DEVELOPMENT OF NON-EFFERVESCENT GASTRIC FLOATING TABLET BY USING SHELLAC AND SHELLAC DERIVATIVES

By

Mr. Noppadol Chongcherdsak

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree

Doctor of Philosophy Program in Pharmaceutical Technology

Graduate School, Silpakorn University

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การพัฒนายาเม็ดลอยตัวในกระเพาะอาหารชนิดไม่เกิดก๊าซฟองฟู่
โดยใช้เชลแล็กและอนุพันธ์ของเชลแล็ก

โดย

นายนพดล จงเจิดศักดิ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรดุษฎีบัณฑิต

สาขาวิชาเทคโนโลยีเภสัชกรรม

บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร

ปีการศึกษา 2559

The Graduate School, Silpakorn University has approved and accredited the thesis title of "Development of non – effervescent gastric floating tablet by using shellac and shellac derivatives" submitted by Mr. Noppadol Chongcherdsak as a partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Technology.

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51353803 : MAJOR : PHARMACEUTICAL TECHNOLOGY
KEY WORDS : SHELLAC / SHELLAC DERIVATIVES / GASTRIC FLOATING TABLET / MATRIX TABLET / THEOPHYLLINE
NOPPADOL CHONGCHERDSAK : DEVELOPMENT OF NON-EFFERVESCENT GASTRIC FLOATING TABLET BY USING SHELLAC AND SHELLAC DERIVATIVES. THESIS ADVISOR : ASSOC. PROF. SONTAYA LIMMATVAPIRAT, Ph.D. 174 pp.

The objective of this study was to develop intra gastric floating tablets by using shellac and it's derivatives as polymers for controlling of drug release. For preparing of shellac derivatives, shellac was partially hydrolyzed with 0.1 N NaOH to form hydrolyzed shellac while shellac salts were fabricated through salt formation with either ammonia or the combination of meglumine and ammonia at the ratio 40 to 60. Shellac and it's derivatives were subsequently used as matrix forming agent in tablets that prepared by direct compression method. The effects of polymer content and annealing temperature on tableting properties including kinetic of drug release were studied. As a result, the physical properties of tablets such as hardness and disintegration time were obviously increased, at 80°C annealing temperature and the polymer content from 30%w/w. The polymerization of shellac and its derivatives to form the molecular network might be a possible explanation for retarded drug release. The main mechanism of drug release was the combination process between Fickian's diffusion and relaxation and approached the Fickian's diffusion as increasing amount of polymer and annealing temperature. With regard to the result from matrix tablets, the shellac was selected as candidate polymer for fabrication of floating matrix tablets. The influence of ammonium carbonate (pore forming agent) content on floating ability was studied. The result showed that ammonium carbonate was completely sublimated at 80°C and the porous structure within matrix tablets was observed. The density of porous tablets was less than 1 g/cm^3 resulting in immediately floating upon contacting with gastric fluid. As increasing amount of ammonium carbonate the floating time was prolonged. However, the floating time was limited to 4 h due to the penetration of water into the porous tablets. Addition of 5 – 10% w/w of HPMC, the floating time was increased to more than 12 h. The gelling structure of HPMC after contacting with gastric fluid could retard water penetration leading to increased floating time as well as sustained drug release.

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51353803 : สาขาวิชาเทคโนโลยีเภสัชกรรม
คำสำคัญ : เชลแล็ก / อนุพันธ์ของเชลแล็ก / ยาเม็ดลอยตัวในกระเพาะอาหาร / ยาเม็ดเมทริกซ์ / ธีโอฟิลีน

นพดล จงเจิดศักดิ์ : การพัฒนายาเม็ดลอยตัวในกระเพาะอาหารชนิดไม่เกิดก๊าซฟองฟู่โดยใช้เชลแล็กและอนุพันธ์ของเชลแล็ก. อาจารย์ที่ปรึกษาวิทยานิพนธ์ : รศ.ดร.ภก.สนทยา ลิ้มมัทวาภิรัติ์. 174 หน้า.

การวิจัยครั้งนี้มีวัตถุประสงค์เพื่อ พัฒนายาเม็ดลอยตัวในกระเพาะอาหารโดยใช้เชลแล็กและอนุพันธ์ของเชลแล็กเป็นพอลิเมอร์สำหรับควบคุมการปลดปล่อ ยยา การเตรียมอนุพันธ์ของเชลแล็กในรูปไฮโดรไลซ์เชลแล็กทำโดยการกระบวนการย่อยสลายด้วยน้ำบางส่วนด้วยสารละลา ยโซเดียมไฮดรอกไซด์ความเข้มข้น 0.1 นอร์มาลิตี้ในขณะที่เชลแล็กในรูปเกลือเตรียมโดยใช้แอมโมเนียหรือส่วนผลมของเมกูมีน :แอมโมเนีย ในอัตราส่วนร้อยละ 60:40 และนำเชลแล็กและอนุพันธ์ของเชลแล็กที่ได้มาเป็นสารก่อเมทริกซ์ในยาเม็ดที่เตรียมด้วยวิธีตอกตรง โดยศึกษาผลของปริมาณพอลิเมอร์และอุณหภูมิต่อการสมบัติของยาเม็ด รวมทั้งศึกษาจลนศาสตร์ของการปลดปล่อยยา ผลการทดสอบพบว่า ปริมาณเชลแล็กและอนุพันธ์ของเชลแล็กในยาเม็ดเมทริกซ์ ตั้งแต่ร้อยละ 30 โดยน้ำหนัก และความร้อนที่อุณหภูมิ 80 องศาเซลเซียสส่งผลต่อการเปลี่ยนแปลงสมบัติทางกายภาพของยาเม็ดอย่างชัดเจน เช่น ยาเม็ดมีความแข็งและระยะเวลาการแตกตัวมากขึ้น อาจเนื่องจากเชลแล็ก และอนุพันธ์ของเชลแล็กเกิดพอลิเมอไรเซชั่น ทำให้ โครงสร้างโมเลกุลเกิดเป็นร่างแห ปริมาณของเชลแล็กและอนุพันธ์ของเชลแล็ก รวมทั้งอุณหภูมิในการอบที่สูงขึ้น ช่วยชะลอการปลดปล่อยยาให้ช้าลง โดยกลไกหลักของการปลดปล่อยยาเป็นกลไกร่วมระหว่างการแพร่และการคลายตัวของยาเม็ดโดยมีลักษณะของการแพร่มากขึ้นเมื่อเพิ่มพอลิเมอร์และอุณหภูมิในการอบ ในส่วนของระบบยาเม็ดลอยตัวในกระเพาะอาหาร ได้เลือกเชลแล็กเป็นพอลิเมอร์สำหรับควบคุมการปลดปล่อยยา และศึกษาผลของปริ มาณแอมโมเนียมคาร์บอเนต (สารก่อรูพรุน) ต่อความสามารถในการลอยตัวของยาเม็ด พบว่าการให้ความร้อนแก่ยาเม็ดที่อุณหภูมิ 80 องศาเซลเซียส สามารถระเหิดแอมโมเนียมคาร์บอเนตได้หมด ทำให้โครงสร้างรูพรุนภายในยาเม็ดเมทริกซ์ ความหนาแน่นของยาเม็ดมีค่าน้อยกว่า 1 กรัมต่อลูกบาศ ก์เซนติเมตร ทำให้ยาเม็ดสามารถลอยตัว ได้ทันทีที่สัมผัสกับกรด ในกระเพาะอาหาร โดยปริมาณแอมโมเนียมคาร์บอเนตที่มากขึ้ นส่งผลให้ยาเม็ดลอยตัวนานขึ้น อย่างไรก็ตามยาเม็ด สามารถลอยตัวได้เพียง 4 ชั่วโมง เนื่องจากน้ำภายนอกสามารถแทรกเข้าไปในรูพรุน ของยาเม็ด การใส่ไฮดรอกซีโพ รพิลเมทิลเซลลูโลสที่ปริมาณร้อยละ 5-10 โดยน้ำหนัก ช่วยยื ดระยะเวลาการลอยตัวของยาเม็ดได้ นานกว่า 12 ชั่วโมง การพองตัวเป็นเจลของไฮดรอกซีโพรพิลเมทิลเซลลูโลสหลังจากสัมผัสกับกรด ในกระเพาะอาหาร ช่วยกีดขวางการแพร่ของน้ำเข้าสู่ยาเม็ด ช่วยเพิ่มระยะเวลาการลอยตัวและช่วยชะลอการปลดปล่อยยา

ACKNOWLEDGEMENTS

The success of my graduate study could not happen without support and invaluable advice from many people who contributed to my valuable experience.

I would like thanks my advisor, Associate Professor Dr. Sontaya Limmatvapirat, for his invaluable suggestion and guidance to adapt my ideas into the well scientific thought, for his assistance in the preparation of my thesis and research manuscript, his incredible creativity and interpretation skills have often inspired me, and especially for his tireless patience throughout my study.

I am very grateful to express my gratitude to Professor Dr. Katsuhide Terada, Professor Dr. Etsuo Yonemochi and Dr. Yasuo Yoshihashi for their valuable guidance and helpful comments, for providing exceptional research facilities and their supports during entire study in Japan.

I also would like to thank Associate Professor Dr. Prasert Akkaramongkolporn and Associate Professor Dr. Thawatchai Phaechamud from Faculty of Pharmacy, Silpakorn University and Associate Professor Dr. Srisagul Sungthongjeen from Faculty of Pharmaceutical Sciences, Naresuan University for their helpful suggestion and their valuable time being my thesis committees.

I would like to acknowledge Siam University for scholarship during my study in Thailand and in Toho University, Japan; the Thailand Toray Science Foundation; Graduate School, Silpakorn University and also the Silpakorn University Research and Development Institute for financial support.

I also record my special appreciation for the kind assistance, support and friendship granted me by all my friends, my colleagues and fellow graduate students in both Thailand and Japan. Finally, I wish to declare my infinite gratitude to my family for their endless love, encouragement, care and precious spiritual support throughout my life.

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LIST OF ABBREVIATIONS

Symbol	Definition
°C	degree Celsius
%w/w	percent weight by weight
AV	acid value
DDS	drug delivery system
DSC	differential scanning calorimetry
et al.	et alii (and others)
etc.	et cetara (Latin); and other thing/ and so on
FTIR	fourier transform infrared spectroscopy
GIT	gastrointestinal tract
GRDF	gastro retentive dosage form
h	Hour
HCl	hydrochloric acid
HPMC	hydroxyl propyl methyl cellulose
HS	hydrolyzed shellac
min	Minute
mm	Millimeter
N	Newton
n	release exponent
NMR	nuclear magnetic resonance
PXRD	powder X – ray diffractrometry
SA	shellac ammonium salt
SHL	Shellac
SMA	shellac meglumine/ammonium salt

CHAPTER 1

INTRODUCTION

1.1 Statement and significance of the research problem

Oral drug delivery system is the most preferred route of drug administration due to its common and convenience. However, the disadvantage of the conventional oral dosage forms is the frequency of dosing regimen which might lead to the fluctuation of the drug levels in the plasma [1]. To reduce the frequency of drug administration and improve patient compliance, the conventional dosage form might be modified. The controlled release drug delivery system has been developed in order to prolong action and also maintain drug levels. Nevertheless, it has shown some limitations. Regarding to previous study, the controlled release system could be easily removed from the gastrointestinal (GI) tract easily prior to the complete drug release as a result of fast gastric emptying time [2]. Therefore, a gastroretentive dosage form (GRDF) has been recently introduced as a mean for overcoming this problem. The system is particularly useful for drugs which are primarily absorbed in the duodenum and upper jejunum region, which is a result of delayed gastric emptying process. The classification of different modes of gastric retention has been listed; high density systems, expandable systems, superporous hydrogel systems, mucoadhesive systems, magnetic systems and floating systems [3 – 7].

With regard to previous researches, floating system has been widely investigated because of its convenient fabrication and prolonging gastric residence time[8, 9]. Floating system could be divided into 2 types which are effervescent floating and non-effervescent floating systems. Due to the bulk density of less than that of gastric fluid (< 1g/cm^3), it could float and remain buoyant in the stomach for a prolonged period of time with the potential continuous drug release [4].

Recently, various dosage forms of gastric floating drug delivery system such as microspheres, granules, films, powders, capsules, pills and tablets have been developed [3]. Polymer, especially synthetic polymer, has been employed as a major excipient for accomplishment of drug delivery. Besides synthetic polymer, the applying of natural polymer seems to be increased even in preparation of gastric floating system because of safety and biodegradability. Chitosan, a biocompatible natural product from crustacean, insect and certain fungi, was used as a polymer membrane for floating microcapsule [10]. Nevertheless, the major problem of chitosan is acid soluble [11]; thus, it cannot be represented as a good polymer for controlled drug release in gastric floating delivery system. Therefore, finding of alternative polymer is still necessary.

Shellac (SHL) is a natural polymer derived from lac insect (*Laccifer Lacca*), which lives on lac host trees found in Thailand, India, Burma and in a minor extent other Asian countries [12]. Due to its excellent film forming and protective property, SHL has been used for sealing and gloss coating of pharmaceutical products [13]. Another outstanding property of SHL is resistance to acid medium; thus, it might be used for enteric coating [14]. However, a major problem of SHL is the slow

dissolution rate in high pH aqueous environment, such as intestinal fluids. Therefore, several structural modifications of SHL molecules have been performed to solve this problem. Hydrolyzed shellac (HS) is one of the modified shellac which could be used for improving the rate of dissolution of coated tablet [15]. The salt formation of SHL is also an approach for enhancing the solubility of SHL film [16 – 18]. Recently, the development of polymer – based matrix tablet for controlled drug release tends to be increased due to ease of fabrication as comparing to polymer based coated tablet. SHL has been used as a polymer – based matrix forming agent for oral controlled release. Some studies showed that SHL could provide retard drug release, especially after annealing process [19]. During the heating of SHL, hydroxyl and carboxyl groups in its structure could polymerize and form more condensed network [19, 20]. Therefore, the effect of annealing temperature might be concerned. Another factor affecting drug release profile is the degree of polymerization. In addition to improving the solubility of SHL, composite salt formation is also used for controlling the degree of polymerization. SHL composite salt formed by 2-amino-2-methyl-1-propanol (AMP) and ammonium hydroxide (AMN) could inhibit the polymerization process by protecting at the carboxyl group [18], the composition of SHL and SHL – succinate might delay the polymerization process by masking at the hydroxyl group of SHL molecule [16]. According to the improved properties of SHL and its derivatives including resistance to acid medium and providing sustained drug release, they should be good alternative polymers for controlled drug release, especially for gastric floating dosage form.

The purpose of this study was to prepare shellac (SHL), hydrolyzed shellac (HS) and SHL salts and subsequently to use them as alternative polymers for controlling of drug release in non – effervescent gastric floating matrix tablet. The factors affecting drug release and floating behavior such as the annealing temperature, SHL and SHL derivatives content, the amount of pore forming agent were studied. In addition, characterization of SHL and its derivatives by several techniques including the determination of acid value, alcohol insoluble solid, FTIR spectroscopy, powder X – ray diffraction, thermal property and nuclear magnetic resonance spectroscopy were also evaluated.

1.2 Objectives of this research

1. To study the effects of annealing temperature and the amount of SHL and its derivatives on drug release from matrix tablet

2 To fabricate SHL and SHL derivatives – based matrix tablet for controlling drug release

3. To fabricate SHL – based floating matrix tablet for controlling drug release

CHAPTER 2

LITERATURE REVIEWS

2.1 Basic Physiology of Gastrointestinal tract

It is well recognized that the stomach can be used as a 'depot' for sustained – release (SR) dosage forms. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, is served as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying The process of gastric emptying occurred both during fasting and fed states; however, the pattern of motility differs markedly in the two states [3]. In the fasted state, it is characterized by an interdigestive series of electrical events which cycled both the stomach and small intestine every 2 – 3 h. This activity is called the inter – digestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases [2, 3].

1. Phase I (basal phase) lasts for 40 to 60 min with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.
3. Phase III (burst phase) lasts for 4 – 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested

material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4. Phase IV lasts for 0 – 5 min. It is a transition period of decreasing activity until the next cycle begins.

The difference between MMC and peristaltic waves is complicated. In the intestine, MMC usually occurs only in the small bowel in the fasted state, it occurs cyclically about every two hours and propagates over large distances of the bowel. In contrast, peristaltic waves in the intestine might occur in the fed or fasted state, they occur with no consistent frequency and usually die out over a few centimeters. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to fed state. This is also known as digestive motility pattern and comprises of continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm) which are propelled toward the pylorus in a suspension form. During the fed state, onset of MMC is delayed resulting in slowdown of gastric emptying rate [3, 21, 22].

2.2 Factor affecting gastric retention of dosage form

Gastric residence time (GRT) of an oral dosage form is affected by several factors. The rate of gastric emptying depends on two major factors, biologic and formulation factors.

Biologic factors

1. Gender

Generally females had slower gastric emptying rate than males

2. Age

Elderly people, especially those over 70 years, had a significant longer GRT

3. Posture

GRT could vary between supine and upright ambulatory states of the patient.

4. Food

GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit could be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. For caloric content, GRT could be increased by 4 to 10 hours with a meal that is high in proteins and fats. The frequency of feeding also affected to GRT. The GRT could increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

5. Drug intake

Intake of anticholinergics liked atropine and propantheline, opiates liked codeine and prokinetic agents liked metoclopramide and cisapride results in prolonged gastric emptying time.

Formulation factors

1. Density of dosage form

The density of dosage form also affects the gastric emptying rate. A buoyant dosage form has density of less than gastric fluids (< 1g/cm^3). Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for prolonged period [23, 24] or the high density of dosage form which nearly closes to 2.5 g/cm^3 is necessarily for significant prolongation of gastric residence time. High density dosage form sinks to the bottom of the stomach and withstand peristaltic wave [4, 25, 26].

2. Size of dosage form

Size is especially important in designing indigestible solid dosage forms. The human pyloric diameter is 12±7mm [27]. It is closed while the stomach is in fed state. The first mouthful thus passes directly into the duodenum, triggering closure of the pyloric sphincter. The pylorus then sorts the gastric contents, large particles are carried away by retrograde flow to the center of the stomach. Solids are evacuated by the pylorus slowly and regularly. Finally, indigestible materials, including solid pharmaceutical dosage forms, are evacuated by a Interdigestive Migration Myoelectric Complex (IMMC) peristaltic wave. Particles with diameter less than 7 mm are efficiently evacuated, and it is generally accepted that a diameter of more than 15 mm is necessary for useful prolongation of retention especially during the fasting state [4].

3. Shape of dosage form

The previous study reported that tetrahedron and ring shaped devices had a better gastric residence time as compared with other shapes [21].

4. Single or multiple unit formulation

Multiple unit formulations showed more predictable release profile and also avoided failure gastroretentive property when compared to single unit dosage forms that called “all or none” effect [24, 83].

2.3 Gastroretentive dosage forms

From the past to present, numerous oral delivery systems have been developed to act as drug reservoirs which the active drug could be slowly released over a period of time at a predetermined and controlled rate. However, the limitation of conventional and modified drug release system was the gastric residence time (GRT) of these dosage forms. Dosage form was diminished from GI tract before completely release of active ingredient and inability to restrain and localize the drug delivery system (DDS) within desired regions of gastrointestinal tract [4, 28, 29]. A gastro retentive dosage form (GRDF) could overcome this problem and was particularly useful for drugs that were primarily absorbed in the duodenum and upper jejunum segments [30, 31]. GRDF might be broadly classified into: high – density (sinking) systems, low – density (floating) systems, expandable systems, superporous hydrogel systems, mucoadhesive systems and magnetic systems [2, 4].

2.3.1 High density system

The density of gastric content was nearly close to 1 g/cm^3 [26]. When the patient was in the upright position, high – density dosage form sank to the bottom of the stomach in the antrum region (Fig 1.) where they became deposit in the folds of the antrum and withstood the peristaltic waves of the stomach wall. The required density of dosage form might be close to 2.5 g/cm^3 that was necessary for significant

prolongation of gastric residence time [32, 33]. The high density excipients including barium sulphate, zinc oxide, iron powder and titanium dioxide were investigated. Although encouraging results were reported in ruminants [34], the effectiveness in human subjects was not clearly indicated and the high density system was not yet marketed.

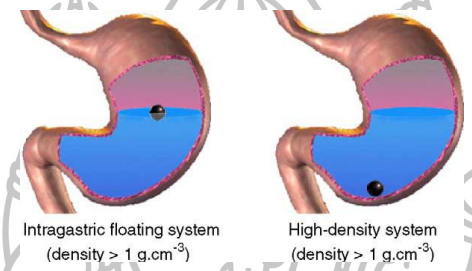

Figure 1 Schematic localization of an intragastric floating system and a high density system in the stomach.

Source : Singh, B.N. and Kim, K.H., "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention." Journal of Controlled Release 63(3): 235 – 259.

2.3.2 Expandable systems

The expandable GRDFs were composed of three configurations [35].

- A small (collapsed) configuration was convenient for oral intake

- Expanded form that was achieved in the stomach and thus prevented passage through the pyloric sphincter

- Another small form that was achieved in the stomach when retention was no longer required.

The expandable system was easily fabricated by inserting a large size of GRDF and folding into a pharmaceutical carrier *i.e.* gelatin capsule. The different geometric forms were compressed within a capsule (Figure 2). When dosage form mobilized to stomach, the carrier was dissolved and the GRDF unfolded to extended configuration [4, 35, 36].

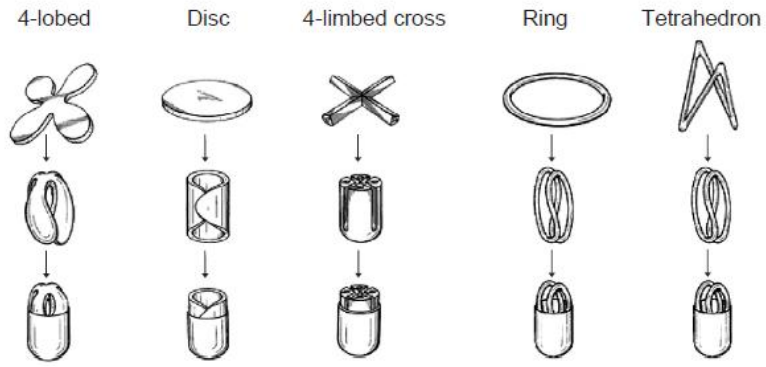

Figure 2 The different geometric forms of unfoldable system inserted into capsule
Source : Singh, B.N. and K.H. Kim. "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention." Journal of Controlled Release 63(3): 235-259.

2.3.3 Superporous hydrogels system

The picture of superporous hydrogels system is shown in Figure 3 – 4. The system indicated an average pore size of more than 100 µm and could swell to equilibrium size within a minute, due to rapid water uptake through numerous interconnected open pores [37, 38]. In addition to high swelling ratio, (~100 or more), the system had sufficient mechanical strength to withstand pressure by gastric contraction. Although the superporous hydrogels were one of swellable systems, they

differed from the conventional types in pore size. The pore size of conventional swellable systems was in the range of 10 nm and 10 μm which was very small as compared to that of superporous hydrogels. Additionally, the absorption of water by conventional hydrogel was a very slow process that took several hours to reach an equilibrium state [39, 40] and therefore might be repelled through pyloric sphincter before completely swelling.

The superporous hydrogels were divided into three different generations as shown in Figure 5. The first generation (conventional superporous hydrogels) was characterized by fast swelling, high swelling ratio and weak mechanical properties. The second generation (superporous hydrogels composites) was characterized by fast swelling, medium swelling ratio and improved mechanical properties. The third generation (superporous hydrogels hybrids) possessed elastic properties that could be highly useful in the development of gastrointestinal devices, as well as in other pharmaceutical and biomedical applications [37, 38, 41]. As compared with conventional superporous hydrogels, superporous hydrogels hybrids were not easily breakable when stretched. Due to elastic and rubbery properties, superporous hydrogel hybrids were therefore a better choice for various applications. The elastic water – swollen superporous hydrogel hybrids could resist various types of stresses, including tension, compression, bending and twisting.

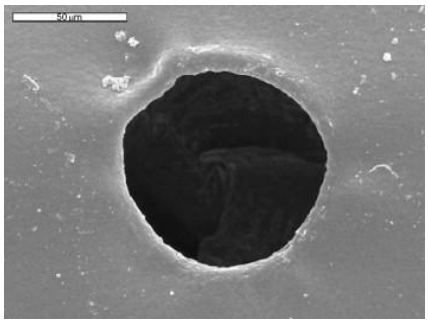

Figure 3 A typical superporous hydrogel

Source : Omidian, H., K. Park, and D. Paul. “Superporous Hydrogels for Drug Delivery Systems.” Comprehensive Biomaterials 563 – 576.

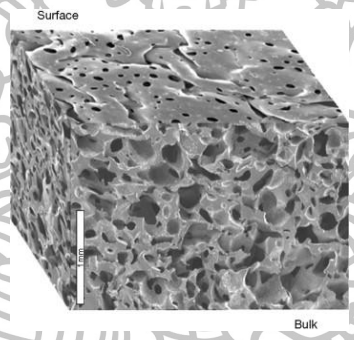

Figure 4 A three – dimensional porous structure of a typical superporous hydrogel

Source : Omidian, H., K. Park, and D. Paul. “Superporous Hydrogels for Drug Delivery Systems.” Comprehensive Biomaterials 563 – 576.

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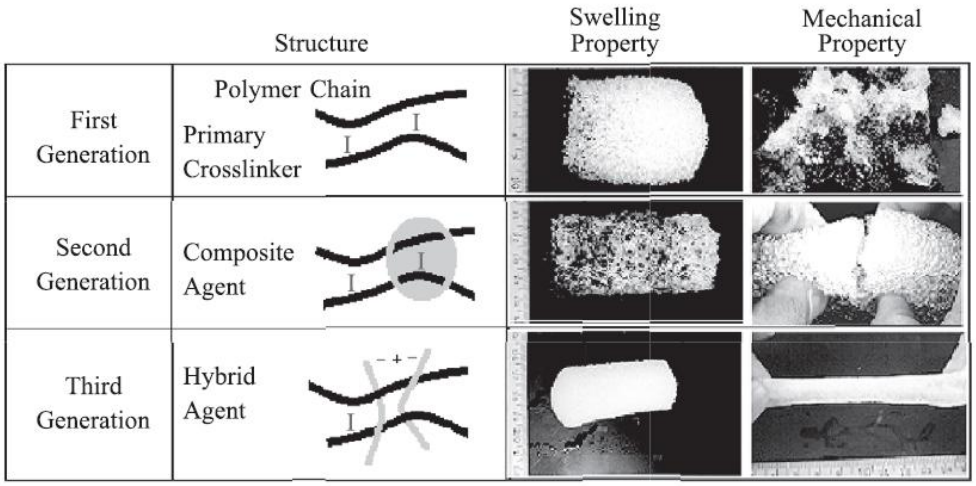


Figure 5 Structural, swelling and mechanical properties of various SPH generations.
Source : Omidian, H., J.G. Rocca, and K. Park. "Advances in superporous hydrogels." Journal of Controlled Release102(1): 3 – 12.

2.3.4 Mucoadhesive system

Mucoadhesive system has been developed to stick onto various types of mucosa, such as ophthalmic, vaginal, nasal, buccal, intestinal and gastric regions. There were six theories of adhesion, which had been adapted for the investigation of mucoadhesive system. Firstly, the electronic theory [43, 44] suggested that electron transfer occurred upon contact of adhering surfaces due to differences in their electronic structure. This was proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces. Secondly, the adsorption theory [43, 44] described the attachment of adhesives on the basis of hydrogen bonding and van der Waals' forces. It had been proposed that these forces were the main contributors to the adhesive interaction. The wetting theory [43 – 46] correlated the surface tension of the mucus and the mucoadhesive system with

the ability of the mucoadhesive system to swell and spread on the mucus layer and indicated that interfacial energy played an important role in mucoadhesion. By calculating the interfacial energy from the individual spreading coefficients of the mucus and the mucoadhesive system or by calculating a combined spreading coefficient, predictions of mucoadhesive performance could be obtained. The wetting theory was significant, since spreading of the mucoadhesive over the mucus was a prerequisite for the validity of all the other theories. The diffusion theory [43, 44, 47 – 49] concerned the interpenetration to a sufficient depth and physical entanglement of the protein and polymer chains of the mucus and the mucoadhesive system, depending on their molecular weight, degree of cross – linking, chain length, flexibility and spatial conformation. The mechanical theory [44, 50] explained that adhesion occurred from an interlocking of a liquid adhesive into irregularities on a rough surface. However, rough surfaces also provided an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which were thought to be more important in the adhesion process than in a mechanical effect. The last theory was the fracture theory [44]. It related the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion.

Materials commonly used for bioadhesion were poly(acrylic acid), chitosan, polymethyl vinyl ether/maleic anhydride copolymers, cholestyramine, tragacanth, sodium alginate, hydroxypropylmethyl cellulose, sephadex, sucralfate, polyethylene glycol, dextran, pectin, poly(alkylcyanoacrylate), poly(vinyl pyrrolidone) / poly(acrylic acid) interpolymer complexes, gelatin and polylactic acid. Even though some of these polymers were effective in producing bioadhesion, it was

very difficult to effectively maintain at target site because of the rapid turnover of mucus in the gastrointestinal tract [4, 51 – 59].

2.3.5 Magnetic system

This system was based on a simple idea: the dosage form contained a small internal magnet, which could be localized by the external magnet that placed on the abdomen over the position of the stomach outside after administration. Fujimori et al. formulated magnetic tablets containing 50%w/w ultra ferrite with hydroxypropylcellulose and cinnarizine. In beagle dog, the tablets remained in the stomach for 8 hr by the application of a magnetic field (1000 to 2600 G). Cinnarizine was extendedly localized at the absorbed area, resulting in the increased area under the plasma concentration – time – curve values (AUC0 – 24 h) increased [60]. Groning *et al.* proposed oral acyclovir depot tablets with internal magnets. The result of *in vivo* human studies showed that, in the presence of an extracorporeal magnet, the plasma concentrations of acyclovir were significantly higher than after 7, 8, 10 and 12 h. Furthermore, the mean $AUC_{0-24\ hr}$ was ~ 2800 ng h/mL with the external magnet and ~ 1600 ng h/mL without the external magnet [61]. Nagano *et al.* prepared magnetic granules containing bleomycin. The compositions of this system consisted of bioadhesive polymer and ultrafine ferrite. The advantage of the combination systems over bioadhesive property alone was that drug delivery system was localized in the target site and had sufficient time to attach the mucus membrane [62]. Although these systems seemed to be worked, the external magnet must be positioned with a degree of precision that might compromise with patient compliance.

2.3.6 Floating system

The systems had a bulk density lower than the gastric content. They remained buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Moreover, the residual system was emptied from the stomach. Gastric emptying was much more rapid than in the fasting state. Floating systems relied heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy [3, 63]. There were four approaches used in designing intragastric floating systems.

2.3.6.1 Hydrodynamically balanced systems: HBS™

Swellable polymer was a major excipient in HBS. Polymer which had been used in this system were hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (NaCMC), agar, carrageenans or alginic acid. The polymer was mixed with drug and incorporated in a gelatin capsule. The capsule was rapidly dissolved in the gastric fluid and the surface polymer was hydrated to produce a floating mass. Drug release was controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allowed water to penetrate the inner layers, maintaining surface hydration and buoyancy [64, 65]. Various approaches had been employed to improve efficacies of the floating HBS. Dorozynski *et al.* formulated HBS by using the combination between carrageenan and HPMC containing L – dopa as a model drug. The polymer mixture were able to maintain satisfactory floating properties for a sufficient long period [66]. Moreover, Krogel and Bodmeier designed an impermeable polypropylene cylinder, which were 10 – 15 mm

long and sealed on both sides by a matrix of hydrophilic polymer (HPMC) containing the drug. Entrapped air in the core of the cylinder provided the buoyancy [67].

2.3.6.2 Gas generating system

Floating ability of this system could be achieved by generation of gas bubbles. Gas forming agent was incorporated in the dosage forms and then covered with polymer outside. After immersion into gastric fluid, the fluid could diffuse through polymer and react with gas forming agent inside. CO_2 gas was then generated and entrapped in swollen polymer leading to floating of the drug system. An alternative technique was achieved through using of citric or tartaric acids for promoting CO_2 bubbles. The study reported that the optimal ratio of citric acid and sodium bicarbonate was 0.76 : 1 [68]. The approach had been used for single and multiple unit systems. In single unit systems, such as capsules or tablets, the floating lag time was less than 1 min and duration of floating was prolonged to 8 – 10 hr [69]. Bilayer or multilayer systems had also been designed [70, 71]. Drug and excipients could be formulated independently and the gas generating unit could be incorporated into any layers. However, the disadvantage of single unit was “all or none” effect [72, 73]. To avoid this problem, multiple units had been formulated. Sungthongjeen *et al.* fabricated floating pellets by using extrusion – spheronization processes. Pellets were coated with double layers of an inner effervescent layer (sodium bicarbonate) and an outer gas – entrapped polymeric membrane. Drug system could float over 24 hr [74]. Hamdani *et al.* also prepared floating pellets by different technique called melt pelletization. The melt pelletization was a solvent free process which granulation was obtained through the addition of an excipient that could be melting or softening at a relatively low temperature. After melting, the excipient acted as a binding liquid.

Good floating capabilities were obtained for formulations containing the gas – generating agent in both the inner matrix and the outer coating layers of the pellets [75]. The floating of multiple unit minitablets coated with insoluble acrylic polymer was also studied by Goole *et al.* The system consisted of a 3 mm levodopa containing gas generating core. The optimized coated minitablets could float within 20 min and remain buoyant for more than 13 hr [76]. The recent study used the combination technique between floating and adhesion process to ensure that drug system was localized in the stomach. Tadros developed drug delivery system with swelling, floating, and adhesive properties. Hydroxypropylmethylcellulose (HPMC K15M) and sodium alginate had been used as release – retard polymer. Sodium bicarbonate ($NaHCO_3$) or calcium carbonate ($CaCO_3$) had been used as a gas former. Tablets containing HPMC K15M (21.42%w/w), sodium alginate (7.14%w/w) and $NaHCO_3$ (20%w/w) or $CaCO_3$ (20%w/w) exhibited excellent floating properties, extended adhesion periods and sustained drug release characteristics [77]. The buoyancy characteristics of the system are shown in Figure 6 – 7.

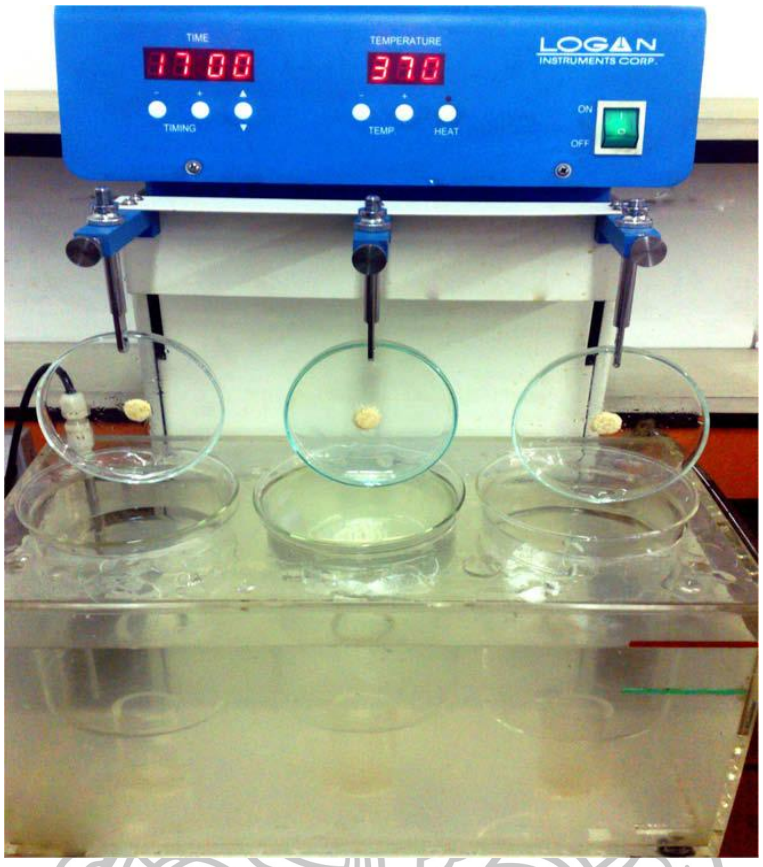


Figure 6 The *in vitro* adhesion study in a USP disintegration test apparatus

Source : Tadros, M.I., "Controlled – release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro – in vivo evaluation in healthy human volunteers." European Journal of Pharmaceutics and Biopharmaceutics 74(2): 332 – 339.

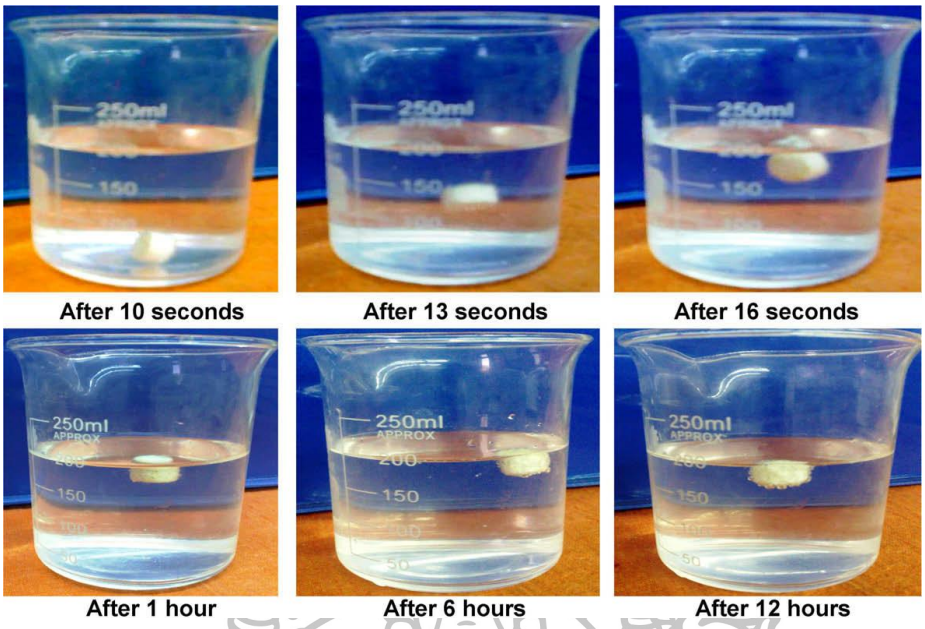


Figure 7 *In vitro* buoyancy study in 200 mL 0.1 N HCl

Source : Tadros, M.I., "Controlled – release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro – in vivo evaluation in healthy human volunteers." European Journal of Pharmaceutics and Biopharmaceutics 74(2): 332 – 339.

2.3.6.3 Raft – forming systems

The raft forming system was one of the approaches that involved the formulation of effervescent floating liquid with in situ gelling properties, which had been assessed for sustaining drug delivery and targeting [78]. The continuous layer containing CO_2 bubbles that called raft – forming systems could float on the gastric fluid due to lower bulk density as compared to gastric fluid. Thus, it increased gastric residence time resulting in prolonged drug delivery. As the system floated on the gastric contents, the drug was released slowly at the desired rate from

the system. Therefore, the system could increase gastroretention time while the better control of the fluctuations in plasma drug concentration was achieved [79].

2.3.6.4 Low – density systems

Lag time or time to float was the disadvantage of gas – generating system. Dosage form might be evacuated through pyloric sphincter before floating if the lag time was too long. To solve this problem, variety of the low density systems with immediate buoyancy had been developed. Most of them used low – density materials and fabricated in multiple unit systems, including, microballoons or hollow microspheres with low density core or hollow core inside [80, 81]. Streubel *et al.* prepared both single unit and multiple unit systems by using polypropylene foam powder. In case of single unit, floating matrix tablets had been established. The porous foam powder provided low density of tablet and the tablets showed a good buoyancy property for at least 8 h [82]. For multiple unit systems, a good in – vitro floating property of microparticles prepared by solvent evaporation method was observed [83]. Sher *et al.* also used low – density microporous polypropylene as a drug carrier in pulsatile floating drug delivery system. Drug was loaded onto porous particle by melt and solvent evaporation technique. Drug system could be floated over 6 h while the biphasic pattern of drug release profile was observed [84]. The low – density system of liquid paraffin entrapped alginate beads was also successfully prepared by emulsion gelation method Drug, liquid paraffin and other excipients were mixed and homogenized to obtain emulsions. The emulsions were then slowly dropped into calcium chloride solution to produce spherical beads. The density of drug system was less than 1 g/cm^3 because of inner porous structure [85]. Yao *et al.* also prepared the porous floating beads by using of poloxamer 188 and alginate as

foaming agent and foaming stabilizer, respectively. The foam solution was dropped into $CaCl_2$ to form beads. The core of beads was composed of uniform bubbles. The beads could immediately float on the surface gastric while the floating time of most beads were more than 6 hr [86].

