วิทยากระแสและคุณสมบัติการแขวนตะกอนของแป้งมันสำปะหลังดัดแปร

นางสาว ปริญญา ธารบุปผา

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RHEOLOGY AND SUSPENDING PROPERTIES OF MODIFIED TAPIOCA STARCHES

Miss Parinya Tharnbupphar

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for the Degree of Master of Science in Pharmacy Program in Industrial Pharmacy
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การศึกษาแป้งมันสำปะหลังดัดแปรทางกายภาพหรือเคมีจำนวน 5 ชนิด ได้แก่ แป้งมันสำปะหลังดัดแปรโซเดียมคาร์บอกซีเมทิล แป้งมันสำปะหลังดัดแปรโซเดียมคาร์บอกซีเมทิลร่วมกับปฏิกิริยาเชื่อมขวางด้วยฟอสเฟต แป้งมันสำปะหลังดัดแปรพรีเจลาติไนซ์ แป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิล และ แป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิลร่วมกับปฏิกิริยาเชื่อมขวางด้วยฟอสเฟต เพื่อเป็นสารช่วยแขวนตะกอนเปรียบเทียบกับสารแขวนตะกอนที่มีจำหน่ายในท้องตลาด เช่น อัลตร้าสเปริส์ แซนแทนกัม และทรากาแคนท์ การเตรียมแป้งมันสำปะหลังดัดแปรโซเดียมคาร์บอกซีเมทิลที่มีระดับการแทนที่ต่างกัน 3 ระดับ คือ 0.11 0.22 และ 0.37 โดยวิธีของฟิลเบิรต์ ส่วนแป้งมันสำปะหลังดัดแปรโซเดียมคาร์บอกซีเมทิลร่วมกับปฏิกิริยาเชื่อมขวางด้วยฟอสเฟตมีปริมาณฟอสเฟตแทนที่ต่างกัน 3 ระดับคือ 0.7, 0.23 และ 0.32 ซึ่งเตรียมด้วยวิธีของเคลอร์และเคลฟแลนด์ เพื่อศึกษาความหนืด และลักษณะการไหล พบว่าสารแขวนตะกอนทุกชนิดมีการไหลแบบซูโดพลาสติก เมื่อศึกษาผลกระทบของความแรงของอิออน ความเป็นกรด-ด่าง ชนิดของบัฟเฟอร์ (ฟอสเฟตและซิเตรตบัฟเฟอร์) ต่อความหนืดและลักษณะการไหลของสารแขวนตะกอนพบว่า แป้งมันสำปะหลังดัดแปรโซเดียมคาร์บอกซีเมทิลร่วมกับปฏิกิริยาเชื่อมขวางด้วยฟอสเฟตมีคุณสมบัติไม่เหมาะสมในการเป็นสารช่วยแขวนตะกอน เนื่องจากสูญเสียความหนืดเมื่อมีความแรงของอิออน บัฟเฟอร์และความเป็นกรด-ด่าง จึงคัดเลือกเฉพาะแป้งมันสำปะหลังดัดแปรโซเดียมคาร์บอกซีเมทิล แป้งมันสำปะหลังดัดแปรพรีเจลาติไนซ์ แป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิล แป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิลร่วมกับปฏิกิริยาเชื่อมขวางด้วยฟอสเฟต เพื่อศึกษาคุณสมบัติการใช้เป็นสารช่วยแขวนตะกอนที่ความเข้มข้นต่างกัน 3 ระดับในตำรับยาน้ำแขวนตะกอนไอบูโพรเฟน และทำการประเมินผลโดยดูลักษณะทางกายภาพ ความเป็นกรด-ด่าง ความหนืด ปริมาตรของตะกอน การกระจายตัวคืนรูป เพื่อหาความเข้มข้นที่เหมาะสมหลังจากเก็บที่อุณหภูมิห้องเป็นเวลา 1 เดือน ตำรับยาไอบูโพรเฟนที่เตรียมจาก 3 % แป้งมันสำปะหลังดัดแปรโซเดียมคาร์บอกซีเมทิล 4 % แป้งมันสำปะหลังดัดแปรพรีเจลาติไนซ์ 6 % แป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิล 3 % และ 4 % แป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิลร่วมกับปฏิกิริยาเชื่อมขวางด้วยฟอสเฟต ให้ตำรับที่มีลักษณะที่ดีใกล้เคียงกับตำรับที่เตรียมจาก 4 % อัลตร้าสเปริส์ 0.4 % และ 0.6 % แซนแทนกัม และ1 % และ 1.5 % ทรากาแคนท์ และนำมาเก็บที่อุณหภูมิห้องเป็นระยะเวลา 3 เดือน และสภาวะเร่ง โดยประเมินผลในหัวข้อลักษณะทางกายภาพ ปริมาตรของตะกอน ความเป็นกรด-ด่าง ความหนืด ลักษณะการไหล การกระจายตัวคืนรูป และปริมาณตัวยาสำคัญ พบว่า ทุกตำรับมีความคงตัวทางเคมีทั้งในสภาวะปรกติและสภาวะเร่ง แป้งมันสำปะหลังดัดแปรโซเดียมคาร์บอกซีเมทิล แป้งมันสำปะหลังดัดแปรพรีเจลาติไนซ์ และแป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิล ไม่เหมาะสมในการเป็นสารช่วยแขวนตะกอนเนื่องจากตำรับยาจะมีความหนืดลดลงมากเมื่อตั้งทิ้งไว้ นอกจากนี้ยังกระจายตัวคืนรูปได้ยาก แป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิลร่วมกับปฏิกิริยาเชื่อมขวางด้วยฟอสเฟตเป็นสารช่วยแขวนตะกอนที่ให้ผลการประเมินเป็นที่น่าพอใจ เนื่องจากทำให้ตำรับมีลักษณะทางกายภาพสวยงาม มีการกระจายตัวคืนรูปได้ง่าย ไม่เกิดการตกตะกอน มีลักษณะการไหลที่เหมาะสมและเทียบเคียงได้รับตำรับที่ประกอบด้วยอัลตร้าสเปริส์ แซนแทนกัม และทรากาแคนท์ แป้งมันสำปะหลังดัดแปรไฮดรอกซีโพรพิลร่วมกับปฏิกิริยาเชื่อมขวางด้วยฟอสเฟตเป็นอีกทางเลือกหนึ่งในการนำมาใช้เป็นสารช่วยแขวนตะกอนในอุตสาหกรรมยา

ภาควิชา เภสัชอุตสาหกรรม ลายมือชื่อนิสิต ปริญญา ธารบุปผา

สาขาวิชา เภสัชอุตสาหกรรม ลายมือชื่ออาจารย์ที่ปรึกษา

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PARINYA THARNBUPPHAR : RHEOLOGY AND SUSPENDING PROPERTIES OF MODIFIED TAPIOCA. THESIS ADVISOR : ASSOC. PROF. POJ KULVANICH, Ph.D., 211 pp. ISBN 974-14-3826-5

Five modified tapioca starches, sodium carboxymethyl tapioca starch (SCMS), cross-linked sodium carboxymethyl tapioca starch (CSCMS), pregelatinized tapioca starch (PGTS), hydroxypropyl tapioca starch (HPTS) and cross-linked hydroxypropyl tapioca starch (CHPTS) were investigated for their properties as suspending agent comparing with commercial suspending agent such as Ultrasperse®2000 (UT), xanthan gum (XG) and tragacanth (TG). SCMS with DS of 0.11, 0.22 and 0.37 were prepared by Filbert's method and CSCMS with % phosphate content of 0.17, 0.23 and 0.32 were obtained from Kerr and Cleveland's method. Those materials were studied for their viscosity and rheological behavior. The pseudoplastic flow was observed in all suspending agents. The effect of ionic strength, pH and type of buffer (phosphate and citrate buffer) on the viscosity and rheological behavior of those materials was evaluated. CSCMS was excluded from the study because it was very sensitive to ionic strength, buffer and pH. SCMS, PGTS, HPTS, CHPTS, UT, XG and TG at three level concentrations were used as suspending agents in ibuprofen formulation. Their physical appearance, pH, viscosity, sedimentation volume and redispersibility were evaluated to find the proper concentration of those suspending agents after keeping in room temperature for 1 month. The ibuprofen preparations containing 3 % w/v SCMS, 4 % w/v PGTS, 6 % w/v HPTS, 3 and 4 % w/v CHPTS provided the preferable suspension comparing with 4 % w/v UT, 0.4 and 0.6 % w/v XG and 1 % and 1.5 % w/v TG. The evaluation parameters including physical appearance, sedimentation volume, pH, viscosity, rheological behavior, redispersibility and % drug content were investigated during storage at room temperature and heating-cooling condition. All preparations provided the acceptable chemical stability after standing 3 months at room temperature and 8 cycles of heating-cooling condition. SCMS, PGTS and HPTS were not suitable as suspending agent because they obviously decreased the viscosity after storage. Moreover, the difficult redispersibility of compact sediment was occurred in their preparations. CHPTS was a promising suspending agent in the preparation due to its good physical appearance, redispersibility, no caking, suitable rheological behavior and comparable to those of UT, XG and TG. CHPTS was a good modified starch candidate for the development as suspending agent in the pharmaceutical industry.

Department Manufacturing Pharmacy Student's signature ปริญญา ธารน์บุพ์ผา
Field of study Manufacturing Pharmacy Advisor's signature
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ABBREVIATIONS

ºC	=	degree Celsius
cps	=	centripoises
cm	=	centimeter
CSCMS	=	cross-linked sodium carboxymethyl tapioca starch
CSCMS-2	=	cross-linked sodium carboxymethyl tapioca starch after 2 hrs of reaction time
CSCMS-8	=	cross-linked sodium carboxymethyl tapioca starch after 8 hrs of reaction time
CSCMS-16	=	cross-linked sodium carboxymethyl tapioca starch after 16 hrs of reaction time
CHPTS	=	cross-linked hydroxypropyl tapioca starch
CV	=	coefficient of variation
DS	=	degree of substitution
e.g.	=	*exemplit gratia*, 'for example'
et al.	=	*et alii* ,'and others'
FT-IR	=	fourier-transform infrared
g	=	gram
HPLC	=	high performance liquid chromatographic
HPTS	=	hydroxypropyl tapioca starch
hr	=	hour
l	=	liter
M	=	molar (concentration)
MFG	=	manufacturing date
mg	=	milligram
MGS	=	modified glutinous rice starch
min	=	minute
ml	=	milliliter
MRS	=	modified rice starch
MTS	=	modified tapioca starch
N	=	normal (concentration)
nm	=	nanometer

No.	=	number
Pa	=	pascal
PGTS	=	pregelatinized tapioca starch
pH	=	the negative logarithm of the hydrogen concentration
qs.	=	quantium sufficiat = sufficient quantity
r^2	=	coefficient of determination
rpm	=	revolution per minute
sec	=	second
SCMS	=	sodium carboxymethyl starch
SCMS-1	=	sodium carboxymethyl starch with DS 0.11
SCMS-2	=	sodium carboxymethyl starch with DS 0.22
SCMS-3	=	sodium carboxymethyl starch with DS 0.37
SD	=	standard deviation
SV	=	sedimentation volume
TG	=	tragacanth
USP	=	The United States Pharmacopeia
UT	=	Ultrasperse®2000
UV	=	ultraviolet
v/v	=	volume by volume
w/v	=	weight by volume
w/w	=	weight by weight
XG	=	xanthan gum
μ	=	micron
μ	=	micrometer
η	=	viscosity
τ	=	shear stress
γ·	=	shear rate

CHAPTER I

INTRODUCTION

Starch is a mixture of two polymers of anhydroglucose units, amylose and amylopectin. Amylose is a linear molecule with 100-10000 α D-(1→4)-linked anhydroglucose unit. Amylopectin has the same basic structure as amylose, but it is heavily branched with a-D-(1→6) bonds, the average branch chain length being 20-60 monomer units. Starch is one of the most important functional food biopolymers. As a natural component, it contributes to the characteristic properties of food products made from cereals, rice, potato and maize. It is also added as a functional ingredient to many products such as sauces, puddings, confectionery, comminuted meat and fish products and a variety of low-fat products. The demands for functionality may vary from product to product. Starch is often added to fluid products to increase their viscosity and stability and also to semisolid products to contribute to their structure and thus improve their fat and water-holding properties.

However, the native starch had some non-suitable properties for industrial manufacture such as narrow range of viscosity, non-smooth texture and low stable in some conditions. For this reason, the native starch would provide low quality product. So, the native starch was modified to produce the product which gave high quality. Modified starches had played a major role in the food and pharmaceutical industry. They possessed some unique properties, not found in natural starches, which were suitable for the development of new products. Examples were the solubility in unheated water, specific changes in rheological profiles, lower gelatinization temperature, less retrogradation, pH stability, etc.

In pharmaceutical, starch is used for manufacturing as a filter, binder (Pitaksuteepons, 1995), disintregrant (Teruya, 1995), lubricant, gelling agent and suspending agent e.g. Ultrasperse® 2000 (National starch & Chemical).

Rheology is involved in the mixing and flow of materials, their packaging into containers, and their removal prior to use, whether this is achieved by pouring from gel in cool water bottle, extrusion from a tube, or passage through a syringe needle. The

rheology of a particular product, which can range in consistency from fluid to semisolid to solid, can affect its patient acceptability, physical stability, and even biologic availability. Thus, viscosity has been shown to affect the absorption rate of drugs from the gastrointestinal tract. The rheological properties of a pharmaceutical system can influence the choice of processing equipment to be used in its manufacture. Furthermore, lack of appreciation for the correct choice of a piece of processing equipment can result in an undesirable product, at least in terms of its flow characteristics (Martin, 1993).

Suspension is a heterogeneous system consisting of two phases. The continuous or external phase is generally a liquid or semisolid, and the dispersed or internal phase is made up of particulate matters that is essentially insoluble in, but dispersed throughout, the continuous phase. Suspending agent is used to suspend the particles that might settle to the bottom of the container. In case of the sediment particles are occurred, the suspension should easy to redisperse and pour freely from the container. The selection of suspending agent in formulation is very important because it influences on the property and rheological behavior of the suspension. The flow pattern of suitable suspending agent is pseudoplastic and thixotropy. Methylcellulose, carboxymethyl-cellulose, alginate, clays, carbopol and some modified starch are used as suspending agent in pharmaceutical preparations.

Sodium carboxymethyl starch, an ester starch derivative prepared by a reaction between native starch and chloroacetic acid in an alkaline condition, is modified chemically starch which can be swell completely in cool water. It yields paste with smooth texture, flexibility, strength and persistence with other chemical materials. In pharmaceutical, this modified starch can be employed as binder in tablet formulation (Filbert, 1952, Robert, 1967, Tasana, 1995). In addition, the pH stability profile of vancomycin at 37 ^{o}C from pH 2-7 was slightly stabilized in the presence of sodium carboxymethyl starch (Claudius, 1998).

Suwannapakul (1996) prepared carboxymethyl starch by a substitution reaction modified using the method described by Filbert (1952). The results indicated that modified glutinous rice starch, modified rice starch and modified tapioca starch with degrees of substitution of 0.16, 0.26 and 0.38 could be used as suspending agent in ibuprofen suspension preparations for 3 months storage. However, it was found that the

viscosity of the preparations decreased as time and those modified starches would lose their suspension property for long storage time (>3 months). Later, Luprasong (2003) used those modified starches as a suspending agent in reconstituted dry syrup. It was found that those modified starches with degrees of substitution of 0.16, 0.26 and 0.38 could be used as suspending agent in reconstituted dry syrup of amoxicillin trihydrate and cephalexin monohydrate.

In addition, it is found that electrolyte, buffer and pH affect on the rheological behavior of suspending agent. Concentration and valency of electrolyte affect on the characteristic rheological properties. Ö Isik Ece (1999) reported that monovalent cations (LiCl, KCl) increased the viscosity of bentonite solution whereas divalent cations ($CaCl_2$, $MgCl_2.6H_2O$) decreased the viscosity of bentonite solution. The recent study by Luprasong (2003) reported that salt of the buffer system decreased the viscosity of sodium carboxymethyl starch in amoxicillin trihydrate and cephalexin monohydrate dry syrup.

Cross-linked sodium carboxymethyl tapioca starch was prepared by Teruya (1995) which was based on the method of Kerr and Cleveland (1957). It was found that this modified starch could from gel in cool water and could be used as superdisintegrant in tablet. However, nobody reported the property of its as suspending agent. So, it was interesting to study the suspending property of this modified starch.

In this study, sodium carboxymethyl tapioca starch with different degree of substitution and cross-linked sodium carboxymethyl tapioca starch were prepared and evaluated their physicochemical properties as potential materials for pharmaceutical industries. They were evaluated as suspending agent in ibuprofen suspension preparations and compared with other commercial modified tapioca starches such as pregelatinized tapioca starch, hydroxypropyl tapioca starch and cross-linked hydroxypropyl tapioca starch.These modified starches were characterized in comparing with other existing suspending agents such as Ultrasperse®2000, xanthan gum, tragacanth. Effect of electrolyte, and type of buffer and pH on rheological behavior of those modified starches was investigated. Then suitable modified starches were selected and applied as suspending agents in formulation of ibuprofen suspension.

Objectives of the study

1. To investigated effect of electrolyte and type of buffer and pH on viscosity and rheological behavior of physically and chemically modified tapioca starches in comparing with commercial suspending agents.
2. To investigated the suspending property of modified tapioca starches in ibuprofen suspension.

CHAPTER II

LITERATURE REVIEW

Starch

Starch is widely distributed in various plant organs as a storage carbohydrate. As an ingredient of many foods, it is also the most important carbohydrate source in human nutrition. In addition, starch and its derivatives are important industrially, for example, in the paper and textile industries. Starches of various origins have individual characteristic properties which go back to the shape, size distribution, composition, and crystallinity of the granules. It is generally accepted the starch is a natural high molecular weight polymeric carbohydrate composed of glucose units as shown in Figure 2-1.

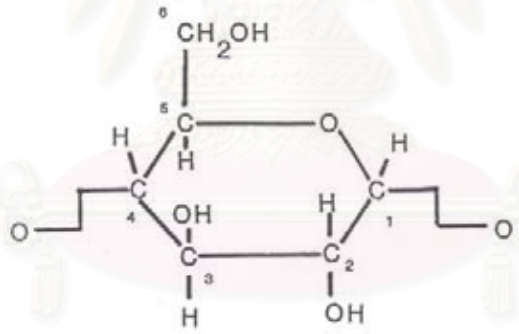


Figure 2-1 Anhydroglucose unit.

Starch can be subdivided into cereal starches (e.g. wheat, rice) and starches derived from roots or tubers (e.g. potato). In plants, starch is stored in the form of semicrystalline granules, with diameters in the range of l-100 μm. Granules from different starch sources vary in composition, size and shape. Cereal starch granules are smaller, and contain more residuals of proteins and lipids; in some species, such as wheat, there is a bimodal distribution, with larger lenticular granules as well as smaller spherical granules. Starch is a mixture of two polysaccharides, the linear amylose and the heavily

branched amylopectin. Variations in the ratio of these polysaccharides, their properties and interactions with other components can explain differences in the swelling behavior of granules and the functionality of starches of different origins (Hermansson and Svegmark, 1996).

Chemically, Starch is a polymeric carbohydrate consisting of anhydroglucose units linked together primarily through α–D-(1➢ 4) glucosidic bonds. While the detailed fine structure has not been fully elucidated, it has been that starch is a heterogeneous material consisting at the extremes of two major types of polymer – amylose and amylopectin (Wurzburg, 1986).

Amylose

Amylose is essentially a linear polymer in which the anhydrousglucose units are predominantly linked through α–D-(1➢ 4) glucosidic bonds (Figure 2-2). 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 an 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).

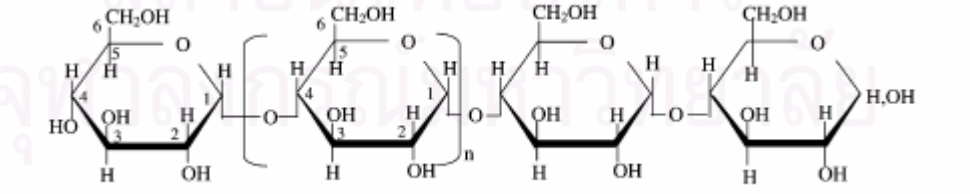


Figure 2-2 Linear-chain structure of amylose molecules (Tester, et al., 2004).

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 2-3.

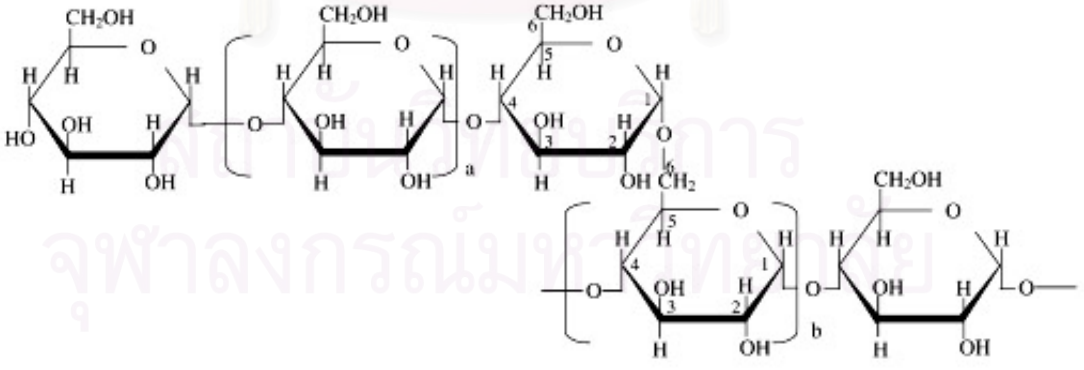


Figure 2-3 Structure of amylopectin branching points (Tester, et al., 2004).

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 and 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).

Modified 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/or physical properties of native starch have been altered might be considered to modified, the range of modifications covered in this volume will be limited to those in which the physical and chemical properties of native starch have been modified through significant molecules scission, molecular rearrangements, oxidation, or introduction of substituent chemical groups into the starch molecules. Modified products which will be covered

include converted starches such as acid fluidities or chlorinations, pyroconversions, cross-linked starches, and all derivatives in which substitutent groups have been introduced onto the starch molecules. Pregelatinized starches, redried starches, extruded starches, and blends or mixes in which the properties of the starch powder have been physically modified will not be specifically covered since they primarily involve modification of the physical properties.

Cross-linked Starch

Starch contains an abundance of hydroxyl groups. Each anhydroglucose unit contains two secondary hydroxyls and a large majority contains primary hydroxyls. These hydroxyls 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 anhydrides, 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 cross-linking between hydroxyls 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 polyfunctional 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 coatings, permanent textiles sizes, wet-strength paper, water resistance adhesives, etc. These involve the use of formaldehyde, glyoxal, urea formaldehyde and other reactive resins or bifunctional 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 treatments such as derivatization with monosubstituents such as acetyl or hydroxypropyl groups.

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 may be 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 introduced 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 300 anhydroglucose units.

The reaction conditions used in making cross-linked starches vary widely depending upon the specific bi- or polyfunctional reagent used for the cross-linking. In general, most of the reactions are run on aqueous suspensions of starch at temperatures ranging from room temperature up to about 50^{o}C. Often an alkali such as sodium hydroxide is used to promote reaction. The reactions are normally run under neutral to fairly alkaline conditions, but below the level which will peptize or swell the starch. In some case, however, such as situations where aldehydes are used, the reactions are run under acidic conditions. If the cross-linking reaction is run in an aqueous suspension of starch, when the desired level of cross-linking (usually as measured by some type of viscosity or rheology test) is reached. The starch suspension is neutralized and the starch is filtered and washed to remove salts, any unreacted reagent, and other impurities produced by side reactions of the cross-linking reagent with water.

A wide variety of chemicals have been reported to cross-link starch, only a limited number are now of commercial significance. The most widely used are the adipic acetic mixed anhydride, which forms distarch adipates; phosphorus oxychloride or sodium trimetaphosphate, which yield distarch phosphates; and epichlorohydrin, which gives distarch glycerols. Of these, only distarch adipates and distarch phosphates are used in making modified food starches.

The distarch adipates are made by esterifying granule starch in aqueous suspension under mildly alkaline conditions with a mixed anhydride prepared by reacting adipic acid with acetic anhydride. 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. In addition to reacting with starch hydroxyls, a portion of the 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.

These are considerable variation in the rate at which these chemicals cross-link starch. The reaction rate with phosphorus oxychloride and adipic acetic mixed anhydride is very rapid. That portion which does not react with the starch is rapidly hydrolyzed. The rate of reaction with sodium trimetaphosphate is somewhat slower, while the rate with epichlorohydrin is much slower. The difference, however, can be minimized by the use of higher reaction temperatures and alkalinity when reacting with epichlorohydrin.

Depending upon the type of cross-link, the sensitivity of the cross-linked starch to pH variation, shear, etc. will vary considerably. The cross-links in distarch glycerol are combined with the hydroxyls in the starch through ether linkages which are resistance to attack by acids, alkalis, and enzymes. As a result distarch glycerols are highly resistance to variations in pH and to mechanical shear. In distarch adipates, the cross-link is combined with the hydroxyls of the starch through organic ester linkages. These are resistance to acid conditions but hydrolyze readily under mildly alkaline conditions. The cross-link in distarch phosphates are linked to the starch through inorganic ester linkages. They show resistance to acidic conditions. Although they show some tolerance to mild alkalinity, the phosphate linkages hydrolyze under moderately alkaline conditions (Wurzburg, 1986).

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 used in combination with other methods for modifying starch, such as acid conversions, oxidations, and derivatizations to introduce monosubstituents.

A major portion of the markets for derivatives such as acetylated or hydroxypropylated starches depends upon the use of cross-linking in order to modify the shortcomings characteristic of these derivatives. These combination treatments and their applications will be covered in the chapters on specific derivatives and on fields of applications. Mention, however, should be made of special applications not normally covered in the major fields of usage such as food, paper, textile, and adhesives. Usage in other application areas is widespread. These include utilization of cross-linked starch in the granule from in surgical dusting powder, as an antiblocking dusting agent for blown films, as an absorbent in the purification of alpha amylases by affinity chromatography, and in combination with treatment of the cross-linked starch with allyl isothiocyanate as an enzyme carrier.

Miscellaneous applications on utilizing pastes prepared from cross-linked starches include their use as gelling agents in the electrolyte for primary cells of the Leclanche type making possible the manufacture of leak-resistant or leak-proof dry cells. The use of cross-linked starches in zinc manganese dioxide dry cell batteries and in anode mixes of zinc alkaline batteries have also been reported. Cross-linked starch derivatives have also used in alkaline batteries. Oven cleaners which are highly alkaline use epichlorohydrin cross-linked starch as thickeners. Combination treatments involving cross-linking potato starch with epichlorohydrin and etherifying with monochloroacetic acid have been used to prepare absorbents for disposable sanitary product (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, carriers, absorbents, 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 mechanical shear

-Resistance to viscosity breakdown at high (retort) temperatures

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

Tapioca starch is an important carbohydrate in tropical countries, worldwide. It has a unique bland flavor and gives a stringy cohesive paste when gelatinized. However, its price in the world market is low when compared to starches from other sources. The potential of tapioca starch for use as filler in pharmaceutical tablets was investigated by Atichokudomchai et al., (2001). Native tapioca starch possesses many desirable filler properties. It is as dry, white, odorless, tasteless, insoluble and neutral; however it has poor flowability and compressibility. Native and acid-modified tapioca starches, hydrolyzed with 6 % w/v HCl at room temperature for various reaction times, were compressed into tablets at various compression forces. It was found that native tapioca starch provided tablets with low crushing strength while the crushing strength of tablets prepared from acid-modified tapioca starches increased inline with crystallinity. Tapioca starch hydrolyzed for 192 h provided tablets with an adequate crushing strength without applying excessive compression force. The next study of Atichokudomchai and Varavinit (2003), acid-modified cross-linked tapioca starch was prepared. Native and cross-linked tapioca starches were hydrolyzed with 6 % w/v HCl at room temperature for 192 hrs. The drying process of all starches studied was by spray drying in order to allow formation of agglomerated starch granules, which provided flowability suitable for direct compression. Acid-modified cross-linked tapioca starch

provided higher crushing strength than that of acid-modified tapioca starch. Acid-modified and acid-modified cross-linked tapioca starches were shown to be useful as fillers in direct-compression tablet preparation.

Cross-linked sodium carboxymethyl tapioca starch was prepared by Teruya (1995) based on the method of Kerr and Cleveland (1957). It was found that this modified starch could from gel in cool water and could be used as superdisintegrant in tablet.

Hydroxylpropylated Starches

The last 30 year has seen hydroxypropyl starches go from a laboratory curiosity to being a mainstay of the highly modified starches supplied to the food processing industry. The unique functionality of these starches introduced a new era in food processing, especially in convenience-type products. New product concepts never before possible became reality through the use of this starch.

Hydroxylpropyl starches did not much to further the development of conventional and new convenience-type food products. Use of hydroxylpropylated starch gives improved shelf-life, freeze-thaw stability, cold storage stability, cold water swelling and reconstituting properties to a formulated product. Maximizing functional properties of these products is based on obtaining the optimum balance between hydroxylpropyl substitution, cross-linking (when used), 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.

Hydroxylpropyl groups are hydrophilic in nature and when introduced into the starch granule, weaken or strain the internal bond structure holding the granule together. This reduction in bond strength is reflected in starch pasting temperature. The higher the level of hydroxypropyl substitution, the lower the pasting temperature until the product becomes cold water swelling. The effect of substitution on internal bond strength is also dramatically evident in paste preparation of these products.

When an 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 a three-dimensional network or gel structure in the paste. Chemical substitution of these chains, however, prevents close alignment resulting in a more fluid pate with improved clarity. Although the substituted starch paste thickens when it cools, reheating will return it to original hot viscosity and clarity.

This unique property of modified starch is also evidenced in improved freeze/thaw or cold storage stability. Here the hydrophilic nature of the hydroxypropyl group keeps the water in the starch paste from separating or syneresing when subjected to freeze/thaw cycling.

Cross-linking of hydroxypropyl 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 hydroxypropyl substitution and cross-linking. Careful control of these steps makes possible the "tailoring" of starch products for very specific application conditions.

Hydroxypropyl-modified starches have a very wide spectrum of application. They are being used or evaluated in products that range from blood extentders 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.

In addition, Visavarongroj and Remon (1991) have evaluated hydroxypropyl and pregelatinized hydroxypropyl starch as disintegrant and binder in tablet formulations. The results showed that pregelatinized hydroxypropyl starch exhibited some good disintegrating properties and could be used as a binder in wet granulation,

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, flexible, water-soluble coating, formed by hydroxypropyl starch is desired. In 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 the starch are utilized.

Pregelatinized Starches

There always has been an interest in starches that swell in cold or warm water without cooking. With the growth and acceptance of convenience products, the need for such starches increase. The major methods involve instantaneous cooking-drying starch suspension on steam-heated rolls, puffing, continuous cooking-puffing-extruding and spray drying.

In the instant food preparations such as cake mixes, instant puddings and fruit pie fillings, cold water swelling starches are increasingly used. Aectylated cross-link types offer improved storage stability as they retard the reassociation of molecules in dry mixes. Pregelatinized type are particularly useful in instant gravies, instant pudding and in dry cake mixes for freshness retention. The inherent lumping tendency of these materials is usually reduced by shipping them in form of coarse powder from which fines have been removed. Another method involves incorporation of small amounts of additives such as orthophosphate salts or polyphosphate salts is claimed to be helpful, probably by sequestering with heavy metal ions.

Pregelatinized starches are used in many industrial applications wherever cooking facilities are not available or rapid hydration is desired. The properties of the cold water swelling product depend greatly on the pregelatinizing process and equipment used.

Wierik, et al. (1997) introduced a pregelatinized starch product in directly compressible controlled-release matrix systems. It was prepared by enzymatic degradation of potato starch followed by precipitation (retrogradation), filtration and washing with ethanol. The advantages of the material include ease of tablet preparation, the potential of a constant release rate (zero-order) for an extended period of time and the possibility to incorporate high percentages of drugs with different physicochemical properties. A work by Sinchaipanid (1989) suggested that pregelatinized mungbean starch had potential as a tablet disintegrant.

Carboxymethyl Starch

The first carboxymethyl starch was made in 1924, by reacting starch in an alkaline solution (40 % NaOH) with sodium monochloroacetate. Carboxylation of starch progressively increases water solubility as the DS increases and at higher substitutions they are cold-water soluble and the solutions are water clear. The value of the derivatization stems from inherent properties of the carboxyl group such as chelation, ion-exchange, polyanion flocculation and the acidity function as well as the solution properties that include thickening, gelation, water absorption, adhesion and film formation (with both grease and water resistance).

Monochloroacetic acid is a crystalline solid, mp 63^{o}C, that is corrosive and soluble in water, alcohols and benzene. The reaction with the starchate nucleophile is a bimolecular displacement (S_N2) and the substitution is said to be preferential at the secondary hydroxyls. The high solubility of the derivatives precludes the preparation of derivatives above DS 0.1 in aqueous systems with retention of the granule form. Therefore, the lower alkyl alcohols and acetone in varying proportions with water have served as reaction media.

Preparation of carboxymethyl starch in aqueous medium has been accomplished by using a high content of swamping salt of DS less than 0.07 that retains the granules or by reacting totally dissolved starch and recovering the derivative by precipitation with methyl alcohol. In aqueous systems, highest yields, product viscosity and acid number were obtained at a NaOH/starch weight ratio of 1 and with 7 % starch concentration. The reaction temperature in water is generally 40 to 50°C. The higher DS products, up to 1 have been obtained in essentially nonaqueous reaction media. For example, potato starch was reacted with sodium monochloroacetate in ethyl alcohol (with 15 % water content) using a NaOH/AGU mol ratio of 1.5 to 2. Temperature in the aqueous systems ranged from 20 to 65°C. At DS 0.5, it was noted that the substituents distorted the helical structure to a point that colored complexes would not form. Large sodium monochloroacetate/starch ratios were inefficient.

The viscosity of cold paste is dependent upon the extent of degradation of the starch and, also, on the carboxyl content. The degradation is directly related to carboxyl content or more exactly is related to the conditions of etherification, and the

viscosity is salt-sensitive because the salt counter ion reduce the repulsive charges on the polyanion and lessen molecular extension. The water-solubilizing properties of the carboxylate group have been applied to special advantage in the preparation of insoluble, cross-linked carboxylmethyl starches. In these, the granule while swelling considerably in water is held together by the secondary chemical cross-links, thereby stabilizating solution viscosity. This type of derivative has been patented in many variations as component in disposable absorbent products for physiological fluids and as a protective colloid for drilling muds. For example, one such absorbent was cross-linked with epichlorohydrin (DS 0.003 to 0.2) and was then carboxymethylated to an extent that the product was only 0.6 % soluble in water; it retained 13 g water per gram dry weight of starch derivative. Also, cross-linked carboxymethyl starch, prepared in one-step process with subsequent addition of epichlorohydrin and sodium chloroacetate, is a cation exchanger having a 1.6 meg/g capacity.

The carboxymethyl starches are not harmful to humans expect for ingestion of extraordinarily large quantities (e.g., 60 g/day of DS 0.4 to 0.5 caused diarrhea) and therefore can be used for medical applications such as anions in salts of certain drugs. Carboxymethyl starch or amylose have, in fact, been injected into mice, resulting in a 50% reduction of malignant tumors. In 1967, the carboxymethyl starches were reported as having use or potential value for paper and textile sizing, for soil-suspending agents and numerous other uses resulting from the ability to form viscous aqueous solutions and gels.

Because carboxymethyl starch in many of its applications becomes a waste product, e.g., in textile sizing and desizing operations, biodegradability is an important property. The biodegradability of carboxymethyl starch is, most likely, inversely related to the DS (carboxyl content), as is true of starch derivatives in general. The BOD_5 (5-day BOD) sodium carboxymethyl starch (DS 0.2, molecular weight 2000), used as a particle dispersant, was found to be 1.38 g/g, while a DS 0.1 (used in a detergent formulation) was 55 % depolymerized within 30 hr. Biodegradability is desirable for enzyme activity in removing sizes and for conversion of organic material in secondary on-site treatments of plant effluents. The BOD_5 of sodium carboxymethyl starch has been compared with other textile sizing agents.

Some of the applications of carboxymethyl starch have been already alluded to in the preceding paragraphs. Proposed or actual usages and an approximation percent of the total references from one period, 1977 to 1981, were components of absorbents; adhesives; medical poultices; papermaking, coating, and pulp refining; tablets, binders, and disintegrants; and thickening agents and textile printing. Other applications are as flocculants, antisoil-deposition agents, chelating agent, size, components of film-formers, and dentrifice powders. Carboxymethyl starch is also compatible with many hydrophilic sizing agents, such as polyvinyl alcohol used in paper sizing, in which oil resistance and water insolubility (multivalent-ion salt form) are important contributions.

Fifteen sodium carboxymethyl mungbean starches (SCMMSs or MMSs) were prepared from native starch through a substitution reaction using monochloroacetic acid, using different modification conditions and solvents as shown in Table 2-1 (Kittipongpatana, et al., 2006). The degree of substitution (DS) of the prepared MMSs ranged from 0.06-0.66. Nine modified mungbean starches were freely soluble in unheated water while the other six were partially soluble or only swelled. The pH of water-soluble MMSs was between 9.0–10.5.

Table 2-1 Degree of substitution (DS) and water solubility of MMSs prepared using four different alcoholic solvents and under different conditions (Kittipongpatana, et al., 2006).

MMS #	Solvent	*T* (°C)	Time of reaction (min)	DS	Solubility in water	pH
M-01	92.4% MeOH	50	20	0.0590	×	
M-02	100% MeOH	60	60	0.1953	×	
M-03	100% MeOH	60	120	0.1725	×	
M-04	100% MeOH	70	60	0.3597	✓	9.0
P-01	1-Propanol	50	60	0.3096	✓	9.1
P-02	1-Propanol	50	120	0.5192	✓	9.6
P-03	1-propanol	81	120	0.5277	×	
I-01	2-Propanol	50	60	0.3443	✓	9.2
I-02	2-propanol	81	30	0.5585	✓	9.7
I-03	2-propanol	81	60	0.5526	×	
I-04	2-Propanol	50	120	0.4374	×	
E-01	92.4% EtOH	50	22	0.2011	✓	9.0
E-02	92.4% EtOH	50	30	0.3696	✓	9.4
E-03	92.4% EtOH	50	40	0.5271	✓	9.8
E-04	92.4% EtOH	81	15	0.6551	✓	10.5

A 1 % w/v solution of MMS-M-04 yielded a viscosity of 149.7±1.5 mPas, a 3–5 times higher than that of other MMS solutions (Table 2-2), which indicated that the ability to dissolve in water and form a thick gel was primarily due to the carboxymethyl modification. Freeze-thaw cycles resulted in a decrease of viscosity, especially MMS-M-04, partly due to the loss of water molecules out of the polymer paste. Phase separation, however, was not observed.

Table 2-2 Viscosity of 1 % w/v solution of water-soluble MMSs under normal (room temperature) and freeze-thaw (FT) conditions (eight cycles of a 2 days storage at 8 °C and 2 days storage at 45°C and the thixotropic values (Kittipongpatana, et al., 2006).

Samples	1% Viscosity–normal (mPa s)	1% Viscosity–FT (mPa s)	Thixotropic value (mPa s)
MMS-M-04	149.7±1.5	59.3±0.6	8795±458
MMS-P-01	31.3±0.6	26.0±2.0	−1137±51
MMS-P-02	29.7±0.6	25.7±1.5	−448±143
MMS-I-01	37.3±0.6	29.7±1.5	−1599±38
MMS-I-02	32.7±0.6	26.0±1.0	−505±90
MMS-E-01	31.3±0.6	27.7±1.5	−1557±16
MMS-E-02	22.0±0.0	17.7±0.6	−102±28
MMS-E-03	31.7±0.6	25.0±1.7	−273±70
MMS-E-04	26.0±2.3	22.7±0.6	369±121

The rheograms of water-soluble MMSs showed a pseudoplastic-type rheology, with the formation of a hysteresis loop between the upcurve and the downcurve (Figure 2-4). At 1 % concentration, MMS-M-04 and MMS-E-04 showed thixotropic behavior (i.e. positive thixotropic value), while other MMSs were rheopexy (i.e. negative thixotropic value). These flow behaviors are important information for pharmaceutical applications of MMSs. For example, the high-viscosity MMS-M-04, which also shows a large area of hysteresis loop (Figure 2-4 (A)), is suitable for use as a suspending agent or a gelling agent (hydrogel). Those with lower viscosity and smaller loop area such as MMS-I-01 and MMS-P-01 (Figure 2-4 (B)), can be used as film-forming agent. MMS-E-04 and MMS-E-02, which are relatively non-viscous and show little hysteresis loop can be employed as binder in tablet formulation. In addition, MMSs that is partially soluble but have a high swelling capacity in water can be employed as a disintegrant.

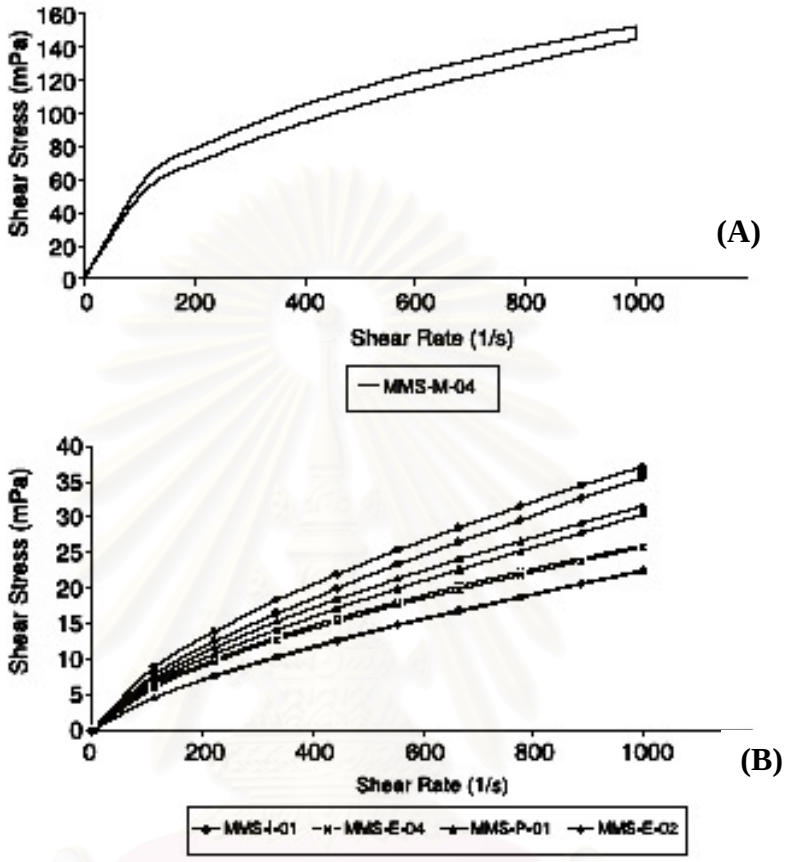


Figure 2-4 Rheograms of selected water-soluble MMSs at 1 % w/v concentration. (A) MMS-M-04 (B) MMS-I-01, MMS-E-04, MMS-P-01, MMS-E-02 (Kittipongpatana, et al., 2006).

High amylose starch (HAS) with more than 70 % amylose and less than 30 % amylopectin was largely used in pharmaceutics as filler, binder or disintegrant (Roper, 1996). The hydroxyl groups play an important role in the organization of the matrix network, which is an important factor in the control of the drug release (Dumoulin, et al., 1998 and Ispas-Szabo, et al., 2000). Many chemical modifications was achieved by partial substitution of hydroxylic groups of HAS with various agents, such as monochloroacetic acid, leading to carboxymethyl groups (Mulhbacher, et al., 2001).

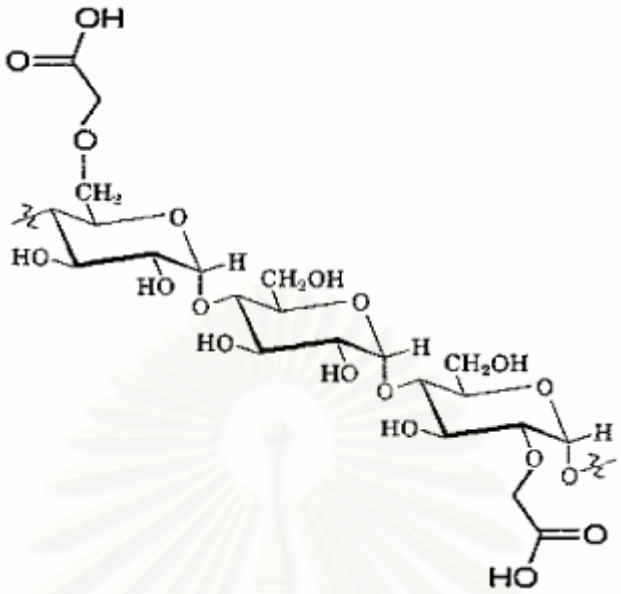


Figure 2-5 Schematic representation of Carboxymethyl High Amylose Starch (CM-HAS).

In addition, carboxymethyl high amylose starch (CM-HAS) (Figure 2-5) appeared to be an interesting excipient-carrier for microorganism transportation through the stomach and delivery in the gut (Calinesc, et al., 2005). The products were dried in powder form and tablets were obtained by direct compression of mixed powders of polymeric excipient and lyophilized Escherichia coli (E. coli) bacteria. Dosage forms of CM-HAS are unswollen and compact in acidic medium, ensuring protection of active agents against acidity. Release of bacteria from CMHAS tablets is based on the fast swelling of the tablets during the passage from gastric acidity to alkaline intestinal medium, enzymatic hydrolysis triggering their rapid, almost total dissolution.

Suwannapakul (1996) prepared carboxymethyl starch by a substitution reaction modified using the method described by Filbert (1952). The results indicated that modified glutinous rice starch, modified rice starch and modified tapioca starch with degrees of substitution of 0.16, 0.26 and 0.38 could be used as suspending agent in ibuprofen suspension preparations for 3 months storage. However, it was found that the viscosity of the preparations decreased as time and those modified starches would lose their suspension property for long storage time (>3 months). The next study of

Luprasong (2003) used those modified starches as a suspending agent in reconstituted dry syrup. It was found that those modified starches with degrees of substitution of 0.16, 0.26 and 0.38 could be used as suspending agent in reconstituted dry syrup of amoxicillin trihydrate and cephalexin monohydrate. In addition, it was found that salt of the buffer system decreased the viscosity of sodium carboxymethyl starch in amoxicillin trihydrate and cephalexin monohydrate dry syrup.

Xanthan Gum

Xanthan gum is a high-molecular-weight, specially designed anionic polysaccharide that functions as a hydrocolloid and suspending agent. Xanthan gum contained three different monosaccharides: mannose, glucose, and glucuronic acid (as salt). Each repeating block of polymer chain has 5 sugar units (2 glucose, 2 mannose, 1 glucuronic acid). The main chain is made of β–D-glucose units linked through the 1 and 4 positions. The two mannose units and glucuronic acid units make up the side chain. The terminal β–D-mannose unit is glycosidically linked to the 4 position of β–D-glucuronic acid which in turn is linked to the 2 position of α-D-mannose. This side chain is linked to the 3 position of every other glucose residue on average in the polymer main chain. Roughly half of the terminal D-mannose residue carries a pyruric acid residue linkeketalically to the 4 and 6 positions. The nonterminal D-mannose unit on the side chain has an acetyl group at the 6 position (Figure 2-6).

Xanthan gum is soluble in hot and cold water and imparts high viscosity at low concentration with pseudoplastic flow characteristics. Aqueous xanthan gum systems exhibit gel behavior at a very low pH. Gel persistence under shear, viscosity, and pseudoplasticity all increase with xanthan gum concentration. Compared to other cellulose agents and/or polysaccharides, xanthan gum solutions are unusually resistant to prolonged shear. A 1% xanthan gum solution sheared at 46,000 reciprocal seconds for one hour exhibited no significant loss of viscosity.

Temperature has very little on the viscosity of xanthan gum solutions. The small change in viscosity that does occur with temperature is reversible. This temperature independence of viscosity is unique to xanthan gum and is a very desirable attribute for product shelf-life. Products containing xanthan gum stored at elevated temperature are

stable and exhibit minimal loss of viscosity. There is no significant change in the viscosity of a solution over a wide pH range of 1-10.

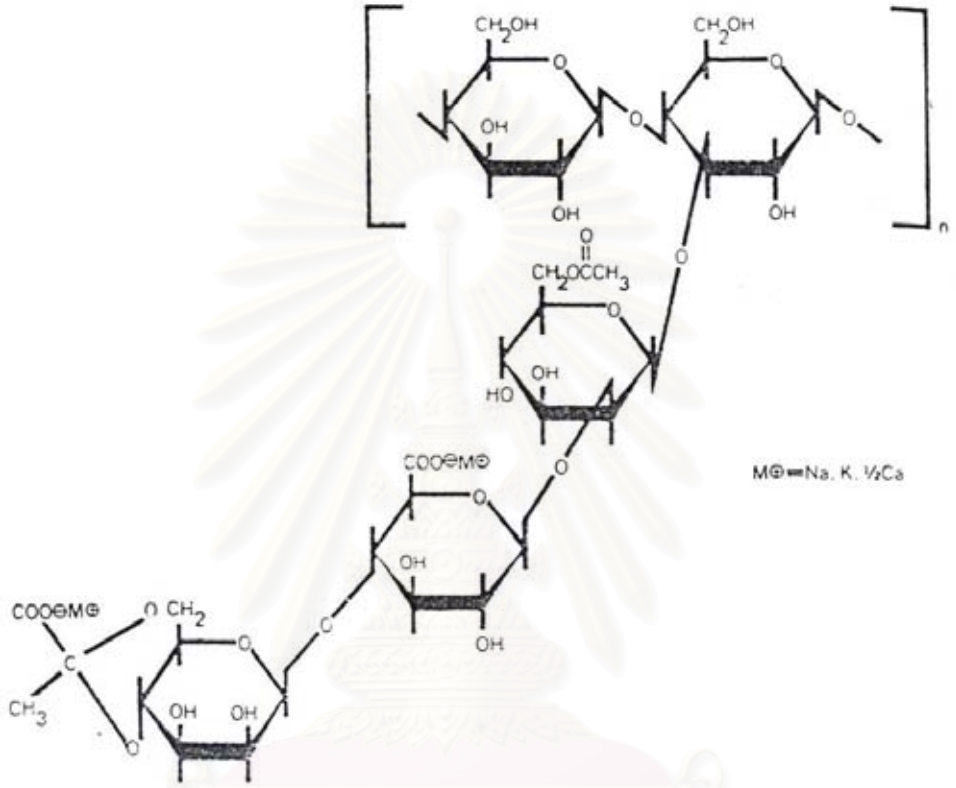


Figure 2-6 Structure of xanthan gum (Bhargava and Nicolai, 1988).

Solutions of xanthan gum are compatible with virtually all mono and divalent cations such as sodium, calcium and magnesium over a wide pH range and with many pharmaceutical adjuvants such as polyols, alcohol, acidulants, chelating agents, and preservatives. Because of its anionic nature, xanthan gum is incompatible with cationic drugs and preservatives. It is not influence by a freeze-thaw cycle and is resistance to enzymatic degradation. However, xanthan gum solutions are susceptible to microbiological degradation on prolonged storage and do require a preservative to maintain the microbial integrity of the product (Bhargava and Nicolai, 1988).

Tragacanth Gum

Gum tragracanth N.F. is an anionic exudates polysaccharide made up of a soluble portion, tragacanthin and an insoluble portion, bassorin. Tragacanth swells in cold water to produce a highly viscous colloidal dispersion. It is insoluble in alcohol or organic solvents. Gum tragacanth is one of the most efficient natural polymer thickeners. The highest viscosities are obtained when solution are made in cold water. The use of heat in solution preparation causes a certain amount of degradation and a loss of at least 1/3 the original viscosity due to chain scisson. Tragacanth is graded by its viscosity in water. Ribbon grade tragacanth exhibits the highest viscosity and flak grade is slightly lower. Solutions of gum tragacanth exhibit pseudoplastic flow.

Tragacanth solutions are stable over a wide pH range. In fact, these solutions exhibit good stability at low pH. For this reason, it is often chosen as the thickener for low pH food products such as salad dressings and sauces. Divalent and trivalent cations, as well as storage at elevated temperature, may cause a reduction in viscosity (Zatz, et al., 1988).

Mohammadifar et al., (2006) studied the rheological behavior of aqueous solutions of gum tragacanth and its insoluble and soluble fractions (bassorin and tragacanthin, respectively). They showed that typical flow curves, at 25°C, for gum tragacanth, tragacanthin and bassorin solutions, in the absence of salt are shown in Figure 2-7. In all cases the behaviour was shear thininng. However, for similar concentrations, (i) bassorin solution was more viscous than tragacanthin solution and gum tragacanth showed a thickening efficiency between these two and (ii) as shown in Figure 2-8 even in the presence of 0.1 M NaCl, at very low or very high shear rates bassorin did not show Newtonian regions but in the case of tragacanthin solutions, a low shear Newtonian region was observed.

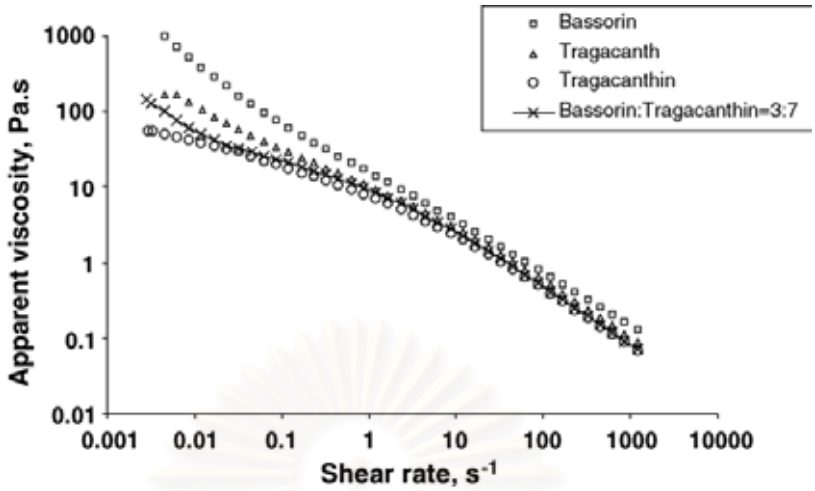


Figure 2-7 Viscosity of 1 % solution of gum tragacanth and its fractions at 25 °C as a function of shear rate.

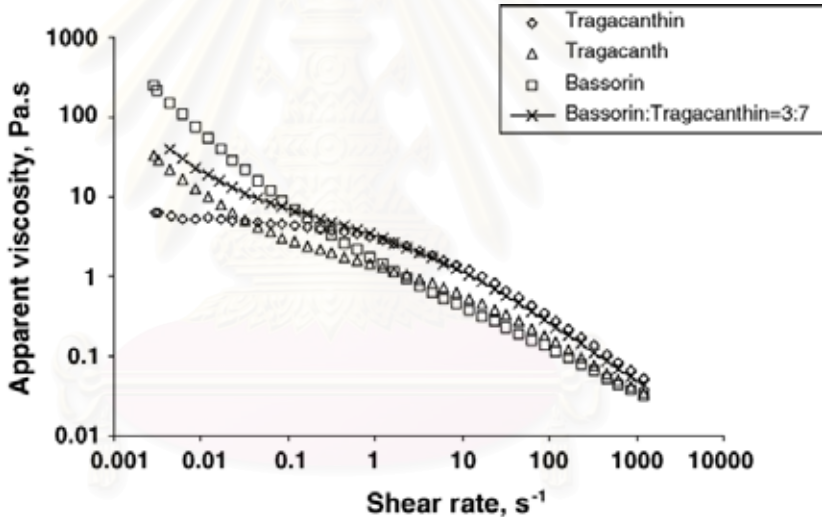


Figure 2-8 Viscosity of 1 % solution of gum tragacanth and its fractions at 25 °C as a function of shear rate in the presence of 0.1M NaCl.

Rheology

In suspension formulation, the rheology of the suspending agent usually dominates the overall properties of the suspension. A study showed that an ideal suspending agent should be shear thinning, should have a high viscosity at low shear for shelf stability and a low viscosity at high shear for easy dispensing (Deem, 1998)

The rheological behavior of a pharmaceutical suspension furnishes the formulator with a means of exercising the greatest control over sedimentation and optimization of the physical stability of the system. The choice of the type of rheology depends to a large extent on the type of bodying agent and its intended application. If the medium is viscous enough, like castor oil or glycerin, a bodying agent may not be necessary to enhance the viscosity. However, if the medium is nonviscous, like alcohol or water, a bodying agent may be necessary to impart the desired viscosity to the medium. For example, a suspension for topical application should be fluid enough to permit proper shaking and pourability yet should not flow readily from the skin. It should also provide sufficient resistance against gravitational settling while in container.

