การดัดแปรแป้งมันสำปะหลังโดยการแทนที่ด้วยกลุ่มไฮดรอกซีโพรพิล, การเชื่อมขวางด้วยฟอสเฟตและพรีเจลาติไนเซชันเพื่อใช้เป็นสารก่อเมทริกซ์ในยาเม็ดออกฤทธิ์นาน

นางสาวพรรณอร ว่องสนั่นศิลป์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2554

MODIFICATION OF TAPIOCA STARCH BY HYDROXYPROPYL SUBSTITUTION, CROSSLINKING WITH PHOSPHATE AND PREGELATINIZATION FOR USE AS A MATRIX FOR SUSTAINED RELEASE DOSAGE FORMS

Miss Pannaon Wongsanansin

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy Program in Industrial Pharmacy
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Faculty of Pharmaceutical Sciences
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Thesis Title	MODIFICATION OF TAPIOCA STARCH BY HYDROXYPROPYL SUBSTITUTION, CROSSLINKING WITH PHOSPHATE AND PREGELATINIZATION FOR USE AS A MATRIX FOR SUSTAINED RELEASE DOSAGE FORMS
By	Miss Pannaon Wongsanansin
Field of Study	Industrial Pharmacy
Thesis Advisor	Associate Professor Poj Kulvanich, Ph.D.

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

……Dean of the Faculty of Pharmaceutical Sciences

(Associate Professor Pintip Pongpetch, Ph.D.)

THESIS COMMITTEE

…….. Chairman

(Associate Professor Kraisri Umprayn, Ph.D.)

…….. Thesis Advisor

(Associate Professor Poj Kulvanich, Ph.D.)

…….. Examiner

(Phanphen Wattanaarsakit, Ph.D.)

…….. Examiner

(Jittima Chatchawalsaisin, Ph.D.)

…….. External Examiner

(Assistant Professor Chutima wiranidchapong, Ph.D.)

พรรณอร ว่องสนั่นศิลป์ : การดัดแปรแป้งมันสำปะหลังโดยการแทนที่ด้วยกลุ่มไฮดรอกซีโพรพิล การเชื่อมขวางด้วยฟอสเฟตและพรีเจลาติไนเซชันเพื่อใช้เป็นสารก่อเมทริกซ์ในยาเม็ดออกฤทธิ์นาน. (MODIFICATION OF TAPIOCA STARCH BY HYDROXYPROPYL SUBSTITUTION, CROSSLINKING WITH PHOSPHATE AND PREGELATINIZATION FOR USE AS A MATRIX FOR SUSTAINED RELEASE DOSAGE FORMS) **อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ดร. พจน์ กุลวานิช, 111 หน้า.**

วัตถุประสงค์ของงานวิจัยนี้ เพื่อพัฒนาแป้งพรีเจลาติไนซ์ครอสลิงค์ไฮดรอกซีโพรพิล (พีซีเอชเอส) เป็นสารควบคุมการปลดปล่อยสำหรับเมทริกซ์ชนิดออกฤทธิ์นาน โดยทำการดัดแปรแป้งมันสำปะหลังโดยปฏิกิริยาแทนที่ด้วยโพรพิลลีนออกไซด์ ที่ความเข้มข้น 3 ระดับร้อยละ 2.5, 5.0, 7.5 จากนั้นนำแป้งไปทำปฏิกิริยาเชื่อมขวางด้วยโซเดียมไตรเมตาฟอสเฟตความความเข้มข้นร้อยละ 0.1 ดัดแปรแป้งต่อด้วยวิธีพรีเจลาติไนเซชันโดยใช้เครื่องดรัมดราย และนำไปประเมินคุณสมบัติทางกายภาพและทางเคมี ได้แก่ สัญฐานอนุภาคภายนอก ความชื้น ความหนืด กำลังการพองตัว วิทยากระแส วิเคราะห์หาหมู่ไฮดรอกซีโพรพิลและหมู่ฟอสเฟตโดยเครื่องฟูเรียร์แทรนฟอร์มอินฟราเรดสเปกโตรสโกปีและวิธีแก๊สโครมาโทกราฟี และการปลดปล่อยตัวยาโปรพาโนลอลไฮโดรคลอไรด์ ในตัวกลางที่มีค่าพีเอช และค่าความแรงไอออนแตกต่างกัน พบว่าอุณหภูมิ พีเอช และความแรงไอออนของตัวกลางมีผลน้อยต่อความหนืดและการพองตัว และที่ระดับการแทนที่สูงสุด 0.106 ให้ค่าความหนืดและกำลังการพองตัวสูงที่สุด รองลงมาคือระดับการแทนที่ 0.074 และ 0.062 ตามลำดับ ในการทดสอบการปลดปล่อยตัวยาพบว่าเมื่อใช้ แป้งพีซีเอชเอสที่ระดับการแทนที่ 0.106 ร่วมกับ10 เปอร์เซ็นต์ HPMC E4Mสามารถปลดปล่อยยาโปรพาโนลอลไฮโดรคลอไรด์ร้อยละ 92.64 ในเวลา12 ชั่วโมงในน้ำกลั่น เทียบเท่ากับการใช้ HPMC E4Mเพียงอย่างเดียว และที่ความแรงไอออน 0.05 และ 0.10 ไม่มีผลต่อการปลดปล่อยยา แต่ที่ความแรงไอออน 0.20 แป้งพีซีเอชเอสปลดปล่อยตัวยาได้ช้ากว่ากว่าในน้ำกลั่น (f_2 เท่ากับ 45.50) และเมื่อเปรียบเทียบการปลดปล่อยตัวยาในสารละลาย 0.1 นอร์แมลไฮโดรคลอริกกับ PBS พีเอช 6.8 พบว่ามีความแตกต่างกัน (f_2 เท่ากับ 32.32) นอกจากนี้การเพิ่มแรงตอกจาก 1000 ไปถึง 3000 ปอนด์ต่อตารางนิ้ว และการเปลี่ยนวิธีทดสอบการปลดปล่อยยา จากวิธีตระกร้าเป็นวิธีใบพัดไม่มีผลต่อการปลดปล่อยตัวยา(f_2 เท่ากับ 57.32) ดังนั้นแป้งพีซีเอชเอสจึงเป็นอีกทางเลือกหนึ่งในการใช้เป็นสารก่อเมทริกซ์แบบชอบน้ำ

ภาควิชา วิทยาการเภสัชกรรมและเภสัชอุตสาหกรรม ลายมือชื่อนิสิต .....

สาขาวิชา เภสัชอุตสาหกรรม ลายมือชื่ออ.ที่ปรึกษาวิทยานิพนธ์หลัก .....

ปีการศึกษา 2554 .....

5176574033 : MAJOR PHARMACEUTICAL AND INDUSTRIAL PHARMACY
KEYWORDS : MODIFIED STARCH / SUBSTITUED REACTION / CROSS-LINKED / PREGELATINIZATION / MATRIX

PANNAON WONGSANANSIN : MODIFICATION OF TAPIOCA STARCH BY HYDROXYPROPYL SUBSTITUTION, CROSSLINKING WITH PHOSPHATE AND PREGELATINIZATION FOR USE AS A MATRIX FOR SUSTAINED RELEASE DOSAGE FORMS . ADVISOR : ASSOC. PROF. POJ KULVANICH, Ph.D., 111 pp.

The objective of this study is to develop pregelatinized cross-linked hydroxypropyl starch (PCHS) for using as a matrix for sustained release tablet. The native tapioca starch was modified by substituted reaction with propylene oxide at three levels 2.5, 5.0, 7.5%, cross-linked with 0.1% sodium trimetaphosphate, and then pregelatinized by using drum dryer method. Physical and chemical properties of PCHS were investigated ie. particle morphology, moisture content, viscosity, swelling power, rheology, analysis of hydroxypropyl and phosphate groups by FT-IR & GC. It was found that temperature, pH, and ionic strength of medium had slightly effected on viscosity and the highest degree of substitution (DS) of PCHS (0.106) provided the highest viscosity and swelling power, following with 0.074 and 0.062, respectively. In dissolution testing, it was found that the PCHS matrix of 0.106 DS combined with 10 % of HPMC E4M released 92.64% of propranolol hydrochloride within 12 hrs in DI water, that similar to matrix which consisted only HPMC E4M. In various Ionic strength of media, at 0.05 and 0.10 had no effect on drug release. However, the PCHS gave slower release rate in 0.20 M NaCl solution when comparing with in DI water (f_2 =45.50). In addition, when comparing drug release in 0.1 N HCl solution with PBS pH 6.8, it was found that the pH of dissolution media had effect on drug released (f_2=32.32). Increasing compression force from 1000-3000 psi and changing the methods of dissolution test from basket to paddle method had no effect on drug release rate that the f_2 was 57.32. Therefore, the PCHS was alternative choices for used as hydrophilic matrix.

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Department : Pharmacuetics and Industrial Pharmacy Student's Signature .....

Field of Study : Industrial Pharmacy Advisor's Signature .....

Academic Year : 2011 .....

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LIST OF ABBREVATIONS

%	percentage
ºC	degree Celsius (centrigrade)
cps	centripoises
cm	centimeter (s)
DI	deionized
DS	Degree of substitution
et.al.	et alli, and others
FT-IR	Fourier transform infrared
g	gram(s)
HCl	hydrochlorid acid
hr	hour (s)
HPMC	Hydroxypropyl methyl cellulose
M	molarity
mg	milligram (s)
min	minute (s)
ml	millliliter (s)
mm	millimeter (s)
N	normality
NaCl	sodium chloride
nm	nanometer (s)

PCHS	pregelatinized hydroxypropyl cross-linked starch
PBS	phosphate buffer solution
pH	the negative logarithm of hydrogen ion concentration
R^2	coefficient of determination
rpm	revolution (s) per minute
®	registered
SD	standard deviation
SEM	scanning electron microscope
SP	swelling power
μ	ionic strength
UV	ultraviolet

CHAPTER 1

INTRODUCTION

Starch is a carbohydrate consisting of a large number of glucose units joined together by glycosidic bonds. This polysaccharide is produced by all green plants as an energy store. It is the most important carbohydrate in the human diet and is contained in such staple foods as potatoes, wheat, maize (corn), rice, and cassava. Pure starch is a white, tasteless and odorless powder that is insoluble in cold water or alcohol. It consists of two types of molecules: the linear and helical amylose and the branched amylopectin. Depending on the plant, starch generally contains 75 to 80% amylose and 15 to 20% amylopectin. Native starch and starch derivatives are widely used in the manufacturing of food, paper, textiles, adhesives, pharmaceuticals and building materials (Korstee et al., 1997).

Cassava (*Manihot esculenta*) is an important food crop in tropical countries such as Brazil, Nigeria, Indonesia and Thailand. The roots of cassava are rich in starch and consumed as human food or animal feed. Only a small amount of roots is converted into other industrial products. Thailand is the only country where most of the roots are processed into chips, pellets and starch. Against the total world root production of 175 million tons. Thailand produces about 18 million tons. Ten million tons are converted to starch, producing approximately 2 million tons starch/year, and the rest to chips and pellets. As the leader of cassava starch production, Thailand is also the only country where modified starches from cassava are produced in large scale. Around 50% of the starches are employed locally in the food and non-food industries, the remainder is exported. This commodity generates significant revenue for the country and the future is promising. Growth of the starch industry sector is, in part, a substantial driving force that has generated large-scale cassava planting for commercial purpose in Thailand (Sriroth et al., 2002).

Figure 1 Export of Thai tapioca starch.

Source: Thai Tapioca starch Association, 2010.

Starch derivatives, are prepared by physically, enzymatically, or chemically treating native starch, thereby changing the properties of the starch. Modified starches are used in practically all starch applications, such as in food products as a thickening agent, stabilizer or emulsifier; in pharmaceuticals as a disintegrant; or in paper as a binder. They are also used in many other applications. Starches are modified to enhance their performance in different applications. Starches may be modified to increase their stability against excessive heat, acid, shear, time, cooling, or freezing; to change their texture; to decrease or increase their viscosity; to lengthen or shorten gelatinization time; or to increase their viscosity-stability.

Starches are used since a long time as excipients in pharmaceutical preparations. Mainly maize starch, potato starch and wheat starch are used and monographed in several pharmacopoeias and pea starch will soon be introduced in the pharmaceutical world. The classical functionalities of native starches in the past are fillers and disintegrants in tablets and fillers in dermatological powders. Also modified (pregelatinized) starches have been used as filler-binders in tablet technology. From the various starch derivates Hydroxyethyl starch exhibit excellent properties as plasma

expander and sodium-carboxymethyl starch is used as disintegrant in tablets and as thickener in several liquid preparation. Starch paste is still widely used as binder in wet granulation. The problem is that the properties of freshly cooked starch paste can hardly be held constant. It is shown, that pregelatinized starches do a better job in this field. (Steffens K.J. & Bonn, 2006)

Hydrophilic matrix (HM) system is a monolithic system prepared by compression of a powdered mixture of a hydrophilic polymer and a drug. When this device is exposed to an aqueous medium, it does not disintegrate, but immediately after hydration it develops a highly viscous gelatinous surface barrier which controls the drug release and the liquid penetration into the centre of the HM system. The overall release rate of a drug from this system is controlled by one or more of the following processes: transport of the solvent into the device, swelling of the associated matrix, diffusion of the solute through the swollen matrix, erosion of the swollen matrix, etc. (Rao & Devi, 1988).

Matrix systems appear to be a very attractive approach from the economic as well as from the process of development and scale up point of view in controlled-release system cellulose derivative is used frequently as a rate controlling polymer in matrix tablets. Starch offers the advantages of being non-toxic, biodegradable and inexpensive. (Takka, Rajbhandari and Sakr, 2001). It processes a variety of interesting properties, like low gelatinization temperature, clarity and bland taste, which make it desirable for both food and industrial applications. However, it also have negative characteristics, such as a long texture (high cohesiveness), sensitivity to shear, high temperature and low pH, which makes it unsuitable for some specific uses. Furthermore, to extend its usefulness, cassava starch has often been modified, and cross-linking is the most widely used technology for this purpose (Wurzburg, 1986).

Characterization of hydroxypropylate crosslinked sago starch (HPST) as compare to commercial modified starch was investigated by Wattanachant et al. (2002). In this study, they found that the phosphorus content, paste clarity, swelling power properties after six freeze thaw cycles of HPST weren't changed. When compare to

commercially modified starch which are normally used in frozen and canned food, the HPST showed the similar viscosity, stability, solubility but the swelling power of HPST was slightly lower than commercial modified starch.

Peerapattana et al. (2009) studied glutinous rice starch (GS) as a sustained release agent for matrix tablet. The GS slurry was physically modified by heat and then dried by spray drying. The pregelatinized GS (PGS) showed odorless fine white powder and poor flowability. The components of tablet were prepared by wet granulation method. Less than 80% of propranolol hydrochloride was released in the period of 10 hr. at the drug to PGS ratio of 1:2 and longer than 14 hr at the ratios of 1:3 and 1:4. Moreover, compaction pressure in the range of 6.9–27.5 MPa did not affect the release of the drug from the matrix. However, there are no study of modification of starch by using the combination of chemical and physical modified method as a new sustained release matrix polymer.

Onofre et al. (2009) investigated effects of structure and modification on sustained release properties of starches, by using starches in different sources and composition. Starches were cross-linked with epichlorohydrin and substituted with carboxymethyl or aminoethyl groups at different levels. Substitution efficiency was overall higher for waxy corn and potato starches than for Hylon VII (high amylase corn starch), and was higher for starches at low cross-linking levels than those at high cross-linking ones. Waxy corn starch displayed better sustained release properties when cross-linked to a lower level, whereas Hylon VII showed better performances when cross-linked to a higher level. Matrices substituted with carboxymethyl and aminoethyl groups at the high level showed better sustained release properties than those substituted at the low level. The proportion and structure of amylose and amylopectin in starches from different botanical sources strongly influenced the level of modification required to produce a satisfactory sustained release matrix.

Modified starch is commonly used as an excipient in sustained release formulations because of their ability to swell and form gel network. Moreover, modified starch is a biocompatible and biodegradable polysaccharide for controlling drug delivery

applications. Although, there are many previous studies of modified starch, but there are no studies on the modification tapioca starch by combination of hydroxypropyl substitution, crosslinking with phosphate and pregealatinization.

In this study, the native cassava starch was modified by substitution reaction with propylene oxide, cross-linked with 0.1% sodium trimetaphosphate (chemical mothod) and then pregelatinized by drum dryer(physical method), in order to improve undesirable properties (sensitivity to shear, high temperature, acidic condition , swelling and viscosity properties) for use as a matrix excipient in controlled release system. Propranolol hydrodrochloride was seclected as a model drug, it is a weak base drug which show good solubility in water. It‘s non-selective beta adrenergic blocking agent use in the treatment of hypertension, angina pectoris, cardiac arrhythemia.

The objective of the present study was to

1. To develop pregelatinized cross-linked hydroxypropyl starch (PCHS) for using as a released controlling agent for sustained release matrix.
2. To study viscosity, swelling power and rheology properties of PCHS after modification.
3. Investigate effect of pH and ionic strength media on the drug released of propranolol hydrochloride from matrix.

CHAPTER 2
LITERATURE REVIEW

1. Starch Sources and Structure

Starch is the reserve carbohydrate of the plant kingdom, where it generally is deposited in the form of minute granule or cell ranging from 1 up to 100 μm or more in diameter. There granule are mainly deposited in the seeds, tubers, or root of plants. Starch granules are insoluble in cold water. They vary in size and shape, depending upon the plant source. Tapioca starch granules usually have round shapes which are truncated at one end. They average about 20 μm in diameter, but may range from 5-35 μm in diameter. Potato starch has the largest granules of commercial starch. (Wurzburg, 1986)

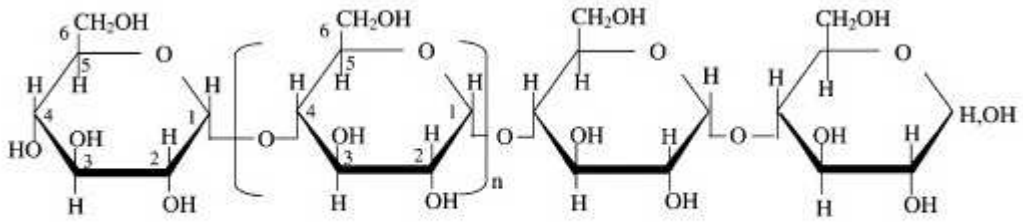
1.1 Structure

Starch molecules arrange themselves in the plant in semi-crystalline granules. Each plant species has a unique starch granular size: rice starch is relatively small (about 2 μm) while potato starches have larger granules (up to 100 μm). Although in absolute mass only about one quarter of the starch granules in plants consist of amylose, there are about 150 times more amylose molecules than amylopectin molecules. Amylose is a much smaller molecule than amylopectin.

Chemically, starch is polymer carbohydrate consisting andhydroglucose units linked togrther primarily to through α-D-(1—>4) glucosidic bonds. (Wurzburg, 1986) most starch contain two types of glucose polymers: amylase amylopectin. There two fractions occur in different amounts in starches from various sources. (Horton et al., 2002). Some cultivated plant varieties have pure amylopectin starch without amylose, known as *waxy starches*. The most used is waxy maize, others are glutinous rice and waxy potato starch. Waxy starches have less retrogradation, resulting in a more stable paste. High amylose starch, amylomaize, is cultivated for the use of its gel strength.

Amylose

Amylose is essentially a linear polymer in which the anhydrousglucose units are predominantly linked through α-D-(1—>4) glucosidic bonds (Figure 2). Its molecular size varies depending upon the plant source and processing conditions employed in extracting the starch. It may contain anywhere from about 200 to 2000 anhydrousglucose units. At one end of the polymeric molecule, the anhydrousglucose unit contains one primary and two secondary hydroxyls as well as an aldehydic reducing group in the form of and inner hemiacetal. This is called the reducing end of the molecule. The opposite end, or nonreducing end, contains an anhydroglucose unit containing one primary hydroxyl and three secondary hydroxyls. The other anhydroglucose units contain one primary and two secondary hydroxyls (Wurzburg, 1986).



Amylose: α-(1→4)-glucan; average n = ca. 1000. The linear molecule may carry a few occasional moderately long chains linked α-(1→6).

Figure 2 Structure of amylose linear –chain (Tester, Karkalas and Qi, 2003)

The abundance of hydroxyls imparts hydrophilic properties to the polymer, giving it an affinity for moisture and dispersibility in water. However, because of their linearity, mobility, and hydroxyl groups, amylose polymers have a tendency to orient themselves in a parallel fashion and approach each other closely enough to permit hydrogen bonding between hydroxyl on adjacent polymers. Amylose is insoluble in cold water but absorbs a large amount of water and swells. In general, the linearity of amylase favors formation of strong flims. Amylose forms complex with iodine giving a characteristic blue color which is used to establish the presence of amylose-containing starch.

Amylopectin

Amylopectin is a branched polymer containing, in addition to anhydroglucose units linked together as in amylose through α-D-(1—>4) glucosidic bonds, periodic branches at the carbon-6 position. These branched are linked to the 6 carbon by α-D-(1—>6) glucosidic bonds. Each branch contains about 20 to 30 anhydroglucose units. A schematic diagram of the amylopectin molecule is shown in Figure 3.

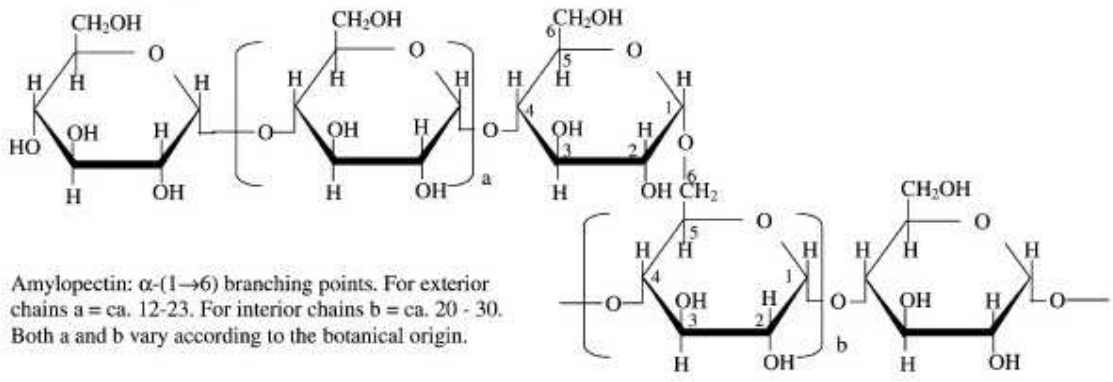


Figure 3 Structure of amylopectin branching points (Tester, Karkalas and Qi, 2003).

In most cases, amylopectin is much larger than amylose. Light scattering measurements indicate molecular weight in million. The large size and branched nature of amylopectin reduce the mobility of the polymers and interfere with any tendency for them to become oriented closely enough to permit significant levels of hydrogen bonding. As a result, aqueous sols of amylopectin are characterized by clarity and stability as measured by resistance to gelling on aging. Amylopectin sols do not form as strong and flexible films as the linear amylose. Amylopectin rapidly forms a viscous colloidal solution at room temperature (Shangraw et al.,1980). They do not form an iodine complex with its associated deep blue coloration.

Starch granules are composed of two types of alphaglucan, amylose and amylopectin, which represent approximately 98-99% of the dry weight. The ratio of the two polysaccharides varies according to the botanical origin of the starch. The “waxy” starches contain less than 15% amylose, “normal” 20-35% and “high” (amylo-) amylose starches greater than about 40%. The moisture content of air-equilibrated starches

ranges from about 10-12% (cereal) to about 14-18% (some roots 0and tubers) (Tester et al., 2004).

The level of amylose found in starch varies depending upon the starch source. Most starches such as regular corn, wheat, potato, and tapioca contain about 18 to 25% amylose. Corn and wheat are at the high end of the range, while potato and tapioca are at the lower end. Certain starches such as genetic modifications of corn, namely, waxy corn and high amylose corn, depart significantly from this range (Wurzburg, 1986).

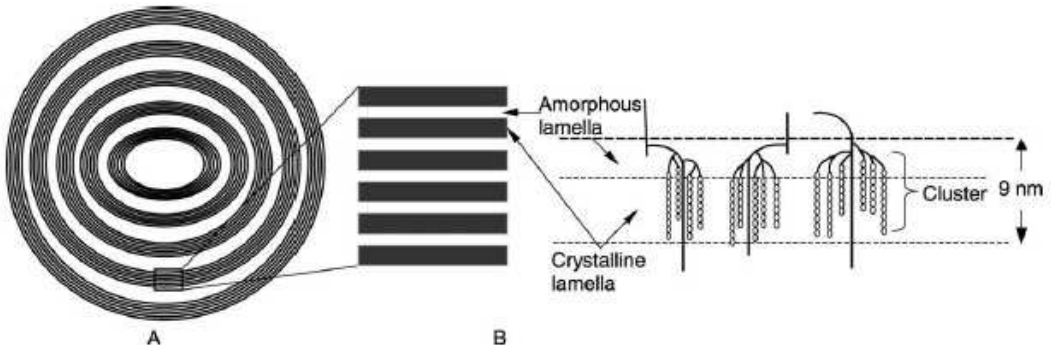


Figure 4 Diagrammatic representation of the lamellar structure of a starch granule according to Donald et al. (1997). (A) Stacks of microcrystalline lamellae separated by amorphous growth rings. (B) Magnified view of the amorphous and crystalline regions. (C) Double helical structures formed by adjacent chains of amylopectin give rise to crystalline lamellae. Branching points constitute the amorphous regions. (Tester, Karkalas and Qi, 2003).

Table 1 Basic properties of raw starch

Solubility	As starch is not soluble in water, it can easily extracts in water from the storage in plant. Its suspension starts to become viscous by heating and turns to transparent paste. It means amylopectin forms crystallized micelle and amylose arranges orderly around the gaps of the micelles in starch particle. This is why starch is not soluble in cold water. However, water molecules are getting into micelles gradually when heating the solution and resulting to loosen hydrogen bond and short molecules of amylose starts to dissolve, then amylopectin swells up.
Gelatinization & Retrogradation	Starch is swelling up by heating and continues to swell up absorbing water and showing more viscosity and clarity along with increase of temperature and then will reach to maximum viscosity. By giving further higher temperatures, the outer shell of starch particle which have highest crystallinity index starts to collapse and amylopectin and amylose inside outer shell are melting out and its viscosity is getting lower by heating and stirring. Viscosity is gradually increasing again when the solution is chilled down and continuous chilling makes the solution cloud and less clarity. Leaving to stand the solution, it shows more white and in case of higher concentration of starch, it gels and in case of low concentration, syneresis and precipitation will be caused. This is the retrogradation of starch caused by recrystallization of amylose through cooling.
Viscosity	The solution of starch which is gelatinized by high temperatures shows high viscosity and non-Newtonian flow. This indicates the decrease of apparent viscosity when the shearing stress is faster and this is considered an interaction of swollen starch particles. Thixotropic viscosity of potato starch, which has thread forming property is termed“long”and plastic flow viscosity such as cornstarch, which has less thread forming property is termed“short”.

Derivative	Starch derivative is a modified starch that hydroxyl group of anhydrous glucose group is substituted with various functional groups. By inducing hydrophilic group, gelatinisation-starting temperature becomes lower. The transparency and the stability of paste are improved. Combining multi-functional groups to more than two hydroxyl groups, heat resistance, chemical resistance and shearing resistance are improved. It is also possible to combine some different modifications and processes. It has extensive applications such as medical, papermaking, textile and other fields.
Decomposition	Decomposing starch by heating with acid and hydrolyzing starch with enzyme are called Dextrin. Soluble in cold water and high concentrated paste is obtainable. Hydrolyzed starch by organic or inorganic acid is called soluble starch and soluble in hot water and high concentrated paste is also obtainable. Being used widely in medical, dyestuffs and many other fields.
Pregelatinization	Pregelatinized starch is obtainable by drying quickly the paste in swollen or dissolved state. This modified starch can be swollen in cold water and easily becomes paste. Pregelatinized starch is classified into two categories; one is pregelatinized maintaining characteristic of native starch and another one is pregelatinized the modified starches such as derivative starch or soluble starch. Food, feed, paper making and many other industries are utilizing them.
Natural Gum Derivative	This is produced inducing functional group into hydroxyl group of natural gum. It is easily swollen up in cold water. High viscosity solution is obtainable even in low concentration, while it is rather hard in starch, and it is suitable to textile printing binders and industrial thickeners. In case of textile printing use, it improves chemical resistance and also very effective in removing printing binder.

2. Modification Starches

Modified starches were developed to overcome one or more of these shortcomings and thus expand the usefulness of starch for a myriad of industrial applications. While in the broadest sense any product in which the chemical and physical properties of native starch have been altered might be considered to be modified. The range of modifications covered in this volume will be limited to those in which the chemical and physical properties of native starch have been modified through significant molecular scission, molecular rearrangement, oxidation or introduction of substitutent chemical group in to the starch molecule. Pregelatinized starches, redried starches, extrude starches and blends or mixes in which the properties of the starch powder have been physically modified will not be specifically conversed since they primary involve modification of the physical properties. (Wurzburg, 1986)

Table 2 Standard Specifications of native cassava starch for modification purpose (Sriroth et al., 2002)

Property	Specification
Moisture content (% maximum)	13 %
Ash (% maximum)	0.2 %
Fiber (cm^3 per 50g wet starch, maximum)	0.2
pH	5.0 to 7.0
Whiteness (Kett scale, minimum)	90
Viscosity (Barbender Unit, minimum)	600
Sulfur dioxide content (ppm, maximum)	100
Residue (ppm, maximum)	300

2.1 Modification of cassava starch in Thailand

The starch modification sector is one of the most important industries in Thailand. This industry began as the production technology of cassava starch developed from small- to large-scale and starch quality improved. One of the main driving forces was the high market demand; both domestically and internationally, for the diversified cassava-based products produced by the modification technology.

The modified cassava starch and derivatives currently produced at the commercial scale can be categorized based on the technology approach as summarized in Figure 5 (Sriroth et al., 2002)

2.2 Reasons for modification of starch

Starches are modified chemically or physically or both to accentuate their positive characteristics, diminish their undesirable qualities, or add new attributes. Common limitation associated with native normal starches are excessive viscosity at low solids content (difficulty in handing, lack of body), high susceptibility to retrogradation (gel opacity, synersis, and lack of freeze-thaw stability), and lack of process tolerance. By proper modification, change can be made in one or more of the following attributes.

