ผลของตัวแปรในกระบวนการผลิตและสูตรตำรับต่อการปลดปล่อยยา
ไดโคลฟีแนคโซเดียมจากไมโครแท็บเล็ต

นางสาว ศุรวีร์ จันทร

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EFFECT OF PROCESSING AND FORMULATION VARIABLES ON THE RELEASE DICLOFENAC SODIUM FROM MICROTABLETS

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ศุรวีร์ จันทร : ผลของตัวแปรในกระบวนการผลิตและสูตรตำรับต่อการปลดปล่อยยาไดโคลฟีแนค โซเดียมจากไมโครแท็บเล็ต (EFFECT OF PROCESSING AND FORMULATION VARIABLES ON THE RELEASE DICLOFENAC SODIUM FROM MICROTABLETS) อ. ที่ปรึกษา : รศ. ดร. กาญจน์พิมล ฤทธิเดช, อ. ที่ปรึกษาร่วม : ผศ. ดร. ชัยโรจน์ คุณพนิชกิจ, 190 หน้า, ISBN 974-17-5014-5.

งานวิจัยนี้ศึกษาผลของตัวแปรในกระบวนการผลิตและสูตรตำรับต่อคุณสมบัติทางกายภาพ และการปลดปล่อยตัวยาของไมโครแท็บเล็ตซึ่งเป็นเภสัชภัณฑ์ในรูปแบบหลายหน่วย และเพื่อพัฒนาสูตรตำรับไดโคลฟีแนค โซเดียมไมโครแท็บเล็ตชนิดออกฤทธิ์นาน ไมโครแท็บเล็ตประกอบด้วยพอลิเมอร์ เช่น เอธิลเซลลูโลส และ ไฮดรอกซีโพรพิลเมธิลเซลลูโลส และ แวกซ์ เช่น คอมไพรตอล 888 เอทีโอ และไตรสเตรียริน เป็นสารก่อเมทริกซ์ และเตรียมด้วยวิธีการทำแกรนูลเปียก โดยพบว่าแกรนูลที่ประกอบด้วยเอธิลเซลลูโลสในปริมาณสูง และการผสมกันระหว่างเอธิลเซลลูโลส และไฮดรอกซีโพรพิลเมธิลเซลลูโลส หรือ เอธิลเซลลูโลส และกลีเซอไรด์แวกซ์ ส่งผลทำให้อัตราการไหลของแกรนูลลดลง แสดงว่าชนิดและปริมาณของสารก่อเมทริกซ์มีผลต่อคุณสมบัติทางกายภาพของไดโคลฟีแนค โซเดียมแกรนูล จากการตรวจสอบคุณสมบัติทางกายภาพของไดโคลฟีแนค โซเดียมไมโครแท็บเล็ต พบว่าความแปรปรวนของน้ำหนักเม็ดยา ความกร่อน ปริมาณตัวยาสำคัญ และความสม่ำเสมอของตัวยาสำคัญ มีคุณสมบัติเข้าตามมาตรฐานเภสัชตำรับของอเมริกา 24 นอกจากนี้พบว่าความแข็งของเม็ดยาขึ้นอยู่กับแรงตอกและขนาดของสากที่ใช้ในกระบวนการผลิต เนื่องจากตัวยามีค่าการละลายที่ต่ำมากทำให้ ไดโคลฟีแนค โซเดียมไมโครแท็บเล็ตมีการปลดปล่อยตัวยาต่ำกว่า 5 เปอร์เซ็นต์ในตัวกลางที่เป็นกรด แต่ในสภาวะที่เป็นด่างปริมาณไดโคลฟีแนค โซเดียมที่ละลายจะค่อยๆเพิ่มมากขึ้นตลอดเวลา 24 ชั่วโมง แรงตอกระหว่าง 400-1200 ปอนด์ ส่งผลเล็กน้อยต่ออัตราการปลดปล่อยตัวยา แต่ในทางตรงกันข้ามเมื่อเพิ่มขนาดเส้นผ่านศูนย์กลางของเม็ดยาให้มากขึ้นทำให้อัตราการปลดปล่อยตัวยาลดลง แสดงว่าเมื่อเปลี่ยนแปลงพื้นที่ผิวของเม็ดยาส่งผลเด่นชัดต่ออัตราการปลดปล่อยตัวยา การเพิ่มปริมาณตัวยาไดโคลฟีแนค โซเดียมในสูตรตำรับจะทำให้มีการปลดปล่อยตัวยาสูงขึ้น การเพิ่มอัตราส่วนของแวกซ์ต่อเอธิลเซลลูโลสมีผลทำให้การปลดปล่อยตัวยาลดลง ขณะที่การผสมกันระหว่างเอธิลเซลลูโลสกับไฮดรอกซีโพรพิลเมธิลเซลลูโลสให้ผลในทางตรงกันข้าม แสดงว่าชนิดและปริมาณของสารก่อเมทริกซ์ส่งผลต่ออัตราการปลดปล่อยตัวยา ไดโคลฟีแนค โซเดียมไมโครแท็บเล็ตทั้งหมดที่ผลิตได้มีจลนศาสตร์การปลดปล่อยแบบอันดับหนึ่ง และมีกลไกการปลดปล่อยตัวยาแบบซูเปอร์-เคสทู การศึกษานี้ยังครอบคลุมถึงการวิเคราะห์รูปแบบการปลดปล่อยตัวยาและนำมาเปรียบเทียบกับผลิตภัณฑ์ที่มีจำหน่ายในท้องตลาด พบว่ารูปแบบการปลดปล่อยตัวยาออกจากไดโคลฟีแนค โซเดียมไมโครแท็บเล็ต มีความแตกต่างจากโวทาเรน เอสอาร์ 75 มิลลิกรัม

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

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SURAWEE CHANTORN : EFFECT OF PROCESSING AND FORMULATION VARIABLES ON THE RELEASE DICLOFENAC SODIUM FROM MICROTABLETS. THESIS ADIVISOR : ASSOC. PROF. GARNPIMOL C. RITTHIDEJ, Ph.D., THESIS COADVISOR : AIST. PROFESSOR CHAIROTE KUNPANITCHAKIT, Ph.D., 190 pp. ISBN 947-17-5014-5

The effect of processing and formulation parameters on properties and drug release of microtablets as subunit in multiparticulate dosage form was investigated in this study. In addition, a sustained release diclofenac sodium (DS) microtablet was formulated. The microtablets contained various polymers such as ethylcellulose (EC) and hydroxypropylmethylcellulose (HPMC K15M), waxes such as compritol 888 ATO and tristearin as matrix former and prepared by wet granulation method. It was found that the flow rates of granules were decreased when the granules contained high amount of EC and combined EC with HPMC K15M or EC with glycerides waxes, indicating that type and amount of matrix former affected the physical properties of the DS granules. The physical properties of DS microtablets such as weight variation, friability, drug content, and content uniformity were passed the specification of official USP 24. In addition, it was noted that the hardness of DS microtablets was depended on the compression force and punch size. Due to its very low solubility in acid medium, DS microtablets exhibited lower than 5% release in 0.1 N HCl, while in phosphate buffer stage, percentage of DS dissolved could gradually increase over 24 hours. The compression forces from 400 to 1,200 lb had negligible effect on the drug release. On the other hand, increasing the tablet diameter decreased the release rate. Hence, the surface area had strong influence on the drug release pattern. Higher DS content gave faster release rate, increasing the proportion of waxes to EC ratio decreased the release rate, while combining EC with HPMC K15M exhibited opposite effect. Therefore, the sustained effect was depended on the types and amount of matrix former. Furthermore, the release model of all formulations was best fit the first-order plot and the mechanism of release was Super Case II transport. The release models of all prepared microtablets were also assessed in comparison with a commercial product (Voltaren® SR 75 mg). It was found that the drug release profiles of DS microtablets were different to that of Voltaren SR tablet.

Department….Manufacturing Pharmacy……Student’s name…….....
Field of study….Industrial Pharmacy…….Advisor’s name……....
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LIST OF ABBREVIATIONS

°C	degree Celsius (centigrade)
cps.	centipoints
cm	centimeter (s)
DS	diclofenac sodium
DSC	differential scanning calorimetry
EC	ethylcellulose
e.g.	exempli gratia
et al.	et alii, and others
g	gram (s)
g/sec	gram/sec
HCl	hydrochloric acid
HPMC	hydroxypropylmethylcellulose
hr	hour (s)
i.e.	id est, that is
IR	infrared
kg	kilogram (s)
KH_2PO_4	potassium dihydrogen phosphate
lb.	pound (s)
min.	minute (s)
mg	milligram (s)
ml	milliliter (s)
MNm^{-2}	mega Newton per square meter
N	normality
NaOH	sodium hydroxide
NF	The Nation Formulary
Nm	nanometer (s)
No.	number
pH	the negative logarithm of the hydrogen ion concentration
pKa	the negative logarithm of the dissociation constant
q.s.	make to volume

r^2	coefficient of determination
%RH	percentage of relative humidity
SD	standard deviation
SEM	scanning electron photomicrograph
USP	The United States Pharmacopiea
BP	The British Pharmacopiea
UV	ultraviolet
w/w	weight by weight
w/v	weight by volume
μg	microgram (s)
μm	micrometer (s)
%	percentage

CHAPTER I

INTRODUCTION

Oral sustained release products are developed in order to enhance safety and extend of action. These may be of greater importance, especially in long term treatment. Sustained release products can decrease fluctuation of serum concentrations, resulting in reduced toxicity and sustained efficacy and also decrease frequency of dosing, resulting in improved patient compliance, reduced patient care time, and possibly reduced total amount of drug used. Drugs that are taken on a chronic or extended basis, such as cardiovascular, arthritic, respiratory, and analgesic products, often have the most potential for controlled release delivery (Ranade and Hollinger, 1996). Multiparticulate dosage forms such as matrix or coated pellets, microtablets or microparticles (microcapsules or microspheres) have gained interests in oral sustained release formulations. Multiparticulates can be filled into capsules, if the capsules dissolved, multiparticulates will be wildly dispersed throughout the gastrointestinal tract. Thus, it is resulting in a more uniform drug absorption and reduced patient-to-patient variability. The dispersion of multiparticulates also reduces the risk of local irritation of gastric mucosa (Kramer and Blume, 1994).

The pellets are one kind of matrix type dosage forms used to achieve sustained release. They are particles of 1-2.5 mm diameters, which contained various hydrophobic or hydrophilic materials. However, the pellets are wildly used as sustained release dosage forms but the pellet production has many drawbacks, which gives undesirable pellet for sustained release dosage form such as broad size distribution, the irregularity of shape and/or the surface structure (Rey H. et al., 2000). Moreover, the solvent in these processes affects the porous structure of the products. The weight of the individual pellet fluctuates greatly. The undesirable characteristics of pellet are not suitable for producing the effective sustained release dosage forms. However, these disadvantages properties could be overcome by the microtablets (Pich C.H. et al., 1989; Ney H. et al., 1991).

Microtablets or minitablets are tablets, which have a diameter and height that are preferably approximately equal and, independently of another, from 1-3 mm, preferably 1.5-2.5 mm. Its shape is nearly spherical or cylindrical with a flat or convex upper and lower side. They are made by ordinary reciprocating or rotary tabletting machines, using a multiple tooling (Lennartz P. et al., 1998). The microtablet according to the invention is produced in conventional techniques, which commonly use to produce the plain tablet. The equipment is similar to that produces the plain tablets, except the tooling of the tabletting machine. The special punches and dies that require precision and mechanical stability must be used. Because the punch station is equipped with a punch holder that containing many small concave punches per punch holder. The most awareness factor for producing the microtablets is the flowability of powder because it affects the properties of microtablets (Lennartz P. et al., 1998; Rey H. et al., 2000).

The characteristics of microtablets are better than the pellets such as narrow size distribution, the uniformity of the shape and surface structure because of the controlling by punch and die. Furthermore, the weight of the individual microtablet is not varied. These advantages are desirable for producing sustained-release dosage form (Brabander C.D. et al., 2000; Rey H. et al., 2000).

At present, there are many research articles about the microtablets. Pich et al. (1989) used various methods to prepare microtablets, such as fluidized bed granulator and coating techniques, extraction method, and direct compression. Rey et al. (2000) prepared sustained-release theophylline microtablets based on a Eudragit RS PO matrix and produced on a rotary tablet press. Brabander et al. (2000) prepared ibuprofen matrix tablets that contained with combination of different microcrystalline waxes with various melting range and starch derivatives. Weyenberg et al. (2003) prepared ocular bioadhesive minitablets of sodium fluorescein and studied the influence of the compression force on the release rate.

Diclofenac sodium is a non-steroidal anti-inflammatory agent used for painful and inflammatory conditions. It has an adverse effect on the gastric mucosa and short biological half-life. Thus, it is usually given two to three times daily (Reynolds et al., 1989), in order to reduce the gastric irritations, maintaining plasma drug levels within

the therapeutic range for longer period and decrease frequency of dosing. Hence, sustained release of diclofenac sodium has been developed. In this study, sustained release diclofenac sodium microtablet was developed using cellulose derivative and glyceride waxes, since the cellulose derivative polymers and waxes have been extensively investigated for sustaining the release of drug and ease of manufacturing (Romero et al, 1991; Zhang and Schwart, 2000; Obaidat et al., 2001; Lin et al., 2001). Although the single-unit matrices of diclofenac sodium sustained-release are widely developed, there are rarely reports on the preparation of sustained release diclofenac sodium microtablets. Sujja-areevath et al. (1996) prepared diclofenac sodium microtablets contained various amount of natural gum by wet granulation method. However, there is no report on the preparation of diclofenac sodium microtablets by using cellulose derivative and glyceride waxes. Therefore, the aim of this study was to study effect of processing and formulation parameters on properties and drug release of microtablets. In addition, diclofenac sodium microtablets containing cellulose derivatives and waxes as sustained release materials were formulated.

Objective of this study

On the basis of rational mentioned above, the objectives of this research are:

1. To study the effect of processing parameters such as compression force, punch size on physicochemical properties of diclofenac sodium microtablets.
2. To study the effect of formulation variables such as drug load, type and amount of matrix formers on the physicochemical properties of diclofenac sodium microtablets.
3. To prepare sustained release diclofenac sodium microtablets with cellulose derivative and glyceride waxes using wet granulation technique and to evaluate the physicochemical properties of diclofenac sodium microtablets.
4. To compare drug release from the capsules containing the prepared microtablets to a commercial product.
5. To investigate the model and mechanism of drug release from the prepared microtablets.

CHAPTER II

LITERATURE REVIEWS

1. Microtablet or minitablet

The microtablets are tablets with a diameter equal to or small than 1-3 mm, preferably 1.50-2.50 mm. Their shapes are nearly spherical and cylindrical with a flat or convex upper side and lower side. It has definite advantages over the single unit dosage forms. These advantages are less risk of dose dumping, less inter- and intra-subject variability, and high degree of dispersion in the digestive tract that reduced the risks of high local drug concentrations. Therefore, microtablets also offer an alternative for pellets because of their uniform size with smooth surface and low porosity structure. The microtablets are made by ordinary reciprocating or rotary tabletting machines. However, it must use the special punches and dies that require high precision and mechanical stability, because the punch station is equipped with a punch holder that contains many small concave punches (Flemming et al., 1996; Kolter et al., 1997; Rey et al., 2000).

Figure 1 The construction of multiple upper punches, lower punch and die for preparing Panzytract® and Ceferro®

Figure 1 shows the special steel rams used for tabletting of 19 microtablets at each compression to produce Panzytract® and Ceferro® by Nordmark Pharma (Normark Arzneimittel GmbH& Co.KG).

The special punch and dies have many punches per holder, which are narrow diameters. Therefore, these tooling require excellent flowability that is an important factor necessary for producing microtablets because it affects the uniformity of weight and content of the microtablets (Flemming and Mielck, 1995; Pich et al., 1989).

2. The techniques of microtablets production

The methods used to produce microtablet are similar to plain tablet production such as the direct compression and wet granulation method. For direct compression method, the active ingredient is mixed with other additives such as diluents and lubricant until homogeneous. Then the powder mixtures are compressed with single punch tabletting machine or rotary tabletting machine that containing with special punches and dies.

Flemming et al. (1995) reported that spray-dried lactose preparations FLOW®, DCL11 was appropriated diluent for preparing microtablets by direct compression method. It was due to free-flowing property. The flow rates of additional materials, namely PHAV, CEMCC, CEPC, and DCL40 were sufficient, when theoretically required flow rates were calculated from the volume of microtablets and filling times available on modern rotary tabletting machine.

Saettone et al. (1995) prepared sustained release timolol maleate microtablets by direct compression and coated with Eudragit RS and Eudragit RL. The microtablets were pressed by a single punch tabletting machine that contained concave punches and dies with a diameter of 3.5 mm. They observed that an adequate control of the drug release from this microtablet could be obtained by adjusting the amount of acrylic polymer coating.

Wet granulation method is more complicated than direct compression method. The granule is either prepared by using ordinary technique (sieving method) or fluidization technique.

Gazzaniga et al. (1993) prepared verapamil and dyphylline mini-matrices. The drug, polymer and filler mixtures were granulated by wetting with an isopropyl alcohol 5% solution of Eudragit® RS. The mixtures were passed through a 710 μm screen and dried at 35°C. The granules were lubricated with magnesium stearate (0.5%) and tableted in a single punch instrument tabletting machine with 3.5 mm diameter of punch.

Rey et al. (2000) prepared sustained-release theophylline microtablets with wet granulation technique that using fluidized bed granulator. In fluidized bed granulator equipped with a 0.8-mm nozzle, the powder blend of 400 g theophylline and Eudragit RS PO were granulated by top-spraying of 6% of Eudragit RS 30D as binder at an atomizing air rate of 1.2 bars. Inlet air temperature was maintained 60 °C, and granulating liquid flow rate was 18-20 g/min. The granules were then dried in the same apparatus for approximately 15 min at 60 °C. The granules were sieved and the fraction below 500 μm was used for preparation of tablets. Then the granules were compressed with rotary tabletting machine that using force feeder and 17 punch station. The punch station was equipped with a punch holder containing 19 small concave punches, each with a diameter of 2 mm.

Brabander et al. (2000) prepared ibuprofen matrix tablets that contained combination of different microcrystalline waxes with various melting range and starch derivative by melt extrusion. The melt extrusion was performed on a MP19TC-25 laboratory scale co-rotating twin screw extruder of APV Baker. The temperature profiles were necessary during extrusion: 58-56-56-53-53 °C from powder feeder towards the die for Paracera® P and IGI® 2291 based formulations, while a higher temperature profile: 64-62-62-59-58 °C was used in Paracera® M formulations The extrudates were then milled by sieving. The fraction of granules sized below 500 μm was used for preparation of tablets by using eccentric tabletting machine (EKO).

3. Evaluation the microtablets

3.1 Apparent tensile strength

At equal applied pressures, powders compress to different degrees, which produce compacts of different thickness. This difference in compact thickness may influence the pressure-crushing force profile (Newton et al., 1968). To overcome this potential problem, Fell and Newton (1968) developed a diametral compression test to determine the tensile strength of tablets. The tensile strength (σ_x) of the compacts was determined according to the method of Fell and Newton:

$$\sigma_x = \frac{2F}{\pi \times d \times t} \qquad [1]$$

where F is the crushing force, d is the compact diameter and t is the compact thickness.

Equation [1] is used frequently for calculation of the tensile strength of flat-faced, but not of convex-faced. Lennartz et al. (1998) used equation [1] even though convex faced tablets were produced, because the tensile strength of these tablets should be closely related to the overall tablet thickness due to the high ratio between central cylinder thickness and diameter (Pitt et al., 1988). Therefore, equation [1] results in an apparent tensile strength produce. This apparent tensile strength, ts_{app}, may be used for comparison of the tablets with differing size, because the error made can be taken as constant due to the geometrical specifications.

The equation [2] for determination of tensile strength, σ_f, of convex-faced tablets was developed by Pitt et al. (1988), which based on analysis with dimensional considerations. The equation [2] could not be used because of the different ratios between central cylinder thickness and diameter, which were between 0.06 and 0.3 for tablets investigated by Pitt et al. (1988) and 0.6 for the tablets produced by Lennartz et al. (1998)

$$\sigma_f = \frac{10F}{\pi d^2} (2.86t/d - 0.126t/w + 3.15\ w/d + 0.01)^{-1} \qquad [2]$$

where F is the crushing force, t is overall tablet thickness, d is diameter and w is central cylinder thickness.

Lennartz et al. (1998) applied equation [2]. Certain simplification was adopted due to the geometric specifications of tablets. Because of the tabletting procedure and the constant relative curvature of the punches, one may assume that the ratio between central cylinder thickness and diameter and the ratio between overall tablet thickness and diameter are constant. Therefore the ratio of t/d, t/w and w/d, and the term insides of the parentheses may be taken as constant.

Equation [2] then transforms into equation [3]

$$\sigma_f = \frac{2F}{\pi dt} \times (K)^{-1} \qquad [3]$$

where K is a constant, which represents the error made by applying equation [1] for the tablets produced in investigation. However, due to the considerations mentioned above, K cannot be determined precisely without stress analysis.

However, the true values of the tensile strength have not been determined. Tablets with same geometrical proportions may be compared, under the assumption that the error is constant. The variable ts_{app} would then correspond to $\sigma_f \times K$ in equation [3].

4. Controlled parameters of the matrix system

Technological factors influencing release from controlled matrix tablets can be states as the following parameters:

A. Amount of drug incorporate in matrix

The influence of the type and amount of drug incorporated in matrix is interesting and of practical importance in the field of controlled release. Fessi et al. (1982) have shown the several systems of loading type obeyed the Higuchi square root equation, such that the slope was approximately proportional to the initial drug loading.

Foster et al. (1990a, 1990b) showed the release of ephedrine hydrochloride and procaine hydrochloride from hydrogenated castor oil matrix tablet. The effect of drug revealed that the release profiles at 25°C in terms of cumulative amount release per unit area versus square root of time were linear. The release increased with increasing the concentration of drug. A similar result was obtained when using to other drug.

Katikaneni et al. (1995) determined the effect of drug load on the release of drug from matrix tablets. Pseudoephendrine hydrochloride was used as a model drug to prepare direct compression sustained release tablets with ethylcellulose 10 cps. Psudoephendrine hydrochloride was varied from 12.5% to 25.5% and compressed at 22.25 kN. Increase in the concentrations of drug in matrix resulted in an increase in the amount of drug release at any time t. It must be noted that a change in concentration of drug would affect the porosity and may possibly affect the tortousity of the matrix.

Rey et al. (2000) prepared sustained-release theophylline microtablets with wet granulation technique that using fluidized bed granulator. The influence of drug content on the release of drug from theophylline matrix microtablets was determined. Microtablets containing 60% to 80% of theophylline in Eudragit RS PO matrix were compressed at 200 MPa. It was found that theophylline content did not affect on the drug release.

Brabander et al. (2000) prepared ibuprofen matrix microtablets that contained combination of microcrystalline wax (Paracera P®), 2.5% of triacetin and

WMD (waxy maltrodextrin) and varied drug content 40%, 60% and 70%. The ibuprofen concentration affected the release rate. It was observed that increasing the ibuprofen concentration to 70% w/w resulted in a faster drug release rate than formulations 40% and 60% probably due to the high drug load and lower concentration of matrix forming materials.

B. Type and amount of matrix material

The matrix material should be met the selection criteria as shown in Table 1 (Phillai et al., 1988). The matrix former should be chemically inert, non toxic, cheap etc.

Emori et al. (1984) reported that the increase in the release rate occurred with increasing amount of polymer in phenacetin wax matrix, because of an increase in the diffusion rate of drug molecules through channels that resulted from leaching of the polymer and also by a shortening of this channel length due to matrix disintegration.

Brabander et al. (2000) prepared ibuprofen matrix microtablets that contained combination of different microcrystalline waxes with various melting range and starch derivative. The drug release rate of IGI® 2291 formulation was higher than those of Paracera P®, Paracera M®, respectively. The amount of drug release was depended on the melting range of microcrystalline waxes (49-52°C for IGI® 2291, 58-62°C for Paracera P®, 68-72°C Paracera M®). Increasing the amount of wax in the formulation showed a slower drug release profile.

Liu et al. (2001) prepared lipophlic matrix tablets containing phenylpropanolamine hydrochloride (PPA) by hot-melt extrusion. At the same wax level, drug release from tablets was decreased in the order of using microcrystalline cellulose, lactose, Emcompress® as the filler excipient, respectively. The observed differences in dissolution properties of the tablets were due to the differences in the solubility, swellability and density of the filler excipients.

C. Influence of the surface area of matrix

Lin et al. (1996) proposed that smaller particles possessed higher dissolution rates than larger particles due to the former possessing a greater available surface area of drug generated may control the release of drug from solid dispersions.

Table 1 The criteria in selection polymers for matrix development

1. Molecular weight, glass-transition temperature, and chemical functionality of the polymer must allow the proper diffusion and release of the specific active agent. 2. Polymer functional group should not react chemically to active agent. 3. The polymer and its degradation product must be not toxic. 4. The polymer must not decompose during the entire shelf-life. 5. The polymer must be easily manufactured or fabricated into a desired product. 6. The cost of polymer should not be expensive as to make controlled drug release device very expensive. 7. It should be readily available.

Shanawany (1993) reported that the release of nitrofurantoin from matrix was reduced when the granule size increased. This effect was mainly due to the reduction in surface area of granules exposed to the dissolution medium. Consequently, granules of 125-200 μm showed the highest drug release of 80% w/w, while granules of 300-450 μm showed the lowest release of 52% w/w after 6 hrs.

Rey et al. (2000) reported that tablets with a low quotient surface area/ tablet weight led to slower release from theophylline matrix tablets. Compared to 2 mm cores, drug release was slower with 6 mm tablets and much slower with 10 mm tablets. Microtablets having a diameter of 2 mm exhibited higher surface area compared to tablets 6 mm and 10 mm in diameter.

D. Influence of the compression force

Stamm and Tritsch (1986) prepared the methocopraminde hydrochloride containing ethylcellulose 20 cp. The matrices made with low crushing strengths had high porosity and gave fast release. Whereas, the tablets prepared higher crushing strengths had lower release rates.

Sarisuta et al. (1994) investigated that the influence of compression force and type of fillers on the drug release of diclofenac sodium matrix tablets containing Emcompress® and lactose as fillers with Eudragit RS PM as a matrix former. The results indicated that the compression forces did not affect on the drug release. Whereas, increasing the amount of Emcompress® in formulation caused to decrease the drug dissolution.

Dabbagh et al. (1996) investigated the effect of compaction pressure on the drug release from matrices containing 285 mg of ethylcellulose 7cp. The drug release from matrices made at 7.8-39.4 MNm^{-2} was very rapid. Whereas, the release rate of matrices compressed at between 78.7 and 393.7 MNm^{-2} were relatively unaffected by pressure. It was due to porosity of matrices made at between 78.7 and 393.7 MNm^{-2} that were not different.

Velasco, et al. (1999) reported that although compression force was a statistically significant factor in tablet hardness, its effect on drug release from HPMC tablets was minimal. It could be assumed that the variation in compression forces should be closely related to a change in the porosity of tablets. However, as the porosity of the hydrate matrix was independent of the initial porosity, the compression force seemed to have little influence on the drug release.

5. The release pattern of matrix system

5.1 Matrix system

A matrix system, as the name implies, consists of drug distributed homogenously throughout a polymer matrix. When the term “matrix device” is used

without qualification, it typically means that the containing polymers doses not chemically disintegrate. If the polymer dose erodes, the device- actually a type of matrix device is referred to as an erodible, bioerodible, or biodegradable system.

Matrix systems have the advantage of generally being easier and less expensive to produce than reservoir systems. In addition, because they do not have a polymer covering that can suddenly break; there is no danger of an abrupt release of a large amount of drug.

There are two principle categories of matrix devices. If the active agent is dissolves in the polymer medium, the device is called a matrix solution. A device of this kind is often used when the active agent is a liquids, some polymer can easily dissolve up to 20% or more in these liquids. If the active agent had a more limited solubility in the polymer medium and the remainder is dispersed as small particles throughout the polymer. A device of this type is called matrix dispersion.

5.2 The release pattern of matrix system

The pattern of delivery achieved by a sustained release system can vary over a wide range but release profiles can be mainly categorized into three types:

1. Zero-order release model
2. Square-root-time release model
3. First-order release model

5.2.1 Zero-order release model

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

$$\frac{dM_t}{dt} = k \qquad [4]$$

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

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

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

$$\frac{dM_t}{dt} = \frac{k}{\sqrt{t}} \qquad [5]$$

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

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

$$Q = [D\varepsilon/ \tau(2A-\varepsilon C_s) C_s t]^{½} \qquad [6]$$

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

The assumptions made deriving equation are as follows:

1. A pseudo-steady state is maintained during release
2. $A>>>C_s$, i.e., excess solute is present
3. The system is in perfectly sink condition in which C, is approximately to zero at all time
4. Drug particles are much smaller than those in the matrix
5. The diffusion coefficient remains constant
6. No interaction between the drug and the matrix occurs

In general Higuchi's equation is usually desired and used as in equation [7]

$$Q = k_h t^{1/2} \quad [7]$$

where k_h = Higuchi constant

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

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

$$\log Q = \log k_h + \tfrac{1}{2} \log t \quad [8]$$

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

5.2.3 First-order release model

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

$$\frac{dM_t}{dt} = k (M_0 - M_t) \quad [9]$$

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

$$\frac{dM_t}{dt} = kM_0 \exp^{-kt} \quad [10]$$

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

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

$$A_t = A_0 e^{-k_1 t} \qquad [11]$$

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

Simplifying and taking the logarithm of equation (11) yields

$$\log A_t = \log A_0 - \frac{k_1 t}{2.303} \qquad [12]$$

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

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

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

$$\frac{dQ}{dt} = \frac{k_h^2 S^2}{2Q'} \qquad [13]$$

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

$$\frac{dQ}{dt} = kA_0 - kQ \qquad [14]$$

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

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

The release model for each classes of device is illustrated in Figure 2 (Baker, 1987). The release models of zero-order, square-root time, and first-order are depicted, respectively [equation 4, 5 and 9].

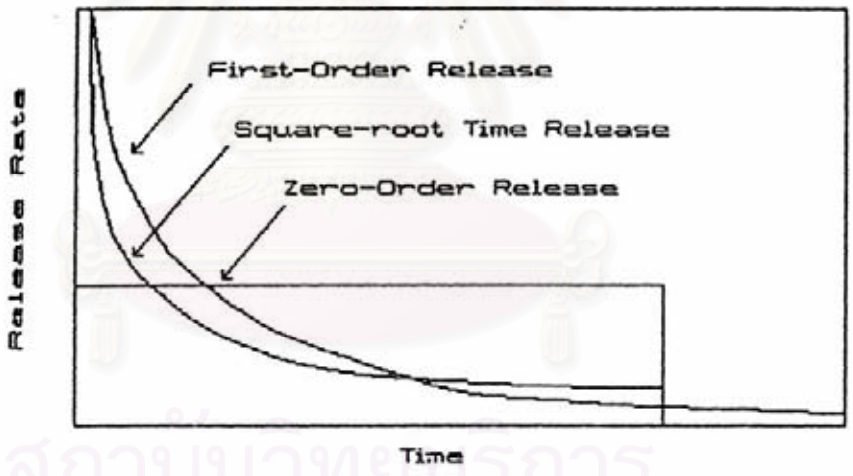


Figure 2 Zero-order, First-order, and Square-root time release patterns from devices containing the same initial active agent content

5.3 Release mechanism of controlled release system

A semi-empirical eq. [15] can be used to analyze data of controlled release of drug under perfect sink conditions. The general form of this equation is given by Peppas (1985).

$$\frac{M_t}{M_\alpha} = kt^n \qquad [15]$$

where, $\frac{M_t}{M_\alpha}$ = the fractional of release of drug up to time t

t = the release time

k = a constant incorporating structure and geometric characteristics of the controlled release device

n = the release exponent, indicative of the mechanism of drug release

The determination of exponent n is valid for the first 60% of total release drug ($M_t/M_\alpha \leq 0.6$), which also applied only the early times of release. Clearly, at desirable mechanism for many applications that which leads to be equals 1, this characterizes zero-order release behavior. Table xxx summarizes the general dependence of n on the diffusional mechanism (Peppas, 1985).

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

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

The empirical equation [15] could be modified for application to non-planar geometric. The relationship between the diffusional exponent *n* and the corresponding release mechanism is clearly depend upon the geometry employed as shown in Table 2 , 3, and 4 (Rittger and peppas, 1987).

In non-swellable matrices, the values of n are 0.45 and 1.0 for Fickian and case–II transport, respectively. Case-II transport is a special case readily identified and characterized by the constant velocity of the moving solvent front and the resulting linear weight gain with time. However, its characteristics are not as well understood, nor are they as fundamental in origin as those of Fickian diffusion. When the value of n is >0.45 and < 1.00, the release was said to be non-Fickian (Rittger and peppas, 1987). A value of n =1, however, means that the drug release is independent of time, regardless of the geometry. Thus, zero- order release can exist for any geometry.

Table 3 Diffusional exponent and mechanisms of diffusional release from various non-swellable controlled release systems

Diffusional exponent, *n*			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
0.5<*n*<1.0	0.45<*n*<1.0	0.43<*n*<1.0	Anomalous (non-Fickian) transport
1.0	1.0	1.0	Zero-order (time-independent)

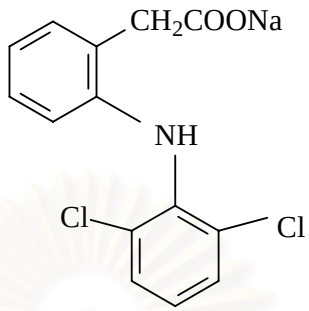
In swellable controlled release systems, case-II (Fickian diffusion) and case-II solute release behaviors are unique in that each can be described in terms of a single parameter. Case-I transport is described by diffusion coefficient, while case-II transport is described by a characteristic relaxation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

In swellable matrices, when the system does not swell more than 25% of its original volume, the values of n are 0.45 and 0.89 for Fickian and case-II transport, respectively. When the value of n is > 0.45 and <0.89, the release was said to be non-Fickian (Rittger and peppas, 1987). When the value of n was greater than that of the case-II transport, the release is said to be super case-II transport. Table 4 summarizes the range of values of diffusional exponent n, and the released transport mechanism for each a geometry (Rittger and peppas, 1987). A value of n = 1, means that the drug release can exist for any geometry; only slabs do this release coincide with case-II transport.

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

Diffusional exponent, *n*			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
0.5<*n*<1.0	0.45<*n*<0.89	0.43<*n*<0.85	Anomalous (non-Fickian) transport
1.0	0.89	0.89	Zero-order (time-independent)

6. Diclofenac sodium



MW. 318.13

Figure 3 Diclofenac sodium ($C_2H_{10}C_{12}NO_2Na$)

Diclofenac sodium (DS) or 2-[2,6-Dichloropheny)amino]benzeneacetic acid monosoduium salt is synthetic, non steroidal anti- inflammatory and analgesic compound. It is widely used for relief of pain and inflammation. DS appears as odorless, white to off white crystalline, slightly hygroscopic powder. Melting point is 283-285°C. The pKa of DS in water is 4 and the partition coefficient in n-octanol/aqueous buffer pH is 13.4. The aqueous solubility of DS is dependent on pH; solubility is poor at low values of pH but when the pH rises above the pKa, rapid increases in solubility occur (Maitani et al., 1991; Herzfeldt and Kummel, 1983).

The presence of cations (sodium ions or potassium ions) markedly affects the solubility of DS. The addition of sodium or potassium chloride to the dissolution decreased the solubility of DS and showed the dissolution rate, with the effect of sodium chloride being greater. The equilibrium solubility performed in various solvents at the room temperature (RT) is shown in Table 5.

Stability

DS tablets film coated with polymers like acrylic and hydroxypropyl cellulose was reported to be stable after storage for one week at 30°C in the relative humidity of 80%. Suppository formulation was also analyzed for stability using thin layer

chromatography and ultraviolet spectroscopy. The formulation was stable for 24 months at room temperature. Stability in biological fluid (serum) was determined and the results demonstrated that DS could be frozen for at least two weeks without degradation (Adeyeye and Li, 1990).

Buffered sodium (pH 7.4) that DS dissolved in either (β-CD) or hydroxyprophyl-β-cyclodextrin (HP-β-CD) were prepared either in presence or absence of oxygen and stored in the dark (Backensfeld et al., 1991). Solution from which oxygen had been removed was claimed to be more stable than those with oxygen. Although precipitation was observed in solution β-CD or HP-β-CD during a short storage time at 21°c no loss of DS was reported after 520 days. At 71°c in solutions (without oxygen) that contained DS alone, or with β-CD or with HP-β-CD, 24.7%, 30.4%, and 34.6% of diclofenac sodium remained, respectively, after 207 days.

Table 5 The solubility of DS

Solvent	Temperature	Solubility(mg/ml)
Deionized water (pH 5.2)	RT	>9
Methanol	RT	>24
Acetone	RT	6
Acetronitrile	RT	<1
Cyclohexine	RT	<1
PH 1.1	RT	<1
PH 7.2 (phosphate buffer)	RT	6

Use and Administration (Reynolds et al., 1993)

DS is used mainly as the sodium salt for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, renal colic, acute gout, and following some surgical procedures. The usual dose by mouth is 75 to 150 mg of DS daily in divided doses. It may be also being given rectally as a

suppository in a usual dose of 100 mg each evening. DS may also be given by intramuscular injection in a dose of 75 mg one daily or, if required in severe conditions, 75 mg twice daily. It is also used intramuscular renal colic in a dose of 75 mg repeated once after 30 minutes if necessary. In children the suggested dose by mouth or rectally for juvenile chronic arthritics is 1 to 3 mg per kg body-weight daily in divided doses.

Adverse effect (Reynolds et al., 1993; Adeyeye and Li, 1990**)**

Due to the activity of inhibit cyclooxygenase, the most frequent adverse of DS are gastro-intestinal disturbances; abdominal discomfort, nausea and vomiting and abdominal pain to serious gastro-intestinal bleeding or activation of peptic ulcer. Other adverse effects include CNS-related side effect; headache, dizziness, nervousness, tinnitus, depression, drowsiness and insomnia. Hypersensitivity reaction may occur occasionally and include fever and rashes.

Commercial product of sustained-released diclofenac sodium

Voltaren SR® tablet (Norvartis) is one of these products, which is certainly the most successful of all the sustained-release DS products. It shows relatively uniform release pattern for 24 hours period of time. Its characteristic is film-coated tablet of two levels of dosed. These products have 75 mg and 100 mg per tablet.

7. Ethylcellulose (Arthur, 2000)

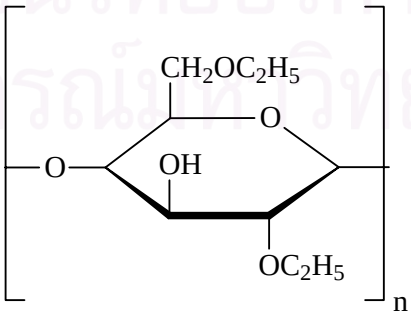


Figure 4 Chemical structure of ethylcellulose

Ethylcellulose (EC) is an inert, hydrophobic polymer and its properties such as lack of toxicity, stability during storage and good compressibility make it suitable for sustained release matrices (Dabbagh et al, 1996).

EC appears as a tasteless, free flowing, white to light tan powder. The various types of EC are not affected by water. EC is insoluble in water, glycerin and propylene glycol, but soluble in varying degrees in certain organic solvents, depending upon the ethoxy content. Its release mechanism is diffusion and erosion. The solubility data of EC is listed in Table 6.

EC is resistant to alkali, both dilute and concentrated, and to salt solutions. It can withstand dilute acid for limited period of exposure. It is subject to oxidative degradation in the present of sunlight or UV light at elevated temperatures. EC is incompatible with paraffin wax and microcrystalline wax. It is presented to be a non-toxic substance.

EC is wildly used to control the dissolution rate of drugs from sustained-release products are as follows, Microencapsules of captopril coated with EC 9, 14, 93 and 300 cps could be directly compressed into tablet. The release pattern was achieved first ordered kinetics followed by Higuchi's equation (Singh et al., 1988). Crowley et al. (2004) prepared EC matrix tablets by either direct compression or hot-melt extrusion of binary mixtures of water soluble drug (guaifenesin). EC was separated into fine or coarse particle size fractions. Tablets containing 30% guaifenesin were prepared at 10, 30 or 50 kN compaction forces and extruded at processing temperatures of 80-90 and 90-110°C. The results were shown that the guaifenesin release rate was slower in tablets prepared with fine EC particle size fraction and tablets prepared by hot-melt extrusion exhibited considerably slower drug release relative to those prepared by direct compression. The guaifenesin release rate also decreased with increasing compaction force in tablets prepared by direct compression. The Higuchi model was found to be the drug release profiles for hot-melt extruded tablets. Tablets prepared by direct compression were found to release guaifenesin by both diffusion and erosion.

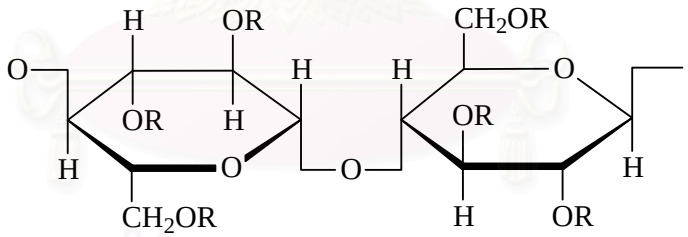
Table 6 Solubility of EC in various solvents (Arthur, 2000)

Solvent	Solubility (g/ml)	
	I*	II*
Water (25°C)	0.010	< 0.001
Water (37°C)	0.012	< 0.001
Alcohol (25°C)	0.015	0.053
Alcohol (37°C)	0.025	0.066
Propylene glycol (25°C)	0.025	0.025
Propylene glycol (37°C)	0.025	0.025
Hexane (25°C)	< 0.002	< 0.002
Hexane (37°C)	< 0.006	< 0.006

Suppliers: I Hercules Ltd.

II Dow Chemical Co

8. Hydroxypropylmethylcellulose



R-H, CH_3- or $CH_3CH(OH)CH_2$

Figure 5 Chemical structure of hydroxypropylmethylcellulose

Hydroxypropylmethylcellulose (HPMC) has been extensively used since the early 1960s as a rate controlling polymer in oral extended-release dosage forms. This popularity can be attributed to the polymer's non-toxic nature, its availability in different chemical substitution and hydration rates (for example, USP Type 2208

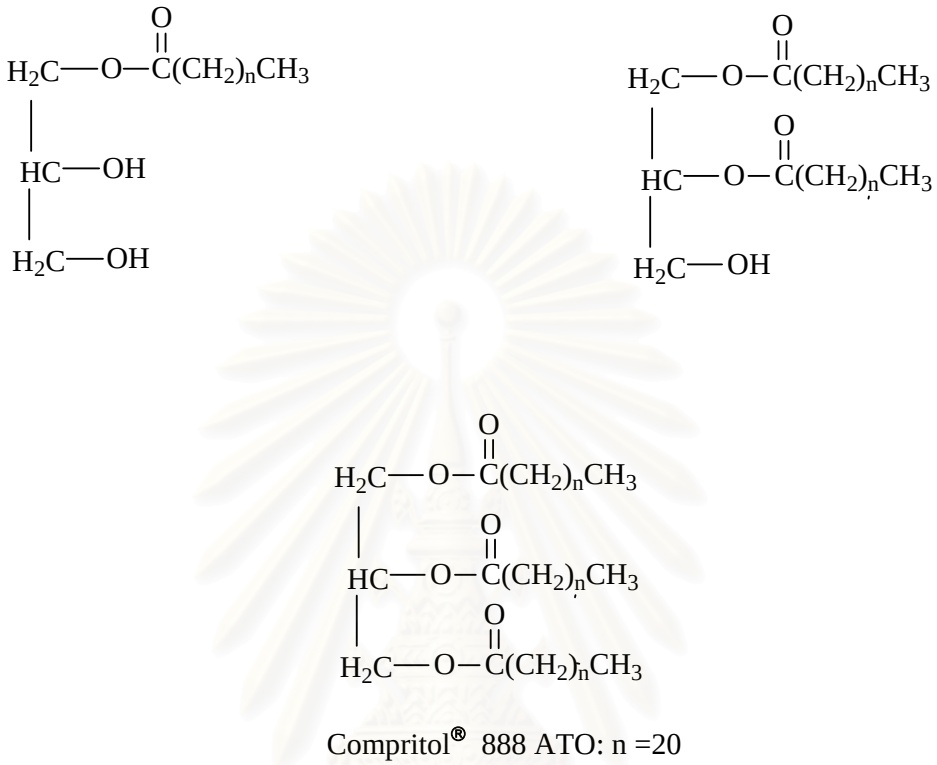
(Methocel K), 2910 (Methocel E), 2906 (Methocel F), good compressibility. These types of HPMC differ by various degrees of substitution of hydroxypropyl (hydrophilic) and methoxy (hydrophobic) group (Rekhi et al., 1999).