A fluid may exhibit Newtonian or non-Newtonian flow. The non-Newtonian type of behavior includes pseudoplastic, plastic thixotropic, or dilalant flow characteristics, as shown in Figure 2-9. The combination of desired attributes requires careful selection of an additive that will impart non-Newtonian flow characteristics to the suspension. (Bhargava and Nicolai, 1988)

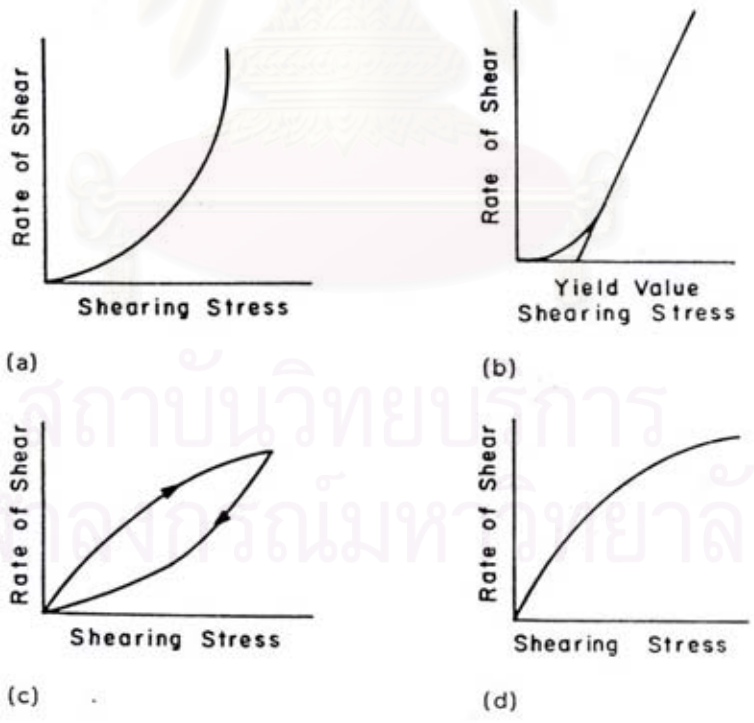


Figure 2-9 Plots of rate of shear as a function of shearing stress for (a) simple pseudoplastic, (b) plastic, (c) thixotropic, and (d) dilatant flow.

Pseudoplasticity

The viscosity of a system exhibiting pseudoplastic flow is inversely proportional to the shear rate. As shear stress is increased, the resistance to flow decrease (Figure 2-9a), and the system becomes more fluid. This shear-thinning behavior is called pseudoplasticity. The apparent viscosity of such a system therefore cannot be defined in terms of on value. Many colloidal systems, especially polymer solutions, exhibit pseudoplastic flow.

Plasticity

Plastic behavior is characterized by the presence of a yield value (Figure 2-9b). Some materials like semisolids do not flow at low shear stress. A Bingham body does not flow until shearing stress equals or exceeds the yield value. Once the shear stress equals or exceeds the yield value, the composition begins to flow. This system exhibits solidlike behavior under quiescent conditions. This property of plastic flow may effectively inhibit sedimentation altogether in a suspension. Agitation temporarily disrupts the rigid network of solids, making it possible to pour or apply the suspensions to skin.

Thixotropy

Thixotropy, which may be seen in both plastic and pseudoplastic systems, is characterized by the fact that the rate of shear at any given shearing stress can vary depending on whether the rate of shear is increasing or decreasing. Thixotropy is a measure of the breakdown and then rebuilding of the structure of the system. Thixotropic systems contain a structural network of colloidal particles. At rest this structure confers some degree of rigidity on the system, but when disrupted by shear, the system begins to flow. Upon removal of shear stress, the structure begins to reform. The reformation of structure is time-dependent and can take from several minutes to hours or days. During this time, the product can be poured from the container. The apparent viscosity of a thixotropic system depends not only on the shear rate and shear stress, but also on duration under shear.

The most apparent characteristic of a thixotropic system is the presence of a hysteresis loop which is formed by the up and down curve of the rheogram (Figure 2-9c). The area of a hysteresis loop has been proposed as a measure of thixotropic breakdown and rebuilding of the structure and can be easily obtained.

Dilatancy

A dilalant system exhibits an increase in the resistance to flow when stress is exerted; thus the system returns to its original state of fluidity when the stress is removed (Figure 2-9d). A dilalant system is the reverse of a pseudoplastic system and is a shear thickening system.

Pharmaceutical suspensions that exhibit plastic or thixotropic rheological behavior generally exhibit good physical stability. Such a suspension may prevent sedimentation, aggregation, and caking by virtue of its high-yield value at rest, yet reduce viscosity significantly to permit its application. On the other hand, pseudoplastic or dilatant flow characteristics are undesirable in a suspension as they impart physical instability to the product (Bhargava and Nicolai, 1988).

Bulges and Spur

Dispersions employed in pharmacy may yield complex hysteresis loops when sheared in a viscometer in which shear rate (rather than shear stress) is increased to a point, then decreased, and the shear stress is read at each shear rate value to yield appropriate rheograms. Two such complex structures are shown in Figure 2-10 and 2-11. A concentrated aqueous bentonite gel, 10 to 15% by weight, produces a hysteresis loop with a characteristic *bulge* in the up-curve. It is presumed that the crystalline plates of bentonite form a “house-of-cards structure” that causes the swelling of bentonite magmas. This three-dimensional structure results in a bulged hysteresis loop as observer in Figure 2-10. In still more highly structured systems, such as a procaine penicillin gel, for intramuscular injection, the bulged curve may actually develop into a spur-like protrusion (Figure 2-11). The structure demonstrates a high yield or *spur value*, Y, that traces out a bowed up-curve when the three-dimensional structure breaks in the viscometer, as observed in Figure 2-11. The spur value represents a sharp point of

structural breakdown at low shear rate. It is difficult to produce the spur, and it may not be observed unless a sample of the gel is allowed to age undisturbed in the cup and bob assembly for some time before the rheologic run is made. The spur value is obtained by using an instrument in which the rate of shear can be slowly and uniformly increased, preferably automatically, and the shear stress read out or plotted on X-Y recorder as a function of shear rate. It was found that penicillin gels having definite Y values were very thixotropic, forming intramuscular depots upon injection that afforded prolonged blood levels of the drug (Martin, 1993).

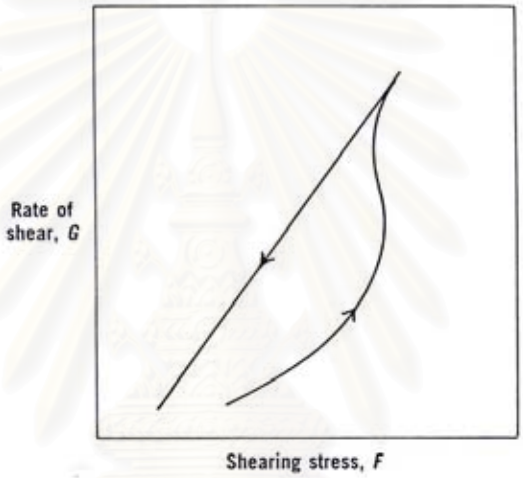


Figure 2-10 Rheogram of a thixotropic material showing a bulge in the hyteresis loop.

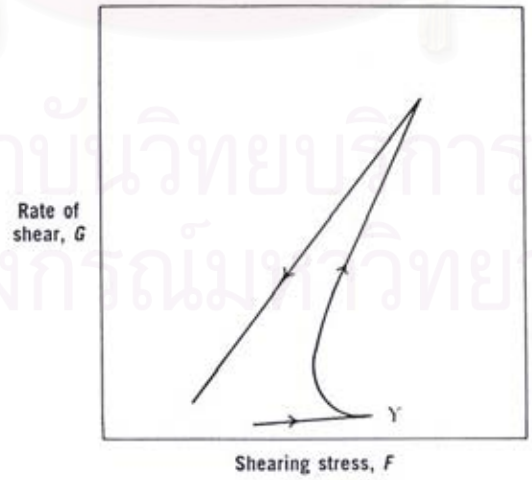


Figure 2-11 Rheogram of a thixotropic material showing a spur value Y in the hyteresis loop.

Negative Thixotropy

From time to time in the measurement of supposedly thixotropic materials, one observes a phenomenon called *negative thixotropy* or *antithixotropy*, which represents an increase rather than a decrease in consistency on the down-curve. This increase in thickness or resistance to flow with increased time of shear was observed in the rheologic analysis of magnesia magma. It was detected at shear rates of greater than 30 sec^{-1}; below 30 sec^{-1} the magma showed normal thixotropy, the down curve appearing to the left of the up-curve. Antithixotropy had been reported by other investigators, but not in pharmaceutical systems.

It was observed that when magnesia magma was alternately sheared at increasing and then decreasing rate of shear, the magma continuously thickened (an increase in shearing stress per unit shear rate) but at a decreasing rate, and it finally reached an equilibrium state in which further cycles of increasing-decreasing shear rate no longer increased the consistency of the material. The antithixotropic character of magnesia magma is demonstrated in Figure 2-12. The equilibrium system was found to be gel-like and to provide great suspendability, yet it was readily pourable. When allowed to stand, however, the material returned to its sol-like properties.

Antithixotropy or negative thixotropy should not be confused with dilatancy or rheopexy. Dilatant systems are deflocculated and ordinarily contain greater than 50 % by volume of solid dispersed phase, whereas antithixotropic systems have low solid content (1 to 10 %) and are flocculated. *Rheopexy* is a phenomenon in which solid forms a gel more readily when gently shaken or otherwise sheared that when allowed to form the gel while the material is kept rest. In a rheopectic system, the gel is the equilibrium form, where as in antithixotropy, the equilibrium state is the sol. Magnesia magma and clay suspensions may show a negative rheopexy, analogous to negative thixotropy. It is believed that antithixotropy result from an increased collision frequency of dispersed particles or polymer molecules in suspension, resulting in increased interparticle bonding with time. This changes the original state consisting of a large number of individual particles and small floccules to an eventual equilibrium state consisting of a small number of relatively large floccules. At rest, the large floccules

break up and gradually return to the original state of small floccules and individual particles (Martin, 1993).

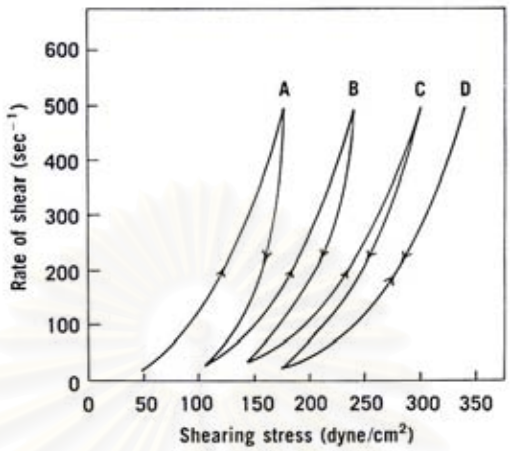


Figure 2-12 Rheogram of magnesia magma showing antithixotropic behavior. The material is sheared at repeated increasing and then decreasing rates of shear. At stage D, further cycling no longer increased the consistency, and the up- and down-curves coincided (Martin, 1993).

CHAPTER III
EXPERIMENTAL

Materials

The following materials were obtained from commercial sources and deionized water was used throughout the study

1. Starch material
   - Tapioca starch (New Grade, Thai Wan Food Products Public Co., Ltd, Thailand)
2. Commercial modified starches
   - Fully pregelatinized tapioca starch (MFG. 20/05/05, Bangkok Starch Industrial Co., Ltd, Thailand)
   - Hydroxypropyl tapioca starch (MFG. 10/08/05, Bangkok Starch Industrial Co., Ltd, Thailand)
   - Cross-linked hydroxypropyl tapioca starch (MFG. 20/05/05, Bangkok Starch Industrial Co., Ltd, Thailand)
   - Ultrasperse®2000 (Batch No. BJ-7537, Supplied by National starch & Chemical(Asia) Pte Ltd.)
3. Commercial suspending agents
   - Xanthan gum (Batch No. 6328501, Pkelco, Germany)
   - Tragacanth (Lot No. TEC 14/382, Srichand United Dispensary Co; Ltd, Thailand)
4. Model drug
   - Ibuprofen (Lot No. 2050-0049D, micronized grade(20µ), Albemarle Corporation, USA)
5. Material used for starch modification
   - Monochloroacetic acid (Lot. No. 452459/1 42004029, Fluka Chemika, Germany)
   - Absolute methanol (Lot No. K31725209, Merck, Germany)
   - Methanol
   - Glacial acetic acid (Lot No. K18049863, Merck, Germany)
   - Sodium hydroxide (Lot No. B460750 412, BDH Laboratory, England)
   - Ethanol (commercial grade)

- Sodium chloride (Batch No. AF309070, Ajax Finechem, Australia)
- m-Cresol purple TS (Aldrich Chemical Co; Inc,USA)
- Hydrochloric acid (Lot No. 538193, J.T. Baker, USA)
- Sulfuric acid (Lot No. 9681-03, J.T. Baker, USA)
- Silver nitrate (E Merck, Germany)
- Sodium trimetaphosphate (Lot No. 012K1712, Sigma, USA)
- Calcium acetate (Batch No. 0525/01/04, Polskie Odczynniki Chemiczne S.A., Germany)
- Nitric acid (Lot No. K31570467 250, BDH Laboratory, England)
- Ammonium metavanadate (Lot No. A365458, BDH Laboratory, England)
- Amonium molybdate (Batch No. AF404332, Ajax Finechem, Australia)
- Potassium phathalate (Lot No. 0689M100, Carlo ERBA, Italy)

6. Suspension additives
   - Tween80 (Lot No.405854, Srichand United Dispensary Co; Ltd, Thailand)
   - Sucrose (Mitrphol, Thailand)
   - 70% Sorbitol solution (Lot No. 70-010946, S. Tong Chemicals Co; Ltd, Thailand)
   - Sodium saccharin (Lot No. 9532, Srichand United Dispensary Co; Ltd, Thailand)
   - Methyl paraben (S. Tong Chemicals Co; Ltd, Thailand)
   - Propyl paraben (S. Tong Chemicals Co; Ltd, Thailand)
   - Pineapple essence (Lot No. 67463, 718609, Bush Boake Allen, England)
   - Sunset Yellow (Lot No. 6-6001, Butterfield Food Ingredients limited, England)
7. Others
   - Citric acid monohydrate (Lot No. K91112639 903, BDH Laboratory, England)
   - Disodium hydrogen phosphate anhydrous (Lot No. 91706290B, Carlo ERBA, Italy)
   - Sodium dihydrogen phosphate monohydrate (Lot No. 941A420746, Merck, England)
   - Orthophosphoric acid (Batch No. A3B017, Ajax Finechem, Australia)

- Trisodium orthophosphate (Batch No. A2220-500G, Ajax Finechem, Australia)
- Acetonitrile HPLC Grade (Lab-scan Analytical Sciences, Ireland)
- Acetonitrile AR Grade (Lab-scan Analytical Sciences, Ireland)

Methods

1. Preparation and Evaluations of Modified Starches

1.1 Preparation of modified starches

Five modified tapioca starches were used in this study, pregelatinized tapioca starch (PGTS), hydroxypropyl tapioca starch (HPTS), cross-linked hydroxypropyl tapioca starch (CHPTS), sodium carboxymethyl tapioca starch (SCMS), and cross-linked sodium carboxymethyl tapioca starch (CSCMS). In this experiment two modified starches (sodium carboxymethyl tapioca starch, and cross-linked sodium carboxymethyl tapioca starch) were made in the laboratory and others were supplied by manufacturing company.

1.1.1 Modification of sodium carboxymethyl tapioca starches

The method of preparation was modified from Filbert's method (1952). Ornanong Suwannapakul (1996) found that sodium carboxymethyl tapioca starch at degree of substitution of 0.16, 0.26 and 0.38 were suitable to be used as suspending agent in liquid preparation. To obtain three different degrees of substitution, methods of preparation were as follows;

1.1.1.1 Degree of substitution of 0.16 (SCMS-1)

The absolute methanol of 254 g and monocholoroacetic acid of 27.6 g were weighed and thoroughly mixed. Tapioca starch of 109 g was added together with continuous mixing by using stirrer (Erweka, Germany) at 200 rpm in closed system. 50 % aqueous solution sodium hydroxide of 110 g was added then heated the mixture to 60°C for 60 minutes, providing good agitation. The product was neutralized with glacial acetic acid to pH 7.0. Removed mother liquor and washed with 80 % methanol for several times until free of sodium chloride in filtrate, tested by silver nitrate. Finally, the product was washed with 100 % methanol and dried in hot air oven (Memmert, type ULSO, Germany) at 50° C overnight .The dried product was sieved through No.80 mesh screen and stored in desiccator.

1.1.1.2 Degree of substitution of 0.26 (SCMS-2)

The absolute ethanol of 286 g and monocholoroacetic acid of 29.2 g were weighed and thoroughly mixed. Tapioca starch of 102 g was added together with continuous mixing by using stirrer at 200 rpm in closed system. The solution of 97 % sodium hydroxide flake 38.4 g in 69 g of water was added. Then, heated the mixture to 50°C and maintained for 20 minutes, providing good agitation. The product was neutralized with glacial acetic acid to pH 7.0. Removed mother liquor and washed with 80 % methanol for several times until free of sodium chloride in filtrate, tested by silver nitrate. Finally, the product was washed with 100 % methanol and dried in hot air oven at 50° C overnight. The dried product was sieved through No.80 mesh screen and stored in desiccator.

1.1.1.3 Degree of substitution of 0.38 (SCMS-3)

The absolute ethanol of 286 g and monocholoroacetic acid of 29.2 g were weighed and thoroughly mixed. Tapioca starch of 102 g was added together with continuous mixing by using stirrer at 200 rpm in closed system. The solution of 97 % sodium hydroxide flake 38.4 g in 69 g of water was added. Then, heated the mixture to 50°C and maintained for 120 minutes, providing good agitation. The product was neutralized with glacial acetic acid to pH 7.0. Removed mother liquor and washed with 80 % methanol for several times until free of sodium chloride in filtrate, tested by silver nitrate. Finally, the product was washed with 100 % methanol and dried in hot air oven at 50° C overnight. The dried product was sieved through No.80 mesh screen and stored in dessicator.

1.1.2 Modification of cross-linked sodium carboxymethyl tapioca starches

Selected the sodium carboxymethyl tapioca starch with DS of 0.22 that was produced in the part 1.1.1 to modify as cross-linked sodium carboxymethyl tapioca starch by Kerr and Cleverland's method (Kerr and Cleveland, 1957) because it provided the highest viscosity compared with three degrees of substitution of sodium carboxymethyl tapioca starch.

One gram of sodium trimetaphosphate were dissolved in 352 ml of 95 % ethanol and thoroughly mixed by using stirrer (Erweka, Germany) at 200 rpm in closed system. Add 162 grams (on dried basis) of the most viscosity of substitution of sodium carboxymethyl tapioca starch that was done in the part 1.1.1 and 66.5 grams of sodium carbonate. Then, heated the mixture to 50°C and maintained for 2, 8 and 16

hours, providing good agitation. After that, the product was adjusted pH to 6.7 with hydrochloric acid. Removed mother liquor and washed with 80 % methanol for several times until free of phosphate in filtrate, tested by silver nitrate. Finally, washed with 100 % methanol and dried in hot air oven at 50° C overnight. The dried product was sieved through No.80 mesh screen and stored in desiccator.

1.2 Evaluation of the physico-chemical properties of modified tapioca starches

1.2.1 Evaluation of sodium carboxymethyl tapioca starch

1.2.1.1 Chemical evaluation

1.2.1.1.1 Determination of a degree of substitution (DS)

The procedure which was used to determine a degree of substitution of sodium carboxymethyl tapioca starch was the same method as for Croscarmellose sodium in USP 28. There were two steps in this method. One is titration step and another is residue on ignition step. Each sample was tested in tripicated. The procedures are as followes;

Step 1 : Titration step

One gram of starch sample was weighed accurately and transferred to 500 ml of glass-stoppered conical flask. Add 300 ml of sodium chloride solution (1 in 10) and 25 ml of 0.1N sodium hydroxide. After that, the stopper was inserted and the mixture was allowed to stand for 5 minutes with intermittent shaking. Five drops of m-cresol purple TS and about 15 ml of 0.1 N sodium chloride were added, insert the stopper in the flask and shake. When the solution was purple, 0.1 N hydrochloric acid in 1 ml portion was added until the solution was yellow, shaking after each addition. Then, the sample was titrated with 0.1N sodium hydroxide until the endpoint was purple. Finally, the net number of milliequivalents (M) of base required for the neutralization of 1 gram of sodium carboxymethyl tapioca starch was calculated on dried basis.

Step 2 : Residue on ignition step

One gram of starch sample was weighed accurately into a suitable crucible. The crucible was previously been ignited, cooled and weighed. The sample was heated at first until the substance was thoroughly charred. The sample was cooled to the room temperature; the residue was moistened with 1 ml of sulfuric acid. After that, the sample was heated gently until white fumes were no longer evolved. The sample was ignited in the Muffle furnace which had the temperature 800±25° C until

the carbon was consumed. Then, sample was took into the desiccator, cooled and weighed. Finally, the percentage of residue on ignition (C) was calculated.

The degree of substitution (DS) could be calculated by (USP 28):

DS = A + S

In which A = degree of acid carboxymethyl substitution

= 1150M / (7102-412M-80C)

S = degree of sodium carboxymethyl substitution

= (162 + 58A) C / (7102-80C)

M = milliequivalent of base required for the neutralization of 1 g of modified starch

C = percentage of residue on ignition

1.2.1.2 Detection of carboxymethyl substitution in modified tapioca starches

Fourier-transformed infrared spectrometer (Perkin Elmer, 1760X, USA.) was used to detect the carbonyl group in the prepared starches. The samples were prepared as KBr pellets and scanned with the speed of three seconds per scan. IR spectrum of native starch was compared with IR spectrum of modified starch. The presence of carbonyl group was used as evidence of substitution of carboxymethyl group in modified starches.

1.2.1.3 Moisture content

The moisture content of modified tapioca starches was determined by moisture determination balance (Mettler Toledo, Switzerland). One gram of sample was weighed and heated at 105 °C until constant weight was achieved.

1.2.2 Evaluation of cross-linked sodium carboxymethyl tapioca starches

1.2.2.1 Chemical evaluation

1.2.2.1.1 Determination of phosphate contents

The phosphate contents were determined by determination of the percentage of phosphorous in the sample. The small amount of phosphorous in sample of modified tapioca starch was determined by using ultraviolet/visible recording spectrophotometry (Model V-530, Jasco, Japan). This method was employed by Corn Industries Research Foundation (Lyne, 1976)

Weighed 10.0 g of starch sample into evaporating dish, added 10 ml of 2% calcium acetate solution in a fine steam. Distributed the solution uniformly in the sample and then evaporated to dryness on hot plate and carbonized the sample. Place the dish in the muffle furnace at 650 °C until free of carbon. Then cooled to room temperature and wetted the ash with 15 ml of water. Slowly washed down the sides of the dish with 5 ml of 29% nitric acid, quantitatively transferred to a 200 ml volumetric flask and rinsed the dish with three 20 ml portions of distilled water. Diluted to the volume with distilled water and mixed thoroughly.

Transferred 2.50 ml of prepared sample to 100 ml volumetric flask, add 50 ml of water to another flask to serve as blank. To each flask, add 10 ml of 29% nitric acid and 10 ml of 0.25% ammonium metavanadate, and then add 10 ml of 5% ammonium molybdate, mixing thoroughly after addition of each reagent. Diluted to volume with distilled water, mixed thoroughly and allowed to stand for 10 minutes.

The sample was determined the absorbance at 460 nm. The phosphorous content was calculated from the absorbance curve which was performed by using standard phosphorous solution.

$$\% \text{ phosphorous} = \frac{(P \times \text{dilution volume in ml} \times 100)}{(\text{aliquot volume in ml} \times \text{sample weight in g} \times 1000)}$$

Where P is phosphorous content (mg/100 ml) from calibration curve.

$$\% \text{ phosphate} = \% \text{ phosphorous} \times 3.065$$

1.2.2.1.2 Detection of phosphate substitution in modified tapioca starches

Fourier-transformed infrared (FIIR) spectrometer was used to detect the phosphate group in the prepared starches. The samples were prepared as KBr pellets and scanned with the speed of three seconds per scan. IR spectrum of native starch was compared with IR spectrum of modified tapioca starches.

1.2.2.1.3 Moisture content

The moisture content of modified tapioca starches was determined by moisture determination balance (Mettler Toledo, Switzerland). One gram of sample was weighed and heated at 105 °C until constant weight was achieved.

2. Evaluations of Modified Tapioca Starches as Suspending Agent

Each of modified tapioca starches (SCMS, CSCMS, PGTS, HPTS and CHPTS), Ultrasperse®2000 (UT), xanthan gum (XG) and tragacanth (TG) were dispersed in water. In order to completely hydrate the modified starches, they were kept at room temperature overnight.

2.1 Viscosity measurement of modified tapioca starches and other suspending agents

The measurement of viscosity was performed by Haake RotoVisco1® rheometer (Haake Mess-Technik GmbH u. Co., Germany) which has measuring plate no. P61, rotor C35/1 and cone with diameter 35 mm, 1°; Titan. The viscosity was determined at shear rate 100 s^{-1} at 90 seconds. The viscosity was measured in triplicate at room temperature.

2.2 Rheological studies of modified tapioca starches and other suspending agents

2.2.1 Rheological determination of modified tapioca starches and other suspending agents.

Rheological behaviors of the dispersion of five modified starches, UT, XG and TG were investigated by Haake RotoVisco1® rheometer at room temperature. The shear rate of sample was increased by step from 0 to 1,000 s^{-1} within 60 seconds and maintained at the shear rate of 1000 s^{-1} for 30 seconds. Then, the shear rate was decreased by step from 1,000 to 0 s^{-1} within 60 seconds. The experiments were performed in triplicate.

2.2.2 Measurement of thixotropic value

The rheogram was constructed from shear rate (sec^{-1}) versus shear stress (Pa) which showed thixotropic loops for two different times intervals (Deem, 1996). The area enclosed within up-curve and down-curve was known as hyteresis loop (Deem, 1996; Falkiewicz, 1996). The thixotropic value could be calculated from the area of hysteresis loop by differentially integrating area between up curve and down curve. In this experiment, the thixotropic value was achieved from Rheo Win3.12 program of Haake RotoVisco1® rheometer.

3. Effect of Electrolytes, Acid-Base and Buffers on Viscosity and Rheological Behaviors of Modified Tapioca Starches and Other Suspending Agents

The similar viscosity of all modified tapioca starches and other suspending agents were selected from the previous part (2.1). The concentration of 6 % w/v SCMS-1, 2.5 % w/v SCMS-2, 3 % w/v SCMS-3, 0.8 % w/v CSCMS-2, 1.15 % w/v CSCMS-8, 1.95 % w/v CSCMS-16, 8.5 % w/v PGTS, 7.5 % w/v HPTS, 5.5 % w/v CHPTS and 4.5 % w/v UT were selected because they gave the viscosity in the range of 413.33-478.67 cps. For XG and TG it could not prepare in the range of those viscosity so, the concentration of 2.5 % w/v of them that provided the viscosities of 529 and 612 cps, respectively were selected. Each concentration of all modified tapioca starches and other suspending agents were dispersed in various media and their rheological characterizations were studied as following:

3.1 Effect of electrolyte

Sodium chloride solutions at concentration of 0.001, 0.01, 0.1, 0.2, and 0.5 M were used as medium. The samples in those media were studied viscosity and rheological behaviors follow as No. 2.1 and 2.2.

3.2 Effect of type of buffer and pH

Two types of buffer (Phosphate and Citrate buffer) which adjusted the total ionic strength to 0.2 M by NaCl were evaluated as following;

3.2.1 Phosphate buffer at pH of 3, 5, 7 and 9 were used as media. Those buffers were fixed at concentration of 0.05 M and adjusted ionic strength to 0.2 M by sodium chloride. The samples in those buffers were studied viscosity and rheological behaviors as previously described in No. 2.1 and 2.2.

3.2.2 Citrate buffer at pH of 2, 4, and 6 were used as media. Those buffers were fixed concentration at 0.04 M and adjusted ionic strength to 0.2 M by sodium chloride. The samples in those buffers were studied viscosity and rheological behaviors as previously described in No. 2.1 and 2.2.

4. Evaluation of Modified Tapioca Starches as Suspending Agent in Ibuprofen Suspension

4.1 Preliminary study suspension preparations

The suitable type and concentration of various modified tapioca starches were used as suspending agents in formulation of ibuprofen suspension (100 mg/5ml) according to the formulation shown below:

Ibuprofen	2 g
Tween 80	0.25 g
Suspending agent	qs.
Syrup USP	15 ml
70 % Sorbitol solution	15 ml
Sodium saccharin	0.02 g
Methyl paraben	0.18 g
Propyl paraben	0.02 g
Propylene glycol	0.8 ml
Pineapple essence	0.2 ml
2 % Sunset yellow	0.1 ml
Purified water qs.	100 ml

Suspending property of modified tapioca starches was compared with that of UT, XG and TG. The percentage of all suspending agents in the preparation was varied at three concentration levels which were selected by the concentration that it started to form gel. All of ingredients were added in the preliminary study except pineapple essence and 2 % sunset yellow.

The preparation procedure was as follows:

1. All suspending agents were hydrated overnight.
2. Wet Ibuprofen with tween 80 in mortar.
3. Add overnight hydrated suspending agent in (2) and mixed thoroughly.
4. Add syrup USP, 70 % sorbitol solution, and 1 ml of stock solution of stock solution containing 18 % w/v of methyl paraben and 2 % w/v propyl paraben in propylene glycol in (3) and mixed thoroughly.

5. Dissolved sodium saccharin in water about 10 ml and add in (4).
6. Add Pineapple essence and 2 % w/v of sunset yellow (in the part of stability test).
7. Adjusted volume to 100 ml.
8. Mixed by high speed dispenser for 15 minutes.

4.2 Evaluation of ibuprofen suspension

The preparations of ibuprofen suspension were stored at room temperature for 4 weeks. Rheological studies of ibuprofen suspension were investigated at start and 4 weeks. The samples were evaluated such as physical appearance, viscosity, sedimentation volume, redispersibility, and pH every week.

4.2.1 Physical appearance

The sample was observed in color, and sediment appearance.

4.2.2 Viscosity

The viscosities of ibuprofen suspension preparations containing of each modified starches, UT, XG and TG at various concentrations were determined by Brookfield viscometer (Brookfield DV-II+ Programmable Viscometer, USA) at 10 rpm of spindle No. S31. The determinations were repeated in triplicate at room temperature.

4.2.3 Sedimentation volume

The sedimentation volume of ibuprofen suspension was determined at room temperature over a period of one month using the cylindrical graduate method (Nasipuri and Ogumlana, 1978). The procedure is as follows: 50 ml suspensions were stored in 100 ml graduated glass cylinders. Each sample was shaken to ensure uniformity prior to the study. Sedimentation height was measured and recorded every week without disturbing the suspension. The sedimentation volume (SV) was calculated from the ratio of the ultimate height (Hu) of the sediment to the initial height (Ho) of the total suspension. The sedimentation volume was measured in triplicate.

$$\text{Sedimentation volume (SV)} = \frac{Hu}{Ho}$$

The total and compact sedimentation volumes were determined. The total sedimentation volume was the part of non transparent plus compact sediment. The total sedimentation volume was the ratio of the height (Hu) of non transparent plus compact sediment to the initial height (Ho) of the total suspension.

The compact sedimentation volume was the part of dense sediment. It was the ratio of the height (Hu) of dense sediment to the initial height (Ho) of the total suspension.

4.2.4 Redispersibility

The ease of redispersion was determined from the number of the times which each test tube had to be inverted by hand under reasonably-controlled conditions, until the suspension was completely resuspended (Farley and Lund, 1976). In this study, 10 ml suspensions were filled in the calibrated test tubes. They were allowed to settle for 1, 2, 3 and 4 weeks. The redispersibility of preparations was evaluated. Based on the number of inversion and the effort required to obtain homogenous suspension. If complete redispersion was not achieved after 12 inversions of the test tube, it was shaken vigorously. If after shaking vigorously the sediment was still present the system was described as “caking”. The redispersibility was done in triplicate.

4.2.5 pH

The pH of ibuprofen suspension preparations containing each modified starches, UT, XG and TG at various concentrations were determined by pH meter at room temperature.

4.3 Stability test of selected ibuprofen suspension

The ibuprofen suspension preparations from No. 4.2 were selected for further study. Preparations were stored at room temperature over a period of three months. In addition, the preparations were also stored in stress conditions (heating-cooling) for eight cycles. Each cycle was stored at $4^{o}C$ over a period of two days and then stored at $45^{o}C$ over a period of two days. The preparations of Ibuprofen suspension were stored at room temperature for 0, 4, 8 and 12 weeks and at stress conditions (heating-cooling). Those samples were evaluated as follows:

4.3.1 Physical properties

4.3.1.1 Physical appearance

The sample was observed in color and sediment appearance.

4.3.1.2 pH

The pH of ibuprofen suspension preparations was determined at room temperature.

4.3.1.3 Viscosity

The viscosities and rheological behaviors of preparations were determined by Brookfield® viscometer as previously described in No.4.2.2.

4.3.1.4 Rheological studies

4.3.1.4.1 Rheological behaviors

Rheological behaviors of ibuprofen suspension were investigated by Brookfield® viscometer at room temperature. The shear rate of sample was increased by step from 0 to 20 rpm within 2 minutes. Then, the shear rate was decreased by step from 20 to 0 rpm within 2 minutes. The experiments were done in triplicate.

4.3.1.4.2 Measurement of thixotropic value

The rheogram was constructed from shear rate (dye/cm^2) versus shear rate (sec^{-1}) which showed thixotropic loops for two different time intervals (Deem, 1996). The area enclosed within up-curve and down-curve was known as hyteresis loop (Deem, 1996; Falkiewicz, 1996). The thixotropic value could be calculated from the area of hysteresis loop by differential integrating area between up-curve and down curve.

4.3.1.5 Sedimentation volume

The sedimentation volume of ibuprofen suspension preparations was evaluated using the same procedure as described in No.4.2.3.

4.3.1.6 Redispersibility

The redispersibility of ibuprofen suspension preparations was evaluated using the same procedure as described in No.4.2.4.

4.3.2 Chemical properties

The High Performance Liquid Chromatographic (HPLC) method was used to determinate percentage of drug in preparations. The assay method described in USP 28. High performance liquid chromatographysystem (Model SCL-10A VP, Shimadzu, Japan) was used to analysis.

4.3.2.1 Chromatographic condition and instrumental settings

HPLC chromatographic conditions as follows:

Column : Hypersil C8 5µ (250mm x 4.6mm) (Thermo Electron Corporation, UK)

Mobile phase : Acetonitrile and 0.01 M phosphoric acid (48:52). Mobile phase was prepared freshly and filtered through a 0.45 µm membrane filter. It was then degassed by sonication for a 30 min prior to use.

Flow rate : 2.0 ml/min

Detector : UV detector at 214 nm

Injection volume : 20 µl

Temperature : ambient

Internal standard : benzophenone

Retention time : 8 min

4.3.2.2 Mobile phase preparation

The 0.7 ml of phosphoric acid was diluted with water to obtain 1,000 ml of 0.01 M phosphoric acid. The mobile phase consisted of this solution and acetonitrile in the ratio of 52:48 v/v, filtered through a 0.45 µm membrane filter and degassed by sonication for a 30 min prior to use.

4.3.2.3 Diluent preparation

The mixture of acetonitrile and distilled water were prepared in the ratio of 50:50 v/v.

4.3.2.4 Internal standard preparation

The 3.2 mg per ml of benzophenone in acetonitrile was prepared.

4.3.2.5 Standard preparation of ibuprofen

Ibuprofen of 120.0 mg was dissolved in diluent in a 100 ml volumetric flask to obtain a concentration of stock solution of 1.2 mg/ml. Each concentration of ibuprofen standard solution was prepared by pipetting 1, 5, 10, 15 and 20 ml of stock solution into 25 ml volume flasks, add 2 ml of internal standard solution and adjusted the volume with diluent, so that the final concentration of standard solution were 0.048, 0.24, 0.48, 0.72 and 0.96 mg/ml, respectively.

4.3.2.6 Calibration curve of ibuprofen aqueous solution

The calibration curve was constructed by plotting the peak area and ibuprofen concentration.

4.3.2.7 Preparation of sample solution

Ibuprofen suspension was weighed accurately, equivalent to about 60 mg of ibuprofen, to a 50 ml volumetric flask, diluted with diluent to volume and mixed (stock solution). Transferred 10 ml of this stock solution and 2 ml of internal standard solution to a second 25 ml volumetric flask, dilute with acetonitrile to volume and mixed and filtered.

4.4 Validations of HPLC method

The typical analytical parameters considering in the validation of the quantitative determination of ibuprofen by HPLC method were modified from USP (United States Pharmacopoeial Convention, 2002). Method validation was performed in term of linearity, precission and accuracy.

4.4.1 Linearity

The linearity was evaluated by plotting the standard curve between the peak area ratio of ibuprofen and the concentrations of ibuprofen. Linear regression analysis was performed. The equation and the coefficient of determination (R-square) were calculated.

4.4.2 Precision

(a) Within Run Precision

The within run precision was evaluated by analyzing peak area ratio of drug of five repetitions of each concentration of standard solution on the same day. The mean, the standard deviation (SD) and the percent coefficient of variation (% CV) of each concentration were determined.

(b) Between Run Precision

The between run precision was evaluated by analyzing peak area ratio of drug of five repetitions of each concentration of standard solution on 3 different days. The mean, the standard deviation and the percentage coefficient of variation of each concentration were determined.

4.4.3 Accuracy

The accuracy of ibuprofen assay was evaluated by analyzing percent recoveries of each concentration of known ibuprofen solutions. The known ibuprofen samples were prepared from physical mixture of ibuprofen and cross-linked hydroxypropyl tapioca starch. Percent recovery of each injection was calculated by comparing the concentration fitted from a calibration curve with the known concentration. The mean, the standard deviation and the percentage coefficient of variation of each concentration were determined.

CHAPTER IV
RESULTS AND DISCUSSION

1. Preparation and Characterization of Modified Tapioca Starches

1.1 Preparation of modified tapioca starches

1.1.1 Sodium carboxymethyl tapioca starches

In this study carboxymethyl ether of tapioca starch were prepared using Filbert's method as described in Suwannapakul (1996). According to Suwannapakul (1996), three degree of substitutions (DS) of sodium carboxymethyl starches (SCMS) from various native starches such as glutinous rice starch, rice starch and tapioca starch were produced. At a certain degree of substitutions, SCMS from different native starches had different property such as viscosity and suspending property. Suwannapakul (1996) reported that modified glutinous rice starch (MGS), modified rice starch (MRS), and modified tapioca starch (MTS) with DS of 0.16, 0.26 and 0.38 could be used as suspending agent. However, those modified starches lost suspending property after storage longer >3 month. In this study only tapioca starch was selected to be investigated for suspending property because of abundant supply, cheap and locally producing in Thailand. Three DS of carboxymethylation reaction were prepared by various the quantities of monochloroacetic acid, temperature and time of reaction by Filbert's method.

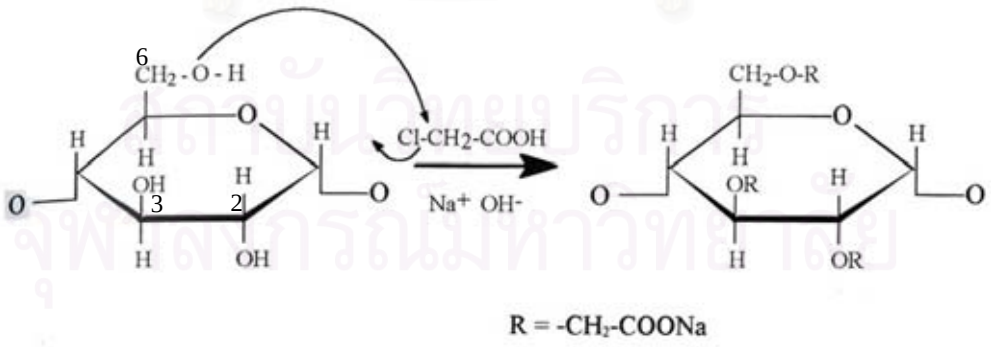


Figure 4-1 Reaction mechanism of the formation of SCMS.

The carboxymethyl substitution reaction is shown in Figure 4-1. Monochloroacetic acid which was a strong electrophile for it had chlorine as a good leaving group was used as etherifying agent to react with starch in the presence of alcohol and alkali solution such as sodium hydroxide at temperature of 50°C or above. Then, maintaining the mixture at elevated temperature during etherification and thereafter purifying the etherified starch. The reaction with the starchate nucleophile was a bimolecular displacement (S_N2) and sodium hydroxide was used as catalyst. There were three reacting positions on one starch unit, i.e. those three –OH group. The number of –OH group that was substituted with $–OCH_2$-COONa or - OCH_2-COOH determined the DS of the modified starches. Each of anhydroglucose unit might be substituted by carboxymethyl group at the primary hydroxyl group on carbon atom 6 and the secondary hydroxyl group on carbon atom 2 and 3 however, carboxymethylation occurred preferentially at the secondary hydroxyl group (Hofreiter, 1987; Radley, 1968; Robert, 1965).

1.1.1.1 Quantitative determination of a degree of substitution (DS)

The DS indicated the average number of sites per anhydroglucose unit on which there was substituted group. Thus, if one hydroxyl on each of the anhydroglucose unit in a starch had been etherified with carboxyl group, the DS was 1. If all three hydroxyls were etherified, the DS was 3. Most of the commercially available modified starch had low DS value ranging up to about DS 0.1, which would represent on average 1 substitute group per every 10 anhydroglucose units (Wurzburg, 1986).

The DS of modified tapioca starch were calculated the same as the method for Croscarmellose sodium in USP 28. This method was calculated from acid/basic titration and residue on ignition experiments. Theoretically, the DS value obtained from this calculation represented the carbonyl group in both acid and salt forms. However, S value contributed to most DS value because the reaction took place in basic condition. One advantage of modified starches preparing by this method was that their salt from improved solubility in water.

The DS of modified tapioca starch are presented in Table 4-1.

Table 4-1 Calculation of DS of SCMS.

Type of modified starches	Predicted DS	C	M	A	S	Calculated DS	SD
SCMS-1	0.13	3.91608	0.08773	0.01494	0.09395	0.10889	0.002
SCMS-2	0.26	8.49382	0.01572	0.00282	0.21446	0.21728	0.001
SCMS-3	0.39	13.19053	0.05564	0.01062	0.35473	0.36536	0.003

M = numbers of milliequivalent of based required to neutralize 1 gram of modified starch

C = residue on ignition (%)

A = degree of acid carboxymethyl substitution

S = degree of sodium carboxymethyl substitution

A+S = degree of substitution

SCMS-1 = sodium carboxymethyl tapioca starch with DS of 0.11

SCMS-2 = sodium carboxymethyl tapioca starch with DS of 0.22

SCMS-3 = sodium carboxymethyl tapioca starch with DS of 0.37

As the result, modified tapioca starches with DS of 0.11, 0.22 and 0.37 were obtained (Table 4-1). The slight different DS was achieved from Filbert's, Suwannapakul's and this experiment. Since those method and condition of reaction might be slightly changed in the reaction conditions (e.g. time interval for adjust pH, the speed of agitation of in reaction) during modification process. The method of calculation was presented in Appendix A.

1.1.1.2 Qualitative determination of carboxymethyl substitution in modified starches

Fourier-Transformed Infrared (FTIR) Spectrophotometer was used to confirm the substitution of carboxymethyl group of modified tapioca starches. In this experiment, three degree of substitution of SCMS and UT were evaluated and compared with native tapioca starch. The carboxymethyl substitution of modified tapioca starch could be confirmed by the presence of carbonyl group (C=O) in infrared spectroscopy. C=O peak appeared as a strong broad peak at the range of

1,600-1,650 cm^{-1}. The FTIR spectrogram of SCMS at three different DS is shown in Figures 4-2. Comparison of the FTIR spectrum between SCMS and native tapioca starch is shown in Figures 4-3.

The FTIR spectrum of SCMS with DS of 0.11, 0.22 and 0.37 showed the C=O peak at 1,606.20, 1,606.89 and 1,618.23 cm^{-1}, respectively (see detail in Appendix A; Figure 5-1 to 5-4). In addition, the intensity of FTIR spectrums increased when modified tapioca starches had higher DS. While, native tapioca starch showed C=O peak at 1,642.43 cm^{-1}. The obtained result was implied that native tapioca starch did not have carbonyl substitute group in their structures. Since the FTIR spectrum of native tapioca starch showed C=O peak over the range (1,606.20-1,618.23 cm^{-1}) of three DS of tapioca starches with carbonyl substitute group in their structures.

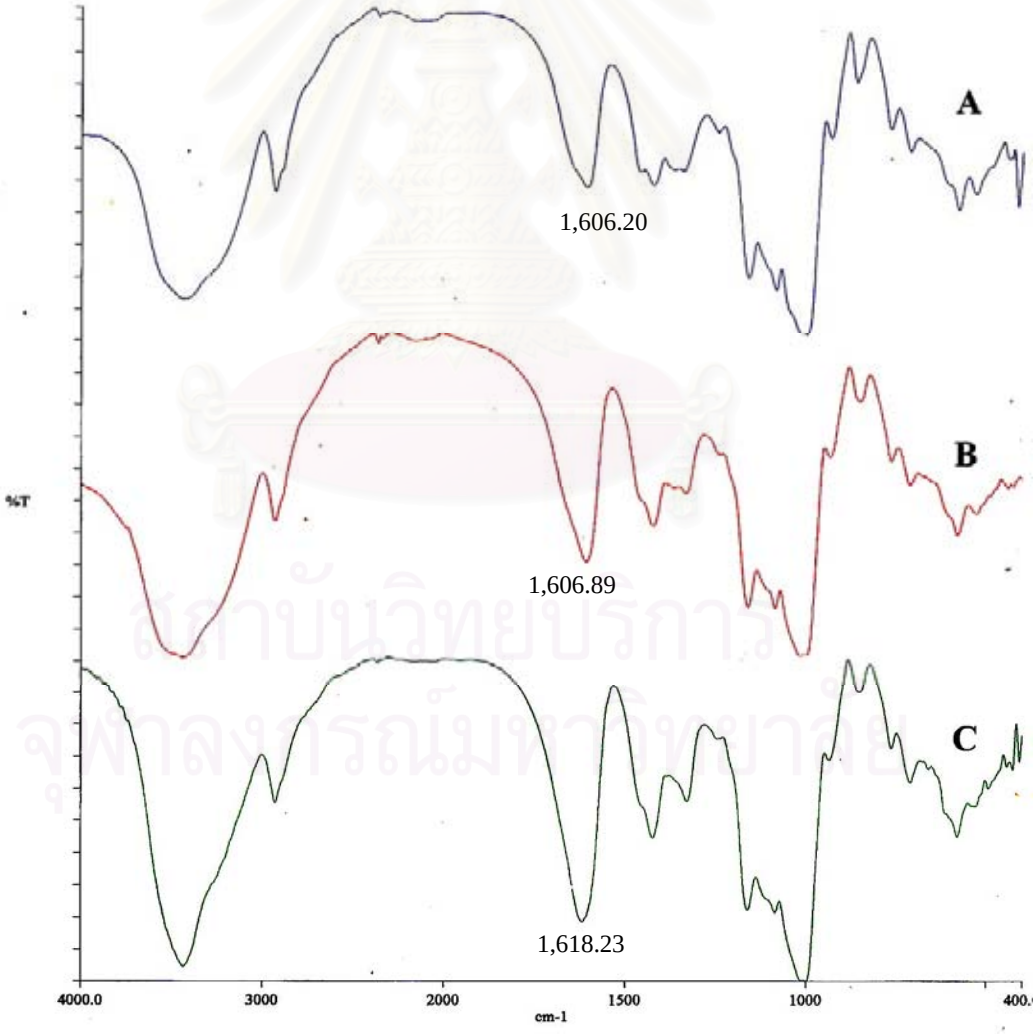


Figure 4-2 FTIR spectrum of SCMS at different DS (A) 0.11; (B) 0.22 and (C) 0.37.

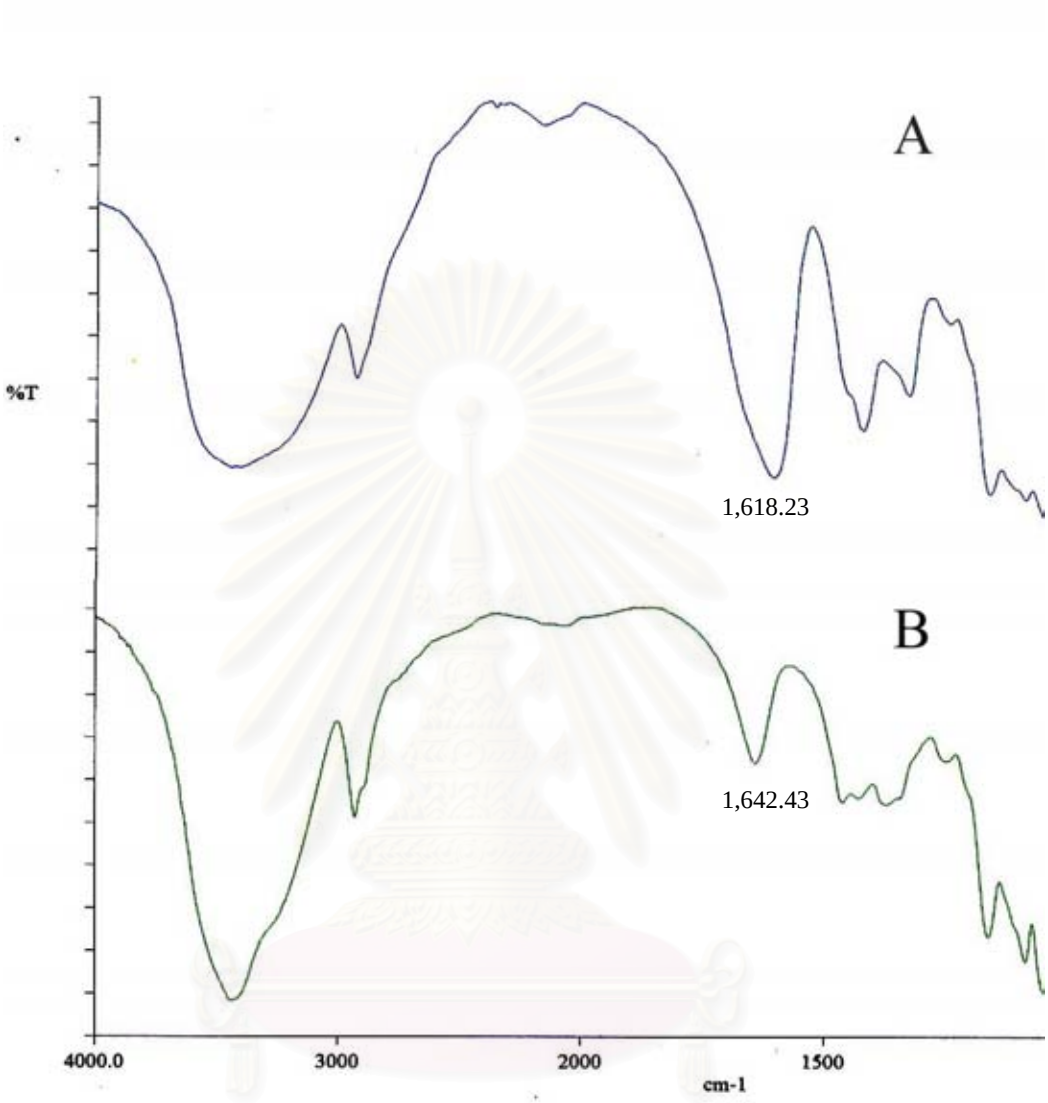


Figure 4-3 Comparison of FTIR spectrum between SCMS (A) and native tapioca starch (B).

1.1.1.3 Moisture content

Moisture content of SCMS with DS of 0.11, 0.22 and 0.37 were evaluated by using moisture balance at the temperature 105°C. The experiments were performed in triplicate. The moisture content of SCMS-1, SCMS-2, SCMS-3, UT and native tapioca starch were 8.90, 9.35, 8.68, 9.88 and 11.19, respectively (as shown in Table 4-2).

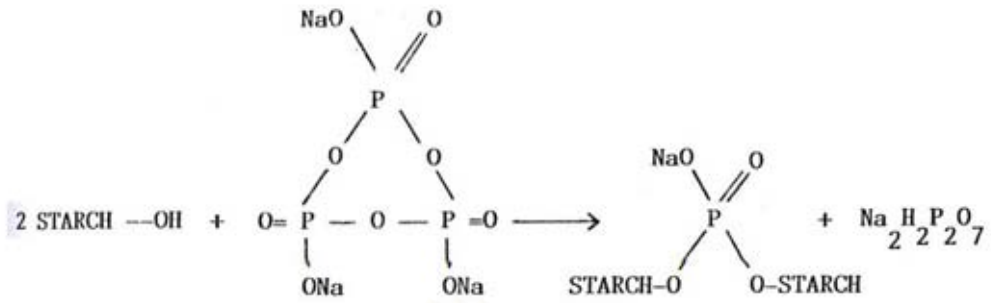
Table 4-2 Moisture content of all DS of SCMS, UT and native tapioca starch.

Type of starches	Average moisture content (% w/w ± SD)
SCMS-1	8.90 (0.14)
SCMS-2	9.35 (0.09)
SCMS-3	8.68 (0.35)
UT	9.88 (0.32)
Native tapioca starch	11.19 (0.04)

SCMS-1 = sodium carboxymethyl tapioca starch with DS of 0.11
SCMS-2 = sodium carboxymethyl tapioca starch with DS of 0.22
SCMS-3 = sodium carboxymethyl tapioca starch with DS of 0.37
UT = Ultrasperse®2000

1.2 Modification of cross-linked sodium carboxymethyl tapioca starches (CSCMS)

Cross-linked starch is a modified starch that bi-or polyfunctional chemicals reacted with hydroxyl groups of starch molecules under alkali condition by etherification or esterification. The cross-linking reagents were used such as sodium trimetaphosphate, phosphorous oxychlorine and apidic acetic. When the specific chemical contained two or more moieties capable of reacting with hydroxyl groups, there was the possibility of reacting at two different hydroxyls resulting in cross-linking between hydroxyls on the same molecule or on different molecules. In this study, sodium trimetaphosphate were used as cross-linking agent because it has been approved for use in food starches by The Food Additive Regulations (Hamilton and Paschall, 1967). The use of sodium trimetaphophate to cross-link starch was reported by Kerr and Cleveland (1957). They treated an aqueous suspension of granular starch with it under alkaline conditions to produce distarch phosphate. The reaction of crosslinking the starch by water soluble trimetaphosphate salts was shown in figure 4-4 (Hamilton and Paschall, 1967).



Starch + Sodium trimetaphosphate ⟶ Distarch phosphate + Sodium dihydrogen pyrophosphate

Figure 4-4 Reaction mechanism of the formation of modified cross-linked starch as distarch phosphate.

The SCMS which had DS 0.22 was selected for further study because it provided the highest viscosity. This SCMS was modified as CSCMS by using Kerr and Cleveland's method as same as of the study by Teruya (1995). Three DS of cross-linked reaction were prepared by various reaction times at 2, 8 and 16 hours.

1.2.1 Quantitative determination of DS

A quantitative determination of starch esters indicated the degree of substitution. The DS was calculated from the phosphorous content (Van der Bij, 1976). The phosphorous and phosphate content are shown in Table 4-3 and the standard curve of phosphorous solution was presented in Appendix A (Table 5-1 and Figure 5-8).

Table 4-3 Phosphate contents of native tapioca starch before and after modification.

Type of starches	% phosphorous	SD	% phosphate	SD
CSCMS-2	0.0568	0.0021	0.1740	0.0065
CSCMS -8	0.0734	0.0017	0.2251	0.0052
CSCMS-16	0.1053	0.0029	0.3228	0.0090
Native tapioca starch	0.0066	0.0003	0.0203	0.0008

CSCMS-2 = cross-linked sodium carboxymethyl tapioca starch after 2 hrs of reaction time

CSCMS-8 = cross-linked sodium carboxymethyl tapioca starch after 8 hrs of reaction time

CSCMS-16 = cross-linked sodium carboxymethyl tapioca starch after 16 hrs of reaction time

When the cross-linked time increased, phosphate content gradually increased as shown in table 4-3. It was found that native tapioca starch had low % phosphate content of 0.0203 comparing with different reaction time of CSCMS.

