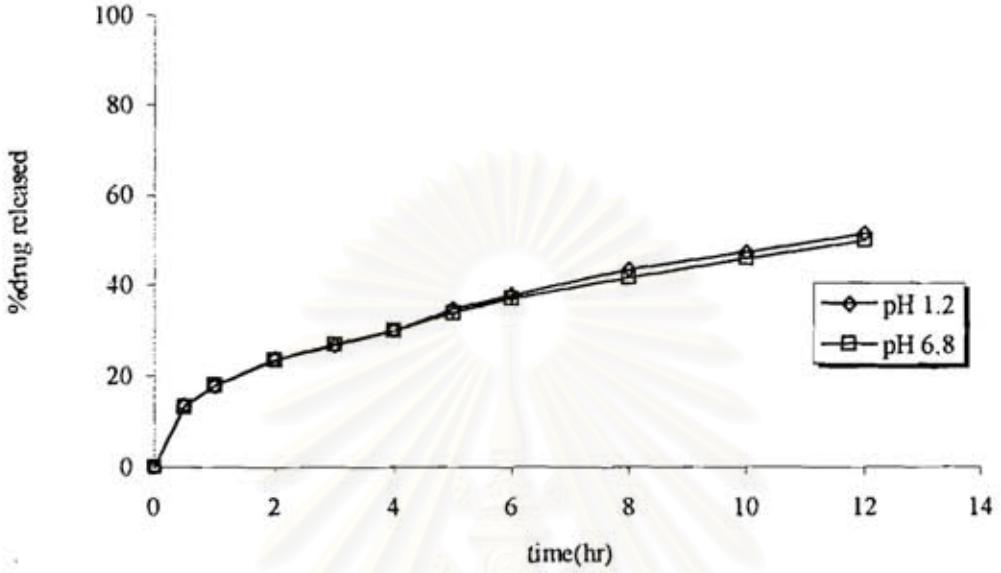

Figure 68 Effect of dissolution media on dissolution profiles of Kollidon® SR with 20 % DBP prepared by method IV

4 Evaluation of physicochemical properties

4.1 The power X-ray diffraction

The x-ray patterns of Eudragit® RS, Kollidon® SR, theophylline, lactose and physical mixture of these materials are shown in **figure 69** and **71.** Eudragit® RS and Kollidon® SR are amorphous in nature due to the absence of complete steroregularity and the presence of bulky side groups. The x-ray diffraction patterns of physical mixture shows a numerous distinct peaks, indicating a crystalline nature of the drug. Characteristic peaks of theophylline appeared at a diffraction angle of 2θ at .the presence of diffraction peaks in the physical mixture demonstrated that the presence of unsolved crystalline drug dispersed.

When the powder mixing of theophylline, lactose and Eudragit® RS100 or Kollidon® SR with 10-20 % TEC or DBP was incorporated into the polymer by method 4 and processed by thermal granulation, the x-ray diffraction patterns of these plasticizer in the granules of Eudragit® RS and Kollidon® SR are shown in **figure70** and **72.** The diffraction patterns of Eudragit® RS and Kollidon® SR containing TEC or DBP exhibited no sharp peak and was identical to those of the pure polymer, suggesting that the TEC or DBP was dissolved in the polymer.

The diffraction peak of crystalline theophylline appeared at the same positions in all formulations. However, the intensity of the diffraction peaks of theophylline decreased following increase in amount of plasticizer. When the temperature of the process increase to 80°C, there was more decrease in the peak intensity but still found the diffraction peaks of theophylline. These results demonstrated that theophylline are not miscible in the polymer. Suggesting that a solid solution was not formed during hot melt granulation processing.

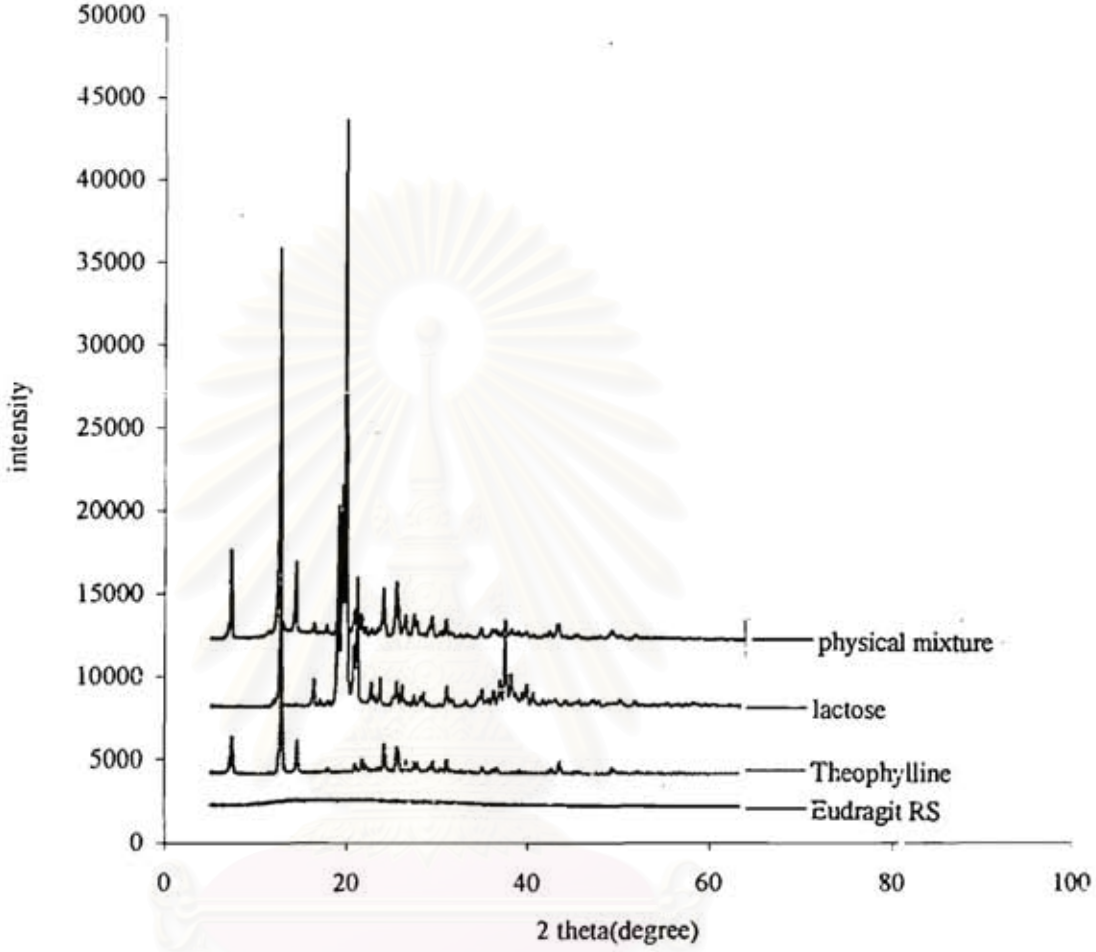

Figure 69 X-Ray diffraction patterns of physical mixture of theophylline and Eudragit® RS

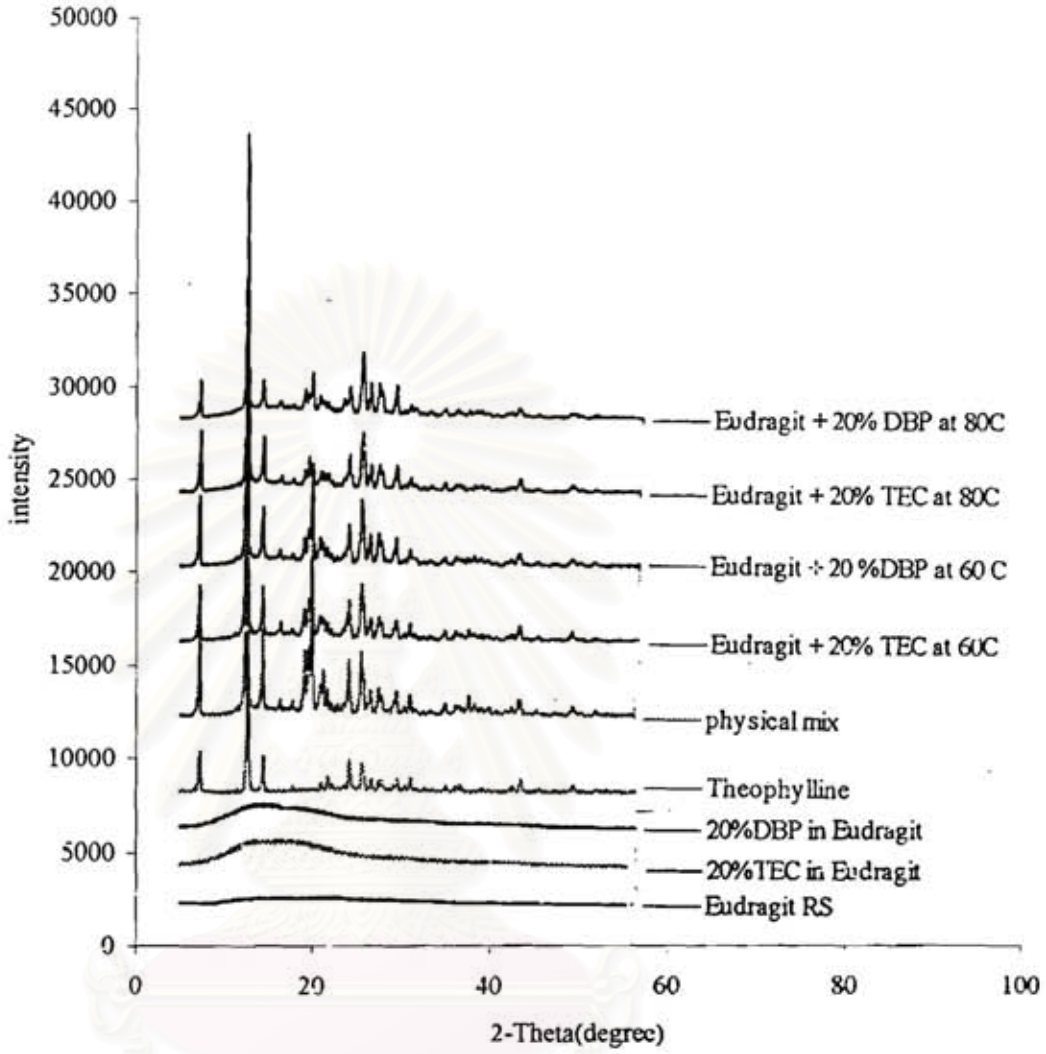

Figure 70 X-ray diffraction patterns of theophylline granules containing Eudragit® RS with 20%plasticizer prepared by method IV