Advantages of gastroretentive dosage forms (GRDF)

1. The retention of dosage forms in the stomach could enhance bioavailability of therapeutic agents when compared to non – gastroretentive dosage forms [87]. Klausner *et al.* showed the more efficient levodopa release of GRDF over non GRDF. Levodopa was slowly released from GRDF and maintained therapeutic level of drug plasma (500ng/mL) over 9 h. However, plasma concentration of levodopa from non GRDF was extremely high at the beginning and gradually dropped under therapeutic level within 4 h [88].

2. GRDF could reduce dosing frequency and improved patient adherence [30, 89].

3. GRDF could resist peristaltic wave of the stomach, resulting in prolong the time of dosage form in the stomach. This was benefit for local treatment of bacteria in stomach *i.e. Helicobacter pylori* or disorder related to stomach and small intestine [90 – 92].

4. GRDF minimized fluctuation of drug concentration and therefore reduced side effect and improved selectivity in receptor activation [64].

Limitation of gastroretentive dosage forms

In case of floating systems, they required a sufficiently high level of fluids in the stomach for the dosage form to float. However, this limitation could be solved by using the combination technique between floating and bioadhesive system

which could be adhered to the mucous lining of the stomach wall [77]. Alternatively, the dosage form might be administered with a glass full of water (200 – 250 mL) [3, 4].

2.4 *In vitro* floating properties evaluation

In vitro floating study of pharmaceutical dosage forms was carried out by the methods described in pharmacopoeia. Simulated gastric fluid with or without pepsin or 0.1 N HCl might be used as the testing solution [93 – 96]. Dissolution apparatus was used for evaluation of floating properties and drug release studies in single unit system. Floating lag time and duration of floating were visual observed by researcher. Arora *et al.* summarized the conditions for evaluation of floating drug system and dissolution performances in Table 1 [97]. For multiple unit system, two methods had been proposed for evaluation *i.e.* counting and resultant weight method. The counting method was based on determination of the percentage remaining of floating multiple unit system [75]. The method was described by Ichikawa *et al.* The accurate number of multiple unit system was immersed into 70 mL of 0.1 N HCl containing 0.05 %w/v polysorbate 20 in a 100 mL beaker. The beaker was then horizontal shaken at temperature of 37°C with speed of 100 cycles/min for 23 h. After that the photographs of the liquid surface in the beaker was taken and the number of floating multiple unit system was counted. The percentage of floating system was calculated compared to initial number of multiple unit system [98]. The resultant weight method was also used for elucidate floating capacity of drug system. The equipment called resultant weight apparatus (Figure 8) was invented by Timmerman and Moes. Drug system was placed in the basket and immersed in the fluid. The total

vertical force (F) was obtained by this method. It could be assumed that drug system had good floating capacities if the resultant weight values were still positives by this equation [75, 99, 100].

$$F = F_{buoy} - F_{grav}$$

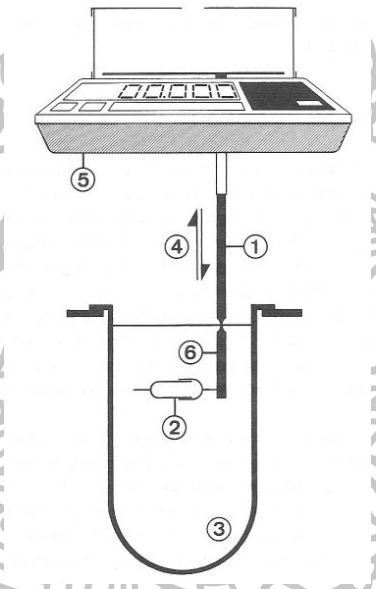


Figure 8 The resultant – weight measuring system

Source : J. Timmermans and A.J.Moes, "How well do floating dosage forms float?" International Journal of Pharmaceutics62: 207 – 216.

Table 1 *In Vitro* Floating and Dissolution Performance

Drug (Polymer Used)	Floating Media/Dissolution Medium and Method
Pentoxyfillin (HPMC K4 M)	500 mL of artificial gastric fluid pH 1.2 (without pepsin) at 100 rpm using USP XXIII dissolution apparatus. The time taken by the tablet to emerge on the water surface (floating lag time) and time until it floats on water surface was measured.
Amoxicillin beads (Calcium alginate)	For dissolution: 900 mL of deaerated 0.1 M HCl (pH 1.2) at 37°C ± 1°C in USP XXII dissolution tester at 50 rpm.
Ketoprofen (Eudragit S100 Eudragit RL)	20 mL of simulated gastric fluid without pepsin, 50 mg of floating microparticles in 50-mL beakers were shaken horizontally in a water bath. % age of floating micro particles was calculated.
	For dissolution: 900 mL of either 0.1 N HCl or the phosphate buffer (pH 6.8) at 37°C ± 0.1°C in USP dissolution apparatus (I) at 100 rpm.
Verapamil (Propylene foam, Eudragit RS, ethyl cellulose, poly methyl meth acrylate)	30 mL of 0.1 N HCl (containing 0.02% wt/wt Tween 20), pH 1.2. Floatation was studied by placing 60 particles into 30-mL glass flasks. Number of settled particles was counted.
Captopril (Methocel K4M)	900 mL of enzyme-free 0.1 N HCl (pH 1.2) in USP XXIII apparatus II (basket method) at 37°C at 75 rpm.
Theophylline (HPMC K4M, Polyethylene oxide)	0.1 N HCl in USP XXIII Apparatus II at 50 rpm at 37°C. Its buoyancy to upper 1/3 of dissolution vessel was measured for each batch of tablet.
Furosemide (β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol)	For dissolution: continuous flow through cell gastric fluid of pH 1.2, 45–50 m N/m by adding 0.02% Polysorbate 20 (to reduce the surface tension), the flow rate to provide the sink conditions was 9mL/min.
Aspirin, Griseofulvin, p-Nitro Aniline (polycarbonate, PVA)	For dissolution: 500 mL of simulated gastric and intestinal fluid in 1000-mL Erlenmeyer flask. Flasks were shaken in a bath incubator at 37°C.
Piroxicam (microspheres) (Polycarbonate)	For dissolution: 900 mL dissolution medium in USP paddle type apparatus at 37°C at 100 rpm.
Ampicillin (Sodium alginate)	For dissolution: 500 mL of distilled water, JP XII disintegration test medium No.1 (pH 1.2) and No.2 (pH 6.8) in JP XII dissolution apparatus with paddle stirrer at 50 rpm.
Diclofenac (HPC-L)	An aliquot of 0.1 g of granules was immersed in 40 mL of purified water in a vessel at 37°C. Dried granules were weighed and floating percentage of granules was calculated.
	For dissolution: flow sampling system (dissolution tester: DT-300, triple flow cell) followed by 900 mL of distilled water in JP XII with paddles at 37 °C ± 0.5°C at 100 rpm.
Sulphiride (CP 934P)	For dissolution: 500 mL of each JP XII disintegration test medium No. 1 (pH 1.2) and No. 2 (pH 6.8) in JP XII dissolution apparatus at 37° C at 100 rpm.
Amoxicillin trihydrate (HPC)	For dissolution: 500–1000 mL (adequate to ensure sink conditions) of citrate/phosphate buffer of variable pH or solution of HCl (pH 1.2) in Erweka DT 6 dissolution tester fitted with paddles.
Ibuprofen, Tranilast (Eudragit S)	For dissolution: 900 mL dissolution medium (disintegration test medium No. 1 (pH 1.2) and No. 2 (pH 6.8) as specified in JP XI and as corresponding to USP XXI, paddle method at 37°C at 100 rpm.
Isardipine (HPMC)	For dissolution: Method 1: 300 mL of artificial gastric fluid in a beaker, which was suspended in water bath at 37°C agitated by magnetic stirrer and by bubbling CO_2 free air. Method 2: 500/1000 mL of 0.1 M HCl and surfactant lauryl sulfate dimethyl ammonium oxide with rotating paddle at 50 rpm.
Potassium chloride (Metolose S.M. 100, PVP)	For dissolution: tablet was mounted onto the perspex holder except one face of the matrix was set flush with one face of the holder at 37°C and the other face of the tablet was prevented from the dissolution media by a rubber closure; good mixing was maintained in the receiver by a magnetic stirrer at 100 rpm.

Source : Arora S., J.A., Alka Ahuja, Roop K. Khar, and S. Baboota, "Floating Drug Delivery Systems: A Review". AAPS PharmSciTech**6**(3): 372 – 390**.**

2.5 Shellac

Shellac is a natural polymer that has been used in many fields, including food, agriculture, confectionary and pharmaceutical industries. Shellac is the final product that made from secretion of lac insect which is parasitic lived on tropical trees in Asia, especially in Thailand, Myanmar and India. *Tachardia lacca* was the first scientific name of the lac insect that had given by J.Kerr since 1782. The other names were *Laccifer lacca* (Kerr) and *Kerria lacca* [101].

Phylum	:	Arthropoda
Class	:	Insecta
Order	:	Hemiptera
Suborder	:	Homoptera
Super family	:	Coccoidea
Family	:	Lacciferidae
Genus	:	*Laccifer*
Species	:	*Lacca*

There are 85 species under 9 genera of lac insects found all over the world. *Laccifer lacca* (Kerr) is the commonest occurring species which secretes lac. For south – east Asia, the common species is *Kerria chinensis* [102].

2.5.1 Lac insect

Lac insect lived on the trees called host plants. It causes impermanent and recoverable damage to the host plant. There are about 30 varieties of host plant in Thailand *i.e. Samanea saman, Butea monosperma, Cajanus cajan, Schleichera oleosa, Combretum quadrangulare, Uncaria gambir, Dalbergia*

cochinchinensis, *Drypetes roxburghii*, *Zizyphus mauritiana*, *Flemingia lineate*, *Ficus racemosa*.

Lac insect has life cycle around half year. The four stages of life cycle are egg, instars nymph, pupa and adult. Female lac insect lay approximate 200 – 500 eggs in each time. Only few hours crawlers come out from eggs. The appearance of nymph might continue for 5 weeks. Nymphs, which live on the sap of the host plant, insert their suctorial beaks into plant tissue and suck the sap, juices and nourishment. Afterward, they grow in size and resinous material is secreted from the nymph body. A number of crawlers locate side by side. Their own bodies are covered with lac in the so called "Cell" and completely encased the twig. After exposure to air, lac is harden that protects lac insect from predators. The lac insect larvae become mature after three molts in about 8 weeks. Only the male transforms to a complete another form; it losses beak and developed antennae, legs and a pair of wings. While the female retains her mouth parts but fails to develop any wing, eye and appendages. After fertilization, the increasing of female size is suitable for growing number of eggs and she assumes a sac like appearance. The female die, the eggs hatch, the crawlers shift to a close uninfected area of the twig, and the process was repeated [103].

2.5.2 Extraction of Lac

Lac cultivation is simple and do not need any large investment requirement. Harvesting is done by removing the lac encrusted twigs. The raw lac is known as "stick lac". The stick lac composes of resin, insect body, sand, coloring matter (lac dye) and twig debris. The stick lac become lump and the quality of lac is decreased by long term storage, so this problem could protect by keeping high

moisture content of stick lac or converting into “seed lac”. Seed lac, which is granular lac and prepared by grinding stick lac in crude mortar, sieving to remove sand and washing to wash out the lac dye and twig debris. The general appearances of seed lac are yellow or reddish brown and small seed (about 10 mesh or smaller). In addition, the seed lac is washed, melted, spread out in a thin layer film and dried. The product obtained is called “shellac”.

2.5.3 Shellac processing

There were three methods for shellac preparing; handmade process, heat process and solvent process.

2.5.3.1 Handmade process

Handmade process is the traditional process. Seed lac is filled into long cloth bag and melted by charcoal – fired hearth. Molten lac is squeezed from twisting the bag and spreaded into thin sheets. Moreover, the molten lac is allowed to solidify in form of discs, and then it is known as “button Lac”.

2.5.3.2 Heat process

This process was step up from handmade process. This process is utilized in manufacturing level. The seed lac is liquefied by hot stream and the molten lac was filtered by hydraulic pressure machine. Shellac sheet is prepared by drying the filtered molten lac and then broken it in the form of pieces called “flakes”.

2.5.3.3 Solvent process

Seed lac is dissolved in ethanol and then impurity and wax are removed by filtering through filter. Alcohol is recovered and the residue shellac is

stretched with a roller. The shellac products from this process are dewaxed platina, dewaxed blonde, dewax lemon, or dewax orange shellac.

According to the United State Pharmacopoeia – National Formulary (USP 38 – NF 33), shellac is categorized into four grades: orange, dewaxed orange, regular bleached, and refined wax-free bleached shellac.

2.5.4 Properties of shellac

2.5.4.1 Low water vapor permeability

Moisture – protective polymer should prepare film which could prevent water vapor from entering the coated products. Several studies reported that shellac had the better effective barrier to water vapor, as compared to other polymers [104, 105]. Hence this characteristic of shellac is the important reason for utilizing shellac as excellent moisture barrier.

2.5.4.2 pH – dependent solubility

The structure of shellac consists of carboxylic groups, resulting in lower solubility at low pH of medium and beginning to dissolve at a higher pH (above pH 7.0). Therefore, shellac could be applied as enteric coating polymer. The solubility of shellac in various solvents is shown in Table 2 [106].

Table 2 Solubility of shellac in various solvents

Solvent	**Solubility at 20°C**
Alkalis	Soluble
Aqueous ethanolamine solution	Soluble
Benzene	1 in 10
Ethanol	1 in 2
Ethanol (95%)	1 in 1.2 (very slowly soluble)
Ether	1 in 8
Hexane	Practically insoluble
Propylene glycol	1 in 10
Water	Practically insoluble

Source : Rowe, R.C., "Handbook of pharmaceutical excipients". Royal Pharmaceutical Society of Great Britain: 98 – 102.

2.5.4.3 Gloss [102, 106]

Gloss is an optical property, which was based on the interaction of light with physical characteristics of a surface. The factors affecting gloss are refractive index, surface topography and angle of incident light. Shellac has gloss properties due to high refractive index (1.5210 – 1.5272) and therefore has been extensively applied for coating of woodwork and fruit.

2.5.4.4 Low thermal conductivity [102, 106]

Shellac had a low thermal conductivity. It also had excellent dielectric properties, high dielectric strength, a low dielectric constant and a good tracking resistance. Shellac was used as an insulator for several decades.

2.5.4.5 Good adhesive property [102, 106]

Alkaline solution and alcoholic solution of shellac provided spreadable films of high adhesive power. Shellac films exhibited well to excellent adhesion to a wide range of surface except Teflon and silicone coated glass.

Based on properties of shellac, it had been used in many fields, including pharmaceutical industries. In the past, shellac only used in sub – coating process but nowadays shellac trend to be valuable polymer for manufacturing. Due to the outstanding resistant to acidic medium, shellac is used as a protective polymer for enteric coating. According to environmental friendly policy, various studies tried to use non organic solvent for preparing shellac film. Chang *et al.* [107] prepared shellac pseudolatex for enteric coating pellets. Shellac was dissolved in the mixture solution between water and miscible organic solvent and then directly dispersed the resin solution in deionized water. Organic solvent and part of water were removed in fume hood. Krause *et al.* [108] also prepared aqueous shellac dispersion by using high pressure homogenisation. Films obtained from both techniques had a good enteric coating property when compared to commercial film [107 – 109]. However, shellac has a comparatively high dissolution pH of about 7.3 which was unsuitable for the application in conventional enteric coated dosage forms. Because of this high dissolution pH the addition of excipients is necessary to achieve a faster drug release in the small intestine. Composite polymer might solve this problem. Stummer *et al.*

improved the enteric coating properties of shellac in order to develop enteric coating formulations. By adding glycerol as plasticizer and sodium alginate as a copolymer, protected the microorganisms against acidic pH and provided the best release profile in simulated intestinal fluid were achieved [110]. Limmatvapirat *et al.* improved dissolution of shellac by formation of shellac succinate. Dry media reaction or solid – state reaction was used for the synthesis of shellac succinate in the concept of solventless reaction. Succinic anhydride would esterified with hydroxyl group on shellac structure resulting in increase the number of carboxylic acid per shellac molecule lead to shellac succinate could dissolve at low pH [16]. By adding shellac to composite film, the poor moisture resistance of high permeable polymer was also improved [111, 112]. In addition to enteric coating, shellac had also been used for controlled drug release. Sheorey *et al.* developed microcapsule from shellac by solvent evaporation technique. After phase separation, microcapsule with shellac shell was occurred [113]. Limmatvapirat *et al.* also used shellac as a major excipient for preparation of matrix tablets. By effect of annealing process, tablet containing high shellac content demonstrated increasing hardness and more sustained drug release [19].

However, the major problem of shellac was stability. After storage shellac was polymerized by effect of aging. The composition of shellac consisted of polyesters and single esters that contained a large amount of hydroxyl and carboxylic moiety. The polymerization could occur by the esterification among the functional groups and was the cause of instability. Since the polymerization occurred via a carboxyl group, the protection at the carboxylic acid should be a possible means for improving the stability of shellac. Limmatvapirat *et al.* reported that 2-amino-2-

methyl-1-propanol (AMP) and ammonium hydroxide (AMN) could protect polymerization when form salt with shellac. But AMP should bind much tighter at the carboxylate binding site as compared with AMN, resulting in more solubility and stability [114]. However, salt formation at carboxyl groups was not yet fully solved since the hydroxyl groups were not completely protected. Danuch and coworker fabricated shellac phthalate (SHL – PHT) by solid state reaction. Shellac was ground with phthalic anhydride and then thermally activated at various conditions. The SHL – PHT demonstrated to improve the thermal stability as compared to native shellac [115]. The protection of carboxyl and hydroxyl groups in shellac structure might be a possible explanation for the improved stability.

2.6 Drug release mechanism

2.6.1 Mechanism of drug release from hydrophilic matrix

Since the appearance of sustained release formulation had occurred. Some dosage forms were based on polymer. Hydrophilic matrix systems were simplest to formulate by using hydrophilic polymer. A hydrophilic matrix was a homogeneous dispersion of drug molecules within a skeleton in which one or several of the excipients incorporated were a hydrophilic polymer, such as cellulose derivatives, sodium alginate, xanthan gum, polyethylene oxide, or carbopol, which swelled after contact with water and became hydrated gel layer. Glass transition temperature (T_g) was decreased, led to change the polymer form from crystalline state to rubbery state. The penetration of medium into matrix caused the series of fronts or layers, swelling front, erosion or dissolution front and diffusion front [116 – 118]. The mechanism of drug release from matrix related several processes: medium enter into

the matrix and then swelling of the matrix, dissolution of the drug in the medium, diffusion of the drug through the gel layer and the final step was erosion of the matrix. Based on the processes that control release, mechanism of drug release classified into four types [119].

1. Fickian diffusion (Type I): The mechanism of diffusion was the process that controls the release of the active principal ingredient (API).

2. Polymer swelling (Type II): Drug release was controlled by the swelling of the polymer.

3. Polymer swelling and polymer and drug dissolution (Anomalous or non – Fickian diffusion): Release of drug involved with matrix swelling and diffusion phenomena.

4. Polymer erosion/degradation (Supra II type): This occurred in matrices in which after the matrix had entered into contact with the dissolution medium these formed a completely hydrated layer at the surface that was subject to continuous erosion.

2.6.2 Mechanism of drug release from lipophilic matrix

The concept of sustain drug release was to manipulate slow rate of drug release from carrier. One approach to accomplish was using the lipophilic drug carrier. Lipophilic carriers such as carnauba wax, glycerides, stearyl alcohol and stearic acid had been reported to formulate. Various manufacturing processes using these lipophilic carriers had been used, including direct compression, hot – melt extrusion, melt granulation and solvent evaporation [120 – 123]. The main mechanisms of drug release were leaching and disintegration depended on preparation method and composition of the formulation. Diffusion – controlled leaching through

the channels of the pores and cracks of the lipophilic matrix tablet (DCT) was a key to the sustained release [123 – 125].

2.7 Mathematic model for analysis of drug release

To understanding the mechanism of drug release from dosage forms, mathematical models had been used in interpretation of drug release data. Models that had been proposed to study drug release *i.e.* zero order, first order, Higuchi, Korsmeyer – Peppas, Hixson – Crowell cube root and Peppas – Sahlin model.

2.7.1 Zero order model

Drug dissolve from dosage forms that did not disaggregate and drug release was slowly, assuming that area did not change and no equilibrium conditions were obtained. In this way, a graphic of drug release versus time would be linear. Equation for this model is expressed in eq. 1.

$$Q = k_o t \quad \text{.....(1)}$$

Where Q was fraction of drug dissolved in time t and k_o was zero order constant [126, 127].

2.7.2 First order model

This model had been used to describe the absorption and/or elimination of some drugs, although it was difficult to conceptualize this mechanism in a theoretical basis. Equation for this model is expressed in eq. 2.

$$\text{Log } Q_t = \text{Log} Q_0 - kt / 2.303 \quad \text{.....(2)}$$

Where Q_t was the amount of drug released at time t, Q_0 was the initial amount of drug in the solution and K was the first order release constant. In this way, a graphic of the decimal logarithm of drug release versus time would be linear [126].

2.7.3 Higuchi model

This model often used to describe the release rate of drug from matrix systems that had been published in 1961 by Higuchi. The basic equation of Higuchi model is shown on Eq.3.

$$M_t/M_\infty = Kt^{1/2} \quad \text{.....(3)}$$

M_∞ was the absolute cumulative amount of drug released at infinite time which should be equal as the amount of drug that incorporate in the drug system. K was a constant and t is a time. Drug release rate was proportional to the square root of time. However, when applied this model to controlled drug delivery system; the following assumption should be concerned [128, 129].

(i) The initial drug concentration in the system was much higher than the solubility of the drug. This assumption was very important, because it provided the basis for the justification of the applied pseudo – steady state approach.

(ii) Mathematical analysis was based on one – dimensional diffusion. Thus, edge effects must be negligible.

(iii) The suspended drug was in a fine state such that the particles were much smaller in diameter than the thickness of the system.

(iv) Swelling or dissolution of the polymer carrier was negligible.

(v) The diffusivity of the drug was constant.

(vi) Perfect sink conditions were maintained.

2.7.4 Korsmeyer – Peppas model

Korsmeyer – peppas or power law equation model was a semi – empirical equation to describe drug release from polymeric systems when the mechanism of drug release was unknown. The equation is shown on Eq.4.

$$M_t/M_\infty = Kt^n \quad \text{.....(4)}$$

M_t and M_∞ were the absolute cumulative amount of drug released at time t and infinite time, respectively; k was a constant incorporating structural and geometric characteristics of the device, and n was the release exponent, indicative of the mechanism of drug release. When the release exponent (n) had the value of 0.5 indicating diffusion-controlled drug release, in case of n = 1.0 indicating swelling – controlled drug release. If the value of n had between 0.5 – 1.0, the mechanism of drug release was anomalous transport which was the mixed mechanism between Fickian diffusion and case II transport. It had to be kept in mind that the two extreme values for the exponent n, 0.5 and 1.0, were only valid for slab geometry. For spheres and cylinders different values had been derived, as list in Table 3 [128, 130].

Table 3 Exponent n of the power law and drug release mechanism

Exponent, *n*			Drug release mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
$0.5<n<1.0$	$0.45<n<0.89$	$0.43<n<0.85$	Anomalous transport
1.0	0.89	0.85	Case-II transport

Source : Siepmann, J. and N.A. Peppas, "Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC)." Advanced Drug Delivery Reviews 64: 163 – 174.

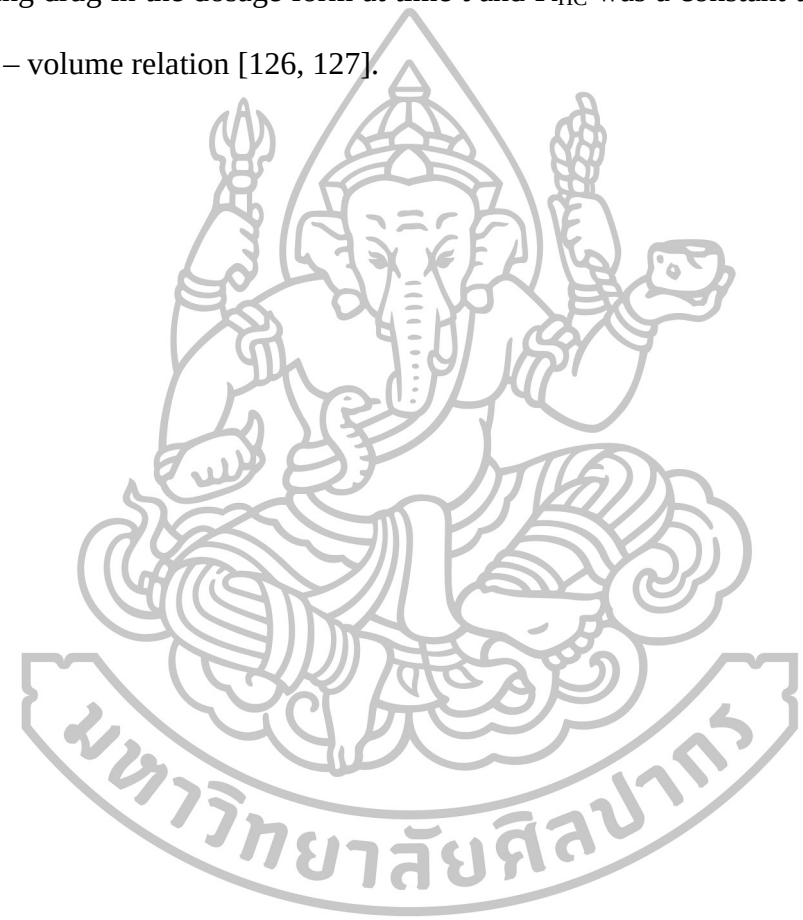
2.7.5 Hixson – Crowell cube root model

This model had been used to explain the release profile while the surface area of dosage was reduced or changed in diameter of dosage form during the

dissolution. The particle area was proportional to the cubic root of its volume**.** The equation is shown on Eq.5.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t \quad \text{.....(5)}$$

Where Q_0 was the initial amount of drug in the dosage form, Q_t was the remaining drug in the dosage form at time t and K_{HC} was a constant that involved the surface – volume relation [126, 127].



CHAPTER 3

MATERIALS AND METHODS

1. Materials

1. Shellac (Thananchai Part., Ltd., Thailand)
2. D(-)-N-methyl-glucamine (Lot No. S5661018243, Merck Darmstadt, Germany)
3. Hydroxypropylmethylcellulose K 100 M (Lot.No. VF 16012N12, Colorcon, Singapore)
4. Ammonium carbonate (Lot.No. 60590, Riedel – de Haen, Germany)
5. Ethyl alcohol absolute (Lot No. J32T04, Mallinckrodt, Malaysia)
6. Sodium hydroxide (Lot No. B0274298827, Merck Darmstadt, Germany)
7. Potassium dihydrogen phosphate (Lot No. A837073707, Merck Darmstadt, Germany)
8. Hydrochloric acid (Lot No. 05070162, Lab scan, Germany)
9. Potassium bromide (Lot No. B0351607905, Merck Darmstadt, Germany)
10. Polyvinylpyrrolidine K 30 (Lot No. 05070162, Lab scan, Germany)
11. Lactose monohydrate (Supertab®) (Lot No. FQ010012T1120, Fonterra, New Zealand)
12. Theophylline (Lot.No. 08107, Taj Pharmaceutical, Ltd., India)

13. Colloidal silica (Aerosil® 200) (Lot No. 5042 0110/069, Degussa AG, Germany)

14. Magnesium stearate (Lot No. YW01M0301, Glaxo Wellcome Vidhyasom, Thailand)

15. Ammonia solution (Lot No. K39606032 910, Merck Darmstadt, Germany)

2. Equipments

1. Analytical balance (Sartorius CP224s, Germany)
2. Moisture balance (Sartorius YTX01L, Germany)
3. Magnetic stirrer (Aris M – 1X, Thailand)
4. Hardness tester (Pharmatest PTB311, Germany)
5. Single punch tableting machine (Yeo Heng Factory, Thailand)
6. Hot air oven (Heraeus UT6060, Germany)
7. Laboratory refrigerator (SANDEN INTERCOOL SNH – 0163, Thailand)
8. Laboratory sieve (sieve size 40,60,80,100 mesh)
9. Vacuum oven (Vaccucell 55, Germany)
10. Planetary ball mill (Retsch PM 100, Germany)
11. Laboratory Centrifuges (Hettich ZENTRIFUGEN, Germany)
12. Disintegration testing apparatus (Sotax DT3, Switzerland)
13. Dissolution testing apparatus (Pharmatest PTWS3C, Germany)
14. UV – VIS spectrophotometer (Lambda 2, Perkin Elmer, USA)
15. pH meter (Mettler Toledo seveneasy, Switzerland)

16. Vortex mixer (Gibthai VX – 100, Thailand)

17. Benchtop magnetic resonance imaging (Pharmasense version 1.0, UK)

18. Laminar fume hood (Hera Safe, Heraeus, Germany)

19. Hydraulic press (Atlas GS15011, USA)

20. Hot stage microscopy (Mettler Toledo FP82HT, Switzerland)

21. Thickness meter (Minitest 600B, Type 80-121-0306, Germany)

22. Desiccator (Biologix Research Company, USA)

23. X-ray microtomography (SkyScan1072 XRCT®, Aartselaar, Belgium)

24. Differential scanning calorimeter (DSC 6200; SII Seiko instruments Inc., Japan)

3. Methods

3.1 Preparation of shellac derivatives

3.1.1 Preparation of HS

SHL was finely ground and passed through 40 – mesh screen. A 200 g of ground SHL was dissolved in 1800 g of 2% (w/w) sodium hydroxide solution and kept at 30±1°C for 15 min. The mixtures were then neutralized with 2 N sulfuric acid and washed with excess water and dried at 25°C. The HS was kept in refrigerator prior used.

3.1.2 Preparation of SHL salts

SHL ammonia and SHL meglumine/ammonia (60:40) were prepared by using a casting/solvent evaporation technique. Each SHL sample was

dispersed in water and then salt forming agent was added. The amount of added salt forming agent was calculated in accordance with the acid value of each SHL sample. The mixture was stirred until the shellac sample was completely dissolved and kept stirring overnight. The final concentration was adjusted to 6%w/w with water. The solution was poured onto a glass plate, whose surface was treated with Aquasil® and allowed evaporating at 50°C for 4 – 5 h. Film prepared from shellac salt was peeled off and then ground into the fine powder. The SHL salts were kept in refrigerator before using.

3.2 Preparation of tablets

3.2.1 Preparation of SHL and SHL derivatives-based matrix tablet

The composition of SHL and SHL derivatives – based matrix tablet are shown in Table 4 – 7. The excipients and theophylline (model drug) were mixed for 10 min. The powder mixture was then directly compressed with 9.53 mm flat-faced punch, using single-punch tableting machine (Yeo Heng, Thailand). The weight and hardness of initial tablets were controlled within 300±10 mg and 70±10 N, respectively. The tablets were annealed at 40, 60 and 80°C for 24 h in an oven (Vaccucell 55, Germany). All tablets were kept in the ambient temperature before evaluated.

Table 4 Composition of SHL – based matrix tablet

Component	Content (%w/w)					
	S0	S10	S20	S30	S40	S50
Theophylline	15	15	15	15	15	15
SHL	0	10	20	30	40	50
PVP K30	3	3	3	3	3	3
Colloidal silica	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1
Super Tab®	80	70	60	50	40	30

Table 5 Composition of HS – based matrix tablet

Component	Content (%w/w)					
	HS0	HS10	HS20	HS30	HS40	HS50
Theophylline	15	15	15	15	15	15
HS	0	10	20	30	40	50
PVP K30	3	3	3	3	3	3
Colloidal silica	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1
Super Tab®	80	70	60	50	40	30

Table 6 Composition of SA – based matrix tablet

Component	Content (%w/w)					
	SA0	SA10	SA20	SA30	SA40	SA50
Theophylline	15	15	15	15	15	15
SA	0	10	20	30	40	50
PVP K30	3	3	3	3	3	3
Colloidal silica	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1
Super Tab®	80	70	60	50	40	30

Table 7 Composition of SMA – based matrix tablet

Component	Content (%w/w)					
	SMA0	SMA10	SMA20	SMA30	SMA40	SMA50
Theophylline	15	15	15	15	15	15
SMA (60:40)	0	10	20	30	40	50
PVP K30	3	3	3	3	3	3
Colloidal silica	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1
Super Tab®	80	70	60	50	40	30

3.2.2 Preparation of SHL – based floating matrix tablet

The composition of SHL – based floating matrix tablet is given in Table 8. The excipients and theophylline were mixed for 10 min. The powder mixtures were then directly compressed with 9.53 mm flat – faced punch, using single-punch tableting machine (Yeo Heng, Thailand). The weight and hardness of

tablets were controlled within 300±10 mg and 70±10 N, respectively. The tablets were annealed at 80°C for 24 h in a vacuum oven (Vaccucell 55, Germany). All tablets were kept in the ambient temperature before evaluated.

In the step of annealing process, ammonium carbonate that was used as a pore forming agent in the tablet vaporized and resulted in the numerous pores within the tablets. The density of tablet in some formula was expected to be less than 1 g/cm^3 and thus the tablet could be immediately floated on the gastric medium.

Table 8 Composition of SHL – based floating matrix tablet

Component	Content (%w/w)							
	FS1	FS2	FS3	FS4	FS5	FS6	FS7	FS8
Theophylline	15	15	15	15	15	15	15	15
SHL	30	30	30	30	0	50	30	30
Ammonium carbonate	0	10	20	30	30	30	30	30
HPMC K100M	0	0	0	0	0	0	5	10
PVP K30	3	3	3	3	3	3	3	3
Colloidal silica	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1
Super Tab®	50	40	30	20	50	0	15	10

3.3 Evaluations of tablet

3.3.1 Weight variation

To study weight variation, 20 tablets of tablets were weighed individually using four decimals digital analytical balance (Sartorius CP 224s, Germany). The mean and standard deviation were determined.

3.3.2 Tablet thickness and diameter

The thickness and diameter of the tablets were determined by using a digital thickness and diameter gauge (Erweka TBH 225 TD, Germany). Ten tablets were used and the mean and standard deviation were calculated.

3.3.3 Density measurements

The apparent densities of the tablets were calculated from their volumes and masses of each tablet (n = 20). The volumes of the cylindrical tablets are calculated from their thickness (t) and diameter (d) using the mathematical equation for a cylinder ($V = \pi d^2 t/4$).

3.3.4 Hardness

Twenty tablets were sampled and individually subjected to test for hardness using a digital hardness tester (Erweka TBH 225 TD, Germany). The mean and standard deviation of the tablet hardness were calculated.

3.3.5 Disintegration

The disintegration test was carried out as described in USP 38. The total of 6 tablets were weighed and placed in each tube of a disintegration basket, using a disintegration testing apparatus (Sotax, DT3, Switzerland) and immersed in 0.1 N HCl for 120 min. At the end of operation, the basket was removed from the 0.1 N HCl and the tablets were checked for the absent or broken tablets. Then, the tablets

were subsequently immersed in phosphate buffer (pH 6.8) for 180 min. The temperature of both media was maintained at 37±0.5°C.

3.3.6 *In vitro* Drug release

Dissolution testing of matrix tablets was carried out according to USP 32 paddle method, using dissolution testing apparatus (Pharmatest PTWS3C, Germany). The dissolution testing was conducted at a revolution speed of 50 rpm in 750 mL of 0.1 N hydrochloric acid at 37°C for 2 h and then adjusted to pH 6.8 by adding 250 mL of tri – basic sodium phosphate and examined for 10 h. The total time of dissolution testing was 12 h. The samples were drawn periodically and replenished with fresh dissolution medium. The amount of drug release is measured by UV/VIS spectrophotometer (Perkin – Elmer, Germany) at 270 nm.

The dissolution of floating matrix tablets was only investigated in 900 mL of 0.1 N hydrochloric acid at 37°C for 12 h and the condition was manipulated in the same method as matrix tablets.

3.3.7 Evaluation of drug release kinetic

To analyze the *in vitro* release data, various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson – Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets and Korsmeyer derived a simple relationship which described drug release from a polymeric system Eq. (5).

$$Q = k_o t \quad \text{.....(1)}$$

$$\text{Log } Q = \text{Log}Q_0 - kt / 2.303 \quad \text{.....(2)}$$

$$Q = Kt^{1/2} \quad \text{.....(3)}$$

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t \quad \text{.....(4)}$$

$$M_t / M_\infty = Kt^n \quad \text{.....(5)}$$

3.3.8 Tablet floating behavior

The floating behavior of the tablets was visually determined. Briefly, a tablet was placed in vessel of dissolution apparatus, containing 900 mL of 0.1 N HCl, maintained temperature at 37±0.5°C. The floating lag time (the time between tablet introduction and its buoyancy) and total floating duration (the time during which tablet remains buoyant) were recorded. The measurement was run in triplicate.

3.3.9 The percentage weight loss of tablet

To study effect of annealing process on ability of sublimation of pore forming agent from tablet, the percentage weight loss was used to evaluate. The initial weights of tablets were recorded and then were annealed at 40, 60 and 80°C in a vacuum oven for 24 h. The annealed tablets were weighed and calculated to find out the percentage weight loss.

3.3.10 X – ray CT imaging

For all tablets, the scanning parameters were operated the X – ray source at a voltage of 40 kV and a current *I* of 50 µA. The exposure time was set at 3 seconds per projection.

3.3.11 ^{1}H NMR imaging experiments

^{1}H NMR imaging was performed on a benchtop MRI spectrometer working at a frequency of 15 MHz having a static magnetic field of strength of 0.5 T. Tablet was placed in the sample holder with 0.1 N HCl and glass beads on the bottom to allow three-dimensional water penetration even in case of sinking tablets. A slice of 10 – mm thickness was selected. A standard spin-echo sequence was used with an echo time (TE) of 9.8 s and repetition time (TR) of 300 ms leading to an acquisition time of about 10 min for each image. Eight scans were accumulated to obtain an image [131].

CHAPTER 4

RESULTS AND DISCUSSION

1. Fabrication and evaluation of tablets containing SHL and its derivatives

In order to study effect of SHL and its derivatives on tablet properties, SHL and SHL derivatives – based matrix tablet were prepared. The formulations are shown in chapter 3 (Table 4 – 7). Each formulation was compressed into tablet by direct compression method. Tablets which contained theophylline with different polymer amount and annealing temperature were comparatively evaluated.

1.1 SHL-based matrix tablet

For SHL-based matrix tablet, the target weight was 300 mg therefore the limit deviation should be within ±15 mg. As shown in Table 9, the weight variation of all tablet formula was within ±2.2 mg, indicating that weight variation of tablets before annealing process (initial) conformed to the specified criteria. After annealing process, the weight of tablets was slightly decreased at high annealing temperature due to loss of moisture, while the S.D. was still at the same level as that before annealing.

Tables 10 and 11 demonstrate the thickness and diameter of tablets before and after annealing process, respectively. The average thickness was increased as increasing the amount of SHL. There were the lower density and compressibility of SHL as compared to direct compression diluents (Supertab®). However, annealing process did not affect the thickness and diameter, suggesting that the relaxation

or contraction of tablets along axial or radial axis did not occur during heating.

Figure 9 shows the effect of SHL content and annealing process on hardness of tablets. The hardness of all tablet formulations before annealing was well controlled within the predetermined range of 80 – 110 N although the formulations containing high percentage of SHL exhibited a lower compressibility. The annealing process at 40^{o}C did not influence on the hardness. The effect of SHL content on hardness was clearly observed at higher annealing temperature. At 60^{o}C, only the formula containing 50%w/w of SHL demonstrated the higher hardness whereas there was no difference in the hardness of the formula containing SHL lower than 50%w/w. However, the change of hardness was more clearly observed in the formula containing lower SHL content after annealing at 80ºC. For example, the tablet containing 30%w/w SHL demonstrated the hardness from 90 to 130 N. The increasing hardness after annealing process was well correlated with the decrement of acid value and the increment of insoluble solid of SHL powder as represent in Figure 55 (APPENDIX). The results suggested that the esterification among the SHL molecule could impart the cohesion within the tablets which were in good agreement with earlier report [19].