1.2.2 Qualitative determination of phosphate in modified tapioca starches

The qualitative determination of phosphate in modified tapioca starches were conducted by using Fourier-Transformed Infrared (FTIR) Spectrophotometer. The FTIR spectrogram of CSCMS at different reaction times is shown in Figures 4-5. The FTIR spectrum of CSCMS-2, CSCMS-8 and CSCMS-16 showed the C=O peak at 1,613.44, 1,606.25 and 1,606.99 cm^{-1}, respectively. A generally characteristic absorption band of starch phosphate ester was illustrated at 1,240-1,200 cm^{-1} (Van der Bij, 1976) which represented the covalent phosphate ($-CH_2-O-P-O$). In fact, at the 1,240-1,200 cm^{-1} was covered by C-OH stretching vibration and a broad C-O stretching band centered at 1,242 cm^{-1}(Pecsok et al., 1976). While, Thavisak Teruya (1995) found $-\overset{|}{P}=O$ peaks of CSCMS at the range of 1,365-1,371 cm^{-1}. In this study the FTIR spectrum of CSCMS which had 0.1740, 0.2251 and 0.3228 % phosphate showed peak at 1,328.91, 1,328.92 and 1,328.37 cm^{-1}, respectively (see detail in Appendix A; Figure 5-5 to 5-7). As the result, $-\overset{|}{P}=O$ peaks might be occurred at the range of 1,328.37-1,328.91 cm^{-1} because the intensity of FTIR spectrums increased when modified tapioca starches had higher DS. However, the quantitative determinations of phosphate content were performed by chemical method.

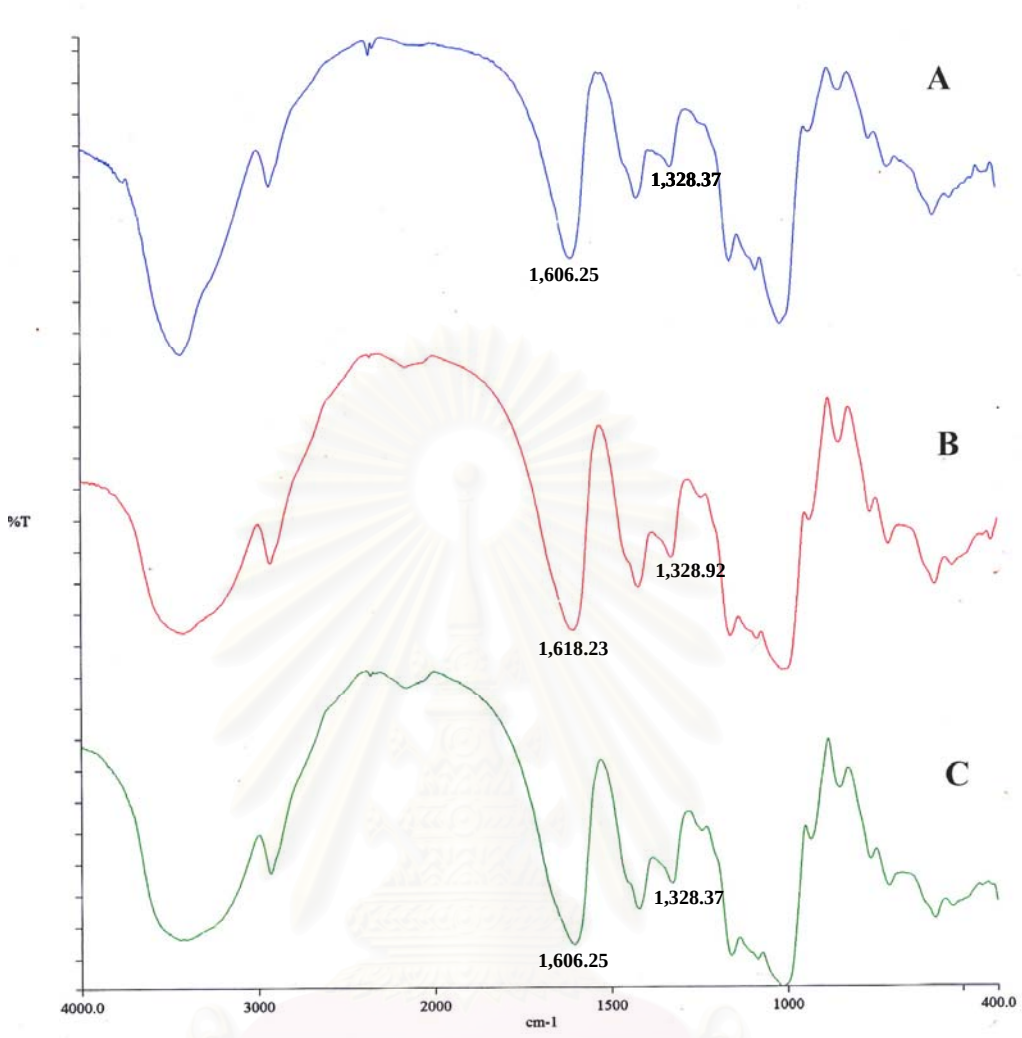


Figure 4-5 FTIR spectrums of CSCMS at different reaction times (A) 2 hrs; (B) 8 hrs and (C) 16 hrs.

Comparison of the FTIR spectrum between CSCMS, SCMS and native tapioca starch is shown in Figures 4-6. The FTIR spectrum of CSCMS displayed the C=O peak at 1,606.25 $cm^{-1}$and –P(=O)– peaks at 1,328.37 cm^{-1} whereas SCMS showed the C=O peak at 1,618.23 $cm^{-1}$and no –P(=O)– peaks. Native tapioca starch did not show those peaks.

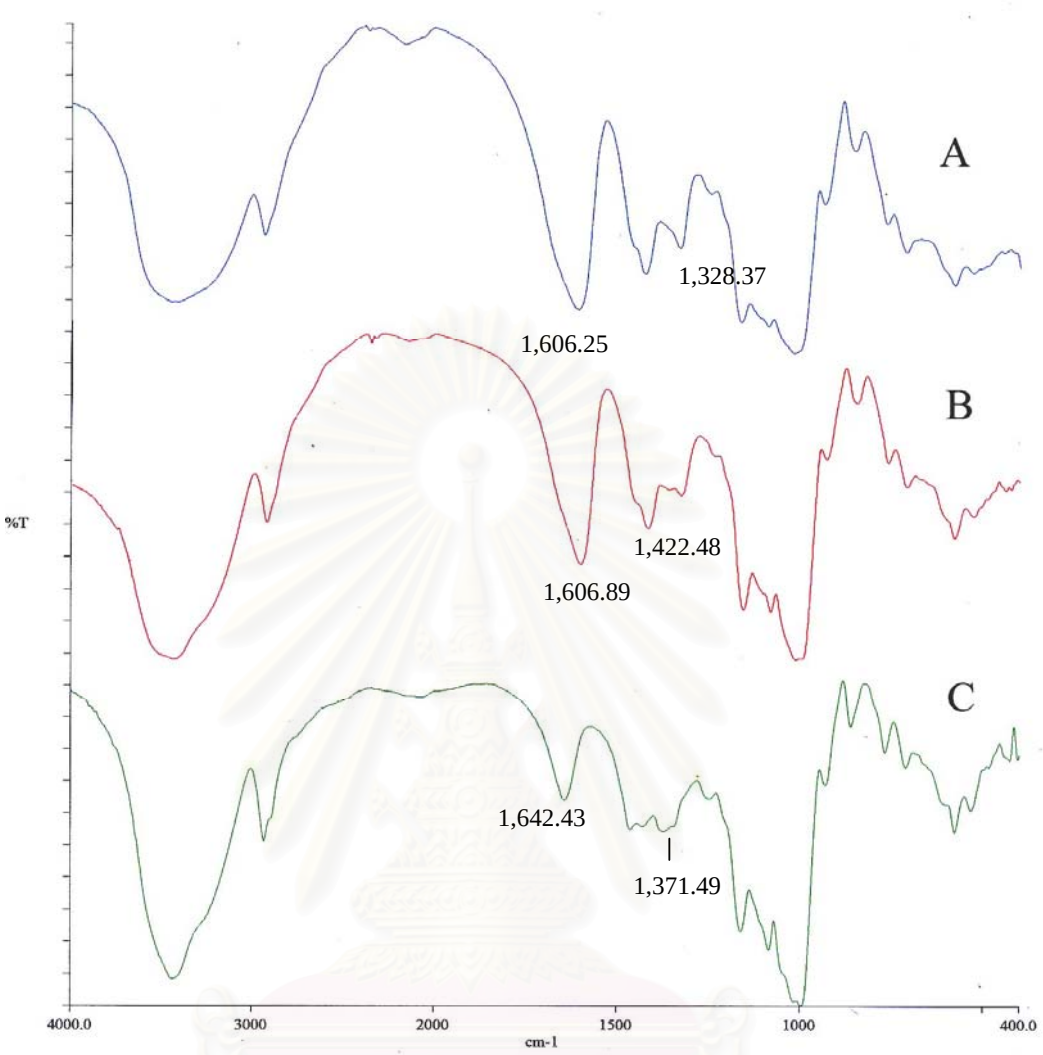


Figure 4-6 Comparison of FTIR spectrum between CSCMS (A), SCMS (B), and native tapioca starch (C).

1.2.3 Moisture content

Moisture contents of CSCMS with reaction time of 2, 8 and 16 hrs were evaluated by using moisture balance at the temperature of 105°C. The moisture content of CSCMS-2, CSCMS-8 and CSCMS-16 were 9.23, 7.82 and 8.16 % w/w, respectively (as displayed in Table 4-4).

Table 4-4 Moisture content of all DS of CSCMS.

Type of starches	Average moisture content (% w/w ± SD)
CSCMS-2	9.23 (0.64)
CSCMS-8	7.82 (0.45)
CSCMS-16	8.16 (0.76)

2. Evaluations of Modified Tapioca Starches as Suspending Agent

2.1 Viscosity measurement of modified tapioca starches and other suspending agents

The preliminary study, the viscosity of our modified tapioca starches (three DS of SCMS and three DS of CSCMS) were evaluated and compared with pregelatinized tapioca starch (PGTS), hydroxypropyl tapioca starch (HPTS), crosss-linked hydroxypropyl tapioca starch (CHPTS), Ultrasperse®2000 (UT), xanthan gum (XG) and tragacanth (TG) at the concentration of 1, 3 and 5% w/v in water. The viscosity of all modified tapioca starches and other suspending agents at various concentrations are shown in Table 4-5.

For all concentrations, the viscosity of all modified tapioca starches, UT, XG and TG increased when the concentration increased. The viscosity of SCMS and CSCMS was not related to the increasing degree of substitution. At the concentration of 1, 3 and 5 % w/v SCMS, DS 0.22 provided the highest viscosity comparing with DS 0.11 and 0.37.This result was according to Suwannapakul (1996). For CSCMS, at low concentration (1 % w/v), the viscosity of CSCMS at different three DS could be ranked in decreasing in order as follows; CSCMS-2 > CSCMS-8 > CSCMS-16.While, at high concentration (5% w/v) the ranging of viscosity were CSCMS-16 > CSCMS-8 > CSCMS-2. This result was not correlated with the result of low concentration because it might be possible that the water was not enough to completely hydrate the starch molecules. PGTS, HPTS, CHPTS, UT gave the similar viscosity at 1 and 3 % w/v while 5 % w/v of UT contained the highest viscosity (792 cps). XG and TG exhibited the higher viscosity than SCMS, PGTS, HPTS, CHPTS, and UT at the concentration of 3 and 5 % w/v but they gave the similar viscosity at the concentration of 1 % w/v.

Table 4-5 Viscosity of various concentrations of modified tapioca starches and the other suspending agents.

Concentration (%w/v)	Average apparent viscosity (cps ± SD)											
	SCMS-1	SCMS-2	SCMS-3	CSCMS-2	CSCMS-8	CSCMS-16	PGTS	HPTS	CHPTS	UT	XG	TG
1	103.44 (4.36)	229.33 (5.03)	156.33 (3.22)	832.00 (7.94)	248.00 (3.00)	25.95 (0.49)	4.68 (0.81)	4.99 (1.84)	3.94 (2.32)	5.75 (0.33)	150.33 (0.58)	65.423 (5.774)
3	217.00 (3.00)	556.33 (5.51)	441.00 (1.73)	3,359.33 (44.43)	5,180.00 (74.51)	3,087.67 (90.12)	39.17 (1.84)	43.87 (1.40)	33.78 (4.04)	48.74 (1.69)	752.00 (14.93)	958.00 (6.245)
5	334.67 (0.58)	995.67 (3.22)	760.33 (5.13)	7,577.00 (183.08)	11,883.33 (178.98)	12,306.67 (210.79)	114.33 (2.31)	168.00 (1.00)	359.33 (4.04)	792.00 (10.44)	1,471.00 (21.17)	3,437.00 (70.89)

Each of modified starches and other suspending agents provided different and wide range of viscosity (3.94-12,306.67 cps). Because of their properties and the quantities of each suspending agents that were not enough to form gel in some concentrations. Since, viscosity affected on rheological behavior, in the further study, the range of viscosity 400-620 cps was selected from each modified starches and other suspending agents by varying concentrations of them. The percent of suspending agent was increased step by step.

The viscosity and graph of three DS of SCMS at various concentrations are shown in Table 4-6 and Figure 4-7, respectively. SCMS-1 at concentration 1-7 % w/v provided the range of viscosity in 103.44-662.33 cps. SCMS-2 and SCMS-3 at concentration 1-5 % w/v provided the range of viscosity in 229.33-995.67 and 156.33-760.33 cps, respectively.

Table 4-6 Viscosity of SCMS at three DS at various concentrations.

Concentration (% w/v)	Average apparent viscosity (cps ± SD)		
	SCMS-1	SCMS-2	SCMS-3
1	103.44 (4.36)	229.33 (5.03)	156.33 (3.215)
2	-*	367.67 (1.53)	277.67 (3.06)
2.5	-*	413.33 (2.08)	-*
3	217.00 (3.00)	556.33 (5.51)	441.00 (1.73)
5	334.67 (0.58)	995.67 (3.22)	760.33 (5.13)
6	457.67 (2.31)	-*	-*
7	662.33 (3.22)	-*	-*

* This concentration was not done in experiment.

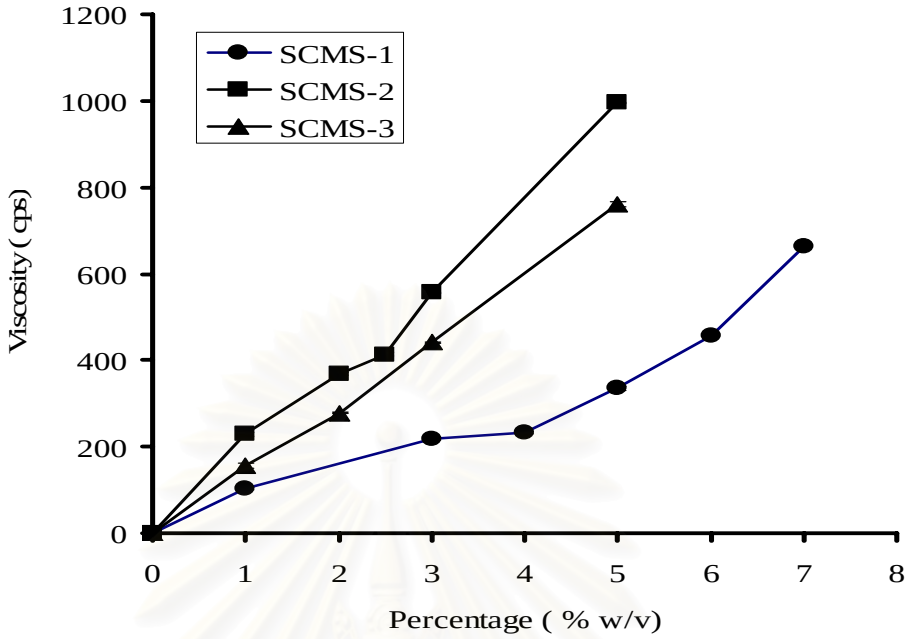


Figure 4-7 Graph of viscosity of SCMS at three DS at various concentrations

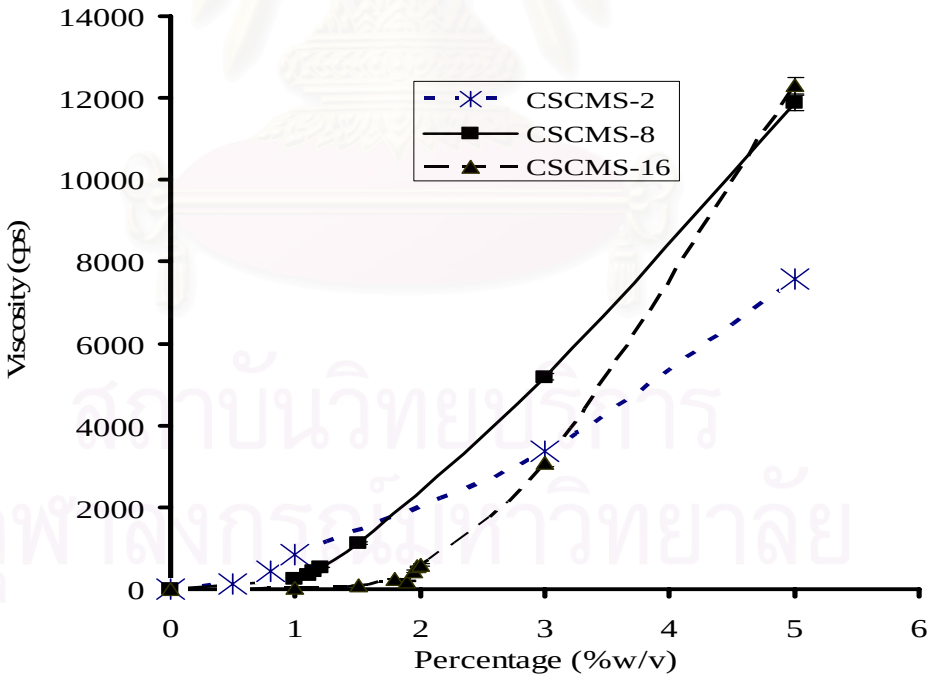


Figure 4-8 Graph of viscosity of CSCMS at three DS at various concentrations.

CSCMS expressed wide range of viscosity therefore the concentrations were varied gradually. The viscosity of CSCMS and graph with three DS at various concentrations are shown in Table 4-7 and Figure 4-8, respectively. CSCMS-2 at concentration 0.5-5 % w/v gave the range of viscosity in 115-7,577 cps. CSCMS and CSCMS-16 at concentration 1-5 % w/v provided the range of viscosity in the range of 248-11,883.33 and 25.95-12,306.67 cps, respectively.

The viscosity of SCMS at all DS was lower than that of three DS of CSCMS. Three DS of CSCMS provided extremely increasing viscosity when the concentration increased (as shown in Figure 4-9).

PGTS, HPTS and CHPTS at concentration of 1-9 % w/v contained the range of viscosity in 4.68-557.33, 4.99-735 and 3.94-3,390.67 cps, respectively (as summarized in Table 4-8 and Figure 4-9)

The viscosity and graph of UT, XG and TG at various concentrations are exhibited in Table 4-9 and Figure 4-9) UT, XG and TG at concentration of 1-5 % w/v contained the range of viscosity in 5.75-792, 150.331,471 and 65.42-3,437 cps, respectively.

The concentration of 6 % w/v SCMS-1, 2.5 % w/v SCMS-2, 3 % w/v SCMS-3, 0.8 % w/v CSCMS-2, 1.15 % w/v CSCMS-8, 1.95 % w/v CSCMS-16, 8.5 % w/v PGTS, 7.5 % w/v HPTS, 5.5 % w/v CHPTS, 4.5 % w/v UT, 2.5 % w/v XG and 2.5 % w/v TG were selected to study in the further part. The concentration of 6 % w/v SCMS-1, 2.5 % w/v SCMS-2, 3 % w/v SCMS-3, 0.8 % w/v CSCMS-2, 1.15 % w/v CSCMS-8, 1.95 % w/v CSCMS-16, 8.5 %w/v PGTS, 7.5 % w/v HPTS, 5.5 % w/v CHPTS and 4.5 % w/v UT provide the range of viscosity in 413.33-478.67 cps while 2.5 % w/v XG and TG gave the viscosity of 529 and 612, respectively.

Table 4-7 Viscosity of CSCMS at three DS at various concentrations.

Concentration (% w/v)	Average apparent viscosity (cps ± SD)		
	CSCMS-2	CSCMS-8	CSCMS-16
0.50	115.00 (2.00)	-*	-*
0.80	440.00 (13.23)	-*	-*
1.00	832.00 (7.94)	248.00 (3.00)	25.95 (0.49)
1.10	-*	348.67 (16.62)	-*
1.15	-*	434.33 (28.50)	-*
1.20	-*	527.33 (6.81)	-*
1.5	-*	1,136.33 (31.26)	103.47 (4.96)
1.8	-*	-*	245.00 (5.00)
1.9	-*	-*	197.33 (8.08)
1.95	-*	-*	450.33 (32.52)
1.98	-*	-*	547.67 (10.50)
2	-*	-*	591.33 (30.67)
3.00	3,359.33 (44.43)	5,180.00 (74.51)	3,087.67 (90.12)
5.00	7,577.00 (183.08)	11,883.33 (178.98)	12,306.67 (210.79)

* This concentration was not done in experiment.

Table 4-8 Viscosity of PGTS, HPTS and CHPTS at various concentrations.

Concentration (% w/v)	Average apparent viscosity (cps ± SD)		
	PGTS	HPTS	CHPTS
1.00	4.68 (0.81)	4.99 (1.84)	3.94 (2.32)
3.00	39.17 (1.84)	43.87 (1.40)	33.78 (4.04)
5.00	114.33 (2.31)	168.00 (1.00)	359.33 (4.04)
5.50	-*	-*	459.00 (1.00)
6	-*	-*	768.67 (7.23)
7.00	288.67 (6.66)	326.00 (7.21)	1,455.33 (17.50)
7.5	-*	420.67 (13.01)	-*
8.00	319.67 (10.60)	-*	-*
8.50	439.67 (5.51)	-*	-*
9.00	557.33 (11.72)	735.00 (4.58)	3,390.67 (23.50)

* This concentration was not done in experiment.

Table 4-9 Viscosity of UT, XG and TG at various concentrations.

Concentration (% w/v)	Average apparent viscosity (cps ± SD)		
	UT	XG	TG
1	5.75 (0.33)	150.33 (0.58)	65.42 (5.77)
2.00	-*	366.33 (9.29)	328.00 (7.00)
2.50	-*	529.33 (8.08)	612.67 (1.16)
3	48.74 (1.69)	752.00 (14.93)	958.00 (6.25)
4	253.67 (4.73)	-*	-*
4.5	478.67 (1.16)	-*	-*
5	792.00 (10.44)	1,471.00 (21.17)	3,437.00 (70.89)

* This concentration was not done in experiment.

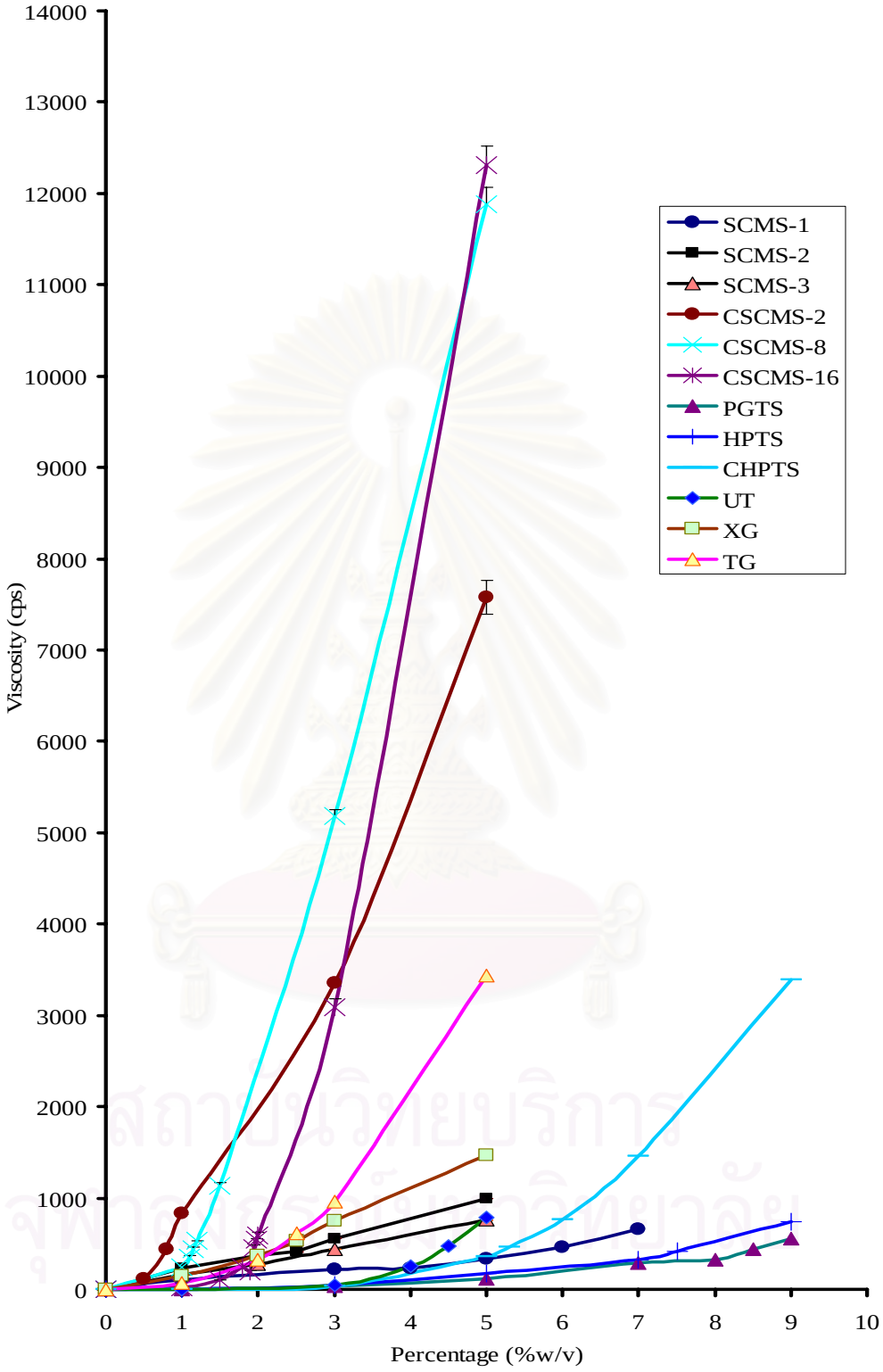


Figure 4-9 Viscosity of various concentrations of suspending agents.

2.2 Rheological studies of modified tapioca starches and other suspending agents

In this experiment, the rheograms of pure suspending agents were derived from Haake RotoVisco1® rheometer. The measurements were performed at 25±2°C. The thixotropic values were achieved from Rheo Win3.12 program of Haake RotoVisco1® rheometer.

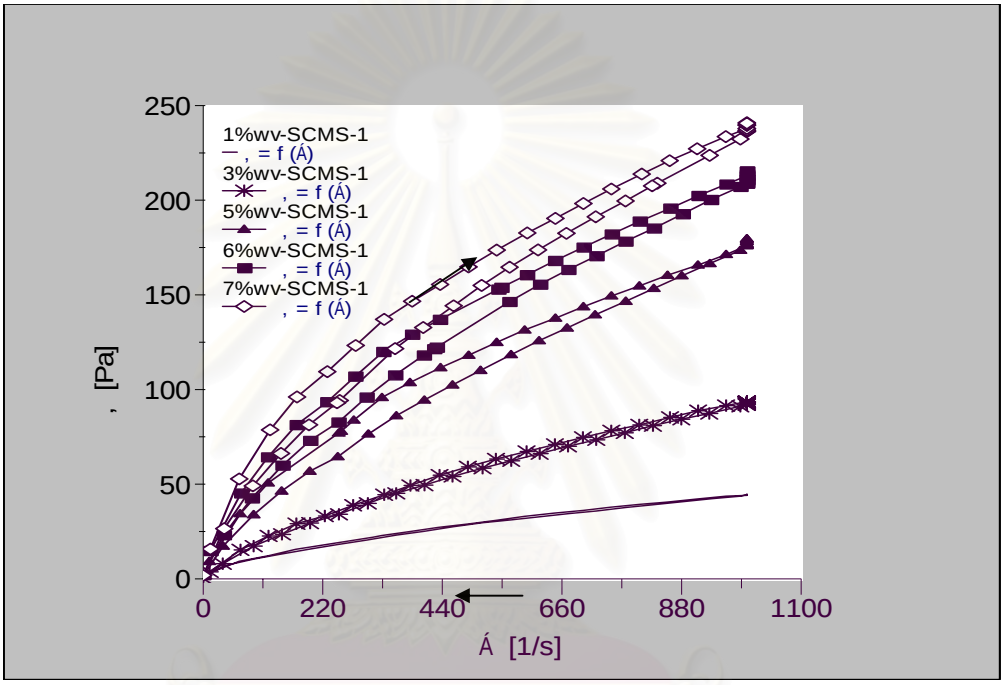


Figure 4-10 The rheograms of SCMS-1 at various concentrations.

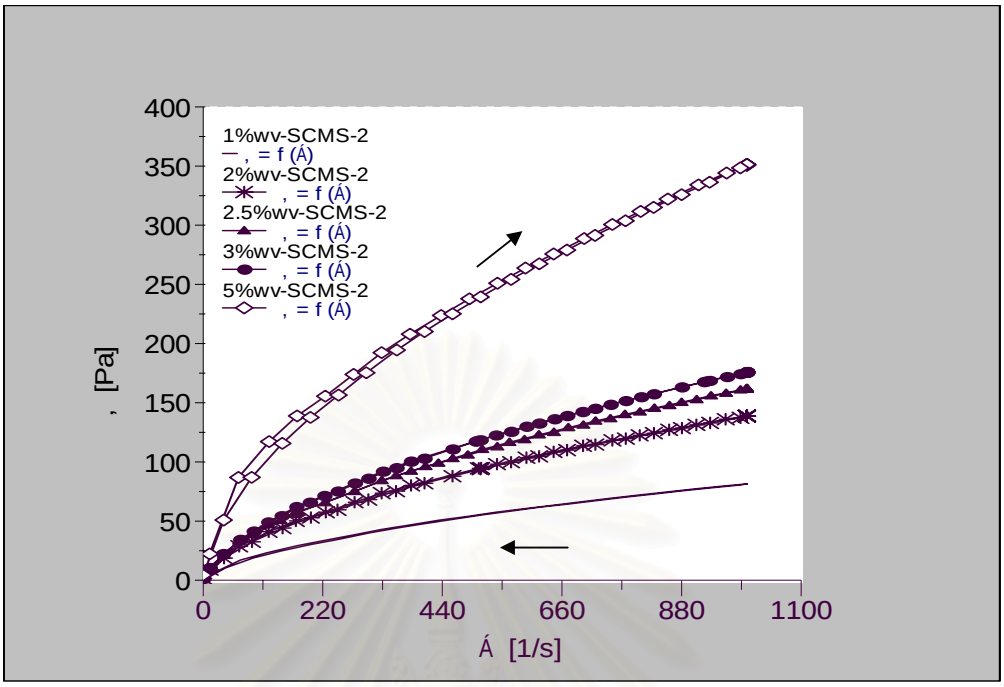


Figure 4-11 The rheograms of SCMS-2 at various concentrations.

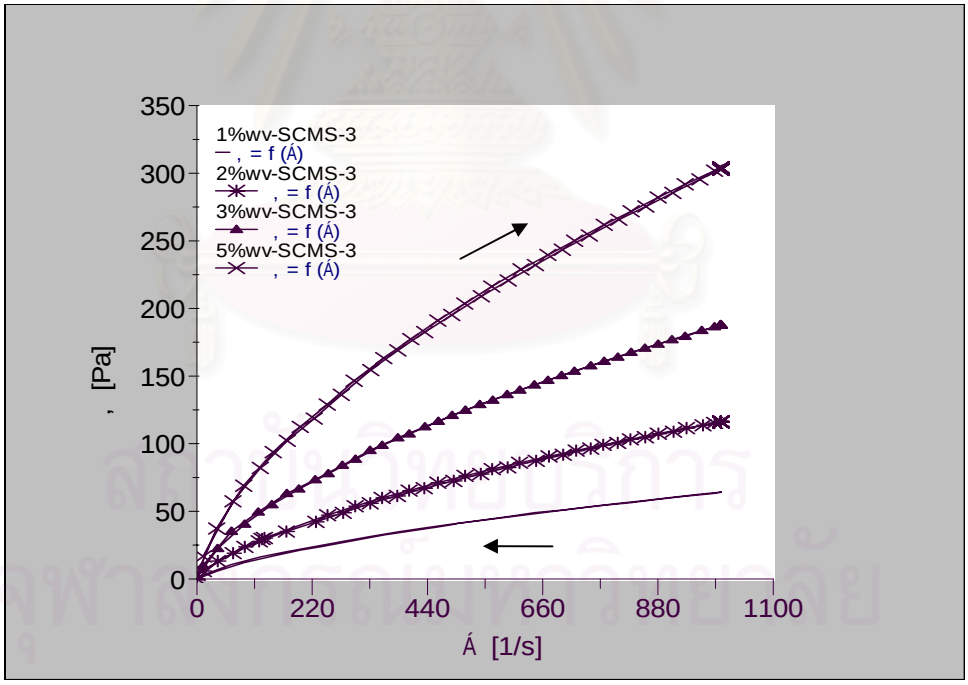


Figure 4-12 The rheograms of SCMS-3 at various concentrations.

As shown in Figure 4-10, 4-11 and 4-12, the rheograms of SCMS with all DS showed a pseudoplastic-type with the formation of a hysteresis loop between the upcurve and the downcurve. All concentrations of SCMS with all DS showed positive thixotropic values as displayed in Table 4-10. The thixotropic values trended to increase when the concentration increased. The highest thixotropic value obtained from SCMS with DS 0.22. The flow behavior is important information for pharmaceutical applications. The large area of hysteresis loop is suitable for use as a suspending agent or a gelling agent.

Table 4-10 Thixotropic values of three DS of SCMS at various concentrations.

Concentration (%w/v)	Average thixotropic value (Pa/s ± SD)		
	SCMS-1	SCMS-2	SCMS-3
1	1,070.47 (162.86)	1,806.33 (91.51)	1,261.00 (97.39)
2	-*	1,777.00 (475.79)	263.90 (13.04)
2.5	-*	1,585.33 (86.38)	-*
3	3,739.00 (407.03)	2,527.33 (295.47)	1,097.00 (42.67)
5	3,832.33 (507.91)	9,495.33 (416.52)	2,581.67 (424.58)
6	4,052.00 (835.06)	-*	-*
7	13,636.67 (2,277.40)	-*	-*

* This concentration was not done in experiment.

The rheograms of CSCMS with all DS showed a pseudoplastic type and positive thixotropic values (see Figure 4-13-4-17). The thixotropic values trended to increase when the concentration increased as summarized in Table 4-11. At the concentration in the range of 1-1.2 % w/v of CSCMS-8 and 1-1.95 % w/v of CSCMS-16 increased gradually, the thixotropic values were not different obviously. While at the concentration of 1, 3 and 5 % w/v, the thixotropic values were different substantially. The high variation of thixotropic values might be occurred because the materials were natural product. The highest thixotropic value obtained from CSCMS-16 at the concentration of 5 % w/v.

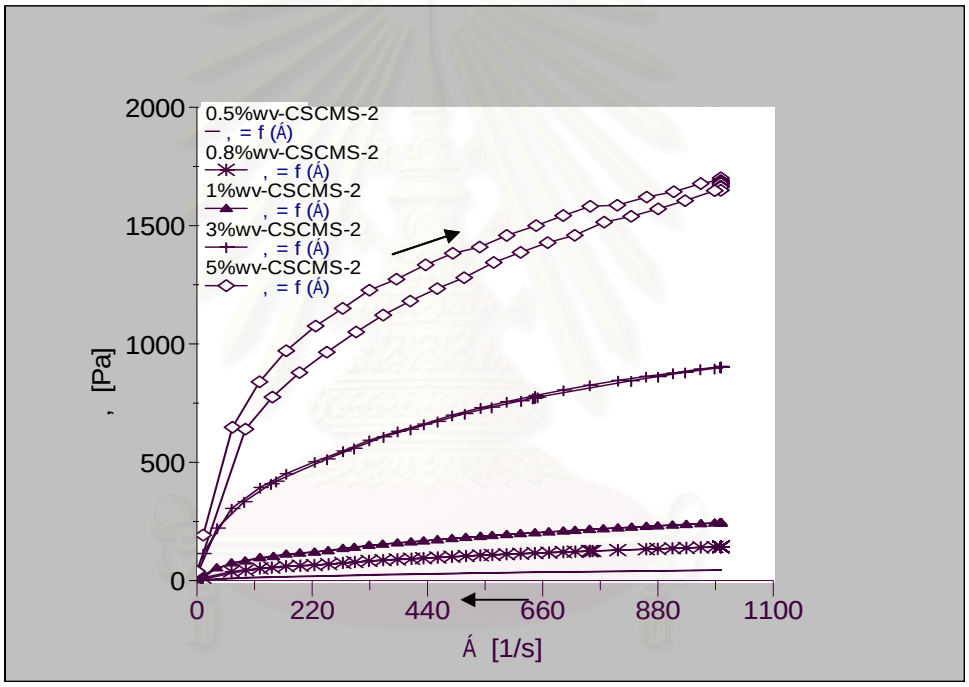


Figure 4-13 The rheograms of CSCMS-2 at various concentrations.

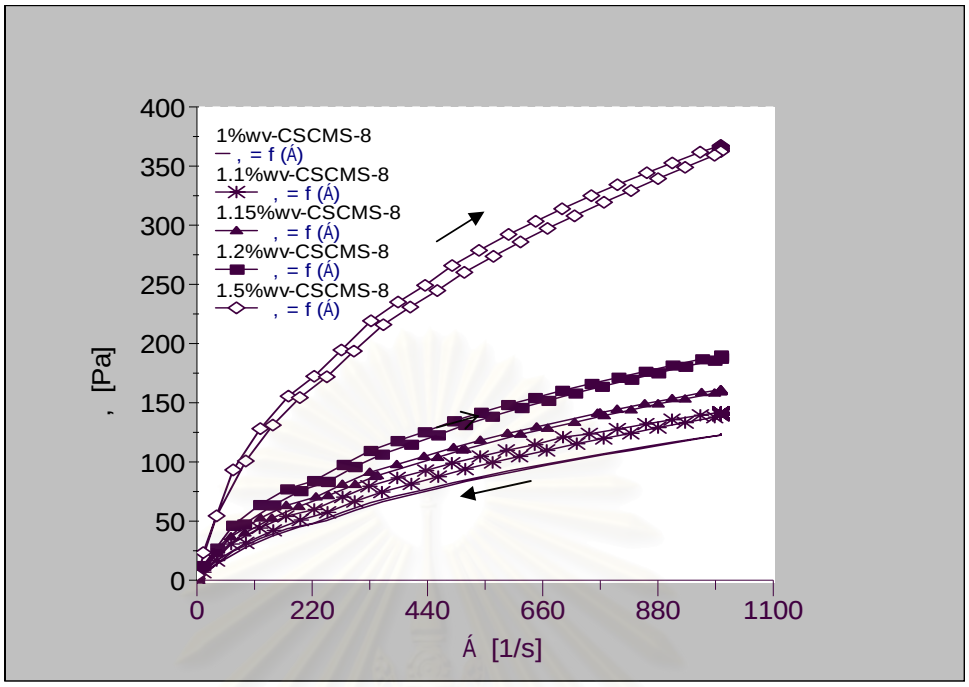


Figure 4-14 The rheograms of CSCMS-8 at various concentrations (1-1.5 % w/v).

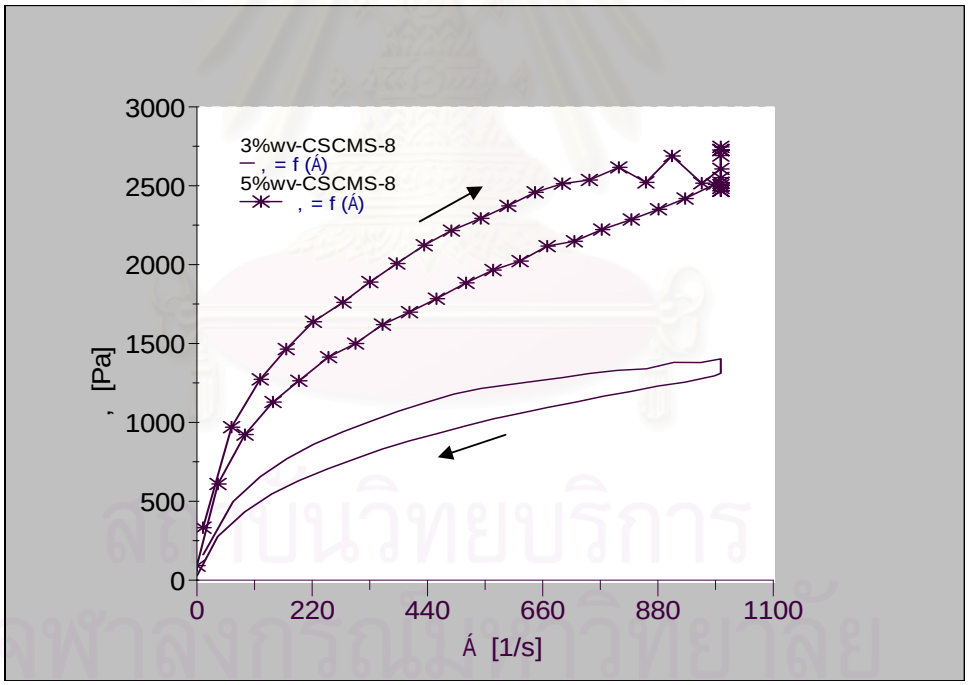


Figure 4-15 The rheograms of CSCMS-8 at the concentration of 3 and 5 % w/v.

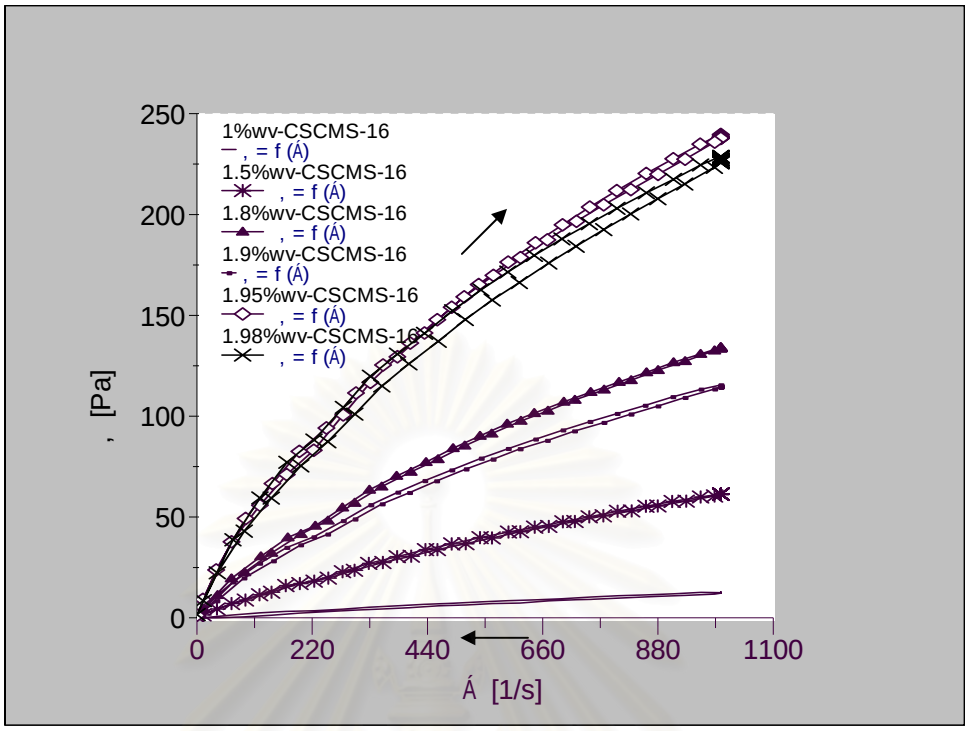


Figure 4-16 The rheograms of CSCMS-16 at various concentrations (1-1.98 % w/v).

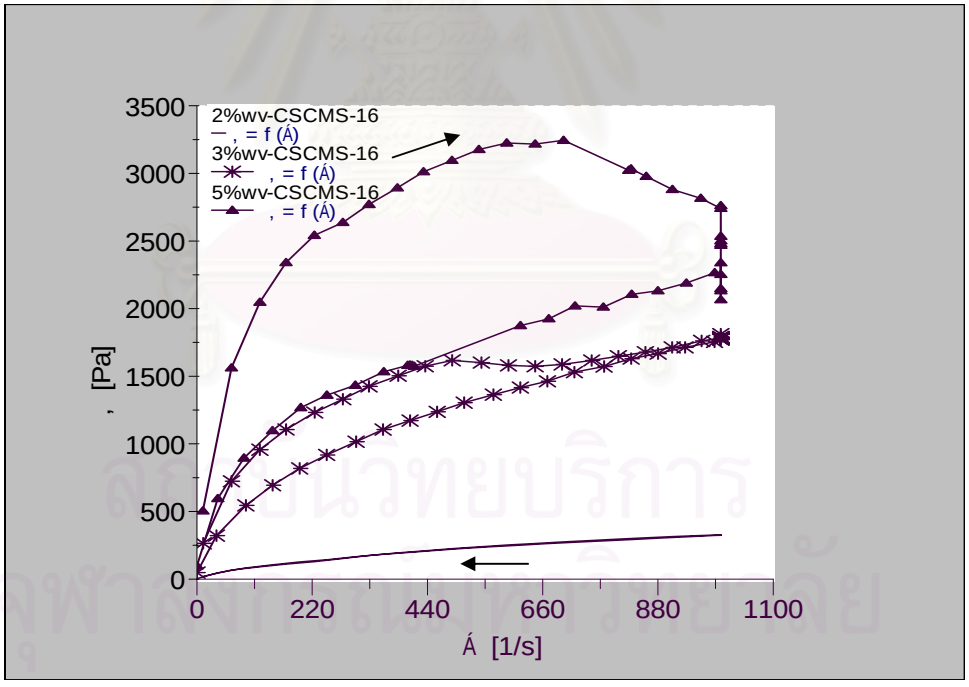


Figure 4-17 The rheograms of CSCMS-16 at various concentrations (2-5 % w/v).

Table 4-11 Thixotropic values of three DS of CSCMS at various concentrations.

Concentration (%w/v)	Average thixotropic value (Pa/s ± SD)		
	CSCMS-2	CSCMS-8	CSCMS-16
0.50	1,963.67 (89.58)	-*	-*
0.80	2,040.67 (237.96)	-*	-*
1.00	3,732.67 (582.61)	6,664.67 (768.63)	1,161.60 (226.65)
1.10	-*	7,452.33 (796.76)	-*
1.15	-*	5,378.00 (162.82)	-*
1.20	-*	7,674.33 (458.87)	-*
1.50	-*	13,510.00 (2,366.79)	1,431.07 (518.03)
1.80	-*	-*	2,532.33 (404.44)
1.90	-*	-*	2,457.33 (353.45)
1.95	-*	-*	3,239.67 (448.93)
1.98	-*	-*	8,729.67 (1,569.67)
2.00	-*	-*	13,876.67 (1,150.01)
3.00	19,756.67 (2,638.38)	174,666.67 (5,577.04)	277,433.33 (42,465.20)
5.00	118,966.67 (6,836.91)	315,100.00 (10,352.29)	1,337,000.00 (218,515.45)

* This concentration was not done in experiment.

The flow patterns of PGTS, HPTS showed a shear-thinning behavior and positive thixotropic values at the concentration of 1 % w/v whereas the higher concentrations (3-9 % w/v) provided negative thixotropic values (see Figure 4-18 and 4-19). It was indicated that the rheological behavior depend on the concentration. At low concentration (1 % w/v) of PGTS and HPTS provided the very low viscosity (4.99 and 3.94 cps, respectively) and the gel formation were not occurred. The thixotropic values of HPTS trended to increase when the concentration increased while the thixotropic values of PGTS were not consistency (see Table 4-12). It was possible that PGTS was physically modified starch so; it did not have consistent property. The rheograms of CHPTS showed a pseudoplastic type and positive thixotropic values at the concentration in the range of 1-5 % w/v whereas the higher concentrations (5.5-7 % w/v) provided negative thixotropic values and gave the pseudoplastic type and positive thixotropic value at the concentration of 9 % w/v (see in Figure 4-20 and Table 4-12).

The rheograms of UT, XG and TG at various concentrations are illustrated in figure 4-21, 4-22 and 4-23, respectively. The thixotropic values of UT, XG and TG at various concentrations are shown in Table 4-13. The rheological behaviors of UT, XG and TG depend on the concentration. For UT, at low concentration (1 and 3 % w/v) the flow patterns showed a pseudoplastic type and positive thixotropic values whereas the higher concentrations (4-5 % w/v) provided negative thixotropic values. For XG, the flow patterns showed a pseudoplastic type and negative thixotropic value at the low concentration (1 % w/v) whereas the higher concentrations (2-5 % w/v) provided positive thixotropic values. For TG, at the low concentration (1 % w/v) it showed a shear thinning behavior and positive thixotropic value while the higher concentrations (2-5 % w/v) provided negative thixotropic values. The areas of hysteresis loop of UT, XG and TG trended to increase when the concentration increased.

Table 4-12 Thixotropic values of PGTS, HPTS and CHPTS at various concentrations.

Concentration (% w/v)	Average thixotropic value(Pa/s ± SD)		
	PGTS	HPTS	CHPTS
1.00	252.40 (67.30)	307.07 (67.35)	660.83 (77.73)
3.00	-2,650.67 (142.68)	-759.63 (294.72)	866.03 (23.20)
5.00	-22,250.00 (1,554.64)	-4,566.67 (268.71)	842.37 (132.74)
5.50	-*	-*	-1,174.70 (282.46)
6.00	-*	-*	-2,521.67 (356.50)
7.00	-71,726.67 (2,947.78)	-19,493.33 (533.79)	-4,291.00 (180.02)
7.5	-*	-19,360.00 (105.36)	-*
8.00	-116,500.00 (2,253.89)	-*	-*
8.50	-64,950.00 (1,181.86)	-*	-*
9.00	-54,600.00 (1,825.02)	-27,303.33 (414.89)	3,931.00 (1,479.18)

* This concentration was not done in experiment.

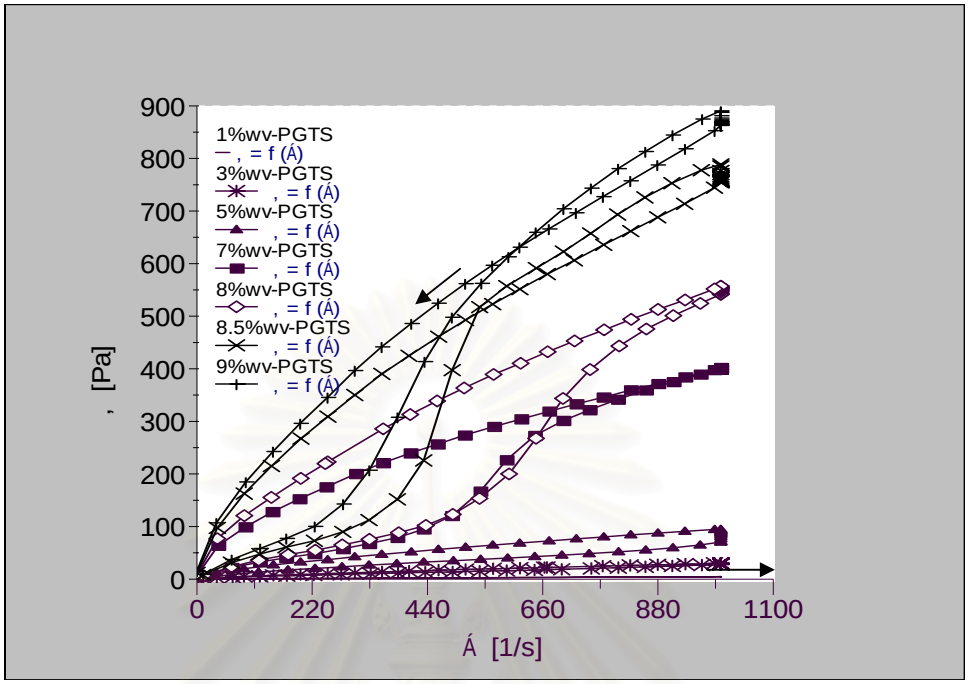


Figure 4-18 The rheograms of PGTS at the various concentrations.

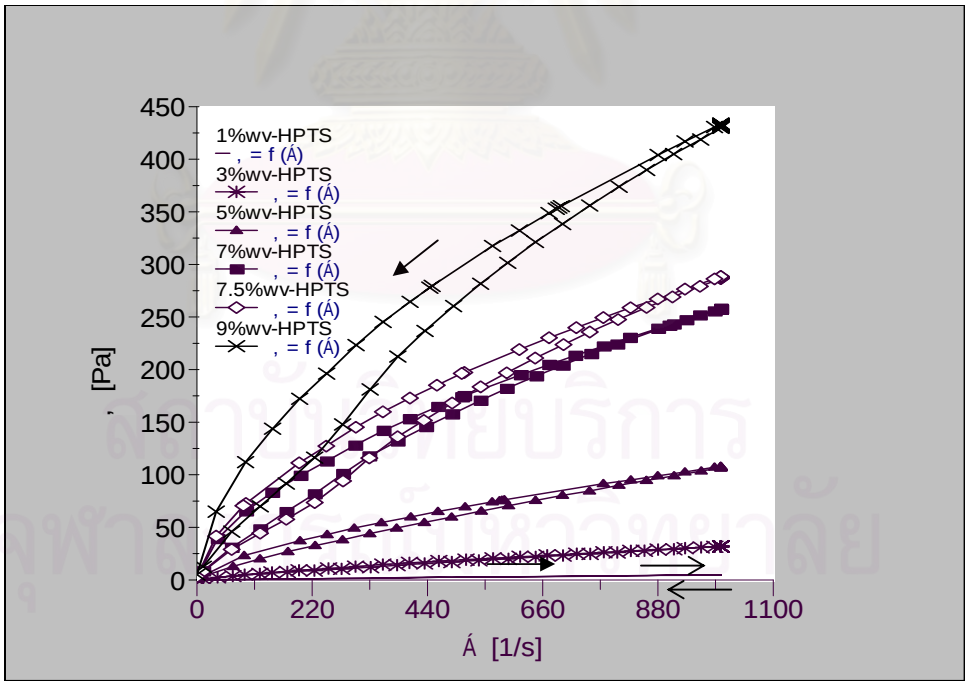


Figure 4-19 The rheograms of HPTS at the various concentrations.

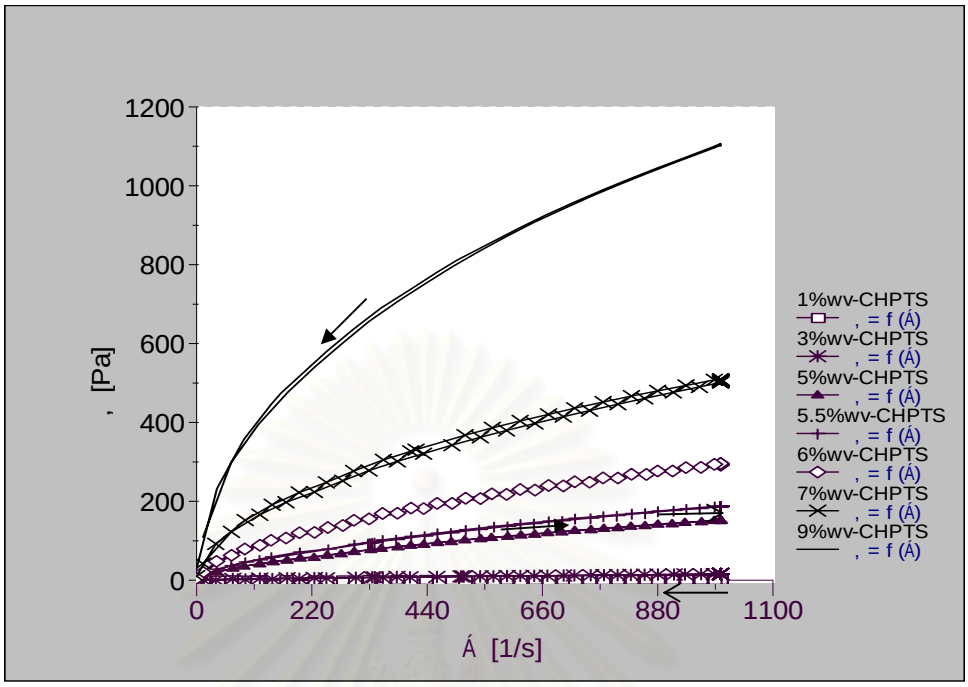


Figure 4-20 The rheograms of CHPTS at the various concentrations.