- Ability to act as an emulsifying agent, emulsion stability, encapsulate
- Cold-water swellability, Film formation, Digestibility, Flowability
- Cooking characteristic (degree of break down, degree of setback retrogradation, energy required to cook, gelatinization, pasting temperature)
- Interactions with other substances
- Paste and gel characteristic (adhesiveness, clarify, freeze-thaw stability, gel strength, rate and extent of syneresis, retrogradation stability, viscoelasicity, viscosity)
- Process tolerance (pH, shear, temperature)
- Solubility in hot and room temperature water
- Stability in high-salt environment s
- Water resistant of films (water resistance or water-holding capacity) (Bertoliny, 2010)

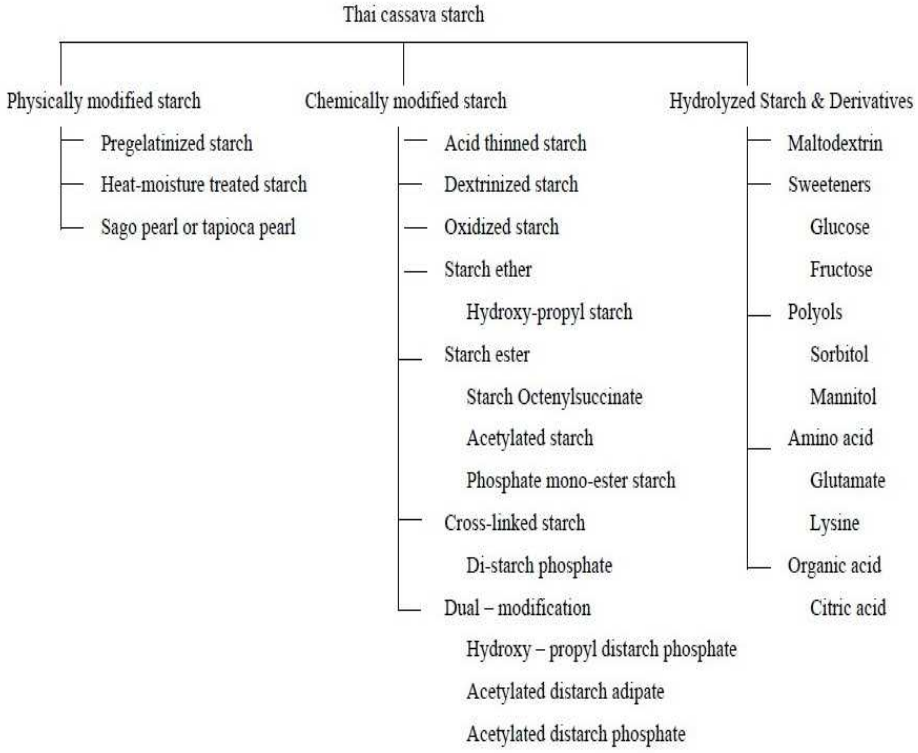


Figure 5 Modified cassava starch and derivatives currently produced at commercial scale in Thailand (Sriroth et al., 2002).

2.3 Applications of starches

As can be seen, there is a great variety of value-added applications for starch in the non-food area, and each application requires very particular functional characteristics. Even in the most basic non-food applications of starch, a great deal of value-addition is employed. Adhesives starches are acid or alkali treated, they are modified with oxidizing agents, salts and different alcohols. Textile starches are esterified, oxidized and are subject to various cross-linking agents. The use of sophisticated, value added starches in paper products is even more noticeable, when one considers the wide range of applications in that industry. Starches are used to provide greater strength to tissues and paper towels, and they allow a greater use of recycled paper in liner board and cardboard. The growing demand for biodegradability promises to provide additional volumes as starch is used in plastic films and sheets as well as in natural fiber formulations that will eventually replace plastic foams. The volume

of starch going into non-food uses is enormous and it is all based upon the functional characteristics of the individual products. The non-food uses of starch are a prime indicator of a country economy. During recessions, the volume of starch going into non-food use drops considerably. On the other hand, an active economy needs construction materials for buildings, industrial plants and housing; it needs paper for the bureaucracy, for packaging and wrapping various products, for corrugated boxes and it need adhesives to stick all this economic activity together. As the economy booms, so does the volume of starches going into non-food uses. As countries develop, so does their demand for high quality, highly functional, value-added starches. Of course, functionality is the key to marketing starches in the wide range of food applications.

Table 3 Utilities of modified starch in non food industrials

Adhesives	- hot-melt glues
	- stamps, bookbinding, envelopes
	- labels (regular and waterproof)
	- wood adhesives, laminations
	- automotive, engineering
	- pressure sensitive adhesives
	- corrugation
	- paper sacks
Explosives Industry	- wide range binding agent
	- match-head binder
Paper Industry	-internal sizing
	- filler retention
	- surface sizing
	paper coating (regular and colour)
	- carbonless paper stilt material
Cosmetic and Pharmaceutical Industry	-dusting powder
	- make-up

	- soap filler/extender
	- face creams
	- pill coating, dusting agent
	- tablet binder/dispersing agent
Construction Industry	-concrete block binder
	- asbestos, clay/limestone binder
	- fire-resistant wallboard
	- polywood/chipboard adhesive
	- gypsum board binder
	- paint filler

2.4 Chemical modification

This group of products is prepared by chemical reaction. The most popular are oxidized starch and acid-modified starch for paper industry. The production of hydroxy ethylated starch, cationic starch and amphoteric starch from cassava for paper industry is prepared only in a small scale. Starch acetate and phosphate are the most produced products for food industry (Sriroth et al., 2002).

2.4.1 Hydroxypropyl starch

Beginning in the late 1930s and early 1940s, the concept of chemically derivertizing starch to enhance or build in functional properties for specific end use applications began to take form. Leaders in this development were National Starch and Chemical Coporation and CPC International, Inc. A key factor in this development was the discovery of a practical way to chemically modify starch in aqueous slurry and still maintain the integrity of the starch granule so that by-product of the reaction could be remove by simple filtration and washing techniques. This, along with increasing demand by customer for starch products with improve and/or unique functional properties, introduced a new era in starch wet milling industry (Wurzburg, 1986).

2.4.1.1 Reaction mechanism

Chemical modification can improve the functional properties of starch for food or nonfood uses. Reaction of starch with propylene oxide to form the hydroxypropyl starch delivertive is used primarily for the food industry. This modification improve the cold-storaged stability, clarity, and textural properties of the starch paste. Besides the propylene oxide treatment, the starch may also be cross-linked with phosphorus oxychloride or epichlorhydrin to improve cooked paste viscosity stability (Wurzburg, 1986).

Substitution so-call stabilized starches are product by reacting starches with mono functional reagent. By converting hydroxyl groups of starch molecules into larger ester or ether groups, interchain associations are blocked, Both ester and ether are made in the same general way. A gelatinzation-inhibiting salt (10-30%) concentration, most often sodium sulfate, sometimes sodium chloride) is added to a stirred slurry of starch granules (30-45% solids). The pH was adjusted to 8-12, the exact value depending on the reaction to be carried out. An alkaline pH converts to hydroxyl groups into alkoxide ions for participation in nucleophillic substitution reactions. The temperature is often adjusted to about 49°C. use of a gelatinization-inhibiting salt and a temperature below the gelatinization temperature of both the native starch and the product prevents pasting, and allows the starch to be recovered in granular form. Following reaction with a mono functional reagent to the desired degree of substituted, the stabilized, starch product was recovered by filtration or centrifugation, washed, and dried (Bertolimi, 2010).

Propylene oxide level generally range from 5-10%based on dry weight of the starch. Most of propylene oxide reacted starches are intended for food use and must confirm to food and drug administration (FDA) guidelines for chemical modification. Swollen or pasted. The product cannot be filtered and washed to removed undesirable by-products. Propylene oxide starch reactions take approximately 24 hr. to complete under the conditions described and are about 60% efficient with respect to the propylene oxide.

2.4.1.2 Properties and uses

Hydroxypropyl starches did much to further the development of conventional and new convenience-type food products. Use of hydroxylpropylated starch gives improve shelf life, freeze/thaw stability, cold storage stability, cold water swelling, and reconstituting properties to a formulate product. Maximizing functional properties of these products is base on obtaining the optimum balance between hydroxypropyl substitution, cross-linking, and inherent properties of the base starch. In general the chemical modifications are carefully adjusted to increase or reinforce properties that already exist to some degree in the base starch.

Hydroxypropyl groups are hydrophilic in nature and when introduced into the starch granule, weaken or strain the internal bold structure holding the granule together this reduction in bond strength is reflected in starch pasting temperature. Until the product become cold water swelling. The effect of substitution on internal bond strength is also dramatically evident in paste preparation of this products. When the unmodified starch paste is formed in water, heat (cooking) is required. As the paste cools, the starch chains (especially amylose) retrograde to form an opanque, stiff paste. This retrograding is caused by close alignment of the starch chains to form three dimensional network or gel structure in the paste. Chemical substitution of these chains, however, prevents close alignment resulting in a more fluid paste with improved clarity. Although the substituted starch paste thickens when it cools, reheating will return it to original hot viscosity and clarity.

Cross-linking of hydroxylpropyl starch imparts viscosity stability and a desired short texture property to paste. Swollen but intact starch granules are usually desired in most food starch applications to maintain rheological properties. In general, the more stringent the cooking conditions, the more cross-linking is required. However, for each application there is an optimum level and balance between hydrxypropyl substitution and cross-linking. Careful control of this steps makes possible the “tailoring” of starch products for very specific application conditions. Hydroxylpropyl-modified starches have a very wide spectrum of application. They are being used or evaluated in products that range from blood extenders to coffee whitener. One of the largest areas of application is as a thickener in a multitude of food and food-

related products. The outstanding storage stability and freeze/thaw properties of these starches make them a premiere product for the food industry.Nonfood uses for hydroxypropyl starch are also numerous. But do not have the commercial impact of the food applications. In many of the nonfood applications the coating or film forming properties of the starches is most important. In the sizing of textile and paper products, for example, the clear, the flexible, water-soluble coating, formed by hydroxypropyl starch is desired. In the other uses such as a binder for building materials or gelling aid for perfumes or organic liquids, the adhesive properties and solvent soluble properties of starch are utilize (Wurzburg, 1986).

Chebli, Cartilier and Hartman, (2001) were Substituted amylose (SA) polymers at amylose chains with 1, 2-epoxypropanol (glycidol). Focus on resisted to biodegradation by α-amylase enzymes that present in the gastro-intestinal tract. Two substituted amylose solid dosage forms were prepared: (i) matrix system and (ii) dry-coated tablets. The results was showed that SA polymers can resist α-amylase biodegradation. Consequently, SA polymer matrix systems can be designed to facilitate colonic drug delivery.

Onofre and Wang (2009) were substituted waxy corn, hylon VII, and common corn starches by hydroxypropyl groups (low and high levels). Moreover, the sustained release properties and matrix characteristics were studied. Hydroxypropylation gave a stronger impact on Hylon VII and common corn starch matrix than on waxy corn ones, suggesting that the behavior of starch tablet was dominated by its amylose content. Hydroxypropylation improved the sustained release ability of amylose-containing starch matrix, and conferred additional resistance to the hydrolytic action of pancreatin under stimulated gastrointestinal conditions. So, hydroxypropylation was an effective way to improve the sustained release properties of amylose-containing corn starches.

2.4.2 Cross-linked starch

Starch contains an abundance of hydroxyl groups. Each andhydroglucose unit contains two secondary hydroxyls and a large majority contains primary hydroxyls. These hydroxyl potentially are able to react with any chemical capable of reacting with alcoholic hydroxyls. This would include a wide range of compounds such as acid anhydride, organic chlorocompound , aldehydes, epoxy, ethylenic compounds, etc. when the specific chemical contains two or more moieties capable of reacting with hydroxyl groups. There is the possibility of reacting at two different hydroxyls resulting in crosslinking between hydroxyl on the same molecular or on different molecules.

The concept of cross-linking solutions or dispersions of starch or dextrin molecules through interaction with bi-or poly functional regents in order to thicken or to reduce the solubility or insolubilize their solutions or films is widely practiced in numerous industrial applications such as the preparation of wet-rub-resistant starch paper coating, permanent textiles sizes, wet strength paper, water resistance adhesives, etc. these involve the use of formaldehyde, glyoxal, urea formaldehyde and other reactive resins or bi-functional chemicals. They may involve not only cross-linking between molecules, but also cross-linking between starch and substrates such as cellulose.Instead, the primary concern will be with those modified starch in which the intact or partially swollen starch granules is cross-linked by chemical means. Cross-linked starches constitute a major class of modified starches. They are marketed simply as cross-linked starches or modified starches in which the cross-linking treatment is combined with other modification treatment such as derivatization with monosubstituents such as acetyl or hydroxypropyl group.

Basically, cross-linking reinforces the hydrogen bonds in the granule with chemical bonds which act as bridges between molecules. As a result, when the cross-linked starch is heated in water, the hydrogen bonds were weakened or destroyed; however, the granule will be kept intact to varying degrees by the chemical bridges. Since the cross- linking involves treatment of the starch in its granular state, the amount of chemical cross-links induced into the starch is usually very small relative to the weight of the starch and the total number of anhydroglucose units present in the

granule. Most of the cross-linked starches will contain about 1 cross-link for every 100 to 3000 anhydroglucoes units. Distarch phosphates may be made by reaction of starch granules in aqueous suspension with either phosphorus oxychloride or sodium trimetaphosphate under alkaline conditions. Distarch glycerols may be made by treating granular starch normally in aqueous suspensions with epichlorohydrin under alkaline conditions. Inaddition to reacting with starch hydroxyls, a portion of cross-linking reagent will be hydrolyzed by water to form free adipic acid or adipate salt or phosphoric acid or its salt or glycerol, respectively. These would be present at very low concentrations since the level of reagents used in the cross-linking treatment is generally very low. Most of any residue left in the aqueous suspension is removed by washing.

Depending upon the type of cross-link, the sensitivity of the cross-linked starch to pH variation, shear, etc. will vary considerably. As a result the cross-link in distarch phosphates are linked to the starch through inorganic ester linkages. They show resistance to acidic conditions. Althought they show some tolerance to mild alkalinity, the phosphate linkages hydrolyze under moderately alkaline conditions (Wurzburg, 1986).

2.4.2.1 Applications of cross-linking

Cross-linking represents a powerful tool for modifying starch. It can be used to modify the granule, permitting utilization of starch granules in applications which would destroy granules of unmodified starch. Cross-linking of the granule can also modify the paste properties of the swollen granule, altering the texture and rheology of the paste. It can also reduce the sensitivity of the swollen granule paste to acidic conditions and shear. In the case of distarch glycerol, it imparts alkali resistance to the paste. It can also be utilized to improve the film forming properties of starch pastes.

Cross-linking plays a very important role when use in combination with other methods for modifying starch, such as acid conversions, oxidations, and derivatizations to introduce monosubsituents. A major portion of the markets for derivatives such as acetylated or hydroxypropylated starches depend upon the use of cross-linking in order to modify the shortcomings characteristic of this derivatives. These

combination treatments and their applications will be covered in the chapters on specific derivatives and on fileds of applications. Mention, however, should be made of special applications not normally covered in the major fields of usage such as food, paper, textile, adhesives. Usage in the granule from in surgical dusting powder, as an anti-blocking dusting agent for blown films, as an absorbent in the purification of alpha amylases by affinity chromatography, and in combination with treatmant of the cross-linked starch with allyl isothiocyanate as an enzyme carrier. (Wurzburg, 1986)

Cross-linking is a key technique for modifying the properties of starch and all types of modified starches:

1. It offers a means for reinforcing the granule to the point where the intact granule can be used as such under conditions which would swell granules of noncross-linked starch. This opens up usages as surgical dusting powder, carrier, absorbent, and ion exchange resins.

2. it toughens the granule so that on swelling, the integrity of the swollen granule is maintained, thus providing

- High-viscosity thickeners
- Short salve-like paste texture
- Resistance to viscosity breakdown and loss of texture in acidic media and, in the case of distarch glycerol, in alkaline media.
- Resistance to chemical shear.
- Resistance to viscosity breakdown at high (retort) temperatures

3. It permits controlled release of amylose from the swollen granule, providing improved film properties.

Aziz et al. (2004) was prepared modified sago starch by using etherification and esterification reaction with propylene oxide followed by a mixture of 2% sodium trimetaphosphate (STMP) and 5% sodium tripolyphosphate (STPP),and acetic anhydride, respectively. FT-IR spectroscopy was use to detected the degree of substitution was relatively low with 0.044 and 0.342 for hydroxypropylation and acetylation respectively. In addition to, thermal analysis was showed that acetylation

increases the gelatinization temperature but reduces the enthalpy although hydroxypropylation cross-linking reduce both temperature and enthalpy.

2.4.3 Pregelatinized starch (alpha starch)

Alpha starch or pregelatinized starch began to be a major industry in the late 1980's during the eel-farming boom when farms required a cold water soluble binder. Alpha starch from cassava gives specific properties such as high transparency, absence of foreign odors, good color carrier properties and high viscosity. The total production capacity for all alpha starch in Thailand is about 50,000 tons/year. The manufacturing process involves drying of 30 – 40 % (dry solid) cassava starch slurry on a roller drum drier heated to 160-170°C by direct steam. Presently alpha starch is produced as food grade, and is used in many industries

The material and tablet formation properties of pregelatinized (thermally modified) forms of four Dioscorea starches have been investigated by Freyer, Schmid and Odeko (2008). Dioscorea starches were pregelatinized followed by either oven drying (PS) or freeze drying (FD) and used as excipient in direct compression. The results indicate that pregelatinization improved the compressibility and flowability of the Dioscorea starches. The high bulk and tap densities of PS coupled with their good flowability offer a unique possibility of the starches being used as filler in capsule formulations. PS exhibited higher elasticity during tableting. FD Chinese and FD Bitter showed higher plasticity and low fast elastic deformation than the PS forms of the starches indicating that the FD starches undergo the highest plastic deformation. Thus, FD White and FD Water starches could be useful when high crushing force and fast disintegration are of concern while FD Chinese and FD Bitter, which were non-disintegrating, could find application as excipients for controlled drug delivery.

Bejenariu et al. (2008) were prepared the xanthan based hydrogels in alkaline medium by using trisodium trimetaphosphate (STMP) as cross-linking agent. Hydrogels with various crosslinking agent : polymer ratios were generated. The highest swelling degree was obtained using an intermediate STMP:Xan ratio. The synthesized networks are pH sensitive. In acid and alkaline media the swelling degrees are lower by comparison to neutral pH. The entrapping and releasing behaviour of the newly

synthesized xanthan networks were studied using methylene blue as a cationic model molecule. The releasing kinetics presented a first-order model. These are creating the premises of obtaining biocompatible pH and ionic strength sensitive substrates suitable for controlled drug delivery systems.

3. Hydrophilic matrix

A hydrophilic matrix is a homogeneous dispersion of drug molecules within a skeleton in which one or several of the excipients incorporated are a hydrophilic polymer, such as cellulose derivatives, sodium alginate, xanthan gum, polyethylene oxide, or carbopol among others, that swells upon contact with water. Most commercial hydrophilic matrices are obtained by compression, such that in most cases one can speak in terms of a matrix tablet. Thus, the basic operations involved in the preparation of the matrices are the same as those used to prepare conventional tablets, such as mixing and compressing the components. Granulation prior to mixing and the coating of matrix tablets are complementary operations widely used to manufacture matrix tablets. As well as the drug and the release-limiting polymer, other excipients are usually added as diluents, lubricants and antiadherents. Although this review focuses on modified starch they are not the only ones: Thus, among others, there are polymers of natural origin, such as agar–agar, alginates or carrageenans and polymers of semisynthetic origin, cellulose derivatives (methylcellulose (MC), ethyl-hydroxyethylcellulose (EHEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC, hypromelose), sodium carboxymethylcellulose (CMC Na)), or derivatives of acrylic and methacrylic acid (Maderuelo et al., 2011).

3.1 Mechanisms of release from hydrophilic matrix

The hydrophilic matrix in contact with water become hydrated instead of disintegrating. This hydration, due to the increase in size of the polymer molecules as a consequence of the entry of solvent (a relaxation of the polymer chains: a decrease in the vitreous transition temperature at 37 °C), leads to the formation of a zone in which the polymer passes from the crystalline state to a “rubbery” state known as a gel layer. Several transport phenomena take place through this gel layer: the entry of the aqueous

medium and the exit of the drug to the outside of the system, and phenomena of matrix erosion. The thickness of the gel layer increases as more and more water enters the system. At the same time, the surface-most polymer chains, which become hydrated earlier than the others, gradually relax until they lose consistency, after which matrix erosion begins (Maderuelo et al., 2011).

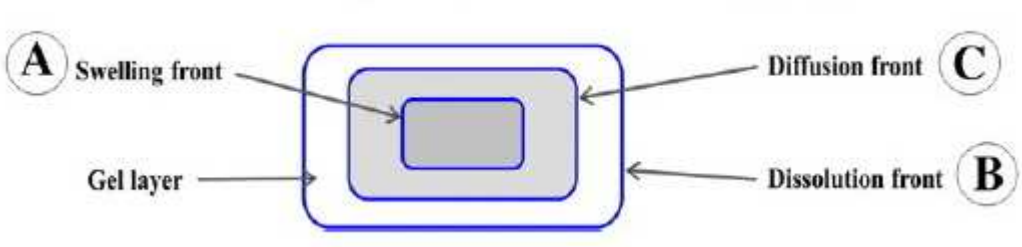


Figure 6 Scheme of the hydrophilic matrix after entry of the dissolution medium.

CHAPTER 3

EXPERIMENTAL

Materials

1. Tapioca starch (BANGKOK STARCH INDUSTRIAL CO., LTD., Thailand)
2. Propranolol Hydrochloride (Lot No. 20091106, Xing Yuang Chemical Plant Julong J iangsu, China)
3. Materials used for starch modification
    - Sodium hydroxide (Merck KGaA, Germany)
    - Sodium sulfate (Lot No. 0706021, Ajax Finechem pty Ltd., Australia)
    - Trisodium metaphosphate (Batch No. 026k0094, Sigma, Germany)
    - Propylene oxide (Lot No. s38857-037, SIGMA-ALDRICH, Germany)
    - Hydrochloric acid (Lot No.b40076, JT. BAKER ANALYZED®, USA)
4. Materials used for matrix preparation
    - Dicalcium phosphate (Batch No. A82220A, BUDENHEIM, USA)
    - Lactose monohydrate (MEGGLE, Germany)
    - Methocel E4M (Rama Production Co.,Ltd., Thailand)
    - 95% ethanol (commercial grade)
    - Magnesium stearate
    - Polyvinyl pyrrolidone K30 (Nanhang Industrial Co.,Ltd., China)
    - Polyvinyl pyrrolidone K90 (Nanhang Industrial Co.,Ltd., China)
5. Others
    - Sodium chloride (Lot No. 08111292, Ajax Finechem pty Ltd., Australia)
    - Potassium chloride (Ajax Finechem pty Ltd., Australia)
    - Potassium dihydrogen orthophosphate (Ajax Finechem pty Ltd., Australia)
    - Deionized water

Equipments

1. Scanning electron microscope
   (Model JSM-5800LV , JEOL , Japan)
2. Dissolution test apparatus
   (Model VK 7000 , VanKel , USA)
3. Ultraviolet/visible spectrophotometer
   (Model V-530 , Jasco , Japan)
4. Tablet friability tester
   (Model TAR 10, Erweka, Germany)
5. Shaking incubator
   (Model Universal Shaking Incubator , DLabTech , India)
6. pH meter
   (Model 210A, Thermo Orion, USA)
7. Disintegration
   (Erweka ZT 31, Germany)
8. Hydraulic pressure
   (CARVER®, USA.)
9. Tablet tester thermonik Model DHT-250
   (Campbell Electronic, India)
10. Moisture content HR 83
    (Mettler Toledo, Switzerland)
11. Haak Roto Viscol® Rheometer
    (GC 2014 shimadzu gas chromatograph, Japan)

Methods

1. Preparation of Modified Starches

The native tapioca starch was modified by substituted reaction with propylene oxide at three levels 2.5, 5.0, 7.5% (based on dry weight of starch), cross-linked with 0.1% sodium trimetaphosphate (based on dry weight of starch) and then pregelatinized by using drum dryer method.

1.1 Preparation of crosslinked hydroxypropyl starch

The native tapioca starch was modified by substituted reaction with propylene oxide, and crosslinked by sodium trimetaphosphate according to the procedure of (Jetsadamaetha, 1991; Tessler, 1975; Wo and Seib, 1997). Thirty grams of sodium sulfate (25% based on dry weight of starch) were added to 300 ml of water and stirred vigorously. When the salt was completely dissolved, 120 g of tapioca starch (equivalent to 40% starch solid in slurry) were slowly added and stirred until the mixture had uniform slurry. Then, the 5% of sodium hydroxide solution was added to the mixture to adjust pH of the slurry to 10.5 ± 0.2, sodium sulfate which added in this mixture in order to prevent starch gelatinized phenomenon. After that the propylene oxide at three levels 2.5, 5.0, 7.5% (volume based on dry weight of starch) were added to prepare low to high levels of substitution, respectively. The slurry was stirred at room temperature for half an hour and then the temperature was raised by magnetic stirrer to 40°C ± 2 with stirring rate of 200 rpm. The condition was allowed to proceed for 24 hours and the pH of slurry was recorded (completed first step substituted reaction).

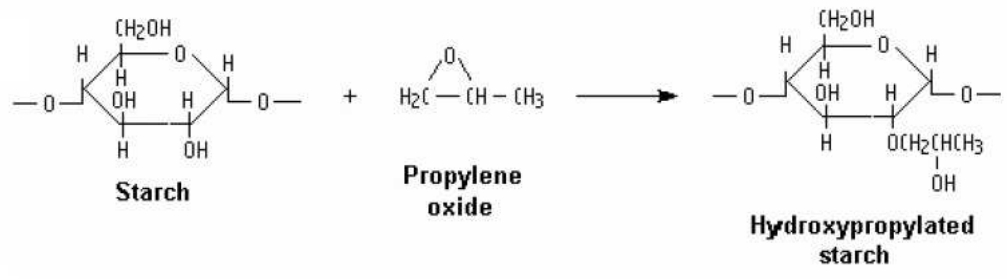


Figure 7 Substituted hydroxypropyl starch reaction (Aziz et al., 2004).

The crosslink reaction was begun when crosslink reagent, 0.1% sodium trimetaphosphate (based on dry weight of starch), was added to the slurry with vigorous stirring (200 rpm) and hold at this speed for 2 hours then added 10% HCl solution to adjust pH to 5.5 to finished the process. Transfer the slurry to recover by vacuum filtering through Whatman filter paper No.1, and the filter cake was washed with distilled water five times. The filter cake was dried at 40°c for 8 hours to control moisture at the range of 5-10%, all levels of substituted starches were passed through a 80-mesh sieve before pregelatinized process which using drum dryer method (the last procedure of the modified process).

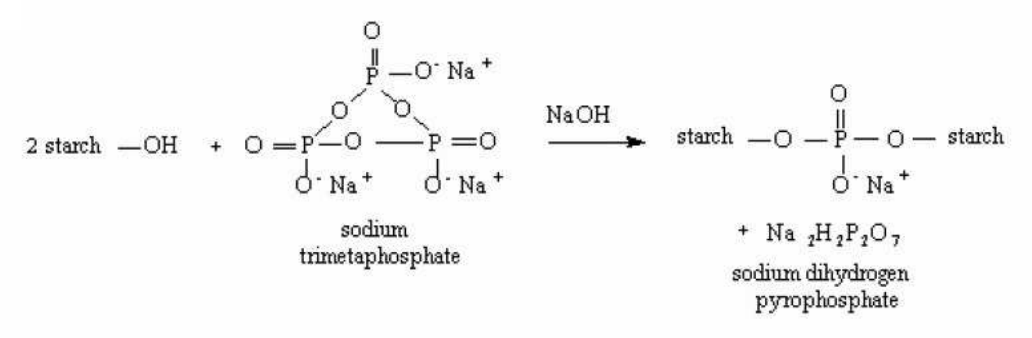


Figure 8 Cross-linked hydroxypropyl starch reaction (Aziz et al., 2004).

1.2 Pregelatinized of cross-linked hydroxypropyl starches

The pregelatinized form of cross-linked hydroxypropyl starches were prepared using drum dryer method. The drums have 0.25 m in diameter and distance between drum is 2 mm. The temperature and rotational speed were set at 120°C and 3 rpm, respectively (Figure 9). Thirty percent w/v aqueous slurry of starch was employed as the dryer feed and the dried mass was powdered in a laboratory mill then passed through 80 mesh sieve before use.

Figure 9 Drum dryer

2. Evaluation of Physicochemical Properties of Pregelatinized Crosslinked Hydroxypropyl Starch (PCHS)

2.1 Scanning electron microscopy (SEM)

The external morphology of modified starches were explored by scanning electron microscopy (SEM). A sample that will fit into the SEM chamber and some accommodation to prevent charge build-up on electrically insulating samples. The electrically insulating samples are coated with gold or some other metal or alloy. Images were taken using a JSM - 5800LV microscope (JEOL, Tokyo, Japan).The accelerating voltage and the magnification are given on the micrographs.

2.2 Polarized light microscopy

Starch birefringence was observed under polarized light using an optical microscope (D-6330, Wild Leitz GmBH, Germany).

2.3 Moisture contents

The moisture contents of all substituted levels of pregelatinized crosslinked hydroxypropyl starch were determined by using moisture balance HR83 apparatus (Mettler Toledo, Switzerland). Three grams of sample were weighted and heated at 105°C (constant weight achieved).

2.4 Viscosity properties

The measurement of viscosity was performed by Haak Roto Viscol® Rheometer (Haak Mess-Technik GmbH u. Co., Germany) using measuring plate no. P61, Rotor C35/1 and cone with diameter 35 mm, 1° Titan. The viscosity of 4, 5 and 6% w/v PCHS (all substituted levels) were dispersed in various media and measured at shear rate 100 s^{-1} at 60 second triplicate at room temperature. The effect of ionic strength and pH of media on viscosity were investigated.

2.4.1 Effect of ionic strength

The deionized water (μ=0) and sodium chloride solution at various concentrations, 0.05 M NaCl (μ=0.05), 0.10 M NaCl (μ=0.10), 0.20 M NaCl (μ=0.20) were used as media.

2.4.2 Effect of pH of media

0.1 N HCl solution pH 1.2 and phosphate buffer solution pH 6.8 were used as media.

2.5 Rheology

Rheological behaviors of dispersion of PCHS (all substituted levels) at three concentrations (4, 5, 6%V/W) were studied by Haak Roto Viscol® Rheometer (Haak Mess-Technik GmbH u. Co., Germany) at room temperature. The shear rate of sample was increased step by step from 0 to 1,000 s^{-1} within 60 seconds and maintained at the shear rate 1000 s^{-1} for another 30 seconds after that the shear rate was decreased step by step from 1,000 to 0 s^{-1} within 60 seconds. The rheology behavior of samples could determine by using the various media as described in section 2.4.1 and 2.4.2 in triplicate at room temperature.

2.6 Swelling power (SP)

Swelling power was determined according to the method described by Leach, et al. (1964). The one gram of PCHS (all substituted levels) was weighed into a centrifuge tube with closed screw cap and then 45 ml of distilled water was added into

the tube, the tube was heated at 37°C in shaker water bath for 30 minutes and moved to centrifuge at 4000 rpm for 15 minutes. The supernatant was poured out from the tube. Only the sample adhering in the tube was considered as the sediment and weighted The swelling power was calculated as the weight of the sediment gel divided by the original dry weight of the starch

SP = weight of the sediment gel / weight of dry starch

The swelling powers of PCHS (all of substitution levels) were studied in various media as described in section 2.4.1and 2.4.2 in triplicate at 37°C and room temperature.

2.7 Determination of hydroxypropyl group and phosphate in pregelatinized crosslinked hydroxypropyl starches

2.7.1 Quantitative determination of hydroxypropyl group and phosphate in pregelatinized cross-linked hydroxypropyl starches.

A gas chromatographic method (GC 2014 shimadzu gas chromatography, Japan) was used for the determination of hydroxypropyl group and phosphate. The sample was injected into a sample injection port and moved into the column, the signal was detected by using thermal conductivity detector and illustrated in chromatogram. The chromatogram of samples were compared with standard curve to identify functional group. Gas chromatography method can be used to analyze both of qualitative and quantitative. The conditions of GC are described as Table 4

Table 4 The conditions of GC 2014 shimadzu gas chromatograph

Temperature of column	100°C
Temperature of injector	150°C
Temperature of detector*	150°C

*thermal conductivity detector.

2.7.2 Quantitative determination of degree of substitution (DS)

The DS indicates the average number of sites per anhydrogluclose unit on which there are substituent groups. Thus, if one hydroxyl on each of the anhydroglucose unit in a starch has been esterified with hydroxypropyl group, the DS is 1. If all three hydroxyl groups are esterified, the DS is 3. Most of the commercially available modified starches have low DS values ranging up to about DS 0.1, which would present on average 1 substituent group per every 10 anhydroglucose units.

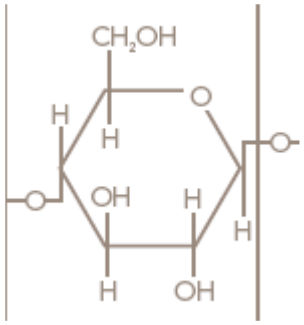


Figure 10 Anhydroglucose unit

The formula for calculating the DS of a starch derivative will vary depending upon the molecular weight and functionality of the substituent group (Wurzburg, 1986).

For hydroxypropylated starch:

$$DS = \frac{162 \times \left(\frac{\%\text{hydroxypropyl}}{58} \right)}{100 - \left(\frac{57 \times \%\text{hydroxypropyl}}{58} \right)}$$

(Molecular weight of anhydroglucose unit = 162 , hydroxypropyl = 58)

2.7.3 Qualitative determination of hydroxypropyl group and phosphate in pregelatinized cross-linked hydroxypropyl starches.

Fourier-transformed infrared (FTIR) spectrometer was used to detect hydroxypropyl group and phosphate group in modified starches. The samples were prepared as KBr pellets and scaned with the speed of three seconds per scan.

3. Preparation of Propranolol Hydrochloride Matrix

3.1 Preliminary study matrix preparation

3.1.1 The formulations of propranolol hydrochloride matrix

After testing the physicochemical of all levels of PCHS, the level of PCHS which had appropriate properties for use as a matrix excipient was chosen to prepare the formulations of sustained release dosage forms, by using lactose and dibasic calcium carbonate as a diluent and using PVP K30 and PVP K90 as a binder.

The composition of the formulations are presented in Table 5 and for more details in Table 7. All of ingredients were passed through 80 mesh sieve before mixing. The mixtures were compressed by hydraulic press equipment (CAVER®, USA.) with 3/8-inch diameter round flat faced punch and die set. The compression forces were 3000 psi. Each total weight of tablet was 300 mg.

Table 5 Formulations of direct compression method.

Ingredient	% w/w and mg. per tablet (300 mg)		
Propranolol	80 mg. (26.67%)		
PCHS	218.50 mg (72.83%)	158.50 mg (52.83%)	143.50 mg (47.83%)
Diluent*	No diluent	60 mg (20%)	60 mg (20%)
Binder **	No binder	No binder	15 mg. (5%)
Lubricant (Mg st)	1.5 mg. (0.5%)		

* Lactose or Dibasic calcium phosphate

** PVP K 30 or PVP K90

The tablet which prepared using direct compression method was too friable and low hardness. As a result, wet granulation method was alternative choice. In addition to, HPMC E4M was added to improving friability and hardness properties.

Table 6 Formulations of wet granulation

Ingredient	% w/w and mg. per tablet (300 mg.)				
Propranolol HCl	(26.67%) 80				
PHCS	210.50mg. (70.17%)	150.50mg. (50.17%)	No starch	135.50mg. (45.17%)	121.85mg. (40.17%)
HPMC E4M	No HPMC	No HPMC	(50.17%) 150.50mg.	(5%) 15mg.	(10%) 30mg.
Diluent	No diluent	60mg. (20%)	60mg. (20%)	60mg. (20%)	60mg. (20%)
Binder	(2.67%) 8 mg.				
Lubricant	(0.5%) 1.5mg.				

* Lactose or Dibasic calcium phosphate

** PVP K30 or PVP K90

The composition of the formulations are presented in Table 6 and for more details in Table 8, the matrix tablets were prepared by wet granulation method. All ingredients were passed through 80 mesh sieve before mixing. The PVP K30 or PVP K90 in 95% alcohol was used as a binder, the damp mass was passed though sieve again and dried at temperature of 60°C for 30 minutes. The dried granules were compressed by hydraulic pressure equipment (CAVER®, USA.) with 3/8-inch diameter round flat faced punch and die set. The compression forces were 3000 psi. Each total weight of tablet was 300 mg.

Table 7 The amount of polymers and diluents used in each formulation of propranolol hydrochloride matrix (direct compression method)

Formulation	%Drug	Polymer (%W/W)			Diluent (%W/W)	
		PCHS	PVP K30	PVP K90	Lactose	Dibasic calcium phosphate
Blank A	26.67	-	-	-	72.83	-
Blank B	26.67	-	-	-	-	72.83
F1	26.67	72.83	-	-	-	-
F2	26.67	52.83	-	-	20	-
F3	26.67	52.83	-	-	-	20
F4	26.67	47.83	5	-	20	-
F5	26.67	47.83	5	-	-	20
F6	26.67	47.83	-	5	20	-
F7	26.67	47.83	-	5	-	20

Table 8 The amount and type of polymers and diluents used in each formulation of propranolol hydrochloride matrix (wet granulation method)

Formulation	%Drug	Polymer (%W/W)			Diluent (%W/W)	
		PCHS	HPMC	PVP K90	Lactose	Dibasic calcium phosphate
F8	26.67	70.17	-	2.67	-	-
F9	26.67	50.17	-	2.67	20	-
F10	26.67	50.17	-	2.67	-	20
F11	26.67	-	50.61	2.67	20	-
F12	26.67	-	50.61	2.67	-	20
F13	26.67	45.17	5	2.67	20	-
F14	26.67	45.17	5	2.67	-	20
F15	26.67	40.17	10	2.67	20	-
F16	26.67	40.17	10	2.67	-	20

4. Evaluation of Propranolol hydrochloride matrix

4.1 Determination of hardness.

Hardness of tablets were evaluated by using hardness tablet tester (Model THERMPNIK, India), ten tablets were measured individually, mean and standard deviation were calculated and reported in term of kilopounds.

4.2 Determination of tablet friability

Friability of tablets were evaluated by using friability tester (Model ERWEKA TAR 10, Germany). The drum was rotated at 25 rpm for 4 minutes. Loss of tablets weight with respect to the initial value was calculated as percent friability.

4.3 Determination of tablet disintegration

Disintegration time of tablets were measured by disintegration test apparatus (Model Erweka ZT 31, Germany). Six tablets were used, at 37°C. The time was recorded when all of tablet were completely disintegrated.

4.4 Assay of propranolol hydrochloride content in matrix

Twenty tablets of each formulation were weighed and pulverized by mortar and pastle. Then, transfer and accurately weighed portion of the powder that equivalent to about 50 mg of propranolol hydrochloride to a 50-ml volumetric flask, add 40 ml of methanol, shaked and sonicated for 5 minutes. Afterward, the volumetric flask was adjusted volume by the same medium and mixed thoroughly. The solution was filtered through filter paper, Whatman No.1, and used as stock solution. This stock solution was appropriately diluted with methanol to obtain a suitable concentration prior to determination by UV/visible spectrophotometer at a wavelength 289 nm.

The propranolol hydrochloride content was calculated from calibration curve of propranolol hydrochloride in methanol and performed in triplicate

4.5 Solubility of propranolol hydrochloride

Solubility of propranolol hydrochloride was studied in different ionic strength media as followed: 0.05, 0.10 and 0.20 M sodium chloride solutions. An excess amount of propranolol hydrochloride was added to each medium in amber glass bottles. The bottles were closed and placed in a shaker maintained at 25°c and rotated at 100 rpm for 30 hours. Ten milliliters of solution were collected at 24, 27 and 30 hours. The solutions were filtered and diluted to suitable concentration and then detected amount of propranolol hydrochloride by UV spectrophotometer at wavelength 289 nm. Solubility of propranolol hydrochloride in each medium was detected in triplicate.

4.6 Determination of drug released form matrix

4.6.1 Calibration curves of propranolol hydrochloride

Calibration curves of propranolol in different medium were made. The medium were; deionized water, 0.05, 0.10, 0.20 M NaCl solution, 0.1 N HCl solution, phosphate buffer pH 6.8 solution and methanol.

Propranolol hydrochloride 80 mg. was accurately weighted into a 100 ml. volumetric flask. The powder was dissolved and adjusted with medium. The solution was used as a stock solution. Stock solution 1.0, 2.0, 3.0, 4.0, 5.0 and 3.0 ml. were transferred into 100, 100, 100, 100, 100 and 50 ml. volumetric flask, then adjusted to the volume with each medium giving the final concentrations of each solution of 8, 16, 24, 32, 40 and 48 mcg/ml respectively. The absorbance was measured by UV spectrophotometer at wavelength 289 nm.

4.6.2 Dissolution tests of formulations (for all formulations)

Dissolution tests of formulations were evaluated by USP 29 apparatus I (basket, model VK7000, VanKel, USA.) and operated at 100 rpm in 37±0.5°C dissolution medium, 900 ml of deionized water. A ten milliliters of sample was withdrawn through a syringe filter (nylon type) and was replaced with the same volume of medium immediately to keep constant volume in vessel throughout the experiment. The dissolution parameters were shown in Table 9.

Table 9 Dissolution testing parameters of propranolol hydrochloride in distilled water

Parameter	value
Basket	100 rpm
Temperature	37±0.5°C
Operating time	12 hrs
Medium volume	900 ml
Sampling volume	10 ml
Sampling time (hours)	0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

Criteria: the formulation with 100% release within 12 hours was chosen for further investigation

4.6.3 Dissolution test of formulation (for formulation within criteria)

The suitable formula which can prolong drug release through 12 hours was chosen for studying the effect of electrolyte and pH media, compression forces and methods of dissolution test on drug release. The dissolution tests were evaluated by USP 29 standard apparatus I (basket, model VK7000, VanKel, USA.) and operated at 100 rpm in 37±0.5°C dissolution medium.

Effect of electrolyte and pH

Nine hundred milliliters of deionized water, 0.05, 0.10, 0.20 M NaCl solutions, 0.1 N HCl solution and phosphate buffer solution pH 6.8 were employed as dissolution media to study the effects of pH and ionic strength of dissolution media on drug released from matrix. A ten milliliters sample was withdrawn through a syringe filter (nylon type) and was replaced with the same volume of medium immediately to keep constant volume in vessel throughout the experiment. The dissolution parameters were shown in Table 10.

Table 10 Dissolution testing parameters of propranolol hydrochloride in various ionic strength and pH of media

Parameter	value
Basket	100 rpm
Temperature	37±0.5°C
Operating time	12 hrs
Medium volume	900 ml
Sampling volume	10 ml
Sampling time (hours)	0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

Effect of compression forces

Effect of compression forces on drug release of Formulation F16 was examined. The formulation was blended as described previously and then compressed at forces of 1000, 2000, 3000 psi using hydraulic pressure equipment (CAVER®) with 3/8-inch diameter round flat faced punch and die set. The total weight of each tablet was about 300 mg. The tablets were tested for hardness, friability, disintegration and dissolution test. The dissolution tests were studied by using criteria as described in 4.6.2.

Effect of methods of dissolution test

Effect of methods of dissolution test was determined by using USP 29 standard apparatus I and II (basket and paddle, model VK7000, VanKel) and operated at 100 rpm in 37±0.5°C dissolution medium. The condition of dissolution test were shown in table 11.

Table 11 Dissolution testing parameters of propranolol hydrochloride for methods of dissolution test

Parameter	value
Basket and paddle	100 rpm
Temperature	37±0.5°C
Operating time	12 hrs
Medium volume	900 ml
Sampling volume	10 ml
Sampling time (hours)	0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

4.7 Statistic analysis

The effect of pH, ionic strength, compaction pressure on drug release and the release rate of propranolol hydrochloride from PCHS matrix were statistically analysed by similarity test. Dissolution testing has become an essential tool in the pharmaceutical industry at various stages of development, manufacturing and marketing. For the comparison of dissolution profiles, similarity factor f_2 is gaining popularity due to its recommendation by various regulatory committees, for testing purposes, a discriminatory medium can be identified by varying stirring rate and parameters of the dissolution medium, including pH, ionic strength, volume, etc. Dissolution profiles are considered similar if the calculated f_2 value is between 50 and 100. This procedure that the dissolution behavior of a number of samples (n) of reference (R) and test (T) products are compared at ttime points (Eq.1).

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\} \quad \text{eq....(1)}$$

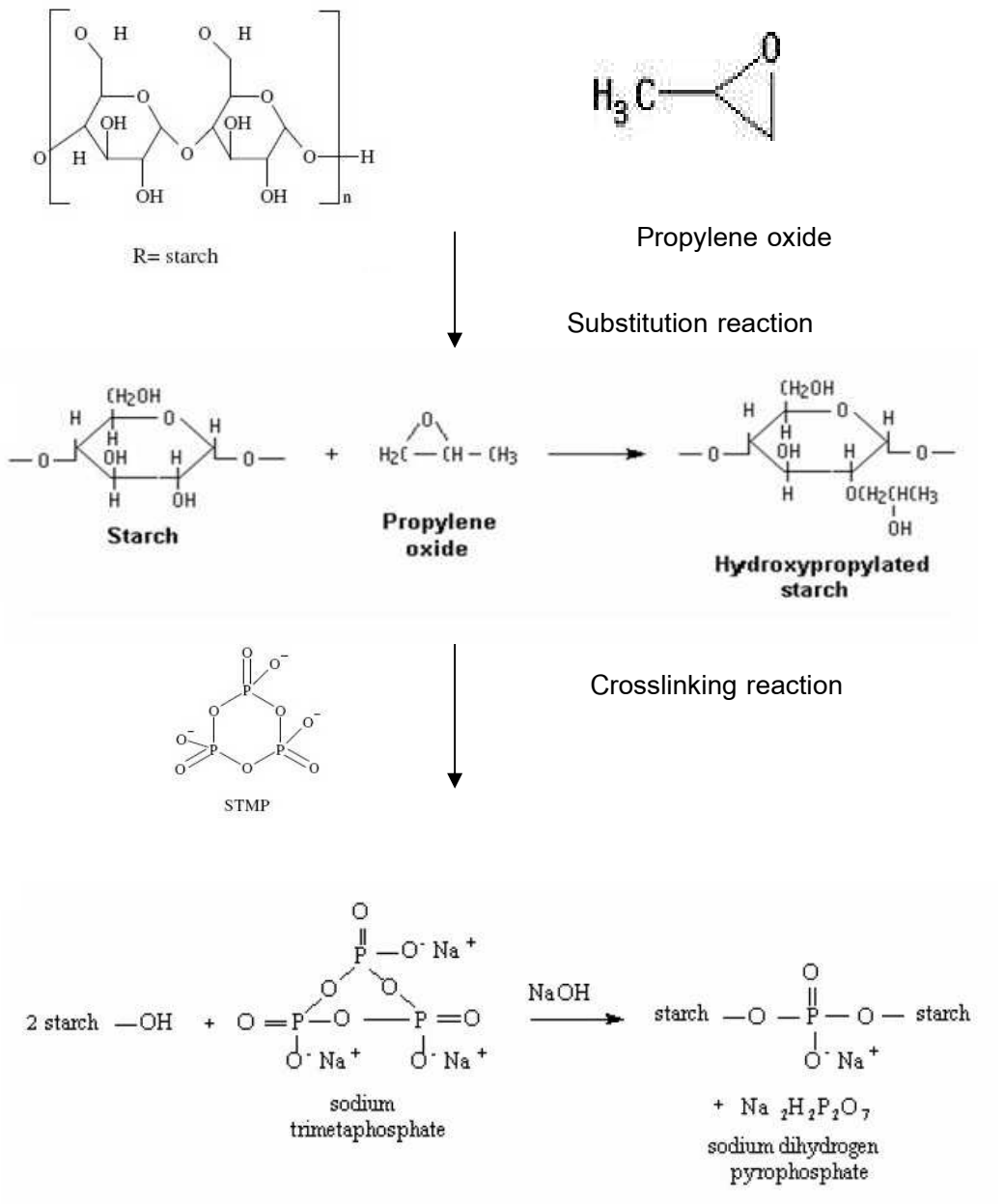
The f_2 values are independent from the sample taken as reference, and they range between 0 and 100, with a higher number indicating better similarity between profiles. Acceptable values are $50 \leq f_2 \leq 100$, which is considered equivalent to a difference in approximately 10% between the dissolution profiles being compared (Shah et al., 1998).

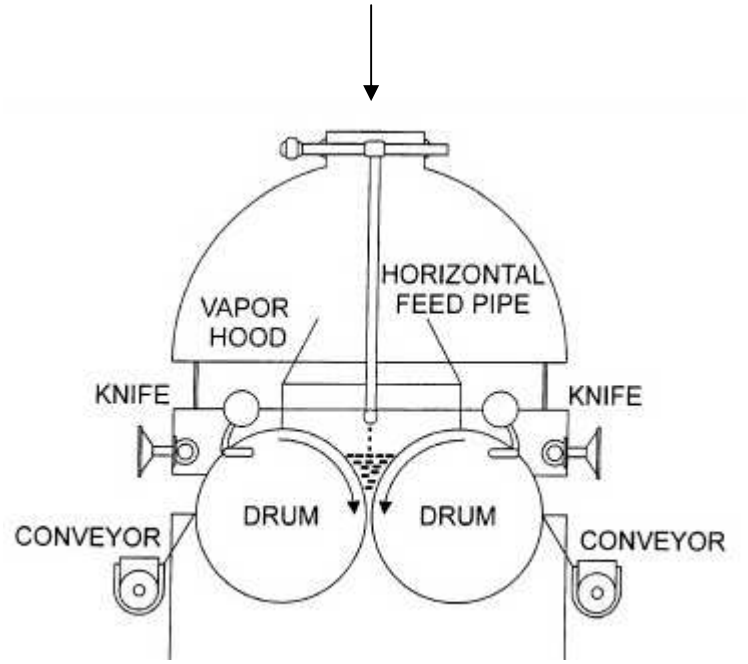
CHAPTER 4

RESULTS AND DISCUSSION

1. Preparation and Characterization of Modified tapioca Starches

Tapioca starches were modified both chemically and physically to accentuate their positive characteristics, diminish their undesirable qualities, or add new attributes. The native tapioca starch were modified by hydroxypropylation with 2.5, 5.0, 7.5% of propylene oxide and then cross-linked with 0.1% of sodium trimetaphosphate (Figure 11).





Drum dryer

Figure 11 The process reaction mechanisms of pregelatinized cross-linked hydroxypropyl starch (Kalogianni, et al., 2002).

The phosphorylation reaction produces either monostarch phosphates via substitution or distarch phosphates via cross-linking depending on the reaction conditions including concentration of sodium trimetaphosphate, amylose content, pH, time and temperature (Singh, et al., 2007).

1.1 Determination of hydroxypropyl group and phosphate in pregelatinized cross-linked hydroxypropyl starches

1.1.1 Quantitative determination of hydroxypropyl group and phosphate

A gas chromatographic method was used for the determination of hydroxypropyl groups and phosphate (as phophorus content) are shown in Table 12. The 2.5, 5.0 and 7.5% of propylene oxide exhibited percent of hydroxypropyl groups 2.18, 2.58 and 3.66, respectively, and showed similar quantity of phosphorus as P around 0.01 at all of substitution levels. The degree of substitution (DS) was calculated from the percent of hydroxypropyl group. The DS of modified starch after substitution with 2.5, 5.0 and 7.5% of propylene oxide were 0.062, 0.074 and 0.106, respectively.

1.1.2 Quantitative determination of degree of substitution (DS)

The DS indicates the average number of sites per anhydrogluclose unit on which there are substituent groups. The DS of PCHS are presented in Table 12, as a result, the DS of PCHS prepared using propylene oxide 2.5%, 5.0% and 7.5% were 0.062, 0.074 and 0.106, respectively. It can imply that when the concentration of propylene oxide was increased, the DS also increased. However, when the concentration of propylene oxide was increased over than 7.5% w/v which resulting in a product that was difficult to filter and wash and remove residual in product.

Table 12 Quantitative of hydroxypropyl group and phosphate and calculation of DS

Sample	Hydroxypropyl group (%)	Phosphorus as P (ppm)	DS
2.5%C_3H_6O + 0.1%$Na_3P_3O_9$	2.18	0.011	0.062
5.0%C_3H_6O + 0.1%$Na_3P_3O_9$	2.58	0.011	0.074
7.5%C_3H_6O + 0.1%$Na_3P_3O_9$	3.66	0.010	0.106

The hydroxypropyl groups and the phosphate as phophorus content which detected by GC 2014 shimadzu gas chromatography were already deducted the quantity of hydroxypropyl groups and phosphorus content that were inside the natural native starch.

1.1.3 Qualitative determination of hydroxypropyl group and phosphate in pregelatinized cross-linked hydroxypropyl starches.

Fourier-transformed infrared (FTIR) spectrophotometer was used to detect hydroxypropyl groups and phosphate groups in modified starches. In this study, three degrees of substitution of PCHS were evaluated and compared with native tapioca starch. From the infrared spectra graph of native starch, the wide band observed at 3411 cm^{-1} can be attributed to the O-H stretching of the starch structure, and its width was ascribed to the formation of inter and intramolecular hydrogen bonds. The bands at 2931 cm^{-1} were attributed to the asymmetric stretching of C-H (Dragunski, and Pawlicka, 2001). The finger print region from 1600 to 250cm^{-1} is dominated from C–H and CH_2 deformation vibrations at 1480–1230cm^{-1} (Passauer, Bender, and Fischer, 2010) while the C-O alcohol bond shows stretching at 1015 cm^{-1}. However, spectra of PCHS showed band of hydroxyl groups and CH aliphatic from structure of starch that OH stretching at 3600-3200 cm^{-1}, CH stretching at 2960-2850 cm^{-1}, respectively.

The native tapioca starch which was substituted by hydroxypropyl groups could be confirmed by the presence of substituted hydroxypropyl groups, CH_3 and CH_2 deformation vibrations at 1470-1400 cm^{-1}, the CH_3 symmetric deformation vibrations at ~1380 cm^{-1}(Socrates, 2001). In addition, after phosphorylation of starch, a new band appeared in the range from 1020 to 920 cm^{-1}, that is the spectral vibrations such as (P–O–P) which representing pyrophosphates and starch diphosphates which lie in regions (Passauer et al., 2010). The phosphate that could display by P=O in polymeric phosphate chains are presented around 1250-1350 cm^{-1} and 525 cm^{-1} (Passauer et al., 2010; Aziz et al., 2004). This bands indicate organically bonded phosphate groups which were introduced into the starch molecule by esterification of the hydroxyl groups of the anyhdroglucose units of starch with sodium

trimetaphosphates. The FTIR spectrum of all PCHS compared with native starch are shown in Figure 12.

The FTIR spectrums of PCHS with DS of 0.062, 0.074 and 0.106 exhibited the CH stretching at 2928, 2929, 2929 cm^{-1}, CH_3 and CH_2 deformation vibrations at 1428, 1420 and 1423 cm^{-1} ,respectively. The CH_3 symmetric deformation vibration all of PCHS appeared at the same wavelength 1371 $cm.^{-1}$

For verified phosphate functional groups of PCHS with DS of 0.062, 0.074 and 0.106, the P=O which located at 1237, 1237, 1238 and 524, 525, 527 cm^{-1}, P-O-P at 1020 cm^{-1}, respectively.

In this experiment, the spectra of native tapioca starch also had spectrum band of phosphate group in their structure, such as, PCHS. Due to the fact that it is known that phosphorus in native tapioca starch is phosphate monoester which are primary found in amylopectin cluster (Atichokudomchai and Varavinit, 2003). Therefore, the FTIR spectrum of native tapioca starch could show similar spectrum bands when comparing with PCHS. Nevertheless, after modification, the FT-IR of PCHS with DS of 0.062, 0.074 and 0.106 exhibited obviously increasing intensity peak of P-O when compared with peak of unmodified starch. In addition, the quantitative determinations of phosphate content could perform by gas chromatography method. (as displayed in Table 12) As a result, It could confirm that after modification, the PCHS were substituted by hydroxypropyl and phosphate groups inside their structure.

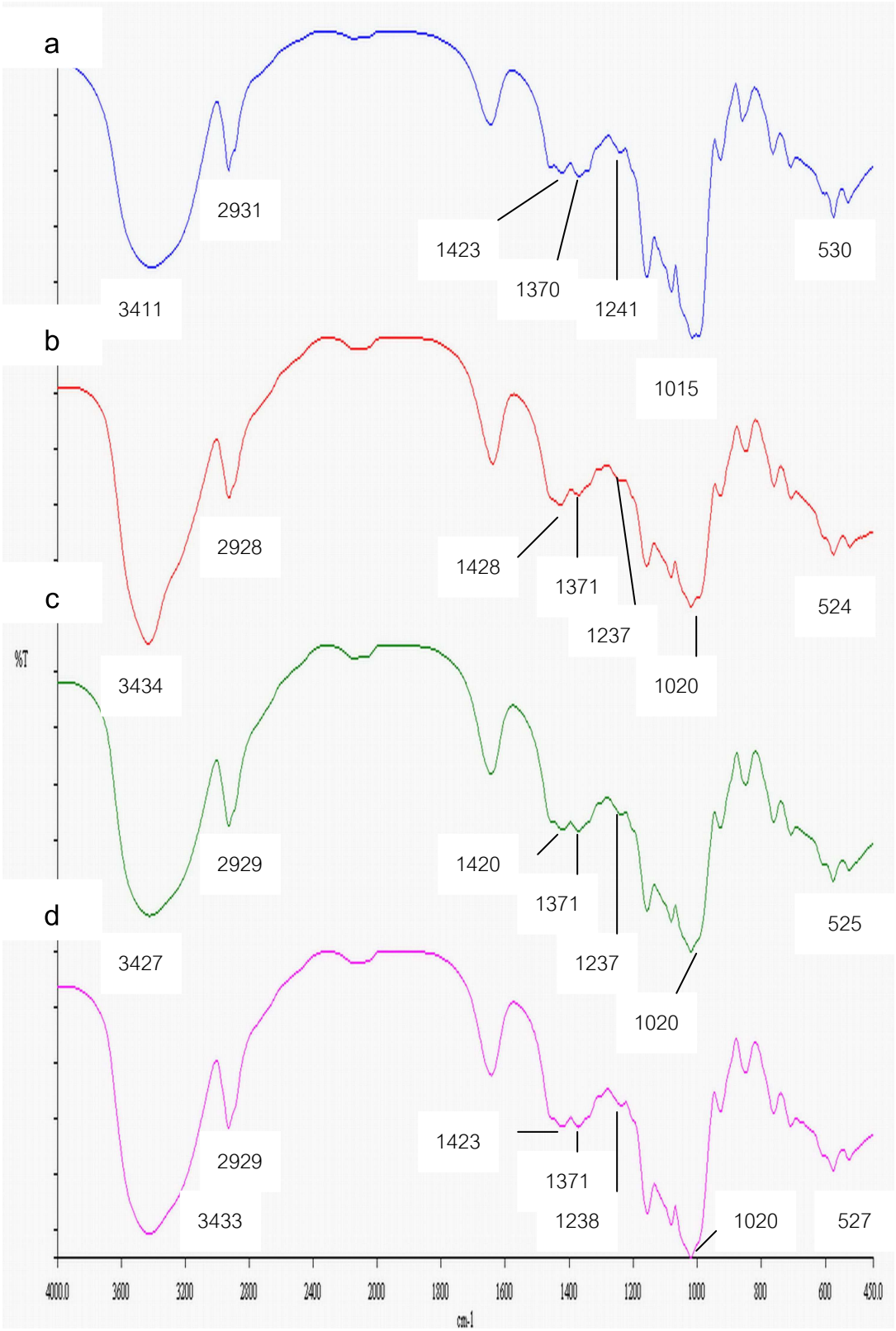
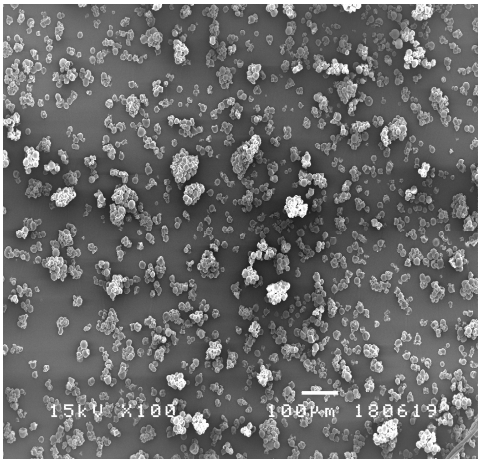


Figure 12 Comparison of FTIR spectrums between native starch (a) and all PCHS after modification (2.5% substitution PCHS (b), 5.0% substitution PCHS (c) 7.5% substitution PCHS (d)).

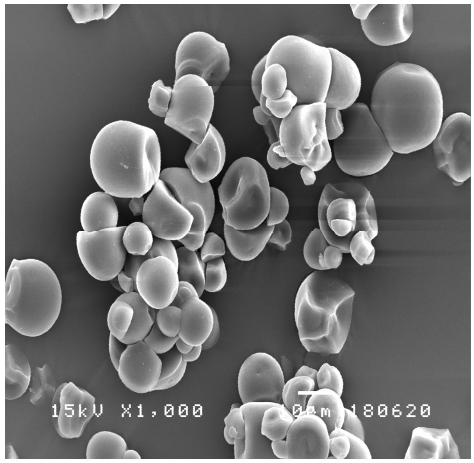
2. Evaluation of Physicochemical Properties of Pregelatinized Crosslinked Hydroxypropyl Starch (PCHS)

2.1 Scanning electron microscopy (SEM) of native tapioca starch and PCHS were illustrated in Figure 13, the native tapioca starch was shown round smooth granule surface (Figure 13a). After being substituted, cross-linked and pregelatinized, they changed in size and surface. After modifying, the size of PCHS granules were increased and it gave irregular rough surface.

(a)

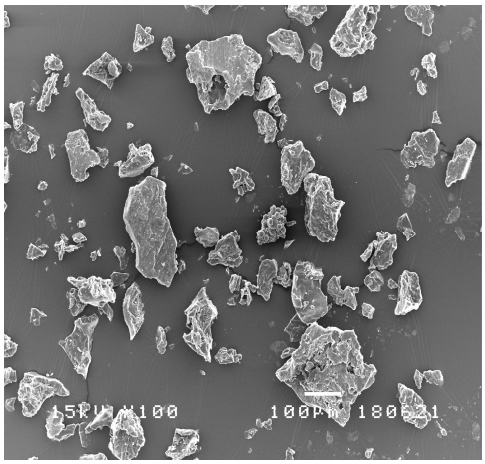


(X100)



(X1000)

(b)



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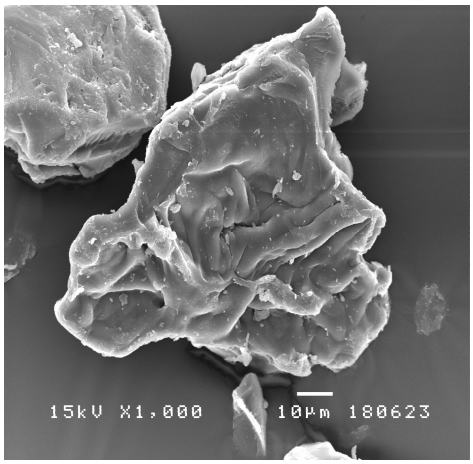
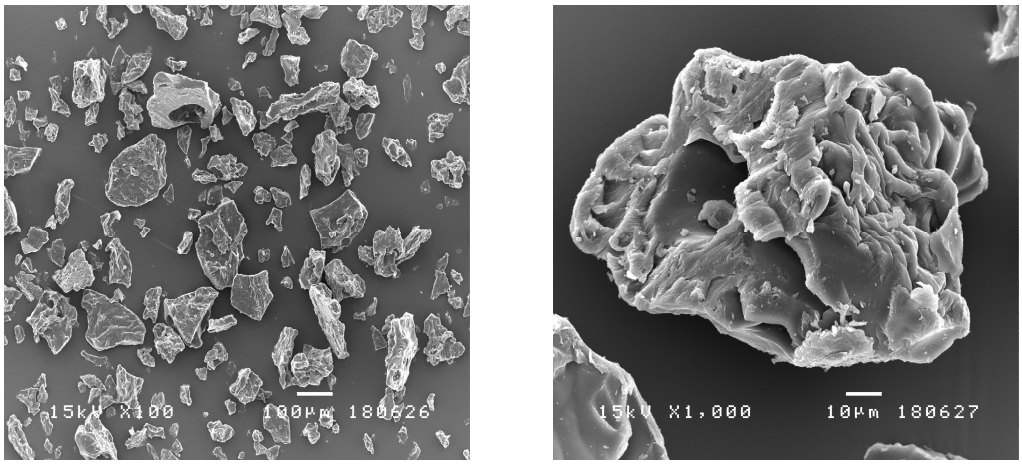


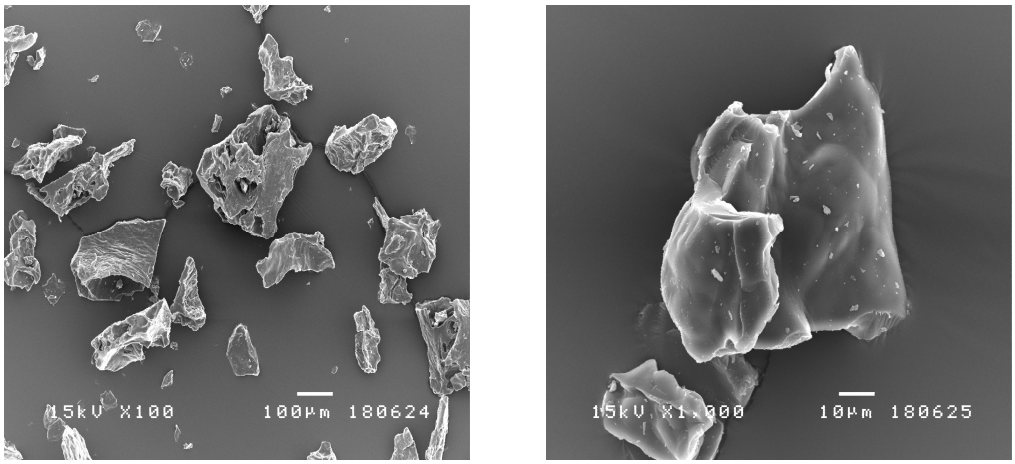
(X1000)

(c)



(X100) (X1000)

(d)



(X100) (X1000)

Figure 13 Electron microscope images of various starch granules, Native tapioca starch(a), 2.5% substitution PCHS (b), 5.0% substitution PCHS (c), 7.5% substitution PCHS (d).

(**Note:** -2.5% substitution PCHS = 2.5% propylene oxide (based on dry weight of starch) substitution of pregelatinized cross-linked hydroxypropyl starch).
-5.0% substitution PCHS = 5.0% propylene oxide (based on dry weight of starch) substitution of pregelatinized cross-linked hydroxypropyl starch).
-7.5% substitution PCHS = 7.5% propylene oxide (based on dry weight of starch) substitution of pregelatinized cross-linked hydroxypropyl starch).

2.2 Polarized light microscopy

The process of gelatinization causes substantial changes in both the chemical and the physical nature of granular starch due to the rearrangement of intra- and intermolecular hydrogen bonding between the water and starch molecules resulting in the collapse or disruption of molecular orders within the starch granule. This results in irreversible changes in the starch properties. Evidence of the loss of an organized structure includes irreversible granule swelling (Odeko, Schmid and Picker-Freyer, 2008 cited in Freitas et al., 2004). Under the microscope in polarized light, starch loses its birefringence and its extinction cross.

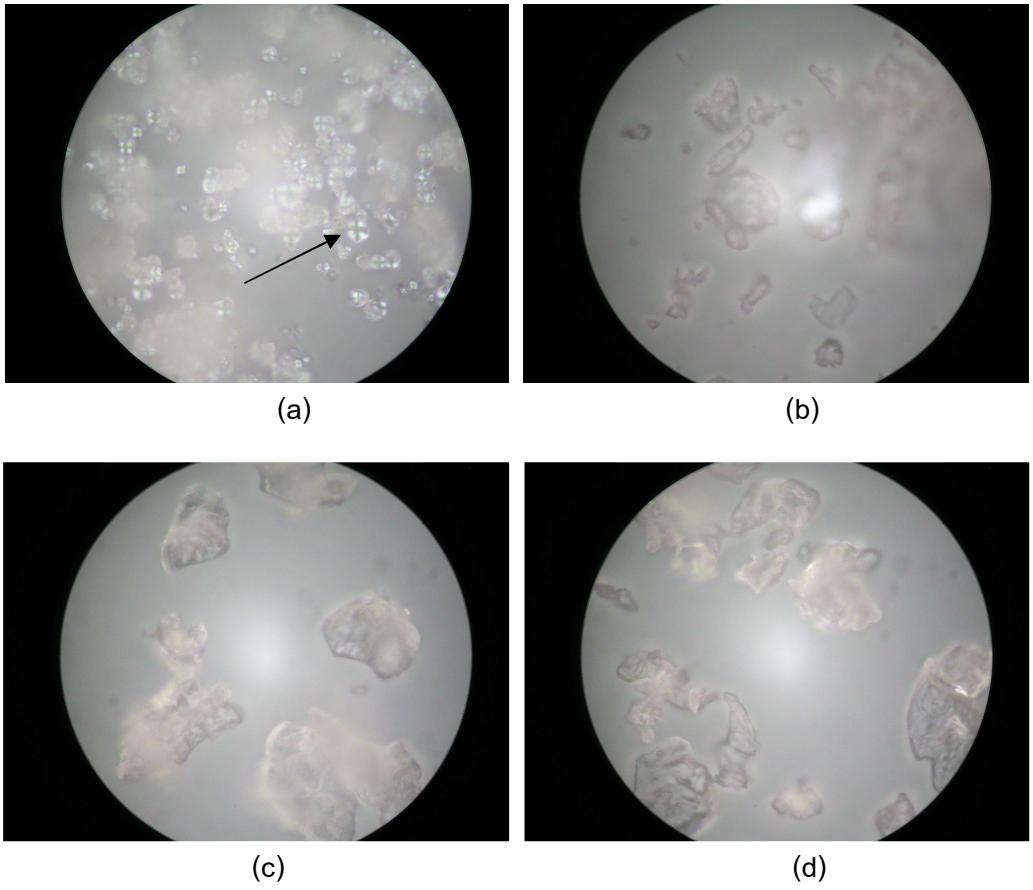


Figure 14 Polarized light microscope images of various starch granules (x40), Native tapioca starch (a), 2.5% substitution PCHS (b), 5.0% substitution PCHS (c), 7.5% substitution PCHS (d).

2.3 Moisture content

The moisture content of PCHS, which kept in the sealed container, were measured by using moisture balance HR83 apparatus at the temperature 105 °C. The moisture content of native tapioca starch, 2.5, 5.0, 7.5% substitution PHCS which were presented at 10.68, 5.04, 5.29 and 4.28% w/w, respectively (Table 13). It was found that the moisture content of PCHS decreased because the starch granules received heat from pregelatinized process.

Table 13 Moisture content all of PCHS

Sample	Moisture content (±SD)
Native tapioca starch	10.68(0.43)
2.5% substitution PCHS	5.04(0.65)
5.0% substitution PCHS	5.29(0.17)
7.5% substitution PCHS	4.28(0.49)

(Note: n=3)

2.4 Viscosity measurement of pregelatinized cross-linking hydroxypropyl straches

The viscosity of all PCHS increased when the concentration of PCHS increased and the 7.5% substitution PCHS provided the highest viscosity comparing with native starch (Table 14 and 15), because it has the highest degree of incorporation hydroxypropyl groups in the starch chains. The hydroxypropyl groups introduced into the starch chains are said to be capable of disrupting inter- and intra-molecular hydrogen bonds, thereby weakening the granular structure of starch leading to an increase in motional freedom of starch chains in amorphous regions (Singh and Kuar, 2003 cited in Choi & Kerr, 2003; Seow and Thevamalar, 1993; Wooton & Manatsathit, 1983). Therefore, substitution tapioca starch with hydroxypropyl groups were changed its granular and molecular structure easily to form H-bond with water and make it gave greater viscosity. It might say that, an increase hydroxypropyl groups of PCHS provided the higher viscosity.

2.4.1 Effect of electrolyte

Sodium chloride solutions at concentration of 0.05, 0.10 and 0.20 M were used as the representative solution ionic strength (μ) of 0.05, 0.10 and 0.20, respectively.

The viscosities of all PCHS in various concentrations of NaCl solution were presented in Table 14. The gel of 2.5%, 5.0% and 7.5% substitution PCHS providing transparent gel, and showed that the viscosity increased when concentration of PCHS increased. Furthermore, an increased DS caused an increased in viscosity of PCHS. However, at the same concentration in various media of PCHS demonstrated close proximity of the viscosity, for instance, the viscosity of 2.5% substitution PCHS at concentration of 6% w/v were 632.2, 833.5, 742.9 and 799.6 cps. 5.0% substitution PCHS at concentration of 6% w/v were 713.2, 809.3, 849.5 and 885.1 cps. 7.5% substitution PCHS at concentration of 6% w/v were 2148.6, 2119.6, 2121.6 and 2253 in DI water, 0.05, 0.10 and 0.20 M NaCl solution, respectively.

Table 14 Viscosity of PCHS in various concentrations of NaCl media

Viscosity (CPS)(±SD)					
sample	Conc (%w/v)	DI Water	0.05 M NaCl	0.10 M NaCl	0.20 M NaCl
2.5% substitution PCHS	4%	138.9 (4.4)	214.9(13.7)	144.7(2.9)	145(12.6)
	5%	351.8 (14.8)	364.4(13.2)	318.7(11.8)	352.7(9.5)
	6%	623.2 (19.4)	833.5(6.9)	742.9(3.01)	799.6(16.6)
5.0% substitution PCHS	4%	148.4(7.1)	219.6(24.4)	185.6(14.7)	173.2(9.0)
	5%	400.3 (40.5)	368.7(7.8)	385(9.6)	392.6(8.3)
	6%	713.2 (16.3)	809.3(13.5)	849.5(10.4)	885.1(6.7)
7.5% substitution PCHS	4%	450.2 (5.03)	467.5(17.5)	478.5(6.9)	496.3(16.7)
	5%	973.4 (7.3)	1085(4.6)	1,050(2.6)	1,049(10.0)
	6%	2,148.6 (15.8)	2119.6(14.6)	2121.6 (10.2)	2,253(10.5)

(Note: n=3)

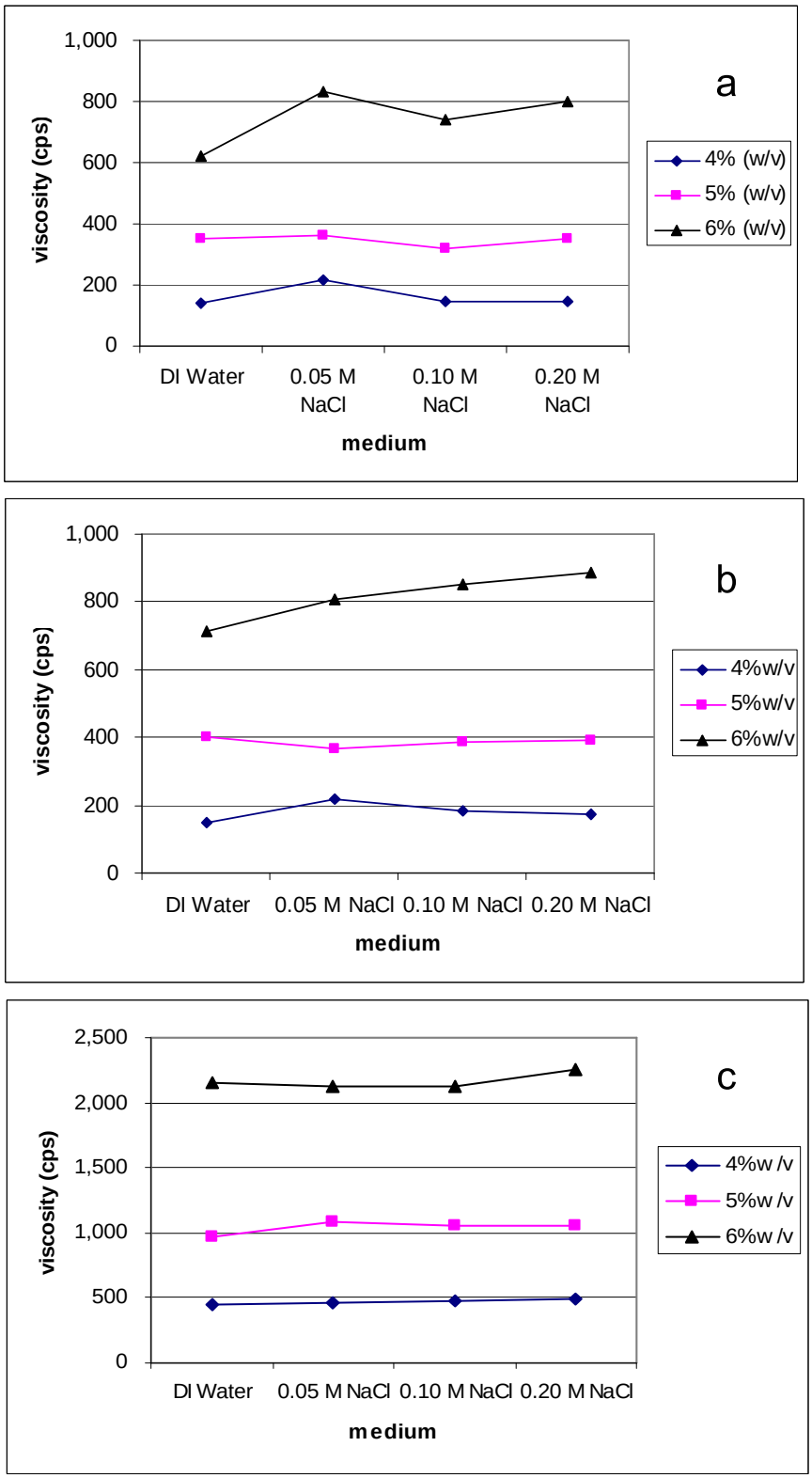


Figure 15 Viscosity of 2.5(a), 5.0(b), 7.5%(c) substitution PCHS comparing with three levels of concentrations in various ionic strength media.

Graphical displays of PCHS in various ionic strength media are shown in Figure 15. It was unlikely that different ionic strength of the media caused viscosity change of PCHS. From the result, when the ionic strength of media increased, there were no changed in viscosity. This may imply that the electrolytes had no effect on the viscosity of all PCHS.

2.4.2 Effect of pH of media

Phosphate buffer solution pH 6.8 and 0.1 N HCl solution were used as a media in this experiment. (ionic strength did not control equally)

The viscosities of PCHS of 2.5, 5.0, 7.5% substitution at concentrations of 4, 5, 6% w/v in various pH media are shown in Table 15. The viscosities of all PCHS increased when concentration of PCHS increase. The 7.5% substitution PCHS at 4, 5 and 6% concentration presented the highest viscosity when comparing with of the same concentration. The viscosities of all PCHS were apparently not affected by the change of pH media (Figure 16).

Table 15 Viscosities of PCHS in various pH media

Viscosity (cps)(±SD)				
sample	Conc (%w/v)	DI Water	0.1 N HCl	PBS pH 6.8
2.5% substitution PCHS	4%	138.9 (4.39)	127.4(4.8)	140.7(4.54)
	5%	351.8 (14.8)	269.5(8.08	304.8(15.02)
	6%	623.2 (19.39)	647.4(8.00)	662.4(4.11)
5.0% substitution PCHS	4%	148.4(7.15)	189.4 (11.75)	177.3 (2.36)
	5%	400.3 (40.52)	311.9 (10.47)	384.9 (6.62)
	6%	713.2 (16.3)	764.1 (10.22))	757.8 (1.36)
7.5% substitution PCHS	4%	450.2 (5.03)	436.5 (6.49)	483.3 (8.41)
	5%	973.4 (7.35)	1,113.3 (10.21)	1,030 (14.10)
	6%	2148.6 (15.82)	2,210.6 (9.60)	2,468 (7.00)

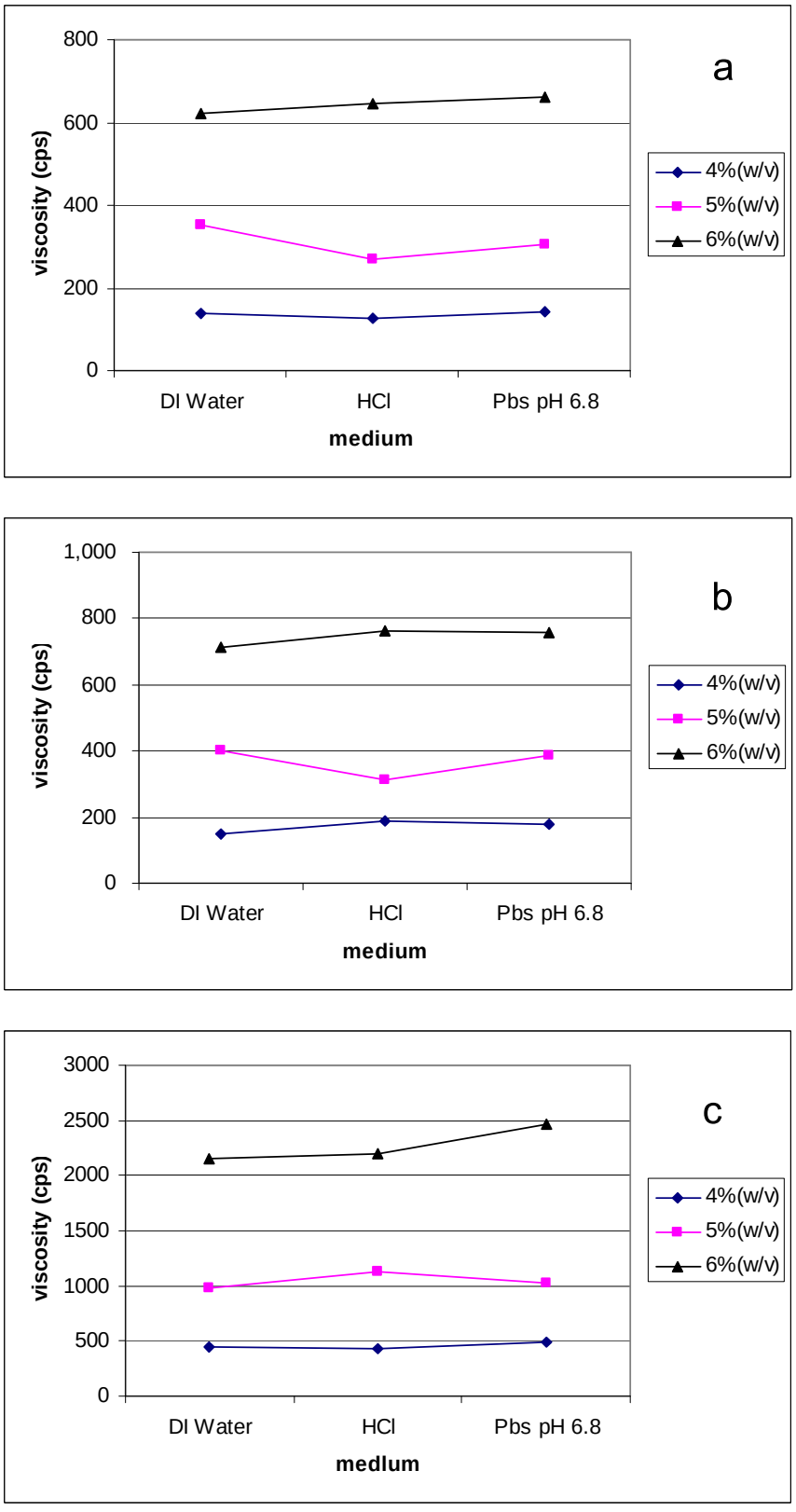


Figure 16 Viscosity of 2.5(a), 5.0(b), 7.5%(c) substitution PCHS comparing at three levels of concentrations in various pH media.

Modified starch (PCHS) can swell and give visco-stability due to a combination of substitution, cross-linking and pregelatinization that provide stability against acid-base, thermal, electrolytes and mechanical degradation of starch, and delay retrogradation during storage (Bertoliny, 2010). Therefore, in this study, it was found that the PCHS remained good swelling and gave visco-stability of gel, even if the media were changed in acid-base and various ionic strength conditions. It can imply that acid-base condition and electrolytes had no effect on viscosity property.

2.5 Rheological studies of pregelatinized cross-linking hydroxypropyl starches

2.5.1 Effect of electrolyte

Rheological behaviors of PCHS dispersion (all substituted levels) at three concentrations (4, 5 and 6%W/V) in various concentrations of sodium chloride comparing with in DI water were illustrated in Figure 17, 18 and 19. The curve began at the origin of shear stress-shear rate plot and was concaved upward. The flow behavior of PCHS presented thixotropic plastic flow pattern that fluids show a time-dependent change in viscosity; the longer the fluid undergoes shear stress, the lower its viscosity. A thixotropic fluid is a fluid which takes a finite time to attain equilibrium viscosity when introduced a step change in shear rate. In conclusion the rheograms patterns of 2.5, 5.0 and 7.5% substitution PCHS were similar, It was indicated that ionic strength had no effect on flow patterns of PCHS.

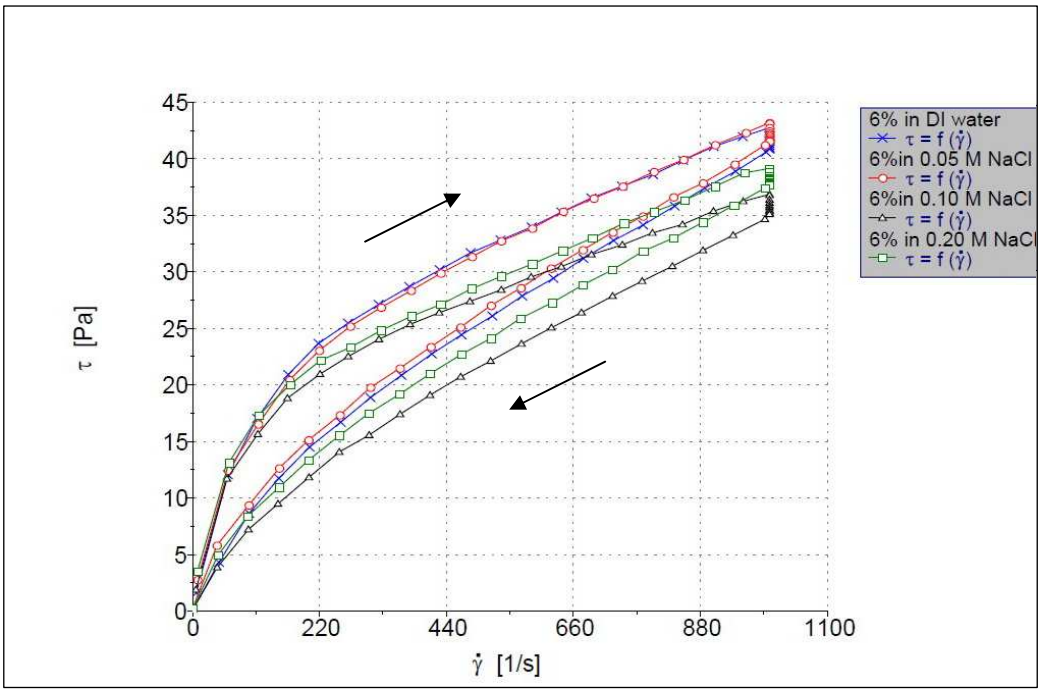


Figure 17 The rheograms of 2.5% substitution PCHS in various concentrations of sodium chloride comparing with DI water.

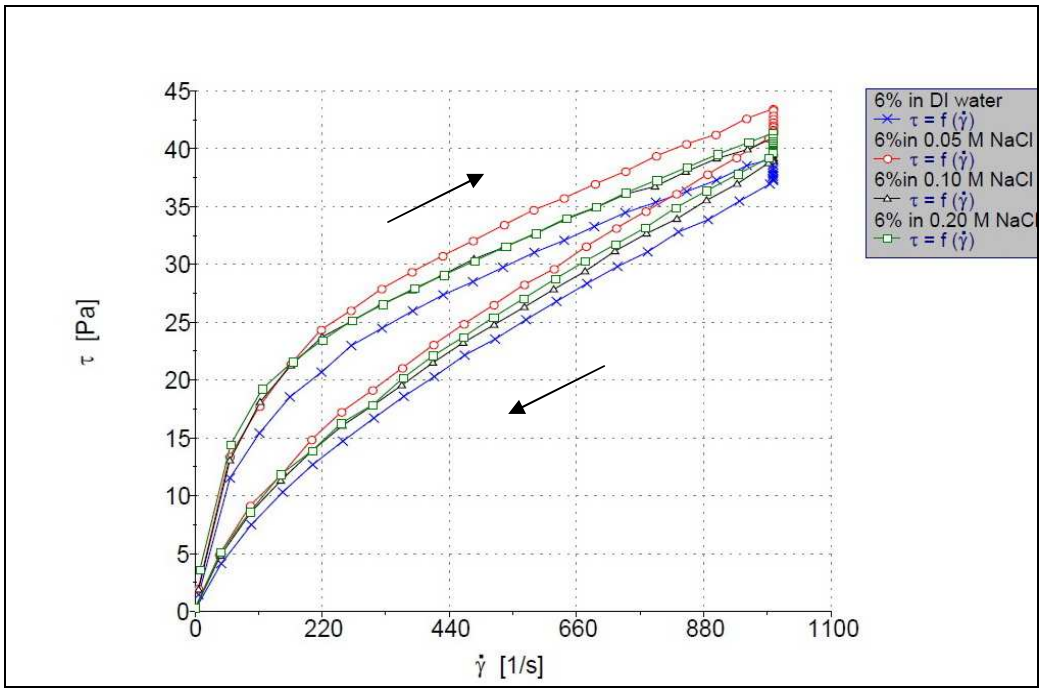


Figure 18 The rheograms of 5.0% substitution PCHS in various concentrations of sodium chloride comparing with DI water.

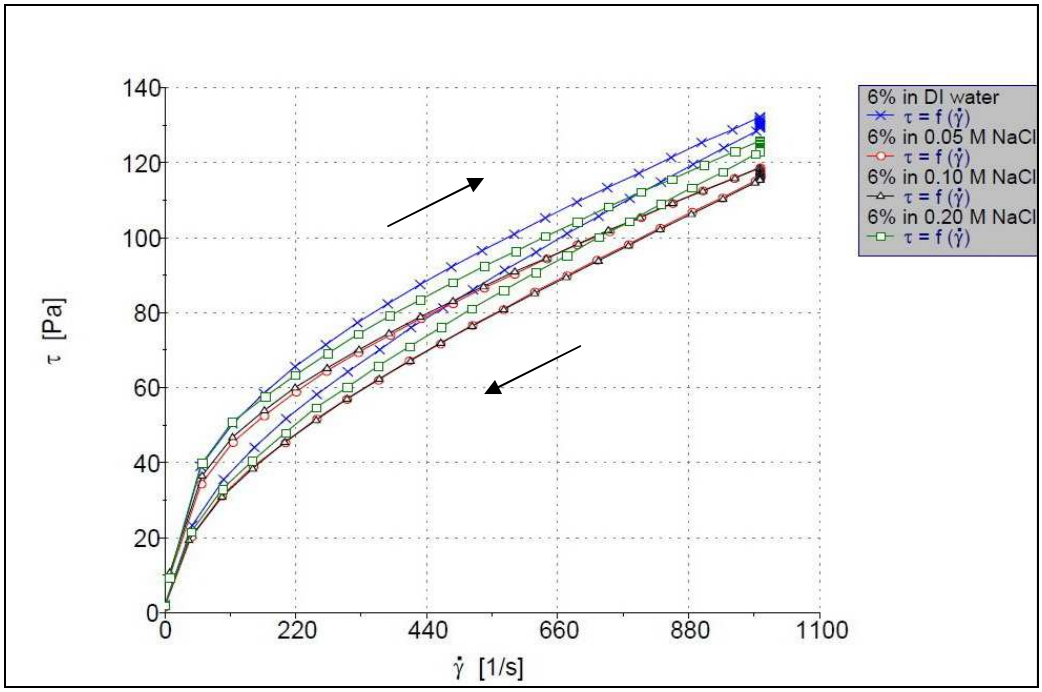


Figure 19 The rheograms of 7.5% substitution PCHS in various concentrations of sodium chloride comparing with DI water.

2.5.2 Effect of pH

Phosphate buffer solution pH 6.8 and 0.1 M HCl solution were used as media by comparing with DI water. The rheograms of all PCHS are shown in Figure 20, 21 and 4. The flow behavior of PCHS exhibited thixotropic plastic flow pattern. The rheograms of 2.5, 5.0 and 7.5% substitution PCHS in various pH media presented rheograms similar to of those in DI water. In this way, it was demonstrated that the pH of media had not changed the flow patterns of PCHS.

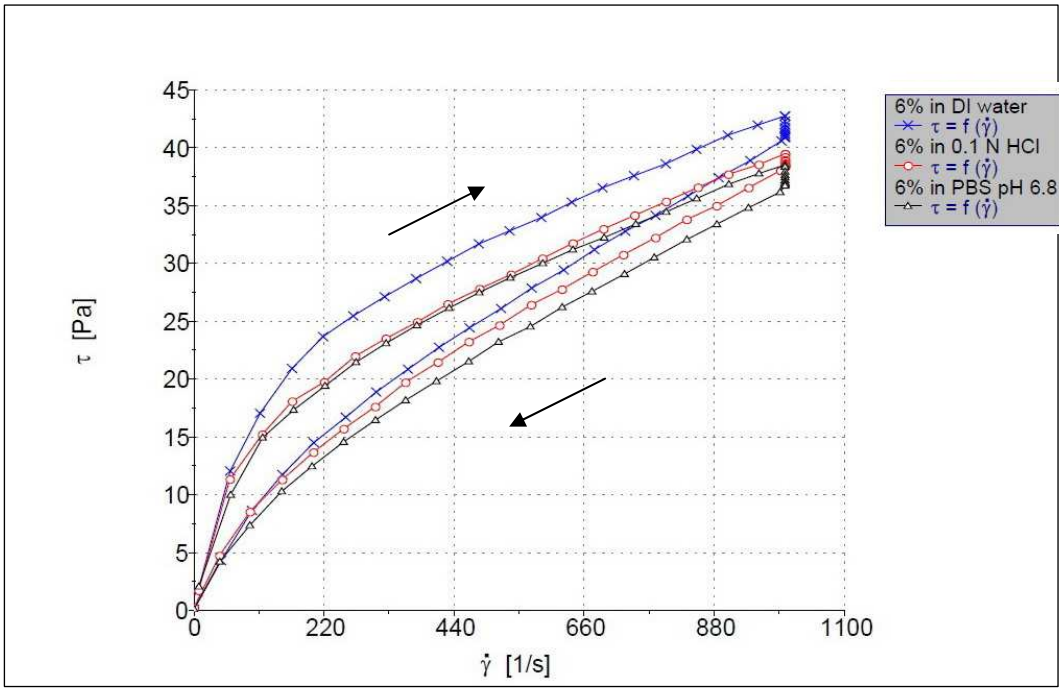


Figure 20 The rheograms of 2.5% substitution PCHS in various pH of media comparing with DI water.

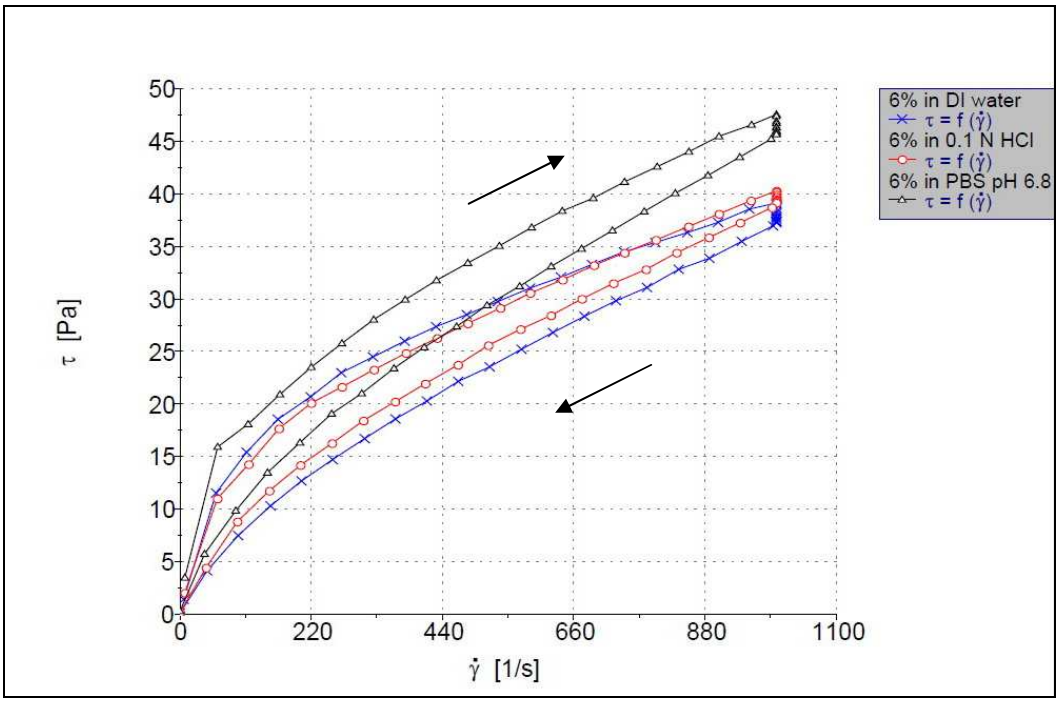


Figure 21 The rheograms of 5.0% substitution PCHS in various pH of media comparing with DI water.

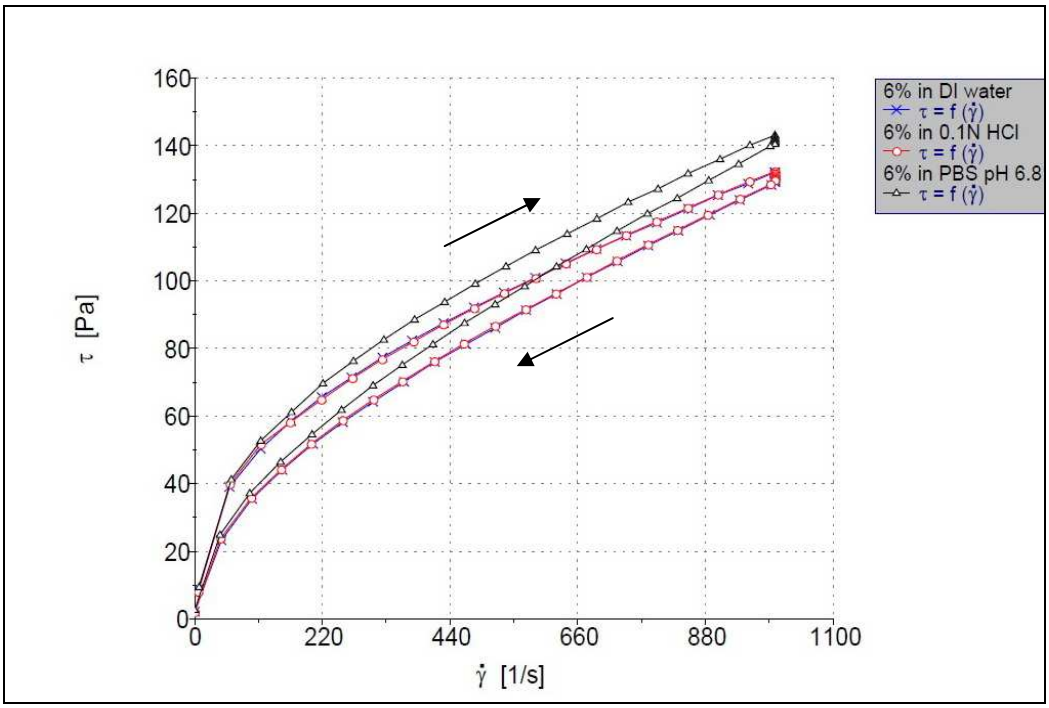


Figure 22 The rheograms of 7.5% substitution PCHS in various pH of media comparing with DI water.

The rheogram of three concentrations (4, 5 and 6%) of all PCHS in various media are shown in Figure 23 to 28, the result illustrated that shear stress and shear rate were increased when concentration of PCHS increased. Furthermore the 6% w/v concentration of PCHS gave the highest shear stress and shear rate in every media.

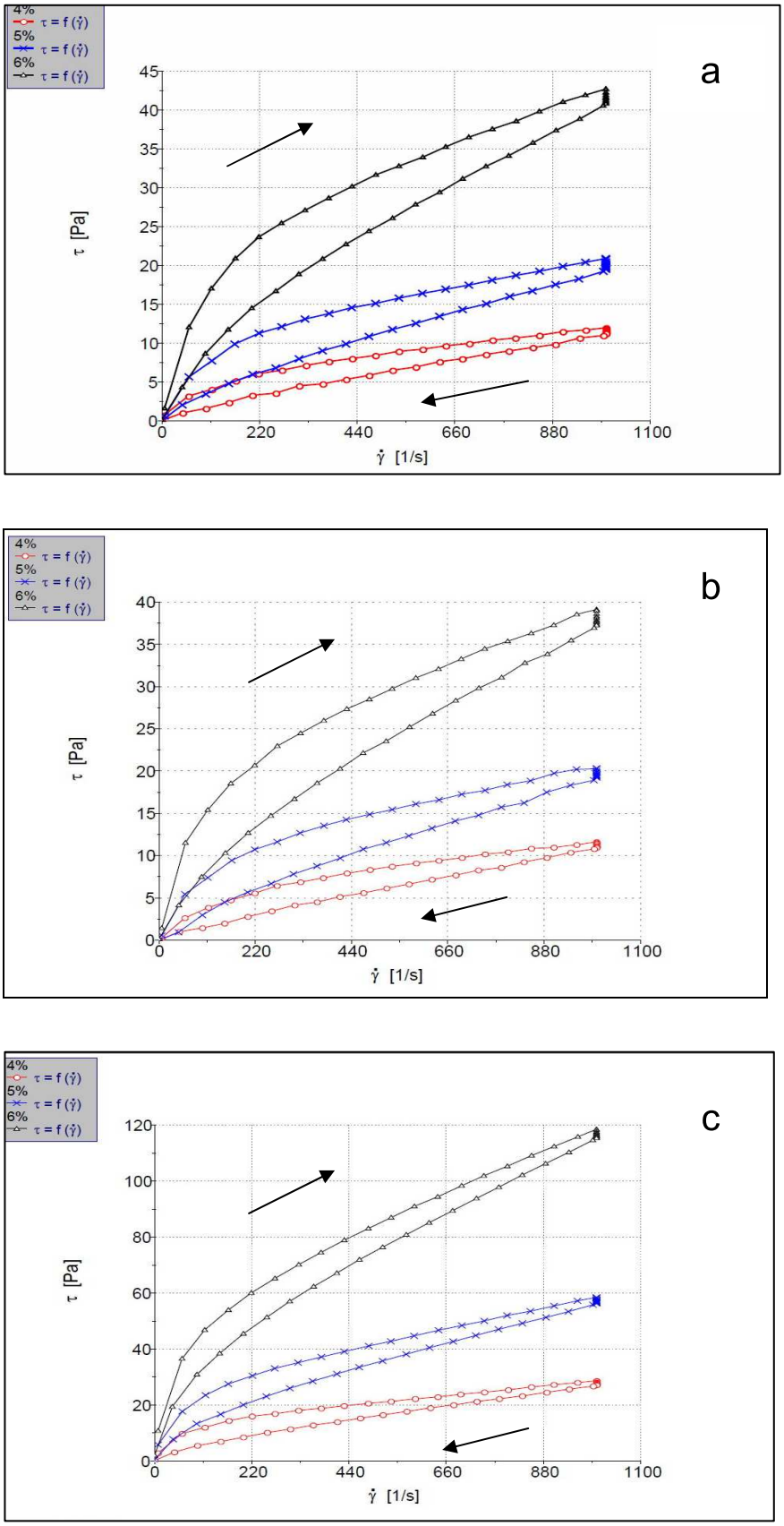


Figure 23 The rheograms of 2.5(a), 5.0(b), 7.5%(c) substitution PCHS in various concentrations in DI water.

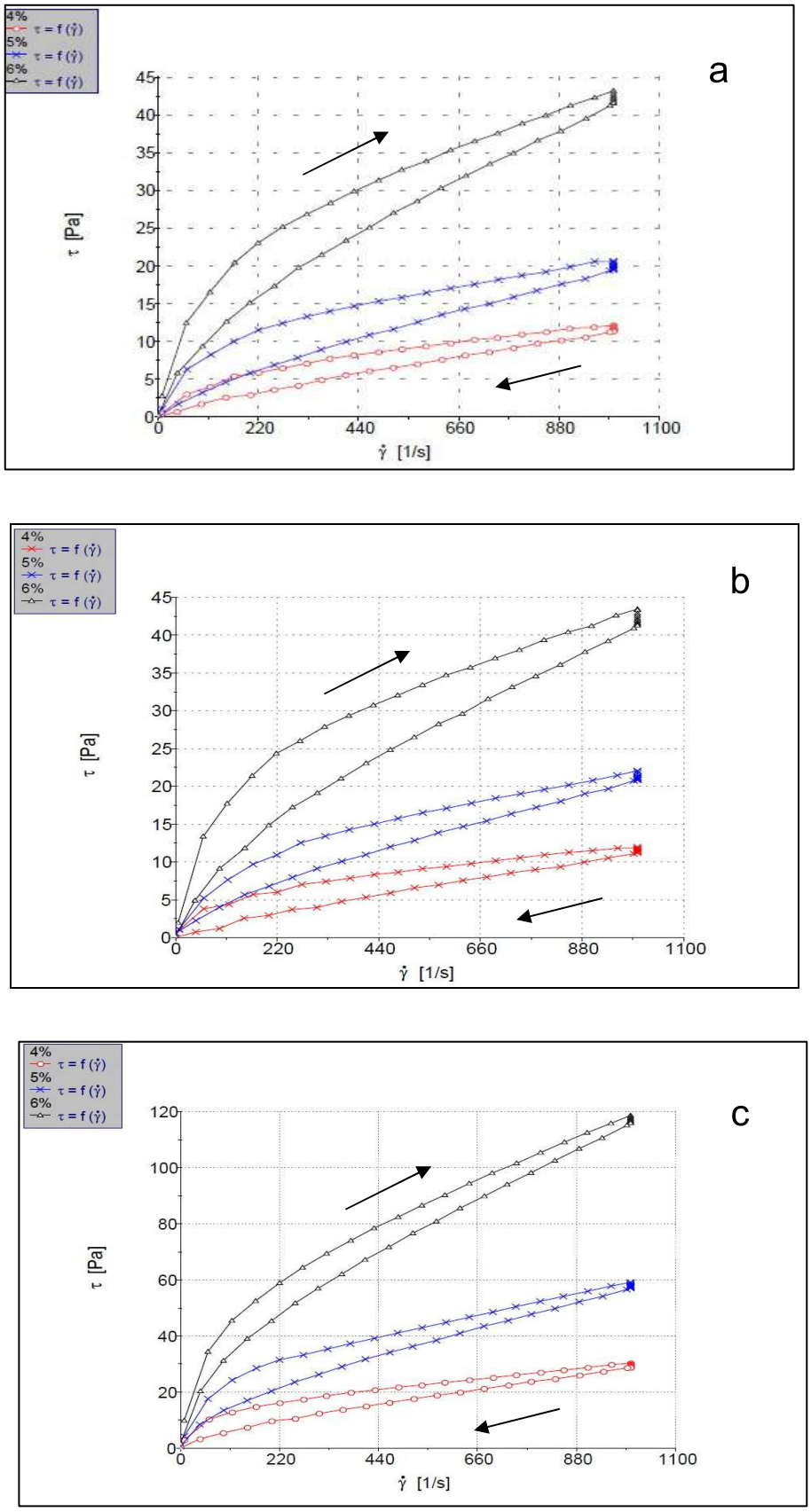


Figure 24 The rheograms of 2.5(a), 5.0(b), 7.5%(c) substitution PCHS in various concentrations in 0.05 M NaCl solution.

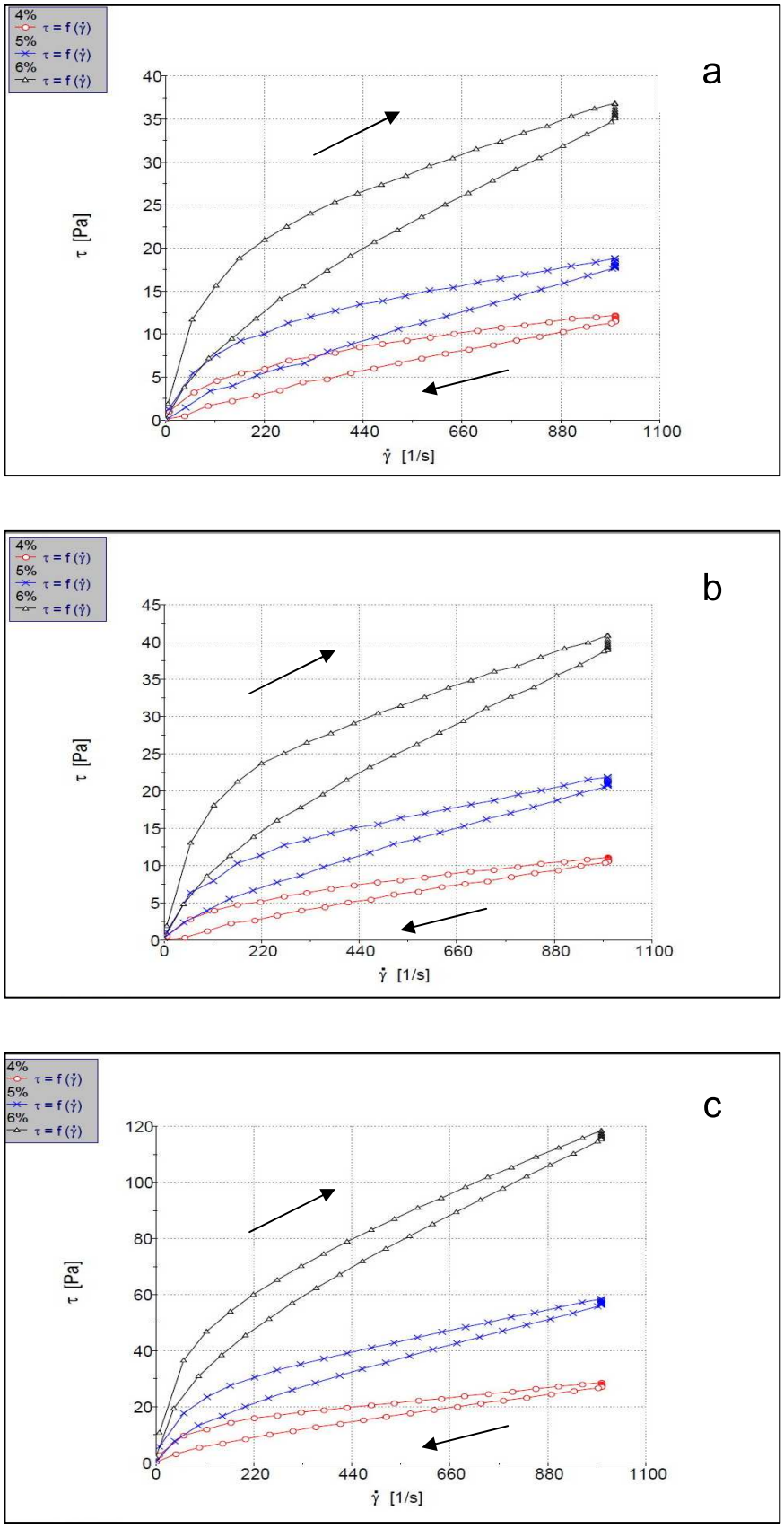


Figure 25 The rheograms of 2.5(a), 5.0(b), 7.5%(c) substitution PCHS in various concentrations in 0.10 M NaCl solution.

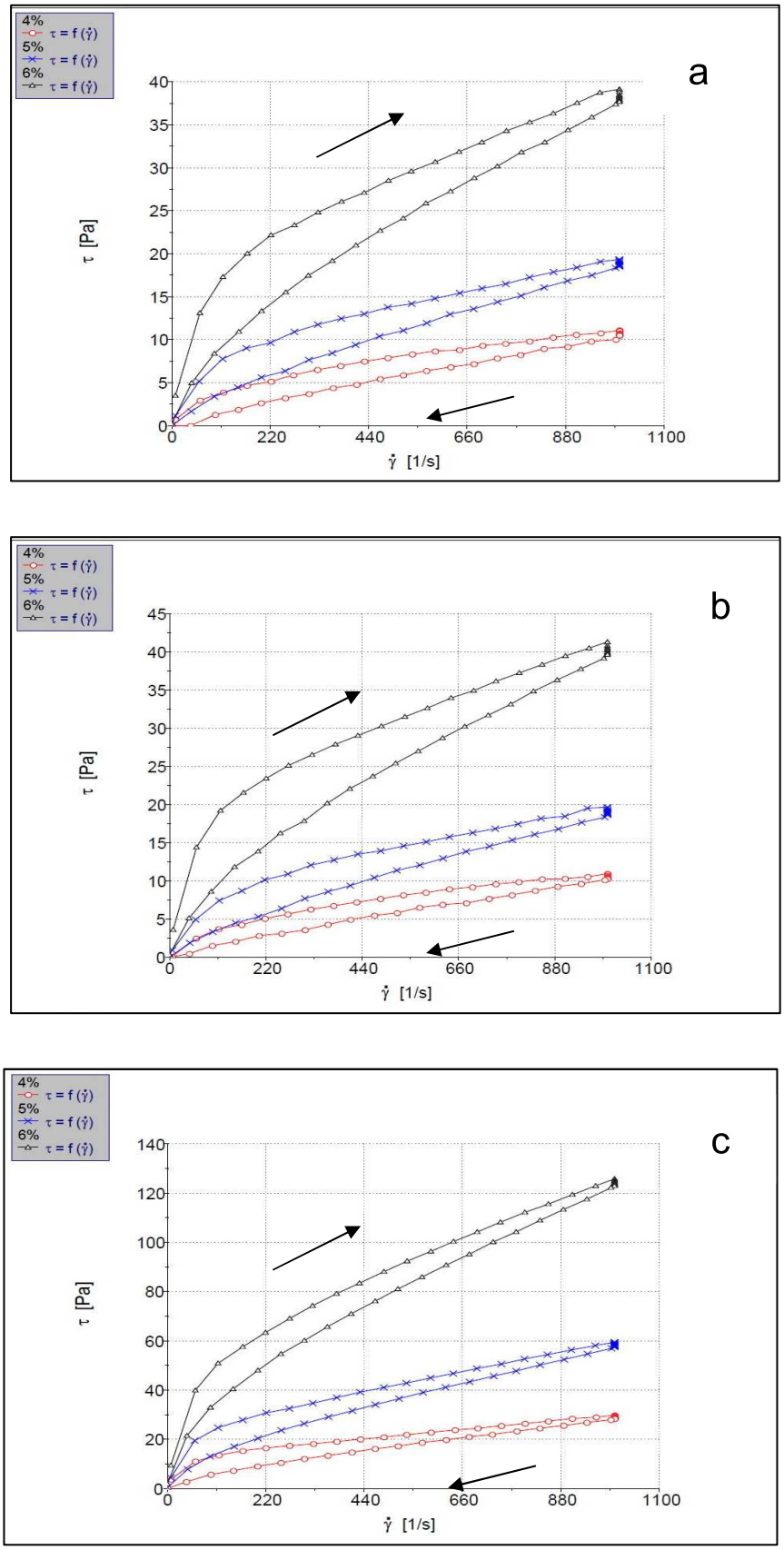


Figure 26 The rheograms of 2.5(a), 5.0(b), 7.5%(c)substitution PCHS in various concentrations in 0.20 M NaCl solution.

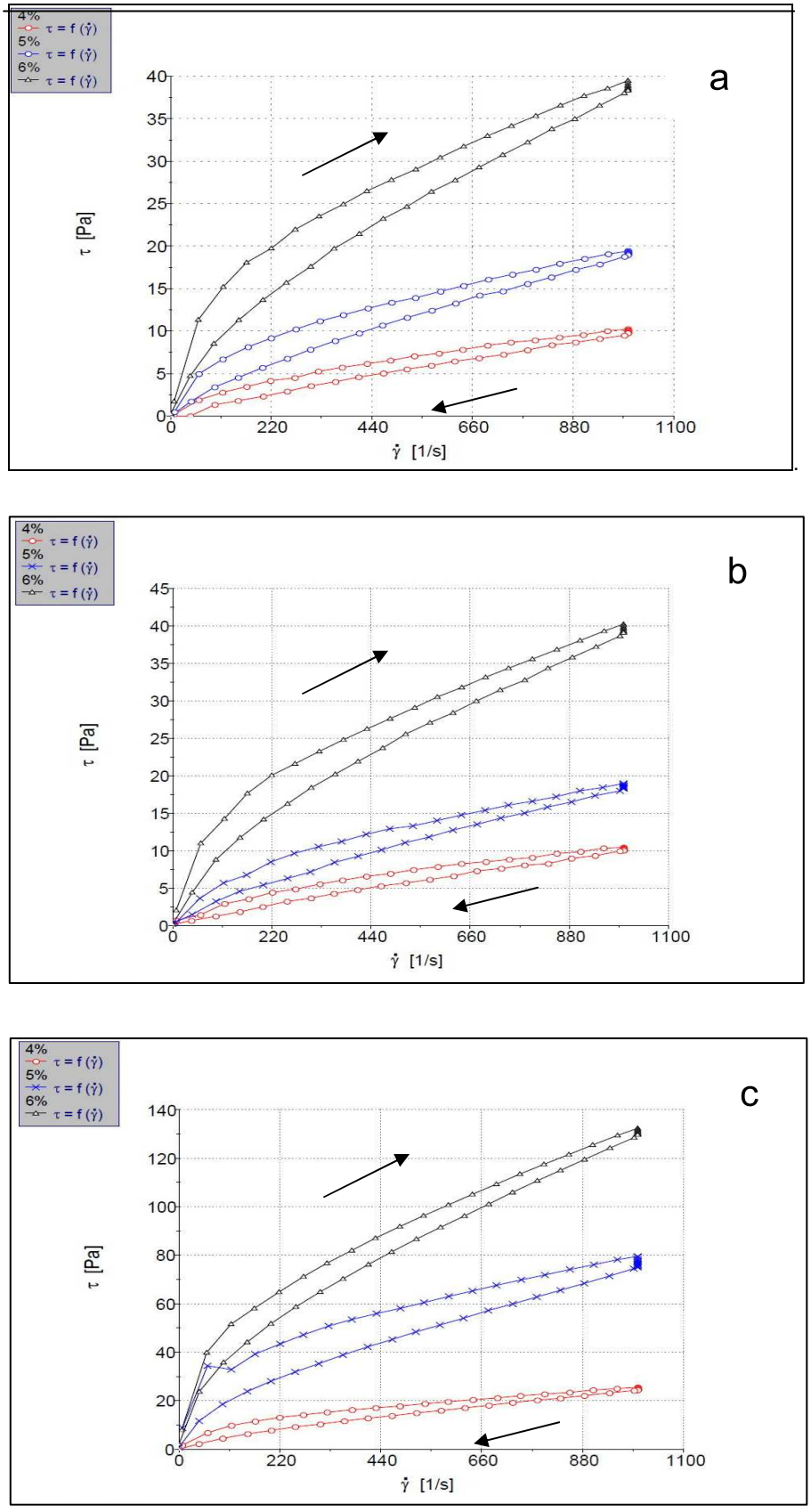


Figure 27 The rheograms of 2.5(a), 5.0(b), 7.5%(c)substitution PCHS in various concentrations in 0.1 N HCl solution.

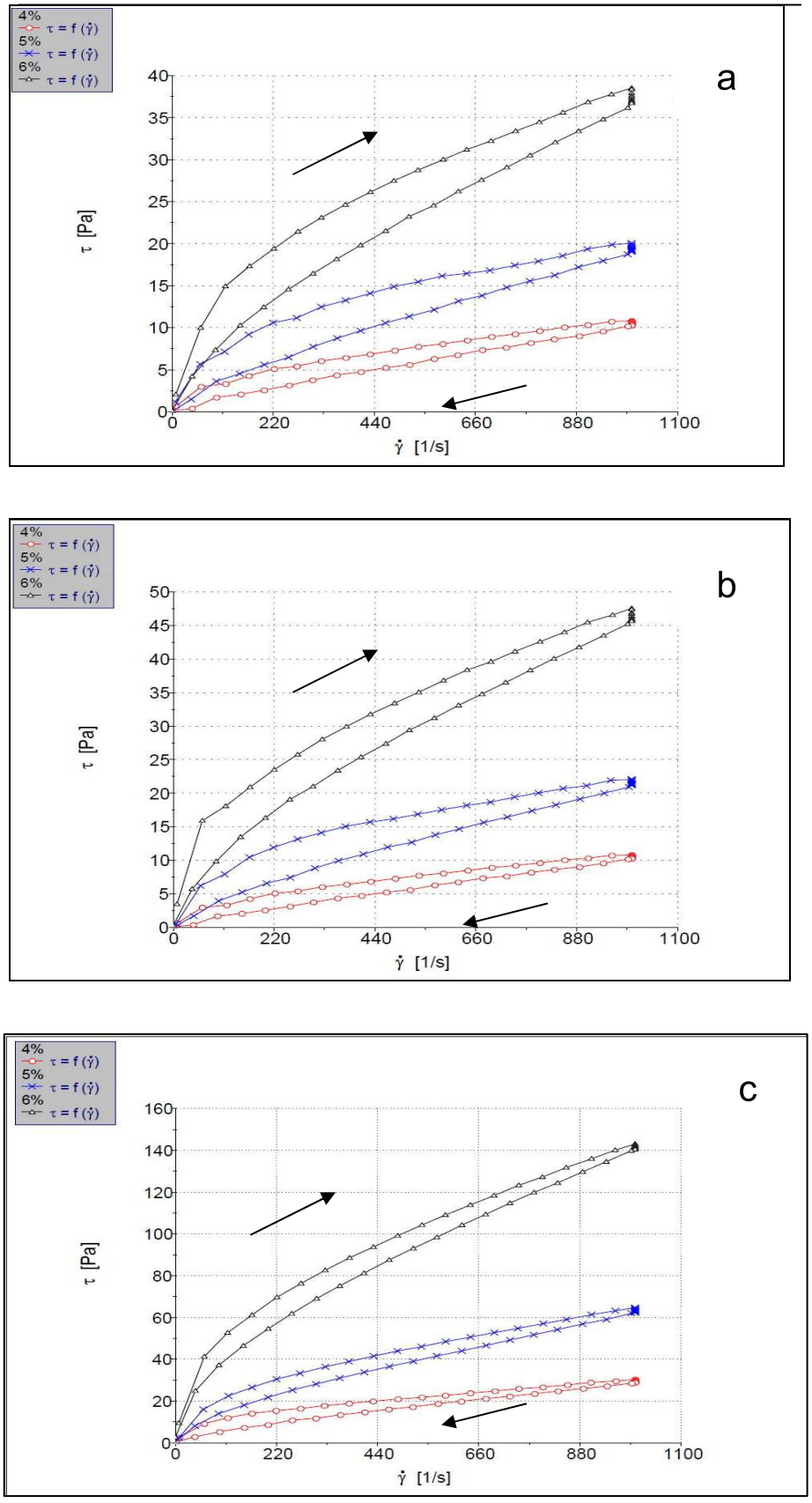


Figure 28 The rheograms of 2.5(a), 5.0(b), 7.5%(c) substitution PCHS in various concentrations in PBS pH 6.8.

2.6 Swelling Power (SP)

The swelling power was studied at room temperature and 37°C in various ionic strength and pH media.

Swelling power of all PCHS at room temperature and 37°C in all media were higher than unmodified tapioca starch. The swelling power of unmodified tapioca starch was around twofold increase, whereas PCHS (all substituted levels) were ranged from sevenfolds to elevenfolds and the 7.5% substitution PCHS gave the highest swelling power at room temperature and 37°C (Table 4-5 to 4-8), due to the 7.5% substitution PCHS has the most of hydroxypropyl groups in structure, hydroxypropyl groups are hydrophilic in nature and when introduced into the starch granule, decreased strength of starch intra-bonds structure holding granule together and reduced pasting temperature therefore, the higher the level of hydroxypropyl substitution, the lower pasting temperature until the product become cold water swelling (Wurzburg, 1986).

2.6.1 Effect of electrolyte

Sodium chloride solutions at concentration of 0.05, 0.10 and 0.20 M were used as the representative solution ionic strength of 0.05, 0.10 and 0.20 M, respectively,

All of PCHS showed better swelling property because hydroxypropyl groups in their structure renders a hydrophilic character by making a weaken internal bond structure which holds the granules together and then molecule of H_2O be able to form bonds easily. Moreover, the cross-links in hydroxypropyl distarch phosphate they show resistance to alkali-acidic condition and tolerance to various ionic strength.

As shown in Table 16, at the same percent of substitution, the PCHS showed slightly different swelling power in various ionic strength media. The SP of native starch displayed about twofold increase while the PCHS at 2.5% and 5.0% substitution demonstrated about ninefold increase. However, the SP of 7.5% substitution of PCHS was shown slightly higher SP than the others which presented approximately ninefold to elevenfold Accordingly, it could be indicated that ionic strength did not altered on SP of matrix.

Table 16 Swelling power all of PCHS and native starch in various ionic strength at room temperature (± SD, n=3)

Type of starch	DI water	0.05 M NaCl	0.10 M NaCl	0.20 M NaCl
Native starch	2.17(0.09)	2.03(0.15)	2.07(0.18)	2.17(0.25)
2.5% substitution	9.63(0.11)	9.37(0.26)	9.24(0.20)	9.10(0.27)
5.0% substitution	9.64(0.17)	9.03(0.29)	9.20(0.18)	9.41(0.11)
7.5% substitution	9.94(0.31)	11.42(0.14)	11.74(0.36)	9.59(0.13)

2.6.2 Effect of pH of medium

Phosphate buffer solution pH 6.8 and 0.1 N HCl solution were used as a medium in this experiment.

The SP in various pH are shown in Table 17, the SP of unmodified starch was ranged from onefold to twofold while all of PCHS showed sevenfold to ninefold. The SP of PCHS at every substituted levels in distilled water and in 0.1 N HCl solution were similar (about ninefold increase) but in the phosphate buffer solution pH 6.8, the PCHS presented a slightly decreased of SP (around sevenfold to eightfold). It might be due to the pH of medium likes phosphate buffer solution pH 6.8 slightly influenced SP of PCHS.

Table 17 Swelling power all of PCHS and native starch in various pH at room temperature (± SD, n=3)

Type of starch	DI water	0.1 N HCl	PBS pH 6.8
Native starch	2.17(0.08)	1.81(0.12)	1.99(0.11)
2.5% substitution	9.63(0.15)	9.98(0.34)	7.68(0.18)
5.0% substitution	9.64(0.16)	9.07(0.21)	8.88(0.24)
7.5% substitution	9.94(0.12)	9.75(0.04)	8.92(0.17)

2.6.3 Effect of temperature

The swelling power of 2.5, 5.0 and 7.5% substitution PCHS at 37 °C in various ionic strength and pH media are shown in Table 18 and 19. The SP did not alter when the temperature was increased. Considering the effect of temperature on SP of PCHS, it was indicated that changing temperature from room temperature to 37°C had no effect on SP.

Table 18 Swelling power all of PCHS and native starch in various ionic strength at 37°C (± SD, n=3)

Type of starch	DI water	0.05 M NaCl	0.10 M NaCl	0.20 M NaCl
Native starch	2.00(0.04)	2.11(0.17)	2.22(0.21)	2.16(0.09)
2.5% substitution	9.59(0.11)	9.30(0.11)	8.36(0.09)	9.86(0.16)
5.0% substitution	9.78(0.19)	9.41(0.17)	9.40(0.14)	9.43(0.27)
7.5% substitution	11.25(0.16)	10.90(0.22)	10.26(0.17)	11.15(0.07)

Table 19 Swelling power all of PCHS and native starch in various pH at 37°C (± SD,n=3)

Type of starch	DI water	0.1 N HCl	PBS pH 6.8
Native starch	2.00(0.15)	2.09(0.05)	1.46(0.14)
2.5% substitution	9.59(0.12)	9.57(0.09)	7.70(0.26)
5.0% substitution	9.78(0.10)	9.36(0.15)	8.15(0.23)
7.5% substitution	11.25(0.21)	10.16(0.15)	8.47(0.19)

In conclusion, all PCHS exhibits better swelling, dispersing and no effect from electrolyte and pH media on swelling at 37 °C and room temperature, in accordance with the previous study on viscosity properties. It might say that effects of hydroxypropylation on the physico-chemical properties of starches are consistent with an overall reduction in bonding between the starch chains and a consequent increase in the ease of hydration of the starch granule (Singh, 2003), resulting in a significant increased swelling and solubility of starch. Cross-linked reaction improved the intergrity of swollen granules and caused resistance of starch granule to acid, alkaline,

electrolytes, temperature and shear. Moreover, pregelatinization of starch was a process that breaks down the intermolecular bonds of starch molecules in the presence of water and heat, allowing the hydrogen bonding sites to engage more water, rendered the PCHS granules ability to disperse and swell in cold water.

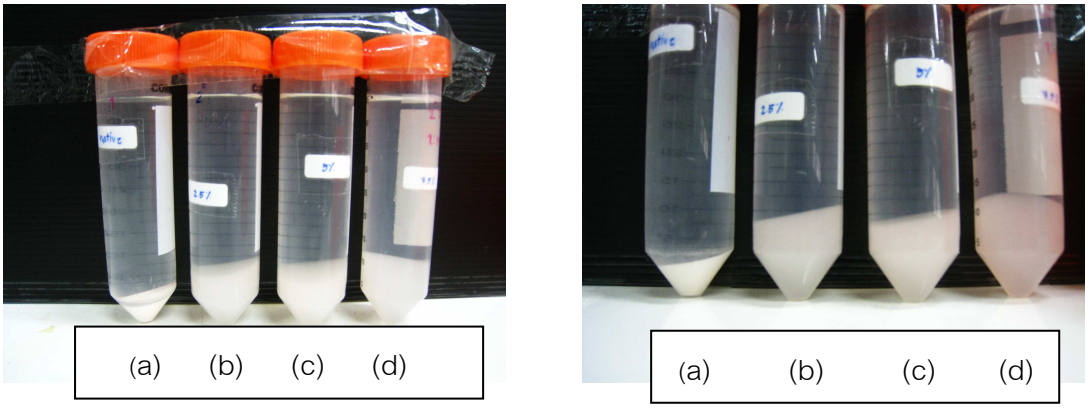


Figure 29 Swelling power of native starch (a), 2.5% substitution PCHS (b), 5.0% substitution PCHS (c), 7.5% substitution PCHS (d) in DI water at room temperature.

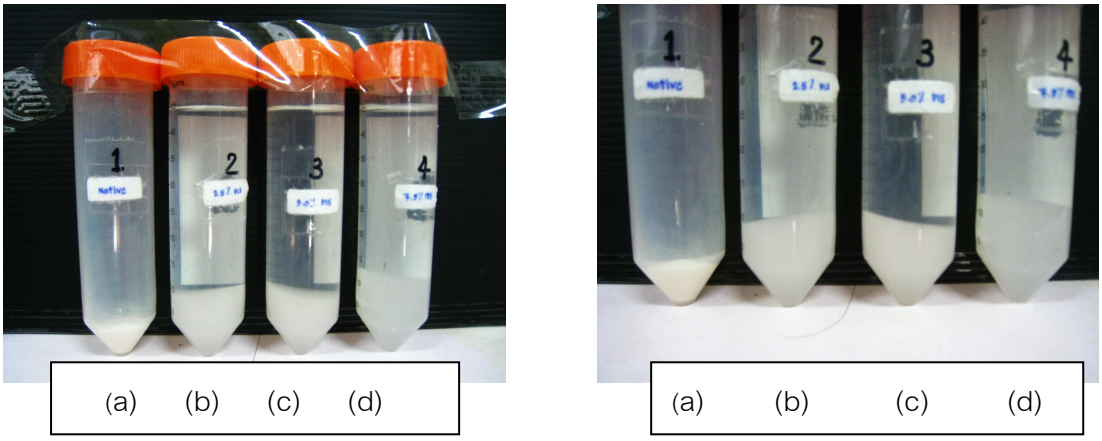


Figure 30 Swelling power of native starch (a), 2.5% substitution PCHS (b), 5.0% substitution PCHS (c), 7.5% substitution PCHS (d) in DI water at 37 °C.

3. Preparation Matrix of Propranolol Hydrochloride Tablet

According to physico-chemical properties from preliminary studied (viscosity, swelling power and rheology properties), indicated that modified starch by substituted with 7.5% propylene oxide followed by cross-linked with 0.1% sodium trimetaphosphate and pegelatinization which provided the highest viscosity and swelling power of PCHS. Therefore, the 7.5% substitution PCHS was selected to prepare propranolol hydrochloride matrix tablet for studying effects of ionic strength, pH, compression forces, methods of dissolution test on drug release continually.

4. Evaluation Matrix of Propranolol Hydrochloride Tablet (Preliminary Studied)

4.1 Determination of hardness and tablet friability

4.1.1Direct compression method

Direct compression method of all formulations (blank1, blank 2 and F1-F7) which varied the amount of polymers and diluents (PCHS, lactose, dibasic calcium phosphate, PVP K 30 and K90), showed very low matrix hardness and highly friable that could not compressed to matrix tablet. Accordingly, they were unsuitable for using to prepare sustained release matrix by direct compression.

4.1.2 Wet granulation method

The tablets of PCHS which manufactured by using direct compression method reported highly friable and low matrix hardness, although the binders were added to improve compactability of matrix. Therefore, the process of manufacture was changed to wet granulation method. It was found that the tablets prepared using wet granulation method demonstrated the decrease of friability and increase of matrix hardness, but it did not form gel of matrix that could prolong drug release in dissolution testing. Therefore, it could imply that the PCHS couldn't use as an exipient for sustained release matrix by itself. However, the formulations which added 5 and 10% of

HPMC E4M combined with PCHS and 5% of PVP K 90 provided good handling properties for sustained release dosage form (as a result presented in Table 20).

Table 20 Physical properties and drug content of propranolol hydrochloride matrix prepared using wet granulation method at compression force 3000 psi.

Formulation	Physical properties of matrix			
	Hardness (kg/cm^2) n=10	% Friability n=20	% Drug content n=3	±SD
F8	11.25(0.71)	0.38	98.33	0.023
F9	11.29(0.77)	0.38	99.71	0.019
F10	13.02(1.07)	0.36	96.42	0.024
F11	11.22(0.66)	0.19	102.06	0.026
F12	13.12(1.17)	0.18	101.06	0.017
F13	12.45(0.86)	0.11	98.56	0.019
F14	13.72(0.50)	0.1	101.28	0.011
F15	12.99(0.75)	0.17	97.08	0.033
F16	13.73(0.50)	0.11	99.34	0.023

Figure 31 displays the PCHS matrix of propranolol hydrochloride tablets after compressed by hydraulic pressure equipment, with 3/8-inch diameter round flat faced punch and die set. The compression forces were 3000 psi. Each total weight of tablet was 300 mg.

Figure 31 The PCHS matrix of propranolol hydrochloride tablets (F16) after compressed by hydraulic pressure at 3000 psi.

4.2 Determination of tablet disintegration

Disintegration time of F16 was observed at 15 min and 1 hrs. It was found that all of six tablets were not disintegrated after 1 hour testing. (Figure 32)

(a) (b)

Figure 32 Images of disintegration of propranolol hydrochloride matrix (F16) at compression force 3000 psi. (a) after 15 minutes (b) after 1 hour testing.

4.3 Determination of drug released from matrix

4.3.1 Dissolution study of matrix (for all formulations)

In this study, it was found that the formulation of F8 which had only PCHS in the formulation and F9, F10 which added diluents such as lactose and dibasic calcium phosphate for increase compactability, did not form gel of matrix and disintegrated when contacted with medium that was similar to the formulations which manufactured using direct compression method. In the formulations of F11, F12, the quantity of PCHS was replaced by HPMC E4M and combined with lactose (F11) or dibasic calcium phosphate (F12) respectively. As a result, the F11 prolonged drug releasing for 7 hrs. while the F12 prolonged drug release up to 12 hrs. Due to the diluents in F 11 consisted of lactose that is soluble diluent in DI water but dibasic calcium phosphate is insoluble (F12).Therefore, the F11 showed faster drug release than F12. Nevertheless, when the 5 and 10% of HPMC E4M was used combine with 45 % of PCHS (F13,F14) and 40 % of PCHS (F15, F16), it was shown that only the F16 (consisted of 10% HPMC E4M, 40 % PCHS, dibasic calcium phosphate) could extend drug release through 12 hrs. That was similar to the release of F12 which consisted of

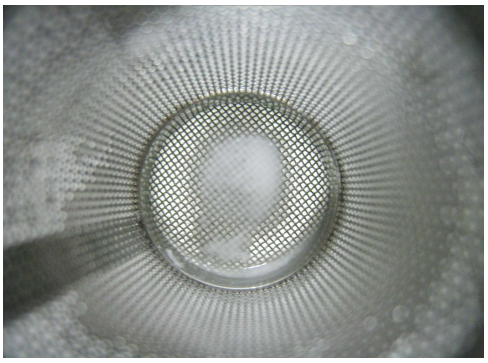
only HPMC E4M (consisted of 50% HPMC E4M) for used as matrix diluent in the formulation. Therefore, it might say that the PCHS could partly replace HPMC E4M for using to prepare sustained release matrix.

Figure 33 Image of propranolol hydrochloride matrix (F16) which prepared by using compression force 3000 PSI, after and before dissolution testing for 12 hrs. in DI water.

Table 21 The dissolution time and percent drug release of formulation of F8-16 in DI water

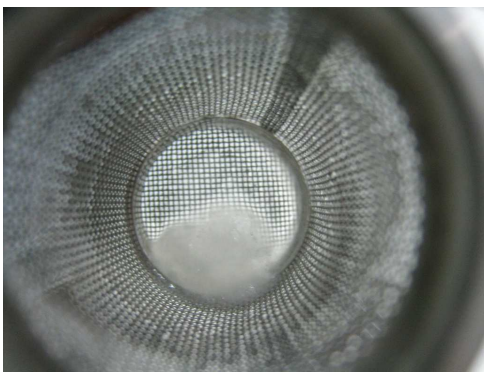
Formulation	Dissolution time(hr.)	% Drug release
F8	-	-
F9	-	-
F10	-	-
F11	7	92.21
F12	12	84.49
F13	7	94.19
F14	8	89.85
F15	7	96.22
F16	12	86.92

The images of propranolol hydrochloride matrix after dissolution testing that manufactured by using wet granulation method (F8-F16) are shown in Figure 34. After dissolution test for 12 hrs. in distilled water, the rapid erosion of the formulation 8, 9 and 10 may be due to the PCHS couldn't form the gel of matrix by itself. The dissolution medium penetrated into the matrix tablets rendered the matrix tablets disintegrated before the obstructive gel was formed. Therefore, formulation 8, 9 and 10 did not have sustained release property. For F11 and F12, The HPMC E4M that combined with lactose or dibasic calcium phosphate was used as a matrix diluents. Normally, the HPMC matrix hydrated upon contact with water and rate controlling gel layer form around the solid inner core. The drug release in soluble drug is controlled by the rate of diffusion though a gel (Takka, et al., 2001). In this study, 50% HPMC E4M combined with dibasic calcium phosphate (F12) presented 85.38% of drug release within 12 hrs. The combination of PCHS with 5-10% of HPMC E4M in formulation of 13, 14, 15 and 16, illustrated an improvement of sustain release property of matrix tablets when comparing with F 8, 9 and 10. The retarding effect was probably caused by adding HPMC E4M to PCHS increased the viscosity and intergrity of gel network.

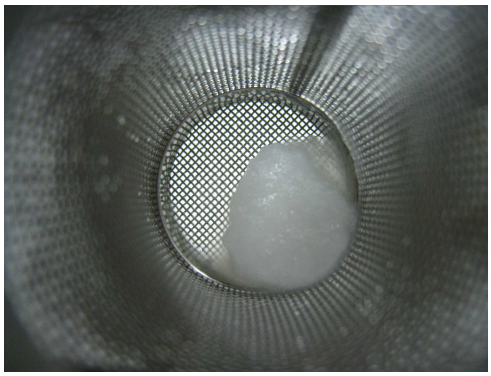


(F8)

(F9)

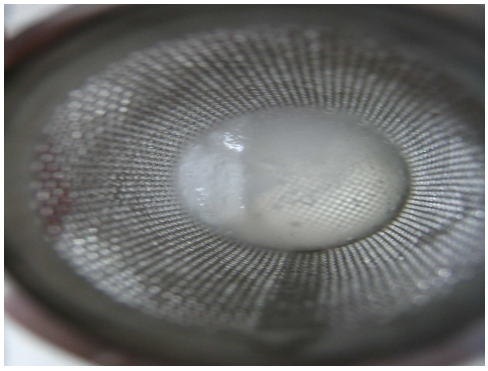


(F10)



(F11)

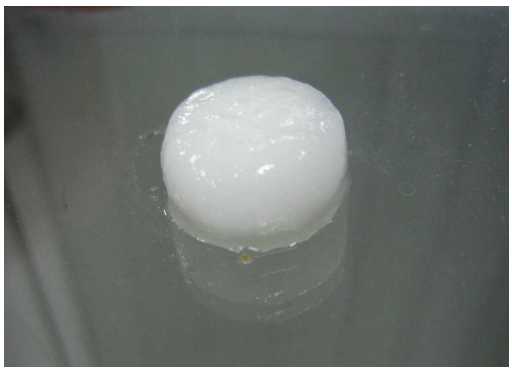
(F12)



(F13)

(F 14)

(F15)



(F16)

Figure 34 Images of propranolol hydrochloride matrix, formulation F8-F16 after finishing dissolution testing for 12 hrs in DI water.

Arise from hydrophilic HPMC matrix systems are widely used for designing oral controlled drug release dosage forms, and in this experiment, the F16 (composed of HPMC E4M : PCHS at ratio 1:4) could prolong drug release for 12 hrs (86.36% drug release) that similar to drug release of F12 which contained only HPMC E4M in the formula (85.38% drug release). Therefore, the F16 was selected to investigate the effects of media, compression forces and methods of dissolution on drug release.

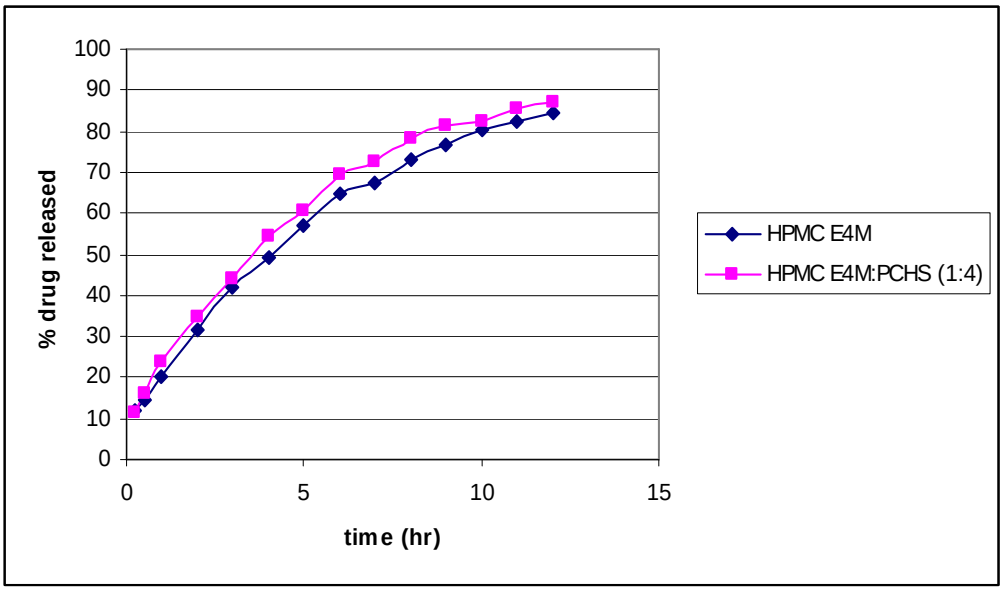


Figure 35 The release profile of propranolol hydrochloride comparing HPMC E4M matrix (F12) with HPMC E4M : PCHS matrix (F16) at compression force 3000 psi. in DI water.

4.3.2 Dissolution test of formulation (only F16)

The aim of experiment is to study the effects of dissolution media, compression forces and methods of dissolution test on drug released. The profiles of dissolution were constructed by plotting cumulative percentage of drug released against time.

Effect of medium ionic strength

In this study, the ionic strength medium were prepared by using NaCl solutions in concentration of 0.05, 0.10 and 0.20 M, giving ionic strengths of 0.05, 0.10 and 0.20, respectively.

The influence of ionic strength of the media on dissolution are shown in Figure 36, 37 and 38. The matrix of propranolol hydrochloride tablets were prepared by using compression force at 1000, 2000 and 3000 psi. The various media, such as, distilled water, 0.5 M, 0.10 M and 0.20 M NaCl solution were used as dissolution media. The percent drug release of matrix prepared using compression force of 1000 psi in distilled water, 0.5 M, 0.10 M and 0.20 M NaCl solution in 12 hrs showed 92.64, 87.97, 87.13 and 79.08%, respectively. It could imply that the release of the drug in 12 hrs. decreased when ionic strength of medium was increased. Especially, in 0.2 M NaCl solution, the release of the drug was decreased significantly when compared to in distilled water, which the result was consistent with the release of the drug of matrix prepared using compression force of 2000 and 3000 psi. The compression force of 2000 psi which demonstrated percent of drug release in 12 hrs were 89.50, 86.42, 85.84, and 80.39% in distilled water, 0.05 M, 0.10, 0.20 M NaCl solution, respectively.The percent of drug release of compression force of 3,000 psi were 88.95, 87.92, 87.09 and 78.19% in distilled water, 0.05, 0.10, 0.20 M NaCl solution, respectively. As a results, the dissolution test in12 hrs gave the highest percent of drug release in distilled water, but slightly lower in 0.05 and 0.10 M NaCl solution. As it was shown, the dilute saline had no effect on drug released. However, at the high ionic strength medium like 0.2 M NaCl solution illustrated decrease percent release of propranolol hydrochloride from the matrix.

From the previous study, the swelling power of PCHS was not affected by ionic strength of media. Normally, the drug solubility is one of the factors which affected drug release. Therefore, this may imply that percent of drug released depends on the solubility of propranolol hydrochloride in various media. The solubility of propranolol hydrochloride in distilled water, 0.05, 0.10 and 0.20 M NaCl solution media

are found to be 360, 296, 264 and 180 mg/ml. Consequently, when the concentration of NaCl solution was raised, the released of propranolol hydrochloride became lower. This was attributed to increase in concentration of NaCl solution providing decease solubility of drug. Then, it effected on decrease percent drug released from matrix of propranolol hydrochloride in dissolution media too. However, from this results, a slight differences in the percent drug release in 0.05 and 0.10 NaCl solution was not markly observed. This finding might be the less difference in ionic strength of dissolution media.

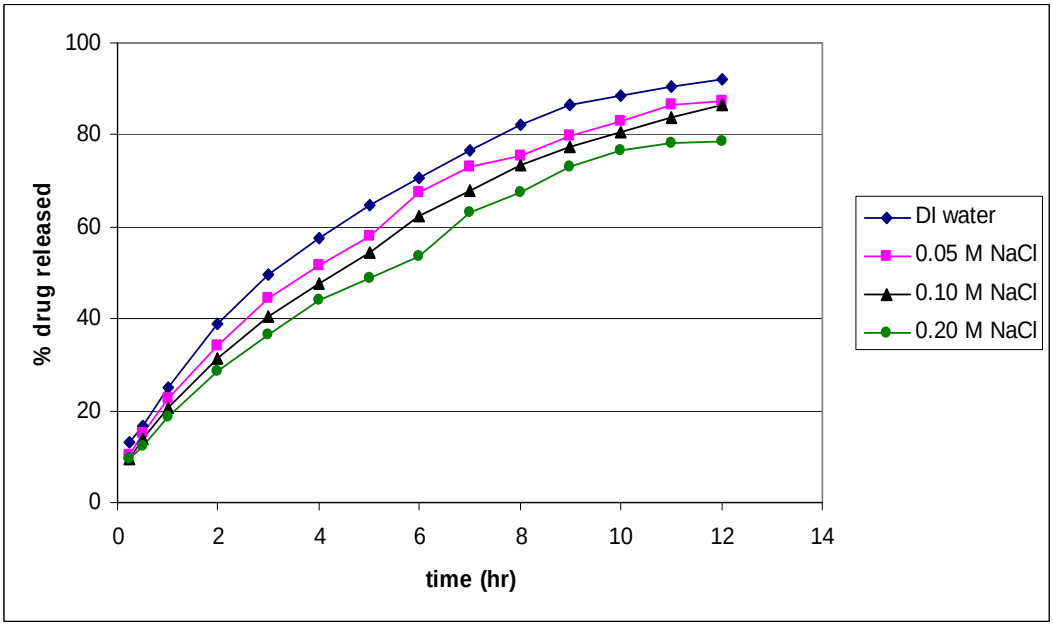


Figure 36 The release profiles of F16 prepared by using compression force 1000 psi in various ionic strength media.

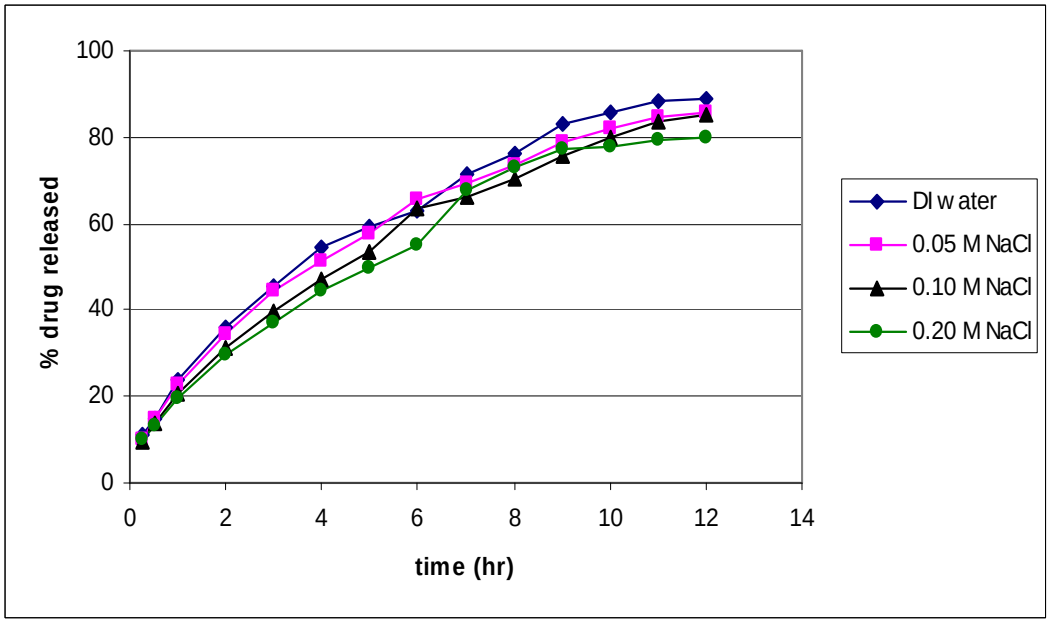


Figure 37 The release profiles of F16 prepared by using compression force 2000 psi in various ionic strength media.

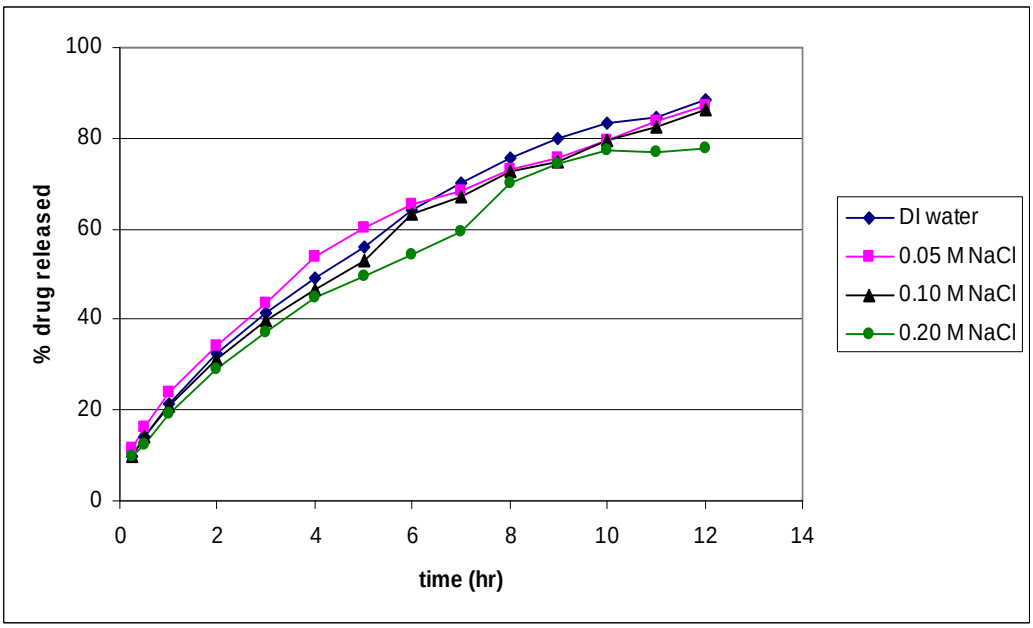


Figure 38 The release profiles of F16 prepared by using compression force 3000 psi in various ionic strength media.

For the comparison of dissolution profiles, similarity factor f_2 is gaining popularity due to its recommendation by various regulatory committees, for testing parameters of the dissolution medium.

As shown in Table 22, the value of similarity factors of drug release profiles in various ionic strength of media, at compaction force of 1000 psi. The release profile of propranolol hydrochloride in distilled water was used as standard reference of similarity test. The f_2 values of 0.05, 0.10 and 0.20 M NaCl media were 65.44, 55.37 and 45.50, respectively. It could indicate that the drug release profiles of 0.05 and 0.10 M NaCl media were quite similar to drug release profile of the reference medium (DI water) that providing the f_2 values more than 50. Conversely, The f_2 value was less than 50 in 0.20 M NaCl medium, which confirmed that the drug release profiles of PCHS matrix in 0.20 M NaCl solution was different from release profile of distilled water.

Table 22 The value of similarity factor of drug release profiles in various ionic strength of media at compaction force of 1000 psi.

Dissolution media	f_2
DI water VS 0.05 M NaCl	65.44
DI water VS 0.10 M NaCl	55.37
DI water VS 0.20 M NaCl	45.50

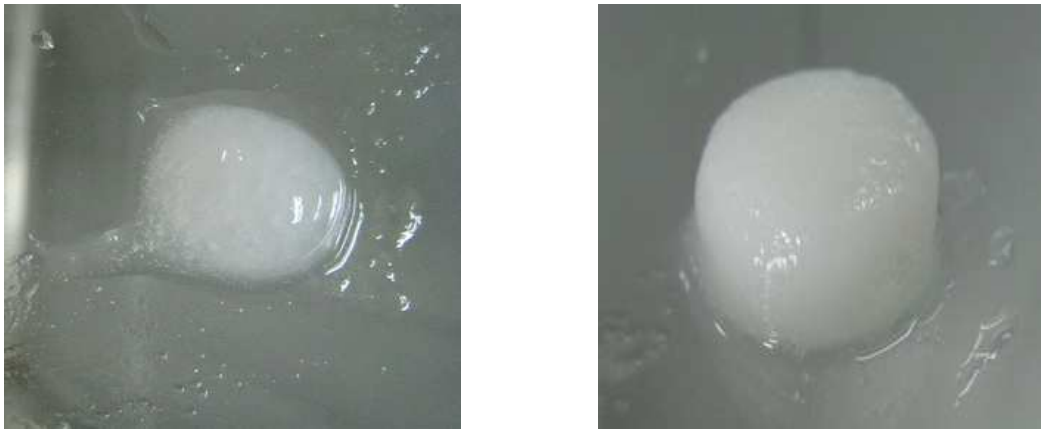
Effect of medium pH

In this case, 0.1 N HCl solution and phosphate buffer solution pH 6.8 were used as a different pH dissolution media.

The pH of the media affected on drug release from matrix of propranolol hydrochloride in dissolution test. The matrix tablets which prepared by using compression force of 1000 psi showed faster releasing in 0.1 N HCl solution medium than in distilled water and phosphate buffer solution pH 6.8 medium. Matrix of propranolol hydrochloride gave 90.57% of drug released within 8 hrs in 0.1 N HCl solution, whereas, 92.64% and 74.14% were released within 12 hrs in the distilled water

and phosphate buffer solution pH 6.8, respectively. Furthermore, the release rates were found to be almost the same for the different compression forces of 2000 and 3000 psi. The matrix tablets which prepared by using compression forces of 2000 and 3000 psi showed drug release of 91.36 and 90.16%, respectively, in 0.1 N HCl solution within 8 hours. While dissolution test in the distilled water and phosphate buffer solution pH 6.8 media of the matrix prepared by using compression force of 2000 psi gave 89.50 and 72.24% drug released, and the matrix which prepared using the compression force of 3000 psi gave 88.95 and 72.65% drug released in distilled water and phosphate buffer solution pH 6.8, respectively (as displayed in Figure 40, 41 and 42).