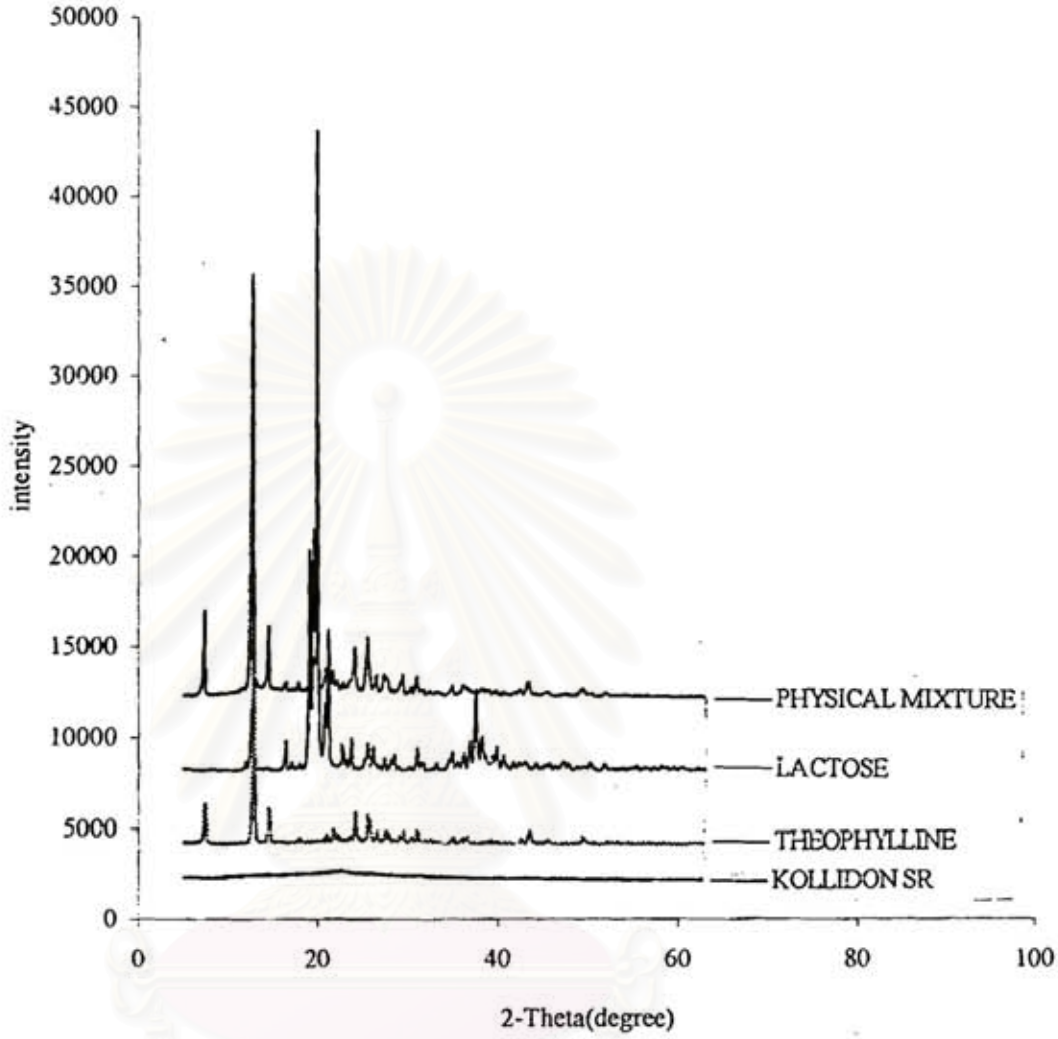

Figure 71 X-Ray diffraction patterns of physical mixture of theophylline and Kollidon® SR

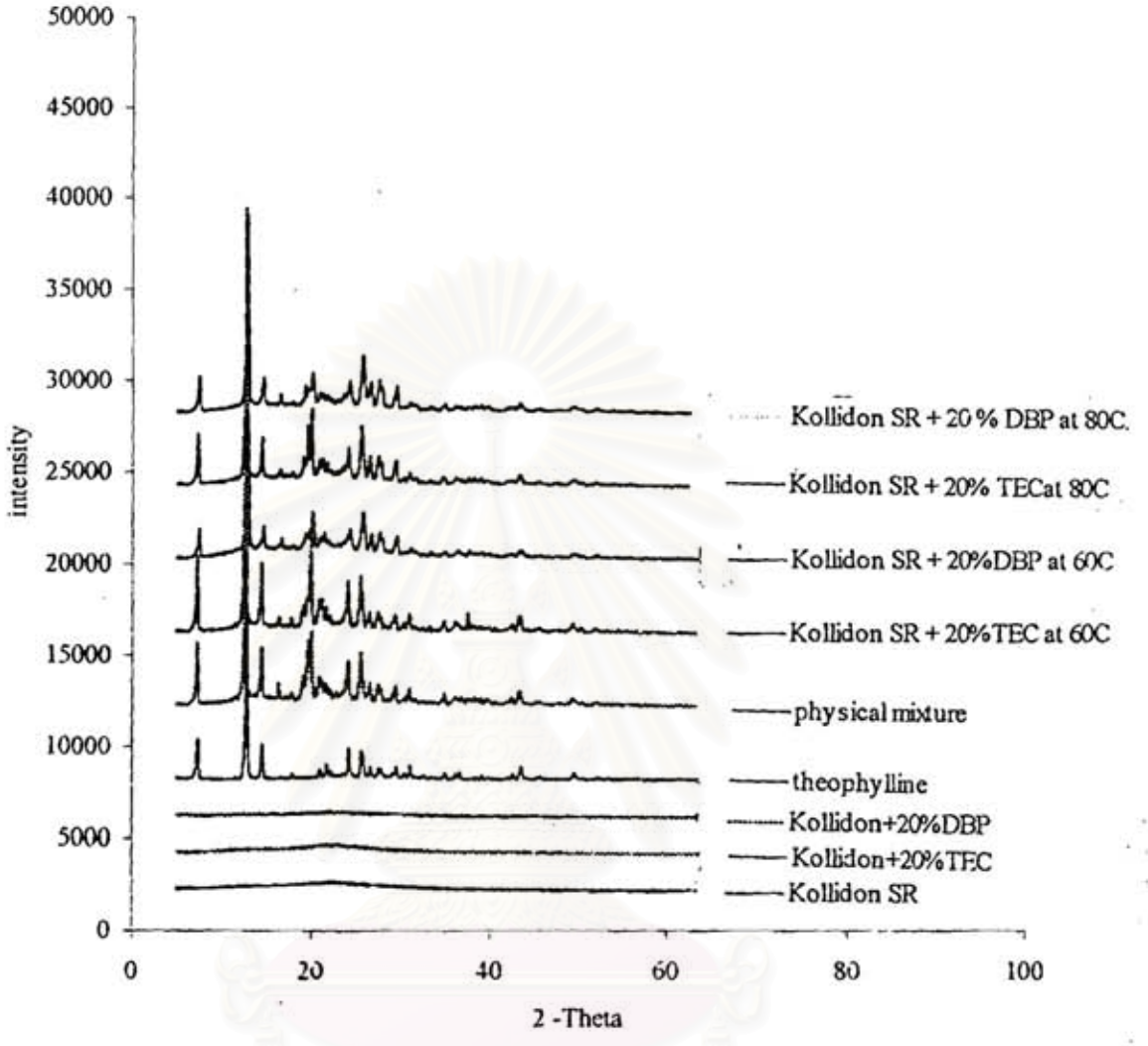

Figure 72 X-ray diffraction patterns of theophylline granules containing Kollidon® SR with 20 % plasticizer prepared by method IV

CHAPTER IV

CONCLUSIONS

Controlled release matrix tablets containing theophylline and Eudragit® RS or Kollidon® SR were successfully prepared by thermal granulation technique.The effect of triethyl citrate (TEC) and dibutyl phthalate (DBP) level, granulation temperature and plasticizer incorporation methods on drug release from matrices tablet were investigated. Plasticizer was incorporated into Eudragit® RS or Kollidon® SR by 4 methods. Based on the finding of this study, the following conclusion could be drawn.

1.Eudragit® RS 100 and Kollidon® SR were plasticized by both TEC and DBP as seen in the differential scanning calorimetry analysis and the plasticization efficiency of TEC was comparable to DBP.

2. The effect of TEC or DBP levels on drug release rates was dependent on the plasticizer incorporation method. As TEC or DBP levels increased, the drug release rates decreased for all formulations. However, the drug release rate from matrix using TEC was faster than DBP for the matrix prepared by method I and III due to TEC leached from the films. Whereas, drug, polymer and plasticizers formed a matrix structure resulting in drug release rate of matrices with TEC prepared by method II and IV was slower than matrices prepared by method I and III.

3.The thermal granulation at 80°C significantly influenced the drug release rate compared to the thermal granulation at 60°C. A significant reduction in drug release rate was found when 10 % and 20 % plasticizer was incorporated into Eudragit® RS matrices prepared by method IV. Whereas, in Kollidon® SR matrices, a significant decrease in drug release rate was found in 10 % plasticizer. An increasing plasticizer level to 20 % did not further decrease in drug release rate from 10 % plasticizer.

4. Morphological studies of the granules revealed drug were adsorbed or adhered on the surface of polymer. This result was agreement with the x-ray diffraction pattern, which demonstrated that a homogenous distribution of drug in the polymer was not found.

5.The drug release data were fitted to the Higuchi equation and the drug release rate constants were calculated and determines to be diffusion-controlled processes for all formulations.

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APPENDICES

APPENDIX A

The concentrations versus absorbances of theophylline in various media were presented in Table 36-38. The calibration curves of theophylline and a linear relationship with the correlation of determination were also in Figures 81.

Table36 Absorbances of theophylline in phosphate buffer pH 6.8 at 270 nm

Concentartio(mcg/ml)	abs(n1)	abs(n2)	abs(n3)	Average (SD)
2.028	0.0842	0.0835	0.0838	0.0838(0.0003)
4.056	0.2189	0.2142	0.2126	0.2152(0.0027)
6.084	0.3377	0.3359	0.3359	0.3365(0.0008)
8.112	0.4589	0.4597	0.4597	0.4594(0.0004)
10.14	0.5881	0.5819	0.5829	0.5843(0.0027)
12.168	0.7142	0.7106	0.7015	0.7087(0.0053)

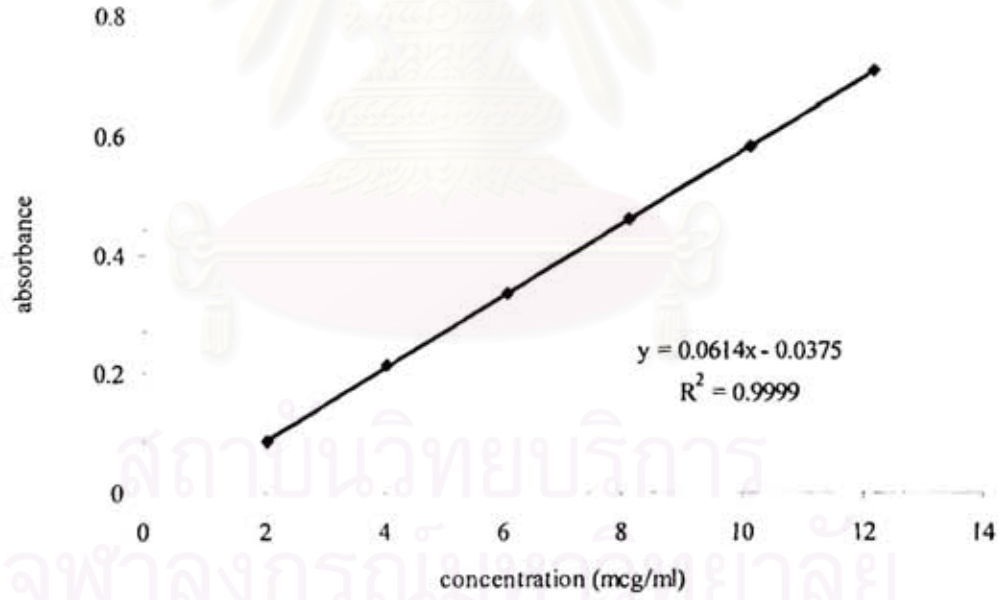

Figure 73 The calibration curve of theophylline in phosphate buffer pH 6.8 at 270 nm

APPENDICES

Appendix A

The concentrations versus absorbances of theophylline in various media were presented in Table 36-38. The calibration curves of theophylline and a linear relationship with the correlation of determination were also in Figures 81.

Table36 Absorbances of theophylline in phosphate buffer pH 6.8 at 270 nm

Concentartio(mcg/ml)	abs(n1)	abs(n2)	abs(n3)	Average (SD)
2.028	0.0842	0.0835	0.0838	0.0838(0.0003)
4.056	0.2189	0.2142	0.2126	0.2152(0.0027)
6.084	0.3377	0.3359	0.3359	0.3365(0.0008)
8.112	0.4589	0.4597	0.4597	0.4594(0.0004)
10.14	0.5881	0.5819	0.5829	0.5843(0.0027)
12.168	0.7142	0.7106	0.7015	0.7087(0.0053)

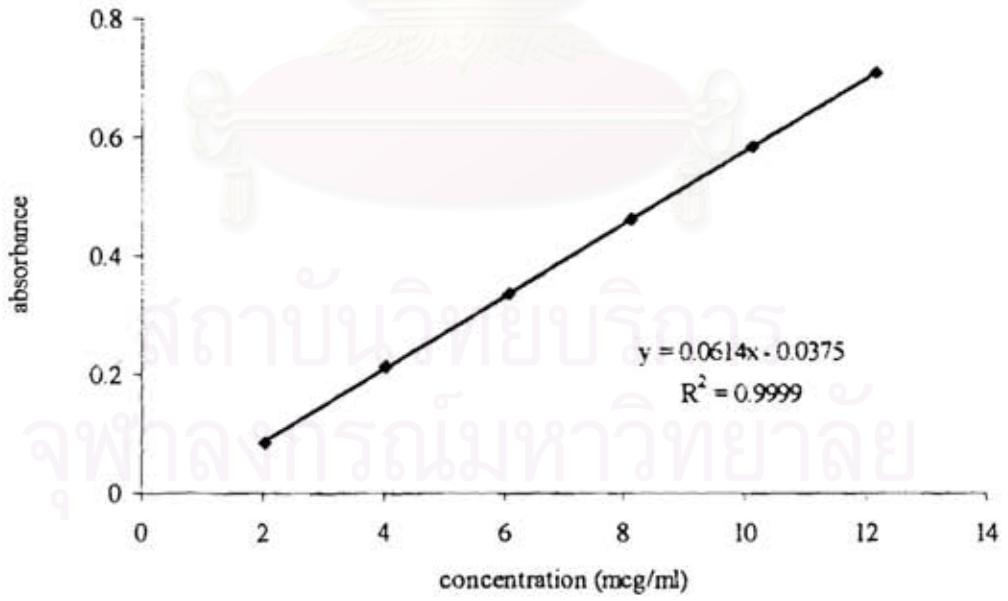

Figure 73 The calibration curve of theophylline in phosphate buffer pH 6.8 at 270 nm

Table 37 Absorbances of theophylline in 0.1 N HCl pH 1.2 at 270 nm

Concentartio(mcg/ml)	abs(n1)	abs(n2)	abs(n3)	Average (SD)
2.0046	0.1322	0.1456	0.1423	0.1399(0.0058)
4.008	0.2445	0.2458	0.2526	0.2476(0.0035)
6.012	0.3468	0.3584	0.3546	0.3532(0.0048)
8.016	0.4498	0.4596	0.4569	0.4554(0.0041)
10.02	0.5624	0.5682	0.5674	0.5660(0.0025)
12.0276	0.6685	0.6755	0.6752	0.6730(0.0032)

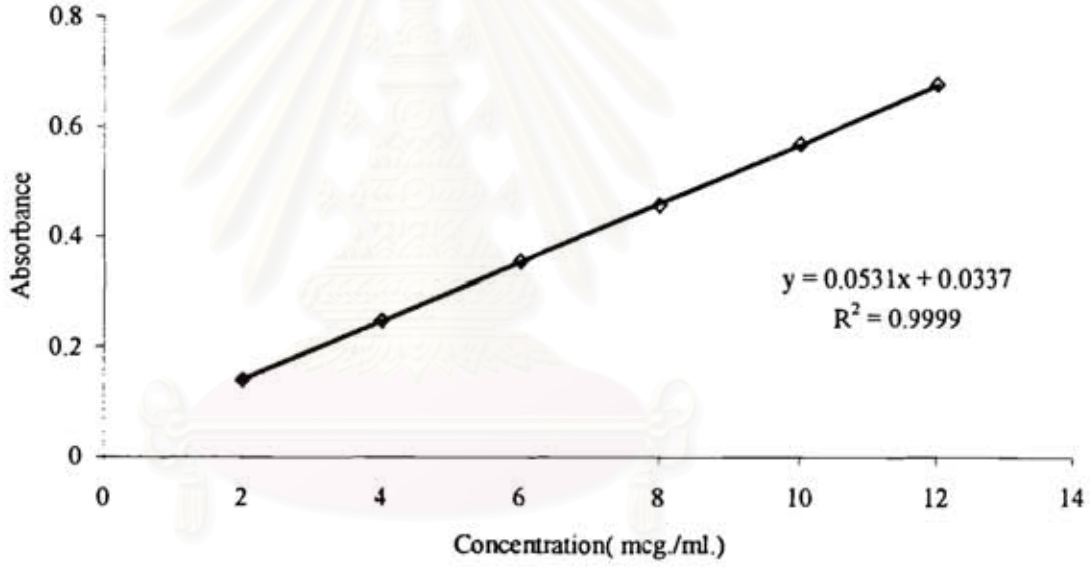

Figure 74 The calibration curve of theophylline in 0.1 N HCl pH 1.2 at 270 nm

Table 38 Absorbances of theophylline in ammonium solution at 273 nm

Concentartio(mcg/ml)	abs(n1)	abs(n2)	abs(n3)	Average (SD)
2.004	0.1429	0.1411	0.1542	0.14607(0.00579)
4.008	0.2712	0.2838	0.2962	0.28373(0.01020)
6.012	0.4062	0.4262	0.4385	0.42363(0.01331)
8.016	0.5423	0.5591	0.5667	0.55603(0.01019)
10.02	0.6712	0.6991	0.7086	0.69296(0.01587)
12.024	0.8003	0.8456	0.8563	0.83406(0.02427)

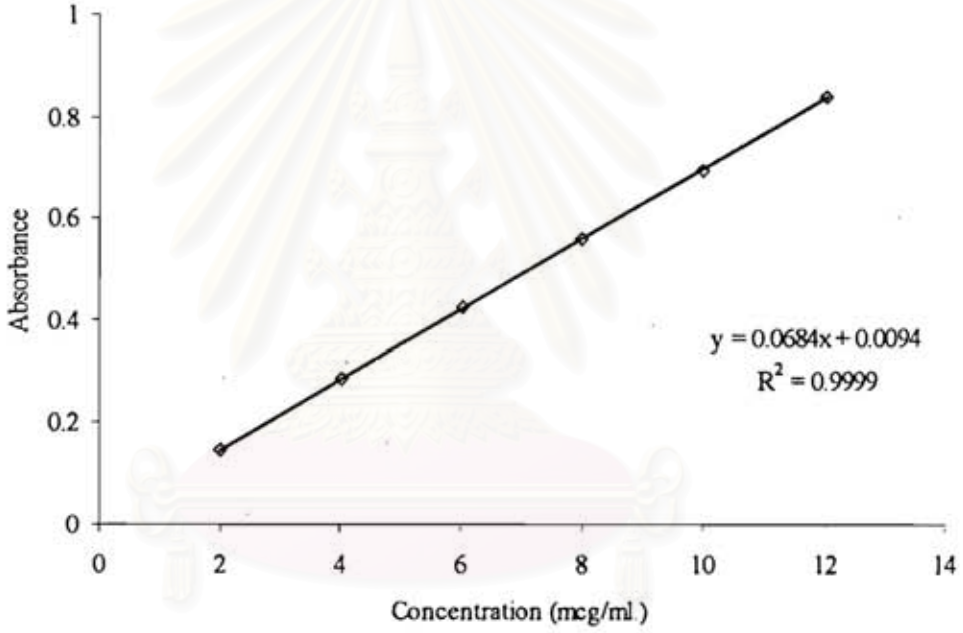

Figure 75 The calibration curve of theophylline in ammonium solution at 273 nm

Appendix B

Percentage amount of dug release

Table 39 Percentage amounts of theophylline from matrices containing Eudragit® RS prepared direct compression

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	16.14	15.74	15.37	15.75	0.31
1	22.54	21.67	21.32	21.84	0.51
2	33.16	31.56	30.61	31.77	1.05
3	40.69	39.61	38.63	39.64	0.84
4	48.36	45.4	44.51	46.09	1.64
5	55.62	54.87	53.85	54.78	0.72
6	60.7	56.94	55.39	57.67	2.22
8	69.8	66.19	65.5	67.16	1.88
10	83.87	79.85	78.31	80.67	2.34
12	95.12	90.5	90.77	92.13	2.11

Table 40 Percentage amounts of theophylline from matrices containing Eudragit® RS prepared by wet granulation

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	16.99	16.12	16.05	16.38	0.42
1	22.54	22.31	22.75	22.53	0.17
2	27.15	28.75	27.75	27.88	0.65
3	33.43	34.5	33.43	33.78	0.50
4	38.45	39.05	38.89	38.79	0.25
5	42.46	42.78	42.47	42.57	0.14
6	47.31	47.32	46.74	47.12	0.27
8	52.04	52.94	53.04	52.67	0.44
10	58.2	58.11	58.29	58.2	0.07
12	68.45	69.72	67.43	68.53	0.93

Table 41 Percentage amounts of theophylline from matrices containing Kollidon® SR prepared by direct compression

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	16.22	18.15	17.11	17.16	0.78
1	22.74	23.89	22.72	23.11	0.54
2	28.77	29.47	28.83	29.02	0.31
3	34.43	37.43	35.17	35.67	1.27
4	38.55	43.15	41.19	40.96	1.88
5	44.46	47.51	45.79	45.92	1.24
6	48.61	50.72	49.99	49.77	0.87
8	54.58	57.54	56.9	56.69	1.64
10	64.79	67.84	65.02	65.88	1.38
12	73.36	76.15	74.16	74.55	1.17

Table 42 Percentage amounts of theophylline from matrices containing Kollidon® SR prepared by wet granulation.

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.45	14.59	14.56	14.53	0.06
1	18.35	18.54	18.49	18.46	0.08
2	25.38	26.79	26.18	26.11	0.57
3	31.59	32.34	33.54	32.49	0.80
4	36.45	37.45	38.43	37.44	0.80
5	39.78	40.75	41.78	40.77	0.81
6	44.29	45.85	46.89	45.67	1.06
8	49.58	50.78	51.25	50.53	0.70
10	55.25	56.89	57.38	56.50	0.91
12	61.89	62.56	63.45	62.63	0.63

Table 43 Percentage amounts of theophylline from matrices containing Eudragit® RS without plasticizer prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	15.15	15.34	15.38	15.29	0.10
1	19.55	19.31	19.69	19.51	0.15
2	24.44	24.35	24.35	24.38	0.04
3	29.04	29.78	30.15	29.65	0.46
4	33.29	33.59	34.26	33.71	0.40
5	37.56	37.75	37.33	37.54	0.17
6	40.48	40.91	41.75	41.04	0.52
8	46.17	46.85	47.19	46.73	0.42
10	51.25	51.67	52.45	51.79	0.49
12	55.62	55.13	56.54	55.76	0.58

Table 44 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10 %TEC prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.56	14.32	14.12	14.33	0.17
1	18.75	18.06	18.36	18.39	0.28
2	23.21	23.96	23.71	23.62	0.31
3	28.15	28.57	29.46	28.72	0.54
4	33.35	32.83	32.69	32.95	0.28
5	36.49	35.86	35.45	35.93	0.42
6	40.48	39.88	39.58	39.98	0.37
8	46.17	45.91	45.28	45.78	0.37
10	51.25	50.74	50.45	50.81	0.33
12	55.62	54.69	54.31	54.87	0.55

Table 45 Percentage amounts of theophylline from matrices containing Eudragit® RS with . 10 % DBP prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.53	14.32	14.12	14.32	0.16
1	17.96	17.55	17.78	17.76	0.16
2	23.45	23.96	23.71	23.70	0.20
3	28.18	28.57	29.46	28.73	0.53
4	32.28	32.83	32.69	32.62	0.23
5	35.45	35.86	35.45	35.58	0.19
6	38.44	38.31	39.58	38.77	0.57
8	44.74	45.91	45.28	45.31	0.47
10	49.09	50.74	50.45	50.09	0.71
12	53.17	54.69	54.31	54.05	0.64

Table 46 Percentage amounts of theophylline from matrices containing Eudragit® RS with . 20 % TEC prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.25	13.11	13.58	13.31	0.19
1	16.48	16.21	16.35	16.34	0.11
2	22.31	21.78	21.49	21.87	0.33
3	27.15	25.89	26.04	26.36	0.56
4	30.46	28.95	29.71	29.70	0.61
5	32.55	29 42	31.89	31.28	1.34
6	35.34	33 21	34.62	34.39	0.88
8	40.57	38.54	39.14	39.41	0.85
10	44.69	42.38	43.52	43.53	0.94
12	48.78	46.75	47.86	47.79	0.82

Table 47 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % DBP prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	10.45	10.87	10.56	10.62	0.17
1	13.21	13.65	13.21	13.35	0.20
2	17.34	17.98	17.4	17.57	0.28
3	20.02	20.75	20.2	20.32	0.31
4	21.75	23.68	22.46	22.63	0.79
5	23.87	25.63	24.64	24.71	0.72
6	26.21	27.33	26.88	26.80	0.46
8	30.18	31.45	30.78	30.80	0.51
10	34.55	35.97	34.78	35.12	0.62
12	37.35	38.72	37.78	37.95	0.57

Table 48 Percentage amounts of theophylline from matrices containing Eudragit® RS without plasticizer prepared by method II melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	
0.5	17.92	17.45	18.24	17.87	0.32
1	24.29	23.78	24.83	24.34	0.42
2	33.03	32.76	34.31	33.36	0.67
3	40.83	39.65	41.05	40.51	0.61
4	46.34	45.28	47.39	46.33	0.86
5	51.67	50.37	52.73	51.59	0.96
6	58.2	57.43	59.71	58.44	0.94
8	68.9	67.32	69.44	68.55	0.89
10	74.54	73.81	75.42	74.59	0.65
12	86.13	85.34	87.27	86.24	0.79

Table 49 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10 % TEC prepared by method II melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	17.33	17.56	17.47	17.45	0.11
1	22.72	23.01	22.68	22.80	0.18
2	31.9	31.84	31.56	31.76	0.18
3	38.85	38.54	38.39	38.59	0.23
4	43.99	43.54	43.96	43.83	0.25
5	48.46	48.06	48.53	48.35	0.25
6	52.95	52.23	52.57	52.58	0.36
8	61.15	61.27	61.67	61.36	0.27
10	66.57	67	67.41	66.99	0.42
12	71.96	72.72	72.42	72.36	0.38

Table 50 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10% DBP prepared by method II melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	16.97	16.95	16.73	16.88	0.13
1	21.89	22.79	21.88	22.18	0.52
2	29.03	30.27	30.52	29.94	0.79
3	36.38	38.03	37.03	37.14	0.83
4	44.45	44.05	44.05	44.18	0.23
5	50.11	50.71	50.08	50.35	0.35
6	55.21	55.71	55.71	55.54	0.28
8	64.78	64.46	64.84	64.69	0.20
10	72.83	72.09	72.55	72.49	0.37
12	78.15	78.88	78.18	78.40	0.41

Table 51 Percentage amounts of theophylline from matrices containing Eudragit® RS100 with 20 % TEC prepared by method II melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	17.66	17.25	17.18	17.36	0.21
1	23.39	22.37	23.5	23.08	0.50
2	29.39	29.42	28.74	29.18	0.31
3	35.92	34.85	34.79	35.18	0.51
4	39.64	39.51	38.73	39.29	0.40
5	42.72	42.82	41.57	42.37	0.56
6	45.84	45.79	45.66	45.76	0.07
8	51.28	53.07	52.27	52.20	0.73
10	57.28	59.55	58.05	58.29	0.94
12	64.9	67.44	65.34	65.89	1.10

Table 52 Percentage amounts of theophylline from matrices containing Eudragit® RS100 with 20 % DBP prepared by method II melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	18.04	17.09	17.18	17.43	0.42
1	24.41	23.65	23.5	23.85	0.39
2	32.89	33.28	32.74	32.97	0.22
3	38.22	40.27	39.34	39.27	0.83
4	43.25	44.45	43.67	43.79	0.49
5	47.74	47.71	47.05	47.5	0.31
6	50.9	50.92	50.27	50.69	0.30
8	57.95	57.58	57.27	57.6	0.27
10	64.26	63.54	63.06	63.62	0.49
12	72.74	73.29	73.1	73.04	0.22

Table 53 Percentage amounts of theophylline from matrices containing Eudragit® RS without plasticizer prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	18.37	17.37	16.35	17.36	1.01
1	22.67	23.06	22.53	22.75	0.27
2	29.23	30.42	29.06	29.57	0.74
3	35.93	36.75	35.72	36.13	0.54
4	42.91	43.4	42.33	42.88	0.53
5	46.5	47.29	46.89	46.89	0.39
6	50.29	52.5	51.58	51.45	1.11
8	59.23	60.03	60.62	59.96	0.69
10	64.26	65.86	66.05	65.39	0.98
12	70.38	72.5	74.21	72.36	1.91

Table 54 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10 % TEC prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	16.37	16.8	15.68	16.28	0.56
1	20.67	21.06	20.53	20.75	0.27
2	27.23	27.42	27.06	27.23	0.18
3	32.93	32.75	32.72	32.8	0.11
4	37.91	37.34	37.33	37.52	0.33
5	41.23	40.46	41	40.89	0.39
6	45.29	44.2	44.58	44.69	0.55
8	52.23	51.03	51.62	51.62	0.60
10	57.26	56.86	57.05	57.05	0.20
12	65.55	65.7	65.44	65.56	0.13

Table 55 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10 % DBP prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	15.43	15.7	15.83	15.65	0.20
1	19.83	20.45	20.8	20.36	0.49
2	26.3	27.12	27.26	26.89	0.51
3	31.81	32.72	32.77	32.43	0.54
4	36.11	37.13	37.79	37.01	0.84
5	39.7	40.81	41	40.50	0.70
6	43.03	44.38	44.66	44.02	0.87
8	49.83	50.79	51.19	50.60	0.69
10	54.4	56.1	56.65	55.71	1.17
12	63.02	64.8	65.02	64.28	1.09

Table 56 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % TEC prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.62	13.31	14.49	14.14	0.58
1	18.24	16.64	18.01	17.63	0.70
2	23.35	21.86	22.91	22.70	0.62
3	27.45	26.18	27.26	26.96	0.55
4	30.65	29.16	30.2	30.00	0.62
5	33.73	31.94	30.2	31.95	1.44
6	35.88	34.81	32.75	34.48	1.29
8	39.79	38.85	38.38	39.00	0.58
10	44.47	42.54	42.76	43.25	0.86
12	47.68	46.77	46.11	46.85	0.64

Table 57 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % DBP prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.33	13.36	13.82	13.50	0.22
1	16.65	16.71	17.2	16.85	0.24
2	21.8	22	22.51	22.10	0.29
3	25.24	25.18	25.65	25.35	0.20
4	28.46	28.12	28.68	28.45	0.23
5	30.56	30.82	31.25	30.87	0.28
6	33.31	33.09	33.68	33.36	0.24
8	37.06	37.3	37.91	37.42	0.35
10	40.88	40.9	41.47	41.08	0.27
12	44.23	44.68	45.12	44.67	0.36

Table 58 Percentage amounts of theophylline from matrices containing Eudragit® RS without plasticizer prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	16.59	16.31	16.65	16.51	0.14
1	21.94	21.23	21.98	21.71	0.34
2	30.43	29.65	31.33	30.47	0.68
3	36.62	35.74	37.72	36.69	0.80
4	41.88	40.48	42.59	41.65	0.87
5	46.57	45.68	47.31	46.52	0.66
6	51.22	50.37	51.67	51.08	0.53
8	59.35	58.42	59.63	59.13	0.51
10	68.04	66.33	70.71	68.36	1.80
12	74.19	72.15	76.28	74.20	1.68

Table 59 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10 % TEC prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	17.35	17.36	17.38	17.36	0.01
1	24.33	24.45	24.45	24.36	0.06
2	32.03	32.55	32.26	32.26	0.21
3	39.12	39.85	39.21	39.39	0.32
4	44.86	44.85	44.21	44.64	0.30
5	48.27	47.72	47.14	47.71	0.46
6	53.23	52.68	52.87	52.92	0.22
8	61.86	61.34	61.22	61.47	0.27
10	64.59	65.73	65.43	65.25	0.48
12	70.11	69.85	69.11	69.69	0.42

Table 60 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10 % DBP prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	17.35	17.36	17.38	17.36	0.01
1	24.33	24.45	24.45	24.36	0.06
2	32.03	32.55	32.26	32.26	0.21
3	39.12	39.85	39.21	39.39	0.32
4	44.86	44.85	44.21	44.64	0.30
5	48.27	47.72	47.14	47.71	0.46
6	53.23	52.68	52.87	52.92	0.22
8	61.86	61.34	61.22	61.47	0.27
10	64.59	65.73	65.43	65.25	0.48
12	70.11	69.85	69.11	69.69	0.42

Table 61 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % TEC prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.04	14.21	14.58	13.94	0.65
1	16.8	17.45	18.29	17.51	0.60
2	22.36	23.56	24.16	23.36	0.74
3	27.85	28.14	30.74	28.91	1.29
4	30.96	31.91	32.83	31.9	0.76
5	35.09	35.5	35.45	35.34	0.18
6	39.27	39.63	39.64	39.51	0.17
8	46.53	46.16	46.14	46.27	0.17
10	52.63	52.6	52.51	52.58	0.05
12	55.42	56.38	56.11	55.97	0.40

Table 62 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % DBP prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.9	14.46	14.11	14.49	0.32
1	20.54	20.99	19.43	20.32	0.65
2	26.93	26.89	26.97	26.93	0.03
3	32.29	31.95	32.07	32.10	0.14
4	36.47	36.5	36.63	36.53	0.06
5	39.61	40.43	39.31	39.78	0.47
6	44.26	43.39	44.13	43.92	0.38
8	49.12	48.13	48.3	48.51	0.43
10	54.87	53.67	53.38	53.97	0.64
12	60.5	59.72	59.55	59.92	0.41

Table 63 Percentage amounts of theophylline from matrices containing Eudragit® RS without plasticizer prepared by method IV, thermal granulation at 80°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	15.67	15.85	15.21	15.57	0.26
1	19.86	20.32	19.43	19.87	0.36
2	28.34	29.37	27.63	28.44	0.71
3	33.74	33.98	32.55	33.42	0.62
4	38.96	39.14	37.18	38.42	0.88
5	43.18	44.56	42.75	43.49	0.77
6	47.27	48.29	46.69	47.41	0.66
8	55.12	56.37	54.63	55.37	0.73
10	62.08	64.13	60.21	62.14	1.60
12	67.59	69.76	65.32	67.55	1.81

Table 64 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10 % TEC prepared by method IV , thermal granulation at 80°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	16.45	16.48	16.87	16.6	0.19
1	23.54	23.15	23.77	24.36	0.50
2	31.56	31.55	31.12	32.26	0.47
3	38.62	38.14	38.46	38.40	0.19
4	43.18	43.01	42.35	42.84	0.35
5	47.32	46.55	45.73	46.53	0.64
6	52.85	51.32	50.57	51.58	0.94
8	60.45	59.78	59.63	59.95	0.35
10	66.37	65.17	64.33	65.29	0.83
12	69.48	68.65	67.12	68.41	0.97

Table 65 Percentage amounts of theophylline from matrices containing Eudragit® RS with 10 % DBP prepared by method IV thermal granulation at 80°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	15.35	15.36	15.38	15.36	0.01
1	20.45	20.45	20.36	20.42	0.04
2	27.03	27.55	27.26	27.28	0.21
3	33.12	33.24	32.47	32.94	0.33
4	37.86	37.85	37.21	37.64	0.30
5	42.27	41.72	41.19	41.72	0.44
6	46.23	45.68	44.87	45.59	0.55
8	52.86	52.34	51.22	52.14	0.68
10	58.59	57.73	56.43	57.58	0.88
12	64.11	62.85	62.11	63.0	0.82

Table 66 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % TEC prepared by method IV thermal granulation at 80°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.95	13.21	13.87	13.67	0.33
1	16.67	16.19	17.43	16.76	0.51
2	22.27	21.38	23.87	22.50	1.03
3	26.3	25.33	27.55	26.39	0.90
4	29.98	28.47	30.21	29.55	0.77
5	32.95	32.18	33.85	32.99	0.68
6	35.56	34.68	36.41	35.55	0.70
8	40.71	40.26	41.87	40.94	0.67
10	44.08	42.35	46.28	44.23	1.60
12	48.03	46.78	50.33	48.38	1.47

Table 67 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % DBP prepared by method IV thermal granulation at 80°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.82	14.35	14.87	14.68	0.23
1	19.21	19.13	19.81	19.38	0.30
2	24.58	23.57	25.33	24.49	0.72
3	29.22	28.31	30.57	29.36	0.92
4	32.88	31.65	33.21	32.56	0.67
5	35.68	34.87	36.84	35.79	0.80
6	38.39	37.21	39.55	38.38	0.95
8	43.5	42.5	44.38	43.46	0.76
10	47.88	46.28	48.53	47.56	0.94
12	51.86	50.55	52.47	51.62	0.80

Table 68 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % TEC prepared by method IV at room temperature

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.12	14.44	14.35	14.30	0.13
1	20.34	20.28	20.65	20.42	0.16
2	26.87	25.5	25.5	25.95	0.64
3	32.92	30.9	30.67	31.49	1.01
4	37.01	35.01	34.21	35.41	1.17
5	41.06	39.06	38.45	39.52	1.11
6	44.22	42.22	41.78	42.74	1.06
8	50.37	48.37	47.95	48.89	1.05
10	55.96	54.51	53.17	54.54	1.13
12	61.04	59.04	58.55	59.54	1.07

Table 69 Percentage amounts of theophylline from matrices containing Eudragit® RS with 20 % DBP prepared by method IV at room temperature

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.9	14.5	14.02	14.47	0.35
1	19.27	19.84	19.21	19.44	0.28
2	26.05	26.75	26.35	26.38	0.28
3	31.28	31.69	31.17	31.38	0.22
4	35.66	36.47	35.13	35.75	0.55
5	38.99	39.21	38.21	38.80	0.42
6	42.86	43.85	41.55	42.75	0.94
8	47.8	48.65	46.23	47.56	1.00
10	52.73	53.72	51.31	52.58	0.98
12	58.1	59.31	57.5	58.30	0.75

Table 70 Percentage amounts of theophylline from matrices containing Kollidon® SR withoutplasticizer prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.25	13.86	13.18	13.43	0.30
1	16.67	16.78	16.35	16.63	0.18
2	22.34	23.45	21.34	22.37	0.86
3	29.12	30.56	28.63	29.43	0.81
4	33.34	34.55	32.75	33.54	0.74
5	36.78	37.69	35.66	36.71	0.83
6	40.29	41.68	39.59	40.52	0.86
8	45.85	46.78	44.75	45.79	0.82
10	50.25	51.23	49.32	50.26	0.77
12	55	56.48	54.81	55.43	0.74

Table 71 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % TEC prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.14	13.56	13.85	13.51	0.29
1	15.46	16.16	17.56	16.39	0.87
2	21.55	22.12	23.65	22.44	0.88
3	25.97	26.87	27.33	26.72	0.56
4	29.64	30.53	31.85	30.67	0.90
5	32.87	33.56	34.73	33.72	0.76
6	36.58	37.31	38.65	37.51	0.85
8	41.21	42.73	43.19	42.37	0.84
10	46.67	47.34	48.65	47.55	0.82
12	51.33	52.17	53.67	52.39	0.96

Table 72 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % DBP prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.19	13.56	13.15	13.3	0.18
1	15.79	16.87	16.55	16.40	0.45
2	19.63	21.58	20.95	20.72	0.81
3	24.16	26.37	25.34	25.29	0.90
4	28.43	30.45	29.03	29.30	0.84
5	31.55	33.68	32.76	32.66	0.87
6	35.41	37.46	36.27	36.38	0.84
8	40.39	42.16	41.46	41.33	0.72
10	44.58	46.55	45.65	45.59	0.80
12	48.37	50.41	49.8	49.52	0.85

Table 73 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % TEC prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	11.56	11.89	11.46	11.63	0.18
1	14.16	15.23	13.75	14.38	0.62
2	20.18	21.46	19.65	20.43	0.75
3	23.54	24.36	22.55	23.48	0.74
4	26.43	27.85	28.33	27.53	0.80
5	28.78	29.61	29.98	29.45	0.50
6	31.89	32.72	33.57	32.72	0.68
8	37.25	38.78	38.61	38.21	0.68
10	42.38	43.14	43.26	42.92	0.38
12	47.56	48.63	49.69	48.62	0.86

Table 74 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % DBP prepared by method I melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	11.85	11.25	11.59	11.56	0.24
1	15.63	14.13	14.55	14.77	0.63
2	19.33	17.59	18.85	18.59	0.73
3	23.68	21.36	22.34	22.46	0.95
4	25.87	24.98	25.03	25.29	0.40
5	29.71	28.67	28.75	29.04	0.47
6	30.55	29.33	30.85	30.24	0.65
8	36.89	35.41	36.78	36.36	0.67
10	41.96	39.72	40.89	40.85	0.91
12	45.73	44.62	44.56	44.97	0.53

Table 75 Percentage amounts of theophylline from matrices containing Kollidon® SR withoutplasticizer prepared by method II melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	20.15	20.48	20.19	20.27	0.14
1	25.79	26.37	25.17	25.77	0.48
2	38.33	39.64	37.62	38.53	0.83
3	46.64	47.55	45.81	46.66	0.71
4	51.26	53.48	49.37	51.37	1.67
5	55.54	57.61	53.19	55.44	1.80
6	60.29	62.39	58.64	60.44	1.53
8	72.39	74.55	70.48	72.47	1.66
10	78.19	81.37	76.88	78.81	1.88
12	84.97	86.21	82.55	84.57	1.51

Table 76 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % TEC prepared by method II melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	18.45	18.23	18.31	18.33	0.09
1	24.65	23.95	22.46	23.68	0.91
2	32.74	31.25	30.69	31.56	0.86
3	38.69	37.28	36.78	37.58	0.80
4	43.84	42.41	41.49	42.58	0.96
5	49.38	48.79	47.76	48.64	0.66
6	56.32	55.03	54.17	55.17	0.88
8	64.87	63.58	62.49	63.64	0.97
10	68.33	67.7	66.55	67.52	0.73
12	72.41	71.45	70.13	71.33	0.93

Table 77 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % DBP prepared by method II melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	18.04	18.67	18.13	18.28	0.27
1	22.61	24.32	23.11	23.34	0.71
2	31.49	33.45	32.57	32.50	0.80
3	39.65	41.62	40.82	40.69	0.80
4	47.55	49.75	48.46	48.58	0.90
5	53.16	55.34	54.12	54.20	0.89
6	59.38	61.75	60.16	60.43	0.98
8	69.96	71.47	70.52	70.65	0.62
10	74.58	76.34	75.77	75.56	0.73
12	80.33	82.64	81.2	81.39	0.95

Table78 Percentage amounts of theophylline from matrices containing Kollidon® SR without plasticizer prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.05	14.75	14.12	14.30	0.31
1	18.67	18.96	18.23	18.62	0.30
2	25.34	26.34	24.75	25.47	0.65
3	33.12	34.62	32.67	33.47	0.83
4	37.94	38.46	36.55	37.65	0.80
5	41.78	42.85	40.81	41.81	0.83
6	45.29	46.24	44.62	45.38	0.66
8	51.55	52.22	50.38	51.38	0.76
10	57.25	58.39	56.45	57.36	0.79
12	63	64.87	62.37	63.41	1.06

Table79 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % TEC prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.35	14.56	14.78	14.56	0.17
1	17.45	18.16	18.65	18.08	0.49
2	24.63	25.12	26.35	25.36	0.72
3	29.33	30.87	31.55	30.58	0.92
4	34.15	35.13	36.81	35.36	1.09
5	37.85	38.56	39.62	38.67	0.72
6	41.73	42.31	43.58	42.54	0.77
8	47.78	48.43	49.32	48.51	0.63
10	52.64	53.34	54.68	53.55	0.84
12	60.28	61.17	62.87	61.44	1.07

Table 80 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % DBP prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	14.26	14.87	14.15	14.42	0.31
1	17.84	19.55	18.55	18.64	0.70
2	22.45	24.65	23.95	23.68	0.91
3	28.62	30.33	29.34	29.43	0.70
4	32.74	34.87	33.63	33.74	0.87
5	36.56	38.27	37.76	37.53	0.71
6	40.55	42.65	41.27	41.49	0.87
8	46.58	48.37	47.16	47.37	0.74
10	50.67	52.92	51.65	51.74	0.92
12	57.29	59.34	58.8	58.47	0.86

Table 81 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % TEC prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	12.56	12.85	12.33	12.58	0.21
1	16.16	16.89	15.75	16.26	0.47
2	23.18	24.65	22.62	23.48	0.85
3	27.54	28.33	26.38	27.41	0.80
4	31.03	32.47	30.54	31.34	0.81
5	33.78	34.96	32.61	33.78	0.95
6	36.89	37.46	35.73	36.69	0.71
8	42.95	43.51	41.42	42.62	0.88
10	48.38	49.63	47.71	48.57	0.79
12	55.23	56.87	54.43	55.51	1.01

Table 82 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % DBP prepared by method III melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	12.16	12.15	12.78	12.36	0.29
1	14.75	15.25	15.84	15.28	0.44
2	20.46	21.21	22.34	21.33	0.77
3	24.35	25.34	26.95	25.54	1.07
4	27.67	28.63	29.64	28.64	0.80
5	30.66	31.75	32.75	31.72	0.85
6	33.49	34.85	35.67	34.67	0.89
8	38.78	39.86	40.52	39.72	0.71
10	43.67	44.56	45.64	44.62	0.80
12	48.23	49.25	50.37	49.28	0.87

Table 83 Percentage amounts of theophylline from matrices containing Kollidon® SR without plasticizer prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	16.05	17.35	15.7	16.36	0.70
1	22.3	22.96	21.46	22.24	0.61
2	30.12	30.62	29.65	30.13	0.39
3	35.96	36.5	36.51	36.32	0.25
4	40.5	40.91	41.19	40.86	0.28
5	44.77	45.12	46.4	45.43	0.70
6	48.46	49.6	50.8	49.62	0.95
8	53.51	56.26	54.9	54.89	1.12
10	62.21	63.52	62.09	62.60	0.64
12	68.52	68.4	67.51	68.14	0.45

Table 84 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % TEC prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.09	13.91	13.26	13.42	0.35
1	15.64	16.96	16.5	16.36	0.54
2	22.55	22.27	22.11	22.31	0.18
3	26.67	26.23	25.99	26.29	0.28
4	29.19	30.8	29.44	29.81	0.70
5	32.39	33.55	32.54	32.82	0.51
6	35.6	36.14	35.22	35.65	0.37
8	38.89	40.78	38.63	39.43	0.95
10	41.99	43.75	42.47	42.73	0.74
12	44.97	46.67	46.89	46.17	0.85

Table 85 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % DBP prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.81	14.86	15.67	14.78	0.76
1	17.71	18.47	18.93	18.37	0.50
2	22.78	23.83	24.67	23.76	0.77
3	27.86	28.36	29.4	28.54	0.64
4	31.44	32.33	32.25	32.00	0.40
5	34.67	35.67	36.4	35.58	0.70
6	37.11	38.47	38.41	37.99	0.62
8	41.46	42.51	43.29	42.42	0.74
10	44.73	46.22	47.96	46.30	1.31
12	48.42	50.28	51.82	50.17	1.39

Table 86 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % TEC prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	12.88	12.03	14.52	13.14	1.03
1	15.26	16.86	16.51	16.21	0.68
2	22.92	21.29	20.95	21.72	0.85
3	25.61	23.67	22.87	24.05	1.15
4	29.84	27.44	26.29	27.85	1.47
5	32.58	30.01	29.51	30.7	1.34
6	35.01	32.47	33.67	33.71	1.03
8	38.22	35.67	37.54	37.14	1.07
10	42.17	39.97	40.99	41.04	0.89
12	45.42	43.11	44.39	44.30	0.94

Table 87 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % DBP prepared by method IV melt granulation at 60°C

Time(hr)	1	2	3	Mean	SD
0	0	0	0	0	0
0.5	13.18	14.86	14.19	14.07	0.69
1	17.81	17.87	19.07	18.25	0.58
2	23.36	22.54	24.54	23.48	0.82
3	26.88	26.99	27.95	27.27	0.48
4	29.87	29.87	31.76	30.5	0.89
5	33.84	32.34	33.73	33.30	0.68
6	36.94	35.11	36.72	36.25	0.81
8	41.52	39.26	40.97	40.58	0.96
10	45.8	44.22	43.99	44.64	0.80
12	49.81	47.47	48.44	48.57	0.95

Table 88 Percentage amounts of theophylline from matrices containing Kollidon® SR with out plasticizer prepared by method IV melt granulation at 80°C

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	16.44	15.19	16.09	15.90	0.52
1	21.72	20.13	21.6	21.15	0.72
2	29.37	28.24	29.94	29.18	0.70
3	35.17	34.52	36.61	35.43	0.87
4	39.75	39.84	41.19	40.26	0.65
5	43.24	43.37	45.11	43.90	0.85
6	46.98	46.6	48.37	47.31	0.76
8	51.71	52.78	53.93	52.80	0.90
10	60.12	61.04	61.02	60.72	0.42
12	64.48	66.81	67.12	66.13	1.17

Table 89 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % DBP prepared by method IV melt granulation at 80°C

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	14.25	14.04	13.34	13.87	0.38
1	17.23	16.81	16.88	16.97	0.18
2	22.32	21.89	22.31	22.17	0.20
3	27.56	26.23	26.58	26.79	0.56
4	30.66	29.87	29.91	30.14	0.36
5	33.83	32.95	33.15	33.31	0.37
6	36.67	36	35.87	36.18	0.35
8	41.23	40.41	39.38	40.34	0.75
10	45.95	44.54	42.98	44.49	1.21
12	48.82	47.15	46.61	47.52	0.94

Table 90 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % TEC prepared by method IV melt granulation at 80°C

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	13.4	13.68	13.27	13.45	0.17
1	17.27	16.9	17.58	17.25	0.27
2	22.79	22.97	23.36	23.04	0.23
3	27.17	26.49	26.88	26.84	0.27
4	31.25	30.16	30.61	30.67	0.44
5	33.92	33.2	33.99	33.70	0.35
6	36.67	35.95	36.82	36.48	0.37
8	40.76	39.75	40.27	40.26	0.41
10	44.73	43.86	43.92	44.17	0.39
12	48.75	47.6	47.74	48.03	0.51

Table 91 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % DBP prepared by method IV melt granulation at 80°C

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	13.18	13.57	13.85	13.53	0.27
1	17.37	18.57	18.61	18.18	0.57
2	20.89	21.98	23.45	22.10	1.04
3	26.35	27.57	28.48	27.46	0.87
4	29.54	30.57	32.33	30.81	1.15
5	32.58	33.85	34.73	33.72	0.88
6	35.94	36.11	37.52	36.52	0.70
8	40.58	41.58	42.95	41.70	0.97
10	44.64	46.57	45.75	45.65	0.79
12	47.58	48.75	49.65	48.66	0.84

Table 92 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % TEC prepared by method IV melt granulation at 80°C

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	12.75	12.09	12.93	12.59	0.36
1	15.24	15.43	15.4	15.35	0.08
2	21.36	21.16	20.38	20.96	0.42
3	25.61	25.19	24.02	24.94	0.67
4	29.55	29.16	28.01	28.90	0.65
5	31.49	30.97	28.51	30.32	1.29
6	34.53	34.34	33.21	34.02	0.58
8	37.74	38.1	36.72	37.52	0.58
10	42.14	41.73	40.13	41.33	0.86
12	45.53	44.97	43.12	44.54	1.02

Table 93 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % DBP prepared by method IV at room temperature

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	14.25	14.04	13.34	13.87	0.38
1	17.23	16.81	16.88	16.97	0.18
2	22.32	21.89	22.31	22.17	0.20
3	27.56	26.23	26.58	26.79	0.56
4	30.66	29.87	29.91	30.14	0.36
5	33.83	32.95	33.15	33.31	0.37
6	36.67	36	35.87	36.18	0.35
8	41.23	40.41	39.38	40.34	0.75
10	45.95	44.54	42.98	44.49	1.21
12	48.82	47.15	46.61	47.52	0.94

Table 94 Percentage amounts of theophylline from matrices containing Kollidon® SR with 10 % TEC prepared by method IV at room temperature.

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	13.85	13.8	13.45	13.7	0.17
1	17.83	16.23	17.55	17.20	0.69
2	22.81	22.38	22.45	22.54	0.18
3	26.18	26.19	26	26.12	0.08
4	29.44	29.29	30.29	29.67	0.44
5	32.74	32.61	33.61	32.98	0.44
6	35.58	34.11	35.11	34.93	0.61
8	40.38	38.29	40.29	39.65	0.96
10	44.1	41.73	42.73	42.85	0.97
12	47.29	46.09	47.08	46.82	0.52

Table 95 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % DBP prepared by method IV at room temperature

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	13.99	13.72	14.32	14.01	0.24
1	17.75	17.74	17.95	17.81	0.09
2	23.65	22.46	22.99	23.03	0.48
3	28.39	26.81	27.6	27.62	0.64
4	32.11	30.57	31.45	31.37	0.63
5	35.21	33.76	34.59	34.52	0.59
6	38.33	36.44	37.51	37.42	0.77
8	42.69	40.61	41.8	41.73	0.85
10	45.49	47.42	46.89	46.61	0.81
12	52.24	49.99	51.95	51.39	0.99

Table 96 Percentage amounts of theophylline from matrices containing Kollidon® SR with 20 % TEC prepared by method IV at room temperature.

Time(hr)	s1	s2	s3	Average	SD.
0	0	0	0	0	0
0.5	14.85	14.54	14.13	14.50	0.29
1	18.36	18.87	18.61	18.61	0.20
2	22.83	22.39	24.85	23.35	1.07
3	26.61	26.67	28.97	27.41	1.09
4	29.74	29.44	32.55	30.57	1.40
5	32.85	32.15	34.32	33.10	0.90
6	35.95	35.18	37.56	36.23	0.99
8	40.56	40.85	42.46	41.29	0.83
10	44.76	44.34	47.89	45.66	1.58
12	47.89	47.33	50.85	48.69	1.54

Appendix C

Table 97 Correlation of determination (r^2) of relationships between percentage drug released versus square root of time (Higuchi rate constant), log percentage drug remained versus time (first order rate constant)and drug released versus time(Zero order rate constant) of Eudragit® RS matrices system prepared by method I and II at 60 °C

Formulation I	Higuchi r^2	First order r^2	Zero order r^2	Formulation II	Higuchi r^2	First order r^2	Zero ord r^2
0 %	0.9958	0.9710	0.8961	0 %	0.9969	0.9828	0.9384
10 % DBP	0.9962	0.9597	0.8969	10 % DBP	0.9983	0.9884	0.9315
10 % TEC	0.9973	0.9357	0.9025	10 % TEC	0.9982	0.9827	0.9372
20 % DBP	0.9938	0.9617	0.8944	20 % DBP	0.9938	0.9662	0.9043
20 % TEC	0.9939	0.9414	0.8865	20 % TEC	0.9931	0.9690	0.9020

Table 98 Correlation of determination (r^2) of relationships between percentage drug released versus square root of time (Higuchi rate constant), log percentage drug remained versus time (first order rate constant)and drug released versus time(Zero order rate constant) of Eudragit® RS matrices system prepared by method III and IV at 60 °C

Formulation III	Higuchi r^2	First order r^2	Zero order r^2	Formulation IV	Higuchi r^2	First order r^2	Zero ord r^2
0 %	0.9985	0.9847	0.9132	0 %	0.9988	0.9888	0.9465
10 % DBP	0.9962	0.9718	0.9110	10 % DBP	0.9938	0.9644	0.8756
10 % TEC	0.9960	0.9747	0.9143	10 % TEC	0.9937	0.9658	0.8807
20 % DBP	0.9880	0.9197	0.8615	20 % DBP	0.9961	0.9590	0.9191
20 % TEC	0.9881	0.9248	0.8638	20 % TEC	0.9970	0.9717	0.8895

Table 99 Correlation of determination (r^2) of relationships between percentage drug released versus square root of time (Higuchi rate constant), log percentage drug remained versus time (first order rate constant)and drug released versus time(Zero order rate constant) of Kollidon® SR matrices system prepared by method I and II at 60 °C

Formulation I	Higuchi r^2	First order r^2	Zero order r^2	Formulation II	Higuchi r^2	First order r^2	Zero or r^2
0 %	0.9981	0.9611	0.9035	0 %	0.9967	0.9890	0.898
10 % DBP	0.9968	0.9592	0.9040	10 % DBP	0.9974	0.9836	0.912
10 % TEC	0.9977	0.9586	0.9100	10 % TEC	0.9944	0.9755	0.896
20 % DBP	0.9960	0.9627	0.9170	20 % DBP	*	*	*
20 % TEC	0.9954	0.9655	0.9240	20 % TEC	*	*	*

*Could not processed

Table 100 Correlation of determination (r^2) of relationships between percentage drug released versus square root of time (Higuchi rate constant), log percentage drug remained versus time (first order rate constant)and drug released versus time(Zero order rate constant) of Kollidon® SR matrices system prepared by method III and IV at 60 °C

Formulation III	Higuchi r^2	First order r^2	Zero order r^2	Formulation IV	Higuchi r^2	First order r^2	Zero or r^2
0 %	0.9986	0.9727	0.9035	0 %	0.9975	0.9740	0.897
10 % DBP	0.9976	0.9703	0.9040	10 % DBP	0.9902	0.9293	0.864
10 % TEC	0.9976	0.9722	0.9100	10 % TEC	0.9912	0.9202	0.861
20 % DBP	0.9983	0.9597	0.9170	20 % DBP	0.9903	0.9306	0.868
20 % TEC	0.9966	0.9699	0.9240	20 % TEC	0.9903	0.9251	0.869

Table 101 Correlation of determination (r^2) of relationships between percentage drug released versus square root of time (Higuchi rate constant), log percentage drug remained versus time (first order rate constant)and drug released versus time(Zero order rate constant) of Eudragit® RS matrices system prepared by method IV at room temperature and at 80 °C

Formulation room temperature	Higuchi r^2	First order r^2	Zero order r^2	Formulation at 80 °C	Higuchi r^2	First order r^2	Zero orc r^2
0 %	0.9905	0.9370	0.9572	0 %	0.9991	0.9842	0.921
10 % DBP	0.9935	0.9675	0.9247	10 % DBP	0.9986	0.9712	0.906
10 % TEC	0.9939	0.9651	0.9301	10 % TEC	0.9981	0.9729	0.902
20 % DBP	0.9964	0.9655	0.8896	20 % DBP	0.9914	0.9348	0.883
20 % TEC	0.9975	0.9565	0.9031	20 % TEC	0.9909	0.9463	0.868

Table 102 Correlation of determination (r^2) of relationships between percentage drug released versus square root of time (Higuchi rate constant), log percentage drug remained versus time (first order rate constant)and drug released versus time(Zero order rate constant) of Kollidon® SR matrices system prepared by method IV at room temperature and at 80 °C

Formulation room temperature	Higuchi r^2	First order r^2	Zero order r^2	Formulation at 80 °C	Higuchi r^2	First order r^2	Zero ord r^2
0 %	0.9952	0.9824	0.8998	0 %	0.9970	0.9708	0.897
10 % DBP	0.9921	0.9310	0.8720	10 % DBP	0.9914	0.9310	0.861
10 % TEC	0.9968	0.9256	0.8661	10 % TEC	0.9902	0.9274	0.864
20 % DBP	0.9948	0.9476	0.8900	20 % DBP	0.9926	0.9352	0.871
20 % TEC	0.9908	0.9337	0.8881	20 % TEC	0.9921	0.9259	0.875

Appendix D

DSC thermograms of Eudragit® RS, Eudragit® RS with 10 % and 20 % plasticizer, Kollidon®SR, Kollidon® SR with 10 % and 20 % plasticizer prepared by method II (ground polymer) and method IV (spray dried)

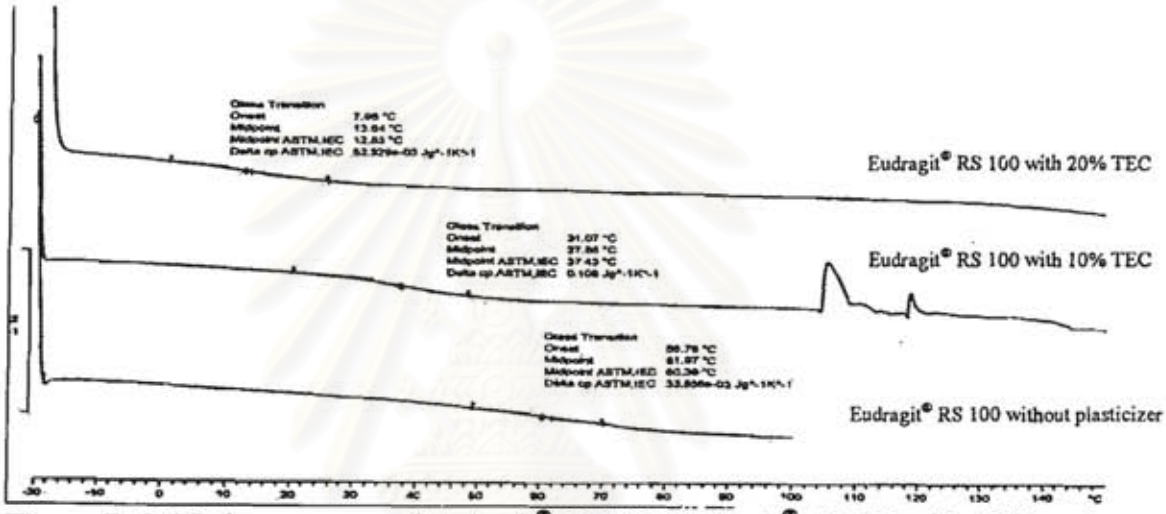

Figure 76 DSC thermograms of Eudragit® RS 100, Eudragit® RS 100 with 10 % and 20 % TEC prepared by method II (ground polymer)

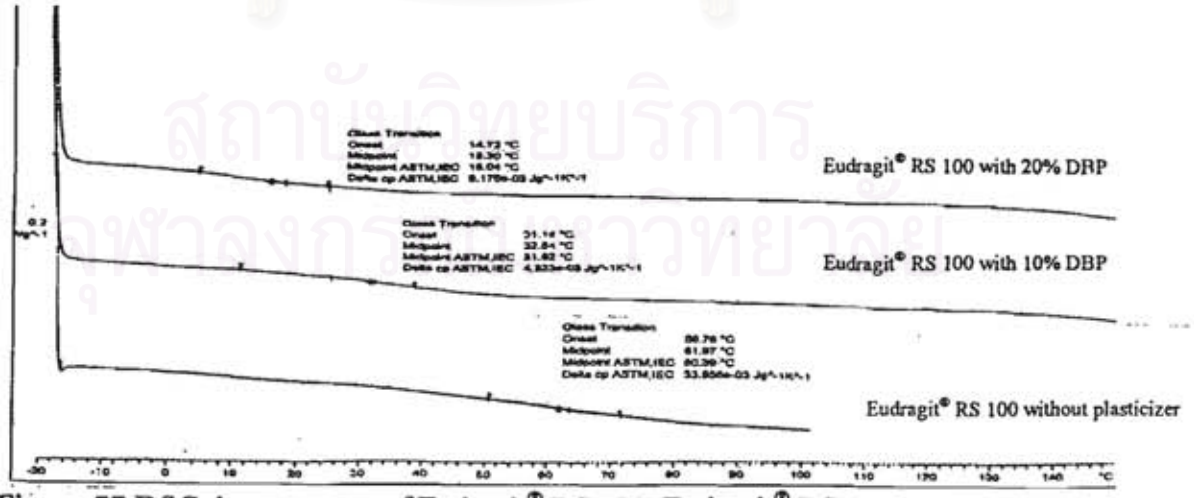

Figure 77 DSC thermograms of Eudragit® RS 100, Eudragit® RS 100 with 10 % and 20 % DBP prepared by method II (ground polymer)

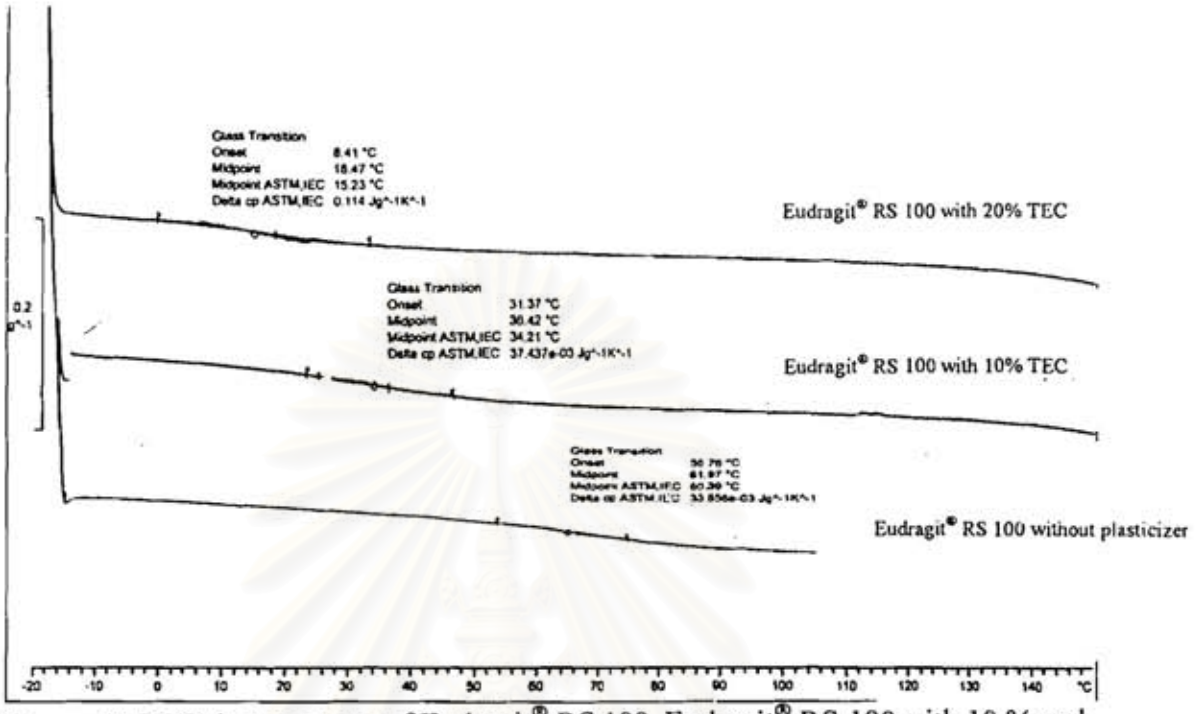

Figure 78 DSC thermograms of Eudragit® RS 100, Eudragit® RS 100 with 10 % and 20 % TEC prepared by method IV (spray dried)

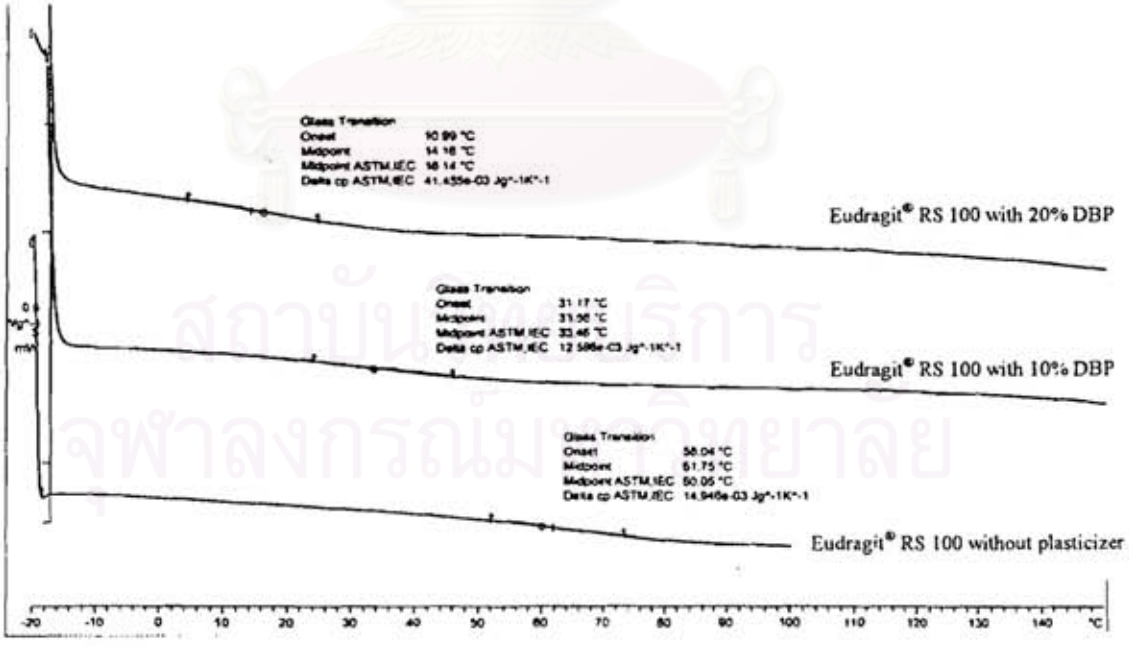

Figure 79 DSC thermograms of Eudragit® RS 100, Eudragit® RS 100 with 10 % and 20 % DBP prepared by method IV (spray dried)

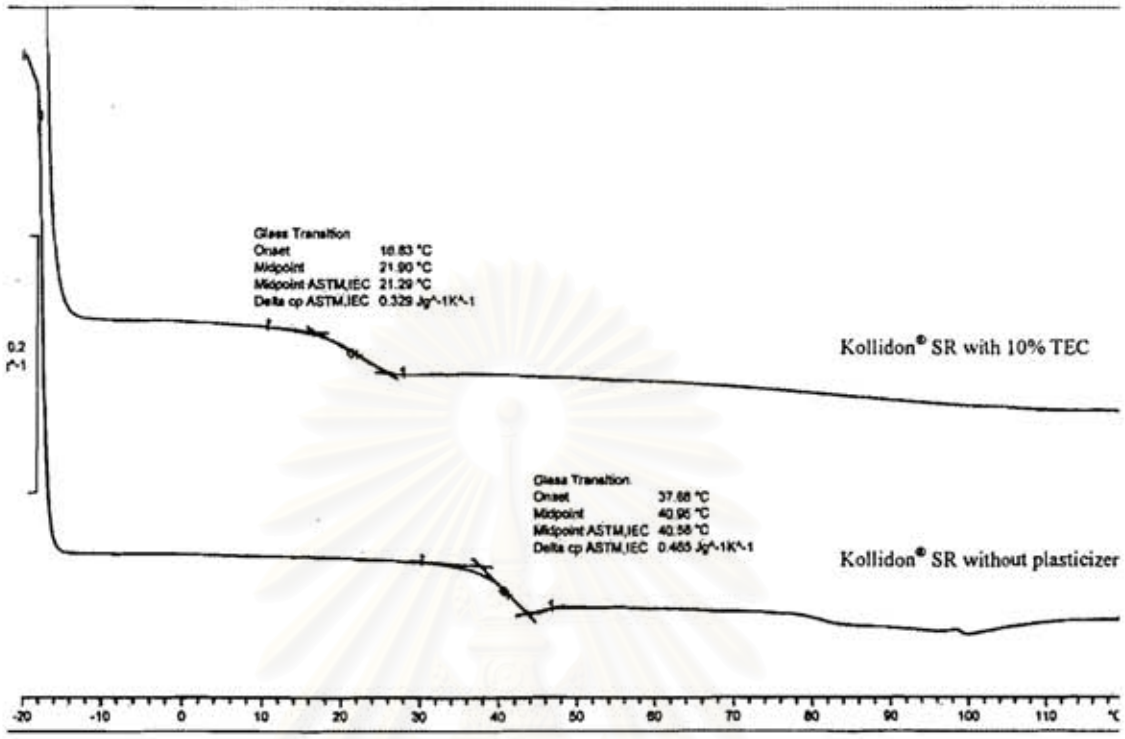

Figure 80 DSC thermograms of Kollidon® SR, Kollidon® SR with 10 % TEC prepared by method II (ground polymer)

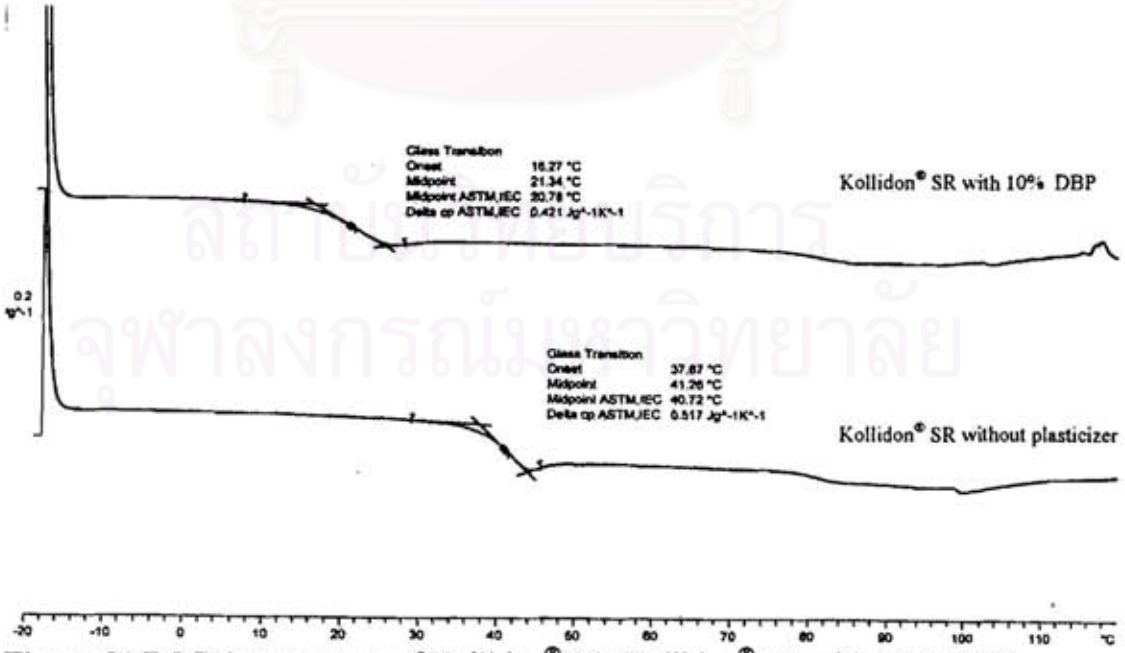

Figure 81 DSC thermograms of Kollidon® SR, Kollidon® SR with 10 % DBP prepared by method II (ground polymer)

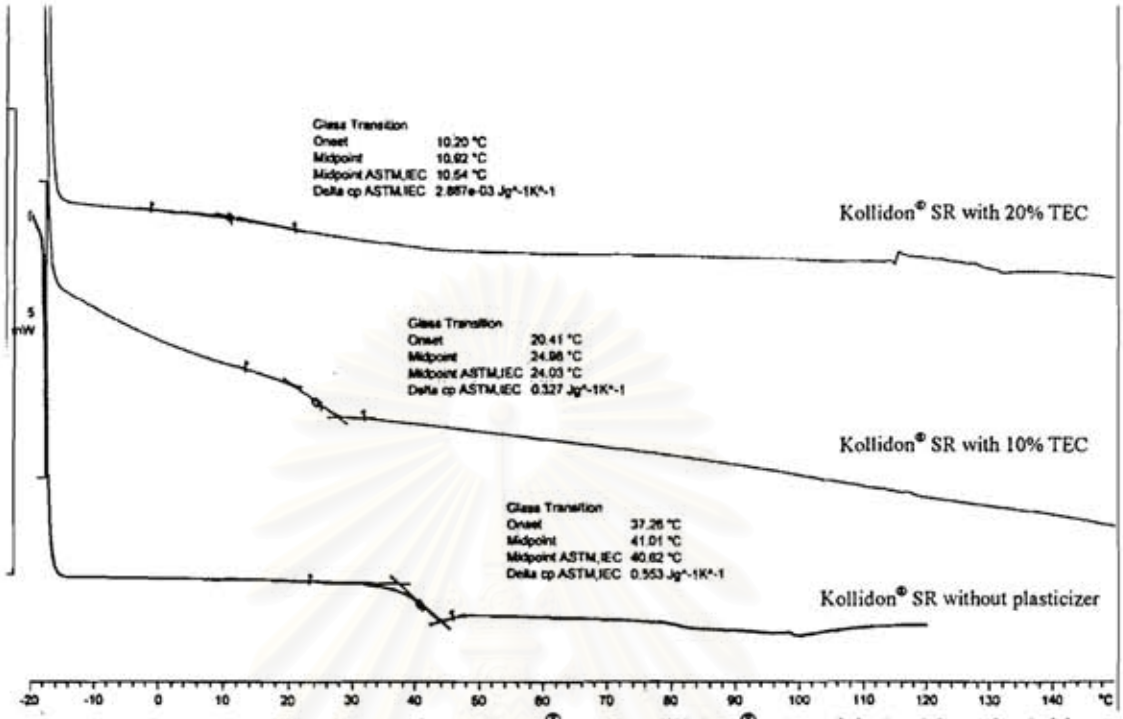

Figure 82 DSC thermograms of Kollidon® SR, Kollidon® SR with 10 % and 20 % TEC prepared by method IV (spray dried)

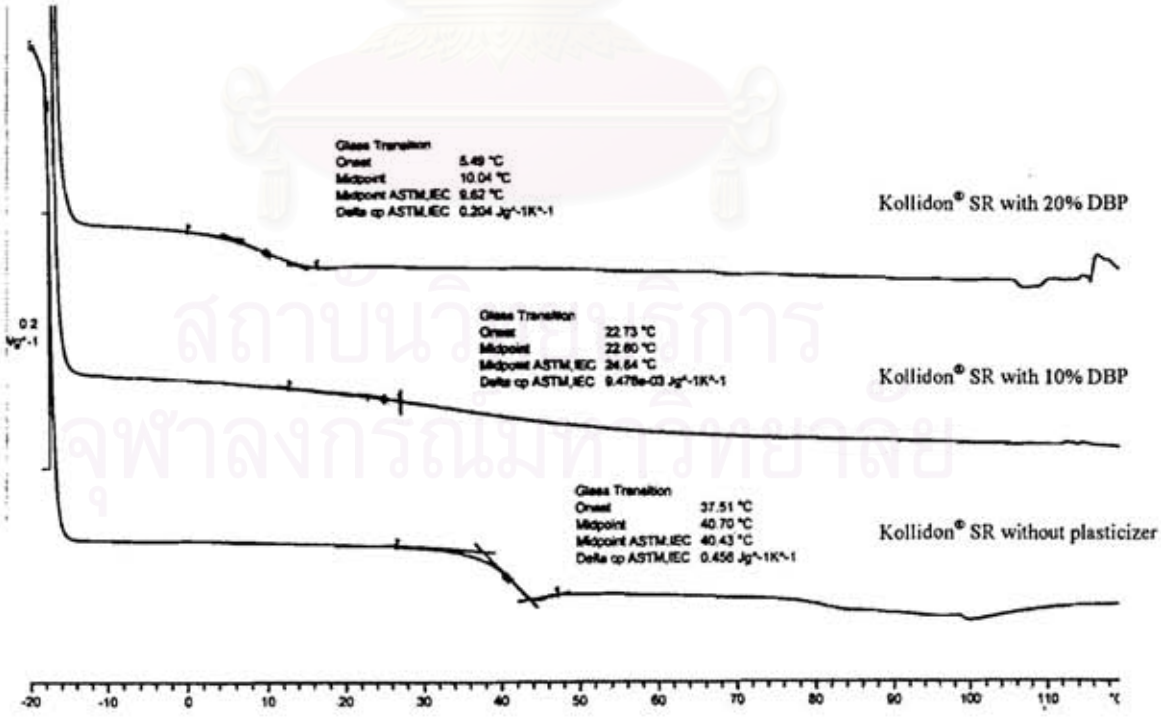

Figure 83 DSC thermograms of Kollidon® SR, Kollidon® SR with 10 % and 20 % DBP prepared by method IV (spray dried)

VITA

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