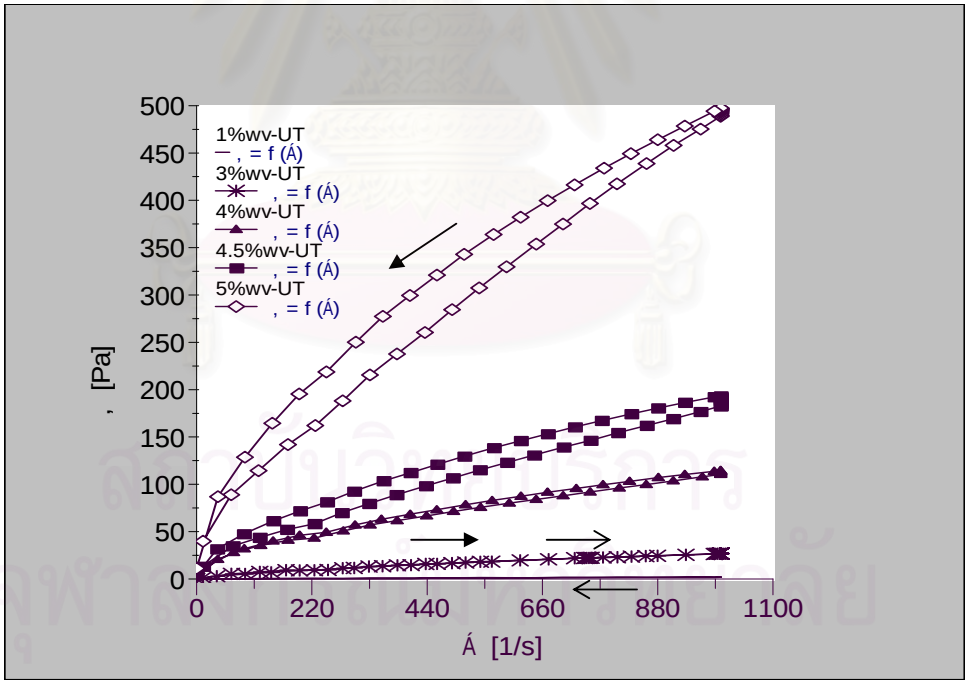


Figure 4-21 The rheograms of UT at the various concentrations.

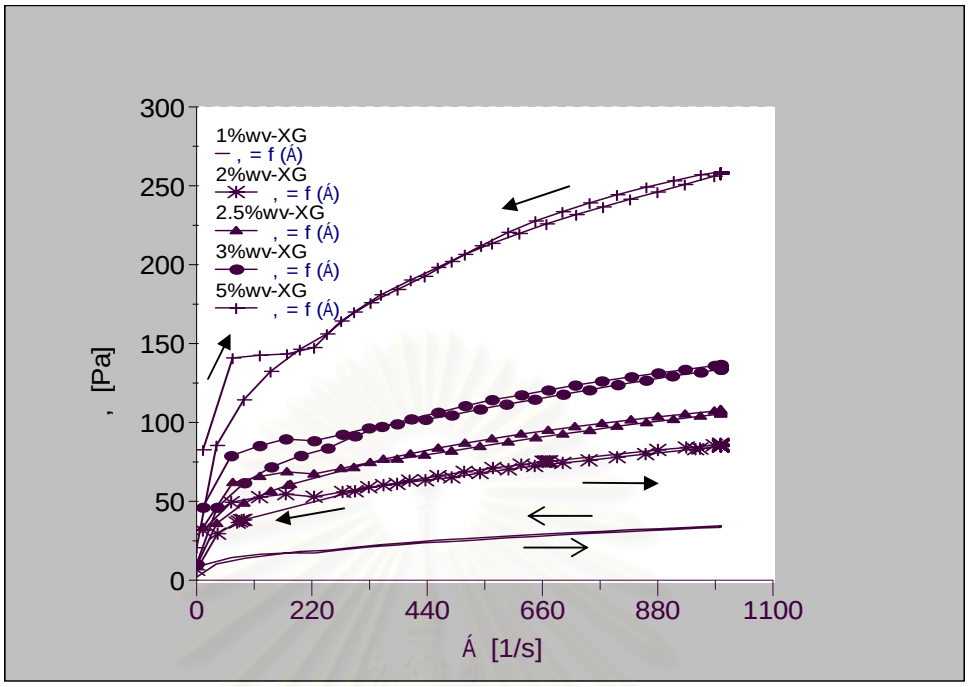


Figure 4-22 The rheograms of XG at the various concentrations.

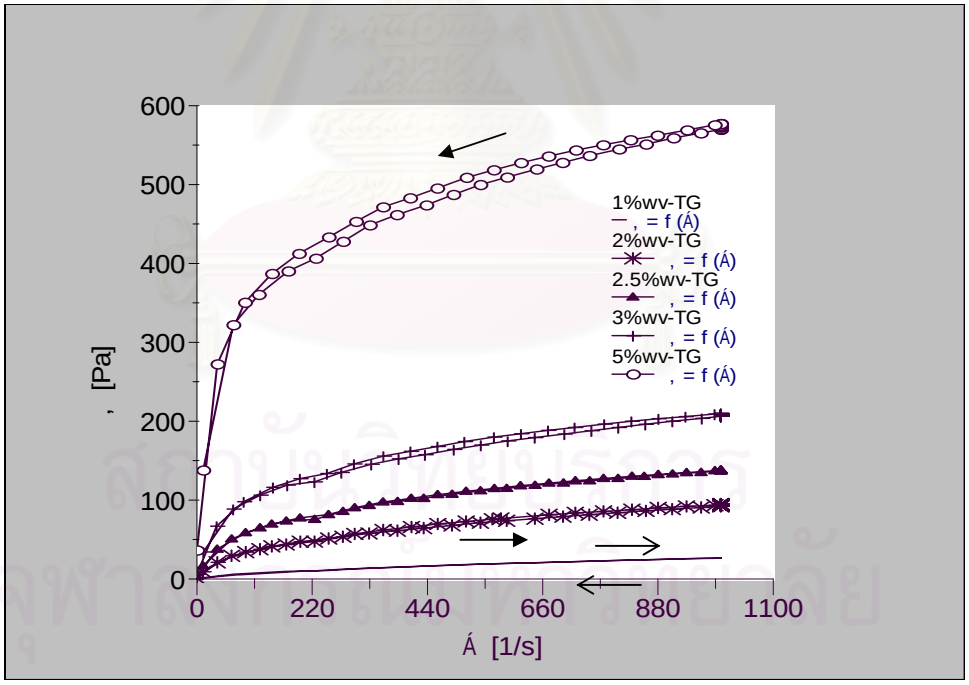


Figure 4-23 The rheograms of TG at the various concentrations.

Table 4-13 Thixotropic values of UT, XG and TG at various concentrations.

Concentration (% w/v)	Average thixotropic value (Pa/s ± SD)		
	UT	XG	TG
1	604.53 (77.99)	-275.70 (98.10)	422.53 (137.62)
2	-*	1,418.57 (811.33)	-924.83 (369.33)
2.5	-*	1,218.20 (495.41)	-1,290.67 (244.73)
3	386.03 (243.05)	2,982.33 (439.56)	-2,930.33 (333.14)
4	- 4,768.33 (271.32)	-*	-*
4.5	- 14,730.00 (646.30)	-*	-*
5	- 28,466.67 (640.34)	6,788.00 (1,050.64)	-5,487.67 (945.02)

* This concentration was not done in experiment.

3. Effect of Electrolyte and Type of buffer and pH on Viscosity and Rheological Behaviors of Modified Tapioca Starches and Other Suspending Agents

In this experiment, the effect of electrolyte and type of buffer and pH on the suspending properties of modified tapioca starches and other suspending agents were investigated. The concentrations of all suspending agents were selected from their viscosity (topic 2). The viscosity and rheological study in the mediums were evaluated.

3.1 Viscosity measurement of modified tapioca starches and other suspending agents

3.1.1 Effect of electrolyte

Sodium chloride solutions at concentration of 0.001, 0.01, 0.1, 0.2, and 0.5 Molar were used as the representative solution at ionic strength of 0.001, 0.01, 0.1, 0.2, and 0.5 Molar, respectively.

Viscosity and in various concentration of NaCl of SCMS with DS 0.11, 0.22 and 0.37 at concentration of 6 %, 2.5 % and 3 % w/v, respectively, are presented in Table 4-14 . The gel of 2.5 % w/v SCMS-2 and 3 % w/v SCMS-3 provided more transparent than that of 6 % w/v SCMS-1 because the high DS (0.22 and 0.37) of SCMS were more hydrophilic than the lower DS and it had more carboxyl group in its structure. The viscosity of all DS of SCMS decreased when sodium chloride concentrations were increased (Figure 4-24). At the lowest DS of SCMS, the viscosity was obviously decreased more than the higher DS when sodium chloride concentrations were increased. Moreover, the starch (6 % w/v SCMS-1) could not form gel and precipitated from the solution at high sodium chloride concentration (>0.2M). It was might be that sodium chloride dehydrated the starch molecule.

Table 4-14 Viscosity of three DS of SCMS in various concentrations of NaCl.

NaCl (M)	Average apparent viscosity (cps ± SD)		
	6 % SCMS-1	2.5 % SCMS-2	3 % SCMS-3
0	457.67 (2.31)	413.33 (2.08)	441.00 (1.73)
0.001	431.33 (1.53)	398.67 (2.08)	428.33 (3.22)
0.01	293.33 (3.22)	313.67 (1.15)	340.67 (6.11)
0.1	102.00 (1.00)	150.00 (2.00)	186.33 (1.53)
0.2	75.46 (0.89)	120.00 (3.61)	150.33 (1.16)
0.5	61.21 (2.07)	91.68 (4.10)	118.33 (5.13)

Table 4-15 Viscosity of three DS of CSCMS in various concentrations of NaCl.

NaCl (M)	Average apparent viscosity (cps ± SD)		
	0.8 % CSCMS-2	1.15 % CSCMS-8	1.95 % CSCMS-16
0.00	589.33 (4.93)	492.67 (13.01)	460.00 (13.00)
0.001	431.67 (11.15)	361.33 (7.23)	378.00 (14.42)
0.01	106.00 (6.25)	96.49 (4.07)	112.00 (9.64)
0.10	16.09 (3.22)	29.51 (4.40)	83.08 (5.59)
0.20	15.50 (4.43)	28.85 (2.49)	85.39 (3.28)
0.50	15.26 (4.92)	23.47 (5.01)	80.40 (3.18)

As summarized in Table 4-14 and Figure 4-24, the viscosity of all DS of CSCMS decreased obviously and the starch precipitation was occurred when sodium chloride concentration was more than 0.01 M and the gel of them was deformed. As the result, CSCMS lose gel structure at lower concentration of sodium chloride than SCMS. It was possible that CSCMS had denser network in the structure than SCMS. Moreover, it was less swelling and hydration than SCMS. Therefore, CSCMS was loss structure deformation than SCMS.

The viscosity of PGTS, HPTS and CHPTS had trend to slightly increase when the concentrations of sodium chloride were increased (see Table 4-16 and Figure 4-24).

Table 4-16 Viscosity of PGTS, HPTS, and CHPTS in various concentrations of NaCl.

NaCl (M)	Average apparent viscosity (cps ± SD)		
	8.5 % PGTS	7.5 % HPTS	5.5 % CHPTS
0.00	439.67 (5.51)	420.67 (13.01)	459.00 (1.00)
0.001	455.33 (4.16)	449.00 (8.718)	476.33 (6.66)
0.01	438.00 (2.00)	475.667 (10.26)	473.67 (6.66)
0.10	467.33 (3.06)	506.00 (9.54)	503.00 (3.61)
0.20	443.67 (4.73)	548.33 (7.51)	532.00 (9.17)
0.50	492.00 (6.25)	574.33 (12.66)	563.67 (2.89)

The viscosity of UT and TG were decreased when the concentrations of sodium chloride were increased (see Table 4-17 and Figure 4-24).Viscosity of TG trended to decrease where presented the ionic salt. This observation was similar to the report of Mohammadifar et al., (2006). TG behaved as a flexible coil in the solution. Anionic polymer when ionized in aqueous solution experience molecular expansion, which is caused by the mutual repulsion of the charges on the polymer backbone. Addition of salt tends to alter the chain flexibility and conformation features of polymer (Mohammadifar et al., 2006). The viscosity of TG was more decreased than the viscosity of UT at the high concentration of sodium chloride (0.5 M).While, the viscosity of XG was increased when the concentrations of sodium chloride were increased. The result agrees with a previous study in that the viscosity of XG in aqueous medium was influence by ionic strength (Talukdar et al., 1996 and Talukdar and Kinget, 1995). The addition of salt to XG solution in the concentration range from 0.2-3 % causes the viscosity to increase (Talukdar and Kinget, 1995). It might be that the salt affect to the conformation of xanthan molecules. The existence of

conformation transition of XG in aqueous solution was established. The disordered random coil conformation loses the ability to form a gel while the ordered elongated conformation is able to form a gel. An increase in concentration of added salt causes an increase in the rate of formation of an ordered structure (Talukdar and Kinget, 1995). In addition, it was also found that the salt screens the electrostatic repulsions of pyruvate and acetate group on the trisaccharide side chains, allowing the adoption of a helical backbone conformation of XG. This in turn promotes the increased association of the ordered XG molecule in solution (Talukdar et al., 1996).

Table 4-17 Viscosity of UT, XG and TG in various concentrations of NaCl.

NaCl (M)	Average apparent viscosity (cps ± SD)		
	4.5 % UT	2.5 % XG	2.5 % TG
0	478.67 (1.16)	529.33 (8.08)	612.67 (1.16)
0.001	474.67 (10.41)	547.33 (5.13)	614.00 (1.73)
0.01	497.00 (9.64)	667.67 (5.13)	589.33 (2.08)
0.1	477.00 (1.00)	1,059.67 (13.20)	549.33 (5.69)
0.2	446.67 (8.145)	1,126.33 (14.05)	537.67 (6.66)
0.5	444.67 (8.74)	1,126.33 (12.90)	499.33 (3.22)

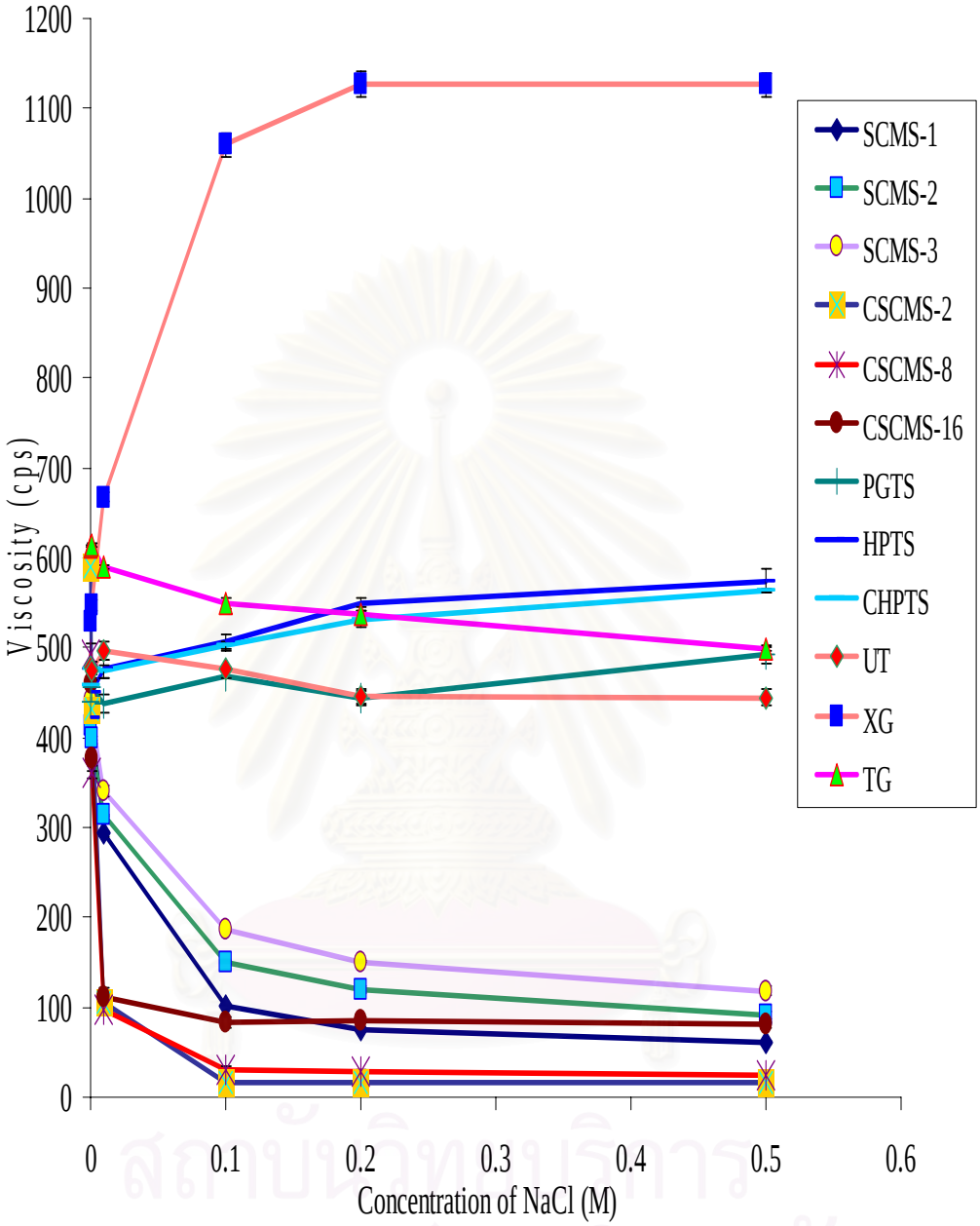


Figure 4-24 Viscosity of all suspending agents in various concentrations of NaCl (M).

3.1.2 Effect of type of buffer and pH

Phosphate and citrate buffer were selected in further study because both of them were widely used in the liquid preparations. The pH of their buffers was varied to study the effect on the property of suspending agent.

3.1.2.1 Phosphate buffer

Phosphate buffer that had 0.05 M of total concentration and 0.2 M of ionic strength were evaluated at pH 3, 5, 7 and 9.

The viscosity and pH change of SCMS with DS 0.11, 0.22 and 0.37 at concentration of 6 %, 2.5 % and 3 % w/v, respectively, in phosphate buffer 0.05 M, ionic strength 0.2 M are shown in Table 4-18. In basic condition (pH 9) all viscosity of SCMS with DS 0.11, 0.22 and 0.37 decreased obviously. While in acid condition (pH 3 and 5), the viscosity of all DS of SCMS were not different (see Figure 4-25). The higher degree of SCMS (0.22 and 0.37) could maintain their viscosity better than the lower DS (0.11) at basic condition. That mean SCMS was suitable as suspending agent in neutral and acid condition.

Table 4-18 Viscosity and pH of three DS of SCMS at different concentrations in 0.05 M phosphate buffer (ionic strength of 0.2 M).

pH of buffer	Average apparent viscosity (cps ± SD)			pH after adding buffer		
	6 % SCMS-1	2.5 % SCMS-2	3 % SCMS-3	6 % SCMS-1	2.5 % SCMS-2	3 % SCMS-3
water	457.67 (2.31)	413.33 (2.08)	449.00 (3.61)	6.72	6.78	6.90
3	72.69 (3.34)	132.33 (2.08)	163.00 (1.00)	4.64	4.65	4.71
5	75.40 (0.35)	133.67 (3.06)	168.00 (2.65)	5.12	5.25	5.12
7	89.62 (0.99)	126.00 (1.00)	142.33 (5.86)	6.90	6.71	6.94
9	49.02 (3.27)	80.11 (1.55)	72.97 (6.70)	8.27	8.44	8.40

As displayed in Table 4-19 and Figure 4-25, the viscosity of all DS of CSCMS decreased obviously and the starch precipitation was occurred because their loosed gel structure beginning at ionic strength of 0.01 M (in previous part 3.1.1). In this section, the total ionic strength was 0.2 M so; the different of pH was not affected on their property. The main effect might be the influence of ionic strength on the viscosity. It was indicated that CSCMS were not suitable as suspending agent because it could not maintain the viscosity when the ionic and salt were added in the solution.

Table 4-19 Viscosity and pH of three DS of CSCMS at different concentrations in 0.05 M phosphate buffer (ionic strength of 0.2 M).

pH of buffer	Average apparent viscosity (cps ± SD)			pH after adding buffer		
	0.8 % CSCMS-2	1.15 % CSCMS-8	1.95 % CSCMS-16	0.8 % CSCMS-2	1.15 % CSCMS-8	1.95 % CSCMS-16
water	645.67 (18.77)	492.67 (13.01)	460.00 (13.00)	6.23	6.49	6.33
3	25.82 (1.96)	26.67 (4.92)	96.57 (4.82)	4.29	4.43	4.61
5	25.17 (2.22)	26.80 (4.75)	60.84 (0.68)	4.99	5.07	5.14
7	18.58 (2.61)	23.57 (1.09)	50.38 (5.11)	6.86	7.01	6.81
9	24.10 (5.18)	28.50 (5.59)	67.22 (1.54)	8.23	8.18	8.17

PGTS, HPTS and CHPTS could form gel in pH 3, 5, 7 and 9 and the viscosity of them were slightly different in acid and basic condition (<100cps). At pH 3 and 5, the viscosity of them were similar and the viscosity of HPTS and CHPTS at pH 7 were similar to those of pH 9 (see Table 4-20 and Figure 4-25).

Table 4-20 Viscosity and pH of PGTS, HPTS, and CHPTS at different concentrations in 0.05 M phosphate buffer (ionic strength of 0.2 M).

pH of buffer	Average apparent viscosity (cps ± SD)			pH after adding buffer		
	8.5 % PGTS	7.5 % HPTS	5.5 % CHPTS	8.5 % PGTS	7.5 % HPTS	5.5 % CHPTS
water	503.67 (7.57)	366.67 (7.10)	450.33 (4.51)	5.96	5.63	6.20
3	584.00 (13.79)	417.00 (6.00)	491.00 (8.00)	3.36	3.04	3.11
5	581.67 (8.51)	403.33 (5.77)	494.00 (4.58)	4.94	4.70	4.82
7	506.67 (13.65)	394.00 (4.36)	506.00 (2.67)	6.80	6.69	6.86
9	593.67 (14.19)	404.33 (0.57)	505.33 (5.03)	8.23	8.28	8.29

Viscosity and pH change of UT, XG and TG at concentration of 4.5 %, 2.5 % and 2.5 % w/v, respectively, in 0.05 M phosphate buffer (ionic strength of 0.2 M) are showed in Table 4-21. Viscosity of UT was slightly different in acid-base condition and water while, the viscosity of XG was increased in pH medium of 3, 5, 7 and 9 comparing with in water (see Figure 4-25). As the result the main effect might be the influence of ionic strength on the viscosity of XG which was discussed in the previous topic (3.1.1). In addition, the little effect of pH on viscosity of XG was observed. At pH 3, 5 and 7 the viscosity of TG was decreased comparing with in water. It might be the effect of ionic strength on the viscosity of TG. The pH of 3, 5and 7 were affected slightly on the viscosity of TG whereas the viscosity was increased at pH 9.

Table 4-21 Viscosity and pH of UT, XG and TG at different concentrations in 0.05 M phosphate buffer (ionic strength of 0.2 M).

pH of buffer	Average apparent viscosity (cps ± SD)			pH after adding buffer		
	4.5 % UT	2.5 % XG	2.5 % TG	4.5 % UT	2.5 % XG	2.5 % TG
water	433.33 (4.04)	531.00 (9.85)	603.33 (16.77)	6.37	6.05	4.48
3	456.67 (3.51)	1042.00 (2.00)	519.33 (4.04)	3.06	3.98	3.76
5	453.33 (2.08)	1,041.00 (12.77)	528.33 (5.51)	4.69	4.93	4.31
7	459.33 (7.51)	1,037.67 (4.51)	579.00 (6.00)	6.73	6.84	6.48
9	493.00 (4.58)	995.67 (9.29)	669.33 (6.43)	8.18	7.85	7.16

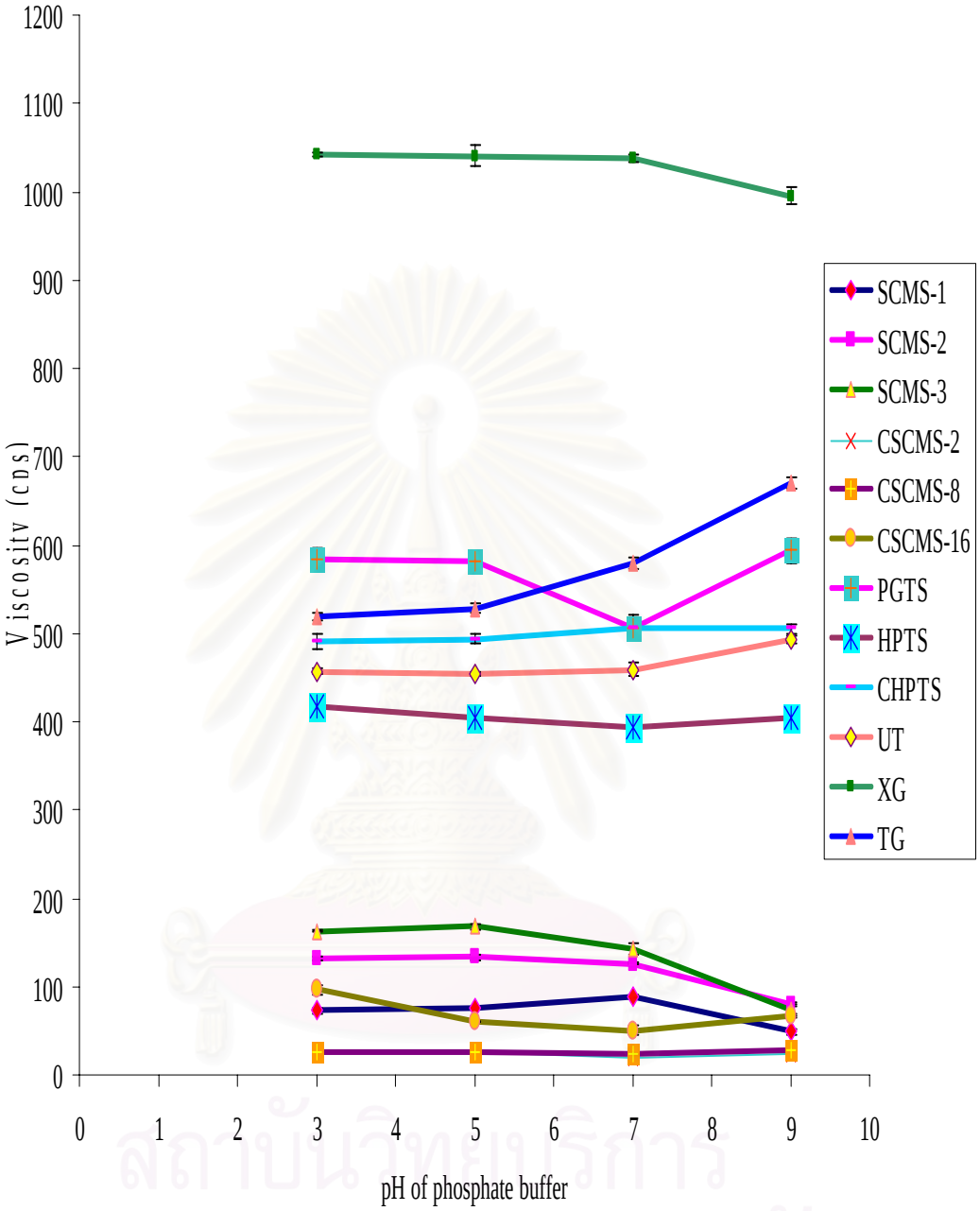


Figure 4-25 Viscosity of all suspending agents in various pH of 0.05 M phosphate buffer (ionic strength of 0.2 M).

3.1.2.2 Citrate buffer

Citrate buffer was used at concentration of 0.04 M having 0.2 M of ionic strength. Its effect on the viscosity and rheological behavior was evaluated at pH 2, 4 and 6.

As shown in Table 4-22 and Figure 4-26, all viscosity of SCMS with DS 0.11, 0.22 and 0.37 in citrate buffer decreased obviously comparing with in the water because the main effect might be the influence of ionic strength on the viscosity (as discussed in previous part 3.1.1). While the viscosity of all DS of SCMS were little decreased at the pH of 2 and 4 in comparing with the pH of 6.The higher DS of SCMS (0.22 and 0.37) could maintain their viscosity in citrate buffer at the pH 2, 4 and 6 better than the lower DS (0.11).

Table 4-22 Viscosity and pH of three DS of SCMS in 0.04 M citrate buffer (ionic strength of 0.2 M).

pH of buffer	Average apparent viscosity (cps ± SD)			pH after adding buffer		
	6 % SCMS-1	2.5 % SCMS-2	3 % SCMS-3	6 % SCMS-1	2.5 % SCMS-2	3 % SCMS-3
water	476.70 (2.21)	464.03 (6.12)	537.30 (8.32)	6.94	6.71	6.20
2	43.72 (5.86)	71.79 (5.08)	128.37 (2.44)	3.20	3.10	3.53
4	68.80 (4.60)	122.17 (4.68)	172.60 (9.70)	4.41	4.39	4.64
6	98.82 (3.61)	165.93 (4.80)	237.33 (9.89)	6.28	6.26	6.21

As shown in Table 4-23 and Figure 4-26, citrate buffer affected on all DS of CSCMS by decreasing the viscosity and precipitation of starch. It might be also the influence of ionic strength on the viscosity (as discussed in previous part 3.1.1). In this section, the different of pH was not obviously affected on their properties. However, the higher DS could be maintained the viscosity better than the lower DS.

Effect of 0.04 M citrate buffer (ionic strength of 0.2 M) on the viscosity and pH change of PGTS, HPTS, and CHPTS at concentration of 8.5 %, 7.5 % and 5.5 % w/v, respectively, is shown in Table 4-24. The viscosity of PGTS, HPTS and CHPTS in citrate buffer at the pH of 6 was not different in comparing with in the water. At the pH of 2 and 4 the viscosity of PGTS was obviously increased whereas the viscosity of HPTS and CHPTS was slightly increased. It was indicated that HPTS and CHPTS were modified starch which were resistible to the ionic and acid condition. This finding was supported by the study of Wattanachant et al. (2003) that cross-linked hydroxypropyl sago starch exhibited no viscosity breakdown and high acid resistance.

Table 4-23 Viscosity and pH of three DS of CSCMS at different concentrations in 0.04 M citrate buffer (ionic strength of 0.2 M).

pH of buffer	Average apparent viscosity (cps ± SD)			pH after adding buffer		
	0.8 % CSCMS-2	1.15 % CSCMS-8	1.95 % CSCMS-16	0.8 % CSCMS-2	1.15 % CSCMS-8	1.95 % CSCMS-16
water	644.37 (14.65)	548.53 (9.50)	459.63 (23.92)	6.59	6.71	6.58
2	6.54 (1.75)	8.34 (2.62)	24.25 (9.50)	2.95	3.08	3.32
4	6.96 (3.11)	19.69 (4.92)	35.86 (4.27)	4.37	4.39	4.44
6	16.70 (6.91)	18.79 (3.53)	48.28 (7.69)	6.17	6.36	6.33

Table 4-24 Viscosity and pH of PGTS, HPTS, and CHPTS at different concentrations in 0.04 M citrate buffer (ionic strength of 0.2 M).

pH of buffer	Average apparent viscosity (cps ± SD)			pH after adding buffer		
	8.5 % PGTS	7.5 % HPTS	5.5 % CHPTS	8.5 % PGTS	7.5 % HPTS	5.5 % CHPTS
water	520.07 (3.55)	320.00 (4.39)	373.77 (8.11)	6.28	6.76	7.09
2	935.10 (11.23)	359.83 (10.10)	416.83 (4.39)	2.59	2.62	2.6
4	960.77 (41.71)	362.73 (5.15)	397.33 (1.82)	4.25	4.39	4.43
6	565.83 (8.08)	318.27 (5.34)	361.33 (4.22)	6.28	6.24	6.38

Viscosity of UT was slightly different in citrate buffer comparing with in the water while, the viscosity of XG in citrate buffer was increased obviously comparing with in water (see Table 4-25 and Figure 4-26). As the result the main effect might be the influence of ionic strength on the viscosity of XG which was discussed in the previous topic (3.1.1). Moreover, the viscosity of XG was not different when pH was decreased. The viscosity of TG in citrate buffer was decreased comparing with in water agreeing with the result in the previous part (3.1.1). As the result the main effect might be the influence of ionic strength on the viscosity of TG. The different pH of 2, 4and 6 were affected slightly on the viscosity of TG.

Table 4-25 Viscosity and pH of UT, XG and TG at different concentrations in 0.04 M citrate buffer (ionic strength of 0.2 M).

pH of buffer	Average apparent viscosity (cps ± SD)			pH after adding buffer		
	4.5 % UT	2.5 % XG	2.5 % TG	4.5 % UT	2.5 % XG	2.5 % TG
water	341.20 (4.95)	533.30 (11.10)	658.00 (28.93)	6.73	6.90	4.44
2	423.63 (8.45)	1,112.67 (21.46)	573.67 (5.14)	2.65	2.89	2.76
4	353.83 (5.31)	1,096.00 (19.47)	580.83 (9.11)	4.39	4.31	4.12
6	329.60 (5.05)	987.47 (27.12)	617.33 (3.99)	6.39	6.52	6.06

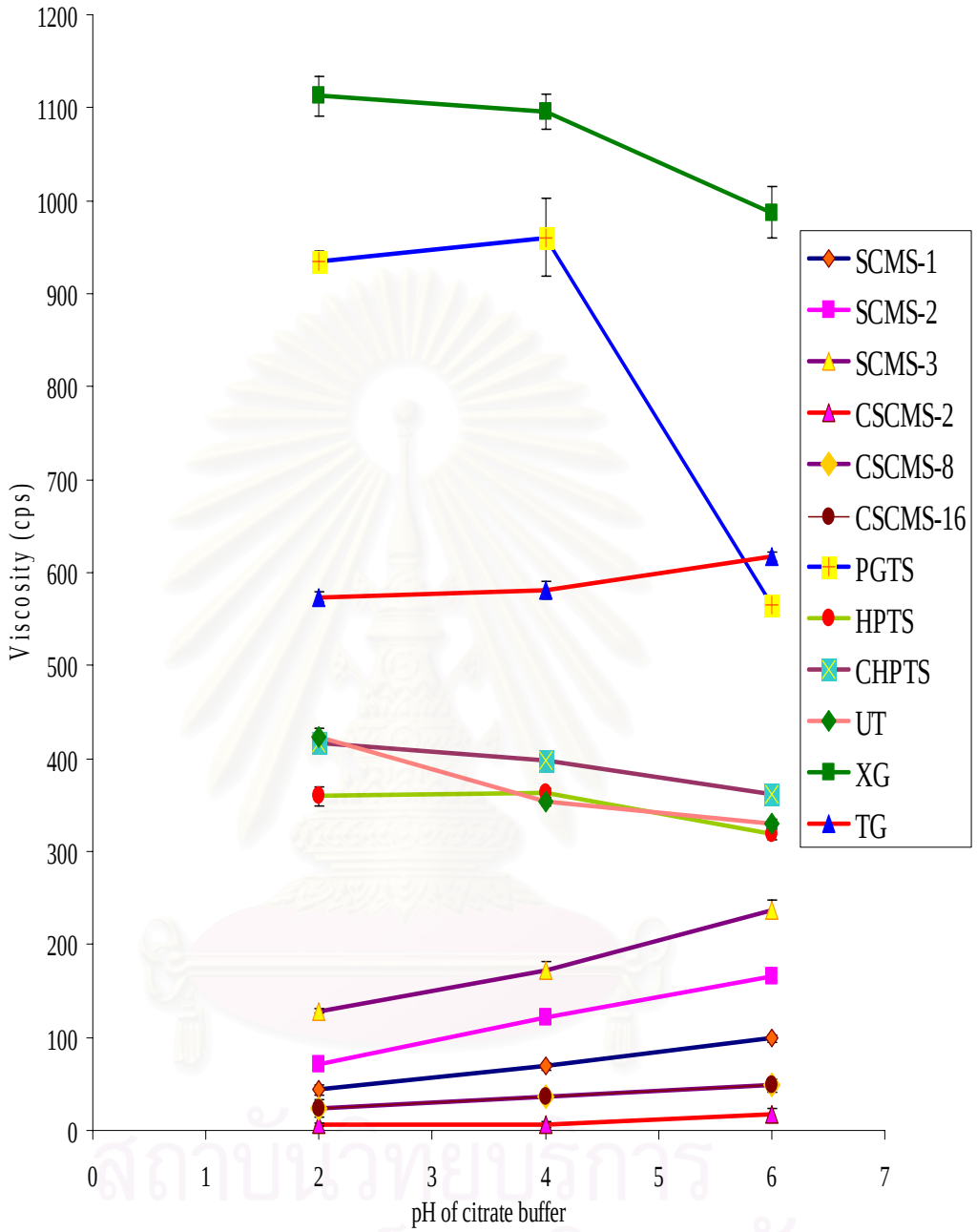


Figure 4-26 Viscosity of all suspending agents in various pH of 0.04 M citrate buffer (ionic strength of 0.02 M).

3.2 Rheological studies of modified tapioca starches and other suspending agents

3.2.1 Effect of electrolyte

The rheograms of SCMS with DS 0.11, 0.22 and 0.37 at the concentration of 6 %, 2.5 % and 3 % w/v in various concentrations of sodium chloride comparing with in water are illustrated in Figure 4-27, 4-28 and 4-29, respectively. When the concentrations of sodium chloride were increased, the curve began at the origin of shear stress-shear rate plot but was concaved upward; that was, an increasing shear rate gave a less than proportional increase in shear stress. The flow behaviors of SCMS with all DS still showed a shear-thinning pattern that provided the positive thixotropic values. As summarized in Table 4-26, the thixotropic values of SCMS with DS of 0.11 and 0.37 trended to decrease obviously while the thixotropic value obtained from SCMS with DS 0.22 were unlikely to be changed. It was indicated that ionic strength was not changed the pattern of flow but it had influence to the viscosity and the thixotropic value of SCMS.

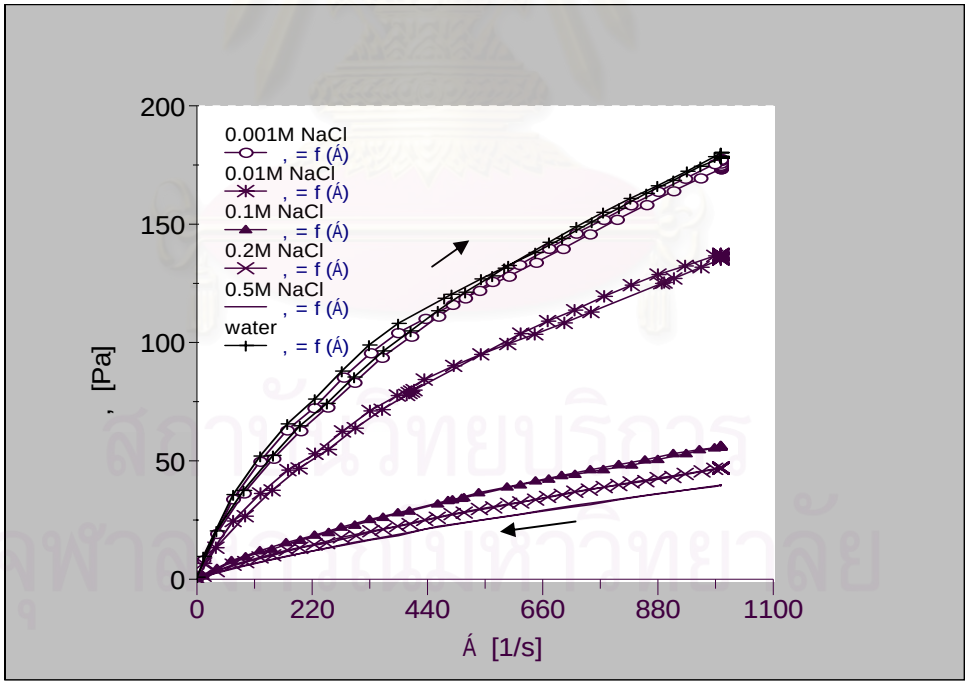


Figure 4-27 The rheograms of 6 % w/v SCMS-1 in various concentrations of NaCl comparing with in water.

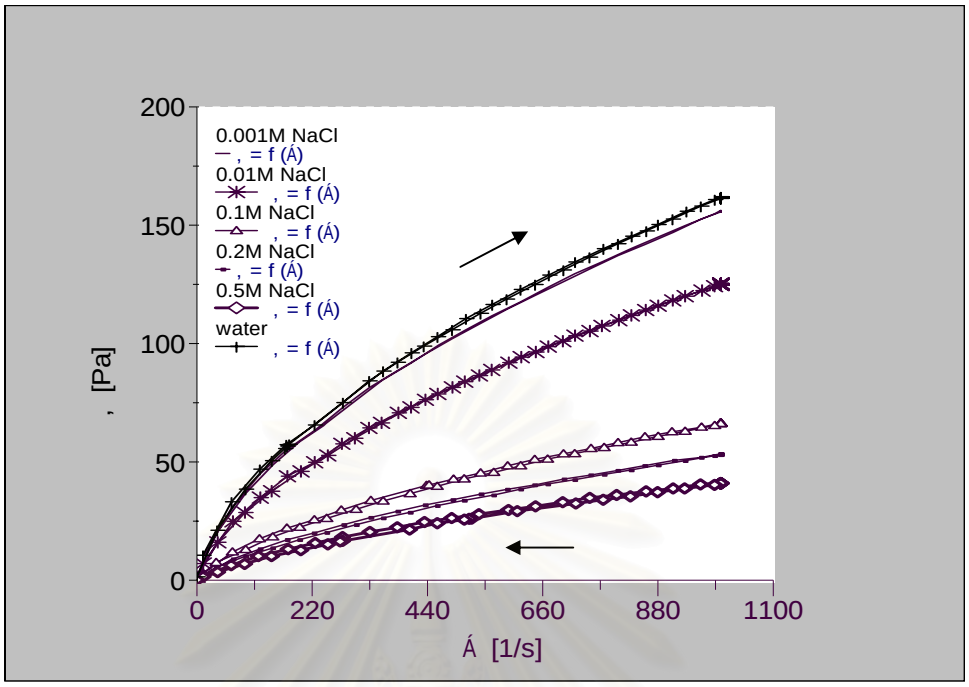


Figure 4-28 The rheograms of 2.5 % w/v SCMS-2 in various concentrations of NaCl comparing with in water.

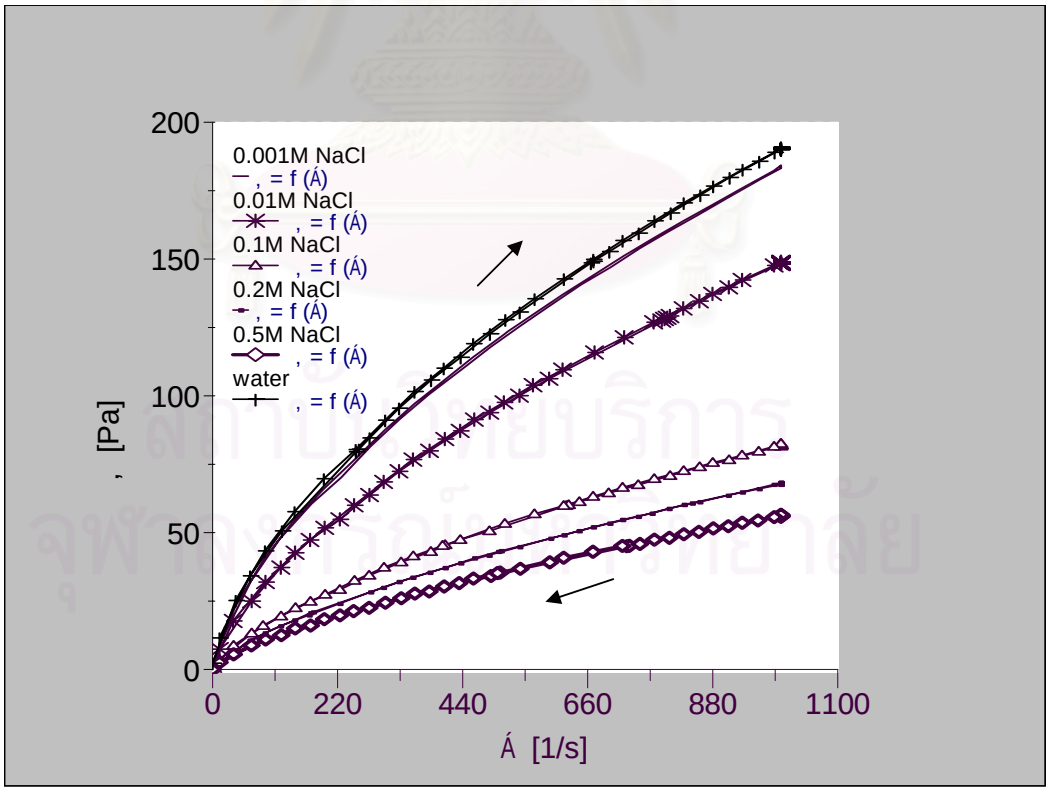


Figure 4-29 The rheograms of 3 % w/v SCMS-3 in various concentrations of NaCl comparing with in water.

Table 4-26 Thixotropic values of three DS of SCMS at different concentrations in various concentrations of NaCl.

NaCl (M)	Average thixotropic value (Pa/s ± SD)		
	6 % SCMS-1	2.5 % SCMS-2	3 % SCMS-3
0	4,052.00 (835.06)	1,585.33 (86.38)	1,097.00 (42.67)
0.001	2,779.00 (437.67)	1,609.33 (260.13)	1,153.00 (84.33)
0.01	2,572.33 (921.87)	1,941.33 (284.30)	1,073.90 (74.66)
0.1	1,251.87 (469.41)	1,802.00 (93.36)	480.80 (24.62)
0.2	829.60 (171.50)	1,680.00 (44.53)	576.80 (114.58)
0.5	449.13 (158.16)	1,739.67 (96.65)	347.17 (54.56)

The rheograms of CSCMS prepared with reaction time of 2, 8 and 16 hrs at the concentration of 0.8 %, 1.15 % and 1.95 % w/v, respectively, in various concentrations of sodium chloride in comparing with in water are shown in Figure 4-30, 4-31 and 4-32, respectively. Their respective thixotropic values respectively are presented in Table 4-27. When the concentrations of sodium chloride were increased, the flow behaviors of CSCMS-2 and CSCMS-8 still showed a pseudoplastic type with positive thixotropic values.

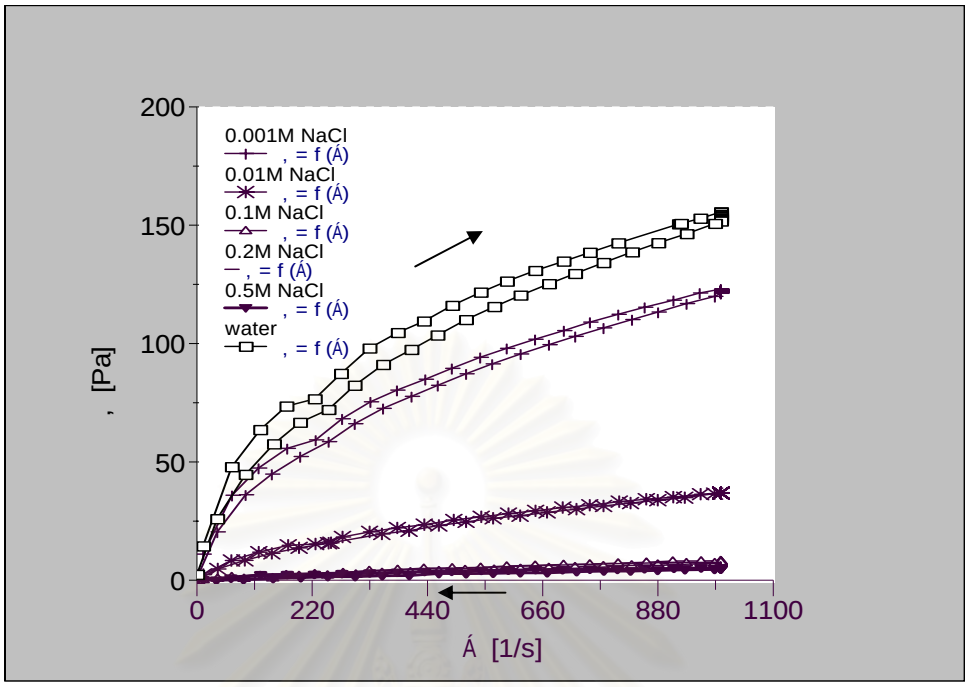


Figure 4-30 The rheograms of 0.8 % w/v CSCMS-2 in various concentrations of NaCl comparing with in water.

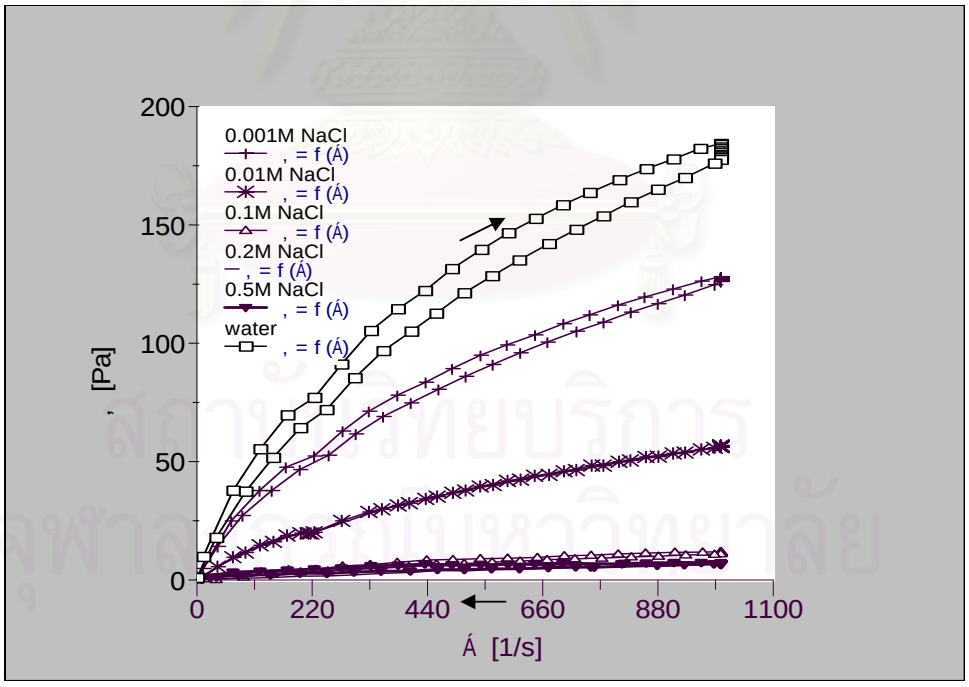


Figure 4-31 The rheograms of 1.15 % w/v CSCMS-8 in various concentrations of NaCl comparing with in water.

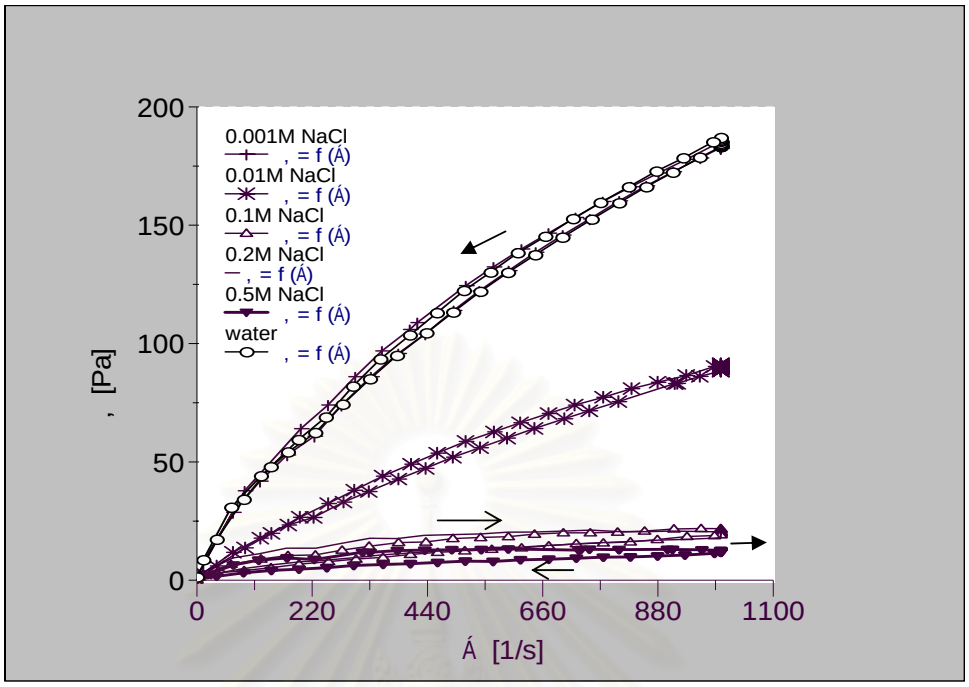


Figure 4-32 The rheograms of 1.95 % w/v CSCMS-16 in various concentrations of NaCl comparing with in water.

Both thixotropic values of CSCMS-2 and CSCMS-8 trended to decrease obviously. The flow patterns of CSCMS-16 were a pseudoplastic type with negative thixotropic values at the concentration of sodium chloride in the range of 0.001-0.01 M, after that the rheograms were changed to the pseudoplastic type with positive thixotropic values at the higher concentration of sodium chloride (> 0.1 M). The thixotropic values of CSCMS-16 increased when the concentrations of sodium chloride increased.

The flow patterns of PGTS, HPTS and CHPTS exhibited antithixotropic type at all concentration of NaCl except CHPTS in 0.2 and 0.5 M of NaCl. They changed the rheograms to a pseudoplastic type with positive thixotropic values (Figure 4-33, 4-34, 4-35 and Table 4-28).

Table 4-27 Thixotropic values of three DS of CSCMS at different concentrations in various concentrations of NaCl.

NaCl (M)	Average thixotropic value (Pa/s ± SD)		
	0.8 % CSCMS-2	1.15 % CSCMS-8	1.95 % CSCMS-16
0.00	7,176.67 (1,165.14)	10,520.33 (769.64)	-2,533.67 (812.17)
0.001	5,182.67 (577.79)	5,238.33 (775.69)	-1,381.20 (903.77)
0.01	1,671.00 (214.01)	1,293.33 (212.49)	-1,338.93 (489.82)
0.10	1,140.67 (122.35)	1,546.00 (251.33)	3,000.67 (1,305.25)
0.20	1,298.40 (368.39)	1,766.00 (211.06)	4,785.33 (1,171.63)
0.50	1,296.67 (165.18)	1,557.67 (313.42)	4,886.67 (1,068.52)

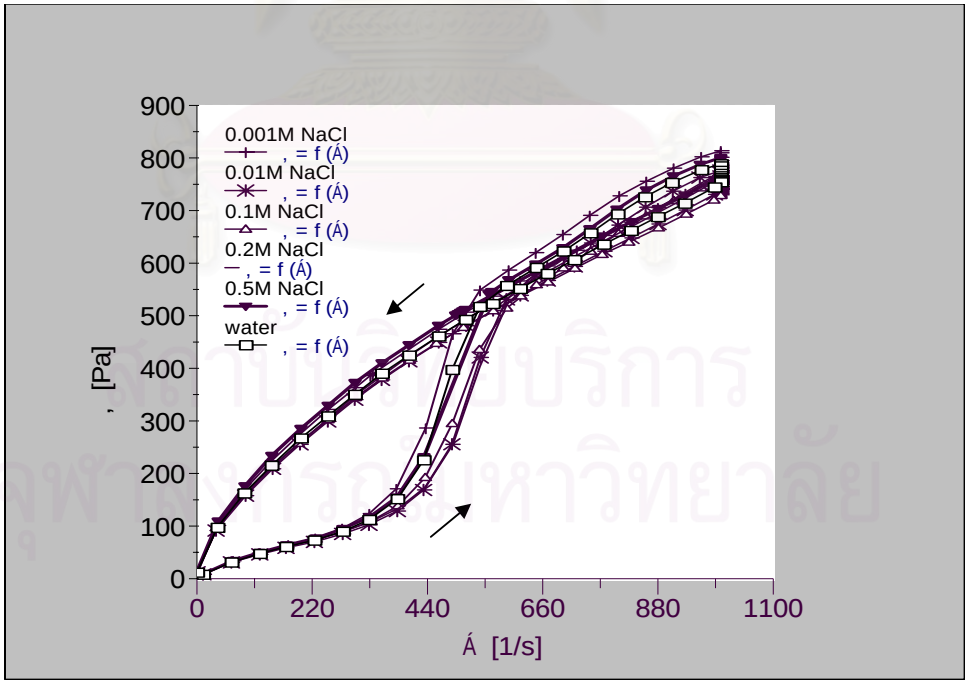


Figure 4-33 The rheograms of 8.5 % w/v PGTS in various concentrations of NaCl comparing with in water.