HPMC is odorless, tasteless white or creamy-white fibrous or granular powder. It is soluble in cold water, forming a various colloidal solution, insoluble in alcohol, ether and chloroform but soluble in alcohol, ether and chloroform but soluble in mixture of methylalcohol and methylene chloride. Certain grades are soluble in aqueous acetone, mixture of methylene chloride and isopropyl alcohol and other organic solvents. HPMC is very stable in dry conditions. Solutions are stable at pH 3.0-11.0. It is compatible in the extreme pH conditions and with oxidizing materials. HPMC can be used as a film-former, thickening agent, protective colloid, emulsifier, suspending agent and stabilizer. High viscosity grades are used to retard the release of water soluble drugs (Arthur, 2000).

Dissolution studies of indomethacin controlled release tablets showed that for a poorly water soluble drug, not only was the polymer to drug ratio important in controlling the release, but both viscosity grade of HPMC and particle size of the drug were to be recognized more than the water soluble drug. Furthermore, erosion of the matrix was suggested to be the only mechanism by which poorly soluble drugs released from matrix tablet (Ford et al., 1985).

Mahaguna et al. (2003) investigated the influence of HPMC molecular weight on pharmacokinetic and pharmacodynamic parameters of controlled release formulations containing alprazolam. Tablet formulations contained alprazolam, excipients, and either HPMC K4MP or HPMC K100LVP. The tablets containing either HPMC K4MP or HPMC K100LVP had similar dissolution profiles and the dissolution profile did not change through 6 months at 40°C/75% RH or 12 months at 25°C/65 RH. The pharmacokinetic and pharmacodynamic parameters were not significantly different between two tablet formulations. In vitro dissolution predicted in vivo pharmacokinetic and pharmacodynamic results irrespective of formulation or diet used in the controlled released tablet.

9. Compritol® 888 ATO (Gattefosse)



Compritol® 888 ATO: n =20

Figure 6 Chemical structure of Compritol® 888 ATO

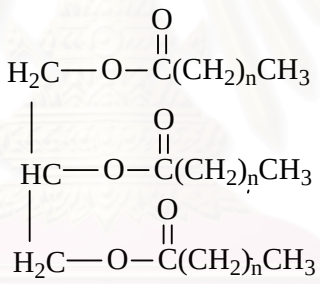
Compritol® 888 ATO is synthesized by esterification of glycerol by behenic acid (C_{22} fatty acid). The raw materials used are of strictly vegetable origin and reaction process involves no catalyst. The product is then atomized by spray-cooling. Compritol® 888 ATO is composed of mono, di and triglycerides of behenic acid, the diester fraction being predominant. Compritol® 888 ATO is fine, white to off-white powder. Melting point (drop point) is 69-74°C. It has faint odor.

Compritol® 888 ATO has several pharmaceutical uses: inert lubricant for tablet and capsule formulations, at use levels from 1% to 3%, binding agent direct tabletting, lipophilic matrix for sustained release tablets or capsule (use level >10%).

Perez et al. (1993) prepared sustained release phenylpropanolamine HCl tablets containing compritol 888 ATO as a retardant material. Two methods were used for the preparation of drug: wax systems; physical mixture and solid dispersion. The drug release was decreased with increasing amounts of compritol 888 ATO. Tablets prepared by physical mixture gave higher drug release than tablets prepared by solid dispersion method. The incorporation of compritol 888 ATO decreased the ejection forces of tablets during compaction. The drug release from tablets prepared by solid dispersion followed the diffusion controlled model.

Barthelemy et al. (1999) investigated the use of compritol 888 ATO as a coating agent to prolong the release of theophylline. Their study confirmed a satisfactory coating potential by this agent and a potential in sustaining the release of theophylline over an extended period of time.

10. Tristearin (Sci-toys)



Tristearin: n=16

Figure 7 Chemical structure of Tristearin®

Tristearin is primary fat in beef. It is a triglyceride; a molecule of glycerine has reacted with three molecules of the fatty acid stearic acid (C18). It is a saturate fat. This mean that every carbon has as many hydrogen atoms as it can hold (it is saturated with hydrogen), and no double bonds between any two carbons.

Tristearin is hard, yellowish while powders. It has slight odor and test suggesting tallow. Tristearin is insoluble in water and melting point is 58-63°C.

11. Stearic acid (Arthur, 2000)

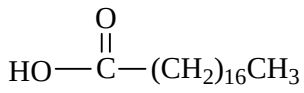


Figure 8 Chemical structure of stearic acid

Stearic acid is hard, white or faintly yellow colored, somewhat glossy, crystalline solid or a white, or yellowish white, powder. It has a slight odor and taste suggesting tallow.

Stearic acid is freely soluble in benzene, carbon tetracholoride, chloroform and ether; soluble in ethanol, hexane and propylene glycol; practically insoluble in water. Stearic acid melts at the temperature higher than 54°C.

Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. Stearic acid is generally regarded as a non toxic and nonirritant material. However, consumption of excessive amount may be harmful.

CHAPTER III

EXPERIMENTAL

1. Materials

The following materials obtained from commercial sources were used.

1.1 Model drug

- Diclofenac sodium BP (bromine free) (Batch No. DS 0006/111, supplied by Amoli organics Ltd., Thailand)

1.2 Additives

- Lactose anhydrous (Lot. No. R1 45/00164, Wyndale, New Zealand)
- Ethyl cellulose 10 cps. (Lot. No. 0K01013T01, Colorcon Co.,Ltd. Singapore)
- Hydroxypropylmethylcellulose (Methocel K15M Premium EP, Lot. No. PB 26012 Colorcon, Co., Ltd., Singapore)
- Glyceryl behenate (Compritol 888 ATO®, Lot. No. 25638, Gattefosse, France)
- Tristearin (Lot. No. 353999/1398, Fluka Chemical, Switzerland)
- Magnesium stearate (Lot. No. F1G 253, Asia Pacific PTE Ltd., Australia)
- Aerosil® 200 (Lot. No. 635912F, Wacker Chemie GMBH, Germany)

1.3 Chemicals

- Acetonitril, HPLC grade (Lot. No. 01 02 0099, Lab-Scan Analytical Sciences, Ireland)

- Hydrochloric acid, AR grade (Lot. No. 03 02 0186 Lab-Scan Analytical Sciences, Ireland)
- Methanol, AR grade (Lot. No. 03 08 1139 Lab-Scan Analytical Sciences, Ireland)
- Methanol, HPLC grade (Lot. No. 02 09 0153 Lab-Scan Analytical Sciences, Ireland)
- Potassium dihydrogen orthophosphate, AR grade (Lot. No. F1F125 Asia Pacific Specialty Chemicals Ltd., Australia)

2. Equipment

- Analytical balance (Model A200s, Sartorius GmbH, Germany And Model PB3002 Mettler, Switzerland)
- Dissolution apparatus (Model DT-6R, Erweka®, Germany)
- Differential scanning calorimeter (Model DSC 7, Perkin-Elmer, USA)
- Friabilator (Erweka TAR 20, Germany)
- High performance liquid chromatography (Model SCL-10A VP, Shimadzu, Japan)
- Infrared spectrometer (Model FT-IR 1760X, Perkin Elmer, Germany)
- Lloyd instruments (Model LR10K, Lloyd, United Kingdom).
- pH meter (Model 210 A+, Thermo Orion, Germany)
- Powder characteristic tester (Model PT-N, Hosokawa/powder tester, Japan)
- Scanning electron microscope (Model JSM-5410LV, Joel Ltd., Japan)
- Sieve shaker (Josef Deckehnann Aschaflenberg, Germany)
- Strain gauge (Type FLA-10-11, Lot NO. A 503811,Tokyo Sokki Kenkyujo Co., Ltd., Japan)
- Strain indicator amplifier (Model 6003-F, Shikoh, Japan)
- Modified tap density tester (Chanchai Engineering, Thailand)

- The single punch tabletting machine (EKO, Viuhang Engineering, Thailand)
- Ultraviolet/visible spectrophotrometer (Model V-530, Jasco, Japan)
- US Standard sieves (Laboratory test sieve ASTM E11, Endecotts, Ltd., USA)
- X-ray diffractometer (Model JDX-8030, Jeol, Japan)
- XY/XY-T recorder (Watanabe Instrument Corp. Model WX 4401 series, Japan)

Methods

1.Tabletting machine

1.1 Tooling

This experiment used a modified single punch tabletting machine (EKO) which was driven at a constant speed of 30 rpm by a 10 horsepower electric motor and pulley system. The machine was equipped with a set of three identical concave punches and matching dies. The radius of curvature of the concave punches and dies were equal to 3 mm. Three sets of punches and dies of 2.0, 2.25 and 2.5 mm diameter were investigated. These special punch and die sets were shown in Figures 9-11.

1.2 Force measurement

The compressive force between punches and dies was measured using strain gauge circuit. The general-purpose type FLA-10-11strain gauge of 10 mm size was used. The strain gauge had an internal resistance of about 120±0.3Ω, with gauge factor of 2.1. The strain gauge was mounted on upper plunger of tabletting machine. The strain gauge was boned using a cyanoacrylate adhesive and was recoated with epoxy adhesive as a protective coating. The strain gauge and the upper plunger assembly are shown in Figure 12. The Shikoh dynamic strain meter, model 6003-F, was used to measure the dynamic compressive force via the variation of the Wheatstone bridge voltage.

The circuitry of Wheatstone bridge with one strain gauge is shown in Figure 13. The dynamic strain meter supplied the variation of the bridge voltage. The voltage variation or the compressive force was recorded using a strip chart recorder.

1.2.1 The calibration of upper plunger

To calibration the compressive force acting on the upper plunger, the “Avery” universal-testing machine was used. The assembly of the upper plunger with the strain gauge was placed within the test section of the testing machine. Using the same measuring equipment setup, a series of known forces was applied to the plunger in the range of 100-1400 pounds force (lb). The applied forces and the corresponding output voltages were recorded. The calibration procedure was repeated a few times. The results were averaged. The curve fitting obtained from the force and voltage relationship are shown in Table 28 and Figure 59, respectively, in Appendix A. The linear relationship and small variations of calibration data was obtained from the force measurement setup.

Figure 9 Special punches and dies of 2.00 mm diameter

Figure 10 Special punches and dies of 2.25 mm diameter

Figure 11 Special punches and dies of 2.50 mm diameter

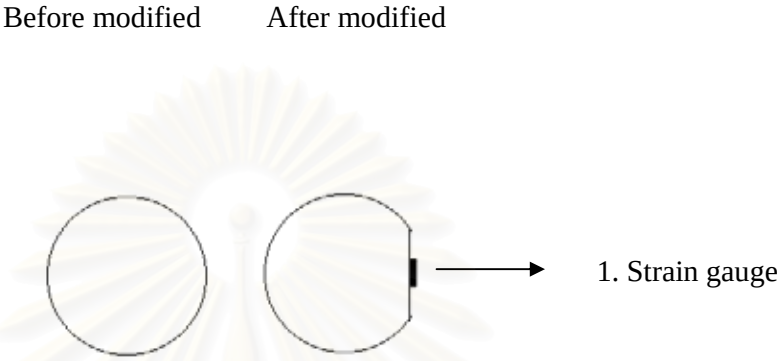


Figure 12 A cross section of the upper plunger

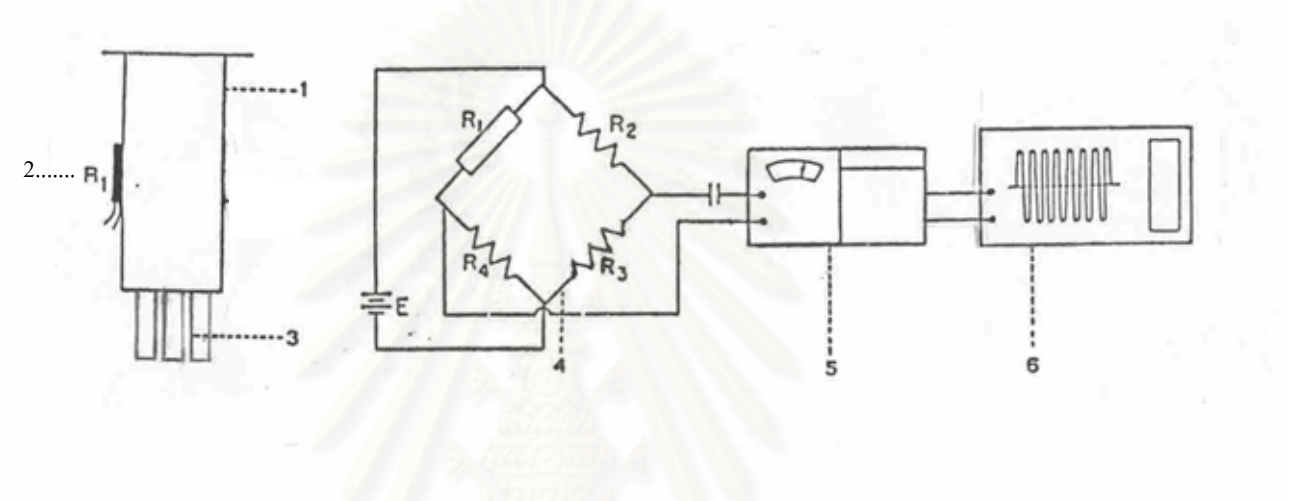


Figure 13 Function blocks diagram of press and associated measuring system

1. Upper plunger 2. Strain gauge 3. Upper punch 4. Wheatstone bridge

5. Strain indicator amplifier 6. Recorder

2. Formulation and preparation of sustained-release diclofenac sodium granule

The compositions of all formulations studied are presented in Table 7.

2.1 Preparation of diclofenac sodium (DS) granules for the studying the effect of processing variable on properties of microtablets.

All materials from formulation F1 in table 1 were passed though a sieve #60 before use. Granules containing 30% w/w of diclofenac sodium (DS) were prepared by wet granulation method. Fraction of DS, ethylcellulose (EC) and lactose, except the magnesium stearate and aerosil were mixed in plastic bag by geometric dilution method for 5 minutes. Then, 95%ethanol was sprayed pass through the nozzle onto the powder and the mixture was mixed in a mortar until wet mass was obtained. The wet mass was screened though a sieve #16 and dried at 50°c for 30 minutes. The dried granules were rescreened through different mesh sizes of sieve #20, #25 or #30. Then, the granules from different mesh size were characterized for their physical properties such as flow rate, angle of repose and compressibility index.

2.2 Preparation of diclofenac sodium (DS) granules for the studying the effect of formulation variable on the properties of microtablets.

Table 7 shows the DS formulations (F1-F11) for studying the effect of drug load, types and amounts of polymers (EC and HPMC K15 M) and glycerides waxes (compritol 888 ATO and tristearin). Granules were prepared by wet granulation method as previously described in 2.1.

Table 7 Composition of diclofenac sodium microtablets

Ingredients (%w/w)	Formulations										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Diclofenac sodium	30	40	50	30	30	30	30	30	30	30	30
Ethocel 10 cps.	30	30	30	40	50	30	30	30	30	30	30
Methocel K15M	-	-	-	-	-	10	-	-	-	-	-
Compritol 88 ATO	-	-	-	-	-	-	10	20	25	-	-
Tristearin	-	-	-	-	-	-	-	-	-	20	-
Stearic acid	-	-	-	-	-	-	-	-	-	-	20
Lactose	37	27	17	27	17	27	27	17	13	17	17
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1	1	1	1

2.3 Evaluation of the granules

2.3.1 Determination of the angle of repose

The powder characteristic tester was used to determine the angles of repose of granule. The angle of repose was measured from a heap carefully built up by dropping the granule samples through a glass funnel to the horizontal plate. When the angle of repose came to the desired condition. Then, the angle measuring arm was moved by fingers to the position at which the angle of repose could be measured in accordance with the display. The angle of repose was averaged from three determinations.

2.3.2 Determination of flow rate

Accurate weight of about 15 g of granules were filled in glass funnel with 6-mm internal stem diameter fixed on the clamp. The time was recorded when the granules started to flow until finished. The flow rate averaged from ten determinations was reported in term of g/sec.

2.3.3 Bulk density, tapped density and compressibility index

The bulk density (ρ_b) of the granules was determined by pouring 10 g of the granule into a 25 ml graduated cylinder and measuring the volume of granule. The graduated cylinder was tapped on a tap density tester through distance of 1.3 cm until no further decrease in the granule volume was seen (approximately 100 times). The tapped density (ρ_t) was then calculated. Both densities were averaged from three determinations. The Carr's compressibility was calculated from the following equation.

$$\text{Compressibility index} = \frac{(\rho_t - \rho_b) \times 100}{\rho_t} \quad [16]$$

2.3.4 Particle size distribution

Particle size distribution was determined by sieve analysis, consisted of set of US standard sieves, ranging from sieve #25, #30, #35, #40, #60, #140, #325 and collection pan respectively. Approximately 50 g of granule was put on the top sieve series. The sieves were placed on the sieve shaker and shaked for 20 minutes. The granules retained on each sieve size were weighed and calculated in percent of total weight.

3. Preparation of microtablets

The uniform dry granules were mixed with the premix of magnesium stearate and aerosil, which were passed through sieve #80, in plastic bag for 5 minutes until homogenous. The final granule blend was then compressed by using modified single punch tabletting machine (EKO) equipped with special punches and dies as previously described in 1.1.

3.1 Effect of processing variables.

3.1.1 Effect of punch's position

The granules (formulation F1, table 7) were compressed into microtablets by using 2.5 mm diameter punches at various forces of 400, 800 and 1,200 lb, respectively. Tablets from different punch positions were characterized for their physicochemical properties such as weight variation, thickness, hardness including drug dissolution.

3.1.2 Effect of compaction pressure and surface area of microtablets

The granules (formulation F1) were compressed into microtablets by using 2.0, 2.25 and 2.5 mm diameter punches at various forces of 400, 800 and 1,200 lb. The tablet weight was adjusted to approximately 10 mg

3.2 Effect of formulation variables.

The granules (all formulations in table 7) were compressed to 10-mg tablet by using concave punches of 2.5 mm in diameter. The mean compaction pressure was 800 lb.

3.3 Evaluation of microtablets

3.3.1 Morphology

The microtablets were examined under a scanning eletron microscope (SEM) for morphological evaluation. The shape and surface topography of microtablets were determined. The samples were prepared by gold sputtering technique before SEM examination.

3.3.2 Friability

The friability of microtablets was determined by a friabilator. Twenty microtablets were weighed by an analytical balance "w_0". Twenty microtablets and five stainless sphere (each sphere weight 1.06 g and diameter 6.34 mm) to increase the mechanical stress on the microtablets, were filled into a PVC container and rotated at 25 rpm for 4 minutes. The microtablets were reweighed again after the dust was eliminated, "w". The percent of friability was calculated based on the following equation. The results were obtained from the average of three determinations.

$$\% \text{ Friability} = \{(w_0 - w) / w_0\} \times 100 \qquad [17]$$

3.3.3 Weight variation

The weight variation of microtablets was determined by an analytical balance. Twenty microtablets were individually weighed. The mean and standard deviation were averaged from twenty microtablets determinations.

Weight variation of capsule

The DS microtablets were filled into hard gelatin capsule size No.1 by using semi-auto capsule filling (Model Panviv. AOI). The weight variation of 20 capsules were selected from 50 capsules of total filling and determined by an analytical balance. The mean weight of DS microtablets which filled into capsule and coefficient of fill weight variation were evaluated.

3.3.4 Hardness and apparent tensile strength

A diametral compression test was performed with an instrumented uniaxial press, Lloyd instrument, equipped with a 100 N load cell and operated at a crosshead rate of 0.5 mm/min. All tablets tested in this manner underwent tensile failure allowing the data (hardness) converted to apparent tensile strength, ts_{app}. The

apparent tensile strength was calculated as describe by Lennartz P. and Mielck J.B. (Lennartz P. et al., 1998)

$$ts_{app} = \frac{2F}{\pi \times D \times t} \times (K^{-1}) \quad [3]$$

where F = crushing force, t is tablets thickness, D is diameter and K is a constant.

3.3.5 Thickness

The thickness of ten individual tablets was determined using a micrometer for each batch. The sample mean and standard deviation of each batch of tablets were calculated.

3.3.6 The X-ray diffraction

The X-ray diffractometer was used to determine the diffraction angle of the substance, which showed crystallinity and interplanar spacing of the crystal planes and determined the interaction between each component in mixing and tabletting process.

The crystallinity of microtablets was examined by X-ray diffractometry. The samples for X-ray diffraction studied were milled and were firmly packed into the cavity of thin rectangular metal plate using two glass slides which was fastened to the metal plate with adhesive tape. The first glass slide was then removed and the prepared sample was taken to expose to the X-ray diffraction chamber. The X-ray diffraction patterns were recorded from 5°-90° terms of 2θ angle.

3.3.7 The IR spectroscopy

Infrared spectroscopy was used to confirm the functional groups of substances and products after production process by observing the intensities of IR peaks.

The IR spectra of microtablets were determined by milling the samples with KBr at a ratio of 1:100. Then, it was detected with an infrared spectrophotometer in range of the wavelength 4000-400 cm^{-1}. The resolution was 8.0.

3.3.8 The differential scanning calorimetry

Thermal analysis is the most common approach to study physicochemical interactions of two or more component system. The thermograms of microtablets were recorded on a thermal analyzer. About 3-4 g of milled sample was put onto the aluminum pan. The sample was taken into the condition that had been purged with liquid nitrogen gas. The condition used the heating rate of 10°C/min and temperature between 30°C and 300°C.

3.3.9 Surface Area Analyzer

The specific surface area of microtablets was determined by BET adsorption method using surface area analytical equipment. The specific surface area was automatically calculated. The amount of nitrogen gas was released into the system at 5%, 12%, 18% and 24%, respectively. The principal of surface area measurement was nitrogen adsorption on the surface area of testing material. Thereby, the resultant record would be shown in term of m^2/g of DS microtablets.

3.3.10 Calculation of surface area and volume of matrix tablets

The surface area of concave tablets can be calculated from following equation (Bauer et al., 1996).

$$O = 2\pi (rw+r^2+h^2) \quad [18]$$

where r = radius of tablet, w = central cylinder thickness h = overall tablets thickness

Moreover, the volume of a concave face tablet can also be computed from the sum of the volume of cylinder and two spherical segments (Bauer et al., 1996).

$$V= \pi\times(r^2w+r^2h+3h^3) \quad [19]$$

where r = radius of tablet, w = central cylinder thickness h = overall tablets thickness

3.3.10 Porosity determination

The porosity of microtablets were calculated following equation (Dabbagh et al., 1994)

$$\varepsilon = (1-\rho_r/\rho_t) \times 100 \quad [20]$$

where : ε = porosity of matrix tablet

ρ_r = the apparent density of the compact at any give pressure

ρ_t = the granules density (mixed granules before compression)

ρ_t of the granules was determined using helium pycnometer (Ultrapycnometer, Quantachorm, USA). The dimensions of the tablets were measured using a vernier caliper and used to calculate the tablet volume in order to determine ρ_r for each tablet. The mean of ten determinations was used for the determination of porosity of matrices tablets at each compaction pressure.

3.3.12 Drug content and uniformity of drug content of DS in microtablets

The drug content and uniformity of drug content of DS in microtablets was quantitatively determined by mean of absorption peak area ratio from HPLC method.

HPLC Analysis

HPLC chromatographic conditions:

Column	: Hypersil® C18 column (250×4.6 mm), 5μm (UK)
Detector	: UV detector was set at 275 nm
Flow rate	: 1.0 ml/min
Injection volume	: 20 μl
Internal standard	: ethyl paraben 5 μg/ml
Mobile phase	: A mixture of 0.1M acetate buffer pH4.2 and acetonitrile, 45:55 % v/v
Retention times	: ethyl paraben 4.3 min diclofenac sodium 6.5 min

The calibration curve of DS is shown in Figure 62, respectively, in Appendix A. Each concentration was determined in triplicate.

Preparation of ethyl paraben internal standard solution, About 50 mg of ethyl paraben was accurately weighed in a 10-ml volumetric flask followed by addition of 5 ml of methanol HPLC grade. The flask was shaken until the compound completely dissolved and then adjusted to volume with methanol HPLC grade. One ml of solution was pipetted to 100-ml volumetric flask and diluted to volume with methanol HPLC grade. The concentration of ethyl paraben was 50 μg/ml.

Preparation of DS standard solutions, About 50 mg of DS was accurately weighed in a 25 ml of volumetric flask. Twenty milliliter of methanol HPLC grade was added to dissolve the drug. After dissolution, the solution was adjusted to volume with the solvent. One ml was pipetted into 100 volumetric flask and further diluted to volume with mobile phase. The final concentration of this standard stock solution was 20 μg/ml.

The 1, 2, 3, 4 and 5 ml of the standard stock solution were separately pipetted and transferred into five 10 ml of volumetric flasks, each containing 1 ml of the internal standard solution. All flasks were subsequently diluted to volume with mobile phase so that the final concentrations were 2, 4, 6, 8 and 10 μg/ml, respectively. The final concentration of ethyl paraben internal standard was equal to 5 μg/ml in all solution.

Preparation of pH 4.2, 0.1M acetate buffer, Sodium acetate (13.608 g) was dissolved in 980 ml of distilled water. The pH of solution was adjusted to 4.2 with dropwise addition of glacial acetic acid. The final volume was subsequently adjusted to 1000 ml with distilled water.

Assay of DS content in matrices, Twenty tablets of each formulation were weighed and pulverized by mortar and pestle. Then, the powder was accurately weighed equivalent to one tablet into a 50-ml volumetric flask, which was then filled with 35 ml of methanol HPLC grade and sonicated for 60 minutes. Afterwards, the volumetric flask was adjusted to volume by methanol HPLC grade and mixed thoroughly. The solution was filtered through 0.45 μm membrane filter paper and used as stock solution. The final concentration of this stock solution was 60 μg/ml. One ml of sample stock solutions was pipetted and mixed with one ml of internal standard solution in 10 ml volumetric flask. Then, adjusted to 10 ml and mixed thoroughly. Finally, the final concentration of sample solution and internal standard were 6 μg/ml and 5 μg/ml, respectively. Each sample was determined in triplicate.

Assay for uniformity of drug content DS in matrices, Ten microtablets was taken by random sampling. Each microtablet was filled into a 10 ml volumetric flask. Then, dissolved with methanol HPLC grade and sonicated for 60 minutes. Each solution was adjusted to 10 ml with methanol HPLC grade and mixed thoroughly. The solution was filtered through 0.45-μm membrane. Then, two ml of this solution was pipetted and transferred into a 10 ml of volumetric flask. Methanol was added to volume and mixed. The solution was used as stock solution. The final concentration of this stock solution was being 60 μg/ml. One ml of sample stock solutions was pipetted and mixed with one ml of internal standard solution in 10 ml

volumetric flask. Then, the volumetric flask was adjusted to volume by mobile phase and mixed thoroughly. Finally, the final concentrations of sample solution and internal standard prior to HPLC analysis were 6 μg/ml and 5 μg/ml, respectively.

Validation of HPLC method

The analytical parameters used for the assay validation were specification, accuracy, precision and linearity (USP24/NF19, 1999).

Specificity

Under the chromatographic condition used, the peak of DS had to be completely separated from and not interfered by the peak of other components in the sample. Non-active ingredients, including EC, HPMC K15M, compritol 888 ATO and tristearin, mixed with internal standard were prepared and injected. The chromatograms were evaluated by comparing with the standard solution of diclofenac sodium.

Accuracy

Standard solutions of DS having concentrations of 6 μg/ml were prepared and injected. The percentage of the analytical recovery of each standard solution was calculated.

Precision

Within Run Precision, The within run precision was determined by analyzing three sets of five standard solutions of DS in the same day. Peak area ratios of DS to ethyl paraben were compared and percentage coefficients of variation (%CV) of each concentration were determined.

Between Run Precision, The between run precision was determined by comparing each concentration of DS standard solutions that were prepared and

injected on different days. The percentage coefficient of variation (%CV) DS to their internal standard peak area ratios from the three sets of standard solutions having the same concentration were determined.

Linearity

DS standard solutions ranging from 2 to 10 μg/ml were prepared and analyzed. Linear regression analysis of peak area ratios versus their concentrations was performed.

3.3.13 Dissolution study

The aqueous solubility of DS is dependent on pH. The solubility is poor at low values of pH but when the pH rises above the pKa (pKa in water is 4), rapid increases in solubility occur (Lund, 1996). For drugs that exhibit pH-dependent solubility and dissolution behaviors, dissolution screening at pH media should be performed (Khan, 1996)

As controlled release tablets were supposed to pass the entire upper gastrointestinal tract, it would be ideal when the release of drug was constant over a wide range of pH values (from 1 to about 7). Therefore, an in vitro test for controlled release tablets for controlled release tablets should at least cover this pH range (Jonkman and De Zeeuw, 1993)

In this study, a special attention was paid to the effect of pH of dissolution medium on the release of diclofenac sodium from microtablets, therefore, the two dissolution system, pH-change and phosphate buffer pH 6.8 system were studied.

Microtablets equivalent to 75 mg of DS was filled into a capsule. Three capsules for each formulation were evaluated. Nine hundred milliliters of 0.1 N HCl (pH change system) or one thousand milliliters of phosphate buffer pH 6.8 (phosphate buffer pH 6.8 system) was placed in a glass vessel specified in USP dissolution test

(apparatus II). In order to study the effect of punch position, dissolution studies were carried out on a single tablet of each punch position. Two hundred and fifty milliliters of 0.1N HCl or 280 milliliters of phosphate buffer pH 6.8 systems were used with apparatus II. In all cases, the medium was equilibrated to 37±0.5°C. The distal paddles were calibrated at 2.5 cm above the bottom of vessel. The apparatus was operated at a speed of 50 rpm.

In the dissolution model with pH change, the pH of the medium was kept at pH 1.2 using 0.1N HCl for two hours, then the pH was increased to 6.8 by adding 4.4064 g of NaOH followed by 6.125 g of KH_2PO_4 dissolved in 100 milliliters of 0.1N HCl. In case of testing single tablet 1.2192 g of NaOH and 1.8375 g of KH_2PO_4 in 30 milliliters of 0.1N HCl were dissolved. Then the solution was added to medium (0.1N HCl) for increasing pH to 6.8. All fluids were deaerated before use by boiling.

Ten milliliters of the specimen were withdrawn at the time interval of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 14, 17, 20 and 24 hours and the medium was replaced immediately after each sampling to keep the volume of the medium constant during the experiment.

Each sample was filtered through paper filter (Whatman® NO.1). The first one milliliter of filtrate was discarded and was diluted to suitable concentration, which gave the absorbance between 0.2-0.8. The absorbance of each sample was spectrophotometrically assayed at 271 nm for 0.1N HCl and 275 nm for phosphate buffer pH 6.8.

The amount of DS release at any time interval was calculated from calibration curve. A cumulative correlation was made for the previously removed sample to determine the total amount of drug release.

Calibration curve of diclofenac sodium

In 0.1N HCl solution

DS 50 mg was accurately weighed into a 200-ml volumetric flask and dissolved with deionized water, then adjusted to volume. The solution was used as stock solution.

The 1, 2, 3, 4 and 5 ml stock solution was individually pipetted into 50 ml volumetric flask and then diluted to volume with 0.1N HCl. The final concentration of each solution was 5, 10, 15, 20 and 25 μm/ml, respectively.

The solution was assayed spectrophotometrically assayed at 271 nm. The absorbance and calibration curve of diclofenac sodium in 0.1N HCl are shown in Table 29 and Figure 60, respectively in Appendix A. Each concentration was determined in triplicate.

In phosphate buffer pH 6.8

DS 50 mg was accurately weighed into a 200-ml volumetric flask and dissolved with phosphate buffer pH 6.8, then adjusted to volume. The solution was used as stock solution.

The 1, 2, 3, 4 and 5 ml stock solution was individually pipetted into 50 ml volumetric flask and then diluted to volume with phosphate buffer pH 6.8. The final concentration of each solution was 5, 10, 15, 20 and 25 μm/ml, respectively.

The solution was assayed spectrophotometrically assayed at 275 nm. The absorbance and calibration curve of diclofenac sodium in phosphate buffer pH 6.80 are shown in Table 30 and Figure 61, respectively in the appendix A. Each concentration was determined in triplicate.

CHAPTER IV

RESULTS AND DISCUSSIONS

1. Selection of appropriate mesh size of sieve for preparing DS granule

The flow properties of DS granules that were prepared by various mesh sizes of sieve were investigated. The results of DS granules investigated by various parameters, which supported for flow properties, are presented in Table 8.

1.1 The flow rate

The flow rates of granule formulations F1#20, F1#25 and F1#30, passed through the sieve in different sizes #20, #25 and #30 respectively, were 2.03, 2.13 and 2.35 g/sec. It was found that the flow rate increased when the granules were screened through smaller aperture. In addition, when tested with the one-way ANOVA, the test showed statistically significant difference ($P<0.05$) in the flow rate of granule of all sample formulations studied (Table 97, appendix D). This was explained by the F1#30 had narrow particle size than that of F1#20 and F1#25, indicating that the formulation F1#30 showed faster flow than F1#20 and F1#25.

1.2 The angle of repose

The angles of repose of the granules from various mesh sizes of sieve are reported in Table 8. The angles of repose of all formulations were within 33°-34°, which indicated of good flowability (Nagel and Peck, 2003).

1.3 Bulk density, Tapped density and Compressibility index

The bulk density and tapped density of granules F1#30 was higher than the granule of formulations F1#25 and F1#20, respectively. Particle with high-density and low-internal porosity tended to posses free-flowing characteristic (Nagel and

Peck, 2003). Thus, the granules F1#30 had better flow than formulation F1#20 and F1#25. The bulk density was described the packing behavior of granules. A higher bulk density had advantage in tabletting because of a reduction in the fill volume of die (Ho et al., 1997).

The Carr's compressibility index was used for prediction of powder flow characteristic. The low percentage of compressibility indicated the free flowing property (Gordon et al., 1990). The compressibility of granules prepared by various mesh sizes are shown in Table 8.

For the DS granule F1#30, the compressibility index was lower than the granule F1#25 and F1#20, respectively. This result indicated that granule F1#30 had better flow property than granules F1#20 and F1#25 because granule F1#30 had the lowest percentage of compressibility.

Table 8 The Physical properties of DS granule for preparing from different mesh size of sieve

Formulation	Flow rate (g/sec) n=5	Angle of repose (X°) n=3	Bulk density(g/ml) n=3	Tapped density(g/ml) n=3	Carr's index (%) n=3
F1#20	2.03(0.019)	33.80(0.058)	0.51 (0.004)	0.57 (0.006)	11.27 (1.380)
F1#25	2.13(0.051)	33.90(0.569)	0.52 (0.004)	0.57 (0.002)	9.34 (0.447)
F1#30	2.35(0.037)	33.20(0.643)	0.59 (0.002)	0.63 (0.002)	6.26 (0.66)

These results of bulk density, tapped density and compressibility index indicated that the granules F1#30 had free flowing properties than granules F1#20 and F1#25.

1.4 The particle size distribution

The particle size distributions of DS granule at various mesh sizes of sieve are shown in Figure 14. It was observed that the particle size of DS granules of formulation F1#30, prepared by sieve #30, was smaller than those formulations prepared by using the sieve #20 and #25. Moreover, it was found that the granules of formulation prepared by sieve #20 and #25 had broader size distribution than granules prepared by using a 30 mesh sieve. The results were related to flow rate determination that the powder and granules had narrow size distribution, which generally indicated good flow (Gordon et al., 1990; Nagel K.M. and Peck, G.E., 2003).

From the results of flow properties and the particle size distributions of DS granules indicated that the DS granules prepared by sieve #30 were more suitable for microtabletting.

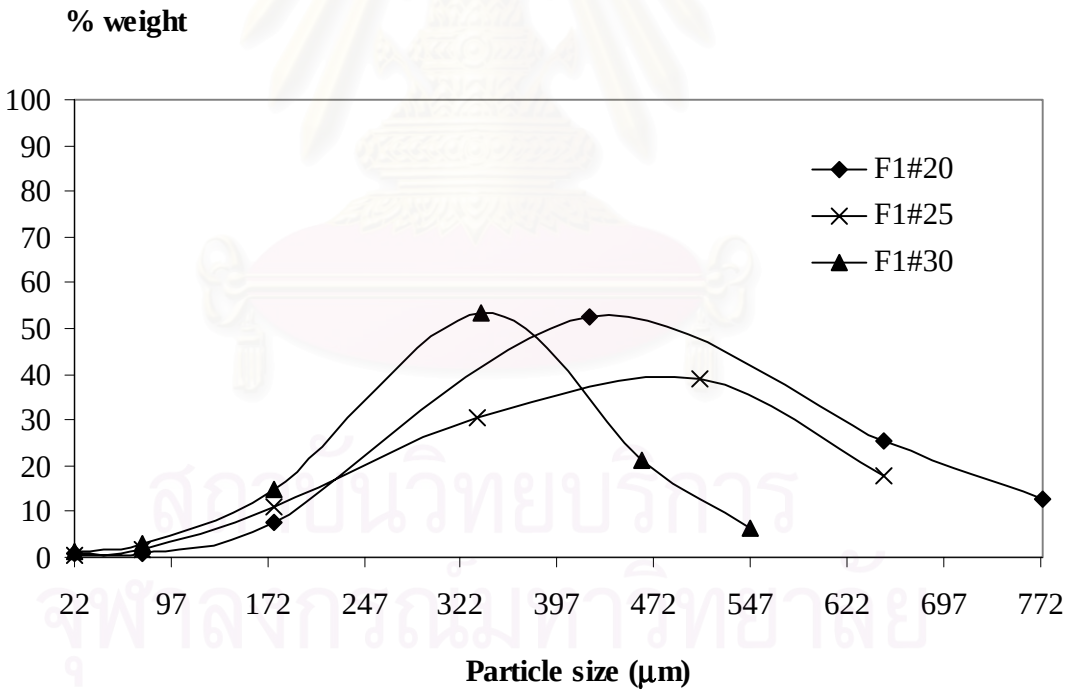


Figure 14 Particle size distributions of DS granules prepared by various mesh sizes of sieve

2. Evaluation of diclofenac sodium granules

All formulations could be prepared as DS granules, except the formulation F11 which produced damp undesirable rubbery and sticky mass on a sieve. This was due to the influence of high amount of stearic acid which had low melting point of 55-59°C (Sci-toys; Arthur, H.K. 2000). Hence, the damp mass could not pass through the sieve. Table 9 shows that the physical properties such as flow rate, angle of repose, bulk density, tapped density, and Carr's compressibility index of DS granules.

2.1 The flow rate

2.1.1 The influence of DS content on the flow property of granules

The flow rates of granules of formulations F1-F3 from Table 9 were decreased from 2.35 to 2.32 and 2.30 g/sec when increasing the amount of DS from 30% to 40% and 50%, respectively. It was observed that the flow rates of granules were decreased when the amounts of DS were increased. This was due to crystal habit of DS is crystalline powder as rod shape which gave poor flowability as seen in Figure 65 in Appendix E. Thus, increasing the drug load caused decrease the flow rate.

2.1.2 The influence of types and amounts of polymers and glycerides on the flow property of granules

For the formulations F4 and F5 which combined 30%DS with various amounts of EC (40%-50%), the flow rate of granules of formulation F4 was 2.36 g/sec whereas, the formulation F5 showed slower flow rate. However, the flow rate of formulation F4 was similar to that of formulation F1, which contained 30%EC in formulation.

For the formulations F6-F10 which contained 30%DS, 30%EC and additional polymer (HPMC K15 M) or glyceride waxes (compritol 888 ATO, tristearin) into the formulations, the flow rates were significantly decreased when the

formulations combined EC with HPMC K15M (formulation F6) or EC with glycerides waxes (formulation F7-F10) as matrices former. The flow rates of granules formulation F6 was 2.12 g/sec, which was faster than that of the formulations F7-F10.

Table 9 The Physical properties of DS granule of all formulation

Formulation	Flow rate (g/sec) n=5	Angle of repose (X°) n=3	Bulk density (g/ml) n=3	Tapped density (g/ml) n=3	Carr's index (%) n=3
F1	2.35 (0.037)	33.20 (0.643)	0.59 (0.002)	0.63 (0.002)	6.26 (0.660)
F2	2.33 (0.019)	33.50 (0.153)	0.60 (0.014)	0.65 (0.020)	8.58 (0.561)
F3	2.30 (0.033)	34.47 (0.231)	0.61 (0.009)	0.67 (0.018)	9.31 (1.954)
F4	2.36 (0.025)	35.17 (1.320)	0.58 (0.003)	0.64 (0.007)	8.19 (0.612)
F5	2.27 (0.028)	35.63 (0.777)	0.54 (0.00)	0.61 (0.000)	10.81 (0.000)
F6	2.13 (0.016)	38.03 (0.586)	0.50 (0.014)	0.55 (0.005)	8.03 (1.934)
F7	2.08 (0.031)	38.47 (0.404)	0.52 (0.005)	0.55 (0.002)	6.04 (1.015)
F8	2.00 (0.032)	38.33 (0.351)	0.49 (0.002)	0.52 (0.002)	6.54 (0.255)
F9	1.95 (0.029)	38.83 (0.603)	0.48 (0.004)	0.52 (0.006)	7.42 (0.333)
F10	1.93 (0.021)	40.77 (0.306)	0.50 (0.009)	0.54 (0.007)	6.05 (0.400)
F11*	-	-	-	-	-

Figures in parentheses represent the standard deviation

* The granule could not be prepared.

Tsai et al. (1998) were explained that when the powder was granulated with different materials, the surface area, morphology and cohesive forces between the particulate might greatly affect on the flowability. A mixture of drug and matrix former might migrate to the surface of treated granules. Consequently, flowability of granules could be altered by the cohesion of the matrix forming materials on the surface of granules. This retardation of flowability would be more significant as the granulating amount increased. The increasing the amount of EC and adding HPMC K15M into the formulation lead to increase the amount of EC or HPMC K15M particles around the surface of granules. In addition, EC was of rod shape and HPMC was fibrous or cylindrical shape (Arthur et al., 2000) which also expressed the poor flowability. Hence, the flow rates of granules were decreased due to both increasing of the cohesive effect and morphological of matrix formers.