Table 9 Weight variation of SHL – based matrix tablet before and after annealing process at 40, 60 and 80°C (n = 20)

Formula	Weight variation (mg)			
	Initial	40°C	60°C	80°C
S0	300.8±0.7	301.2±1.1	300.7±1.2	300.6±1.6
S10	301.3±2.2	300.7±1.2	300.6±1.5	300.1±2.1
S20	299.7±1.8	299.9±1.5	299.8±1.7	299.6±1.7
S30	299.2±1.4	299.8±1.7	299.1±1.3	297.7±1.6
S40	299.4±2.0	298.9±1.4	300.7±2.0	298.5±1.4
S50	300.2±1.0	300.0±1.6	298.5±2.0	297.6±1.1

Table 10 Thickness of SHL – based matrix tablet before and after annealing at 40, 60 and 80°C (n = 20)

Formula	Thickness (mm)			
	Initial	40°C	60°C	80°C
S0	3.43±0.04	3.42±0.04	3.44±0.04	3.42±0.04
S10	3.50±0.04	3.48±0.04	3.45±0.02	3.47±0.05
S20	3.56±0.01	3.56±0.02	3.57±0.03	3.58±0.04
S30	3.59±0.03	3.62±0.03	3.62±0.04	3.62±0.03
S40	3.67±0.05	3.70±0.06	3.71±0.05	3.68±0.05
S50	3.76±0.02	3.77±0.03	3.79±0.02	3.76±0.02

Table 11 Diameter of SHL – based matrix tablet before and after annealing process at 40, 60 and 80°C (n = 20)

Formula	Diameter (mm)			
	Initial	40°C	60°C	80°C
S0	9.26±0.01	9.12±0.04	9.20±0.04	9.18±0.04
S10	9.17±0.02	9.20±0.04	9.12±0.02	9.15±0.05
S20	9.15±0.01	9.16±0.02	9.17±0.03	9.19±0.04
S30	9.15±0.03	9.15±0.03	9.23±0.04	9.19±0.03
S40	9.20±0.05	9.21±0.01	9.17±0.04	9.19±0.05
S50	9.28±0.02	9.18±0.03	9.18±0.02	9.19±0.02

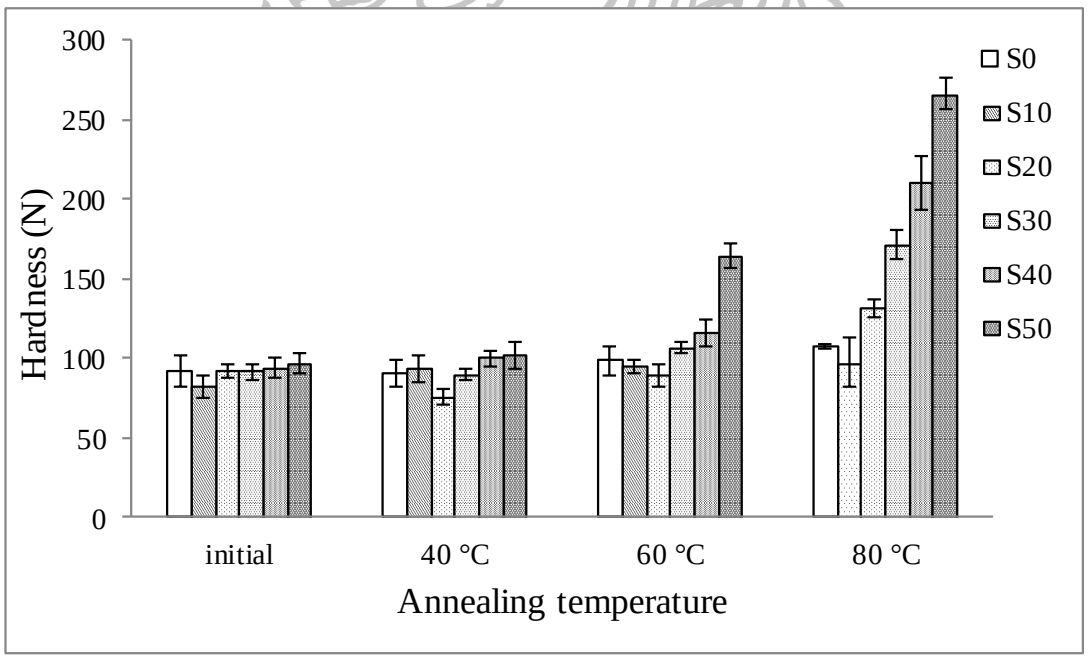


Figure 9 Effect of SHL content and annealing processes on hardness (n = 20)

For a drug to be absorbed from a solid dosage forms after oral administration, the liberation process of drug must be occurred. Tablet disintegration testing is used as a preliminary tool to assure that drug is further dissolved and absorbed through the GI tract [2,4]. Hence, the disintegration of tablets containing different amounts of SHL was also comparatively evaluated in various media simulated the conditions in GI tract as explained below.

Disintegration time of SHL – based matrix tablets in 0.1 N HCl is shown in Table 12. Before annealing process, the tablets without SHL were completely disintegrated in acidic media within 20 min. While, those containing 30%w/w or more of SHL were partially eroded even after testing for 120 min. As increasing amount of SHL, the more disintegration time was observed. This can be explained by the acid resistance of SHL. In this case, SHL could be acted as the barrier for the acid permeation through the tablets, resulting in the increased disintegration time. The results agreed well with some previous findings [106, 131].

The effect of annealing temperature on the disintegration time in 0.1 N HCl of SHL – based matrix tablets is also shown in Table 12. The disintegration time of formulation without SHL (S0) was not clearly changed even annealing at 80°C. However, annealing process directly impacted on the formulation containing SHL. The increased annealing temperature retarded the tablet disintegration. At higher temperature, the non-disintegrated tablets (within 120 min) were found at lower concentration of SHL. For example, 20%w/w SHL – loaded tablets (S20), the disintegration was extended to 77 min and more than 120 min after annealing at 60 and 80^{o}C, respectively. The results correlated well with the increased hardness. The more hardness could reduce the corrosion and breaking of tablet in acidic medium.

Additionally, the non – disintegrated tablets from acid medium were further investigated in phosphate buffer (pH 6.8) for 180 min. The disintegration time of tested tablets in phosphate buffer (pH 6.8) is shown in Table 13. The tablets containing SHL less than 40%w/w were completely dissolved within 180 min which was due to the high solubility of SHL at increased pH [14 – 16, 18]. The increased disintegration time in phosphate buffer was also observed as increasing SHL contents. Additionally, the effect of annealing process on disintegration time of tablets in phosphate buffer (pH 6.8) was more clearly indicated at high temperature. For example, the tablet containing 30%w/w SHL was not completely disintegrated after annealing at 60°C or more. The result suggested that SHL content as well as annealing temperature were critical factors controlling disintegration of tablets. The results were in good agreement with those from some previous findings [19, 134].

As indicated in Tables 12 and 13, the disintegration time of some tablet formulations exceeded 120 min and 180 min in 0.1 N HCl and phosphate buffer, respectively and therefore could not be used for comparison the effects of SHL contents and annealing temperature on disintegration of tablets. In order to further investigation, the percent weight loss of non – disintegrated tablets was determined after disintegration in each medium was recorded and used as a parameter for the comparative characterization.

Figure 10 demonstrates the percentage weight loss of tablets after disintegration test in 0.1 N HCl. As increasing either amount of SHL or annealing temperature, a decreasing tendency of weight loss was observed. The percentage weight loss of tablet before annealing was decreased from 85% to 30% as escalating the amount of SHL from 30% to 50%w/w. The more reduced weight loss was

indicated when combined with the annealing at high temperature, especially at 80°C. For 30%w/w of SHL containing tablet, the percentage weight loss was reduced from 90% to 40%, after increasing annealing temperature from 40 to 80°C. Similar result was also observed in phosphate buffer pH 6.8 (Figure 11). The decreased percentage weight loss was clearly indicated after increasing SHL content and annealing temperature. The result was also later confirmed by the total percentage weight loss in both media (Figure 12), revealing the significant effect of SHL content and annealing temperature on retardation for disintegration of tablets.

Table 12 Effect of SHL content and annealing process on disintegration time of tablets in 0.1 N HCl (n = 6)

Formula	Disintegration in 0.1 N HCl (min)			
	Initial	40°C	60°C	80°C
S0	19.0±2.2	19.0±1.6	25.0±1.5	20.2±1.5
S10	30.5±6.7	31.0±4.2	35.6±2.8	57.3±3.6
S20	54.8±1.7	58.6±4.1	77.0±5.1	> 120
S30	> 120	> 120	> 120	> 120
S40	> 120	> 120	> 120	> 120
S50	> 120	> 120	> 120	> 120

Table 13 Effect of SHL content and annealing process on disintegration time of tablets in buffer (pH 6.8) (n = 6)

Formula	Disintegration in buffer (pH 6.8) (min)			
	Initial	40°C	60°C	80°C
S0	-	-	-	-
S10	-	-	-	-
S20	-	-	-	> 180
S30	108.5±2.6	165.0±4.3	> 180	> 180
S40	143.4±6.7	172.9±12.1	> 180	> 180
S50	> 180	> 180	> 180	> 180

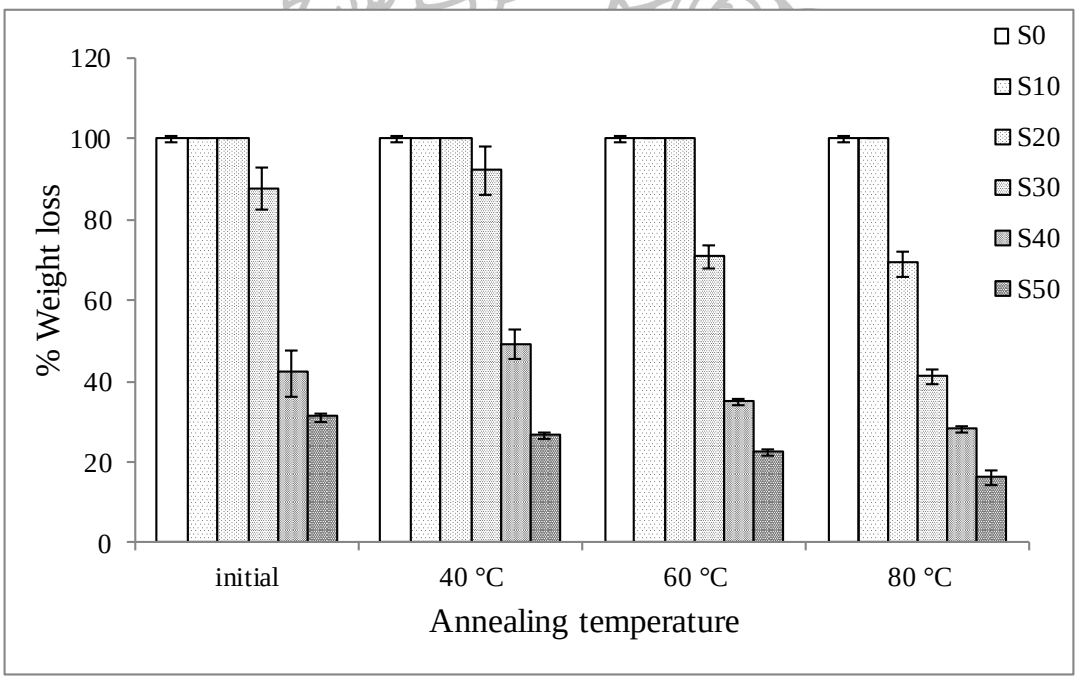


Figure 10 Percentage weight loss in 0.1 N HCl of SHL – based matrix tablets before and after annealing at 40, 60 and 80°C (n = 6)

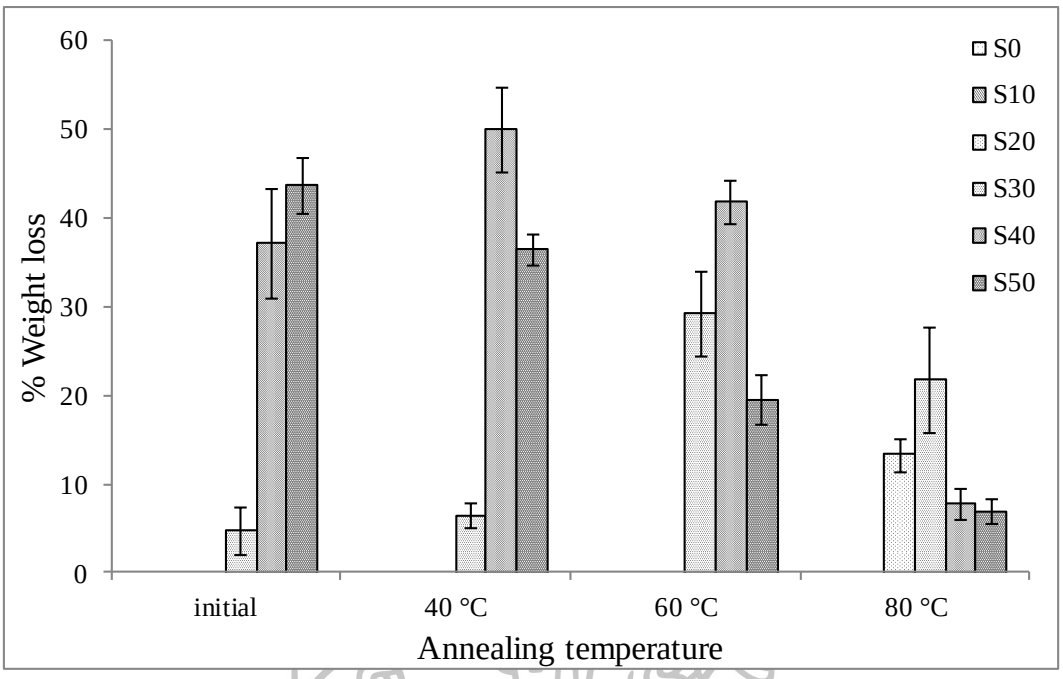


Figure 11 Percentage weight loss in phosphate buffer (pH 6.8) of SHL – based matrix tablets before and after annealing at 40, 60 and 80°C (n = 6)

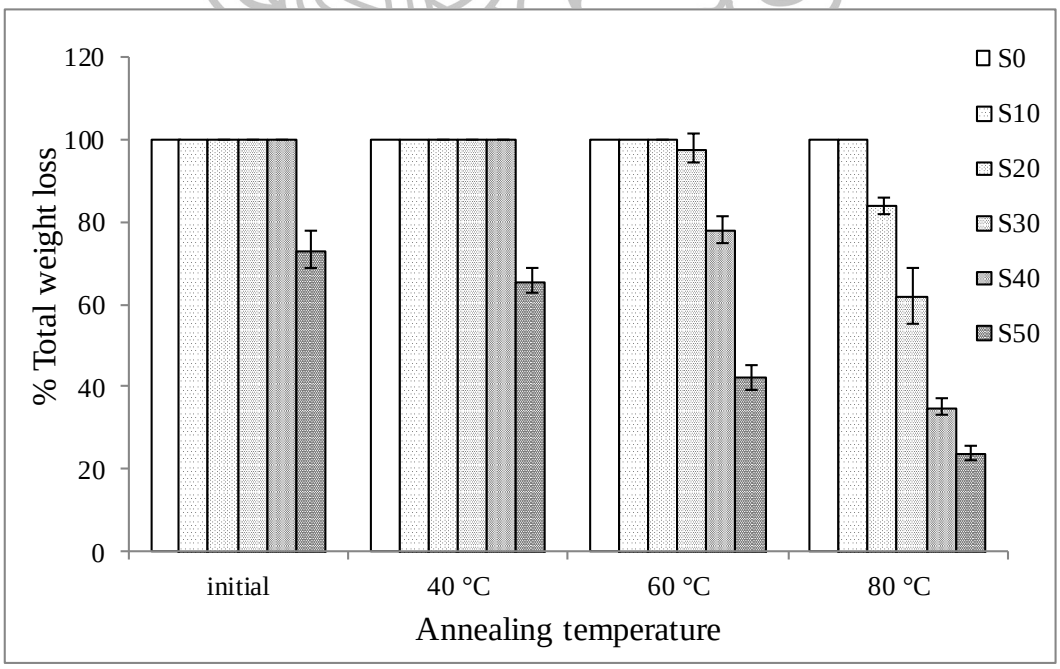


Figure 12 Total weight loss in both media of SHL – based matrix tablets before and after annealing at 40, 60 and 80ºC (n = 6)

In order to visualize the SHL – based tablets with varied amounts of SHL, prepared at different annealing temperatures and after disintegration in both media, the photomicrographs of all tablets were recorded as tabulated in Tables 14 – 17.

As indicated in Table 14, the good distribution of SHL in the tablets (before disintegration) was clearly indicated in all formulation. The darker tablets due to SHL were also observed as increasing SHL content. The results suggested the good blending of SHL with other components in the formulations. Additionally, there was no evidence of chipping or cracking even the S50 which possessed a low compressibility. After disintegration test in 0.1 N HCl, the tablets except S30, S40 and S50 were completely disintegrated. It was also noted that the erosion of S30 was clearly observed even the disintegration time was more than 120 min. The tablets from S40 formulation were completely dissolved after continued disintegration test in phosphate buffer while those of S50 were partially eroded, suggesting the prolonged dissolution of SHL as increasing pH.

The physical appearance of tablets after annealing at 40°C was not clearly different as compared to that of unannealed tablets (Table 15). After disintegration test, the complete disintegration and partial erosion of tablet were also occurred at the same level of SHL. However, the partial disintegrated tablets at lower amount of SHL were observed after annealing at 60°C and above. For example, the S30 was completely disintegrated after annealing at 40°C but partially disintegrated at higher temperature. Additionally, the slower erosion was observed at 80°C as compared to 60°C. The 80°C annealed tablets containing 30% SHL and above were

almost intact even after disintegration in 0.1 N HCl and phosphate buffer. The results were in good agreement with those of disintegration time and percent weight loss, confirming the significant effect of annealing temperature. As described in earlier section, the SHL was melted at above 50°C and therefore could impart the cohesion to the 60 and 80°C annealed tablets, resulting in slower disintegration. It was also noted that polymerization was also a possible cause of delayed disintegration since the SHL was obviously occurred at 80°C and above.

Table 14 Photographs of unannealed SHL – based matrix tablets both before and after disintegration test in 0.1 N HCl and phosphate buffer pH 6.8

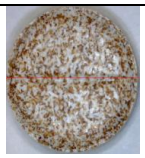
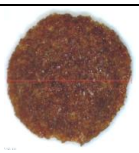
Formula	Appearance of Tablet before and after disintegration test		
	Initial	0.1N HCl (2 h)	Phosphate buffer pH 6.8 (3 h)
S0	 D = 9.262 mm	Completely disintegrated within 2 h	-
S10	 D = 9.174 mm	Completely disintegrated within 2 h	-
S20	 D = 9.152 mm	Completely disintegrated within 2 h	-
S30	 D = 9.152 mm	 D = 8.008 mm	Completely disintegrated within 3 h
S40	 D = 9.196 mm	 D = 8.888 mm	Completely disintegrated within 3 h
S50	 D = 9.284 mm	 D = 9.262 mm	 D = 8.668 mm

Table 15 Photographs of 40°C annealed SHL – based matrix tablets both before and after disintegration test in 0.1 N HCl and phosphate buffer pH 6.8

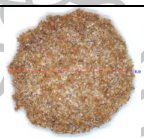
Formula	Appearance of Tablet before and after disintegration test		
	Initial	0.1N HCl (2 h)	Phosphate buffer pH 6.8 (3 h)
S0	 D = 9.260 mm	Completely disintegrated within 2 h	-
S10	 D = 9.312 mm	Completely disintegrated within 2 h	-
S20	 D = 9.209 mm	Completely disintegrated within 2 h	-
S30	 D = 9.286 mm	 D = 8.924 mm	Completely disintegrated within 3 h
S40	 D = 9.235 mm	 D = 9.137 mm	Completely disintegrated within 3 h
S50	 D = 9.235 mm	 D = 9.212mm	 D = 8.492 mm

Table 16 Photographs of 60°C annealed SHL – based matrix tablets both before and after disintegration test in 0.1 N HCl and phosphate buffer pH 6.8

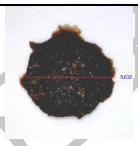
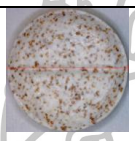
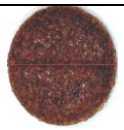
Formula	Appearance of Tablet before and after disintegration test		
	Initial	0.1N HCl (2 h)	Phosphate buffer pH 6.8 (3 h)
S0	 D = 9.271 mm	Completely disintegrated within 2 h	-
S10	 D = 9.286 mm	Completely disintegrated within 2 h	-
S20	 D = 9.258 mm	Completely disintegrated within 2 h	-
S30	 D = 9.260 mm	 D = 9.232 mm	 D = 5.632 mm
S40	 D = 9.261 mm	 D = 9.034 mm	 D = 8.558 mm
S50	 D = 9.261 mm	 D = 9.260 mm	 D = 8.954 mm

Table 17 Photographs of 80°C annealed SHL – based matrix tablets both before and after disintegration test in 0.1 N HCl and phosphate buffer pH 6.8

Formula	Appearance of Tablet before and after disintegration test		
	Initial	0.1N HCl (2 h)	Phosphate buffer pH 6.8 (3 h)
S0	 D = 9.232 mm	Completely disintegrated within 2 h	-
S10	 D = 9.177 mm	Completely disintegrated within 2 h	-
S20	 D = 9.174 mm	 D = 9.172 mm	 D = 9.134 mm
S30	 D = 9.352 mm	 D = 9.350 mm	 D = 9.180 mm
S40	 D = 9.265 mm	 D = 9.262 mm	 D = 9.035 mm
S50	 D = 9.240 mm	 D = 9.237 mm	 D = 8.954 mm

As suggested by the slow erosion of tablets as increasing either SHL content or annealing temperature, therefore the retarded drug release from SHL based matrix might be occurred. In order to study the consequence of these factors on drug release, the dissolution of model drug (theophylline) release from SHL based matrix prepared from different amount of SHL and annealing temperature were comparatively investigated. The drug release profiles from unannealed SHL – based matrix tablets in continuous media (0.1 N HCl for 2 h and pH 6.8 buffer for 10 h) are shown in Figure 13. Drug release from tablets without SHL (S0) was complete within 1 h whereas the formulation containing SHL (S10 – S50) showed a tendency of retarded drug release. As increasing the amount of SHL, the more sustained drug release profiles were observed. Tablet containing more than 40%w/w of SHL demonstrated a controlled drug release in both media over 12 h, suggesting the good possibility for applying SHL as a matrix forming agent for sustained drug release.

The effects of annealing temperature on drug release profiles are shown in Figure 14 – 17. The annealing temperature did not clearly affect the drug release of shellac – free matrix tablets. The completely drug release was observed within 1 h, even annealing at 80°C. However, the SHL-based tablets demonstrated temperature dependent drug release. At lower SHL content (less than 20%w/w), the annealing temperature slightly affected drug release. While the tablets containing high SHL content showed obviously sustained drug release after annealing process, especially at 80^{o}C. The results well agreed with change of related tablet properties, including increased hardness and extended disintegration. It should be noted that the acid value and percent insoluble solid of SHL was rapidly changed at the temperature 80°C. Therefore, it was reasonable that the polymerization of SHL at high

temperature was also a key factor that governed the sustained drug release through the matrix tablets. These suggested the good possibility for applying SHL as a matrix forming agent for sustained drug release dosage forms.

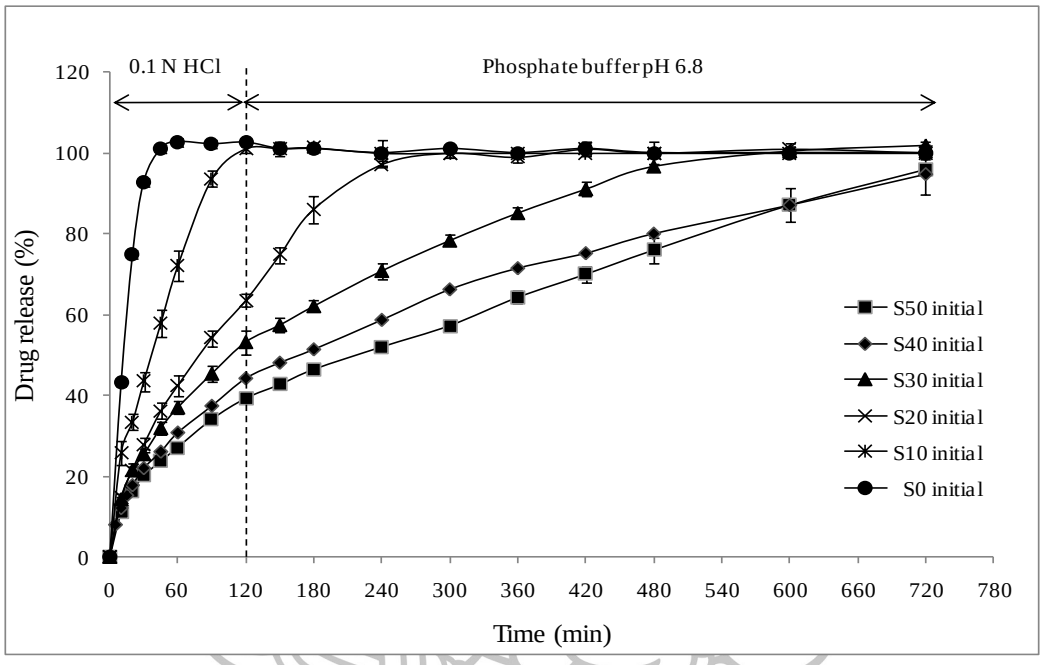


Figure 13 Drug release profiles of unannealed SHL – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

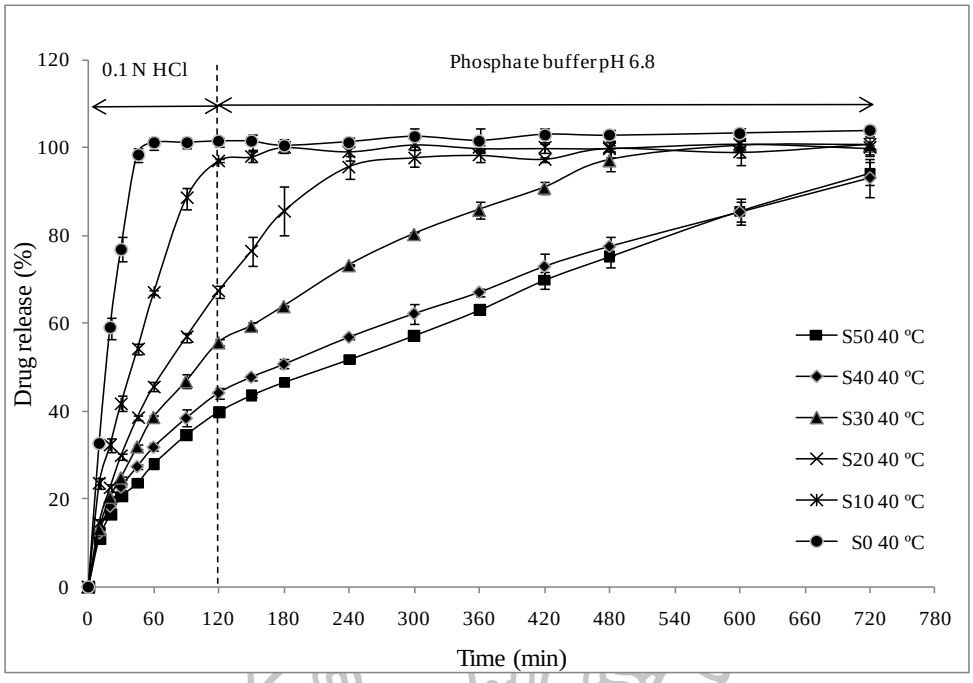


Figure 14 Drug release profiles of 40°C annealed SHL – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

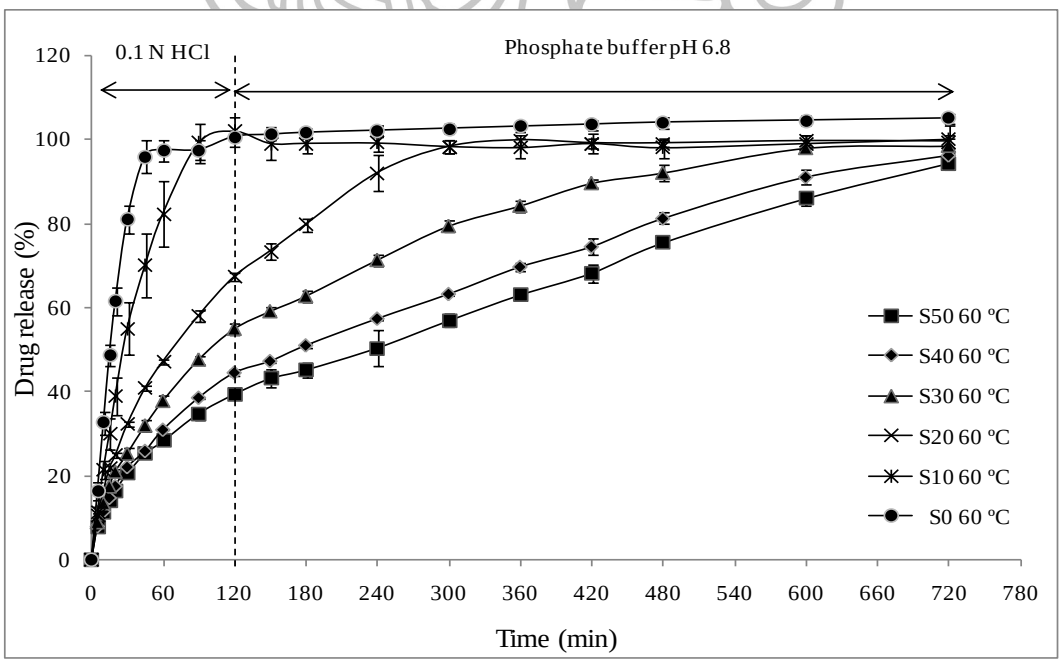


Figure 15 Drug release profiles of 60°C annealed SHL – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

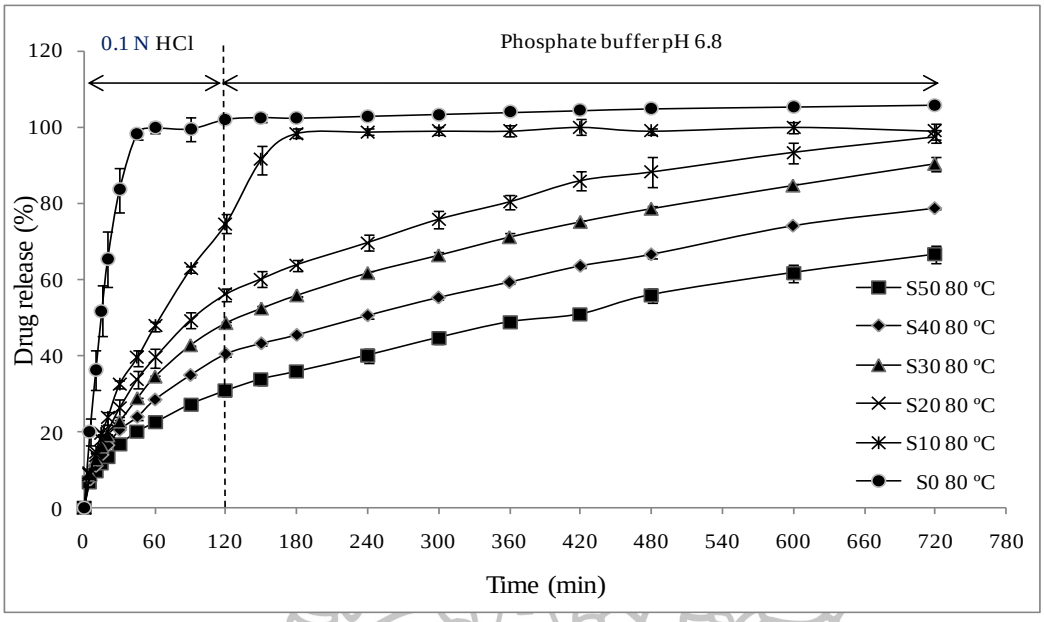


Figure 16 Drug release profiles of 80°C annealed SHL – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

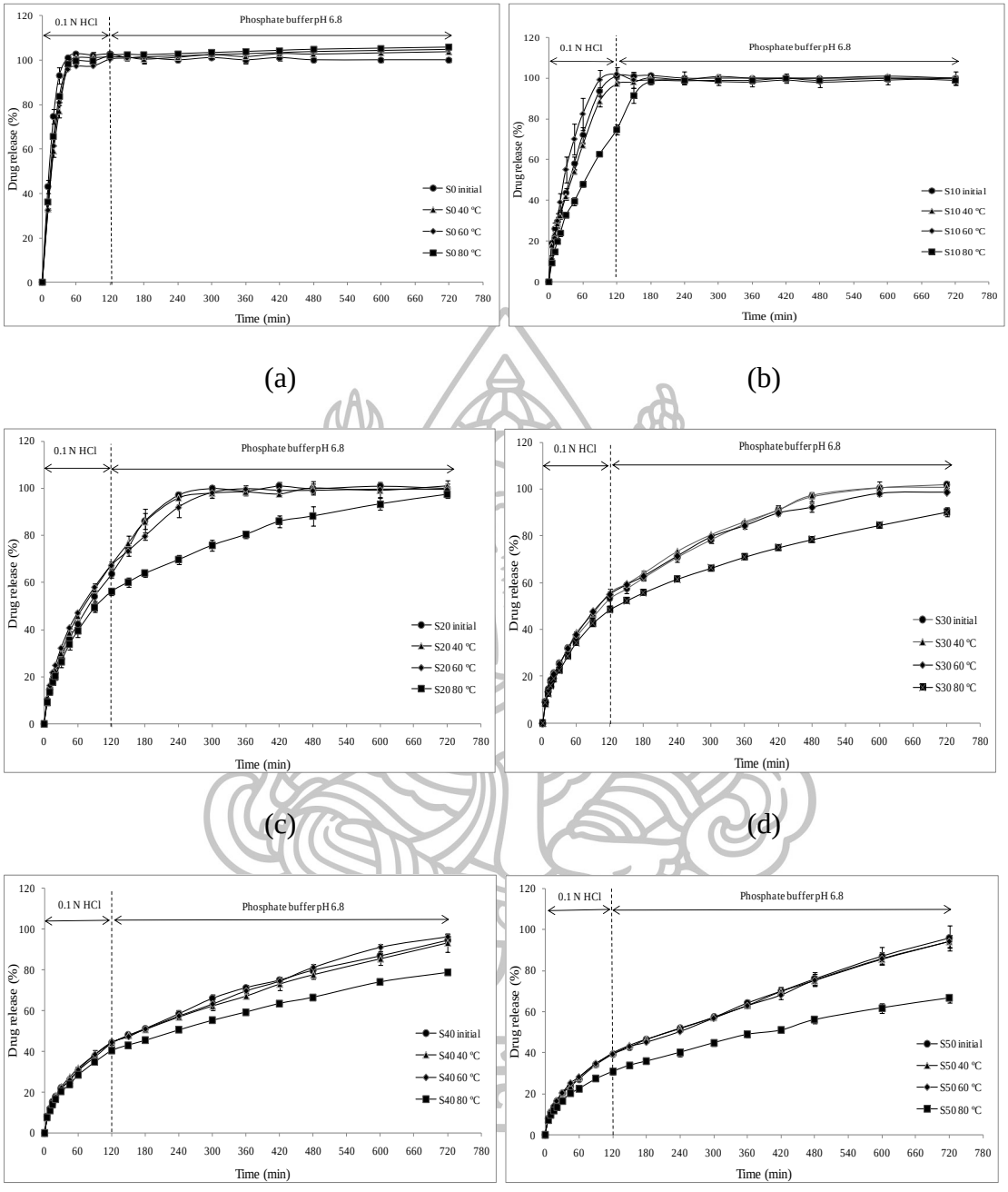


Figure 17 Effect of annealing temperatures on drug release profiles of tablets with different amounts of SHL (a) 0% SHL, (b) 10% SHL, (c) 20% SHL, (d) 30% SHL, (e) 40% SHL, (f) 50% SHL (n = 3)

Studies on drug release kinetics provide important information into the function of material systems [144]. As described above, SHL – based tablets showed retarded drug release while the detailed transport mechanism and the structure-function relationship were not yet established. In this study, the dissolution profiles of theophylline containing SHL based tablets in both 0.1 N HCL or phosphate buffer pH 6.8 for 12 h were constructed. The mechanism of drug release from SHL – based tablet was investigated by using various mathematical models, including zero order, first order, Higuchi, Hixson – Crowell and power law models. The correlation coefficient or coefficient of determination (r^2) from drug release profiles were comparatively evaluated both in 0.1 N HCl and phosphate buffer pH 6.8 as shown in Tables 19 and 20, respectively.

As indicated in Table 19, the theophylline release from SHL free tablets in 0.1 N HCl showed the best fit with the Hixson – Crowell model as indicated by the r^2 value close to 1. As increasing temperature, the release profiles still fitted with Hixson – Crowell model, confirming the release mechanism of SHL free tablets was not affected by annealing temperature. As previously reported, the Hixson – Crowell model describes the release systems controlled by dissolution in which changes in surface area and diameter of tablets [126, 127]. This model was compatible with the SHL – free tablets where the tablets were gradually eroded resulting in decreasing of surface area during the first 60 min in acidic medium.

However, the release mechanism was changed after incorporation of SHL. The SHL – based tablets demonstrated different release mechanism as compared to SHL – free tablets. The release characteristic was better characterized by Higuchi and Korsmeyer – Peppas models, especially at high level of SHL.

In case of Higuchi model, drug release is governed by diffusion through water – filled pores in the matrix or dissolution of solute into liquid-filled pore [19, 143]. As indicated by r^2 of Higuchi model, the values were approached 1.0 as increasing SHL content, indicating the more diffusion controlled drug release. As increasing annealing temperature, the r^2 of tablets with low amount of SHL had also a tendency to increase. However, the annealing temperature did not clearly influence the r^2 of tablets with 30% or more of SHL. It might be possible that the matrix diffusion control of SHL – based tablet with lower SHL content was caused by polymerization of SHL. For tablets with high amount of SHL, e.g. 30%w/w or more, on the other hand, the matrix diffusion control was achieved by the acid insoluble condensed network of SHL.

Korsmeyer – Peppas model is often used to determine drug release behavior of polymeric drug delivery system by considering the release exponent (n) [126, 128]. The n value is affected by the shape of system as shown in Table 18

Table 18 Exponent n of the power law and drug release mechanism from polymeric controlled delivery systems of different geometry

Exponent (n)			Drug release mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
0.5 <n< 1.0	0.45 <n<0.89	0.43 <n<0.85	Anomalous transport
1.0	0.89	0.85	Case II transport

Source : Siepmann, J. and N.A. Peppas, "Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC)." Advanced Drug Delivery Reviews 64: 163 – 174.

For SHL based tablet, the cylinder shape was applied as the geometry shape for selection of criterion to explain the release mechanism. As indicated in Table 19, most release exponents of SHL based tablets were within the range of 0.45 – 0.89, suggesting the anomalous transport or the non Fickian diffusion in which the combination of both diffusion and erosion controlled rate release were observed. The n value was decreased as increasing the amount of SHL. The result suggested that the release mechanism was changed from erosion control to more predominantly diffusion control as increasing amount of SHL. It was also noted that n value, especially at 40 – 50%w/w SHL – based tablets, was substantially close to 0.45 as increasing annealing temperature. The result indicated that the release mechanism was approached Fickian diffusion although the data was not clearly indicated by r^2 value of Higuchi's model. Since SHL was not soluble in acidic media and rapidly

polymerized at high temperature, it might be possible that the release of theophylline was diffusional control via the polymerized matrix of SHL polymer chains.