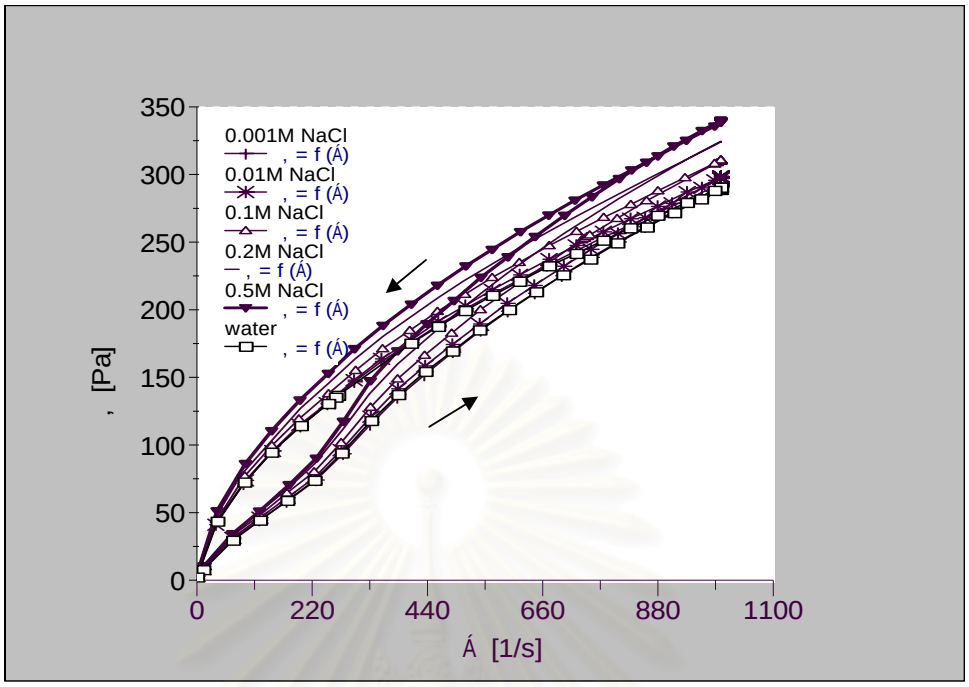


Figure 4-34 The rheograms of 7.5 % w/v HPTS in various concentrations of NaCl comparing with in water.

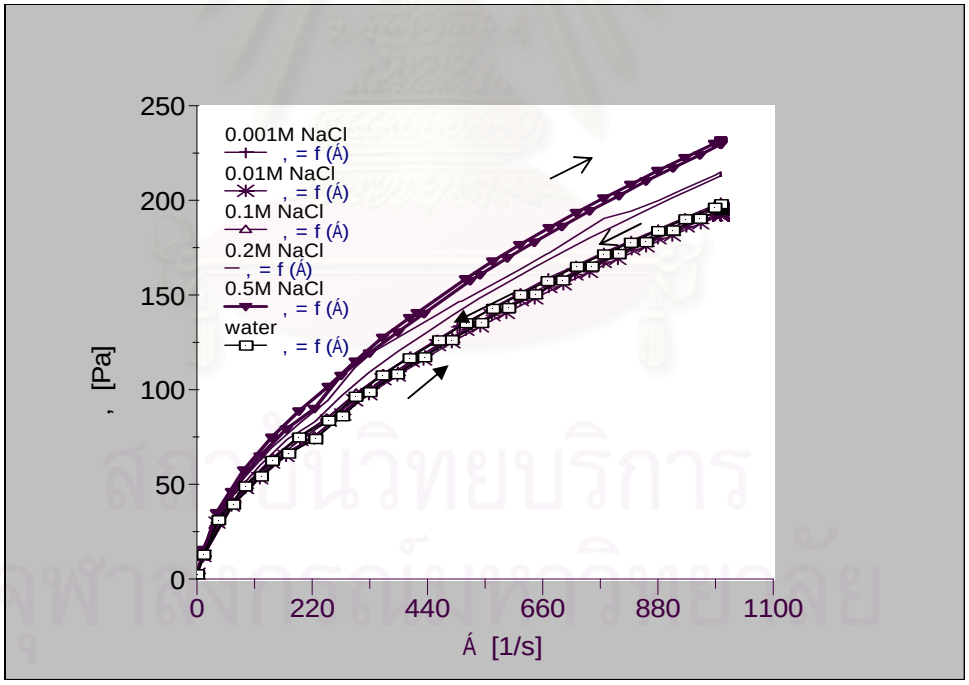


Figure 4-35 The rheograms of 5.5 % w/v CHPTS in various concentrations of NaCl comparing with in water.

The thixotropic values of PGTS were not consistency showing high standard deviation of the repeated measurement. It was possible that PGTS was physically modified starch therefore; it did not have consistent property. The areas of hysteresis loop of HPTS trended to slightly decrease after adding sodium chloride. Ionic strength was not changed the pattern of flow behaviors of PGTS and HPTS but it had influence to the viscosity and the thixotropic values of them, while the flow patterns of CHPTS were changed from negative to positive pseudoplastic type after adding 0.2 M of ionic strength in the system.

Table 4-28 Thixotropic values of PGTS, HPTS and CHPTS at different concentrations in various concentrations of NaCl comparing with in water.

NaCl (M)	Average thixotropic value (Pa/s ± SD)		
	8.5 % PGTS	7.5 % HPTS	5.5 % CHPTS
0.00	-91,846.67 (1,988.73)	-19,360.00 (105.36)	-1,174.67 (282.52)
0.001	-56,513.33 (1,681.68)	-20,860.00 (199.25)	-908.90 (385.04)
0.01	-80,803.33 (1,235.69)	-18,920.00 (633.80)	-585.07 (606.91)
0.10	-83,483.33 (3,796.98)	-18,390.00 (521.15)	-532.40 (247.36)
0.20	-91,386.67 (3,763.67)	-17,440.00 (476.97)	106.97 (716.65)
0.50	-79,620.00 (1,036.77)	-17,083.33 (265.77)	110.38 (175.08)

The rheograms of UT, XG and TG at the concentration of 4.5 %, 2.5 % and 2.5 % w/v, respectively, in various concentrations of sodium chloride comparing with in water are shown in Figure 4-36, 4-37 and 4-38. Their respective thixotropic values are presented in Table 4-29. Each concentration, the flow behaviors of UT, XG and TG exhibited a pseudoplastic type with negative thixotropics values in water.

Adding 0.5 M sodium chloride, the rheogram of UT still showed a pseudoplastic type with negative thixotropic value. While, the flow patterns of XG altered from negative to positive thixotropic values at 0.01 M to 0.5 M sodium chloride. Hysteresis loop areas of XG trended to increase after increasing the salt. At high concentration of NaCl (0.5 M) it changed the thixotropic value of TG from negative to positive and decreased the area of hysteresis loop.

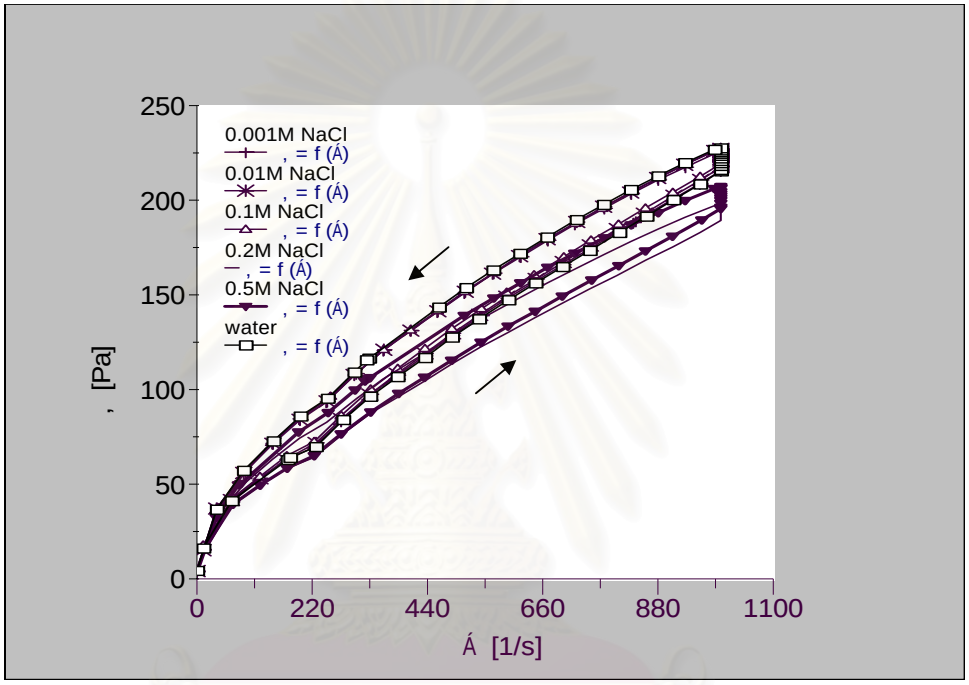


Figure 4-36 The rheograms of 4.5 % w/v UT in various concentrations of NaCl comparing with in water.

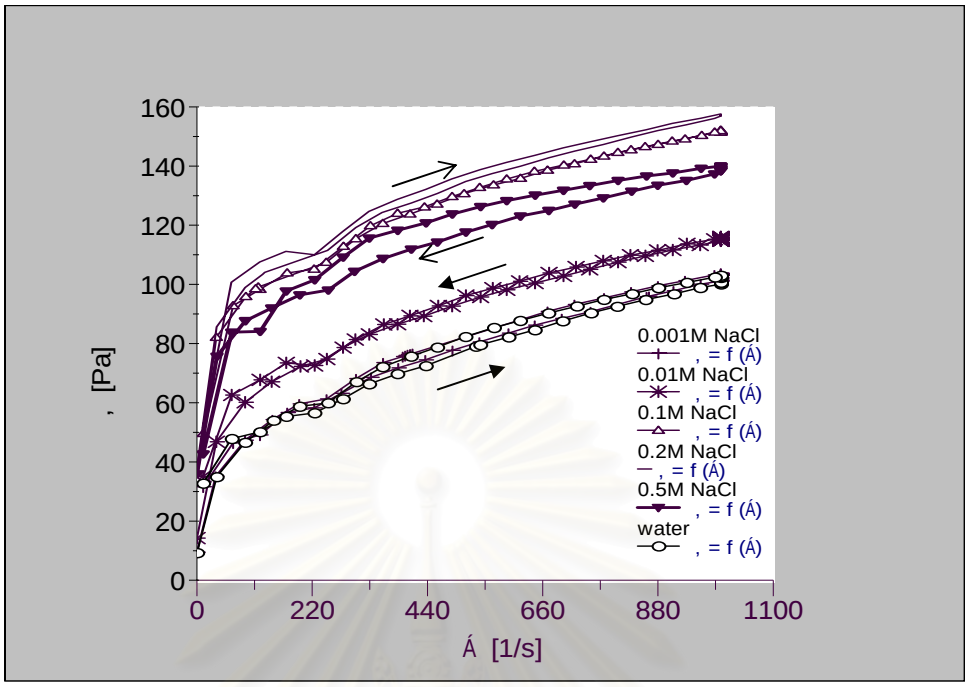


Figure 4-37 The rheograms of 2.5 % w/v XG in various concentrations of NaCl comparing with in water.

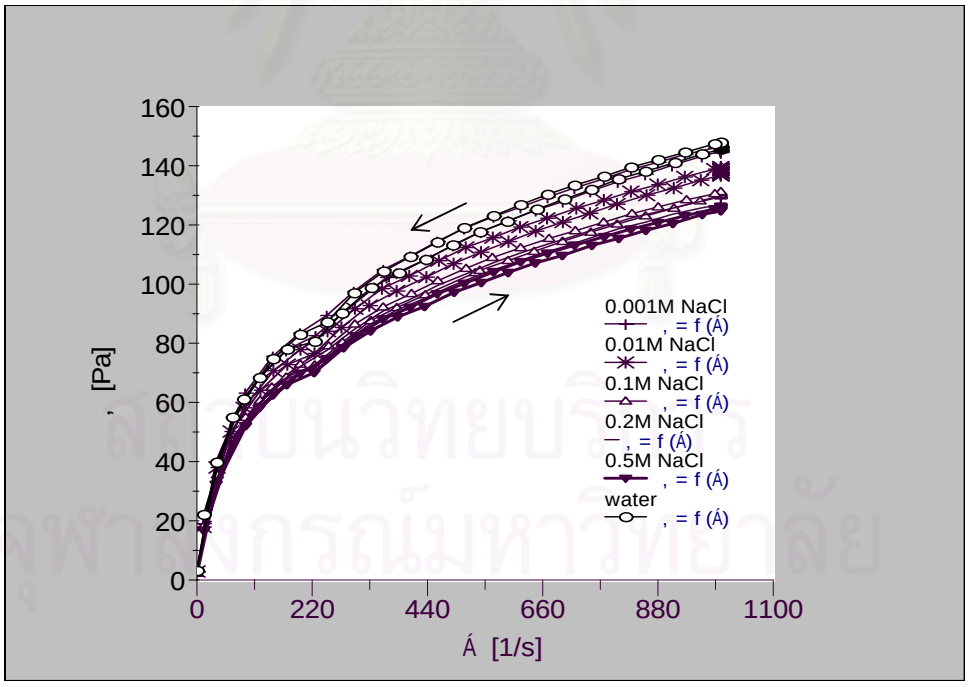


Figure 4-38 The rheograms of 2.5 % w/v TG in various concentrations of NaCl comparing with in water.

Table 4-29 Thixotropic values of UT, XG and TG at various concentrations of NaCl.

NaCl (M)	Average thixotropic value(Pa/s± SD)		
	4.5 % UT	2.5 % XG	2.5 % TG
0	- 14,730.00 (646.30)	-1,699.00 (286.61)	-1,290.67 (244.73)
0.001	- 13,513.33 (1,156.26)	-1,293.03 (527.65)	-1,076.67 (129.07)
0.01	- 15,056.67 (3,631.18)	833.93 (280.01)	-1,259.67 (112.81)
0.1	- 10,443.33 (90.74)	1,201.87 (259.15)	-553.60 (95.30)
0.2	- 10,386.67 (244.20)	3,213.67 (294.61)	-476.50 (205.33)
0.5	- 13,520.00 (225.17)	5,736.00 (360.02)	114.25 (231.44)

3.2.2 Effect of type of buffer and pH

3.2.2.1 Phosphate buffer

The rheograms of SCMS with DS 0.11, 0.22 and 0.37 at concentration of 6 %, 2.5 % and 3 % w/v, respectively, at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) are shown in Figure 4-39, 4-40 and 4-41. The thixotropic values of them are presented in Table 4-30. The flow patterns of all DS of SCMS still showed a shear-thinning type with positive thixotropic values in acid-base condition. The thixotropic values of all DS of SCMS in phosphate buffer were obviously different comparing with in water because the main effect might be the influence of ionic strength on the viscosity (as shown in previous part 3.1.1). In addition, the thixotropic values of all DS of SCMS in phosphate buffer at pH of 3 and 5 were not different and less than the thixotropic values at pH 7 and 9.

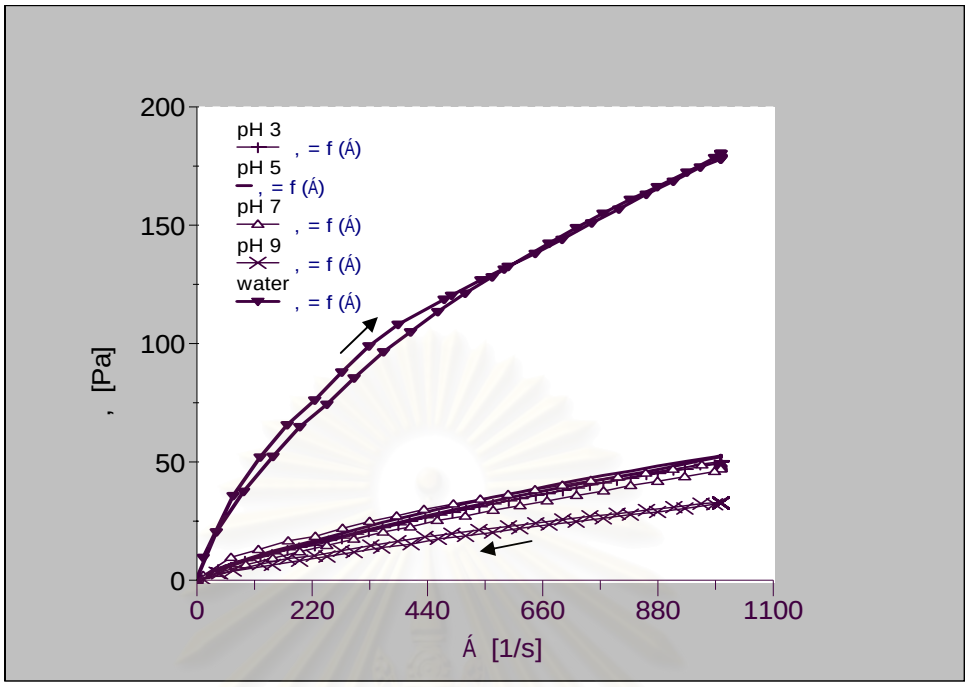


Figure 4-39 The rheograms of 6 % w/v SCMS-1 at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

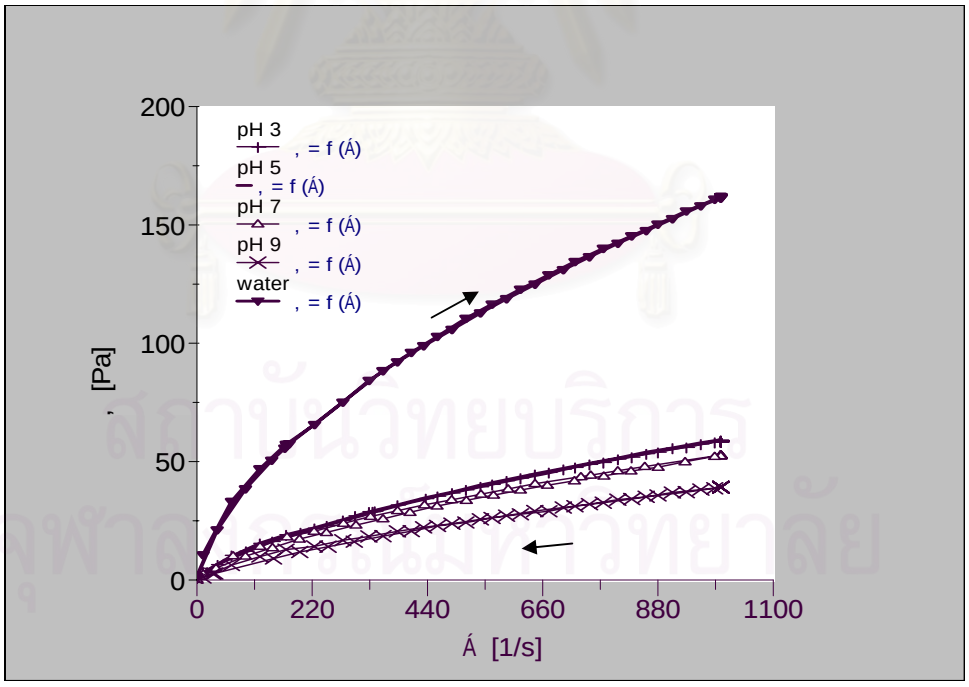


Figure 4-40 The rheograms of 2.5% w/v SCMS-2 at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

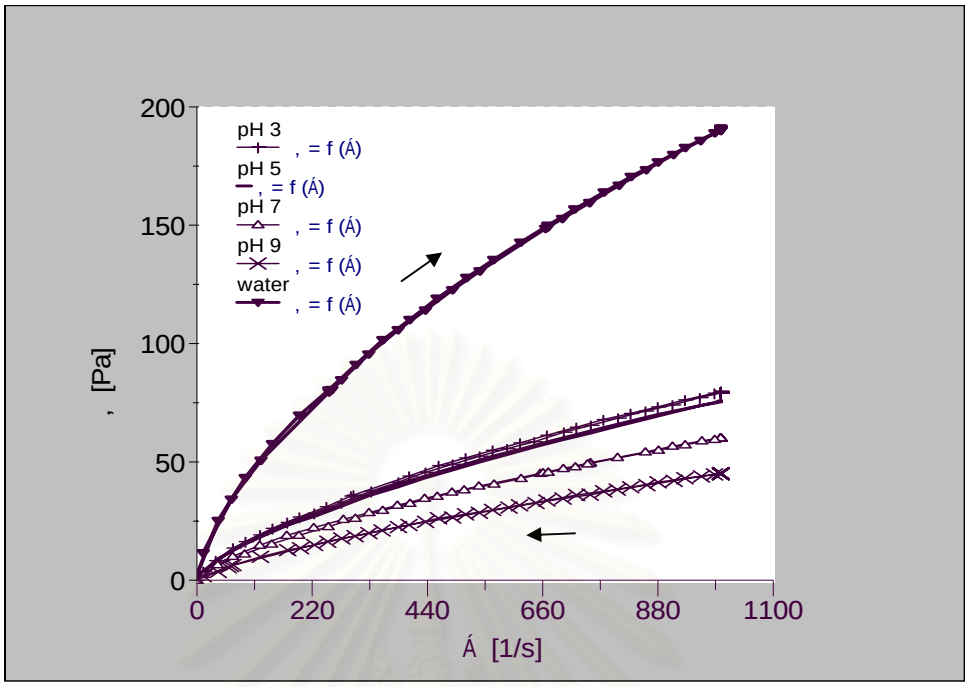


Figure 4-41 The rheograms of 3 % w/v SCMS-3 at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

Table 4-30 Thixotropic values of all DS of SCMS at different concentrations at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M).

pH	Average thixotropic value (Pa/s ± SD)		
	6 % SCMS-1	2.5 % SCMS-2	3 % SCMS-3
water	4,052.00 (835.06)	1,585.33 (86.38)	831.60 (286.83)
3	104.63 (180.19)	1,110.33 (71.39)	227.87 (114.72)
5	- 384.10 (224.05)	1,250.33 (124.94)	249.50 (61.51)
7	5,320.00 (340.69)	2,035.33 (182.51)	1,107.00 (151.56)
9	1,604.33 (90.96)	1,192.00 (31.48)	526.80 (112.86)

The flow behaviors of CSCMS-2, CSCMS-8 and CSCMS-16 at concentration of 0.8 %, 1.15 % and 1.95 % w/v, respectively, at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) are shown in Figure 4-42, 4-43 and 4-44. The thixotropic values of them are displayed in Table 4-31.The rheograms of CSCMS-2 and SCMS-8 showed a pseudoplastic type and positive thixotropic values in acid-base condition, while CSCMS-16 gave the flow patterns from negative to positive pseudoplastic type when the system was ionic. The thixotropic values of all DS of CSCMS in phosphate buffer were obviously different comparing with in water because the main effect might be the influence of ionic strength on the viscosity. However; the thixotropic values of all DS of CSCMS in all pH of phosphate buffer pH were not much different.

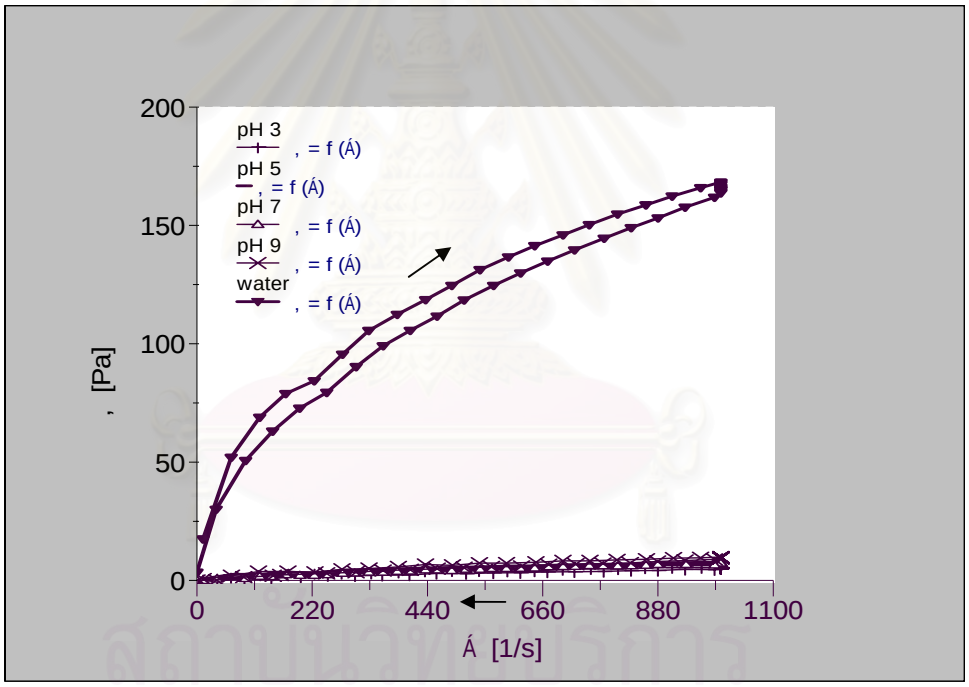


Figure 4-42 The rheograms of 0.8 % w/v CSCMS-2 at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

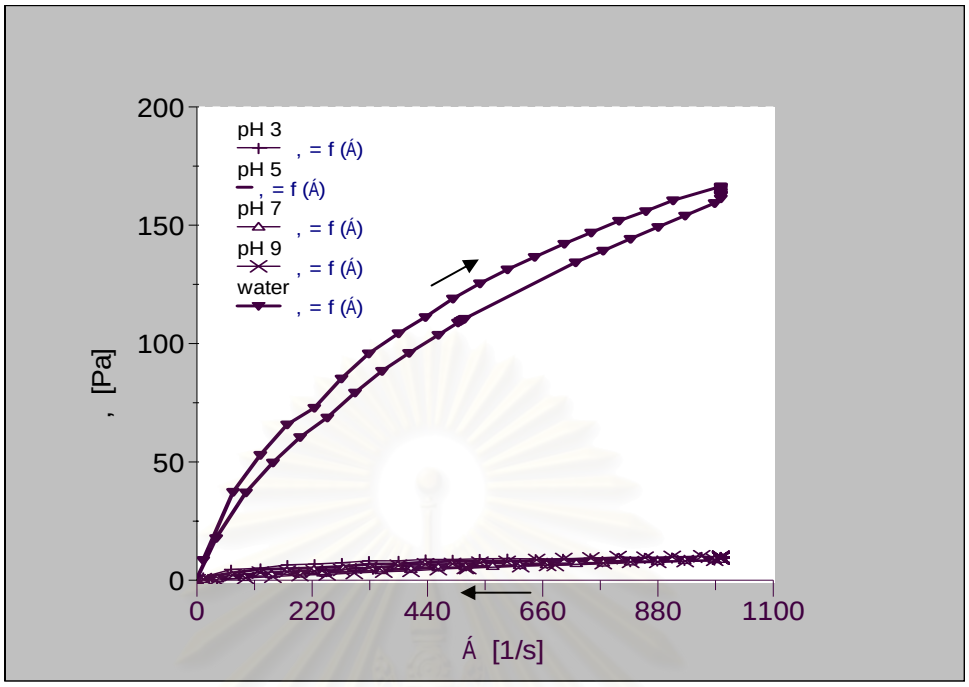


Figure 4-43 The rheograms of 1.15 % w/v CSCMS-8 at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

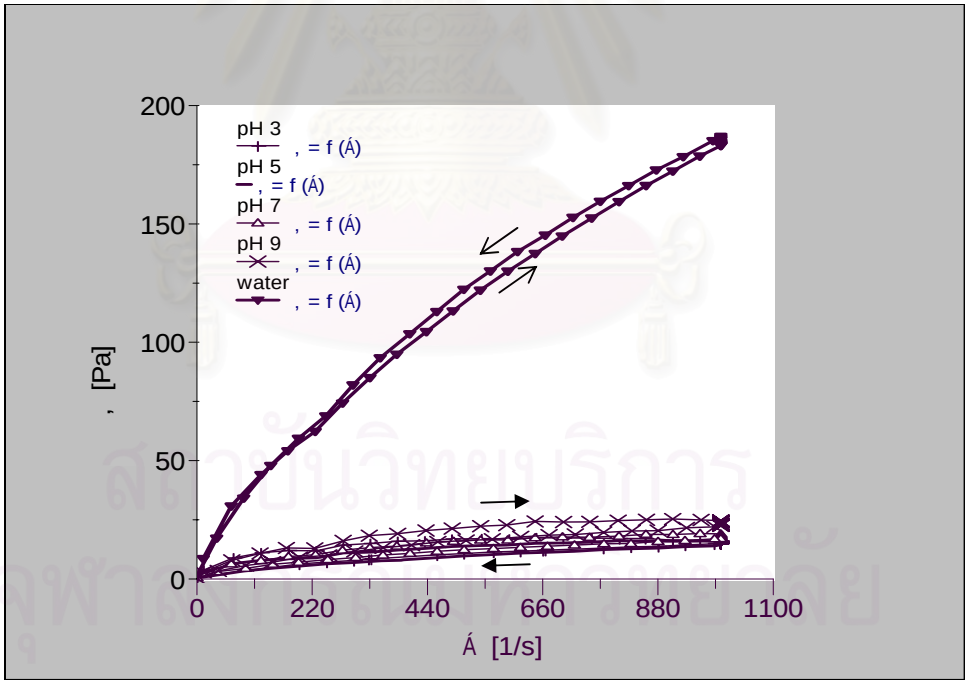


Figure 4-44 The rheograms of 1.95 % w/v CSCMS-16 at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

Table 4-31 Thixotropic values of three DS of CSCMS at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M)

pH	Average thixotropic value(Pa/s ± SD)		
	0.8 % CSCMS-2	1.15 % CSCMS-8	1.95 % CSCMS-16
water	10,886.67 (313.74)	10,520.33 (769.64)	- 2,533.67 (812.17)
3	666.33 (333.08)	2,325.67 (265.21)	4,717.00 (529.64)
5	1,045.03 (391.89)	1,864.67 (136.62)	3,634.00 (81.47)
7	901.83 (366.64)	1,621.00 (200.75)	2,699.67 (593.08)
9	1,178.50 (215.19)	2,122.67 (103.47)	1,661.67 (210.51)

As displayed in Figure 4-45, the rheograms of PGTS showed a pseudoplastic type and positive thixotropic value in water while in acid-base condition the flow patterns were changed to negative pseudoplastic type. Area of hysteresis loop of PGTS at the pH of 3 was decreased greater than of the pH of 5 and 7. In basic condition, area of hyterisis loop of PGTS at the pH 9 was higher than those of pH 7 (see Table 4-32). PGTS provided the high standard deviation of thixotropic values because it was a physical modified starch that did not have consistent property. The flow behaviors of HPTS and CHPTS in phosphate buffer are displayed in Figure 4-46 to 4-47. They provided a pseudoplastic-type and thixotropic values were negative in water and acid-base condition. In addition, the thixotropic values of HPTS were similar all pH. The thixotropic values of CHPTS were not obviously different in water and acid condition. In basic condition, the thixotropic value of CHPTS was decreased in greater degree than in acid condition.

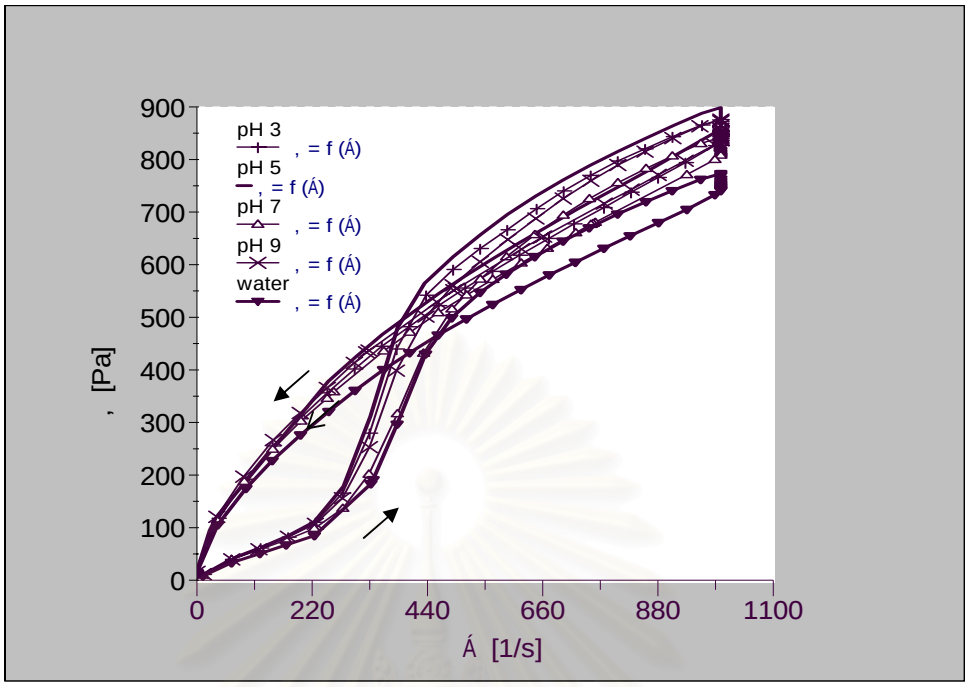


Figure 4-45 The rheograms of 8.5 % w/v PGTS at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

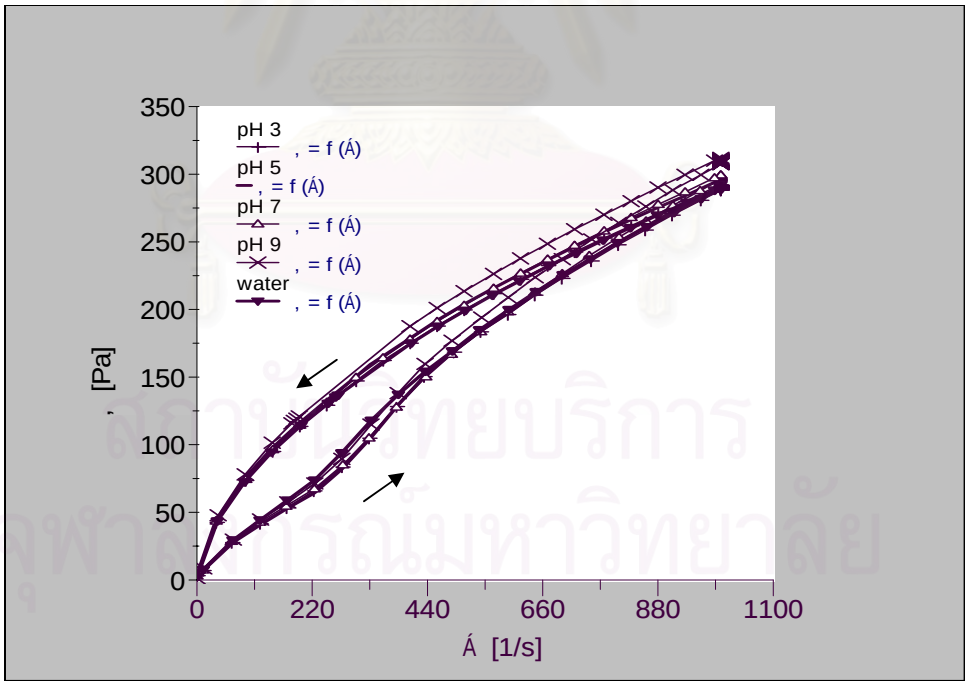


Figure 4-46 The rheograms of 7.5 % w/v HPTS at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

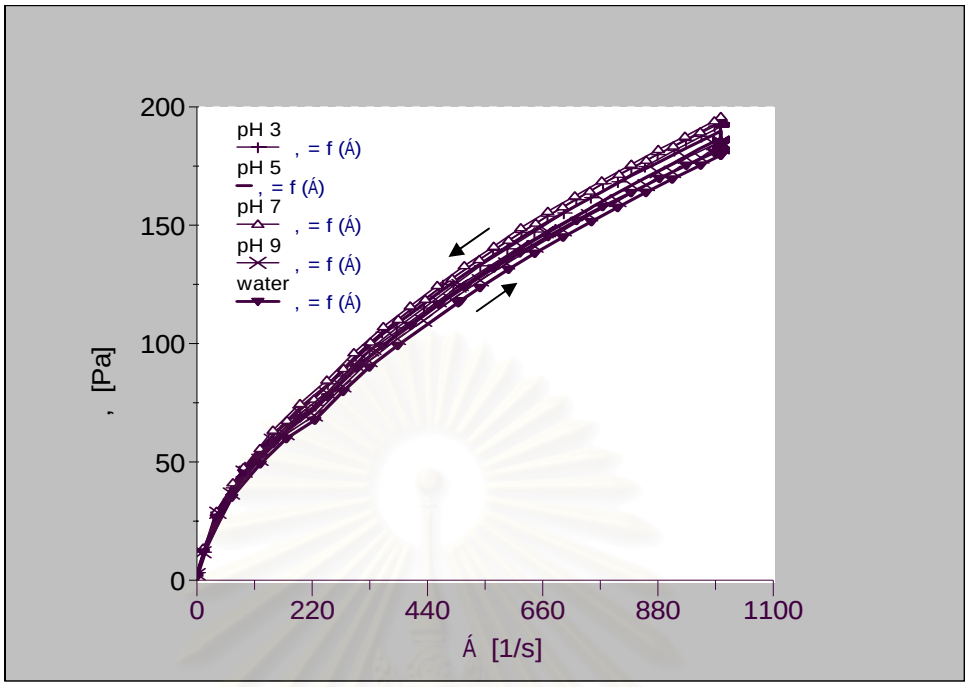


Figure 4-47 The rheograms of 5.5 % w/v CHPTS at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

Table 4-32 Thixotropic values of PGTS, HPTS and CHPTS at the various concentrations at various pH 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

pH	Average thixotropic value (Pa/s ± SD)		
	8.5 % PGTS	7.5 % HPTS	5.5 % CHPTS
water	4,412.35 (4,585.32)	- 25,796.67 (627.72)	-1,880.00 (584.52)
3	-9,650.00 (3,278.48)	- 24,780.00 (1,235.76)	-1,230.97 (739.42)
5	-14,583.33 (810.08)	- 25,823.33 (758.57)	- 1895.93 (1,033.47)
7	-47,043.33 (3,450.82)	- 25,630.00 (910.60)	-114.63 (654.31)
9	-36,863.33 (3,230.45)	- 25,833.33 (411.87)	- 681.00 (484.81)

The rheograms of UT, XG and TG at the concentration of 4.5 %, 2.5 % and 2.5 % w/v in various pH of 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water are illustrated in Figure 4-48, 4-49 and 4-50, respectively. Thixotropic values are presented in Table 4-33. The flow patterns of UT, XG and TG displayed a pseudoplastic type and negative thixotropic values in water. The pH of phosphate buffer and ionic strength did not affect on the flow behavior of UT, while the flow patterns of XG and TG were changed to positive thixotropic values. The thixotropic values of UT, XG and TG were slightly increased in the acid-base condition comparing with in the water.

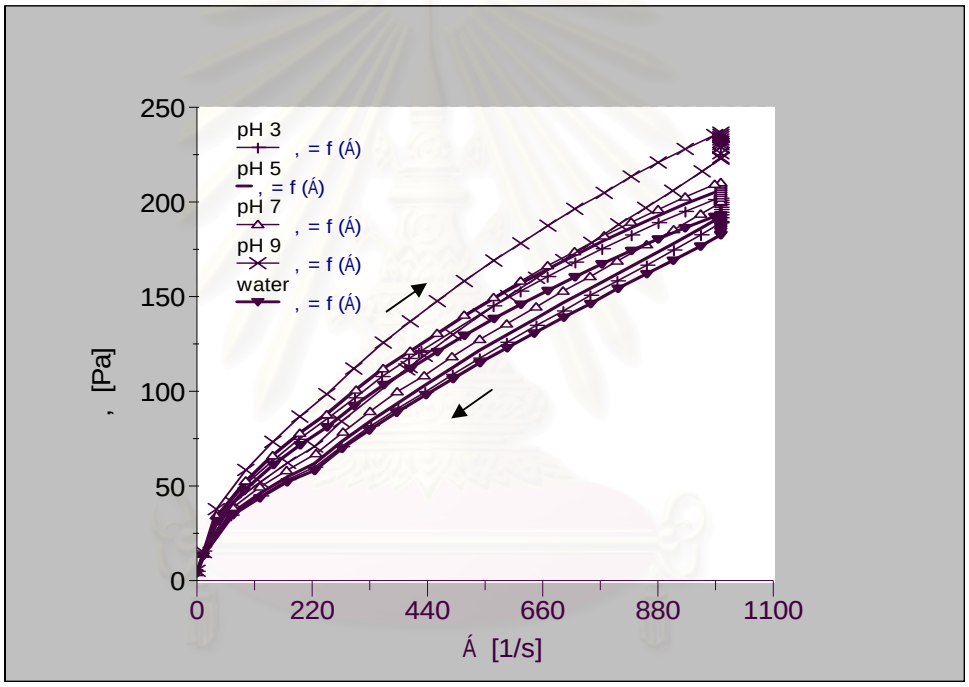


Figure 4-48 The rheograms of 4.5 % w/v UT at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

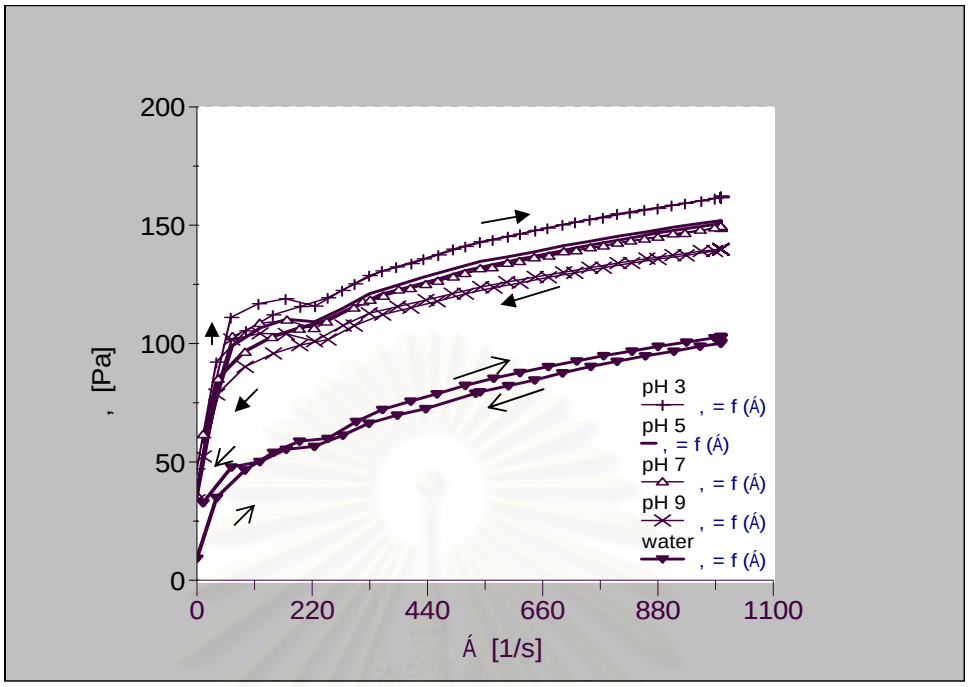


Figure 4-49 The rheograms of 2.5 % w/v XG at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

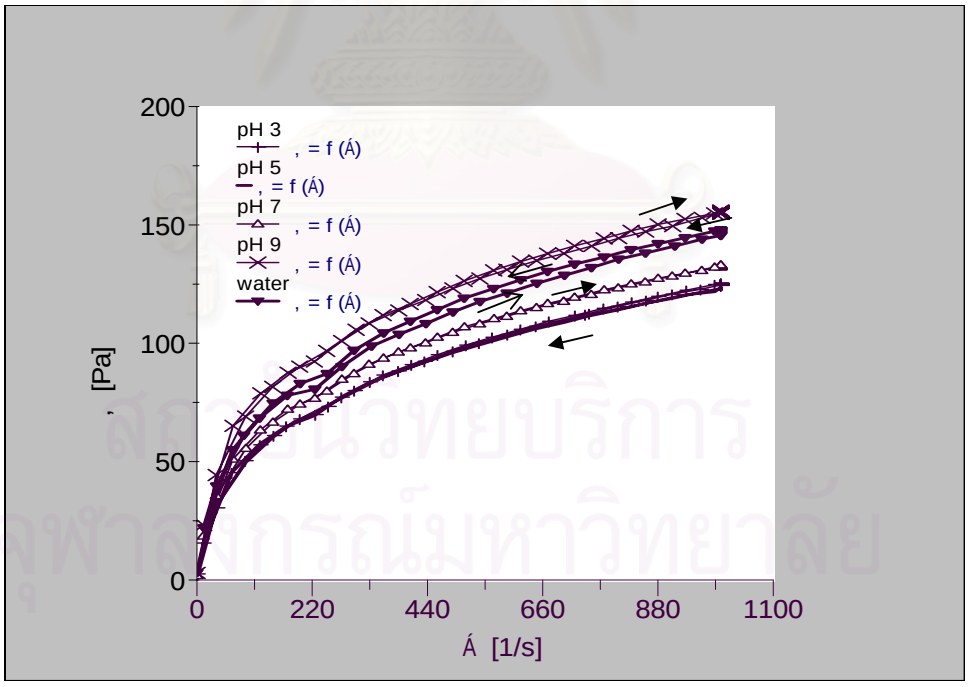


Figure 4-50 The rheograms of 2.5 % w/v TG at various pH in 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

Table 4-33 Thixotropic values of UT, XG and TG at different concentrations in various pH of 0.05 M phosphate buffer (ionic strength of 0.2 M) comparing with in water.

pH	Average thixotropic value (Pa/s ± SD)		
	4.5 % UT	2.5 % XG	2.5 % TG
water	-13,533.33 (230.07)	-1,699.00 (286.6)	- 1,294.00 (245.1)
3	-15,466.67 (1,210.06)	2,796.33 (650.5)	1,553.00 (473.3)
5	- 15,843.33 (1,141.29)	3,268.33 (370.2)	875.63 (454.3)
7	- 13,766.67 (808.85)	2,973.67 (397.2)	1,316.33 (168.6)
9	- 16,440.00 (965.66)	3,669.67 (822.1)	1,152.33 (220.6)

3.2.2.2 Citrate Buffer

The flow patterns of SCMS with three DS at different concentrations in 0.04 M citrate buffer (ionic strength of 0.2 M) were compared with in water (as shown in Figure 4-51, 4-52 and 4-53). Thixotropic values are summarized in Table 4-34. The flow behaviors of SCMS with DS of 0.11 were changed from a positive pseudoplastic in water to negative pseudoplastic type in citrate buffer pH 2 and 4. While, at the pH 6 the flow pattern was a positive pseudoplastic type. The thixotropic values of all DS of SCMS in citrate buffer were obviously different comparing with in water because the main effect might be the influence of ionic strength on the viscosity. However, areas of hysteresis loop were not much different at all pH of citrate buffer. The rheograms of SCMS with DS of 0.22 and 0.37 still showed a pseudoplastic type and positive thixotropic values in the water and in all pH of citrate buffer. The thixotropic values of them at pH 6 were higher than the pH 4 and 2.

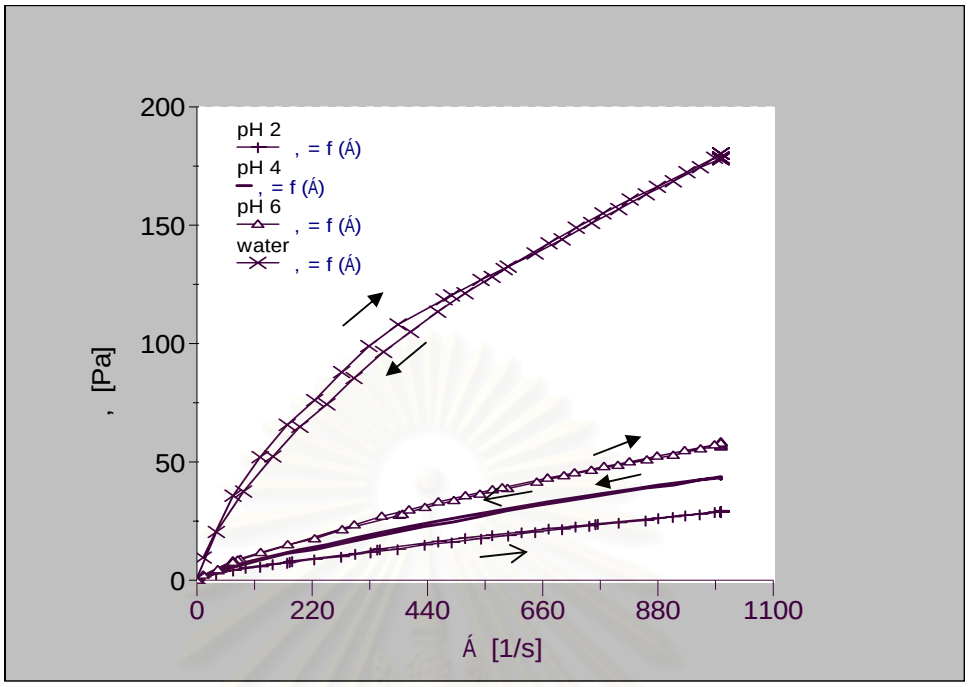


Figure 4-51 The rheograms of 6 % w/v SCMS-1 at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

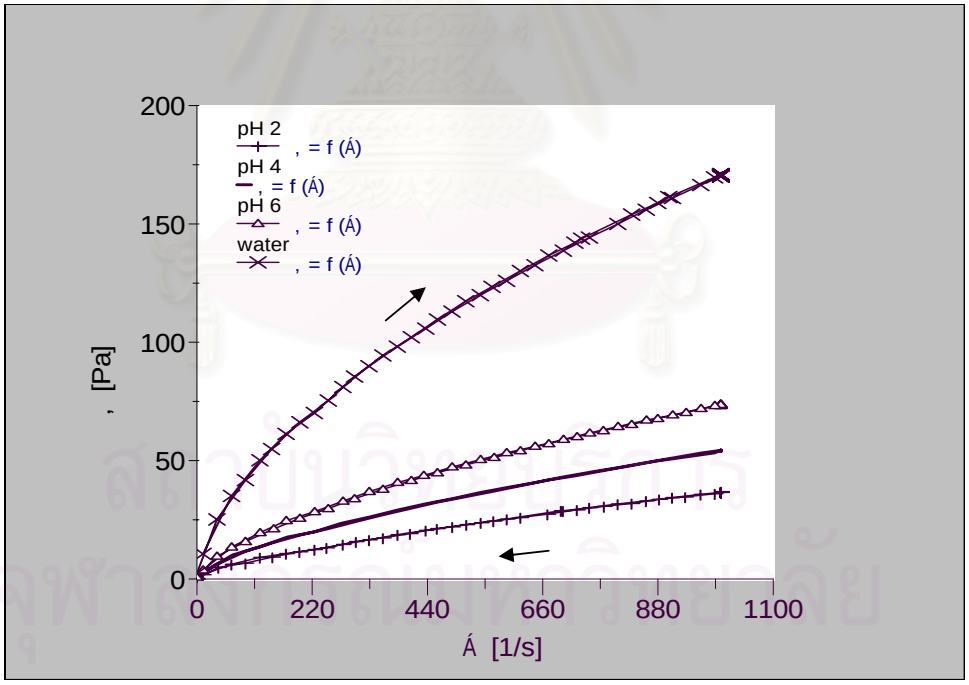


Figure 4-52 The rheograms of 2.5 % w/v SCMS-2 at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

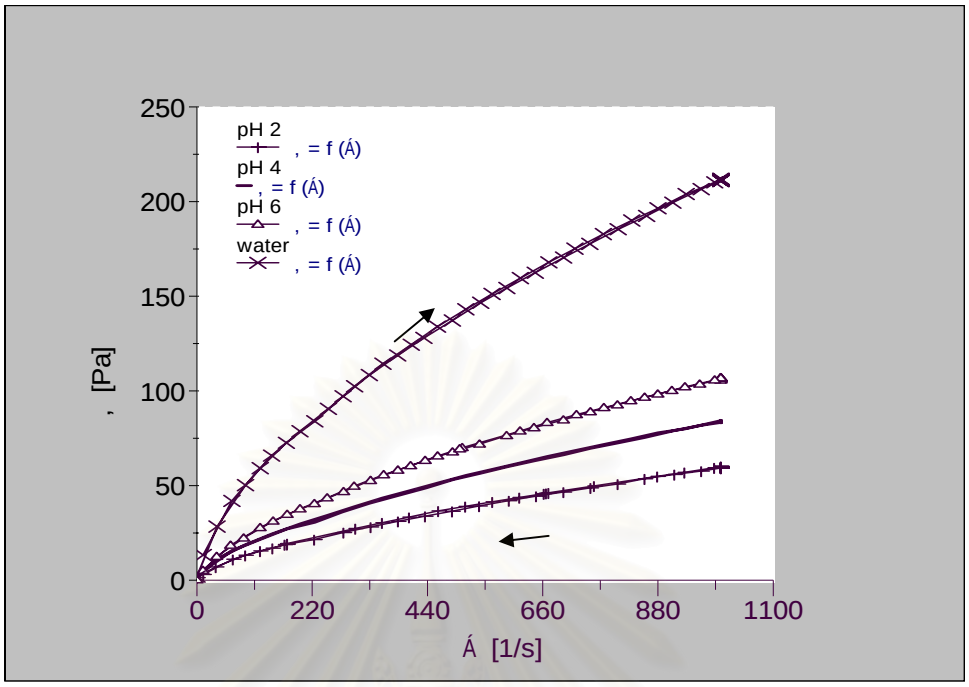


Figure 4-53 The rheograms of 3% w/v of SCMS-3 at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

Table 4-34 Thixotropic values of SCMS with three DS at various concentrations in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

pH	Average thixotropic value (Pa/s ± SD)		
	6 % SCMS-1	2.5 % SCMS-2	3 % SCMS-3
water	1,565.77 (723.75)	1,713.00 (329.36)	1,154.00 (381.32)
2	- 263.53 (71.96)	808.03 (139.05)	266.48 (264.79)
4	-191.47 (382.18)	880.77 (125.37)	445.57 (237.92)
6	79.14 (63.57)	1,404.00 (64.09)	814.67 (118.85)

Rheograms of CSCMS with different reaction times at various concentrations in 0.04M citrate buffer (ionic strength of 0.2M) comparing with in water are shown in Figure 4-54 to 4-56. The thixotropic values at various pH in 0.04M citrate buffer comparing with in water are expressed in Table 4-35. The rheograms of CSCMS with reaction time of 2 and 8 hrs gave a pseudoplastic type and thixotropic values were positive in all pH of citrate buffer. While, CSCMS with reaction time of 16 hrs changed the flow behaviors from negative pseudoplastic type to positive pseudoplastic type when the system containing ionic salt. The thixotropic values of all DS of CSCMS in citrate buffer were obviously different in comparison with in water because the main effect might be the influence of ionic strength on the viscosity. However, the thixotropic values of all DS of CSCMS in citrate buffer at pH 2, 4 and 6 were slightly different.