For the formulations F7-F9 with the increasing amount of compritol 888 ATO, it was observed that the flow rates were decreased from 2.08 to 2.0 and 1.95 g/sec, respectively. It might be explained that the higher amount of waxy materials such as compritol 888 ATO and tristearin in the inner part of granules were directly reduced the binding activity of granules and also lead to decrease lubrication property. It was due to the fact that maximum capacity of lubrication effect would be occurred as the smallest particle size of lubricants were used and homogeneously distributed around the outer of granules. But in this study, compritol 888 ATO were placed in the inner granule by conventional wet granulation process thus maximum lubrication effect could not take place. Moreover, the flow rate of formulation F10 that combined EC with tristearin at 3:2 weight ratios was 1.93 g/sec. While comparison to the compritol formulation (F7-F9), it was appeared that tristearin formulation (F10) showed slower flow rate. Since the formulation F10 had boarder size distribution and lower bulk density than the others.

2.2 The angle of repose

The angles of repose of granules of formulation F1-F5 were within the range of 33.23°-35.63°, which indicated of good flowability. The angles of repose of granules of formulations F6-F10 were ranged from 35.16°-40.76° indicating of fair

flowability (Gordon et al., 1990). The angle of repose of formulation contained EC alone was lower than that of the formulations combined EC with HPMC K15M or EC with glyceride waxes. It could be seen that the results of angle of repose and flow rate were related in all formulations.

2.3 Bulk density and tapped density

The bulk density of a powder depended on the particle size distribution, particle shape, and the tendency of the particle to adhere together (Martin et al., 1993). The bulk density and tapped density of DS granules at various percentages of drug load, types and amounts of polymers or glycerides waxes are presented in Table 9. The bulk density and tapped density of DS granule from formulations F1-F5 were higher than those of formulations F6-F10. It was observed that the bulk and tapped densities of granules were decreased when the composition of granules were admixed with EC and HPMC K15M or EC and glycerides waxes. Harwood and Pilpel (1968) investigated the effect of granule size and shape on the bulk density of griseofluvin granulations. The bulk density of granules decreased when particle size of granules was increased. The smaller granules were able to form a closer, more intimate packing than were larger granules. For this study, it was found that the amount of large granules and fine particles were both increased when the formulations comprised of EC with HPMC K15M or glyceride waxes. Hence, formulation F6-F10 had broader particle size distribution and higher amount of large particle size of granule than F1, it caused lower of bulk density when compared with formulation F1.

2.4 Compressibility index

The compressibility index was to predict the powder flow characteristics. Low percentage of compressibility indicated free flowing property (Gordon et al., 1990). The compressibility indexes of granule formulations F1-F10 are presented in Table 9. It could be seen that the compressibility indexes were increased when increasing the amounts of glyceride waxes or polymers in formulation. Furthermore, the compressibility indexes were decreased by additional with glyceride

waxes at low amount. However, increasing the glyceride waxes at higher concentration would result in higher compressibility indexes.

2.5 Particle size distribution

The particle size distributions of DS granules are shown in Figures 15-16. The particle size distributions were affected by the composition in the formulation such as amounts and types of polymers or glycerides waxes as illustrated in Figures 16. The amount of large granules and fine particle were increased when the formulations combined EC with HPMC K15M or glyceride waxes and increasing the amount of matrix former. As a result, the amount of fine particle was increased and had broad size particle distribution that affected to poor flowability. Different drug loading (30% to 50%) had little effect on the particle size distribution as shown in Figure 15.

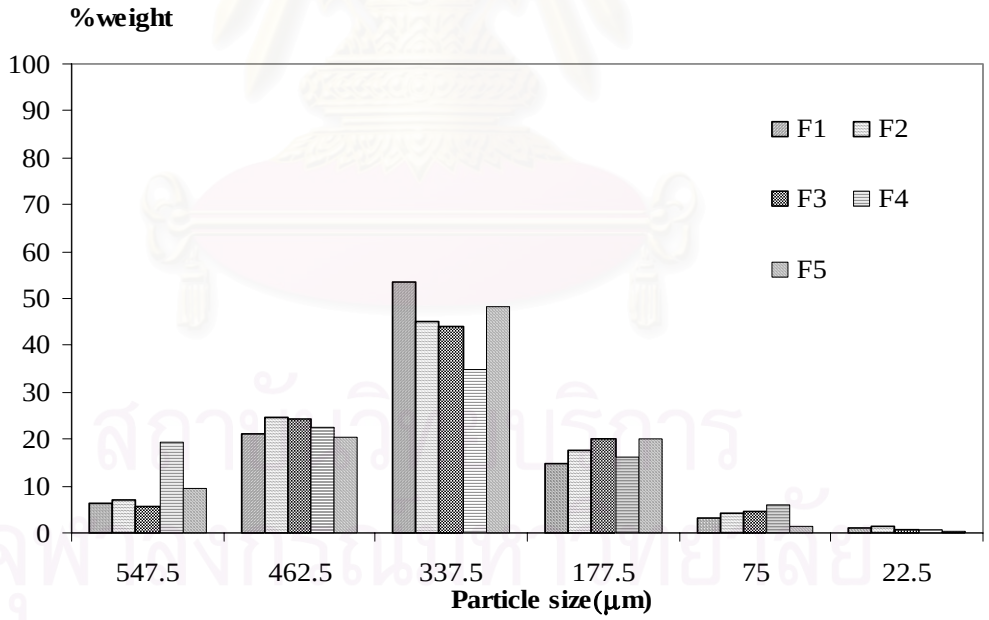


Figure 15 Particle size distribution of granules from formulations F1 (DS: EC; 3:1), F2 (DS: EC; 4:1), F3 (DS: EC; 5:1), F4 (DS: EC; 1:4), F5 (DS: EC; 1:5)

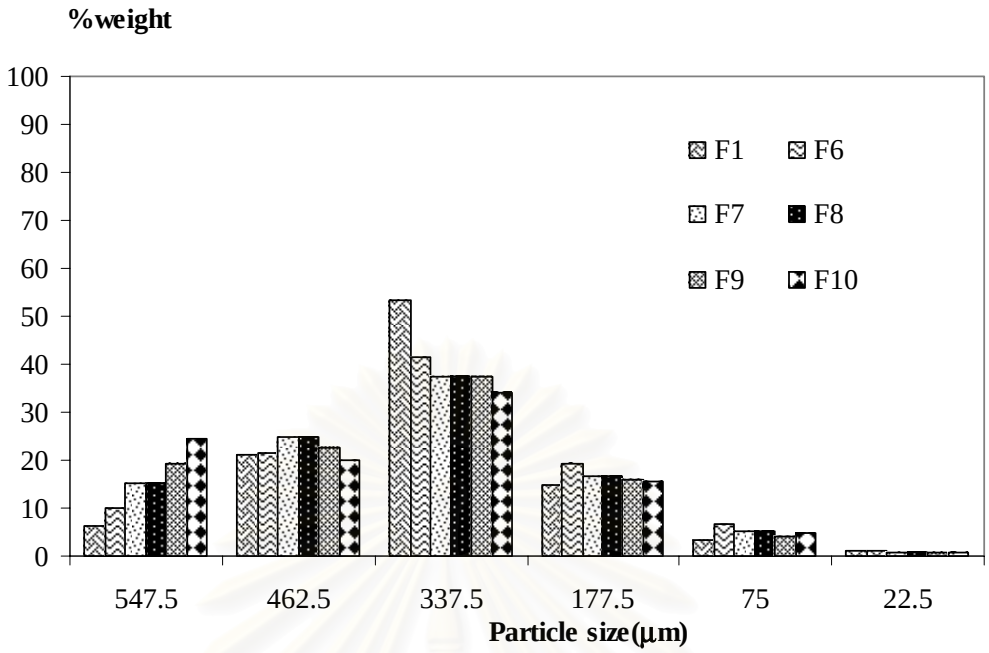


Figure 16 Particle size distribution of granules from formulations F1 (DS: EC; 3:1), F6 (DS: HPMC K15M; 3:1), F7 (DS: Compritol® 888 ATO; 3:1), F8 (DS:Compritol® 888 ATO; 3:2), F9 (DS: Compritol® 888 ATO; 3:2.5), F10 (DS: Tristearin®; 3:2)

3. Evaluation of DS microtablets

3.1 Effect of punch positions on the properties of microtablets

3.1.1 Weight variation and friability

The mean and standard deviation in weight of microtablets prepared from different punch position, P1, P2 and P3 at various compression forces are presented in Table 10. The weight of microtablets at various punch position was not different and was passed the specification in official standard USP XXIV (average difference of less than 10%).

The % friability of microtablets from different punch position at different compression forces were in the range of 0.09-0.1% that less than 0.6% as presented in Table 10. Therefore, the % friability passed the specification in official standard USP XXIV.

3.1.3 Hardness

The mean and standard deviation of hardness of microtablets are displayed in Table 10 and Figure 17. The One-way ANOVA showed no statistically significant difference (P>0.05) in hardness of microtablets that were prepared from different punch positions at the same compression force (Table 98, 99, and 100 in Appendix D). The results indicated that each microtablet which was prepared from different punch position received equivalent pressure for compressing microtablet. Moreover, the hardness of microtablets increased when increasing the compression forces.

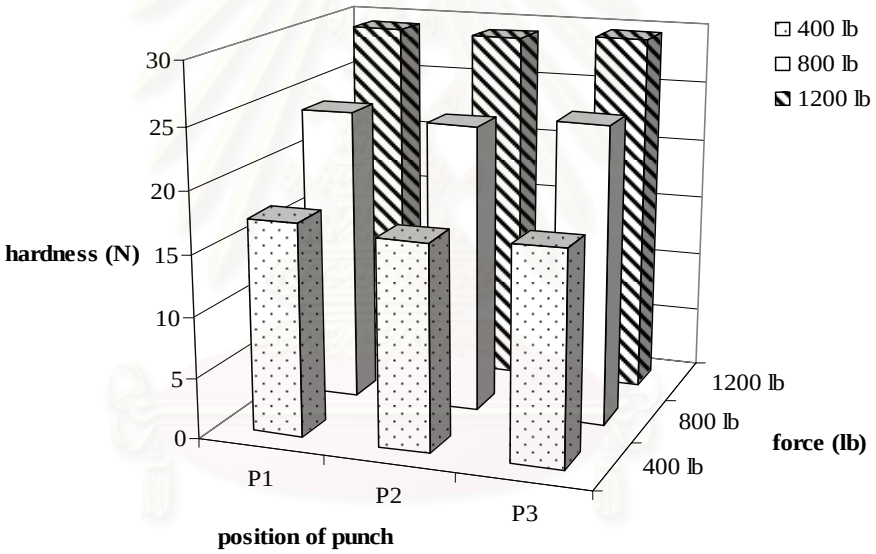


Figure 17 Effect of punch positions (P1, P2 and P3) on the hardness of microtablets prepared with various compression forces

Table 10 Physical properties of diclofenac sodium microtablets prepared from different punch position

	400 lb			800 lb			1,200 lb		
	P1	P2	P3	P1	P2	P3	P1	P2	P3
weight variation (mg/tab)	15.502 (0.183)	15.638 (0.309)	15.994 (0.258)	16.652 (0.446)	15.862 (0.324)	16.657 (0.234)	15.727 (0.193)	15.366 (0.148)	15.700 (0.232)
Thickness (mm)	2.9316 (0.008)	2.8950 (0.008)	2.8917 (0.026)	2.7083 (0.014)	2.6900 (0.009)	2.6933 (0.060)	2.5550 (0.176)	2.5617 (0.031)	2.5850 (0.0509)
% friability	0. 091	0.098	0.094	0.092	0.095	0.093	0.095	0.092	0.100
Hardness (N)	17.420 (1.690)	16.795 (1.270)	17.320 (1.394)	24.02 (1.136)	23.663 (1.071)	24.485 (1.773)	29.281 (0.964)	29.082 (1.012)	29.550 (1.347)

Figures in parentheses represent the standard deviation

P1, P2 and P3 were arranged in order from left-hand to right-hand side, respectively.

3.1.4 Thickness

The thickness of microtablets prepared from punch position P1, P2 and P3 at the same compression force were not different. The thickness of microtablets was decreased when increasing the compression forces because of the induction among particles closely attached with each other and interparticulate bonding. The mean and standard deviation of thickness of microtablets are displayed in Table 10.

3.1.5 Dissolution study

The matrix tablets formulation F1 that contained 30% DS, 30% EC and 40% diluents was used in this study. The dissolution studies were carried on a single microtablet of each punch position (P1, P2 and P3) which was compressed at the same compression force. All release studies of DS microtablets were evaluated in pH-change dissolution system. The dissolution profiles of microtables from different punch position at compression forces of 400, 800 and 1,200 lb are shown in Figures 18, 20, and 22, respectively. In pH- change system, these microtablets were tested in acid stage (0.1N HCl, pH 1.2) for 2 hours. The percentages of drug released of all punch positions at the same compression force were less than 1% that the amount released was almost negligible. When the dissolution medium was changed to pH 6.8 (phosphate buffer), the percentage of drug release were rapidly raised to 30%-50% in all cases (shown in Figures 18, 20, and 22). The mean times for 50% drug release ($T_{50\%}$ values) of microtablets from different punch position are presented in table 11. The results from dissolution profiles and $T_{50\%}$ indicated that the release of DS from microtablets was strongly medium dependent. DS was a salt of a weak acid (2-[2, 6-dichloropheny) amino] benzeneacetic acid monosodium salt). Therefore, the solubility was strongly depended on the ionization constant, K_a, and the pH of the dissolution medium (Kincl et al., 2004). In 0.1N HCl medium, DS was neutralized with hydrogen ion and precipitated on or in the matrix. Most DS could dissolve in phosphate buffer pH 6.8 therefore most drugs were in this medium (Sheu et.al, 1992).

In order to study the drug release kinetics of the investigated microtablets, the dissolution profiles were analyzed according to the zero-order, first-

order and Higuchi's square root equations which were analyzed the first 80% of release curve (Table 11 and 12). In all cases, the most suitable mathematical model for describing the experimental data was the first-order. In addition, when tested with the ANOVA, the statistic test showed no statistically significant difference ($P>0.05$) in the drug release rate constant, Kr (the slope of log percentage drug remained as a function of time) of microtablets from each punch position (P1, P2 and P3) that were compressed at the same condition (Table 101 in appendix D). Thus the punch position did not affect the dissolution rate when the microtablets were produced at the same condition. The first order release profiles of DS microtablet from different punch position (P1, P2 and P3) at compression forces of 400, 800 and 1,200 lb (phosphate buffer pH 6.8) are depicted in Figures 19, 21, and 23, respectively.

From this study, all results indicated that different punch positions in this study did not affect physicochemical properties of DS microtablets, if the microtablets were prepared at the same compression force.

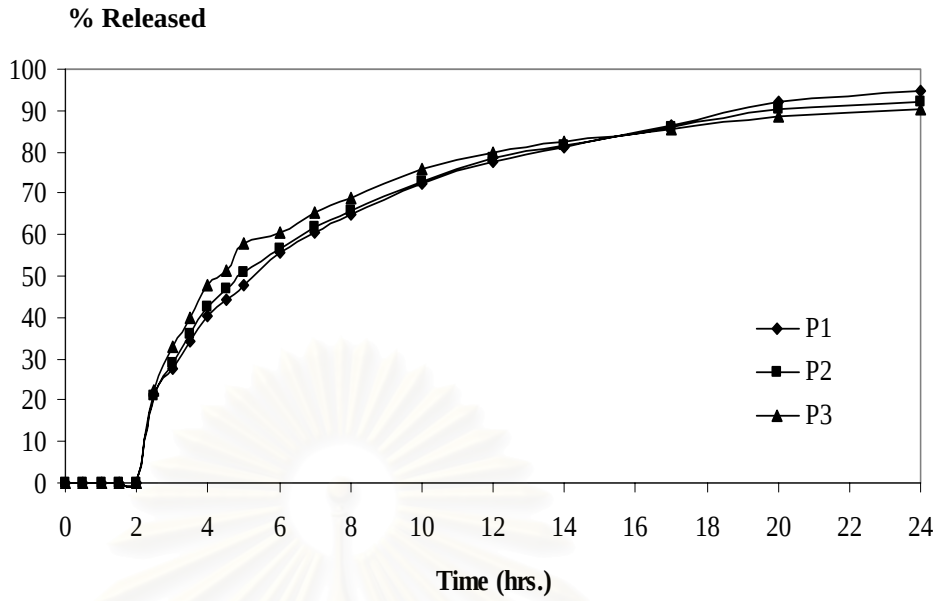


Figure 18 Dissolution profiles of DS microtablets from punch positions P1, P2 and P3 at compression force of 400 lb in pH-change system

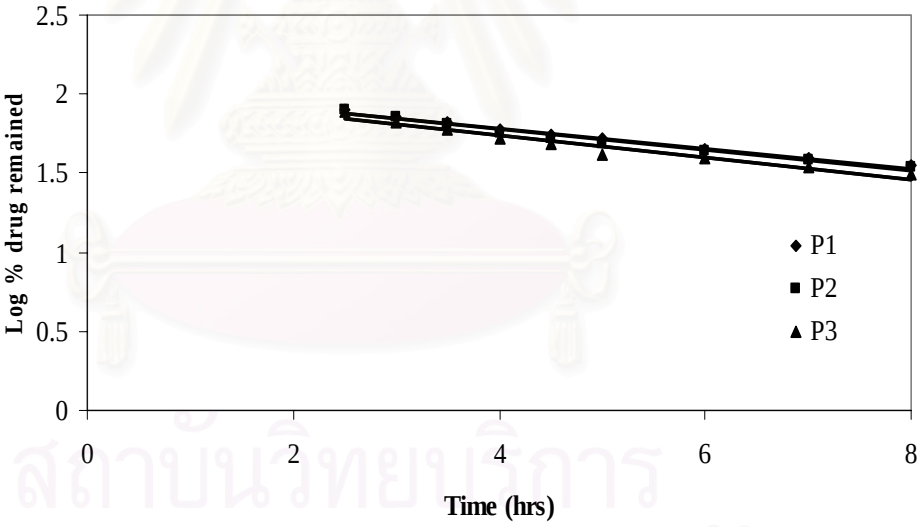


Figure 19 The first order plot of DS microtablets from punch positions P1, P2 and P3 at compression force of 400 lb in pH-change system

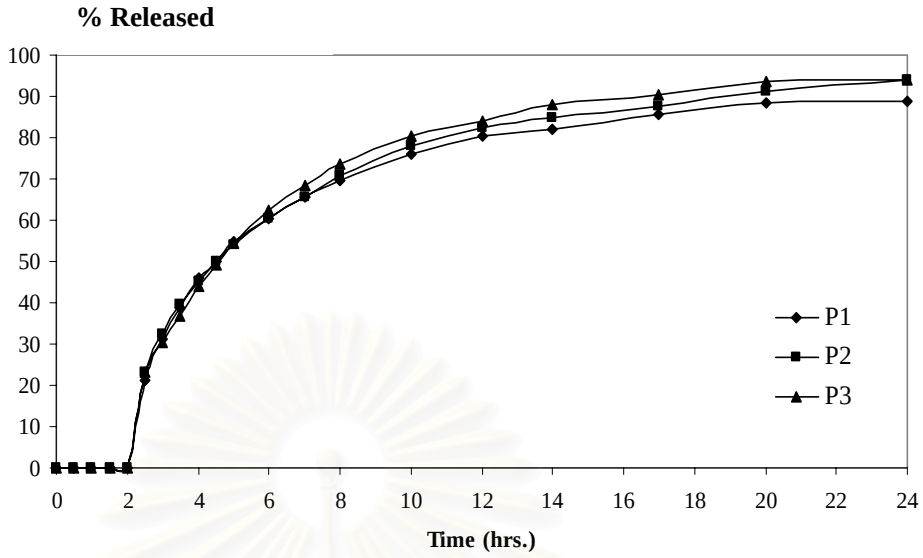


Figure 20 Dissolution profiles of DS microtablets from punch positions P1, P2 and P3 at compression force of 800 lb in pH-change system

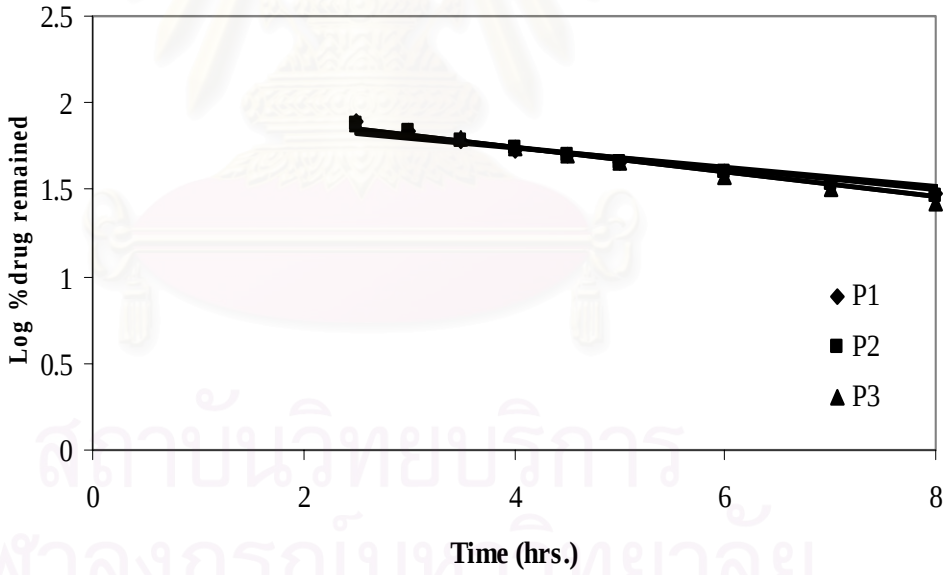


Figure 21 The first order plot of DS microtablets from punch positions P1, P2 and P3 at compression force of 800 lb in pH-change system

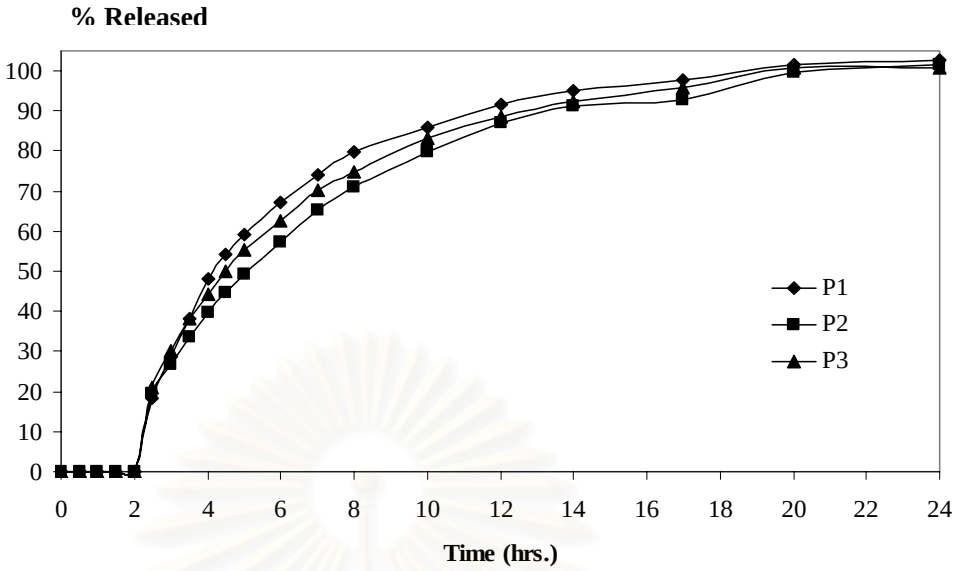


Figure 22 Dissolution profiles of DS microtablets from punch positions P1, P2 and P3 at compression force of 1,200 lb in pH-change system

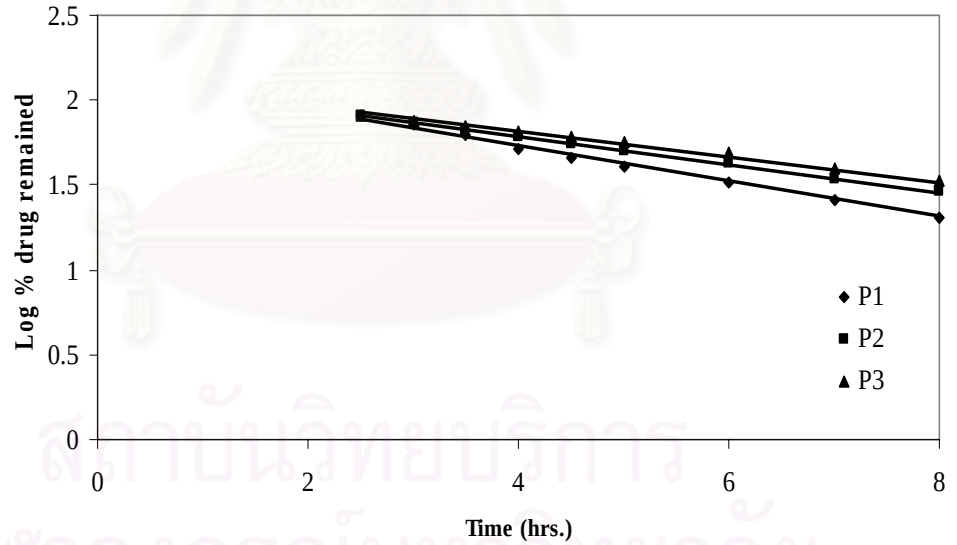


Figure 23 The first order plot of DS microtabltes from punch positions P1, P2 and P3 at compression force of 1,200 lb in medium pH 6.8

Table 11 Value of $T_{50\%}$ (hrs.) and the first-order release rate, Kr (hr^{-1}) of DS microtablets

	400 lb			800 lb			1,200 lb		
	P1	P2	P3	P1	P2	P3	P1	P2	P3
$T_{50\%}$ (hrs.)	4.48	4.36	4.03	4.47	4.51	4.36	4.07	5.03	4.31
Kr (hr^{-1}) (mean±sd.)	0.0614 ±0.0261	0.0608 ±0.0223	0.0606 ±0.0175	0.0725 ±0.0378	0.0711 ±0.0279	0.0735 ±0.0275	0.1111 ±0.0167	0.0829 ±0.0195	0.0970 ±0.0374

Table 12 Correlation of determination (r^2) of relationships between log percentage drug remained versus time (first-order), percentage drug released versus square root time (Higuchi's equation), and drug released versus time (zero-order)

r^2	400 lb			800 lb			1,200 lb		
	first order	Higuchi	zero order	first order	Higuchi	zero order	first order	Higuchi	zero order
P1	0.9924	0.9657	0.9133	0.9642	0.9470	0.8555	0.9962	0.9694	0.9357
P2	0.9842	0.9529	0.8953	0.9837	0.9642	0.8870	0.9998	0.9905	0.9624
P3	0.9624	0.9147	0.8457	0.9884	0.9242	0.8556	0.9994	0.9558	0.8983

3.2 Effect of compression forces and punch sizes on the properties of microtablets

3.2.1 Morphology of DS microtablets

The observation of surface, dimension and shape was done by scanning electron microscopy. The scanning electron photomicrographs of microtablets containing 30% EC, 30% DS and 40% diluents (formulation F1) that were prepared by various compression forces (400-1,200 lb) and punch sizes (2.00-2.50 mm) are shown in Figure 24. The surface area of microtablets prepared with higher compression force was smoother than that of microtablets compressed with

lower compression force. More fissures were seen at the surface of DS microtablets compressed at the lowest compression force. Moreover, the compression forces and punch sizes were varied thus the dimensions of DS microtablets were changed. Therefore, it affected the surfaces area and volumes of microtablets. The results of calculated surfaces area and volumes of microtablets are presented in Table 13. The results showed that the volumes of the matrix microtablets tended to increase when increasing the diameter of punches and decrease with the increasing compression force. This caused the surface area to volumes ratio of microtablets to decrease. As the diameter of the punch increases, the same compression force used to be has distributed more over the increase compression area and less force was therefore transmitted through the compact mass. This resulted in higher porosity as well as volumes of tablets.

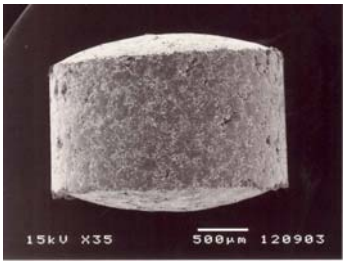
Table 13 The results of calculated surface area, volume and surface area-volume ratio of DS microtablets prepared by various compression forces and punch sizes

	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb
Surface area (mm^2)	20.873 (0.205)	20.658 (0.111)	20.261 (0.198)	20.934 (0.164)	20.331 (0.175)	20.124 (0.201)	21.799 (0.104)	21.390 (0.145)	20.739 (0.218)
Volume (mm^3)	7.789 (0.102)	7.682 (0.055)	7.484 (0.099)	8.104 (0.093)	7.765 (0.099)	7.648 (0.099)	8.729 (0.066)	8.474 (0.091)	8.067 (0.136)
Surface area to volume ratio	2.679 (0.008)	2.689 (0.005)	2.707 (0.009)	2.583 (0.009)	2.618 (0.011)	2.631 (0.013)	2.497 (0.006)	2.524 (0.009)	2.572 (0.016)

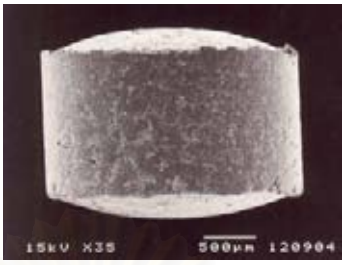
Parentheses represent the standard deviation, n=10

3.2.2 Weight variation and friability

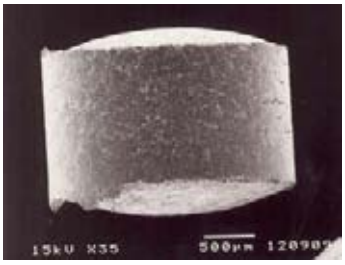
Table 14 shows the results of the physical properties of microtablets which were prepared from various compression forces and punch sizes. The results showed that the mean weight and friability of DS microtablets were within the limit of standard official USP XXIV.



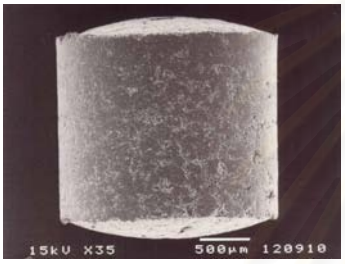
400 lb, 2.50mm



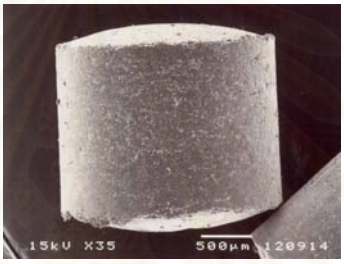
800 lb, 2.50mm



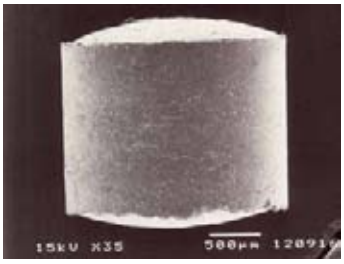
1,200 lb, 2.50mm



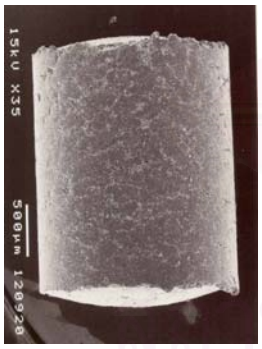
400 lb, 2.25mm



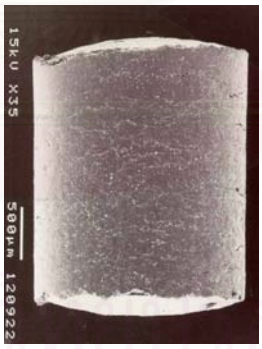
800 lb, 2.25mm



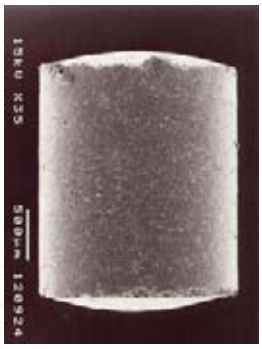
1,200 lb, 2.25mm



400 lb, 2.00 mm



800 lb, 2.00mm



1,200 lb, 2.00mm

Figure 24 Scanning electron photomicrograph of DS microtablet prepared from punch sizes 2.00, 2.25 and 2.50 mm and various the compression forces (400-1,200 lb) (the surface of microtablet ×35)

Table 14 Physical properties of DS microtablets from formulation F1

	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1,200 lb	400 lb	800 lb	1,200 lb	400 lb	800 lb	1,200 lb
Weight variation mg±SD (%RSD) n =20	10.465 ± 0.263 (2.51)	10.435 ±0.308 (2.96)	10.489 ± 0.200 (1.91)	10.181 ± 0.177 (1.73)	10.049 ± 0.167 (1.66)	10.131 ± 0.271 (2.78)	10.336 ± 0.201 (1.96)	10.382 ± 0.224 (2.15)	10.463 ± 0.203 (1.944)
Friability (%)	0	0	0	0	0	0	0	0	0
Thickness (mm) n =10	2.638±0.03	2.603±0.02	2.540±0.03	2.233±0.02	2.148±0.02	2.118±0.03	2.013±0.02	1.961±0.02	1.878±0.03
Hardness (N)	19.097±0.32	23.183±1.56	26.034±1.72	14.741±2.04	17.210±2.16	18.693±1.65	11.050±3.30	14.842±2.63	16.449±1.26
Porosity (% ± SD)	6.475±1.17	4.277±1.34	1.432±1.31	11.496±0.99	9.593±0.86	8.859±0.91	15.483±0.63	13.192±0.93	8.782±1.54

3.2.3 Thickness

The thicknesses of microtablets at high pressure were less than the thickness of microtablets at low pressures. In case of microtablets compressed with different punch sizes, the thicknesses were decreased when increasing the punch size as displayed in Table 14.

In addition, the tablet thickness was also useful to determine the apparent density of tablet compacts. The volume of a concave face tablet could be calculated from the formula for the volume of cylinder and two spherical segment ($V=\pi (r^2w+r^2h+3h^3)$, where r = radius of tablet, w = central cylinder thickness, and h = overall tablets thickness). Density was equaled to mass per unit volume, where mass was determined by weighing the individual tablets. Thus, thickness was related to the density of tablet (Rosanske et al., 1990, Newton et al., 2000). These results of thickness indicated that the compression force and punch size might affect the density or porosity of microtablet because of thickness changing of microtablets.

3.2.4 Porosity

The porosity of microtablets was calculated from measurements of microtablet dimensions, weight and the true density of the DS granules (F1). The density of granules was 1.4185 g/cc and % porosity was calculated from equation [19]. The results of % porosity are presented in Table 14.

The porosity of DS microtablets was decreased when increasing the compression force while increasing the punch size tended to increase the porosity of microtablet. Hence, it could be concluded that the porosity of microtablets was depended on the compression force and dimensions of punch, indicating that the porous distribution of microtablet were different (Al-Nasassrah et al., 1996; Newton et al., 2000). The applied pressure was increased and the porosity of tablets was decreased. This was explained that by the interparticular distances through which bonding forces operate was shorter. Thus, the bonding force of material was stronger than at low porosity (Parrott, 1990) and caused harder microtablets.

3.2.5 Specific surface area of DS microtablets

The specific surface area and the total pore volume of DS microtablets (formulation F1) were measured by BET method. The specific surface area and the total pore volume of DS microtablets (formulation F1) prepared from various compression forces (400-1,200 lb) and punch sizes (2.00-2.50 mm) are displayed in Table 15.

For the punch sizes 2.00 and 2.50 mm, the specific surface area was minimally decreased when increasing the compression force within the range of 400-1200 lb. At the punch size 2.25 mm, the specific surface area was increased to maximal value when increasing the compression force from 400 lb to 800 lb, indicating the formation of new clean surface area due to fragmentation of the granules. Further increased in applied pressure (to 1200 lb) produce a progressive decreased in specific surface area as the particle bonding (Parrott, 1990). For this study, these results indicated that the compression force and punch size did not clearly affect to specific surface area of DS microtablets. Surface area of tablet was determined by both BET and tablet dimensional calculation techniques. The results from both methods were quite different due to BET analysis obviously gave higher values than calculation. BET method generally uses gas adsorption on the surface of materials principle, if some parameters are changed (such as pressure) it provides a different surface area value. The crack or opened pore of microtablets was one of the most important factors that perturbed the surface area determination from such analysis. The result from BET analysis of microtablets was the sum of the surface around the tablet and all of cracking portions including open pores (Nystrom et al., 1993). Meanwhile, the surface area calculation from tablet geometry is only used the outer tablet dimension as main parameter in computation. So, BET method was normally giving a higher value than the calculation of tablet dimension.

Table 15 Specific surface area of DS microtablets

	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb
Specific surface area (m^2/g)	5.05	4.38	4.27	3.26	3.84	3.38	4.53	4.48	3.94

3.2.6 Hardness and apparent tensile strength (ts_{app})

The mean and standard deviation of hardness of DS microtablets are displayed in Table 15. Figure 25 exhibits the hardness-compression profile of DS microtablets compressed at various compression forces (400-1,200 lb) and punch sizes (2.00-2.50 mm). The hardness of DS microtablets was increased when increasing the compression force for preparing the microtablets at each punch diameter. Moreover, smaller punch size produced microtablets with higher hardness than that of larger punch size under the same compression forces.

The apparent tensile strength (ts_{app}) of DS microtablets was calculated from the equation 3. The results of ts_{app} were plotted against compression forces at each punch size as shown in Figure 26. It was seen that the ts_{app} of all punch sizes was increased with increasing the compression pressure. In addition, smaller punch produced tablets had higher ts_{app} values than larger punch under the same condition. This could be explained by the density and porosity of microtablets as previously described in 3.2.4. Al-nasassrah and Newton (2000) reported a linear relationship was obtained when plotted the natural log of tensile strength against tablet porosity, indicating that the tablet tensile strength was decreased when porosity of tablets was increased. It was found that tensile strength decreased with increasing the punch diameter from 10 mm to 12 mm. Hence, it could be concluded that the tensile strength was depended on the dimension of punch, because of the porous distribution of tablets was different.

Both increasing the compression force and decreasing the punch size reduced the volume of microtablets as shown in Table 13 in 3.2.4 that led to increase

the densities and decrease porosities of microtablets and caused harder microtablets. The higher compression force produced the closer packing structure of powder bed in the die due to particle rearrangement and volume reduction. Subsequently, it directly affected increase the interparticulate bonding at the point of contraction among granule within compacted mass. The higher the compression force the higher the bonding and the hardness of tablet. Thus, interparticulate bonding and volume reduction were playing a major role on the microtablet formulation. Figure 27 shows the relationship of the compression force and %porosity, indicating that the porosity of microtablets was decreased when increasing the compression force.

Figure 28 shows the relationship of the ts_{app} and % porosity of microtablets that prepared with various compression forces (400-1200 lb) and punch sizes (2.00-2.50 mm). It was shown that decreasing in porosity tends to increase the ts_{app} of microtablets. Conclusively, ts_{app} was depended on the porosity of microtablets.

The compaction profiles in Figures 25 and 26 showed a non-linear relationship between compression force and hardness, compression force and ts_{app}, respectively. Figure 25 and 27 showed that, the slopes of graphs were not straight line. At low pressure, increase pressure tended to increase hardness and ts_{app} more than that at high pressure. Padmaja and Sprockel (1992) explained that the rate of increase in tensile strength with pressure was related to the predominating mechanism of compression in that pressure range. At low pressure, the major mechanisms for densification were particle rearrangement and elastic deformation, which caused a large volume reduction with small increasing in pressure. The rate of increase in tensile strength with pressure was rapid even though the magnitude was small. At higher compression pressures, the plastic deformation of particle became the predominant mechanism for volume reduction. Since deformation was required more energy input than particle rearrangement, the rate of volume reduction with pressure was less. This explained that the lower rate of increase in tensile strength with pressure in the range where deformation was dominated. The hardness of tablets was correlated with ts_{app} (Figures 25 and 26). Hence, these results could be concluded that the hardness and ts_{app} depended on the compression forces and diameter of punches.

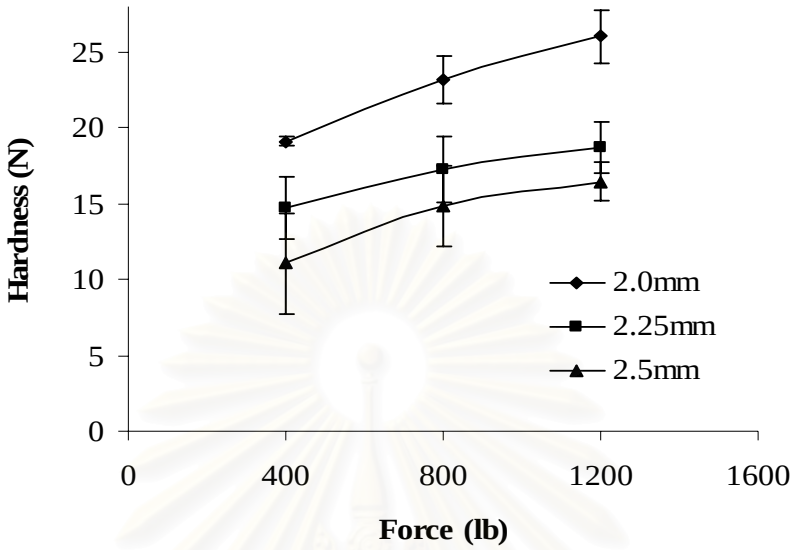


Figure 25 Effect of the compression pressures on the hardness of DS microtablets prepared with different punch size of 2.00, 2.25 and 2.5

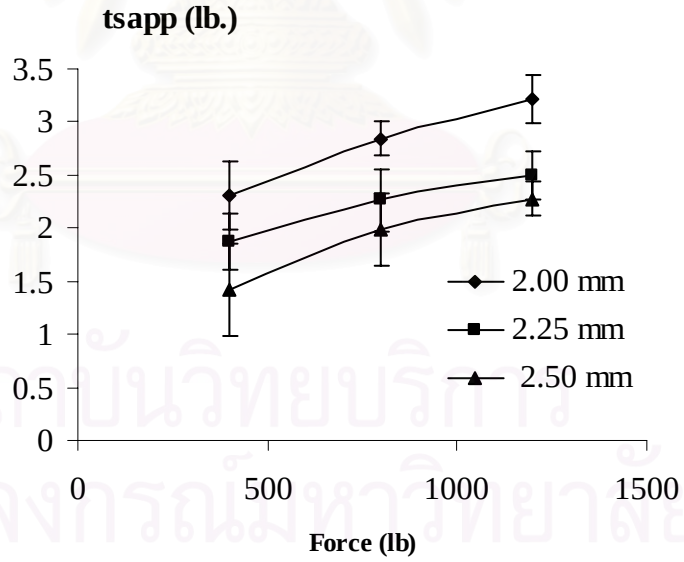


Figure 26 Effect of compression pressures on apparent tensile strength, ts_{app}, of DS microtablets prepared with different punch diameters (2.00, 2.25 and 2.50 mm)

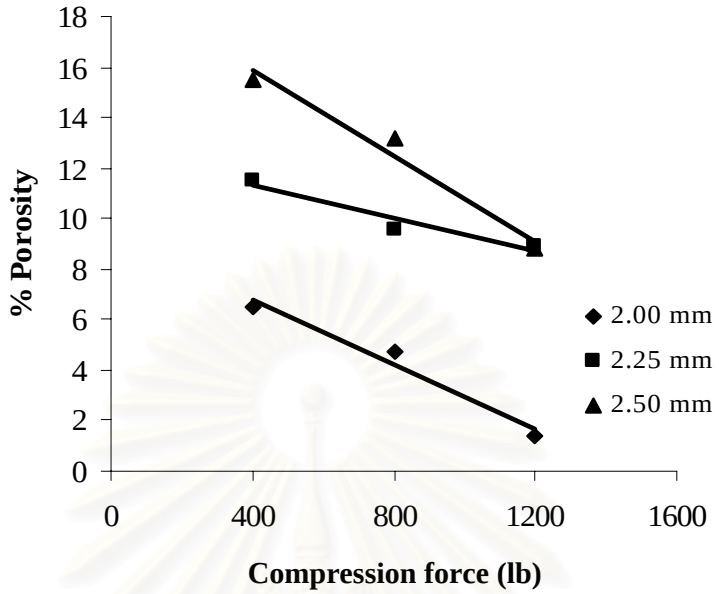


Figure 27 Effect of compression pressures on % porosity of DS microtablets prepared with different punch diameters (2.00, 2.25 and 2.50 mm)

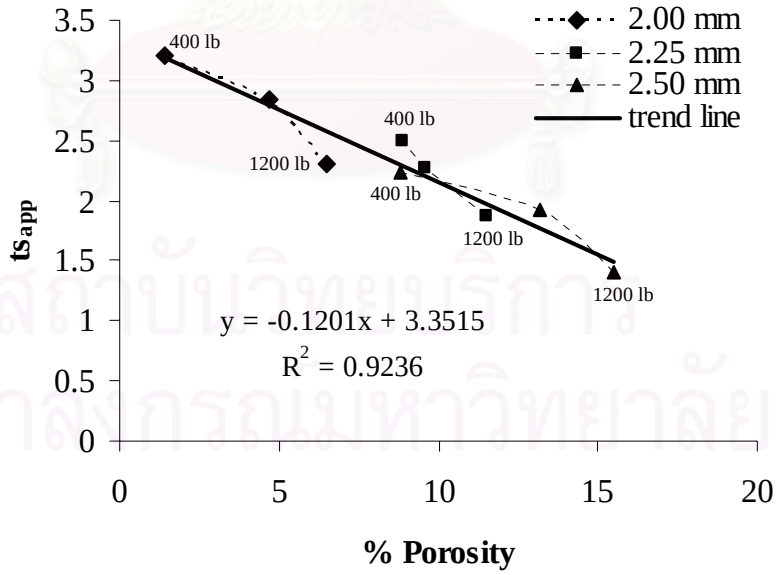


Figure 28 Porosity of DS microtablets prepared with different punch size and various compression force as a function of the natural logarithm of apparent tensile strength

3.2.7 Effect of the compaction pressure and punch sizes on the drug release

To study the effect of compaction pressure and punch sizes on drug release, microtablets containing 30% EC, 30%DS and 40% diluents (formulation F1) were prepared from punch sizes of 2.00, 2.25 and 2.50 mm and compressed at various forces of 400, 800 and 1,200 lb. The DS microtablets equivalent to 75 mg of DS that were filled into a capsule were evaluated in pH-change system. The release profiles of DS microtablets from various the compression forces of DS microtablets that were prepared from punch sizes of 2.00, 2.25 and 2.50 mm in pH-change system are shown in Figures 29-40, respectively.