In order to study the drug release mechanism of SHL – based tablets in the condition simulating the environment in small intestine, the dissolution profiles in phosphate buffer pH 6.8 were also fitted with various models as tested in 0.1 N HCl. The r^2 of each model and some selected parameters are shown in Table 20. The release profiles of SHL – free tablet were well fitted with Hixson – Crowell model, suggesting the erosion controlled rate release as also observed in 0.1 N HCl. The release profiles were also well characterized by Korsmeyer – Peppas model with the release exponent of nearly 0.89 (case II transport), confirming the erosion mechanism. However, the release profiles of SHL – based tablet were more fitted with the Higuchi model and Korsmeyer – Peppas model with low n value. Additionally, the r^2 of Higuchi approached 1.0 and the n value of Korsmeyer – Peppas model was decreased as increasing SHL content and annealing temperature. The results were similar with those observed in acid medium, suggesting the diffusion controlled release rate. Nevertheless, the mechanism of drug release of SHL based tablets in phosphate buffer pH 6.8 was more fitted to Hixson – Crowell model as compared to that of 0.1 N HCl. For examples, the r^2 values from Hixson – Crowell model of 10, 20, 30, 40 and 50% SHL based tablet (before annealing) in phosphate buffer pH 6.8 were 0.998, 0.970, 0.817, 0.892, 0.753 while those in 0.1 N HCl were 0.834, 0.872, 0.784, 0.787, 0.688, respectively. Moreover, the n values from Korsmeyer – Peppas of SHL based tablets (before annealing) in phosphate buffer 6.8 were higher as compared with those obtained from drug release in 0.1 N HCl. The results suggested the more erosion rate control in phosphate buffer pH 6.8 which could be explained by the higher solubility

of SHL as increasing pH [14 – 16, 18]. It was also noteworthy to observe the decrement of n values after annealing, especially at 80°C and lower content of SHL, which suggested the more diffusion rate control. Therefore, it might be reasonable to conclude that SHL directly affected drug release mechanism through the matrix network formed during melting and polymerization.

Table 19 Curve fitting of drug release from SHL – based tablets in 0.1 N HCl (n = 3)

Formulations		Zero order model	First order model	Higuchi model	Hixson-Crowell model	Power law Equation model		
%SHL	annealing temperature					r^2	n	k
0	initial	r^2 = 0.8330	r^2 = 0.9427	r^2 = 0.9909	r^2 = 0.9924	0.9888	0.675	9.505
	40°C	r^2 = 0.9247	r^2 = 0.9795	r^2 = 0.8974	r^2 = 0.9991	0.9951	0.755	5.962
	60°C	r^2 = 0.9528	r^2 = 0.9547	r^2 = 0.8728	r^2 = 0.9900	0.9937	0.802	5.377
	80°C	r^2 = 0.9016	r^2 = 0.9684	r^2 = 0.9059	r^2 = 0.9972	0.9915	0.732	6.973
10	initial	r^2 = 0.6593	r^2 = 0.8852	r^2 = 0.9627	r^2 = 0.8342	0.9787	0.582	6.075
	40°C	r^2 = 0.6625	r^2 = 0.8972	r^2 = 0.9776	r^2 = 0.8421	0.9933	0.580	5.867
	60°C	r^2 = 0.9448	r^2 = 0.9957	r^2 = 0.8904	r^2 = 0.9887	0.9994	0.778	3.415
	80°C	r^2 = 0.8623	r^2 = 0.9806	r^2 = 0.9453	r^2 = 0.9581	0.9982	0.673	3.682
20	initial	r^2 = 0.7091	r^2 = 0.9191	r^2 = 0.9806	r^2 = 0.8724	0.9972	0.584	4.206
	40°C	r^2 = 0.6896	r^2 = 0.9073	r^2 = 0.9852	r^2 = 0.8554	0.9992	0.576	4.077
	60°C	r^2 = 0.6392	r^2 = 0.9046	r^2 = 0.9906	r^2 = 0.8436	0.9991	0.557	4.798
	80°C	r^2 = 0.5808	r^2 = 0.8700	r^2 = 0.9959	r^2 = 0.7993	0.9980	0.528	4.733
30	initial	r^2 = 0.5807	r^2 = 0.8524	r^2 = 0.9975	r^2 = 0.7843	0.9995	0.527	4.590
	40°C	r^2 = 0.6284	r^2 = 0.8686	r^2 = 0.9945	r^2 = 0.8079	0.9992	0.542	4.104
	60°C	r^2 = 0.5923	r^2 = 0.8612	r^2 = 0.9964	r^2 = 0.7933	0.9990	0.531	4.436
	80°C	r^2 = 0.5825	r^2 = 0.8550	r^2 = 0.9981	r^2 = 0.7853	0.9982	0.504	4.483
40	initial	r^2 = 0.6100	r^2 = 0.8495	r^2 = 0.9973	r^2 = 0.7868	0.9977	0.513	4.046
	40°C	r^2 = 0.5729	r^2 = 0.8332	r^2 = 0.9981	r^2 = 0.7643	0.9981	0.501	4.289
	60°C	r^2 = 0.5567	r^2 = 0.8215	r^2 = 0.9986	r^2 = 0.7508	0.9986	0.496	4.371
	80°C	r^2 = 0.4288	r^2 = 0.7792	r^2 = 0.9917	r^2 = 0.6913	0.9973	0.458	4.581
50	initial	r^2 = 0.4619	r^2 = 0.7681	r^2 = 0.9936	r^2 = 0.6876	0.9963	0.470	4.336
	40°C	r^2 = 0.5015	r^2 = 0.7955	r^2 = 0.9954	r^2 = 0.7195	0.9967	0.480	4.246
	60°C	r^2 = 0.4995	r^2 = 0.7832	r^2 = 0.9972	r^2 = 0.7085	0.9986	0.479	4.090
	80°C	r^2 = 0.4473	r^2 = 0.7579	r^2 = 0.9882	r^2 = 0.6749	0.9989	0.442	4.036

Table 20 Curve fitting of drug release from SHL – based tablets in buffer pH 6.8 (n = 3)

Formulations		Zero order model	First order model	Higuchi model	Hixson-Crowell model	Power law Equation model		
%SHL	annealing temperature					r^2	n	k
0	initial	r^2 = 0.9938	r^2 = 0.9802	r^2 = 0.8124	r^2 = 0.9930	0.9941	0.935	4.327
	40°C	r^2 = 0.9683	r^2 = 0.9913	r^2 = 0.8623	r^2 = 0.9993	0.9937	0.829	6.490
	60°C	r^2 = 0.9977	r^2 = 0.9734	r^2 = 0.7949	r^2 = 0.9883	0.9962	0.977	3.738
	80°C	r^2 = 0.9855	r^2 = 0.9845	r^2 = 0.8401	r^2 = 0.9973	0.9969	0.878	5.603
10	initial	r^2 = 0.9603	r^2 = 0.9981	r^2 = 0.8863	r^2 = 0.9982	0.9994	0.798	5.400
	40°C	r^2 = 0.9483	r^2 = 0.9995	r^2 = 0.8876	r^2 = 0.9933	0.9993	0.783	5.945
	60°C	r^2 = 0.9923	r^2 = 0.9930	r^2 = 0.8378	r^2 = 0.9979	0.9991	0.903	3.114
	80°C	r^2 = 0.8751	r^2 = 0.9793	r^2 = 0.9322	r^2 = 0.9567	0.9962	0.694	4.592
20	initial	r^2 = 0.8959	r^2 = 0.9887	r^2 = 0.9236	r^2 = 0.9703	0.9964	0.711	3.594
	40°C	r^2 = 0.9134	r^2 = 0.9962	r^2 = 0.9144	r^2 = 0.9832	0.9968	0.730	3.637
	60°C	r^2 = 0.8499	r^2 = 0.9739	r^2 = 0.9491	r^2 = 0.9463	0.9963	0.659	3.832
	80°C	r^2 = 0.6895	r^2 = 0.9011	r^2 = 0.9894	r^2 = 0.8481	0.9950	0.551	4.292
30	initial	r^2 = 0.6584	r^2 = 0.8708	r^2 = 0.9913	r^2 = 0.8165	0.9976	0.551	4.492
	40°C	r^2 = 0.6949	r^2 = 0.9029	r^2 = 0.9883	r^2 = 0.8520	0.9985	0.565	4.490
	60°C	r^2 = 0.7336	r^2 = 0.9197	r^2 = 0.9854	r^2 = 0.8737	0.9961	0.570	3.891
	80°C	r^2 = 0.6949	r^2 = 0.8819	r^2 = 0.9960	r^2 = 0.8327	0.9991	0.536	3.941
40	initial	r^2 = 0.7847	r^2 = 0.9270	r^2 = 0.9862	r^2 = 0.8921	0.9993	0.580	3.297
	40°C	r^2 = 0.7293	r^2 = 0.8922	r^2 = 0.9931	r^2 = 0.8501	0.9989	0.551	3.670
	60°C	r^2 = 0.7888	r^2 = 0.9264	r^2 = 0.9884	r^2 = 0.8912	0.9985	0.571	3.028
	80°C	r^2 = 0.6672	r^2 = 0.8671	r^2 = 0.9973	r^2 = 0.8157	0.9973	0.510	3.669
50	initial	r^2 = 0.6197	r^2 = 0.8053	r^2 = 0.9988	r^2 = 0.7529	0.9988	0.494	4.116
	40°C	r^2 = 0.6557	r^2 = 0.8248	r^2 = 0.9979	r^2 = 0.7774	0.9978	0.506	3.851
	60°C	r^2 = 0.6066	r^2 = 0.8078	r^2 = 0.9992	r^2 = 0.7539	0.9997	0.486	3.888
	80°C	r^2 = 0.5964	r^2 = 0.8129	r^2 = 0.9965	r^2 = 0.7553	0.9997	0.465	3.618

1.2 Hydrolyzed shellac – based matrix tablet

As indicated in the previous chapter, hydrolyzed shellac (HS) demonstrated some different properties from SHL. The lower acid value was observed in SHL while HS was more rapidly polymerized as compared to SHL. As a result, the different properties of tablet containing HS might be observed. In order to investigate the effect of HS on the tableting properties, the HS based tablets were prepared by the same method (as described in section of SHL based tablets) and evaluated for their tableting properties. With regard to the influence of polymerization, the HS based tablets were also annealed at 80°C and comparatively evaluated for their tableting properties.

The tableting properties of tablets containing different amounts of HS (before annealing) are shown in Table 21. The weight, hardness and diameter of HS based tablets could be controlled in the desired range by using the same criteria as specified in SHL – based tablets. The weight variation was less than 1%. The average thickness was in the range of 3.61 – 3.66 mm while slight increase of thickness was observed as increasing amount of HS. The result related to low density and compressibility of HS as compared to other excipients in the formulation. However, the average of diameter was in the range of 9.52 – 9.54 mm and did not differ among formulations.

The tableting properties of 80°C annealed HS tablets are shown in Table 22. With regard to the result of unannealed HS tablets, similar tableting properties of annealed HS tablets were observed. The result suggested that the annealing process did not significantly affect weight variation, thickness and diameter.

Figure 18 shows the effect of HS content and annealing process on hardness of tablets. The initial hardness of all formulations was controlled within the range of 60±10 N. However, the formulations containing high amount of HS (40%w/w and 50%w/w) showed a poor ability to compress into the tablets which might be a consequence of lower compressibility of HS. Additionally, tablets with high amount of SHL also showed a low decreased hardness. Therefore, the elastic recovery of tablet might be occurred after removal of the compression force [131, 144]. The result was correlated well with increased thickness after increment of HS content and storage.

After annealing at 80^{o}C, the hardness of tablet formulations containing HS less than 40%w/w was not clearly changed. However, the effect of annealing process on hardness was obviously observed in tablets with 40 and 50% w/w HS. The results were similar as observed in SHL based tablets, suggesting that the HS also formed the cohesive matrix that increased the strength of tablets. Nevertheless, the hardness of HS based tablets was relatively lower as compared to SHL based tablets.

As described in previous section, HS was a partially hydrolyzed product of SHL. It contained the higher free carboxyl and hydroxyl groups which were readily esterified to form the condensed network after annealing [19, 131, 134]. By this reason, the HS should rapidly form the network and provide more tablet hardness than SHL. However, opposite results were observed. It might be possible that the increased hardness was not simply due to the formation of polymerized network. As reported by some works, the compressibility of tablets was a result of the bond formation among the excipients and incorporated drug. For examples, the hydroxyl groups of microcrystalline cellulose could form the H – bond, resulting in

the increased tablet hardness [145]. In this case, the reduced number of carboxyl and hydroxyl groups due to rapid polymerization of HS might also decrease the possibility of bond formation among functional groups which negatively affected the hardness of tablets.

Table 21 Properties of HS – based tablet (n = 20)

Formula	Weight (mg)	Thickness (mm)	Diameter (mm)
HS0	302.7±0.5	3.61±0.01	9.53±0.01
HS10	302.4±1.3	3.61±0.01	9.54±0.01
HS20	302.4±1.0	3.65±0.02	9.53±0.02
HS30	303.1±1.6	3.63±0.05	9.52±0.01
HS40	303.2±1.3	3.65±0.01	9.52±0.01
HS50	304.4±1.0	3.66±0.01	9.54±0.02

Table 22 Properties of HS – based matrix tablet after annealing at 80°C (n = 20)

Formula	Weight (mg)	Thickness (mm)	Diameter (mm)
HS0	300.9±1.5	3.66±0.01	9.52±0.01
HS10	301.5±0.9	3.66±0.02	9.54±0.02
HS20	300.6±1.5	3.74±0.03	9.54±0.02
HS30	299.2±0.9	3.75±0.03	9.54±0.04
HS40	300.2±1.2	3.82±0.01	9.52±0.01
HS50	299.9±1.4	3.76±0.01	9.53±0.02

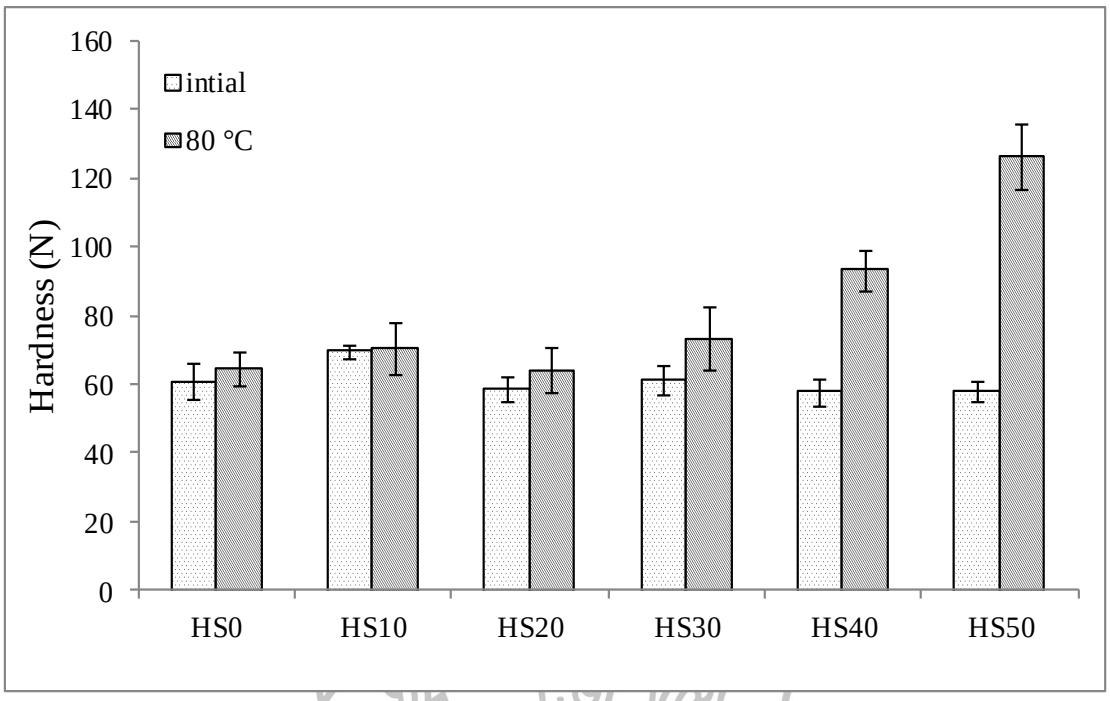


Figure 18 Effect of HS content and annealing on tablet hardness (n = 20)

To study the influence of HS content and annealing on disintegration time, six tablets from each formulation were randomly selected and tested in 0.1 N HCl for 2 h. The non – disintegration tablets from acid media were further investigated in phosphate buffer pH 6.8 for 3 h. The disintegration time of HS based tablets in 0.1 N HCl and phosphate buffer pH 6.8 are shown in Tables 23 and 24, respectively.

As indicated in Table 23, the tablets without HS were rapidly disintegrated in 0.1 N HCl within 2 min whereas the extended disintegration was observed as increasing the amount of HS. At 50%w/w of HS, the disintegration time was more than 120 min. This might be explained by the insolubility of HS in acidic medium which also observed in the case of SHL. When compared disintegration time between SHL and HS – based matrix tablets, the result showed that the tablets

containing HS disintegrated more rapidly than SHL – based matrix tablets. For example, the disintegration time of S30 (30%w/w of SHL) in 0.1 N HCl was more than 120 min whereas that of HS30 (30%w/w of HS) was about 47 min, suggesting the lower binding properties of HS as compared to SHL. The results were in good agreement with the lower compressibility of HS based tablets during tableting process. As previously reported, the solubility of films prepared from HS was significantly higher as compared to those prepared from SHL [131]. Therefore, the faster disintegration of HS based tablets might be also due to the enhanced solubility of HS.

The effect of annealing process on the disintegration time in 0.1 N HCl of HS-based matrix tablets is shown in Table 23. At the low content of HS (HS0 – HS20), disintegration time was not affected by annealing process. However, the tablets containing more than 20%w/w of HS (HS30 – HS50) were tolerated with acid environment for more than 120 min. The results were in good agreement with the increased hardness as described above.

The disintegration time in phosphate buffer (pH 6.8) of some selected HS tablets formulations with incompletely disintegrated in 0.1 N HCl is shown in Table 24. The HS50 tablets before annealing were completely disintegrated within 20 min. However, the annealed tablets with more than 30%w/w HS were not disintegrated. These results suggested that both HS content and annealing process were important factors for controlling the erosion of tablets. Similar results were also observed in SHL based tablets as descried earlier.

Figures 19 – 21 demonstrate the percentage weight loss of HS based tablets after disintegration test in 0.1 N HCl phosphate buffer pH 6.8 and both media, respectively. In acid condition, tablet containing HS less than 50%w/w (HS0, HS10, HS20, HS30, and HS40) was completely disintegrated, resulting in 100% weight loss while the weight loss of HS50 was about 20%w/w and not different from that of S50. The result suggested that the acid resistance of HS was still remaining even after partial hydrolysis. In contrast, the mass of HS50 tablets was lost around 80%w/w whereas that of S50 tablets was lost only 45%w/w in buffer condition. Therefore, the partial hydrolysis of SHL might improve the solubility of SHL in buffer condition [15], resulting in more erosion. With regard to the result of total weight loss (Figure 21), annealing process directly affected the reduced weight loss especially at high level of HS. The same finding was also observed in SHL – based tablets, confirming that HS content and annealing process directly controlled disintegration of tablets.

Table 23 Effect of HS content and annealing process on disintegration time of tablets in 0.1 N HCl (n = 6)

Formula	Disintegration in 0.1 N HCl (min)	
	Initial	80°C
HS0	1.91±0.86	7.86±2.90
HS10	18.72±12.22	9.12±8.88
HS20	38.11±6.88	15.59±11.69
HS30	46.55±10.57	>120
HS40	101.08±12.35	>120
HS50	>120	>120

Table 24 Effect of HS content and annealing process on disintegration time of tablets in phosphate buffer pH 6.8 (n = 6)

Formula	Disintegration in buffer pH 6.8 (min)	
	Initial	80°C
HS0	-	-
HS10	-	-
HS20	-	-
HS30	-	65.47±2.50
HS40	-	> 120
HS50	14.42±5.24	> 120

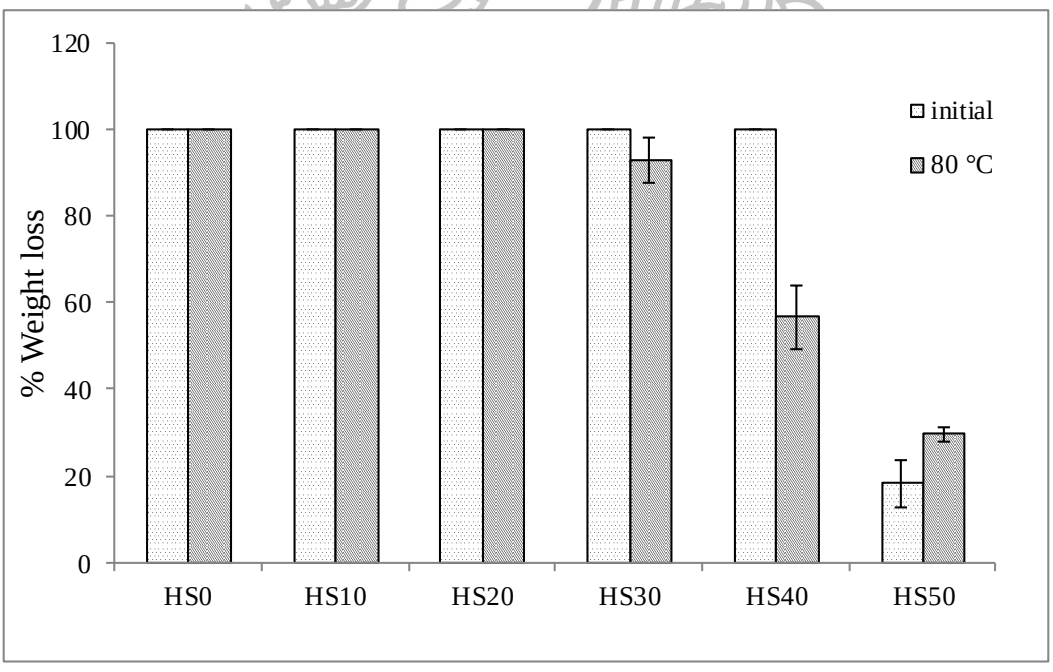


Figure 19 Percentage weight loss in 0.1 N HCl of HS – based tablets before and after annealing at 80°C (n = 6)

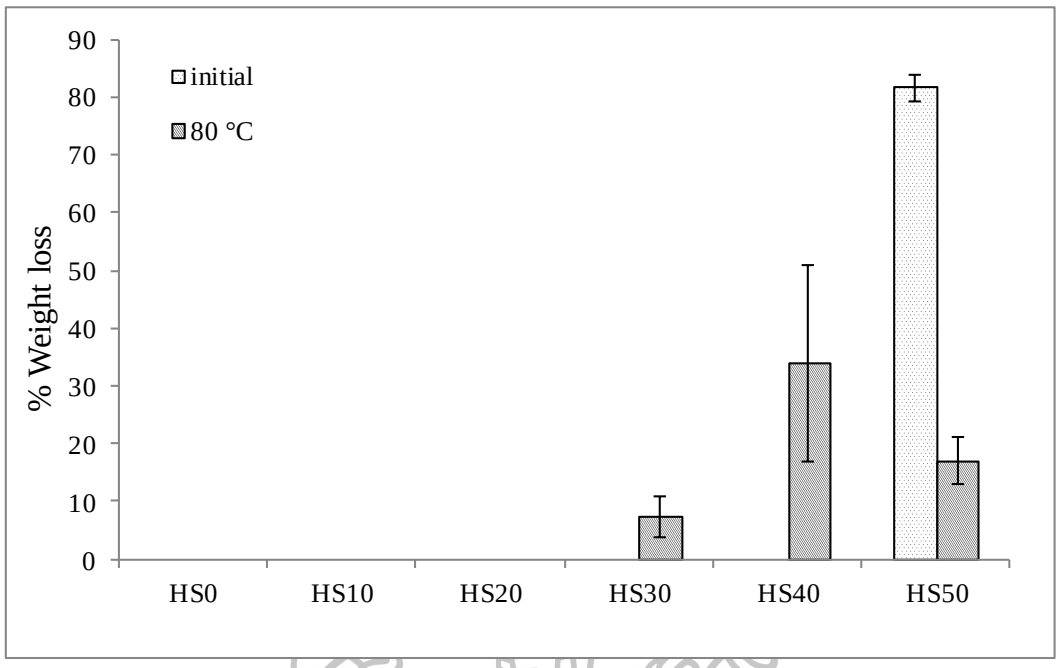


Figure 20 Percentage weight loss in phosphate buffer pH 6.8 of HS – based tablets before and after annealing at 80°C (n = 6)

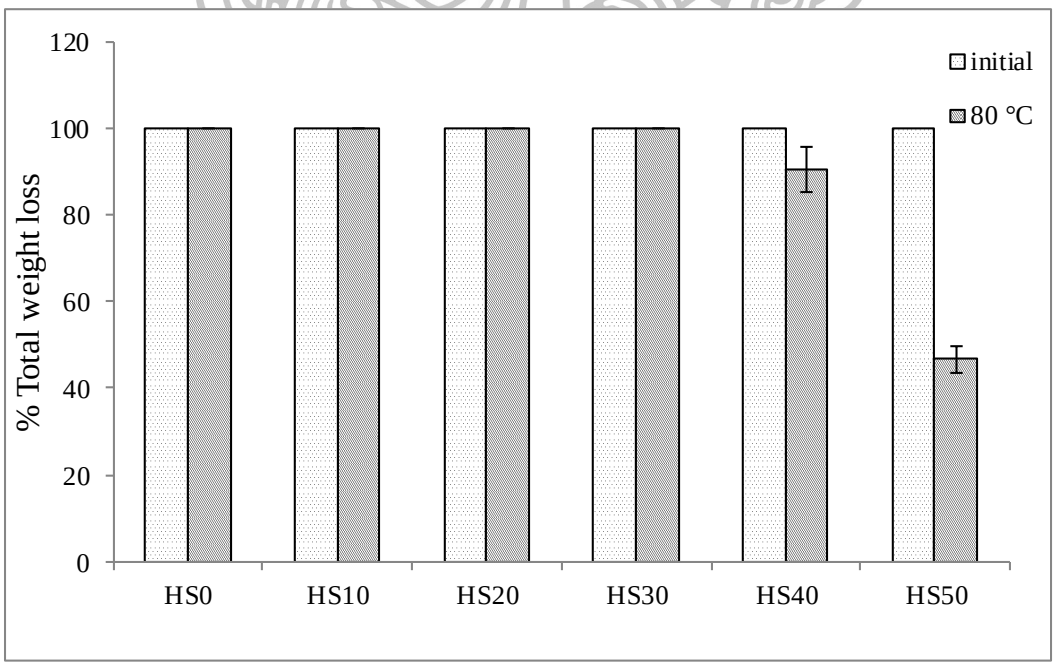


Figure 21 Total weight loss in both media of HS – based tablets before and after annealing at 80°C (n = 6)

In order to further investigate the effect of HS content and annealing process on the drug release, the dissolution profiles of all HS formulations were comparatively evaluated as presented in Figures 22 – 24. Drug release was continuously studied in 0.1N HCl for 2 h and phosphate buffer pH 6.8 for 10 h.

Figure 22 shows drug release profile of unannealed tablets with different amounts of HS. The completed drug release from HS0 formulation was observed within 1 h. However, the retarded drug release was clearly indicated for formulation containing HS. For HS10, HS20 and HS30 formulations, the completed drug release was extended to 120, 240 and 600 min, respectively while the sustained drug release over 12 h was observed for HS40 and HS50 formulations. The result suggested that HS also could also act a matrix forming agent for controlled drug release. With regard to the results of disintegration test and percent weight loss of HS and SHL based tablet, the enhanced drug release of HS based tablets over SHL based tablets was expected. However, the amount of drug released was not clearly increased especially for formulation containing high amount of HS. In this case, it might be possible that theophylline was still trapped in the eroded parts of HS based tablets.

Drug release profiles of HS based tablet after annealing process at 80^{o}C are shown in Figures 23 – 24.The drug release profiles of annealed HS0 and HS10 were similar as compared to those of unannealed tablet while the more sustained release of annealed tablets over unannealed tablet was clearly observed as increasing HS content to 20%w/w. The result suggested that the drug release profile depended on both HS content and annealing process. At lower content of HS, the polymerized network due to HS might be not sufficient to trap the drug in sinuosity of the polymer chain. Additionally, annealing processes directly affected the increment

of tensile and shear moduli properties resulting in improved packing between polymer chains that also retarded drug release from HS based tablets [19, 131, 145]. It was also noted that the annealing process had a lower effect on drug release of HS based tablets as compared to those of SHL based tablets. At 80°C annealing temperature, the SHL annealed tablets showed more remarkably controlled drug release as compared to HS annealed tablets. The results well agreed with the lower hardness of annealed HS based tablets as previously discussed in Figure 18. In this case, the improved packing in SHL based tablets should more influence on retardation of drug release although the polymerization of SHL was lower as compared to HS.

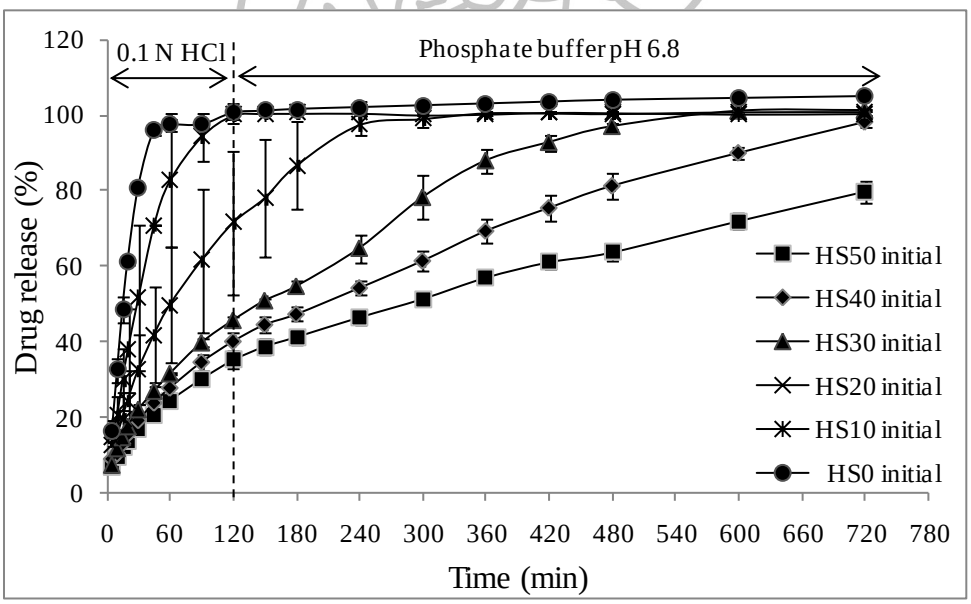


Figure 22 Drug release profiles of unannealed HS – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

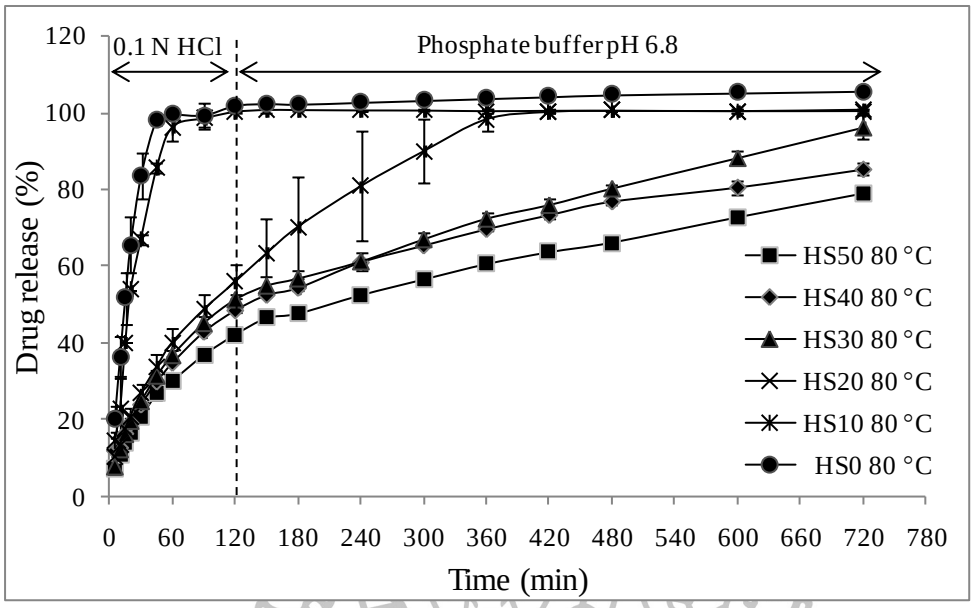


Figure 23 Drug release profiles of 80°C annealed HS – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

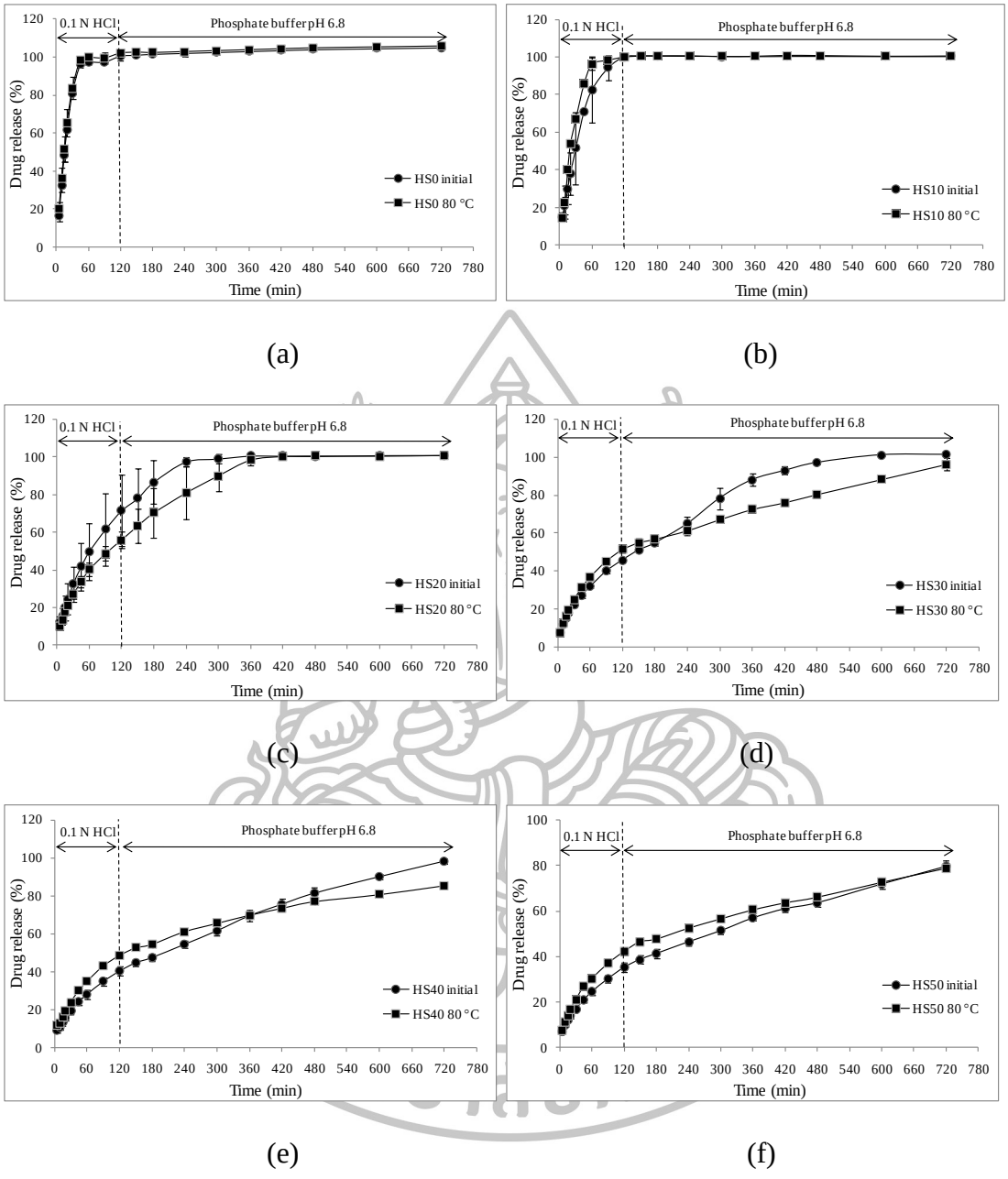


Figure 24 Effect of annealing process on drug release profiles of tablets with different amounts of HS (a) 0% HS, (b) 10% HS, (c) 20% HS, (d) 30% HS, (e) 40% HS, (f) 50% HS (n = 3)

1.3 Shellac ammonium – based tablet

Due to its acidic character, SHL was mainly dissolved in alcoholic solution and dissolved in the solution above pH 7.0 that it was not suitable controlled drug release in GI tract. SHL also pronounced hardening induced by a continuing polymeriazation process. This resulted in changing gastric resistance and decreasing intestinal fluid solubility, both leading to major change in drug dissolution profiles. To solve these problems, salts formation was used to improve SHL solubility and diminish polymerization during storage.

Shellac ammonium salt (SA) based tablets at various content were fabricated and evaluated by the same method as previous described in section 1.1 and 1.2 (SHL and HS based tablets). The properties of SA tablets (before annealing) are presented in Table 25. The weight variation of tablets with different amount of SA (0% to 50%w/w) could be controlled in the desired range by using the same criteria as specified in SHL and HS – based tablets. The average thickness was slightly increased as increasing amount of SA which was resulted from the lower bulk density of SA as compared to other excipients.

The effect of annealing on properties of SA – based tablets is shown in Table 26. Except for the hardness, weight, thickness as well as diameter were not clearly changed even after annealing at 80°C. To study consequence of SA content and annealing on change of hardness, the initial hardness of SA – based tablets was controlled within the range of 60±10 N (Figure 25). As compared with the results of annealed SHL and HS – based tablets (Figures 10 and 18), the hardness of annealed SA tablets was not obviously increased as raising amount of SA. The increased hardness was clearly observed for only SA50 based tablets. The result suggested the

less cohesive property after annealing of SA. With regard to the result of thermal analysis (Figure 56), SHL and HS showed clearly melting characteristic at the temperature less than 80°C. However, the SA did not show clear melting peak although heating up to 200°C. Therefore, the less cohesive property of SA might be involved with the melting. After annealing process, SHL and HS could be melted and possibly acted as binding agent, resulting in the increased hardness of tablet over SA. Additionally, the increased hardness of tablets containing SHL and HS was also resulted from polymerization as previously discussed in earlier sections. For SA, the polymerization could be protected by salt formation with ammonium [114]. Therefore, the hardness of annealed SA tablets was not clearly increased as compared to that of SHL and HS annealed tablets. It was noted that hardness of SA50 tablets was increased from 70 N to more than 100 N after annealing. In this case, it might be possible that the large amount of SA could also provide the polymeric network that could partially impart the compressibility of the tablets. Moreover, the ammonium groups might be partly leached out due to weak interaction with carboxylate resulting in free carboxyl group after annealing [114]. Consequently, the polymerization among free carboxyl and hydroxyl groups occurred and caused the increased hardness of annealed SA tablets.

Table 25 Properties of SA – based tablets (n = 20)

Formula	Weight (mg)	Thickness (mm)	Diameter (mm)
SA0	300.5±0.1	3.44±0.12	9.56±0.01
SA10	300.5±0.1	3.48±0.03	9.55±0.01
SA20	301.1±0.1	3.68±0.03	9.54±0.01
SA30	300.7±0.2	3.71±0.04	9.54±0.01
SA40	301.7±0.2	3.83±0.04	9.54±0.05
SA50	300.6±0.3	3.87±0.04	9.53±0.01

Table 26 Properties of SA – based tablets after annealing at 80°C (n = 20)

Formula	Weight (mg)	Thickness (mm)	Diameter (mm)
SA0	300.5±0.1	3.39±0.04	9.56±0.01
SA10	299.3±0.1	3.47±0.04	9.55±0.01
SA20	300.0±0.2	3.72±0.04	9.55±0.01
SA30	299.0±0.1	3.76±0.05	9.54±0.01
SA40	300.8±0.1	3.92±0.06	9.55±0.01
SA50	299.4±0.1	3.95±0.04	9.55±0.01

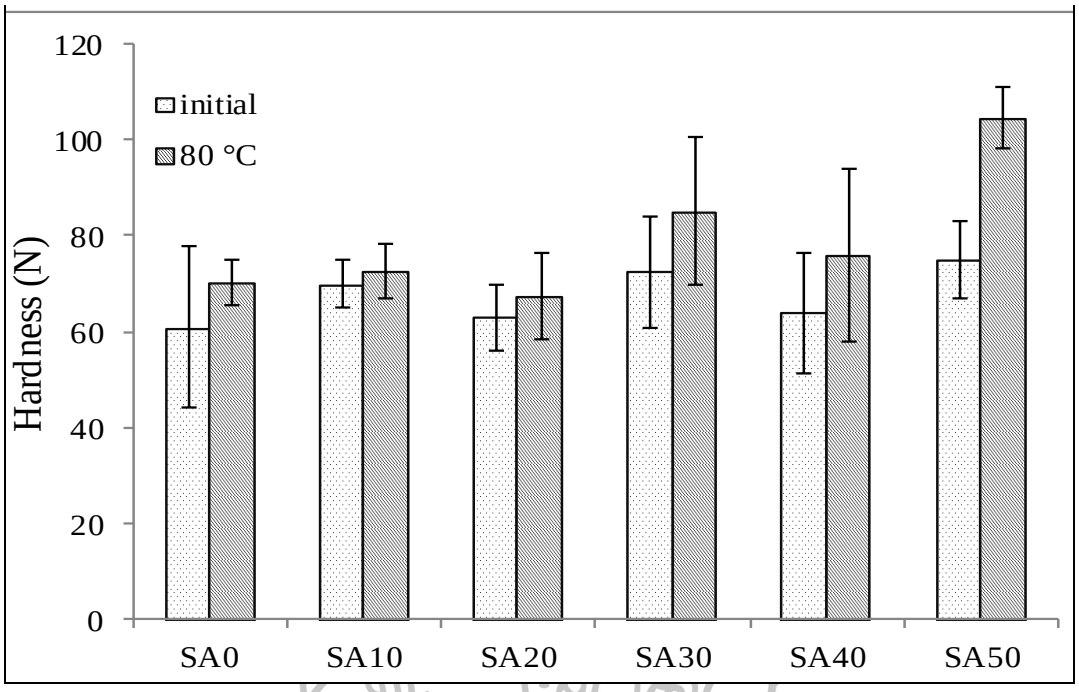


Figure 25 Effect of SA content and annealing on hardness of tablets (n = 20)

In order to study consequence of the SA content and annealing process on the disintegration properties, the tablets was evaluated in 0.1 N HCl and followed by phosphate buffer pH 6.8 by the same method as previously described for SHL and HS tablets. Table 27 indicates the disintegration time in 0.1 N HCl of tablets with different amounts of SA. With increasing amount of SA, the extended disintegration time was observed. At the level from 30%w/w SA, disintegration time of tablets in acid condition was more than 120 min. However, the less retardation of disintegration was observed as compared to SHL – based tablets. This might be mainly due to the fact that the solubility of SA was improved after salt formation [114, 132]. The disintegration time of SA based tablets after annealing at 80°C was also evaluated. For SA10, annealing process had not clearly an effect on disintegration time. However, the disintegration time was slightly increased as increasing SA content to

20%w/w although the shorter disintegration time was observed as compared to that of SHL annealed tablets. The result agreed well with the increased hardness as described above.

The non – disintegrated SA based tablets (SA30, SA40 and SA50) from acid medium were further investigated in phosphate buffer pH 6.8 as shown in Table 28. The result demonstrated that tablets containing SA at level from 30%w/w with or without annealing were not completely disintegrated over 180 min, suggesting the reduced erosion of tablets even at higher pH.

Table 27 Effect of SA content and annealing process on disintegration time of tablets in 0.1 N HCl (n = 6)

Formula	Disintegration in 0.1 N HCl (min)	
	Initial	80°C
SA0	17.4±2.9	19.1±5.8
SA10	33.9±4.7	35.3±3.1
SA20	40.6±1.8	67.7±4.9
SA30	>120	>120
SA40	>120	>120
SA50	>120	>120

Table 28 Effect of SA content and annealing process on disintegration time of tablets in phosphate buffer pH 6.8 (n = 6)

Formula	Disintegration in buffer pH 6.8 (min)	
	Initial	80°C
SA0	-	-
SA10	-	-
SA20	-	-
SA30	> 180	> 180
SA40	> 180	> 180
SA50	> 180	> 180

The percentage weight loss of non – disintegrated tablets after disintegration test is shown in Figures 26 – 28. The weight loss had a tendency to decrease in all media as increasing amount of SA content and after annealing. The results correlated well with increased hardness and disintegration and similar to those obtained from SHL and HS based matrix tablets.

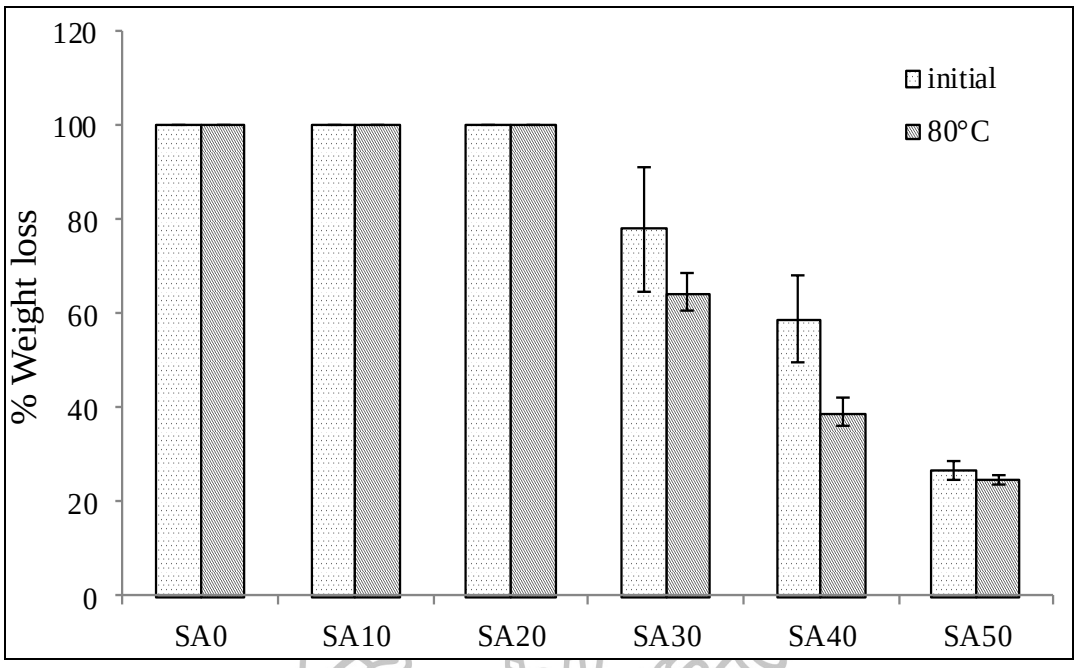


Figure 26 Percentage weight loss in 0.1 N HCl of SA – based tablets before and after annealing at 80°C (n = 6)

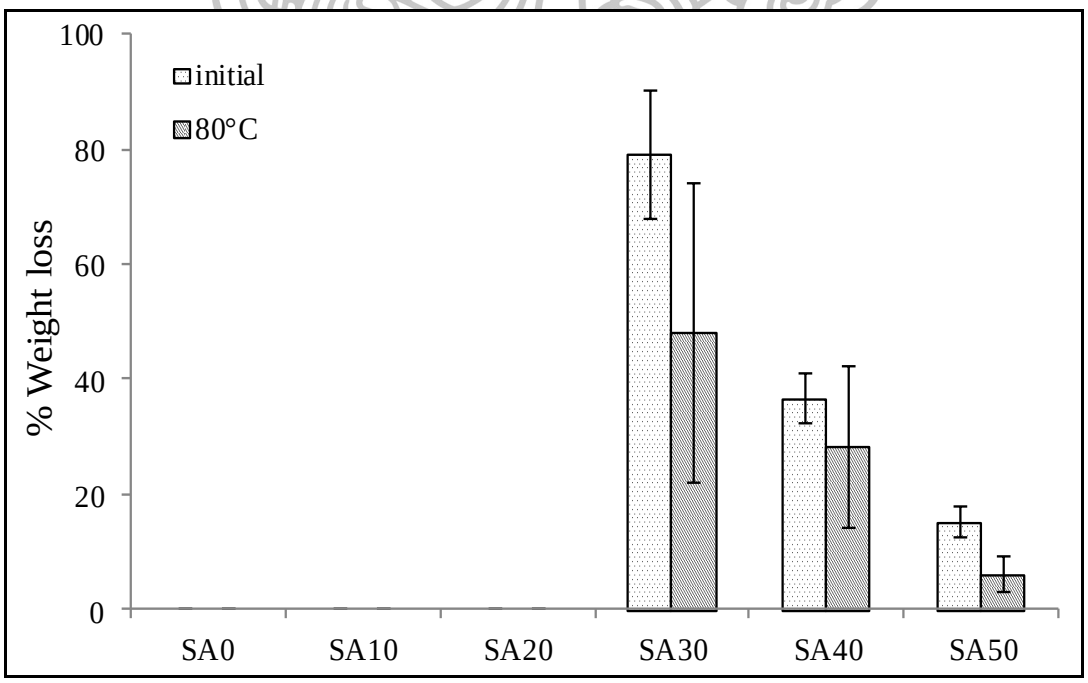


Figure 27 Percentage weight loss in phosphate buffer pH 6.8 of SA – based tablets before and after annealing at 80°C (n = 6)

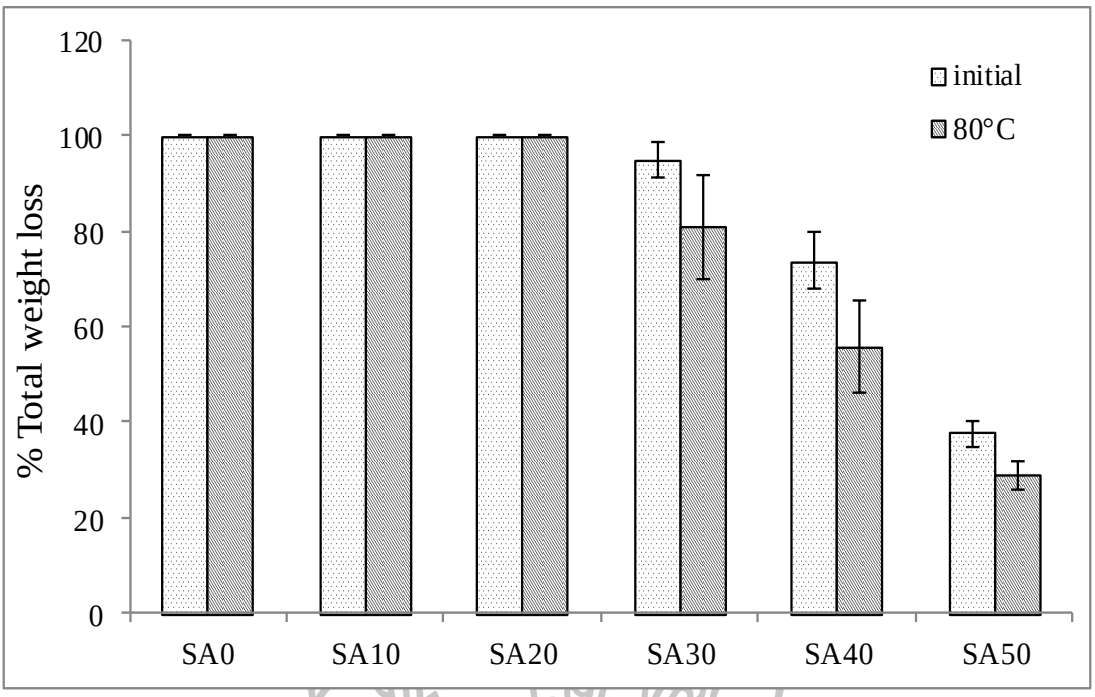


Figure 28 Total weight losses in both media of SA – based tablets before and after annealing at 80°C (n = 6)

Figure 29 expresses *in vitro* drug release profiles of theophyline from unannealed SA – based tablets. The SA0 and SA10 based tablets demonstrated complete drug release within 120 min. As increasing the amount of SA, the more retarded drug release was observed. However, only SA40 and SA50 based tablets could extend drug release over 12 h. It was also noted that the drug release profiles in phosphate buffer region of SA – based tablets showed more concave up characteristic as compared to those of SHL – based tablets. The result might be explained by the increased solubility of SA after salt formation.

Drug release profiles of SA – based tablets after annealing process at 80^{o}C is shown in Figure 30 – 31. Drug release patterns from SA0 and SA10 annealed tablets were similar to those of unannealed tablets. For SA20, SA30, SA40 and SA50

annealed tablets, the drug release patterns in 0.1 N HCl were not obviously different as compared to unannealed tablets while the slower drug release was observed for in buffer region. The result suggested the retarded drug release due to polymerization of SA. As previously reported, the salt formation increased solubility of SHL at intestinal pH while was not clearly affected the solubility in acid media [18]. Therefore, it might be possible that the pronounced effect of annealing on drug release was more clearly observed in buffer region.

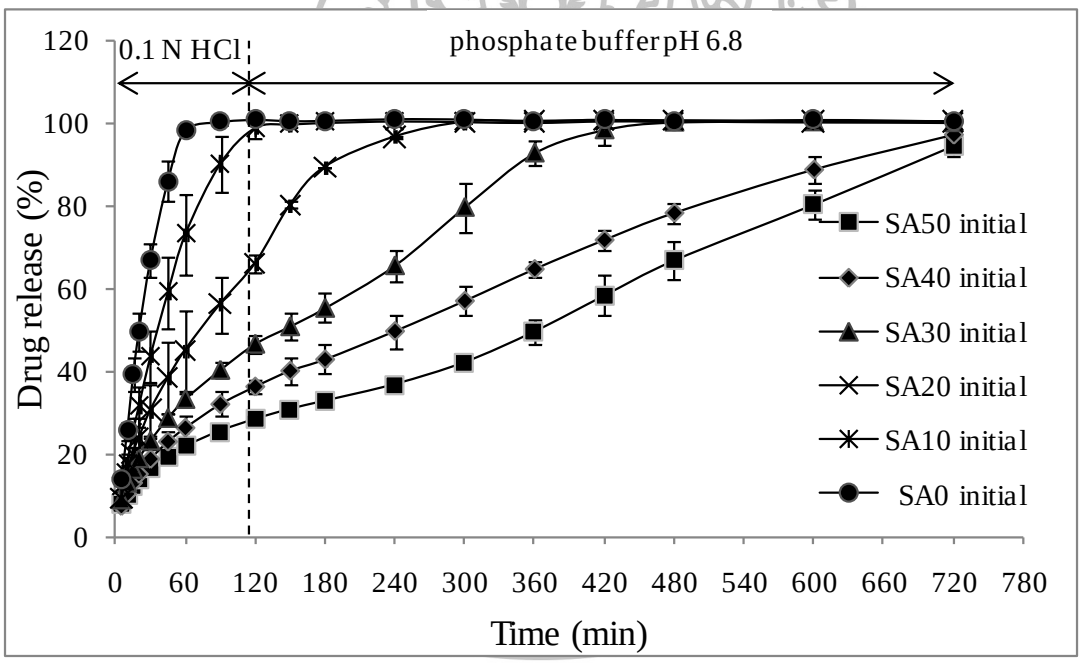


Figure 29 Drug release profiles of unannealed SA – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

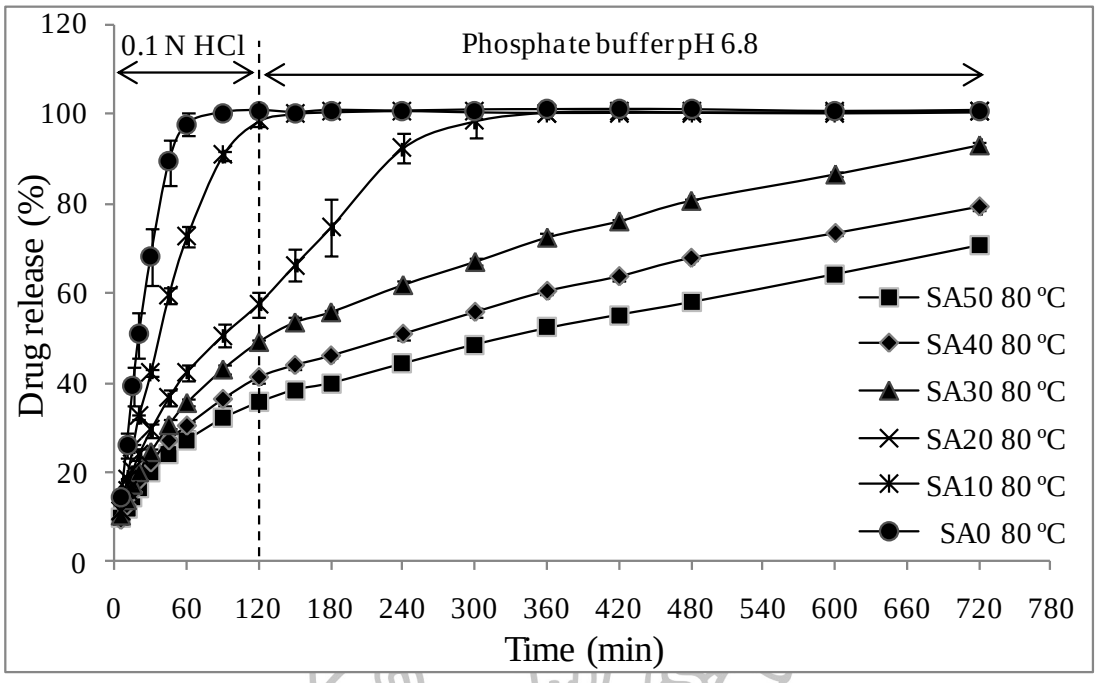


Figure 30 Drug release profiles of 80°C annealed SA – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

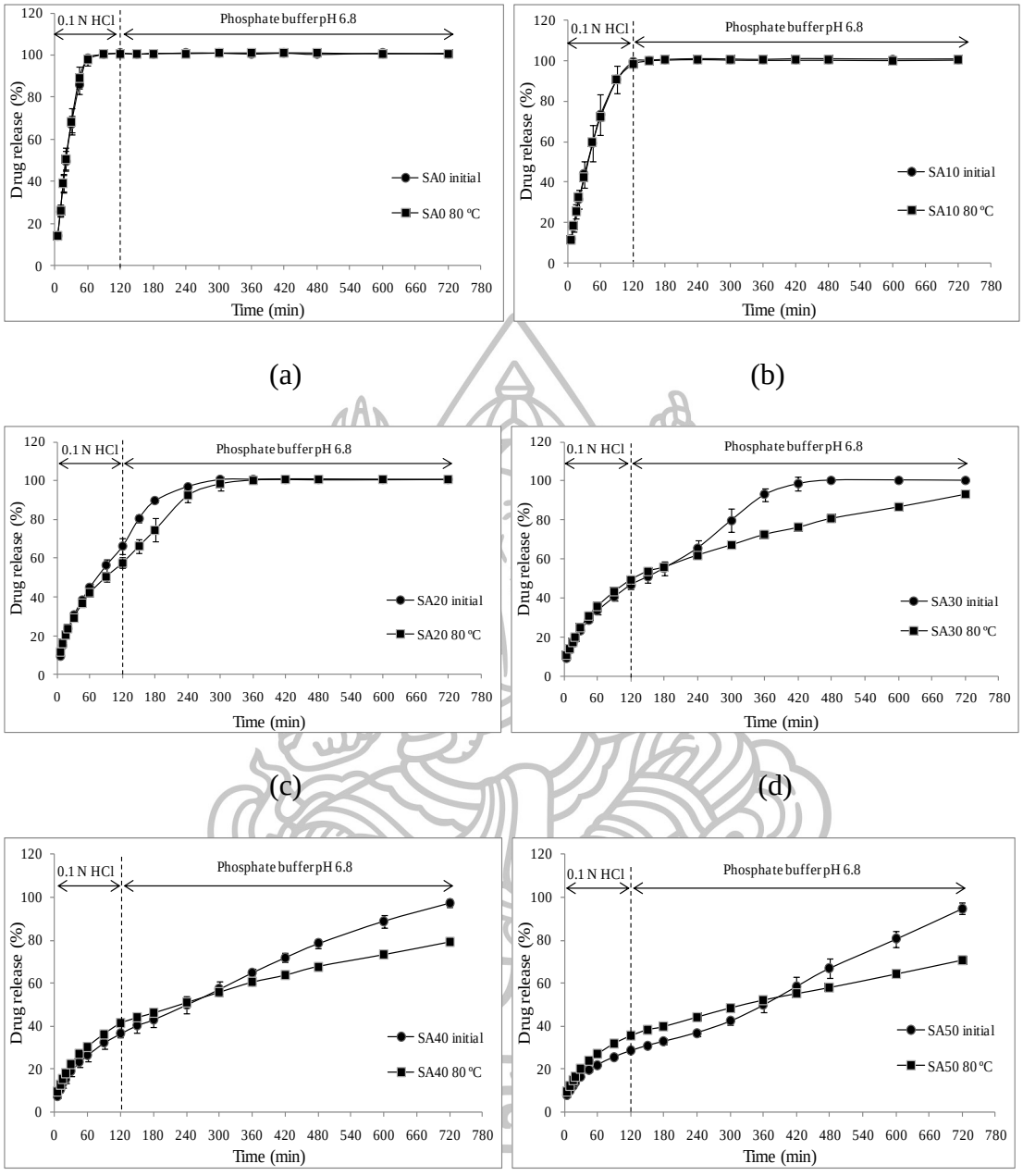


Figure 31 Effect of annealing process on drug release profiles of tablets with different amount of SA (a) 0% SA, (b) 10% SA, (c) 20% SA, (d) 30% SA, (e) 40% SA, (f) 50% SA (n = 3)

1.4 Shellac meglumine/ammonium – based matrix tablet

According to the previous reports, the salt formation with various bases could improve solubility and stability of SHL [18]. Among the bases used, the meglumine demonstrated the most probable salt forming in terms of stability and solubility. However, shellac meglumine salt was too soft, sticky and difficult to grind into fine particle. Meanwhile, the shellac ammonium salt (SA) showed the brittle characteristic although the less stability was observed. Therefore, the use of composite salt formation could compensate the disadvantage of each salt. With regard to the results of Limmatvapirat *et al.*, the SHL salt with meglumine:ammonium at the ratio 60:40 showed the optimized properties in terms of stability and mechanical properties [18]. In this study, shellac meglumine ammonium salt (SMA) was selected to further study as a matrix forming agent for controlled drug release. The SMA salt was pulverized and formulated into the tablets by the same methods as previously described in sections of SHL, HS, SA based tablets.

The tablets containing different amount of SMA were successfully fabricated although the sticking problem was observed during compression process. The tablet properties were evaluated by the same methods as previous described in sections 1.1 – 1.3. The weight variation, thickness and diameter of SMA based tablets before and after annealing are presented in Table 29 and 30, respectively. The weight variation of SMA – based tablets was well controlled in the specified range. The average thickness has a tendency to increase as increasing SMA content which was a result of low bulk density of SMA. The results were similar to those described in SHL, HS and SMA – based tablets, suggesting that the SMA was also could be used

as a material for fabricating of tablets although sticking problem needed to be concerned.

The effect of annealing on the change of hardness of SMA – based tablets is shown in Figure 32. The initial hardness could be controlled within the range of 60±10 N although tablets with high amount of SMA needed more compression force as compared to SHL. After annealing, the hardness had a tendency to increase for tablets containing 30% SMA or more (SMA30, SMA40 and SMA50). However, it was not significantly different. These might be explained by the protect polymerization due to salt formation [16, 114, 132]. The results were well agreed with the lesser amount of percent insoluble solid of SMA as compared to SHL as discussed in section.

Table 29 Properties of SMA – based tablets (n = 20)

Formula	Weight (mg)	Thickness (mm)	Diameter (mm)
SMA0	300.5±0.1	3.44±0.12	9.56±0.01
SMA10	300.5±0.3	3.64±0.05	9.54±0.07
SMA20	302.1±0.4	3.76±0.03	9.53±0.04
SMA30	302.5±0.1	3.73±0.06	9.52±0.06
SMA40	303.4±0.2	3.86±0.07	9.51±0.05
SMA50	299.7±0.2	3.98±0.06	9.52±0.04

Table 30 Properties of SMA – based tablets after annealing at 80°C (n = 20)

Formula	Weight (mg)	Thickness (mm)	Diameter (mm)
SMA0	300.5±0.1	3.39±0.04	9.56±0.02
SMA10	300.5±0.2	3.65±0.18	9.53±0.01
SMA20	301.3±0.1	3.73±0.06	9.53±0.01
SMA30	301.8±0.3	3.73±0.07	9.52±0.01
SMA40	301.8±0.1	3.79±0.05	9.52±0.01
SMA50	300.3±0.1	3.89±0.03	9.52±0.01

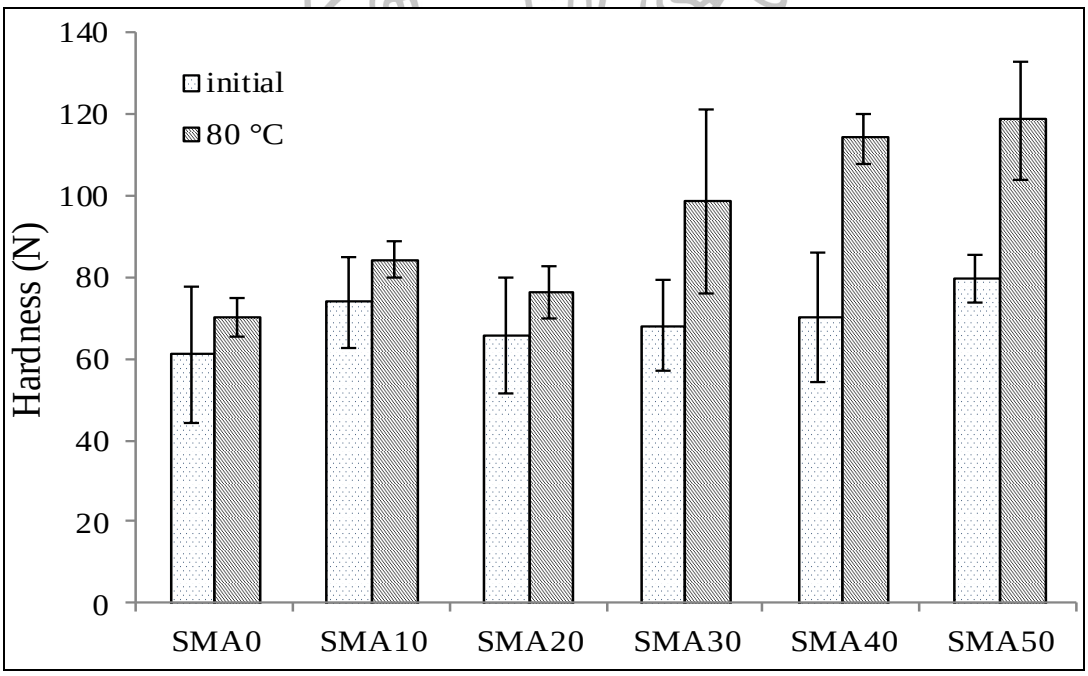


Figure 32 Effect of SMA content and annealing on hardness of tablets (n = 20)

Table 31 Effect of SMA content and annealing process on disintegration time of tablets in 0.1 N HCl (n = 6)

Formula	Disintegration in 0.1 N HCl (min)	
	Initial	80°C
SMA0	17.4±2.9	19.1±5.8
SMA10	11.7±4.7	12.6±4.7
SMA20	31.8±5.2	35.8±3.7
SMA30	>120	>120
SMA40	>120	>120
SMA50	>120	>120

Table 32 Effect of SMA content and annealing process on disintegration time of tablets in phosphate buffer pH 6.8 (n = 6)

Formula	Disintegration in buffer pH 6.8 (min)	
	Initial	80°C
SMA0	-	-
SMA10	-	-
SMA20	-	-
SMA30	>180	>180
SMA40	>180	>180
SMA50	>180	>180

The consequence of SMA content and annealing process on the disintegration properties was also evaluated in 0.1 N HCl and followed by phosphate buffer pH 6.8 by the same method as previously described. Table 31 shows the

disintegration time in 0.1 N HCl of tablets with different amounts of SMA. The extended disintegration time was observed as increasing amount of SMA. At the level from 30%w/w of SMA, disintegration time of tablets in acid condition was more than 120 min. As compared to SA based tablets, the shorter disintegration time was observed for tablets containing SMA lower than 30%w/w. The results were correlated with the higher solubility of SMA as compared to SA [18].

The effect of annealing on disintegration time in 0.1 N HCl was also studied. The disintegration time of annealed SMA10, SMA20 tablets was almost the same as those obtained from unannealed tablets, suggesting that annealing process did not affect the disintegration of tablets, especially alt low content of SMA. For SMA30, SMA40 and SMA50, the tablets were not disintegrated and further investigated in phosphate buffer pH 6.8.

To determine disintegration in phosphate buffer pH 6.8, the remained tablets were dried at ambient temperature before evaluated by the same method as described for SHL, HS, SA – based tablets. The remained tablets from both conditions were not disintegrated in phosphate buffer pH 6.8 over 180 min (Table 32), suggesting that high amount of SMA (SMA30, SMA40 and SMA50) could also perform as a good carrier for sustained drug release.

The percentage weight loss in 0.1N HCl and phosphate buffer pH 6.8 was summarized in Figures 33 and 34, respectively. In case of acid media, as the amount of SMA was increased, the loss weight was decreased. In contrast, the percentage of weight loss for SMA – based tablets before and after annealing was not significantly different (Figure 33). This finding was similar to the data of percent weight loss in phosphate buffer pH 6.8 (Figure 34). As expected, the annealed tablet

should be lost its weight less than unannealed tablet. In fact, the annealed tablets were large lost of their weight. This revealed that the advantage of salt formation were prevented polymerization and improved solubility of shellac. A total weight loss of shellac meglumine/ammonium – based matrix tablets is depicted in Figure 35.

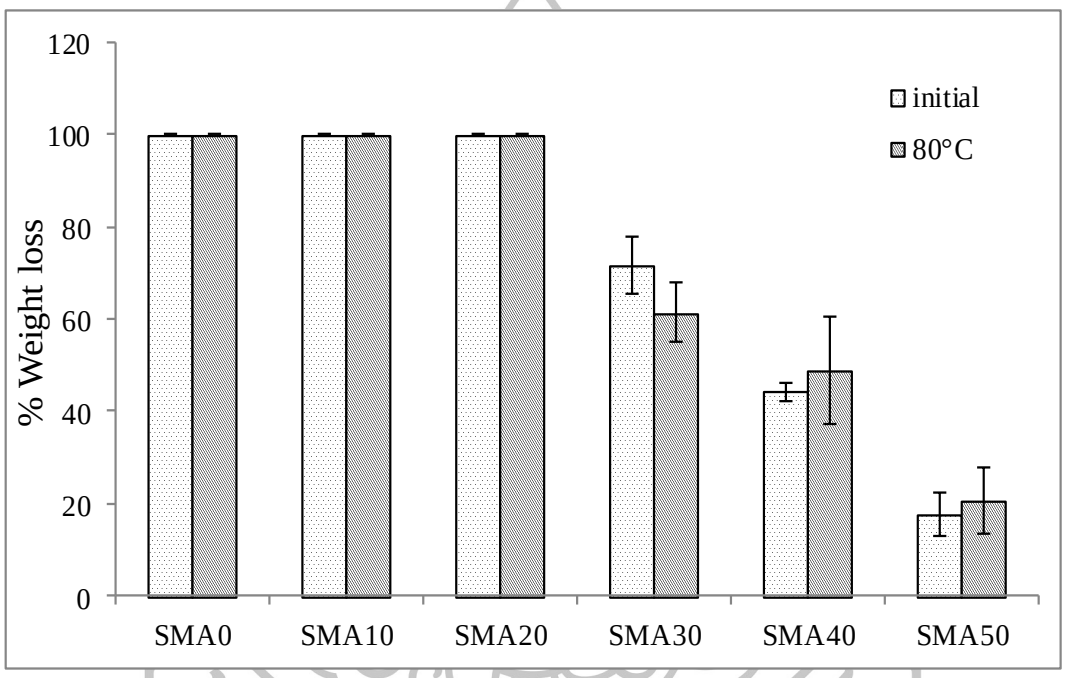


Figure 33 Percentage weight loss in 0.1 N HCl of SMA – based tablets before and after annealing (n = 6)

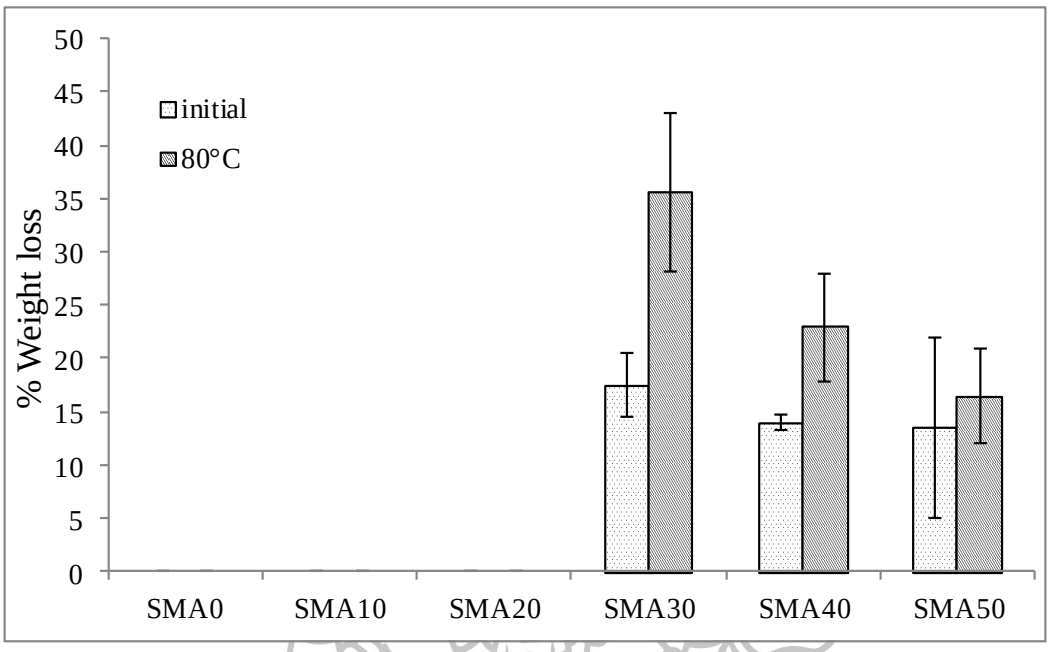


Figure 34 Percentage weight loss in phosphate buffer pH 6.8 of SMA – based tablets before and after annealing (n = 6)

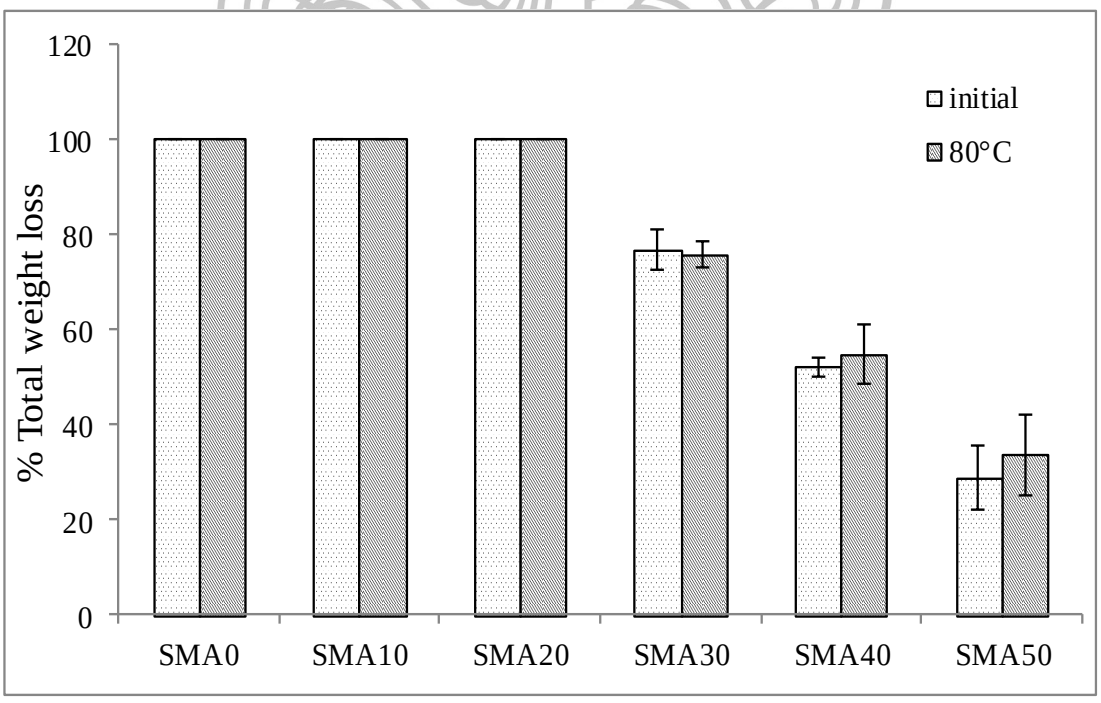


Figure 35 Total weight losses in both media of SMA – based tablets before and after annealing (n = 6)

In order to investigate the effect of SMA contents and annealing on drug release, the dissolution profiles of SMA – based tablets were also evaluated in continuous media of 0.1 N HCl followed by phosphate buffer pH 6.8 by the same method as described for SHL, HS, SA – based tablets

Figure 36 shows the influence of SMA content on the drug release profiles of unannealed tablets. The drug release profiles from SMA0, SMA10 and SMA20 based tablets were similar as indicated by complete release within 60 min. However, the drug release was remarkably decreased by increasing of SMA content from 30%w/w. The results agreed well with those of hardness and disintegration. Additionally, SMA30, SMA40 and SMA50 tablets showed a biphasic drug release. In 0.1 N HCl and early buffer stage, the gradual drug release as indicated by smooth curved lines was observed. However, the inflected curves resulting from elevated drug release were indicated after soaking in phosphate buffer for a certain period. The time to inflection point had a tendency to increase as increasing amount of SMA. Since the solubility of SMA was increased after salt formation, the faster erosion of SMA based tablets after soaking in phosphate buffer might be a possible explanation. The biphasic characteristic was also observed in SA – based tablets but less pronounced than that as indicated in SMA system. It was also noted that SMA – based tablet could not prolong drug release to 12 h. The time to complete drug release of SMA30, SMA40 and SMA50 based tablets was 300, 360 and 600 min, respectively.

Drug release profiles from SMA – based tablet after annealing process are illustrated in Figures 37 – 38. The drug release pattern of annealed SMA10 tablets was similar to that of unannealed tablets. However, the retarded drug release of annealed tablets was more clearly observed as increasing amount of SMA. For

example, the time to complete drug release of SMA50 tablets was increased from 600 min to 720 min after annealing process. It was also noted that annealing process had more influence on drug release in buffer stage as compared to acid stage. The results were similar with that of SA – based tablets, suggesting that the retarded drug release was also indicated in spite of lesser extent of polymerization of SMA after annealing. Therefore, it might be possible that the controlled release characteristic after annealing was not only governed by polymerization but also by some other related mechanisms. In this case, it might be possible that partial melting of SMA might impart some hardness of tablets and therefore reduced the dissolution of drug especially in buffer stage.

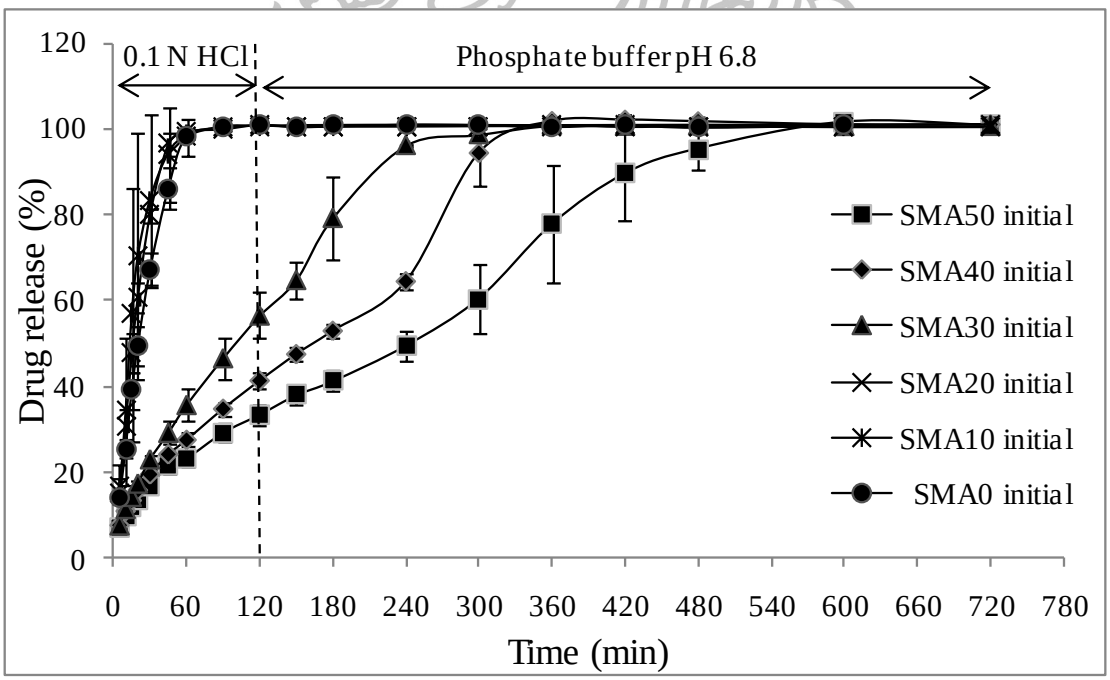


Figure 36 Drug release profiles of unannealed SMA – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

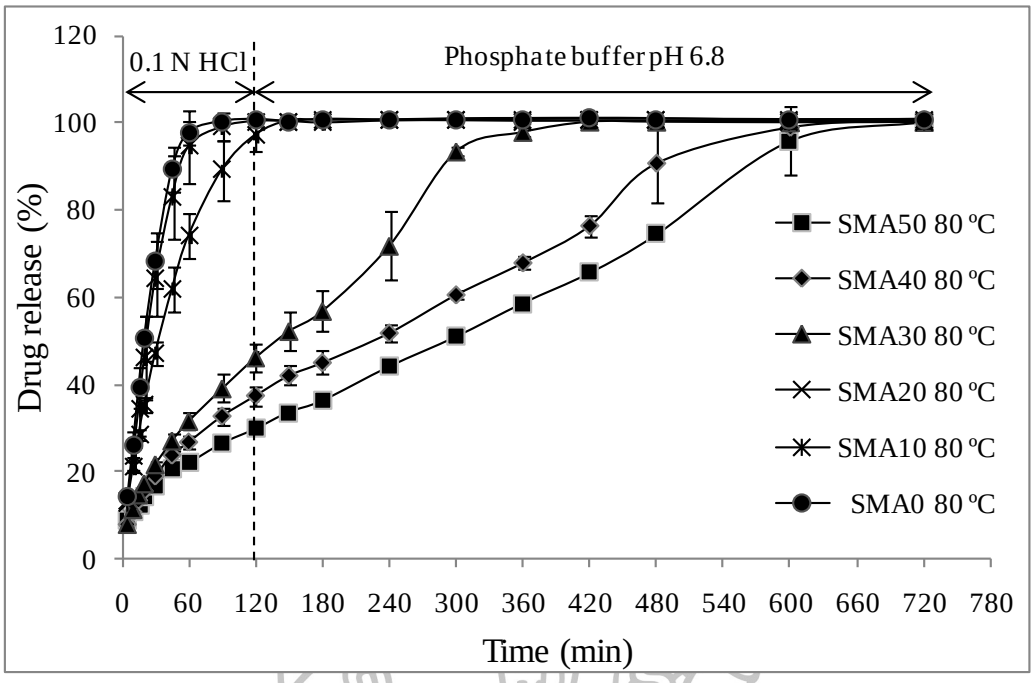


Figure 37 Drug release profiles of 80°C annealed SMA – based tablets in 0.1 N HCl followed by phosphate buffer pH 6.8 (n = 3)

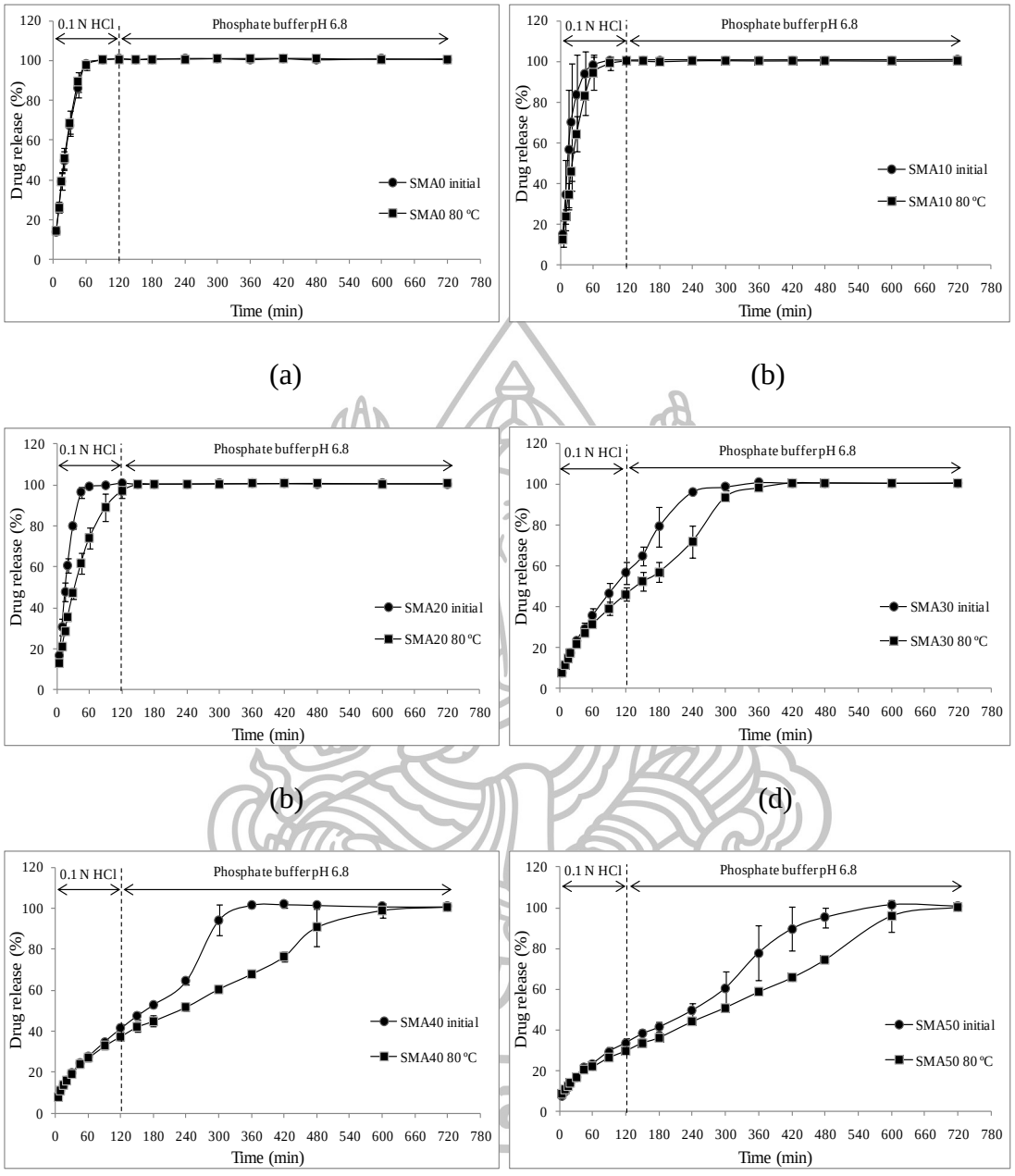


Figure 38 Effect of annealing process on drug release profiles of tablets with different amount of SMA (a) 0% SMA, (b) 10% SMA, (c) 20% SMA, (d) 30% SMA, (e) 40% SMA, (f) 50% SMA (n = 3)

1.5 Fabrication and evaluation of SHL – based floating tablets

SHL and SHL derivatives were successfully used as a matrix forming agent for controlling of drug release as showed in the previous results. Drug release of some formulations were presented over 12 h. Unfortunately, sustained release tablet was diminished out from the GI tract prior to completely released. To avoid this limitation, the development of oral sustained – controlled release formulation was an attempt to residence inside the GI tract. Various approaches used to increase the GI residence time including mucoadhesive system, flotation system or swellable system.

Gastric floating devices might be highly useful for the drug delivery system. For many drugs that absorbed mainly from the proximal small intestine, controlled release in the stomach would result in improve bioavailability. Based on mechanism of floating, gastric floating devices could divide into 2 types; effervescent floating and non – effervescent floating type. As compared between 2 types, non – effervescent floating devices represented more benefit due to lack of time to float. Hence, in this part would be focused on fabrication of non – effervescent floating tablets. However the ability of SHL and SHL derivatives for controlling of drug release were differed. The properties of SHL were changed after modification. The solubility of HS, SA and SMA was improved consequence to rapidly release of drug from tablet and modified SHL powder showed tougher than SHL that caused the problem of tablet compression. To fabrication of floating tablet, SHL was further used as an excipient for controlling of drug release.

The SHL – based floating tablets were fabricated thorough formation of porous matrix after annealing process. The influence of amount of SHL, ammonium carbonate (pore forming agent) and HPMC as well as the annealing

conditions on tablet properties and buoyancy properties were comparatively evaluated.

The effects of ammonium carbonate, SHL and HPMC contents on properties of tablets (before annealing) are shown in Tables 33, 34, and 35, respectively. All tablet formulations (FS1 – FS8) were compressed without any cracking and sticking problems although less compressibility of tablets with high amount of SHL was observed. The weight variation of all formulations was found satisfactorily within limit, suggesting the good flow ability of powder mixtures. The average thickness was in the range of 3.57 – 3.98 mm and had a tendency to increase as increasing the amount of ammonium carbonate or SHL. This might be due to the lower compressibility of ammonium carbonate and SHL as compared to drug and other excipients in the powder mixtures. However, the average diameter was not different among formulations and was in the range of 9.56 – 9.65 mm.

Table 33 Effect of ammonium carbonate content on properties of SHL – based floating matrix tablets (before annealing) (n = 20)

Ammonium carbonate content	Tablet properties			
	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)
(FS1) 0%	298.37±2.59	3.565±0.003	9.564±0.001	67.360±2.141
(FS2) 10%	299.80±2.51	3.592±0.031	9.563±0.002	74.401±1.634
(FS3) 20%	296.85±2.14	3.761±0.102	9.644±0.120	54.648±9.820
(FS4) 30%	297.02±2.28	3.767±0.154	9.648±0.124	54.238±5.825

Table 34 Effect of SHL content on properties of SHL – based floating matrix tablets (before annealing) (n = 20)

SHL content	Tablet properties			
	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)
(FS5) 0%	298.40±3.88	3.302±0.008	9.594±0.051	69.474±11.210
(FS4) 30%	297.02±2.28	3.767±0.154	9.648±0.124	54.238±5.825
(FS6) 50%	297.81±2.50	3.983±0.080	9.635±0.070	38.216±4.040

Table 35 Effect of HPMC content on properties of SHL – based floating matrix tablets (before annealing) (n = 20)

HPMC content	Tablet properties			
	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)
(FS4) 0%	297.02±2.28	3.767±0.154	9.648±0.124	54.238±5.825
(FS7) 5%	298.22±2.41	3.642±0.030	9.549±0.010	64.583±2.741
(FS8) 10%	299.24±2.10	3.716±0.042	9.539±0.011	65.467±2.761

In order to remove the AMN and study the consequence of annealing temperature, the tablets with different compositions were annealed in a vacuum oven at 40, 60 and 80°C for 24 h AMN and then comparatively evaluated for tableting properties.

With increasing annealing temperature, the weight loss due to sublimation of AMN was observed. However, the total weight loss was less than calculated value after annealing at the temperature below 80°C. For example, the

percentage weight loss of FS4 tablets after annealing at 40 and 60°C was 22.53±0.99 and 16.98±0.90; respectively which was less than the expected value of 30%w/w. The result suggested that annealing temperature at 80°C was more suitable in term of completed sublimation. The percentage weight loss of tablet after annealing at various temperature is shown in Table 36.

Table 36 The percentage weight loss of tablet after annealing at 40, 60 and 80°C for 24 h (n = 20)

Formula	Annealing temperature		
	40°C	60°C	80°C
FS1(0%AMM)	0	0	0.29±0.15
FS2(10%AMM)	5.27±1.21	4.49±1.29	9.54±0.11
FS3(20%AMM)	12.58±1.01	10.65±1.07	18.20±0.24
FS4(30%AMM)	22.53±0.99	16.98±0.90	28.24±0.34
FS5(30%AMM)	21.78±1.38	17.52±1.82	28.90±0.45
FS6(30%AMM)	20.04±1.12	18.17±0.99	27.70±0.46
FS7(30%AMM)	24.88±1.66	17.37±1.19	29.06±0.19
FS8(30%AMM)	21.92±0.67	15.94±1.04	27.73±0.13

With regarded to the result of SHL – based tablets (section 1.1), annealing temperature directly increased the hardness of tablets through melting and polymerization of SHL. In this study, the porous structure of SHL – based tablets was expected after removal of AMN and might also had a negative impact on tablet hardness. Therefore, the influence of annealing temperature on hardness of SHL –

based floating matrix tablets with different composition was investigated as shown in Figure 39 – 41.

After annealing, tablets without AMN (FS1) demonstrated an increased hardness which was a result of melting and polymerization of SHL as described in previous section (Figure 10). However, the hardness had a tendency to decrease as increasing amount of AMN, especially at the temperature more than 40°C (Figure 39). The result suggested the porous formation due to sublimation of AMN. The porous structure of annealed tablets could be easily cracked during testing, resulting in reduced hardness as compared with unannealed tablets.

Figure 40 shows the influence of SHL content on hardness of tablets containing fixed amount of 30% AMN. Regardless of SHL content, the reduced hardness was observed after increasing annealing temperature. After annealing at 80°C, the hardness of tablets containing 50%w/w SHL (FS6) was not clearly different as compared to that containing 0% (FS5) and 30%w/w SHL (FS4). According to the result of SHL – based tablets (section 1.1), the increased hardness was clearly indicated after annealing or increasing amount of SHL. The results seem to disagree with that of SHL – based floating tablets. In this case, it might be possible that porous structure was fragile and could not withstand with the breaking force although the denser polymerized matrix structure due to increased SHL content.

The effect of HPMC content on hardness of annealed tablets is shown in Figure 41. The hardness of tables with 0%w/w (FS4), 5%w/w (FS7) and 10%w/w HPMC (FS8) was not obviously different after annealing at the same temperature although the decreased hardness was observed in all formulation. The results suggested that HPMC did not clearly affect the hardness of tablets. Among the studied

parameters, AMN content should be the major parameter that controlled the hardness of tablet since it directly affected the porous structure in SHL – based floating matrix tablets. The detail of porous structure would be further discussed in next section.

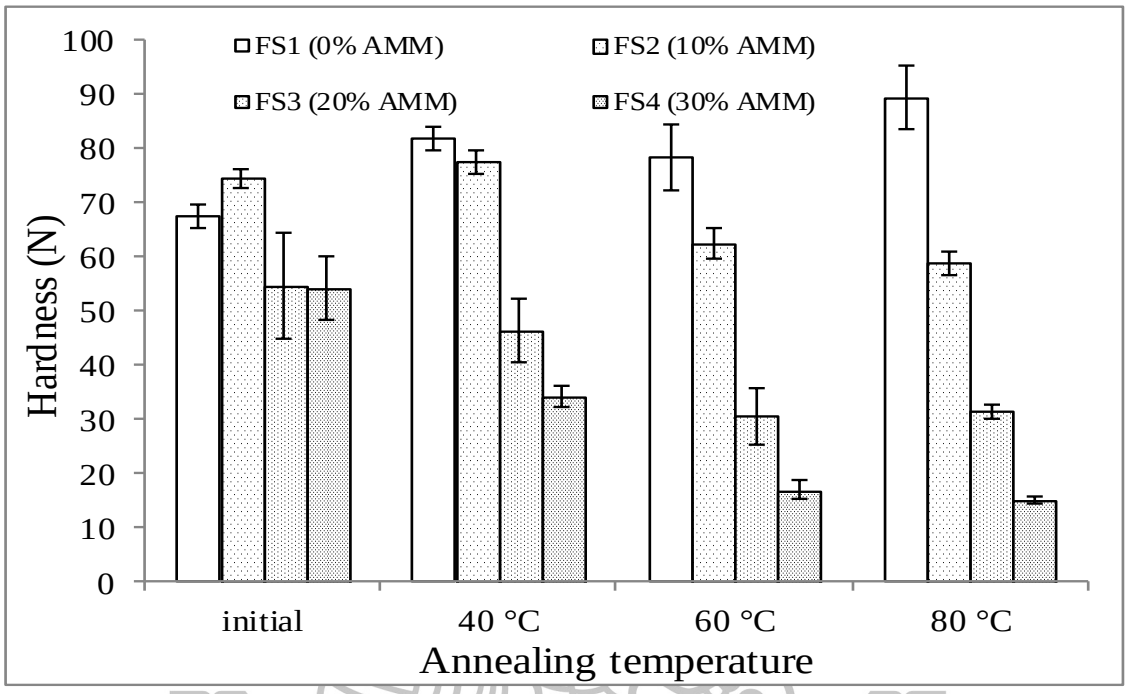


Figure 39 Effect of AMN content and annealing temperature on hardness of SHL – based floating matrix tablets (n = 20)

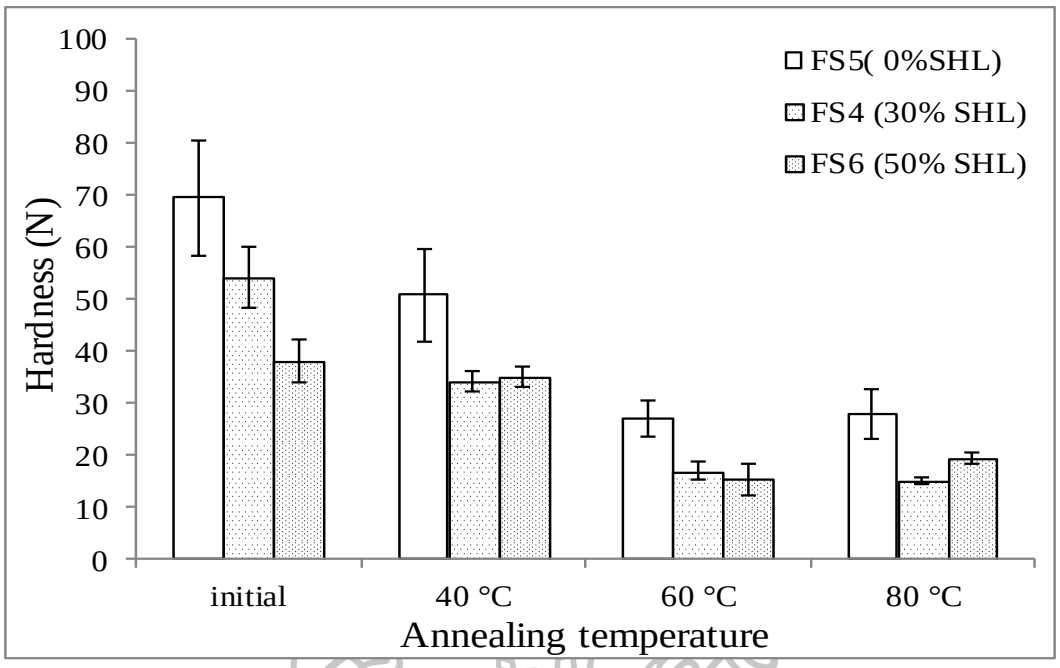


Figure 40 Effect of SHL content and annealing temperature on hardness of SHL – based floating matrix tablets (n = 20)

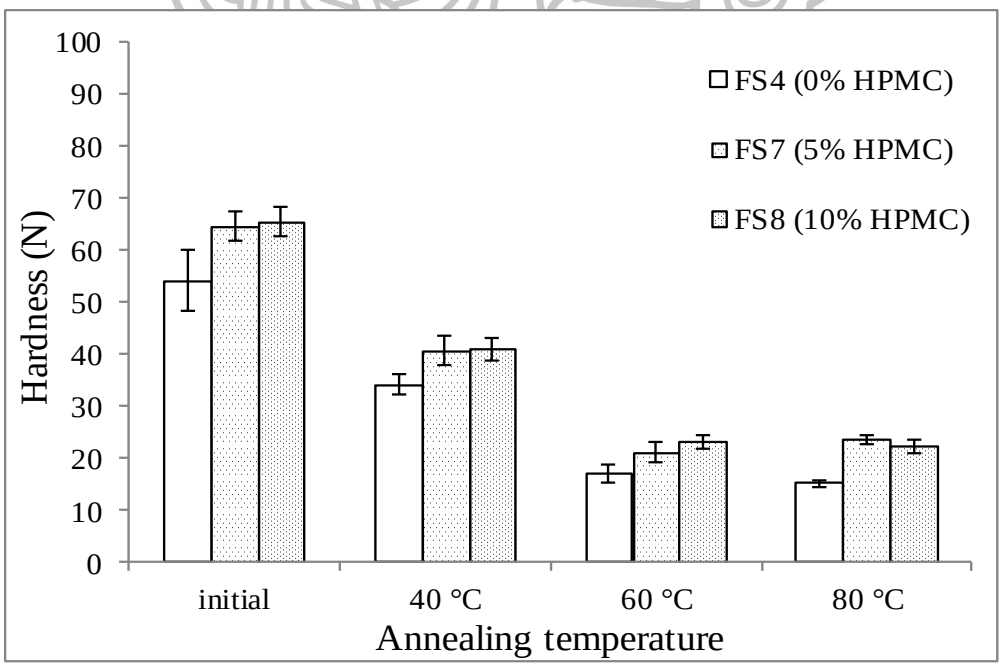


Figure 41 Effect of HPMC content and annealing temperature on hardness of SHL – based floating matrix tablets (n = 20)

In order to clarify the porous structure of SHL based floating matrix tablets with different composition, the tablets before and after annealing at 80°C were comparatively investigated by scanning electron microscopy (SEM) and X – ray Computed Tomography (X – ray CT) techniques.

Figures 42 – 43 show the SEM images for the cross sectional view of SHL – based floating matrix tablets. As expected, the porous structure was observed in the tablet containing AMN (FS2 – FS8) after annealing while was not clearly indicated in the tablet without AMN (FS1). As increasing the amount of AMN from 10%w/w to 30%w/w (FS2, FS3 and FS4), the number of pores had a tendency to increase. However, the porous structure could not be clearly seen since it was easily cracked during sample preparation. To study the porosity of tablets, the X – ray CT was used to evaluate. The X – ray CT allowed 3D characterization of micro – structure and thus had some advantages compared to other methods. The sample was placed on a precision turntable in a divergent beam of X – rays. A detector was used to measure the local intensity distribution of a diverging X – ray beam transmitted through the sample. This scan could be decomposed in a series of cross – sectional images in a chosen plane

In this study, the X – ray CT scan was also used as a non – destructive tool for clarifying the pore and its distribution in the SHL – based floating tablets. Figure 44 expresses the X – ray CT images of FS1 and FS4 after sublimation at 80°C. The pores were clearly observed and uniformly distributed through the matrix of tablet containing AMN (FS4) while the tablet without AMN (FS1) indicated the dense non porous matrix after sublimation at 80°C.

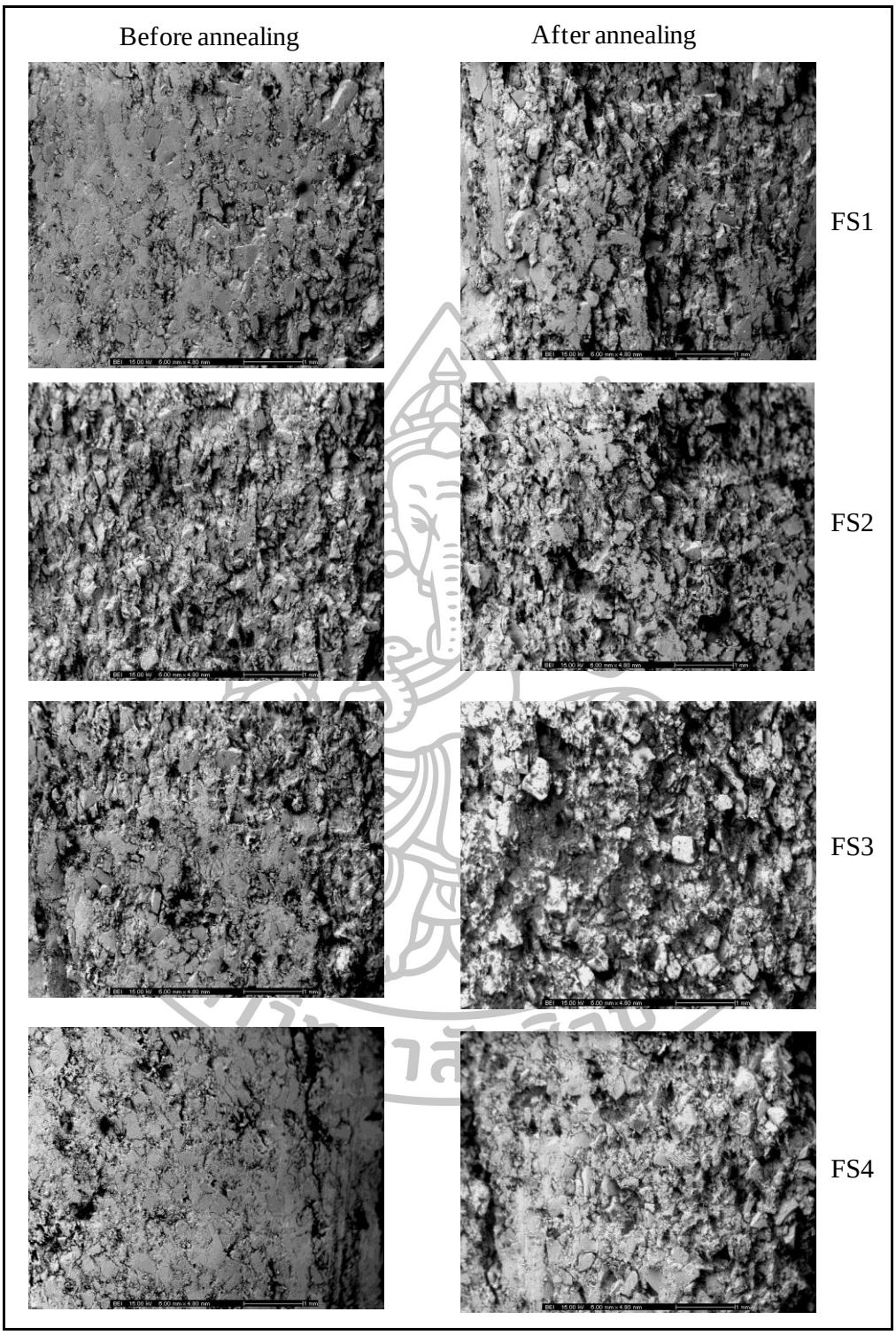


Figure 42 SEM images of SHL – based floating matrix tablets (FS1, FS2, FS3 and FS4) before and after annealing at 80°C. (The result revealed the formation of porous structure in SHL – based floating matrix tablets)

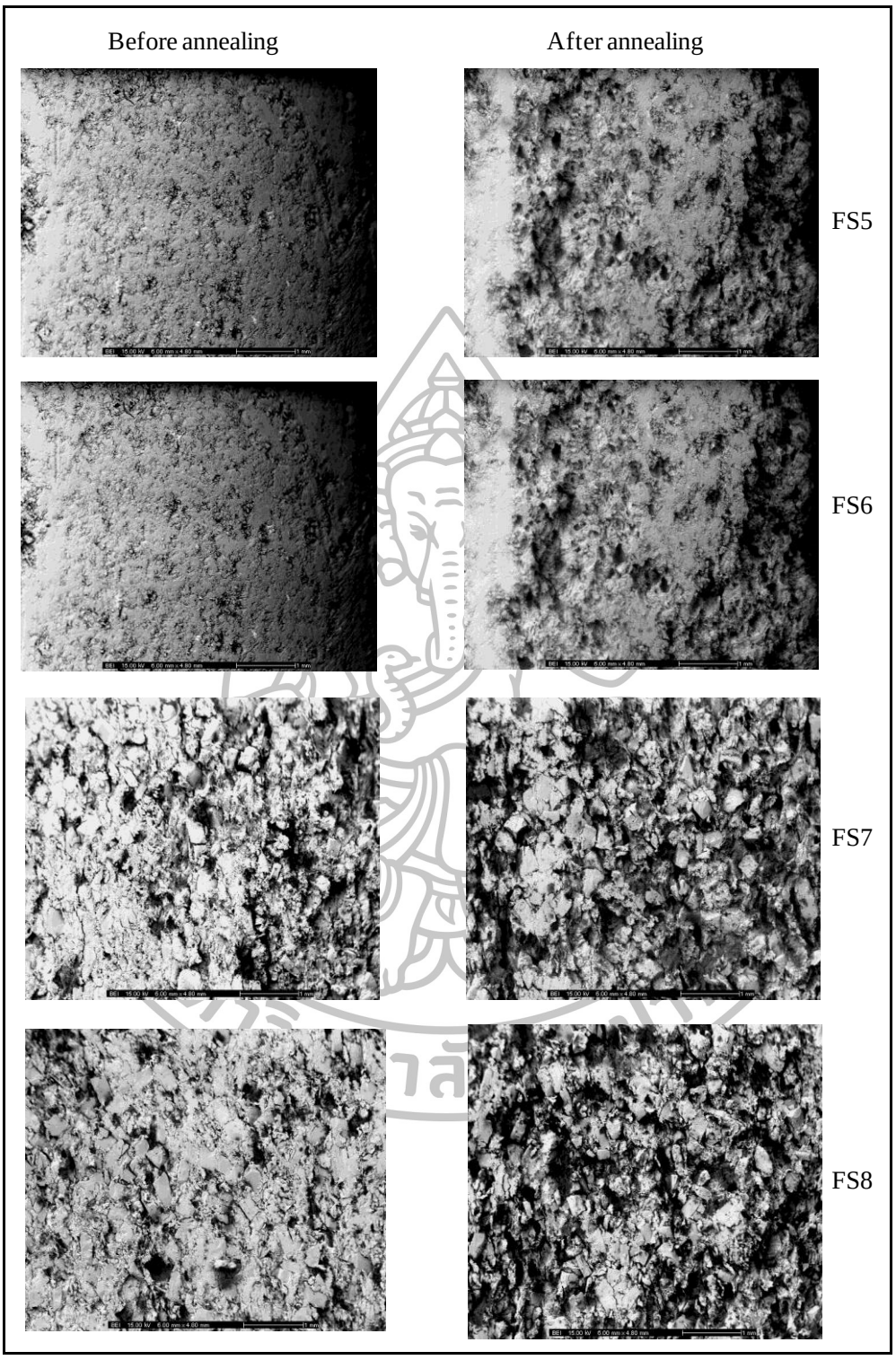
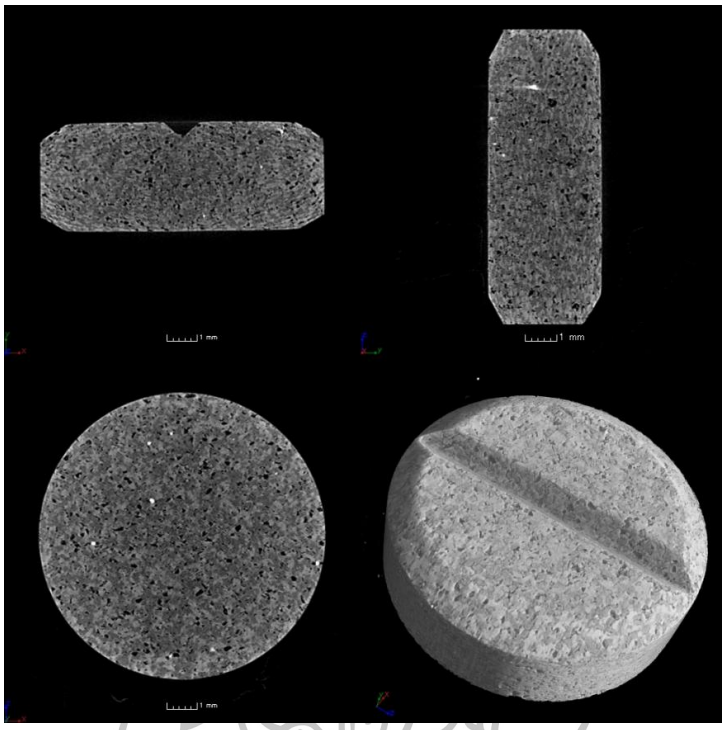
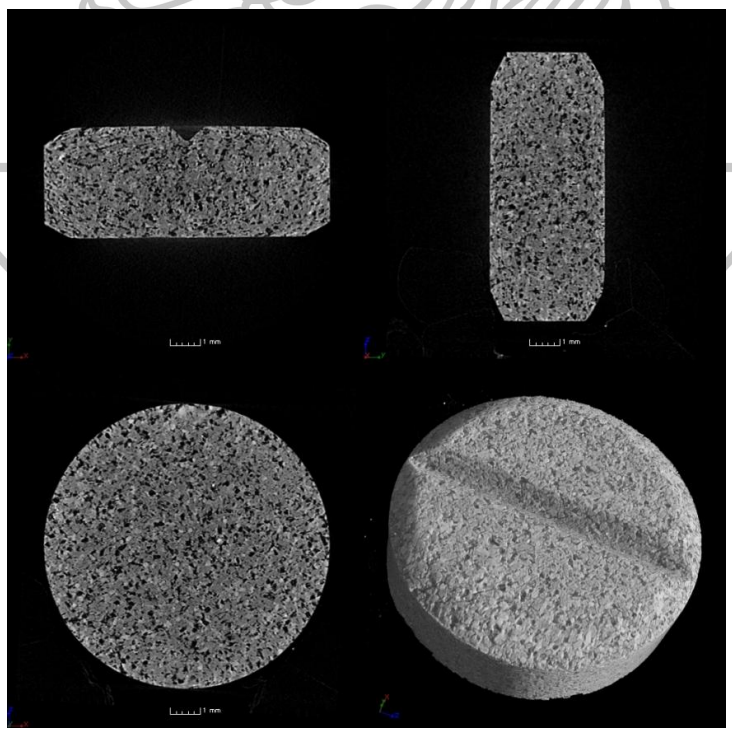


Figure 43 SEM images of SHL – based floating matrix tablets (FS5, FS6, FS7 and FS8) before and after annealing at 80°C



FS1



FS4

Figure 44 X – ray CT image of FS1 and FS4 after annealing at 80°C

The buoyancy of floating drug delivery system depends on the density of the dosage forms. The system is expected to be floated on the gastric fluid if the density is less than the density of gastric fluid (≈1 g/cm^3). Hence, the density of the system is the key factor for designing the floating drug delivery system. [2 – 4, 82 – 84]. In order to study the floating ability of SHL – based floating matrix tablets, the density was also determined based on the volume and weight of tablets before and after annealing process.

Table 37 shows the effect of AMN content and annealing process on density of tablets. Regardless of tablet formulation, the initial density of tablets was more than 1 g/cm^3. As increasing annealing temperature, the density of the tablets with AMN has a tendency to decrease. However, the density of tablets with AMN less than 20%w/w was greater than 1 g/cm^3. The result suggested that porous SHL base tablets could be floated if AMN at least 20%w/w was incorporated into the formulation and then sublimed at 80°C.

The influence of SHL content on density of tablets with fixed amount of AMN to 30%w/w is shown in Table 38. The initial density of tablets was decreased as increasing amount of AMN. This could be explained by the density of excipient. The density of SHL was markedly lower than that of Supertab® (1.035 and 1.567 g/cm^3, respectively). Therefore, this might facilitate the application of SHL as a carrier for floating dosage form.

Table 39 shows the effect of HPMC content and annealing process on density of SHL – based floating matrix tablet. SHL and AMN were fixed at the level 30%w/w. After adding HPMC in the formulation, the density was slightly increased. The density of tablets after sublimation was also not different from that of tablets

without HPMC. This might be due to low percentage of HPMC in the formulation. However, HPMC was benefit to the floating property that would be further described.

Table 37 Effect of AMN content and annealing temperature on density of SHL – based floating matrix tablets (n = 20)

AMN content	Density (g/cm^3)			
	Initial	40°C	60°C	80°C
(FS1) 0%	1.17±0.01	1.19±0.00	1.19±0.02	1.17±0.01
(FS2) 10%	1.16±0.01	1.09±0.02	1.12±0.01	1.04±0.02
(FS3) 20%	1.08±0.05	0.97±0.02	1.01±0.01	0.94±0.02
(FS4) 30%	1.08±0.06	0.87±0.01	0.94±0.03	0.81±0.02

Table 38 Effect of SHL content and annealing temperature on density of SHL – based floating matrix tablets (n = 20)

SHL content	Density (g/cm^3)			
	Initial	40°C	60°C	80°C
(FS5) 0%	1.25±0.03	0.98±0.02	1.02±0.08	0.89±0.02
(FS4) 30%	1.08±0.06	0.87±0.01	0.94±0.03	0.81±0.02
(FS6) 50%	1.03±0.03	0.83±0.01	0.86±0.03	0.77±0.02

Table 39 Effect of HPMC content and annealing temperature on density of SHL – based floating matrix tablets (n = 20)

HPMC content	Density (g/cm^3)			
	Initial	40°C	60°C	80°C
(FS4) 0%	1.08±0.06	0.87±0.01	0.94±0.03	0.81±0.02
(FS7) 5%	1.14±0.01	0.85±0.01	0.94±0.01	0.79±0.02
(FS8) 10%	1.13±0.01	0.86±0.24	0.94±0.01	0.81±0.01

Gastroretentive floating tablets were one of the promising approach for enhancing the bioavaiability and controlled delivery of drug. Density of tablets was not sufficient to confirm floating ability due to water could penetrate through the porous matrix resulting in unsuccessful floating. Concerning floating tablets, several authors concluded that the buoyancy was the major factor in determining the gastric floating tablets. Floating tablets could be emerged on the gastric fluid surface and constantly floated for a long period of time. For preventing the ejection of tablets through the pyrolic sphincter, tablets should take a short time to float. Therefore, the main parameters that used to evaluate floating ability were floating lag time and duration of floating.

In order to evaluate the buoyancy characteristic of SHL – based floating matrix tablets with different porous structure and composition, the lag time and duration of floating (floating time) were comparatively investigated. Table 40 expresses the effect of AMN content and annealing temperature on floating properties of SHL – based floating matrix tablets. For tablets containing less than 30%w/w of AMN, the tablets could not float after immersion in 0.1 N HCl. The result agreed with

the bulk density of tablets (>1.0 g/cm^2) as indicated in Table 37. However, the tablets with 30%w/w AMN (FS4) were immediately floated. Additionally, the floating time of FS4 tended to increase as increasing annealing temperature. The more porous structure along with lower bulk density as increasing annealing temperature should be a possible explanation. However, the maximum floating time of FS4 was less than 60 min and not sufficient for controlled drug release over intended period. The result suggested the existence of medium accessible pores in the tablets. The acid medium might slowly fill in the pores, increased the bulk density and finally resulted in the sinking of tablets over prolonged period.

Table 41 represents the influence of SHL content and annealing process on floating properties of SHL – based floating matrix tablets with fixed amount of AMN to 30%w/w. Tablets without SHL (FS5) did not float despite the density of tablet after sublimation at 80°C was more than 1 g/cm^3 (Table 38) while the tablets containing SHL (FS4 and FS6) were immediately floated after contacting with acid medium, suggesting that the medium was quickly penetrated into the porous structure of tablets without SHL as matrix forming agent. The results were corresponded with the higher solubility and density of Supertab®. It was also noted that the floating time showed a tendency to increase as increasing annealing temperature and SHL content. The result might be possibly explained by the increased strength of porous SHL matrix tablet resulting in more trapping of air inside.

As previously described, the presence of porous structure after sublimation in SHL matrices facilitated the floating of dosage form. However, the FS1 – FS6 tablets were still sunk before the expected period of at least 720 min since the media could still permeate into the pores. In order to extend the duration of

floating, HPMC was incorporated into tablets. The swelling of incorporated HPMC after contact with gastric fluid was expected to prevent a liquid uptaking into the pores and might be also act as a barrier for drug diffusion process. Table 42 indicates the effect of HPMC content and annealing process on floating properties of SHL – based floating matrix tablets**.** After adding HPMC in the formulation, the duration of floating was significantly increased. The SHL based tablets containing at least 5%w/w HPMC (FS7 and FS8), were floated on 0.1 N HCl for more than 720 min although the density was not different from that of other formulations. The result suggested the blocking of penetration of medium into the porous structure by the swelling of HPMC. However, the process or mechanism of media diffusion was still needed to be further clarified.

Table 40 Effect of AMN content and annealing temperature on floating properties of SHL – based floating matrix tablets (n = 3)

AMN content	Floating properties					
	40°C		60°C		80°C	
	Floating lag time (min)	Duration of floating (min)	Floating lag time (min)	Duration of floating (min)	Floating lag time (min)	Duration of floating (min)
(FS1) 0%	sank	-	sank	-	sank	-
(FS2) 10%	sank	-	sank	-	sank	-
(FS3) 20%	sank	-	sank	-	sank	-
(FS4) 30%	immediately float	12.11±4.25	immediately float	30.70±6.46	immediately float	55.06±3.95

Table 41 Effect of SHL content and annealing temperature on floating properties of SHL – based floating matrix tablets (n = 3)

SHL content	Floating properties					
	40°C		60°C		80°C	
	Floating lag time (min)	Duration of floating (min)	Floating lag time (min)	Duration of floating (min)	Floating lag time (min)	Duration of floating (min)
(FS5) 0%	sank	-	sank	-	sank	-
(FS4) 30%	immediately float	12.11± 4.25	immediately float	30.70± 6.46	immediately float	55.06± 3.95
(FS6) 50%	immediately float	342.32±5 .69	immediately float	459.33± 13.50	immediately float	454.12± 16.70

Table 42 Effect of HPMC content and annealing temperature on floating properties of SHL – based floating matrix tablets (n = 3)

HPMC content	Floating properties					
	40°C		60°C		80°C	
	Floating lag time (min)	Duration of floating (min)	Floating lag time (min)	Duration of floating (min)	Floating lag time (min)	Duration of floating (min)
(FS4) 0%	immediately float	12.11±4.25	immediately float	30.70±6.46	immediately float	55.06±3.95
(FS7) 5%	immediately float	> 720	immediately float	> 720	immediately float	> 720
(FS8) 10%	immediately float	> 720	immediately float	> 720	immediately float	> 720

In order to clarify the mechanism of media diffusion through the porous structure of matrix tablets as well as the process of drug release, the other non – invasive technique need to be employed for further study. MRI is one of outstanding technique for medical application based on detection of the nuclear magnetic resonance signal of the hydrogen nucleus. It could be also applied for pharmaceutical fields, including the drug delivery system [146 – 148]. The MRI is the best choice for visualizing the dynamic process during drug release. Based on detection of proton in water or acid medium, it was applied to monitor water penetration and swelling properties of dosage form containing various polymers such as hydroxypropyl methylcellulose (HPMC), poly(vinyl acetate), starch and xanthan gum [146,149].

MRI was therefore could be used for monitoring the medium permeation into the SHL based floating tablets. The 2D MR images of SHL – based floating tablets after immersion in acid medium are illustrated in Figure 45. Dark blue areas in the ^{1}H NMR images could refer to low spin densities or short T1 relaxation times, which was related to dry parts of the tablet or trapped air. While green or yellow areas represented the medium or liquid zone. The bottom of flow cell was covered with glass beads (as indicated by small blue spheres) to allow laminar flow of the medium and also to position the tablet without restricting the swelling [142]. FS1 represented tablet without pores (0%w/w of AMN). After immersion of FS1 tablets into 0.1 N HCl, the tablets did not float. At initial time, the dark blue area was observed over the entire part of tablets. With prolongation of immersion time, the pale blue and green area was extended from the outside to the inside of the tablets. The dark blue area was totally replaced by green area after immersion from 6 – 12 h. Additionally, the size of tablets had a tendency to decrease as increasing of immersion

time. The result suggested the diffusion of medium from the outer surface into the inner part followed by erosion of tablets.

For FS2 and FS3 formulations, the tablets also did not float. However, the medium was more rapidly penetrated into the inner part of the tablets than that of FS1 as indicated by the faster appearance of green areas. The results were in good agreement with the more porous structure as previously described. In the case of FS4 formulation, the tablets were immediately floated while the medium was gradually filled into the inner part similarly as observed in FS2 and FS3 tablets. However, the dry part (as indicated by blue area) was still observed even soaking for over 12 h. The result revealed the immediate and extended buoyancy was a result of entrapped air in the porous matrix formed by SHL. It was noted that the floating time in dynamic conditions was not equal to those obtained from static conditions as previously described in Tables 40 – 42. For example, the floating time of FS4 tablets in dynamic conditions (during MR study) was over 12 h while that from static conditions was around 55 min. In this case, it might be possible that the driving force from liquid flow from the bottom could maintain the buoyancy.

In order to study the effect of shellac content on floating properties and its mechanism, tablets containing fixed amount of AMN and varied amount of SHL including FS5 (0%w/w SHL), FS4 (30%w/w SHL) and FS 6 (50%w/w SHL) were comparatively evaluated for their MRI after soaking in 0.1 N HCl for various time. As expected, the porous FS5 tablets was not floated and dissolved as prolonged soaking time since it mainly consisted of water soluble lactose (Supertab®). The medium could easily access through the pores followed by fast dissolving of the soluble excipients. As increasing the amount of SHL to 30%w/w (FS4) and 50%w/w (FS6), the

immediate float was observed in both tablet formulations. However, the more erosion was observed in FS4 tablets as indicated by smaller size of floated tablets. It was also noted that FS4 tablets were still floated although the liquid was almost completely filled in the tablets. This might be explained by the lower density of SHL could facilitate the floating ability.

The FS7 and FS8 tablets were formulated in order to solve the problem of short floating time of FS4 tablets by incorporation of HPMC at the level of 5, and 10%w/w, respectively. The HPMC was postulated to swell and act as barrier for medium diffusion into the porous structure of SHL matrix.

As shown by the MRI, both FS7 and FS8 tablets were immediately floated and not different from FS4 tablets. However, the penetration of medium into the FS7 and FS8 tablets was significantly slower as compared to FS4 tablets. Additionally, the more delayed diffusion as increasing the amount of HPMC was observed which was clearly indicated by the longer existence of dry area in the inner core of tablets. The swelling of HPMC after contacting with the medium should be a possible explanation for the results. The gel layer of HPMC, as indicated by the green area around the core, retarded the penetration of medium into the porous matrix and thus increased the floating time of the tablets. Therefore, the MR images could reveal the floating mechanism of SHL – based matrix tablets with different compositions.

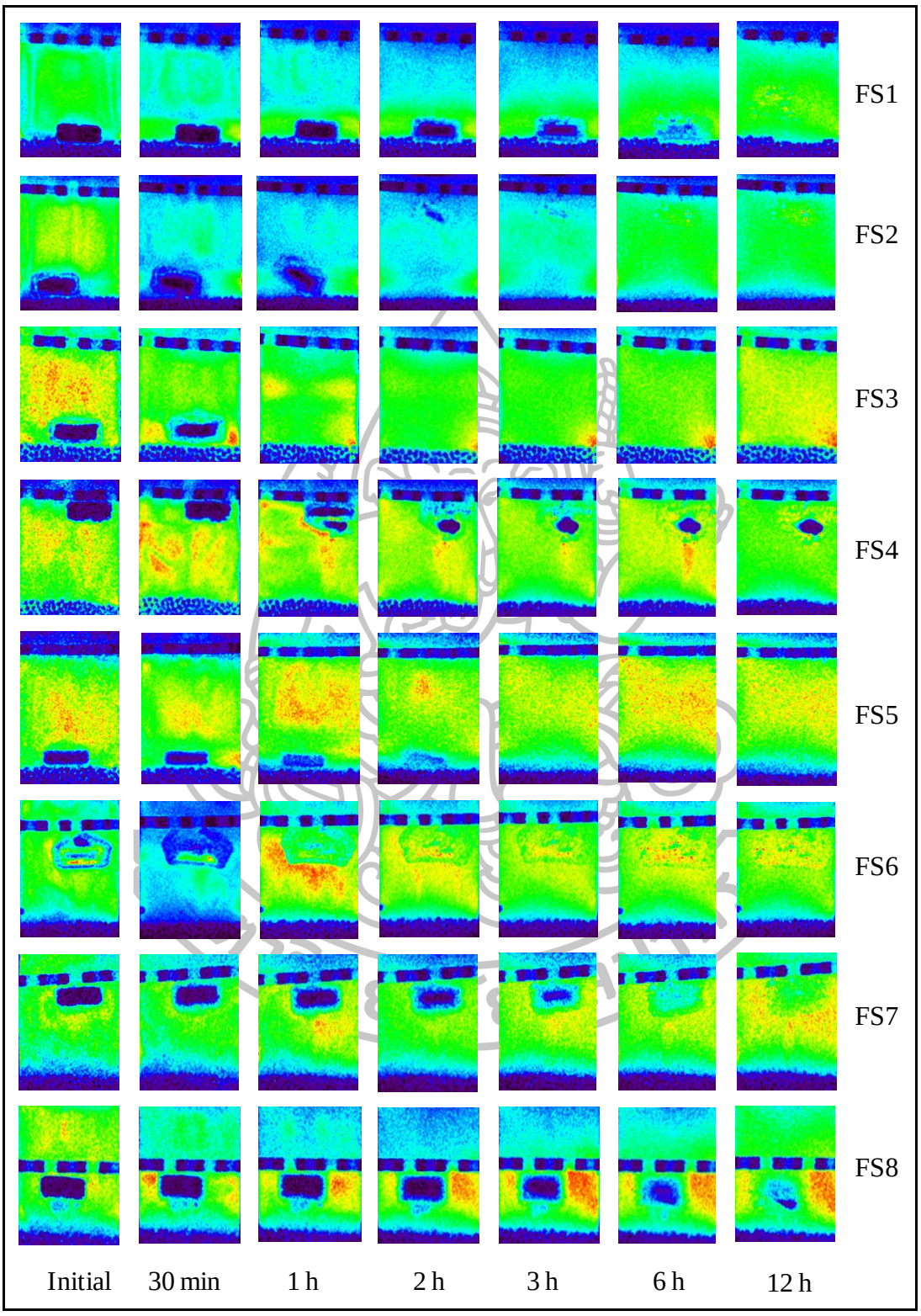


Figure 45 MRI of FS1 – FS8 after immersed to 0.1 N HCl at various times

As previously described in section 1.1, the drug release from non-porous SHL – based tablets was directly influenced by formulation and process parameters. In this study, the different SHL – based tablets with porous structure were fabricated and therefore need to be further characterized for drug release characteristic. The consequence of AMN, SHL, HMPC contents and annealing process on dissolution profiles was investigated as shown in Figures 46 – 54.

The effects of AMN content and annealing temperature on drug release profile are presented in Figures 46 – 48. At annealing temperature of 40°C, the faster drug release was observed as increasing AMN contents in SHL based tablets. For examples, the completed drug release from FS4 tablets (AMN 30%w/w) was observed within 1 h while FS1 tablets showed less than 90% drug release at 12 h. Similar results were also observed in 60°C annealed SHL based tablets although the less pronounced effect of AMN on drug release was indicated. However, the drug release from 80°C annealed SHL based tablets showed similar profiles regardless of AMN contents.

As previously discussed in section 1.5, the AMN was completely removed from the tablets after annealing at 80°C while 30% and 50% of AMN were left after annealing the SHL – based tablets at 40 and 60°C, respectively. Therefore, it should be possible that the acid – base reaction between residual AMN and acid media should promote erosion of tablet and consequently increased the drug dissolution. Additionally, the salt formation of SHL with residual AMN might also increase the solubility of SHL and also promote the erosion of matrix. The result was consistent with the previous report [114]. It was also noted that the similar release profiles were

observed regardless of porosity at high annealing temperature. Therefore, it might be possible to explain that the drug was tightly entrapped by polymerized network of SHL and was slowly diffused after leaching by the medium through the pores.

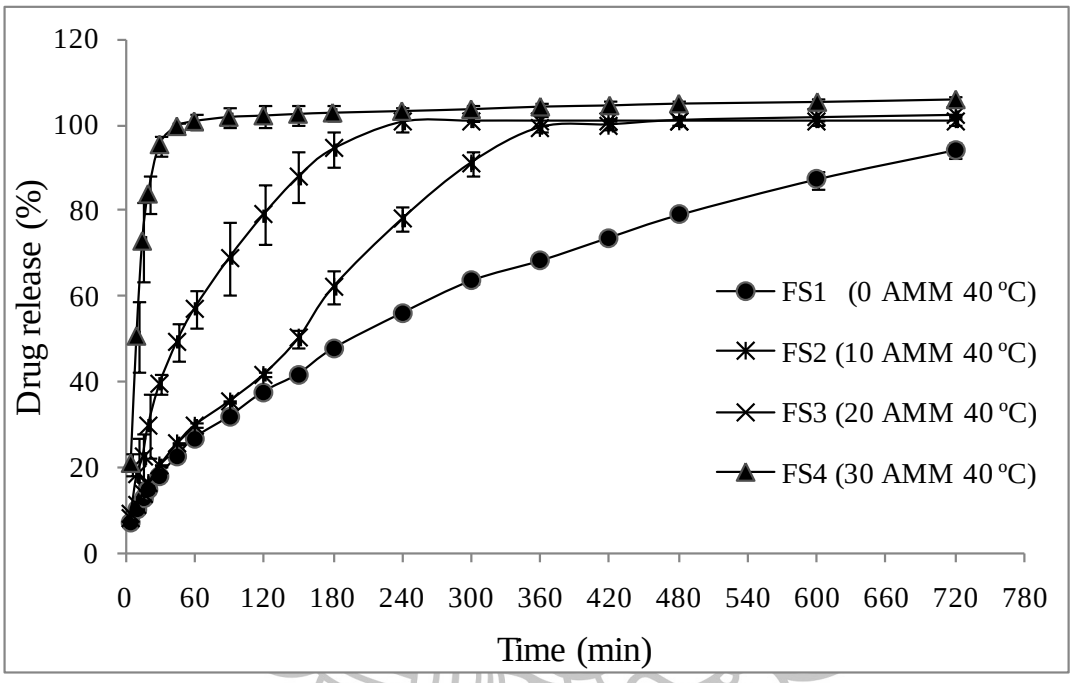


Figure 46 Effect of AMN content and annealing at 40°C on drug release profiles of SHL – based floating matrix tablets (n = 3)

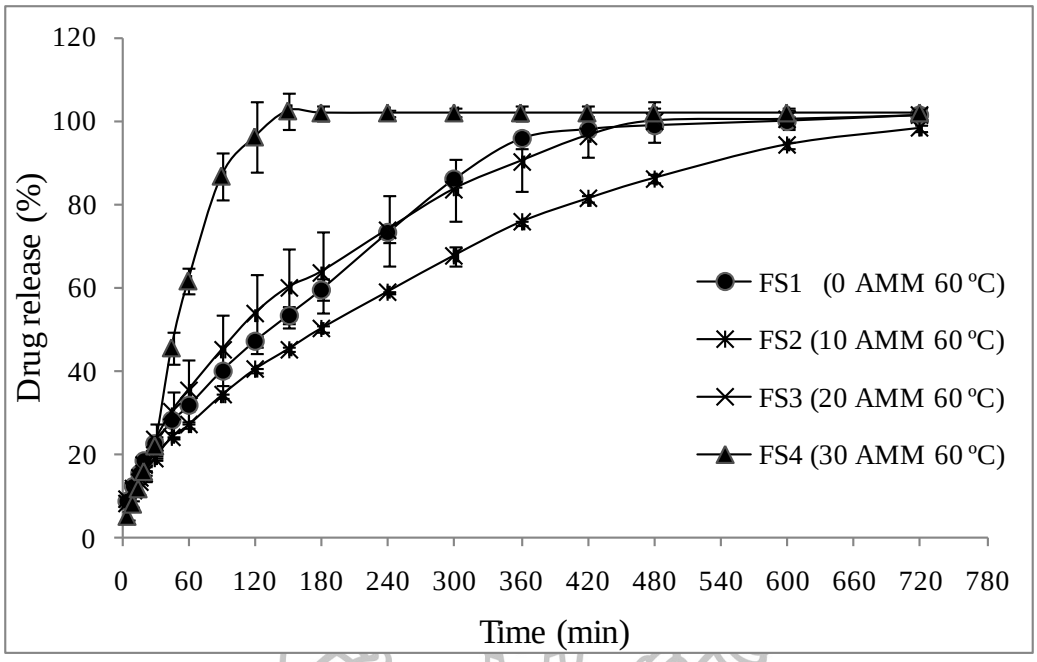


Figure 47 Effect of AMN content and annealing at 60°C on drug release profiles of SHL – based floating matrix tablets (n = 3)

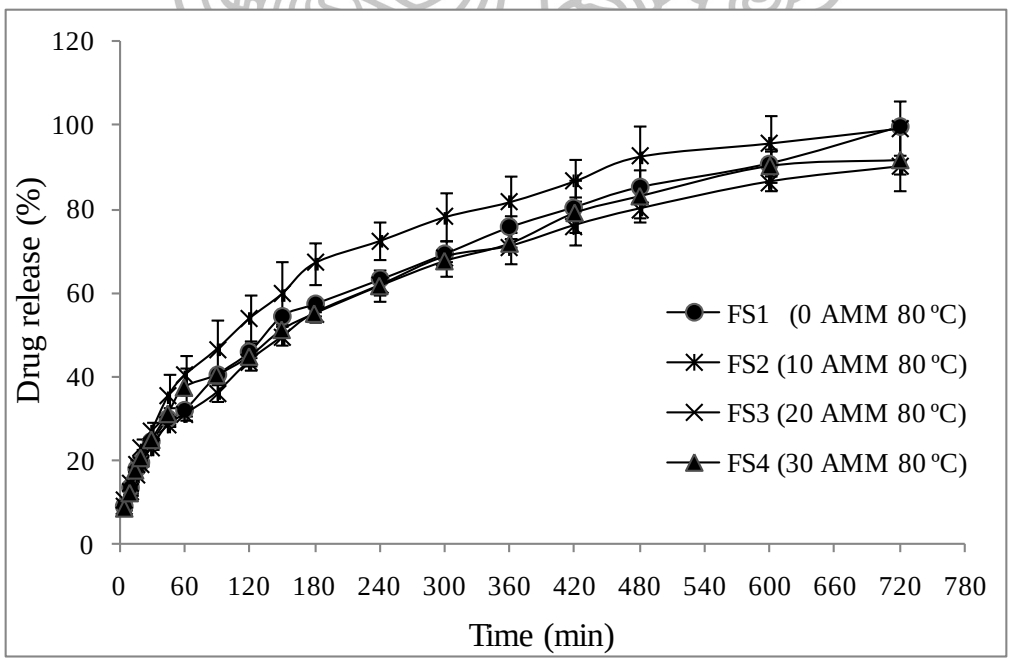


Figure 48 Effect of AMN content and annealing at 80°C on drug release profiles of SHL – based floating matrix tablets (n = 3)

Effects of SHL content and annealing process on drug release profiles are presented in Figures 49 – 51. At 40°C annealing temperature (Figure 49), the fast drug release was observed in all tablet formulations regardless of SHL content because of residual AMN as described above. However, the retardation of drug release was clearly observed after increasing of SHL content and annealing at higher temperature, especially at 80°C in which the AMN was completely removed. The result was correlated with the result from nonporous SHL – based matrix tablet as described in section 1.1, suggesting that the SHL was the critical factor affecting the controlled drug release through the polymerized network [19, 134]

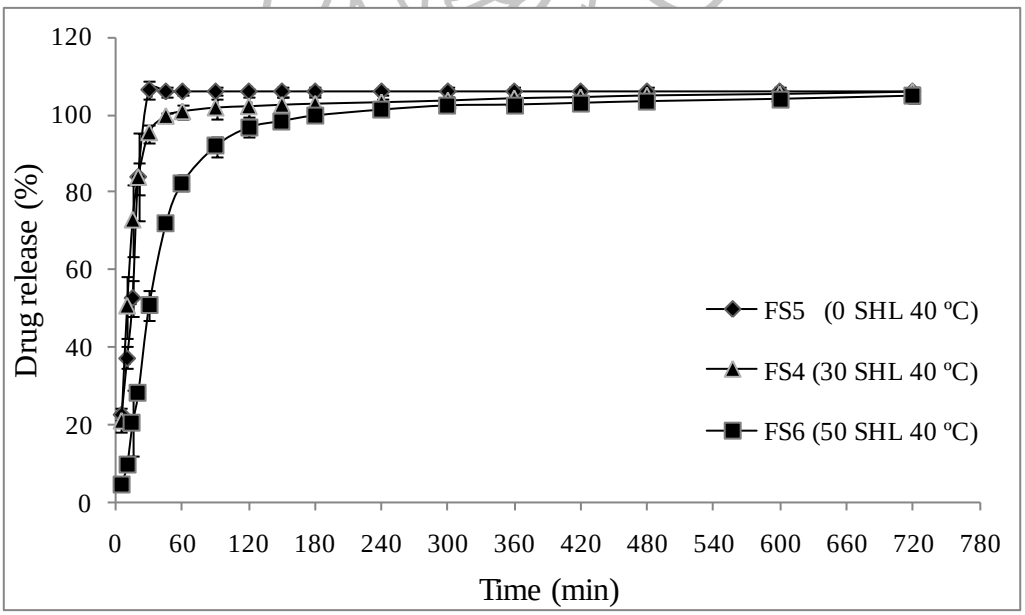


Figure 49 Effect of SHL content and annealing at 40°C on drug release profiles of SHL – based floating matrix tablets (n = 3)

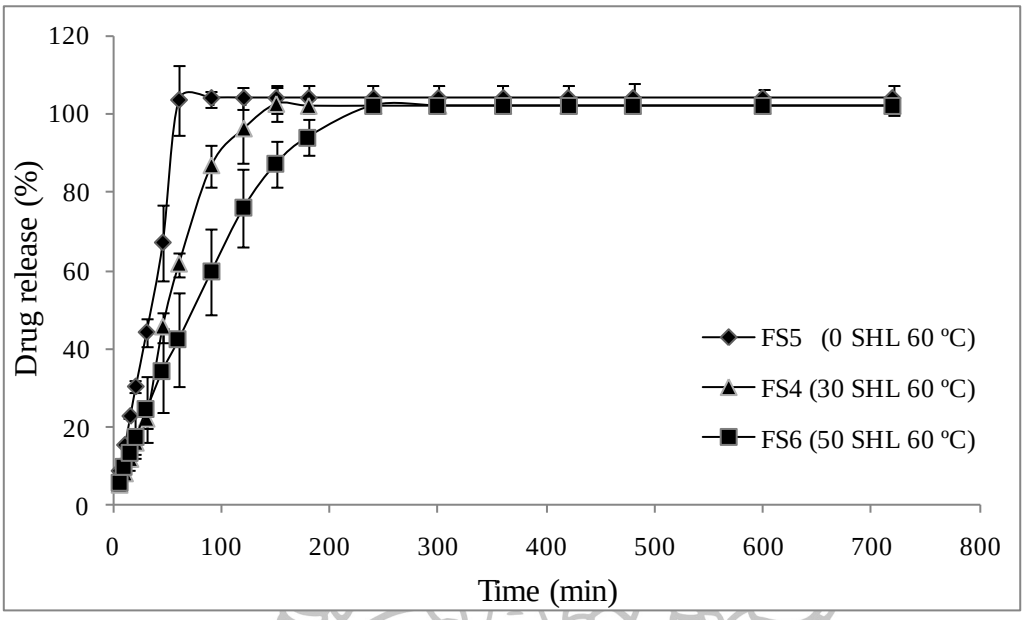


Figure 50 Effect of SHL content and annealing at 60°C on drug release profiles of SHL – based floating matrix tablets (n = 3)

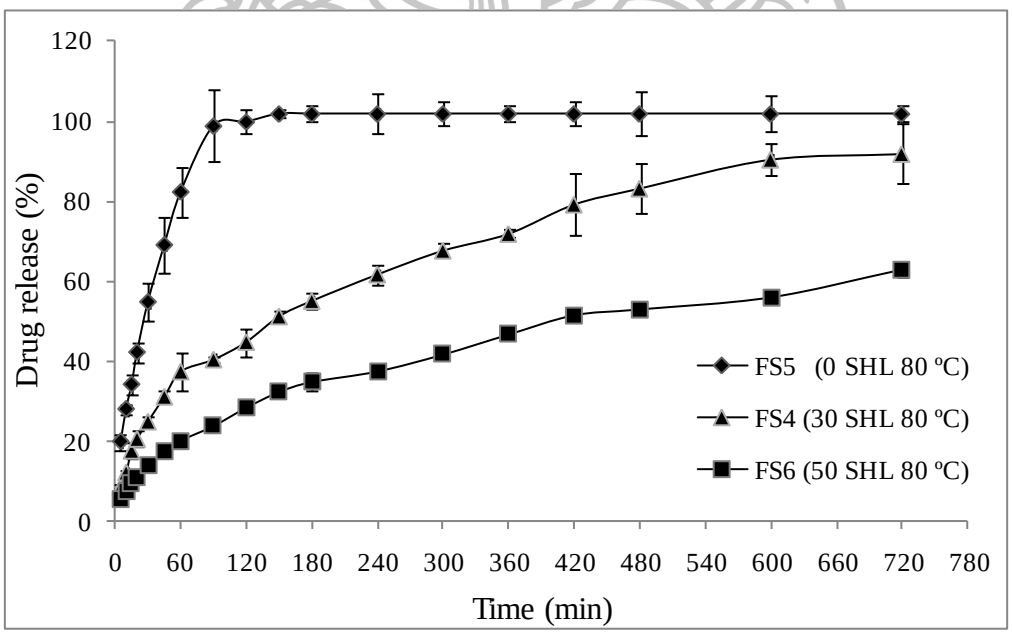


Figure 51 Effect of SHL content and annealing at 80°C on drug release profiles of SHL – based floating matrix tablets (n = 3)

With regard to the result of floating ability and MRI of SHL – based floating tablets, HPMC had directly influenced on the floating time by swelling and blocking of water channel in the matrix and therefore might also affect the drug release. In order to study the consequence of HPMC on drug release, the dissolution profiles of tablets with and without HMPC were comparatively evaluated. Additionally, the drug release from the tablets with different residual AMN (annealing at 40 and 60°C) was also evaluated.

Effect of HPMC content and annealing process on drug release profile is presented in Figures 52 – 54. At annealing temperature of 40 and 60°C, the drug release from SHL – based tablets was significantly reduced as increase amount of HMPC. For example, the FS4 tablets demonstrated a complete drug release within 2 h whereas the FS5 and FS7 tablets could prolong a drug release over 12 h. In this case, the swelling of HPMC to form the integrity matrix might prevent the erosion of tablets due to residual AMN and sustain a drug release [89]. However, the less pronounced effect of HMPC on the drug release of SHL based tablets annealed at 80°C was observed. The result suggested that the drug release was mainly controlled by SHL. Although swelling of HPMC in the pore of polymerized matrix might act as a barrier for drug release especially at high content of HPMC, the diffusion process through polymerized matrix of SHL might be a more rate controlled step as compared to the diffusion through gel layer of HPMC.

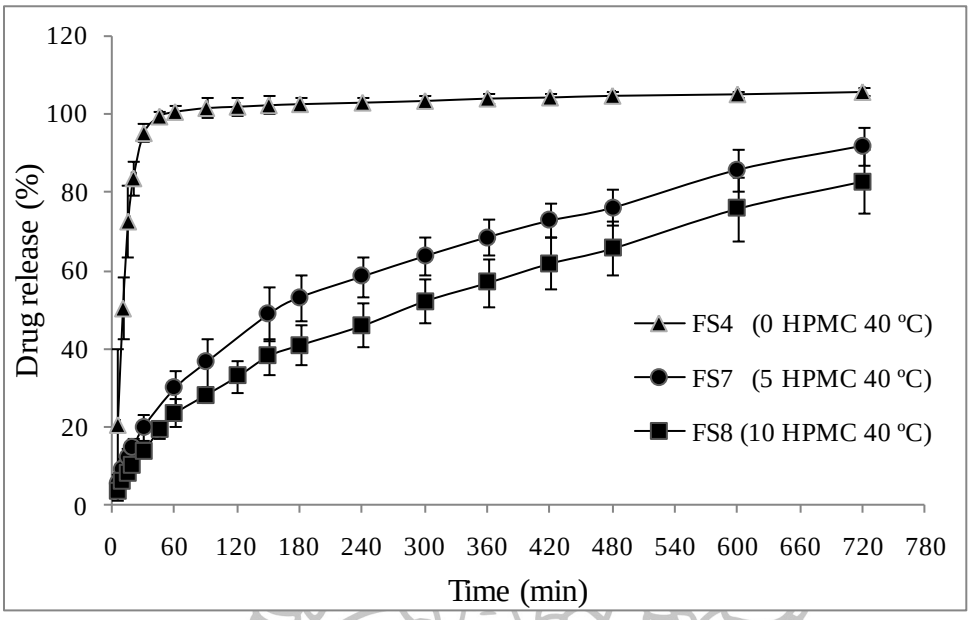


Figure 52 Effect of HPMC content and annealing at 40°C on drug release profiles of SHL – based floating matrix tablet (n = 3)

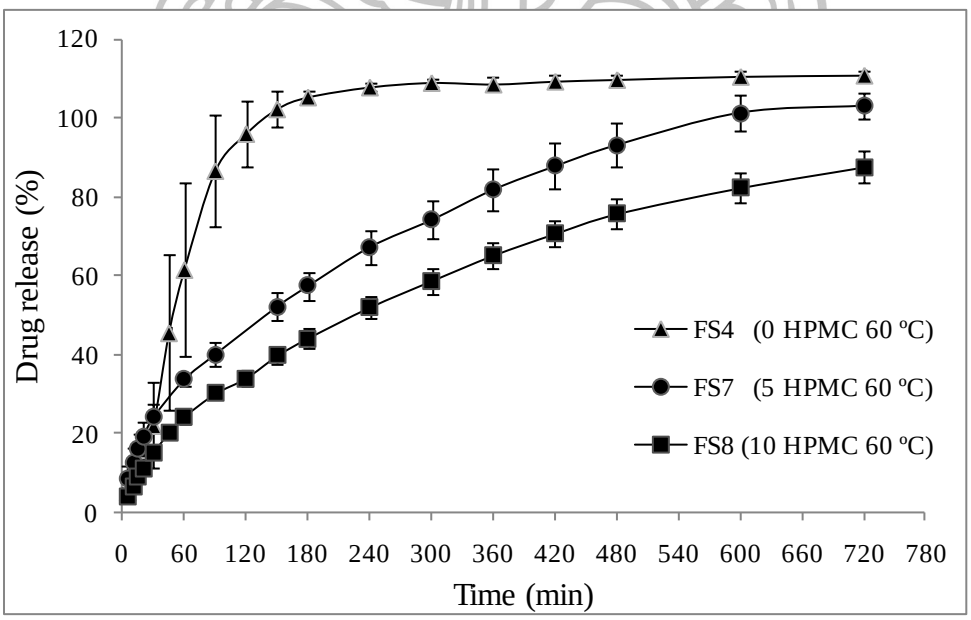


Figure 53 Effect of HPMC content and annealing at 60°C on drug release profiles of SHL – based floating matrix tablet (n = 3)

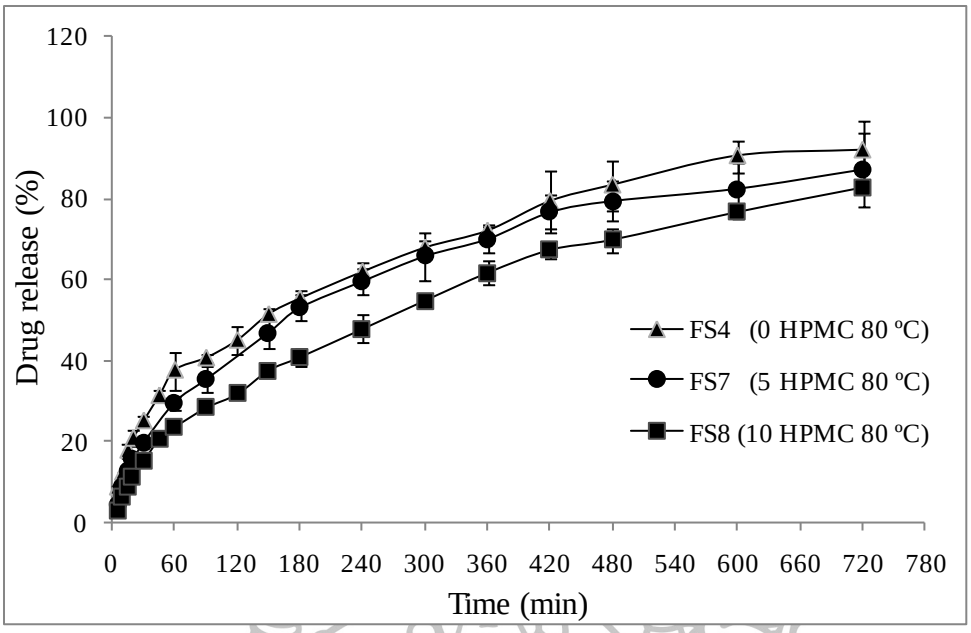


Figure 54 Effect of HPMC content and annealing at 80°C on drug release profiles of SHL – based floating matrix tablet (n = 3)

In order to study the consequence of tablet formulation and annealing temperature on the drug release mechanism, the dissolution profiles of SHL – based tablet matrices with different amount of AMN, SHL and HPMC were fitted with various mathematical models, including zero order, first order, Higuchi, Hixon – Crowell and power law models. The correlation coefficient or coefficient of determination (r^2) from drug release profiles was comparatively evaluated as shown in Tables 43 – 45.

The influence of AMN content and annealing process on drug release kinetics from SHL – based floating matrix tablets in 0.1 N HCl is presented in Table 43. The kinetic of drug release was depended on both amount of AMN and annealing temperatures. For tablets without AMN (FS1), the release kinetics were well fitted with the Higuchi and the power law models with the n value closed to 0.5, regardless

of annealing temperature. The result suggested the main mechanism of drug release was matrix diffusion through the network of SHL. However, the kinetic of drug release of tablets was depended on the annealing temperature for tablets with AMN. At low annealing temperature, the n – value from power law model was closed to 1 while the release kinetic was more fitted with zero order. For examples, FS4 showed the n value of 1.069 and 0.460 and the correlation coefficient of zero order was 0.998 and 0.494, after annealing at 40°C and 80°C, respectively. At low annealing temperature, the residual ammonium carbonate could promote erosion of matrix and disturbed the diffusion process caused by SHL network. However, the matrix diffusion process was clearly indicated in tablets annealed at 80°C due to completely removal of ammonium carbonate and polymerization of SHL.

Table 43 Effect of ammonium carbonate content and annealing process on drug release kinetics from SHL – based floating matrix tablet in 0.1 N HCl

Formulations		Zero order kinetic	First order kinetic	Higuchi model	Hixson-Crowell model	Power law equation		
Ammonium carbonate content (%)	Annealing temperature					r^2	n	k
(FS1) 0	40°C	0.7364	0.8787	0.9956	0.8414	0.9987	0.537	2.902
	60°C	0.7347	0.8905	0.9958	0.8496	0.9993	0.540	3.570
	80°C	0.6265	0.8246	0.9963	0.7705	0.9963	0.497	4.363
(FS2) 10	40°C	0.7075	0.8485	0.9924	0.8087	0.9963	0.541	3.223
	60°C	0.7336	0.8871	0.9963	0.8483	0.9992	0.536	3.091
	80°C	0.6195	0.8026	0.9956	0.7509	0.9957	0.494	4.140
(FS3) 20	40°C	0.8431	0.9739	0.9450	0.9456	0.9901	0.657	3.992
	60°C	0.8072	0.9423	0.9809	0.9098	0.9987	0.595	3.083
	80°C	0.5668	0.8271	0.9960	0.7576	0.9962	0.493	5.126
(FS4) 30	40°C	0.9881	0.9007	0.7504	0.9407	0.9909	1.069	4.081
	60°C	0.9458	0.9006	0.6752	0.9164	0.9723	1.266	0.355
	80°C	0.4904	0.7453	0.9825	0.6722	0.9875	0.460	5.132

The effect of SHL content and annealing process on drug release kinetics from SHL – based floating matrix tablet in 0.1 N HCl is shown in Table 44. As increasing the amount of SHL, drug release profile was more fitted with Higuchi model and the n value from Korsemeyer – Peppas model was decreased and approached to 0.45, especially at high annealing temperature. The result suggested the release mechanism was changed from anomalous transport to Fickian diffusion. The similar results were also observed in the non – porous SHL – based tablet (Table 19),

confirming the diffusion of drug through polymerized SHL matrix after annealing. It was also noted that the porous structure did not clearly affect the mechanism of high SHL load matrix since the n value obtained from release profile of non – or porous matrix, after removal of residual AMN, were almost the same.

Effect of HPMC content and annealing process on drug release kinetics from SHL – based floating matrix tablet in 0.1 N HCl is shown in Table 45. The release mechanism was significantly changed after addition of small amount of HPMC. For tablets annealed at 40°C, the n – value was decreased from 1.069 (FS4) to 0.549 (FS7) and 0.550 (FS8) after addition of 5% and 10% HPMC, respectively. The result suggested the swelling of HPMC prevented the erosion of tablets and the mechanism was changed to diffusion process though the gel layer. At 80°C annealing temperature, the main mechanism was diffusion process regardless of HPMC content while the lower n – value of SHL based tablet without HPMC was observed. The result suggested that drug was diffused through both the polymerized matrix of SHL and swelling layer of HPMC. The higher n – value of HPMC containing SHL tablets might be resulted from more erosion control of swelling HPMC in the porous structure of SHL tablet.

Table 44 Effect of SHL content and annealing process on drug release kinetics from SHL – based floating matrix tablet in 0.1 N HCl

Formulations	Annealing temperature	Zero order kinetic	First order kinetic	Higuchi model	Hixson-Crowell Model	Power law equation		
Shellac content (%)						r^2	n	k
(FS5) 0	40°C	0.9452	0.9915	0.8865	0.9878	0.9971	0.782	6.308
	60°C	0.9957	0.9911	0.8199	0.9967	0.9992	0.931	1.864
	80°C	0.7203	0.9161	0.9706	0.8721	0.9934	0.600	7.025
(FS4) 30	40°C	0.9881	0.9007	0.7504	0.9407	0.9909	1.069	4.081
	60°C	0.9458	0.9006	0.6752	0.9164	0.9723	1.266	0.355
	80°C	0.4904	0.7453	0.9825	0.6722	0.9875	0.460	5.132
(FS6) 50	40°C	0.9415	0.8795	0.6436	0.9009	0.9971	1.405	0.427
	60°C	0.9733	0.9970	0.8793	0.9970	0.9996	0.818	1.506
	80°C	0.6135	0.8166	0.9924	0.7624	0.9954	0.466	2.980

Table 45 Effect of HPMC content and annealing process on drug release kinetics from SHL – based floating matrix tablet in 0.1 N HCl

Formulations		Zero order kinetic	First order kinetic	Higuchi model	Hixson-Crowell model	Power law equation		
HPMC content (%)	Annealing temperature					r^2	n	k
(FS4) 0	40°C	0.9881	0.9007	0.7504	0.9407	0.9909	1.069	4.081
	60°C	0.9458	0.9006	0.6752	0.9164	0.9723	1.266	0.355
	80°C	0.4904	0.7453	0.9825	0.6722	0.9875	0.460	5.132
(FS7) 5	40°C	0.7801	0.9195	0.9891	0.8832	0.9934	0.549	3.017
	60°C	0.6628	0.8414	0.9988	0.7905	0.9989	0.504	4.191
	80°C	0.8010	0.9248	0.9884	0.8927	0.9954	0.560	2.839
(FS8) 10	40°C	0.7674	0.9128	0.9875	0.8753	0.9926	0.550	2.294
	60°C	0.8318	0.9459	0.9817	0.9185	0.9976	0.594	2.005
	80°C	0.7935	0.9145	0.9852	0.8831	0.9943	0.569	2.143

CHAPTER 5

CONCLUSIONS

This study was designed to fabricate gastric floating drug delivery tablets by using SHL and SHL derivatives as carriers for controlling of drug release. The porous floating matrix tablets were successfully prepared by using sublimation technique. In this work, we divided into 2 parts. The first section was to prepare and evaluate SHL and SHL derivatives – based matrix tablet. The factors affecting drug controlled release in this system were investigated. The results obtained from the first section were further used as a basic knowledge for fabrication of porous SHL – based matrix tablet in the second section. The major finding in this study could be summarized as follows:

1. The SHL or SHL derivatives content in the formulation was the major factor that directly affected the physical properties of tablet. The increment of SHL or SHL derivatives content, especially at level of 30%w/w or more, significantly promoted the hardness and extended the disintegration time of tablet.

2. The properties of annealed SHL or SHL derivatives – based matrix tablets differed from unannealed tablets. The annealed tablets demonstrated more hardness and longer disintegration time as compared to those of unannealed tablets.

3. The more sustained drug release was observed as increasing annealing temperature, suggesting the polymerization of SHL could provide the network that retarded the drug release.

4. The annealing temperature demonstrated less effect on tableting properties containing SHL salts as matrix forming agent which could be explain by the reduced polymerization due to protection of function groups of SHL after salt formation.

5. The main mechanism of drug release from SHL or SHL derivatives – based matrix tablet was anomalous transport. In addition, anomalous transport was coupled of diffusion and relaxation control.

6. The floating SHL – based matrix tablets were successfully fabricated through sublimation technique and specific selection of amount of SHL, AMN and HPMC.

7. At annealing temperature of 80°C for 24 h, the AMN was completely sublimed resulting in the porous structure of SHL – based tablet as observed through SEM and X – ray CT imaging.

8. The hardness of tablets was decreased as increasing amount of AMN while it was compensated by increasing amount of SHL and annealing temperature.

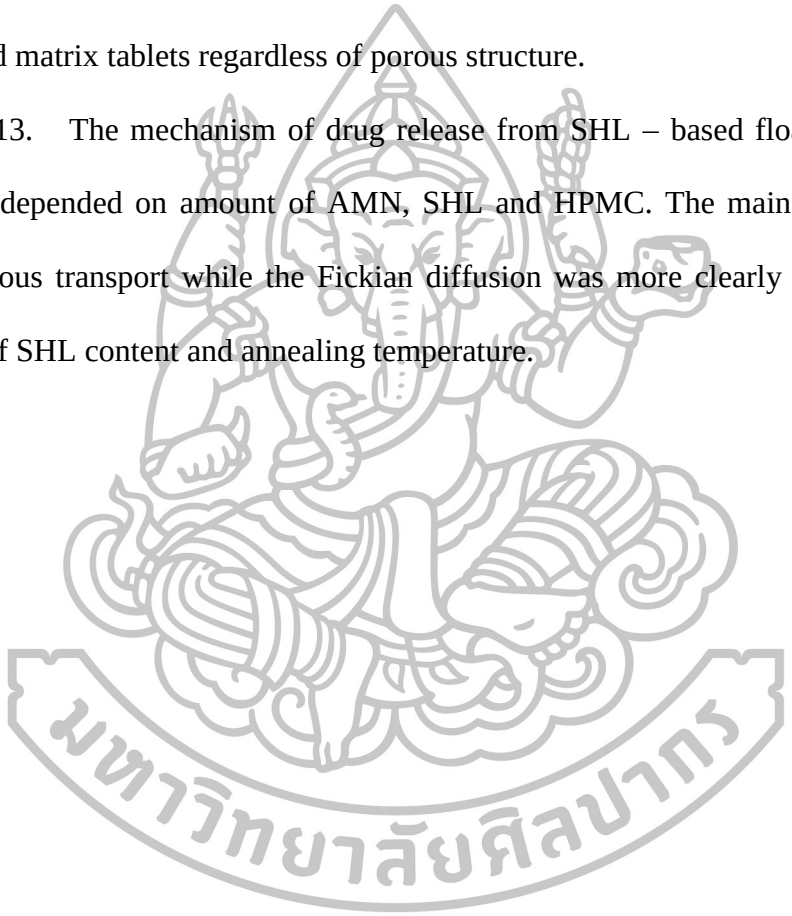
9. The SHL – based floating tablets with at least 30%w/w of AMN were immediately floated due to the density of less than 1 g/cm^3. However, the duration of floating was less than 12 h due to medium penetration through the pore.

10. HPMC was the key success material to extend the floatation. The minor amount of HPMC in the range of 5 – 10%w/w supported floating duration for more than 12 h. The gel layer of HPMC could retard the water filled pore and also sustained the drug release.

11. The floating properties were also influenced by SHL content. As increasing the amount of SHL or SHL derivatives, the floatability was improved due to the lower density of SHL as compared to other incorporated excipients.

12. The more sustained drug release from SHL – based floating matrix tablets was observed as increasing amount of SHL in the same manner as observed in SHL – based matrix tablets regardless of porous structure.

13. The mechanism of drug release from SHL – based floating matrix tablets was depended on amount of AMN, SHL and HPMC. The main mechanism was anomalous transport while the Fickian diffusion was more clearly observed as increasing of SHL content and annealing temperature.



REFFERENCES

[1] Lobenberg, R., et al. (2005). "Pharmacokinetics of an immediate release, a controlled release and a two pulse dosage form in dogs." **European Journal of Pharmaceutics and Biopharmaceutics** 60(1): 17 – 23.

[2] Sauzet, C., et al. (2009). "An innovative floating gastro retentive dosage system: Formulation and in vitro evaluation." **International Journal of Pharmaceutics** 378(12): 23 – 29.

[3] Singh, B.N., and K.H. Kim. (2000). "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention." **Journal of Controlled Release** 63(3): 235 – 259.

[4] Bardonnet, P.L., et al. (2006). "Gastroretentive dosage forms: Overview and special case of Helicobacter pylori." **Journal of Controlled Release** 111(1 – 2): 1 – 18.

[5] Sato, Y., et al. (2004). "In vitro and in vivo evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans." **International Journal of Pharmaceutics** 275(1 – 2): 97 – 107.

[6] Sato, Y., et al. (2004). "Pharmacoscintigraphic evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans." **Journal of Controlled Release** 98(1): 75 – 85.

[7] Sato, Y., et al. (2003). "In vivo evaluation of riboflavin-containing microballoons for floating controlled drug delivery system in healthy human volunteers." **Journal of Controlled Release** 93(1): 39 – 47.

[8] Whitehead, L., et al. (1998). "Floating dosage forms: an in vivo study demonstrating prolonged gastric retention." **Journal of Controlled Release** 55(1): 3 – 12.

[9] Fukuda, M., et al. (2006). "Floating hot-melt extruded tablets for gastroretentive controlled drug release system." **Journal of Controlled Release** 115(2): 121 – 129.

[10] El-Gibaly, I. (2002). "Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres." **International Journal of Pharmaceutics** 249(1 –2): 7 – 21.

[11] Dash, M., et al. (2011). "Chitosan – A versatile semi – synthetic polymer in biomedical applications." **Progress in Polymer Science** 36(8): 981 – 1014.

[12] Brydson, J.A. (1999). "Miscellaneous plastics materials." **Plastics Materials**: 867 – 869.

[13] Agyilirah, G.A., and G.S. Banker. (1991). "Polymer for enteric coating applications." **Polymers for controlled drug delivery**: 41 – 44.

[14] Pearnchob, N., et al. (2004). "Improvement in the disintegration of shellac – coated soft gelatin capsules in simulated intestinal fluid." **Journal of Controlled Release** 94(2 – 3): 313 – 321.

[15] Limmatvapirat, S., et al. (2004). "Modification of physicochemical and mechanical properties of shellac by partial hydrolysis." **International Journal of Pharmaceutics** 278(1): 41 – 49.

[16] Limmatvapirat, S., et al. (2008). "Formation of shellac succinate having improved enteric film properties through dry media reaction." **European Journal of Pharmaceutics and Biopharmaceutics** 70(1): 335 – 344.

[17] Farag, Y. and C.S. Leopold. (2011). "Development of shellac – coated sustained release pellet formulations." **European Journal of Pharmaceutical Sciences** 42(4): 400 – 405.

[18] Limmatvapirat, S., et al. (2007). "Enhanced enteric properties and stability of shellac films through composite salts formation." **European Journal of Pharmaceutics and Biopharmaceutics** 67(3): 690 – 698.

[19] Limmatvapirat, S., et al. (2008). "Modulation of drug release kinetics of shellac – based matrix tablets by in-situ polymerization through annealing process." **European Journal of Pharmaceutics and Biopharmaceutics** 69(3): 1004 – 1013.

[20] Coelho, C., et al. (2012). "Molecular changes during natural biopolymer ageing – the case of shellac." **Polymer Degradation and Stability** 97: 936 – 940.

[21] Arora, S. (2005). "Floating drug delivery system: A review." **The American Association of Pharmaceutical Sciences PharmSciTech** 6(3): 374 – 390.

[22] O'Reilly, S., et al. (1987). "The influence of food on the gastric emptying of multiparticulate dosage forms." **International Journal of Pharmaceutics** 34(3): 213 – 216.

[23] Jiminez-Martinez, I., et al. (2008). "Sustained delivery of captopril from floating matrix tablets." **International Journal of Pharmaceutics** 362(1-2): 37 – 43.

[24] Stops, F., et al. (2008). "Floating dosage forms to prolong gastro-retention – The characterisation of calcium alginate beads." **International Journal of Pharmaceutics** 350(1 – 2): 301 – 311.

[25] Rouge, N., et al. (1998). "Comparative pharmacokinetic study of a floating multiple – unit capsule, a high – density multiple – unit capsule and an immediate – release tablet containing 25 mg atenolol." **Pharmaceutica Acta Helvetiae** 73(2): 81– 87.

[26] Clarke, G.M., et al. (1995). "Comparative gastrointestinal transit of pellet systems of varying density." **International Journal of Pharmaceutics** 114(1): 1 – 11.

[27] Timmermans, J., et al. (1993). "The cutoff size for gastric emptying of dosage forms." **Journal of Pharmaceutical Science** 82(8): 854.

[28] Jang, S.W., et al. (2008). "Gastroretentive drug delivery system of DA-6034, a new flavonoid derivative, for the treatment of gastritis." **International Journal of Pharmaceutics** 356(1 – 2): 88 – 94.

[29] Kagan, L., et al. (2006). "Gastroretentive Accordion Pill: Enhancement of riboflavin bioavailability in humans." **Journal of Controlled Release** 113(3): 208 – 215.

[30] Streubel, A., et al. (2006). "Drug delivery to the upper small intestine window using gastroretentive technologies." **Current Opinion in Pharmacology** 6(5): 501 – 508.

[31] Rouge, N., et al. (1996). "Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery." **International Journal of Pharmaceutics** 136(1 – 2): 117 – 139.

[32] Clarke, G.M., et al. (1993). "Gastrointestinal transit of pellets of differing size and density." **International Journal of Pharmaceutics** 100(1 – 3): 81 – 92.

[33] Tuleu, C., et al. (1999). "Gastrointestinal transit of pellets in rats: effect of size and density." **International Journal of Pharmaceutics** 180(1): 123 – 131.

[34] Cardinal, J.R. (1985). "Controlled drug delivery: Veterinary applications." **Journal of Controlled Release** 2(0): 393 – 403.

[35] Klausner, E.A., et al. (2003). "Expandable gastroretentive dosage forms." **Journal of Controlled Release** 90(2): 143 – 162.

[36] Groning, R., et al. (2007). "Compressed collagen sponges as gastroretentive dosage forms: In vitro and in vivo studies." **European Journal of Pharmaceutical Sciences** 30(1): 1 – 6.

[37] Chen, J., et al. (2000). "Gastric retention properties of superporous hydrogel composites." **Journal of Controlled Release** 64(1 – 3): 39 – 51.

[38] Omidian, H., et al. (2011). "Superporous Hydrogels for Drug Delivery Systems." **Comprehensive Biomaterials**: 563 – 576.

[39] Sen, M., et al. (2000). "Controlled release of terbinafine hydrochloride from pH sensitive poly(acrylamide/maleic acid) hydrogels." **International Journal of Pharmaceutics** 203(1 – 2): 149 – 157.

[40] Aikawa, K., et al. (1998). "Hydrogel formation of the pH response polymer polyvinylacetal diethylaminoacetate (AEA)." **International Journal of Pharmaceutics** 167(1 – 2): 97 – 104.

[41] Chen, J. and K. Park. (2000). "Synthesis and characterization of superporous hydrogel composites." **Journal of Controlled Release** 65(1 – 2): 73 – 82.

[42] Omidian, H., et al. (2005). "Advances in superporous hydrogels." **Journal of Controlled Release** 102(1): 3 – 12.

[43] Dodou, D., et al. (2005). "Mucoadhesives in the gastrointestinal tract: revisiting the literature for novel applications." **European Journal of Pharmaceutics and Biopharmaceutics** 60(1): 1 – 16.

[44] Smart, J.D. (2005). "The basics and underlying mechanisms of mucoadhesion." **Advanced Drug Delivery Reviews** 57(11): 1556 – 1568.

[45] Peppas, N.A. et al. (1985). "Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues." **Journal of Controlled Release** 2: 257 – 275.

[46] Lehr, C.M., et al. (1993). "A surfaceenergy analysis of mucoadhesion. II. Prediction of mucoadhesiveperformance by spreading coefficients." **European Journal of Pharmaceutics and Biopharmaceutics** 1: 19 – 30.

[47] Park, K., et al. (1984). "Bioadhesive polymers as platforms for oralcontrolled drug delivery: method to study bioadhesion." **International Journal of Pharmaceutics** 19: 107 – 127.

[48] Park, H., et al. (1985). "Physico-chemical properties of water insoluble polymers important to mucin/epithelial adhesion." **Journal Controlled Release** 2: 47 – 57.

[49] Leung, S.H.S. (1990). "Polymer structure features contributing to mucoadhesion II." **Journal of Controlled Release** 12: 187 – 194.

[50] Peppas, N.A. and J.J. Sahlin. (1996). "Hydrogels as mucoadhesive and bioadhesive materials: a review." **Biomaterials** 17(16): 1553 – 1561.

[51] Darandale, S.S. and P.R. Vavia. (2012). "Design of a gastroretentive mucoadhesive dosage form of furosemide for controlled release." **Acta Pharmaceutica Sinica B** 2(5): 509 – 517.

[52] Sogias, I.A., et al. (2012). "Chitosan-based mucoadhesive tablets for oral delivery of ibuprofen." **International Journal of Pharmaceutics** 436: 602 – 610.

[53] Tao, Y., et al. (2009). "Development of mucoadhesive microspheres of acyclovir with enhanced bioavailability." **International Journal of Pharmaceutics** 378(1 – 2): 30 – 36.

[54] Chun, M.K., et al. (2002). "Mucoadhesive drug carrier based on interpolymer complex of poly(vinyl pyrrolidone) and poly(acrylic acid) prepared by template polymerization." **Journal of Controlled Release** 81: 327 – 334.

[55] Cao, Q.R., et al. (2012). "Enhanced oral bioavailability of novel mucoadhesive pellets containing valsartan prepared by a dry powder – coating technique." **International Journal of Pharmaceutics** 434(1 – 2): 325 – 333.

[56] Mahesh, D., et al. (2006). "Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin." **International Journal of Pharmaceutics** 316: 86 – 92.

[57] Wang, J., et al. (2001). "Evaluation of gastric mucoadhesive properties of aminated gelatin microspheres." **Journal of Controlled Release** 73(2 – 3): 223 – 231.

[58] Han, H.K., et al. (2012). "Improved oral bioavailability of alendronate via the mucoadhesive liposomal delivery system." **European Journal of Pharmaceutical Sciences** 46(5): 500 – 507.

[59] Hagesaether, E., et al. (2009). "Mucoadhesion and drug permeability of free mixed films of pectin and chitosan: An in vitro and ex vivo study." **European Journal of Pharmaceutics and Biopharmaceutics** 71: 325 – 331.

[60] Fujimori, J., et al. (1994). "Preparation of a magneticallyresponsive tablet and confirmation of its gastric residence in beagle dogs." **Sciences techniques et pratiques pharmaceutiques sciences** 4: 425 – 430.

[61] Groning, R., et al. (1998). "Acyclovir serum concentrations, et al., Acyclovir serum concentrations following peroral administration of magnetic depot tablets and the influence of extracorporal magnets to control gastrointestinal transit." **European Journal of Pharmaceutics and Biopharmaceutics** 46(3): 285 – 291.

[62] Nagano, H., et al. (1997). "Preparation of magnetic granules containing bleomycin and its evaluation using model esophageal cancer." **International Journal of Pharmaceutics** 147: 119 – 125.

[63] Mazer, N., et al. (1988). "Intragastric behavior and absorption kinetics of a normal and ‘‘floating’’ modified – release capsule of isradipine under fasted and fed conditions," **Journal of Pharmaceutical Science** 77(8): 647 – 657.

[64] Nayak, A.K., et al. (2013). "Gastroretentive hydrodynamically balanced systems of ofloxacin: In vitro evaluation." **Saudi Pharmaceutical Journal** 21(1): 113 – 117.

[65] Ali, J., et al. (2007). "Formulation and development of hydrodynamically balanced system for metformin: In vitro and in vivo evaluation." **European Journal of Pharmaceutics and Biopharmaceutics** 67(1): 196 – 201.

[66] Dorozynski, P., et al. (2011). "Gastroretentive drug delivery systems with l – dopa based on carrageenans and hydroxypropylmethylcellulose." **International Journal of Pharmaceutics** 404(1 – 2): 169 – 175.

[67] Krogel, I. and R. Bodmeier. (1999). "Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder." **Journal of Controlled Release** 61(1 – 2): 43 – 50.

[68] Garg, S., et al. (2003). "Gastroretentive drug delivery systems." **PharmaTech**: 160 – 166.

[69] Baumgartner, S., et al. (2000). "Optimisation of floating matrix tablets and evaluation of their gastric residence time." **International Journal of Pharmaceutics** 195(1 – 2): 125 – 135.

[70] Krogel, I. and R. Bodmeier. (1999). "Floating or pulsatile drug delivery systems based on coated effervescent cores." **International Journal of Pharmaceutics** 187(2): 175 – 184.

[71] Yang, L., et al. (1999). "A new intragastric delivery system for the treatment of Helicobacter pylori associated gastric ulcer: in vitro evaluation." **Journal of Controlled Release** 57(3): 215 – 222.

[72] Gattani, Y.S., et al. (2009). "Formulation and evaluation of Gastro retentive Multiparticulate Drug delivery system of Aceclofenac." **International Journal of ChemTech Research** 1: 1 – 10.

[73] Choi, B.Y., et al., (2002). "Preparation of alginate beads for floating drug delivery system: effects of CO_2 gas – forming agents." **International Journal of Pharmaceutics** 239(1 – 2): 81 – 91.

[74] Sungthongjeen, S., et al. (2006). "Preparation and in vitro evaluation of a multiple – unit floating drug delivery system based on gas formation technique." **International Journal of Pharmaceutics** 324(2): 136 – 143.

[75] Hamdani, J., et al. (2006). "Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization." **International Journal of Pharmaceutics** 322(1 – 2): 96 – 103.

[76] Goole, J., et al. (2008). "New levodopa sustained – release floating minitablets coated with insoluble acrylic polymer." **European Journal of Pharmaceutics and Biopharmaceutics** 68(2): 310 – 318.

[77] Tadros, M.I. (2010). "Controlled – release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro – in vivo evaluation in healthy human volunteers." **European Journal of Pharmaceutics and Biopharmaceutics** 74(2): 332 – 339.

[78] Ibrahim, H.K. (2009). "A novel liquid effervescent floating delivery system for sustained drug delivery." **Drug Discoveries and Therapeutics** 3(4): 168 – 175.

[79] Prajapati, V.D., et al. (2013). "Raft forming system – An upcoming approach of gastroretentive drug delivery system." **Journal of Controlled Release** 168(2): 151 – 165.

[80] Kawashima, Y., et al. (1991). "Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (in vivo)." **Journal of Controlled Release** 16(3): 279 – 289.

[81] Sato, Y., et al. (2004). "In vitro evaluation of floating and drug releasing behaviors of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method." **European Journal of Pharmaceutics and Biopharmaceutics** 57(2): 235 – 243.

[82] Streubel, A., et al. (2003). "Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release." **European Journal of Pharmaceutical Sciences** 18(1): 37 – 45.

[83] Streubel, A., et al. (2002). "Floating microparticles based on low density foam powder." **International Journal of Pharmaceutics** 241(2): 279 – 292.

[84] Sher, P., et al. (2007). "Low density porous carrier based conceptual drug delivery system." **Microporous and Mesoporous Materials** 102(1 – 3): 290 – 298.

[85] Malakar, J., et al. (2012). "Development of cloxacillin loaded multiple – unit alginate – based floating system by emulsion – gelation method." **International Journal of Biological Macromolecules** 50(1): 138 – 147.

[86] Yao, H., et al. (2012). "Preparation and evaluation of a novel gastric floating alginate/poloxamer inner – porous beads using foam solution." **International Journal of Pharmaceutics** 422(1 – 2): 211 – 219.

[87] Xu, X., et al. (2006). "Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers." **International Journal of Pharmaceutics** 310(1 – 2): 139 – 145.

[88] Klausner, E.A., et al. (2003). "Novel levodopa gastroretentive dosage form: in – vivo evaluation in dogs." **Journal of Controlled Release** 88(1):117 – 126.

[89] Hu, L., et al. (2011). "Floating matrix dosage form for dextromethorphan hydrobromide based on gas forming technique: In vitro and in vivo evaluation in healthy volunteers." **European Journal of Pharmaceutical Sciences** 42(1 – 2): 99 – 105.

[90] Ishak, R.A.H., et al. (2007). "Preparation, in vitro and in vivo evaluation of stomach-specific metronidazole-loaded alginate beads as local anti – *Helicobacter pylori* therapy." **Journal of Controlled Release** 119(2): 207 – 214.

[91] Rajinikanth, P.S. and B. Mishra. (2008). "Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate H. pylori." **Journal of Controlled Release** 125(1): 33 – 41.

[92] Singh, B., et al. (2010). "Gastroretentive floating sterculia alginate beads for use in antiulcer drug delivery." **Chemical Engineering Research and Design** 88(8): 997 – 1012.

[93] Chen, Y.C., et al. (2013). "Physical characterizations and sustained release profiling of gastroretentive drug delivery systems with improved floating and swelling capabilities." **International Journal of Pharmaceutics** 441(1 – 2): 162 – 169.

[94] Hascicek, C., et al. (2011). "Assemblage of drug release modules: Effect of module shape and position in the assembled systems on floating behavior and release rate." **European Journal of Pharmaceutics and Biopharmaceutics** 77(1): 116 – 121.

[95] Jain, S.K., et al. (2005). "Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: Preparation and in vitro characterization." **Journal of Controlled Release** 107(2): 300 – 309.

[96] Mouzam, M.I., et al. (2011). "Preparation of a novel floating ring capsule – type dosage form for stomach specific delivery." **Saudi Pharmaceutical Journal** 19(2): 85 – 93.

[97] Arora, S., et al. (2005). "Floating Drug Delivery Systems: A Review." **The American Association of Pharmaceutical Sciences PharmSciTech** 6(3): 372 – 390.

[98] Ichikawa, M., et al. (1991). "A new multiple – unit oral floating dosage system. I. Preparation and in vitro evaluation of floating and sustained – release characteristics." **Journal of Pharmaceutical Science** 80: 1062 – 1066.

[99] Timmermans, J., et al. (1990). "How well do floating dosage forms float ?" **International Journal of Pharmaceutics** 62: 207 – 216.

[100] Li, S., et al. (2003). "Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design." **International Journal of Pharmaceutics** 253: 13 – 22.

[101] Rajendra, S. (2006). "Elements of Entomology." **Meerut : Rastogi Publications**: 23 – 45.

[102] Bechtold, T.a.R.M. (2009). "Handbook of Natural Colorants." **West Sussex Wiley**: 67 – 72.

[103] Jabde, P.V. (2005). "Text Book Of Applied Zoology." **New Delhi Discovery**: 89 – 95.

[104] Phan , D., et al. (2008). "Moisture barrier, wetting and mechanical properties of shellac/agar or shellac/cassava starch bilayer bio – membrane for food applications." **Journal of Membrane Science** 325(1): 277 – 283.

[105] Pearnchob, N. and R. Bodmeier. (2003). "Dry polymer powder coating and comparison with conventional liquid – based coatings for Eudragit RS, ethylcellulose and shellac." **European Journal of Pharmaceutics and Biopharmaceutics** 56(3): 363 – 369.

[106] Rowe, R.C., et al. (2006). "Handbook of pharmaceutical excipients" **Royal Pharmaceutical Society of Great Britain**: 98 – 102.

[107] Chang, R.K., et al. (1990). "Preparation and evaluation of shellac pseudolatex as an aqueous enteric coating system for pellets." **International Journal of Pharmaceutics**: 171 – 173.

[108] Krause, K.P. and R.H. Muller. (2001). "Production of aqueous shellac dispersions by high pressure homogenisation." **International Journal of Pharmaceutics** 223(1 – 2): 89 – 92.

[109] Farag, Y., et al. (2011). "Development of shellac – coated sustained release pellet formulations." **European Journal of Pharmaceutical Sciences** 42: 400 – 405.

[110] Stummer, S., et al. (2010). "Application of shellac for the development of probiotic formulations." **Food Research International** 43: 1312 – 1320.

[111] Chauhan, O.P., et al. (2011). "Shellac and aloe – gel – based surface coatings for maintaining keeping quality of apple slices." **Food Chemistry** 126(3): 961 – 966.

[112] Byun, Y., et al. (2012). "Formation and characterization of shellac – hydroxypropyl methylcellulose composite films." **Food Hydrocolloids** 27(2): 364 – 370.

[113] Sheorey, D.S., et al. (1991). "Effect of variables on the preparation of shellac microcapsules by solvent evaporation technique: Part 1." **International Journal of Pharmaceutics** 68(1 – 3): 19 – 23.

[114] Limmatvapirat, S., et al. (2007). "Enhanced enteric properties and stability of shellac films through composite salts formation." **European Journal of Pharmaceutics and Biopharmaceutics** 67: 690 – 698.

[115] Panchapornpon, D., et al. (2011). "Fabrication of thermally stabilized shellac through solid state reaction with phthalic anhydride." **Materials Letters** 65(8): 1241 – 1244.

[116] Colombo, P., et al. (1999). "Observation of swelling process and diffusion front position during swelling in hydroxypropyl methyl cellulose (HPMC) matrices containing a soluble drug." **Journal of Controlled Release** 61(1 – 2): 83-91.

[117] Bin, C., et al. (2009). "Bio – fluid uptake and release of Indomethacin of direct – compressed HPMC tablets." **Carbohydrate Polymers** 75(2): 282 – 286.

[118] Wan, S.C., et al. (1995). "Matrix swelling: A simple model describing extent of swelling of HPMC matrices." **International Journal of Pharmaceutics** 116(2): 159 – 168.

[119] Maderuelo, C., et al. (2011). "Critical factors in the release of drugs from sustained release hydrophilic matrices." **Journal of Controlled Release** 154(1): 2 – 19.

[120] El-Shanawany, S. (1993). "Sustained release of nitrofurantoin from inert wax matrixes." **Journal of Controlled Release** 26(1): 11 – 19.

[121] Hamdani, J., et al. (2003). "Physical and thermal characterisation of Precirol and Compritol as lipophilic glycerides used for the preparation of controlled – release matrix pellets." **International Journal of Pharmaceutics** 260(1): 47 – 57.

[122]. Liu, J., et al. (2001). "Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot – melt extrusion." **European Journal of Pharmaceutics and Biopharmaceutics** 52(2): 181 – 190.

[123] Pallagi, E., et al. (2004). "Iron(II) sulfate release from drop – formed lipophilic matrices developed by special hot – melt technology." **European Journal of Pharmaceutics and Biopharmaceutics** 57(2): 287 – 294.

[124] Cao, Q.R., et al. (2007). "Photoimages and the release characteristics of lipophilic matrix tablets containing highly water-soluble potassium citrate with high drug loadings." **International Journal of Pharmaceutics** 339(1 – 2): 19 – 24.

[125] Dredan, J., et al. (1998). "Effect of chemical properties on drug release from hydrophobic matrices." **International Journal of Pharmaceutics** 160(2): 257 – 260.

[126] Costa, P. and J.M. Sousa Lobo. (2001). "Modeling and comparison of dissolution profiles." **European Journal of Pharmaceutical Sciences** 13(2): 123 – 133.

[127] Dredan, J., et al. (1996). "Evaluation of mathematical models describing drug release from lipophilic matrices." **International Journal of Pharmaceutics** 145(1 – 2): 61 – 64.

[128] Siepmann, J. and N.A. Peppas. (2001). "Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC)." **Advanced Drug Delivery Reviews** 64: 163 – 174.

[129] Ferrero, C., et al. (2003). "Drug release kinetics and fronts movement studies from methyl methacrylate (MMA) copolymer matrix tablets: effect of copolymer type and matrix porosity." **Journal of Controlled Release** 92(1 – 2): 69 – 82.

[130] Siepmann, J. and F. Siepmann. (2008). "Mathematical modeling of drug delivery." **International Journal of Pharmaceutics** 364(2): 328 – 343.

[131] Strubing, S., et al. (2008). "New insights on poly(vinyl acetate) – based coated floating tablets: Characterisation of hydration and CO_2 generation by benchtop MRI and its relation to drug release and floating strength." **European Journal of Pharmaceutics and Biopharmaceutics** 69(2): 708 – 717.

[132] Limmatvapirat, S. et al. (2004). "Modification of physicochemical and mechanical properties of shellac by partial hydrolysis." **International Journal of Pharmaceutics** 278: 41 – 49.

[133] Chongcherdsak, N., et al. (2012). "Factors affecting design of shellac – based matrix tablet through annealing process." **Advanced Materials Research** 506: 421 – 424.

[134] Arifin , D.Y., et al. (2006). "Mathematical modeling and simulation of drug release frommicrospheres: Implications to drug delivery systems." **Advanced Drug Delivery Reviews** 58: 1274 – 1325.

[135] Dominique M.R., et al. (2008). "A study on maize proteins as a potential new tablet excipient." **European Journal of Pharmaceutics and Biopharmaceutics** 69: 718 – 726.

[136] Ward, T., et al. (1998). "A comparison of the effect of annealing on two liquid crystalline polymers." **Polymer** 39(2): 315 – 317.

[137] Soradech, S., et al. (2013). "Stability enhancement of shellac by formation of composite film: Effect of gelatin and plasticizers." **Journal of Food Engineering** 116(2): 572 – 580.

[138] Tack-Oon O., et al. (2013). "Preparation of highly porous gastroretentive metformin tablets using a sublimation method." **European Journal of Pharmaceutics and Biopharmaceutics** 83(3): 460 – 467.

[139] Nott, K.P. (2010). "Magnetic resonance imaging of tablet dissolution." **European Journal of Pharmaceutics and Biopharmaceutics** 74(1): 78 – 83.

[140] Oh, T.O., et al. (2013). "Preparation of highly porous gastroretentive metformin tablets using a sublimation method." **European Journal of Pharmaceutics and Biopharmaceutics** 83(3): 460 – 467.

[141] Ito, Y., et al. (2003). "Coerced photodimerization reaction in the solid state through amine salt formation." **Tetrahedron** 59(37): 7323 – 7329.

[142] Mostafavi, A., et al. (2011). "Development of a prolonged – release gastroretentive tablet formulation of ciprofloxacin hydrochloride: Pharmacokinetic characterization in healthy human volunteers." **International Journal of Pharmaceutics** 409(1 – 2): 128 – 136.

[143] Lifang Yina, C.Q., et al. (2013). "Gastro – floating tablets of cephalexin: Preparation and in vitro/in vivo evaluation." **International Journal of Pharmaceutics** 452: 241 – 248.

[144] Zhang, F., et al. (2016). "Properties and mechanisms of drug release from matrix tablets containing poly(ethylene oxide) and poly(acrylic acid) as release retardants." **European Journal of Pharmaceutics and Biopharmaceutics** 105: 97 – 105.

[145] Thoorens G., et al. (2014). " Microcrystalline cellulose, a direct compression binder in a quality by design environment – A review." **International Journal of Pharmaceutics** 473: 64 – 72.

[146] Clarke L.P., et al. (1995). "MRI Segmentation: method and applications." **Magnetic Resonance Imaging** 13: 343 – 368.

[147] Baumgartner S., et al. (2005). "Quantitative evaluation of polymer concentration profile during swelling of hydrophilic matrix tablets using 1H NMR and MRI methods." **European Journal of Pharmaceutics and Biopharmaceutics** 59: 299 – 306.

[148] Richardson J.C., et al. (2005). "Pharmaceutical applications of magnetic resonance imaging (MRI)." **Advanced Drug Delivery Reviews** 57: 1191 – 1209.

[149] Dvinskikh S.V., et al. (2009). " MRI profiles over very wide concentration ranges: Application to swelling of bentonite clay." **Journal of Magnetic Resonance** 198: 146 – 150.

APPENDIX

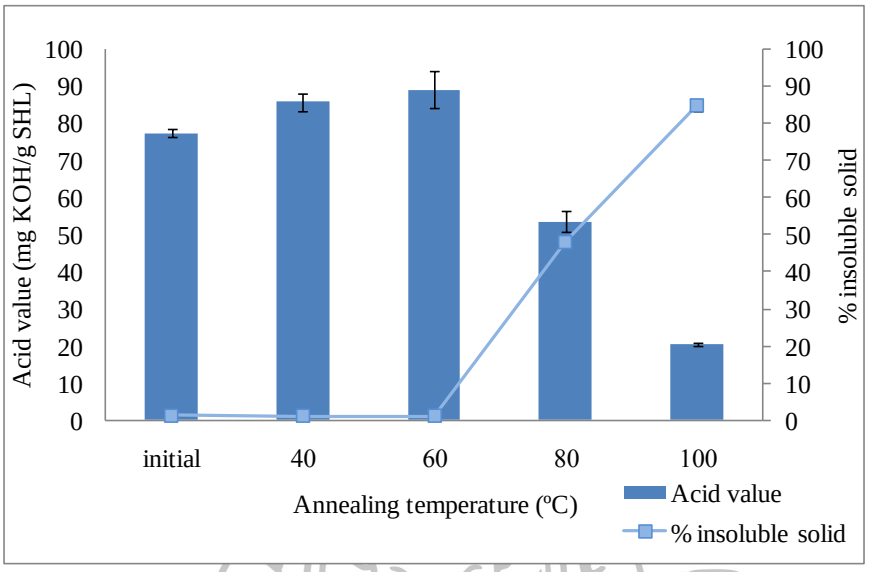


Figure 55 Acid value and insoluble solid of SHL powder at various annealing temperature

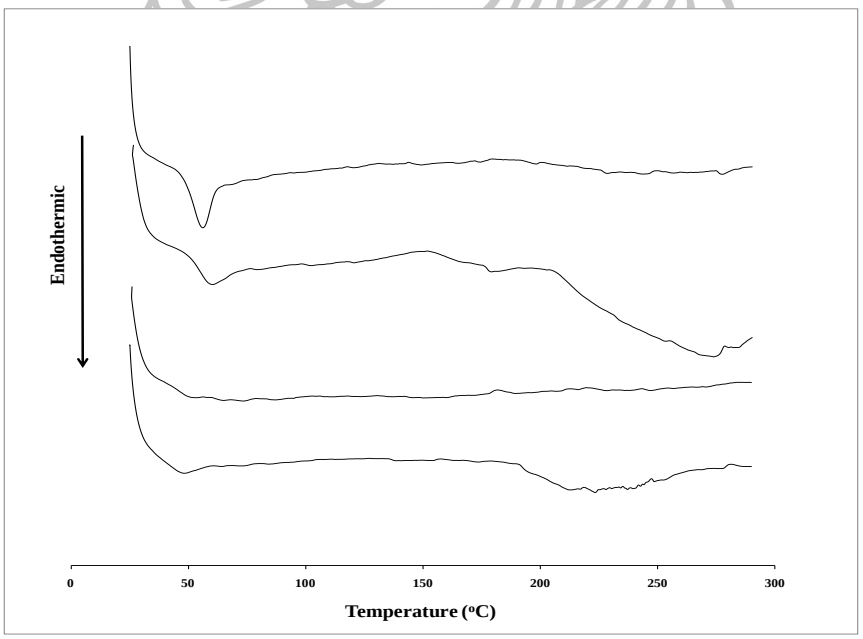


Figure 56 DSC curves of SHL and its derivatives

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Refereed journals

1. N. Chongcherdsak, C. Limmatvapirat, S. Limmatvapirat, Factors Affecting Design of Shellac – Based Matrix Tablet Through Annealing Process, Advanced Materials Research Vol. 506 (2012) pp 421 – 424.

Conference proceedings

1. Limmatvapirat S, Chongcherdsak N, Nunthanid J, Luangtana-Anan M, Limmatvapirat C, Sriamornsak P. Evaluation of porous shellac matrices as a carrier for non-effervescent floating drug delivery. 22nd Federation of Asian Pharmaceutical Associations Congress (FAPA 2008) 7 – 10 November 2008. Singapore.

2. Panchapornpon D, Chongcherdsak N, Nunthanid J, Luangtana-anan M, Limmatvapirat C, Puttipipatkhachorn S, Limmatvapirat S., Solid state formation of shellac phthalate having improved enteric property and stability., 22nd Federation of Asian Pharmaceutical Associations Congress (FAPA 2008) 7 – 10 November 2008. Singapore.

3. Chongcherdsak N, Sriamornsak P, Limmatvapirat C and Limmatvapirat S, Effect of Shellac Content and Temperature on Physical Properties of Matrix Tablet. The 4th Silpakorn University Research Fairs (SURF), 19 – 21 January 2011, Silpakorn University, Nakhon Pathom, Thailand.

4. Chongcherdsak N., Ngamsil J., Sutsuy A., Pothitirat W., Sirikun W., Limmatvapirat C. Limmatvapirat S., Effect of Shellac Content and Gas Forming Agent on Properties of Effervescent Gastric Floating Dosage Forms, The 7th Indochina Conference on Pharmaceutical Sciences "ADVANCING PHARMACY FOR ASEAN COMMUNITY" 14 – 16 DEC 2011, Arnoma Hotel, Bangkok, Thailand.

Conference abstract

1. Chongcherdsak N., Sritrinimit P., Sakullimcharoen R., Khusuwan W., Siribamrungsuk W., Limmatvapirat C., Limmatvapirat S., Effect of Hydrolysis and Annealing Process on *in situ* Polymerization of Shellac and Consequence on Drug controlled Release. The 5th Thailand Pharmacy Congress: Thailand Vision of Pharmacy Profession 2020, 27 – 28 November 2009, Bangkok, Thailand.

2. Chongcherdsak N., Limmatvapirat C., Limmatvapirat S., Effect of Shellac Content and Annealing Temperature on Kinetics of Drug Release from Matrix Tablets. The 3rd Annual Northeast Pharmacy Research Conference 2011, "Integrated Pharmacy: From research to Practice", 12 – 13 February 2011, Ubonrajathanee University, Ubonratchathani, Thailand.

3. N. Chongcherdsak, P. Suriyaampor, V. Laksananukul, A. Keawchuthamani, D. Panjapornpon, S. Limmatvapirat, Fabrication of Shellac as Matrix Forming Agent for Floating Drug Delivery System, 2nd International Symposium Frontiers in Polymer Science 29 – 31 May 2011, Centre de Congrès, Lyon, France

4. Chongcherdsak N., Limmatvapirat C., Limmatvapirat S., Factors Affecting Design of Shellac – Based Matrix Tablet Through Annealing Process, Chiang Mai International Conference on Biomaterials & Applications (CMICBA 2011) 9 – 10 AUG 2011, Chiang Mai, Thailand.