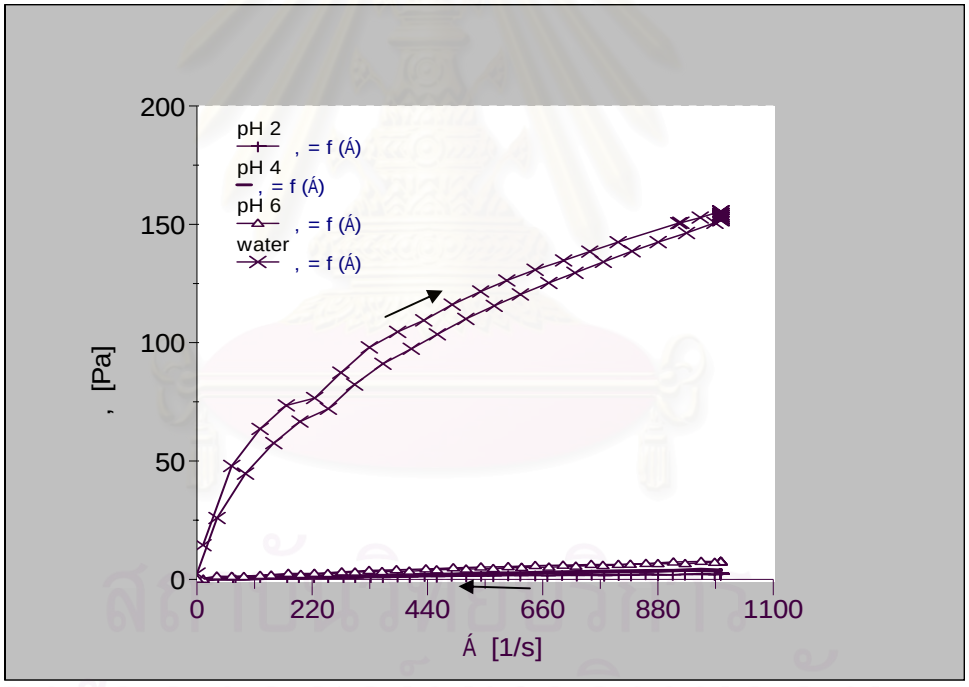


Figure 4-54 The rheograms of 0.8 % w/v CSCMS-2 at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

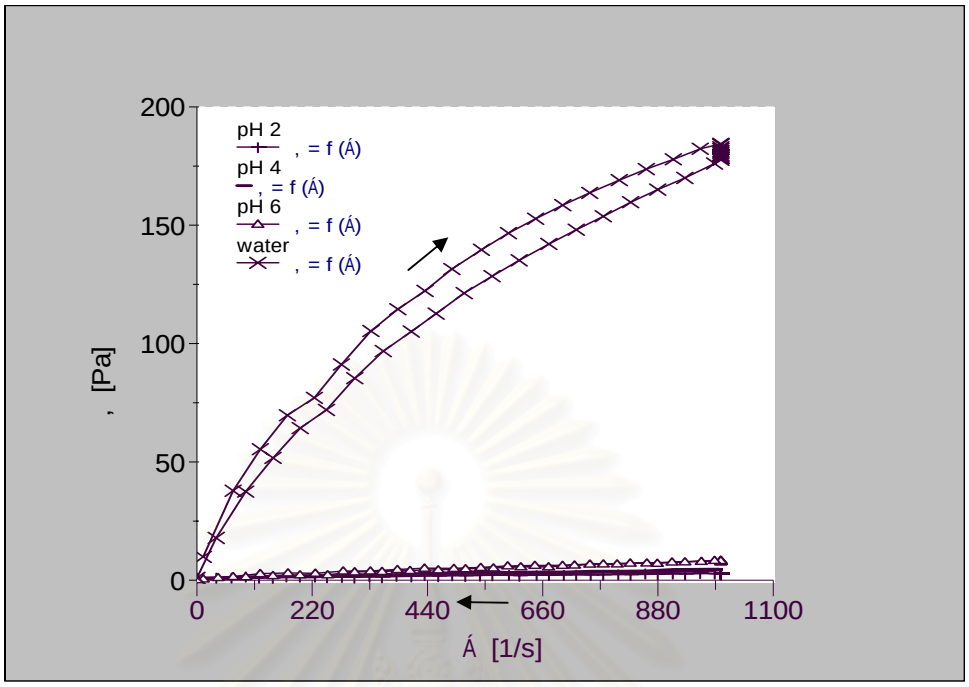


Figure 4-55 The rheograms of 1.15% w/v CSCMS-8 at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

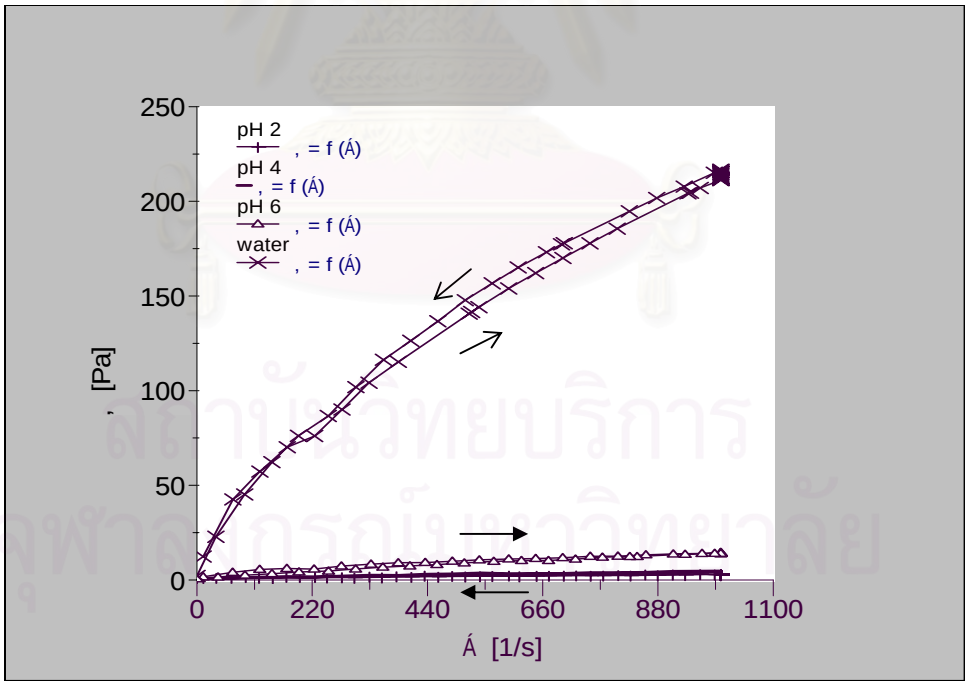


Figure 4-56 The rheograms of 1.95% w/v CSCMS-16 at various pH in 0.04M citrate buffer (ionic strength of 0.2M) comparing with in water.

Table 4-35 Thixotropic values of CSCMS with three different reaction times at various concentrations in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

pH	Average thixotropic value (Pa/s ± SD)		
	0.8 % CSCMS-2	1.15 % CSCMS-8	1.95 % CSCMS-16
water	9,073.67 (584.16)	13,356.67 (636.11)	-1,992.13 (1,238.91)
2	360.87 (42.64)	370.63 (143.58)	3,277.67 (327.34)
4	627.70 (217.73)	530.70 (101.53)	3,721.00 (469.37)
6	372.07 (135.90)	718.43 (235.16)	2,396.00 (839.10)

Rheograms of PGTS, HPTS and CHPTS at the different concentrations in 0.04M citrate buffer (ionic strength of 0.2M) were compared with in water as shown in Figure 4-57, 4-58 and 4-59. The thixotropic values of PGTS, HPTS and CHPTS at various pH of 0.04M citrate buffer in comparison with in water are presented in Table 4-36. The rheograms of PGTS showed a pseudoplastic type and the thixotropic values were negative in water and in citrate buffer at the pH 6 while at the pH 2 and 4 the flow patterns was changed to positive pseudoplastic type. Areas of hysteresis loop of PGTS at all pH were not different. The rheograms of HPTS and CHPTS displayed a pseudoplastic type and negative thixotropic values in water and in citrate buffer. In addition, areas of hysteresis loop of HPTS trended to increase when pH was increased. The thixotropic values of CHPTS were similar at all pH of citrate buffer.

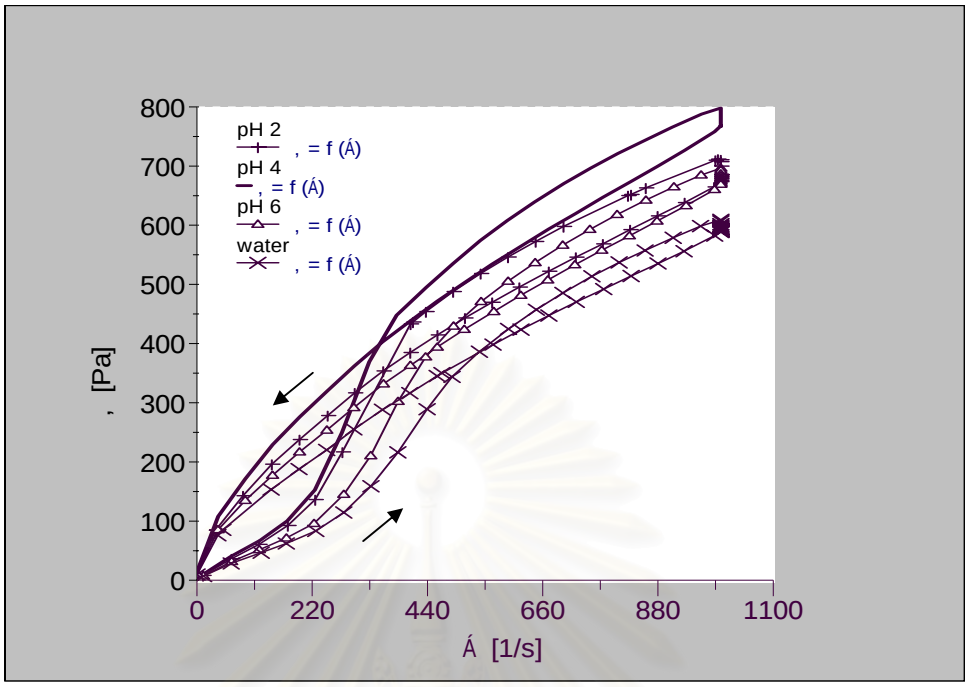


Figure 4-57 The rheograms of 8.5 % w/v PGTS at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

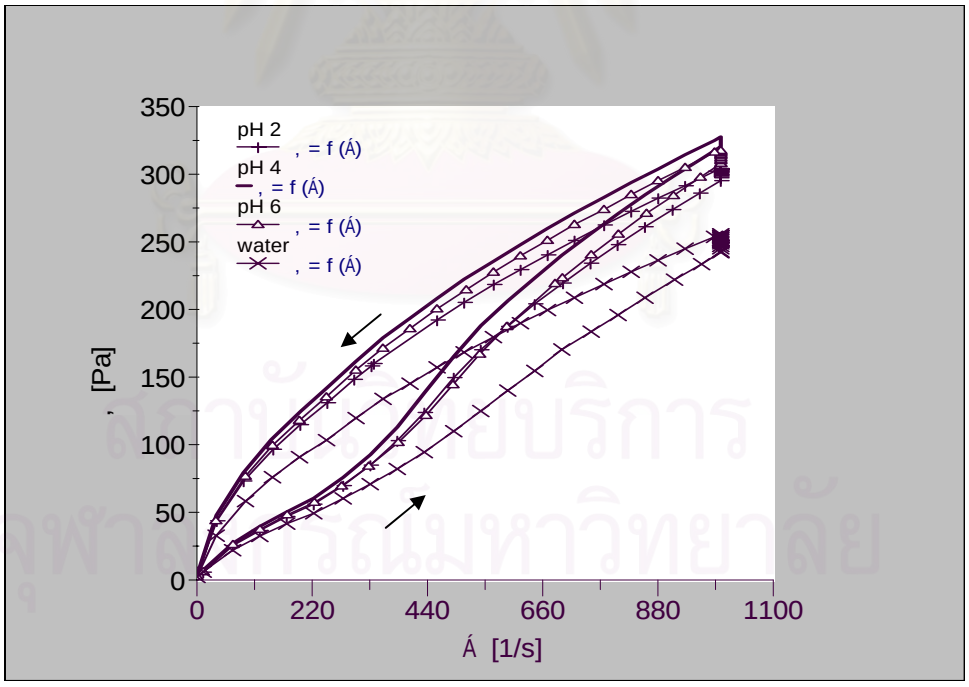


Figure 4-58 The rheograms of 7.5 % w/v HPTS at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

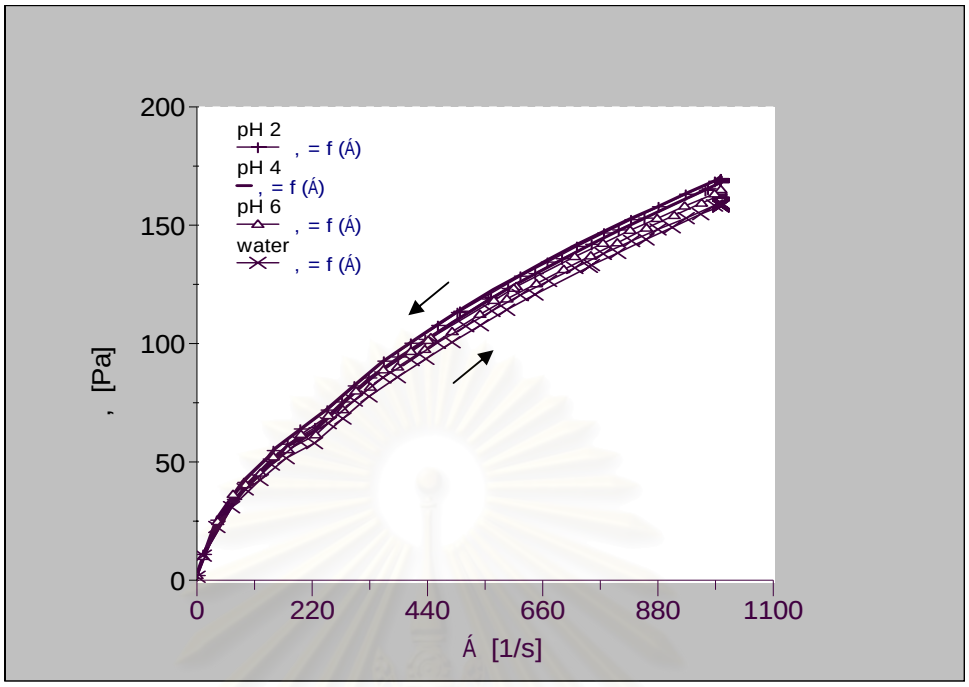


Figure 4-59 The rheograms of 5.5 % w/v CHPTS at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

Table 4-36 Thixotropic values of PGTS, HPTS and CHPTS at the different concentrations in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

pH	Average thixotropic value (Pa/s ± SD)		
	8.5 % PGTS	7.5 % HPTS	5.5 %CHPTS
water	-20,733.33 (3,419.19)	-34,720.00 (1,527.87)	-1,218.83 (464.10)
2	11,278.67 (2,527.20)	- 37,133.33 (751.42)	- 787.37 (340.10)
4	10,821.33 (2,848.20)	- 38,776.67 (516.17)	- 756.02 (595.80)
6	-10,294.00 (3,350.63)	- 41,630.00 (1,182.92)	- 639.33 (219.24)

Flow behaviors of UT, XG and TG at the various concentrations in 0.04 M citrate buffer (ionic strength of 0.2 M) in comparison with water are shown in Figure 4-60 to 4-62. Thixotropic values of UT, XG and TG at the concentration of 4.5 %, 2.5 % and 2.5 % w/v, respectively, in 0.04 M of citrate buffer are summarized in Table 4-37. The flow patterns of UT and XG provided a pseudoplastic type and negative thixotropic values in water while the flow pattern of TG was pseudoplastic type and positive thixotropic value. The pH of citrate buffer and ionic strength did not affect on the flow behavior of UT while the flow patterns of XG were changed to positive thixotropic value at the pH 2 and 4. The thixotropic value of XG at the pH 2 was higher than pH 4 and 6. The rheograms of TG in the water and in citrate buffer showed a pseudoplastic type and the thixotropic values were positive. The thixotropic values of TG were similar when pH was increased.

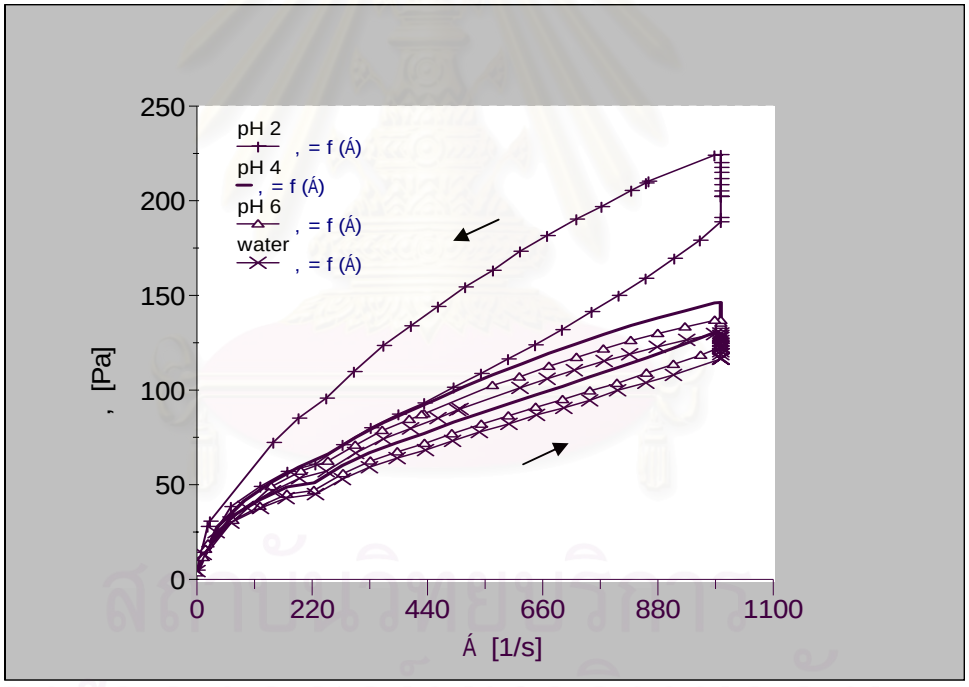


Figure 4-60 The rheograms of 4.5 % w/v UT at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

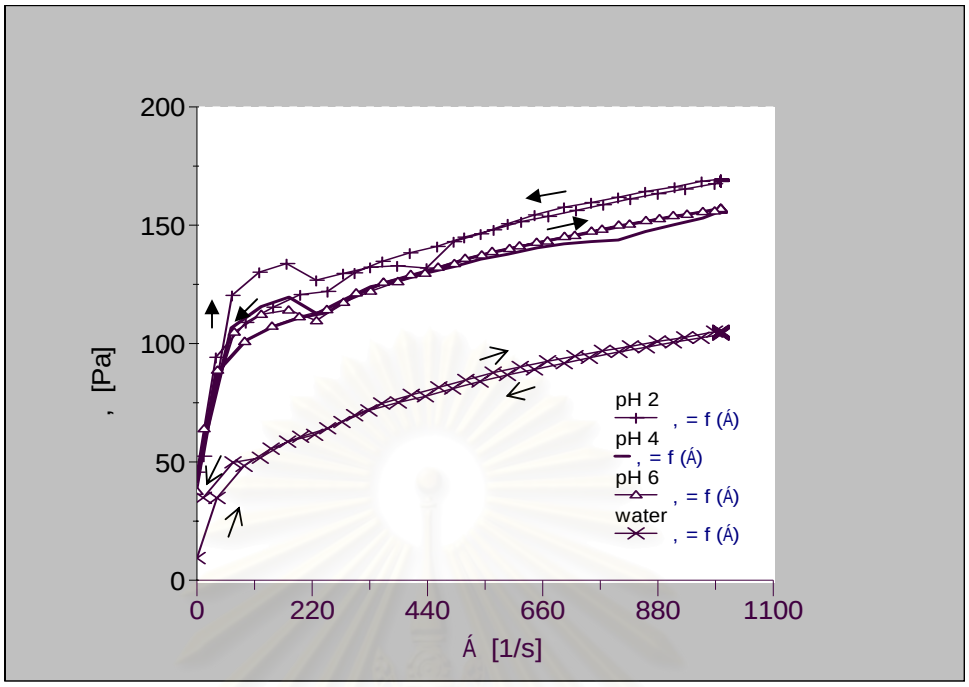


Figure 4-61 The rheograms of 2.5 % w/v XG at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

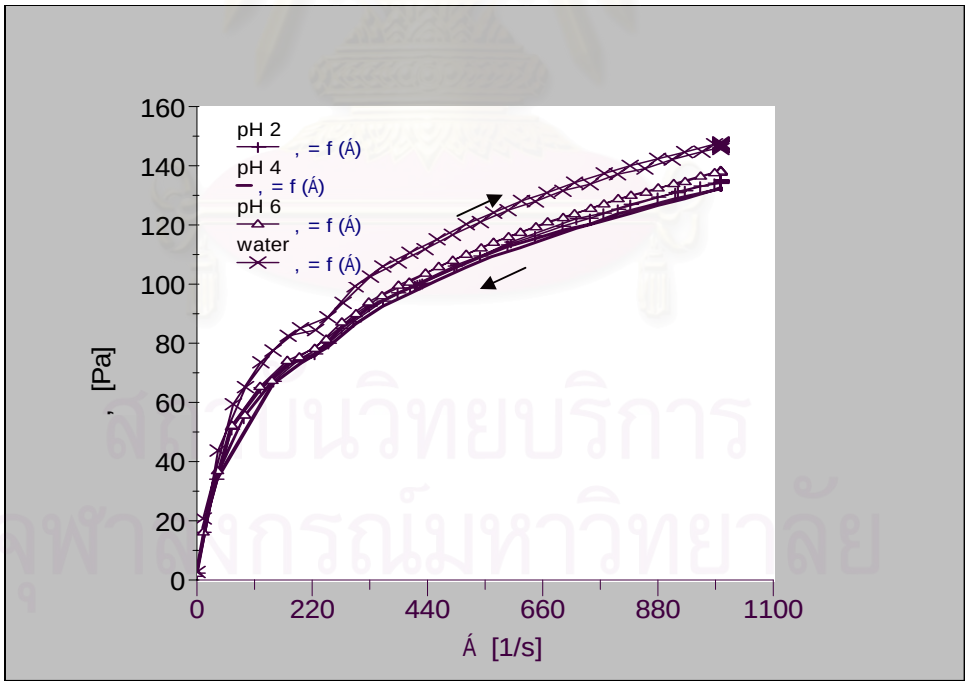


Figure 4-62 The rheograms of 2.5 % w/v TG at various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

Table 4-37 Thixotropic values of UT, XG and TG at the different concentrations various pH in 0.04 M citrate buffer (ionic strength of 0.2 M) comparing with in water.

pH	Average thixotropic value (Pa/s ± SD)		
	4.5 % UT	2.5 % XG	2.5 % TG
water	- 13,036.67 (2,756.96)	- 278.03 (171.20)	374.10 (710.32)
2	- 38,990.00 (1,960.08)	5,526.33 (1,496.46)	2,384.00 (428.45)
4	- 13,580.00 (2,773.39)	1,977.00 (1,388.65)	2,593.33 (285.37)
6	- 11,943.33 (1,321.56)	- 511.50 (78.69)	2,646.67 (405.56)

4. Evaluation of Modified Tapioca Starches as Suspending Agent in Ibuprofen Suspension

4.1 Preliminary studied

As the result from the previous part (3.1 and 3.2), SCMS with DS of 0.22 was selected in this section because it provided the highest viscosity comparing with SCMS with DS of 0.11 and 0.37. However, all DS of CSCMS was discarded from the study in this part because they loosed gel structure when added ionic salt in the system. CSCMS were used as superdisintregrant (Teruya, 1995) but not suitable for suspending agent. In the preparation of ibuprofen suspension contained various suspending agents such as SCMS-2, PGTS, HPTS, CHPTS, UT, XG and TG. The percent of each suspending agent was selected by the concentration that it started form gel. SCMS-2, PGTS, HPTS, CHPTS, UT, XG and TG were used at the concentration of 1-3 %, 3-5 %, 4-6 %, 3-4.5 %, 2-4 %, 0.2-0.6 % and 0.5-1.5 %, respectively.

4.2 Evaluation of ibuprofen suspension

The preparations of ibuprofen suspensions that contained those suspending agent were stored at room temperature for 4 weeks. The physical properties of them were investigated.

4.2.1 Physical appearance

Physical appearance of ibuprofen suspension stored at room temperature for 4 weeks are described in Table 4-38.

4.2.2 Viscosity of ibuprofen suspension

The Table 4-39 shows the viscosity of ibuprofen suspension after storage for 1 month. The preparations of suspension containing SCMS-2, PGTS, HPTS, CHPTS, UT, XG and TG provided viscosity in range of 145-770, 981.80-1,271, 1,1028-1,707, 967.8-2,007, 884.8-2,108, 1,177-1,877, and 45-1,100 cps., respectively. The viscosity of ibuprofen suspension increased when the percentage of all suspending agents increased. The viscosity remained constant in the second week. Their viscosity decreased after storage for 1 month at room temperature, except for 4, 4.5 % w/v CHPTS and 1.5 % w/v TG. The viscosity increased after storage of those suspending agents, it was possible that the hydration of polymer was not saturated at starting date. The viscosity increased when standing for longer time, it might be that saturated network of polymer formed rigid structure.

Table 4-38 Physical appearance of ibuprofen suspension after standing at room temperature for 4 weeks.

Suspending agent	%	Initial	1 weeks	2 weeks	3 weeks	4 weeks
SCMS-2	1	White homogenous suspension	White homogenous suspension	← Clear supernatant was occurred above white compact sediment →		
	2	White homogenous suspension	White homogenous suspension	Non- transparent supernatant was occurred above white compact sediment	Clear supernatant was occurred above white compact sediment	Clear supernatant was occurred above white compact sediment
	3	White homogenous suspension	White homogenous suspension	← Non- transparent supernatant was occurred above white compact sediment		
PGTS	3	White homogenous suspension	← Non- transparent supernatant was occurred above white compact sediment →			
	4	← White homogenous suspension →				
	5	← White homogenous suspension →				

Table 4-38 (cont.)

Suspending agent	%	Initial	1 weeks	2 weeks	3 weeks	4 weeks
HPTS	4	White homogenous suspension.	← Non- transparent supernatant was occurred above white compact sediment. →			
	5	← White homogenous suspension. →				
	6	← White homogenous suspension. →				
CHPTS	3	← White homogenous suspension. →				
	4	White homogenous suspension.	White homogenous suspension.	← White homogenous suspension and the surface formed a rigid gel. →		
	4.5	White homogenous suspension.	← White homogenous suspension and the surface formed a rigid gel. →			

Table 4-38 (cont.)

Suspending agent	%	Initial	1 weeks	2 weeks	3 weeks	4 weeks
UT	2	White homogenous suspension.	White homogenous suspension.	White homogenous suspension.	The suspended floccules were observed in the suspension.	The suspended floccules were observed in the suspension.
	3	← White homogenous suspension. →				
	4	← White homogenous suspension. →				
XG	0.2	White homogenous suspension.	White homogenous suspension.	← The suspended floccules and the compact white sediment were observed in the suspension.		
	0.4	← White homogenous suspension. →				
	0.6	← White homogenous suspension. →				

Table 4-38 (cont.)

Suspending agent	%	Initial	1 weeks	2 weeks	3 weeks	4 weeks
TG	0.5	← White homogenous suspension. →				The clear supernatant was slightly occurred above the white sediment.
	1	← White homogenous suspension. →				
	1.5	← White homogenous suspension. →				

Table 4-39 The viscosity of ibuprofen suspension after storage for 1 month at room temperature.

Suspending agent	%	Average apparent viscosity (cps ± SD)				
		Initial	1 week	2 weeks	3 weeks	4 weeks
SCMS-2	1	145.00 (1.73)	129.00 (0.00)	112.00 (3.46)	119.00 (1.73)	117.00 (0.00)
	2	538.90 (12.12)	456.90 (13.86)	434.90 (13.08)	431.90 (0.00)	446.90 (13.08)
	3	770.80 (9.00)	667.90 (17.32)	631.90 (12.12)	602.90 (6.00)	633.90 (24.06)
PGTS	3	1,020.00 (0.00)	159.00 (3.00)	167.00 (1.73)	168.00 (3.00)	167.00 (1.73)
	4	981.80 (4.58)	1,117.00 (11.36)	300.90 (1.73)	311.90 (5.20)	328.90 (9.17)
	5	1,271.00 (27.87)	1,459.00 (6.93)	627.90 (10.54)	662.90 (5.20)	679.90 (14.18)
HPTS	4	1,028.00 (1.73)	203.00 (3.46)	187.00 (3.46)	197.00 (14.18)	183.00 (3.00)
	5	1,494.00 (54.99)	526.90 (13.53)	443.90 (7.94)	412.90 (3.46)	374.90 (6.00)
	6	1,707.00 (12.00)	839.80 (7.94)	753.80 (27.22)	726.83 (22.06)	714.87 (62.47)
CHPTS	3	967.80 (1.73)	172.00 (1.73)	201.00 (0.00)	225.00 (3.00)	232.97 (6.19)
	4	473.90 (7.94)	1,512.00 (46.18)	741.80 (22.91)	762.83 (107.05)	978.87 (128.67)
	4.5	2,007.00 (13.75)	2,051.00 (34.77)	2,100.00 (54.58)	2,310.67 (52.00)	2,412.00 (46.51)
	3	988.80 (1.73)	154.00 (4.58)	149.00 (4.58)	157.00 (1.73)	171.00 (10.39)

Table 4-39 (cont.)

Suspending agent	%	Average apparent viscosity (cps ± SD)				
		Initial	1 week	2 weeks	3 weeks	4 weeks
UT	2	884.80 (0.00)	21.00 (0.00)	21.00 (0.00)	20.00 (1.73)	24.00 (0.00)
	3	988.80 (1.73)	154.00 (4.58)	149.00 (4.58)	157.00 (1.73)	171.00 (10.39)
	4	2,108.00 (8.66)	1,119.93 (124.00)	1,170.00 (59.77)	1,221.00 (28.62)	1,253.00 (1.73)
XG	0.2	1177.00 (3.46)	290.90 (3.00)	288.90 (3.46)	284.90 (6.00)	276.90 (1.73)
	0.4	1,821.00 (0.00)	917.80 (7.94)	915.80 (6.93)	916.80 (15.39)	909.80 (11.36)
	0.6	1,877.00 (6.24)	1,867.00 (37.99)	1,801.00 (28.83)	1,831.00 (24.06)	1,809.00 (18.25)
TG	0.5	45.00 (0.00)	45.00 (0.00)	45.00 (0.00)	48.00 (0.00)	49.00 (1.73)
	1	1,100.00 (17.06)	329.90 (7.07)	309.90 (6.93)	312.90 (8.66)	337.90 (17.06)
	1.5	791.80 (13.08)	802.80 (18.33)	860.80 (20.78)	921.80 (49.87)	893.80 (26.15)

4.2.3 pH of ibuprofen suspension

The pH of ibuprofen suspensions after storage for 1 month is shown in Table 4-40. The preparations of suspension containing SCMS-2, PGTS, HPTS, CHPTS, UT, XG and TG provided pH in range of 4.91-5.36, 3.73-3.96, 3.80-3.95, 3.86-4.03, 3.82-3.94, 4.38-4.72, and 4.08-4.17, respectively. After standing for 4 weeks, it was founded that pH of the preparations were not changed significantly.

Table 4-40 The pH of ibuprofen suspension after storage for 1 month at room temperature.

Suspending agent	%	pH				
		Initial	1 weeks	2 weeks	3 weeks	4 weeks
SCMS-2	1	4.91	4.68	4.97	4.96	4.94
	2	5.20	5.17	5.25	5.27	5.25
	3	5.36	5.31	5.47	5.47	5.48
PGTS	3	3.89	3.83	3.87	3.83	3.95
	4	3.96	3.87	4.03	4.01	3.99
	5	3.73	3.90	4.05	4.02	4.00
HPTS	4	3.80	3.90	3.99	3.72	3.81
	5	3.94	3.96	4.04	3.81	3.85
	6	3.95	4.03	4.20	3.93	3.97
CHPTS	3	4.03	4.13	3.86	3.99	3.95
	4	3.86	4.10	4.19	4.03	4.05
	4.5	3.96	3.98	4.03	3.97	4.29
UT	2	3.94	4.02	3.94	3.90	4.06
	3	3.83	3.89	3.94	3.71	3.90
	4	3.82	3.99	4.06	3.85	3.97
XG	0.2	4.38	4.47	4.16	4.22	4.39
	0.4	4.63	4.67	4.40	4.47	4.55
	0.6	4.72	4.54	4.40	4.58	4.73
TG	0.5	4.08	3.87	3.62	3.89	4.24
	1	4.16	4.10	3.83	3.89	4.08
	1.5	4.17	4.03	4.01	4.01	4.23

4.2.4 Determination of sedimentation volume

The total and compact sedimentation volume (Hu/Ho) of ibuprofen suspension containing SCMS-2, PGTS, HPTS, CHPTS, UT, XG and TG at various concentrations is shown in Table 4-41 and Figure 4-63.

The total sedimentation volume of ibuprofen suspension containing 1-2 % w/v SCMS-2 was decreased after keeping between 1-4 weeks, but at concentration of 3 % w/v the total sedimentation volume was not changed. At concentration of 2 % w/v, the total sedimentation volume gradually decreased when compare to at concentration of 1 % w/v.

The total sedimentation volume of ibuprofen suspension containing 3-5 % w/v PGTS, 4-6 % w/v HPTS, 3-4.5 % w/v CHPTS, 2-4 % w/v UT, 0.2-0.6 % w/v XG and 1-1.5 % w/v TG remained constant and equal to 1 after keeping between 1-4 weeks. It was indicated that those suspending agent could be suitably suspended ibuprofen in the preparation for 4 weeks.

For compact sedimentation volume, higher concentration of SCMS-2 showed larger compact sediment at 1 week storage. The compact sedimentation volume of concentrations of 1-3 % w/v SCMS-2 decreased slowly with time. The highest compact sedimentation volume of high polymer concentration was still greater than that of low polymer concentration after keeping between 1-4 weeks.

The ibuprofen suspension containing 4-5 % w/v PGTS, 5-6 % w/v HPTS, 3-4.5 % w/v CHPTS, 3-4 % w/v UT, 0.4-0.6 % w/v XG and 0.5-1.5 % w/v TG did not give compact sediment after keeping between 1-4 weeks while the ibuprofen suspension containing 3 % w/v PGTS ,4 % w/v HPTS, 2 % w/v UT and 0.2 % w/v XG provided compact sediment. This result indicated that those concentrations of some polymers were not enough for suspending ibuprofen particles in the preparation.

Table 4-41 The total and compact sedimentation volume of ibuprofen suspension containing various concentrations of suspending agents after standing at room temperature for 4 weeks.

Suspending agent	%	Total sedimentation volume ± SD				Compact sedimentation volume ± SD			
		1 week	2 weeks	3 weeks	4 weeks	1 week	2 weeks	3 weeks	4 weeks
SCMS-2	1	1(0)	0.87(0.01)	0.87(0.02)	0.86(0.01)	0.04(0)	0.05(0)	0.05(0)	0.05(0)
	2	1(0)	1(0)	0.94(0.01)	0.89(0)	0.84(0.02)	0.13(0)	0.11(0.01)	0.09(0.01)
	3	1(0)	1(0)	1(0)	1(0)	0.91(0.01)	0.18(0)	0.15(0)	0.12(0.01)
PGTS	3	1(0)	1(0)	1(0)	1(0)	0(0)	0.006(0)	0.03(0.01)	0.03(0.01)
	4	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
	5	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
HPTS	4	1(0)	1(0)	1(0)	1(0)	0.12(0.01)	0.10(0.01)	0.08(0)	0.07(0.01)
	5	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
	6	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
CHPTS	3	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
	4	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
	4.5	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
UT	2	1(0)	1(0)	1(0)	1(0)	0.09(0)	0.09(0.01)	0.07(0)	0.06(0.01)
	3	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
	4	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
XG	0.2	1(0)	1(0)	1(0)	1(0)	0(0)	0.12(0)	0.10(0)	0.08(0)
	0.4	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
	0.6	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)
TG	0.5	1(0)	1(0)	1(0)	0.99(0.01)	0(0)	0(0)	0(0)	0(0)
	1	1(0)	1(0)	1(0)	1(0)	0(0)	0(0)	0(0)	0(0)

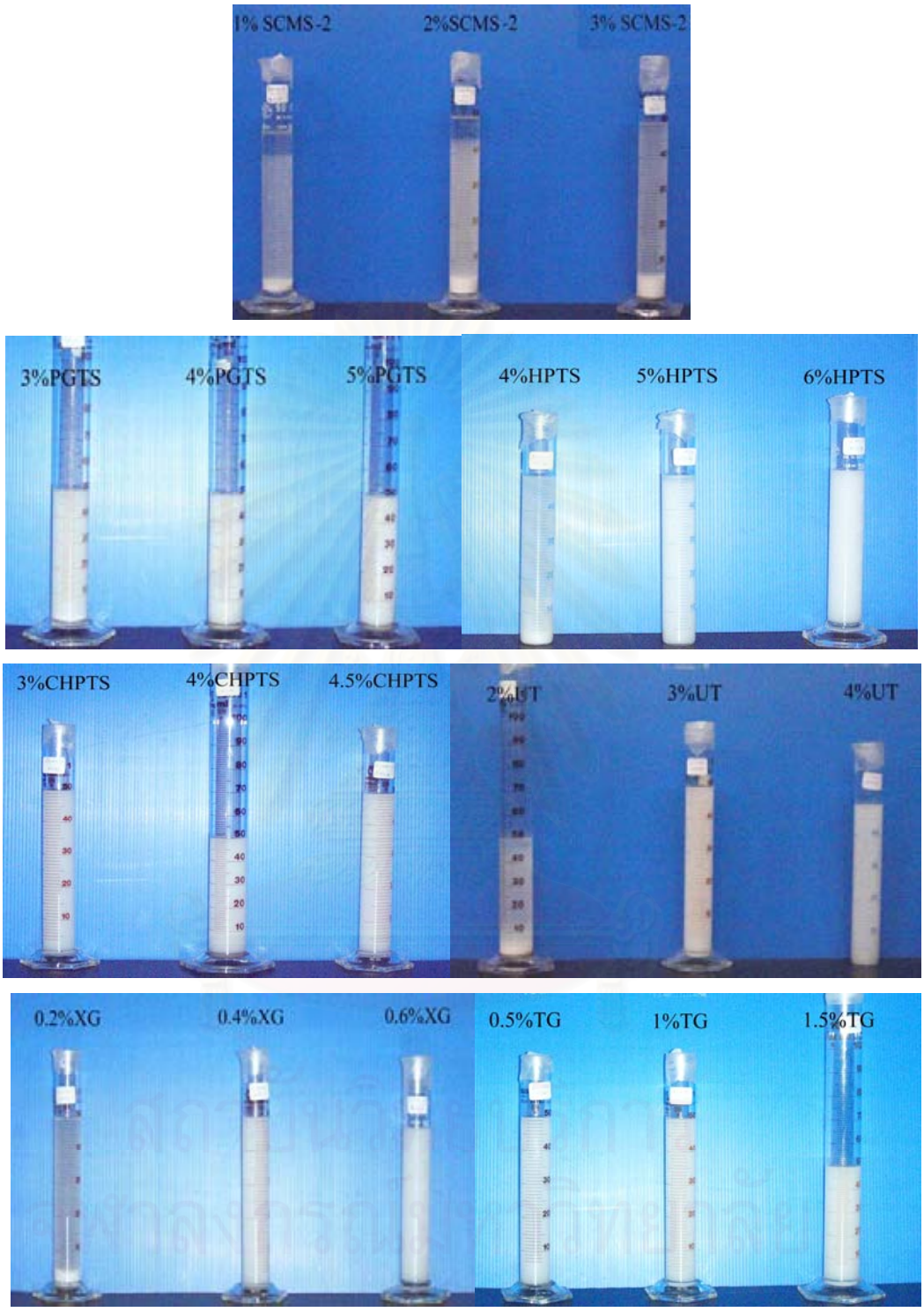


Figure 4-63 Photograph of final sedimentation volume of ibuprofen suspension containing various suspending agents and different concentrations after standing for 4 weeks at room temperature.

4.2.5 Determination of redispersibility

The redispersibility of ibuprofen suspension containing SCMS-2, PGTS, HPTS, CHPTS, UT, XG and TG at various concentrations is summarized in Table 4-42. The less number of inversions indicated the better of the redispersibility. The lowest number of inversion of ibuprofen suspension containing 4-5 % w/v PGTS, 5-6 % w/v HPTS, 3 % w/v CHPTS, 3-4 % w/v UT, 0.4-0.6 % w/v XG and 0.5-1.5 % w/v TG were equal to 1 after keeping between 1-4 weeks. It was indicated that those concentrations and polymer types were suitable as suspending agent.

The highest number of inversion of ibuprofen suspension was the preparation containing SCMS-2. The number of inversion at all concentrations decreased in accordance with the increasing concentration used. More number of inversions was required for storage. At 4 weeks, the number of inversion of preparation containing SCMS-2 did not different.

The suspension containing CHPTS as suspending agent at the concentration of 4 % w/v and 4.5 % w/v after keeping for 1 week required the force for its redispersion. This result might be indicated that it was the specific properties of CHPTS which formed rigid gel on the surface of preparation. At 3 % w/v CHPTS as suspending agent it could flow freely when inversed the tube because this concentration was not enough for forming rigid gel on the surface.

The ibuprofen suspension containing 3 % w/v PGTS, 4 % w/v HPTS, 2 % w/v UT and 0.2 % w/v required more number of inversions than 4-5 % w/v PGTS, 5-6 % w/v HPTS, 3-4 % UT and 0.4-0.6 % w/v XG after keeping between 1-4 weeks. The obtained results revealed that compact sedimentation forming at low concentration of suspending agent caused the more number of inversions.

Table 4-42 Number of inversion required to redisperse ibuprofen suspension after storage at room temperature for 4 weeks.

Suspending agent	%	Number of inversion (times)			
		1 week	2 weeks	3 weeks	4 weeks
SCMS-2	1	9-10	9-10	8-10	9-11
	2	7	8	9-10	11-12
	3	4-5	6	7-8	10-11
PGTS	3	1	4	4-5	4-5
	4	1	1	1	1
	5	1	1	1	1
HPTS	4	5	6-7	6-7	7-8
	5	1	1	1	1
	6	1	1	1	1
CHPTS	3	1	1	1	1
	4	1-2	2	3-4	3-5
	4.5	3-4	1*	1*	1*
UT	2	7-8	7-8	8	8-9
	3	1	1	1	1
	4	1	1	1	1
XG	0.2	2	4	5	6
	0.4	1	1	1	1
	0.6	1	1	1	1
TG	0.5	1	1	1	1
	1	1	1	1	1
	1.5	1	1	1	1

* could redisperse at the first time by using shaking force.

4.3 Selection of modified tapioca starch as suspending agent

Selection of modified tapioca starches and other suspending agents was made based on the results obtained from basic suspending properties such as viscosity, sedimentation volume and redispersibility of ibuprofen suspension containing modified tapioca starches and other suspending agents according to the studies in 4.4 and 4.2. In each property evaluation, a rank of 1, 2 and 3 was used as the score. Modified tapioca starch that showed the best result among the different concentrations was given score of 3 while the one that possessed the poorest result was given score of 1. The selection of modified tapioca starch of each concentration was made on the basis of the obtained score number of three evaluated properties. Maximum score of each modified tapioca starch as suspending agent was selected for further study in the part of stability test. The summary of preliminary evaluation was shown in Table 4-43 to 4-49.

Table 4-43 Selection of SCMS-2

Parameter	Score number		
	1.0 % w/v	2.0 % w/v	3.0 % w/v
Viscosity	1	2	3
Sedimentation volume	1	2	3
Redispersibility	1	3	2
Total score	3	7	8

Table 4-44 Selection of PGTS

Parameter	Score number		
	3.0 % w/v	4.0 % w/v	5.0 % w/v
Viscosity	1	3	2
Sedimentation volume	1	3	3
Redispersibility	1	3	3
Total score	3	9	8

Table 4-45 Selection of HPTS

Parameter	Score number		
	4.0 % w/v	5.0 % w/v	6.0 % w/v
Viscosity	1	2	3
Sedimentation volume	1	3	3
Redispersibility	1	3	3
Total score	3	8	9

Table 4-46 Selection of CHPTS

Parameter	Score number		
	3.0 % w/v	4.0 % w/v	4.5 % w/v
Viscosity	2	3	1
Sedimentation volume	3	3	3
Redispersibility	3	2	2
Total score	8	8	6

Table 4-47 Selection of UT

Parameter	Score number		
	2.0 % w/v	3.0 % w/v	4 % w/v
Viscosity	1	2	3
Sedimentation volume	1	3	3
Redispersibility	1	3	3
Total score	3	8	9

Table 4-48 Selection of XG

Parameter	Score number		
	0.2 % w/v	0.4 % w/v	0.6 % w/v
Viscosity	1	2	3
Sedimentation volume	1	3	3
Redispersibility	1	3	3
Total score	3	8	9

Table 4-49 Selection of TG

Parameter	Score number		
	0.5 % w/v	1 % w/v	1.5 % w/v
Viscosity	1	2	3
Sedimentation volume	1	3	3
Redispersibility	3	3	3
Total score	5	8	9

Among three concentrations of SCMS-2, at 3 % w/v gave the maximum score in the term of viscosity, sedimentation volume and redispesibility. It required lowest number of inversion and the highest sedimentation volume.

5 % w/v PGTS provided the highest viscosity but it was difficult to prepare the preparation. This concentration of PGTS was very viscous and difficult to disperse by using high speed disperser. So, 4 % w/v PGTS was selected in the further study because the score number in the term of sedimentation volume and redispersibility were equal to the score of 5 % w/v PGTS.

5 % w/v HPTS provided the same score number in the term of sedimentation volume and redispersibility as of 6 % w/v HPTS but 6 % w/v HPTS gave the higher score number in the term of viscosity more 5 % w/v HPTS. The total score number of HPTS at different three concentrations could be ranked in decreasing order as follows; 6 % w/v > 5 % w/v > 4 % w/v.

At the different three concentrations of CHPTS, 4.5 % w/v CHPTS gave the highest viscosity but this concentration of CHPTS formed a very rigid gel on the surface of suspension. CHPTS at the concentration of 4 % w/v trended to formed a rigid gel on the surface of the suspension but it could flow by itself when tube inversion. Whereas 4.5 % w/v CHPTS needed more agitation to stimulate the flowing of gel rigid on the surface. The score number of 3 and 4 % w/v CHPTS were equal and higher than 4.5 % w/v CHPTS. Therefore, 3 and 4 % w/v of CHPTS were selected in the further study.

Although, UT at the concentration of 4 % w/v gave the score number in the term of sedimentation volume and redispersibility similar to the concentration of 3 % w/v but it gave the highest score in the term of viscosity.

Although 0.4 % w/v XG provided the total score number in the term of viscosity, sedimentation volume and redispersibility lower than those of 0.6 % w/v XG but the physical appearance was good and was not different from 0.6 % w/v XG. So, the preparations that contained 0.4 and 0.6 % w/v XG were selected. TG at 1 % and 1.5 % w/v provided the same result of XG therefore they were selected.

In summary, ibuprofen suspension that contained 3 % w/v SCMS-2, 4 % w/v PGTS, 6 % w/v HPTS, 3-4 % w/v CHPTS, 4 % w/v UT, 0.4-0.6 % w/v XG and 1-1.5 % w/v TG as suspending agent were tested for their stability after storage for 12 weeks.

4.4 Stability test of selected ibuprofen suspensions

Ten formulations of ibuprofen suspension that contained suspending agents which was selected in the previous part were stored in two conditions. One was stored at room temperature for 12 weeks and another was stored at stress condition (heating-cooling) for eight cycles. Each cycle comprised storage at 4° C over a period of two days and then stored at 45° C over a period of two days. The evaluation was performed on five properties including physical appearance, pH, viscosity, sedimentation volume determination, redispersibility and content of active ingredient.

4.4.1 Physical properties

4.4.1.1 Appearance

The appearance of ibuprofen suspensions that were stored at room temperature for 3 months and at heating-cooling condition are shown in Table 4-50, 4-51 and Figure 4-64 to 4-66.

Table 4-50 Physical appearance of ibuprofen suspension after standing at room temperature for 3 months

Suspending agent	%	Initial	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
SCMS-2	3	Orange homogenous suspension.	Non- transparent supernatant was occurred.	← Clear orange supernatant was occurred with white compact sediment. →				
PGTS	4	Orange homogenous suspension.	Cluster of particles and non- transparent supernatant were observed in suspension.		← Clear supernatant was occurred above white compact sediment. →			
HPTS	6	Orange homogenous suspension.	Cluster of particles and non- transparent supernatant were observed in suspension.	← Cluster of particles and clear supernatant was occurred above white compact sediment. →				
CHPTS	3	Orange homogenous suspension.	← Clear slight supernatant on the top, suspended particles and no compact sediment were observed. →					
	4	Orange homogenous suspension.	← Orange homogenous suspension and the surface formed a rigid gel. →					

Table 4-50 (cont.)

Suspending agent	%	Initial	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
UT	4	← Orange homogenous suspension. →						
XG	0.4	← Orange homogenous suspension. →						Clear slight supernatant on the top, suspended particles and no compact sediment were observed.
	0.6	← Orange homogenous suspension. →						
TG	1	← Orange homogenous suspension. →				← Clear slight supernatant on the top, suspended particles and no compact sediment were observed. →		
	1.5	← Orange homogenous suspension. →						

Table 4-51 Physical appearance of ibuprofen suspension after keeping at heating-cooling condition.

Suspending agent	%	Initial	Heating-cooling condition
SCMS-2	3	Orange homogenous suspension.	← Clear supernatant and increasing intensity of color → were observed above white compact sediment.
PGTS	4	Orange homogenous suspension.	← Cluster of particles and non- transparent supernatant were observed → over the white compact sediment, the intensity of color was decreased.
HPTS	6	Orange homogenous suspension.	← Cluster of particles and non- transparent supernatant → were observed in suspension.
CHPTS	3	Orange homogenous suspension.	← Cluster of particles and non- transparent supernatant → were occurred over the compact sediment.
	4	← Orange homogenous suspension. →	
UT	4	Orange homogenous suspension.	← Slightly separated orange suspension, no compact sediment was occurred →
XG	0.4	Orange homogenous suspension.	← Cluster of particles and clear supernatant was occurred → above white compact sediment.
	0.6	← Orange homogenous suspension. →	
TG	1	Orange homogenous suspension.	← Slightly separated orange suspension, no compact sediment was occurred. →
	1.5	Orange homogenous suspension.	← Slightly separated orange suspension, no compact sediment was occurred. →

Under heating-cooling condition, ibuprofen suspension containing 4 % w/v CHPTS exhibited a good physical appearance and no sedimentation was observed. On the other hand, those of 6 % w/v HPTS, the cluster of particles and non-transparent supernatant were observed in the suspension. This result was similar to Wattanachant et al. (2003). They reported that cross-linked hydroxypropyl sago starch had better heating-cooling condition stability than native sago starch. In addition they explain that crosslinking with hydroxypropylation caused in substantial freeze thaw condition stability and it would be very much dependent on hydroxypropylation. Hydroxypropylation introduced mono functional hydroxypropyl groups to the hydroxyl group of the starch molecule, thus preventing dissolved linear starch molecules from associating closely by reduction of the attractive forces between hydroxyl groups on adjacent chains during cooling and freezing.

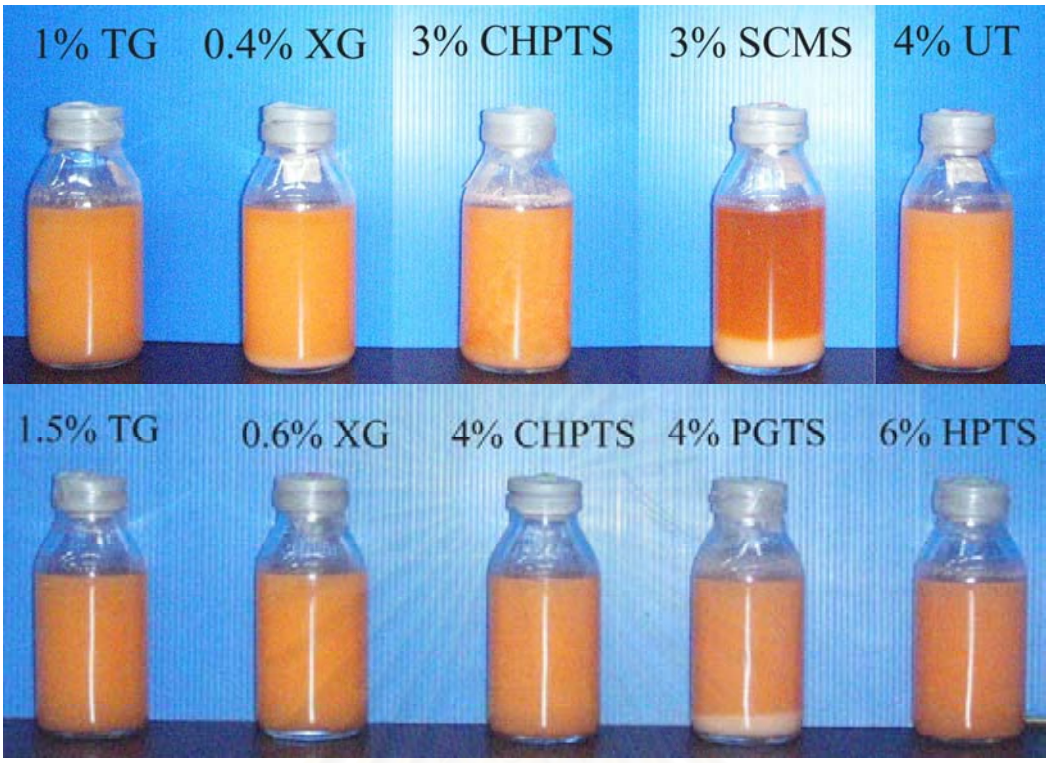


Figure 4-64 Photograph of ibuprofen suspension containing different suspending agents after heating-cooling condition.

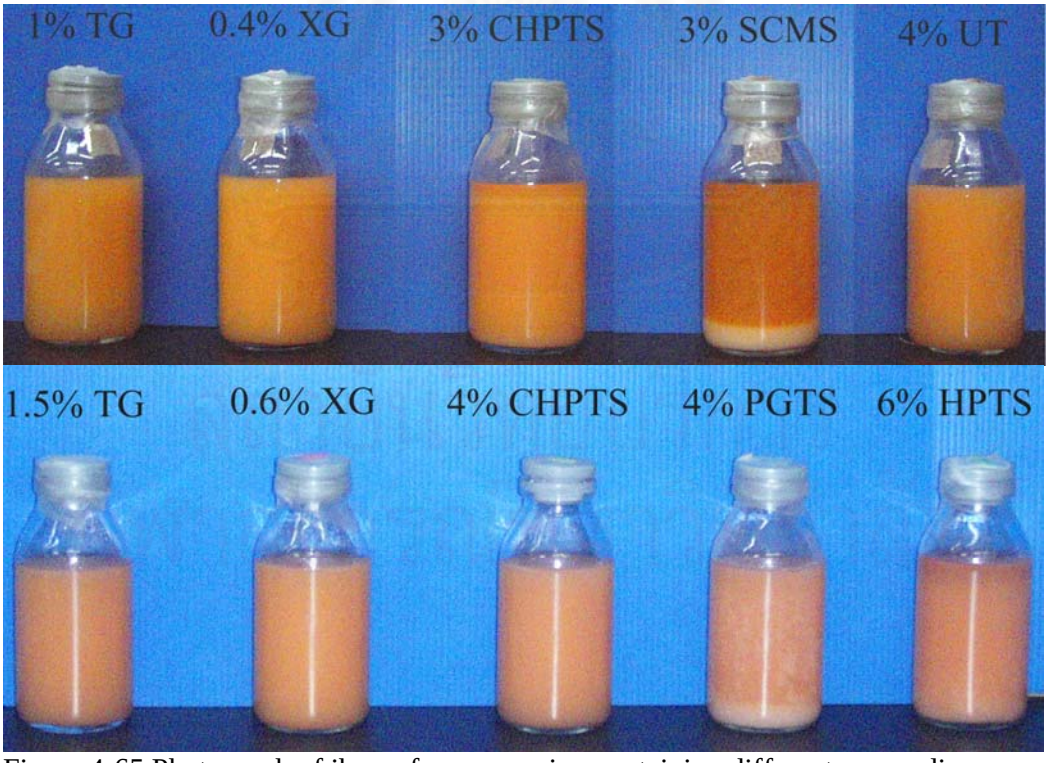


Figure 4-65 Photograph of ibuprofen suspension containing different suspending agents after standing at room temperature for 1 month.