It was observed that even though the solubility is found to be 360 mg/ml in distilled water, 225 mg/ml in 0.1 N HCl solution and 130 mg/ml in phosphate buffer solution pH 6.8 (Takka, 2001). In acidic condition, hydrogen bond intra structure of PCHS might be brake up by acid hydrolysis reaction, so the gel layer of matrix eroded causing loss of matrix intergrity, resulting in rapid release than the other media. In general, the drug solubility is an important factor that affected the drug release. In this experiment, the solubility of propranolol in 0.1 N HCl medium was higher than in phosphate buffer solution pH 6.8 because of its basic nature. The higher release profile obtained with propranolol hydrochloride can be attributed to the rapid ionization and higher solubility of the drug in acidic medium. Increment of pH of the dissolution media reduced the extent of ionization and solubility of propranolol hydrochloride (Reza and Datta, 2005). Moreover, The slower release of propranolol hydrochloride in phosphate buffer solution pH 6.8 could explain by previous studied that the PCHS presented the lower of SP in phosphate buffer solution pH 6.8 than the other media. As a result, both the rate and extent of propranolol hydrochloride released from PCHS matrix was decreased in basic media. Accord with previous study (Uko-Nne et al., 1989 cite in Srinarong, 2000) refer to phosphate ions in dissolution medium caused the dehydration of cellulose ether. Heyman et al., 1938 (cite in Mitchell et al., 1990) mentioned that the reduction of drug released is explained by the ions which have a greater affinity than the polymer removing water from polymer and thus dehydrating polymer. Thus, it might say that the pH of dissolution media had effected on drug release from matrix of PCHS.



(a) (b)

Figure 39 Images of PCHS matrix (f16) after finished dissolution testing in 0.1 N HCl solution (a) in PBS pH 6.8 (b).

Dissolution profiles comparison of propranolol hydrochloride in various pH media using similarity factor (f_2), shown in Table 23. The value of similarity factor presented 32.32 that under acceptant value. Therefore, dissolution profiles of PCHS matrix in 0.1 N HCl solution medium and in phosphate buffer solution pH 6.8 were dissimilar.

Table 23 The value of similarity factor of drug release profiles in various pH of media at compaction force of 1000 psi.

Dissolution media	f_2
0.1 N HCl VS PBS pH 6.8	32.32

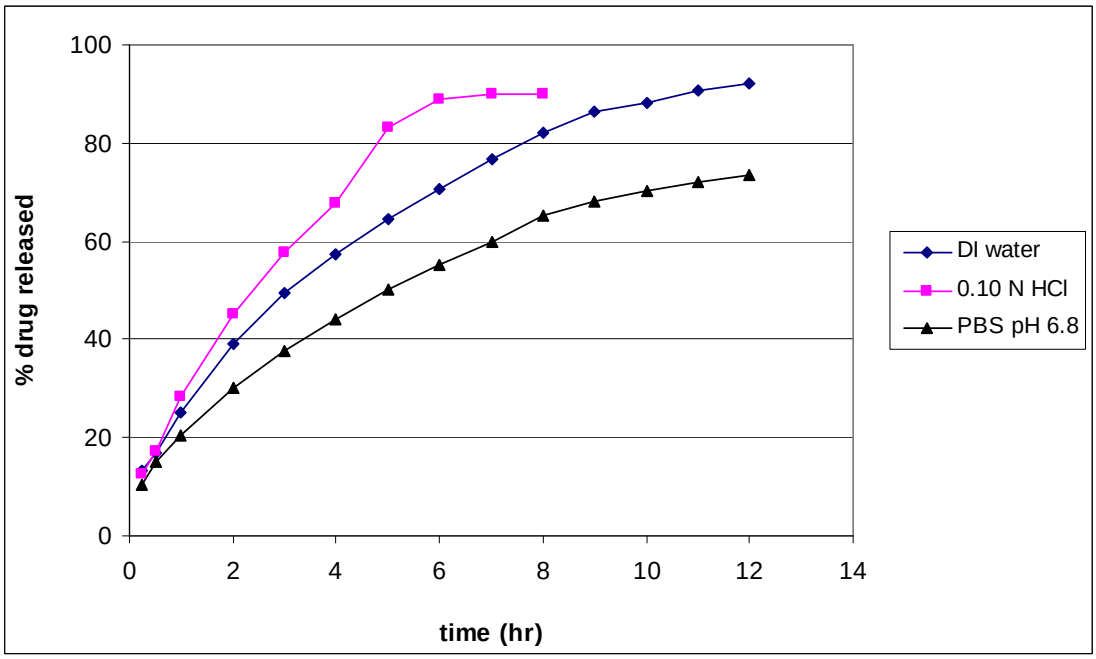


Figure 40 The release profiles of F16 prepared by using compression force 1000 psi in various pH media.

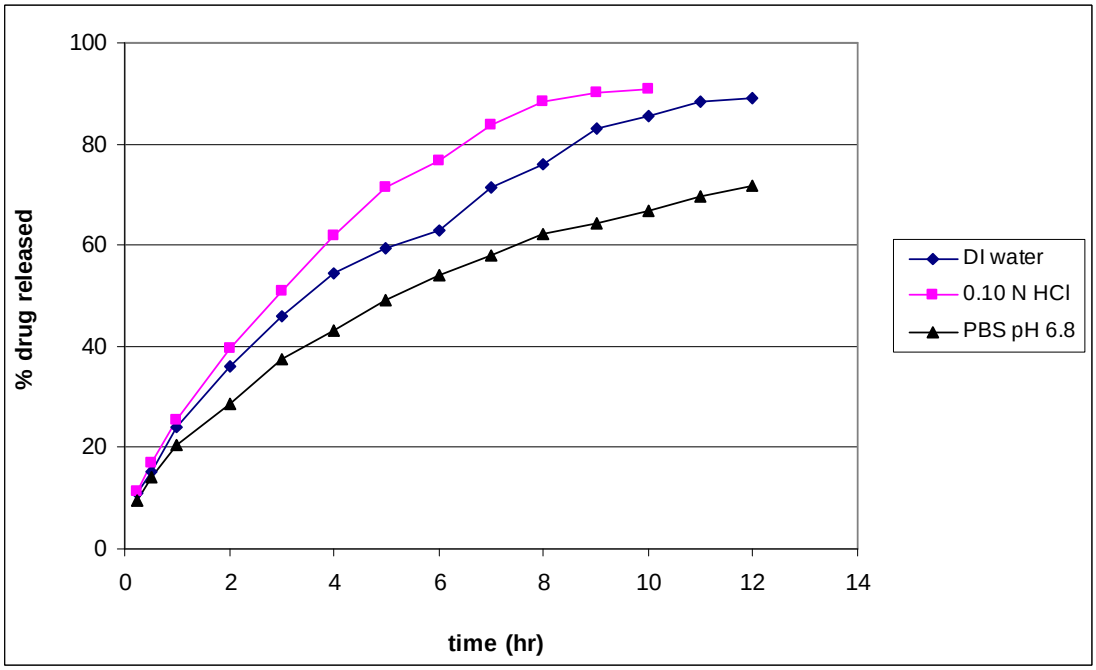


Figure 41 The release profiles of F16 prepared by using compression force 2000 psi in various pH media.

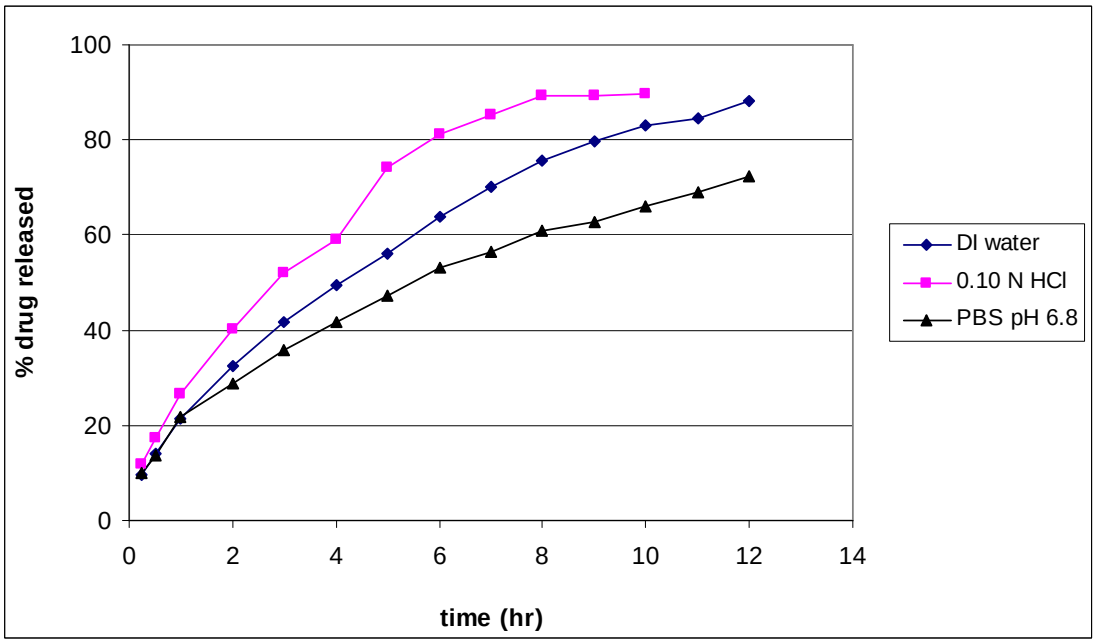


Figure 42 The release profiles of F16 prepared by using compression force 3000 psi in various pH media.

Effect of compression forces

The compression force is usually a significant factor affecting tablet hardness. However, in this study, when the compaction pressure was changed from 1000 to 3000 psi, its effect on drug release from PCHS matrix tablets was minimal.

The release of the drug of PCHS matrix in distilled water and in various ionic strength and pH media which varied compression forces of 1000, 2000 and 3000 psi are shown in Figure 43 and 44. It was observed that the percent release of drug release in 12 hrs from the matrix of PCHS prepared using different compression forces was similar in every media. Consequently, It can mention that the increase of compression force has no effect on the release of the drug from PCHS matrix. In various pH media (0.1 N HCl and PBS pH 6.8), they showed a slightly change of drug release. The compression forces in range of 1000-3000 psi did not affect the release rate of drug. This might be due to the matrix of PCHS was hydrated and swelled fast enough to compensate for the difference in porosity and tortuosity under varying compression forces. (Peerapattana, 2009). Although the compression force is one of important factors which influence on drug release, its effect on drug release from PCHS matrix tablets was minimal.

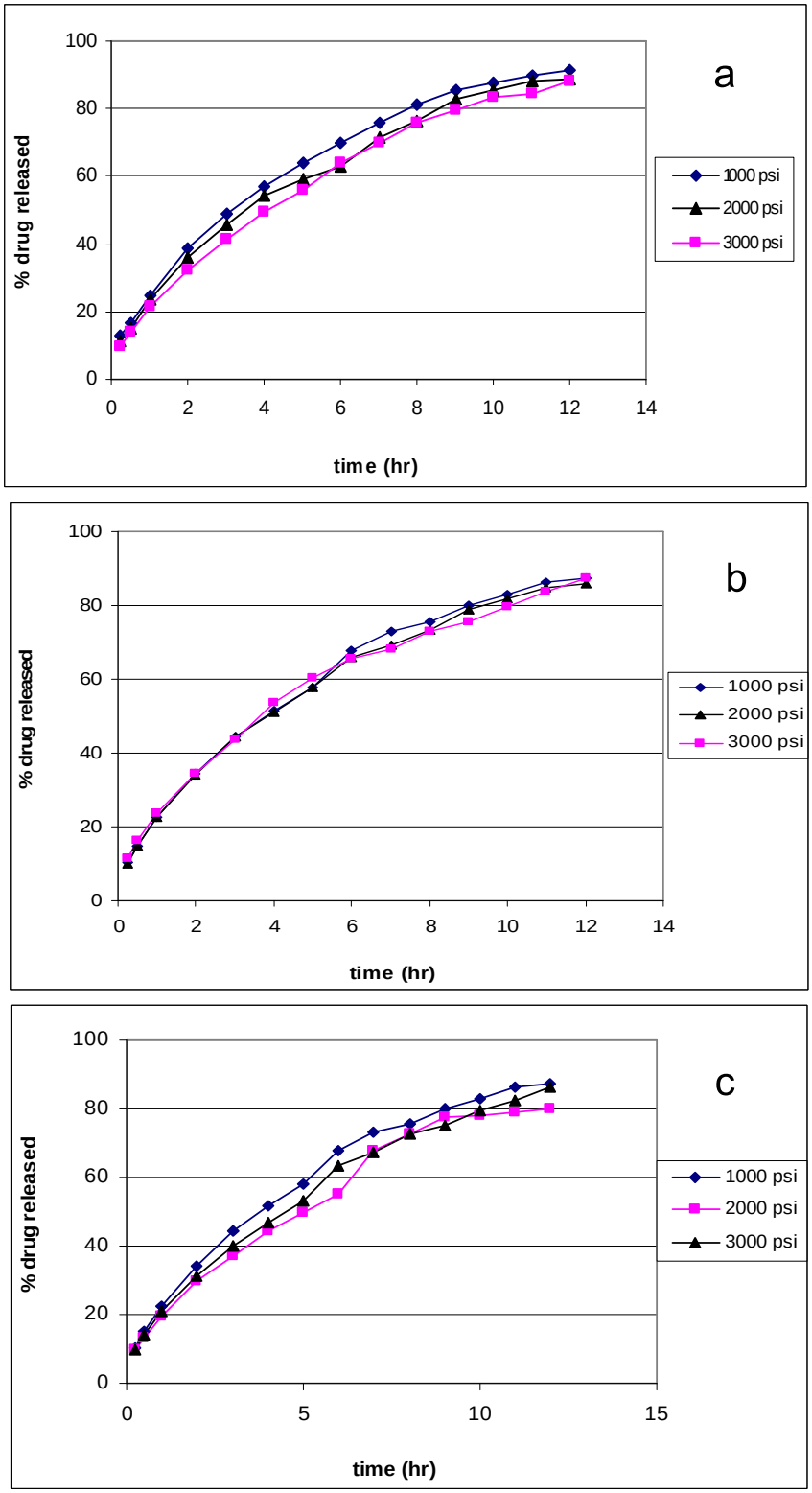


Figure 43 The release profile of F16 in DI water(a), 0.05 M(b) , 0.10 M NaCl solution (c) at three different compression forces.

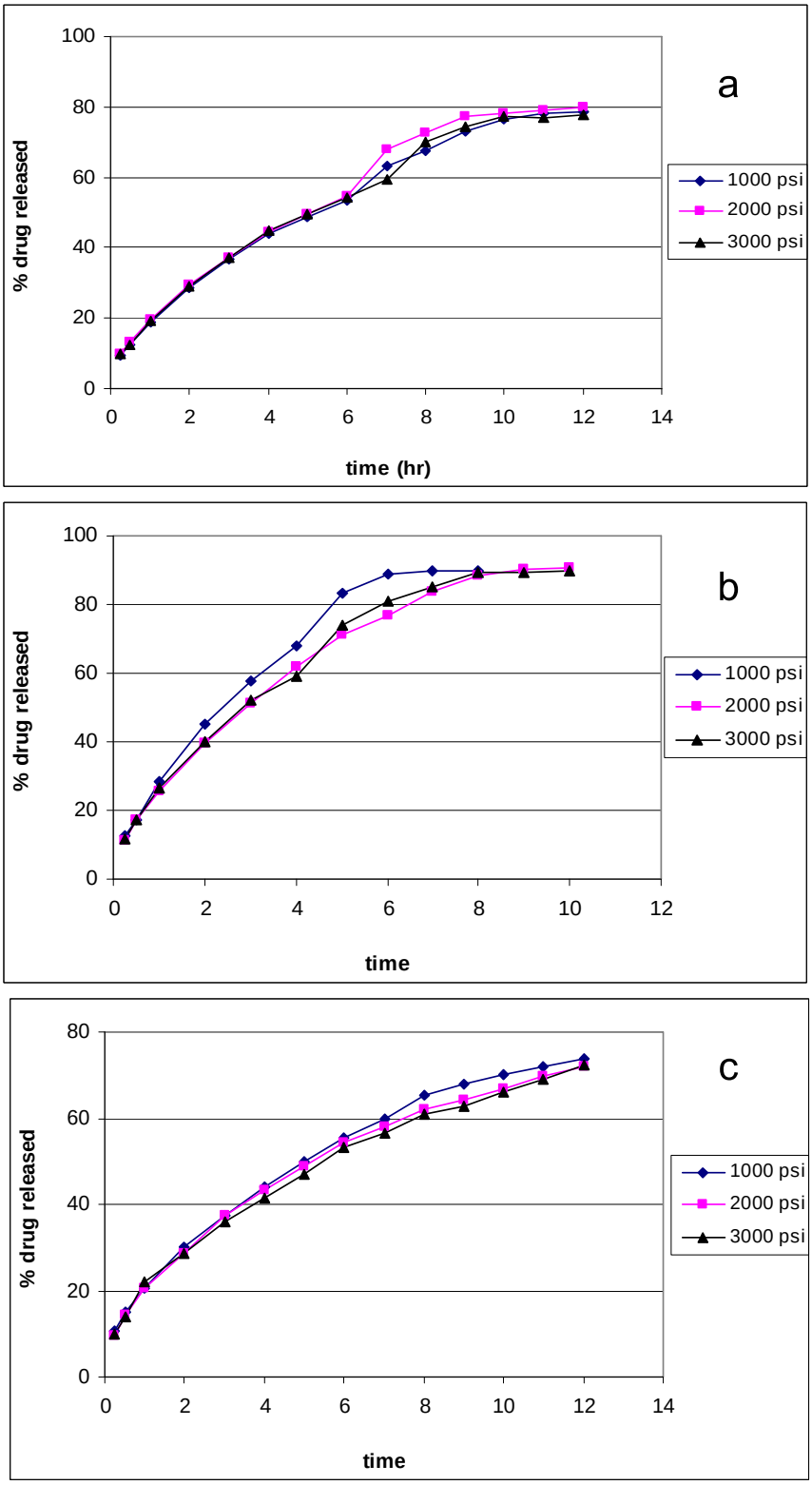
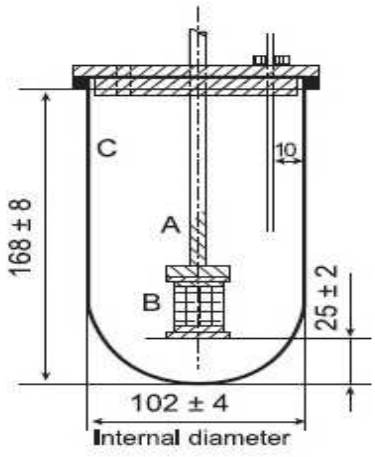


Figure 44 The release profile of F16 in 0.20 M NaCl solution(a), 0.10 N HCl solution(b), PBS pH 6.8 at three different compression forces.

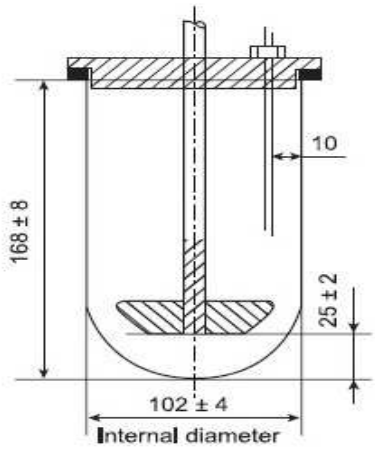
Effect of method of dissolution test

Dissolution rate of the matrix of PCHS, which compression foce of 1000 psi were examined by using Apparatus I and II (basket and paddle) of USP XXVIII at 100 rpm. The dissolution media was 900 ml in distilled water and in various ionic strength and pH media at a temperature of 37±0.5 °C.

(a)



(b)



(c)

Figure 45 Dissolution apparatus (a), basket (b), paddle(c) dimensions in millimeters (European pharmacopoeia, 2005).

A comparison of drug release profiles for matrix of propranolol hydrochloride was also investigated among two different dissolution methods. Release profiles obtained from all methods in every media were similar (Figure 46 and 47).

The value of similarity factor that comparison of drug release profiles of PCHS matrix between using USP dissolution apparatus I (basket method) and using USP dissolution apparatus II (paddle method) was determined at compression force of 1000 psi in distilled water. The f_2 values showed 57.18 (Table 24) that more than 50. This might imply that the release profile of propranolol matrix by using paddle method was similar to basket method.

Table 24 The value of similarity factor of drug release profiles in distilled water by using basket comparing with paddle method at compaction force of 1000 psi.

dissolution method	f_2
basket vs paddle	57.18

In summary, drug release rates dependence water penetration, polymer swelling, drug dissolution, and matrix erosion. Nevertheless, the result of dissolution by using apparatus II (paddle method) always give slightly higher percent of drug release for 12 hrs than using apparatus I (basket method). Due to dissolution test by using basket method, the higher matrix surface exposure to the medium, resulting in building up and swelling of gel layer better than using paddle method. The gel must be capable of preventing matrix disintegration and reducing additional water penetration hence prolonged diffusion of drug release. Moreover, the dynamic force induced by rotating paddle caused the rapid erosion surface of matrix. Thus, using paddle method caused higher erosion of matrix than using basket method.

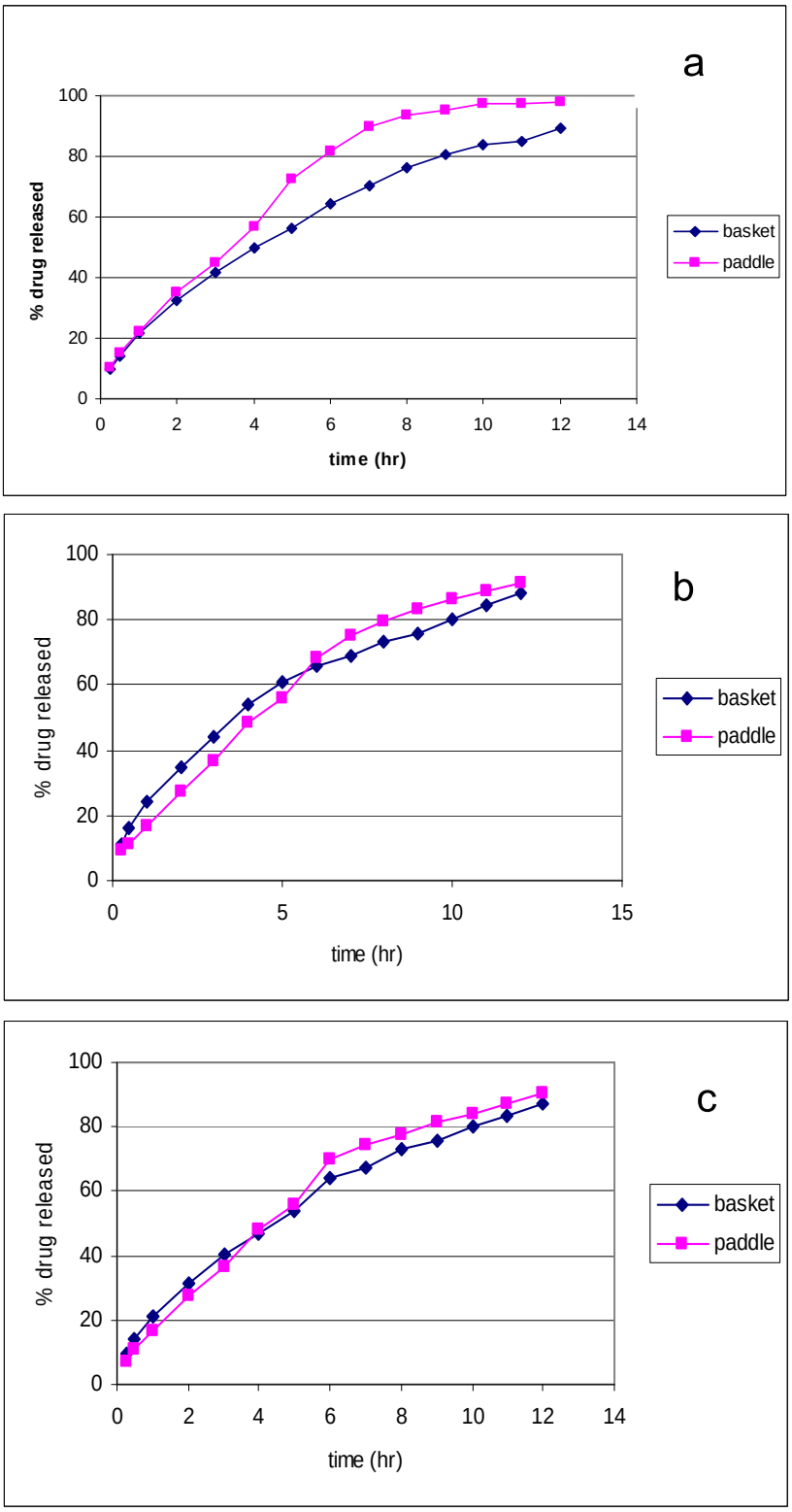


Figure 46 The release profile of F16 by using basket comparing with paddle in DI water(a), 0.05 M (b), 0.10 M NaCl solution(c) at compression force 1000 psi.

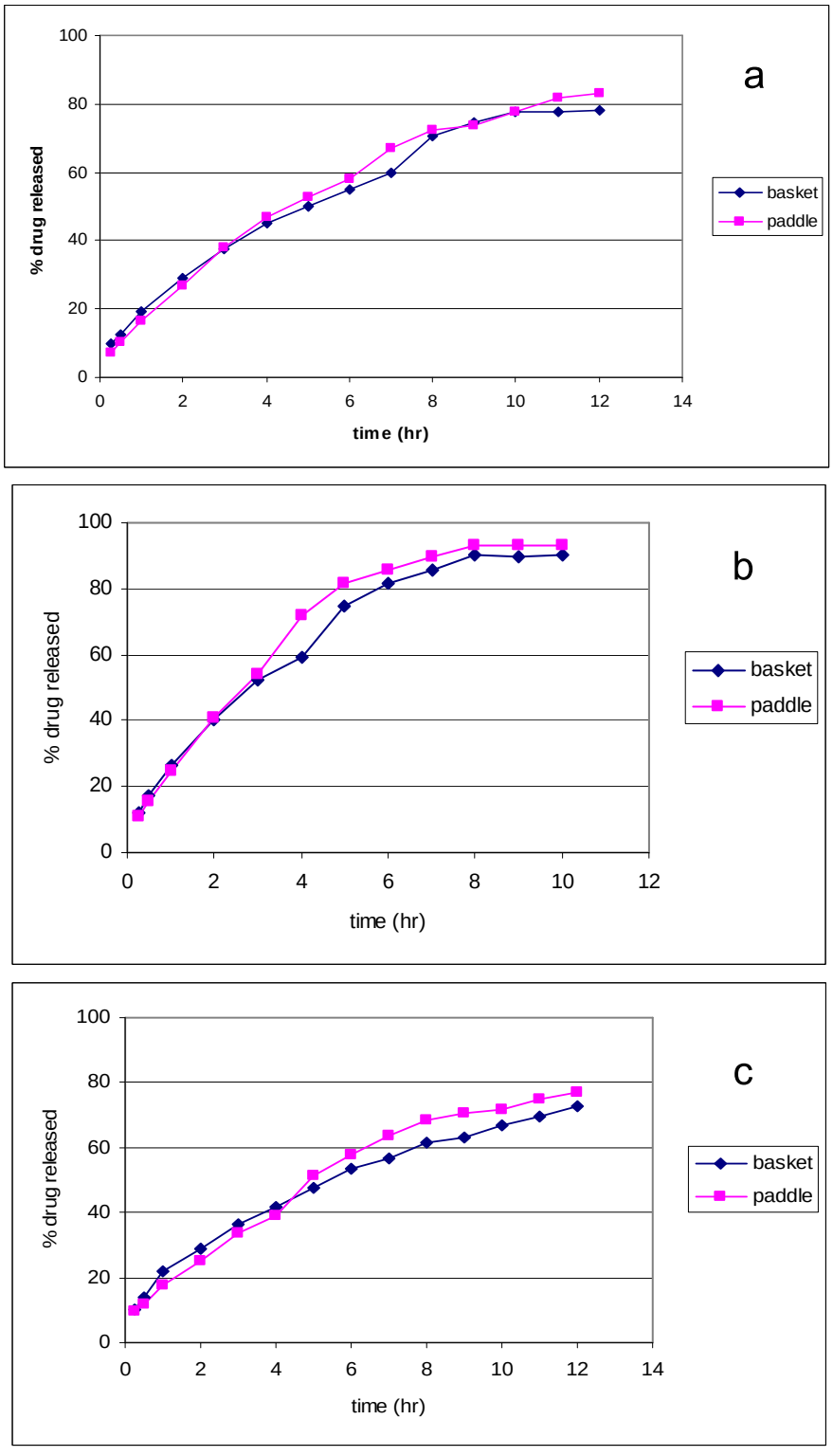


Figure 47 The release profile of F16 by using basket comparing with paddle in 0.20 M NaCl solution(a), 0.10 N HCl solution(b), PBS pH 6.8(c) at compression force 1000 psi.

CHAPTER V
CONCLUSIONS

To date, most studies on the production of modified starches have been limited to widely available starches such as corn, potato, wheat, tapioca and rice. Modified starches from other botanical sources may yield starches with special properties and offer a wide range of functional properties permitting numerous applications (Odeku, Schmid and Freyer, 2008). The aim of this study was to modify the native tapioca starch as a released controlling agent for sustained release matrix. The PCHS was prepared by substituted reaction with propylene oxide at three levels, and crosslinked by 0.1% sodium trimetaphosphate. The last step, the modified starch slurry was physically modified by pregelatinization method. The PCHS was investivated for the physico-chemical properties and effect of electrolytes and pH media on viscosity, rheology, swelling power. The F16 formula containing PCHS and HPMC E4M (ratio 4:1) prepared by wet granulation method was selected to study effects of media, compression forces and methods of dissolution on drug release. It can be conclude as below:

1. The physical appearance of PCHS by using scanning electron microscopy and polarized light microscopy showed a larger in size, irregular rough surface and lost of birefringence property.

2. The hydroxypropyl groups content of 2.5, 5.0 and 7.5% substitution PCHS exhibited percent of hydroxypropyl groups at 2.18, 2.58 and 3.66 respectively. The degree of substitution (DS) was calculated from the percent of hydroxypropyl group which exhibited DS of 0.062, 0.074 and 0.106 when using 2.5, 5.0 and 7.5% propylene oxide, respectively. It could mention that, increasing the percent of propylene oxide, resulting in increase of DS.

3. Degree of substitutions had effects on the viscosity. The more degree of substitution of PCHS, the higher viscosity since the 7.5% substitution PCHS provided the highest viscosity, follow by 5.0%, 2.5% and native starch, respectively. The viscosities of all PCHS were shown similar. This might imply that the electrolytes had no

effect on the viscosity. However, the viscosities of all PCHS just had a little change when the pH changed. Therefore, it might say that the pH of media had no effect on the viscosity of PCHS.

4. The flow behavior of PCHS presented thixotropic flow patterns that fluids showed a time-dependent change in viscosity. The results demonstrated that shear stress and shear rate increased when concentration of PCHS increased. Therefore the 6% w/v concentration of PCHS gave the highest shear stress and shear rate in every media. Rheological behaviors in various ionic strength media (0.05, 0.10 and 0.20 M NaCl solution) and in various pH media (0.1 N HCl solution, PBS pH 6.8) comparing with in DI water showed similar rheograms. It was indicated that ionic strength and pH of media had no effect on flow patterns of PCHS.

5. A result of swelling power (SP) of PCHS after modification showed that the SP was increased when the concentration was increased and 7.5% substitution gave the highest of SP. Due to the 7.5% substitution had the more of hydroxypropyl groups in structure which made it good solubility in water. Its solution was transparent, colorless and gave more swelling property better than native tapioca starch. The SP presented ninefold to elevenfold increase in various of ionic strength media (0.05, 0.10, 0.20 M NaCl) and in 0.1 N HCl solution, however, in the phosphate buffer solution pH 6.8, the PCHS showed a slightly decreased of SP (sevenfold to eightfold). It could imply that pH of medium, such as, phosphate buffer solution pH 6.8 gave slight influence on SP of PCHS.

The 7.5% substitution PCHS was selected to prepare propranolol hydrochloride matrix tablet, and the effects of ionic strength, pH, compression forces, methods of dissolution test on drug release were investigated. As results, it was shown that the F16 which consisted of PCHS and HPMC E4M (4:1) (Table 25) could extend drug release through 12 hrs. that was similar to the release of F12 which consisted of only HPMC E4M (50% HPMC E4M) for used as matrix agent in the formulation. Therefore, it might say that the PCHS could partly replace HPMC E4M for using as sustained release matrix.

Table 25 The formulation F16 was chose to study in dissolution test

F16	mg/tab
Propranolol hydrochloride	80.00
PCHS	121.85
Dibasic calcium phosphate	60.00
HPMC E4M	30.00
PVP K90	8.00
Mg. stearate	0.15

6. At the high ionic strength of medium in dissolution test influenced drug release from PCHS matrix. In the 0.20 M NaCl solution (μ=0.20), the percent of drug release was lower than in distilled water clearly observed. Furthermore, the comparison of dissolution profile using the f_2 value to be 45.50 which was lower than 50. It was indicated that drug release profiles of PCHS matrix in 0.20 M NaCl solution was different from in distilled water. However, the percent of drug release in 0.05 M NaCl solution (μ=0) and 0.10 M NaCl solution (μ=0.10) were resemble in distilled water. This finding might be due to the less difference in ionic strength of dissolution media.

7. The release rate from PCHS matrix in 0.1 N HCl solution showed the fastest following by distilled water and phosphate buffer pH 6.8 and the release rates were found almost the same at different compression forces. However, in acid condition, the PCHS matrix could prolong drug release for only 8 hrs while it could prolong for 12 hrs in distilled water and phosphate buffer pH 6.8. Due to the PCHS tended to break down in acid condition. The gel layer of matrix was eroded, resulting in rapid release of drug. Moreover, the solubility of propranolol hydrochloride in 0.1 N HCl solution (225mg/ml) was higher than in phosphate buffer solution pH 6.8 (130mg/ml), hence the rapid release in 0.1 N HCl solution. When comparison of dissolution profile by using similarity factor between in 0.1 N HCl solution with phosphate buffer pH 6.8 solution. The value of similarity factor was 32.32, It could confirm that drug release profile of PCHS matrix in both media were different.

8. The compression forces in the range of 1000-3000 psi. had no effect on drug release of PCHS matrix. The compression forces probably did not change porosity inside the PCHS matrix that was the important factor on drug release, or the PCHS could hydrated and swelled fast enough to compensate the difference in porosity and tortuosity under varying compression forces.

9. The value of similarity factor which comparison of drug release profiles of PCHS matrix between using basket method and paddle method was 57.18 that greater than 50. This might imply that the release profile of propranolol hydrochloride matrix using paddle method was comparable to basket method.

The results suggested that the introduction of hydroxypropyl groups to amylose chains improved their solubility and viscosity properties, water holding capacity. Cross-linked starches with phosphate groups support the hydrogen bonds and act as brides between the starch molecules, which increase the gel intergrity. The cross-linked starches are resistant to shear, high temperature, electrolytes and acid-base condition. Moreover, the swelling capacity of pregelatinized starches obtained were increased so the PCHS is able to swell and dissolve in cold water. However, this study did not clarify those property change of each step of modification.

From this study, the PCHS couldn't use as matrix agent for sustained drug release by itself. However, it could use to combine with HPMC E4M (ratio PCHS : HPMC E4M 4:1) which sustained drug release for 12 hrs. In acid condition, the matrix of PCHS could sustain drug release for only 8 hrs. Due to the hydrogen bond of PCHS was broke down by acid hydrolysis reaction, causing of rapid release. It might say that low crosslinked starch could not resist to acid condition.

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Appendices

Appendix A

Propranolol hydrochloride

β- Adrenergic blockers are one of the most frequently prescribed cardiovascular drugs. Propranolol hydrochloride is non-selective beta-blocker with no intrinsic sympathomimetic activity (ISA) that is widely used in the treatment of angina pectoris, cardiac arrhythmias and hypertension. It is available as either an immediate release or sustained release product, with a variety of both innovator and generic forms available on various National and International markets

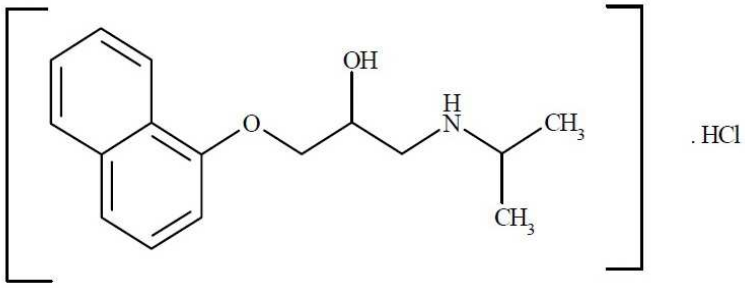

Figure 1(A) Chemical structure of propranolol hydrochloride

Empirical name	$C_{16}H_{21}NO_2 \cdot HCl$
Chemical name	(±)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride
Molecular weight	295.8
Description	white to off white crystalline powder, odorless with a bitter taste
Melting point	163 to 166 °C
Dissociation constant (pKa)	9.5
Stability	Propranolol hydrochloride solutions are most stable at pH of 3 and decompose rapidly under alkaline conditions. Light has effect on propranolol hydrochloride.

Ultraviolet Absorption Spectrum

Organic molecules that are in solutions and that are exposed to light in the visible and ultraviolet regions of the light spectrum can absorb radiation of particular wavelengths depending on the type of electronic transition that is associated with the absorption. The electronic transitions depend on the electron bonding within the molecule. A molecule can have more than one characteristic absorption band, and the complete spectrum in the ultraviolet and visible wavelength regions can provide information for the positive identification of a compound. The absorption maximum or lambda maximum wavelength Absorbance (λmax) for PHCL is 288 nm in aqueous acidic media and 290 nm in methanolic solution (Chetty, 2006).

APPENDIX B

Calibration curve

The amounts of propranolol hydrochloride were determined by the spectrophotometer. The calibration curve and the linear relationship with the correlation of determination in each medium propranolol hydrochloride were displayed in Figure 1(B) -7(B).

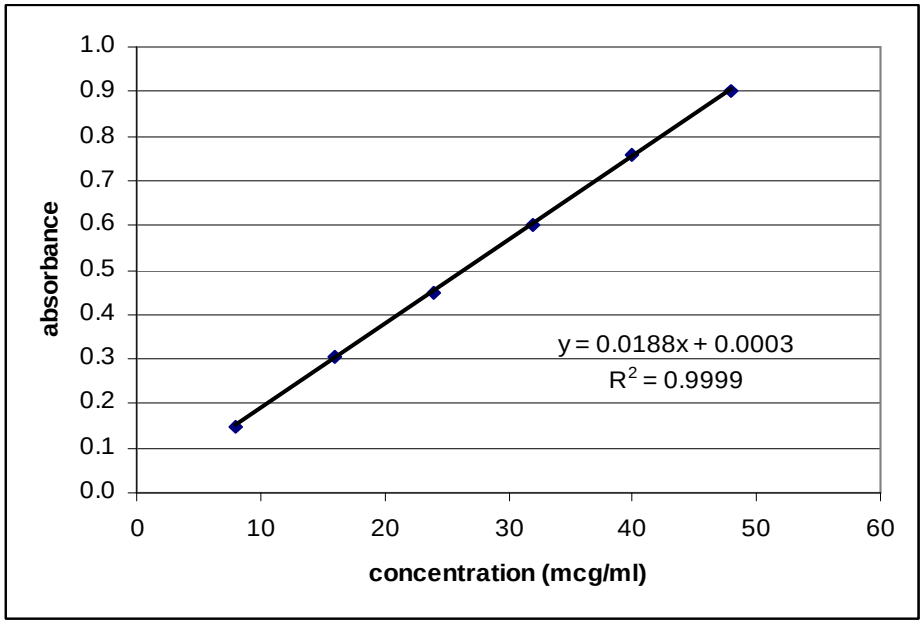

Figure 1(B) Calibration curve of propranolol hydrochloride in DI water at 289nm.

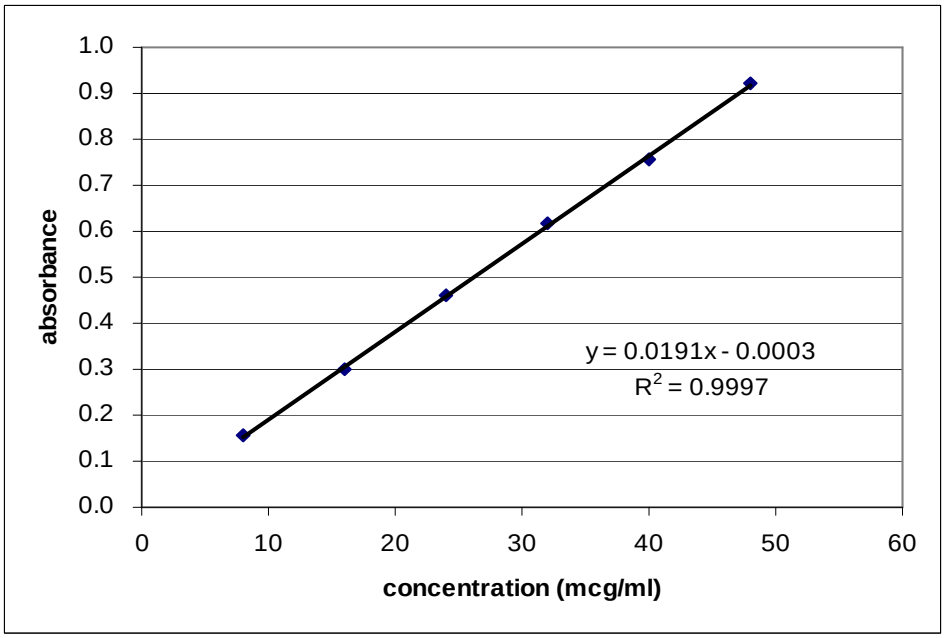

Figure 2(B) Calibration curve of propranolol hydrochloride in 0.05 M NaCl solution at 289 nm.

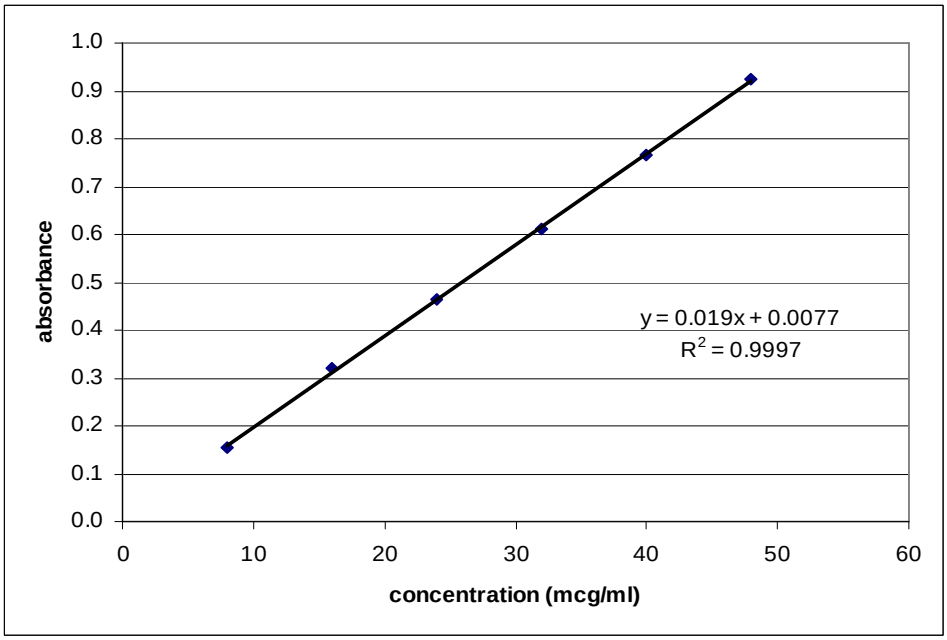

Figure 3(B) Calibration curve of propranolol hydrochloride in 0.10 M NaCl solution at 289 nm.

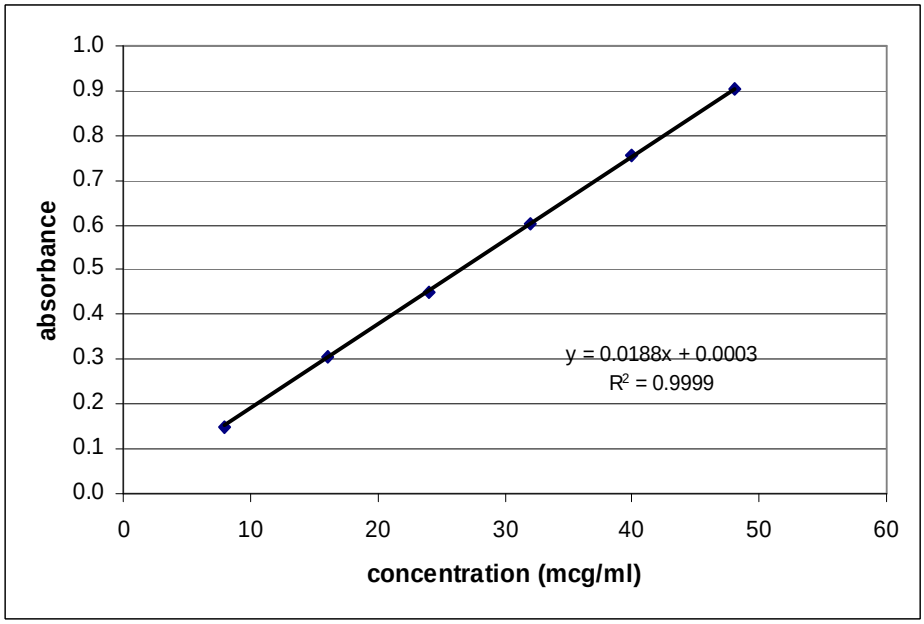

Figure 4(B) Calibration curve of propranolol hydrochloride in 0.20 M NaCl solution at 289 nm.

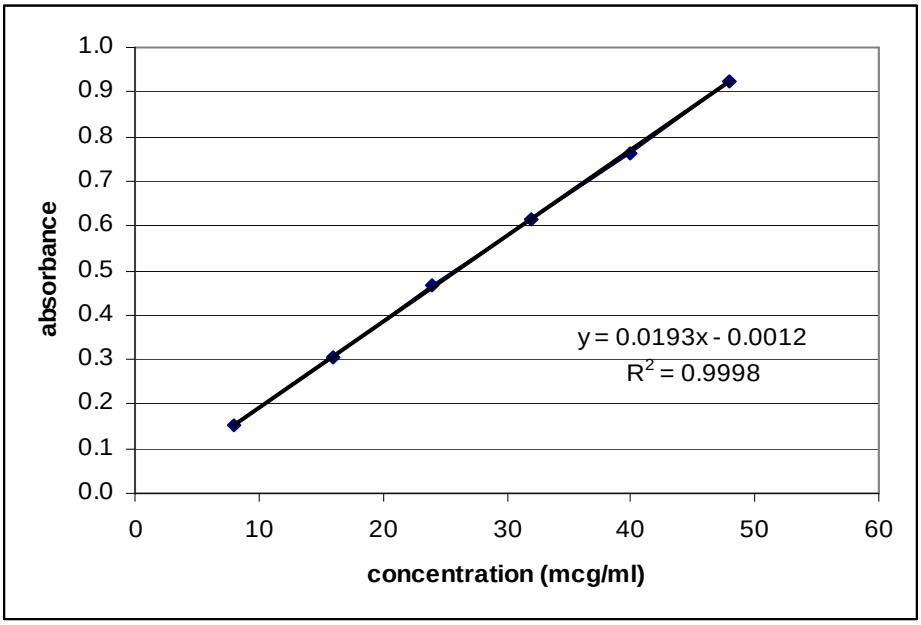

Figure 5(B) Calibration curve of propranolol hydrochloride in 0.1 N HCl solution pH 1.2 at 289 nm.

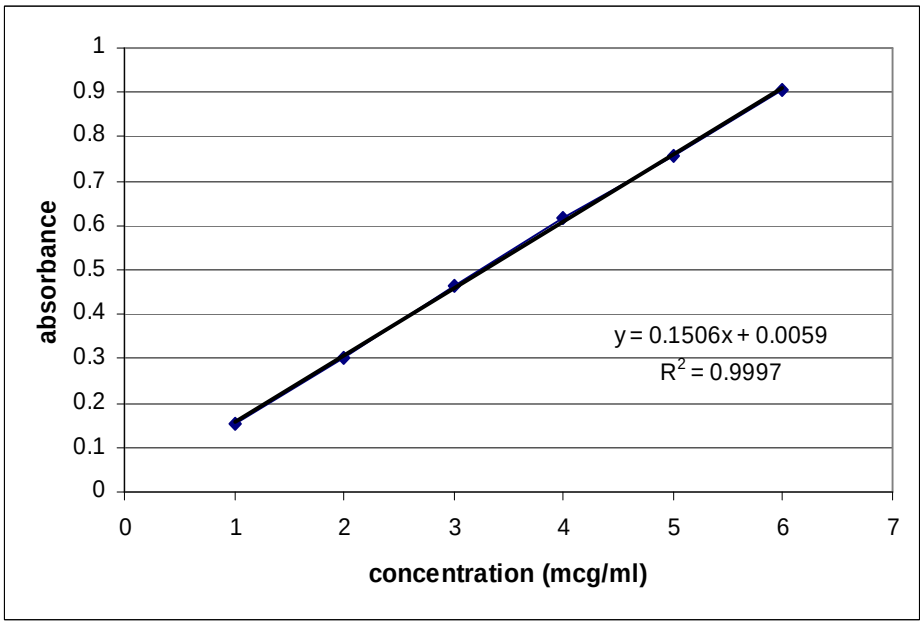

Figure 6(B) Calibration curve of propranolol hydrochloride in phosphate buffer solution pH 6.8 at 289 nm.

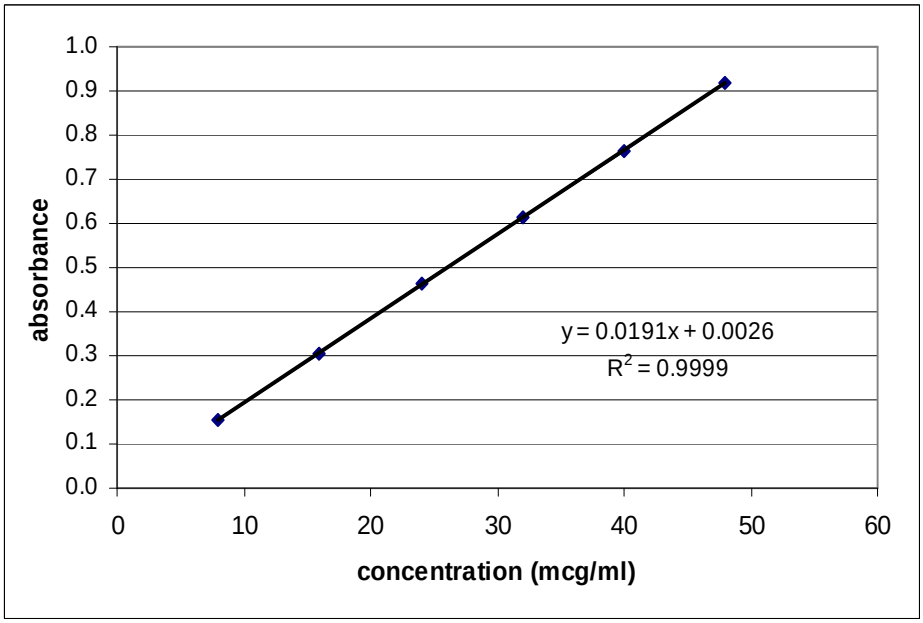

Figure 7(B) Calibration curve of propranolol hydrochloride in methanol at 289 nm.

APPENDIX C

Fourier-transformed infrared (FT-IR)

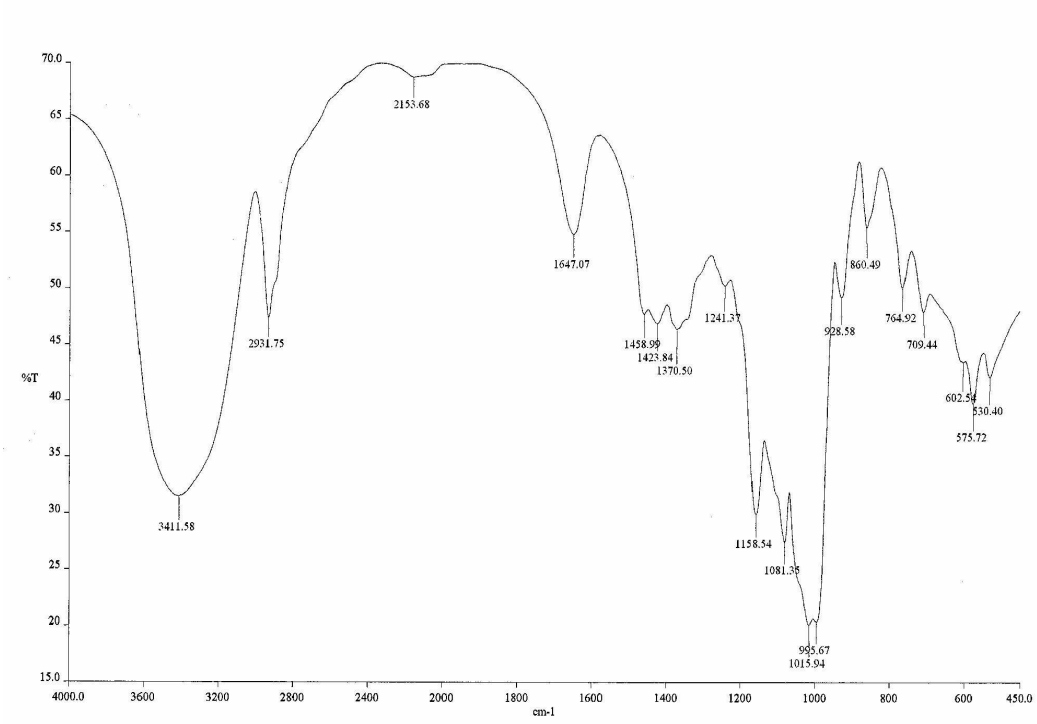

Figure 1(C) FT-IR of native starch

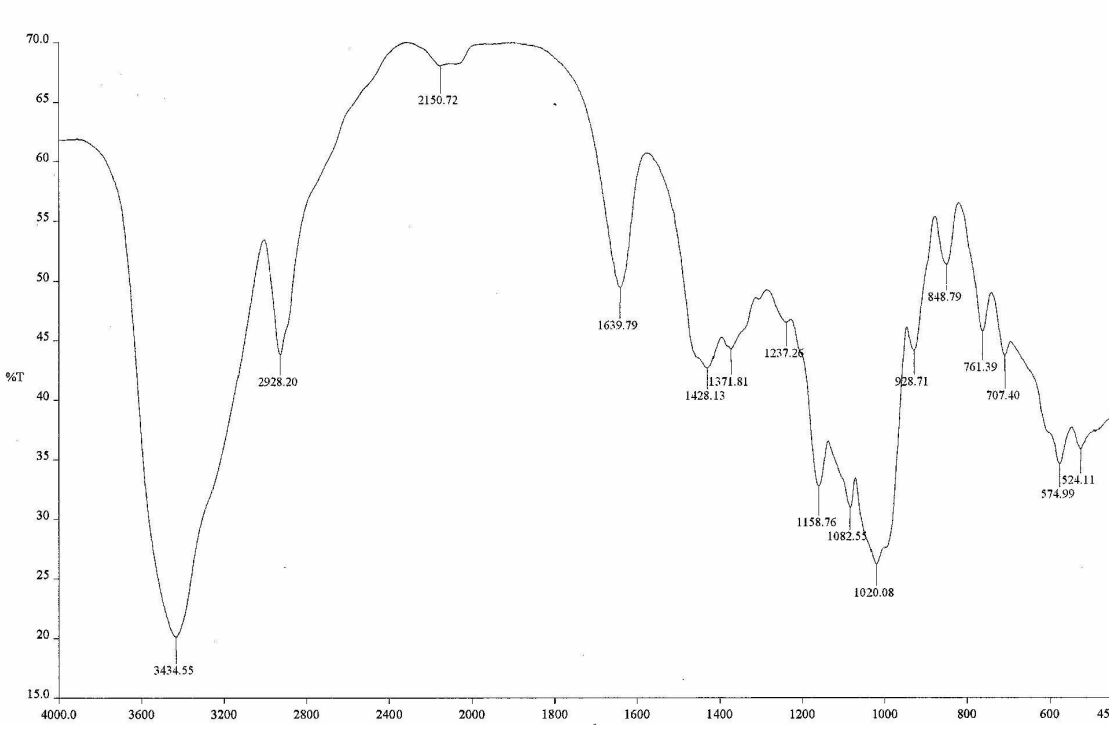

Figure 2(C) FT-IR of 2.5% substitution PCHS

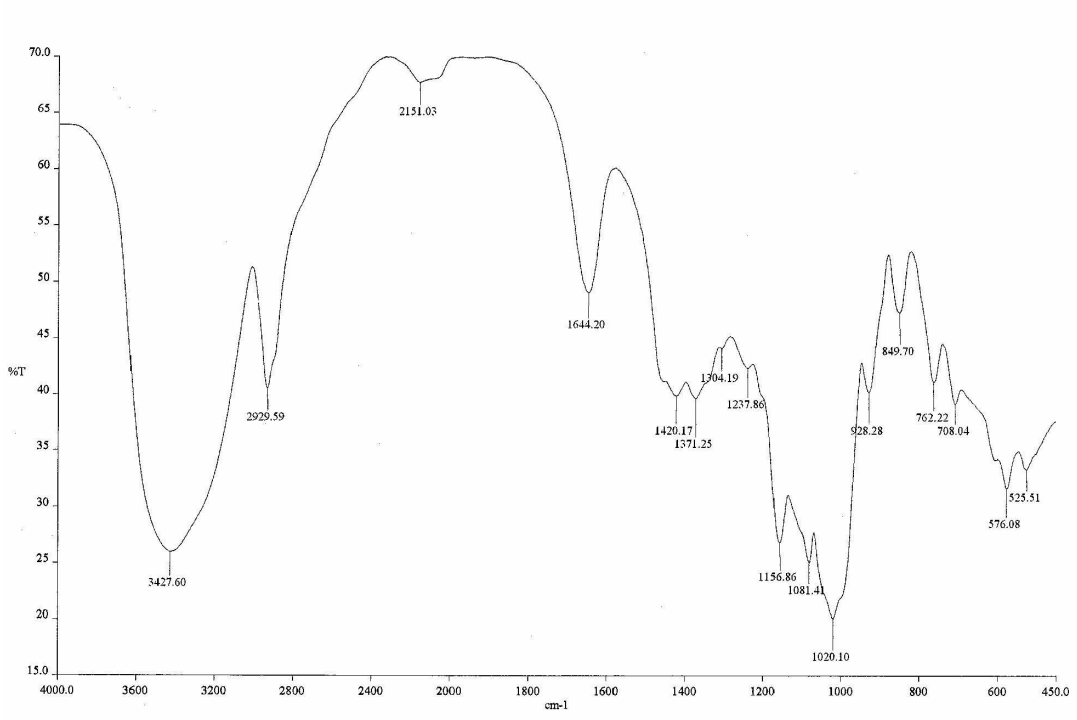

Figure 3(C) FT-IR of 5.0% substitution PCHS.

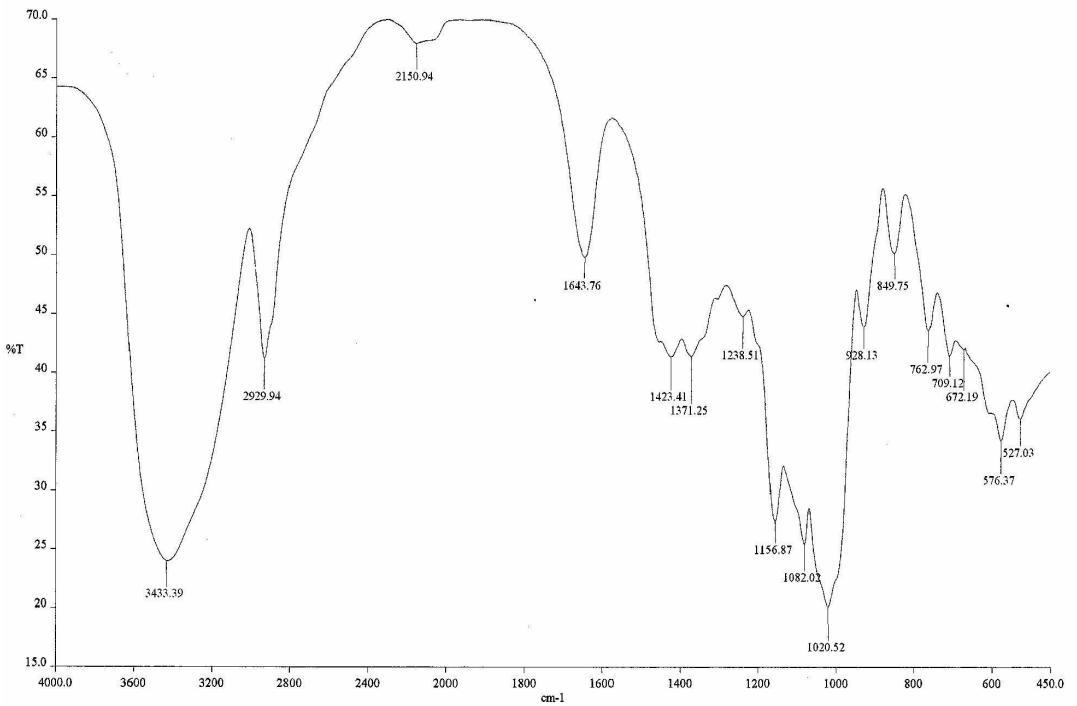

Figure 4(C) FT-IR of 7.5% substitution PCHS.

VITAE

Miss Pannaon Wongsanansin was born on February 9, 1981. She received the Bachelor of Sciences in Pharmacy in 2004 from the faculty of pharmaceutical Sciences, Silpakorn University, Thailand. She entered studying in the Master's Degree in Industrial Pharmacy Program in the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand in 2008.