In pH-change system, these DS microtablets were tested in acid stage (0.1 N HCl, pH 1.2) for 2 hours; the percentages of drug release from all cases were less than 5 %. When the pH of medium was raised to pH 6.8 by addition of the phosphate buffer, the amounts of drug release in the first 2 hours were increased to 30-40%. This indicated that the release of DS from microtablets was depended on the pH of dissolution medium as previously described in 3.1.5.

The dissolution profiles indicated that the compression forces had minimal effect on drug release profile when the microtablets were produced with the same punch size. The drug release profiles were nearly superimposed, indicating that the compression force within the range of 400-1,200 lb was not an important factor in modifying the release pattern of drug from matrix microtablets (Figures 29-34). The similarity factors (f_2) for the drug release profiles for varying the compression force were found to be more than 50, indicating that an average difference was not more than 10% at initial 80% of drug release. However, the dissolution profiles of microtablets that were prepared by using different punch sizes depicted the difference on drug release when compressed at the same compression force (Figures 35-40). The similarity factors (f_2) for the dissolution profiles from various the punch sizes were more than 50. From the results were indicated that different punch size would be resulted for unequal f_2 value. As increasing punch size it would be made f_2 value decrease. However, all of f_2 in the experiments were in the acceptable limitation.

It might be indicated that punch size is one of the crucial factor for microtablets formulation.

All cases showed similar release model. The first-order plot showed linearity with correlation plot of greater than 0.99 in pH-change system as seen in Table 16. Furthermore, the first- order constant release rates (Kr) were tested with ANOVA, it was found that the compression force had no significant effect ($P>0.05$) on the first-order release rate constant when the microtablets produced by using punch size 2.25 and 2.50 mm, whereas, the microtablets compressed by using punch size 2.00 mm, it was found that the compression force at 800 lb had significantly difference effect ($P<0.05$) on the first-order release rate when compared with force of 400 lb and 1200 lb (Table 102-105, Appendix D). However, the first- order constant release rates (Kr) were tested with ANOVA, it was found that the punch size had significant effect on the release rate ($P<0.05$) when compressed at same force (Table 106-111, Appendix D). This was indicating that the punch size had influence on the drug release pattern.

At the same punch size, the changing of compression forces for preparing microtablets had little influence on the drug-release. These results were agreed with those previous papers, Cameron and McGinity (1987), Fassihi (1987) and Sarisuta and Mahahpunt (1994) stated that compression force and tablets hardness had minimal effect the drug release, which could be explained by porosity of tablets which was decreased when increasing the compression force. However, at optimum point (critical limit), the compression force did not affect porosity due to the occurrence of elastic deformation. Dabbagh et al. (1996) reported that compaction pressures up to 39.4 MNm^{-2} affected the propranolol release from matrices containing EC 7 cps. Whereas compression pressure from 78.7 to 393.4 MNm^{-2} did not further modify the release rate. Initially, increasing the compression pressure would decrease the porosity resulting in decreasing the dissolution release rate. While the porosity of matrices made at pressure between 78.7 and 393.4 MNm^{-2} were similar therefore the drug release was not significant different. Furthermore, Rey et al. (2000) reported that the compression pressure (from 200-250 MPa) had no effect on the theophylline release from microtablets due to the plastic behavior of Eudragit RS PO during compression.

Calculation of tablets porosity showed a difference of only 0.5% between microtablets compressed at 200 and 250 MPa. For this study, the compression force within the range of 400-1200 lb produced the DS microtablets with similar the porosity and surface area as seen in Table 13, 14 and 15. The compression force within the range of 400-1200 lb might be over critical limit to produce microtablets with similar porosity and surface area. Therefore, the compression force (400-1200 lb) had little influence on the drug release of DS microtablets. However, a contrast with the results was reported by other study. Stamm and Tritsch (1986) reported that EC matrices tablets made with low crushing strengths had high porosity and gave quick release of metoclopramide hydrochloride whereas the drug release was lower when the tablets made to higher crushing strength.

On the other hand, smaller punch size at constant applied compression force increased the surface area to volume ratio than larger punch size. Therefore, the drug release would be increased. In a previous paper, Sujja-areevath (1996) showed that an increase in matrix volume with increasing the punch size could account for slower drug release. It was due to the decrease of surface area to volume ratio. Figure 41 showed that the first-order release rate constant was decreased when decreasing the surface area to volume ratio. This was indicated that the surface area had strongly influence on the drug release. The surface area of different tablet sizes, and therefore have different areas, should also be considered. The larger contact surface area of tablet and less diffusion path length should result in faster dissolution rates. As any matrix system was undergone the diffusion and erosion, the size and shape of a tablet might affect on the drug dissolution (Rekhi et al., 1999). The relationship of the first-order drug release rate constant and surface area to volume ratio is shown in Figure 41.

In addition, dissolution studies showed that formulations with 800 lb compression forces gave a superior dissolution rate than 400 lb formulations. It might be indicated that higher compression force resulted in tiny fragmentation of each granules and also led to increase new clean surface area that was potential bonding area. Even though the higher compression force normally provided higher specific surface area via granule fragmentation, but excess amount of compression force

would generate the bonding formation between each particles as well. Subsequently, the porosity of tablet after exposure to excess compression force would decrease because of predominant bonding formation over fragmentation mechanism. Therefore the results from formulation of the highest compression force of 1200 lb formulations could express a lower release rate than 400 and 800 lb formulations. However, changing of surface and porosity had slightly affect to release rate when were varied the compression force within the range of 400-1200 lb. Parrott (1990) reported that the dissolution became faster as the pressure was increased to maximum and then further increased in applied pressure slowed dissolution when a gelatin solution was used as granulating agent for preparing sulfadimide tablets. This was explained that if the fragmentation occurred during in compression, the dissolution was faster as the applied pressure was increased since the fragmentation increased the specific surface area. If the bonding of particles was predominated phenomena in compression, increasing the applied pressure caused decrease in the dissolution.

The exponent value (n) of DS microtablets at various compression force and punch size are presented in Table 17. The released data were evaluated according to the equation of Ritger and Peppas (1987) fitting the data from the initial 60% of drug release. In non-swellable matrices, the value of $n = 0.45$ indicated square root of time kinetics (Case I or Fickian diffusion), $n = 1.0$ indicated Case II transport, $0.45<n<1.0$ indicated anomalous (non- Fickian) diffusion and $n>1.0$ for Super Case II transport (Peppas, 1987). The exponent values (n) of all cases from various compression forces and punch size were Super Case II transport. However, the released mechanism of this study might combine with another mechanism due to low correlation of determination (r^2=0.95-0.96). The values of n remained almost unchanged, indicating that the processing variables did not influence the released mechanism. Dabbagh et al. (1996) reported that propanolol matrix tablets containing 3:1 NaCMC: EC gave a released exponent value of 1.45. This value indicates Super Case II transport. The reason for this value might be the high swelling nature of the polymer at this ratio.

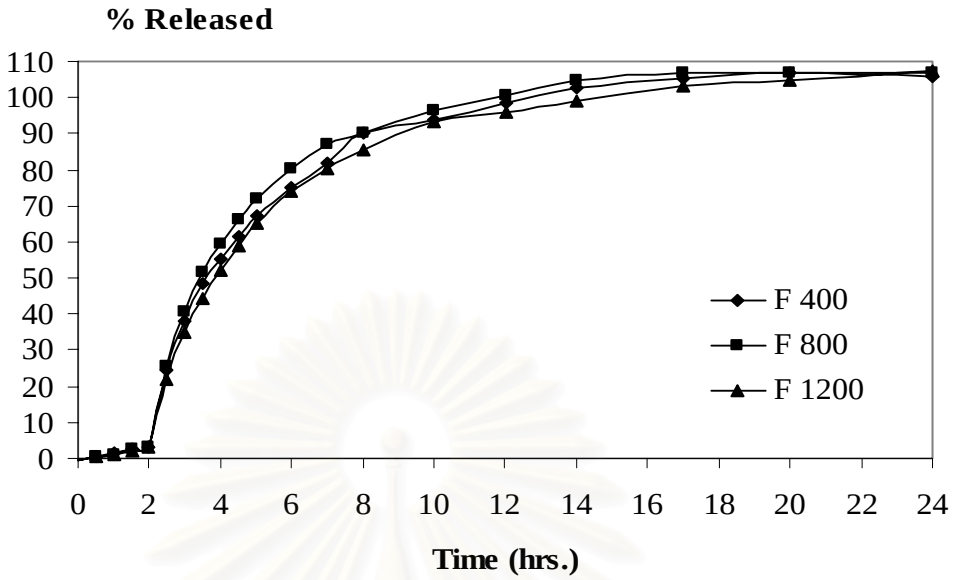


Figure 29 Dissolution profiles of DS microtablets that were prepared by using punch diameter 2.00 mm at various forces of 400-1200lb

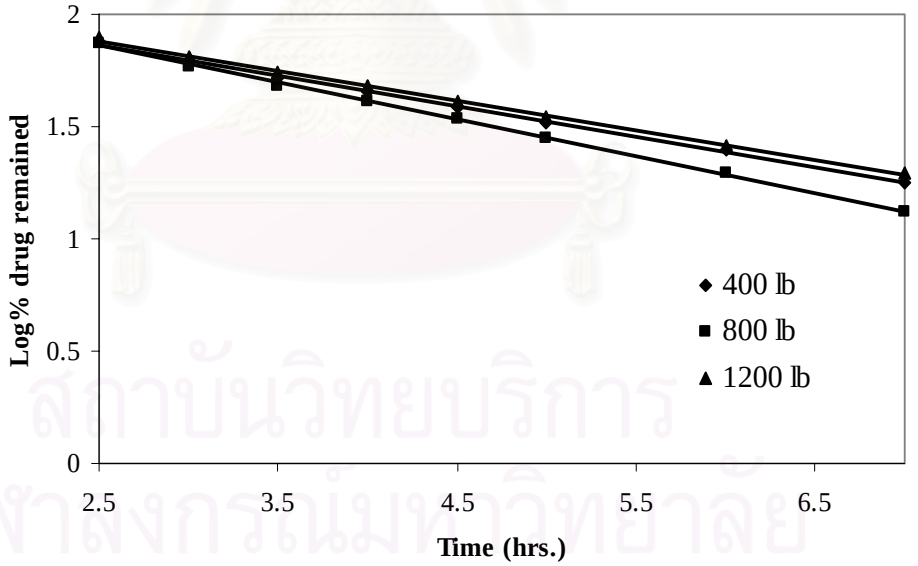


Figure 30 Log % drug remained against time for DS microtablets with 2.00 mm at compression forces of 400, 800 and 1200 lb

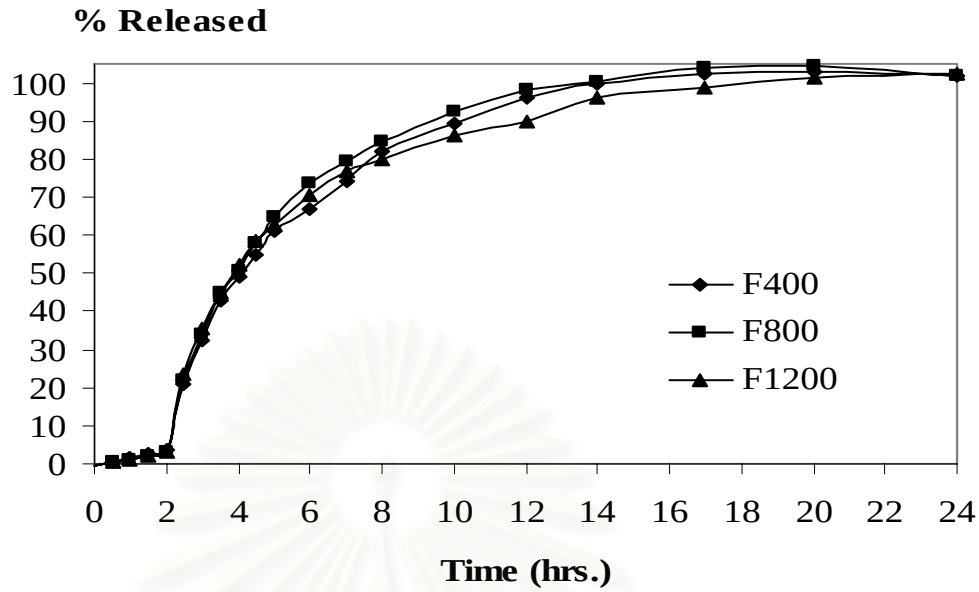


Figure 31 Dissolution profiles of DS microtablets that were prepared by using punch diameter 2.25 mm at various forces of 400-1200lb

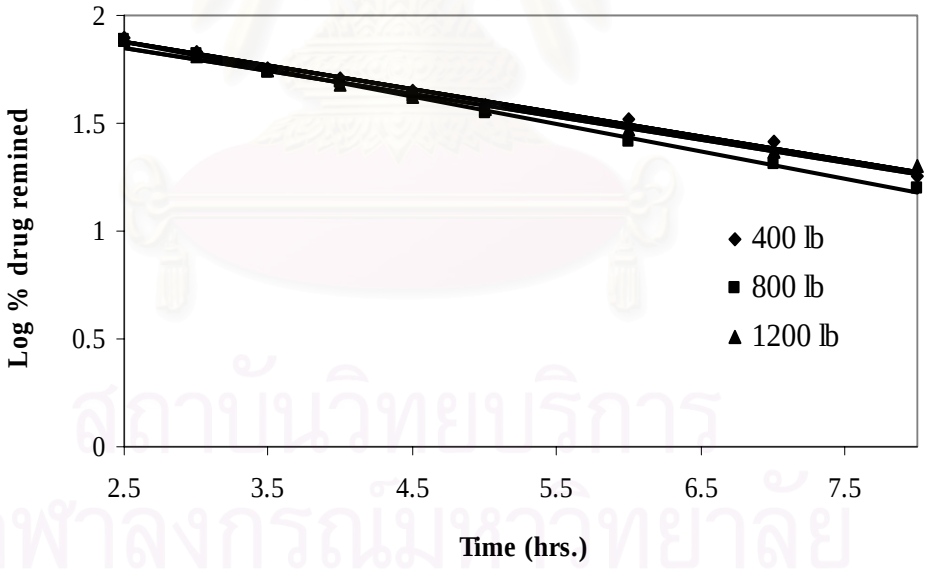


Figure 32 Log % drug remained against time for DS microtablets with 2.25 mm at compression forces of 400, 800 and 1200 lb

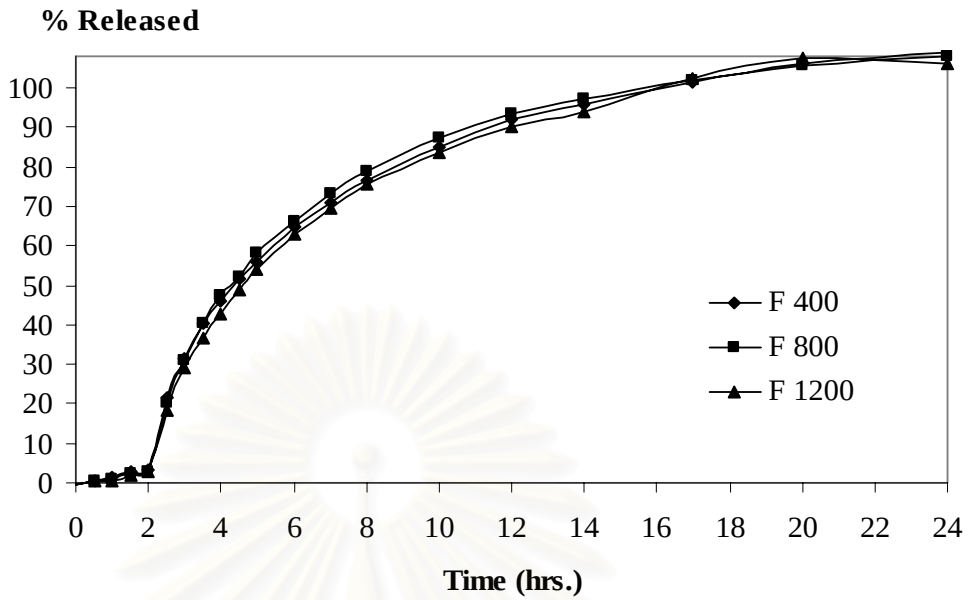


Figure 33 Dissolution profiles of DS microtablets that were prepared by using punch diameter 2.50 mm at various forces of 400-1200lb

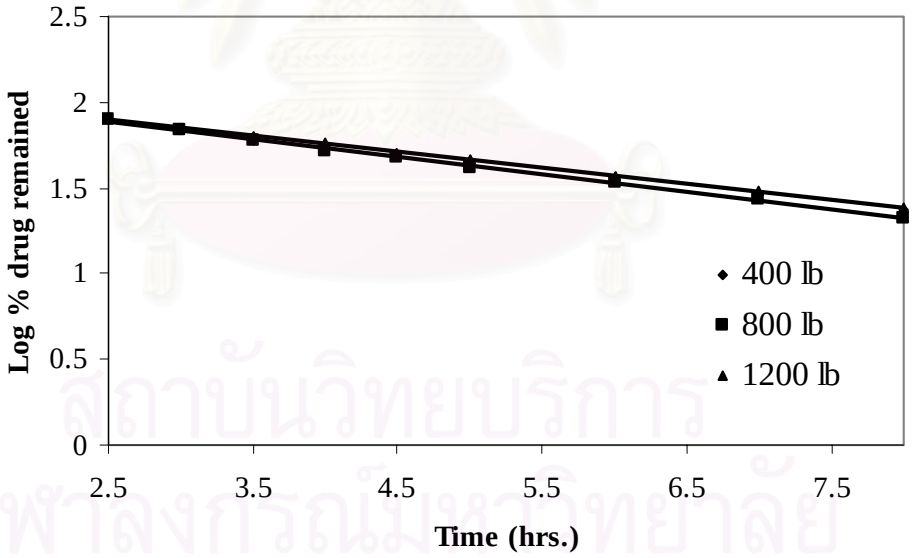


Figure 34 Log % drug remained against time for DS microtablets with 2.50 mm at compression forces of 400, 800 and 1200 lb

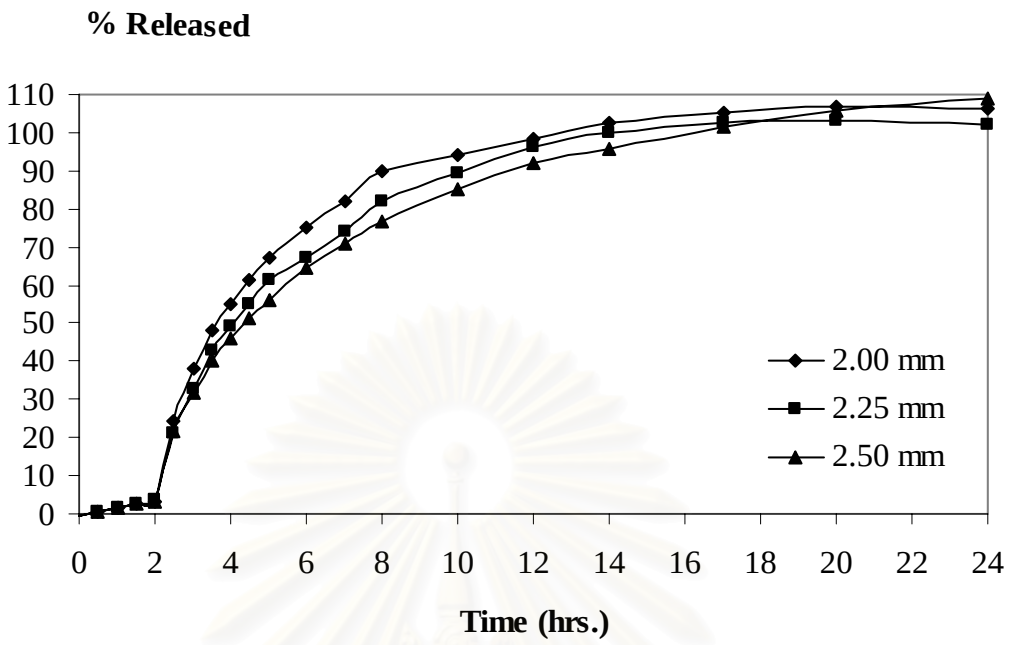


Figure 35 Dissolution profiles of DS microtablets prepared various punch sizes at force of 400 lb

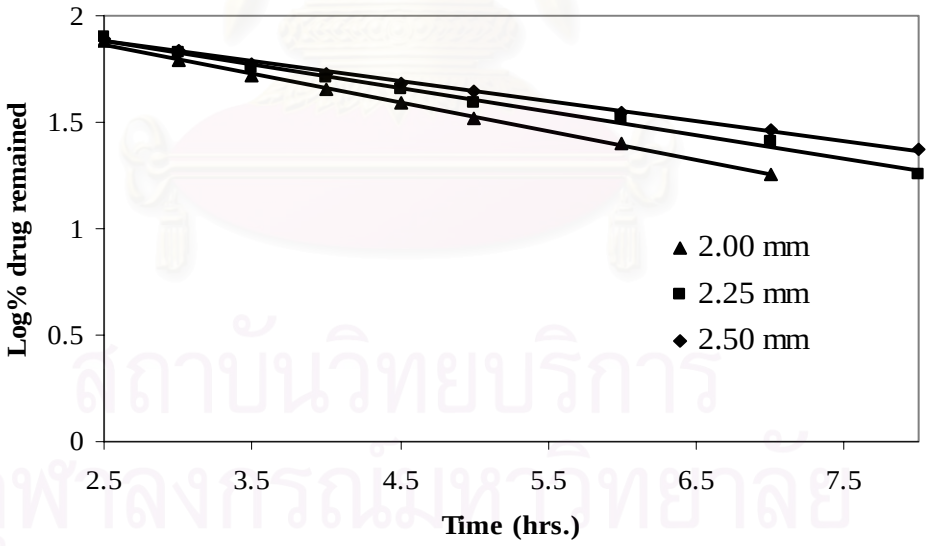


Figure 36 Log % drug remained against time for DS microtablets compressed with 400 lb at punch size of 2.00, 2.25 and 2.50 mm

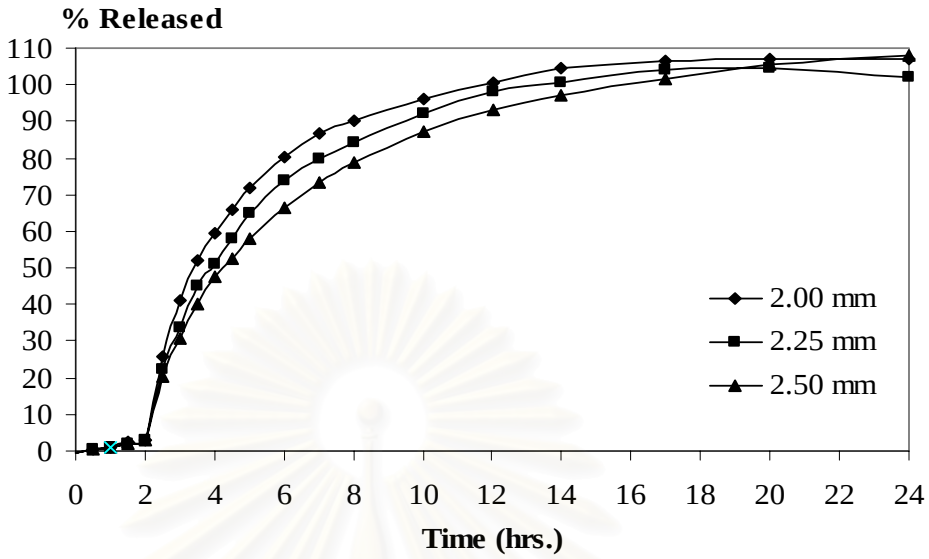


Figure 37 Dissolution profiles of DS microtablets prepared various punch sizes at force of 800 lb

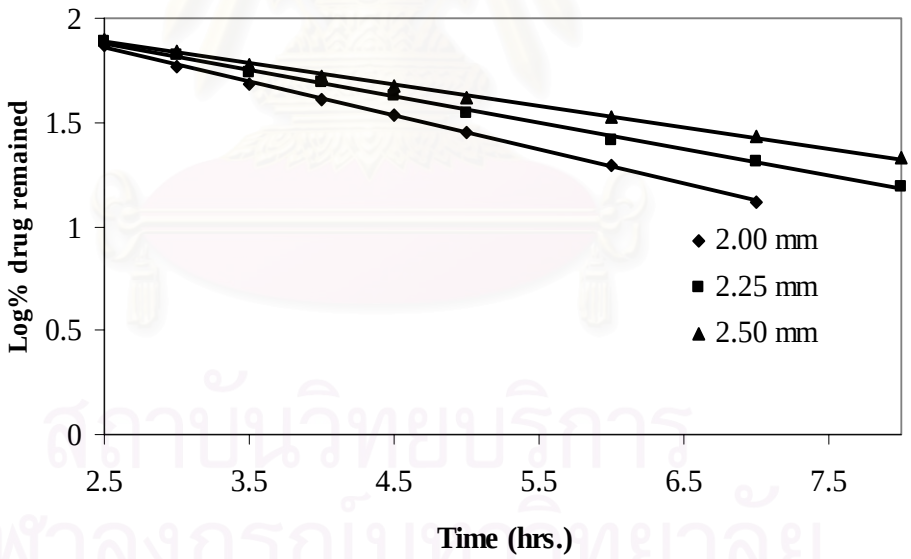


Figure 38 Log % drug remained against time for DS microtablets compressed with 800 lb at punch size of 2.00, 2.25 and 2.50 mm

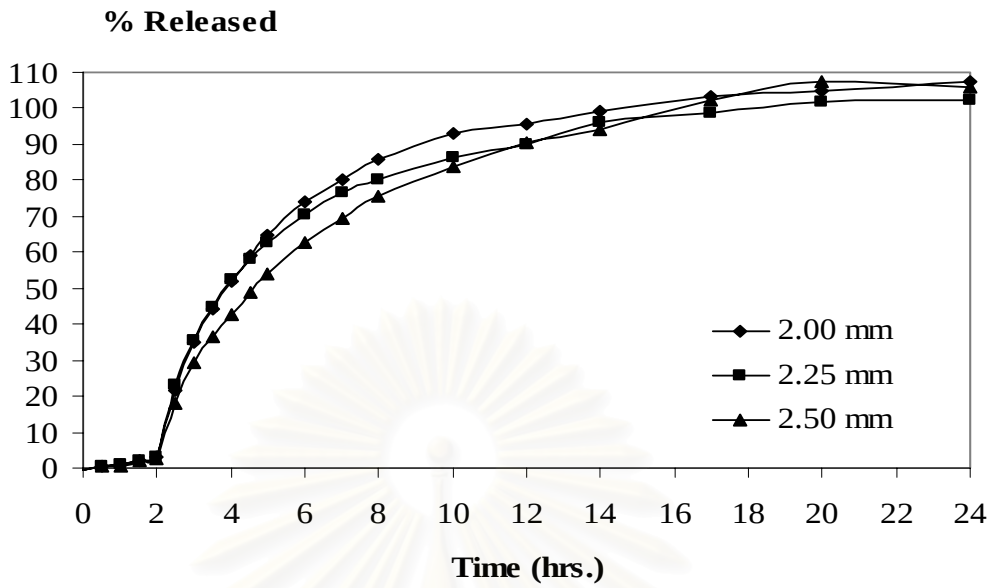


Figure 39 Dissolution profiles of DS microtablets prepared various punch sizes at force of 1,200 lb

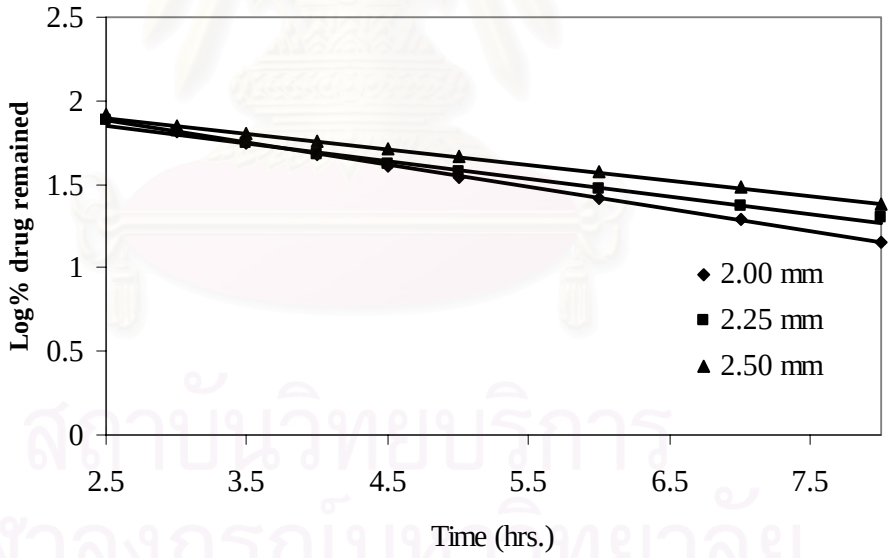


Figure 40 Log % drug remained against time for DS microtablets compressed with 1,200 lb at punch size of 2.00, 2.25 and 2.50 mm

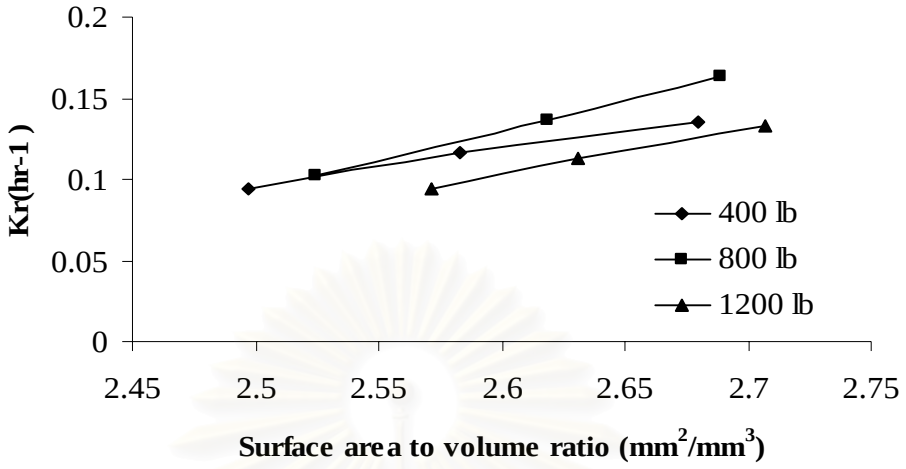


Figure 41 Relationship of the first-order release rate constant and surface area to volume ratio of DS microtablets prepared with different compression forces

Table 16 Correlation of determination (r^2) of relationships between percentage log percentage drug remained versus time (first-order), percentage drug released versus square root time (Higuchi's equation), and drug released versus time (zero-order)

r^2	2.00 mm			2.25 mm			2.50 mm		
	first order	Higuchi	zero order	first order	Higuchi	zero order	first order	Higuchi	zero order
400 lb	0.9981	0.9724	0.9495	0.9916	0.9724	0.9419	0.9979	0.9814	0.9534
800 lb	0.9965	0.9690	0.9423	0.9978	0.9671	0.9322	0.998	0.9776	0.9475
1,200 lb	0.9989	0.9751	0.9461	0.9900	0.9554	0.9159	0.9988	0.9859	0.9607

Table 17 Influence of compression force and punch size on the first-order release rate constant, release exponent (*n*) and correlation of determination (r^2) for DS microtablets

	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200lb	400 lb	800 lb	1200lb	400 lb	800 lb	1200lb
Kr (hr^{-1})[a]	0.1357 ±0.0036	0.1636 ±0.0042	0.1329 ±0.0051	0.1159 ±0.0042	0.1367 ±0.0129	0.1131 ±0.0087	0.0941 ±0.0085	0.1029 ±0.0106	0.0938 ±0.0066
n	1.5379 ±0.0858	1.7797 ±0.0189	1.6648 ±0.1323	1.4891 ±0.0634	1.5142 ±0.1858	1.4039 ±0.0209	1.3563 ±0.0538	1.4819 ±0.0290	1.3596 ±0.0321
r^2	0.9566	0.9611	0.9606	0.9576	0.9597	0.9559	0.9628	0.9625	0.9509

[a] The release rate (hr^{-1}) was calculated from slope of the plot of log percentage drug remained versus time (mean ± sd; n=3)

3.3 Effect of formulation variable on the properties of microtablets

For this study, a compression force of 800 lb and punch size of 2.5 mm were selected for preparing the matrix microtablets.

3.3.1 Weight variation of microtablets

The mean and standard deviation in weight variation of DS microtablets of all formulations (F1-F10) are displayed in Table 18. The weight variations of all formulations passed the specification of standard official USP XXIV.

The weight variation of obtained microtablets was within acceptable limits, reflecting the favorable flowability that conferred by wet granulation method (Cheng et al., 1993). Moreover, the single punch tabletting machine had low speed that would not affect to weight variation because slow speed increased time intervals for upper punches to enter into die cavity. Therefore, feed shoes had enough time to uniformly fill the granules into all die cavities (Katikaneni, Upadrashta, Rowlings et.al., 1995.; Wray, 1992).

Table 18 Physical properties of DS microtablets with varying composition in formulation and with compression of 800 lb

	Physical properties			
	Weight variation (mg) mean±SD. (%RSD)	Thickness (mm) mean±SD	% Friability mean±SD.	Hardness (N) mean±SD.
F1	10.43±0.31 (2.96)	1.90±0.04	0±0	14.84±2.63
F2	10.05±0.20 (1.97)	1.82±0.01	0.03±0.06	14.60±1.13
F3	10.25±0.08 (0.75)	1.82±0.02	0.26±0.15	14.75±1.17
F4	10.18±0.14 (1.36)	1.92±0.04	0.24±0.04	7.98±1.62
F5	10.05±0.10 (0.95)	1.92±0.04	18.99±0.50	6.00±0.84
F6	10.02±0.26 (2.15)	1.90±0.01	0.14±0.29	10.65±1.67
F7	10.33±0.11 (1.04)	1.90±0.02	0.24±0.15	13.18±0.75
F8	10.13±0.13 (1.30)	1.93±0.03	0.18±0.12	13.08±0.72
F9	10.08±0.19 (1.9)	2.00±0.04	0.20±0.13	12.80±0.44
F10	10.03±0.26 (2.60)	1.90±0.02	0.24±0.06	14.76±1.04

Weight variation of capsule

The DS microtablets formulations F4 and F5 were filled into hard gelatin capsule size 1 by using semi-auto capsule filling machine. The coefficient of fill weight variation (%cv) of F4 and F5 were 2.900 and 2.3031, respectively. The percentage of weight variation of F4 and F5 were 5.413 and 2.3031, respectively that passed along with the specification of standard official BP (percentage deviation <10). It was indicated that DS microtablets could be uniformly filled into hard gelatin capsule. Table 19 show the mean and standard deviation of average weight of capsule.

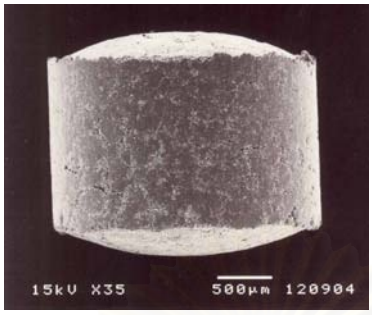
Table 19 The mean of fill weight and the coefficient of fill weight variation

Formulation	F4	F5
mean±SD.	287.54±8.34 (2.90*)	290.02±6.68 (2.30*)

* the numbers in parentheses mean %RSD

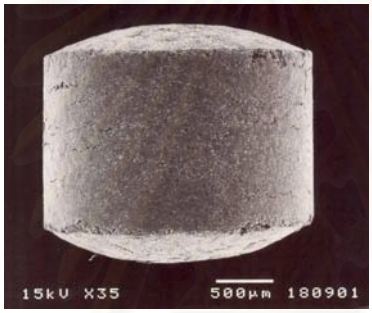
3.3.2 Morphology of DS microtablets

The scanning electron photomicrographs of DS microtablets of formulations F1, F6-F10 which varied the components are presented in Figure 42. The surfaces area of DS microtablets of formulations F7-F10 which combined EC with glyceride waxes (compritol 888 ATO, tristearin) were smoother and polisher than formulation F1 which contained EC alone, since, some glyceride waxes might be melted due to heat occurring in compression process and caused smoother surface tablet. On the other hand, more pores were seen at the surface of the DS microtablets formulation F6 which combined EC with HPMC K15M. This was explained by the lower hardness of microtablets (F6). Because of adding the HPMC K15M resulted in the increased of elastic deformation after compression. Therefore, the deformation recovery was increased resulting in decreased hardness of microtablets and caused more porous on the surface tablets (Banker et al, 1990).

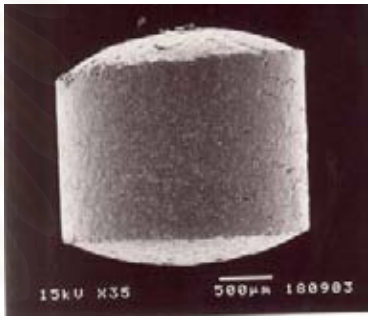


F1

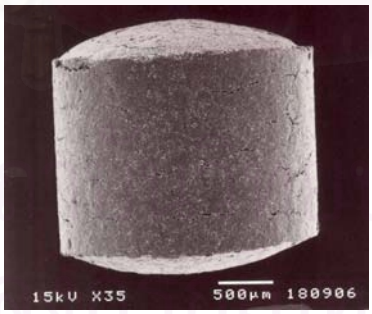
F6



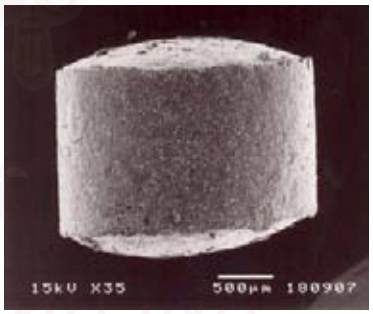
F7



F8



F9



F10

Figure 42 Scanning electron photomicrograph of DS microtablet prepared from various compositions in formulation (×35)

3.3.3 Thickness

The thickness of microtablets of formulations F1-F10 is presented in Table 18. Thickness of microtablets was increased when increasing the amount of EC in formulation and combining EC with glyceride waxes. Whereas increasing the amount DS in formulations did not affect the thickness of microtablets. It indicated that amount of polymer and types of compositions in formulation had an effect on the thickness of microtablets. This could be explained by the granules properties including bulk density, particle size and particle size distribution (Rosanske et al., 1990). If the granule of lower bulk density and larger particle sizes were compressed at the same conditions, they would be thicker than the tablets which were prepared from granules of higher bulk density and smaller particles. Table 9 and figures 15-16 showed that the granules from formulations of higher amount of EC (F4 and F5) and formulations that combined EC with glyceride waxs (F7-F10) had lower bulk density and higher large particle size than the granules from formulation F1 which contained low amount of EC. Thus, the microtablets prepared from granules formulation F4-F10 would be thicker than microtablets formulation F1.

In addition, the tablet thickness was also useful to determine the density of tablet compacts. The consolidation characteristics of various materials or tablet formulations were evaluated by measuring the density of tablet compacts under standard pressures and loading conditions. The thickness could be used to calculate the volume of tablet for converting to density of tablet. The volume of a concave face tablet could be calculated from the formula for the volume of cylinder and two spherical segment ($V=\pi\ (r^2w+r^2h+3h^3)$, where r = radius of tablet, w = central cylinder thickness, and h = overall tablets thickness). Hence, thickness might predict the consolidation characteristics of tablets. Formula or processing modifications of drug that was produced to increase the tablet density under applied compression conditions generally reflected to improve the consolidation of the formula and was expected to yield a more cohesive tablet compact (Rosanske et al., 1990; Duberg et al., 1986).

These results of thickness that were increased when the formulations of DS microtablets contained high amount of EC or combined EC with HPMC or glyceride waxes indicated that the consolidation characteristics of DS microtablets were changed when the formulations were modified (Malamataris et al., 1996; Veen et al., 2000).

3.3.4 Hardness and apparent tensile strength

The hardness of DS microtablets from all formulations (F1-F10) is presented in Table 18. The results showed that the microtablets prepared from granules with additional HPMC K15M (F6) or glyceride waxes (F7-F10) was shown to decrease in hardness. Furthermore, the hardness was clearly decreased when the amount of EC in formulation was increased. Whereas, increasing the percentage of drug load had no effect on the hardness of the microtablets. The results of apparent tensile strength were similar to the hardness. Figure 43 depicts the effect of formulation modification on the hardness and ts_{app} of DS microtablets. These results were explained by the consolidation mechanisms of material in compression process. In compression studies of binary mixtures, the effect on hardness of a second component was depended on the dominating consolidation mechanisms involved (Duberg et al., 1986).

The hardness of DS microtablets was reduced when increasing the amount of EC from 30% to 50%, respectively. It might be due to a decrease in the compressibility of the matrix tablet resulting from the higher EC proportion.

The hardness of formulations F6-F10 which combined EC with HPMC K15M or glyceride waxes (compritol 888 ATO, tristearin) was decreased due to the plastic deformation was the predominant mechanism of EC to compact after compression whereas the elastic deformation was the predominant for HPMC and glyceride waxes (Kantikaeni et al., 1995; Dasai et al., 2001). Therefore, the elastic recovery of tablets was occurred to increase when the formulations of DS microtablets mixed EC with HPMC K15M or glyceride waxes. It was clearly seen in formulations F7-F10 that increasing the amount of glyceride waxes decreased the hardness of

microtablets. Furthermore, the tablet hardness was decreased with an increase in particle size, since the smaller particle size showed greater packing density and greater number of contact points for interparticulate bonding (Katikaneni et al., 1995). The formulations F6-F10 had more higher of large particle size than formulation F1, therefore the hardness of F1 was greater than that of formulation F6-F10.

In addition, compritol 888 ATO was normally used as lubricant in compressed tablets. It could reduce the tablet hardness which was composed of plastic materials due to the decrement of interparticle interactions in the presence of lubricant, which prevented bond formation and increased the elastic nature of powder blend (Jarosz et al., 1984; Shah et al., 1986; Katikaneni et al., 1995).

Katikaneni et al. (1995) reported that hardness of EC matrix tablets was reduced 1.7-fold when increasing the amount of magnesium stearate from 0.5% to 3%. The tablet strength was more sensitive to the presence of magnesium stearate than glyceryl behenate as a result agreed with Shah et al. (1986).

3.3.5 Friability

The mean and standard deviation of microtablets of formulations F1-F10 are presented in Table 18. The percentage friability of all formulations passed the specification in official standard USP XXIV (0.6-1%) except for DS microtablets formulation F5 which did not pass official standard USP XXIV because the hardness of microtablet formulation F5 was very low compared to other formulations. Thus, the microtablets formulation F5 was very friable.

3.3.6 Drug content and content uniformity of DS microtablets

The percentages of drug content of the DS microtablets prepared from various formulations are shown in Table 20. The percentage of drug contents of all formulations passed the specification in official standard USP XXIV that the percentage drug content for delay-release DS tablet was not less than 90.0 percent and not more than 110.0 percent.

The formulations that passed the specification of drug content must be examined on the uniformity of content. The content uniformity was determined by percentages of coefficient variation (%CV) as shown in Table 20. The percentages of coefficient variation were less than 6%, which passed the specification official standard USP XXIV. All formulation had percentages coefficient variation less than 6 percent that indicated the uniformity of drug content.

The percentage drug content and content uniformity passed the specification in USP XXIV. This was due to the uniformity distribution of drug substance throughout the granulation, good properties of granules such as flowability and compressibility.

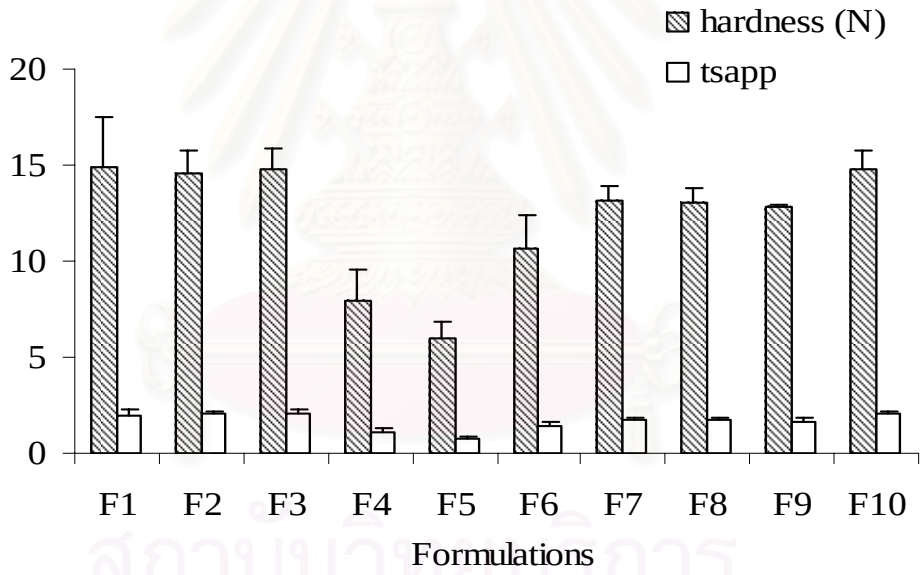


Figure 43 Effect of formulation modification on hardness and apparent tensile strength of DS microtablets

Table 20 Drug content and content uniformity of DS microtablets

Formulation	% Drug content	% Coefficient variation (%RSD)
F1	105.84 (0.48)	2.68
F2	97.03 (1.16)	1.65
F3	97.83 (0.51)	1.24
F4	96.60 (0.76)	1.66
F5*	-	-
F6	98.67 (0.48)	1.47
F7	97.97 (1.17)	2.23
F8	97.65 (0.07)	1.13
F9	99.91 (1.35)	2.00
F10	93.93 (0.66)	0.89

* The content and content uniformity were not determined because % friability did not passed the specification official standard USP XXIV.

3.3.8 Infrared Spectrometry

The IR spectrum of DS is illustrated in Figure 44 and 45. The principle peaks were observed at wave numbers of 747, 767, 1284, 1306, 1506 and 1576 cm^{-1}. The peaks at 747 and 767 cm^{-1} were resulted from C-H out of plane blending. The IR absorption band at 1284 and 1306 cm^{-1} were resulted from C-N stretching. The peaks at 1506 and 1575 cm^{-1} were resulted from C=C stretching (Mofflat et. al 1986). The IR spectra of HPMC and EC are shown in Figure 44. They showed a broad band of O-H stretching at the wavenumber rang of 3300-3400 cm^{-1}.

The IR spectra of two glyceride waxes (compritol 888ATO and tristearin) are shown in Figure 45. They showed the same characteristics of IR spectra because of having the same structure bone. The C-O stretching peak was presented at 1176 cm^{-1}. The aliphatic CH_2 blending was represented at 1739 cm^{-1}. The IR peaks at 2851 and 2918 cm^{-1} were resulted from aliphatic C-H stretching. There was a little different in position of peaks.

The IR spectra of DS microtablets contained EC and DS microtablets which combined EC with HPMC or glyceride waxes (compritol 888ATO and tristearin) are illustrated in Figures 44 and 45. The IR spectra of DS microtablets showed the combination of drug peak and matrix forming substances, while the principle peaks of drug and matrix forming substances were also still presented. Some positions of peak were very slightly shifted from original material. It could be concluded that interaction between drug and matrix former substances were unlikely to occur and type of matrix former had no effect on the IR spectra.

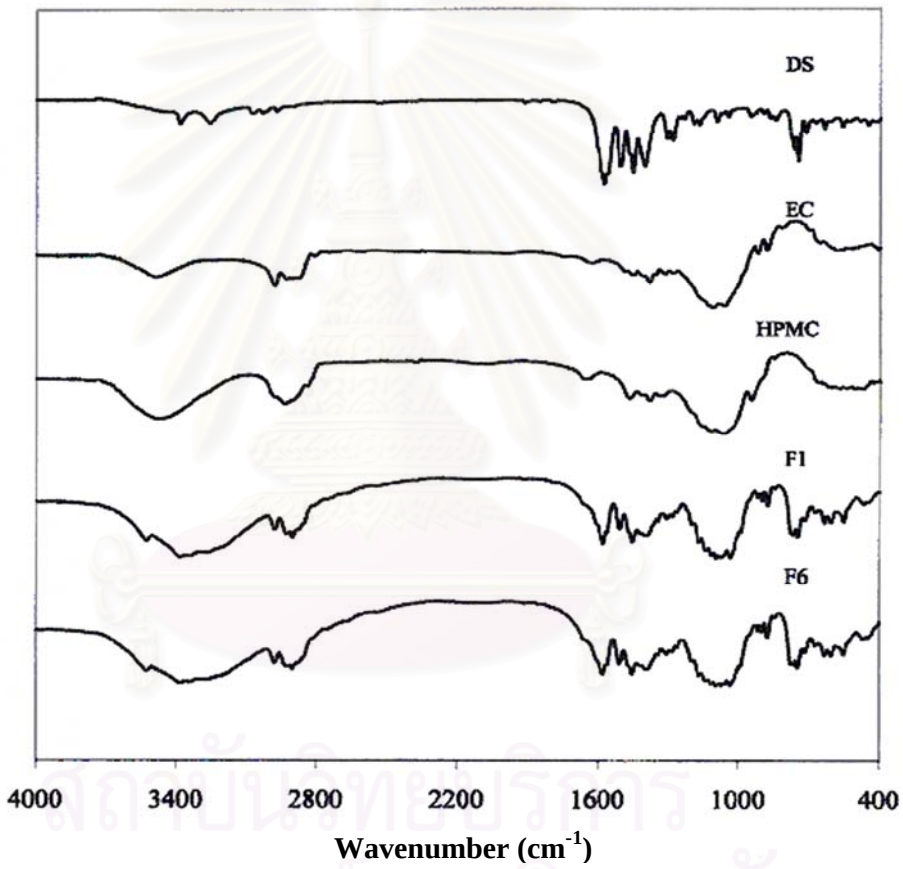


Figure 44 IR spectra of DS microtablets contained EC and DS microtablets with combined EC and HPMC K15M

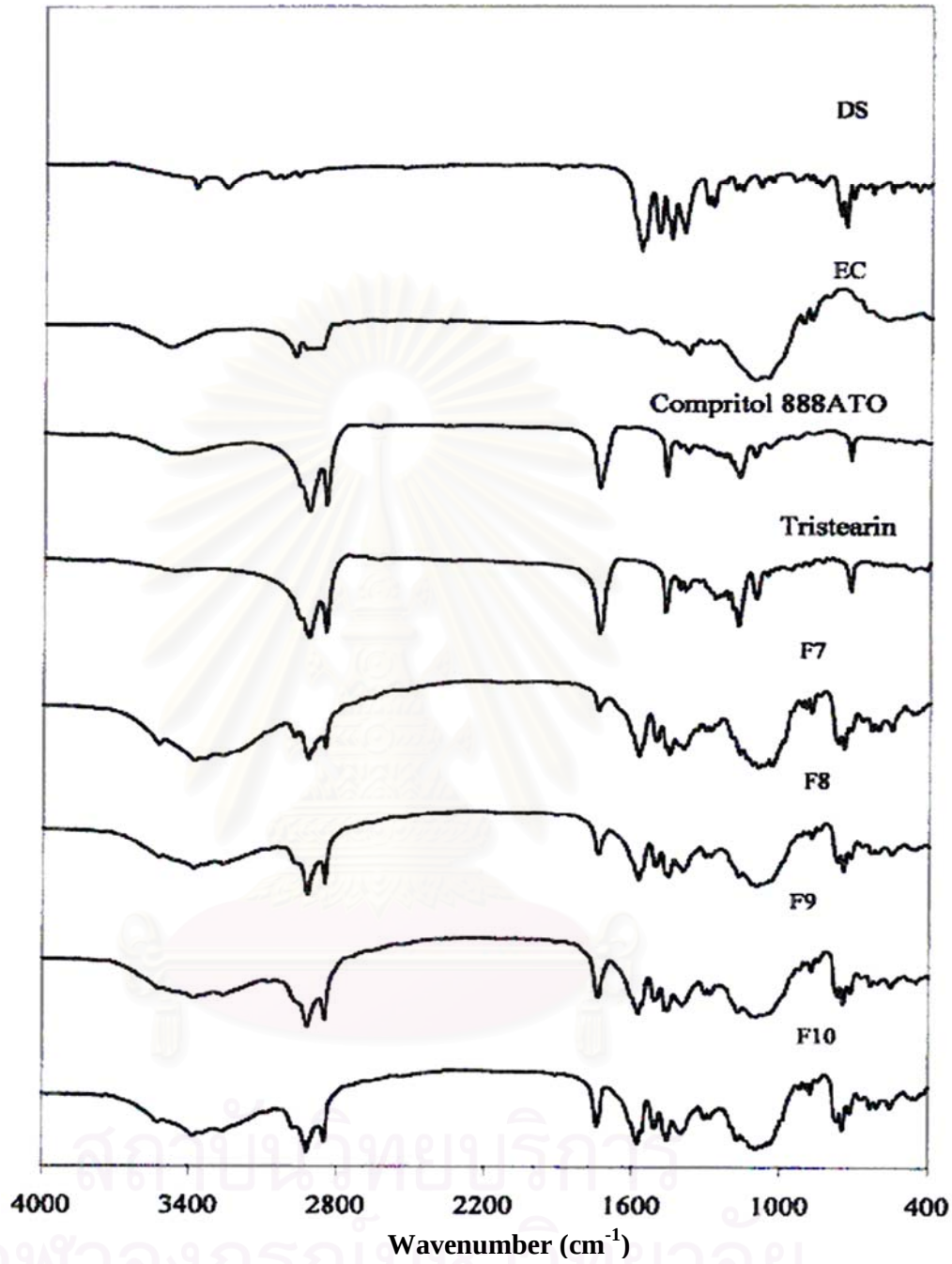


Figure 45 IR spectra of DS microtablets with combined EC and compritol 888 ATO and DS microtablets with combined EC and tristearin

3.3.9 Powder X-ray diffraction

The X-ray diffraction pattern of DS is illustrated in Figure 46-49.The X-ray diffraction pattern of EC, HPMC, tristearin and compritol 888ATO are presented in Figure 46-49. The X-ray diffraction patterns of DS microtablets, which were produced from various formulations, are illustrated in Figure 46-49.

Transformation of drug crystal into amorphous state was confirmed by the powder X-ray diffractometry. The X-ray diffraction pattern of pure DS showed sharp peaks at 6.7°, 8.7° and 11.2° and also showed the heap of sharp at diffraction angle between 20 and 30°. It was observed that the intensities of diffraction peaks of DS microtablets (F1, F6-F10) were weaker than that of DS and exhibited absence of some predominant pure DS peaks. In contrast, it exhibited some new peaks that were different from pure DS peaks. However, the characteristic peaks of DS at the diffraction angle of 6.7°, 8.7° and 11.2° were detected. This indicated that these products were still in crystalline form but some crystals of DS had converted to amorphous form. It was possible due to the mixing and compression processes of tablets (Yoshinari et al., 2003). Furthermore, DS in the microtablets displayed less peak intensities because there were large amount of additive that compounded with DS. Hence, interfering of other additives may decrease intensity DS peaks (Betageri et al., 1996).

3.3.10 Differential scanning calorimetry

The DSC thermograms of DS and DS microtablets with various types and amounts of matrix former substances are shown in Figures 50-52. The DSC thermogram of pure DS gave an endothermic at 289°C. The DSC thermograms of DS microtablets contained EC and the DS microtablets that combined EC with HPMC or EC with glyceride waxes in different proportion were disappeared. But it could detect the heap of endothermic peaks at 100°-150°C in all formulation.

DSC analysis could be used as a quick screening tool for preformulation studies to study the potential incompatibilities in solid state (Fassihi,

1985). From thermograms of microtablets, all formulation did not show major peaks of DS whereas minor peaks were detected. These minor peaks might be the peaks of components in formulations but the X-ray diffraction peak and IR spectra exhibited major peaks of DS. This was perhaps due to equipment and method of detection.

There were several reports about disadvantage of differential scanning calorimetry (DSC). Yonemochi et al (1997) found that differential scanning calorimetry and X-ray diffraction could not measure the difference of two amorphous states of ursodeoxycholic acid whereas isothermal microcalorimetry could measure it.

Differential scanning calorimetry (DSC) results were also reported to be not correlated to other methods. Carstensen et al. (1995) studied and distinguished polymorphic forms of N-[2-{-5-{(Dimethylamino)methyl}}-2-furanyl]ethyl-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride. They found that two polymorphic were not distinguished by DSC and solubility. Only X-ray diffraction was possible to detect the difference. William (1994) found that the ability to detect form I and II of stanozolol and mixtures of these crystal forms was shown to be very difficult with differential scanning calorimetry due to the ability of form II to transform to form I. When transformation occurred prior to melting, there was a tendency to misinterpret DSC data, whereas the X-ray diffraction and Fourier transform infrared spectroscopy could analyze and resolve patterns of each form.

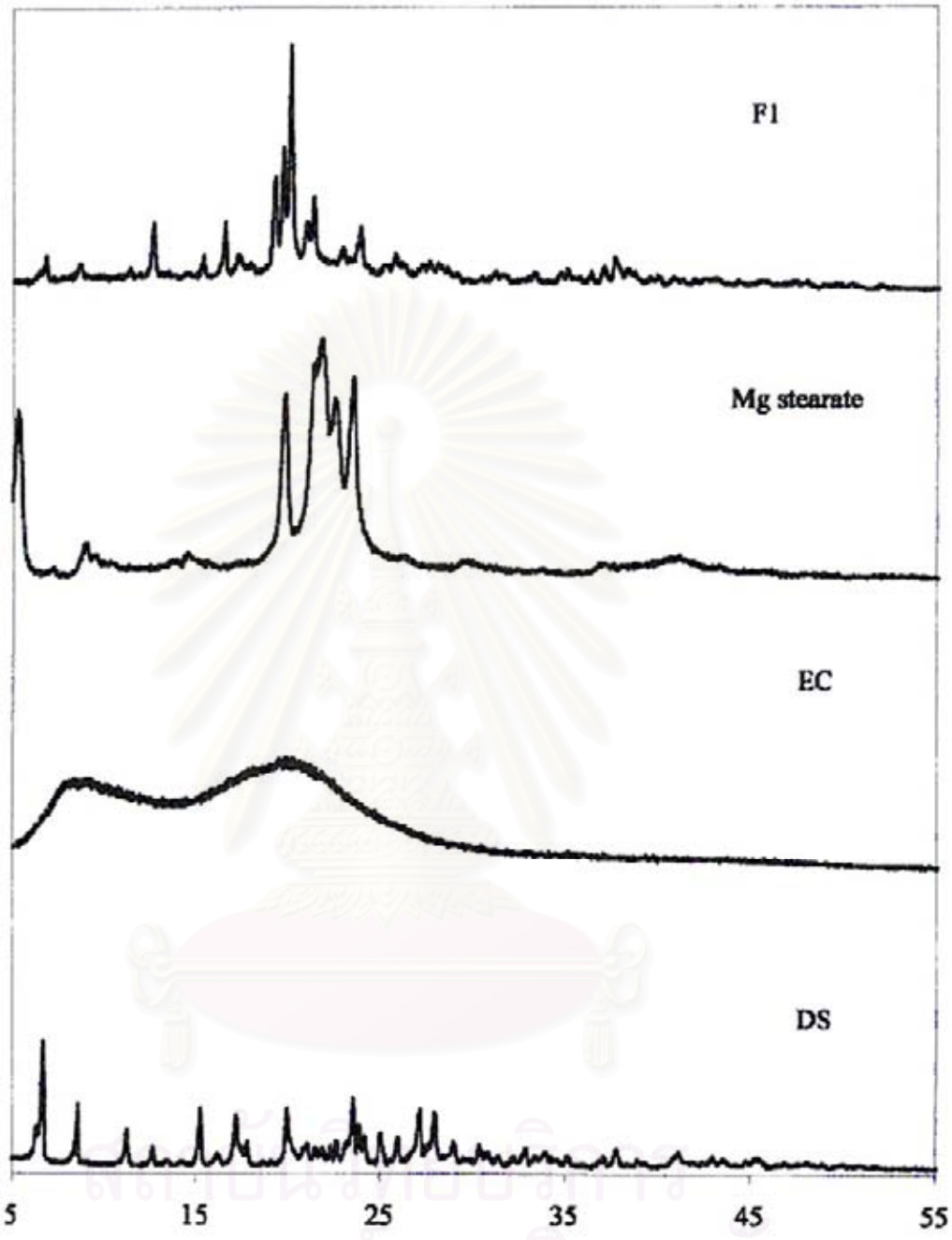


Figure 46 X-ray diffraction spectra of DS microtablets containing with EC

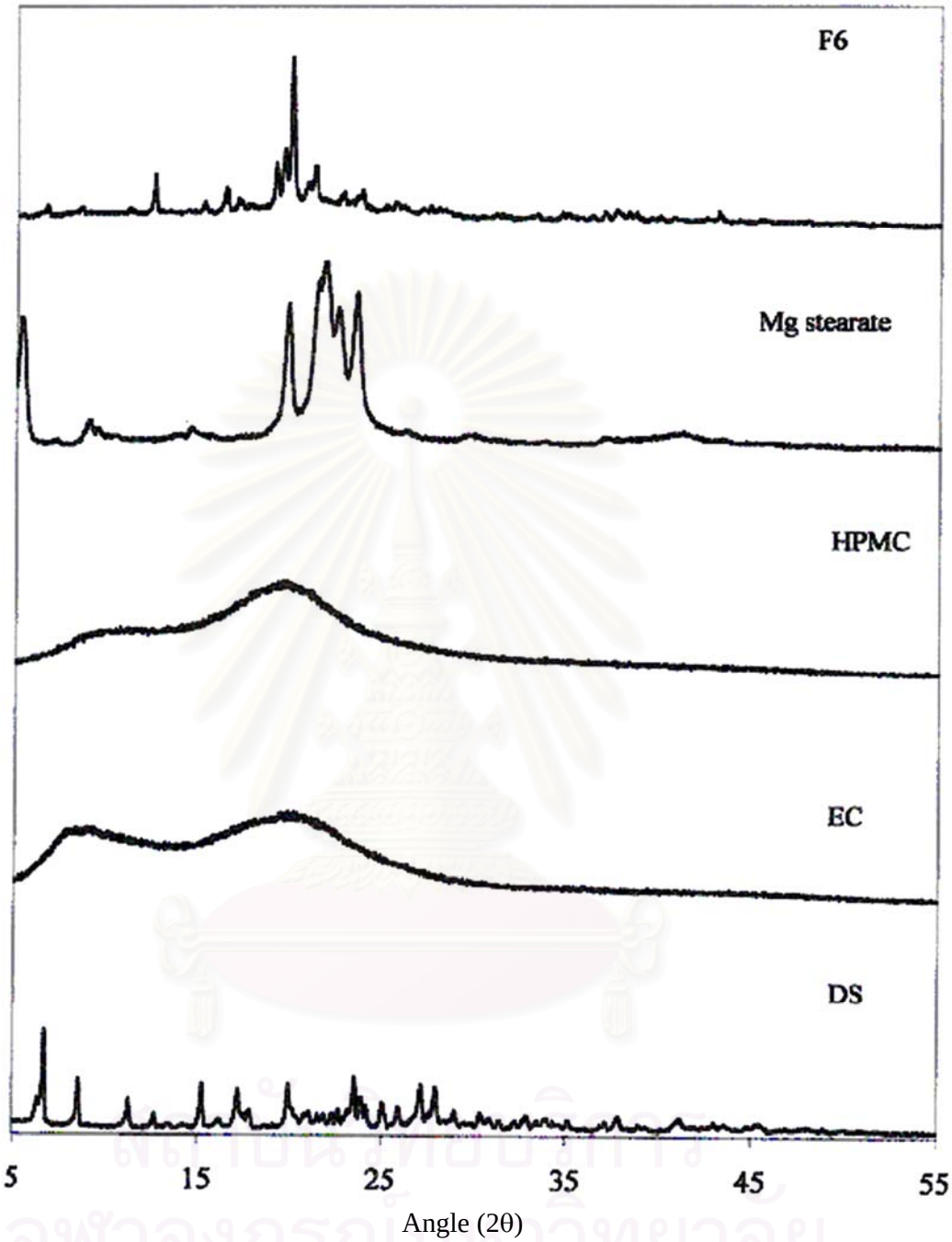


Figure 47 X-ray diffraction spectra of DS microtablets containing with EC and HPMC K15M

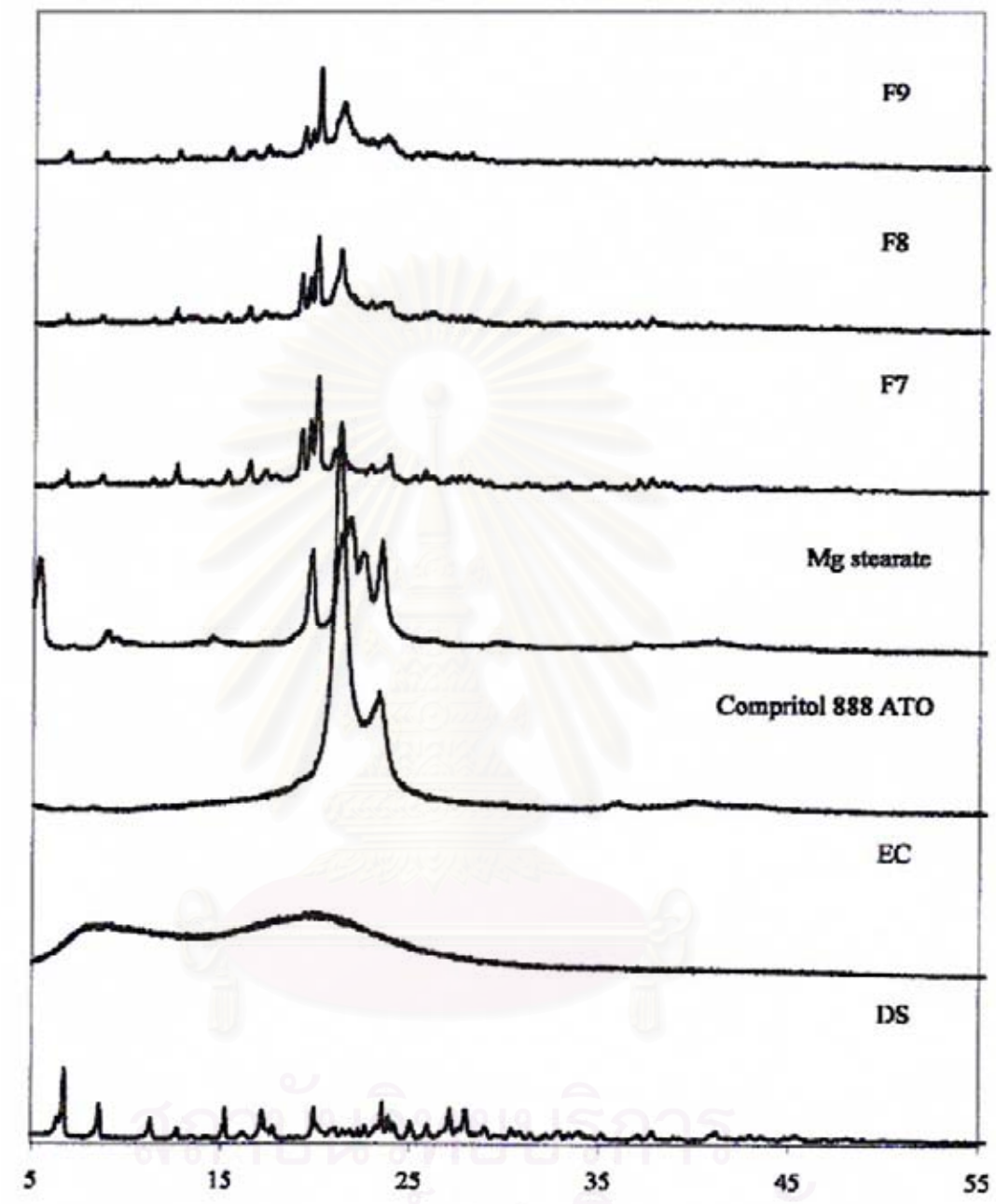


Figure 48 X-ray diffraction spectra of DS microtablets containing with EC and compritol 888 ATO at various ratios of 3:1, 3:2 and 3:2.5

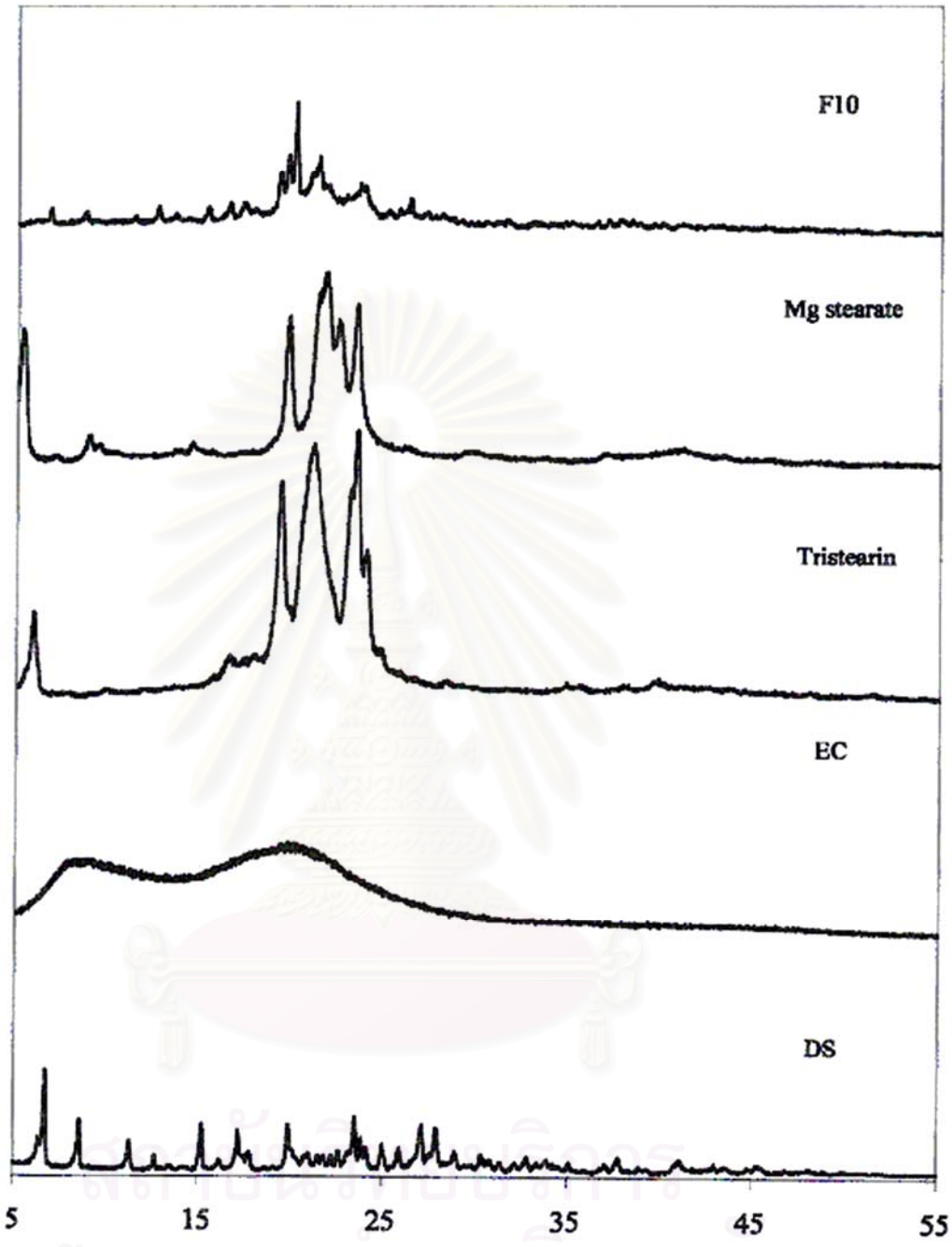


Figure 49 X-ray diffraction spectra of DS microtablets containing with EC and tristearin

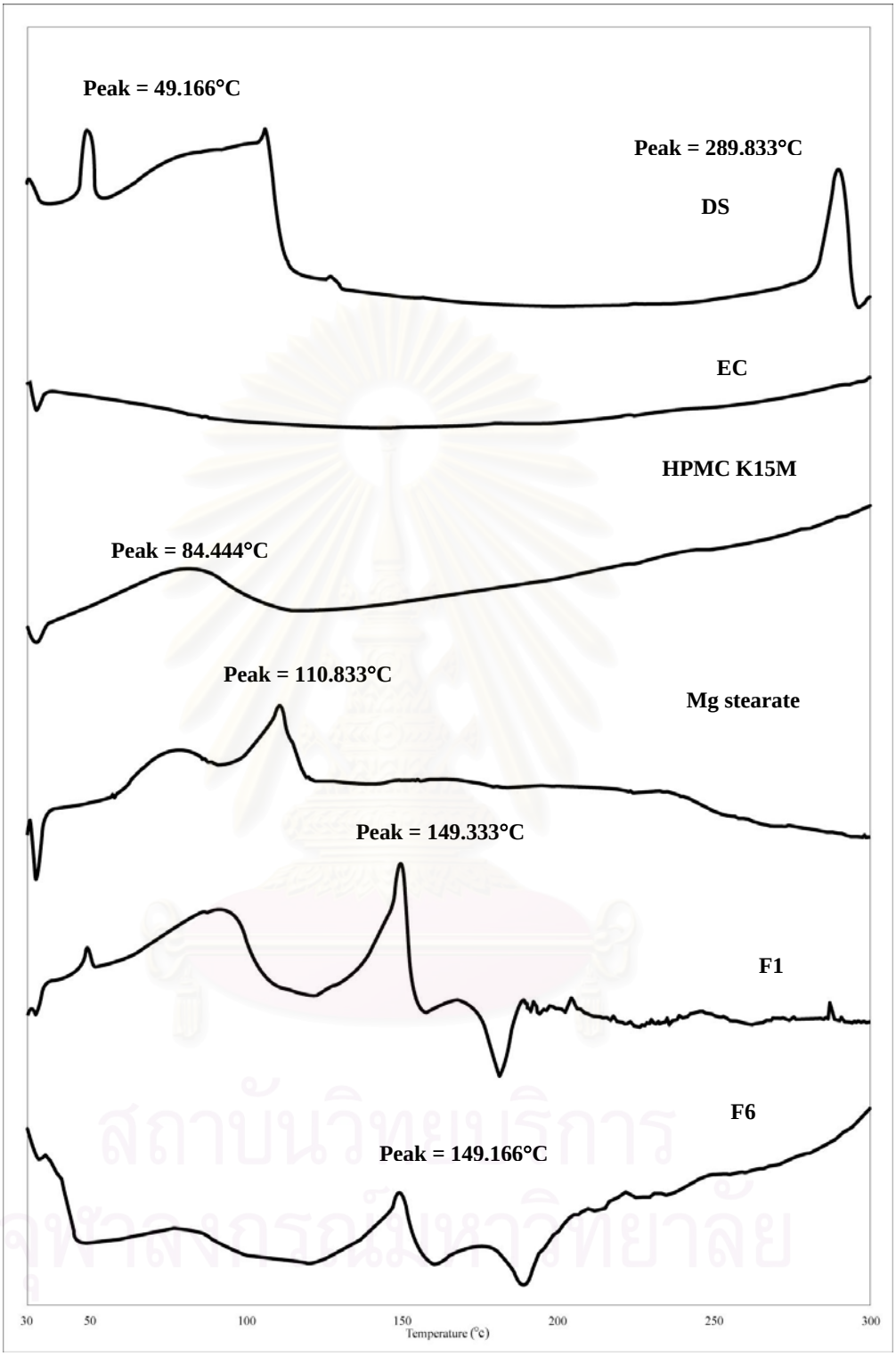


Figure 50 DSC thermograms of DS microtablets contained EC and DS microtablets with combined EC and HPMC K15M

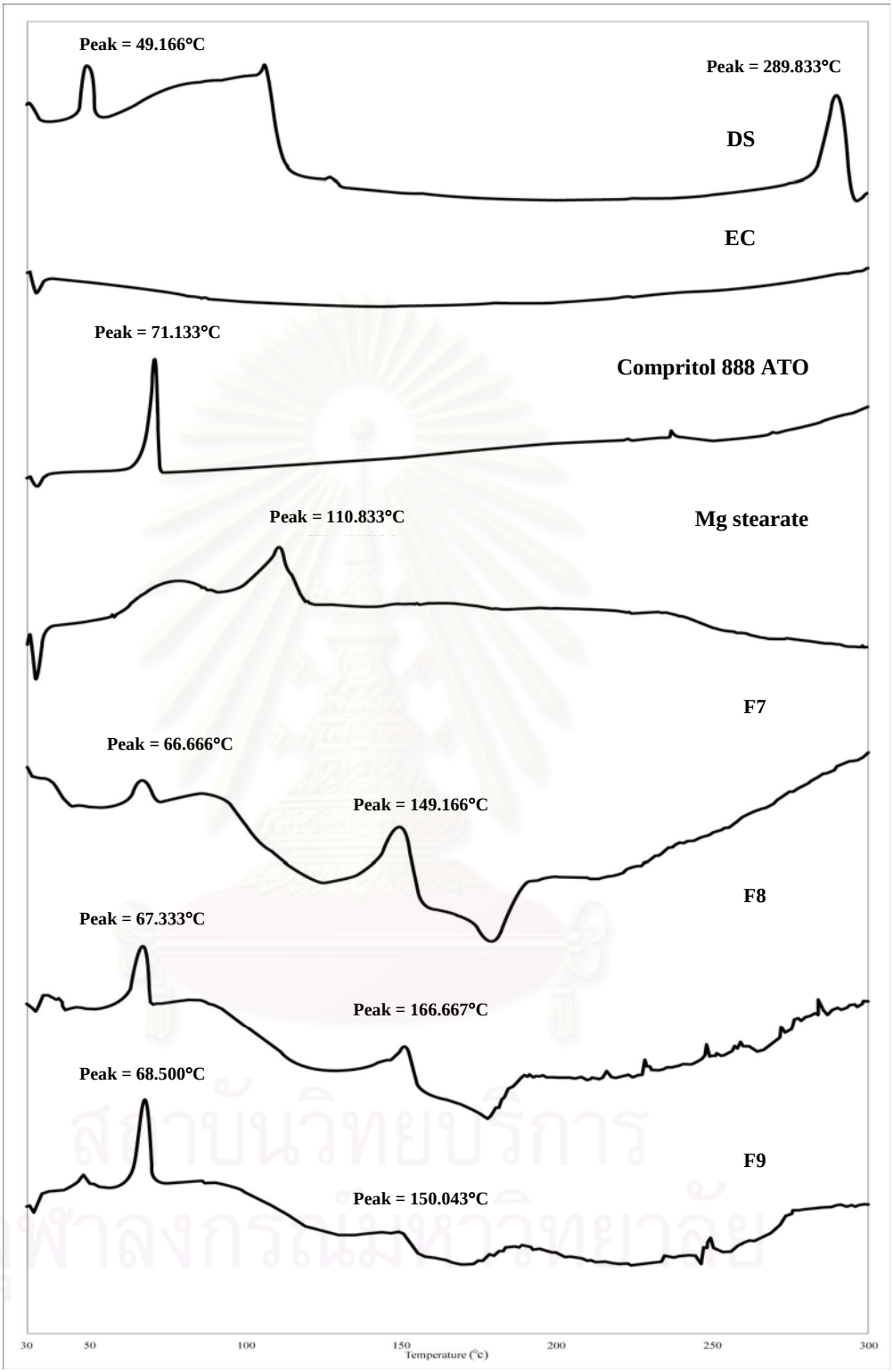


Figure 51 DSC thermograms of DS microtablets with combined EC and compritol 888 ATO and DS microtablets with combined EC

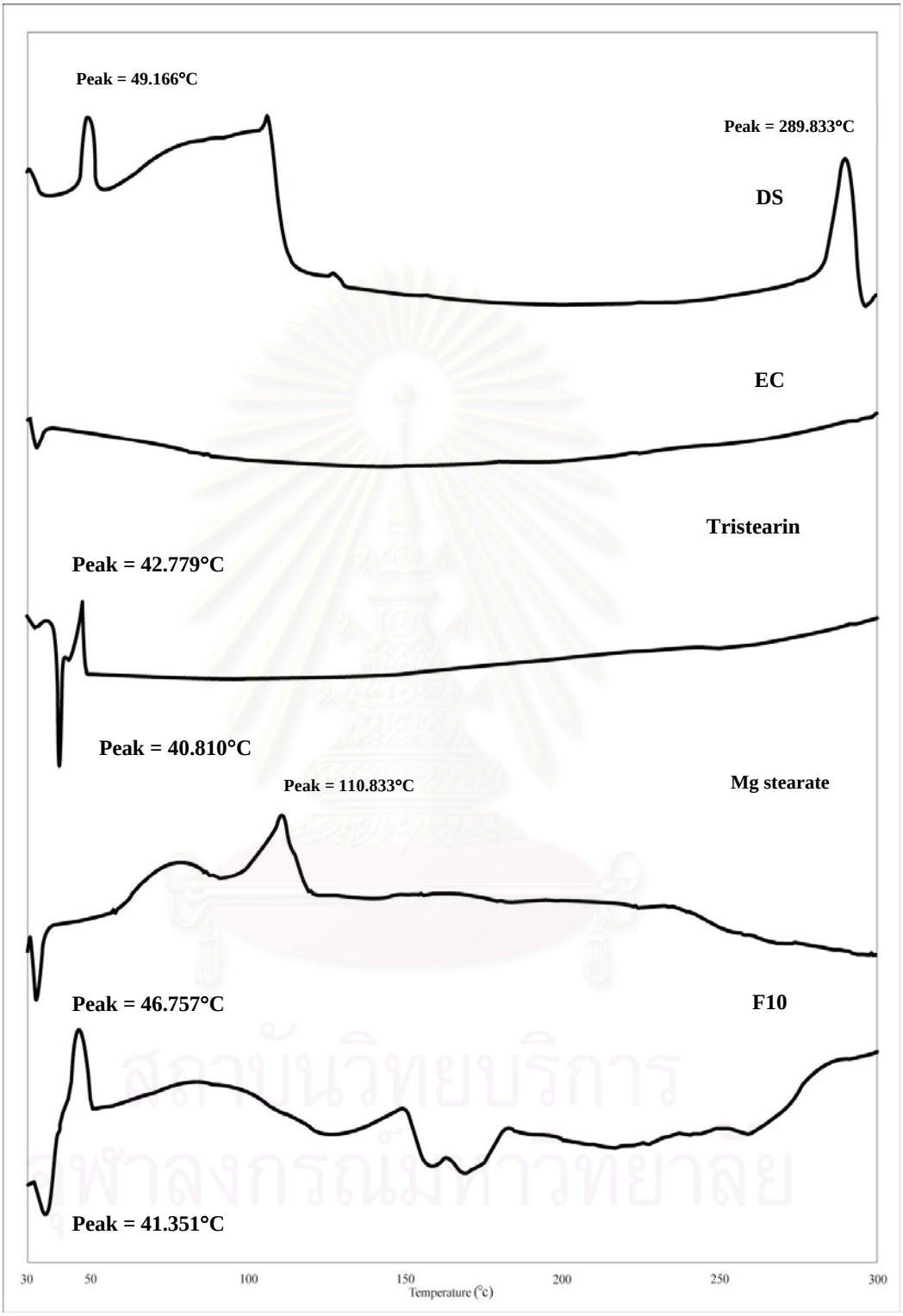


Figure 52 DSC thermograms spectra of DS microtablets containing with EC and tristearin

3.3.11 Effect of formulation modification on the drug release

All formulations of sustained release DS microtablets equivalent to 75 mg of DS that were filled into a capsule were evaluated in pH-change system.

3.3.11.1 Effect of drug load

The release of 30%, 40% and 50% DS load from DS microtablets with 30%EC in pH- change system is exhibited in Figure 53.

In acid stage (0.1N HCl) for 2 hours, the percentages of drug release from these formulations were less than 5%. Then the pH of dissolution medium was changed to pH 6.8, the percentages of drug release were increased to 40%-50% It was shown that the DS released from microtablets was much slower in acid stage than phosphate buffer stage (pH 6.8), presumably due to lower solubility of DS in 0.1 N HCl. In all cases, the release profiles were closely related to first order model (Table 21). The drug release rate constant (Kr) formulations F1, F2 and F3 were 0.1029, 0.141 and 0.1981, respectively. This indicated that the drug release was increased with increasing drug load. It could be described in terms of Fick's first law.

Fick's first law explained that the rate of diffusion or transport was directly proportioned to the concentration gradient (Stavchansky et al., 1990). As the amount of drug in matrix was increased, the concentration gradient was more different between medium and drug in matrix. Therefore, the drug released rate was proportionally increased when increasing the amount of drug in matrix.

Figure 54 depicts the relationship between release rate and percentage of DS in matrix microtablet. A linear relationship was obtained (r^2= 0.992) and accordance along with Fick's first law. The law revealed that first-order release rates constant was a linear function of percentage drug in matrix.

Table 21 Correlation of determination (r^2) of relationships between percentage log percentage drug remained versus time (first-order), percentage drug released versus square root time (Higuchi's equation), and drug released versus time (zero-order)

Formulation	First-order	Zero-order	Higuchi model
F1	0.9980	0.9475	0.9776
F2	0.9922	0.7042	0.8156
F3	0.9995	0.9482	0.9725

Table 22 Effect of drug load on the first order release rate constant of DS microtablets

Formulation	Kr (hr^{-1})
F1	0.1029±0.0106
F2	0.1410±0.0244
F3	0.1931±0.029

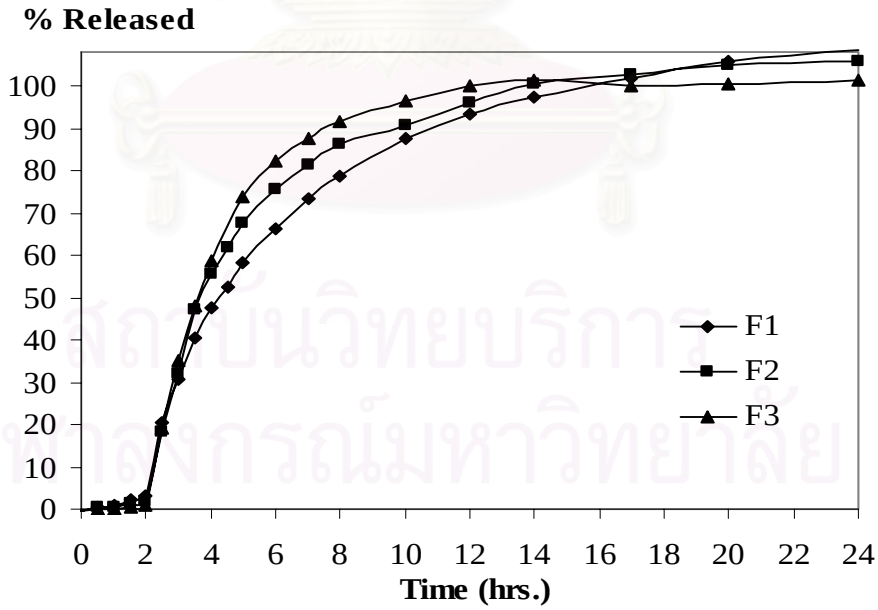


Figure 53 Dissolution profile of DS microtablets prepared from various the drug loads 30% (F1), 40% (F2) and 50% (F3) in pH-change system

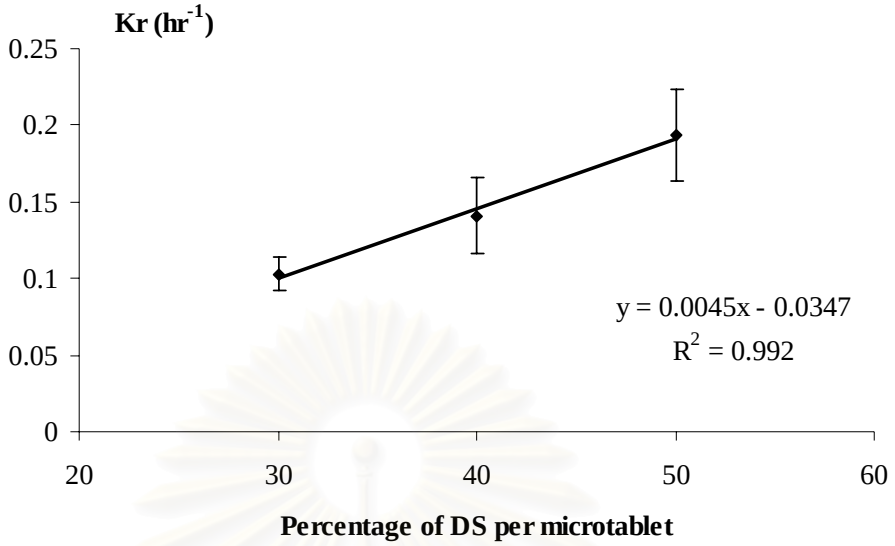


Figure 54 Relationship between release rate of DS microtablet and percentage of DS contained in each microtablet

3.3.11.2 Effect of EC concentration

The dissolution studies were carried out on formulations F1, F4 and F5 which increased the amount of EC from 30% to 50%, respectively. The dissolution profiles of DS microtablets with 30%, 40% and 50% EC compressed at 800 lb in pH-change are shown in Figure 55.

In acid stage (0.1 N HCl), the amount released was almost negligible (< 5% after 2 hrs). Whereas in all cases the drug released in phosphate buffer stage (pH 6.8) was risen to 40-50% and released complete in 24 hours. It was shown that the DS released from microtablets was slower in acid stage than phosphate buffer stage (pH 6.8), presumably due to lower solubility of DS in 0.1 N HCl (Kincl M. et al., 2004). Furthermore, all these cases showed similar release model. The first-order plot was linearity with correlation plot was greater than 0.99 in pH-change system as seen in Table 23. The drug release rate constant (Kr) was changed from 0.1029 hr^{-1} for the formulation F1 to 0.0904 hr^{-1}, 0.0828 hr^{-1} for the formulations F4 and F5, respectively (Table 24). Figure 56 depicted that the relationship between release rate and percentage of EC in matrix microtablet. A linear relationship was

obtained when plotting the first-order release rate constant and amount of EC. The higher the amount of EC the lower was the release rate constant. Therefore, adjusting the EC contents in the microtablets could modify the drug release rate. Increasing the amount of EC increased the hydrophobicity of dosage and then the diffusion of dissolution medium (phosphate buffer) was retarded. Consequently, the dissolution of drug passed through the pores near the surface of microtablets was reduced (Katikaneni, Upadrashta, Neau, et al., 1995; Chambin et al., 2004). It could be seen that increasing the amount of EC had a slightly effect on the release but it had strong influence on hardness and friability of microtablets. This could be explained by the counteraction of two effects. Decreasing the hardness of microtablets resulted in an increase in porosity and a decrease in tortuosity which would consequently increase the release rate. The counter effect was retarded by the influence of the hydrophobicity of EC. It the retarding influence of hydrophobicity was minimally exceeded the increase porosity. Thus, it would lead to negligible decrease in the drug release rate (Katikaneni et al., 1995). Microtablets which contained high amount of EC was very soft and had friability values greater than 0.3% which limited the potential for future development of microtablets containing with EC (Rekhi et al., 1999)

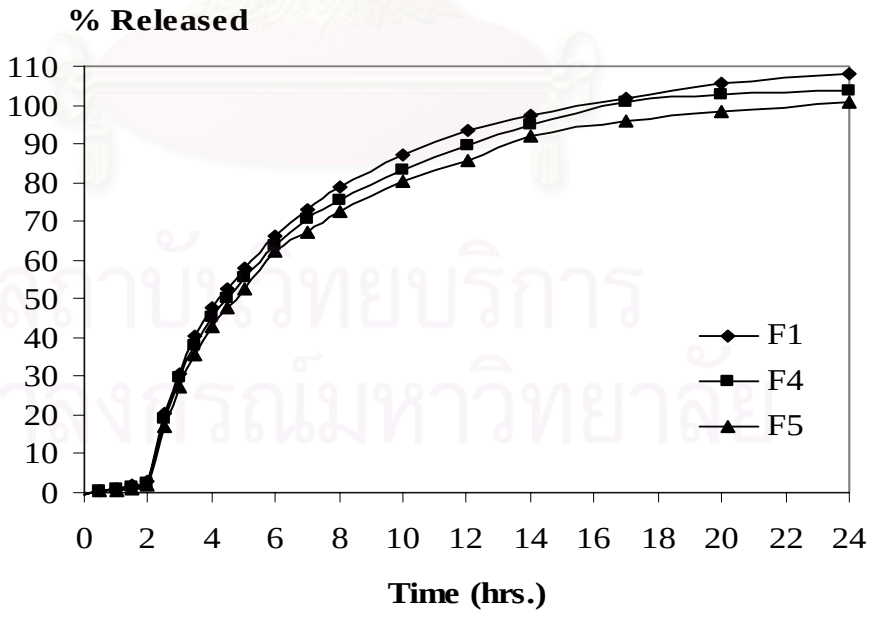


Figure 55 Dissolution profiles of DS microtablets prepared from various concentrations of EC in pH-change system

Table 23 Correlation of determinations (r^2) of relationships between percentage log percentage drug remained versus time (first-order), percentage drug released versus square root time (higuchi's equation), and drug released versus time (zero-order)

	First-order	Zero-order	Higuchi model
F1	0.9980	0.9475	0.9776
F4	0.9970	0.9242	0.9674
F5	0.9939	0.9229	0.9665

Table 24 Influence of EC content on the first-order release rate constant (Kr) for DS microtablets

Formulation	Kr (hr^{-1})
F1	0.1029±0.0106
F4	0.0904±0.0035
F5	0.0828±0.0042

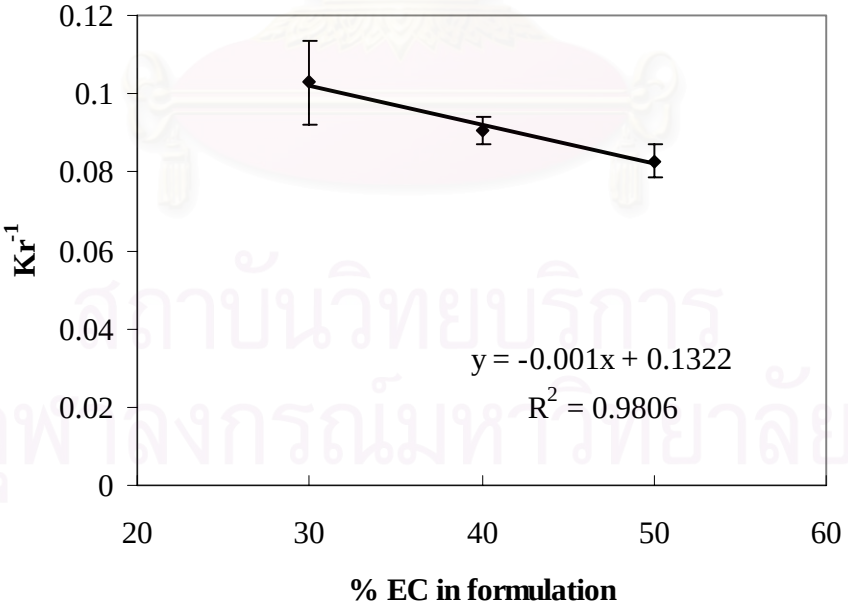


Figure 56 Relationship between release rate of DS microtablet and percentage of EC contained in each microtablet

3.3.11.3 Effect of addition of HPMC or glyceride waxes on the drug release

The dissolution studies were carried out on formulations F1, F6-F10 which contained 30%EC (F1) and combined EC with HPMC K15M (F6), compritol 888 ATO (F7-F10) or tristearin (F10), respectively. The dissolution profile of DS microtablets with various types and amount of matrix former into pH-change system are displayed in Figure 57.

All formulations of sustained release that filled into capsule were observed in the pH-change system. Very low percentages of drug release that less than 5% was remarked in the first 2 hours (acid stage, 0.1 N HCl). Then the pH of dissolution medium was changed to 6.8 (Buffer stage). The percentages of drug release at the buffer stage were more than in acid stage and continuously increased until 24 hours. In order to describe the dissolution profiles, mathematical models were applied to data. In all cases, the best fit was found with first-order model (r^2>0.99) as presented in Table 25. The release rate constant of all formulations that were examined are displayed in Table 26 and Figure 58.

Figure 57 and 58 showed that the drug released was significantly increased when the formulation combined EC with HPMC K15M. Comparison of the drug release rate between F1 formulation and glyceride waxes formulations (F7-F10) that combined EC with compritol 888 ATO (F7-F9) or tristearin (F10) showed that the drug release rate was significantly decreased when adding glyceride waxes into formulations due to the increase of hydrophobicity of compritol 888 ATO and tristearin.

Effect of combination of EC with HPMC K15M on the drug release

The dissolution profile of DS microtablets that combined EC with HPMC K15M in pH-change system is shown in Figure 57. The proportion of polymer in matrix was 1:3 (HPMC K15M: EC, F6), a burst was observed and more

than 60% drug was released during the first prior of phosphate buffer stage (pH 6.8). Since the proportion of HPMC K15M in the matrix was low, therefore the particles were separated from each other and formation of protective gel layer around the matrix did not occur effectively. Consequently the drug was released rapidly (Dabbagh et al., 1996). Furthermore, the SEM study showed the more porous structure and larger contact surface area of microtablets prepared from EC mixed with HPMC K15M. Thus the medium could flow easily through the network of the polymer and caused fast release (Weyeberg, 2003).

Effect of combination of EC with compritol 888 ATO or tristearin on the drug release

The dissolution studies were carried out on the formulations F7-F10. Formulations F7-F9 contained 30%EC with various amount of compritol 888 ATO 10-25% and F10 combined 30%EC with 20% tristearin.

Figure 57 and 58 also shows the effect of combining EC with compritol 888 ATO (F7-F9) and tristearin (F10) for preparing DS microtablets on the release of drug. All examined DS microtablets exhibited a considerable retardation effect on the release of drug. The drug release rates were significant decreased when the formulations combined EC with glyceride waxes.

The release rate from DS microtablets formulation F7 which contained 10% compritol 888 ATO was negligibly decreased, since the hardness of microtablets was decreased when adding compritol 888 ATO. It caused to increase in porosity of microtablets and led to increase the penetration of dissolution medium into the microtablet (Romero et al, 1991). Thus, the hydrophobicity of increasing 10% of compritol 888 ATO was not enough for retarding the drug release. At 20% compritol 888 ATO, the drug release rate was significantly decreased. This indicated that the hydrophobicity of matrix microtablets was sufficiently retarded the drug release. Whereas, increasing amount of compritol 888 ATO up to 25% (F9), the hardness was lower than formulation F7 and F8, because the elastic deformation was predominant mechanism for compritol 888 ATO after compression (Wray et al, 1992). This

deformation provided the shape of tablet as same as the former before applied the compression force. Higher content of compritol 888 ATO in the EC based formulation gave an elastic deformation mechanism much more over than plastic deformation. Therefore, increasing the amount of compritol 888 ATO would provide friable and porous microtablets. The drug release rate was slightly increased. It was explained that the increasing amount of compritol 888 ATO in formulation could affect the increasing in porosity more than hydrophobicity property of glyceride wax in microtablets. Therefore, more dissolution medium could penetrate into microtablets resulting in an increase the release rate. Furthermore, the SEM depicted the smoothness of surface area of wax matrix microtablet that caused the slower drug released than from another formulations.

It was observed that the drug release rate from formulation F10 which combined EC with tristearin was lower than those of F1 and compritol 888 ATO formulations (F7-F9). This could be explained by hydrophobicity of tristearin. Tristearin had more hydrophobicity than compritol 888 ATO. The compritol 888 ATO was composed of mono, di and triglyceride of behenic acid but tristearin was of triglyceride. Therefore, compritol 888 ATO exhibited more hydrophilicity than tristearin. Because of the structure of mono and di glycerides had hydroxyl group (-OH) resulting in faster dissolution rate than formulation F10 that contained EC with tristearin.

All formulations could be manufactured successfully except the formulation F10 that combined EC with tristearin. According to physicochemical properties of tristearin which had low melting point (58-63°C) and exhibited softness, the compression process could hardly be done. It caused abnormal noise during compression process and stickiness of wax between punch and die. Thus, the formulation F10 was not suitable for further preparing and development DS microtablets.

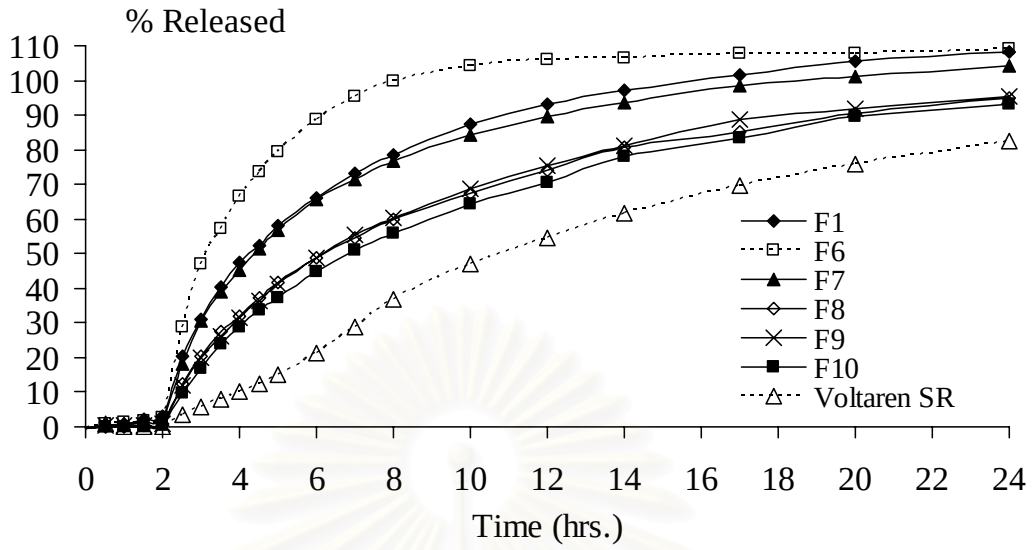


Figure 57 The release profiles of DS microtablets combined EC with HPMC K15 M or glyceride waxes in pH-change system

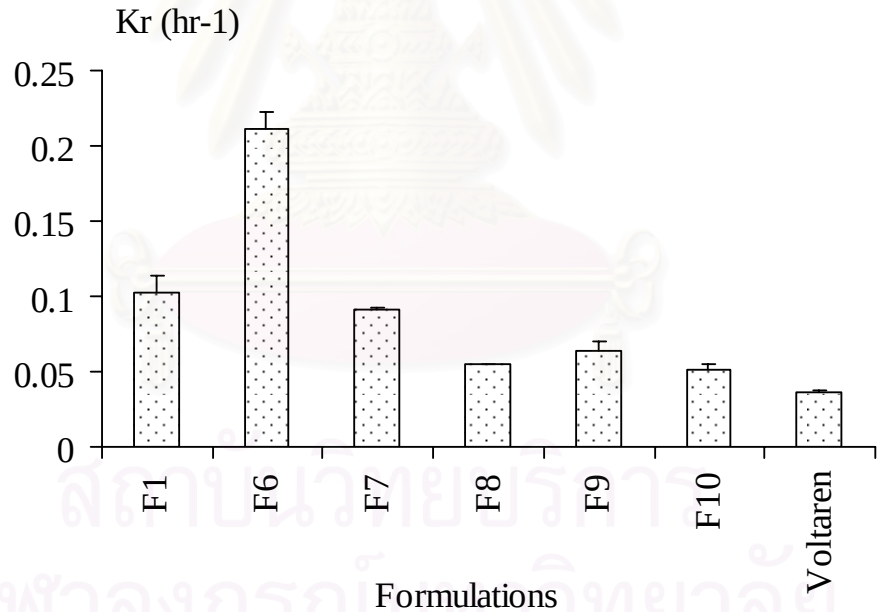


Figure 58 Comparison of the first-order release rate constant of DS microtablets formulations F1, F6, F7, F8, F9, F10 and Voltaren® SR

Table 25 Correlation of determination according to the different kinetic equations used for describing DS release behavior

	First-order	Zero-order	Higuchi model
F1	0.9980	0.9475	0.9776
F6	0.9985	0.9569	0.9745
F7	0.9959	0.9146	0.9607
F8	0.9954	0.9325	0.9772
F9	0.9973	0.9343	0.9788
F10	0.9959	0.9416	0.9825
Voltaren® SR	0.9980	0.9528	0.9877

Table 26 Effect of type and amount of matrix former on the first-order release rate constant for DS microtablets

Formulation	Kr (hr^{-1})
F1	0.1029±0.0106
F6	0.2115±0.0115
F7	0.0913±0.0132
F8	0.0546±0.0004
F9	0.0642±0.0059
F10	0.0513±0.0033
Voltaren® SR	0.0357±0.0013

3.3.12 Effect of formulation modification on the release exponent (*n*)

The release mechanism of all formulations of DS microtablet was super case-II transport. However, the release mechanism of this study might combined with another mechanism due to low correlation of determination (r^2=0.93-0.96), whereas Voltaren® SR tablet was clearly Super Case-II transport due to correlation of determination > 0.99. These results indicated that formulation and

variables studied did not alter the drug release mechanism. The release exponents (n) are shown in Table 27.

The *n* values suggested that the drug release of all formulations was predominantly erode-controlled because of the containing of EC. EC had a natural tendency to erode in water due to a separation of the surface particles of the matrix as the classical concept of a plastic or hydrophobic material (Pather et al., 1998). Moreover, the n values were decreased with increasing the amount of matrix former and adding glyceride waxes in formulation. Thus, the erosion of DS microtablets was reduced when amount of waxes was increased and the glyceride waxes were added in the formulations.

Table 27 Effect of formulation modification on the release exponent (*n*)

Formulation	*n*	r^2
F1	1.4822±0.0181	0.9624
F2	2.0740±0.0417	0.9486
F3	2.3989±0.0889	0.9676
F4	1.3338±0.0098	0.9443
F5	1.4191±0.0325	0.9513
F6	2.0708±0.0622	0.9641
F7	1.3966±0.0199	0.9337
F8	1.2540±0.0236	0.9361
F9	1.3023±0.0029	0.9438
F10	1.3943±0.0027	0.9311
Voltaren® SR	1.6638±0.0396	0.9913

3.3.13 Comparison between the microtablets produced with combined EC and glyceride waxes and a commercial product DS (Voltaren® SR 75 mg)

The Voltaren® SR tablet

The release of DS from Voltaren® SR tablet was affected by dissolution medium as illustrated in Figure 57. In pH-change system, the percentage of drug release from Voltaren® SR tablet at first 2 hours (acid stage) was less than 2%. Whereas, the percentage of drug release at the first 2 hours (buffer stage) was more than 10% and continuously increased until 24 hours in phosphate buffer pH 6.8 stage. The amount of drug released in 24 hours was 80%. The elucidated of drug release model, the first-order was obtained. The correlation of determination of Voltaren® SR 75 mg tablet was 0.998 from the first-order plot. The release mechanism was super case II transport with n values of 1.664 and release rate of 0.0357 hr^{-1}.

The comparison between the Voltaren® SR tablet and the microtablet contained EC with compritol 888 ATO (F8) found that the drug release profiles of DS microtablets were different to the drug release profile of Voltaren® SR tablet. There were more than 10% difference in the average cumulative drug release between DS microtablets and Voltaren® SR.

CHAPTER V

CONCLUSIONS

Matrix microtablets can be used as subunits to prepare multiple-unit dosage forms. DS microtablets provided high reproducibility with respect to weight uniformity, hardness, and dissolution. The preparations of DS microtablets were successfully prepared by conventional tablet production method of wet granulation. The formulations contained DS with various cellulose derivative polymers such as ethylcellulose (EC), hydroxypropylmethyl cellulose (HPMC) and glyceride waxes such as glyceryl behenate as matrix forming agent.

1. Type and amount of matrix former affected the physical properties of granules. The flow rates of granules were significant decreased when the formulations were combined EC with HPMC K15M or EC with glycerides waxes as matrix formers.

2. The physical properties of DS microtablets were depended on the compression force, the type and amount of matrix former. The hardness of DS microtablets was increased with increasing of the compression force. This was due to the decreasing in the porosity of microtablets. Whereas the low hardness and high friability of DS microtablets were obtained when increasing the amount of EC and combining EC with HPMC K15M or EC with glycerides waxes.

3. The compaction pressure (from 400 lb to 1,200 lb) had negligible effect on the drug release profile. Whereas decreasing the tablet diameter increased the release rate. This was due to a greater dissolution surface area resulting from a large number of particles exposed to the dissolution medium.

4. The drug release from microtablets was dependent on the compositions in the formulation. Drug release from microtablets was increased when increasing the drug load (30%-50%) and combining EC with HPMC K15M. Whereas the drug

release from DS microtablets as significant decreased when increasing the proportion of glyceride waxes.

5. The release model of all formulations of DS microtablets, best fitted the first-order plot and the mechanism of release was Super Case II transport. Their percentage of the drug release passed the specification in USP XXIV but their drug release patterns were different from the pattern of Voltraren SR 75 mg.

REFERENCES

Adeyeye, C.M., and Li. P. 1990. Diclofenac sodium In K. Florey, A.A., Al-Badr, and T.J., Wozniak (eds), **Analytical profiles of drug substances** (Vol. 19). pp. 123-144. New York: Accademic press.

Al-Nasasarah, M., and Newton, J.M. 1996. Effect of punch size on the mechanical strength of binary mixtures of PEGs with microcrystalline cellulose. **Eur. J. Pharm. Biopharm.** 4(S1): S186.

Arthur, H.K. 2000. **Handbook of pharmaceutical excipients**. (3rd ed.). Washinton, D.C.: The pharmaceutical press.

Banker, G.S., Peck, G.E., Baley, G. 1990. Tablet formulation and design. In H.A. Lieberman, L. Lachman and J.B. Scgwaetz (eds.), **Pharmaceutical dosage forms: tablet** (1 vols 2nd. ed.). pp. 61-107. New York: Marcel Dekker.

Barthelemy, P., Laforet, J.P., Farah, N. and Joachim, J. 1999. Compritol 888 ATO: an innovative hot-melt coating agent for prolonged- release drug formulations. **Eur. J. Pharm. Biopharm.** 47(1): 87-90.

Bauer, K.H., Lehmann, K., Osterwald, H. P., and Rothgang G. 1996. The core or Substrate. In Raton, B. (ed.)**, Coated Pharmaceutical Dosage Forms**, pp. 19-28. Florida: CRC Press.

Betageri, G.V., and Makarla, K.R. 1996. Characterization of glyburide-polyethylene glycol solid dispersion. **Drug. Dev. Ind. Pharm.** 22(7): 731-734.

Brabander, C. De, Vervaet, C., Fiermans L. and Remon, J.P. 2000. Matrix mini-tablets based on starch/microcrystalline wax mixtures. **Int. J. Pharm.** 199: 195-203.

British Pharmacopeia Commission. 1988. **British Pharmacopeia**. London. Her Majesty's Stationery at the university press.

Cameron, G.C. and McGinity, J.W. 1987. Controlled-release theophylline tablet formulations containing acrylic resins, II. Combination resin formulations. **Drug. Dev. Ind. Pharm.** 13(8): 1409-1427.

Carstensen, J.T., and Franchini, M.K. 1995. Isoenergetic polymorphs. **Drug. Dev. Ind. Pharm.** 21(5): 523-536.

Chambin, O., Champion, D., Debray, C., Rochat-Gonthier, M.H., Le Meste, M, and Pourcelot, Y. 2004. Effect of different cellulose derivatives on the drug release mechanism studied at a preformulation stage. **J. Controlled. Release.** 95: 101-108.

Cheng, H.L., Chen, S.C., Kao, Y.H., Kao, C.C., Sokoloski, T.D., and Sheu, M.T. 1993. Properties of hydroxypropylmethylcellulose granules produced by water spraying. **Int. J. Pharm.** 100: 241-248.

Cox, P.J., Khan, K.A., Munday, D.L., and Sujja-areevath, J. 1999. Development and evaluation of multiple-unit oral sustained release dosage form for S(+)-ibprofen: preparation and release kinetics. **Int. J. Pharm.** 193: 73-84.

Crowley, M.M., Schroeder, B., Fredersdorf, A., Obara, S., Talarico, M., Shawn, K. and McGinity J.W. 2004. Physicochemical properties and mechanism of drug release from ethylcellulose matrix tablets prepared by direct compression and hot-melt extrusion. **Int. J. Pharm.** 269: 509-522.

Dabbagh, M.A., Ford, J.L., Rubinstein, M.H., and Hogan, J.H. 1996. Effect of polymer particle size, compaction pressure and hydrophilic polymers on drug release from matrices containing ethylcellulose. **Int. J. Pharm.** 140: 85-95.

David, E.B., and Paul-Findlay, W. 1991. Pharmaceutical excipients, characterization by IR, Raman, and NMR spectroscopy. **Drug and The Pharmaceutical Sciences.** 94: 225-393.

Desai, R.P., Neau, S.H., Pather, and Johnson, T.P. 2001. Fine-particle ethylcellulose as a tablets binder in direct compression, immedieate-release tablets. **Drug. Dev. Ind. Pharm.** 27(7): 633-641.

De Brabander, C., Verveaet, C., Gortz, J.P. 2000. Matrix mini-tablets base on starch/microcrystalline wax mixtures. **Int. J. Pharm.** 199: 195-203.

Duberg, M., and Nyström, C. 1986. Studies on direct compression of tablets XVII. Porosity-pressure curves for the characterization of volume reduction mechanisms in powder compression. **Powder. Technol.** 46; 67-75.

Emori, H., Ishizaka, T., and Koishi, M. 1984. Effect of acrylic polymer and its arrangement on drug release from wax matrix. **J. Pharm. Sci.** 73: 910-914.

Fassihi, A.R. 1987. Kinetic of drug release from solid matrices: effect of compaction pressure. **Int. J. Pharm.** 37: 119-125.

Fell, J.T., and Newton, J.M. 1968. The tensile strength of lactose tablets. **J. Pharm. Pharmacol.** 20: 657-658.

Fell, J.T., and Newton, J.M. 1968. Determination of tablet strength by dametral-compression test. **J. Pharm. Sci.** 59 (5). 1970.

Fessi, H., Marty, J.P., Pusisienx, F., and Cartensen, J. T. 1982. Square root of time dependendence of matrix formulations with low drug content. **J. Pharm. Sci.** 71: 749-752.

Flemming, J, and Mielck, J.B. 1995. Requirements for the production of microtablets: suitability of direcet-compression excipients estimated from powder characteristics and flow rates. **Drug. Dev. Ind. Pharm.** 21(19): 2239-2251.

Flemming, J, and Mielck, J.B. 1996. Experimental microtabletting: construction of an instrument punch holder for an eccentric tabletting machine. **Eur. J. Pharm. Biopharm**. 43(3): 212-213.

Ford, J.L., Rubinstein, M.H., and Hogan, J.E. 1985. Propanolol hydrochloride and aminophylline release from matrix tablets containing hyroxypropylmethylcellulose. Int. J. Pharm. 24: 339-350.

Foster, T.P., and Paarrott, E. L. 1990a. Release of highly water-solluble medicinal compounds from inert, heterogenous matrix I physical mixture. **J. Pharm. Sci**. 79(9): 806-810.

Gazzaniga, A., Sanglli M.E., Conte, U., Colombo, P., and Manna, A. La. 1993. On the release mechanism from coated swellable minimatrices. **Int. J. Pharm**. 91: 167-171.

Gordon, R.E., Rosanske, T.W. and Fonner, D.E. 1990. Granulation technology and characteristization. In H.A. Lieberman, L. Lachman, J.B. Schwartz (eds.), **Pharmaceutical dosage forms: Tablets** (3 vols 2nd. ed.). Marcel Dekker, Inc. New York: 245-347.

Herzfeldt, C.D., and Kummel, R. 1989. Dissociation constant solubilities and dissolution rates of some selected non-steroidal anti inflamatories. **Drug. Dev. Ind. Pharm.** 9(5): 767-793.

Ho, H., Wang, H, and Sheu, M. 1997. The evaluation of granulated excipients as matrix material for controlled delivery of captopril. 49(1): 243-251.

Gattefosse. **Compritol 888 ATO lubricant and controlled-release**[online]. Available from: http://www.gattefosse.com/pharma/products/comp888a.html [2004, Feb18].

Normark Arzneimittel GmbH& Co.KG. **Manufacture of all solid dosage form: microtablets[**online]. Available from: http://www. Nordmark pharma.de/eleistungen/b02_02.htm[2003, Jun 19].

Sci-toys. **Ingredients-tristearin**[online]. Available from http://www.sci-toy.com/ingreadients/tristearin.html[2004, Feb18].

Jorosz, P.L. and Parrott, E.L. 1984. Effect of tablet lubricants on tensile strength of tablets. **Drug. Dev. Ind. Pharm**.10: 259-273.

Katikaneni, P.R., Upadrashta, S.M., Rowlings, C.E., Neau, S.H., and Hileman, G.A. 1995. Consolidation of ethylcellulose: effect of partical size, press speed, and lubricants. **Int. J. Pharm**. 117:13-21.

Katikaneni, P.R., Upadrashta, S.M., Neau, S.H., and Mitra, A.K. 1995. Ethylcellulose matrix controlled release tablets of water-soluble drug. **Int. J. Pharm**. 123:119-125.

Kincl, M., Vrecer, F., and Veber, M. 2004. Characterization of factors affecting the release of low-solubility drug from prolonged release tablets. **Ana. Chimica. Act**. 502: 107-113.

Kolter, et al. 1997. **Delay release microtablet of beta-phenylpropionone derivative**. U.S Patent No. US5681588. October 28: 1-14.

Kramer, J., and Blume, H. Biopharmaceutical aspects of multiparticulates. In I. Gnrebre-sellassie (ed.), **Multiparticulate oral drug delivery**. pp. 307-332. New York: Marcel dekker.

Lennartz, P., and Mielck, J.B. 1998. Minitabletting: improving the compactibility of paracetamol powder mixtures. **Int. J. Pharm**. 173(1-2): 75-85.

Lin, K.H., Lin, S.Y., and Li, M.J. 2001. Compression force and amount of outer coating layer affecting the time-controlled disintegration of compression coated tablets prepared by direct compression with micronized ethylcellulose. **J. Pharm. Sci**. 90(12): 21-26.

Lin, S.Y., Lin, K.H., and Li, M.J. 2001. Micronized ethylcellulose used for designing a directly compressed time controlled disintregation tablet. **J. Controlled. Release**. 70(Feb 23): 321-328.

Liu, J., Zheng, F., and McGinity, J.W. 2001. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. **Eur. J. Pharm. Biopharm.** 52: 181-190.

Maitani, Y., Nakagaki, M., and Naigai, T. 1991. Determination of the acid dissolution constants in ethanol-water mixtures and partition coeffients for diclofenac sodium. **Int. J. Pharm.** 74: 105-114.

Malamataris, S., Hatjichristos, Th., and Rees, J.E. 1996. Apparent compressive elastic modulus and strength isotropy of compacts formed from binary powder mixes. **Int. J. Pharm**. 141: 101-108.

Mahaguna, V., Talbert, R.L., Peters, J.I., Adams, S., Reynolds, T.D., Lam F. L.W. and Williams, R.O. 2003. Influence of Hydroxypropylmethylcellulose polymer on in vitro and in vivo performance of controlled release containing alprazolam. **Eur. J. Pharm. Biopharm**. 56(3): 461-468.

Martin, A., Bustamane, P., and Chun, A.H.C. (1993). **Physical Pharmacy** (4^{th} ed.). Lea&Febiger. Philadelphia. London.

Moffat, A., Jackson, J.V., Moss, M.S., and Widdop, B. (eds). 1986. **Clarke's isolation and identification of drug** (2nd ed.). London: The pharmaceutical press.

Munday, D.L. 1994. A comparison of the dissolution characteristics of theophylline from film coated granules and mini-tablets. **Drug. Dev. Ind Pharm**. 20(15): 2369-2379.

Nagel, K.M., and Peck, G.E. 2003. Investigating the excipients on the powder flow characteristics of theophylline andydrous powder formulations. **Drug. Dev. Ind. Pharm**. 29(3): 277-287.

Newton, J.M., Haririan, I. and Podczeck, F. 2000. The determination of mechanical properties of elongated tablets of varying cross section. **Eur. J. Pharm. Biopharm**. 49(1): 59-64.

Ney, H. 1991. Microtablets as an alternative to pellets. **Manu. Chem**. 62(Jul): 24-25.

Nystrom, C., Alderborn, G., and Karehill, Per-G. 1993. Bonding surface area and boning mechanism-two important factors for the understanding of powder compactibility. **Drug. Dev. Ind. Pharm**. 19(17&18): 2143-2196.

Obaidat, A.A., and Obaidat, R.M. 2001. Controlled release of tramadol hydrochloride from matrices prepared using glyceryl behenate. **Eur. J. Pharm. Biopharm**. 52: 231-235.

Padmaja, S., and Sprockel, O.L. 1992. Compaction behaviour of cellulose polymers. **Powder. Technol.** 69: 177-184.

Parrott, E.L. 1990. Compression**.** Pharmaceutical dosage forms: In H.A. Lieberman, L. Lachman, J.B. Schwartz (eds.), **Pharmaceutical dosage forms: Tablets** (2 vols 2nd. ed.), Marcel Dekker, Inc. New York: 202-243.

Pather, S.I., Russell, I., Syce, J.A., and Neau, S.H. 1998. Sustained release theophylline tablets by direct compression Part 1: formulation and in vitro testing. **Int. J. Pharm**. 164: 1-10.

Perez, M.A., Ghaly, E.S. and Marti, A. 1993. Sustained release phenylpropanolamine HCl from ATO 888 matrix. **P.R. Health Sci. J.** 12(4): 263-267.

Pich, C.H. and Moest, T. 1989. **Cylindrical microtablets.** U.S Patent No. US4797287. January 10: 1-7.

Pillai, J.C., Brabar, A., and Plakogiannis, F.M. 1988. Polymers in cosmetic and pharmaceutical industries. **Pharm. Acta. Helv.** 63: 46-53.

Pitt, K.G. and Newton, J.M. 1988. Tensile fracture of doubly-convex cylindrical discs under diamentral loading. **Powder. Technol.** 23: 2723-2728.

Ranada, V.V., and Hollinger, M.A. 1996. Raton, B. (ed.), **Drug deliverly system**. pp. 127-173. Florida: CRC Press.

Rekhi, G.H., Nellore, R.V., Hussain, A.S., Tillman, L.G., Malinowski, H.J., and Augsburger, L.L. 1999. Identification of critical formulation and processing variables for metoprolol tartrate extended-release (ER) matrix tablets. **J. Controlled. Release**. 59(1): 327-342.

Rey, H., Wagner, K.G., Wehrle, P., and Schmidt, P.C. 2000. Development of matrix-based theophylline sustained-release microtablets. **Drug. Dev. Ind. Pharm**. 26(1). 21-26.

Reynolds, E.F., Parfitt, K., Parsons, A.V., and Sweetman, S.C., eds. 1989. **Martindale: the extra pharmacopoiea** (29th ed.). pp. 12-13. London. The pharmaceutical Press.

Ritger, P.L., and Peppas, N.A. 1987a. A simple equation for description of solute release I Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. **J. Controlled Release**. 5: 23-26.

Ritger, P.L., and Peppas, N.A. 1987a. A simple equation for description of solute release II Fickian and non-Fickian release from swellable devices. **J. Controlled Release**. 5: 37-42.

Rosanske, T.W., Gordon, R.E., and Fonner, D.E. 1990. Granulation technology and characteristization. In H.A. Lieberman, L. Lachman, J.B. Schwartz (eds.), **Pharmaceutical dosage forms: Tablets** (2 vols 2nd. ed.). Marcel Dekker, Inc. New York: 245-347.

Romero, A.P., Caramella, C., Ronchi, M., Ferrari, F. and Chulia, D. 1991. Water uptake and force development in an optimized prolonged release formulation. **Int. J. Pharm**. 73(Jul 21): 239-248.

Saettone, M.F., Chetoni, P., Mariotti, Bianchi, L., Ginnaccini, B., Conte, V., and Sanglli, M.E. 1995. Controlled release of timolol maleate from coated ophthalmic mini-tablets prepared by compression. **Int. J. Pharm**.126: 79-82.

Sánchez-Lafuente, C., Faucci, M.T., Fernández-Arévalo, M., Álvarez-Fuentes, Rabasco, A.M., and Mura, P. 2002. Development of sustained release matrix tablets of didanisine containing methacrylic and ethylcellulose polymers. **Int. J. Pharm**. 234: 213-221.

Sa, B., Bandyopadhyay, A.K., and Gupta, B.K. 1990. Development and in vitro evaluation of ethylcellulose micropellets as acontrolled release dosage form theophylline. **Drug. Dev. Ind. Pharm**. 16: 1153-1169.

Sarisuta, N., and Mahahpun, P. 1994. Effect of compression force and type of fillers on the release of diclofenac sodium. **Drug. Dev. Ind. Pharm**. 20(6): 1049-1061.

Schwartz, J.B., Simonelli, A.P., and Higuchi, W.I. 1968. Drug release from wax matrices I analysis of data with first-order kinetics and with the diffusion-controlled model. **J. Pharm. Sci.** 57: 274-277.

Singh, J., and Robinson, D.H. 1988. Controlled release kinetics of captopril from tableted microcapsules. **Drug. Dev. Ind. Pharm**. 14(4): 545-560.

Shah, N.H., Stiel, D., Infeld, M.H., and Malick, A.W. 1986. Evaluation of two new lubricants-sodium fumarate and glyceryl behenate. Mesurements of physical parameters (compaction, ejection and residual forces) in the tableting process and effect on the effect on the dissolution rate. **Drug. Dev. Ind. Pharm.** 12: 1329-1346.

Shanawany, S.L. 1993. Sustained release of nitrofurantoin from inert wax matrix. **J. Controlled Release.** 26: 11-19.

Shue, M.T., Chou, H.L., Kao, C.C., Liu, C.H., and Sokoloski, T.D. 1992. Dissolution of diclofenac sodium from matrix tablets. **Int. J. Pharm**. 85: 57-63.

Stavchansky, S.A. and McGinity J.W. Tablet formulation and design. In H.A. Lieberman, L. Lachman and J.B. Scgwaetz (eds.), **Pharmaceutical dosage forms: tablet** (2 vols 2nd. ed.), pp. 349-569. New York: Marcel Dekker.

Sujja-areevath, J., Munday, D.L., Cox, P.J., and Hhan, K.A. 1996. Release characteristics of diclofenac sodium from encapsulated natural gum mini-matrix formulations. **Int. J. Pharm.**139: 53-62.

Stamm, A., and Tritsch, J.C. 1986. Some concentrations on the libration of drugs froms from inert matrices. **Drug. Dev. Ind. Pharm.** 12: 2337-2353.

The United States Pharmacopeial Convention. 1995. **The United States Pharmacopoiea (USP)** (24th. Rev. ed.). Massachusetts: 546-547

Thomsen, L.J., Schæfer T., and Kristensen H.G. 1994. Prolonged release matrix pellets prepared by melt pelletization II. Hydrophobic substances as meltable binders. **Drug. Dev. Ind. Pharm.** 20(7): 1179-1197.

Tsai, T., San, Y., Ho, H., Wu, J., and Shue, M. 1998. Film-forming polymer-granulated excipients as the matrix materials for controlled release dosage forms. **J. Controlled. Release**. 51: 289-299.

Upadrashta, S.M., Katikaneni, P.R., Hileman, G.A., and Keshary, P.R. 1993. Direct compression controlled release tablets using ethylcellulose matrices. **Drug. Dev. Ind. Pharm.**19(4): 449-460.

Upadrashta, S.M., Katikaneni, P.R., Hileman, G.A., Neau, S.H., and Rowlings, C.E. 1995. Compressibility and compatibility properties of ethylcellulose. **Int. J. Pharm.** 112: 173-179.

Veen, B.V., Maarschalk, K.V., Bolhuis, G.K., and Frijlink, H.W. 2004. Predicting mechanical properties of compacts containing two components. **Powder. Technol.** 139: 156-164.

Velasco, M.V., Ford, J.L., Rowe, P. and Rajabi-Siahboomi, A.R. 1999. Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. **J. Controlled. Release**. 57: 75-85.

Weyenberg, W., Vermeire, A., Remon, J.P. and Ludwig, A. 2003. Characterization and in vivo evaluation ocular bioadhesive minitablets compressed at different forces. **J. Controlled. Release.** 89(1): 329-340.

William, L. R. 1994. Solid state characterization of stanzolol. **Drug. Dev. Ind. Pharm.** 20(11): 1831-1849.

Yoshinari, T, Forbes, R.T., York, P., and Kawashima, Y. 2003. The improved compaction properties of manitol after moisture-induced polymorphic transition. **Int. J. Pharm.** 258. 121-131.

Yoshino, H., Hagiwara, Y., Kabayashi, M., and Samejima, M. 1984. Estimation of polymorphic transition degree of pharmaceutical raw materials. **Chem. Pharm. Bull.** 32(4): 1523-1536.

Zhang, Y., and Schwartz, J.B. 2000. Effect of diluents on tablet integrity and controlled drug release. **Drug. Dev. Ind. Pharm.** 26(7): 761-765.

APPENDICES

Appendix A

Calibration curve

1. Calibration Curve of force measurement

Table 28 The calibration data of voltage measured on the strain indicator amplifier and force applied on the upper plunger

Force (lb)	Voltage (mV)
100	9.5
200	19.5
300	26.75
400	36.25
500	43
600	52.5
700	61.75
800	70.75
900	80
1000	88
1100	95
1200	103.75
1300	112.25
1400	121.25

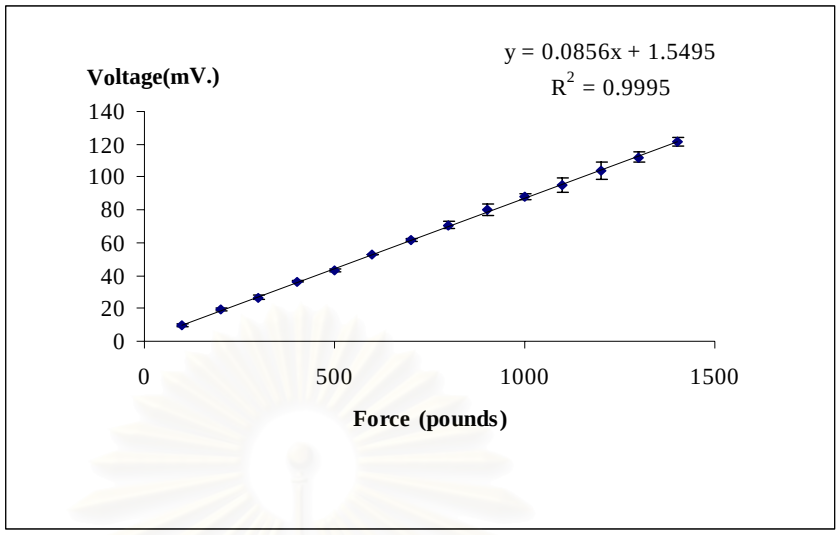


Figure 59 Calibration curve of to show linearity between the force applied on to upper plunger versus voltage measured

2. Calibration curve of diclofenac sodium for dissolution studied

The concentration versus absorbance of diclofenac sodium in 0.1N HCl at 271 nm and in phosphate buffer pH 6.8 at 275 nm are presented in Table 3-4. The standard curves of diclofenac sodium in these mediums are illustrated in Figures 3-4.

Table 29 Absorbance of diclofenac sodium in 0.1N HCl at 271 mn

Concentration (μg/ml)	Absorbance
5	0.1412
10	0.2747
15	0.4082
20	0.5417
25	0.6752

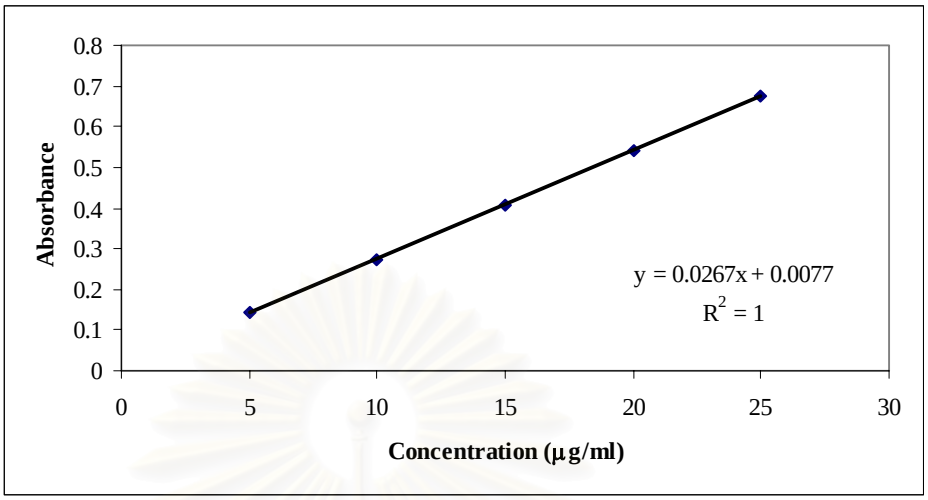


Figure 60 Calibration curve of diclofenac sodium in 0.1N HCl at 271

Table 30 Absorbance of diclofenac sodium in phosphate buffer pH 6.8 at 275 nm

Concentration (µg/ml)	Absorbance
5	0.1622
10	0.3242
15	0.4862
20	0.6482
25	0.8102

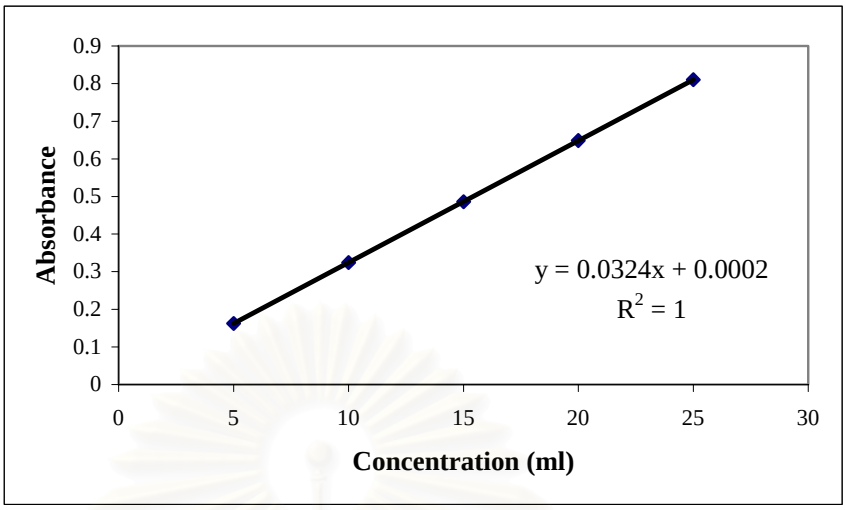


Figure 61 Calibration curve of diclofenac sodium in phosphate buffer pH 6.8 at 275 nm

3. Validation of HPLC method

The DS concentrations for drug content and content uniformity of DS microtablets could be determined by HPLC assay with UV detection. The wavelength used to analyze DS in this study was 275 nm. The validation of HPLC method used are presented as follows:

1.1 Specificity

Ethylparaben (EP) and DS were eluted at 4.00-5.00 min and 6.00-7.00, respectively. Figure 63 shows the chromatogram in presence of internal standard (ethylparaben) and non- active ingredients, including EC, HPMC K15M, compritol 888 ATO, tristearin. It indicated that the other ingredients did not interfere with peaks of DS.

1.2 Accuracy

Table 31 shows the percentage of analytical recovery at actual concentration of DS was 6 μg/ml. The mean percentage of analytical recovered closely to 100%, with a low %RSD (<2.00%) indicated the high accuracy of this method.

1.3 Precision

Table 32 shows data of within run precision and between run precision of DS by HPLC method. The percentage of coefficient of variation (%RSD) values of peak area ratios both within run and between run were low (0.11% and 0.22%) which indicated that the HPLC methods could be used to determine the amount of DS over period of time studied.

Table 31 Percentage of analytical recovery of DS at actual concentration of DS was 6 μg/ml

Formulation	Analytical concentration (μg/ml)			% Recovery			Mean (sd)	%CV
EC	6.1298	6.1529	6.0888	100.819	102.548	101.1442	101.504 (0.919)	0.955
HPMC	5.9541	5.9356	5.9969	97.9296	98.9276	99.9488	98.9354 (1.009)	1.020
Compritol 888 ATO	6.1955	5.9196	5.9170	101.9003	98.6611	98.2901	99.6171 (1.986)	1.986
tristearin	5.9586	6.0162	6.0434	98.0035	100.2713	100.3888	99.5546 (1.344)	1.350

Table 32 Data within run precision at concentration of DS was 6 μg/ml

	Peak area ratio
1	1.1425
2	1.1434
3	1.1408
4	1.1418
5	1.1443
mean	1.1425
SD	0.0013
%RSD	0.1170

Table 33 Data between run precision

Concentration (μg/ml)	Peak area ratio				
	day1	day2	mean	sd	%RSD
2	0.372	0.379	0.376	0.005	1.251
4	0.741	0.760	0.750	0.013	1.789
6	1.117	1.145	1.131	0.020	1.805
8	1.489	1.529	1.509	0.028	1.880
10	1.855	1.895	1.875	0.029	1.530

1.4 Linearity

The linearity of analysis method is its ability to elicit test results that directly, or by well-defined mathematical transformation, proportional to the concentration of analysis in samples within a given range. Figure 62 showed that the relationship between peak area ratios and DS concentrations is linearity with correlation of determination value of 1. This result indicated that HPLC method was acceptable for qualitative analysis of DS in range studied. Figure 64 shows HPLC chromatograms of standard solutions of DS

Calibration curve of diclofenac sodium for HPLC studied

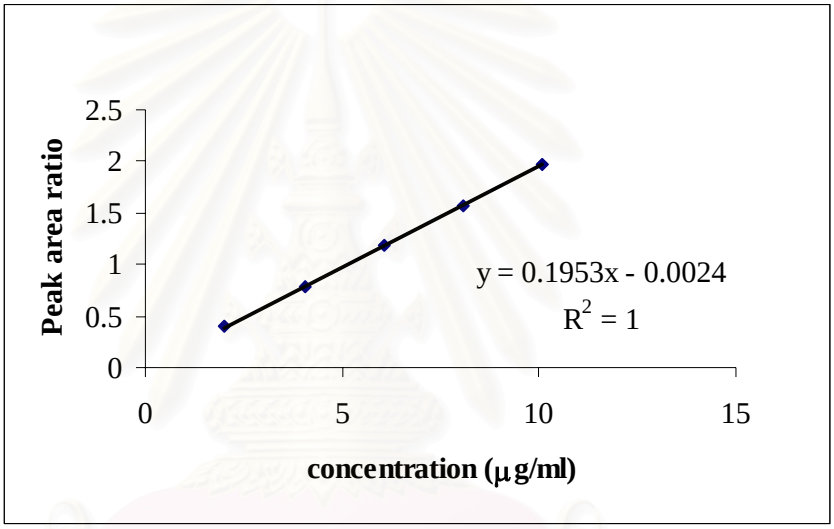


Figure 62 Calibration curve showing linearity between concentration and peak area ratio of diclofenac sodium and ethyl paraben (internal standard)

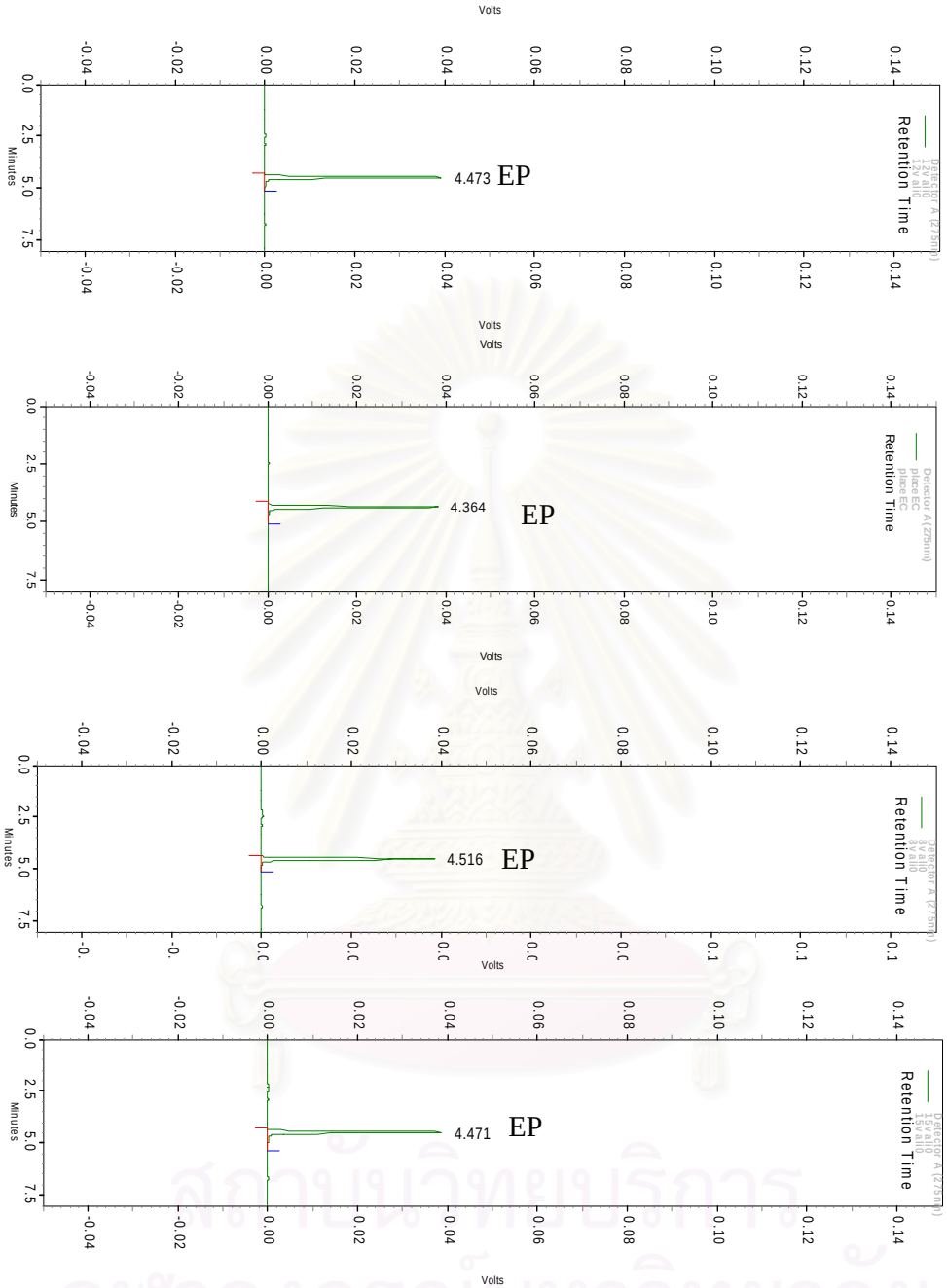


Figure 63 The chromatogram in presence of internal standard (ethylparaben) and non- active ingredients, including EC, HPMC K15M, compritol 888 ATO, tristearin.

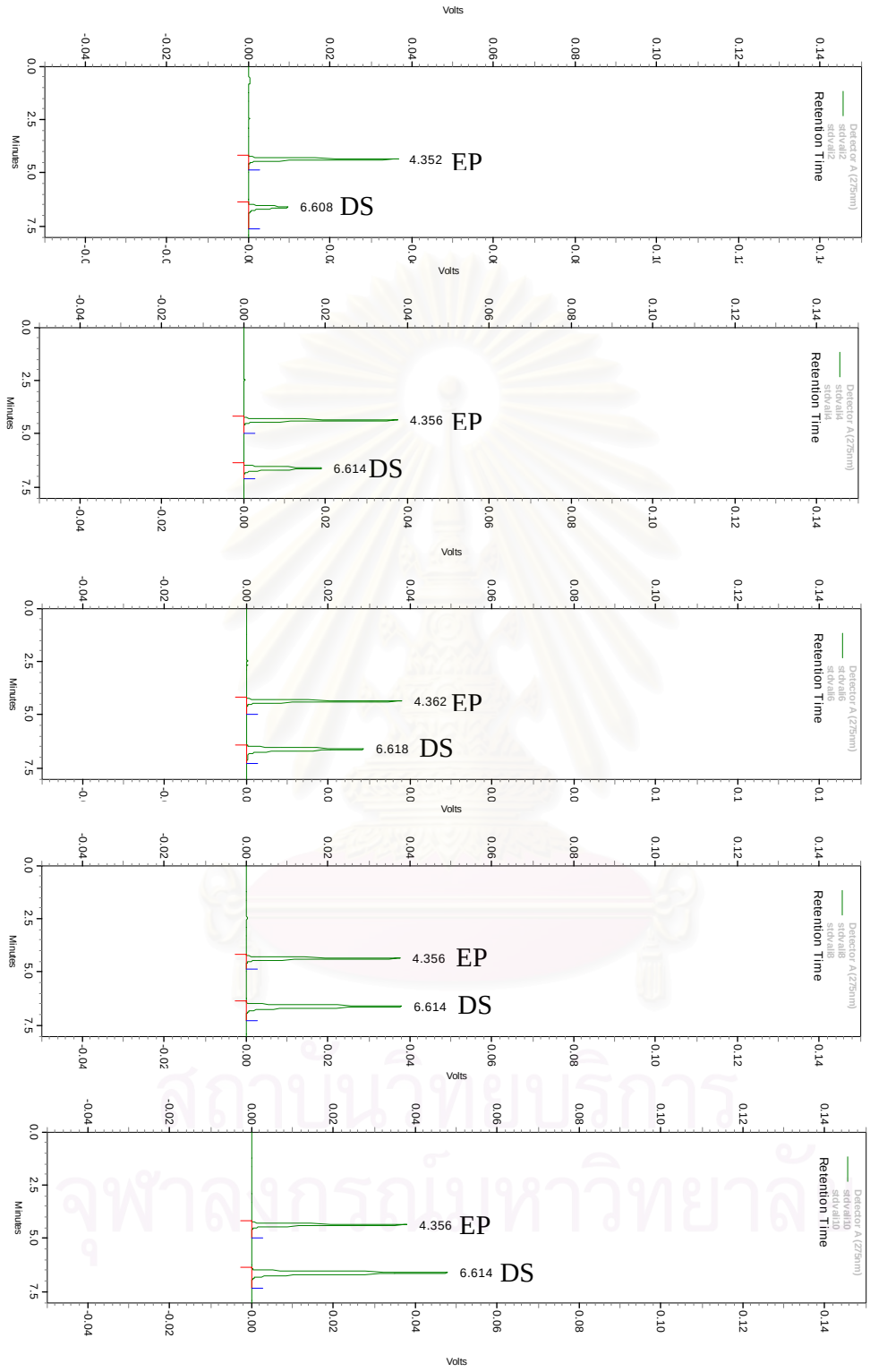


Figure 64 HPLC chromatograms of standard solutions of DS

Appendix B

The physical properties of DS granule and DS microtablets

1. The physical properties of DS granules

Table 34 The physical properties of granules which were prepared from various mesh size #20, #25, #30

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Flow rate (g/sec)	Angle of repose (x°)
F1#20	0.5076 0.5128 0.5050	0.5797 0.5681 0.5714	12.4366 9.7435 11.2654	2.0547 2.0270 2.0000 2.0270 2.0270	33.8 33.9 33.8
F1#25	0.5181 0.5236 0.5154	0.5714 0.5747 0.5714	9.3264 8.9005 9.7938	2.0833 2.0833 2.2058 2.1127 2.1428	34.4 33.3 34.1
F1#30	0.5882 0.5882 0.5847	0.625 0.625 0.6289	5.8823 5.8823 7.0175	2.3438 2.3438 2.3809 2.3809 2.3077	32.5 33.5 33.7

Table 35 Particle size distribution of granule that were prepared from various mesh size #20, #25, #30

Formulation	% average weight retained							
	707µm (sd)	595µm (sd)	500µm (sd)	425µm (sd)	250µm (sd)	106µm (sd)	45µm (sd)	Base (sd)
F1#20	12.676 (0.83)	25.502 (0.04)	*	*	52.430 (3.27)	7.426 (2.33)	1.008 (0.26)	0.958 (0.11)
F1#25	*	17.782 (1.68)	*	39.069 (0.51)	30.359 (4.03)	10.890 (1.48)	1.557 (0.66)	0.342 (0.21)
F1#30	*	*	6.264 (0.79)	21.111 (1.56)	53.351 (2.52)	14.951 (1.57)	3.174 (0.56)	1.148 (0.03)

* The sieve not used in experiment.

Table 36 The physical properties of DS granules

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Flow rate (g/sec)	Angle of repose (x°)
F1	0.5882 0.5882 0.5847	0.625 0.625 0.6289	5.8823 5.8823 7.0175	2.3438 2.3438 2.3809 2.3809 2.3077	32.5 33.5 33.7
F2	0.6153 0.5917 0.5882	0.6779 0.6451 0.6410	9.2308 8.2840 8.2352	2.3437 2.3437 2.3076 2.3076 2.3437	33.7 33.4 33.5
F3	0.6172 0.5988 0.6061	0.6756 0.6493 0.6849	8.6419 7.7844 11.5151	2.3278 2.2854 2.3157 2.2854 2.2864	34.6 34.2 34.6
F4	0.5882 0.5847 0.5813	0.6451 0.6329 0.6329	8.8235 7.6023 8.1395	2.3437 2.3809 2.3437 2.3809 2.3809	34.9 36.6 34.0
F5	0.5405 0.5405 0.5405	0.6060 0.6060 0.6060	10.8108 10.8108 10.8108	2.2727 2.2727 2.2727 2.2388 2.3076	36.5 35.4 35.0

Table 37 The physical properties of DS granules

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Flow rate (g/sec)	Angle of repose (x°)
F6	0.5128 0.4878 0.5128	0.5494 0.5435 0.5525	6.6666 10.2439 7.1794	2.1126 2.1428 2.1428 2.1126 2.1126	37.8 38.7 37.6
F7	0.5235 0.5128 0.5181	0.5525 0.5523 0.5495	5.2356 7.1794 5.6995	2.0833 2.0833 2.0547 2.1428 2.0547	38.1 38.4 38.9
F8	0.4878 0.4926 0.4902	0.5236 0.5263 0.5236	6.8293 6.4039 6.3725	2.0000 1.9480 1.9736 2.0270 1.9480	38.7 38.4 30.0
F9	0.4831 0.4808 0.4878	0.5208 0.5181 0.5291	7.2463 7.2115 7.8049	1.9736 1.9230 1.9736 1.9480 1.9230	38.9 38.2 39.4
F10	0.4951 0.5051 0.5128	0.5376 0.5435 0.5291	6.4356 6.0606 5.6410	1.9230 1.9480 1.9230 1.9230 1.9480	41.1 40.5 40.7

Table 38 Particle size distribution of DS granule

Formulation	% average weight retained					
	500 μm	425 μm	250 μm	106 μm	45 μm	base
F1	6.264 (0.79)	21.111 (1.56)	53.351 (2.52)	14.951 (1.57)	3.174 (0.56)	1.148 (0.03)
F2	7.178 (0.81)	24.730 (0.44)	45.002 (0.31)	17.653 (0.09)	4.078 (0.14)	1.359 (0.05)
F3	5.806 (0.02)	24.429 (0.32)	44.173 (0.28)	20.244 (0.19)	4.705 (0.28)	0.641 (0.12)
F4	19.414 (1.25)	22.622 (1.23)	34.922 (0.75)	16.107 (1.49)	6.0751 (0.79)	0.859 (0.04)
F5	9.532 (1.01)	20.341 (1.18)	48.250 (0.88)	19.912 (2.80)	1.526 (0.24)	0.439 (0.13)
F6	10.001 (0.44)	21.415 (0.88)	41.447 (3.02)	19.160 (1.78)	6.7241 (1.01)	1.252 (0.11)
F7	16.215 (1.09)	25.772 (0.22)	36.622 (0.77)	16.155 (0.34)	4.473 (0.12)	0.762 (0.11)
F8	15.046 (1.43)	24.737 (0.71)	37.441 (0.38)	16.839 (1.56)	5.046 (0.69)	0.891 (0.01)
F9	19.206 (2.36)	22.569 (1.24)	37.347 (2.19)	16.081 (1.37)	4.149 (1.33)	0.649 (0.03)
F10	24.629 (2.12)	19.833 (2.18)	34.071 (2.11)	15.709 (0.91)	4.906 (1.03)	0.851 (0.04)

Table 39 The hardness of DS microtablets that prepared from various punch position and compression force

hardness(N)	400 lb			800 lb			1200 lb		
	P1	P2	P3	P1	P2	P3	P1	P2	P3
1	14.67	16.77	18.42	24.71	23.82	25.94	29.7	27.54	29.54
2	19.65	15.12	19.3	24.88	23.21	24.56	27.64	29.54	27.26
3	16.77	17.94	16.77	23.69	22.53	26.47	30.12	28.42	29.57
4	17.33	18.56	17.5	22.79	24.87	24.73	28.64	30.41	30.75
5	18.6	15.96	16.5	22.68	22.18	23.73	29.54	28.94	29.14
6	17.5	16.42	15.43	25.37	25.37	21.48	30.05	29.64	31.04

2. The physical properties of DS microtablets

Table 40 The hardness of DS microtablets that prepared from various punch size (2.00, 2.25, and 2.5 mm) and compression force (400, 800, 1,200 lb)

hardness(N)	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb
1	21.45	23.38	24.56	14.07	17.56	20.08	11.99	16.49	16.11
2	12.86	19.71	25.62	14.33	17.85	16.43	16.72	15.06	15.42
3	20.87	22.59	26.41	19.95	16.5	20.45	9.75	11.42	17.6
4	19.31	22.84	26.08	13.19	18.08	16.53	10.56	17.35	18.33
5	22.69	23.86	23.91	13.82	18.52	17.61	8.102	18.37	17.01
6	21.10	23.44	26.12	14.15	13.79	20.95	10.69	12.02	15.53
7	18.25	24.37	29.45	15.29	19.19	20.32	8.058	11.72	17.82
8	17.46	25.13	25.69	12.64	20.09	18.46	16.99	15.5	15.55
9	18.30	24.6	28.25	14.18	17.14	18.13	9.102	12.92	16.73
10	18.68	21.91	24.25	15.79	13.38	17.97	8.543	17.57	14.39

Table 41 The apparent tensile strength (ts_{app}) of DS microtablets that prepared from punch size 2.00, 2.25, and 2.5 mm and compression force 400, 800, 1,200 lb

ts_{app}	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb
1	2.549	2.875	3.0083	1.77	2.28	2.694	1.551	2.247	2.231
2	1.600	2.491	3.1872	1.811	2.35	2.153	2.173	2.03	2.147
3	2.527	2.821	3.2727	2.533	2.173	2.693	1.23	1.581	2.373
4	2.329	2.808	3.2318	1.645	2.381	2.176	1.359	2.267	2.58
5	2.727	2.900	2.94	1.747	2.461	2.385	1.032	2.45	2.394
6	2.545	2.871	3.301	1.772	1.791	2.824	1.369	1.587	2.162
7	2.202	2.997	3.6637	1.959	2.575	2.713	1.011	1.614	2.39
8	2.106	3.055	3.1959	1.626	2.633	2.431	2.197	2.046	2.165
9	2.199	2.990	3.5987	1.792	2.226	2.479	1.159	1.732	2.292
10	2.245	2.663	2.9818	2.023	1.778	2.400	1.088	2.381	2.026

Table 42 Thickness of DS microtablets that prepared from various punch size (2.00, 2.25, and 2.5 mm) and compression force (400, 800, 1,200 lb)

Thickness (mm)	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb
1	2.68	2.59	2.52	2.25	2.18	2.11	2.03	1.94	1.89
2	2.56	2.59	2.56	2.24	2.15	2.16	2.01	1.94	1.91
3	2.63	2.62	2.57	2.23	2.15	2.15	2.00	1.95	1.83
4	2.64	2.60	2.52	2.27	2.13	2.15	2.01	1.98	1.85
5	2.65	2.63	2.50	2.24	2.18	2.09	2.00	1.96	1.92
6	2.64	2.59	2.52	2.26	2.11	2.12	2.03	1.99	1.86
7	2.64	2.62	2.56	2.21	2.16	2.15	2.00	1.94	1.87
8	2.64	2.58	2.56	2.22	2.18	2.07	2.02	1.96	1.90
9	2.65	2.62	2.50	2.22	2.11	2.07	2.03	1.98	1.87
10	2.65	2.59	2.59	2.21	2.13	2.12	2.00	1.97	1.88

Table 43 Surface area of DS microtablets that prepared from various punch size (2.00, 2.25, and 2.5 mm) and compression force (400, 800, 1,200 lb)

surface area (mm^2)	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb
1	21.14	20.58	20.14	21.05	20.27	20.35	21.93	21.23	20.83
2	20.39	20.58	20.39	20.98	20.56	20.27	21.78	21.23	20.99
3	20.83	20.76	20.45	20.91	20.56	20.56	21.70	21.3	20.36
4	20.89	20.64	20.14	21.19	20.49	20.56	21.78	21.54	20.52
5	20.95	20.83	20.01	20.98	20.49	20.7	21.70	21.38	21.07
6	20.89	20.58	20.136	21.12	20.49	20.49	21.93	21.62	20.60
7	20.89	20.76	20.39	20.77	20.27	20.56	21.70	21.23	20.68
8	20.89	20.51	20.39	20.7	20.42	20.35	21.85	21.38	20.91
9	20.95	20.76	20.01	20.98	20.7	20.27	21.93	21.54	20.68
10	20.95	20.58	20.575	20.77	20.35	20.49	21.70	21.46	20.75

Table 44 The volume of DS microtablets that prepared from various punch size (2.00, 2.25, and 2.5 mm) and compression force (400, 800, 1,200 lb)

volume(mm^3)	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb
1	7.924	7.641	7.4216	8.17	7.733	7.773	8.812	8.371	8.126
2	7.547	7.641	7.5472	8.131	7.892	7.733	8.714	8.371	8.224
3	7.767	7.736	7.5786	8.091	7.892	7.892	8.665	8.42	7.831
4	7.798	7.673	7.4216	8.25	7.853	7.892	8.714	8.567	7.929
5	7.83	7.767	7.3588	8.131	7.853	7.972	8.665	8.469	8.273
6	7.798	7.641	7.4216	8.21	7.853	7.853	8.812	8.616	7.978
7	7.798	7.736	7.5472	8.011	7.733	7.892	8.665	8.371	8.027
8	7.798	7.61	7.5472	7.972	7.813	7.773	8.763	8.469	8.175
9	7.83	7.736	7.3588	8.131	7.972	7.733	8.812	8.567	8.027
10	7.83	7.641	7.6414	8.011	7.773	7.853	8.665	8.518	8.077

Table 45 The porosity of DS microtablets that prepared from various punch size (2.00, 2.25, and 2.5 mm) and compression force (400, 800, 1,200 lb)

% porosity	2.00 mm			2.25 mm			2.50 mm		
	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb	400 lb	800 lb	1200 lb
1	8.045	4.215	0.6136	12.15	8.393	8.122	16.29	12.13	9.466
2	3.454	4.215	2.2675	11.72	10.24	7.650	15.34	12.13	10.550
3	6.186	5.381	2.6725	11.29	10.24	9.510	14.87	12.64	6.063
4	6.564	4.607	0.6136	13.00	9.784	9.510	15.34	14.15	7.226
5	6.938	5.764	0.2346	11.72	9.784	10.41	14.87	13.15	11.080
6	6.564	4.215	0.6136	12.58	9.784	9.052	16.29	14.63	7.796
7	6.564	5.381	2.2675	10.41	8.393	9.510	14.87	12.13	8.360
8	6.564	3.82	2.2675	9.961	9.325	8.122	15.82	13.15	10.010
9	6.938	5.381	0.2346	11.72	11.13	7.650	16.29	14.15	8.360
10	6.938	4.215	3.4723	10.41	8.861	9.052	14.87	13.65	8.917

Table 46 The hardness (N) of DS microtablets that prepared from various the type and amount of compositions in the formulation

F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
16.49	14.77	13.96	8.789	7.019	8.34	13.09	12.79	11.42	16.15
15.06	14.73	14.64	6.691	5.905	11.72	12.35	11.76	12.05	13.86
11.42	15.26	16.05	6.264	5.966	12.23	14.45	12.69	12.5	14.31
17.35	15.36	14.98	9.521	5.135	12.27	14.02	12.36	13.05	15.59
18.37	14.27	14.76	9.178	6.02	8.865	13.24	13.31	12.03	15.82
12.02	12.00	15.18	11.06	5.035	8.89	13.46	13.5	13.62	14.86
11.72	15.52	11.94	7.599	7.637	10.57	13.49	13.98	10.50	13.41
15.5	15.19	16.08	6.233	5.295	13.24	12.38	13.03	15.46	15.75
12.92	13.37	14.79	6.744	5.531	10.09	12.09	14.09	13.02	13.32
17.57	15.48	15.13	7.721	6.454	10.25	13.27	13.3	14.37	14.48

Table 47 The thickness (mm) of DS microtablets that prepared from various the type and amount of compositions in the formulation

F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.87	1.8	1.86	1.95	1.9	1.85	1.9	1.93	1.97	1.89
1.89	1.81	1.81	1.88	1.86	1.87	1.89	1.9	2.03	1.91
1.84	1.79	1.8	1.88	1.89	1.85	1.89	1.91	2.04	1.88
1.95	1.83	1.82	1.95	1.9	1.88	1.93	1.9	1.96	1.90
1.91	1.83	1.82	1.91	1.97	1.85	1.90	1.98	1.95	1.92
1.93	1.81	1.83	1.96	1.93	1.86	1.93	1.95	1.99	1.89
1.85	1.83	1.82	1.91	1.99	1.84	1.89	1.95	1.96	1.92
1.93	1.82	1.82	1.89	1.93	1.86	1.87	1.96	2.06	1.92
1.90	1.82	1.82	1.91	1.95	1.87	1.90	1.94	1.97	1.89
1.88	1.83	1.81	1.91	1.88	1.86	1.90	1.89	2.05	1.89

Appendix C

Percentage of drug release

Table 48 Percentage of DS release of microtablets from position P1 at 400 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	21.289	6.484	1.896
3	1.732	27.849	11.302	1.858
3.5	1.871	34.358	14.721	1.817
4	2.000	40.453	15.255	1.775
4.5	2.121	44.157	17.198	1.747
5	2.236	47.981	18.068	1.716
6	2.449	55.556	19.183	1.648
7	2.646	60.693	19.594	1.594
8	2.828	64.790	18.679	1.547
10	3.162	72.332	16.037	1.442
12	3.464	77.461	12.257	1.353
14	3.742	81.250	9.179	1.273
17	4.123	86.596	8.532	1.127
20	4.472	92.302	6.648	0.886
24	4.899	94.721	4.074	0.723

Table 49 Percentage of DS release of microtablets from position P2 at 400 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	21.106	5.723	1.897
3	1.732	28.806	11.410	1.852
3.5	1.871	35.878	15.217	1.807
4	2.000	42.690	19.801	1.758
4.5	2.121	46.975	21.253	1.724
5	2.236	50.971	21.204	1.690
6	2.449	56.674	20.910	1.637
7	2.646	61.679	19.715	1.583
8	2.828	65.647	18.422	1.536
10	3.162	72.938	15.561	1.432
12	3.464	78.328	13.268	1.336
14	3.742	81.594	10.777	1.265
17	4.123	85.811	6.619	1.152
20	4.472	90.188	6.039	0.992
24	4.899	92.000	2.967	0.903

Table 50 Percentage of DS release of microtablets from position P3 at 400 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	22.536	6.526	1.889
3	1.732	32.915	15.099	1.827
3.5	1.871	39.758	20.311	1.780
4	2.000	47.928	23.741	1.717
4.5	2.121	51.253	23.056	1.688
5	2.236	58.101	19.409	1.622
6	2.449	60.687	21.406	1.595
7	2.646	65.177	20.290	1.542
8	2.828	68.696	19.131	1.496
10	3.162	75.876	15.903	1.382
12	3.464	79.638	12.583	1.309
14	3.742	82.360	10.404	1.246
17	4.123	85.700	7.006	1.155
20	4.472	88.706	5.688	1.053
24	4.899	90.199	3.398	0.991

Table 51 Percentage of DS release of microtablets from position P1 at 800 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	21.345	5.892	1.896
3	1.732	31.279	10.631	1.837
3.5	1.871	38.915	15.355	1.786
4	2.000	46.085	17.636	1.732
4.5	2.121	49.802	19.450	1.701
5	2.236	54.749	19.153	1.656
6	2.449	60.246	19.951	1.599
7	2.646	65.449	19.369	1.538
8	2.828	69.513	19.402	1.484
10	3.162	76.188	17.073	1.377
12	3.464	80.379	14.085	1.293
14	3.742	81.970	11.501	1.256
17	4.123	85.732	8.287	1.154
20	4.472	88.486	6.062	1.061
24	4.899	88.993	3.887	1.042

Table 52 Percentage of DS release of microtablets from position P2 at 800 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	23.274	5.427	1.885
3	1.732	32.346	10.611	1.830
3.5	1.871	39.739	14.580	1.780
4	2.000	45.318	15.999	1.738
4.5	2.121	49.893	15.835	1.700
5	2.236	54.166	16.421	1.661
6	2.449	60.304	16.787	1.599
7	2.646	65.519	16.203	1.538
8	2.828	70.817	15.371	1.465
10	3.162	77.902	13.626	1.344
12	3.464	82.360	11.517	1.247
14	3.742	84.784	8.285	1.182
17	4.123	87.633	7.691	1.092
20	4.472	91.220	8.096	0.944
24	4.899	93.843	5.301	0.789

Table 53 Percentage of DS release of microtablets from position P3 at 800 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	23.345	3.882	1.885
3	1.732	30.290	8.409	1.843
3.5	1.871	36.961	10.771	1.800
4	2.000	44.188	11.706	1.747
4.5	2.121	49.343	13.789	1.705
5	2.236	54.305	15.746	1.660
6	2.449	62.596	15.184	1.573
7	2.646	68.347	15.324	1.500
8	2.828	73.506	14.612	1.423
10	3.162	80.385	12.605	1.293
12	3.464	83.957	11.153	1.205
14	3.742	88.119	8.999	1.075
17	4.123	90.539	6.959	0.976
20	4.472	93.685	5.370	0.800
24	4.899	94.030	4.546	0.776

Table 54 Percentage of DS release of microtablets from position P1 at 1200 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	18.273	1.769	1.912
3	1.732	28.481	4.395	1.854
3.5	1.871	38.118	6.224	1.792
4	2.000	47.998	8.158	1.716
4.5	2.121	54.117	8.136	1.662
5	2.236	59.182	7.996	1.611
6	2.449	67.280	7.725	1.515
7	2.646	74.204	5.609	1.412
8	2.828	79.842	4.721	1.304
10	3.162	86.099	4.002	1.143
12	3.464	91.589	3.847	0.925
14	3.742	95.251	2.960	0.677
17	4.123	97.660	2.738	0.369
20	4.472	101.661	1.228	#NUM!
24	4.899	102.876	2.148	#NUM!

Table 55 Percentage of DS release of microtablets from position P2 at 1200 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	19.543	2.352	1.906
3	1.732	26.657	3.219	1.865
3.5	1.871	33.413	4.945	1.823
4	2.000	39.543	5.923	1.781
4.5	2.121	44.502	6.983	1.744
5	2.236	49.348	7.679	1.705
6	2.449	57.209	8.015	1.631
7	2.646	65.331	7.351	1.540
8	2.828	70.875	7.111	1.464
10	3.162	79.967	8.066	1.302
12	3.464	87.010	8.127	1.114
14	3.742	91.270	6.013	0.941
17	4.123	92.699	4.384	0.863
20	4.472	99.518	3.528	-0.317
24	4.899	101.574	2.002	#NUM!

Table 56 Percentage of DS release of microtablets from position P3 at 1200 lb in pH-change method

Time(hr)	SQRT(t)	Ave	sd	Log% drug remained
0	0.000	0.000	0.000	2.000
0.5	0.707	0.000	0.000	2.000
1	1.000	0.000	0.000	2.000
1.5	1.225	0.000	0.000	2.000
2	1.414	0.000	0.000	2.000
2.5	1.581	20.873	1.293	1.898
3	1.732	30.195	0.679	1.844
3.5	1.871	38.202	1.370	1.791
4	2.000	44.455	2.368	1.745
4.5	2.121	50.024	3.278	1.699
5	2.236	55.333	4.210	1.650
6	2.449	62.602	4.614	1.573
7	2.646	70.092	5.196	1.476
8	2.828	74.787	5.971	1.402
10	3.162	83.083	7.923	1.228
12	3.464	88.749	7.779	1.051
14	3.742	92.530	5.510	0.873
17	4.123	95.855	4.190	0.618
20	4.472	100.766	2.653	#NUM!
24	4.899	100.697	2.172	#NUM!

Table 57 Percentage of DS release from microtablets which prepared from punch 2.00 mm at 400 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f400	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.348	0.001	2.002	#NUM!
0.5	0.707	-0.301	0.733	0.255	1.997	-2.135
1	1.000	0.000	1.361	0.091	1.994	-1.866
1.5	1.225	0.176	2.522	0.067	1.989	-1.598
2	1.414	0.301	3.135	0.073	1.986	-1.504
2.5	1.581	0.398	24.565	1.806	1.878	-0.610
3	1.732	0.477	37.821	3.241	1.794	-0.422
3.5	1.871	0.544	48.268	3.388	1.714	-0.316
4	2.000	0.602	55.106	2.266	1.652	-0.259
4.5	2.121	0.653	61.314	1.769	1.588	-0.212
5	2.236	0.699	67.123	2.942	1.517	-0.173
6	2.449	0.778	75.085	1.979	1.396	-0.124
7	2.646	0.845	82.068	1.132	1.254	-0.086
8	2.828	0.903	89.946	1.031	1.002	-0.046
10	3.162	1.000	93.923	1.371	0.784	-0.027
12	3.464	1.079	98.296	0.565	0.231	-0.007
14	3.742	1.146	102.466	1.108	#NUM!	0.011
17	4.123	1.230	105.489	1.643	#NUM!	0.023
20	4.472	1.301	106.675	0.372	#NUM!	0.028
24	4.899	1.380	106.039	1.659	#NUM!	0.025

Table 58 Exponential value of DS microtablets which prepared from punch 2.00 mm at 400 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.231	-1.225	-1.105	-1.187	0.071
slope(n)	1.586	1.589	1.439	1.538	0.086
k	0.059	0.060	0.079	0.066	0.011
r2	0.971	0.962	0.936	0.957	0.018

Table 59 Percentage of DS release from microtablets which prepared from punch 2.00 mm at 800 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f800	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.346	0.001	2.001	#NUM!
0.5	0.707	-0.301	0.710	0.158	1.997	-2.148
1	1.000	0.000	1.225	0.127	1.995	-1.912
1.5	1.225	0.176	2.481	0.179	1.989	-1.605
2	1.414	0.301	3.211	0.176	1.986	-1.493
2.5	1.581	0.398	25.679	0.846	1.871	-0.590
3	1.732	0.477	40.915	1.585	1.771	-0.388
3.5	1.871	0.544	51.838	2.112	1.683	-0.285
4	2.000	0.602	59.264	2.281	1.610	-0.227
4.5	2.121	0.653	66.058	1.770	1.531	-0.180
5	2.236	0.699	71.821	2.219	1.450	-0.144
6	2.449	0.778	80.205	1.547	1.297	-0.096
7	2.646	0.845	86.852	1.089	1.119	-0.061
8	2.828	0.903	90.378	0.935	0.983	-0.044
10	3.162	1.000	96.213	0.937	0.578	-0.017
12	3.464	1.079	100.624	0.192	#NUM!	0.003
14	3.742	1.146	104.596	1.517	#NUM!	0.020
17	4.123	1.230	106.712	1.430	#NUM!	0.028
20	4.472	1.301	106.959	0.552	#NUM!	0.029
24	4.899	1.380	107.116	1.827	#NUM!	0.030

Table 60 Exponential value of DS microtablets which prepared from punch 2.00 mm at 800 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.292	-1.290	-1.311	-1.298	0.011
slope(n)	1.801	1.765	1.773	1.780	0.019
k	0.051	0.051	0.049	0.050	0.001
r2	0.958	0.964	0.961	0.961	0.003

Table 61 Percentage of DS release from microtablets which prepared from punch 2.00 mm at 1200 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f800	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.344	0.000	2.001	#NUM!
0.5	0.707	-0.301	0.497	0.091	1.998	-2.304
1	1.000	0.000	0.823	0.310	1.996	-2.085
1.5	1.225	0.176	2.096	0.045	1.991	-1.679
2	1.414	0.301	2.966	0.106	1.987	-1.528
2.5	1.581	0.398	21.770	1.720	1.893	-0.662
3	1.732	0.477	35.119	2.362	1.812	-0.454
3.5	1.871	0.544	44.413	0.980	1.745	-0.352
4	2.000	0.602	51.928	1.209	1.682	-0.285
4.5	2.121	0.653	59.157	1.108	1.611	-0.228
5	2.236	0.699	64.925	0.683	1.545	-0.188
6	2.449	0.778	74.170	0.497	1.412	-0.130
7	2.646	0.845	80.366	1.262	1.293	-0.095
8	2.828	0.903	85.667	0.726	1.156	-0.067
10	3.162	1.000	93.227	2.652	0.831	-0.030
12	3.464	1.079	95.774	0.756	0.626	-0.019
14	3.742	1.146	99.011	0.766	-0.005	-0.004
17	4.123	1.230	103.104	1.388	#NUM!	0.013
20	4.472	1.301	104.960	0.377	#NUM!	0.021
24	4.899	1.380	107.451	0.851	#NUM!	0.031

Table 62 Exponential value of DS microtablets which prepared from punch 2.00 mm at 1200 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.212	-1.382	-1.268	-1.287	0.087
slope(n)	1.541	1.804	1.650	1.665	0.132
k	0.061	0.042	0.054	0.052	0.010
r2	0.963	0.965	0.954	0.961	0.006

Table 63 Percentage of DS release from microtablets which prepared from punch 2.25 mm at 400 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f400	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.342	0.001	2.001	#NUM!
0.5	0.707	-0.301	0.543	0.214	1.998	-2.265
1	1.000	0.000	1.405	0.080	1.994	-1.852
1.5	1.225	0.176	2.602	0.061	1.989	-1.585
2	1.414	0.301	3.530	0.170	1.984	-1.452
2.5	1.581	0.398	21.130	1.675	1.897	-0.675
3	1.732	0.477	32.615	2.370	1.829	-0.487
3.5	1.871	0.544	43.007	2.266	1.756	-0.366
4	2.000	0.602	49.019	2.188	1.707	-0.310
4.5	2.121	0.653	54.975	2.372	1.653	-0.260
5	2.236	0.699	61.203	2.429	1.589	-0.213
6	2.449	0.778	66.927	4.250	1.519	-0.174
7	2.646	0.845	74.082	4.436	1.414	-0.130
8	2.828	0.903	82.158	3.087	1.251	-0.085
10	3.162	1.000	89.494	1.083	1.021	-0.048
12	3.464	1.079	96.102	0.771	0.591	-0.017
14	3.742	1.146	99.956	3.077	-1.357	0.000
17	4.123	1.230	102.426	1.160	#NUM!	0.010
20	4.472	1.301	103.141	0.859	#NUM!	0.013
24	4.899	1.380	101.971	1.189	#NUM!	0.008

Table 64 Exponential value of DS microtablets which prepared from punch 2.25 mm at 400 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.220	-1.165	-1.284	-1.223	0.059
slope(n)	1.480	1.431	1.557	1.489	0.063
k	0.060	0.068	0.052	0.060	0.008
r^2	0.980	0.977	0.979	0.979	0.001

Table 65 Percentage of DS release from microtablets which prepared from punch 2.25 mm at 800 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f800	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.345	0.001	2.001	#NUM!
0.5	0.707	-0.301	0.734	0.123	1.997	-2.134
1	1.000	0.000	1.161	0.115	1.995	-1.935
1.5	1.225	0.176	2.143	0.278	1.991	-1.669
2	1.414	0.301	3.141	0.161	1.986	-1.503
2.5	1.581	0.398	22.141	3.408	1.891	-0.655
3	1.732	0.477	33.810	4.891	1.821	-0.471
3.5	1.871	0.544	45.109	5.320	1.740	-0.346
4	2.000	0.602	50.828	6.266	1.692	-0.294
4.5	2.121	0.653	57.987	4.358	1.623	-0.237
5	2.236	0.699	64.740	2.858	1.547	-0.189
6	2.449	0.778	73.785	1.608	1.419	-0.132
7	2.646	0.845	79.612	1.585	1.309	-0.099
8	2.828	0.903	84.371	0.939	1.194	-0.074
10	3.162	1.000	92.357	0.354	0.883	-0.035
12	3.464	1.079	98.334	1.800	0.222	-0.007
14	3.742	1.146	100.355	0.372	#NUM!	0.002
17	4.123	1.230	103.883	0.550	#NUM!	0.017
20	4.472	1.301	104.438	1.570	#NUM!	0.019
24	4.899	1.380	101.882	1.077	#NUM!	0.008

Table 66 Exponential value of DS microtablets which prepared from punch 2.25 mm at 800 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.146	-1.119	-1.390	-1.219	0.149
slope(n)	1.453	1.367	1.723	1.514	0.186
k	0.071	0.076	0.041	0.063	0.019
r^2	0.947	0.953	0.979	0.960	0.017

Table 67 Percentage of DS release from microtablets which prepared from punch 2.25 mm at 1200 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f1200	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.343	0.001	2.001	#NUM!
0.5	0.707	-0.301	0.278	0.052	1.999	-2.556
1	1.000	0.000	0.936	0.043	1.996	-2.029
1.5	1.225	0.176	2.256	0.122	1.990	-1.647
2	1.414	0.301	3.294	0.078	1.985	-1.482
2.5	1.581	0.398	23.258	0.525	1.885	-0.633
3	1.732	0.477	35.375	1.181	1.810	-0.451
3.5	1.871	0.544	44.915	1.974	1.741	-0.348
4	2.000	0.602	52.319	1.585	1.678	-0.281
4.5	2.121	0.653	58.323	1.998	1.620	-0.234
5	2.236	0.699	62.793	2.247	1.571	-0.202
6	2.449	0.778	70.448	2.572	1.471	-0.152
7	2.646	0.845	76.588	2.136	1.369	-0.116
8	2.828	0.903	80.127	1.908	1.298	-0.096
10	3.162	1.000	86.423	1.514	1.133	-0.063
12	3.464	1.079	89.723	0.290	1.012	-0.047
14	3.742	1.146	95.867	0.808	0.616	-0.018
17	4.123	1.230	98.729	1.135	0.104	-0.006
20	4.472	1.301	101.586	1.656	#NUM!	0.007
24	4.899	1.380	102.474	0.799	#NUM!	0.011

Table 68 Exponential value of DS microtablets which prepared from punch 2.25 mm at 1200 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.140	-1.143	-1.160	-1.148	0.011
slope(n)	1.420	1.380	1.412	1.404	0.021
k	0.072	0.072	0.069	0.071	0.002
r^2	0.951	0.959	0.956	0.956	0.004

Table 69 Percentage of DS release from microtablets which prepared from punch 2.50 mm at 400 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f400	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.341	0.001	2.001	#NUM!
0.5	0.707	-0.301	0.535	0.208	1.998	-2.272
1	1.000	0.000	1.453	0.268	1.994	-1.838
1.5	1.225	0.176	2.590	0.240	1.989	-1.587
2	1.414	0.301	3.167	0.068	1.986	-1.499
2.5	1.581	0.398	21.492	1.185	1.895	-0.668
3	1.732	0.477	31.468	1.243	1.836	-0.502
3.5	1.871	0.544	40.218	2.520	1.777	-0.396
4	2.000	0.602	46.111	1.564	1.732	-0.336
4.5	2.121	0.653	51.478	1.551	1.686	-0.288
5	2.236	0.699	56.006	1.825	1.643	-0.252
6	2.449	0.778	64.577	1.528	1.549	-0.190
7	2.646	0.845	71.075	2.501	1.461	-0.148
8	2.828	0.903	76.471	2.708	1.372	-0.117
10	3.162	1.000	84.949	1.686	1.178	-0.071
12	3.464	1.079	92.051	1.853	0.900	-0.036
14	3.742	1.146	95.670	1.755	0.636	-0.019
17	4.123	1.230	101.332	0.896	#NUM!	0.006
20	4.472	1.301	105.957	1.632	#NUM!	0.025
24	4.899	1.380	108.797	0.956	#NUM!	0.037

Table 70 Exponential value of DS microtablets which prepared from punch 2.50 mm at 400 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.121	-1.202	-1.186	-1.170	0.043
slope(n)	1.299	1.379	1.392	1.356	0.050
k	0.076	0.063	0.065	0.068	0.007
r^2	0.954	0.968	0.966	0.963	0.007

Table 71 Percentage of DS release from microtablets which prepared from punch 2.50 mm at 800 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f800	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.348	0.000	2.002	#NUM!
0.5	0.707	-0.301	0.332	0.034	1.999	-2.479
1	1.000	0.000	0.815	0.092	1.996	-2.089
1.5	1.225	0.176	2.113	0.107	1.991	-1.675
2	1.414	0.301	3.047	0.052	1.987	-1.516
2.5	1.581	0.398	20.327	0.651	1.901	-0.692
3	1.732	0.477	30.874	1.488	1.840	-0.510
3.5	1.871	0.544	40.240	1.517	1.776	-0.395
4	2.000	0.602	47.478	2.059	1.720	-0.324
4.5	2.121	0.653	52.338	2.257	1.678	-0.281
5	2.236	0.699	58.086	2.456	1.622	-0.236
6	2.449	0.778	66.266	3.038	1.528	-0.179
7	2.646	0.845	73.131	2.891	1.429	-0.136
8	2.828	0.903	78.717	3.084	1.328	-0.104
10	3.162	1.000	87.336	2.922	1.103	-0.059
12	3.464	1.079	93.316	2.191	0.825	-0.030
14	3.742	1.146	97.215	2.442	0.445	-0.012
17	4.123	1.230	101.790	2.724	#NUM!	0.008
20	4.472	1.301	105.693	0.680	#NUM!	0.024
24	4.899	1.380	108.228	0.271	#NUM!	0.034

Table 72 Exponential value of DS microtablets which prepared from punch 2.50 mm at 800 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.259	-1.222	-1.238	-1.240	0.018
slope(n)	1.484	1.452	1.510	1.482	0.029
k	0.055	0.060	0.058	0.058	0.002
r^2	0.965	0.964	0.959	0.962	0.003

Table 73 Percentage of DS release from microtablets which prepared from punch 2.50 mm at 1200 lb in pH-change method

Time(hr)	SQRT(t)	Log(t)	Ave f1200	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.345	0.000	2.001	#NUM!
0.5	0.707	-0.301	0.503	0.090	1.998	-2.299
1	1.000	0.000	0.631	0.157	1.997	-2.200
1.5	1.225	0.176	1.954	0.091	1.991	-1.709
2	1.414	0.301	2.798	0.176	1.988	-1.553
2.5	1.581	0.398	18.192	1.029	1.913	-0.740
3	1.732	0.477	29.109	2.171	1.851	-0.536
3.5	1.871	0.544	36.679	2.377	1.802	-0.436
4	2.000	0.602	42.550	2.317	1.759	-0.371
4.5	2.121	0.653	48.826	2.547	1.709	-0.311
5	2.236	0.699	53.925	2.551	1.663	-0.268
6	2.449	0.778	62.805	3.071	1.570	-0.202
7	2.646	0.845	69.280	2.246	1.487	-0.159
8	2.828	0.903	75.697	2.552	1.386	-0.121
10	3.162	1.000	83.745	2.084	1.211	-0.077
12	3.464	1.079	90.250	2.454	0.989	-0.045
14	3.742	1.146	94.137	1.400	0.768	-0.026
17	4.123	1.230	102.194	1.532	#NUM!	0.009
20	4.472	1.301	107.323	1.119	#NUM!	0.031
24	4.899	1.380	106.007	0.636	#NUM!	0.025

Table 74 Exponential value of DS microtablets which prepared from punch 2.50 mm at 1200 lb in pH-change method

mechanism	1	2	3	ave	sd
intercept(logk)	-1.190	-1.195	-1.263	-1.216	0.041
slope(n)	1.328	1.358	1.393	1.360	0.032
k	0.065	0.064	0.055	0.061	0.006
r^2	0.945	0.948	0.959	0.951	0.007

Table 75 Percentage of DS release from microtablets formulation F1 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.348	0.000	2.002	#NUM!
0.5	0.707	-0.301	0.332	0.034	1.999	-2.479
1	1.000	0.000	0.815	0.092	1.996	-2.089
1.5	1.225	0.176	2.113	0.107	1.991	-1.675
2	1.414	0.301	3.047	0.052	1.987	-1.516
2.5	1.581	0.398	20.327	0.651	1.901	-0.692
3	1.732	0.477	30.874	1.488	1.840	-0.510
3.5	1.871	0.544	40.240	1.517	1.776	-0.395
4	2.000	0.602	47.478	2.059	1.720	-0.324
4.5	2.121	0.653	52.338	2.257	1.678	-0.281
5	2.236	0.699	58.086	2.456	1.622	-0.236
6	2.449	0.778	66.266	3.038	1.528	-0.179
7	2.646	0.845	73.131	2.891	1.429	-0.136
8	2.828	0.903	78.717	3.084	1.328	-0.104
10	3.162	1.000	87.336	2.922	1.103	-0.059
12	3.464	1.079	93.316	2.191	0.825	-0.030
14	3.742	1.146	97.215	2.442	0.445	-0.012
17	4.123	1.230	101.790	2.724	#NUM!	0.008
20	4.472	1.301	105.693	0.680	#NUM!	0.024
24	4.899	1.380	108.228	0.271	#NUM!	0.034

Table 76 Exponential value of DS microtablets from formulation F1

mechanism	1	2	3	ave	sd
intercept(logk)	-0.947	-1.023	-1.011	-0.993	0.041
slope(n)	0.969	1.043	1.062	1.024	0.049
k	0.113	0.095	0.097	0.102	0.010
n+1	1.969	2.043	2.062	2.024	0.049
r2	0.934	0.943	0.946	0.942	0.006

Table 77 Percentage of DS release from microtablets formulation F2 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.341	0.002	2.001	#NUM!
0.5	0.707	-0.301	0.372	0.137	1.998	-2.429
1	1.000	0.000	0.606	0.082	1.997	-2.217
1.5	1.225	0.176	1.293	0.033	1.994	-1.888
2	1.414	0.301	1.965	0.048	1.991	-1.707
2.5	1.581	0.398	18.375	1.905	1.912	-0.736
3	1.732	0.477	32.146	3.139	1.832	-0.493
3.5	1.871	0.544	47.304	4.801	1.722	-0.325
4	2.000	0.602	55.645	5.454	1.647	-0.255
4.5	2.121	0.653	61.783	5.600	1.582	-0.209
5	2.236	0.699	67.707	5.643	1.509	-0.169
6	2.449	0.778	75.662	5.892	1.386	-0.121
7	2.646	0.845	81.189	5.173	1.274	-0.091
8	2.828	0.903	86.391	5.023	1.134	-0.064
10	3.162	1.000	90.624	4.344	0.972	-0.043
12	3.464	1.079	95.958	3.650	0.607	-0.018
14	3.742	1.146	100.591	3.808	#NUM!	0.003
17	4.123	1.230	102.820	3.357	#NUM!	0.012
20	4.472	1.301	104.932	2.363	#NUM!	0.021
24	4.899	1.380	105.780	1.246	#NUM!	0.024

Table 78 Exponential value of DS microtablets from formulation F2

mechanism	1	2	3	ave	sd
intercept(logk)	-1.512	-1.461	-1.571	-1.513	0.055
slope(n)	2.118	2.021	2.087	2.074	0.050
k	0.031	0.035	0.027	0.031	0.004
R^2	0.940	0.954	0.952	0.949	0.008

Table 79 Percentage of DS release from microtablets formulation F3 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.337	0.000	2.001	#NUM!
0.5	0.707	-0.301	0.117	0.182	1.999	-2.931
1	1.000	0.000	0.068	0.029	2.000	-3.170
1.5	1.225	0.176	0.303	0.044	1.999	-2.518
2	1.414	0.301	0.675	0.111	1.997	-2.171
2.5	1.581	0.398	18.920	0.646	1.909	-0.723
3	1.732	0.477	35.074	1.953	1.812	-0.455
3.5	1.871	0.544	47.815	1.555	1.718	-0.320
4	2.000	0.602	58.679	4.151	1.616	-0.232
5	2.236	0.653	73.634	4.744	1.421	-0.133
6	2.449	0.699	82.401	3.696	1.245	-0.084
7	2.646	0.778	87.603	3.391	1.093	-0.057
8	2.828	0.845	91.544	3.073	0.927	-0.038
10	3.162	0.903	96.539	1.567	0.539	-0.015
12	3.464	1.000	99.940	2.130	-1.225	0.000
14	3.742	1.079	101.541	1.547	#NUM!	0.007
17	4.123	1.146	99.865	0.883	-0.869	-0.001
20	4.472	1.230	100.310	0.935	#NUM!	0.001
24	4.899	1.301	101.212	0.556	#NUM!	0.005

Table 80 Exponential value of DS microtablets from formulation F3

mechanism	1	2	3	ave	sd
intercept(logk)	-1.609	-1.667	-1.656	-1.645	0.031
slope(n)	2.296	2.433	2.462	2.399	0.089
k	0.025	0.022	0.022	0.023	0.002
R^2	0.974	0.954	0.971	0.968	0.011

Table 81 Percentage of DS release from microtablets formulation F4 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.340	0.001	2.001	#NUM!
0.5	0.707	-0.301	0.280	0.116	1.999	-2.553
1	1.000	0.000	0.821	0.093	1.996	-2.086
1.5	1.225	0.176	1.699	0.067	1.993	-1.770
2	1.414	0.301	2.536	0.078	1.989	-1.596
2.5	1.581	0.398	19.016	0.151	1.908	-0.721
3	1.732	0.477	29.925	0.833	1.846	-0.524
3.5	1.871	0.544	38.195	0.858	1.791	-0.418
4	2.000	0.602	45.422	0.859	1.737	-0.343
4.5	2.121	0.653	50.186	0.756	1.697	-0.299
5	2.236	0.699	55.294	0.822	1.650	-0.257
6	2.449	0.778	63.840	0.132	1.558	-0.195
7	2.646	0.845	70.552	0.763	1.469	-0.151
8	2.828	0.903	75.428	0.835	1.390	-0.122
10	3.162	1.000	83.383	1.029	1.221	-0.079
12	3.464	1.079	89.497	1.228	1.021	-0.048
14	3.742	1.146	94.779	1.080	0.718	-0.023
17	4.123	1.230	100.955	2.790	#NUM!	0.004
20	4.472	1.301	102.899	1.008	#NUM!	0.012
24	4.899	1.380	103.876	1.233	#NUM!	0.017

Table 82 Exponential value of DS microtablets from formulation F4

mechanism	1	2	3	ave	sd
intercept(logk)	-1.194	-1.179	-1.182	-1.185	0.008
slope(n)	1.343	1.335	1.324	1.334	0.010
k	0.064	0.066	0.066	0.065	0.001
R^2	0.950	0.930	0.951	0.944	0.012

Table 83 Percentage of DS release from microtablets formulation F5 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.346	0.001	2.001	#NUM!
0.5	0.707	-0.301	0.509	0.088	1.998	-2.293
1	1.000	0.000	0.526	0.077	1.998	-2.279
1.5	1.225	0.176	1.179	0.142	1.995	-1.928
2	1.414	0.301	1.769	0.260	1.992	-1.752
2.5	1.581	0.398	17.233	0.305	1.918	-0.764
3	1.732	0.477	27.205	0.229	1.862	-0.565
3.5	1.871	0.544	35.654	0.327	1.809	-0.448
4	2.000	0.602	42.627	0.311	1.759	-0.370
4.5	2.121	0.653	47.897	0.861	1.717	-0.320
5	2.236	0.699	52.778	0.894	1.674	-0.278
6	2.449	0.778	62.119	1.180	1.578	-0.207
7	2.646	0.845	67.363	1.368	1.514	-0.172
8	2.828	0.903	72.533	1.354	1.439	-0.139
10	3.162	1.000	80.389	1.354	1.293	-0.095
12	3.464	1.079	85.475	0.933	1.162	-0.068
14	3.742	1.146	91.821	1.345	0.913	-0.037
17	4.123	1.230	95.827	1.480	0.620	-0.019
20	4.472	1.301	98.119	0.650	0.274	-0.008
24	4.899	1.380	100.935	0.986	#NUM!	0.004

Table 84 Exponential value of DS microtablets from formulation F5

mechanism	1	2	3	ave	sd
intercept(logk)	-1.27155	-1.27451	-1.24379	-1.26329	0.016945137
slope(n)	1.440171	1.435496	1.381731	1.419193	0.032475151
k	0.053511	0.053148	0.057044	0.054539	0.002151722
R^2	0.952798	0.94656	0.954067	0.951308	0.004018183

Table 85 Percentage of DS release from microtablets formulation F6 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.347	0.001	2.002	#NUM!
0.5	0.707	-0.301	0.756	0.148	1.997	-2.122
1	1.000	0.000	1.301	0.134	1.994	-1.886
1.5	1.225	0.176	1.900	0.120	1.992	-1.721
2	1.414	0.301	2.441	0.110	1.989	-1.612
2.5	1.581	0.398	28.762	0.558	1.853	-0.541
3	1.732	0.477	46.984	0.867	1.724	-0.328
3.5	1.871	0.544	57.359	0.150	1.630	-0.241
4	2.000	0.602	66.606	0.985	1.524	-0.176
4.5	2.121	0.653	73.425	1.022	1.424	-0.134
5	2.236	0.699	79.357	1.540	1.315	-0.100
6	2.449	0.778	88.898	1.817	1.045	-0.051
7	2.646	0.845	95.410	1.768	0.662	-0.020
8	2.828	0.903	99.988	1.118	-1.929	0.000
10	3.162	1.000	104.323	0.594	#NUM!	0.018
12	3.464	1.079	106.198	0.672	#NUM!	0.026
14	3.742	1.146	106.351	0.320	#NUM!	0.027
17	4.123	1.230	107.930	0.213	#NUM!	0.033
20	4.472	1.301	107.861	0.663	#NUM!	0.033
24	4.899	1.380	109.240	1.758	#NUM!	0.038

Table 86 Exponential value of DS microtablets from formulation F6

mechanism	1	2	3	ave	sd
intercept(logk)	-1.337	-1.324	-1.389	-1.350	0.034
slope(n)	2.044	2.027	2.142	2.071	0.062
k	0.046	0.047	0.041	0.045	0.003
R^2	0.965	0.955	0.971	0.964	0.008

Table 87 Percentage of DS release from microtablets formulation F7 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.349	0.000	2.002	#NUM!
0.5	0.707	-0.301	0.493	0.105	1.998	-2.307
1	1.000	0.000	0.840	0.017	1.996	-2.076
1.5	1.225	0.176	1.535	0.015	1.993	-1.814
2	1.414	0.301	2.341	0.095	1.990	-1.631
2.5	1.581	0.398	18.097	0.459	1.913	-0.742
3	1.732	0.477	30.607	0.880	1.841	-0.514
3.5	1.871	0.544	38.850	1.335	1.786	-0.411
4	2.000	0.602	45.305	0.962	1.738	-0.344
4.5	2.121	0.653	51.389	1.602	1.687	-0.289
5	2.236	0.699	56.672	1.201	1.637	-0.247
6	2.449	0.778	65.473	1.881	1.538	-0.184
7	2.646	0.845	71.424	1.472	1.456	-0.146
8	2.828	0.903	76.665	1.334	1.368	-0.115
10	3.162	1.000	84.189	1.327	1.199	-0.075
12	3.464	1.079	89.657	1.638	1.015	-0.047
14	3.742	1.146	93.684	1.437	0.800	-0.028
17	4.123	1.230	98.432	1.724	0.195	-0.007
20	4.472	1.301	101.223	1.316	#NUM!	0.005
24	4.899	1.380	104.215	1.077	#NUM!	0.018

Table 88 Exponential value of DS microtablets from formulation F7

mechanism	1	2	3	ave	sd
intercept(logk)	-1.205	-1.213	-1.237	-1.218	0.017
slope(n)	1.374	1.407	1.409	1.397	0.020
k	0.062	0.061	0.058	0.060	0.002
R^2	0.934	0.931	0.935	0.934	0.002

Table 89 Percentage of DS release from microtablets formulation F8 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.340	0.000	2.001	#NUM!
0.5	0.707	-0.301	0.130	0.574	1.999	-2.887
1	1.000	0.000	0.054	0.188	2.000	-3.272
1.5	1.225	0.176	0.474	0.160	1.998	-2.325
2	1.414	0.301	0.884	0.157	1.996	-2.054
2.5	1.581	0.398	12.547	0.537	1.942	-0.901
3	1.732	0.477	20.450	0.552	1.901	-0.689
3.5	1.871	0.544	27.473	0.645	1.861	-0.561
4	2.000	0.602	32.004	0.698	1.832	-0.495
4.5	2.121	0.653	37.379	0.627	1.797	-0.427
5	2.236	0.699	41.809	0.554	1.765	-0.379
6	2.449	0.778	49.003	0.722	1.708	-0.310
7	2.646	0.845	54.603	0.593	1.657	-0.263
8	2.828	0.903	59.706	0.785	1.605	-0.224
10	3.162	1.000	67.444	0.420	1.513	-0.171
12	3.464	1.079	73.943	0.424	1.416	-0.131
14	3.742	1.146	80.655	0.333	1.287	-0.093
17	4.123	1.230	85.185	0.162	1.171	-0.070
20	4.472	1.301	90.613	0.802	0.973	-0.043
24	4.899	1.380	94.865	0.641	0.711	-0.023

Table 90 Exponential value of DS microtablets from formulation F8

mechanism	1	2	3	ave	sd
intercept(logk)	-1.307	-1.267	-1.310	-1.294	0.024
slope(n)	1.264	1.227	1.271	1.254	0.024
k	0.049	0.054	0.049	0.051	0.003
R^2	0.935	0.938	0.936	0.936	0.002

Table 91 Percentage of DS release from microtablets formulation F9 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.342	0.001	2.001	#NUM!
0.5	0.707	-0.301	0.499	0.102	1.998	-2.302
1	1.000	0.000	0.355	0.036	1.998	-2.450
1.5	1.225	0.176	0.646	0.014	1.997	-2.190
2	1.414	0.301	0.992	0.041	1.996	-2.003
2.5	1.581	0.398	12.079	0.166	1.944	-0.918
3	1.732	0.477	19.810	0.245	1.904	-0.703
3.5	1.871	0.544	26.386	0.436	1.867	-0.579
4	2.000	0.602	31.322	0.306	1.837	-0.504
4.5	2.121	0.653	36.574	0.479	1.802	-0.437
5	2.236	0.699	41.420	0.836	1.768	-0.383
6	2.449	0.778	48.614	0.582	1.711	-0.313
7	2.646	0.845	55.286	0.695	1.650	-0.257
8	2.828	0.903	60.460	1.010	1.597	-0.219
10	3.162	1.000	68.830	1.011	1.494	-0.162
12	3.464	1.079	75.599	0.856	1.387	-0.121
14	3.742	1.146	81.214	0.793	1.274	-0.090
17	4.123	1.230	88.670	1.663	1.054	-0.052
20	4.472	1.301	91.978	0.687	0.904	-0.036
24	4.899	1.380	95.400	1.111	0.663	-0.020

Table 92 Exponential value of DS microtablets from formulation F9

mechanism	1	2	3	ave	sd
intercept(logk)	-1.334	-1.336	-1.328	-1.333	0.004
slope(n)	1.304	1.299	1.304	1.302	0.003
k	0.046	0.046	0.047	0.046	0.000
R^2	0.944	0.942	0.944	0.944	0.001

Table 93 Percentage of DS release from microtablets formulation F10 in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.349	0.001	2.002	#NUM!
0.5	0.707	-0.301	0.010	0.139	2.000	-4.013
1	1.000	0.000	-0.149	0.026	2.001	#NUM!
1.5	1.225	0.176	0.064	0.053	2.000	-3.192
2	1.414	0.301	0.375	0.092	1.998	-2.426
2.5	1.581	0.398	9.818	0.315	1.955	-1.008
3	1.732	0.477	17.023	0.788	1.919	-0.769
3.5	1.871	0.544	23.855	0.996	1.882	-0.622
4	2.000	0.602	28.787	2.115	1.853	-0.541
4.5	2.121	0.653	33.549	1.506	1.823	-0.474
5	2.236	0.699	37.383	1.657	1.797	-0.427
6	2.449	0.778	44.968	2.133	1.741	-0.347
7	2.646	0.845	51.136	2.267	1.689	-0.291
8	2.828	0.903	55.924	1.856	1.644	-0.252
10	3.162	1.000	64.122	2.632	1.555	-0.193
12	3.464	1.079	70.727	2.851	1.466	-0.150
14	3.742	1.146	77.892	2.206	1.345	-0.109
17	4.123	1.230	83.169	1.935	1.226	-0.080
20	4.472	1.301	89.513	2.288	1.021	-0.048
24	4.899	1.380	93.018	2.008	0.844	-0.031

Table 94 Exponential value of DS microtablets from formulation F10

mechanism	1	2	3	ave	sd
intercept(logk)	-1.427	-1.463	-1.431	-1.440	0.020
slope(n)	1.397	1.395	1.391	1.394	0.003
k	0.037	0.034	0.037	0.036	0.002
R^2	0.921	0.938	0.934	0.931	0.009

Table 95 Percentage of DS release from voltraren® SR in pH-change method

Time(hr)	SQRT(t)	log(t)	Ave	sd	Log% drug remained	Log(fraction)
0	0.000	#NUM!	-0.346	0.000	2.002	#NUM!
0.5	0.707	-0.301	0.880	0.271	1.996	-2.055
1	1.000	0.000	0.130	0.065	1.999	-2.885
1.5	1.225	0.176	0.151	0.073	1.999	-2.821
2	1.414	0.301	0.108	0.059	2.000	-2.967
2.5	1.581	0.398	3.459	0.043	1.985	-1.461
3	1.732	0.477	5.948	0.077	1.973	-1.226
3.5	1.871	0.544	8.062	0.285	1.963	-1.094
4	2.000	0.602	10.083	0.677	1.954	-0.996
4.5	2.121	0.653	12.357	1.177	1.943	-0.908
5	2.236	0.699	14.922	1.703	1.930	-0.826
6	2.449	0.778	21.388	2.960	1.895	-0.670
7	2.646	0.845	28.892	3.375	1.852	-0.539
8	2.828	0.903	36.726	3.124	1.801	-0.435
10	3.162	1.000	46.900	2.304	1.725	-0.329
12	3.464	1.079	54.577	2.091	1.657	-0.263
14	3.742	1.146	61.529	1.533	1.585	-0.211
17	4.123	1.230	69.846	1.144	1.479	-0.156
20	4.472	1.301	75.879	1.214	1.382	-0.120
24	4.899	1.380	82.518	1.193	1.243	-0.083

Table 96 Exponential value of DS microtablets from formulation voltraren®

mechanism	1	2	3	ave	sd
intercept(logk)	-2.006	-1.992	-2.039	-2.012	0.024
slope(n)	1.623	1.667	1.702	1.664	0.040
k	0.010	0.010	0.009	0.010	0.001
n+1	2.623	2.667	2.702	2.664	0.040
R^2	0.986	0.992	0.995	0.994	0.004

Appendix D

Data in statistical process

1. The statistic test of flow rate for DS granule were prepared by various mesh size of sieve (#20, #25, #30)

Table 97 Multiple Comparisons of flow rate for DS granule were prepared by various mesh size of sieve (#20, #25, #30)

Dependent Variable: flow rate

	(I) mesh size	(J) mesh size	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Scheffe	#20	#25	-.099854(*)	.022912	.003	-.163723	-.035984
		#30	-.325668(*)	.022912	.000	-.389538	-.261799
	#25	#20	.099854(*)	.022912	.003	.035984	.163723
		#30	-.225815(*)	.022912	.000	-.289684	-.161945
	#30	#20	.325668(*)	.022912	.000	.261799	.389538
		#25	.225815(*)	.022912	.000	.161945	.289684

* The mean difference is significant at the .05 level.

2. The statistic test for hardness of DS microtablets from various the punches positions

Table 98 ANOVA test for hardness of DS microtablets from punch position P1, P2 and P3 which compressed at force 400 lb

HARDNESS	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1.353	2	.676	.316	.734
Within Groups	32.145	15	2.143		
Total	33.497	17			

Table 99 ANOVA test for hardness of DS microtablets from punch position P1, P2 and P3 which compressed at force 800 lb

HARDNESS	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2.037	2	1.019	.505	.613
Within Groups	30.262	15	2.017		
Total	32.299	17			

Table 100 ANOVA test for hardness of DS microtablets from punch position P1, P2 and P3 which compressed at force 1200 lb

HARDNESS	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.663	2	.331	.264	.772
Within Groups	18.835	15	1.256		
Total	19.498	17			

3. The statistic test for Kr of DS microtablets with various punches positions and force

Table 101 Multiple Comparisons test for the first-order release rate constant of DS microtablets that were prepared from different punch position (P1, P2 and P3)

Dependent Variable: KR

Scheffe

(I) POSITION	(J) POSITION	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
P1	P2	.004011	.0119554	.945	-.027865	.035888
	P3	-.004333	.0119554	.937	-.036210	.027543
P2	P1	-.004011	.0119554	.945	-.035888	.027865
	P3	-.008344	.0119554	.786	-.040221	.023532
P3	P1	.004333	.0119554	.937	-.027543	.036210
	P2	.008344	.0119554	.786	-.023532	.040221

Based on observed means

4. The statistic test for Kr of DS microtablets which were prepared from various the compression forces and punch sizes

Table 102 ANOVA test for study the effect of compression force on the first-order drug release rate of DS microtablets which were prepared by using punch size 2.00 mm

K (2.00 mm)	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.002	2	.001	32.262	.001
Within Groups	.000	6	.000		
Total	.002	8			

Table 103 Multiple comparison tests for study the effect of compression force on the first-order drug release rate of DS microtablets which were prepared by using punch size 2.00 mm

Dependent Variable: Kr (2.00 mm)

Scheffe

(I) Force	(J) Force	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
400 lb	800 lb	-.027900(*)	.0042704	.002	-.041596	-.014204
	1200 lb	.003333	.0042704	.748	-.010363	.017030
800 lb	400 lb	.027900(*)	.0042704	.002	.014204	.041596
	1200 lb	.031233(*)	.0042704	.001	.017537	.044930
1200 lb	400 lb	-.003333	.0042704	.748	-.017030	.010363
	800 lb	-.031233(*)	.0042704	.001	-.044930	-.017537

* The mean difference is significant at the .05 level.

Table 104 ANOVA test for study the effect of compression force on the first-order drug release rate of DS microtablets which were prepared by using punch size 2.25 mm

Kr (2.25 mm)	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.001	2	.000	1.664	.266
Within Groups	.001	6	.000		
Total	.002	8			

Table 105 ANOVA test for study the effect of compression force on the first-order drug release rate of DS microtablets which were prepared by using punch size 2.50 mm

Kr (2.50 mm)	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.000	2	.000	1.057	.404
Within Groups	.000	6	.000		
Total	.001	8			

Table 106 ANOVA test for study the effect of punch size on the first-order drug release rate of DS microtablets which were compressed at 400 lb

Kr (400 lb)	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.003	2	.001	9.398	.014
Within Groups	.001	6	.000		
Total	.004	8			

Table 107 Multiple comparison tests for study the effect of punch size on the first-order drug release rate of DS microtablets which were compressed at 400 lb

Dependent Variable: Kr (400 lb)
Scheffe

(I) Diameter	(J) Diameter	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
2.50 mm	2.25 mm	-.0323000	.01007832	.050	-.0646238	.0000238
	2.00 mm	-.0416333(*)	.01007832	.018	-.0739571	-.0093095
2.25 mm	2.50 mm	.0323000	.01007832	.050	-.0000238	.0646238
	2.00 mm	-.0093333	.01007832	.670	-.0416571	.0229905
2.00 mm	2.50 mm	.0416333(*)	.01007832	.018	.0093095	.0739571
	2.25 mm	.0093333	.01007832	.670	-.0229905	.0416571

* The mean difference is significant at the .05 level.

Table 108 ANOVA test for study the effect of punch size on the first-order drug release rate of DS microtablets which were compressed at 800 lb

Kr (800 lb)	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.006	2	.003	25.722	.001
Within Groups	.001	6	.000		
Total	.006	8			

Table 109 Multiple comparison tests for study the effect of punch size on the first-order drug release rate of DS microtablets which were compressed at 800 lb

Dependent Variable: Kr (800lb)
Scheffe

(I) Diameter	(J) Diameter	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
2.50 mm	2.25 mm	-.033800(*)	.0084812	.021	-.061001	-.006599
	2.00 mm	-.060700(*)	.0084812	.001	-.087901	-.033499
2.25 mm	2.50 mm	.033800(*)	.0084812	.021	.006599	.061001
	2.00 mm	-.026900	.0084812	.052	-.054101	.000301
2.00 mm	2.50 mm	.060700(*)	.0084812	.001	.033499	.087901
	2.25 mm	.026900	.0084812	.052	-.000301	.054101

* The mean difference is significant at the .05 level.

Table 110 ANOVA test for study the effect of punch size on the first-order drug release rate of DS microtablets which were compressed at 1200 lb

Kr (1200 lb)	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.002	2	.001	17.222	.003
Within Groups	.000	6	.000		
Total	.003	8			

Table 111 Multiple comparison tests for study the effect of punch size on the first-order drug release rate of DS microtablets which were compressed at 1200 lb

Dependent Variable: Kr (1200 lb)
Scheffe

(I) DI	(J) DI	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
2.50 mm	2.25 mm	-.020700	.0065717	.054	-.041777	.000377
	2.00 mm	-.038533(*)	.0065717	.003	-.059610	-.017456
2.25 mm	2.50 mm	.020700	.0065717	.054	-.000377	.041777
	2.00 mm	-.017833	.0065717	.090	-.038910	.003244
2.00 mm	2.50 mm	.038533(*)	.0065717	.003	.017456	.059610
	2.25 mm	.017833	.0065717	.090	-.003244	.038910

* The mean difference is significant at the .05 level.

Table 112 The f_2 analysis of the release profiles of DS microtablets which were prepared from various compression forces at punch size 2.50, 2.25 and 2.00 mm

	2.50 mm			2.25 mm			2.50 mm		
	400*800	800*1200	400*1200	400*800	800*1200	400*1200	400*800	800*1200	400*1200
f_2	87.013	71.947	77.887	71.587	79.927	77.391	69.920	59.868	76.197

Table 113 The f_2 analysis of the release profiles of DS microtablets which were prepared from various punch sizes at force of 400, 800, and 1200 lb

	400 lb			800 lb			1200 lb		
	2.00*2.25	2.25*2.50	2.00*2.50	2.00*2.25	2.25*2.50	2.00*2.50	2.00*2.25	2.25*2.50	2.00*2.50
f_2	59.395	72.545	50.779	57.933	63.376	45.947	76.871	55.597	51.486

Appendix E

Morphology of diclofenac sodium

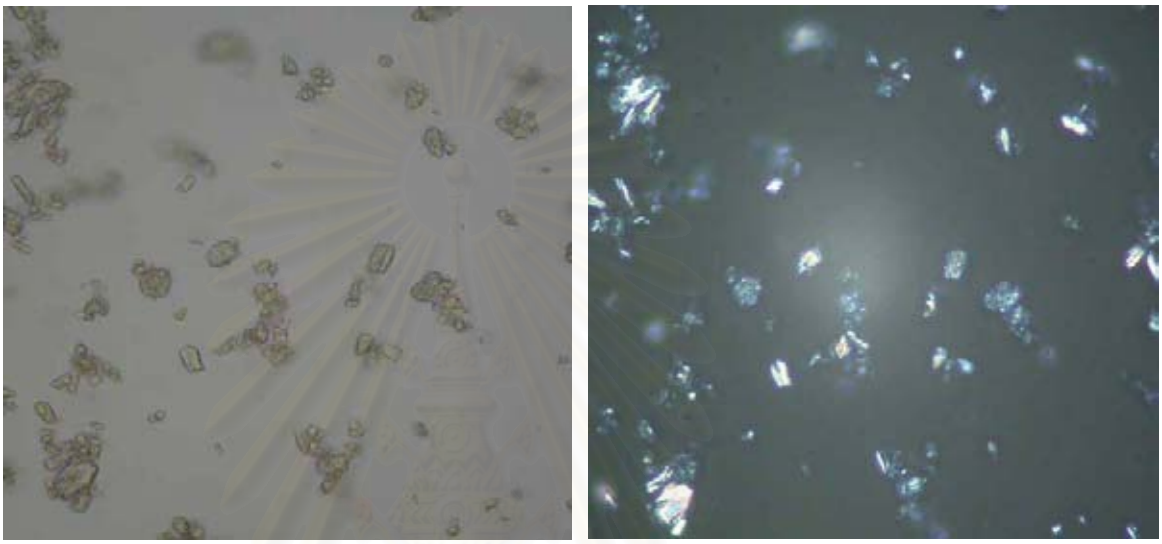


Figure 65 Crystal habit of diclofenac sodium

VITA

Miss Surawee Chantorn was born on March 16, 1977. She got her degree in Bachelor of Science in Pharmacy in 1999 from Faculty of Pharmacy, Silpakorn University, Sanam Chandra Palace, Nakhon Phathom, Thailand. After graduated she worked as a pharmacist in Bungsamphan Hospital for 1 year. In 2001, she entered the Master's Degree program in Manufacturing Pharmacy of Chulalongkorn University.