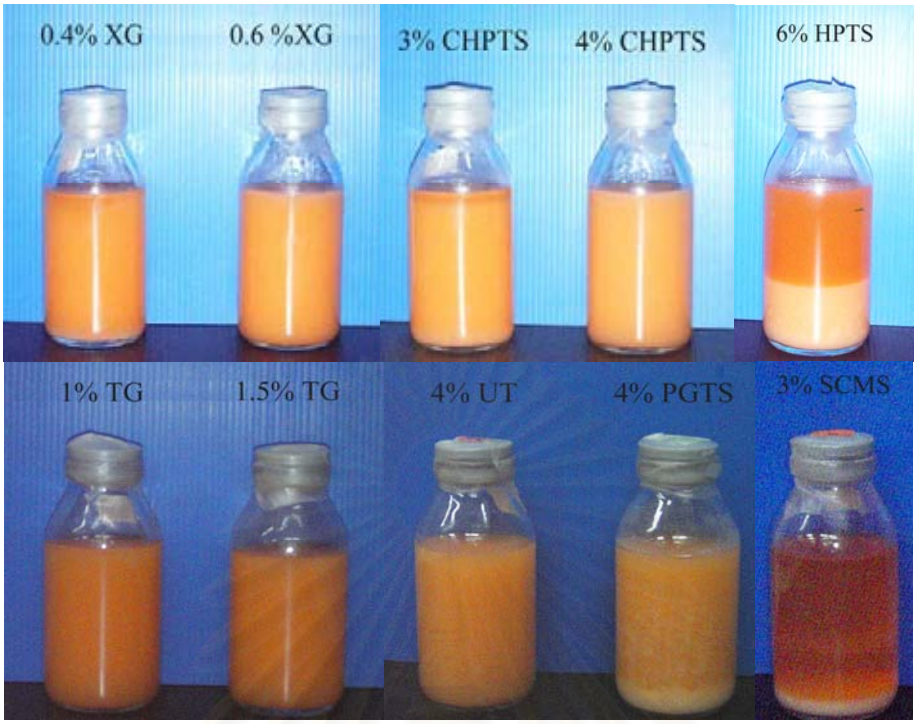


Figure 4-66 Photograph of ibuprofen suspension containing different suspending agents after standing at room temperature for 3 months.

4.4.1.2 pH

As displayed in Table 4-52, the preparations of ibuprofen suspension containing SCMS-2, PGTS and HPTS at each of concentration provided pH in the range of 5.56-5.30, 3.87-3.94 and 3.99-4.15, respectively after standing at room temperature for 3 months and provided the pH of 5.34, 3.89, and 4.02 respectively at heating-cooling condition. The ibuprofen suspension that contained 3 and 4 % w/v CHPTS, 0.4 and 0.6 % w/v XG and 1 and 1.5 % w/v TG gave the pH in the range of 3.99-4.08, 3.83-4.03, 4.34-4.68, 4.39-4.62, 4.11-4.29 and 4.14-4.28, respectively. While at heating-cooling condition they provided the pH of 4.03, 3.92, 4.10, 4.25, 4.30, 4.11 and 4.14, respectively. The pH of all preparations trended to slightly decrease after standing at room temperature for 3 months and at heating-cooling condition.

Table 4-52 The pH of ibuprofen suspension after storage at the room temperature for 3 months and heating-cooling condition.

Suspending agent	%	pH of ibuprofen suspension				
		Room temperature condition				Heating-cooling condition
		Initial	1 month	2 months	3 months	
SCMS-2	3	5.56	5.30	5.36	5.38	5.34
PGTS	4	3.94	3.87	3.91	3.92	3.89
HPTS	6	4.15	4.04	3.99	3.99	4.02
CHPTS	3	4.08	4.07	4.04	3.99	4.03
	4	4.03	3.93	3.88	3.83	3.92
UT	4	4.22	4.09	4.13	4.19	4.10
XG	0.4	4.68	4.37	4.34	4.35	4.25
	0.6	4.62	4.44	4.43	4.39	4.30
TG	1	4.29	4.11	4.17	4.20	4.11
	1.5	4.28	4.14	4.15	4.17	4.14

4.4.1.3 Viscosity and rheological behavior

4.4.1.3.1 Viscosity

The average apparent viscosity of modified starch containing ibuprofen suspensions evaluated at initial after storage at room temperature for 3 months and heating-cooling condition are presented in Table 4-53 and Figure 4-67 to Figure 4-68. The results showed that the viscosity of suspension that contained 3 % w/v SCMS-2, 6 % w/v HPTS, 0.4 % and 0.6 % w/v XG at initial conditions was higher than that of suspension at room temperature while 4 % w/v PGTS, 3 % w/v CHPTS, 4 % w/v CHPTS, 4 % w/v UT , 1 and 1.5 % w/v TG after standing at room temperature condition for 3 months gave the viscosity higher than at initial.

The viscosity of suspension that contained 4 % w/v PGTS, 3 % w/v CHPTS and 1 % w/v TG were slightly increased when the time of storage was increased while the viscosity of 4 % w/v CHPTS was extremely increased in the range of 1,156.93-1,913.67 cps. The increase in viscosity of PGTS, CHPTS, UT and TG containing suspensions was due to either the loss of water or the fully swelling of the gum or saturated network of polymer forming a rigid structure.

The order of decreasing viscosity of suspension that contained 3 % w/v SCMS-2 was: at initial > room temperature for 3 months > heating-cooling condition. This result was similar to the report by Suwannapakul (1996) and was suggested that this modified starch underwent regular degrading pattern in which degradation took place as time proceeded and occurred the most under stress condition (Zatz, 1985).

The order of decreasing viscosity of suspension containing 4 % w/v PGTS, was room temperature for 3 months > initial > heating-cooling condition.

For 6 % w/v HPTS and 4 % w/v CHPTS, the order of decreasing viscosity was heating-cooling condition > room temperature for 3 months > initial. Whereas the viscosity of 3 % w/v CHPTS was not significant different between at heating-cooling condition and room temperature for 3 month but they were higher than that of at initial condition.

The order of decreasing viscosity of suspension that contained 4 % w/v UT, was room temperature for 3 months > heating-cooling condition > initial. For 0.4 and 0.6 % w/v XG, the order of decreasing viscosity was initial > room temperature for 3 months > heating-cooling condition. For 1 % w/v TG, the order of decreasing viscosity was heating-cooling condition = room temperature for 3 months > initial while the order of decreasing viscosity of 1.5 % w/v was heating-cooling condition> room temperature for 3 months > initial.

Table 4-53 Viscosity of ibuprofen suspension after storage at the room temperature for 3 months and heating-cooling condition at 10 rpm of Brookfield® viscometer.

Suspending agent	%	Average apparent viscosity (cps ± SD)				
		Room temperature condition				Heating-cooling condition
		Initial	1 month	2 months	3 months	
SCMS-2	3	875.80 (26.15)	669.90 (9.64)	644.90 (15.88)	674.87 (57.89)	520.90 (6.93)
PGTS	4	218.00 (8.66)	222.00 (13.75)	247.93 (17.52)	237.93 (16.47)	196.00 (6.25)
HPTS	6	493.90 (6.99)	480.90 (16.52)	471.90 (16.52)	464.90 (18.00)	525.90 (4.59)
CHPTS	3	87.00 (0.00)	110.00 (6.93)	142.00 (6.25)	156.00 (7.94)	146.00 (10.54)
	4	1,156.93 (236.18)	1,745.00 (33.05)	2,038.00 (63.59)	1,913.67 (109.20)	1,964.00 (168.92)
UT	4	1,193.00 (66.57)	1,285.00 (114.01)	1,262.00 (81.30)	1,306.00 (99.51)	1,285.00 (26.89)
XG	0.4	964.80 (24.06)	904.80 (10.54)	866.80 (7.94)	847.80 (1.73)	785.80 (10.39)
	0.6	1,934.00 (53.78)	1,850.00 (6.25)	1,788.00 (13.75)	1,765.00 (7.55)	1,720.00 (22.91)
TG	1	226.00 (4.58)	233.97 (2.95)	294.90 (1.73)	299.90 (3.00)	288.90 (10.54)
	1.5	859.80 (26.89)	982.87 (27.99)	1,075.00 (9.17)	1,133.00 (22.52)	1,175.00 (16.52)

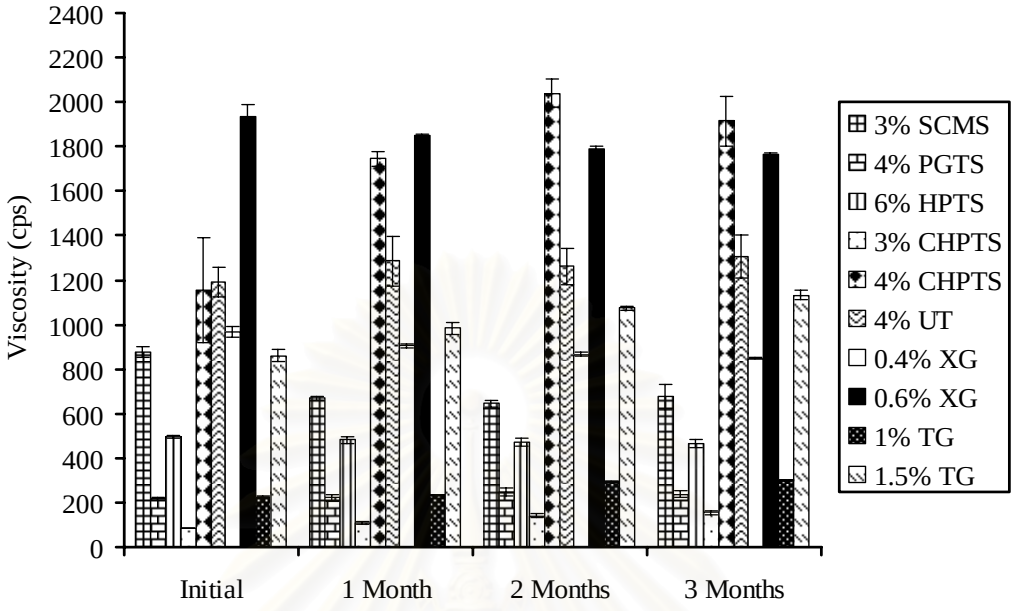


Figure 4-67 The comparative appearance viscosity for ibuprofen suspension using various suspending agents under room temperature storage.

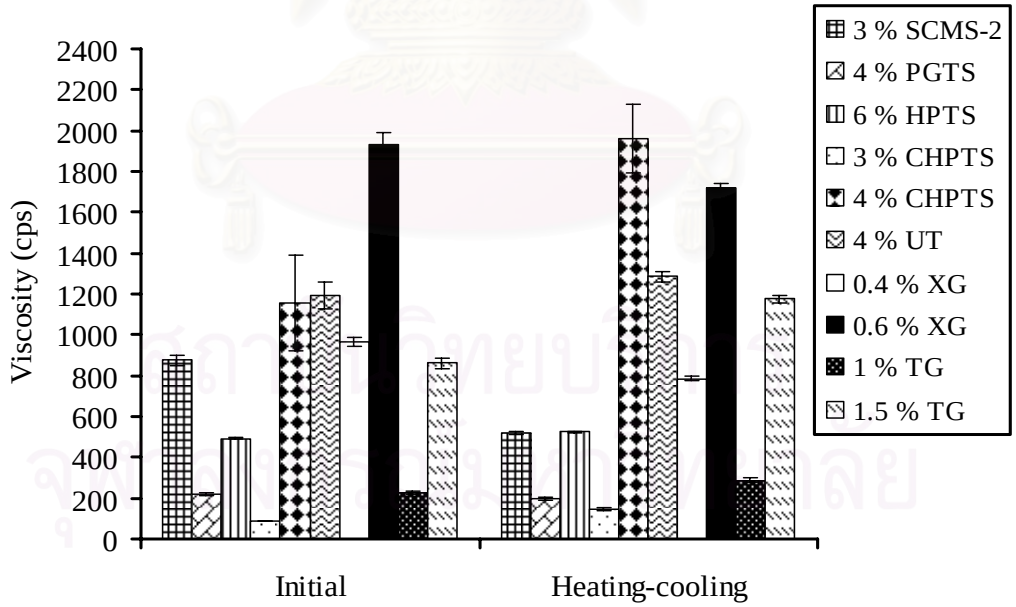


Figure 4-68 The comparative appearance viscosity for ibuprofen suspension using various suspending agents under heating-cooling condition.

4.4.1.3.2 Rheological behavior

As summarized in Table 4-54, the thixotropic values of ibuprofen suspension containing 3 % w/v SCMS-2, 0.4 and 0.6 % w/v XG and 1.5 % w/v TG as suspending agent trended to increase at the first month and decreased at the second and the third month. Whereas the ibuprofen suspension containing 4 % w/v PGTS, 6 % w/v HPTS and 3 and 4 % w/v CHPTS obtained the maximum thixotropic values at the second month and decreased when the storage time increased.

The thixotropic values of ibuprofen suspension containing 1 % w/v TG trended to increase when the storage time increased. While, ibuprofen suspension containing 4 %w/v UT provided the decreasing thixotropic values comparing with the `initial preparation.

At heating-cooling condition, the preparation containing 3 % w/v SCMS-2, 4 % w/v UT, 0.4 and 0.6 % w/v XG exhibited the decreasing thixotropic values comparing with the initial preparation. Whereas the thixotropic values of heating-cooling preparation containing 4 % w/v PGTS, 6 % w/v HPTS, 3 and 4% w/v CHPTS and 1 and 1.5 % w/v TG increased comparing with the initial preparation. Preparing using 4 % w/v CHPTS exhibited highest thixotropic property.

Table 4-54 Thixotropic values of ibuprofen suspension after storage at the room temperature for 3 months and heating-cooling condition.

Suspending agent	%	Average thixotropic value (dynes/cm^2.sec ± SD)				
		Room temperature condition				Heating-cooling condition
		Initial	1 month	2 months	3 months	
SCMS	3	1.77 (0.85)	2.01 (0.54)	1.94 (0.61)	0.42 (0.74)	0.42 (0.55)
PGTS	4	-0.12 (0.16)	-0.05 (0.17)	0.52 (0.38)	-0.27 (0.15)	0.05 (0.06)
HPTS	6	-0.45 (0.13)	-0.09 (0.16)	0.02 (0.22)	-0.05 (0.58)	0.30 (0.32)
CHPTS	3	0.01 (0.23)	0.32 (0.78)	1.00 (0.49)	0.43 (0.04)	0.22 (0.30)
	4	32.80 (23.59)	44.68 (17.42)	51.86 (11.59)	23.61 (6.30)	44.54(30.47)
UT	4	-1.82 (0.52)	-3.30 (1.03)	-4.00 (1.62)	-2.53(1.04)	-3.39 (0.95)
XG	0.4	1.66 (0.19)	2.07 (2.06)	0.85 (0.22)	0.78 (0.07)	1.14 (0.38)
	0.6	4.18 (0.76)	4.39 (0.21)	4.07 (0.90)	3.53 (0.54)	3.82 (0.60)
TG	1	2.49 (0.19)	3.52 (0.35)	4.92 (0.79)	5.67 (0.58)	4.53 (1.03)
	1.5	12.94 (0.51)	15.70 (0.62)	11.08 (1.33)	11.69 (0.88)	14.42 (2.04)

The flow patterns of all ibuprofen suspension were not changed after standing at room temperature for 3 months (Figure 4-69 to 4-78). The rheograms of ibuprofen suspension containing 3 %w/v SCMS-2, 3 and 4 % w/v CHPTS, and 0.4 and 0.6 % w/v XG were a pseudoplastic type with positive thixotropic values. While the rheograms of ibuprofen suspension containing 4 % w/v PGTS, 6 % w/v HPTS, and 4 % w/v UT displayed a pseudoplastic type with negative thixotropic values. Almost the rheograms of ibuprofen suspension at heating-cooling condition did not alter except ibuprofen suspension containing 4 % w/v PGTS and 6 % w/v HPTS.

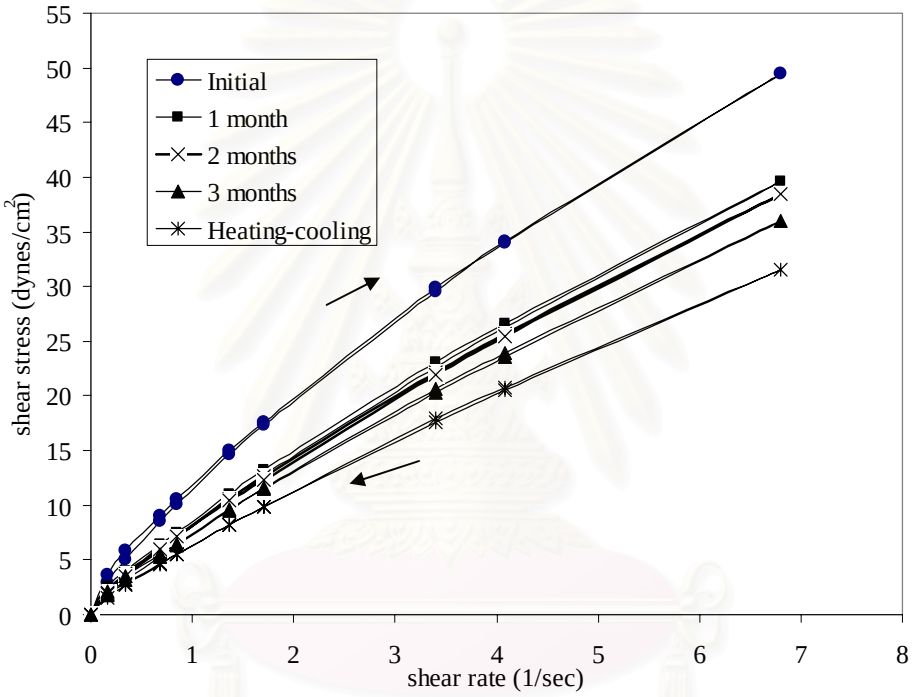


Figure 4-69 Rheograms of ibuprofen suspension containing 3 % w/v SCMS-2 at different storage conditions.

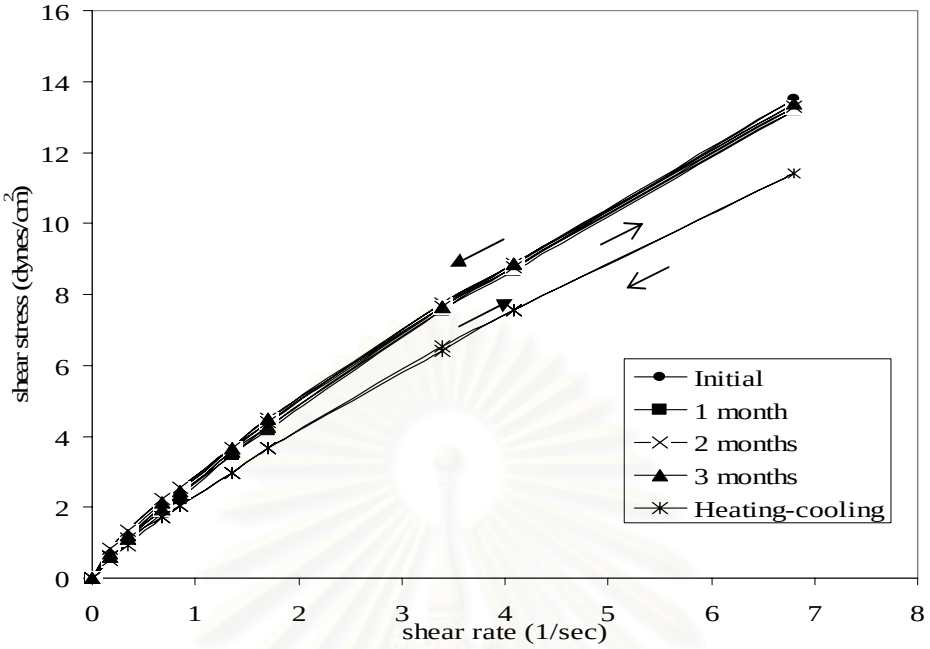


Figure 4-70 Rheograms of ibuprofen suspension containing 4 % w/v PGTS at different storage conditions.

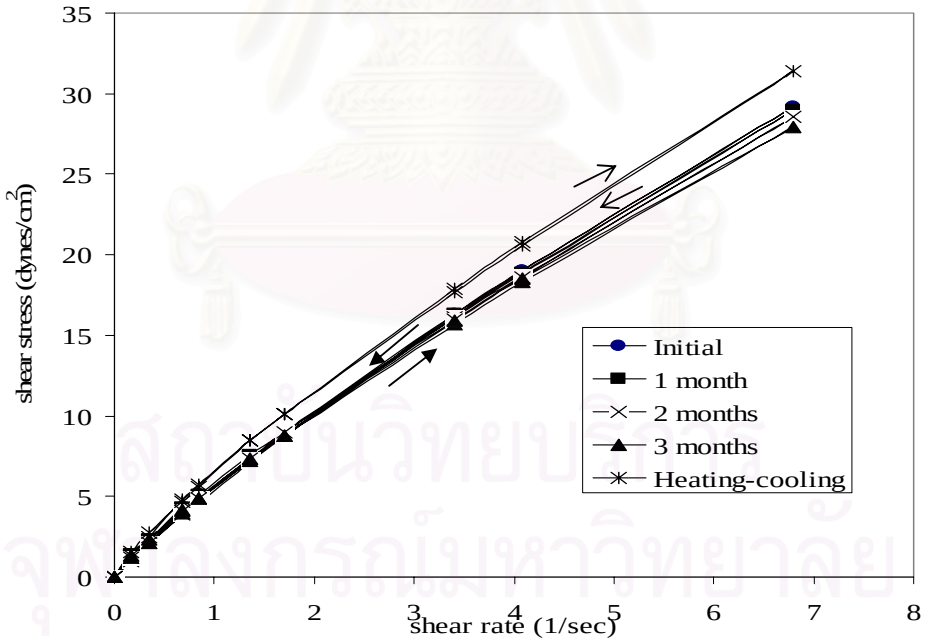


Figure 4-71 Rheograms of ibuprofen suspension containing 6 % w/v HPTS at different storage conditions.

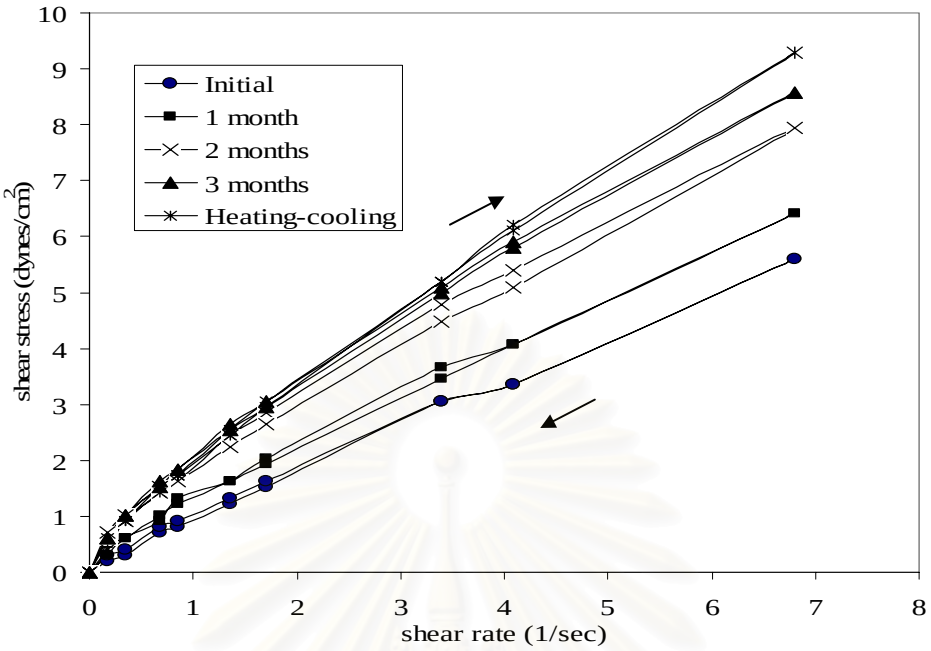


Figure 4-72 Rheograms of ibuprofen suspension containing 3 % w/v CHPTS at different storage conditions.

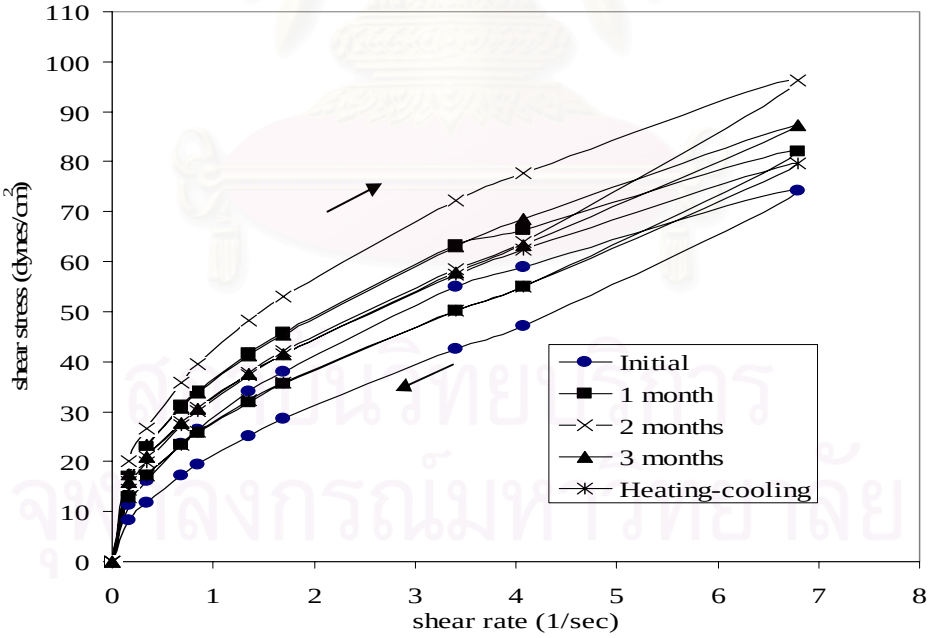


Figure 4-73 Rheograms of ibuprofen suspension containing 4 % w/v CHPTS at different storage conditions.

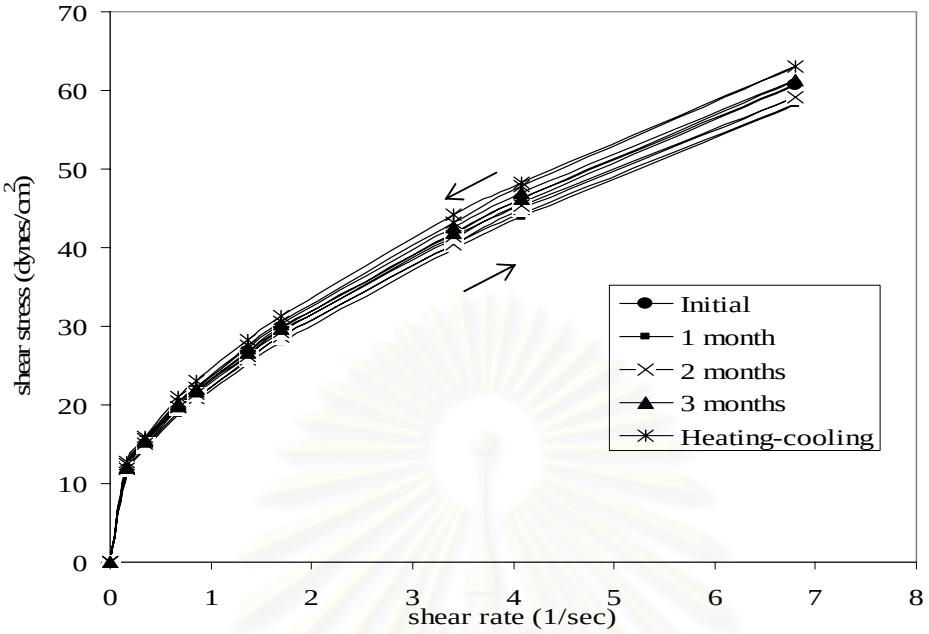


Figure 4-74 Rheograms of ibuprofen suspension containing 4 % w/v UT at different storage conditions.

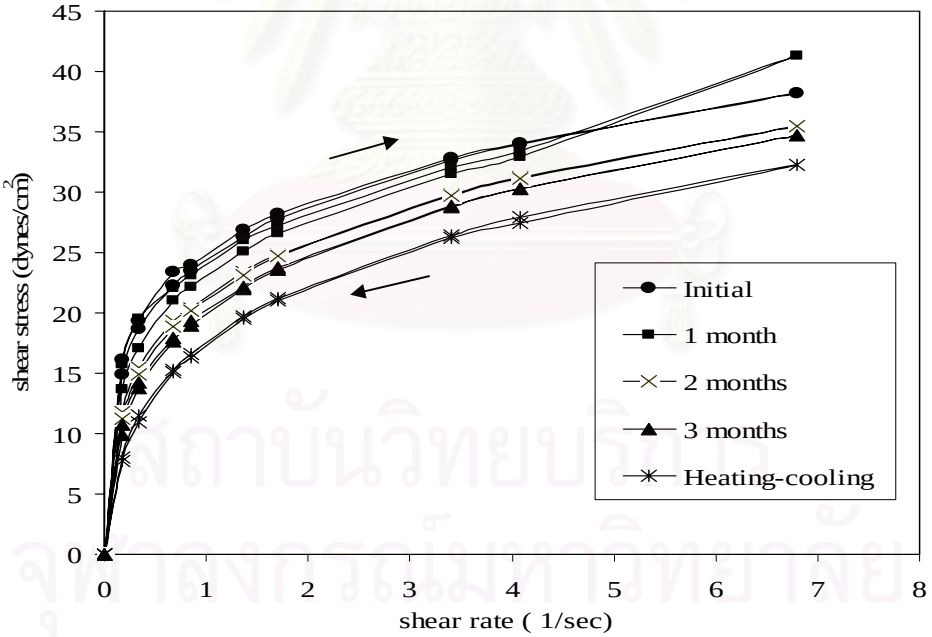


Figure 4-75 Rheograms of ibuprofen suspension containing 0.4 % w/v XG at different storage conditions.

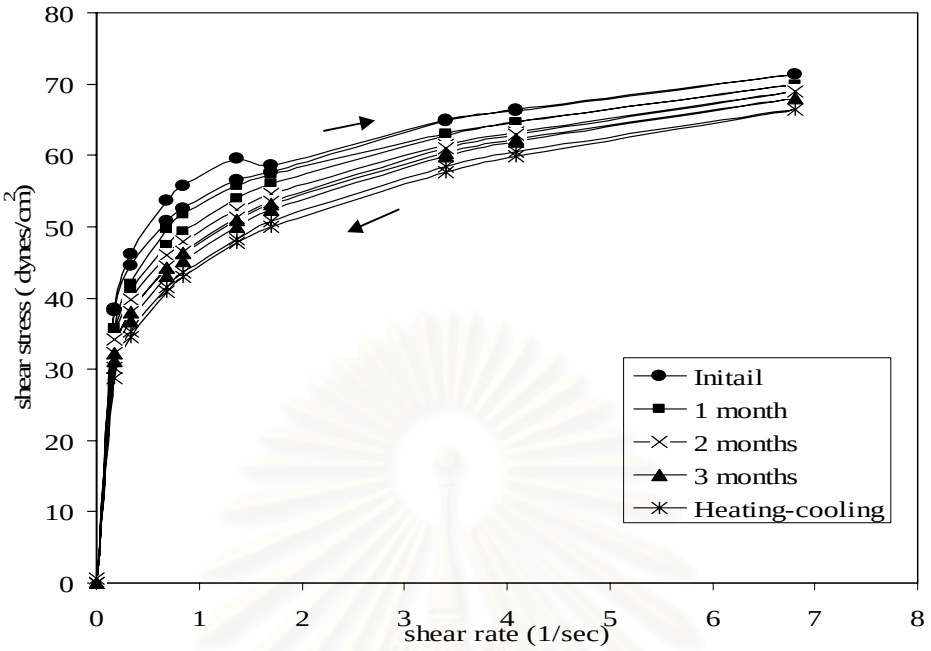


Figure 4-76 Rheograms of ibuprofen suspension containing 0.6 % w/v XG at different storage conditions.

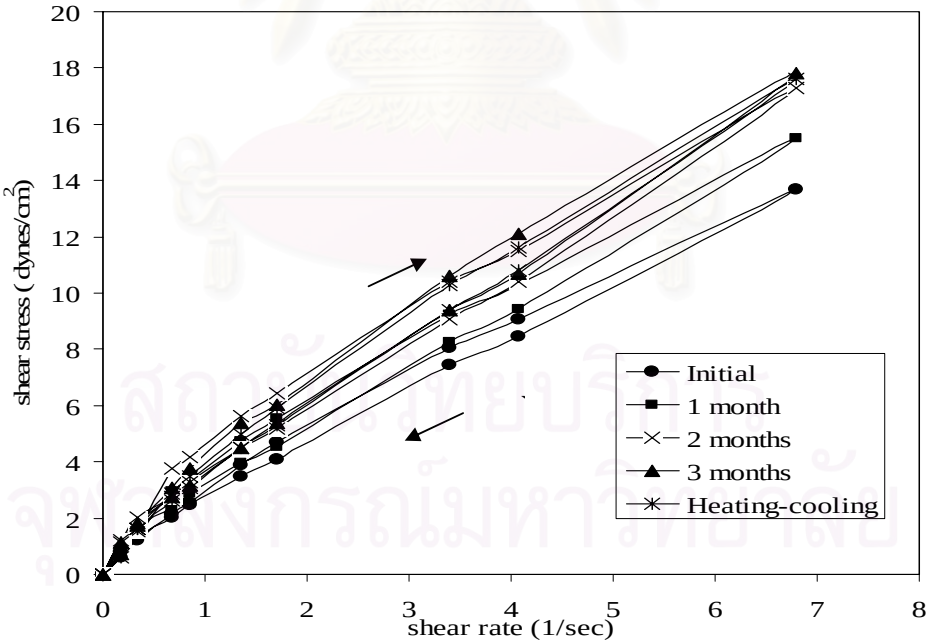


Figure 4-77 Rheograms of ibuprofen suspension containing 1 % w/v TG at different storage conditions.

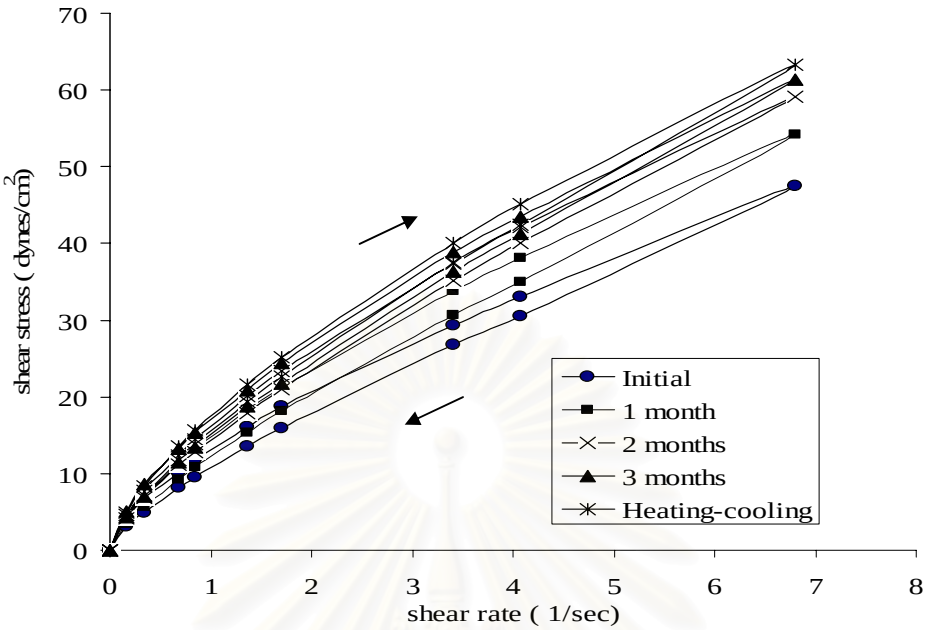


Figure 4-78 Rheograms of ibuprofen suspension containing 1.5 % w/v TG at different storage conditions.

4.4.1.4 Sedimentation volume

The total and compact sedimentation volume (Hu/Ho) of ibuprofen suspension containing various suspending agents after standing at room temperature for 12 weeks and heating-cooling condition are displayed in Table 4-55 and 4-56, respectively. The total sedimentation volume of ibuprofen suspension containing 3 % w/v SCMS-2 was decreased at the sixth week at room temperature; the compact sediment was occurred in the fourth week and decreased when the storage time increased. At heating-cooling condition the total sedimentation volume of ibuprofen suspension containing 3 % w/v SCMS-2 was lower than those of initial preparation but higher than the preparation after standing at room temperature for 12 weeks. The compact sediment was occurred in this preparation at heating-cooling condition but higher than the preparation after standing at room temperature for 12 weeks.

For 4 % w/v PGTS, the total sedimentation volume of ibuprofen suspension was decreased at the sixth week at room temperature and slowly decreased when the storage time increased. The compact sediment occurred at the second week and increased when the storage time increased until the eighth week. After that the compact sediment decreased. Under heating-cooling condition the total sedimentation

volume of ibuprofen suspension containing 4 % w/v PGTS was not changed comparing with those of initial preparation (equal to 1) and lower than the preparation after standing at room temperature for 12 weeks. At heating-cooling condition, the compact sediment was higher than the preparation after standing for 12 weeks.

For ibuprofen suspension containing 6 % w/v HPTS, the total sedimentation volume was decreased at the fourth week at room temperature and extremely decreased when the storage time increased. The compact sediment occurred after 4 weeks storage and the compact sediment was remained unchanged at the sixth weeks. Under heating-cooling condition the total sedimentation volume was not changed comparing with those of initial preparation (equal to 1) but higher than the preparation at room temperature after standing for 12 weeks. No compact sediment of the preparation was observed under heating-cooling condition.

The total sedimentation volume of ibuprofen suspension containing 3 % w/v CHPTS was slightly decreased at the second week after standing at room temperature and was not changed significantly when the storage time increased. While at 4 % w/v CHPTS the total sedimentation volume was equal to 1 and was not changed after standing at room temperature for 12 weeks comparing with the initial preparation. No compact of both suspensions containing 3 and 4 % w/v CHPTS was observed after standing at room temperature for 12 weeks. The total sedimentation volumes of ibuprofen suspension containing 3 and 4 % w/v CHPTS were not changed after standing for 12 weeks under heating-cooling condition comparing with those of initial preparation (equal to 1). Very low compact sediment of ibuprofen suspension containing 3 % w/v CHPTS was found in the preparation at heating-cooling condition whereas the compact sediment did not occurred in ibuprofen suspension containing 4 % w/v CHPTS.

The total sedimentation volume of ibuprofen suspension containing 4 % w/v UT was equal to 1 and did not alter after standing at room temperature for 12 weeks and at heating-cooling condition. The compact sediment of this preparation did not occur after standing at room temperature for 12 weeks and at heating-cooling condition.

The total sedimentation volume of ibuprofen suspension containing 0.4 % w/v XG was equal to 1 in the period of 2-10 weeks and slightly decreased to 0.98 after 12 weeks at room temperature. However, the compact sediment did not found after standing at room temperature for 12 weeks. Under heating-cooling condition, the total sedimentation volume of ibuprofen suspension containing 0.4 % w/v XG was 0.93 and it was lower than those of initial preparation and the preparation after storage in room temperature for 12 weeks (0.98). For 0.6 % w/v XG as suspending agent, the total sedimentation volume of the preparation was equal to 1 and did not alter after standing at room temperature for 12 weeks and at heating-cooling condition. No compact sediment of the preparation was found after standing at room temperature for 12 weeks and at heating-cooling condition.

The total sedimentation volume of ibuprofen suspension containing 1 % w/v TG was equal to 1 in the period of 2-6 weeks and constant at 0.98 after standing at room temperature for 8 weeks. In addition, the compact sediment did not occur after standing at room temperature for 12 weeks. The total sedimentation volume of ibuprofen suspension containing 1.5 % w/v TG was equal to 1 and did not alter after standing at room temperature for 12 weeks and at heating-cooling condition. The compact sediment of both preparations containing 1 and 1.5 % w/v TG did not occur after standing at heating-cooling condition.

Table 4-55 The total and compact sedimentation volume of ibuprofen suspension containing various suspending agents after standing at room condition for three months.

Suspending agent	%	Total sedimentation volume ± SD						Compact sedimentation volume ± SD					
		2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
SCMS-2	3	1.00 (0.00)	1.00 (0.00)	0.17 (0.00)	0.15 (0.00)	0.15 (0.00)	0.15 (0.00)	0.00 (0.00)	0.21 (0.02)	0.17 (0.00)	0.15 (0.00)	0.15 (0.00)	0.15 (0.00)
PGTS	4	1.00 (0.00)	1.00 (0.00)	0.91 (0.00)	0.86 (0.02)	0.83 (0.02)	0.85 (0.00)	0.11 (0.00)	0.21 (0.01)	0.21 (0.01)	0.22 (0.00)	0.20 (0.02)	0.19 (0.00)
HPTS	6	1.00 (0.00)	0.97 (0.01)	0.88 (0.01)	0.64 (0.01)	0.52 (0.00)	0.46 (0.00)	0.00 (0.00)	0.11 (0.00)	0.15 (0.00)	0.15 (0.00)	0.15 (0.00)	0.15 (0.00)
CHPTS	3	0.94 (0.00)	0.93 (0.01)	0.93 (0.01)	0.94 (0.00)	0.94 (0.00)	0.94 (0.01)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	4	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
UT	4	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
XG	0.4	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	0.98 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	0.6	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
TG	1	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	0.98 (0.00)	0.98 (0.00)	0.98 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	1.5	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)

Table 4-56 The total and compact sedimentation volume of ibuprofen suspension containing various suspending agents under heating-cooling condition.

Suspending agent	%	The total sedimentation volume ± SD	The compact sedimentation volume ± SD
SCMS-2	3	0.22 (0.005)	0.22 (0.005)
PGTS	4	1 (0.000)	0.13 (0.005)
HPTS	6	1 (0.000)	0 (0.000)
CHPTS	3	1 (0.000)	0.11 (0.000)
	4	1 (0.000)	0 (0.000)
UT	4	1 (0.000)	0 (0.000)
XG	0.4	0.93 (0.000)	0.11 (0.005)
	0.6	1 (0.000)	0 (0.000)
TG	1	1 (0.000)	0 (0.000)
	1.5	1 (0.000)	0 (0.000)

4.4.1.5 Determination of redispersibility

The redispersibility of ibuprofen suspension containing various suspending agents after standing at room temperature for 3 months and 8 cycles of heating-cooling condition are presented in Table 4-57. The number of inversion of ibuprofen suspension containing 3 % w/v SCMS-2 was more than 12 times after 6 weeks and increased to 23-24 times at 12 weeks at room temperature condition. This result indicated that this preparation produced the cake at the bottom of the container and was not easy to redisperse. It was indicated that this system might be produced deflocculating particles. It might be caused that SCMS and ibuprofen had similar charge (anionic) so; ionic repulsion would be occurred and enriched deflocculation of particles. The 3 % w/v SCMS-2 was not suitable as suspending agent for ibuprofen suspension.

Ibuprofen suspension containing 4 % w/v PGTS and 6 % HPTS after storage at room temperature condition exhibited the increasing of number of inversion when the storage time increased. For 4 % w/v PGTS, the number of inversion of this preparation was not more than 12 times after standing at room temperature for 12 weeks while caking was observed at 6 % w/v HPTS.

The number of inversion of ibuprofen suspension containing 3 % w/v CHPTS after storage at room temperature condition was gradually increased when the storage time increased. It increased in the range of 2-4 times after standing at room temperature condition for 12 weeks. This preparation could flow freely when inversed the tube through out the period of storage (12 weeks) while those if 4 % w/v CHPTS could not. It required the first shaking force to breakdown the rigid gel on the surface of the preparation. After that, the suspension could flow freely. This result might be indicated that it was the specific properties of CHPTS which formed rigid gel on the surface of preparation. The formation of rigid gel on the surface might be possible that CHPTS occupied high degree of cross-linked which provided dense network and less hydrophilic of its molecules. At high concentration of CHPTS (4 and 4.5 % w/v), it might be that the water content in the molecules was less than that of 3 % w/v. Therefore, it was easy to loss water molecule and form rigid gel.

HPTS and CHPTS had no charge. HPTS produced the cake in the preparation while CHPTS did not. It might be possible that cross-linked reaction provided the longer chain which could act as polymer bridge between drug particles.

The number of inversion of the ibuprofen suspension containing 4 % w/v UT, 0.6 % w/v XG, 1 and 1.5 % w/v TG were equal to 1 and was not changed after storage at room temperature condition except the preparation containing 0.4 % w/v XG. The number of inversion of the ibuprofen suspension containing 0.4 % w/v XG increased from 1 to 2 times at the 12 weeks.

The number of inversion of ibuprofen suspension containing various suspending agent after standing at room temperature for 3 months could be ranked in decreasing order as follows; 3 % w/v SCMS-2 > 6 % w/v HPTS > 4 % w/v PGTS > 3 % w/v CHPTS > 0.4 % w/v XG > 4 % w/v UT = 0.6 % w/v XG = 1% w/v TG = 1.5 % w/v TG = 4 % w/v CHPTS.

Heating-cooling condition provided the increasing of the number of inversion of all preparations comparing with the initial preparation. The ibuprofen suspension containing 4 % w/v PGTS gave the highest number of inversion (more than 12 times) under heating-cooling condition. It was indicated that this preparation produced the caking that difficult to redisperse at stress condition. PGTS was physical modified starch so, its property was similar to native starch that was not stable in stress condition. Although PGTS had no charge, caking was observed. It might be that the deflocculating system was occurred because the property of PGTS could not act as polymer bridge between the drug molecules. Moreover, the preparation containing 3 % w/v SCMS-2, 6 % w/v HPTS, 0.4 and 0.6 % w/v XG, 1 and 1.5 % w/v TG gave the number of inversion not more than 12 times at heating-cooling condition. While, the ibuprofen suspension containing 3 and 4 % CHPTS and 4 % w/v UT could not flow by normal inversion the tube. It required the initial shaking force to breakdown the rigid gel on the surface of the preparation, after that the suspension could flow freely.

The number of inversion of ibuprofen suspension containing various suspending agents after standing at heating-cooling condition could be ranked in decreasing order as follows; 4 % w/v PGTS > 3 % w/v SCMS-2 > 6 % w/v HPTS = 0.4 % w/v XG > 0.6 % w/v XG = 1 % w/v TG = 1.5 % w/v TG > 3 % w/v CHPTS = 4 % w/v CHPTS = 4 % w/v UT.

Table 4-57 Number of inversion required to redisperse ibuprofen suspension containing various suspending agents after standing at room condition for 12 weeks and heating-cooling condition.

Suspending agent	%	Number of inversion (times)						
		Room condition						Heating-cooling condition
		2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	
SCMS-2	3	3-5	10	15-16	16	19-20	23-24	9-8
PGTS	4	5	6	6	6	7-8	7-8	17-18
HPTS	6	1	2-3	11-13	14-15	15	17-18	3
CHPTS	3	2	2	2-3	3	3-4	4	*
	4	*	*	*	*	*	*	*
UT	4	1	1	1	1	1	1	*
XG	0.4	1	1	1	1	1	2	3
	0.6	1	1	1	1	1	1	2
TG	1	1	1	1	1	1	1	2
	1.5	1	1	1	1	1	1	2

* could redisperse at the first time by using shaking force.

4.4.2 Chemical property

Ibuprofen content of 10 preparations were presented in term of percentage of the label amount after standing in room temperature for 3 months and 8 cycles of heating-cooling condition at shown in Table 4-58 and Figure 4-79 to Figure 4-80). For each suspension, a triplicate result of ibuprofen content determining from three difference samples was reported every 1 month over a period of 3 months. The theoretical concentration of ibuprofen in all suspensions was 2g/100 ml.

Percent drug content of 10 preparations were ranging from 96.33-104.68. The preparation containing 3 % w/v SCMS-2 after keeping in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 100.70, 99.59, 96.74, 97.98 and 99.44 %LA, respectively. For the statistical analysis, it was found that % LA at storage condition of initial and heating-cooling was not significantly different while those of initial preparation was significantly different from the storage time of 2 and 3 months (see detail in Appendix B). However, the % LA of all preparations at difference storage conditions was in accepted range of USP which was ranging from 90-110 % LA.

The preparation containing 4 % w/v PGTS after keeping in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 103.86, 97.91, 97.94, 97.52 and 96.33 % LA, respectively. For the statistical analysis, it was found that % LA of initial was significantly different from that of 1 month, 2 months, 3 months at room condition and heating-cooling condition (see detail in Appendix B).

Percent drug content of the preparation containing 6 % w/v HPTS after keeping in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 104.68, 101.38, 99.75, 99.10 and 100.24, respectively. For the statistical analysis, it was found that % LA of initial was significantly different from that of 1 month, 2 months, 3 months at room condition and heating-cooling condition (see detail in Appendix B).

The preparation containing 3 % w/v CHPTS after keeping in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 100.61, 99.27, 98.91, 98.58 and 98.81 % LA, respectively. For the statistical analysis, it was found that % LA of initial was significantly different from that of 1 month while those of initial preparation was significantly different from the storage

time of 2 months, 3 months at room condition and heating-cooling condition (see detail in Appendix B).

The preparation containing 4 % w/v CHPTS after keeping in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 100.27, 98.10, 97.81, 98.86 and 98.00 % LA, respectively. For the statistical analysis, it was found that % LA of initial was not significantly different from that of 1 month, 2 months, 3 months at room condition and heating-cooling condition (see detail in Appendix B).

Percent drug content of the preparation containing 4 % w/v UT after standing in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 100.73, 99.35, 99.59, 100.79 and 98.24, respectively. For the statistical analysis, it was found that %LA of initial was not significantly different from that of 1 month, 2 months, 3 months at room condition and heating-cooling condition (see detail in Appendix B).

The preparation containing 0.4%w/v of XG after standing in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 98.75, 101.25, 100.85, 100.08 and 99.58 % LA, respectively. For the statistical analysis, it was found that %LA of initial was not significantly different from that of 1 month, 2 months, 3 months at room condition and heating-cooling condition (see detail in Appendix B).

Percent drug content of the preparation containing 0.6 % w/v XG after standing in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 104.02, 102.14, 101.19, 101.17 and 99.51 % LA, respectively. For the statistical analysis, it was found that % LA of initial was significantly different from that of 1 month, 2 months, 3 months at room condition and heating-cooling condition (see detail in Appendix B).

The preparation containing 1 % w/v of TG after standing in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 99.40, 99.59, 98.01, 100.10 and 98.16 % LA, respectively. For the statistical analysis, it was found that %LA at of initial was significantly different from that of 2 months at room condition and heating-cooling condition (see detail in Appendix B).

The preparation containing 1.5 % w/v TG after standing in room temperature at initial, 1 month, 2 months, 3 months and heating-cooling condition were 102.59, 100.48, 100.73, 99.84 and 99.60 % LA, respectively. For the statistical

analysis, it was found that % LA of initial was not significantly different from that of 1 month, 2 months and 3 months at room condition but it was significantly different from heating-cooling condition (see detail in Appendix B).Through the % LA of these preparation at difference storage conditions were in accepted range of USP (90-110 % LA), but long term stability study should be performed. However, some modified tapioca starches were applicable as suspending agent.

Table 4-58 Percent drug content of ibuprofen suspension containing various suspending agents at different storage conditions.

Suspending agent	%	Drug content (% LA ± SD)				
		Room temperature condition				Heating-cooling condition
		Initial	1 month	2 months	3 months	
SCMS-2	3	100.70 (0.28)	99.59 (0.62)	96.74 (0.29)	97.98 (1.00)	99.44 (1.17)
PGTS	4	103.86 (3.06)	97.91 (0.85)	97.94 (1.45)	97.52 (0.31)	96.33 (0.54)
HPTS	6	104.68 (0.65)	101.38 (1.15)	99.75 (1.48)	99.10 (0.97)	100.24 (0.31)
CHPTS	3	100.61 (0.70)	99.27 (0.55)	98.91 (0.66)	98.58 (0.43)	98.81 (0.52)
	4	100.27 (0.60)	98.10 (1.02)	97.81 (0.14)	98.86 (1.17)	98.00 (1.40)
UT	4	100.73 (0.87)	99.35 (1.17)	99.59 (0.87)	100.79 (1.84)	98.24 (1.62)
XG	0.4	98.75 (0.80)	101.25 (0.47)	100.85 (0.34)	100.08 (1.30)	99.58 (1.37)
	0.6	104.02 (0.33)	102.14 (0.87)	101.19 (0.31)	101.17 (0.63)	99.51 (0.30)
TG	1	99.40 (0.33)	99.59 (0.15)	98.01 (0.27)	100.10 (0.53)	98.16 (0.31)
	1.5	102.59 (0.54)	100.48 (0.27)	100.73 (1.72)	99.84 (0.83)	99.60 (0.82)

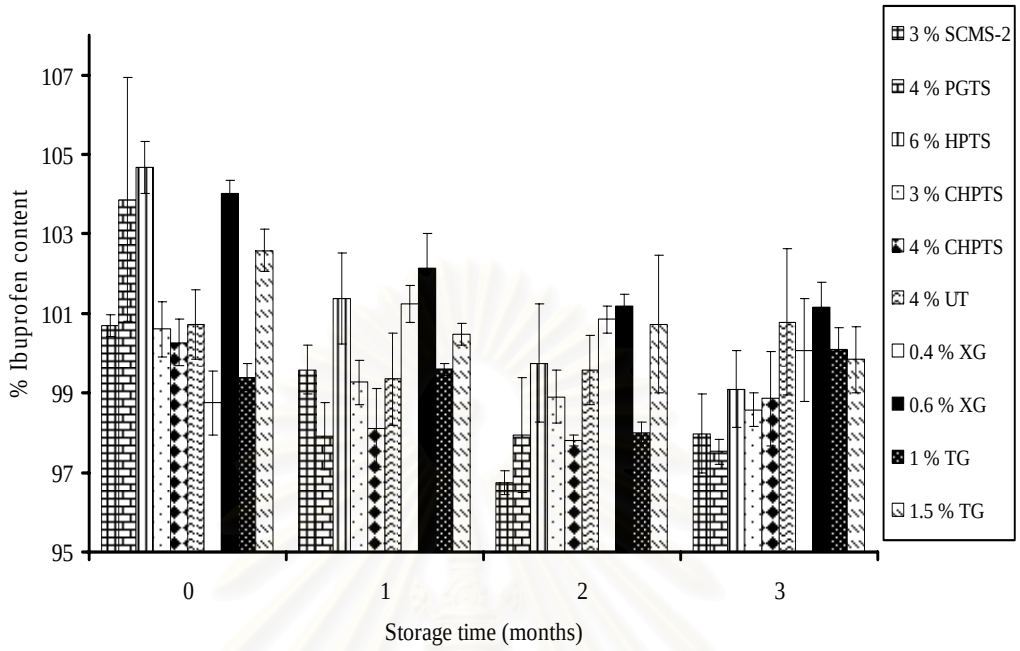


Figure 4-79 Percent drug content of ibuprofen suspension containing various suspending agents at different storage time of room conditions.

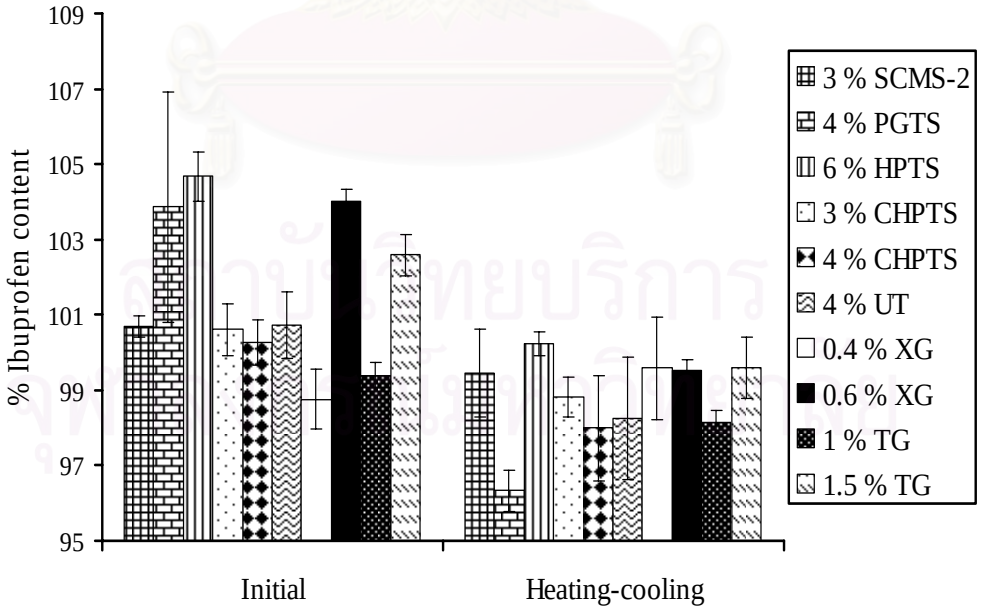


Figure 4-80 Percent drug content of ibuprofen suspension containing various suspending agents under heating-cooling conditions.

CHAPTER V

CONCLUSIONS

In this study, sodium carboxymethyl tapioca starch and cross-linked sodium carboxymethyl tapioca starch with different degree of substitution were prepared in the laboratory. Effect of electrolyte and type of buffer and pH on rheological behavior of these modified tapioca starches and other commercial modified tapioca starches such as pergelatinized tapioca starch, hydroxypropyl tapioca starch and cross-linked hydroxypropyl tapioca starch were investigated in comparing with other commercial suspending agents such as Ultrasperse2000®, xanthan gum and tragacanth. The suspending property of these modified tapioca starches as suspending agent in ibuprofen suspension preparations comparing with other commercial suspending agents was evaluated. The following conclusions can be drawn from the study;

1. The procedures according to Filter (1952) did not yield the modified starch with expected degree of substitution. In order to obtain the desired DS, we have modified the procedure for each DS in the following manner; Filbert's procedure for 0.23 and 0.34 was employed to prepare SCMS at DS 0.11 and 0.37. Filbert's procedure for preparation of SCMS at DS 0.34 was reduced the reaction time from 120 minutes to 20 minutes to have modified by reduction of SCMS at DS 0.22.The slight different DS was achieved from Filbert's, Suwannapakul's and this experiment. Since those method and condition of reaction might be slight change in the reaction conditions (e.g. time interval for adjust pH, the speed of agitation of stirrer in reaction) during modification processing. In addition, the ratio of amylose and amylopectin in the structure of each native starch affected on a position and amount of chemical agent in the etherification reaction. In the case of the high molecular weight starch, it was possible that the steric effect was occurred.

2. Degree of substitution of SCMS affected on the viscosity of those in solution. The SCMS with higher of DS provided the viscosity more than that of the lower DS because the carboxymethyl substitution caused starch hydrophilic and more soluble in cold water produced a high viscosity.

3. Degree of phosphate substitution of CSCMS affected on the viscosity of those in solution. The CSCMS with higher DS gave the viscosity less

than that of the lower DS because phosphate crosslinking caused the starch molecule to form network which decreased the swelling due to steric effect and more complex structure lattice. Moreover, the viscosity of CSCMS was higher than that of SCMS.

4. All modified tapioca starches and the other suspending agents in this experiment displayed a pseudoplastic type rheogram. At all concentrations of SCMS and CSCMS provided positive thixotropic values. The concentration of suspending agent affected on the thixotropic value such as PGTS, HPTS, UT and TG showed negative thixotropic values at high concentration (> 3 % w/v PGTS and HPTS, > 4 % w/v UT and > 2 % w/v TG). CHPTS expressed the positive thixotropic values at the concentration of 1-5 % w/v, 9 % w/v whereas it provided the negative thixotropic values at the concentration of 5.5-7 % w/v. XG gave the negative thixotropic value at low concentration (1% w/v) whereas it provided the positive thixotropic values at the concentration of 2-5 % w/v.

5. Increasing ionic strength affected extremely on decrease in the viscosity of SCMS and CSCMS but slightly affected on that of UT and TG. When ionic strength was increased, the viscosity of PGTS, HPTS and CHPTS were slightly increased. Moreover, increasing ionic strength affected significantly on an increase of viscosity of XG.

6. The viscosity of SCMS and CSCMS containing the buffers decreased obviously comparing with in the water. The main effect was the influence of ionic strength on the viscosity. The acid condition of phosphate buffer in the range of pH 3-5 was not significantly affected the viscosity of SCMS while in the basic condition the viscosity was decreased. In acid condition of citrate buffer in the range of pH 2-6, the viscosity was decreased when the pH decreased. The acid-base condition did not affected on the viscosity of CSCMS.

The acid-base condition of phosphate buffer did not significantly alter on the viscosity of PGTS, HPTS and CHPTS while in the citrate buffer the viscosity of them were increased when the pH decreased.

The acid condition of phosphate buffer did not affect on the viscosities of UT and TG but the viscosity was slightly increased in basic condition. The acid condition of citrate buffer caused a decrease in viscosity of UT when increased pH. The acid condition of citrate buffer increased the viscosity of TG when increased pH.

The acid condition of phosphate and citrate buffer did not affect on the viscosities of XG while the viscosity was slightly decreased in basic condition of phosphate buffer.

7. No effect of ionic strength on the flow pattern of SCMS, CSCMS, UT, PGTS and HPTS except CSCMS-16, CHPTS, XG and TG.

8. No acid-base effect of phosphate and citrate buffer on the flow pattern of SCMS-2, SCMS-3, CSCMS-2, CSCMS-8, HPTS, CHPTS and UT except SCMS-1, CSCMS-16, PGTS, XG and TG.

9. CSCMS was not selected as suspending agent in the preparation because it was sensitive to ionic strength, buffer and pH by losing the gel property. The suspension preparing from SCMS, PGTS and HPTS exhibited poor physical appearance, compacted sediment and was difficult to redisperse after storage at room temperature for 3 months and heating-cooling condition. The suspension containing 4%w/v of CHPTS was preferred preparation because it showed good physical appearance, no compacted sediment and good redispesibility. Moreover, 4%w/v of CHPTS gave the highest thixotropic value. So it was suitable as suspending agent in the preparation which was comparable to commercial suspending agents such as xanthan gum, tragacanth and Ultrasperse®2000.

10. Chemical stability of all preparations after storage at room temperature for 3 months and heating-cooling condition was acceptable in the range of USP.

The results have suggested the use of CHPTS as suspending agent and the application in pharmaceutical should be concerned. In addition, degree of cross-linked and the concentration of CHPTS would be varied to find more preferable suspending agent. In this experiment, preliminary physical study was only investigated. However, there were many factors that influenced the stability of suspension. So, in further study should be evaluated the crystallinity change, particle size, zeta potential, etc.

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Appendices

Appendix A

Determination of degree of substitution

(Method of calculation)

Sample from SCMS-3

Normality of NaOH VS. = 0.10025 N

Normality of HCl VS. = 0.10461 N

Average residue on ignition (C) = 13.1906

Sample 1

Weight of SCMS-3 = 0.4521 g

Volume of $NaOH_1$ (added first) = 12.00 ml

Volume of HCl used = 15.00 ml

Volume of $NaOH_2$ (for back titration) = 3.9 ml

$NaOH_2$ (=excess HCl) = 3.9*0.10025 = 0.3910 meq

HCl used (=total HCl-excess HCl) = (15*0.10461) - 0.3910 = 1.1782 meq

Excess $NaOH_1$ (react with HCl used) = 1.1782 meq

$NaOH_1$ used (=total $NaOH_1$-excess $NaOH_1$) = (12*0.10025) - 1.1782 = 0.0248 meq

meq of NaOH used to react with sample 0.4521 g = 0.0248 meq

meq of NaOH used to react with sample 1 g = 0.0248/0.4521 = 0.0549 meq (M)

Calculation of degree of acid carboxymethyl substitution (A)

$$A = \frac{1150M}{7{,}102 - 412M - 80C}$$

$$= \frac{1150M}{7{,}102 - (412*0.0549) - (80*13.1906)} = 0.0105$$

Calculation of sodium carboxymethyl substitution (S)

$$S = \frac{(162 + 58A)\,C}{7{,}102 - 80C}$$

$$= \frac{(162 + 58\,(0.0105))\,*\,13.1906}{7{,}102 - 80\,(13.1906)} = 0.3547$$

Calculation of degree of substitution (DS)

$$DS = A + S$$

$$= 0.0105 + 0.3547 = 0.3652$$

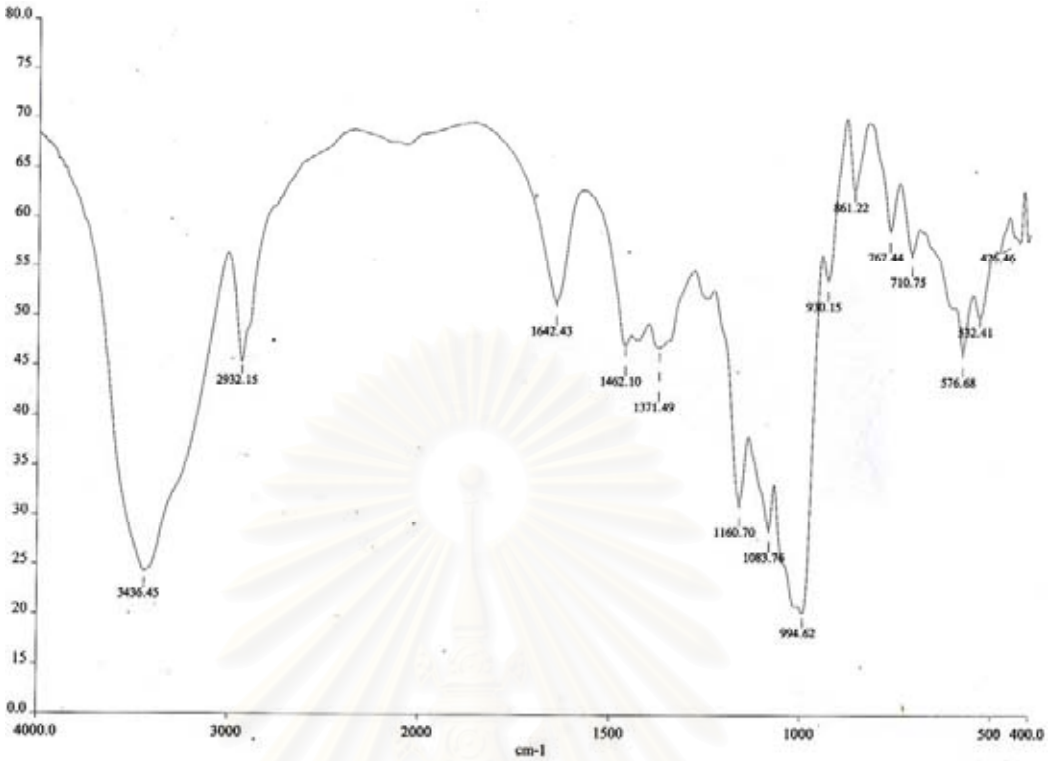


Figure 5-1 FTIR spectrum of native tapioca starch.

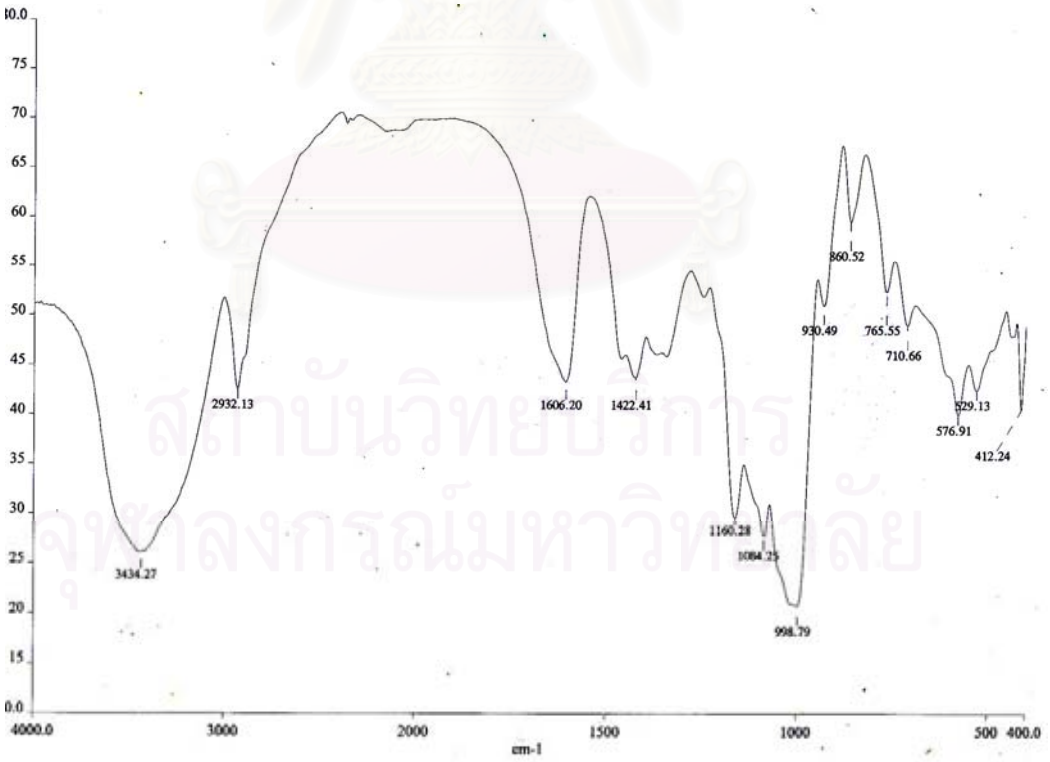


Figure 5-2 FTIR spectrum of SCMS-1.

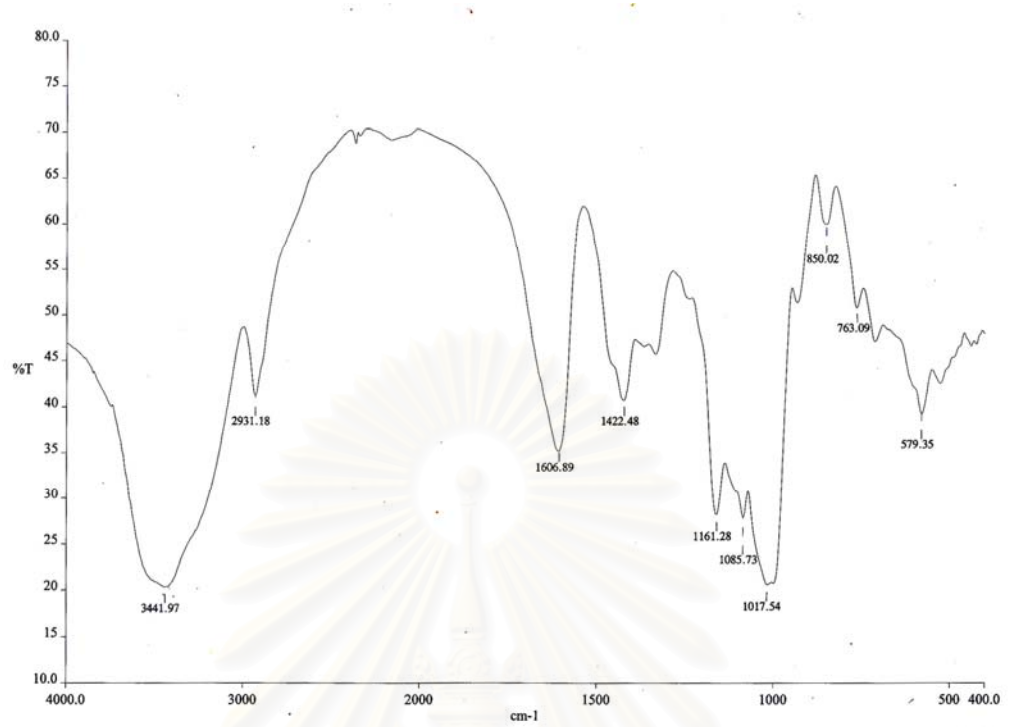


Figure 5-3 FTIR spectrum of SCMS-2.

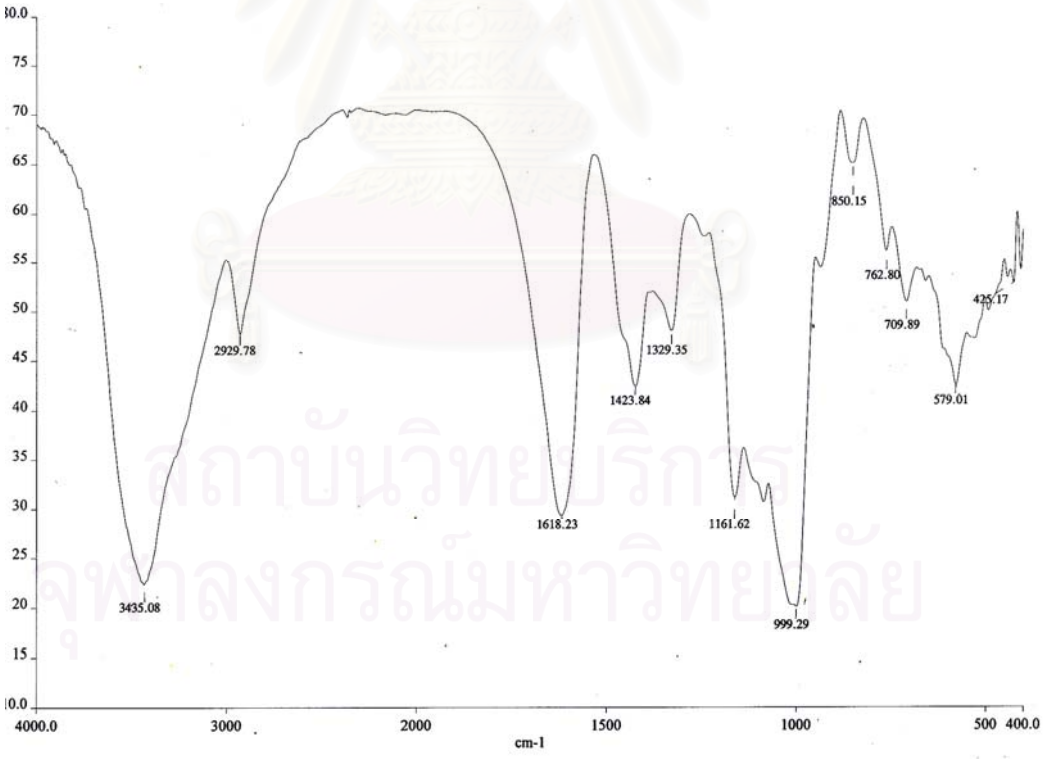


Figure 5-4 FTIR spectrum of SCMS-3.

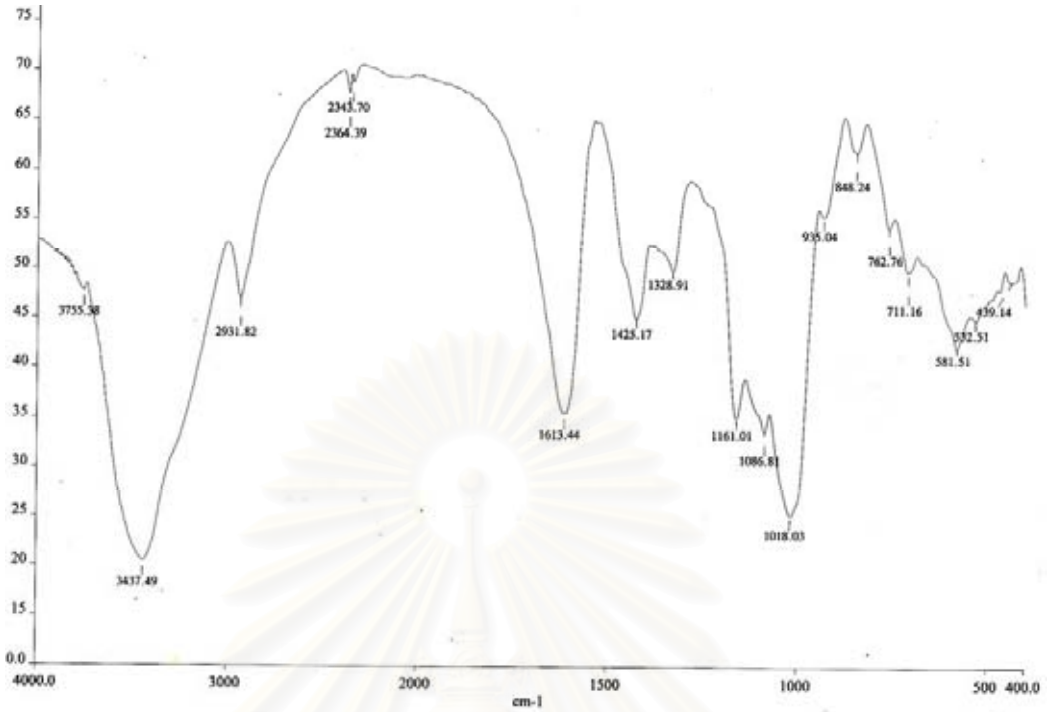


Figure 5-5 FTIR spectrum of CSCMS-2.

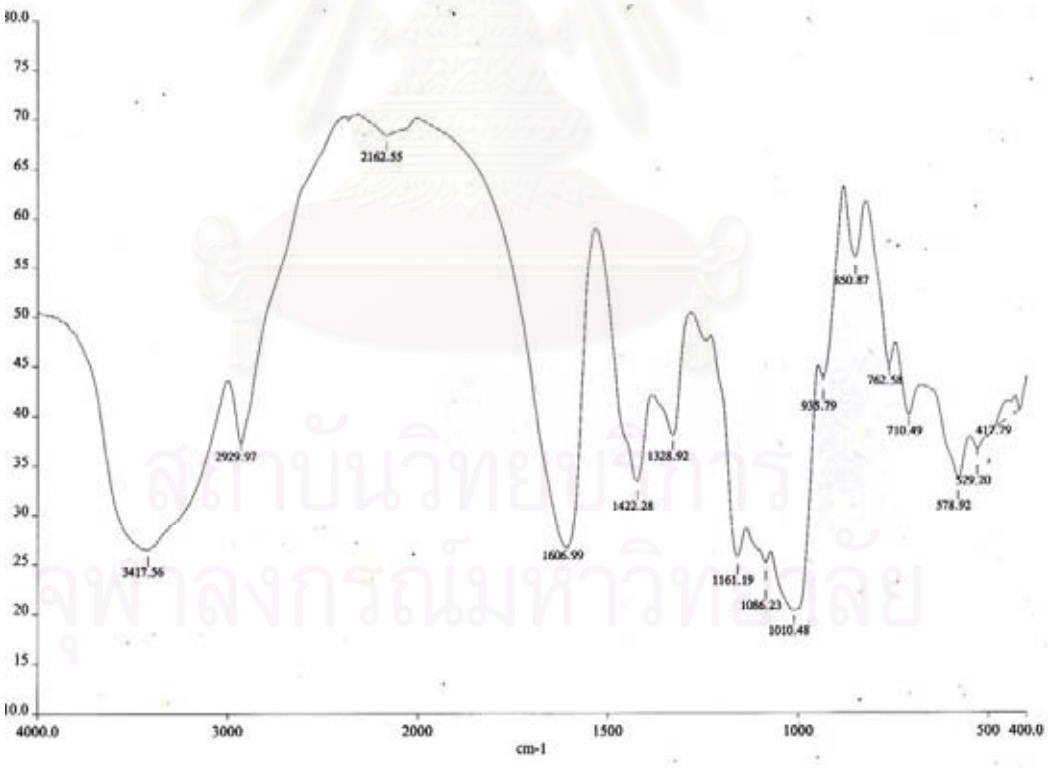


Figure 5-6 FTIR spectrum of CSCMS-8.

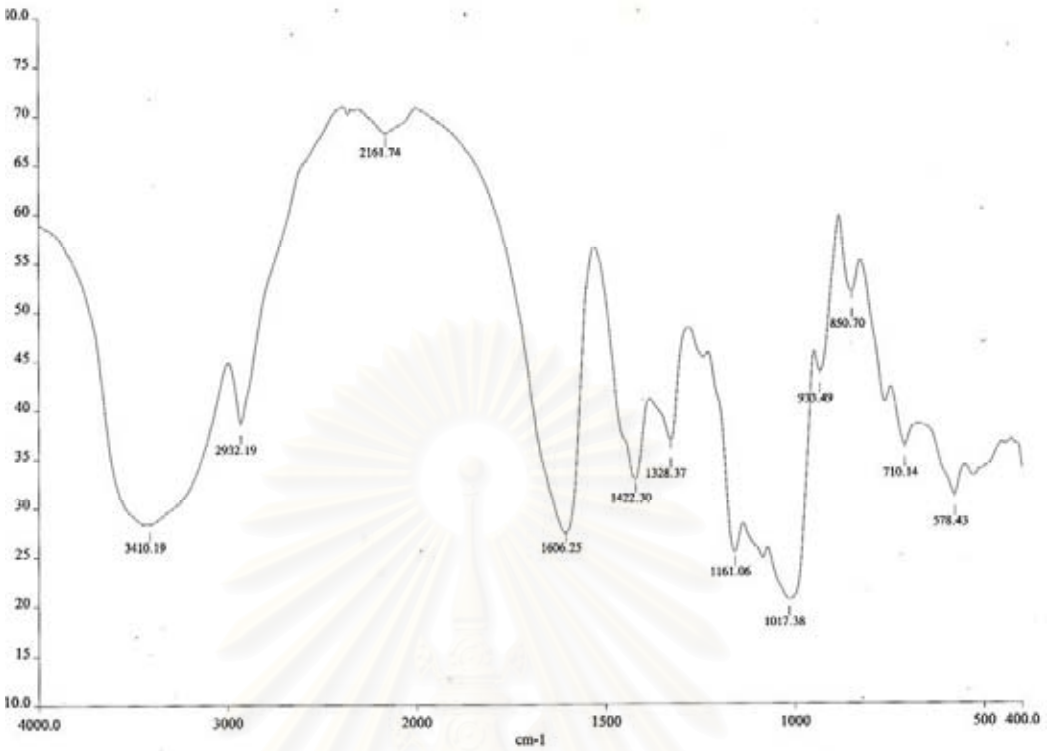


Figure 5-7 FTIR spectrum of CSCMS-16.

Table 5- 1 Absorbance of phosphorous standard solution at 460 nm.

Concentration (mg/100ml)	Absorbance
1	0.2190
2	0.4261
3	0.6436
4	0.8528
5	1.0529

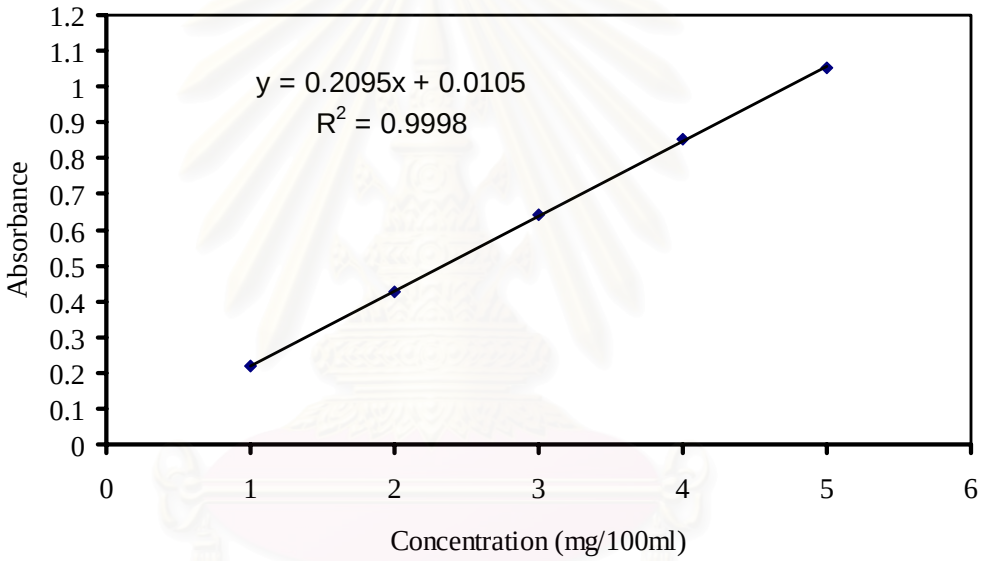


Figure 5-8 Standard curve of phosphorous solution at 460nm.

Appendix B

Table 5-2 ANOVA test of % drug content of 3 % w/v SCMS at different storage conditions.

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	28.509	4	7.127	12.241	.001
Within Groups	5.822	10	.582		
Total	34.331	14			

% drug content

Scheffe

time	N	Subset for alpha = .05		
		1	2	3
2 months	3	96.7416		
3 months	3	97.9815	97.9815	
freeze thaw	3		99.4409	99.4409
1 month	3		99.5898	99.5898
initial	3			100.6979
Sig.		.456	.233	.444

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5-3 ANOVA test of % drug content of 4 % w/v PGTS at different storage conditions.

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	104.575	4	26.144	10.385	.001
Within Groups	25.175	10	2.518		
Total	129.750	14			

% drug content

Scheffe

time	N	Subset for alpha = .05	
		1	2
freeze thaw	3	96.3312	
3 months	3	97.5241	
1 month	3	97.9136	
2 months	3	97.9434	
initial	3		103.8647
Sig.		.813	1.000

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5-4 ANOVA test of % drug content of 6 % w/v HPTS at different storage conditions.

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	58.230	4	14.558	14.639	.000
Within Groups	9.944	10	.994		
Total	68.174	14			

% drug content

Scheffe

time	N	Subset for alpha = .05	
		1	2
3 months	3	99.1013	
2 months	3	99.7501	
freeze thaw	3	100.2372	
1 month	3	101.3802	
initial	3		104.6770
Sig.		.177	1.000

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5- 5 ANOVA test of % drug content of 3 % w/v CHPTS at different storage conditions.

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	8.557	4	2.139	8.460	.003
Within Groups	2.529	10	.253		
Total	11.086	14			

% drug content

Scheffe

time	N	Subset for alpha = .05	
		1	2
3 months	3	98.5819	
freeze thaw	3	98.8109	
2 months	3	98.9088	
1 month	3	99.2657	99.2657
initial	3		100.6979
Sig.		.613	.070

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5-6 ANOVA test of % drug content of 4 % w/v CHPTS at different storage conditions.

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	12.335	4	3.084	3.235	.060
Within Groups	9.533	10	.953		
Total	21.868	14			

% drug content

Scheffe

time	N	Subset for alpha = .05
		1
2 months	3	97.8056
freeze thaw	3	97.9956
1 month	3	98.1018
3 months	3	98.8574
initial	3	100.2736
Sig.		.120

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5- 7 ANOVA test of % drug content of 4 % w/v UT at different storage conditions.

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	13.510	4	3.378	1.893	.188
Within Groups	17.840	10	1.784		
Total	31.350	14			

% drug content

Scheffe

time	N	Subset for alpha = .05
		1
freeze thaw	3	98.2440
1 month	3	99.3472
2 months	3	99.5875
initial	3	100.7315
3 months	3	100.7911
Sig.		.314

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5-8 ANOVA test of % drug content of 0.4 % w/v XG at different storage conditions.

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	10.059	4	2.515	2.429	.116
Within Groups	10.355	10	1.036		
Total	20.414	14			

% drug content

Scheffe

time	N	Subset for alpha = .05
		1
initial	3	98.7532
freeze thaw	3	99.5826
2 months	3	99.5875
3 months	3	100.0765
1 month	3	101.2494
Sig.		.135

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5-9 ANOVA test of % drug content of 0.6 % w/v XG at different storage conditions.

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	32.678	4	8.170	28.159	.000
Within Groups	2.901	10	.290		
Total	35.580	14			

% drug content

Scheffe

		Subset for alpha = .05		
time	N	1	2	3
freeze thaw	3	99.5077		
3 months	3		101.1656	
2 months	3		101.1878	
1 month	3		102.1395	
initial	3			104.0219
Sig.		1.000	.360	1.000

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5-10 ANOVA test of % drug content of 1 % w/v TG at different storage conditions

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	10.142	4	2.535	21.727	.000
Within Groups	1.167	10	.117		
Total	11.309	14			

% drug content

Scheffe

		Subset for alpha = .05	
time	N	1	2
2 months	3	98.0087	
freeze thaw	3	98.1630	
initial	3		99.3966
1 month	3		99.5932
3 months	3		100.0961
Sig.		.988	.256

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Table 5-11 ANOVA test of % drug content of 1.5 % w/v TG at different storage conditions

ANOVA

% drug content

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	16.701	4	4.175	4.462	.025
Within Groups	9.358	10	.936		
Total	26.059	14			

% drug content

Scheffe

		Subset for alpha = .05	
time	N	1	2
freeze thaw	3	99.5967	
3 months	3	99.8389	99.8389
1 month	3	100.4813	100.4813
2 months	3	100.7344	100.7344
initail	3		102.5901
Sig.		.724	.070

Means for groups in homogeneous subsets are displayed.
a Uses Harmonic Mean Sample Size = 3.000.

Appendix C

Validation of High Performance Liquid Chromatographic Technique for Drug Analysis

The HPLC method for the quantitative determination of ibuprofen was validated as follows:

1.1 Precision

The chromatogram of ibuprofen standard solution is shown in Figure 5-9. Internal standard (benzophenone) and Ibuprofen were eluted at 6.162 and 7.834 minutes, respectively.

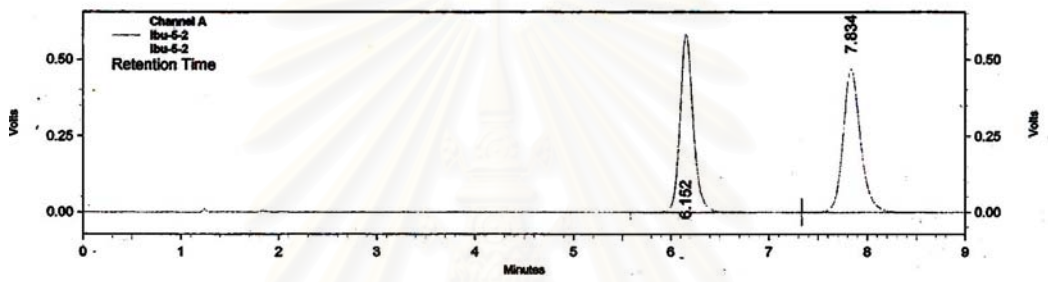


Figure 5-9 HPLC chromatograms of standard solution of ibuprofen.

The precision of the analysis of ibuprofen by HPLC method were determined for both within-run and between run as illustrated in Table 5-12 and Table 5-13, respectively. The percent coefficients of variation (% CV) of all determinations were ranging from 0.03-1.27 %. The accepted criteria of % CV are not more than 2%. It was indicated that HPLC method could be used to determine the amount of ibuprofen over the range of studies.

Table 5-12 Data of within-run precision of ibuprofen assayed by HPLC method.

Ibuprofen concentration (mg/ml)	Calculated concentration from calibration curve (mg/ml)	Mean	% CV
0.048	0.0479 0.0476 0.0477 0.0476 0.0477	0.0477	0.28
0.24	0.2352 0.2353 0.2351 0.2356 0.2354	0.2353	0.07
0.48	0.4857 0.4854 0.4858 0.4856 0.4855	0.4856	0.03
0.72	0.7239 0.7243 0.7237 0.7240 0.7243	0.7241	0.03
0.96	0.9556 0.9552 0.9551 0.9555 0.9555	0.9554	0.03

Table 5-13 Data of between-run precision of ibuprofen assayed by HPLC method.

Ibuprofen concentration (mg/ml)	Day	Calculated concentration from calibration curve (mg/ml)	Mean	% CV
0.048	1 2 3	0.0477 0.0481 0.0469	0.0476	1.27
0.24	1 2 3	0.2353 0.2384 0.2408	0.2382	1.16
0.48	1 2 3	0.4856 0.4842 0.4834	0.4844	0.23
0.72	1 2 3	0.7241 0.7159 0.7149	0.7183	0.70
0.96	1 2 3	0.9554 0.9613 0.9620	0.9596	0.38

1.2 Accuracy

The accuracy of the analysis of ibuprofen by HPLC method was performed by analyzing percent recoveries of five sets of 0.048, 0.24, 0.48, 0.72 and 0.96 mg/ml of actual ibuprofen solutions. The actual ibuprofen samples were prepared by dissolving of ibuprofen and cross-linked hydroxypropyl tapioca starch in the diluent that containing 50%v/v of acetonitrile and 50%v/v of water. Percent recovery of each concentration is showed in Table 5-14. The percent recovery was ranging from 98.05-101.43 %. The percent coefficient of variation of percent recoveries was 1.01 %. It was indicated that the HPLC method could be used to determine the amount of ibuprofen within the concentration range studied.

Table 5-14 The percentage of analytical recovery of ibuprofen assayed by HPLC method.

Actual concentration of ibuprofen (mg/ml)	Analytical concentration of ibuprofen (mg/ml)	% recovery
0.048	0.0474	98.67
	0.0471	98.05
	0.0475	98.88
	0.0473	98.46
	0.0472	98.26
0.24	0.2380	99.18
	0.2378	99.08
	0.2383	99.29
	0.2383	99.30
	0.2383	99.28
0.48	0.4866	101.37
	0.4864	101.34
	0.4866	101.38
	0.4869	101.43
	0.4868	101.41
0.72	0.7162	99.48
	0.7155	99.37
	0.7153	99.34
	0.7161	99.46
	0.7160	99.45
0.96	0.9602	100.02
	0.9586	99.85
	0.9591	99.91
	0.9589	99.89
	0.9589	99.89
	Mean	99.68
	SD	1.00
	% CV	1.01

1.3 Linearity

Table 5-15 shows the standard curve data of ibuprofen assayed by HPLC method. A standard curve plotted between the area and concentration in mg/ml is shown in Figure 5-10.

The linear regression analysis was applied for fitting the data obtained. The straight line was provided with a coefficient of determination (R^2) of 0.9999. The regression equation of the line is

$$y = 4.2639x + 0.0422$$

where y is the ratio of ibuprofen peak area and internal standard peak area and x is the concentration of ibuprofen solution in mg/ml.

Table 5-15 The standard curve data of ibuprofen assayed by HPLC method.

Ibuprofen concentration (mg/ml)	Peak area ratio of ibuprofen and internal standard	Mean	% CV
0.048	0.2470 0.2474 0.2470 0.2478 0.2478	0.2474	0.17
0.24	1.0579 1.0585 1.0592 1.0592 1.0590	1.0588	0.05
0.48	2.1063 2.1063 2.1066 2.1069 2.1071	2.1066	0.02
0.72	3.0977 3.0985 3.0933 3.0930 3.0916	3.0948	0.10
0.96	4.1410 4.1424 4.1412 4.1402 4.1416	4.1413	0.02

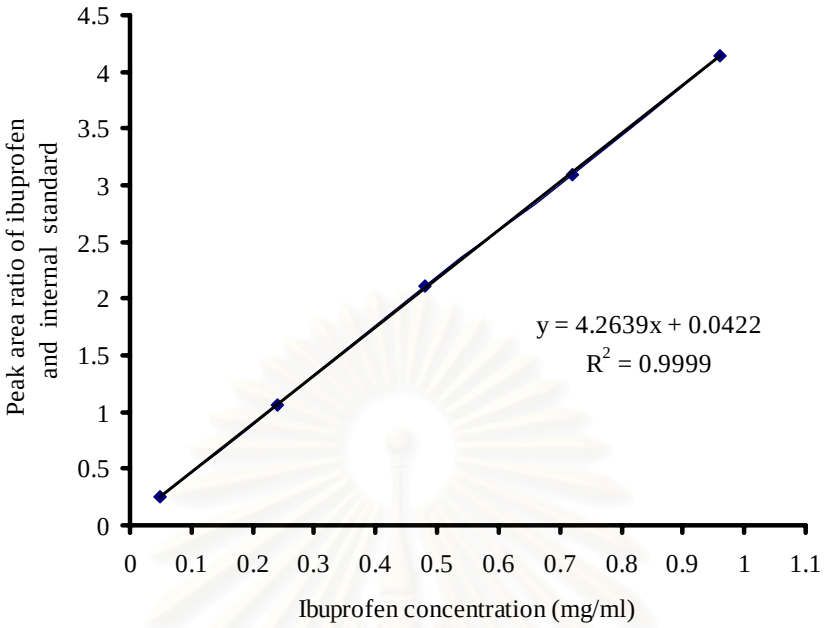
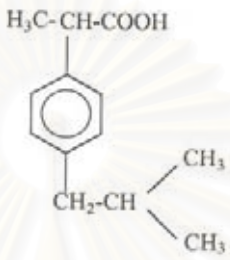


Figure 5-10 The standard curve of peak area ratio of ibuprofen and internal standard against concentration of ibuprofen.

Appendix D

Ibuprofen

Chemical Name	:	α-methl-4(2-methlllpropyl)-benzeneacetic acid 2-(4-Isobutylphenyl)propionic acid
Chemical Formula	:	$C_{13}H_{18}O_2$
Structural Formula	:	



CAS No.	:	15687-27-1
Molecular Weight	:	206.29
Description	:	white crystalline powder or colorless crystals
Solubility	:	practically insoluble in water soluble in 1.5 parts of ethanol and of acetone, 2 parts of Ether freely soluble in dichloroethane readily soluble in most organic solvents soluble in dilute solution of alkali hydroxides and carbonates
Melting Range	:	75-78° C
Dissociation Constant	:	pKa 5.3 pKa (ethanol 60%) 5.3
Stability	:	In the absence of oxygen, Ibuprofen was found to be stable, even at high temperatures (105-110° C) for at least four days.

ALBEMARLE CORPORATION
725 Cannon Bridge Road
Orangeburg, South Carolina (U.S.A.) 29115-1028

P.O. # 017/2005 S.O. # 519848

Certificate of Analysis
Ibuprofen, 20 Grade

Lot Number: 2050-0049D Container: 50 Kg. drums

USP Requirements	Units	Minimum	Maximum	Results
Identification				
a) Infrared Spectral Match		Pass		Pass
b) Ultraviolet Absorptivity Match	BP melting point replaces this UV test for identification purposes			
c) Assay Retention Time Match		Pass		Pass
Water	wt. %		1.0	0.0
Residue on Ignition	wt. %		0.5	0.0
y Metals	%		0.002	<0.001
...matographic Purity, Total Impurities	%		1.0	0.1
Single Largest Impurity	%		0.5	0.1
"Other Impurities": Total	%		0.4	0.0
4,4'-Dihydroxyhexanoic acid	%		0.2	0.0
Any Other Impurity	%		0.1	0.0
Total Impurities: USP/EP + all "Others"	%		1.0	0.1
Organic Volatile Impurities				Meets requirements
Assay	wt. % Ibuprofen	97.0	103.0	100.1
4-isobutylacetophenone (IBAP)	wt. % IBAP		0.1	0.0

BP/EP Requirements	Units	Minimum	Maximum	Results
Identification				
a) Melting Point	Degrees Celsius	75	78	76
b) Ultraviolet Test	not required when tests a) and c) performed			
c) Infrared Spectral Match		Pass		Pass
d) Thin Layer Chromatography Test	not required when tests a) and c) performed			
Appearance of Solution				
Clarity		Pass		Pass
Color		Pass		Pass
Optical Rotation	Degrees	-0.05	0.05	0.00
Related Substances, Total Impurities	%		1.0	0.1
Single Largest Impurity	%		0.5	0.1
2-(4-hydroxyphenyl)propionic acid	%		0.5	0.0
Heavy Metals	ppm		10	<10
Loss on Drying	wt. %		0.5	0.0
Sulfated Ash	wt. %		0.1	0.0
Assay	wt. %	98.5	101.0	99.4
Residual Solvents (as hexane)	ppm		100	29

Other Requirements	Units	Minimum	Maximum	Results
Bulk Density				
Before pack	g/mL	0.15	0.35	0.24
After pack	g/mL	0.37	0.49	0.44
Particle Size, median	microns	17	27	26

Date of Manufacture: December 22, 2004 Retest Date: Four Years from Date of Manufacture Albemarle AP General

Quality Assurance: B Wayne Haigler COA Issue Date: March 15, 2005

Xanthan Gum

Chemical Name	:	Xanthan gum
CAS Registry Number	:	11138-66-2
Empirical Formula	:	Each xanthan gum repeat unit contains five sugar residues: two glucose; two mannose and one glucuronic acid. The polymer backbone consists of four β-D-glucose units linked at the 1 and 4 positions, and is therefore identical in structure to cellulose
Molecular Weight	:	2×10^6
Appearance	:	a cream or white-colored, odorless, free-flowing, fine powder
Solubility	:	soluble in cold or warm water Practically insoluble in ethanol and ether
Specific gravity	:	1.600 at 25 °C
Stability	:	Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3-12) and temperature between 10-60° C.
Incompattibility	:	Xanthan gum is an anionic material and is not usually compatible with cationic surfactant, polymers and preservatives since precipitation occurs.

Tragacanth

Chemical name	:	Tragacanth gum
CAS Registry Number	:	9000-65-1
Molecular weight	:	~840,000
Appearance	:	flattened, lamellated, frequently curved fragments or straight or spirally twisted linear pieces from 0.5-2.5 mm in thickness; it may also be obtained in a powder form. White to yellowish in color, tragacanth is a translucent, odorless substance, with an insipid mucilaginous taste.
Solubility	:	practically insoluble in water, 95% ethanol and other organic solvents. Although insoluble in water, tragacanth gum swells rapidly in 10 times its own weight of cold water to produce viscous colloidal sols or semi-gels.
Specific gravity	:	1.250-1.385
Stability	:	Flanked and powdered forms of tragacanth are stable. Tragacanth gels are luable to microbial contamination with enterobacterial species, stock solutions should contain suitable antimicrobial preservatives. Tragacanth dispersions are most stable at pH 4-8 although stability is satisfactory at low pH. For this reason, it is often chosen as the thickener for low pH food products such as salad dressings and sauces.
Incompatibility	:	At pH7, tragacanth reduces the efficacy of the antimicrobial preservatives benzalkonium chloride, chlorobutanol and methylparaben, and to the leeser extent phenol and phenylmercuric acetate. At pH ⟨5, tragacanth has no adverse effects on the preservative efficacy of benzoic acid, chlorobutanol or methlparaben. The addition of strong mineral and organic acids can reduce the viscosity of tragacanth dispersions.

บริษัท กรุงเทพสตาช อินดัสเทรียล จำกัด
BANGKOK STARCH INDUSTRIAL CO., LTD.

24 GP 14 PETCHKASEM ROAD, RAIKING, SAMPHRAN, NAKORNPRATHOM 73210, THAILAND
Tel: (66) 02-811-5015~9 Fax: (66) 02- 811-5601~2 e-mail: info@bkkstarch.com

GENERAL SPECIFICATION

" THAI FLOWER BRAND "

PREGEL HYDROXYPROPYLATED TAPIOCA STARCH

SPECIFICATION	RANGE
APPEARANCE	FINE WHITE POWDER
WHITENESS	80 (MIN.)
MOISTURE CONTENT	8.0 % (MAX.)
pH VALUE (3% SUSPENSION)	6.00 - 8.50
VISCOSITY (5% WET BASE)	200 B.U.(MIN)
ASH	0.50 % (MAX.)
PARTICLE SIZE (PASS 48 MESH)	98.0 % PASS
MICROBIOLOGY	
TOTAL PLATE COUNT/G	1×10^3 COL./G
YEAST AND MOLD/G	1×10^2 COL./G
E.coli/G	NEGATIVE

STORAGE CONDITION :

1. PLEASE KEEP IN A CLEAN AND DRY AREA AT AMBIENT TEMPERATURE.
2. PLEASE KEEP AWAY FROM MOISTURE AND HEAVILY AROMATIC MATERIAL.

ISSUE DATE:2006/MAR/21
PREPARED AND APPROVED BY
BANGKOK STARCH LABORATORY

BANGKOK STARCH INDUSTRIAL CO., LTD.

24 GP 14 PETCHKASEM ROAD, RAIKING, SAMPHRAN, NAKORNPRATHOM 73210, THAILAND

Tel: (66) 02-811-5015~9 Fax: (66) 02- 811-5601~2 e-mail: info@bkkstarch.com

GENERAL SPECIFICATION

" THAI FLOWER BRAND "

PREGEL CROSSLINKED HYDROXYPROPYLATED TAPIOCA STARCH

SPECIFICATION	RANGE
APPEARANCE	FINE WHITE POWDER
WHITENESS	80 (MIN.)
MOISTURE CONTENT	8.0 % (MAX.)
pH VALUE (3% SUSPENSION)	6.00 - 8.50
VISCOSITY (5% WET BASE)	100 - 300 B.U.
ASH	0.50 % (MAX.)
PARTICLE SIZE (PASS 60 MESH)	90.0 % PASS
MICROBIOLOGY	
TOTAL PLATE COUNT/G	1 X 10 ^{5} COL/G
YEAST AND MOLD/G	1 X 10 ^{2} COL/G
COLIFORMS/G	NEGATIVE
E.coli/G	NEGATIVE

STORAGE CONDITION :

1. PLEASE KEEP IN A CLEAN AND DRY AREA AT AMBIENT TEMPERATURE.
2. PLEASE KEEP AWAY FROM MOISTURE AND HEAVILY AROMATIC MATERIAL.

ISSUE DATE : 15-Sep-2005

PREPARED AND APPROVED BY

BANGKOK STARCH LABORATORY

National Starch
FOOD INNOVATION

TECHNICAL SERVICE BULLETIN

ULTRA-SPERSE® 2000

ULTRA-SPERSE 2000 is a high performance, cold water swelling modified food starch derived from waxy maize. It is particularly well suited for instant food preparations where high viscosity and creamy mouthfeel are desired. It exhibits excellent dispersibility and imparts superior sheen and smoothness when compared to traditional pregelatinized starches.

Physical Properties:

Color	White to off-white
Form	Free-flowing coarse powder
Moisture	Approximately 8%
pH	Approximately 6

Features and Benefits:

ULTRA-SPERSE 2000 disperses easily in hot or cold water without lumping and yields a heavy bodied, short texture with excellent sheen. The procuct is well suited for mild to moderate processing conditions, yielding rapid, high viscosity development.

Applications:

ULTRA-SPERSE 2000 is recommended for many instant food applications where excellent dispersibility, high viscosity and rich mouthfeel are required. ULTRA-SPERSE 2000 is ideally suited for instant cream style soups, cheese sauces, and savory gravies that are to be microwave reconstituted or kept on a steam table for long periods of time.

Since ULTRA-SPERSE 2000 is particularly resistant to heating, it is also recommended for use in turnover fillings, etc., to retard boilout during cooking.

ULTRA-SPERSE 2000 is strongly recommended when an instant thickener with excellent dispersibility is required. Additionally, it delivers rapid high viscosity and premium cook-up textural characteristics.

Label Declaration:

"Food Starch-Modified"

National Starch and Chemical Company · 10 Finderne Avenue, Bridgewater, NJ 08807 · 908-685-5000 · www.foodinnovation.com

National Starch
FOOD INNOVATION

*** MATERIAL SAFETY DATA SHEET ***

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NUMBER	59-3118
PRODUCT NAME	ULTRA-SPERSE ® 2000 modified food starch
Manufacturer	National Starch & Chemical Company P.O. Box 6500, 10 Finderne Avenue Bridgewater, NJ 08807 USA
	EMERGENCY PHONES: MEDICAL: 866-359-5657 (Health & Safety Call Center-24 hours) TRANSPORT: CHEMTREC: 800-424-9300 (24 hours) CHEMTREC International: 703-527-3887 (call collect) Corporate Emergency Phone: 908-685-5100 (24 hours) MSDS Requests/Customer Service: See phone numbers in Section 16

2. COMPOSITION/INFORMATION ON INGREDIENTS

CHEMICAL FAMILY	Modified Starch		
COMPONENT		CAS NUMBER	CONCENTRATION, (% by weight)

None classified as hazardous under the OSHA Hazard Communication Standard (29CFR 1910.1200).

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

Possible physical irritant from dust particles. Potential for dust explosion.
White Powder. Starch odor

EYE	Particulates may scratch eye surfaces and cause mechanical irritation.
SKIN CONTACT	Low order of toxicity.
INHALATION	This product can produce a nuisance dust which should be maintained below a time weighted average of 10 mg/m3.
INGESTION	Low oral toxicity.

4. FIRST-AID MEASURES

EYE	Remove particles by irrigating with eye wash solution or clean water, holding the eyelids apart. If symptoms develop, obtain medical attention.
SKIN CONTACT	Wash skin with soap and water.
INHALATION	Remove to fresh air. Get medical attention if irritation persists.
INGESTION	None required.

5. FIREFIGHTING MEASURES

AUTOIGNITION	Not available
FLASH POINT	Not applicable
EXTINGUISHING MEDIA	Dry Chemical; CO_2; Water Fog; Foam
SPECIAL FIREFIGHTING PROCEDURES	No special procedures are required.
FIRE & EXPLOSION HAZARDS	Minimum ignition temperature of dust cloud- approx. 390 C. Minimum explosive concentration- approx. 62 mg/l. Minimum energy to ignite cloud by electrical spark- approx. 0.045 joules.
HAZARDOUS COMBUSTION PRODUCTS	This product does not undergo spontaneous decomposition. Typical combustion products are carbon monoxide, carbon dioxide, nitrogen and water.
LOWER EXPLOSION LIMIT (%)	Not applicable
UPPER EXPLOSION LIMIT (%)	Not applicable

6. ACCIDENTAL RELEASE MEASURES

SPILL AND LEAK PROCEDURES	Normal precautions for "nuisance dust" should be observed. Avoid prolonged inhalation of dust. Sweep up or vacuum up and place in suitable container for disposal.

For safety and environmental precautions, please review entire Material Safety Data Sheet for necessary information.

7. HANDLING AND STORAGE

STORAGE TEMPERATURE	Ambient.
SENSITIVITY TO STATIC ELECTRICITY	Yes
SENSITIVITY TO MECHANICAL IMPACT	No
OTHER PRECAUTIONS	Use care to minimize dust generation in normal use conditions. Avoid dispersing the powder in the air. Prevent buildup of powder on surfaces.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

	ACGIH	OSHA	Mfg Working Standard

VENTILATION REQUIREMENTS	General.
EYE PROTECTION REQUIREMENTS	Safety glasses recommended.
GLOVE REQUIREMENTS	Gloves are not normally required for foreseable conditions of use.
CLOTHING REQUIREMENTS	Not applicable.
CHANGE/REMOVAL OF CLOTHING	Not normally required.
WASH REQUIREMENTS	Wash before eating, drinking, or using toilet facilities.
RESPIRATOR REQUIREMENTS	NIOSH approved dust mask.

9. PHYSICAL AND CHEMICAL PROPERTIES

PURE SUBSTANCE OR MIXTURE	Pure
PHYSICAL FORM	Powder.
COLOR	White
ODOR	Starch
ODOR THRESHOLD	Not available
MOLECULAR WEIGHT	> 10000
PH AS IS	Not applicable
pH IN (1%) SOLUTION	Approximately 6
OXIDIZING PROPERTIES	Not applicable
BOILING POINT	Not applicable
MELTING/FREEZING POINT	Not applicable
SOLUBILITY IN WATER	Soluble
PARTITION COEFFICIENT (n-octanol/water)	Not applicable
VISCOSITY	Not applicable
SPECIFIC GRAVITY (WATER=1)	1.5
BULK DENSITY	Not available
EVAPORATION RATE	Not applicable
VAPOR PRESSURE (mmHg)	Not applicable
VAPOR DENSITY (air = 1)	Not applicable
VOLATILES	None
VOLATILE ORGANIC COMPOUNDS	Not applicable
AUTOIGNITION	Not available
FLASH POINT	Not applicable

10. STABILITY AND REACTIVITY

STABILITY	Stable
HAZARDOUS DECOMPOSITION PRODUCTS	This product does not undergo spontaneous decomposition. Typical combustion products are carbon monoxide, carbon dioxide, nitrogen and water.

11. TOXICOLOGICAL INFORMATION

ROUTE OF ENTRY		Eye Contact; Skin Contact; Inhalation; Ingestion	
CARCINOGEN	IARC (group)	NTP	OSHA Substance Specific Regulation

PRODUCT NUMBER 50-3118 Print date: 08-April-2005

COMPONENT

There is no evidence that this product poses a carcinogenic risk under normal conditions of handling and use.

CHRONIC (LONG TERM) EFFECTS OF EXPOSURE

EFFECTS OF CHRONIC EXPOSURE	This product is considered as being non-toxic. Use of good industrial hygiene practices is recommended.
TARGET ORGANS	Not applicable.

12. ECOLOGICAL INFORMATION

POTENTIAL TO BIOACCUMULATE	Unknown.
AQUATIC TOXICITY	None Established

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHODS	Disposal should be in accordance with local, state or national legislation.
EMPTY CONTAINER WARNINGS	Empty containers may contain product residue; follow MSDS and label warnings even after they have been emptied.

14. TRANSPORTATION INFORMATION

This section provided for general information only.
FOR NON-BULK SHIPMENTS.

VITA

Parinya Tharnbupphar was born in Bangkok, Thailand, on September 23, 1974. She received the degree of Bachelor of Science in Pharmacy in 1997 from the faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand.