การประเมินคุณสมบัติทางการไหลของมวลเปียกที่ไม่มีไมโครคริสตัลลีนเซลลูโลสสำหรับการเตรียมเพลเลตโดยกระบวนการเอ็กซ์ทรูชันและสเฟียโรไนเซชัน

นางสาวเยาวเรศ จีระเรืองรัตนา

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาเภสัชอุตสาหกรรม
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2549

EVALUATION OF RHEOLOGICAL PROPERTIES OF WET MASS WITHOUT MICROCRYSTALLINE CELLULOSE FOR PREPARATION OF PELLETS BY EXTRUSION/SPHERONIZATION PROCESS

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy Program in Industrial Pharmacy
Department of Manufacturing Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Academic Year 2006

Thesis Title	EVALUATION OF RHEOLOGICAL PROPERTIES OF WET MASS WITHOUT MICROCRYSTALLINE CELLULOSE FOR PREPARATION OF PELLETS BY EXTRUSION/SPHERONIZATION PROCESS
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เยาวเรศ จีระเรืองรัตนา : การประเมินคุณสมบัติการไหลของมวลเปียกที่ไม่มีไมโครคริสตัลลีนเซลลูโลสสำหรับการเตรียมเพลเลตโดยกระบวนการเอ็กซ์ทรูชันและสเฟียโรไนเซชัน. (EVALUATION OF RHEOLOGICAL PROPERTIES OF WET MASS WITHOUT MICROCRYSTALLINE CELLULOSE FOR PREPARATION OF PELLETS BY EXTRUSION/SPHERONIZATION PROCESS) อ.ที่ปรึกษา : อ.ดร.จิตติมา ชัชวาลย์สายสินธ์ 213 หน้า.

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาสูตรตำรับเพลเลตที่ไม่มีไมโครคริสตัลลีนเซลลูโลส ซึ่งเตรียมโดยกระบวนการเอ็กซ์ทรูชันและสเฟียโรไนเซชัน และศึกษาคุณสมบัติการไหลของมวลเปียกที่ใช้เตรียมเพลเลต สูตรตำรับเพลเลตที่ทำการศึกษาประกอบด้วย สารช่วยในการเตรียมเพลเลต ได้แก่ โซเดียมคาร์บอกซีเมทิลเซลลูโลส (NaCMC 1180) เมทิลเซลลูโลส (Methocel®A-15) ไฮดรอกซีเอทิลเซลลูโลส (HEC 4000) ไฮดรอกซีโพรพิลเซลลูโลส ชนิดหมู่แทนที่ต่ำ (HPC-L®) ไฮดรอกซีโพรพิลเมทิลเซลลูโลส (Methocel®E15 LV) ปริมาณ 0.25-2.0 % โดยน้ำหนัก สารตันแบบได้แก่ แล็กโทส ไดเบสิกแคลเซียมฟอสเฟต โพรพราโนลอลไฮโดรคลอไรด์ หรือไอบูโพรเฟน และของเหลวยึดเกาะ ได้แก่ น้ำ หรือ 50% เอทานอล และศึกษาคุณสมบัติการไหลของมวลเปียกโดยใช้เครื่องรีโอมิเตอร์ที่สามารถให้แรงกระทำที่คงที่แก่วัสดุที่ต้องการทดสอบ (controlled stress rheometer) ทดสอบค่า instantaneous compliance (J_0) storage modulus (G') loss modulus (G'') และ loss tangent ($\tan \delta$)

ผลการศึกษา พบว่า เพลเลตของแล็กโทสสามารถเตรียมได้โดยใช้สารช่วย คือ โซเดียมคาร์บอกซีเมทิลเซลลูโลส เมทิลเซลลูโลส หรือ ไฮดรอกซีโพรพิลเมทิลเซลลูโลส ปริมาณ 0.5-1.0% โดยน้ำหนัก เพลเลตของโพรพราโนลอลไฮโดรคลอไรด์สามารถเตรียมได้โดยใช้เมทิลเซลลูโลส ปริมาณ 1.0-2.0% โดยน้ำหนัก และเพลเลตของไอบูโพรเฟน สามารถเตรียมได้โดยใช้เมทิลเซลลูโลส 4.0-8.0% โดยน้ำหนัก สำหรับเพลเลตไดเบสิกแคลเซียมฟอสเฟตนั้นไม่สามารถเตรียมได้ เนื่องจากต้องแรงดันสูงมากเพื่อจะอัดมวลเปียก นอกจากนี้พบว่า คุณสมบัติทางการไหลที่เหมาะสมของมวลเปียกที่สามารถเตรียมเพลเลตได้มีค่า loss tangent อยู่ในช่วง 0.07-0.49 เมื่อใช้น้ำหรือ 50% เอทานอล เป็นของเหลวยึดเกาะ ซึ่งคุณสมบัติการไหลของมวลเปียกจะเปลี่ยนแปลงไปตามตัวแปรของสูตรตำรับ ได้แก่ ชนิดและปริมาณของสารช่วย สารตันแบบ และของเหลวยึดเกาะ สูตรตำรับเพลเลตที่ได้จากการศึกษาครั้งนี้อาจนำมาประยุกต์ใช้ในการเตรียมเพลเลตยาที่เข้ากันไม่ได้กับไมโครคริสตัลลีนเซลลูโลส และ/หรือสลายตัวง่ายเมื่อมีความชื้นสูง และเพลเลตที่มีปริมาณตัวยามากในตำรับ การประเมินคุณสมบัติทางการไหลโดยใช้เครื่องรีโอมิเตอร์ที่สามารถให้แรงกระทำที่คงที่แก่วัสดุที่ต้องการทดสอบอาจมีประโยชน์ในการควบคุมคุณภาพของมวลเปียกเพื่อผลิตเพลเลตโดยกระบวนการเอ็กซ์ทรูชันและสเฟียโรไนเซชัน

ภาควิชา เภสัชอุตสาหกรรม ลายมือชื่อนิสิต เยาวเรศ จีระเรืองรัตนา
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ปีการศึกษา 2549

4676587333 : MAJOR MANUFACTURING PHARMACY
KEY WORD: RHEOLOGY/ WET MASS / PELLETS/ EXTRUSION-SPHERONIZATION/

YOWWARES JEERARAUNGRATTANA : EVALUATION OF RHEOLOGICAL PROPERTIES OF WET MASS WITHOUT MICROCRYSTALLINE CELLULOSE FOR PREPARATION OF PELLETS BY EXTRUSION/SPHERONIZATION PROCESS THESIS ADVISOR : JITTIMA CHATCHAWALSAISIN, Ph.D.213 pp.

The objectives of this study were to study pellet formulation containing no microcrystalline cellulose (MCC) prepared by extrusion-spheronization process and to study the rheological properties of wet mass for preparation of the pellets. The pellet formulations composed of 0.25-2.0% w/w of the formulation aids, i.e. sodium carboxymethyl cellulose (NaCMC 1180), methylcellulose (Methocel®A-15 (MC 15)), hydroxyethyl cellulose (HEC 4000), hydroxypropyl cellulose low-substituted (HPC-L®(HPC-L)) or hydroxypropyl methylcellulose (Methocel®E15 LV (HPMC E15)); model substances, i.e. lactose, dibasic calcium phosphate ($CaHPO_4$), propranolol hydrochloride or ibuprofen; and liquid binders, i.e. water or 50% w/w ethanol. The rheological properties, in terms of the instantaneous compliance (J_0), storage modulus (G′), loss modulus (G″) and loss tangent (tan δ) of the wet mass were measured using a controlled stress rheometer.

The results showed that lactose pellets could be prepared with 0.5-1.0%w/w of NaCMC1180, MC 15 or HPMC E15. Propranolol hydrochloride pellets could be prepared with 1.0-2.0% w/w MC 15, while ibuprofen pellets could be prepared with 4.0-8.0% w/w MC 15. It was not possible to prepare $CaHPO_4$ pellets because too high pressure was required for extruding the wet mass. There appeared to be an optimum rheological property of the wet mass that could produce lactose pellets. The tan δ values of 0.07-0.49 were required for the wet mass granulated with either water or 50% ethanol in order to obtain the pellets. The rheological properties of the wet mass, however, were varied with the formulation variables, i.e. type and amount of the formulation aids, model substances and liquid binders. The formulation in this study may be applied for drugs which are incompatible with MCC and/or are degraded when exposed to high level of moisture as well as for pellets with high-drug loading. The approach of evaluation of rheological properties by the controlled stress rheometer may be useful in quality control of the wet mass for pellets preparation by extrusion-spheronization process.

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Field of study Industrial pharmacy Advisor's signature J. Chatchawalsaisin
Academic year 2006

ACKNOWLEDGEMENTS

I would like to express my grateful and thankfulness to my thesis advisor, Jittima Chatchawalsaisin, Ph.D. for her invaluable attention, guidance, encouragement and support throughout this research. Her generosity and helpfulness are really appreciated.

I am most grateful to Metrohm Siam Ltd. for supporting Rheometer to me. I wish to thank for all staff in Metrohm Siam Ltd., especially, Mr. Passakorn Woonwiriyakit, whom I am very grateful for his guidance and discussion.

A special appreciation is also given to Graduate school, Chulalongkorn University for granting partial support to fulfill this investigation and being the place for learning, participating activities, which is one of the valuable experience in my life.

My special thank is send to all staff and members in the department of Manufacturing Pharmacy and all of my friends in Master's degree for their encouragement and assistance.

Finally, I would like to express my tremendous gratitude to my family for their love and encouragement given to me.

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LIST OF ABBREVIATIONS

α	angle of repose
°	degree
°C	degree celsius (centrigrade)
$CaHPO_4$	dibasic calcium phosphate
cps	centipoises
CR	controlled rate or controlled strain
CS	controlled stress
DS	degree of substitution
δ	phase-lag
g	gram
G*	complex modulus
G′	storage or elastic modulus
G″	loss or viscous modulus
G_0	instantaneous elastic modulus
HEC 4000	hydroxyethylcellulose 4000 cp.
HPC-L	hydroxypropyl cellulose low substituted
HPMC E15	hydroxypropyl methylcellulose 15 cp.
Hz	hertz
IQR	interquartile range
J	compliance
LOD	loss on drying
LVE	linear viscoelasticity
MC15	methylcellulose 15 cp.

MCC	microcrystalline cellulose grade Avicel PH 101
μm.	micrometer
mg	milligram
ml	milliter
Mm	millimeter
mNm	milinewton
NaCMC1180	sodium carboxymethylcellulose grade 1180
NaOH	sodium hydroxide
η	viscosity
ω	frequency
Pa	pascal
pH	the negative logarithm of the hydrogen ion concentration
% v/v	percentage volume by volume
% w/v	percentage weight by volume
% w/w	percentage weight by weight
PVC	polyvinylchloride
rpm	round per minutes
s^{-1}	1/second
sec	second
SEM	scanning electron microscope
tan δ	loss tangent
τ	torque

CHAPTER I

INTRODUCTION

Nowadays, the multiparticulate dosage form such as pellets has been more considered. Pellets can be defined as free-flowing spherical particles or granules that are produced by agglomerating fine powder or granule with an appropriated method. They usually range in size from 0.5-1.5 mm, high density and narrow particle distribution, so that they are useful to be filled in capsule or compacted to tablet. They are also used as cores for coating. There are many advantages of these dosage forms: 1) they are dispersed freely in gastrointestinal tract (GI-tract), so that they decrease dose dumping effect and local irritation; 2) they also reduce gastric emptying time.

Pellets may be manufactured by varying methods, i.e. spray drying, rotor granulator or fluidized-bed. Extrusion-spheronization is currently one of techniques used to produce pellets in pharmaceutical industry. The preparation of pellets by extrusion and spheronization process has many advantage such as producing narrow size distribution, high density and low friability of pellets. The process is a multi-step procedure, involving dry mixing, wet granulation, extrusion, spheronization and drying. The wet mass is necessary to give plastic deformation that can be extruded and shaped into spheres by spheronizer.

Generally, the formulation of pellets consists of 50-90% active ingredients and/or diluents, 5-50% pelletization aid and liquid binder. Microcrystalline cellulose (MCC) is the most widely used pelletization aid. It can modify the rheological properties of the formulations and imparts plasticity deformation to form pellets. Kleinebudde (1997) proposed crystallite-gel model to described mechanism of MCC as a formulation aid, while Ek and Newton (1998) proposed molecular sponge model. However, Kleinebudde et al. (2000) concluded that the molecular sponge model was suitable for cellulose that had high degree of polymerization, and the crystallite-gel-model was used for low degree of polymerization cellulose. Although, MCC is very useful as the pelletization aid but it is incompatibility with some drug such as ranitidine (Basit et al., 1999) and alcohol (Chatlapalli and Rohera, 1998a, Millili and

Schwartz, 1990). It can also form the matrix resulting in slow disintegration. Currently, there is no material that has manner like MCC. Therefore, the research is still ongoing to find a substitution material for MCC.

The research for MCC substitution is classified into two methods. The first method is trying to decrease the MCC in formulation by using hydrophobic polymer (Agrawal et al., 2004) or hydrophilic polymer as a binder (Law and Deasy, 1998; Neau et al., 1996; Kleinebudde et al., 1993). Another approach is finding a material to substitute MCC in formulation (Linder and Kleinebudde, 1994; Alvarez, 2003; Chatlapalli and Rohera, 1998a). Besides cellulose, there are many materials that are used to substitute MCC such as pectinic acid (Tho et al., 2002), glyceryl monosterate (Chatchawalsaisin et al., 2005; Newton et al., 2004), chitosan (Steckel and Nogly, 2004), κ-carrageenan (Thommes and Kleinebudde, 2006; Bornhöfta, et al., 2005). Recently, Prieto et al. (2004) could prepare pellets by using starch-dextrin.

Early, the preparation of pellets by extrusion-spheronization is trial and error. Fielden and Newton (1992) stated that the rheological properties of an extrudate depended on the properties of the material and the liquid content of the wet mass. To design an optimal formulation for extrusion-spheronisation, it is necessary to characterise the mechanical and rheological properties of the wet mass.

The measurement of the rheological property of wet mass can be divided into torque method and rheological method. The torque method is widely used to determine the property of mass for wet granulation. It measures either the power consumption or torque of equipment (Rowe and Sadeghnejad, 1987; Chatlapalli and Rohera, 1998b; Luukkonen et al., 1999). However, the extrusion-spheronization process is different from wet granulation due to this process concerns with high shear forced. Kleinebudde et al. (1999) found that extrusion-spheronization process needs the liquid content more than wet granulation process.

The capillary rheometer (Luukkonen, 2001), ram extruder and compresso-rheometer are employed in the rheological method. The principle of this method is similar with extrusion process. It is useful if water migration could be avoided during

the rheological measurement. A classical rheogical approaches to study materials with the consistency of the wet mass is the application of controlled stress rheometry, either as creep or oscillation test. The rheological property of wet mass, mixture of lactose and MCC, was studied by MacRitchie et al. (2002). They concluded that the controlled stress rheometer could evaluate the wet mass in extrusion-spheronization process for pellet formation.

In present study, rheological properties of wet mass without MCC was evaluated. The results could identify possibility to prepare pellets without MCC by controlling the rheological properties

Objectives of the study

1. To study pellets formulation containing no microcrystalline cellulose prepared by extrusion-spheronization process
2. To study the rheological properties of wet mass containing no microcrystalline cellulose for preparation of pellets by extrusion-spheronization process
3. To study the relationship between the rheological properties of wet mass and pellet formation.

CHAPTER II

LITERATURE REVIEW

1. Pellets

Pellets can be defined as free-flowing spherical particles or granules that are produced by agglomerating fine powders or granules with an appropriated method. They usually range in size from 0.5-1.5 mm, possessing high density and narrow particle distribution. In some applications, They may be large as 3.0 mm. Pellets are found not only in pharmaceutical industry but also in agribusiness (such as fertilizer and feedstuff) and in the polymer industry (Vervaet et al., 1995).

Pellets are easily mixed when a combination of ingredient or various drug release rates from a particular drug delivery system is desired (Ghebre-sellassie, 1989). They disperse freely in the gastrointestinal (GI) tract, so that the maximum drug absorption is obtained. They also reduce local irritation, reduce variations in gastric emptying rate (Bechgaard and Nielsen, 1978) and avoid the dose dumping effect (Reynold, 1997). Furthermore, they offer an advantage of flexibility for modification such as compression into tablet or coating to achieve the desired dosage form.

1.1 Pelletization technique

Pelletization can be performed in different techniques according to the application. The most common pelletization processes are layering (solution, suspension, powder) and extrusion-spheronization. Other techniques are used occasionally such as, spray-drying, spray-congealing and balling. Pelletization technique can be classified following diagram:

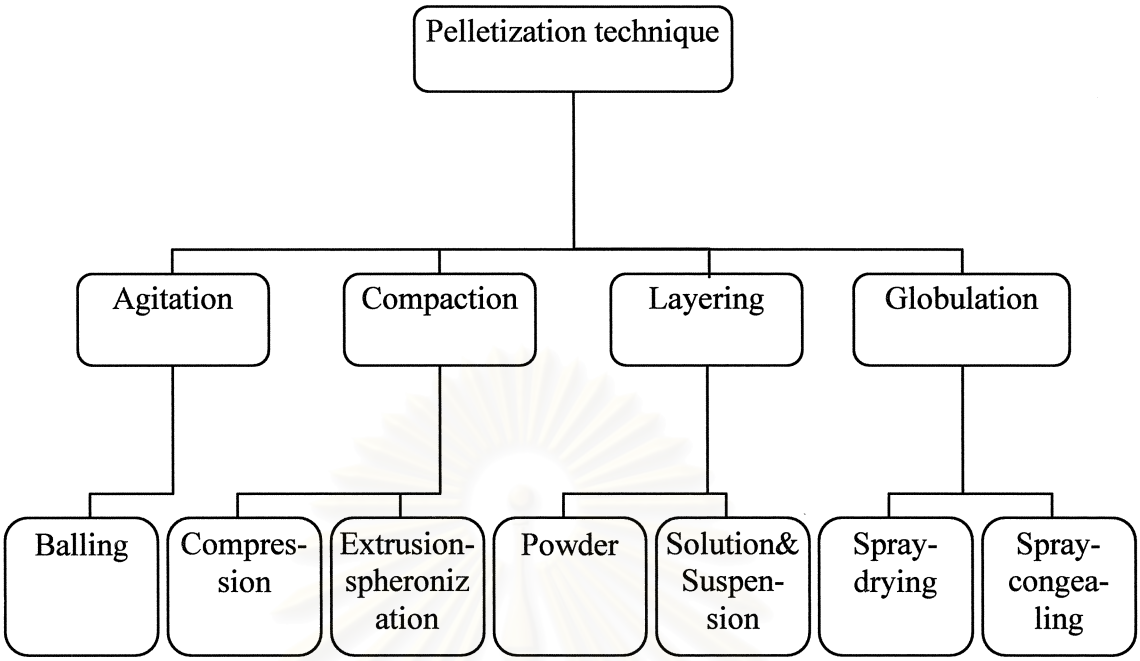


Figure 1. Pelletization techniques.

In a spray-drying process, aqueous solution of core materials and hot solution of polymer is sprayed into hot air, the water then evaporates and the dry solid is separated in the form of pellets, usually by air suspension. Generally, a spray-drying process produces hollow pellets if the liquid evaporates at a rate faster than the diffusion of the dissolved substances back into the droplet interior or if due to capillary action dissolved substances migrate out with the liquid to the droplet surface, leaving behind a void (Ghebre-sellassie, 1989).

In spray congealing, the slurry of drug material that is insoluble in a molten mass is sprayed into the lower temperature after that it is congealed to obtain discrete particles of the insoluble materials coated with congealed substances. A critical requirement for this process is that the substance should have a well-defined melting point or small melting range (Ghebre-sellassie, 1989).

In fluidized bed technology a dry drug is suspended in a stream of hot air. An amount of binder or granulating liquid is sprayed and causes a momentary reaction before vaporization. This causes the ingredients to react to a limited extent, thereby

forming pellets of active components. Govender and Dangor (1997) using this technique to prepared pellets of Salbutamol.

In the rotary processor (roto granulator, or centrifugal fluidized bed granulator), the principle of this equipment based on centrifugal force, fluidization air velocity and gravity force. This equipment is performed the whole cycle in one closed system. It can be used to prepared pellet by direct pelletization technique (or balling) and layering technique. Robinson and Hollenbeck (1991) prepared acetaminophen pellets by roto granulator and compared with pellet from extrusion–spheronization process, they demonstrated that acceptable, immediate release pellets could be produced.

In balling technique, the liquid binder was sprayed into rolling powder. The powder will agglomerate and form the pellet. Melt pelletization is one of this technique based on agglomerated by melted binder (Schaefer and Mathiesen, 1996). Rongrongmuang (2005) used this method to prepared diclofenac pellets.

1.2 Extrusion-spheronization

Extrusion and spheronization technique is the most commonly used, an appropriate method for producing pellets with desired qualities. This technique was developed in early 1960s, and since then has been extensively researched and discussed. Extrusion and spheronization process is multi-step procedure. There are four steps involved in pellet preparation:1) dry mixing and granulation, 2) extrusion, which shapes the wet mass into cylinders, 3) spheronization, which is refered to the rounding of the cylindrical particles into spheres and 4) drying the pellets (Figure 2). According to Vervaet et al. (1995), this process was first reported by Reynolds (Reynolds, 1970) and Conine and Hadley (Conine and Hadley, 1970). The properties of the pellets obtained can be related to the formulation composition (Sousa, et al., 2002), the processing conditions (Alvarez, et al., 2002, Chopra, et al., 2001, Sousa, et al., 1996) and the equipment used (Pinto, et al., 2001).

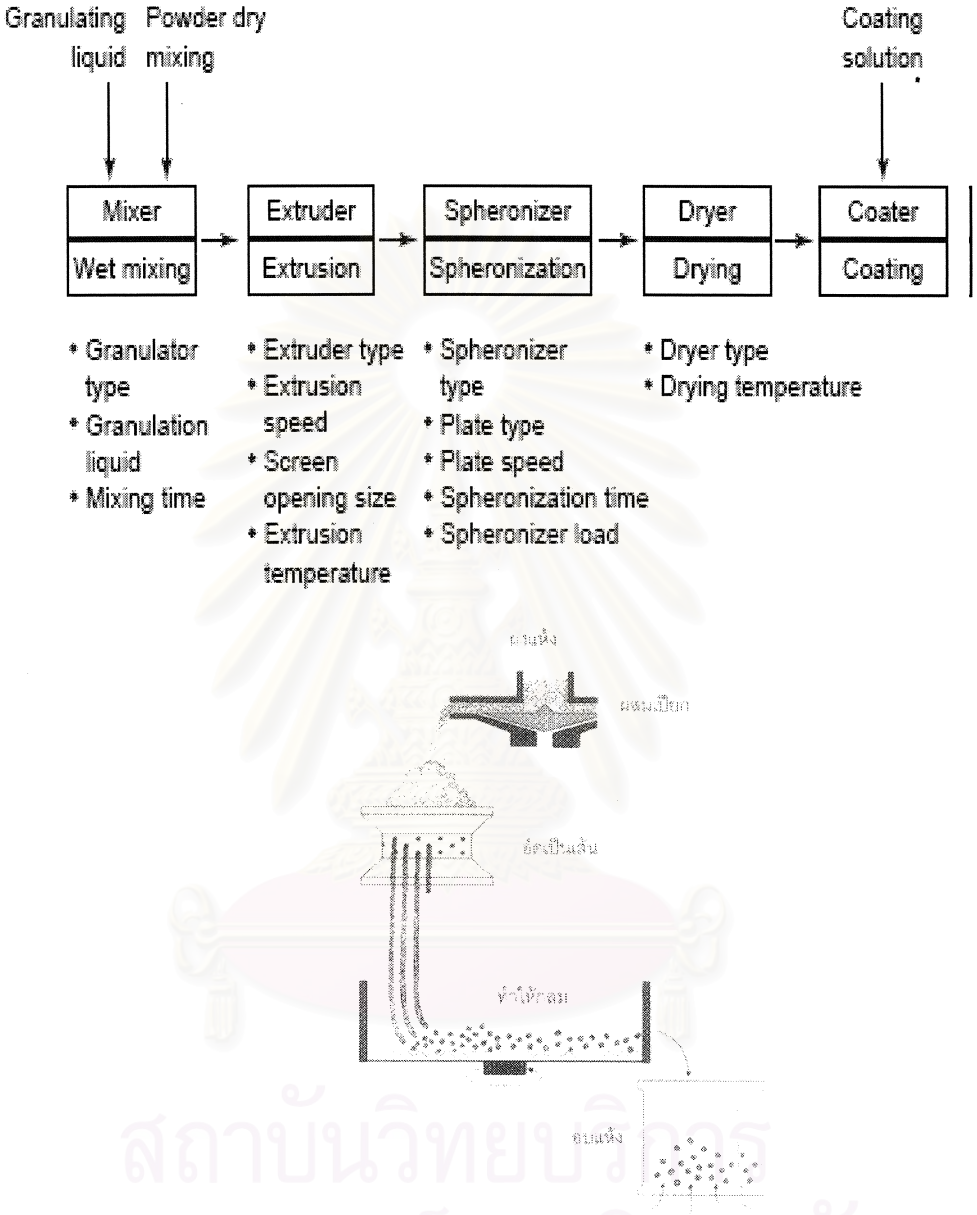


Figure 2. Flow diagram showing different steps, process parameters and equipments (Erkoboni, 1997).

1.2.1 Dry mixing and granulation operation.

The overall process begins with a dry mixing or blending operation of the drug and excipients in a suitable mixer to prepare a uniform, heterogeneous mixture. After that, the mixture is granulated with granulating liquid or liquid binder.

There are two major differences in the granulation step compared with conventional granulation; the amount of granulation fluid, and the uniform dispersion of fluid. The amount of fluid need to achieve spheres of uniform size and sphericity is greater than tablet granulation. Poor liquid dispersion will produce a poor quality product. Typically, dry mixing and wet granulation are performed in the same equipment, i.e. a planetary mixer is commonly used (Vervaet, 1995; Grandhi et al., 1999).

1.2.2 Extrusion

Extrusion produces rod-shaped product, similar to short strands of spaghetti. The wet mass is forced through dies of extruder and the extrudated is obtained. The extrudate may vary in length and characteristics, depending on the physical property of material to be extruded, the method of extrusion and how the particles are manipulated after manipulated after extrusion. There are many designs of extruder, but generally they can be divided into three classes based on their feed mechanism; 1) screw-feed extruder (axial or end-plate, dome and radial), 2) gravity-feed extruder (gear roll, cylinder roll, radial), 3) piston-feed extruder (ram) (Figure 3) (Summers and Aulton, 2002). The first two classes are used for both development and production, especially radial type, but the latter is only used for experimental development work (Erkoboni, 1997).

The extrusion process variables are: feed rate of wet mass, the diameter of die, the length of die and the water content of wet mass. The extrudate must have enough plasticity to deform, but the extruded particles did not adhere to other particles when collected or rolled in the spheronizer (Summers and Aulton, 2002).

1.2.3 Spheronization

The function of spheronization is to round off the rods from extrusion process into spherical particles. The extrudates are transported to a spheronizer then the friction plate breaks up the extrudate into short cylindrical rods. After that, these rods are pushed toward and up the stationary wall of the processing chamber by centrifugal force. Finally, due to gravity, the particle fall back to the friction plate and the cycle repeats until spherical pellets or desired sphericity are obtained. Thus, the extrudate is spheronized by interparticle collision and particle-to-wall friction forces.

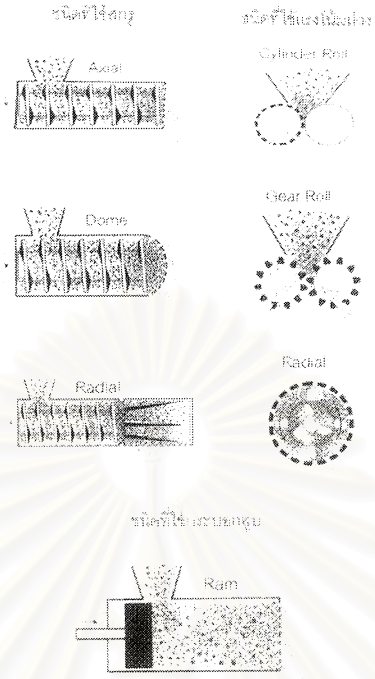


Figure 3. Schematic representation of extruder (Erkoboni, 1997)

A spheronizer is a device that consists of a bowl with a friction plate which located inside. The friction plate has a grooved surface to increase the frictional forces. Two types of geometry of the grooves exist; more common is the cross-hatch geometry in which the grooves intersect each other at 90° angles, whereas the other pattern is radial geometry in which grooves emanate from the centre like the spokes of a bicycle wheel. The spheronization of a product usually takes 2–10 minutes, and a rotational speed of between 200–400 rpm for the friction plate is satisfactory to obtain highly spherical pellets ((Vervaet, 1995; Conine and Hadley, 1970)

1.2.4 Drying

The final step of the process is the drying of the pellets. It is required in order to achieve the desired moisture content. The pellets can be dried at room temperature or at an elevated temperature in the fluidized-bed drier, in an oven or in a microwave oven. Pellet quality is dependent on the type of dryer used. According to Bataille et al. (1993), oven drying provides less porous and harder granules and a more

homogenous surface than those dried by a microwave oven. Dyer et al. (1994) prepared ibuprofen pellets that were dried either by tray drying or fluidized-bed drying, and they showed that the drying technique has a effect on the crushing strength and surface characteristics of ibuprofen pellets. If solute migration during drying, this may result in: 1) an increased initial rate of dissolution; 2) stronger pellets; 3) modified surfaces which might reduce the adhesion of any added film coats.

1.3 Pellet formation

The wet mass must be plastic and could be deform when extruded. Then, the extrudates was broken to form uniformly size cylindrical particles which are easily deformed into pellet. There are two mechanisms of pellet formation have been suggested. First mechanism was suggested by Rowe, the extrudates are rounded into the form of pellets because of frictional forces. Cylinders transform into cylinders with rounded edges then to dumb-bells and elliptical particles and eventually to perfect spheres. Baert and Remon suggested that another mechanism of pellet forming. It is also based on frictional forces. In this mechanism a twisting of the cylinder occurs after the formation of a cylinder with rounded edges, finally resulting in the breaking of the cylinder into two parts with cavity and fold together by spheronization process. The pellet with cavity was obtained by this mechanism (Figure 4).

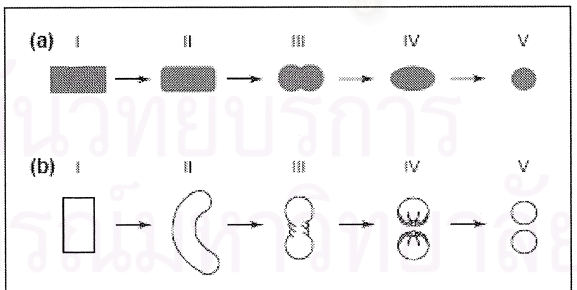


Figure 2. Pellet-forming mechanism according to: (a) Rowe[35] – I. Cylinder; II. Cylinder with rounded edges; III. Dumb-bell; IV. Ellipse; V. Sphere. (b) Baert – I. Cylinder; II. Rope; III. Dumb-bell; IV. Sphere with a cavity outside; V. Sphere. [Reproduced with permission from Ref. 9.]

Figure 4. Pellet forming mechanism (Gandhi, 1999)

1.4 Extrusion-spheronization aid

The physical property of the ingredient influences the particle size, hardness, sphericity and drug release. The different of ingredient even through the source of same ingredient was affected to pellet quality (Fechner, 2003; Heng and Koo, 2001a; Kleinebudde, 2000; Funck et al, 1991).

Microcrystalline cellulose (MCC) is described as a purified, partially depolymerized cellulose. The requirements for the formation of pellets from a wet mass are following (Fielden and Newton, 1992): 1) the wet mass must be brittle enough for extrudate could be broken down, but not be friable. 2) the wet mass must be sufficiently plastic to enable the formation. The function of MCC herein is controlling the distribution of water through the wet mass during pelletization process, and to modify the rheological properties of wet mass.

The rheological properties of wet mass highly depend on the liquid content of the wet mass. If the liquid content was lower than optimum liquid content, the plasticity of the wet mass is insufficient and pellet could not be formed. While the exceeding liquid content results in coalescence of pellets

There are three models was used to explain the mechanism of MCC as a extrusion-spheronization aid.

1.4.1 Liquid saturation model

The liquid saturation model describes the relationship between the amount of powder and liquid content. This model is based on the different liquid saturation stages; i.e. pendular, funicular, capillary, and droplet stage (Figure 5).

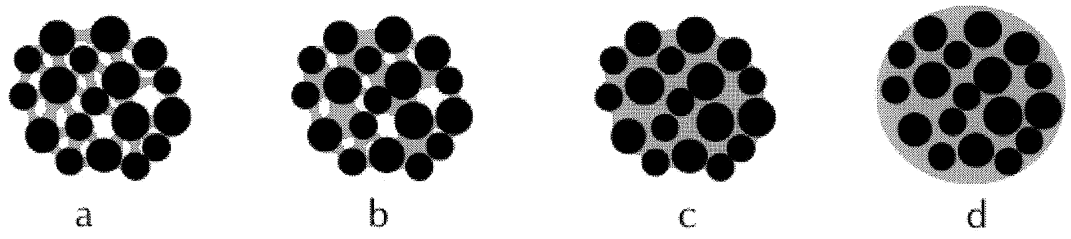


Figure 5. Different stages of saturation for liquid in granule: a. pendular stage, b. funicular stage, c. capillary stage and d. droplet stage (Ramaker, 2001).

Some restrictions of the liquid saturation model are: 1) the liquid saturation is about 25 % and 90 %.; 2) particles are assumed to be spherical; 3) dissolving of the solid by the liquid is not included in this model; 4) porosity is assumed to be constant during process, and swelling of the solid in the liquid is not included in the liquid saturation model. During the extrusion and spheronization process with MCC, it was observed that the liquid saturation can be about 100 % (Jerwanska et. al., 1995), the size and shape of MCC is not spherical and rigid and pellets containing MCC shrink during drying process (Kleinebudde, 1994). For these reasons, the saturation model is not valid to explain the behaviour of MCC during extrusion-spheronization process.

1.4.2 The sponge model

This model MCC would behave as a porous sponge (Figure 6) and it would be able to absorb a large quantity of water. The water is absorbed in the pores of MCC. All pores are supposed to be completely filled with water. It holds a lot of water in its structure although under high pressure; i.e. extrusion process the water would be partly squeezed out and acts as the lubricant. Water can also be taken-up again after releasing the pressure while the volume increases. MCC particles remain intact during the process of pelletization, extrusion and spheronisation and should be of the same size, shape and volume in the finished product compared to the original MCC powder.

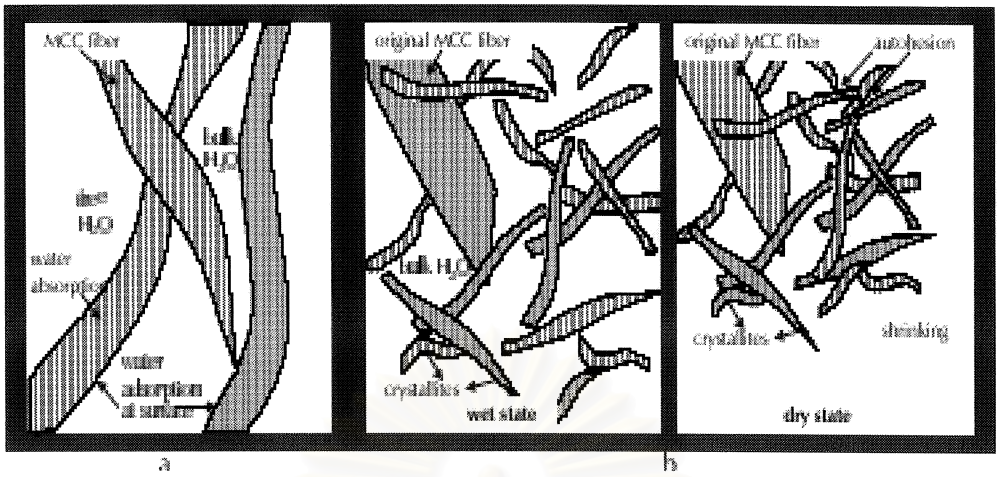


Figure 6. Schematic illustration of water in the cellulose samples.
a. sponge model; b. crystallite-gel model (Ramaker, 2001).

1.4.3 Crystallite-gel model

Kleinebudde (1997) proposed the crystallite-gel model in which a gel is formed during extrusion-spheronisation with MCC. During granulation and extrusion, MCC are broken down into smaller. Single crystallites with a size in micron can be obtained. They are able to form a crystallite-gel and immobilise the water (Figure 6). The crystallites or their agglomerates can form a network by cross-linking with hydrogen bonds at the amorphous ends. The viscosity of the gel depends on the water content and the degree of cross-linking. At increasing liquid content, the fraction of gelling agent in the gel decreases and the deformability increases. The gel is not sticky because the gelling agent is not soluble in water. The formation of hydrogen bonds in the amorphous ends of the crystallites during drying results in a stable matrix. These results provide an explanation for the disintegrating and dissolution properties of pellets (O'connor and Schwartz, 1993).

Heng and Koo (2001b) reports that the particle size of the MCC powder have a little influence to extrusion-spheronization process. These results could be suggested by using the crystallite-gel concept. Moreover, this model was explained the different between the surface structure of MCC pellets and the structure of MCC powder. This showed the formation of a network during pelletization and shrinking of the pellets

during drying. However, Kleinebudde et al. (2000) concludes that the molecular sponge model is suitable for cellulose that has high degree of polymerization, and the crystallite-gel-model is used for low degree of polymerization cellulose. Although, MCC is very useful as the pelletization aid but it is incompatibility with some drug such as ranitidine. It can also form the matrix resulting in slow disintegration. Today, there is no material that has manner like MCC. Therefore, the research is still ongoing to find a substitution material for MCC.

The research for MCC substitution is classified into two methods. The first method is trying to decrease the MCC in formulation by using hydrophobic polymer or hydrophilic polymer as a binder. Agrawal et al. (2004) prepared pellets by using fine particle ethylcellulose (60-90 %), Caffeine (10-40%) and water. These formulations can not be form pellets. It shows that the water absorbing of polymer is necessary to plastic deformation. For hydrophilic polymer, Kleinebudde et al. (1993) using the mixture of MCC (50-70%) and low-substituted hydroxypropyl cellulose (L-HPC) (0-20%), and Acetaminophen (30%) to prepared pellet by extrusion-spheronization process, it was found that HPC-L decreased water-sensitivity of the process and the good dissolution properties of acetaminophen from the pellets was obtained. However, MCC in these formulations is reached 50%. Law and Deasy (1998) prepared the pellet by using MCC 19% combine with binder 1% i.e., Sodium carboxymethylcellulose (NaCMC), Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC) and Polyvinylpyrrolidone (PVP), either spray-drying or physical mixing. This combined exipients (20%), lactose (80%) and water can produced spherical pellet and better sphericity when increase water content. They conclude that the HPC or PVP containing exipients are the most satisfactory because they had the least adhesive strength in spheronizer so that, favouring high yield of spherical pellets. Moreover, Neau et al. (1996) used Carbopol® 974P NF resin, MCC (10-50%) and electrolyte to prepare pellet. They found that it can produce the pellet by extrusion-spheronization when the ionic strength is decreased because of the adhesive force of wetted mixture is increased.

Another method is finding a substitution material for MCC. Linder and Kleinebudde (1994) compared the powder cellulose (PC) with MCC, it shows that PC

pellets has more porosity and fast dissolution rate. These results agree with Alvarez (2003). There are many studies that using other cellulose except PC for substituted MCC. Chatlapali et al. (1998) can not prepare pellets by using HPMC or Hydroxyethycellulose (HEC) and water as the granulating liquid but it can form pellets when using Isopropyl alcohol (IPA) as the granulating liquid. In addition to decrease friability of these pellets, HPC in IPA is used instead of IPA. According to Kanbe et. al. (2007) study, HPC-L (10-90%) and diphenhydramine were used to prepared the pellet with the diameter less than 500 μm. The highest sphericity was found when using HPC-L more than 50%. Besides cellulose, there are many materials that are used to substitute MCC such as Pectinic acid. The pectinic acid has a capacity as a pelletization aid, even through further study is needed to optimize sphericity and reduce the size distribution (Tho et al., 2002). Newton et al. (2004) prepared pellet of Barium sulfate ($BaSO_4$) by using only Glyceryl monosterate (GMS). It is similar with Chatchawalsaisin et al. (2005) study. This study GMS (90%) could be prepared diclofenac sodium (10%) pellets. Recently, Bornhöft et al. (2005) studied the carrageenan i.e., iota-carrageenan (ι-carrageenan), lambda-carrageenan (λ-carrageenan) and kappa-carrageenan (κ-carrageenan) which different in molecular weight, solubility and gelling properties, as a pelletization aid. In addition to Bornhöft et al. (2005), Thommes et al. (2006) reported that κ-carrageenan was used to prepare acetaminophen (20%) pellet results in the high yield, spherical, narrow distribution and fast release in compares with MCC in preparation acetaminophen (20%). Moreover, corn starch and wheat starch addition to white dextrin are also studied compare to MCC as pelletization aid (Prieto et al., 2004).

1.5 Evaluation of wet mass for extrusion-spheronization process

Early, the preparation of pellets by extrusion-spheronization is trial and error. Jerwanska (1995) suggests that the liquid should be fill interparticular space between particle before extrude whereas Benhow and Bridgwater described that the ease of extrusion process depends on the excess of the liquid that fill the interparticular space. Fielden and Newton (1992) stated that the rheological properties of an extrudate depend on the properties of the material and the liquid content of the wet mass. If the wet mass is too dry, the plasticity of the extrudate is insufficient and the extrudate does

not round in the spheronisation. On the other hand, if the wet mass is too wet the pellets will agglomerate during spheronisation. To design an optimal formulation for extrusion-spheronisation, it is necessary to characterise the mechanical and rheological properties of the wet mass. In the same way, Bornhöft et al. (2005) reports that only κ-carrageenan has a suitable property to prepare pellets so that, it means the rheological properties of material influences of pellet formation. Subsequently, the rheological property of wet mass to form the pellet has been interested.

The rheology is defined as the study of the deformation and flow properties of material how responds to an applied stress or strain. It is used to describe the relation of the material structure and the process. So that, it is applied to assume the rheological behaviour of wet mass. The measurement of the rheological property of wet mass can divided into torque method and rheological method.

1.5.1 Torque method

The torque method is widely used. It measures either the power consumption or torque of equipment. The mixer torque rheometer (MTR) as presented in Figure, is has been used to study the source variation of MCC grades (Rowe and Sadeghnejad, 1987; Parker and Rowe, 1991) and for the evaluation of the optimum water level for extrusion-spheronization (Prieto, et al., 2004; Chatlapalli and Rohera, 1998; Luukkonen et al., 1999). The MTR measures torque range which reflects the heterogeneity of the wet mass; and mean torque which described the resistance of the mass to mixing. Apart from MTR, powder rheometer also uses the torque method. This equipment can measure both dry and wet powder masses. It is able to identify similarities and differences in the flow, shear and packing properties of dry powders. So that, it is used to study the capsule filling properties. The torque method is suitable to find the liquid content for wet granulation process. The torque increases with increasing the water content, and it decreases when the material becomes overwetted. However, the extrusion-spheronization process is different from wet granulation due to this process concerns with high shear forced. Kleinebudde et al. (1999) found that this process needs the liquid content more than wet granulation process.

(a) (b)

Figure 7. Instrument of torque method: (a). Mixer torque rheometer and (b) Powder rheometer (Lukkonen, 2001)

1.5.2 Rheological method

The capillary rheometer uses the rheological method. According to Ovenston and Benbow, the parameters necessary to characterize the flow of material through a die during extrusion can be measured directly using capillary rheometer. The ram extruder and compresso-rheometer also use rheological method. The principle of this method is similar with extrusion process, the wet mass moves from the wide barrel to the narrow die and flow through the die, so that these equipments are suitable more than MTR. Luukkonen (2001) compared the capillary rheometer with MTR for the evaluation of rheological property of MCC and silicified microcrystalline cellulose (SMCC) wet mass. This study shows that MTR is suitable for the evaluation of wet granulation whereas capillary rheometer is suitable for extrusion process. The application of a capillary rheometer to evaluation the wet mass, under high stress, the water can separate from solid and move freely in the solid mass thus, the consistency of the mass changes during the measurements. It is useful if water migration could be avoided during the rheological measurement. A classical rheogical approaches to study materials with the consistency of the wet mass is the application of controlled stress rheometry, either as creep or oscillation test. The creep test is useful to indicate the deformation of viscoelastic material but it can not indicate the wet mass which can or can not form the pellet. The oscillation test gives the information about structure of

material. The parameter from these test is storage modulus (G′) and loss modulus (G″). The rheological property of wet mass, mixture of lactose and MCC, is studied by MacRitchie et al. (2002). They conclude that the controlled stress rheometer can evaluate the wet mass in extrusion-spheronization process for pellet formation.

Considering to the extrusion of pastes can result in the phenomenon of liquid migration, which causes change in liquid content in wet mass. Water movement and liquid retention has been studied by centrifugation techniques (Tomer et al., 2001; Tomer and Newton, 1999a). Water movement during extrusion has been followed by measuring the moisture content of extrudate fractions (Tomer and Newton, 1999b)

2. Rheology

Rheological measurements have become essential tool in many industries, because a direct assessment of processability can be obtained.

The term of rheology was invented by Bingham and formally adopted in 1929 (Mariott, 2002). It is defined as the study of the deformation and flow properties of material which includes solids, liquids, and gases (Steven et al., 2004; Fuongfuchat, 2002; Ghooray, 2002; Mezger, 2002). The classical definition of rheology divided into two parts: (1) deformation which is usually applied to materials that are predominantly solid-like in nature; (2) flow which is usually applied to materials that are predominantly fluid-like in nature (Carter, 1998).

A proper understanding of the rheological properties of pharmaceutical materials is useful for preformulation, development, preparation and evaluation of dosage forms, typically consisting of many ingredients to produce a desired texture product. However, for many pharmaceutical dosage forms, such as paste, ointment, cream and gel that has the properties of both solids and fluid, the measuring their properties is sometime difficult.

Viscosity

The viscosity is a property that describes a resistance to flow of substance when sheared. The high viscosity is the high resistance to flow (Laba, 1993). It is a subject in part of the rheology (Dinger, 2002).

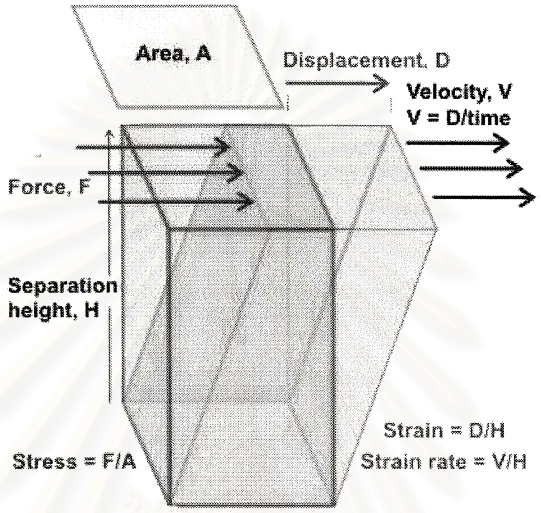


Figure 8. Definition of shear stress, shear strain, shear rate and viscosity. ("Rheology Primer for Hydrocolloid Science", 2006).

The shear is the relative movement of parallel adjacent layer. A stress is a forced applied over an area. The fundamental diagram used to define and explain the terms shear stress, shear strain, shear rate and viscosity is Figure 8. If two plates (area, A) separated by distance (separation height, H) are moved at velocity, V and force, F. The shear stress is the force divided by area parallel to force (F/A). The shear strain is quantified by displacement per unit height, (D/H) and strain rate is the velocity per unit height (V/H). The coefficient of viscosity, or viscosity (η) is the ratio of shear stress to shear rate under simple steady shear and is defined by following equation (1).

$$\eta = \frac{\text{Shear stress}\,(\sigma)}{\text{Strain rate}\,(\dot{\gamma})} \quad (\text{Pa}\cdot\text{s}) \qquad \ldots(1)$$

The abbreviated form "viscosity" is used most often in practice, and is frequently employed without discriminating between Newtonian and non-Newtonian

behavior. When the quotient is independent of shear rate (i.e., follows the Newtonian model), it is considered a material constant. When the quotient is dependent on shear rate (i.e., non-Newtonian), it should be referred to as the non-Newtonian viscosity.

The fundamental unit of viscosity measurement is "poise". It will encounter viscosity measurement expressed in "Pascal-seconds" (Pa·s) or "milli-Pascal-seconds" (mPa·s). One Pascal-second is equal to ten poise; one milli-Pascal-seconds is equal to one centipoise.

Viscoelasticity

The elasticity is the tendency of a body to return to its original shape after it has been stretched or compressed. It explains by using a spring model (Figure 9). The elastic samples are studied by pulling the spring with a force, F. When force F is removed the sample returns to original shape and position (Graule, 2004; Cellulosic Specialties, 2004)

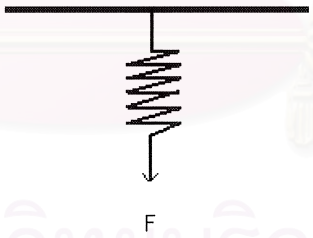


Figure 9. A spring model

The plasticity is the property of being deformed by exterior forces and staying deformed. The plastic materials shows flow properties in the same way as viscous samples. It explains by using a sliding block model, when the minimum critical shear stress is exceeded, i.e. yield stress, plastic materials will flow. If the force is lower than the yield point, the flow will cease (Figure 10).

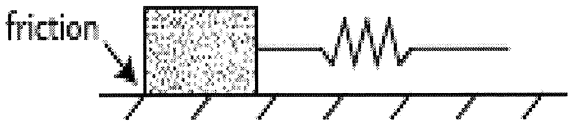


Figure 10. Sliding block model (http//ocw.mit.edu.)

The viscoelastic is a time-dependent property in which a material under stress produces both viscous and elastic response. A viscoelastic material will exhibit viscous flow under constant stress but a portion of mechanical energy is conserved and recovered. After the stress is released, the viscoelastic properties are usually measured as response to an instantaneously applied or removed constant stress or stain or dynamic stress or strain.

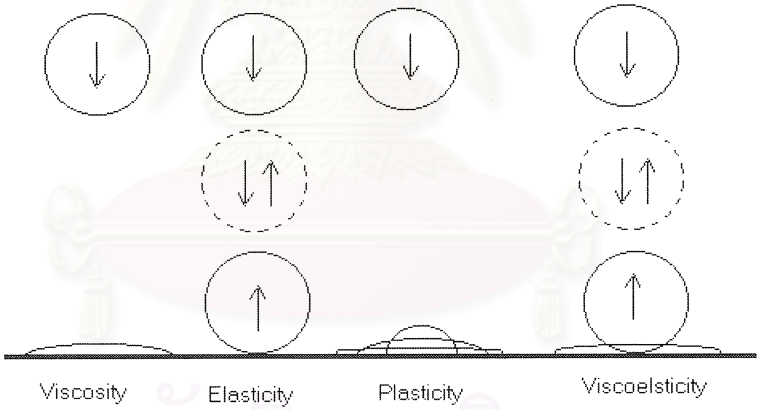


Figure 11. Deformation behavior after hitting the floor. (Mezger, 2002)

The material property may be summarized as shown in Figure 11. (1) viscosity, the viscous sample flows on the surface until surface tension stops further flow (surface tension > gravitational force); (2) elasticity, the elastic sample will bounce at contact with table; (3) plasticity, the plastic sample will deform at impact with surface. Deformation will depend on the yield stress (yield stress compared with gravitational force); (4) viscoelasticity, the viscoelastic sample will initially bounce upon contact

with surface (short time scales). After longer times the sample will come to rest on surface and will start to flow (long time scales).

Flow behavior

The flow behavior can classified into two part: (1) Newtonian; (2) Non-Newtonian.

1. Newtonian

Newtonian materials have a constant viscosity dependent on temperature but independent of the applied shear rate. The Newtonian flow curve is represented in Figure 12. Graph A which is plotted between shear stress and shear rate will be a straight line. The slop of a straight line is viscosity of fluid at a specified temperature. Graph B shows that the material's viscosity remains constant as the shear rate is varied. Water, mineral oil and sucrose solutions are examples of Newtonian materials.

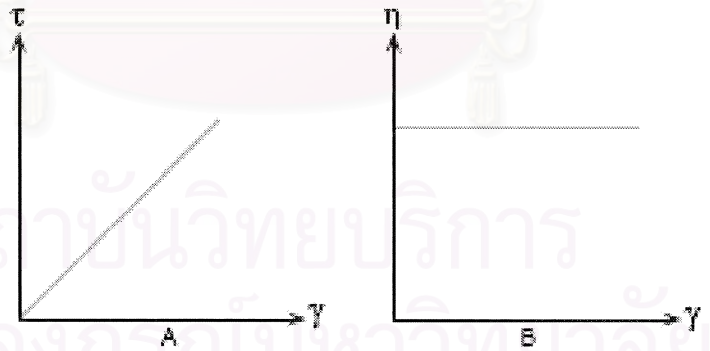


Figure 12. Flow curve or rheogram representing the newtonian flow behavior (Brookfield Engineering Laboratory, 2004).

2. Non-Newtonian

Materials, which cannot be defined by a single viscosity value at a specified temperature, are called non-Newtonian. These materials must always be stated together with a corresponding temperature and shear rate. If the shear rate is changed the viscosity will also change. Non-Newtonian materials may also be time-dependent. They are defined as pseudoplastic, dilatant or plastic. Thixotropic, rheopectic or anti-thixotropic are also defined for time-dependent non-newtonian materials (Bolmstedt, 2000).

2.1 Time-independent flow behavior.

The viscosity of pseudoplastic materials decreases with an increasing shear rate as shown in Figure 13. This type of flow behavior is sometimes called "shear-thinning". The reason for shear thinning flow behavior is that an increased shear rate deforms and/or rearranges particles, resulting in lower flow resistance and consequently lower viscosity (Figure 14).

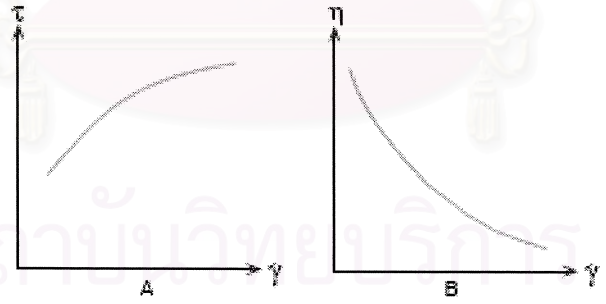


Figure 13. Flow curve or rheogram representing the pseudoplastic flow behavior (Brookfield Engineering Laboratory, 2004).

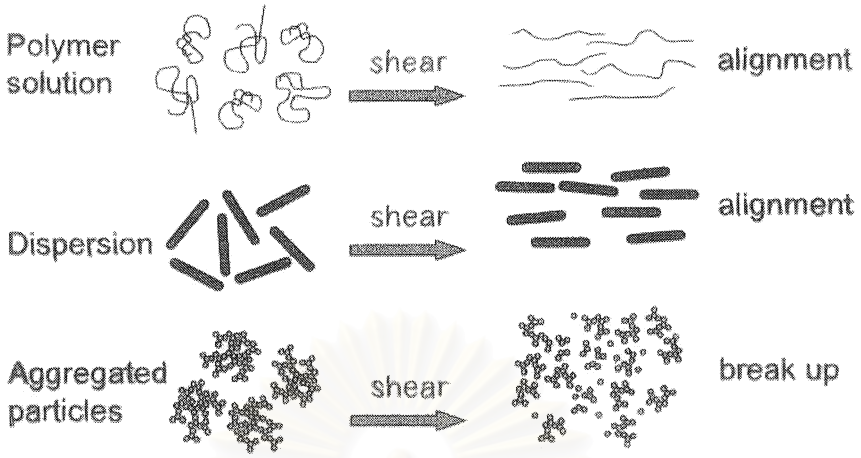


Figure 14. Mechanism of shear-thining system (Stading, 2004).

The viscosity of dilatant materials increases with an increasing shear rate (Figure 15). This type of flow behavior is generally found in suspension with high concentration. At low shear rates the solvent acts as a lubricant between suspended particles but it is squeezed out at high shear rates, resulting in denser packing of particles. Dilatant is also referred to as "shear-thickening" flow behavior.

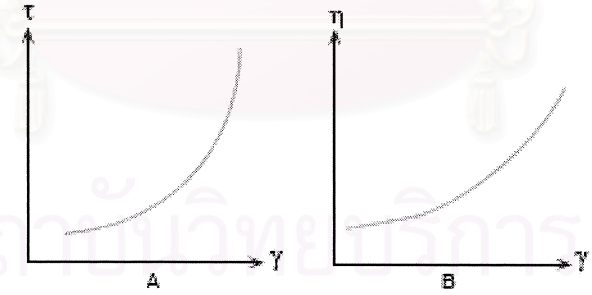


Figure 15. Flow curve or rheogram representing the dilatant flow behavior (Brookfield Engineering Laboratory, 2004).

An amount of stress must be applied to a plastic materials before any flow is induced; this stress is called the "yield stress". If the stress is smaller than yield stress, the material behaves as a solid. When the yield stress is exceeded, the material can flow like a Newtonian, pseudoplastic or dilatant. A Bingham plastic

describes for Newtonian flow and a viscoplastic describes for shear thinning flow. A plastic flow behavior is represented in Figure 16.

Figure 16. Flow curve or rheogram representing the dilatant flow behavior. (Brookfield Engineering Laboratory, 2004)

2.2 Time-dependent flow behavior.

The viscosity of some materials changes with time under conditions of constant shear rate. A thixotropic material undergoes a decrease in viscosity with time at constant shear rate. A thixotropic systems begins to flow under shearing and reform again when shear is removed. As shown in Figure 17, The rigid structure appears to be broken by shear forces and the interparticular bonds tends to reestablish themselves with time. The time-dependent thixotropic flow behavior is seen in the difference between the ascending and descending viscosity of shear stress curve. The thixotropic flow behavior is normally studied in a loop test, called hysteresis loop (Figure 18) (Rao, 1999; Bolmstedt , 2000; Neaman, 2000).

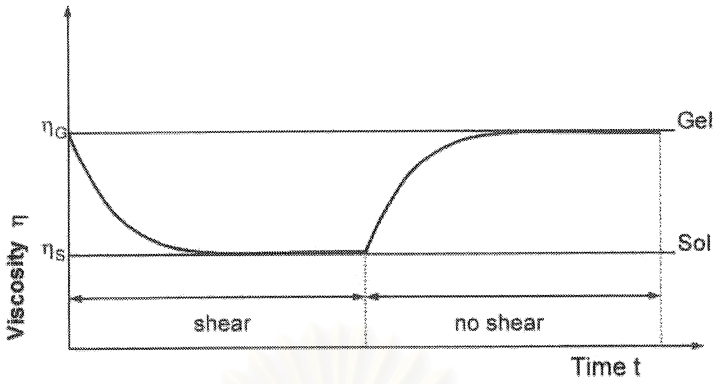


Figure 17. Thixotropy flow behavior (Graule, 2004).

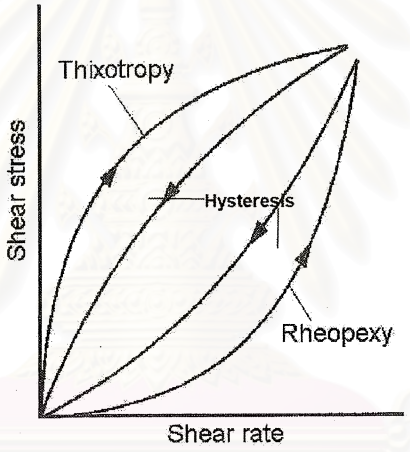


Figure 18. Hysteresis loop of thixotropy and rheopexy (Granule, 2004).

Rheopexy and anti-thixotropic behavior is a phenomenon that opposite to thixotropic behavior, the material's viscosity increases with time at constant shear rate (Figure 19). The increase in the rate of stiffening due to shearing of suspension enhances collision frequency, particle may be linked together into network and form gel. Anti-thixotropic or negative thixotropy should not be confused with rheopexy. Rheopexy systems are deflocculated and contain greater than 50% by volume of solid disperse phase whereas anti-thixotropic systems have low solid content (1%-10%) and are flocculated (Sinko, 2006; Arslan, 2003; Kreiba, 2000).

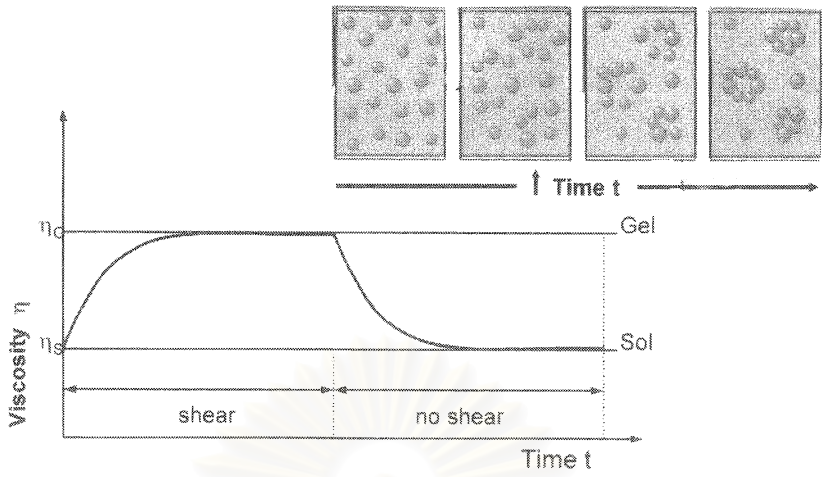


Figure 19. Rheopexy and anti-thixotropic flow behavior (Graule, 2004).

Rheological instrument

The instruments which measure the viscosity are called viscometers, whereas the rheometer can measure further rheological tests such as creep and oscillation tests (Mezger, 2002). The instruments can be classified according to the principle of measuring system.

Bubble and cup method

The viscosity may be obtained by using a bubble method, in which the liquid streams downward in a sealed glass tube against a rising air bubble. The rate of the bubble rises is a direct measurement of the kinematic viscosity, the ratio of the viscosity of a fluid to its density. This instrument is obtained the relative viscosity by comparing with known material. The example is BYK-Gardner bubble viscometer (Laba, 1993).

The cup or the orifice method has specific dimensions and an orifice at the bottom. The example of the orifice viscometers are the dipping-type Zahn viscometer and the Ford cup viscometer (Figure 20). The time for a known volume of sample to flow through the orifice is measured and the viscosity is obtained. The diameter of the

orifice and the type of the cup ha to be given with the result in "seconds", e.g. "240s with DIN cup 4".

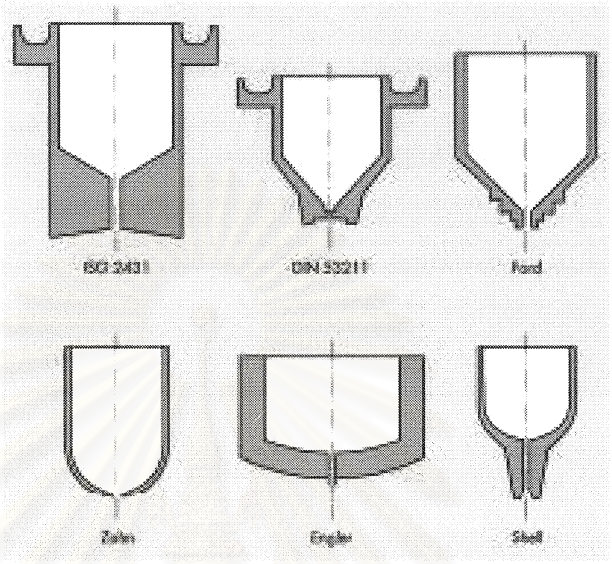


Figure 20. The cup viscometer (Mezger, 2002)

Capillary method

In capillary method, the sample is flowed through a capillary tube and the time is measured. The viscosity of the sample is obtained by used Hagen-Poisseuille equation:

$$\eta = \frac{\pi P r^4 t}{8VL} \qquad ...(2)$$

Where η is viscosity; P, is the driving pressure or the pressure difference across the ends of the tube; r, is the radius of the capillary; t, is the time of flow; V, is the volume of the sample and L is the length of the capillary (Marriott, 2002.; Carter, 1998; Laba, 1993). This equation assumes a laminar and isothermal flow. The driving pressure is usually generated by the gravity force, by compressed air or by mechanical. For a given geometry and pressure, the viscosity of sample is calculated relative to a standard fluid that known viscosity, e.g. water. This is a one-point measurement and

is widely used for Newtonian fluids (Blair, 1969). The various geometries are available commercially, e.g. Ostwald viscometer, as seen in Figure 21.

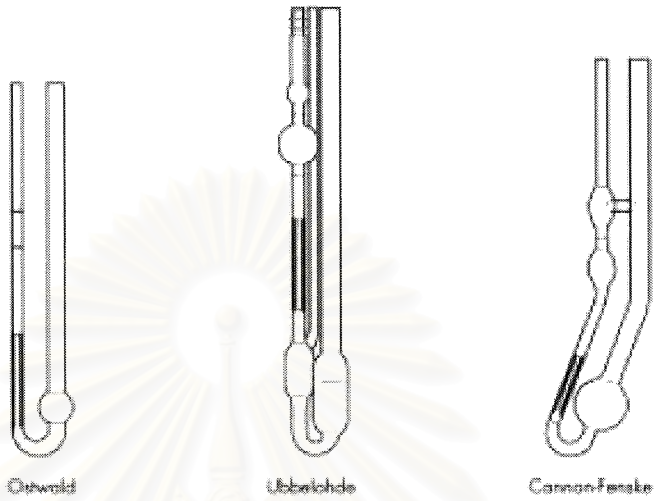


Figure 21. The capillary viscometers (Mezger, 2002)

Falling sphere or falling rod method

The principle of this instrument is measuring the time for a ball or rod that known dimension to fall through in a tube that filled with sample. In general, this method is used for comparative measurement and not for absolute viscosity determination. So that, it requires the ball or rod to cover various viscosity. It is suitable for newtonian sample that has a viscosity range of 0.5-200000 poise. The sample has to be transparent in order to follow the movement of the ball or rod. The best result is obtained when the falling time not less than 30 second (Faculty of pharmacy, Khon Kaen University, 2006; Blair, 1969; Laba, 1993).

This instrument can be easily applied in laboratory. The sample is filled in graduated cylinder and drop the ball or rod in the center of the cylinder. The well known of this instrument is the Hoeppler falling ball viscometer (Figure 22), a sphere rolls or slide down the side of an inclined tube that slightly wider than the sphere (Blair, 1969). The Hoeppler viscometer can give result reproducible to 0.5% or better with newtonian sample (Carter, 1998).

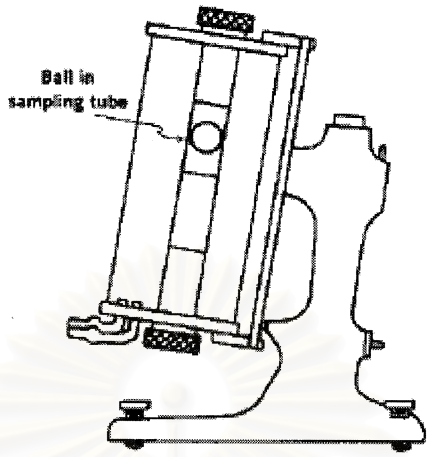


Figure 22. The Hoeppler falling ball viscometer (Faculty of Pharmacy, Khon Kaen University, 2006).

Rotational viscometers/rheometers

The principle of the rotational viscometers/rheometers is based on rotating the sample and measuring its response to the applied stress by variety of sensors (Narongrakdaj, 2004:). There are many different instruments of rotational method which allows the design of excellent and versatile, so that the rheological criteria and conditions are mentioned before use such as type of instruments, design features and application. (Schramm, 2002)

The rotational method consists of two operating systems: 1) controlled stress - the resulting shear rate or the speed is measured at certain constant torque. It is named "Controlled stress method or CS-method"; 2) controlled shear rate - the resulting shear stress or the torque is measured at certain constant speeds. It is named "Controlled rate method, controlled strain method or CR-method" (Läuger et al, 2005; Schramm, 2002). Some rheometers can operate into both modes.

The rotational viscometers/rheometers have two other additional designs for operating system: 1) the Searle system, the torque input and rotor speed acts on the same rotor shaft axis, e.g. the bob rotates while the cup is stationary. The torque data

and rotor speed can be transformed to shear stress and shear rate, respectively. The disadvantage of this system is the Taylor vortices can occur with low-viscosity materials at high speed. 2) The Couette system, the outer of sensor is driven while the shaft of inner sensor measures the torque which is proportional to the viscosity. For example, the cup is driven and the viscous drag on the bob (passive sensor) causes it to turn. This method, the Taylor vortices don't occur. However, the cup must be sealed to control the temperature, therefore the friction of seal has an effect on the measuring result. So as to achieve accurate results, the test must be without equipment for direct temperature control, i.e. in a temperature controlled room (Sinko, 2006; Schramm, 2002; Mezger, 2002).

For controlled stress rheometer (CS-rheometer) with Searle type which may be assemblecoaxial cylinder, cone and plate or parallel plate measuring system, the outer cylinder is stationary and the inner cylinder is driven by a motor at the applied torque value. The resistance of the sample against the applied torque or shear stress will allow the rotor to rotate at a speed or shear rate which correlates to the viscosity of the sample.

For controlled rate rheometer (CR-rheometer) with Searle type, it is similar to CS-rheometer with Searle type but the inner cylinder is driven by a motor at constant or programmed speed and there is a torque detector, normally a spring that twists as the torque applied. The twist angle of the spring is a direct measurement of the viscosity. Another operating system is controlled rate rheometer (CR-rheometer) with Couette type. The outer cylinder rotates at defined speed by the motor. The inner cylinder is induced to rotate by the resistance of the liquid when sheared. The torque is measured by determining the counteracting torque which required to hold the inner cylinder at a stand-still. The outer cylinder may be a cup or a stationary lower plate and the inner cylinder may be a bob, rotating cone or plate (Sinko, 2006; Schramm, 2002; Mezger, 2002).

For identical non-thixotropic material both CS and CR-rheometer with either Searle or Couette provide identical flow curve. The important differences between CS and CR-rheometer when determines rheological properties of viscoelastic material: 1)

CS-rheometer is higher sensitivity to differentiate similar samples at very low values of shear rate; 2) CS-rheometer can differentiate the non-newtonian material better than CR-rheometer; 3) CS-rheometer is especially designed to determine the viscoelastic sample which subjected to small strain in a creep test or to small oscillation amplitude in a dynamic test. Conclusion, the CS-rheometer has the higher potential in characteristic of samples than CR-rheometer (Schramm, 2002; Bhattacharya, Vasudha and Murthy, 1999). Chang, Koo and Song (2003) found that the CS-rheometer is more useful than CR-rheometer to investigate the steady shear rheological properties of vaseline which have lower values of critical shear rate or shear stress.

1. Coaxial cylinder measuring system

The coaxial cylinder measuring system consists of a bob and a cup that are aligned in the same symmetry axis of rotation, sometime it is called a concentric cylinder measuring system (Figure 23).

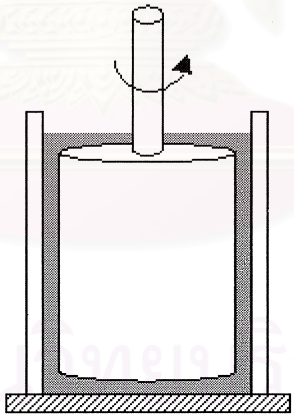


Figure 23. The coaxial cylinder measuring system (Hackley and Ferraris, 2001).

In order to increase the sensitivity of measuring device, many special geometries such as double-gap geometry and tapered plug geometry. The double-gap geometry consists of a hollow inner cylinder which placed in a cylindrical groove in the outer cylinder (Figure 24). The sample is contained in the double annular gap

between the cylinders. This geometry, a large shear area is provided so that is designed for low-viscosity material.

The taper-plug geometry or high shear measuring system, is designed for high shear rates. It consists of a very narrow shear gap. The shear rates of 10^5-10^6 s^{-1} may be obtained from this geometry. However, it is not suitable if the particle of the sample is bigger than the gap or the sample is very elastic.

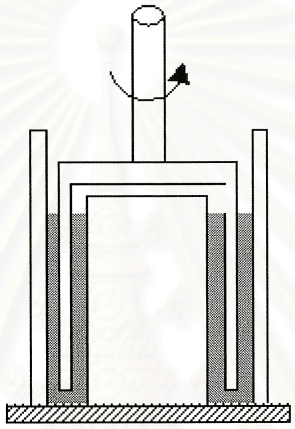


Figure 24. The double-gap geometry (Hackley and Ferraris, 2001).

2. Cone and plate measuring system

This geometry consists of a flat plate with a cone placed centrally above it. (Figure 25). The cone is rotated and the torque is measured at various speed of rotation. The angle between the cone and the plate has to be extremely small, usually 0.1°-4° (Marriott, 2002; Rao, 1999; Carter, 1998; Laba, 1993). There is a small gap between the cone and the plate to fill the sample so that, a small volume (typically 1-5 ml) of sample is needed (Rao, 1999; Laba, 1993). Since the amount of sample is very small, this instrument is very sensitive to sample drying and temperature change. The advantage of cone and plate measuring system is providing uniform shear rate across the sample. It is not suitable for emulsion or dispersed system that has particle size more than 30 μm (Khon Kaen University, Faculty of pharmacy, 2006).

The modification of this instrument is tip truncated. The cone tip is truncated because there is no friction between the cone and the plate, but the measurement of the torque is included not only the torque which produces by the sample but also the torque comes from the friction between the cone and the plate. It causes falsify the test result (Mezger, 2002). Another advantage of this geometry is the measurement of material that containing particles with large dimension (outside colloidal range). Lapasin et al. (1998) used truncated cone and plate system for investigate viscoelastic properties of two solder pastes, material used in an electronic card.

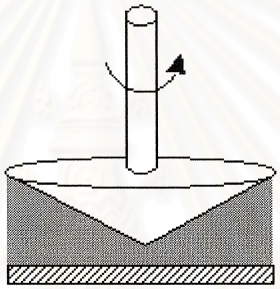


Figure 25. The cone and plate measuring system (Hackley and Ferraris, 2001).

3. Plate and Plate or Parallel plate measuring system

The plate and plate or parallel plate measuring system is consists of two plate (Figure 26). It is useful in handling small sample and dispersion that contain large size particles, such as gelatinize starch dispersion. Taylor et al. (2004) used this instrument to obtained rheological data of mixed gels of mucin and alginate. The guide for a suitable gap width is 10 time particle diameter (Rao, 1999). In addition to study rheological property of gum or dispersion, this geometry can also study the wet mass (MacRitchie et al., 2002).

The disadvantage of this geometry is the shear rate is not constant, but varies from the center to a maximum at the edge.

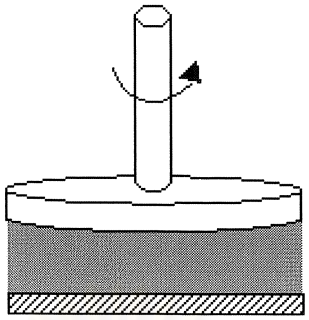


Figure 26. The plate and plate or parallel plate measuring system (Hackley and Ferraris, 2001).

Other method

Over and above mention, there are many designs of instruments. For example, a vibro viscometer, the principle of this instrument is measurement the amplitude that gets from immerse the vibrator in the sample. Another method is "Tuning-fork vibration". It is similar to the vibro viscometer, but this method is vibrating the light wave (Narongrakdaj, 2004).

Measurement of viscoelastic materials

The viscoelastic measurement is based on the properties of material that exhibit both viscous properties (liquid) and elastic properties (solid). There are many pharmaceutical formulations such as cream, paste, lotion and colloidal dispersion which show viscoelastic properties. The steady shear in rotational instruments may produce false result so that, oscillatory and creep methods is applied to determine viscoelastic properties (Sinko, 2006). Barry (1974) reviewed these methods for pharmaceutical and cosmetic semisolids. Several rheological techniques, including die swell and melt fracture, shear stress ramp test, creep and recovery and oscillation, are used for viscoelastic materials.

Creep and recovery test

The useful of controlled-stress is well-known and particularly useful in low-stress and long-term test, is called creep test (Barne and Bell, 2003). This method has been introduced for viscoelastic material. The creep test refers to the application of a given stress to a material and monitoring of the subsequent deformation. The typical response is an immediately deformation on the application of the stress and then the movement towards a steady-state, but very slow continual deformation, so slow that it was called creep. It used to differentiate between the viscous and the elastic responses of material. It is mostly used to examine unlinked polymer in form of melt and solution. It is also suitable for determining the behavior of chemically cross-linked polymer, gels and dispersions with a physical network of force. The material is investigated by performing two shear stress steps. Figure 27. shows the two shear stress steps as preset for a creep test: 1) step from $\tau = 0$ to τ_0 = constant and time interval t_0 to t_2 – this step is stress input; 2) step from τ_0 back to $\tau = 0$ and time interval t_2 to t_4 – this step is removing the stress.

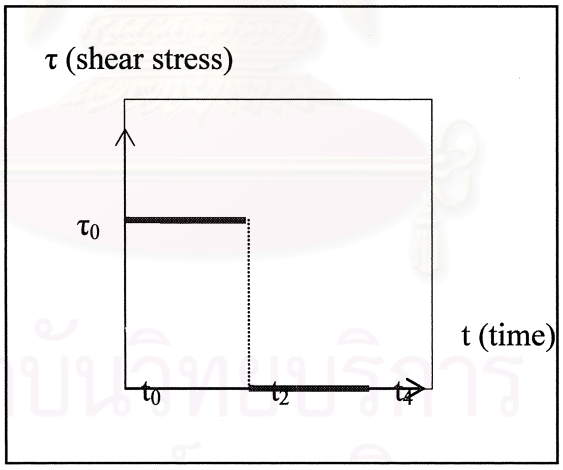


Figure 27. The two shear stress steps as preset for a creep test

A constant shear stress (τ_0), is provided the deformation is sufficiently small that the material does not change appreciably (in linear viscoelasticity, LVE, range), is applied on the material then causing the deformation of material. The resulting of this method is described by using creep and creep recovery curve (Figure 28).

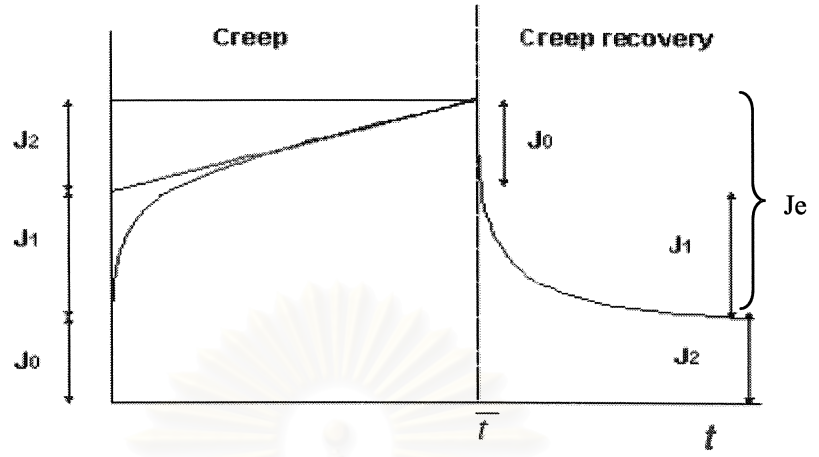


Figure 28. The creep and creep recovery curve (Gabriele, 2006).

The resulting time-dependent deformation is measured. The first part of the curve in the time interval t_0 to t_2 (Figure 28) is called creep curve or deformation curve. The second part of the curve in the time interval t_2 to t_4 (Figure 28) is referred to as creep recovery curve or reformation curve. In creep phase, the material responds to constant shear stress load, J_0 is purely elastic deformation. It is occurring immediately after start the test without time delay. The Je in reformation curve represents the elastic portion of material and the deformation J_2 which remains at the end of the test is viscous portion. Figure 29 shows the response of material which several properties, i.e. solid, fluid or viscoelastic in creep test.

It is difficult to apply a constant stress in less than 0.5 to 1 sec therefore; the creep data begin at 5 to 10 sec. A test from 10 sec to 3 hours, it covers three decades and 28 hours, requires for four decades. The length of time for creep interval of creep test is limited by the experimenter's patience. In zero load or stress removing interval, the period of time should be monitored to make sure strain for material has recovered (Lakes, 2004).

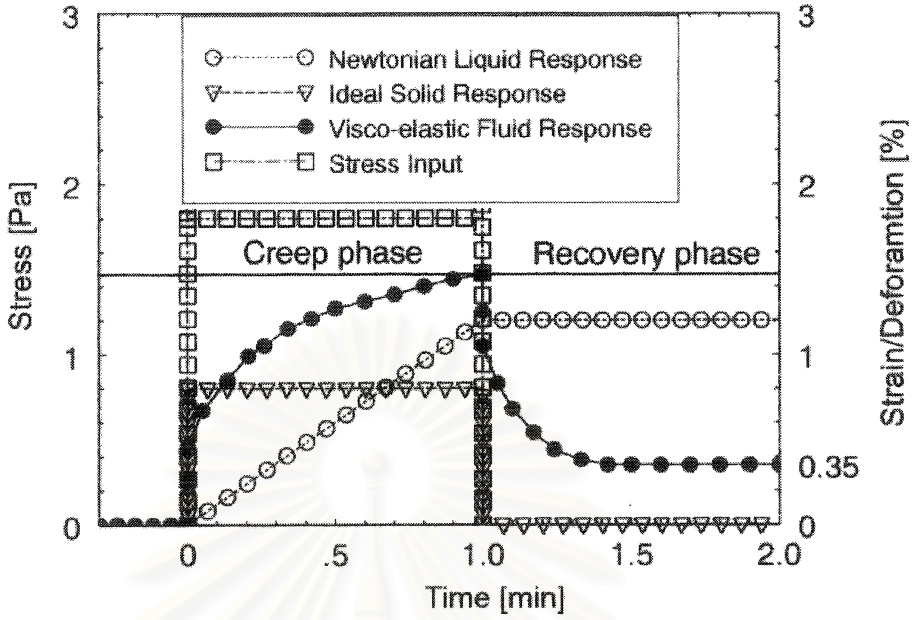


Figure 29. Stress and strain responses of several materials (Schramm, 2002)

Oscillation test

Oscillation is a dynamic measurement of viscoelasticity. It provides a different approach for the viscoelastic measurement in comparison to creep test. Some aspect of viscoelasticity are better described by the dynamic test and others by creep test. In oscillation test the material is subjected to a sinusoidal oscillating stress or strain with a frequency (ω), and the phase difference between oscillating stress and strain is measured.

This test can be divided into two groups: 1) large deformation test; 2) small deformation test. The large deformation measurement involves large stress or strain that beyond the LVE limit and show how the structure is broken down while the small deformation measurement stay with in LVE.

For the small amplitude controlled stress, the resulting strain response is a sine wave and the value of the measurement rheological parameter is independent of stress amplitude. The amplitude and phage-lag (δ), the angular displacement between the applied stress and the strain response, of the resulting strain can resolve the viscous

and elastic components of the shear modulus or complex modulus (G*) as following equation:

$$G^* = G' + iG'' \quad \ldots(3)$$

The G′ is storage or elastic modulus, the portion of the oscillation energy that is stored in elastically; G″ is loss or viscous modulus, representing the energy dissipated by the system.

For an elastic material (Hookean solid), G″ << G′ and the strain response is in phase with the applied stress; whereas a fluid, G″ >> G′ and a δ value is ¶/2 radians (90°). Any material having a δ value between 0 and ¶/2 radians is classified as viscoelastic material. (Figure 30)

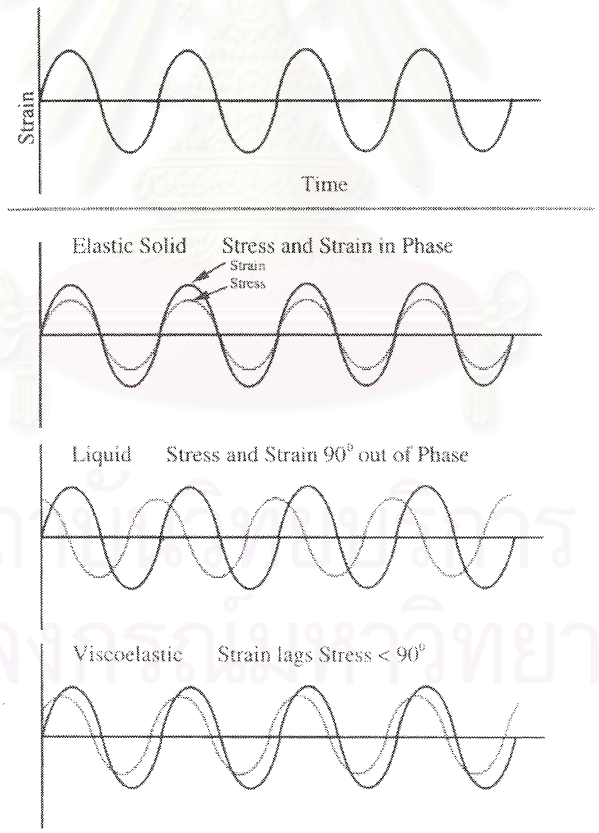


Figure 30. Stress versus strain response in oscillation test (Rao, 1999).

There are four types of oscillation test: 1) frequency sweep - G′ and G″ are determined as a function of frequency at fixed temperature, it is used to determine how the viscous and elastic of material change with the rate of application of stress or strain.; 2) temperature sweep - G′ and G″ are determined as a function of temperature at fixed frequency, this test is suitable for studying gel formation during cooling of heated dispersion; 3) time sweep - G′ and G″ are determined as a function of time at fixed temperature and frequency, this test is suitable for studying structutrer development in physical gel; 4) amplitude sweep – the applied stress or strain is constantly increasing, it is used to determine the linear viscoelastic (LVE) range.

LVE range is referred to G′ and G″ that remains constant over a certain strain or stress range. In this LVE range, the structure of material is not damaged (Figure 31). This is important parameter for setting up time test, temperature test, frequency sweep test and creep test.

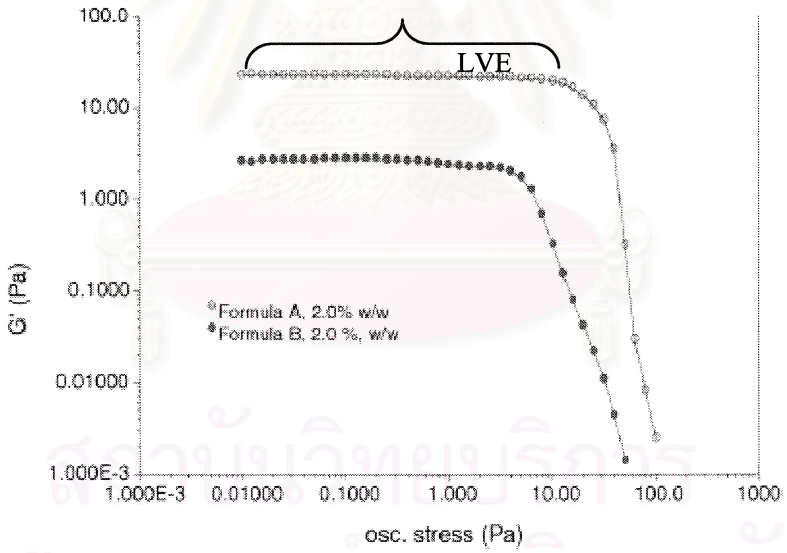


Figure 31. The Amplitude sweep on elastic modulus (G′) of different grades of MCC/NaCMC hydrogels (Rudraraju and Wyandt, 2005)

3 Materials

3.1 Lactose

Lactose, Lactosum, milk sugar or saccharum lactis is a nature disaccharide obtained from mammal's milk, e.g. cow, human, whale (Smolinske, 1992). It consists of glucose and galactose (Figure 32). Commercially, lactose is produced from whey of cow's milk (Wade and Weller, 1994). Lactose is white to off-white crystalline particles or powder, odorless and less sweet than sugar. When lactose is hydrolyzed by ß -D-galactosidase (lactase), an enzyme-splits these monosaccharides resulting in increased sweetness and depressed freezing point (Smolinske, 1992).

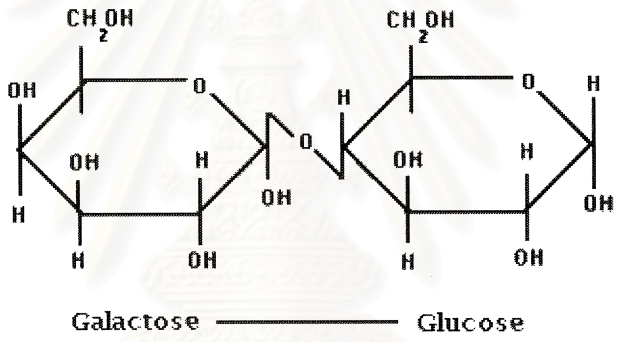


Figure 32. Structure of lactose

Lactose has three crystallized forms: α-lactose monohydrate, α-lactose anhydrous and β-lactose anhydrous. The α-lactose monohydrate form is more common than other forms (Raymond and Othmer, 1954b). The empirical formula of α-lactose monohydrate is $C_{12}H_{22}O_{11}H_2O$ with a molecular weight of 360.31. The melting point of α-lactose monohydrate is about 201-202 C°. It is soluble in water (1 in 4.63 at 25 C°) and more soluble at high temperature; slightly soluble in 85 % methanol and pyridine; insoluble in ethanol, ether, absolute methanol and chloroform (Raymond and Othmer, 1954b; Wade and Weller, 1994).

Lactose is widely used as an excipient in foods, drugs and cosmetics. There are many lactose grade are commercially, thus the grade of lactose chosen is dependent on the objective.

When the lactose is stored at high moisture content (more than 80% relative humidity), mold growth may occur. Lactose may develop a brown coloration on storage, the reaction, called Millard-type condensation, is acceleration by heat and damp conditions This reaction occur between lactose and compounds with a primary amine group (Wade and Weller, 1994)

3.2 Dibasic calcium phosphate

Dibasic calcium phosphate dihydrate, also named calcium monohydrogen phosphate dehydrate or calcium hydrogen orthophosphate is a white, odorless, tasteless powder or crystalline solid (Wade and Weller, 1994). It occurs as monoclinic crystals (O′ Neil et al., 2001). The empirical formula is $CaHPO_4.2H_2O$ with a molecular weight of 172.09. It is non-hygroscopic at 25 C° and relative humidity up to 90%. When the temperature is higher than 45 C°, it starts to lose its water of crystallization. It is prepared by reacting phosphoric acid with limestone and precipitation at a suitable temperature to obtain dibasic calcium phosphate dihydrate. It is practically insoluble in 95% ethanol and water; soluble in dilute acid such as gastric acid(O′ Neil et al., 2001; Wade and Weller, 1994).

Dibasic calcium phosphate dihydrate is used in oral pharmaceutical formulations, especially tabletting excipient because it has good compaction characteristics, desirable flow, and low cost. It is also used in calcium supplement and in dental preparations for its abrasive qualities. (O′ Neil et al., 2001; Wade and Weller, 1994)

3.3 Cellulose derivatives

Cellulose is a polysaccharide with the empirical formula $C_6H_{10}O_5$. It is the most abundant of all naturally occurring organic compounds (Raymond and Othmer, 1954a). Its structure is a polymer chain composed of the repeating anhydroglucose units as shown in Figure 33. In the structure, n is the number of anhydroglucose unit or the degree of polymerization of cellulose. The manufacture of cellulose used in pharmaceutics is divided into four groups as showed in Figure 34. These consist two

type of naturally cellulose: cellulose floc, powdered or microfine cellulose and microcrystalline cellulose; and two type of chemical derivative: cellulose ester and cellulose ether (Wallace, 1943).

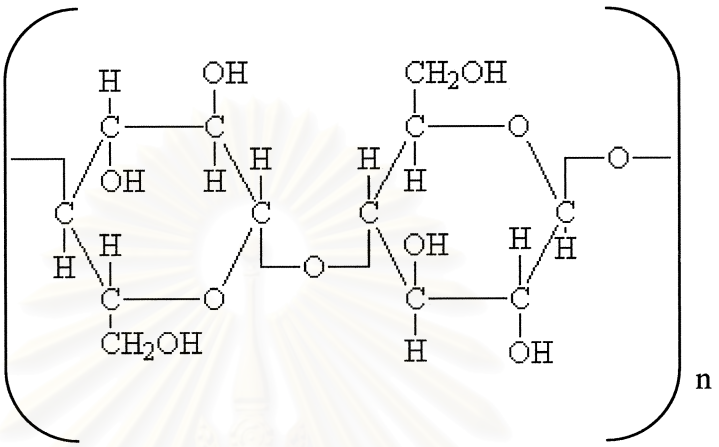


Figure 33. Structure of cellulose

3.3.1 Microcrystalline cellulose (MCC)

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose, with the empirical formula $(C_6H_{10}O_5)_n$; n ≈ 200 and the molecular weight ≈ 36000. It is a white-colored, odorless, tasteless, crystalline, and hygroscopic powder. It is slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acid and the most organic solvent (Wade and Weller, 1994).

In manufacturing process, the alpha-cellulose, obtained as a pulp from plant, are hydrolyzed by mineral acid to remove the amorphous region, then purified by filtration and the slurry is spray-dried to form dry, porous particles. It is commercially available in different particle size grade which has different properties and application. MCC products are very deformable and can be compressed into extremely hard tablet. It is widely used in pharmaceuticals as diluents, binder and disintegrant in tablets and capsules. In pellet formulation, it is known as an extrusion and spheronization aid. It is also used in cosmetics and food products (Wallace, 1943).

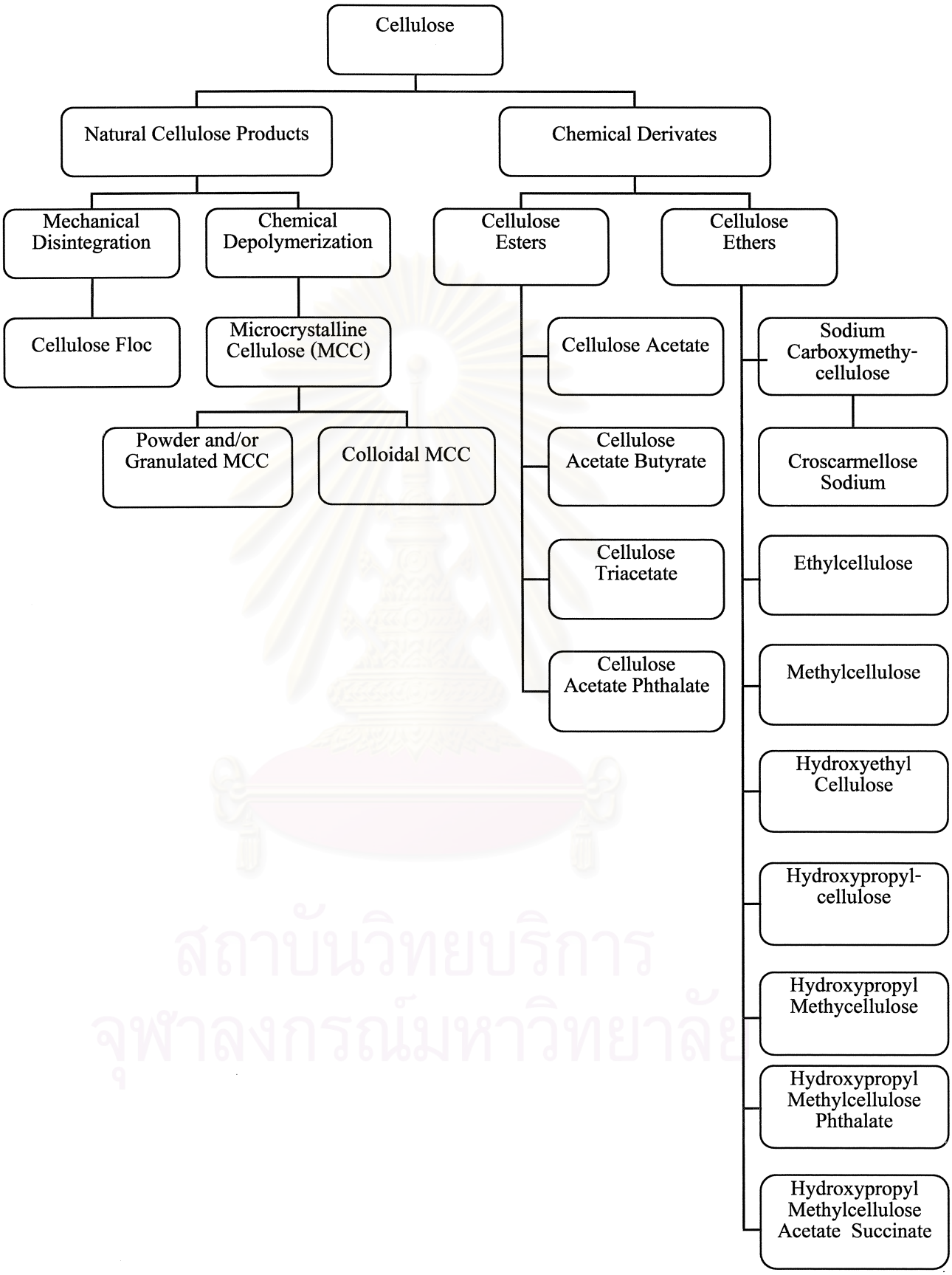


Figure 34. Cellulose products utilized in pharmaceutics

3.3.2 Carboxymethylcellulose sodium (NaCMC)

Carboxymethylcellulose sodium (NaCMC), also called sodium cellulose glycolate or cellulose gum is an ionic cellulose ether, prepared by the reaction of monochloroacetate with alkali cellulose that formed by reacting cellulose with sodium hydroxide (Raymond and Othmer, 1954). The structure of NaCMC is similar to cellulose but hydroxyl group of each anhydroglucose unit is substituted by carboxymethy (CH_2COOH) group (Figure 35). It occurs as a white to almost white color, odorless, granular and hygroscopic powder. Under high humidity, it can absorb a large quantity (>50%) of water. It is practically insoluble in acetone, ethanol, ether and toluene; and easily dispersed in water at all temperature, forming clear, colloidal solution (Wade and Weller, 1994). A number of grades of NaCMC are commercially available. The most frequently used grade in pharmaceuticals having a degree of substitution (DS) of 0.7. The DS is defined as the average number of hydroxyl group substituted of each anhydroglucose unit and it determines the solubility of polymer in water. NaCMC grades can be classified as low, medium and high viscosity. The viscosity, 1% solution, is 5-4000 cps depending on grade of CMC are shown in Table 1. The solutions of medium and high viscosity type of CMC exhibit pseudoplastic behavior (Wallace, 1943).

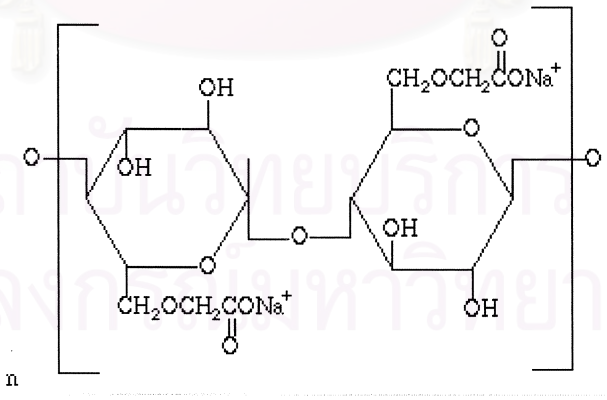


Figure 35. Structure of carboxymethylcellulose sodium

NaCMC is widely used in pharmaceutical formulations such as oral, topical or parenteral products. It is used as a tablet binder, disintegrant, stabilizing

agent, suspending agent and viscosity increasing agent. The concentration of medium viscosity grade about 4-6% is used to produce gel which can be the base for pharmaceutical formulation such as gel, suppository and paste. It is also used in cosmetics, toiletries and food products. Since it is hygroscopic, this has been associated with a decrease tablet hardness and increase disintegration time.

Table 1. Viscosity of aqueous carboxymethylcellullose sodium solution at 25 C°
(Wade and Weller, 1994)

Grade	**Concentration (% w/v)**	**Viscosity (mPas)**
Low viscosity	4	50-200
Medium viscosity	2	400-800
High viscosity	1	1500-3000

3.3.3 Methylcellulose (MC)

Methylcellulose (MC) or cellulose methyl ether is a semi-synthetic, non-ionic, hydrophilic polymer. The molecular weight varies from 40000-180000. It is a grayish-white, odorless, tasteless, fibrous powder (Lewis, 1997). It is prepared by treating alkali cellulose with methylchloride, and then purified with hot water (Raymond and Othmer, 1954). The methyl group, $-CH_3$, substitutes the hydroxyl group of anhydroglucose unit (Figure 36). The maximum DS is 3.0, however, the typical value is 1.3-2.6. The higher value of DS involves the lower solubility, because the polar hydroxyl groups are concealed. The DS value that gives good solubility is 1.8 (Raymond and Othmer, 1954).

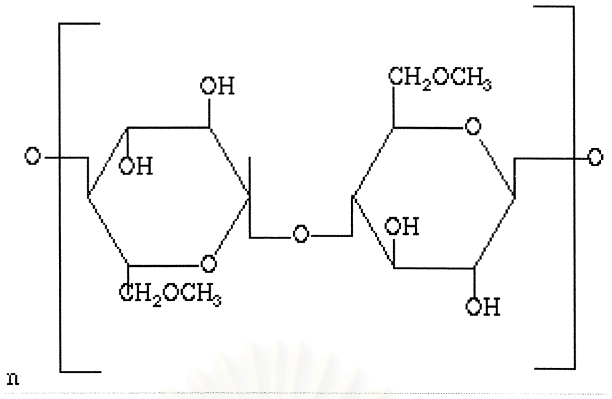


Figure 36. Structure of methylcellulose

MC dissolves in cold water, not in hot water. The clear viscous solution or gel is obtained by dispersing it in hot water, then chilling to 5-10 C°. It is insoluble in alcohol, ether, chloroform and the water with temperature higher than 50.5 C° and soluble in glacial acetic acid. The commercial products are different in DS and the length of backbone polymer. Usually, the commercial product has the DS of 1.6-1.8. It is useful in pharmaceutical, food and cosmetic as the thickener, emulsifier, protective colloid and binder. It is compatible with many water soluble materials such as starch, and natural gum (Raymond and Othmer, 1954).

3.3.4 Hydroxyethyl cellulose (HEC)

Hydroxyethyl cellulose (HEC) or 2-hydroxyethyl ether is long-established, nonionic, water soluble cellulose ether (Wallace, 1943). It is a light tan or cream to white, odorless, tasteless, hygroscopic powder. It is made by swelling cellulose with sodium hydroxide (NaOH) and reacting with ethylene oxide. The hydroxyethyl groups attaches to the hydroxyl (-OH) groups of the cellulose structure by ether linkages (Figure 37). (Wade and Weller, 1994; Zhejiang Shangyu Haishen Chemical, Company, online)

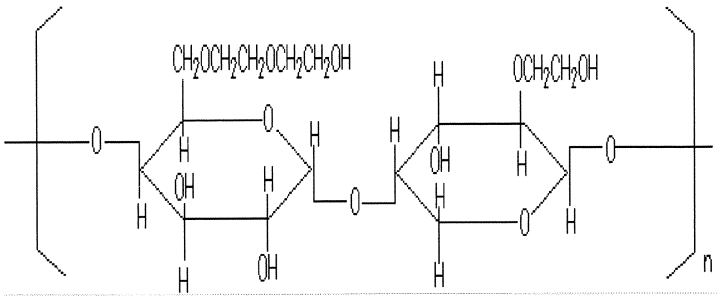


Figure 37. Structue of hydroxyethyl cellulose

HEC is soluble in ether, hot or cold water and forms clear, colorless, smooth and uniform solution. It is practically insoluble in the most organic solvent such as ethanol, acetone, ether and toluene. In some polar organic solvents such as glycols, HEC is partially soluble or swells (Wade and Weller, 1994).

HEC is available in several grades varying in viscosity and degree of substitute. The viscosity ranges from 2 to 800000 cps at 2% w/v (R. T. Vanderbilt Company, 2006). Its dispersible is the worst when compared with MC and HPMC (Zhejiang Shangyu Haishen Chemical, Company, online), so that the aqueous solution may be prepared by dispersing HEC in mildly agitated water at 20-25 C° and increases the temperature of the solution to 60-70 C° to increases the rate of dispersion. After that, the dispersion process is increased by making the solution slightly alkaline. Typically, the solution is completed dispersion in approximately an hour by controlling the temperature, pH and rate of agitation (Wade and Weller, 1994). The rheological behavior of the aqueous solution is pseudoplastic. When the temperature is elevated, the viscosity is decreased (R. T. Vanderbilt, Company, online).

HEC is compatible with the most organic salt, water soluble gums and resins due to its nonionic property. The viscosity of HEC is stable when the pH is between 2 to 12. HEC is tolerance to bacterial and enzyme degradation (Wade and Weller, 1994). NaCMC and sodium alginate can be added to HEC to increase viscosity (Wallace, 1943). HEC is widely used in cosmetics and pharmaceutics formulation. It is primarily used as a thickening agent, binder, film-former and modified release (Wade and Weller, 1994). The medium and high viscosity grade are

used as thickening agent, stabilizer, suspending agent, the low viscosity grade are used as film-former and high viscosity are also used as modified release.

3.3.5 Hydroxypropyl cellulose, low-substituted (HPC-L)

Hydroxypropyl cellulose, low-substituted (HPC-L) or 2-hydroxypropyl ether, low-substituted is a nonionic polymer. When HPC is dried at 105 C° for 1 hour and determined the hydroxypropyl content, HPC contains the content of hydroxypropyl about 50-80% by weight whereas HPC-L contains 5-16% of hydroxypropyl content (Obara, online). It occurs as a white to yellowish white fibrous powder or granular. It is odorless or has a slight, characteristic odor. It is tasteless (Joint FAO/WHO Expert Committee on Food Additives[JECFA], online). It is prepared by reacting alkali cellulose with propylene oxide at elevated temperature. Following the reaction, the reactant is recrystallized by neutralization, washed and milled (Rowe et al., 2003). Figure 38. shows the hydroxypropyl substitution of HPC

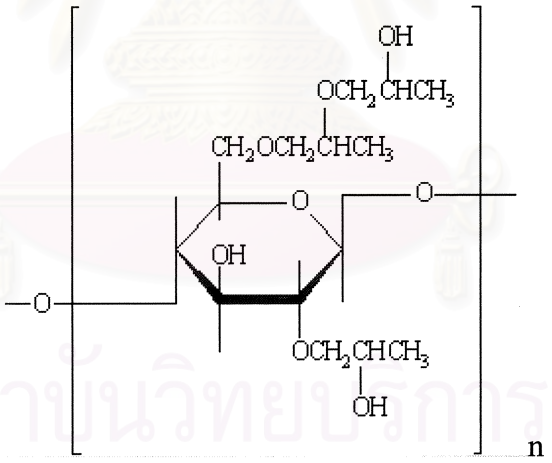


Figure 38. Structue of hydroxypropyl cellulose

While HPC is readily soluble in water, ethanol and other solvent, HPC-L is insoluble in these solvents but it absorbs water and swells. Due to this property, it is used as disintegrant in solid dosage form (Wallace, 1943). It is dissolve in 10% NaOH solution to give viscous solution (Shin-Etsu, Company, online).

HPC-L can be used as a dry binder. It can increase the hardness of tablet because it is in fibrous form. It can also be used as a wet binder (Obara, online). The modification of the substitute content and particle size of HPC-L causing changes in binding and disintegrating property. Therefore, there is many type of HPC-L to allow the selection of the most suitable for application. Typical content of HPC-L that use in the formulation is 5-25% (Rowe et al., 2003).

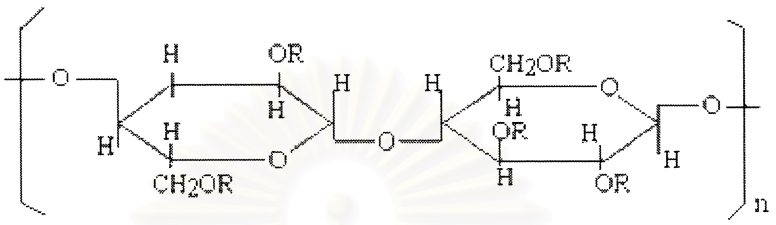
3.3.6 Hydroxypropyl Methylcellulose (HPMC)

Hydroxypropyl Methylcellulose (HPMC) or hypromellose is non-ionic cellulose ether, so that it is not form complex with metal salts (Wallace, 1943). It is an odorless, tasteless, white or creamy-white colored, fibrous and granular powder (Wade and Weller, 1994). The manufacture of HPMC is similar to MC but HPMC uses propylene oxide instead of methyl chloride.

Figure 39. shows the structure of HPMC, it substituents with methoxy group ($-OCH_3$) and hydroxy propoxy group ($-OCH_2CHOHCH_3$). Its molecular weight is approximately 10,000-1,500,000 (Wade and Weller, 1994). It dissolves readily in water in all proportion (Wallace, 1943). It is soluble in cold water and gives clear, odorless, surface-active solution of neutral pH (R. T. Vanderbilt, Company, online). It is practically insoluble in chloroform, 95% ethanol and ether. It is also soluble in binary organic-water solvent system such as mixture of methanol and dichloromethane, ethanol and dichloromethane (Wade and Weller, 1994; Wallace, 1943).

HPMC has many grade that difference in methoxy and hydroxypropoxy content. It is available in grades from very low to extremely high viscosity. The HPMC solution is pseudoplastic behavior. It has characteristic gelation or gel point temperature between 50-90 °C, depend on the grade of HPMC (R. T. Vanderbilt, Company, online; Wade and Weller, 1994). It is incompatible with some oxidizing agent. It tolerate for electrolyte concentration than MC (R. T. Vanderbilt, Company, online). It is more resistant to bacterial and enzyme degradation than other cellulose.

HPMC forms clear, flexible films that useful in coating tablets. It also utilizes as suspending agent, protective colloids, emulsion stabilizers and binder. For high viscosity grade may be used to retard the release of water-soluble drug form a matrix.



n: degree of polymerization; R:-H,-CH_3 or $CH_2CHOHCH_3$

Figure 39. Structue of hydroxypropyl Methylcellulose

3.4 Propranolol hydrochloride (propranolol hydrochloride)

Chemical name : (±) 1- (Isopropylamino)-3-(1-naphthyloxy) propan-2-ol hydrochloride or 1-(1-methylethylamino)-3-naphthalen-1-yloxy-propan-2-ol

Chemical formula : $C_{16}H_{21}NO_2.HCl$

Structural formula

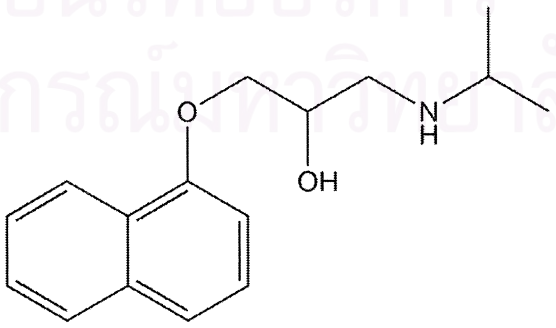


Figure 40. The chemical structure of Propranolol hydrochloride (http://en.wikipedia.org)

Molecular weight : 295.80

Description : A white or off-white, odorless or almost odorless, crystalline powder with bitter taste

Melting point : 163-164 C°

Solubility : 1 in 20 ml of water and alcohol, slightly soluble in chloroform and practically insoluble in ether, benzene and ethyl acetate.

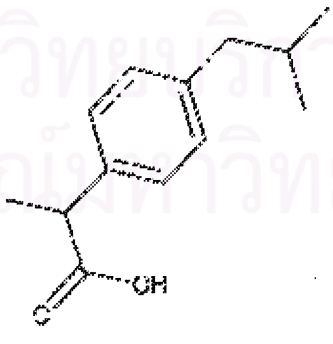
Propranolol is developed from the early β-adrenergic antagonists dichloroisoprenaline and pronethalol in the late 1950 by James W. Black. It is a non-selective beta blocker, which can block the action of epinephrine on both β_1- and β_2-adrenergic receptors. It is mainly used in hypertension, phaeochromocytoma, angina pectoris, myocardial infarction and cardiac arrhythmia. It is rapidly and completely absorbed from GI tract and appears in plasma within 30 min. The peak plasma levels achieved approximately 1–3 hours after ingestion. The bioavailability is increased by food. It has a variable bioavailability due to extensive first-pass metabolism. The hepatic impairment will increase its bioavailability (Martindale, 1996).

3.5 Ibuprofen

Chemical name : (±)-2-(4-isobutylphenyl) propionic acid

Chemical formula : $C_{13}H_{18}O_2$

Structural formula



Chemical Formula: $C_{13}H_{18}O_2$

Figure 41. The chemical structure of Ibuprofen (http://www.3dchem.com).

Molecular weight : 206.28

Description : A white or almost white crystalline powder or colorless crystals with a slight characteristic odor (Martindale, 1996).

Melting point : 75-77 C°

Solubility : Practically insoluble in water but very soluble in organic solvent such as alcohol, acetone, ether and methylene chloride. It dissolves in dilute aqueous solution of alkali hydroxides and carbonates.

Ibuprofen is a nonsteroidal anti-inflammatory (NSAID) drug, introduced in 1969. It is sought as a safer, more effective alternative to either corticosteroid or aspirin for rheumatoid arthritis. There are two ways for the synthesis of Ibuprofen: the Boot process and the Hoechst process. The synthesis of Ibuprofen uses isobutylbenzene as the starting material and Friedel-Crafts acylation. The Boot process requires six steps, while the Hoechst process requires only three steps (Figure 42). Ibuprofen is a chiral compound, the racemic ibuprofen is usually used, but only the s-isomer is an active form (O′ Neil, 2001). However the human body can convert the inactive (R) form into the (S) form, so eventually 100% of the ibuprofen taken becomes active.

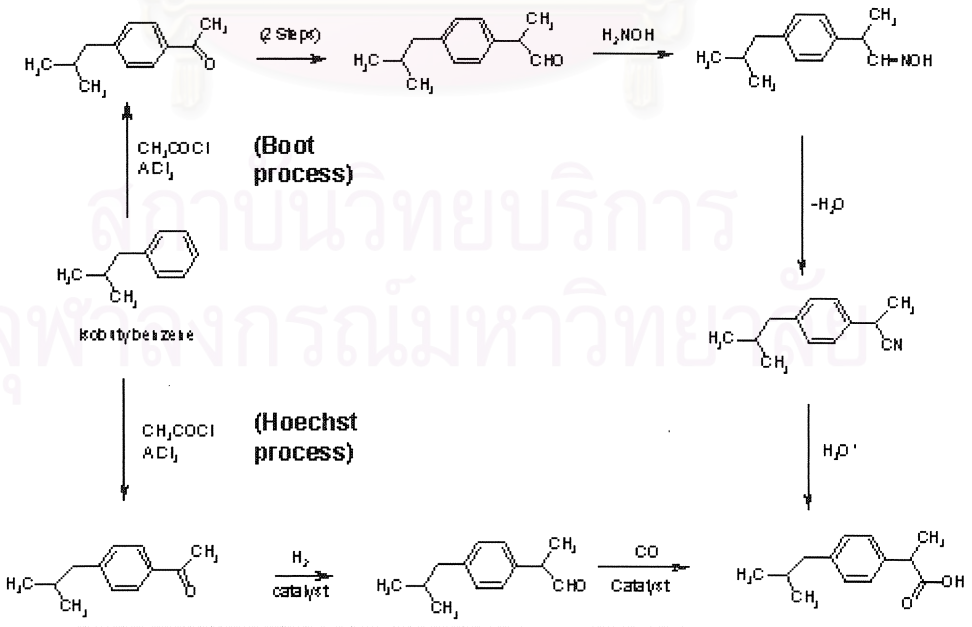


Figure 42. Synthesis of ibuprofen (http://www.chm.bris.ac.uk)

Ibuprofen inhibits the action of cyclooxygenase enzyme, causes inhibiting synthesis of prostaglandin, a compound involved in the inflammatory response. It is used as anti-inflammatory, analgesic and anti-pyretic. It is relieved mild to moderate pain such as headache, muscle pain, dysmenorrheal, and toothache.

Ibuprofen is absorbed from the gastro-intestinal tract and the peak plasma concentration occurs in 1-2 hours after ingestion. Generally, the oral dose is 200–400 mg (5–10 mg/kg in children) every 4–6 hours, up to a usual maximum daily dose of 800–1200 mg. Sometime, a maximum daily dose of 3200 mg may be used. It can also administer by topical and rectal. It is rapidly excreted in the urine. The main adverse effect is gastro-intestinal upset, so that it should be given with food. It is available in tablet, suspension, effervescent granule, cream and gel preparation. It is also available as modified release preparation (Martindale, 1996).

CHAPTER III

EXPERIMENTAL

1. Materials

The following materials obtained from commercial sources were used.

1.1 Drugs and Excipients

- Propranolol hydrochloride (Batch No.060520, Changzhou, China, purchased from Utopian Co., Ltd.)
- Ibuprofen (Batch No. IBU/0806/442, Barnala, India, purchased from Utopian Co., Ltd.)
- Lactose hydrous USP/NF/BP/EP 200 mesh (Lot.No. NZ9370, Whyndale, Auckland, New Zealand)
- Dibasic calcium phosphate (Lot.No. 25489, Total Chemical Co., Ltd., Bangkok, Thailand)
- Microcrystalline cellulose (Avicel PH 101®, Lot.No. 1824, Asahi Chemical Industry Co., Ltd., Japan)
- Sodium carboxymethylcellulose (NaCMC 1180®, Lot.No. B3058054, Diacel Chemical Industry Co., Ltd., Japan)
- Methylcellulose (Methocel A-15 ®, Lot.No. RQ19012496, Colorcon, Inc., UK)
- Hydroxyethylcellulose (HEC 4000, Lot.No. 4533, S. Tong Chemicals Co., Ltd., Bangkok, Thailand)
- Hydroxypropylcellulose (HPC-L®, Lot.No. BC-101, Nippon Soda Co., Ltd., Tokyo, Japan)
- Hydroxypropyl methylcellulose (Methocel E-15 LV®, Lot.No. RD19012404, Colorcon, Inc., UK)
- Deionized water
- 95% Ethyl alcohol (Ayudthaya Spirit Factory, Excise Department, Thailand)

2. Equipment

- Analytical balance (Model PB3002, Metler Toledo, Switzerland and Model A200s, Sartorious GMbh, Germany)
- Planetary mixer (Model 5K5SS, KitchenAid, Michigan, USA)
- Extruder (Model EXKS-1, Fuji Paudal Co., Ltd., Osaka, Japan)
- Spheronizer (Model S320, Aeromatic-Field, Hampshire, England)
- Hot air oven (Model UL 80, Memmert, Germany)
- Moisture balance (Model HR83, Metler Toledo, Switzerland)
- Scaning electron microscope (Model JSM-5800 HV/LV, Joel Ltd., Tokyo, Japan)
- Sieve shaker (Filtra, Spain)
- Jolting volumeter (modified by Department of Manufacturing Pharmacy, Chulalongkorn University, Thailand)
- Laser diffraction particle size (Mastersizer 2000, Malvern instruments, UK)
- Rheometer (Physica MCR 301, Anton PAar, Graz, Austria) and Temperature Controller (Viscotherm VT-2, Paar Physica, Stuttgart, Germany)
- Dissolution Apparatus I (model VK 7000, Vankel, USA)
- Friabilator (Erweka TAR2 20, Germany)
- Ultrapynometer 1000 (Quantachrome, USA)
- Ultraviolet/visible spectrophotrometer (model V-530, Jasco, Japan)
- Ultrasound transonic digital sonicator (model T680/H, Elma, Germany)
- pH meter (model 210A+, Thermo orion, Germany)
- Viscometer DV II+ (Brookfield, USA)
- Image analysis software (Image-Pro® plus version 4.5 for Windows, Media Cybernetic, Inc.)

3. Methods

1. Characterization of raw materials used in pelletization

The physical properties of raw materials including morphology, particle size and its distribution, flowability, density, moisture content and viscosity were investigated.

1.1 Morphology

The shape and surface topography of raw materials were determined by scanning electron microscopy (SEM). The samples were mounted on the aluminum stubs using double-sided sticky tape, then vacuum coated with gold film (gold sputtering technique) before SEM examination. Scanning electron photomicrographs of raw materials were taken in magnification of 75.

1.2 Particle size and size distributions

The particle size and particle size distributions of raw materials were studied by using a laser light diffractometer equipped with a wet dispersion part. Approximately, 0.5-1.0 g of sodium carboxymethyl cellulose, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose (low-substituted), hydroxypropyl methylcellulose were dispersed in approximated 500 ml of ethanol which were used as dispersion medium. Mineral oil and water were used as dispersion medium for propranolol hydrochloride and ibuprofen, respectively. The geometric mean particle size by volume of raw materials was averaged from five determinations

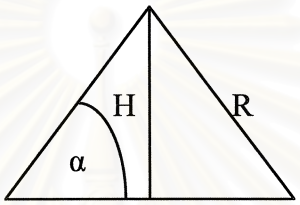
1.3 Flowability and angle of repose

Flowability was determined by funnel method. The amount of 5.0 g of raw material was filled in a glass funnel with 15 mm orifice fixed on a clamp above a smooth surface 10 cm. The time was recorded when the material started to flow until finished. Flow rate was calculated in g/sec. The angle of repose was calculated from the height and

radius of heap as following equation. Flow rate and angle of repose were measured in triplicate.

$$\text{Flow rate} = \frac{\text{Weight of raw materials (g)}}{\text{Flow time (sec)}} \quad \ldots(4)$$

$$\alpha = \tan^{-1}\left[\frac{H}{R}\right] \quad \ldots(5)$$



α = the angle of repose, H = height of heap, R = radius of heap

1.4 Bulk and tapped densities and percent compressibility

Bulk and tapped densities were determined according to the test of apparent volume. Five grams of raw material was accurately weighed and poured into 25 ml cylinder. Then, the filled cylinder was tapped by using jolting volumeter (tap 44 times/min) until the volume did not further decrease. Bulk and tapped volume were obtained, respectively. Bulk densities, tapped densities and percent compressibility were calculated according to following equations. The value of bulk densities, tapped densities and percent compressibility were averaged from three determinations.

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of raw material (g)}}{\text{Bulk volume (ml)}} \quad \ldots(6)$$

$$\text{Tapped density (g/ml)} = \frac{\text{Weight of raw material (g)}}{\text{Tapped volume (ml)}} \quad \ldots(7)$$

$$\text{\% Compressibility (Carr's index)} = \left(\frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}\right) \times 100 \quad \ldots(8)$$

Table 2. Flowability according to Carr's (Saenz et al., 2001).

Flow character	Angle of Repose (degree)	Compressibility (%)
Excellent	25-30	≤ 10
Good	31-35	11-15
Fair	36-40	16-20
Passable	41-45	21-25
Poor	46-55	26-31
Very poor	56-65	32-37
Extremely poor	> 66	> 38

1.5 Apparent density

Apparent densities were determined by using Ultrapycnometer 1000 by helium gas displacement. The sample was dried at 45°C overnight before analysis, then 0.4 g of sample was weighed and filled in a micro cell. The apparent density was averaged from five determinations and reported in term g/cm^3.

1.6 Moisture content

Moisture content in terms of loss on drying (LOD) was measured by using a moisture balance. Three grams of raw materials were used. Moisture content was averaged from three determinations.

1.7 Viscositity of binder solution

The binders were dispersed in deionised water with gently agitation. The binders solutions were equilibrated overnight to ensure the solution was homogeneous and free of

bubble. The viscosities of binders were determined by Brookfield DV II+ viscometer with following condition:

Concentration of binder solution	:	1 % w/v
Volumn of binder solution	:	500 ml
Spindle number	:	S31
Torque range	:	10-100 %

1.8 Rheological property of gel

The NaCMC gels were prepared corresponding to the formulations which shown in Table 3. and equilibrated for 18 hours to ensure full hydration. The period of time for gel hydration was equal to the equilibrium time for the wet mass before extrusion. (MacRitchie, Newton and Rowe, 2002). The rheological property of samples was examined by using a controlled stress rheometer (Physica MCR 301) with parallel plate (PP 25, Part No.79044, Serial no.3145, concentricity ± 2 μm, parallelity ±1 μm). Each gel sample was gently loaded onto lower plate using a dispensing spoon. The upper plate of 20.0 mm in diameter was lowered onto gel sample until 1 mm gap between lower and upper plate. Before the test was carried out, excess sample was removed. All rheological measurements were studied at 20 ± 0.1°C by Viscotherm VT2, the temperature controlled unit, in triplicate.

Preliminary studies were conducted to optimize instrument parameters for creep and oscillation experiment. An initial amplitude sweep, stress range 0.01-10 mNm and frequency of oscillation 1 Hz, was carried out to determine shear independent plateau of the elastic modulus (G'). The stress range used was recommended by company for gel system (Passakorn Woonwiriyakit, personal communication, July 6, 2006). The torque value that provides steady state of the elastic modulus was selected for creep and oscillation experiment.

Table 3. Formulations of gel used in characterization of rheological property by using the controlled stress rheometer

Code	Polymer	% w/w	
		Polymer	Water
CMC1-G/W30	NaCMC1180	0.25	30
CMC1-G/W32			32
CMC1-G/W34			34
CMC1-G/W35			35
CMC1-G/W36			36
CMC2-G/W49	NaCMC1180	0.50	49
CMC2-G/W50			50
CMC2-G/W51			51
CMC2-G/W52			52
CMC3-G/W43	NaCMC1180	0.50	43
CMC3-G/W46			46
CMC3-G/W49			49
CMC3-G/W51			51
CMC4-G/W40	NaCMC1180	0.50	40
CMC4-G/W43			43
CMC4-G/W46			46
CMC4-G/W52			52
CMC4-G/W55			55

1.8.1 Creep experiment

The creep experiment condition was taken from preliminary studies. The stress or torque was applied to the sample is in range of 0.001-0.01 mNm. The retardation and relaxation time for this experiment was 200 and 300 sec, respectively. The experiment was repeated on five samples. It was standard practice for the applied stress to be sufficiently low for the compliance to be within the linear viscoelastic range, LVE (stress

independent) and it was usual to quote the results in the form of the creep compliance, *J(t)* as following equation:

$$J(t) = \frac{\gamma}{\tau} \qquad \ldots(9)$$

, where γ is strain and τ is stress

The results values were calculated separately for creep (Equation 10.) and recovery phase (Equation 11.), *J(t)* can be considered as below :

$$J(t) = J_o + J_m(t) + J_n(t), \tau > 0 \qquad \ldots(10)$$

$$J(t) = J_{max} - J_o - J_m(t), \tau = 0 \qquad \ldots(11)$$

, where J_o is the instantaneous compliance, i.e. J at t = 0; $J_m(t)$ is a viscoelastic compliance,; $J_n(t)$ is a newtonian compliance and J_{max} is a maximum creep compliance. For *Jm(t)* and *Jn(t)* can be calculated by following equations:

$$J_m(t) = J_m \cdot (1 - \exp(-t / \lambda)) \qquad \ldots(12)$$

$$J_n(t) = \frac{t}{zero\ shear\ viscosity} \qquad \ldots(13)$$

, where λ is retardation time and zero shear viscosity is viscosity at no shear condition

In present study, the value of J_o, the instantaneous compliance; was averaged from the experiment on five samples.

1.8.2 Oscillation experiment

The torque value used in this experiment was same as the torque which was used in the creep experiment. The oscillation frequency was 1.0 Hz and time for each run experiment was 200 sec. The viscous and elastic components of the shear modulus can be resolved by monitoring the amplitude and phase-lag, δ, of the resultant strain response of the material. The shear modulus or complex modulus, G*; and phase-lag, δ, can be defined by following equation:

$$G^* = G' + iG'' \quad \ldots (14)$$

$$\tan\delta = \frac{G'}{G''} \quad \ldots(15)$$

,where G′ is storage modulus; and G″ is loss modulus

The value of G′, storage modulus; and G″, loss modulus were determined. The experiment was also repeated on five samples.

2. Pelletization

2.1 Formulation

In general, the formulation composed of a model substances and formulation aid. Lactose hydrous and propranolol hydrochloride were used as models for water soluble substances, whereas dibasic calcium phosphate and ibuprofen were used as models for water insoluble substances. Formulation aids studied were sodium carboxymethylcellulose (NaCMC 1180), methylcellulose (MC 15), hydroxyethylcellulose (HEC 4000), hydroxypropylcellulose (low-substituted) (HPC-L) and hydroxypropyl methylcellulose (HPMC E15). The liquid binder studied were water and 50 % w/w ethanol in water (equivalent to 55.42 % v/v). The amount of model substances was replaced with 0.25, 0.50, 1.00 and 2.00 % w/w formulation aid (Table 4.).

The control formulation contained 50% lactose, 50% microcrystalline cellulose (MCC) and using water as a granulating liquid.

MC 15 was used as a formulation aid for propranolol hydrochloride and ibuprofen. When water was used as liquid binder, propranolol hydrochloride and ibuprofen pellets were prepared by using 2% and 4% w/w of MC 15. When 50% w/w ethanol was liquid binder, MC 15 in the formulation of propranolol hydrochloride and ibuprofen formulation was 1% and 8% w/w, respectively (Table 5).

2.2 Preparation of pellets

Pellets were prepared by extrusion/spheronization process. The batch size was 300 g of dry powders.

The amounts and various types of raw material were weighed and mixed in a planetary mixer at a lowest speed for 10 minutes. The dry mixture was gradually added with water or 50% w/w ethanol in water and mixed for 15 minutes. After that, the wet mass was allowed to equilibrate for 18 hours in the plastic bags in a closed container.

After equilibration, the wet mass was extruded by a radial single screw extruder with a die of 1 mm diameter and 1 mm length. The extrudates were obtained and transferred to a spheronizer with a radial type friction plate. The spheronizer was operated at 800 rpm for 10 minutes. For propranolol hydrochloride and ibuprofen pellets the spheronization time was 3 minutes. The product was dried overnight in a hot air oven at 55C°. When 50%w/w ethanol in water used as a liquid binder, the wet mass was extruded and spheronized immediately.

Table 4. Formulations of pellets using cellulose derivative as the formulation aid and water or 50% w/w ethanol in water as a liquid binder.

Code	Polymer	% w/w	
		Polymer	Lactose (L) or $CaHPO_4$(C)
CMC1	NaCMC1180	0.25	99.75
CMC2		0.50	99.50
CMC3		1.00	99.00
CMC4		2.00	98.00
MC1	MC15	0.25	99.75
MC2		0.50	99.50
MC3		1.00	99.00
MC4		2.00	98.00
HEC1	HEC4000	0.25	99.75
HEC2		0.50	99.50
HEC3		1.00	99.00
HEC4		2.00	98.00
HPC1	HPC-L	0.25	99.75
HPC2		0.50	99.50
HPC3		1.00	99.00
HPC4		2.00	98.00
HPMC1	HPMC E15	0.25	99.75
HPMC2		0.50	99.50
HPMC3		1.00	99.00
HPMC4		2.00	98.00
CT	MCC PH101	50.00	50.00

$CaHPO_4$ = Dibasic calcium phosphate
NaCMC1180 = Sodium carboxymethylcellulose grade 1180
MC15 = Methylcellulose 15 cp.
HEC 4000 = Hydroxyethylcellulose 4000 cp.
HPC-L = Hydroxypropyl cellulose low substitued
HPMC E15 = Hydroxypropyl methylcellulose 15 cp.
MCC PH101 = Microcrystalline cellulose grade Avicel PH 101

Table 5. Formulations of propranolol hydrochloride and ibuprofen pellets using MC 15 as the formulation aid and water or 50% w/w ethanol in water as a liquid binder.

Code	Liquid binder	%w/w		
		MC 15	Propranolol HCl	Ibuprofen
MC2-P/W41	water	2.00	98.00	-
MC4-I/W70		4.00	-	96.00
MC1-P/A58	50% w/w ethanol	1.00	99.00	-
MC8-I/A106		8.00	-	92.00

Propranolol HCl = Propranolol hydrochloride

3. Evaluation of wet mass

The wet mass were prepared according to the formulation which shown in Table 6. and equilibrated for 18 hours to ensure moisture equilibrium. The period of 18 hours was equal to the equilibrium time of the wet mass before extrusion. (MacRitchie, Newton and Rowe, 2002: 44). First, 8.0 g of wet mass was filled into die of 25.0 mm in diameter, and compressed with 1 bar by hydraulic compressor to form a plug having about 11-13 mm in thickeness. Each sample is wrapped in plastic and aluminium and stored in well-closed container . These samples were transferred to the lower plate of a controlled stress rheometer (Physica MCR 301) with parallel plate (PP 25, Part No.79044, Serial no.3145, concentricity ± 2 μm, parallelity ±1 μm).

The rheological property of samples was examined by using a controlled stress rheometer (Physica MCR 301) with parallel plate. Each sample was gently loaded onto lower plate. The upper plate 20.0 mm in diameter was lowered onto sample until the upper plate contact with the sample. All rheological measurments were studied at 20 ± 0.1°C in triplicate.

Preliminary studies were conducted to optimize instrument parameters for creep and oscillation experiment. An initial amplitude sweep, stress range 0.0001-10 mNm and frequency of oscillation 1 Hz, was carried out to determine shear independent plateau of the elastic modulus (G'). The stress range used was recommended by company for solid sample system (Passakorn Woonwiriyakit, personal communication, July 6, 2006). The torque value that provided steady state of the elastic modulus, G′, was selected for creep and oscillation experiment.

3.1 Creep experiment

The creep experiment condition was taken from preliminary studies. The stress or torque was applied to the sample is in range of 0.1-2.6 mNm. The retardation and relaxation time for this experiment is 200 and 300 sec, respectively. The experiment was repeated on five samples and the value of the instantaneous compliance, J_o, were averaged.

3.2 Oscillation experiment

The torque used in this experiment was the same as the torque which was used in the creep experiment. The oscillation frequency was 1.0 Hz and time for each run was 200 sec. This experiment was repeated on five samples and the values of G′, storage modulus; and G″, loss modulus were averaged.

4. Characterization of products

The pellets were characterized that main sieve of each pellets formulation. The main sieve was selected from two sieve fraction that connected and the percent retained more than 70%.

4.1 Morphology

Photomicrographs of shape and size of pellets were taken in magnification of 7, with a digital camera (EOS 100, Cannon, Tokyo, Japan), linked with a stereomicroscope system (ML9300, Meiji, Tokyo, Japan)

Scanning electron microscopy (SEM) topographies were taken to examine morphology, surface and internal structure of cross-sectioned of rounded pellets. The pellets were mounted on the aluminum stubs using lacquer, then vacuum coated with gold film (gold sputtering technique) prior to SEM examination and photomicrographs were taken in magnification of 75.

Table 6. Formulations used in investigating rheological properties by using the controlled stress rheometer

Formulation	Solvent	
	H_2O	50% w/w Ethanol
NaCMC1180	CMC2-L/W45	CMC1-L/A65
	CMC2-L/W50	CMC1-L/A70
	CMC2-L/W51	CMC2-L/A70
	CMC2-L/W52	CMC2-L/A83
	CMC2-L/W55	CMC2-L/A84
	CMC3-L/W43	CMC2-L/A86
	CMC3-L/W45	CMC2-L/A90
	CMC3-L/W50	CMC3-L/A68
	CMC3-L/W52	CMC3-L/A90
	CMC4-L/W43	
	CMC4-L/W45	
	CMC4-L/W52	
MC 15	MC2-L/W39	MC3-L/A58
	MC2-L/W45	MC3-L/A64
	MC2-L/W50	MC3-L/A72
	MC3-L/W45	
HPMC E15		HPMC2-L/A65
		HPMC3-L/A62
		HPMC3-L/A65
		HPMC3-L/A68
MCC	CT-L/W195	CT-L/W195
propranolol HCl	MC2-P/W41	MC1-P/A58
ibuprofen	MC4-I/W70	MC8-I/A106

4.2 Particle size and size distribution

Particle size distribution of pellet was determined by sieve analysis, consisting of a set of US standard sieves, ranging from 10 mesh (2.00 mm), 12 mesh (1.70 mm), 14 mesh (1.40 mm), 16 mesh (1.18 mm), 18 mesh (1.00 mm), 25 mesh (0.71 mm), 35 mesh (0.50 mm) sieves and collection pan. The sieve aperture was based on a $\sqrt{2}$ change in diameter between adjacent sieves (Staniforth, 2002). The total amounts of resultant pellets were put on the top of the sieve set. The sieves were placed on the sieve shaker and shaken for 10 minutes. The pellets retained on each sieve size were weighed and calculated for the percentage of weight retained according to equation (1) and the cumulative percentage weight under size.

$$\%\text{Retained} = \frac{\text{Retained weight (g)}}{\text{Total pellet weight (g)}} \times 100 \qquad \ldots(16)$$

When the cumulative percent frequency was plotted against particle size diameter, the particle size cumulative frequency distribution curve was obtained. The particle diameter (median diameter) corresponded to the point that separated the cumulative frequency distribution curve into two equal halves, above and below which 50% of particle lies (point *a* in Figure 43). The lower and upper quartile points at 25% and 75% divided the upper and lower range of a symmetrical curve into equal part (points *b* and *c*, respectively, in Figure 43). In order to quantify the interquartile range (IQR) can be determined as following equation:

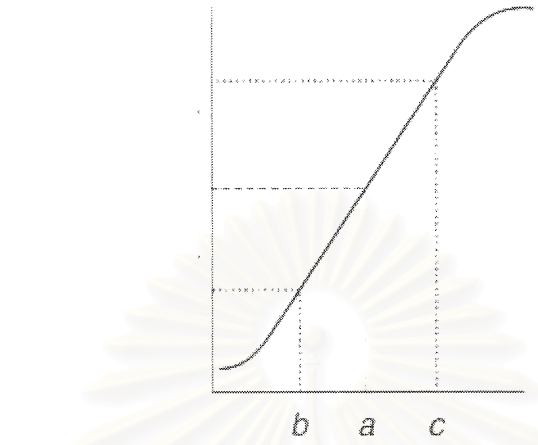


Figure 43. Cumulative frequency distribution

$$IQR = c - b \qquad \ldots(17)$$

,where b and c are lower and upper quartile points.

4.3 Flowability and angle of repose

Flow rate and angle of repose have been used as methods of quantifying flowability. The angle of repose and flow rate was measured by fixed funnel and fixed bed cone method. The 10.0 g of pellets were filled in a glass funnel with 12 mm orifice fixed on a clamp above a smooth surface 7 cm. The angle of repose was measured from heap carefully built up by dropping the sample through a glass funnel to plate. The time was recorded when the pellets started to flow until finished. Flow rate was calculated in g/sec and the angle of repose was calculated from high of heap and radius of plate. Flowability of pellets was determined in triplicate.

4.4 Bulk and tapped densities and percent compressibility

Bulk and tapped densities of pellet were determined by pouring 10 g of pellets into 25 ml graduated cylinder; the initial volume was recorded. Then, the filled cylinder was tapped by jolting volumeter until the volume did not further decrease. The tapped volume was recorded. Both densities were calculated according to equation (6, 7) and averaged from three determinations.

The percent compressibility was another indirect method of measuring flowability. It was calculated from bulk and tapped densities according to equation (8).

4.5 Apparent densities

The apparent densities of pellets were determined using Ultrapycnometer 1000 by helium gas displacement. The sample was dried at 45°C over night before analysis. Then, accurately weighed sample of 0.4 g was filled in a micro cell. The apparent density averaged from five determinations and reported in term g/cm^3.

4.6 Friability

Five grams of pellets were filled with 5 metals spheres into polyvinylchloride (PVC) container. The container was firmly closed with the cap and rotated in friabilator at 25 rpm for 4 minutes. After that, the dust and smaller particles were sieved off and the remained pellets were weighed again. The percent of friability was calculated from the following equation:

$$\text{Percent of friability} = \frac{\text{Weight loss} \times 100}{\text{Initial weight}} \quad \ldots(18)$$

4.7 Sphericity

Pellet size and shape were determined using an image analysis system. Photomicrographs of pellets were taken in magnification of 7, with a digital camera (EOS 100, Cannon, Tokyo, Japan), linked with a stereomicroscope system (ML9300, Meiji, Tokyo, Japan). The sphericity of pellet was determined by using imaging analyzer. One hundred and twenty pellets were analyzed by software Program Image Pro Plus® (Image-Pro® plus version 4.5 for windows). The feature parameters, longest diameter or Feret maximum, smallest diameter or Feret minimum, area and perimeter were determined. Aspect ratio and roundness which gave the degree of pellet sphericity were derived from those parameters and could be calculated by following equations:

$$Aspect\ ratio = \frac{Longest\ diameter\ or\ Feret\ \max imum}{Smallest\ diameter\ or\ Feret\ \min imum} \quad \ldots(19)$$

$$Roundness = \frac{[Perimeter]^2}{4\pi[Area]} \quad \ldots(20)$$

4.8 Moisture

Moisture content in terms of loss on drying (LOD) was measured by using a moisture balance. Three grams of pellets were used. Moisture content was averaged from three determinations.

4.9 Dissolution test

Determination of drug release by using USP Dissolution Apparatus as following condition :

Condition	Propranolol HCl	Ibuprofen
Medium	900 ml diluted hydrochloric acid (1:100)	900 ml pH 7.2 phosphate buffer
Apparatus (rpm)	Apparatus I (100 rpm)	Apparatus I (100 rpm)
Temperature (°C)	37±0.5	37±0.5
Time	1.5 hour	3 hour
UV wavelength (nm)	286	269

An accurate weight of propranolol hydrochloride and ibuprofen pellets equivalent to 20 mg of drug content was filled in the basket. Ten milliliters of samples were withdrawn at time intervals of 5, 15, 30, 45, 60, and 90 for propranolol hydrochloride pellets; or time interval was 5, 15, 30, 45, 60, 90 and 180 minutes for ibuprofen pellets. Fresh medium was added immediately after each sampling to keep the volume of medium constant. The sample was determined by ultraviolet/visible spectrophotometer. The dissolution data was evaluated from three samples of each formulation.

CHAPTER IV

RESULTS AND DISSCUSSION

1. Characterization of raw materials used in pelletization

1.1 Morphology

Lactose, dibasic calcium phosphate ($CaHPO_4$), microcrystalline cellulose (MCC), sodium carboxymethyl cellulose (NaCMC 1180), methylcellulose (MC 15), hydroxyethyl cellulose (HEC 4000), hydroxypropyl cellulose (low-substituted) (HPC-L), hydroxypropyl methylcellulose (HPMC E15), propranolol hydrochloride (propranolol HCl) and ibuprofen were examined by scanning electron microscopy (SEM) for morphology. The shape and surface topography were present in Figures 44-46.

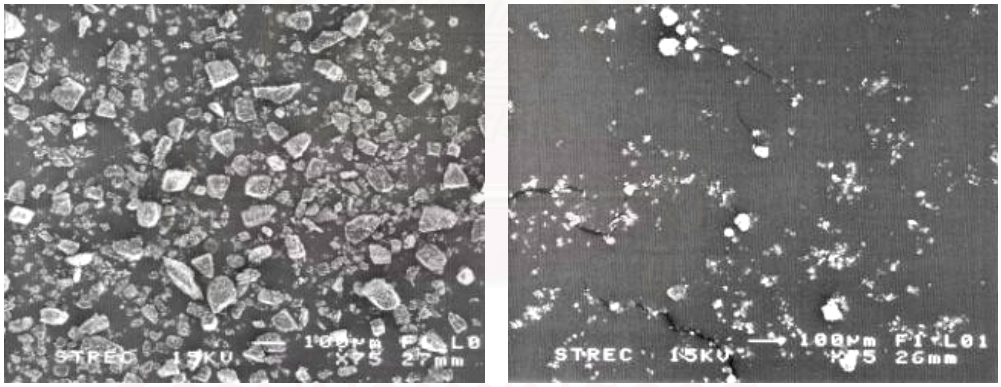
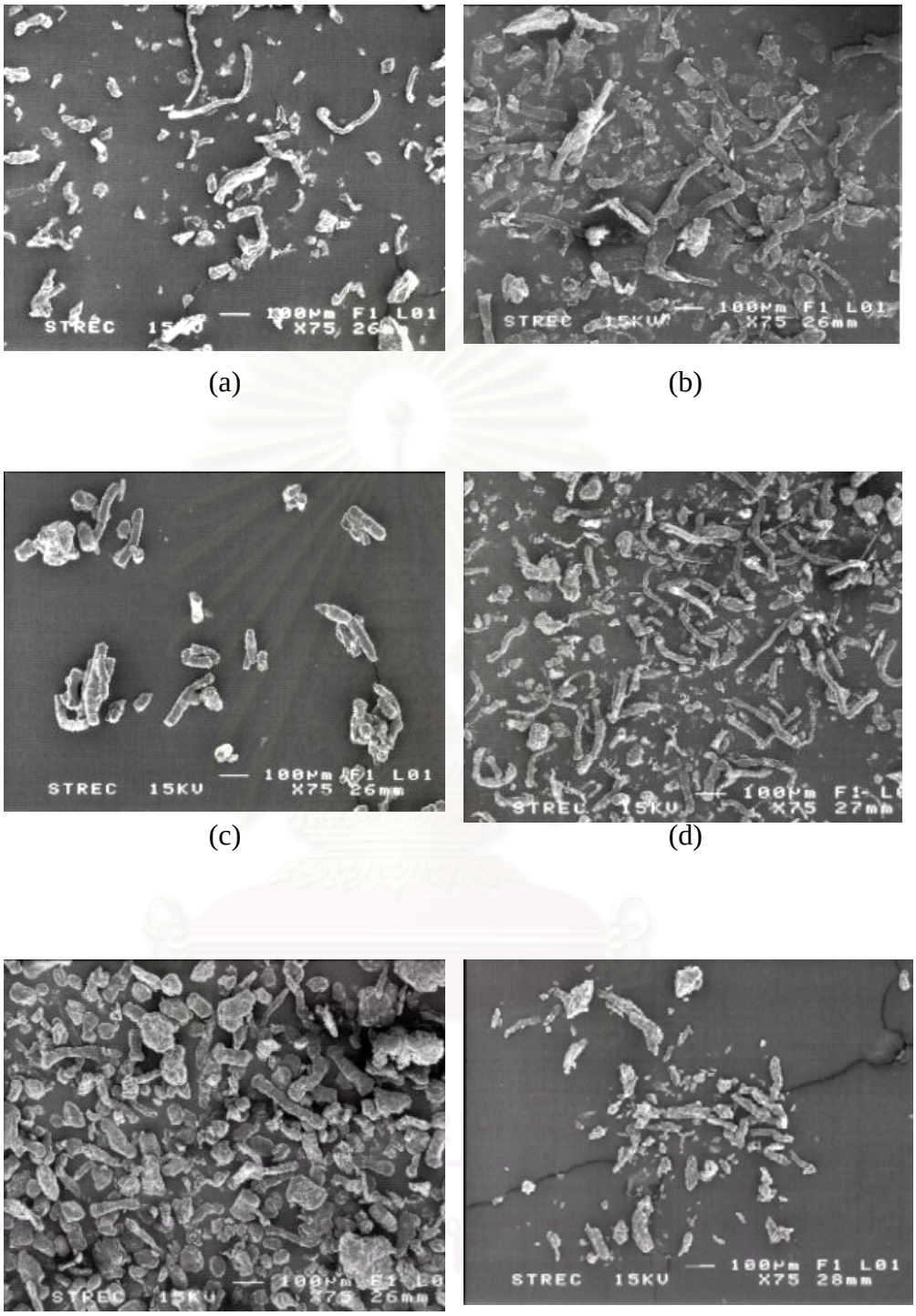


Figure 44. Scanning electron photomicrographs of (a) lactose and (b) dibasic calcium phosphate, in magnification of x75.

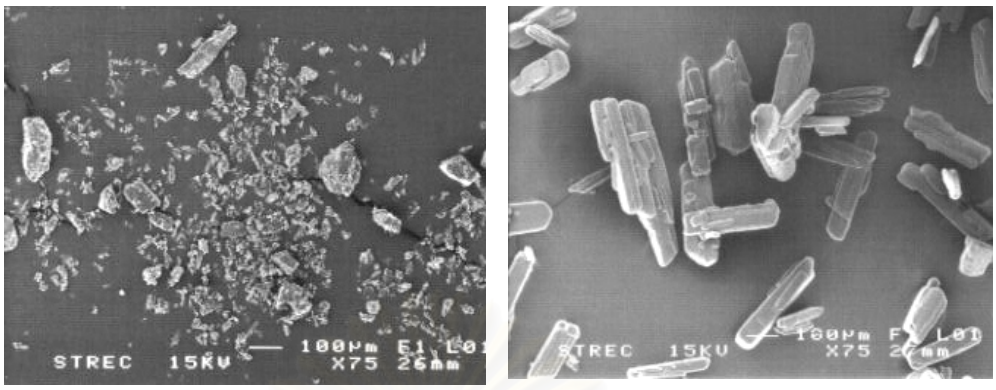


(a) (b)

(c) (d)

(e) (f)

Figure 45. Scanning electron photomicrographs of (a)NaCMC 1180, (b) MC 15, (c) HEC 4000, (d) HPC-L, (e) HPMC E15 and (f) MCC in magnification of x75.



(a) (b)

Figure 46. Scanning electron photomicrographs of (a) propranolol HCl and (b) ibuprofen in magnification of x75.

The shape of lactose, dibasic calcium phosphate and propranolol hydrochloride was irregular while the cellulose ethers were fibrous. Ibuprofen showed crystalline rod shape. The particle size from scanning electron photomicrographs of dibasic calcium phosphate compared with that of other materials was relatively small and agreed with the results obtained from a laser light diffractometer.

1.2 Particle size and size distributions

The particle size and particle size distributions of raw materials were measured by using a laser light diffractometer and the results are shown in Table 7.

The particle size distribution profile of $CaHPO_4$ showed a bimodal distribution. Lactose and HEC 4000 had a normal distribution. MC 15, HPC-L, HPMC 15 exhibited negative skewness whereas NaCMC 1180 was positively skewed. The material which had the smallest particle size, 21.89±3.61 μm, was $CaHPO_4$.

1.3 Flowability and angle of repose

The flowability and angle of repose of raw material were presented in Table 8. Only HPMC E15 could flow through a glass funnel with 15 mm orifice, so that it had the less interparticular cohesion than other materials.

Table 7. The geometric mean particle size of distribution by volume, (n=5).

Material	D[4,3] [a]μm mean (SD)	Span[b] mean (SD)
Lactose	98.65 (1.64)	2.11 (0.01)
$CaHPO_4$	21.89 (3.61)	4.41 (0.15)
NaCMC 1180	112.51 (17.61)	2.16 (0.08)
MC 15	105.40 (2.21)	1.95 (0.04)
HEC 4000	180.00 (1.94)	1.59 (0.03)
HPC-L	71.19 (2.87)	2.26 (0.07)
HPMC E15	212.26 (5.63)	1.88 (0.07)
MCC	102.26 (0.73)	1.83 (0.01)
Propranolol HCl	56.99 (1.46)	3.10 (0.04)
Ibuprofen	237.46 (4.33)	1.75 (0.02)

Note: Propranolol HCl = Propranolol hydrochloride
[a]D[4,3] is the volume mean diameter.
[b]The span is defined as the difference between the diameters at the 90 and the 10 percentage points relative to the median diameter.

1.4 Bulk and tapped densities and percent compressibility

Percent compressibility or Carr's index is a one-point determination and does not always reflect the ease or speed with which the powder consolidates. Indeed, some materials have high index, suggesting poor flow, but may consolidate rapidly. Rapid consolidation is essential for uniform material which posses compressibility, would be the less flowable. As the results in Table 9, MCC and propranolol hydrochloride was a free-flowing material while other materials could be non-free flowing. The HPMC

E15 results disagreed with the flow character of flow rate and angle of repose from which HPMC E15 showed excellent flowability. It might be due to that HPMC had better the bridge strength (Saenz et al., 2001)

Table 8. Flowability and angle of repose of raw materials, (n=3).

Physical properties	Flow rate (g/sec) mean (SD)	Angle of repose (degree) mean (SD)
Lactose	NA	NA
$CaHPO_4$	NA	NA
NaCMC1180	NA	NA
MC15	NA	NA
HEC4000	NA	NA
HPC-L	NA	NA
HPMC E15	10.1 (0.74)	23.3 (0.51)
MCC	NA	NA
Propranolol HCl	NA	NA
Ibuprofen	NA	NA

Note: NA = The material could not flow.

1.5 Apparent density

The apparent density of raw materials was determined by using helium gas displacement. The result was shown in Table 10. This technique was not only for material volume and density determination, but also as a mean for porosity determination (Webb, 2001). The $CaHPO_4$ possessed the highest apparent density than other materials. It can be described that it has the less apparent volume (the total volume of solid matter, open pores and closed pores and interstices) and porosity.

Table 9. Bulk and tapped densities and percent compressibility of raw materials, (n=3).

Physical properties	Bulk density (g/ml) mean (SD)	Tapped density (g/ml) mean (SD)	% Compressibility mean (SD)
Lactose	0.56 (0.02)	0.74 (0.00)	25.0 (2.09)
$CaHPO_4$	0.45 (0.01)	0.72 (0.03)	36.4 (2.00)
NaCMC1180	0.48 (0.01)	0.65 (0.02)	26.2 (2.15)
MC15	0.28 (0.00)	0.44 (0.00)	36.6 (0.57)
HEC4000	0.24 (0.33)	0.33 (0.44)	25.0 (0.52)
HPC-L	0.35 (0.00)	0.53 (0.00)	32.9 (0.69)
HPMC E15	0.45 (0.00)	0.59 (0.00)	24.9 (1.57)
MCC	0.31 (0.00)	0.38 (0.01)	18.5 (0.98)
Propranolol HCl	0.47 (0.01)	0.56 (0.00)	15.9 (0.60)
Ibuprofen	0.39 (0.00)	0.49 (0.00)	21.5 (0.30)

Table 10. Apparent density and moisture content of raw materials, (n=5).

Physical properties	Apparent density (g/ml) mean (SD)	Moisture content (%LOD) mean (SD)
Lactose	1.41 (0.00)	0.1 (0.01)
$CaHPO_4$	2.85 (0.02)	2.0 (0.05)
NaCMC1180	1.54 (0.00)	12.7 (0.11)
MC15	1.29 (0.00)	5.7 (0.06)
HEC4000	1.29 (0.00)	7.8 (0.06)
HPC-L	1.36 (0.01)	9.4 (0.02)
HPMC E15	1.23 (0.00)	4.1 (0.04)
MCC	1.23 (0.00)	4.32 (0.05)
Propranolol HCl	1.21 (0.00)	0.19 (0.05)
Ibuprofen	1.13 (0.00)	0.25 (0.06)

Note: % LOD = % Loss on drying

1.6 Moisture content

The results of moisture content in terms of loss on drying (LOD) are presented in Table 10. The moisture content of NaCMC 1180 is the highest, 12.70±0.11 %, due to hygroscopic property of this material.

1.7 Viscosity of binder solution

The viscosity of NaCMC 1180, MC 15, HEC 4000, HPC-L and HPMC E15 solution was measured by using Brookfield viscometer DV II+. The viscosities of solutions are presented in Table 11. The value in bracket were obtained from commercial source

Table 11. Viscosity of binder solutions.

Polymer	Concentration (%w/v)	Viscosity (cps)	Temp. (˚C)
NaCMC1180	1	680.1 (1300-2000) [a]	26.8
MC15	2	7.7 (12-18)[b]	27.0
HEC4000	2	N/A (4000)[c]	27.2
HPC-L	2	N/A (6-10)[d]	27.1
HPMCE15	2	11.0 (12-18)[e]	27.1

Note : [a]Diacel Chemical Industries, Ltd. (1% w/v, Brookfield 60 rpm at 25˚C)
[b]Dow Chemical Company (2% w/v at 20˚C)
[c]Sigma (2% w/v at 25 ˚C)
[d]Nippon Soda Co., Ltd (2% w/v at 20˚C)
[e]Dow Chemical Company (2% w/v at 20˚C)
N/A = The viscosity could not be measured because the polymer could not be fully hydrated in present study

1.8 Rheological property of gel

The NaCMC 1180 gel was used as a model to study the effect of rheological property of gel due to that NaCMC 1180 has been used to facilitate extrusion and bind moisture in formulation of pellet (Hoefler, 2000). It also reduced MCC content in

formulation for extrusion-spheronization process (Funck et al., 1991). The results are shown in Table C-1, C-6 and C-11 in Appendix C

1.8.1 Creep experiment

The creep and recovery curve of NaCMC 1180 gel exhibited a typical viscoelastic behavior combining both viscous and elastic component. The instantaneous compliance (J_o) is a compliance or deformation in which the bonds between the structural units were stretched elastically. This value reciprocated to instantaneous elastic modulus (G_0), (Equation 21.).

$$J_o = \frac{1}{G_o} \qquad \ldots(21)$$

When the concentration of NaCMC 1180 gel increased, the instantaneous compliance decreased (Figure 47.). It represented that the gel structure was more elastic with increased concentration of gel (Rao, 1999). In Figure 48, it was shown that the NaCMC 1180 gel content in wet mass should have, J_0 value of 5.52E-3, 7.60E-3, and 5.55E-4 1/Pa for CMC2-G/W50, CMC2-G/W51 and CMC3-G/W46 respectively, so that the lactose pellets could form.

1.8.2 Oscillation experiment

The results of the oscillation experiment for NaCMC 1180 gel (Table C-11 in Appendix C) showed that the storage modulus (G') was larger than loss modulus (G") for all concentration studied, indicating the NaCMC 1180 gel was a viscoelastic material that showing a elastic behavior rather than viscous behavior. The concentration of NaCMC 1180 gel increased causing G', which expressed the elastic portion of material, also increased (Figure 48). This agrees with the results from creep experiment.

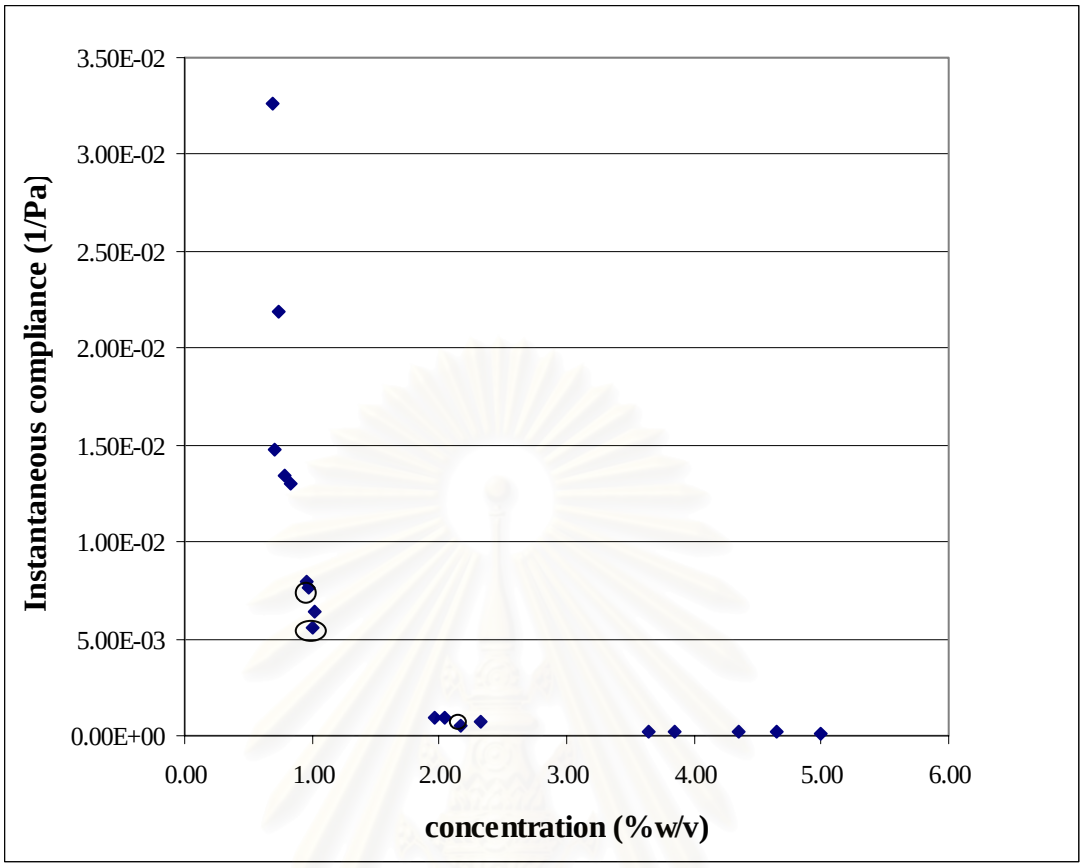


Figure 47. Creep experiment-effect of NaCMC 1180 concentration (%w/v) on the instantaneous compliance (1/Pa), circled bullets: rounded pellet were formed.

In Figure 49, the storage modulus (G') was larger than loss modulus (G") over the time range of 200 sec. It indicated that the NaCMC 1180 gel structure was stable when it was sheared over the time. Moreover, when the content of NaCMC 1180 was constant, the water content had more effect on storage modulus than loss modulus.

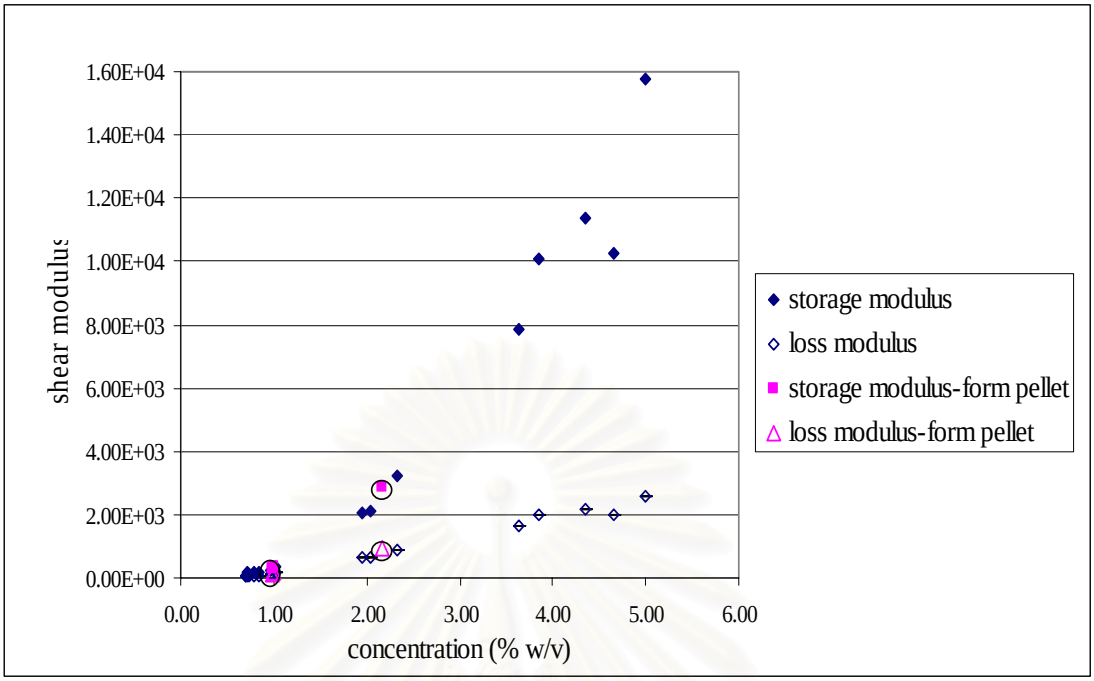


Figure 48. Oscillation experiment-effect of NaCMC 1180 concentration (%w/v) on shear modulus (Pa).

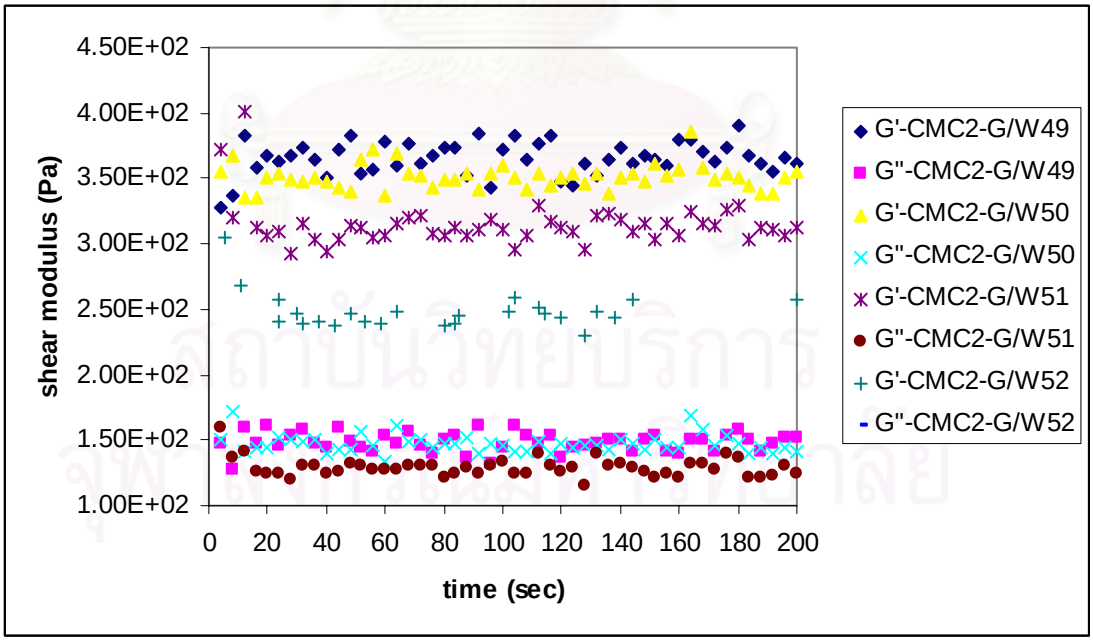


Figure 49. Oscillation experiment-effect of time on shear modulus for NaCMC 1180 gel at different water contents

2. Pelletization

2.1 Preparation of pellets

In present study, dibasic calcium phosphate (99.75-98 %) could not be prepared the pellets by using NaCMC 1180, MC 15, HEC 4000, HPC-L and HPMC E15 (0.25-2.0% w/w) as formulation aids and water or 50% ethanol as liquid binder because of the wet mass of these formulations was very rigid and difficult to be extruded, requiring high pressure. On the contrary, lactose pellets could be prepared by using some of these formulation aids with water and/or 50% ethanol and liquid binders as presented in Table 12. The processibility was identified when rounded granules could be prepared.

The lactose pellets were prepared by using NaCMC 1180, MC 15 and HPMC E15 as formulation aids. However, when HPMC E15 was the formulation aid, the pellets could be prepared with 50% ethanol only.

The lactose pellets could be prepared with NaCMC 1180 (0.5 and 1.0% w/w) as the formulation aid and either water or 50% ethanol as a liquid binder. When water was used, the water content decreased with increased NaCMC 1180 in the formulations. On the contrary, the content of 50% ethanol increased with an increasing NaCMC 1180. The formulation was sensitive to change in water content as the range of liquid binder that could produce pellets was narrow. Increasing NaCMC 1180 content affected sensitivity formulation to 50% ethanol content; only one level of this liquid binder could form pellets. In the same way, MC 15 (0.5-1.0%w/w) could prepare the lactose pellets by using either water or 50% ethanol. At 1.0% MC the range of liquid binder was wider than that required for NaCMC 1180 formulations. For the formulation with HPMC E15, the lactose pellet could be prepared by using 0.5-1.0% w/w of HPMC E15 and 50% ethanol. The liquid binder range of MC 15 and HPMC E 15 was wilder than NaCMC 1180, so that the formulations were less sensitive to change in liquid binder content. This might be due to the fact that the viscosity of NaCMC 1180, 680.1 cps, was more than MC 15 and HPMC E15, 7.7 cps. and 11 cps.

Table 12. Formulations of lactose pellets.

Code	Polymer	Polymer %w/w	Lactose %w/w	H_2O g (%w/w)*	50% Ethanol g (%w/w)*
CMC1-L	NaCMC1180	0.25	99.75	-	-
CMC2-L		0.50	99.50	50-51 (16.6-17.0)	82-87 (27.3-28.0)
CMC3-L		1.00	99.00	45-46 (15.0-15.3)	90 (30.0)
CMC4-L		2.00	98.00	-	-
MC1-L	MC15	0.25	99.75	-	-
MC2-L		0.50	99.50	45 (15.0)	-
MC3-L		1.00	99.00	42-45 (14.0-15.0)	62-68 (20.6-22.6)
MC4-L		2.00	98.00	-	-
HEC1-L	HEC4000	0.25	99.75	-	-
HEC2-L		0.50	99.50	-	-
HEC3-L		1.00	99.00	-	-
HEC4-L		2.00	98.00	-	-
HPC1-L	HPC-L	0.25	99.75	-	-
HPC2-L		0.50	99.50	-	-
HPC3-L		1.00	99.00	-	-
HPC4-L		2.00	98.00	-	-
HPMC1-L	HPMC E15	0.25	99.75	-	-
HPMC2-L		0.50	99.50	-	65-66 (21.6-22.0)
HPMC3-L		1.00	99.00	-	63-67 (21.0-22.3)
HPMC4-L		2.00	98.00	-	-
CT-L	MCC	50.00	50.00	195 (65.0)	-

*% based on dry weight

Table 13. Formulations of propranolol hydrochloride and ibuprofen pellets.

Code	Model drug	Model drug %w/w	MC 15 %w/w	H_2O g (%w/w)*	50% Ethanol g (%w/w)*
MC1-P	Propranolol HCl	99.00	1.00	-	58 (19.33)
MC2-P		98.00	2.00	41 (13.66)	-
MC4-I	Ibuprofen	96.00	4.00	70 (23.33)	-
MC8-I		92.00	8.00	-	106 (35.33)

*% based on dry weight

In present study, pellets could not be produced from the formulations with 0.25-2.0% w/w HEC 4000 and HPC-L using water or 50% ethanol as liquid binder. The amount of the cellulose may be too small to bind lactose powder. However, Kanbe et al. (2006) showed that diphenhydramine pellets could be prepared without MCC by using HPC-L (10-90%) and 15% ethanol as liquid binder. Chatlapalli and Rohera (1998) reported that HEC 4000 and HPMC E15 (95%) could not prepare the pellet by using water as liquid binder due to tacky mass. These results were similar to this study. The formulation of HPMC E15 gave rod shaped product, while extrudate of HEC 4000 formulation stick on the plate during spheronization until spheronization time was over (10 minutes). In this study, it was found that HPMC E15 could form pellets by using 50% ethanol as liquid binder while HEC 4000 could not form. This may be attributed to solubility of HEC 4000 and HPMC E15. HEC 4000 and HPMC E15 are practically insoluble in ethanol but HPMC E15 is soluble in binary organic-water solvent system, 50% ethanol. The presence of ethanol in liquid binder might aid to reduce stickiness in the formulation of pellets using water as liquid binder as reported earlier (Chatlapalli and Rohera, 1998)

Liquid contents in the formulations of the lactose pellets with NaCMC 1180, MC 15 and HPMC E15 and using water as liquid binder were less than those in the formulation of pellets using 50% ethanol. On the other hand, ethanol in formulation of pellets resulted in increase in liquid content required to form pellets. This might be

that these celluloses could be practically insoluble with ethanol, thus they did not cause tackiness or decrease viscosity. The binding property of the cellulose was reduced (Hongprapas, 2002; Chatlapalli and Rohera, 1998).

In general, MCC has known as the formulation aid for formulation of pellets by using water as liquid binder (Fechner, 2003). However, it was not suitable as a formulation aid by using alcohol or hydro-alcoholic mixture as liquid binder (Agrawal et al., 2004; Millili and Schwartz, 1990). Schröder and Klienebudde (1995) reported that MCC could not prepare the pellets by using 70%w/w 2-propanol. In present study, the results showed that the water content, based on dry weight, in MCC formulation (CT-L/W195) was higher than the formulation using NaCMC 1180 and MC 15. This may be due to high amount of MCC which could absorb, water, in the structure, in the formulation. However, the ratios of water content to formulation aids indicated that MCC (1.3:1) was less than NaCMC 1180 (33-46:1) and MC 15 (30-45:1). According to Jerwanska et al. (1995), the water was taken up and included in the cellulose structure and form gel while MCC could absorb and swell. The variation of water content in formulation affected the production, the quality of the extrudate and the ability to form pellets (Pinto et. al., 2001). The water should be available for the filling of the void space.

For propranolol hydrochloride and ibuprofen, MC15 was selected as a formulation aid, due to this formulation aid could form pellet either water or 50% ethanol and the sensitivity of liquid content was less than NaCMC 1180. Propranolol hydrochloride pellets could produce from the formulation with 2% w/w MC 15 using 41 g (13.66%), MC2-P/W41, and 1% w/w MC 15 using 58 g (19.33%) of 50% ethanol, MC1-P/A58. On the other hand, ibuprofen pellets were prepared by 4% w/w MC 15 using 70 g (23.33%), MC4-I/W41, and 8%w/w MC 15 using 106 g (35.33%) of 50% ethanol, MC8-I/A58. As these results, it was observed that MC 15 in ibuprofen formulation was at least 2 times that required for propranolol hydrochloride formulation; similar to liquid binder content in these formulations. These results might be due to that propranolol hydrochloride was soluble in water so that, the binding property increased, while ibuprofen was not soluble in aqueous binder.

3. Evaluation of wet mass

3.1 Creep experiment

The creep and recovery curve of wet mass also exhibited a typical viscoelastic behavior combining both viscous and elastic component. The instantaneous compliance of NaCMC 1180 wet mass was lower than NaCMC 1180 gel (Figure 50), ensuring solid property of wet mass.

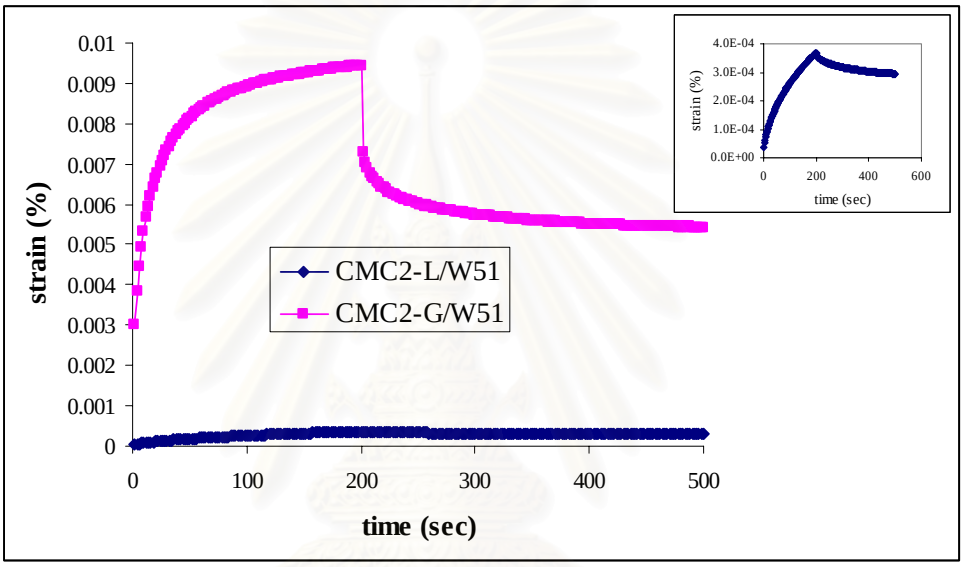


Figure 50. Creep experiment curve of NaCMC 1180 gel (CMC2-G/W51) and wet mass (CMC2-L/W51); inset shows the creep experiment for CMC2-L/W51 at large scale.

The higher contents of NaCMC 1180 in wet mass containing constant water level (15.0% w/w) resulted in higher instantaneous compliance (Figure 51), while those in wet mass containing 50% ethanol (30.0% w/w) caused lowered instantaneous values (Figure 52). This indicated that the content of NaCMC 1180 had some influence on elasticity of the wet mass. The elastic character of the wet mass was changed by more NaCMC 1180, depending on the type of liquid binder used. In present study, there was an appropriate amount of the cellulose, i.e. 1.0% w/w NaCMC 1180 that could form pellets with 15% w/w water.

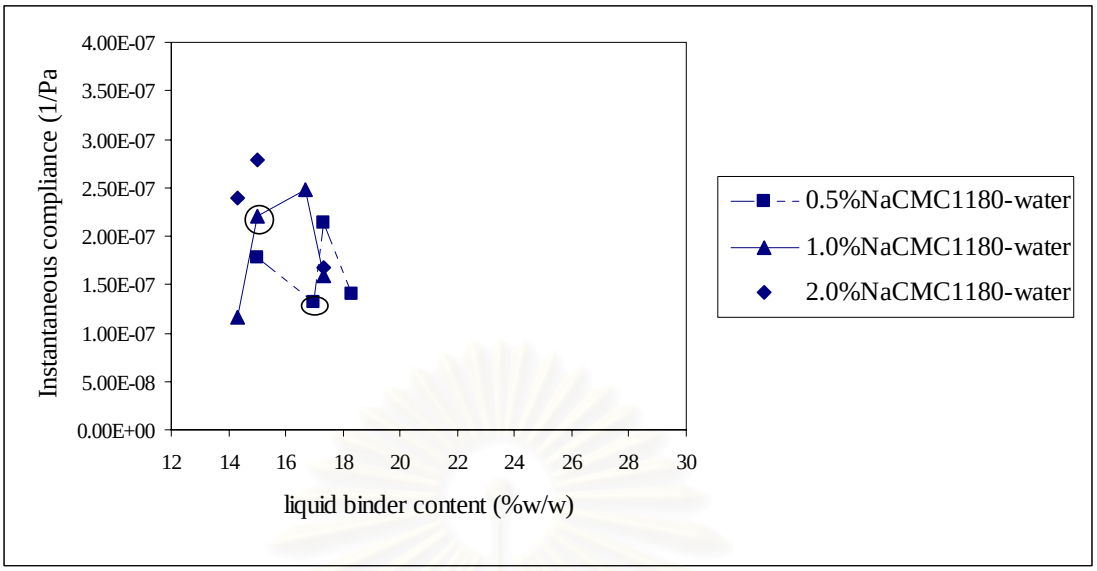


Figure 51. Creep experiment- effect of NaCMC 1180 and water contents in the wet mass on the instantaneous compliance (1/Pa); circled bullets: rounded pellets were formed.

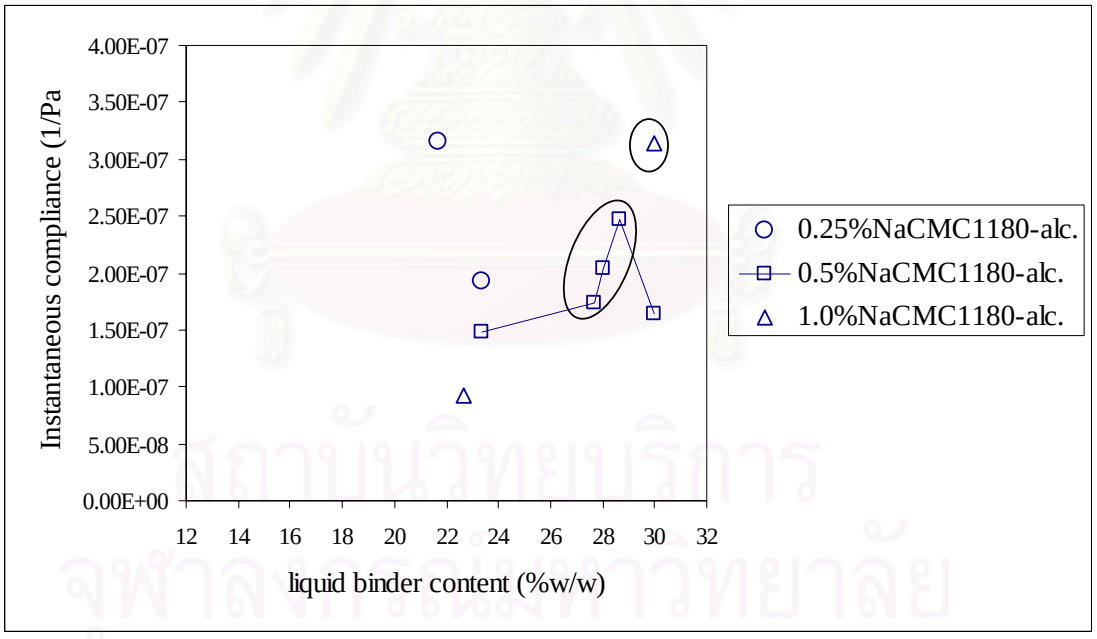
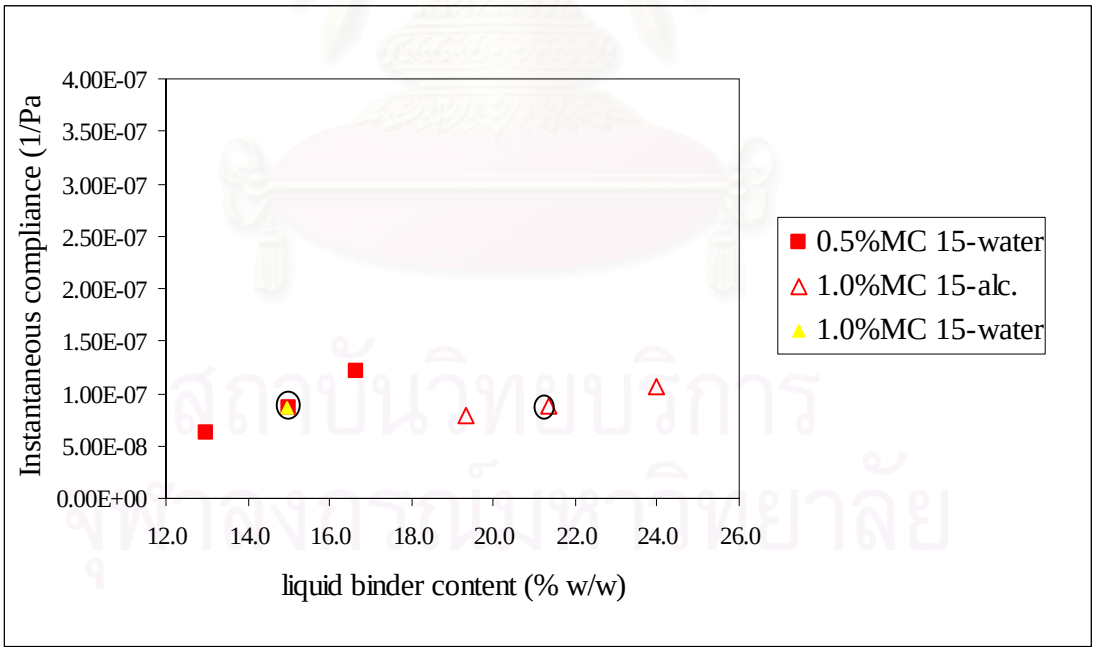


Figure 52. Creep experiment- effect of NaCMC 1180 and 50% ethanol contents in the wet mass on the instantaneous compliance (1/Pa); circled bullets: rounded pellets were formed.

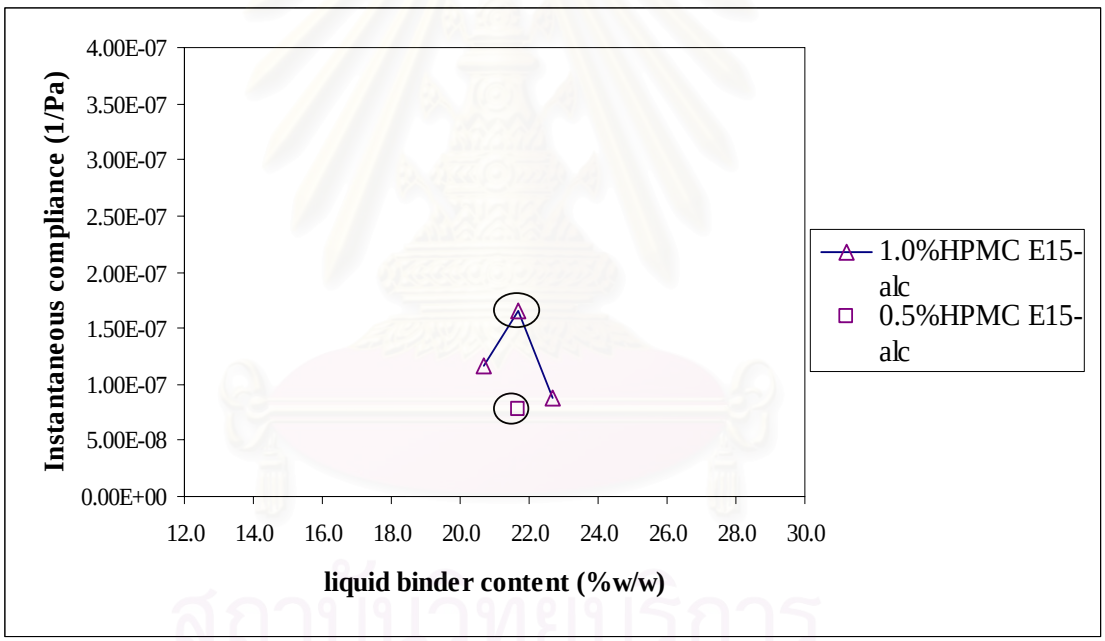
When the amount of NaCMC 1180 in the wet mass was kept constant and the content of liquid binders was varied, the instantaneous compliance value were likely to increase with increased liquid content and then decreased when the liquid content was too high. This could be observed with 1.0% NaCMC 1180 wet mass granulated with water and 0.5% NaCMC 1180 wet mass granulated with 50% ethanol. According to these results, there appeared to be an optimum liquid content, hence instantaneous compliance value of wet mass that could form the pellets. These values, however, would be different, depending on the amount of the NaCMC 1180 and type of liquid in the formulations.

In general, the instantaneous compliance values of the wet mass that could form pellets were varied, depending on the formulations, i.e. the amount of NaCMC 1180 as well as type and amount of liquid content. The measurement of the instantaneous compliance might be useful to identify an appropriate amount of liquid that could form pellets with certain amount of NaCMC 1180.



Figurer 53. Creep experiment- effect of MC 15 and water or 50% ethanol contents in the wet mass on the instantaneous compliance (1/Pa); circled bullets: rounded pellet were formed.

The result of creep experiment of MC 15 wet mass was illustrated in Figure 53. It was shown that the formulation which had same water content (15% w/w) and varied MC content, i.e. 0.5-1.0% w/w MC 15, the instantaneous compliance was rather similar (8.71 E-08 1/Pa and 8.70E-08 1/Pa). This suggested that the values of instantaneous compliance was related to water content. In addition, the wet mass of these instantaneous compliance values could produce pellets, regardless of MC 15 contents. The values seemed to be closed to those of 1.0% w/w MC 15 wet mass granulated with 50% ethanol. Therefore, in the case of using MC 15 as formulation aid, it was possible that the wet mass which would produce possessed the values of instantaneous compliance within range 8.70E-08 to 8.77E-08 1/Pa which not sensitive to the formulation variables studied, i.e. type of liquid and the amount of MC 15.

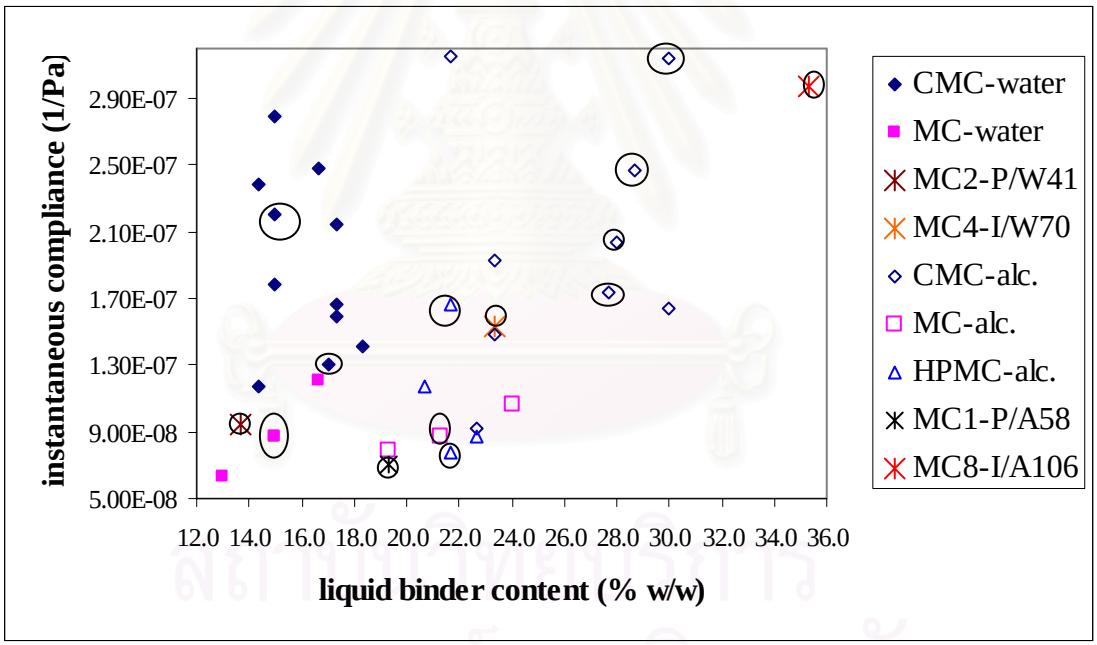


Figurer 54. Creep experiment- effect of HPMC E15 and 50% ethanol contents in the wet mass on the instantaneous compliance (1/Pa); circled bullets: rounded pellets were formed.

As described earlier, HPMC E15 could aid the formulation of lactose pellets when 50% ethanol was used as liquid binder (Figure 54). The instantaneous compliance of the wet mass granulating with the same liquid content, i.e. 21.7% w/w, was higher with increased HPMC E15 contents from 0.5% w/w to 1.0% w/w. In the other words, the presence of more HPMC E15 in the wet mass caused a less elastically

wet mass. The results disagreed with the results for the NaCMC1180 wet mass granulated with the hydroalcoholic solution of 23.3%w/w content, where the elasticity was enhanced with the increased amount of NaCMC1180.

In addition, the instantaneous compliance values were varied with the 50% ethanol content of 1.0 % w/w HPMC E15 wet mass. Similar to the results for the 0.5% w/w NaCMC 1180 wet mass granulating with 50% ethanol, the instantaneous compliance modified the deformation of wet mass appeared to show an optimum value that could produce pellets. In Figure 55, it could be observed that the higher liquid binder, result in the higher instantaneous compliance, in general, regardless of the type and quantity of polymer because of the liquid binder was one of the significant factor that wet mass could form pellets.



Figurer 55. Creep experiment- effect of type of formulation aid and water or 50% ethanol contents in the wet mass on the instantaneous compliance (1/Pa); circled bullets: rounded pellets were formed.

3.2 Oscillation experiment

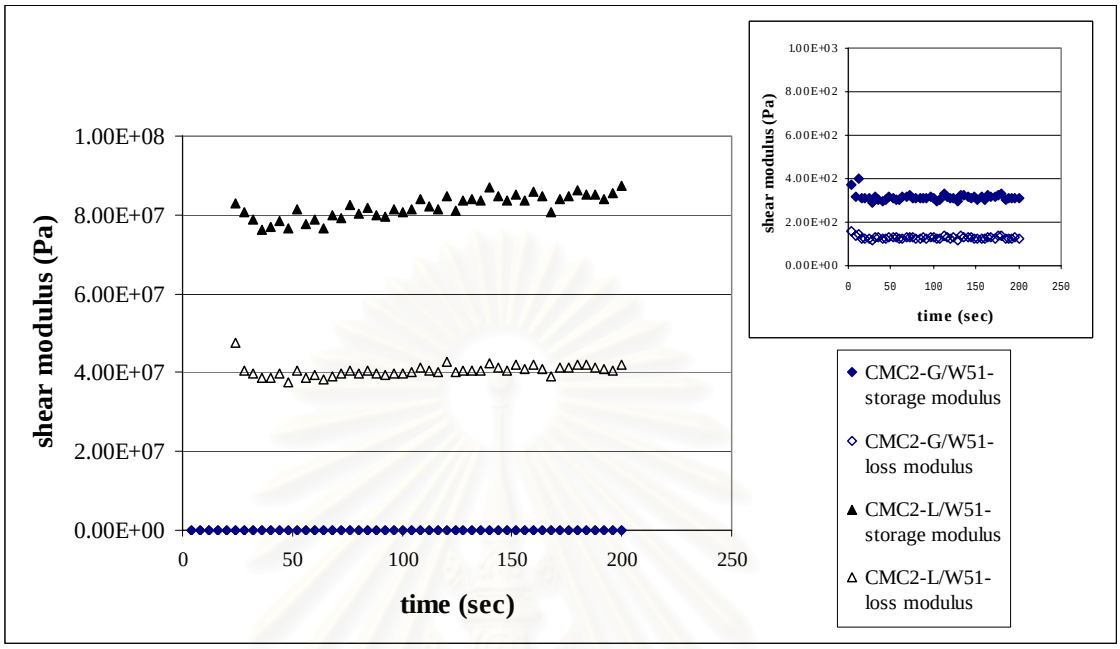


Figure 56. Oscillation experiment curve of NaCMC 1180 gel (CMC2-G/W51) and wet mass (CMC2-L/W51); inset shows the oscillation experiment for CMC2-G/W51 at large scale.

The oscillation curve showed that the shear modulus, storage modulus (G') and loss modulus (G"), of NaCMC 1180 wet mass is higher than NaCMC 1180 gel (Figure 56). This indicated that the elastic character of NaCMC 1180 wet mass was higher than NaCMC 1180 gel. In general, the pattern of oscillation curve of wet mass formulation that used in this experiment was similar; i.e. storage modulus was higher than loss modulus, signifying rather elastic mass.

In Figure 57-60, it was shown that overall the shear modulus of NaCMC 1180 wet mass could not directly be related to the processablilty. However, there were optimum values of the shear modulus of the wet mass granulated with water that could form pellets; these values were changed when the NaCMC 1180 was increased from 0.5 % w/w to 1.0 % w/w (Figure 57-58). The results agreed with the instantaneous compliance values of the wet mass. However, this effect was not clearly observed for

the wet granulated with 50% ethanol as the slight change in the value of shear modulus (Figure 59-60).

For the MC 15 wet mass, it was found that with the same water content, and increase from 0.5% w/w to 1.0% w/w of MC 15 content caused lower shear modulus. The pellets could be formed with the same amount of water even though the MC15 content was changed. For certain amount of MC 15 in the formulation e.g. 0.5% w/w, there appeared to be optimum values of shear modulus that could form pellets; relatively low values for both storage and loss moduli were observed when the formulation was too wet or too dry. Likewise, for the wet mass granulated with 50% ethanol, there were also appropriate range of 50% ethanol content providing the viscoelastic property that were suitable to form pellets. However, in this case it was observed that the too dry formulation gave relatively high value of storage modulus, and the too wet formulation gave relatively low value of storage modulus (Figure 61-62).

The higher contents of NaCMC 1180 in wet mass containing constant water level (15.0% w/w) resulted in higher instantaneous compliance (Figure 51.), while those in wet mass containing 50% ethanol (30.0% w/w) caused lowered instantaneous values (Figure 51-52.). This indicated that the content of NaCMC 1180 had some influence on elasticity of the wet mass. The elastic character of the wet mass was changed by more NaCMC 1180, depending on the type of liquid binder used. In present study, there was an appropriate amount of the cellulose, i.e. 1.0% NaCMC 1180 that could form pellets with 15% w/w water.

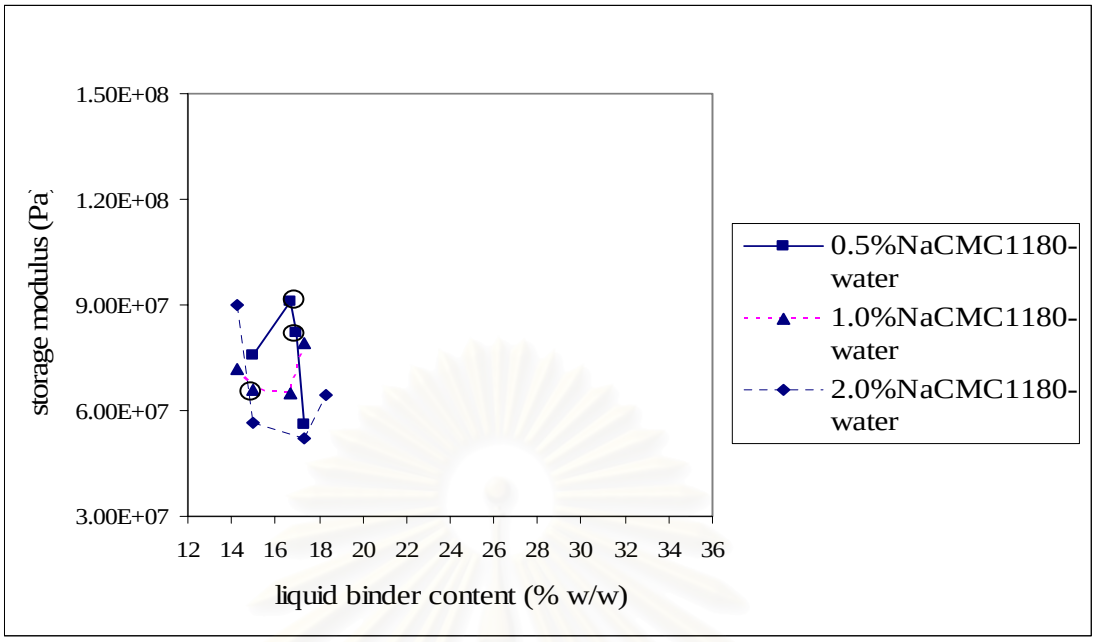


Figure 57. Oscillation experiment-storage modulus (G′) of wet mass with NaCMC 1180 as the formulation aid and water as liquid binder; circled bullets: rounded pellets were formed.

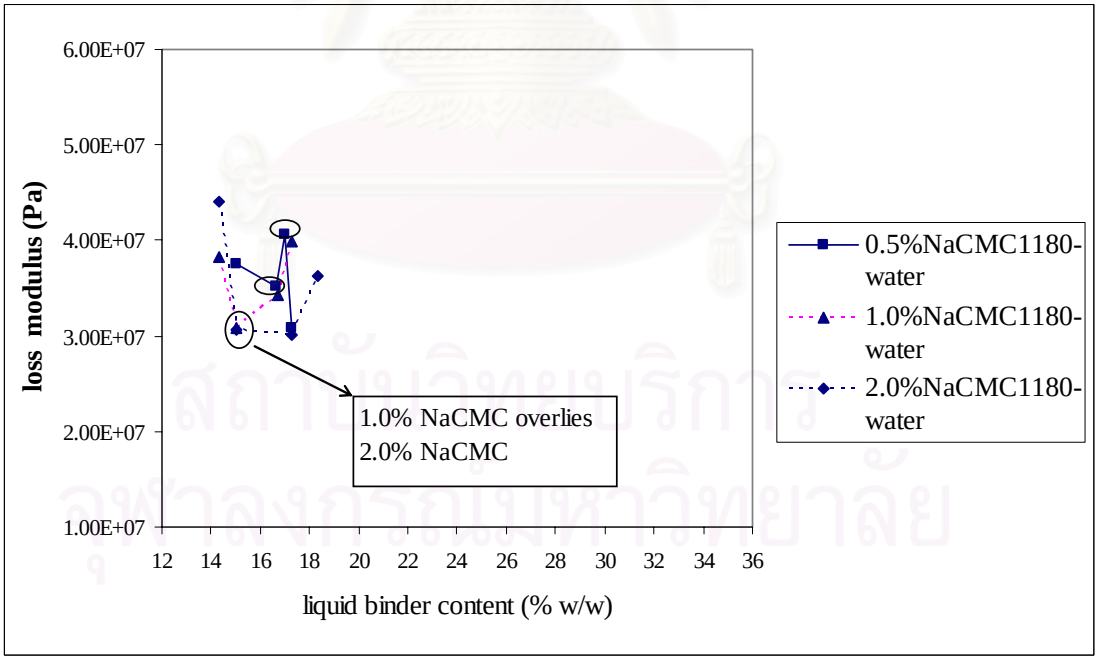


Figure 58. Oscillation experiment-loss modulus (G″) of wet mass with NaCMC 1180 as the formulation aid and water as liquid binder; circled bullets: rounded pellets were formed.

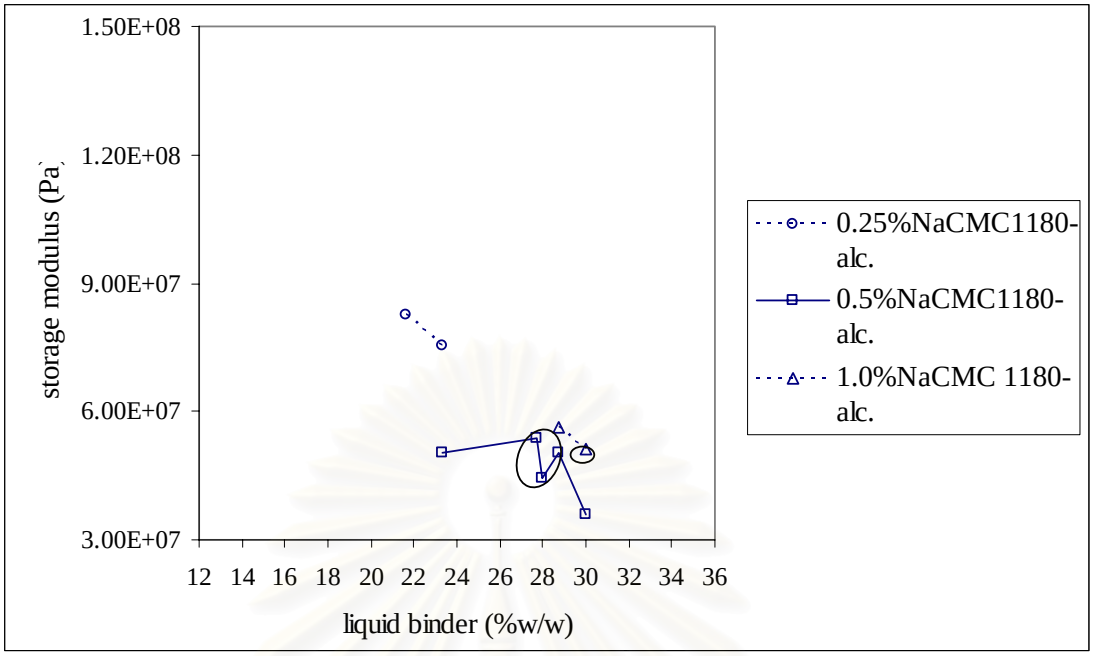


Figure 59. Oscillation experiment-storage modulus (G′) of wet mass with NaCMC 1180 as the formulation aid and 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

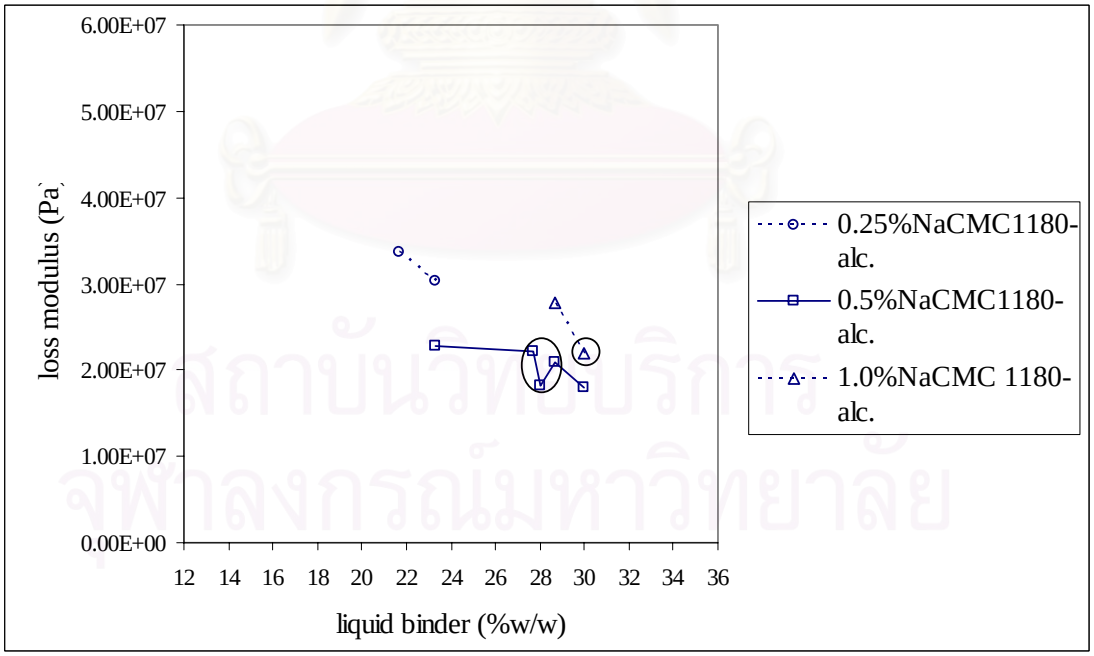


Figure 60. Oscillation experiment-loss modulus (G″) of wet mass with NaCMC 1180 as the formulation aid and 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

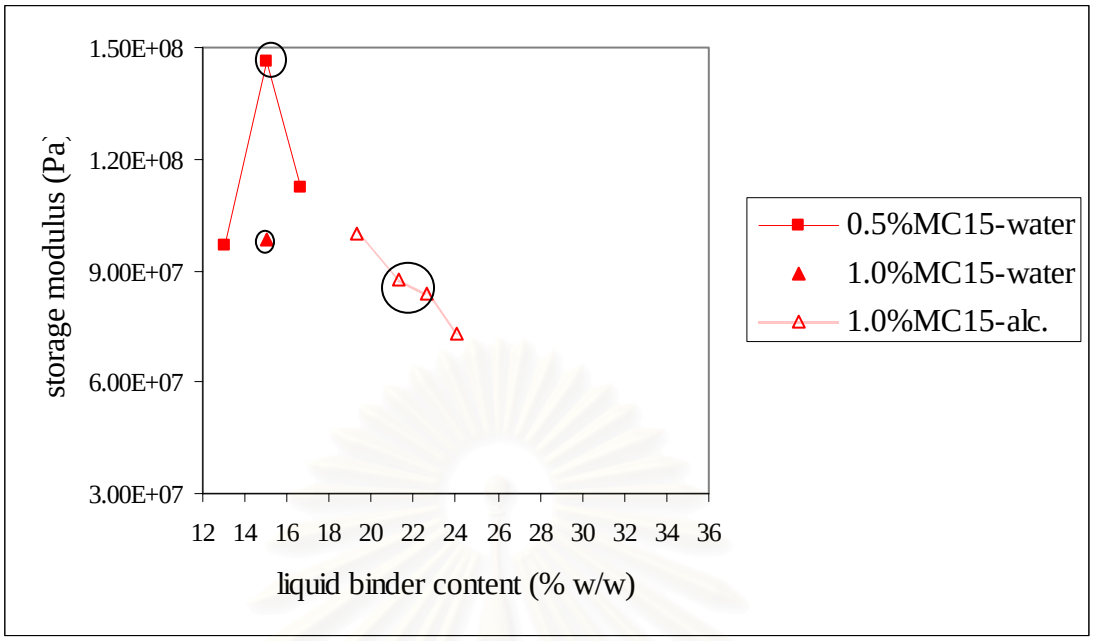


Figure 61. Oscillation experiment-storage modulus (G′) of wet mass with MC 15 as the formulation aid and water or 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

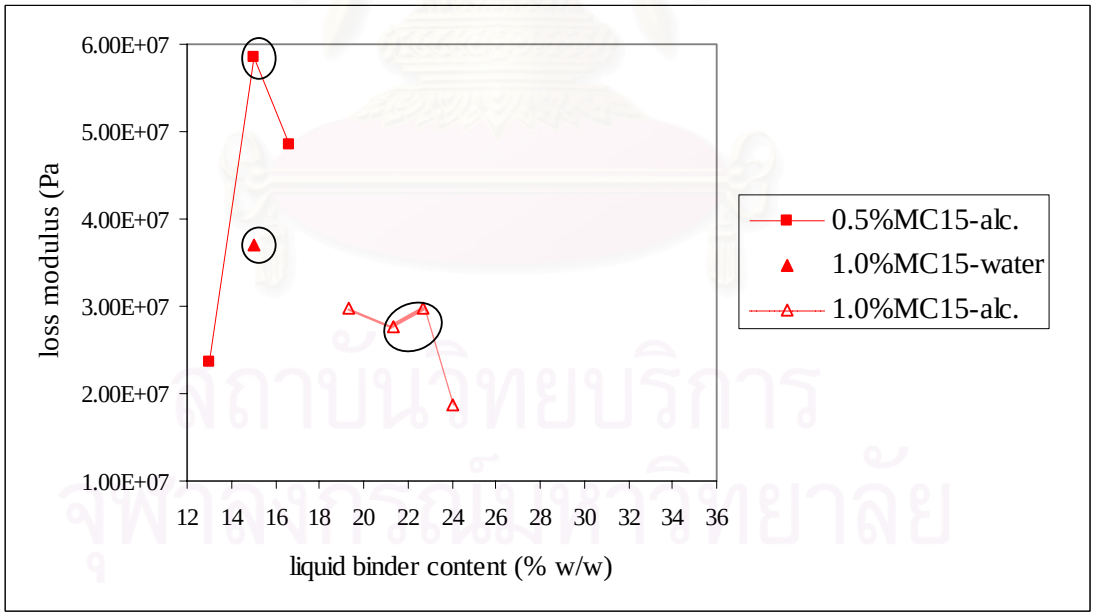


Figure 62. Oscillation experiment-loss modulus (G″) of wet mass with MC 15 as the formulation aid and water or 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

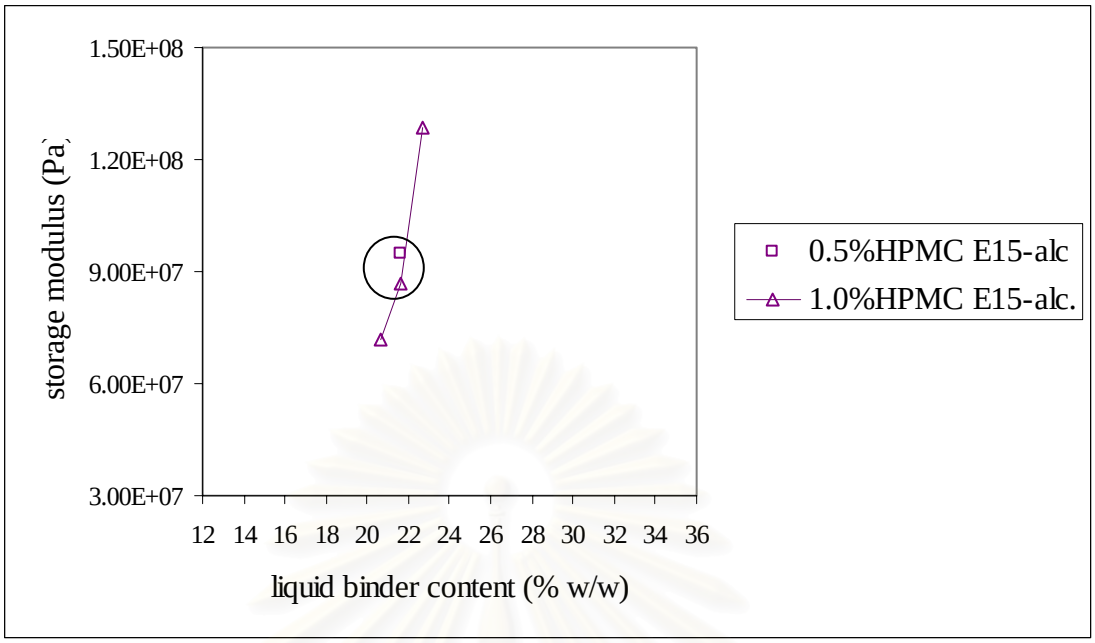


Figure 63. Oscillation experiment-storage modulus (G′) of wet mass with HPMC E15 as the formulation aid and 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

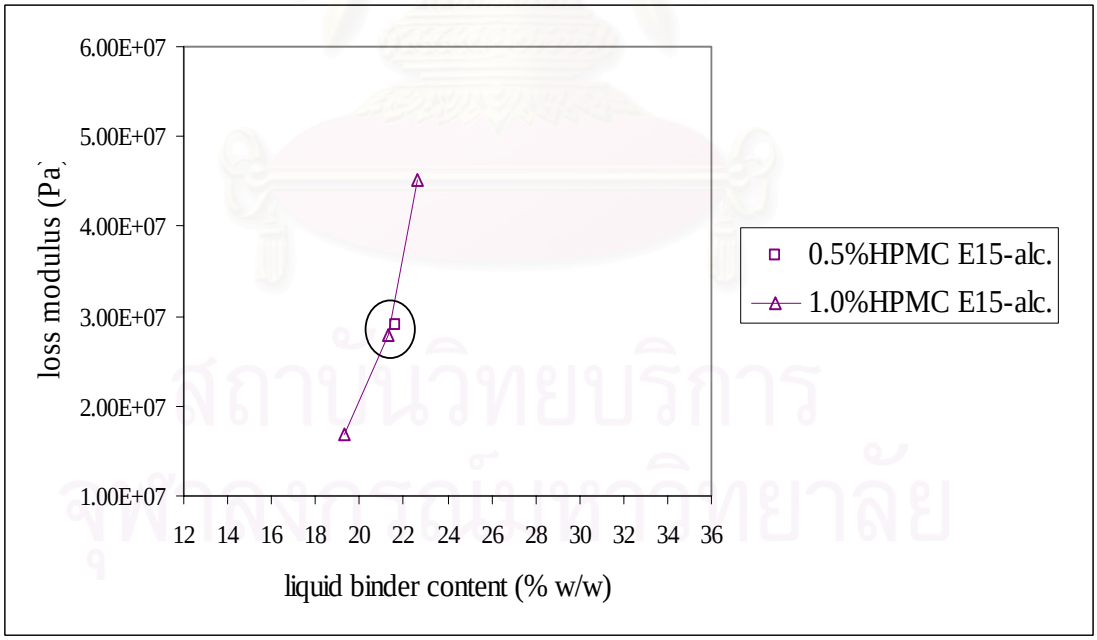


Figure 64. Oscillation experiment-loss modulus (G″) of wet mass with HPMC E15 as the formulation aid and 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

The loss tangent (tan δ) is a dimensionless parameter which is a measure of the ratio of energy lost to the energy stored in an oscillation experiment. It was defined by equation (21). Data for the loss tangent (tan δ) provided a comparative measurement of both the elastic and viscous contributions. The biggest in loss tangent (tan δ) could be indicated the predominantly viscous nature of the material, and a lesser degree of particle association (Rudraraju and Wyandt, 2005).

$$\tan\delta = \frac{G''}{G'} \qquad \ldots(21)$$

The loss tangent (tan δ) values of 0.39-0.49 and 0.41-0.43 for NaCMC 1180 wet mass granulated with water and 50% ethanol, respectively, were required to form lactose pellets. In case of MC 15 as the formulation aid, it found that the loss tangent (tan δ) which could form the lactose pellets were 0.38-0.40 and 0.31-0.35, for water and 50% ethanol, respectively (Figure 67). When HPMC E15 was used to prepare lactose pellets, the loss tangent (tan δ) could form the pellets was 0.31-0.32 (Figure 68). These results showed that the loss tangent which could form the pellets depending on type and quantity of the formulation aids and liquid binders. It was observed that the loss tangent (tan δ) of water formulation was higher than 50% ethanol formulation when NaCMC 1180 or MC 15 as the formulation aids; i.e. the loss tangent (tan δ) of MC 15 were 0.38-0.40 and 0.31-0.35, for water and 50% ethanol, respectively. It suggested that ethanol reduced solubility of the formulation aid resulting in a decrease in viscous property relative to elastic property of wet mass.

The loss tangent of the wet mass granulated by water and 50% ethanol are illustrated in Figure 69-70. It was observed that the loss tangent (tan δ) of 0.38-0.49 and 0.30-0.43 of the wet mass granulated with water and 50% ethanol, respectively, were required to form pellets. If the loss tangent (tan δ) exceeded than 0.50 or 0.43, for water and ethanol, respectively, the pellets could not be formed. Likewise, when the loss tangent (tan δ) was lower than 0.38 or 0.30, for water and ethanol, respectively, the lactose pellets could not be formed. However, for all of formulations which could form pellets, the loss tangent would be within the range of 0.07-0.49. Moreover, it could be observed that for 50% ethanol containing formulations, the loss

tangent values of MC 15 and HPMC E15 formulation were overlied. It might be possible that the viscosity of MC 15 and HPMC E15 was similar, i.e. 7 and 11 cps, respectively.

Propranolol hydrochloride had the loss tangent of 0.07 and 0.10 for water and 50% ethanol, respectively. These results indicated that wet mass of propranolol hydrochloride contributed elastic property more than viscous property. It might cause the propranolol hydrochloride pellets had the dumbbell shape due to it could not be break off and sphere into pellets. In case of ibuprofen formulation, it had the loss tangent of 0.23 and 0.33 for water and 50% ethanol, respectively. These results indicated that wet mass of ibuprofen contributed elastic property more than viscous property, however, the elastic property of ibuprofen was less than propranolol hydrochloride wet mass. These results might be due to that propranolol hydrochloride was soluble in the aqueous binder so that the binding property increased while ibuprofen was not soluble in aqueous binder. Because of the less elastic property of ibuprofen wet mass, the extrudates could be broken off into smaller strand and easier deformed into pellets. These results might cause the smaller size and rather rounder shape ibuprofen pellets in comparison with propranolol hydrochloride pellets.

When lactose in the formulation of pellets formed with MC 15 was replaced with propranolol hydrochloride and ibuprofen, the rheological properties of the wet mass, in terms of instantaneous compliance, storage modulus, loss modulus and loss tangent were changed. The amounts of MC 15 and liquid content which was change in this formulation might cause the rheological properties of the wet mass changed in formulation. Although both lactose (1 in 4.6 ml) and propranolol hydrochloride (1 in 20 ml) was water soluble material. The presence of these materials in the pellets formulation could contribute to rheological properties of wet mass differently. These must be some other properties of the material, apart from the solubility, that affect the consistency of the wet mass. For ibuprofen, it was not soluble in water so that the rheological property of wet mass was different from lactose and propranolol hydrochloride, reflecting might be assumed to be in that the MC quantity required to forming pellets were at least twice that of propranolol hydrochloride.

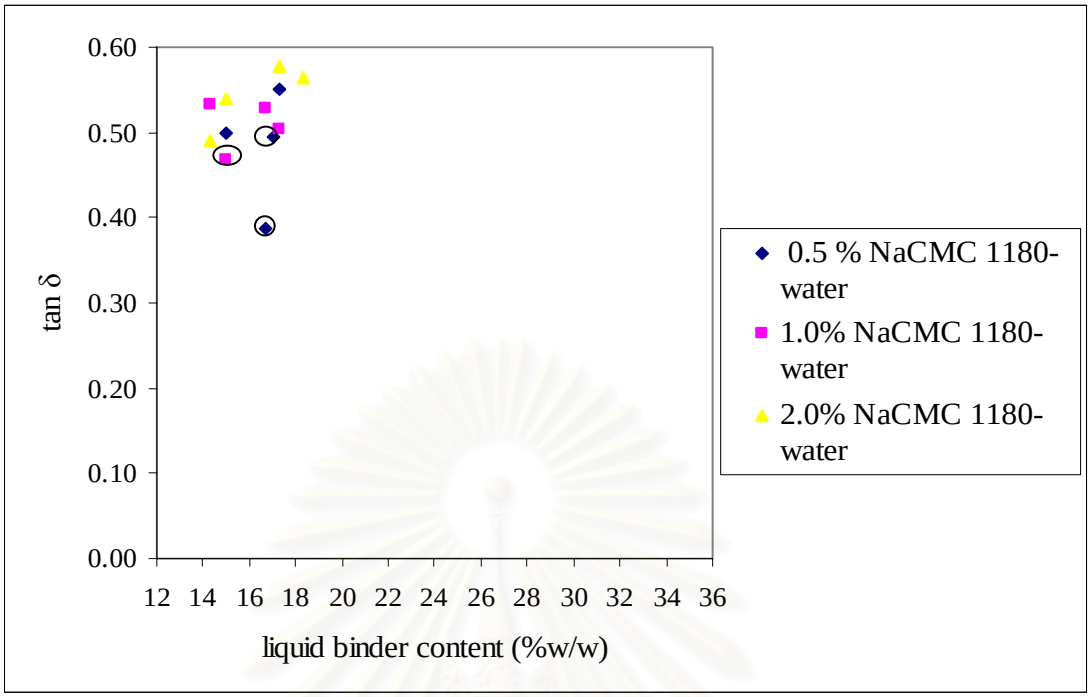


Figure 65. Oscillation experiment-loss tangent (tan δ) of wet mass with NaCMC 1180 as the formulation aid and water as liquid binder; circled bullets: rounded pellets were formed.

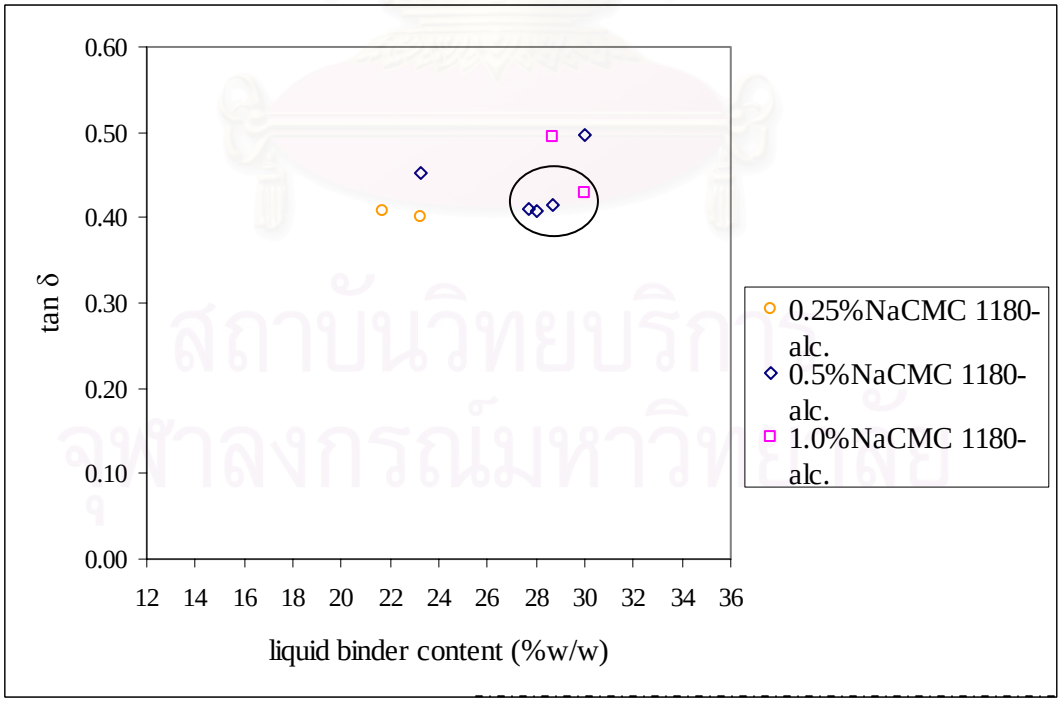


Figure 66. Oscillation experiment-loss tangent (tan δ) of wet mass with NaCMC 1180 as the formulation aid and 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

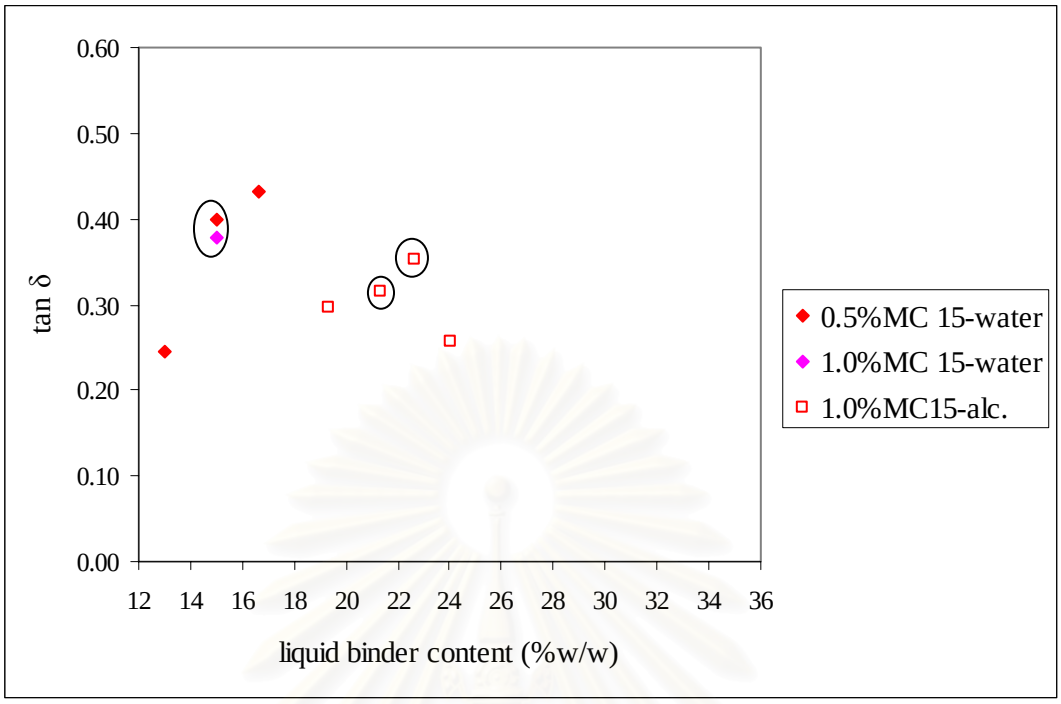


Figure 67. Oscillation experiment-loss tangent (tan δ) of wet mass with MC 15 as the formulation aid and water or 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

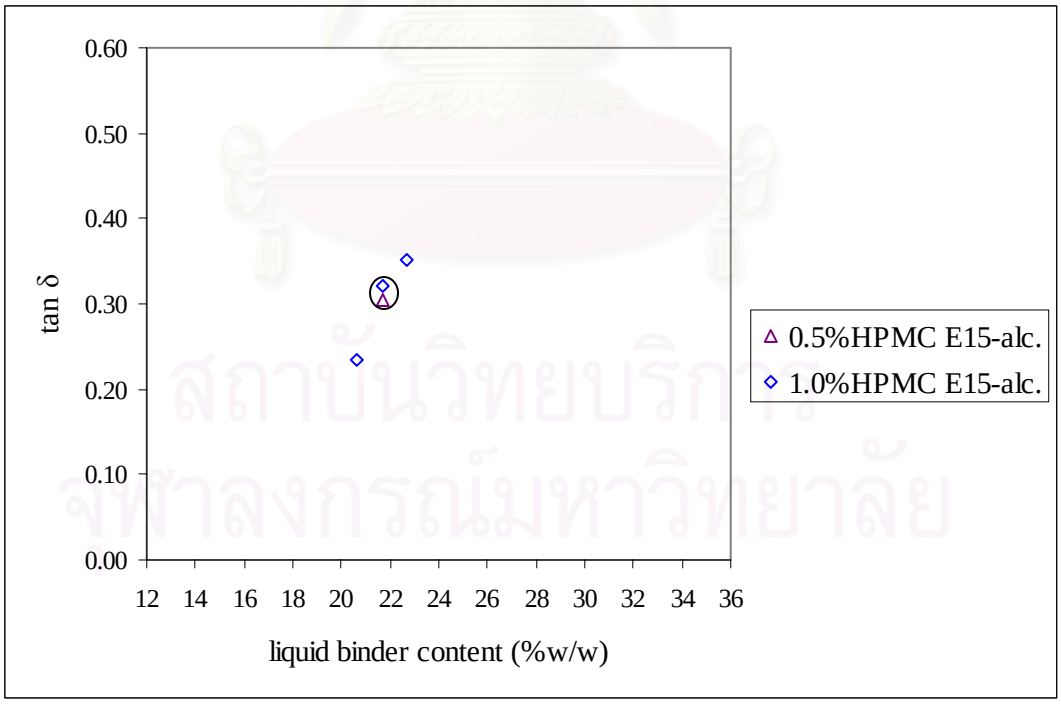


Figure 68. Oscillation experiment-loss tangent (tan δ) of wet mass with HPMC E15 as the formulation aid and 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

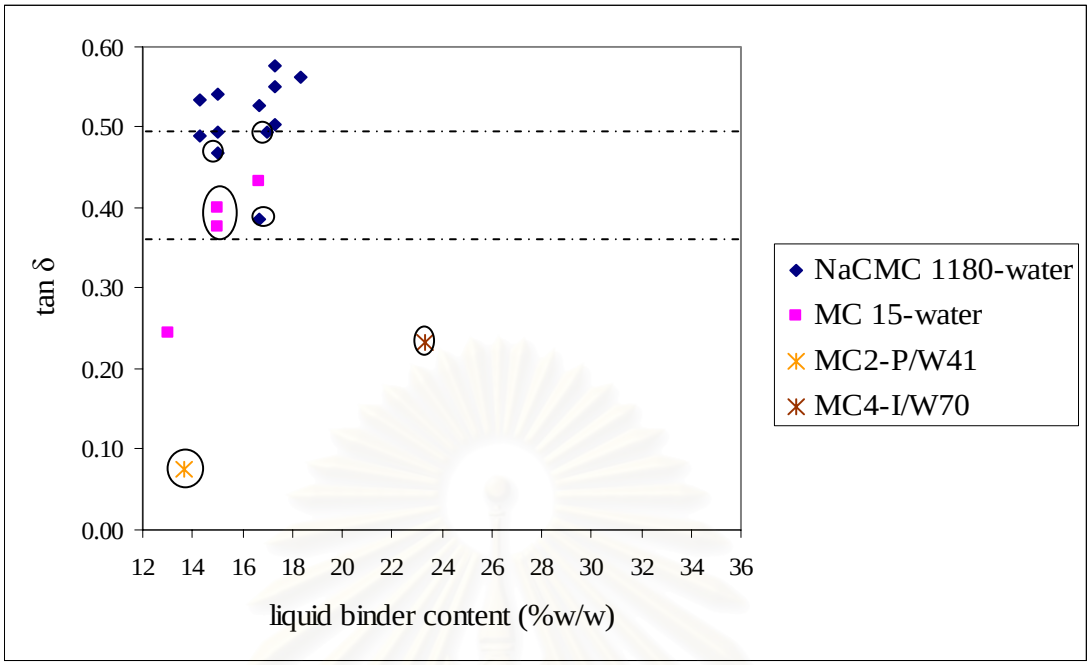


Figure 69. Oscillation experiment-loss tangent (tan δ) of wet mass with NaCMC 1180, MC 15 and HPMC E15 as the formulation aids and water as liquid binder; circled bullets: rounded pellets were formed.

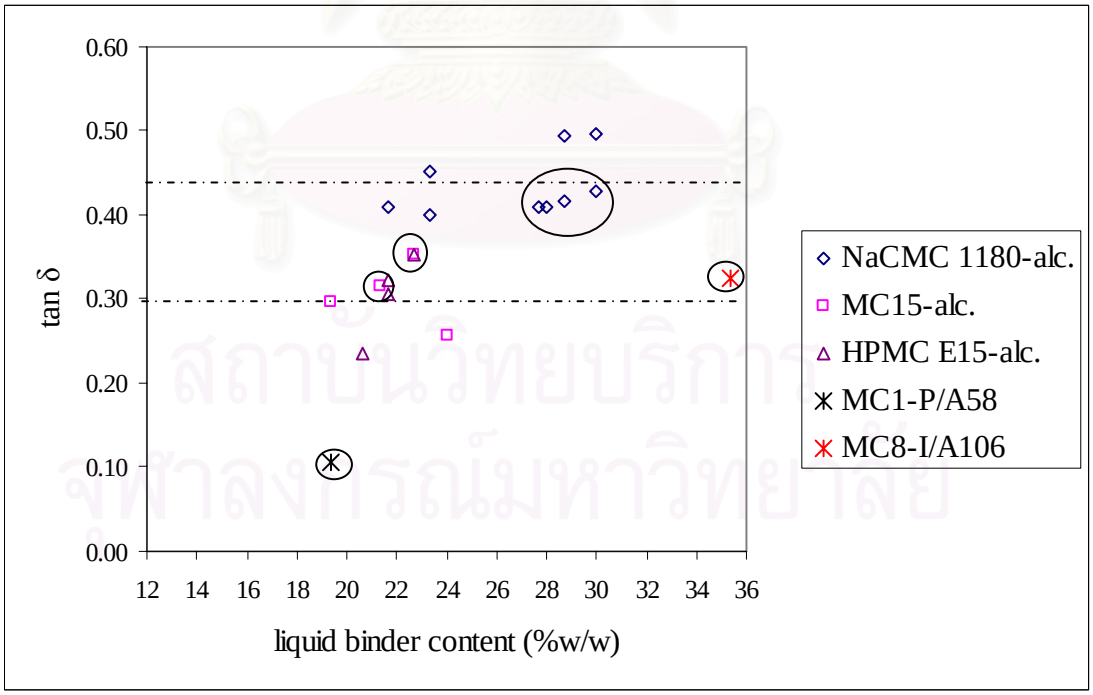


Figure 70. Oscillation experiment-loss tangent (tan δ) of wet mass with NaCMC 1180, MC 15 and HPMC E15 as the formulation aid and 50% ethanol as liquid binder; circled bullets: rounded pellets were formed.

4. Characterization of products

4.1 Morphology

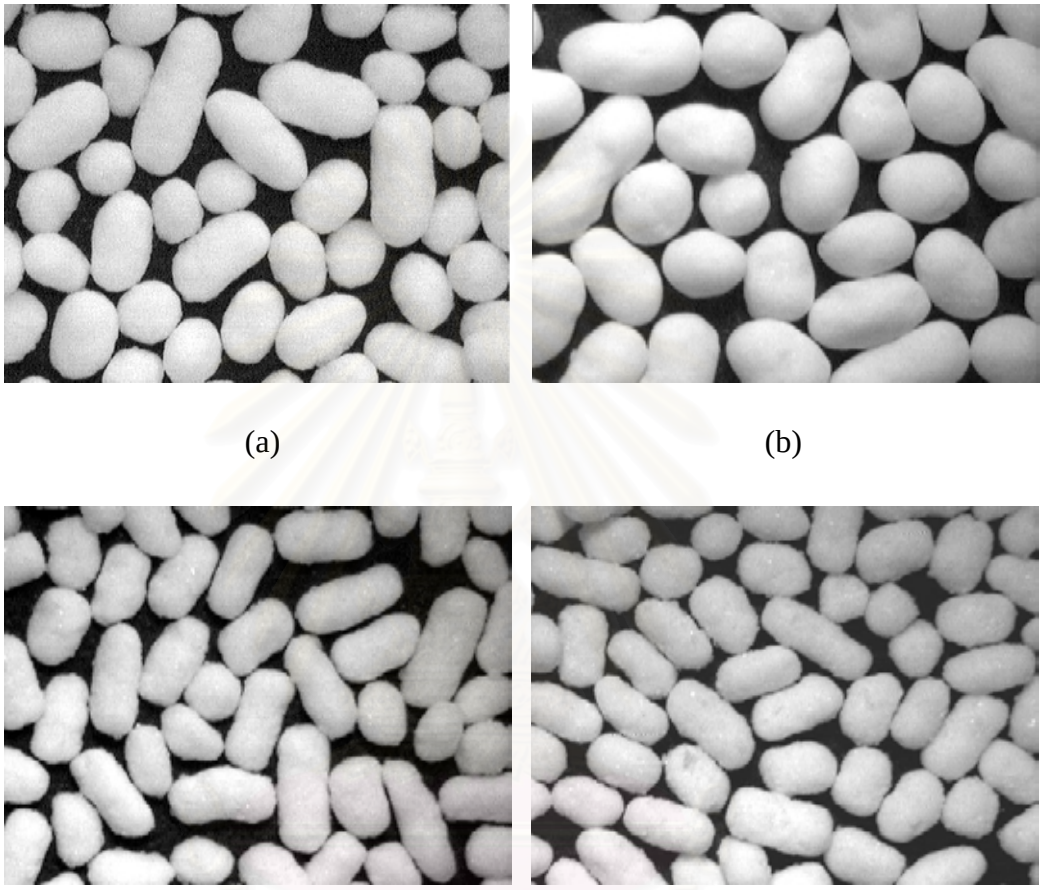
Photomicrographs of shape and size of pellets from main sieves were taken with a digital camera (EOS 100, Cannon, Tokyo, Japan), linked with a stereomicroscope system (ML9300, Meiji, Tokyo, Japan). The morphology and surface topography of pellet were investigated by scanning electron microscopy and a stereomicroscope (ML9300, Meiji, Tokyo, Japan).

In present study, the lactose pellets could be formed with 0.5-1.0% of NaCMC 1180, MC 15, HEC 4000, HPC-L and HPMC E15 was used to prepare pellet as formulation aids. Only, NaCMC 1180, MC 15 and HPMC E15 could be form pellet.

When NaCMC 1180 was used as the formulation aid and water was used as liquid binder, rod shaped (Figure 71) and rough surfaces of pellets (Figure 78-79) were obtained. When 50% ethanol was used as a liquid binder, the pellets seemed to have rounder shape (Figure 72) and smoother surface (Figure 80-81) than using water as liquid binder, except for CMC3-L/A90 which contained 1% NaCMC 1180. The pellets of CMC3-L/A90 had rough surfaces (Figure 72 and 81). It might be caused by balling effect.

The pellets were prepared by using MC 15 as the formulation aid and water as liquid binder, had round shape and smooth surface. The shape and surface of pellets which were prepared by using 50% ethanol as liquid binder were rounder (Figure 73) and smoother (Figure 82-83).

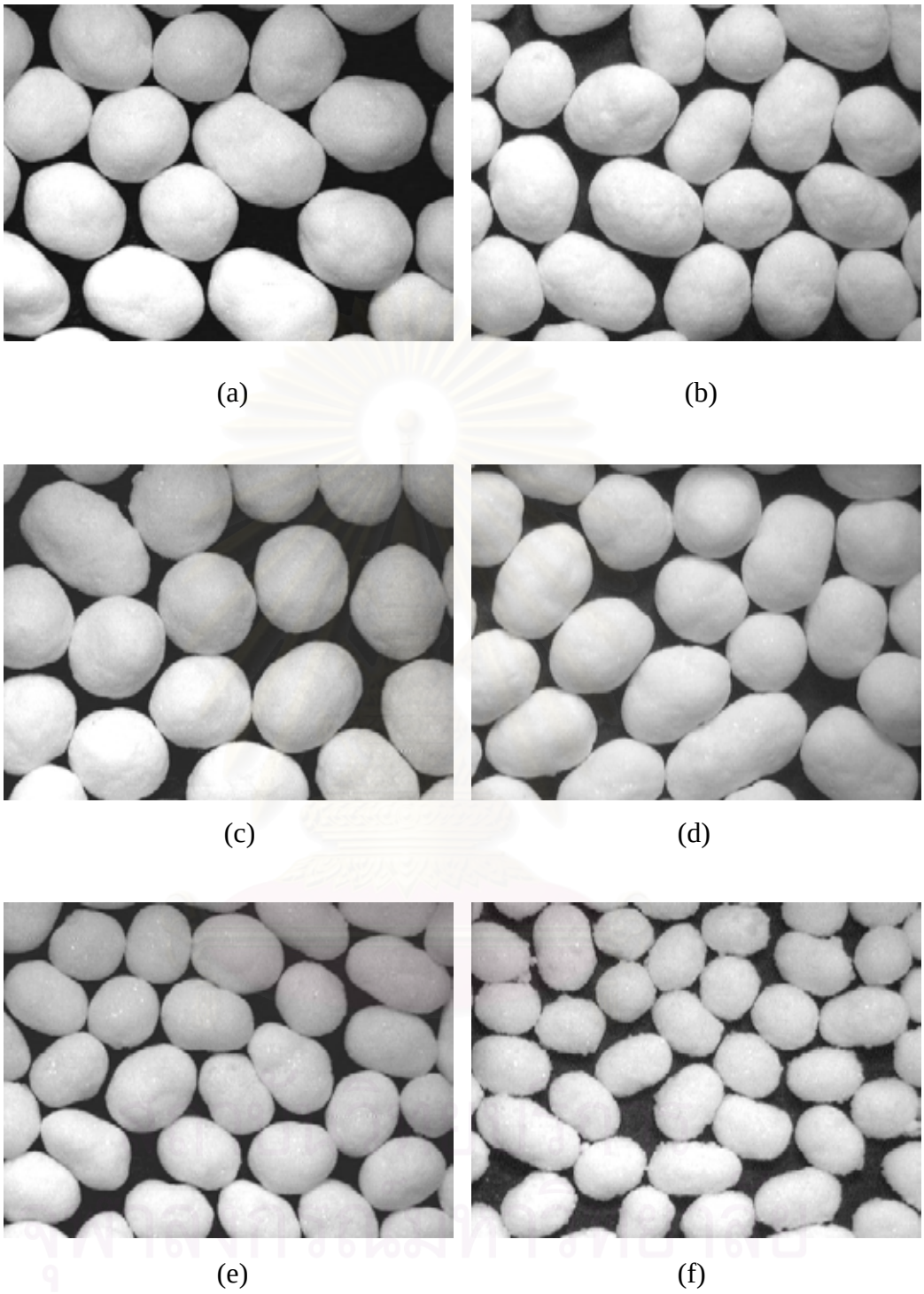
When HPMC E15 was used as the formulation aid and 50% ethanol as liquid binder, round shape (Figure 74) and smooth surface of pellets (Figure 84-85) were obtained. Increasing HPMC E15 content caused the rod shape pellet. This might suggest that the higher HPMC E15 resulted in increasing elastic property of extrudates. Hence, in spheronization process, extrudates could not be broken off into cylindricals and easily deformed into pellets.



(a) (b)

(c) (d)

Figure 71. Photomicrographs of lactose pellets formed with NaCMC 1180 and water in magnification x7: (a) CMC2-L/W50, (b) CMC2-L/W51, (c) CMC3-L/W45 and (d) CMC3-L/W46.

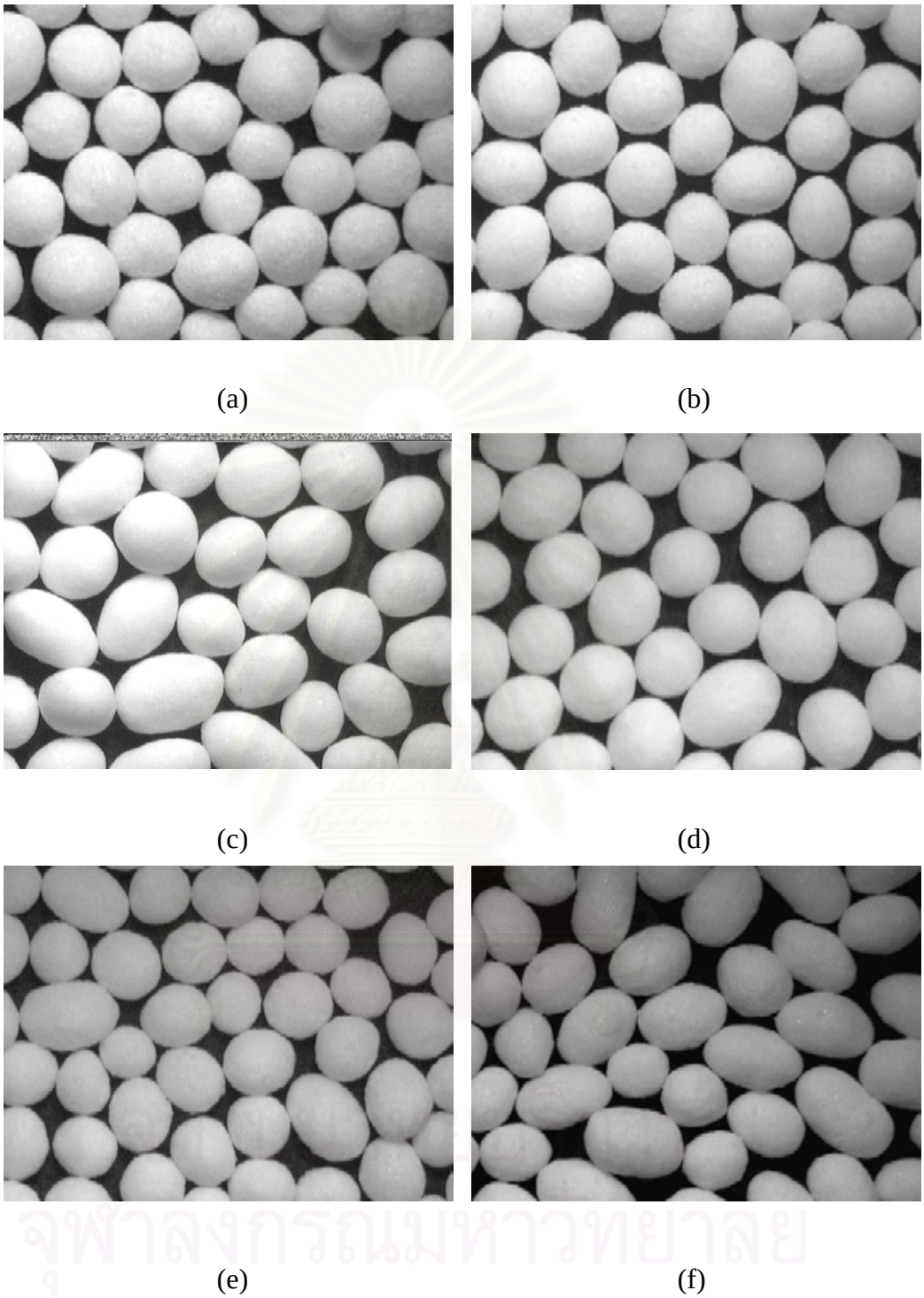


(a) (b)

(c) (d)

(e) (f)

Figure 72. Photomicrographs of lactose pellets formed with NaCMC 1180 and 50% ethanol in magnification x7: (a) CMC2-L/A83, (b) CMC2-L/A84, (c) CMC2-L/A85, (d) CMC2-L/A86, (e) CMC2-L/A87 and (f) CMC3-L/A90.

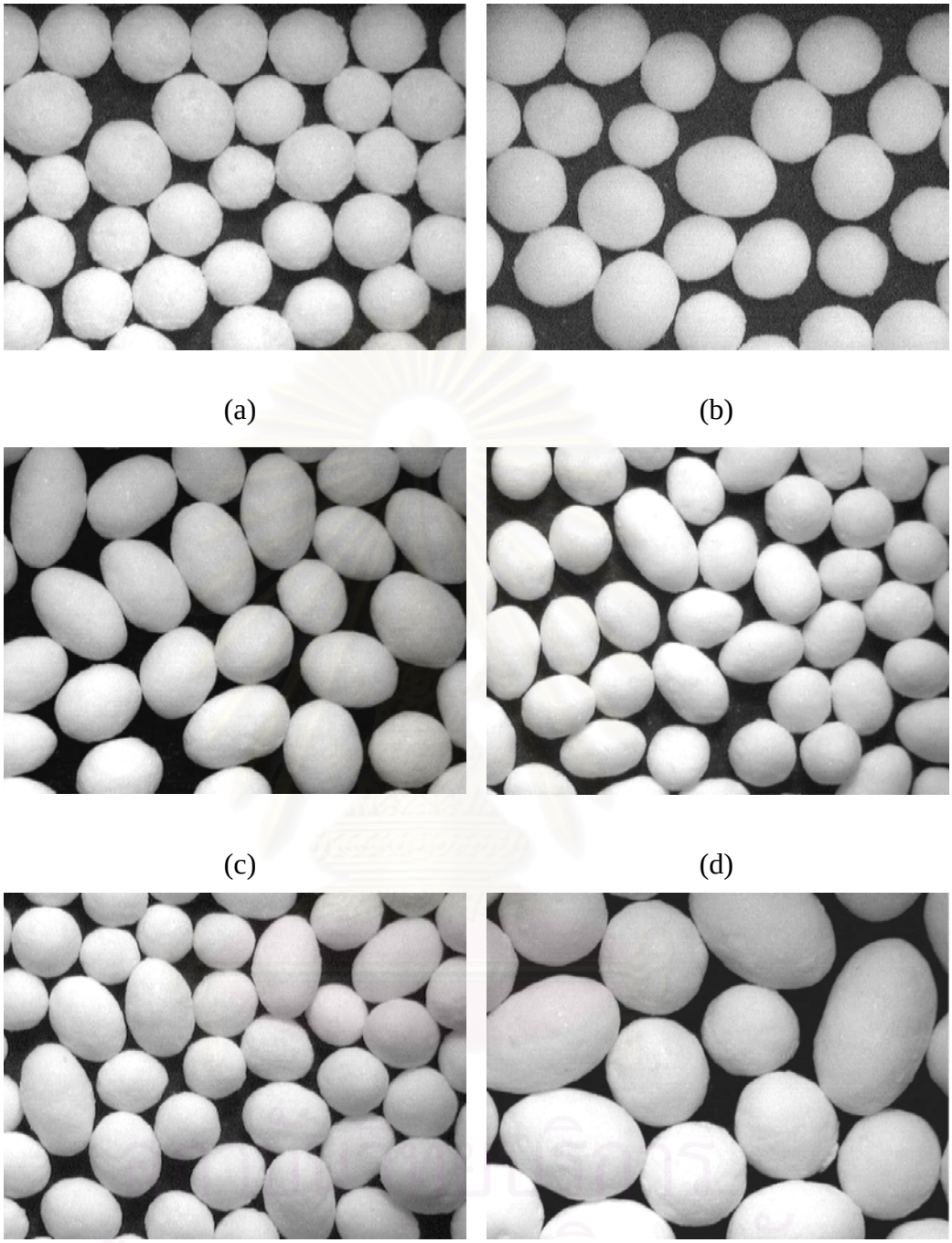


(a) (b)

(c) (d)

(e) (f)

Figure 73. Photomicrographs of lactose pellets formed with MC 15 and water in magnification x7: (a) MC2-L/W45, (b) MC3-L/W42 and (c) MC3-L/W45. Photomicrographs of lactose pellets formed with MC 15 and 50% ethanol in magnification x7: (d) MC3-L/A64, (e) MC3-L/A66 and (f) MC3-L/A68.



(a) (b)

(c) (d)

Figure 74. Photomicrographs of lactose pellets formed with HPMC E15 and 50% ethanol in magnification x7: (a) HPMC2-L/A65, (b) HPMC2-L/A66, (c) HPMC3-L/A64, (d) HPMC3-L/A65, (e) HPMC3-L/A66 and (f) HPMC3-L/A67.

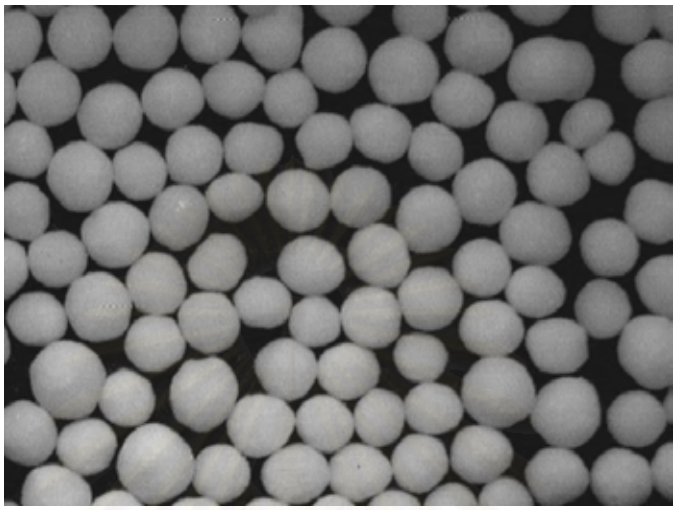


Figure 75. Photomicrograph of lactose pellets formed with MCC and water (CT-L/W195) in magnification x7.

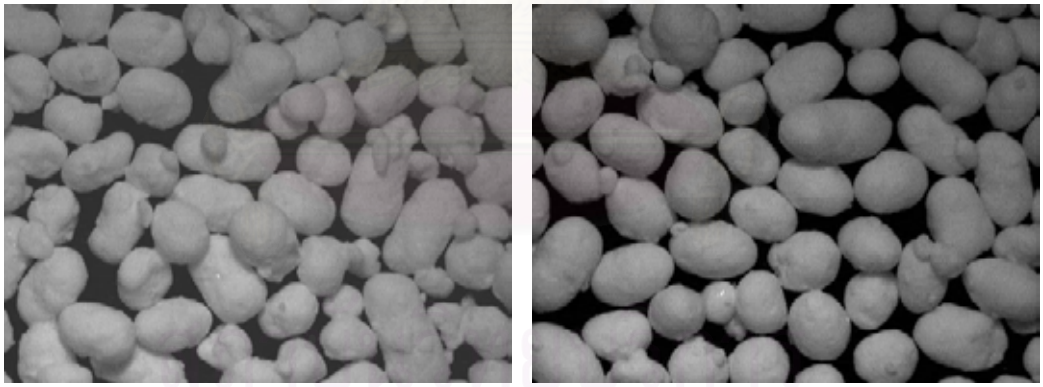
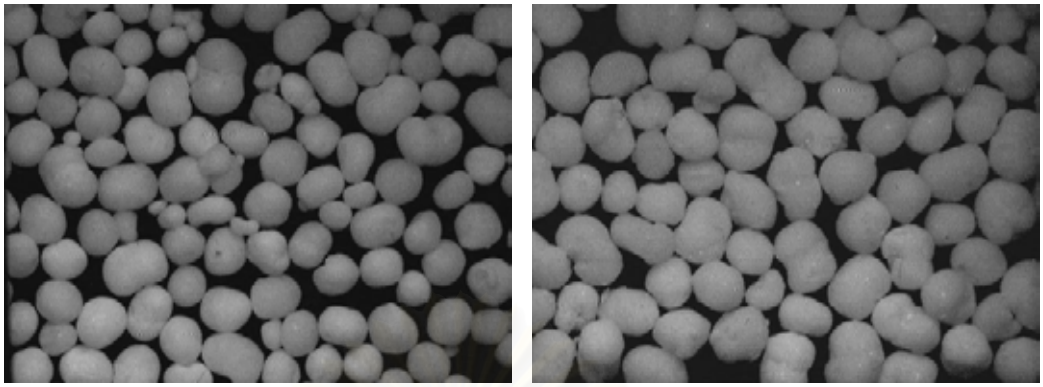


Figure 76. Photomicrographs of propranolol hydrochloride pellets formed with MC 15 in magnification x7: (a) MC2-P/W415 and (b) MC1-P/A58.



(c) (b)

Figure 77. Photomicrographs of ibuprofen pellets formed with MC 15 in magnification x7: (a) MC4-I/W70 (b) MC8-I/A106

For propranolol hydrochloride and ibuprofen pellets, they seemed to have irregular shape and rather remained at rod or dumbelled shape (Figure 76-77). These results might be due to the loss tangent of propranolol hydrochloride is very low, 0.07 and 0.10 for water and 50% ethanol, respectively. It indicated that propranol hydrochloride wet mass is very elastic and could not be broken off and deformed into pellets. As these results, propranolol hydrochloride had larger and agglomeration more than ibuprofen pellets both water and 50% ethanol as liquid binder. Due to stickiness of the pellets, the small particles adhered to large pellets. This might be lead to balling and uncontrollable process in late stage. Spheronization time for these formulations was limited at 3 min because of product adhered to spheronization plate. The formulation of pellet which prepared by using microcrystalline cellulose, CT-L/W195, had the best size, shape and smooth surface as shown in Figure 75 and 86.

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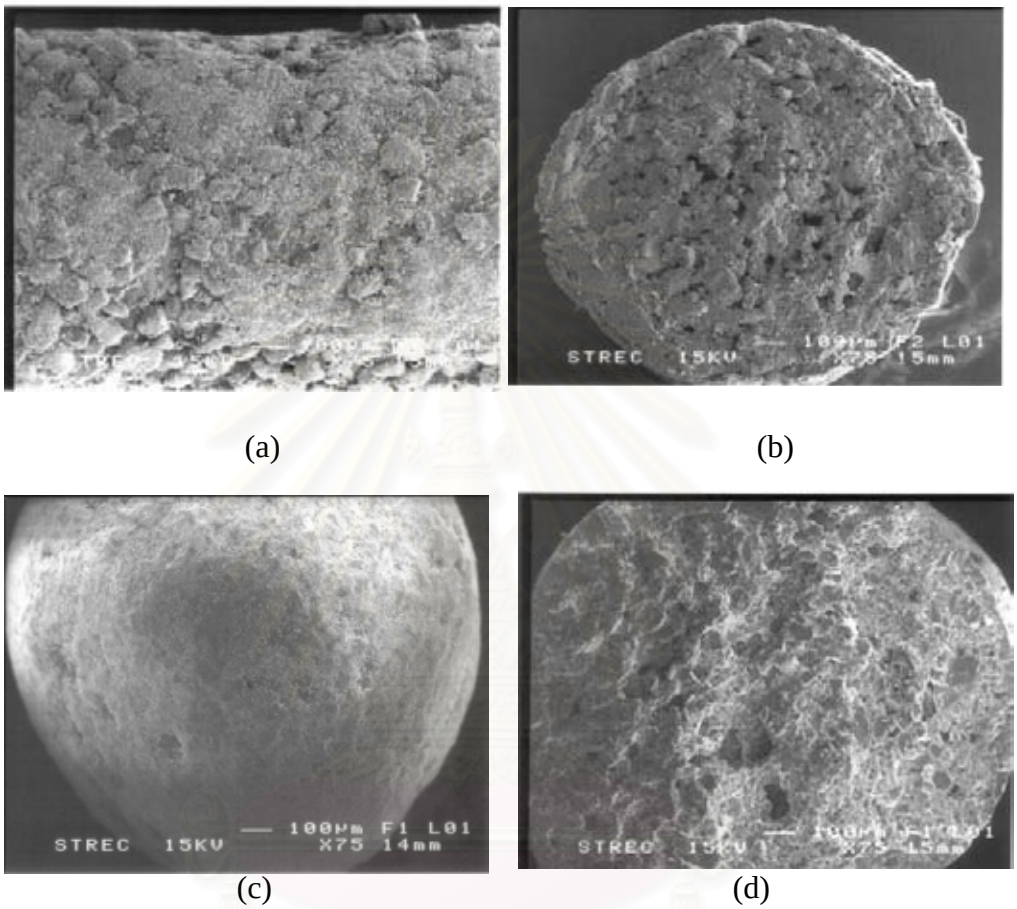
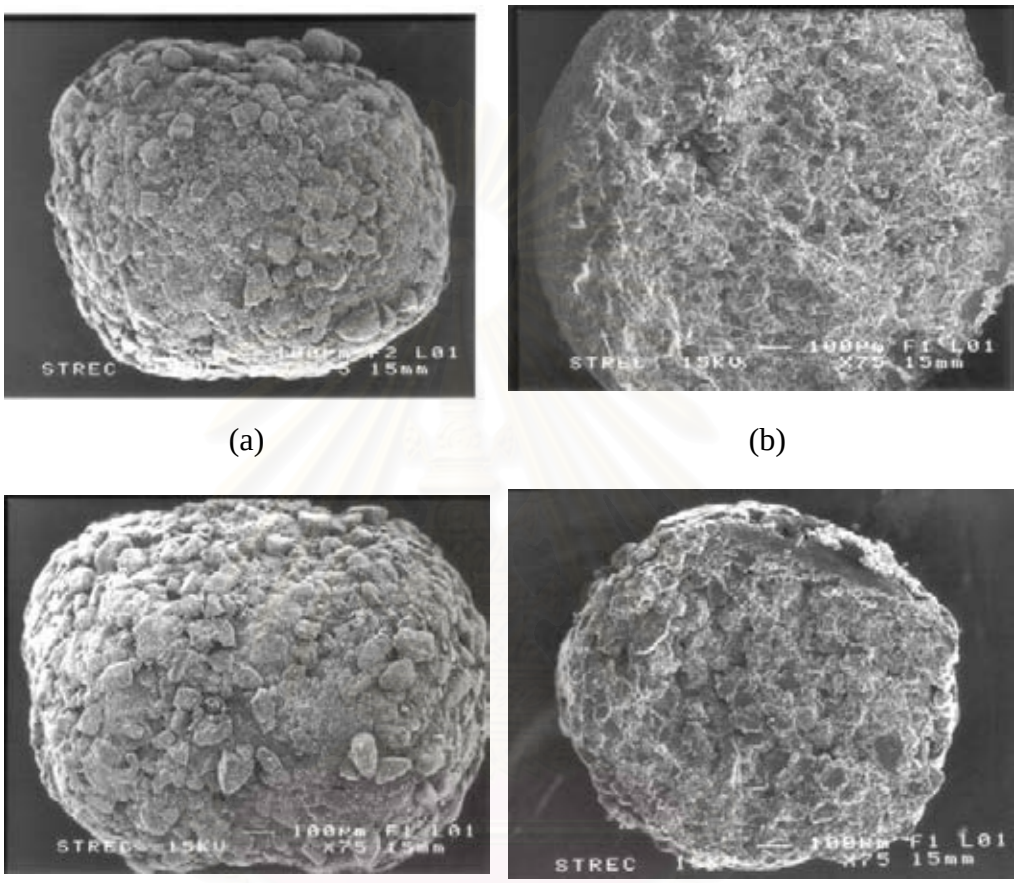


(a) (b)

(c) (d)

Figure 78. Scanning electron photomicrographs of lactose pellet formed with NaCMC 1180 and water in magnification x75: (a) CMC2-L/W50, (b) cross-section of CMC2-L/W50, (c) CMC2-L/W51 and (d) cross-section of CMC2-L/W51.



(a) (b)

(c) (d)

Figure 79. Scanning electron photomicrographs of lactose pellet formed with NaCMC 1180 and water in magnification x75: (a) CMC3-L/W45, (b) cross-section of CMC3-L/W45, (c) CMC3-L/W46 and (d) cross-section of CMC3-L/W46.

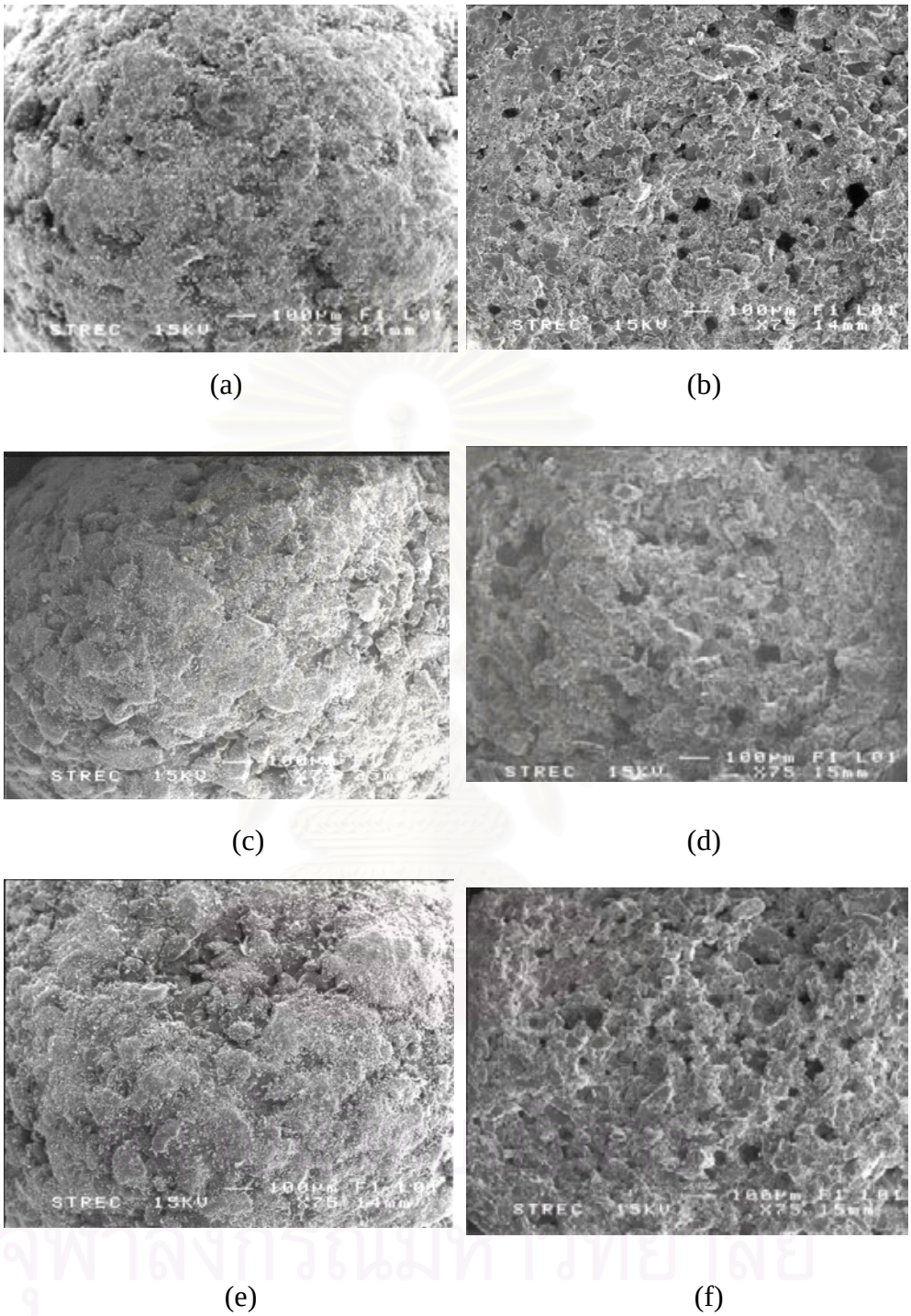


Figure 80. Scanning electron photomicrographs of lactose pellet formed with NaCMC 1180 and 50% ethanol in magnification x75: (a) CMC2-L/A83, (b) cross-section of CMC2-L/A83, (c) CMC2-L/A84, (d) cross-section of CMC2-L/A84, (e) CMC2-L/A85 and (f) cross-section of CMC2-L/A85.

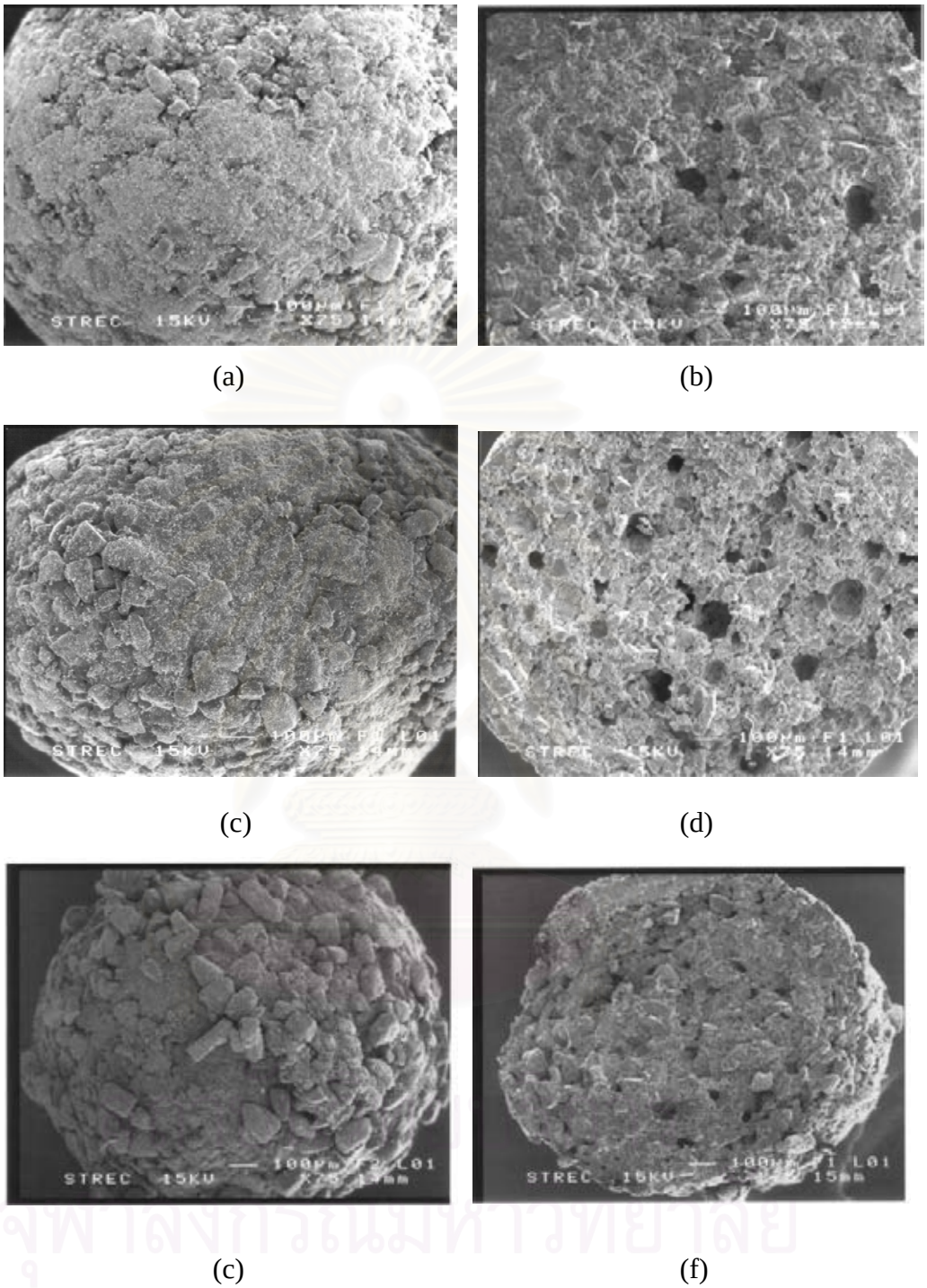
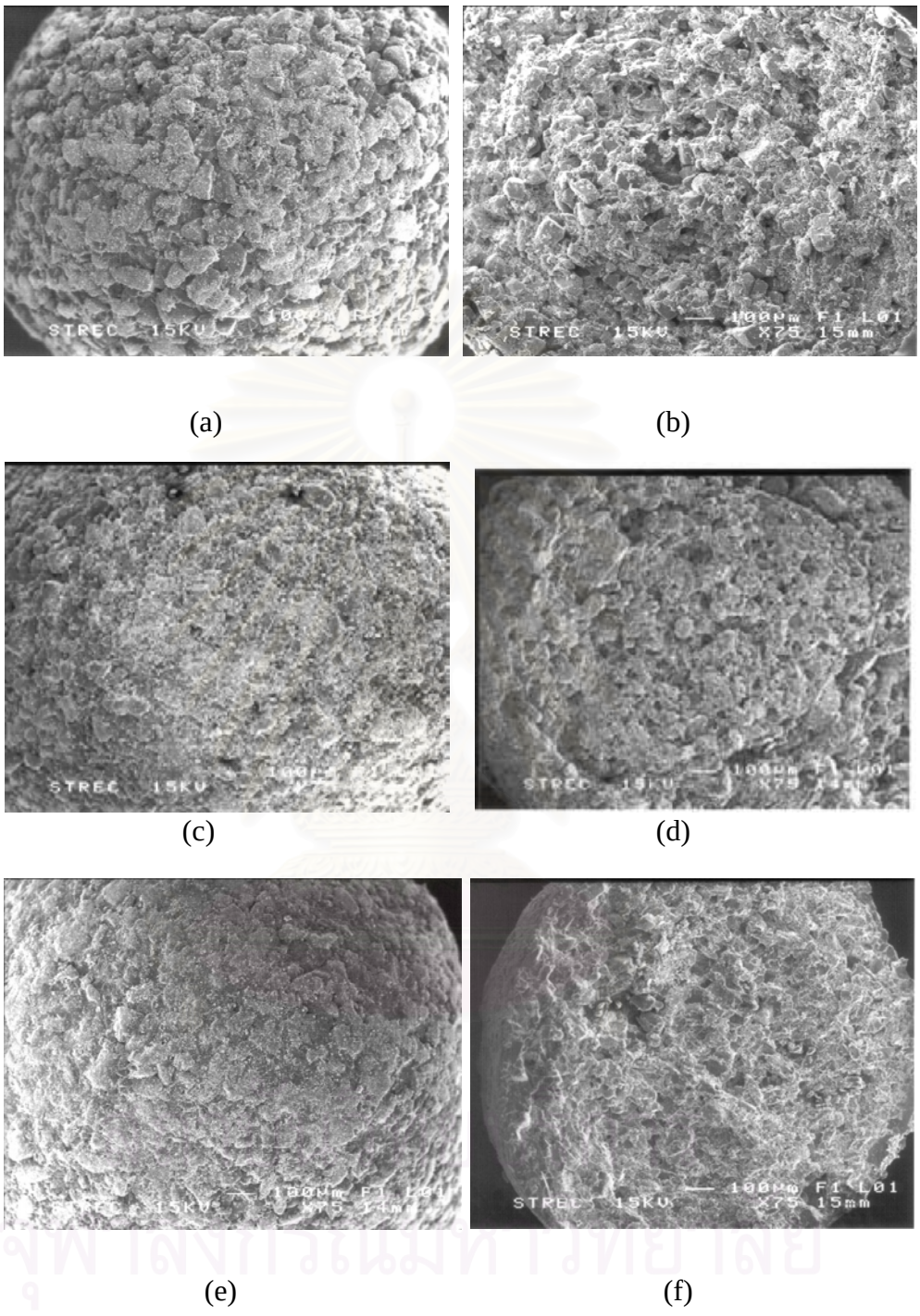


Figure 81. Scanning electron photomicrographs of lactose pellet formed with NaCMC 1180 and50% ethanol in magnification x75: (a) CMC2-L/A86, (b) CMC2-L/A86, (c) CMC2-L/A87 and (d) cross-section of CMC2-L/A87, (e) CMC3-L/A90 and (d) cross-section of CMC3-L/A90.

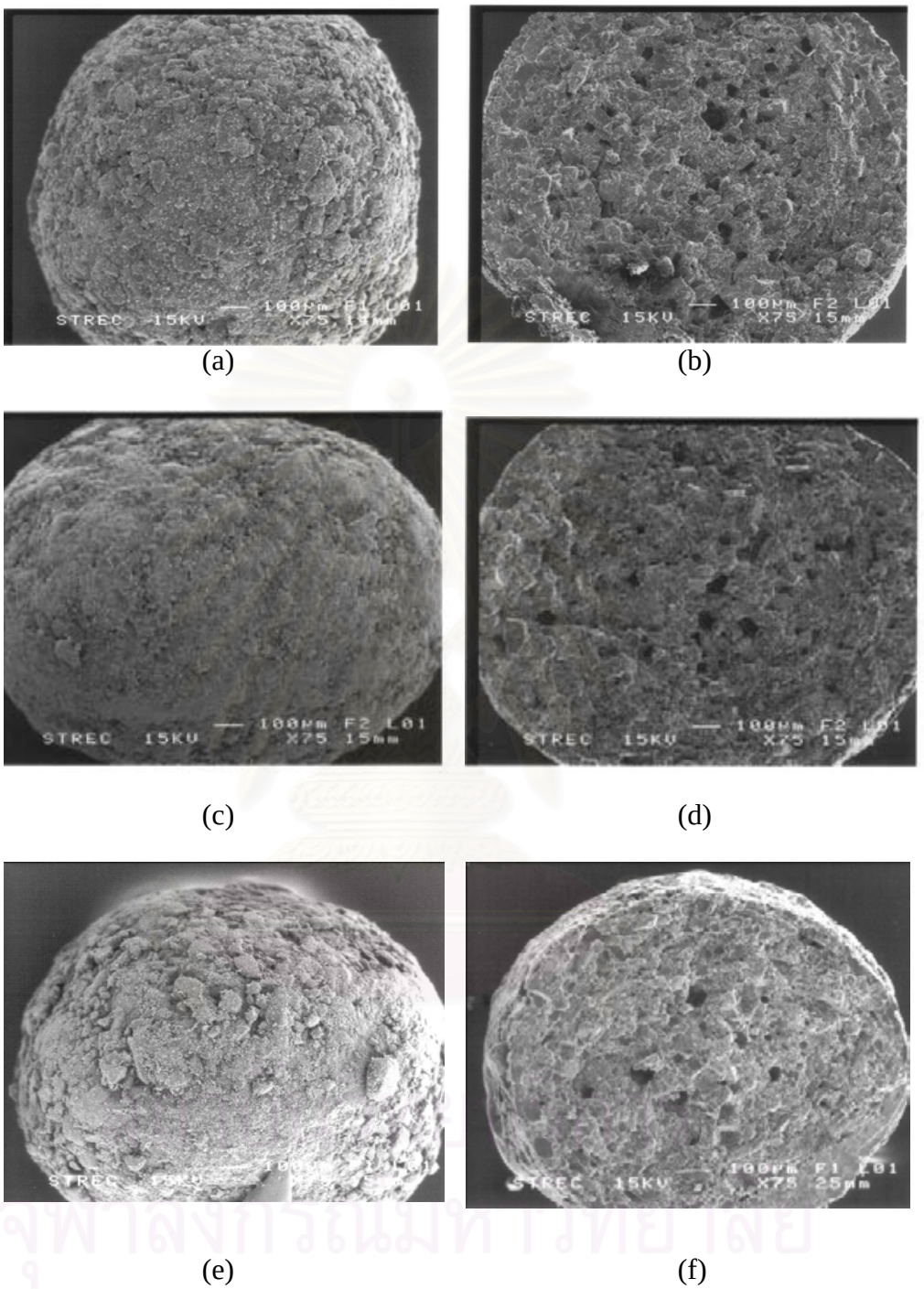


(a) (b)

(c) (d)

(e) (f)

Figure 82. Scanning electron photomicrographs of lactose pellet formed with MC 15 and water in magnification x75: (a) MC2-L/W45, (b) cross-section of MC2-L/W45, (c) MC3-L/W42, (d) cross-section of MC3-L/W42, (e) MC3-L/W45 and (f) cross-section of MC3-L/W45.



(a) (b)

(c) (d)

(e) (f)

Figure 83. Scanning electron photomicrographs of lactose pellet formed with MC 15 and 50% ethanol in magnification x75: (a) MC3-L/A64, (b) cross-section of MC3-L/A624, (c) MC3-L/A66, (d) cross-section of MC3-L/ A66, (e) MC3-L/A68 and (f)cross-section of MC3-L/ A68.

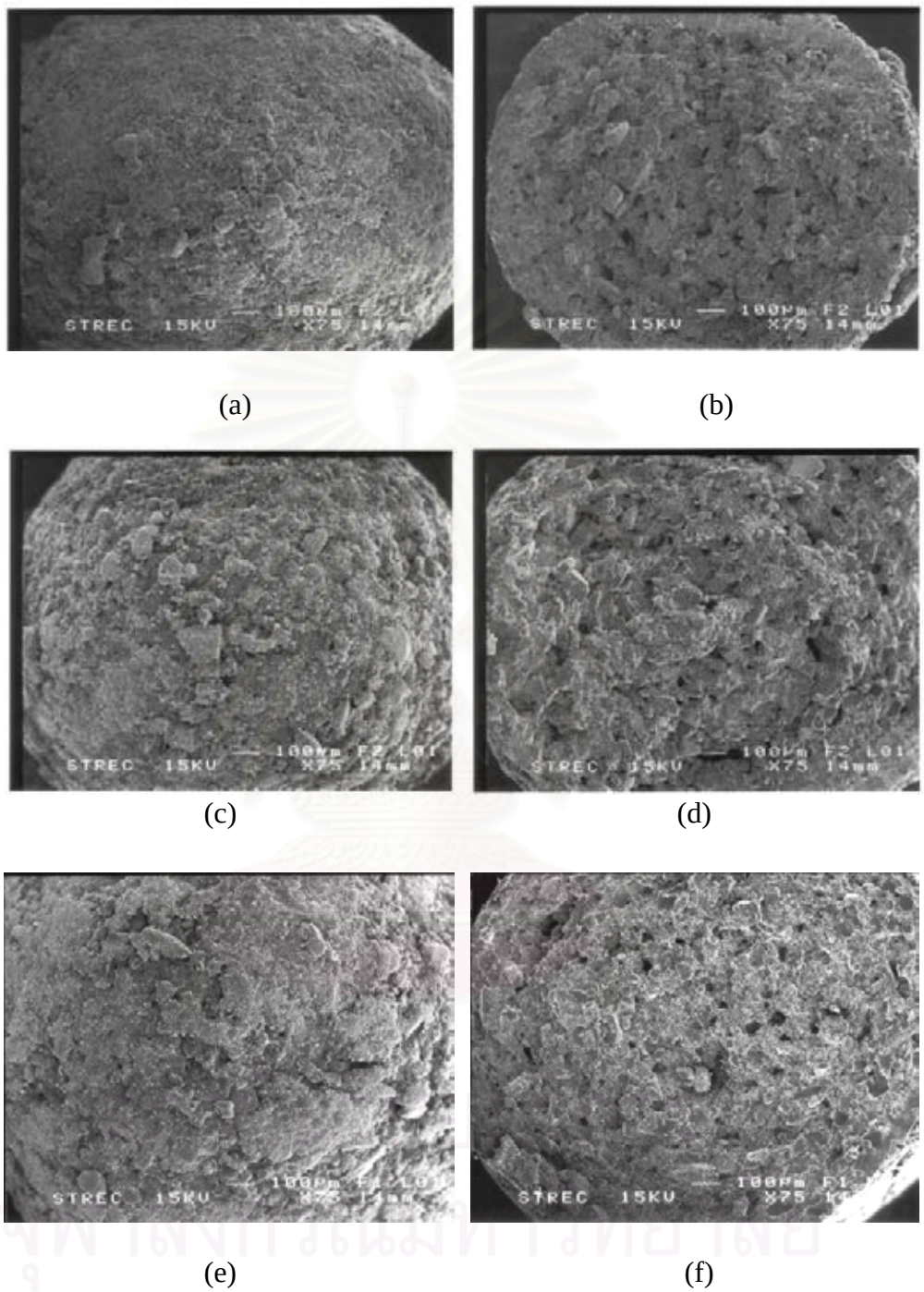
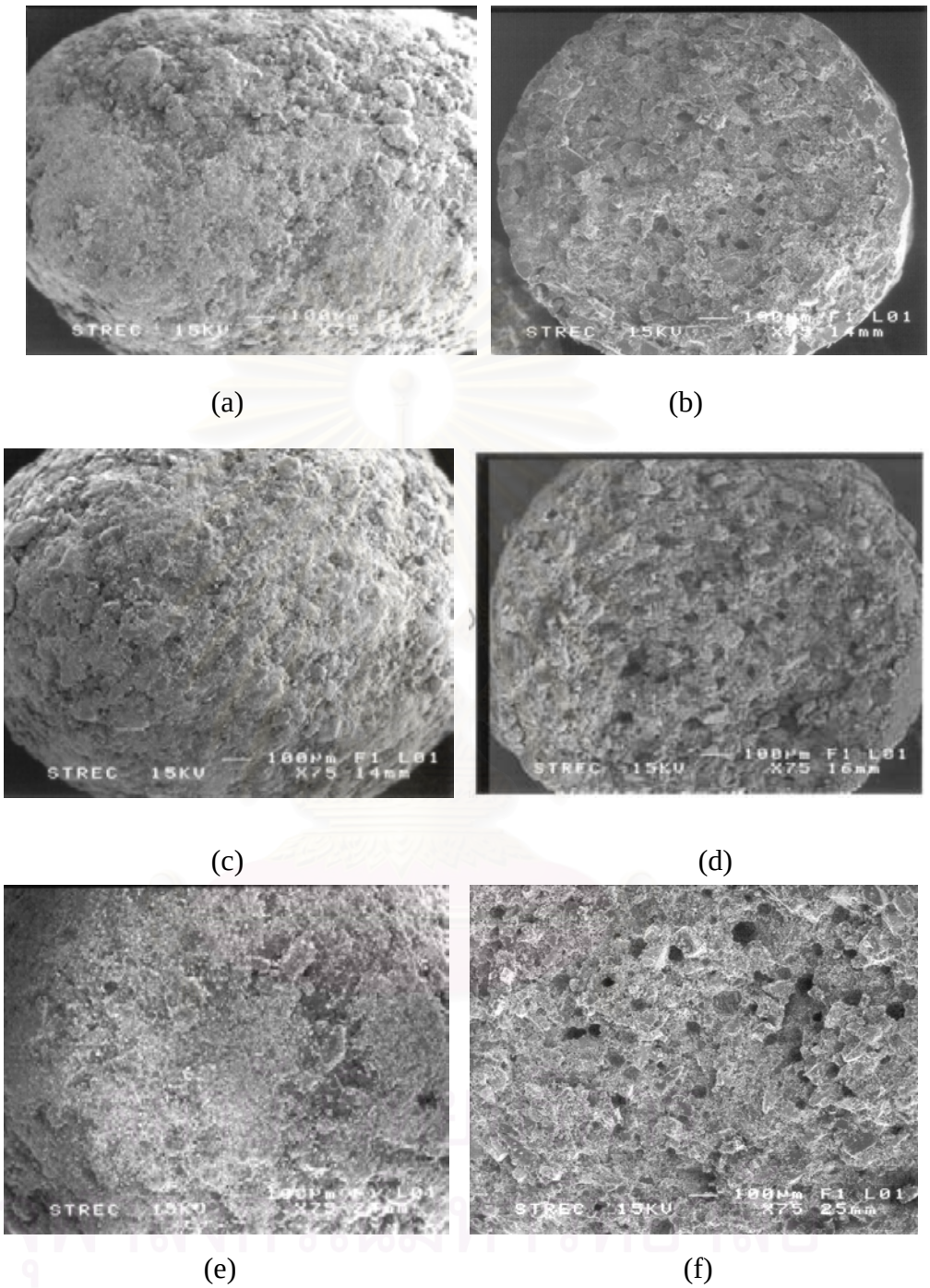


Figure 84. Scanning electron photomicrographs of lactose pellet formed with HPMC E15 and 50% ethanol in magnification x75: (a) HPMC2-L/A65, (b) cross-section of HPMC2-L/A65, (c) HPMC2-L/A66, (d) cross-section of HPMC2-L/A66, (e) HPMC3-L/A64 and (f)cross-section of HPMC3-L/A64

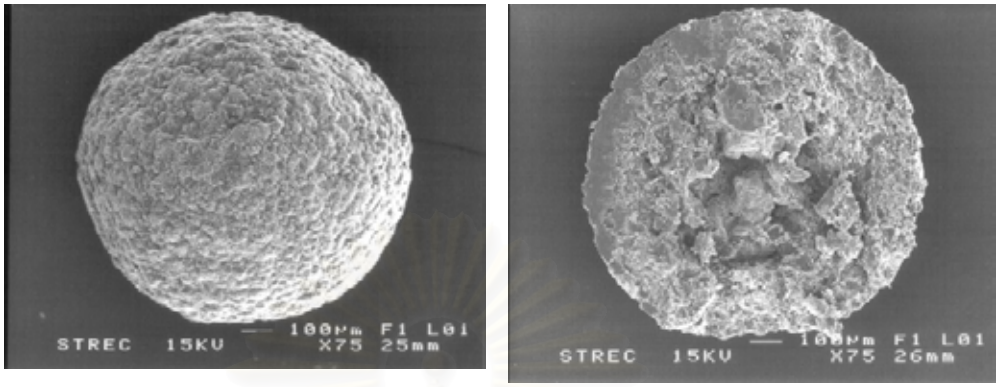


(a) (b)

(c) (d)

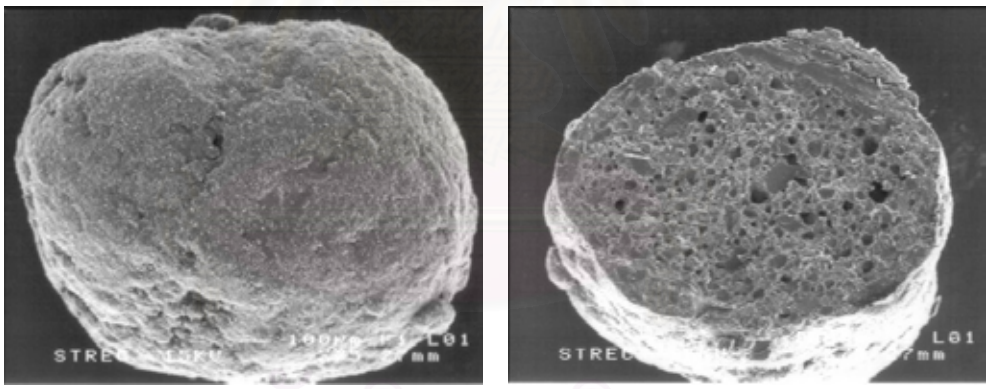
(e) (f)

Figure 85. Scanning electron photomicrographs of lactose pellet formed with HPMC E15 and 50% ethanol in magnification x75: (a) HPMC3-L/A65, (b) cross-section of HPMC3-L/A65, (c) HPMC3-L/A66, (d) cross-section of HPMC3-L/A66, (e) HPMC3-L/A67 and (f) cross-section of HPMC3-L/A67



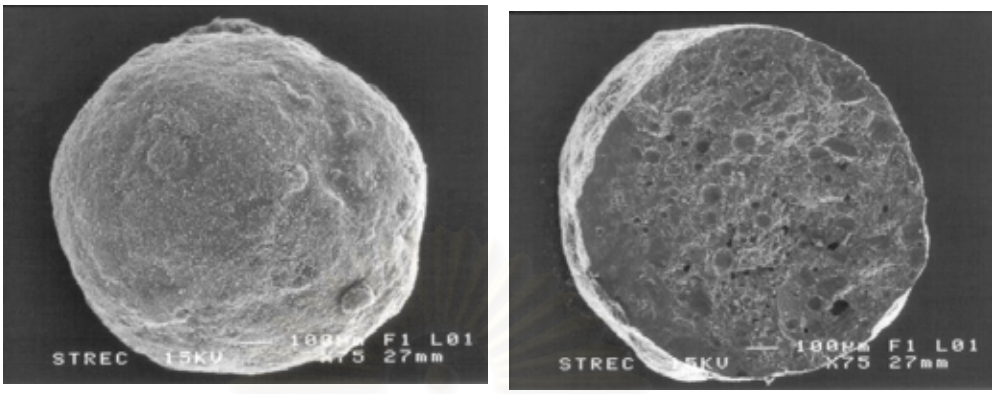
(a) (b)

Figure 86. Scanning electron photomicrographs of lactose pellet formed with MCC and water in magnification x75: (a) CT-L/W195 and (b) cross-section of CT-L/W195



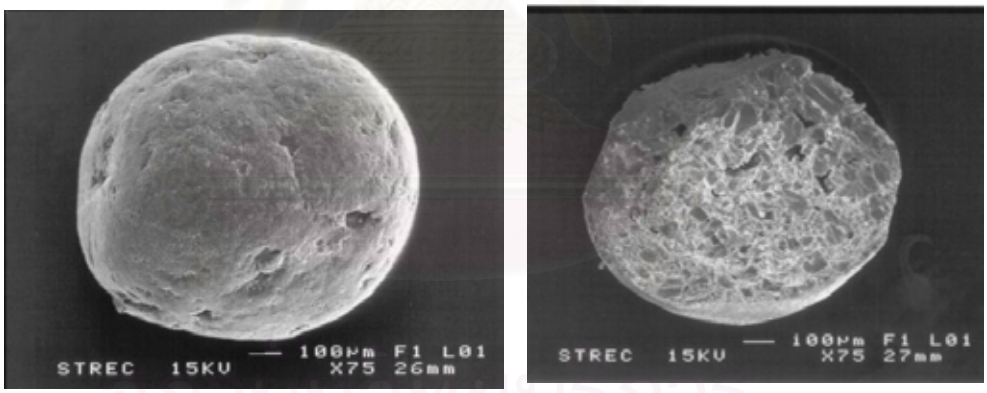
(a) (b)

Figure 87. Scanning electron photomicrographs of propranolol hydrochloride pellet formed with MC 15 and water in magnification x75: (a) MC2-P/W41 and (b) cross-section of MC2-P/W41 in magnification x75



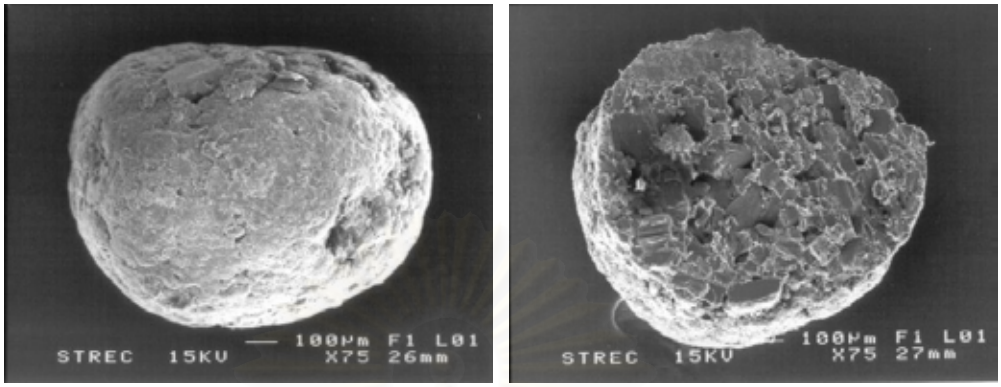
(a) (b)

Figure 88. Scanning electron photomicrographs of propranolol hydrochloride pellet formed with MC 15 and 50% ethanol in magnification x75: (a) MC1-P/A58 and (b) cross-section of MC1-P/A58



(a) (b)

Figure 89. Scanning electron photomicrographs of ibuprofen pellet formed with MC 15 and water in magnification x75: (a) MC4-I/W70 and (b) cross-section of MC4-I/W70



(a) (b)

Figure 90. Scanning electron photomicrographs of lactose pellet formed with MC 15 and 50% ethanol in magnification x75: (a) MC8-I/A106 and (b) cross-section of MC8-I/A106

4.2 Particle size and size distribution

The median size diameter and interquartile range (IQR) representing size distribution of pellets prepared by using various cellulose ethers, i.e. NaCMC 1180, MC 15 and HPMC E15 was determined by using sieve analysis method. The percent retained on each sieve was calculated and plotted against sieve size as illustrated in Figure 87-93. The value of median size diameter and IQR were also determined and the results were shown in Table 14.

In general, as presented in Table 14, For the size distribution of pellets prepared by using NaCMC 1180 as the formulation aid and water as liquid binder, it was found that 1.0% w/w NaCMC 1180 formulations were likely to form smaller size than 0.5% w/w NaCMC 1180. The median size diameter of pellet of NaCMC 1180 as formulation aid was shown in Table 14. The result agreed with those prepared with 50% ethanol. When 1.0% w/w MC 15 and 45 g (15.00%) water was used to prepare pellet, MC3-L/W45, had the largest size, 2.1 mm. This because the higher either MC 15 or water content in wet mass resulted in increased the elastic property of wet mass.

Thus, the extrudates could not be broken off and deformed into spherical. These results agreed with the lower value of loss tangent in case of water formulation (Figure 69). For 50% ethanol formulation, the median size diameter was rather similar with increased liquid binder content. The pellets formed by using HPMC E15 and 50% ethanol were found to have bigger size when the amount of formulation aid was increased, except for HPMC3-L/A67 which was 1.0% w/w HPMC E15 and 67 g (22.33%) of 50% ethanol.

The size distribution of pellets using NaCMC 1180, MC 15 and HPMC E15 as formulation aid reflected in the value of interquartile range (IQR), were not clearly different and rather similar both water and 50% ethanol as liquid binder (Table 14), Except for 0.5% w/w HPMC E 15 and 65g (21.66%) ethanol, HPMC2-L/A65. This formulation had the broadest size distribution, IQR 0.74 mm.

For propranolol hydrochloride or ibuprofen formulation containing MC 15 as the formulation aid, the median size diameter was smaller than using lactose pellets. Due to the physico-chemical property of propranolol hydrochloride, ibuprofen and lactose were different, e.g. solubility and particle size, could change the rheological properties of wet mass. Ibuprofen was insoluble in water so that the quantity of MC 15 used in formulation was more than that required for propranolol hydrochloride.

For MCC formulation, because of the amount of MCC in formulation was high (50%), It absorbed the water and then swell. After drying those pellets would shrink (Kleinebudde, 1994). As the result of that effect, the pellets prepared from MCC was rather small, 0.78 mm.

The rheological property of wet mass might affect on size and size distribution as presented in Figure 94-95. It showed that the higher storage modulus resulted in the larger size of pellets due to elastic property. This result same as IQR, the higher storage modulus resulted in the broadest particle size distribution. For 50% ethanol formulation the tended was not clearly.

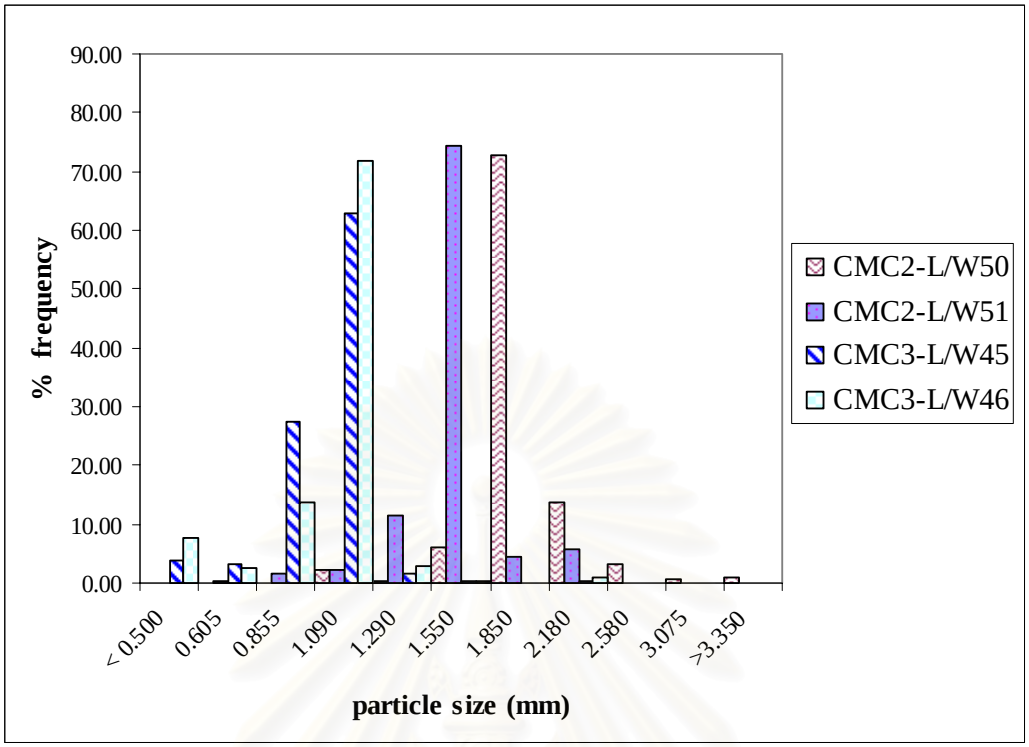


Figure 91. Size distributions of lactose pellets prepared by using NaCMC 1180 as the formulation aid and water as liquid binder.

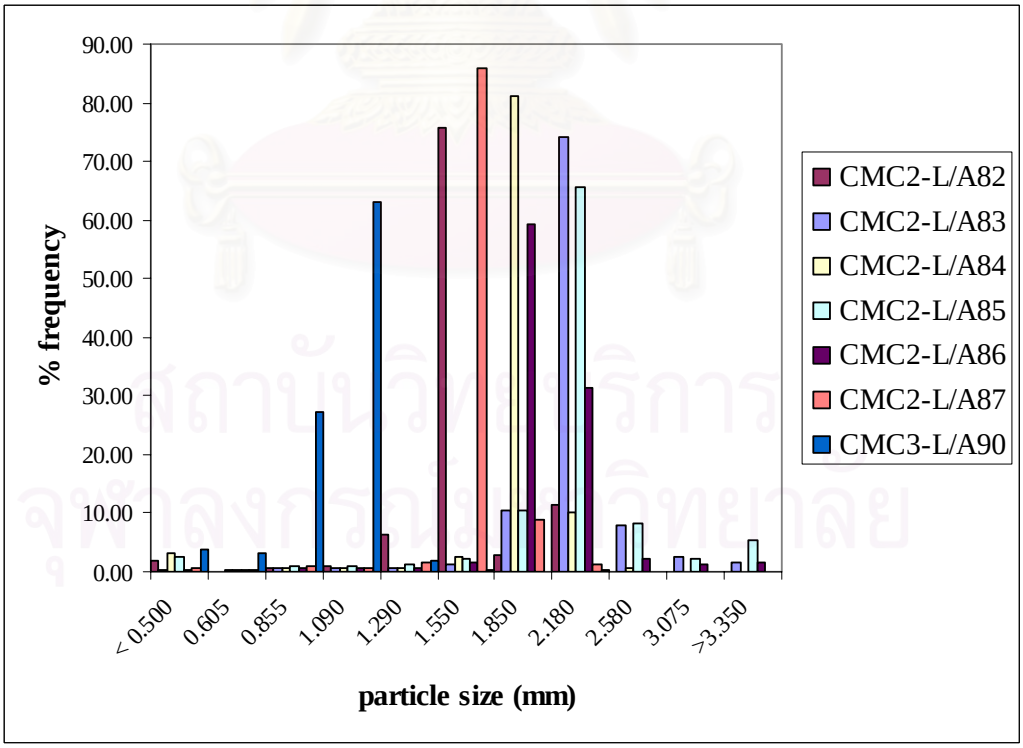


Figure 92. Size distributions of lactose pellets prepared by using NaCMC 1180 as the formulation aid and 50% ethanol as liquid binder.

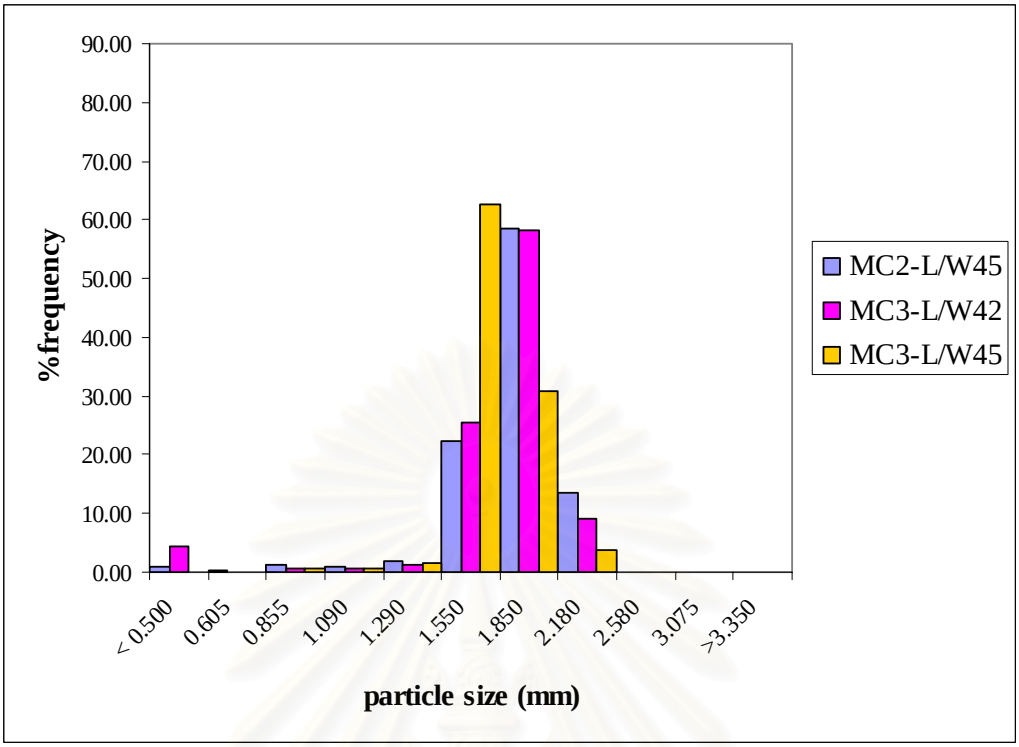


Figure 93. Size distributions of lactose pellets prepared by using MC 15 as the formulation aid and water as liquid binder.

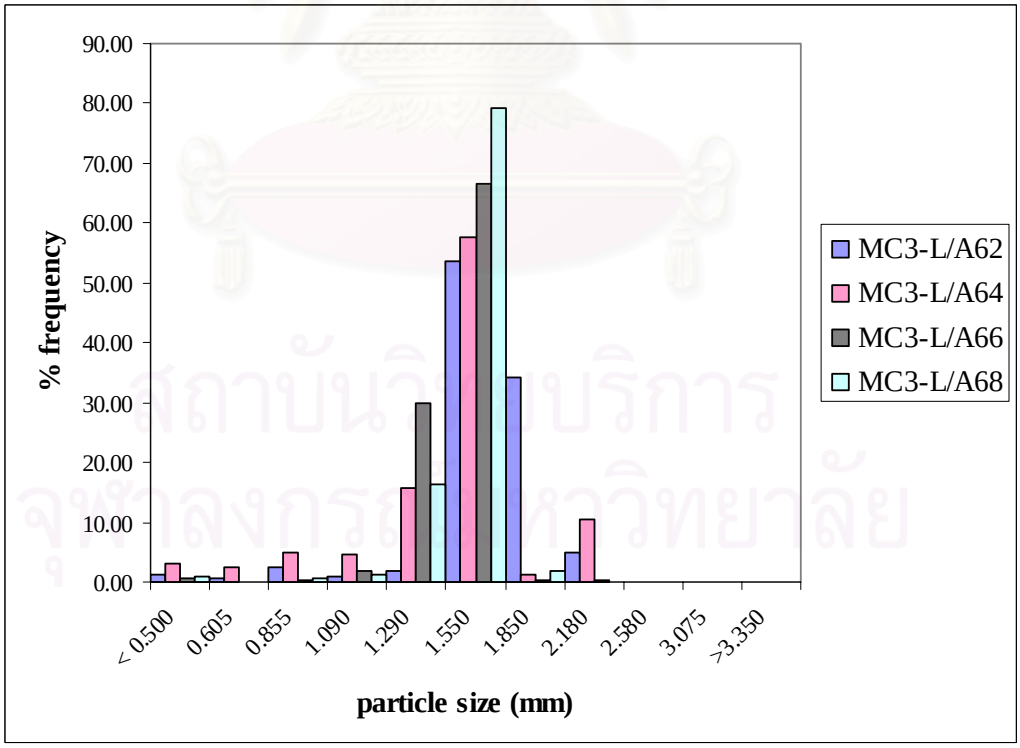


Figure 94. Size distributions of lactose pellets prepared by using MC 15 as the formulation aid and 50% ethanol as liquid binder.

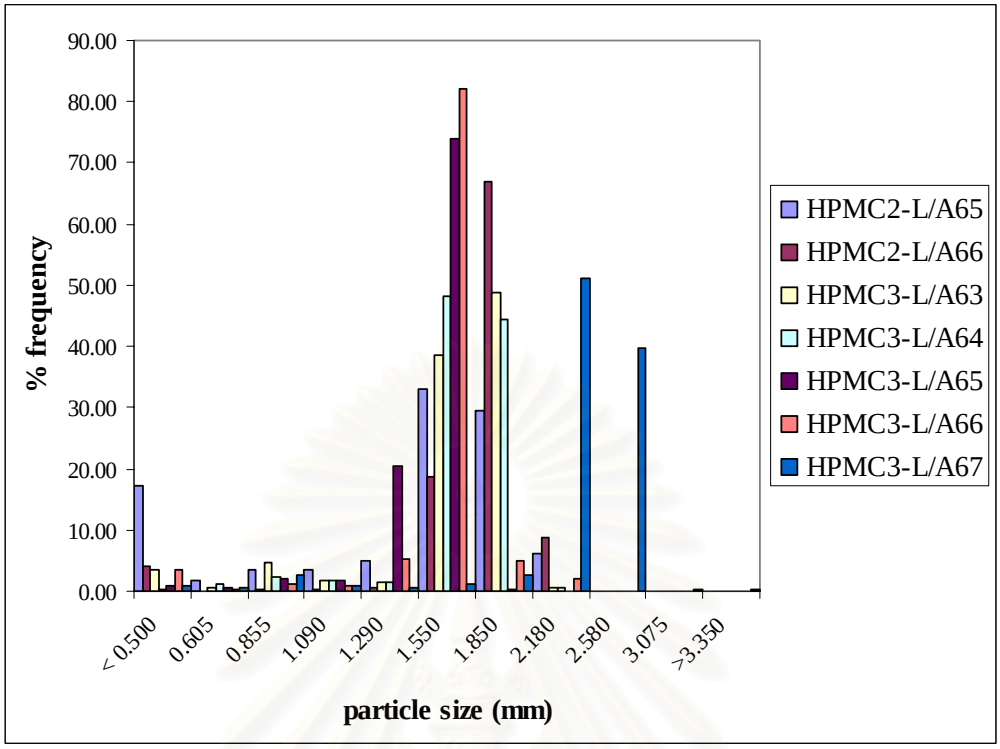


Figure 95 Size distributions of lactose pellets prepared by using HPMC E15 as the formulation aid and 50% ethanol as liquid binder.

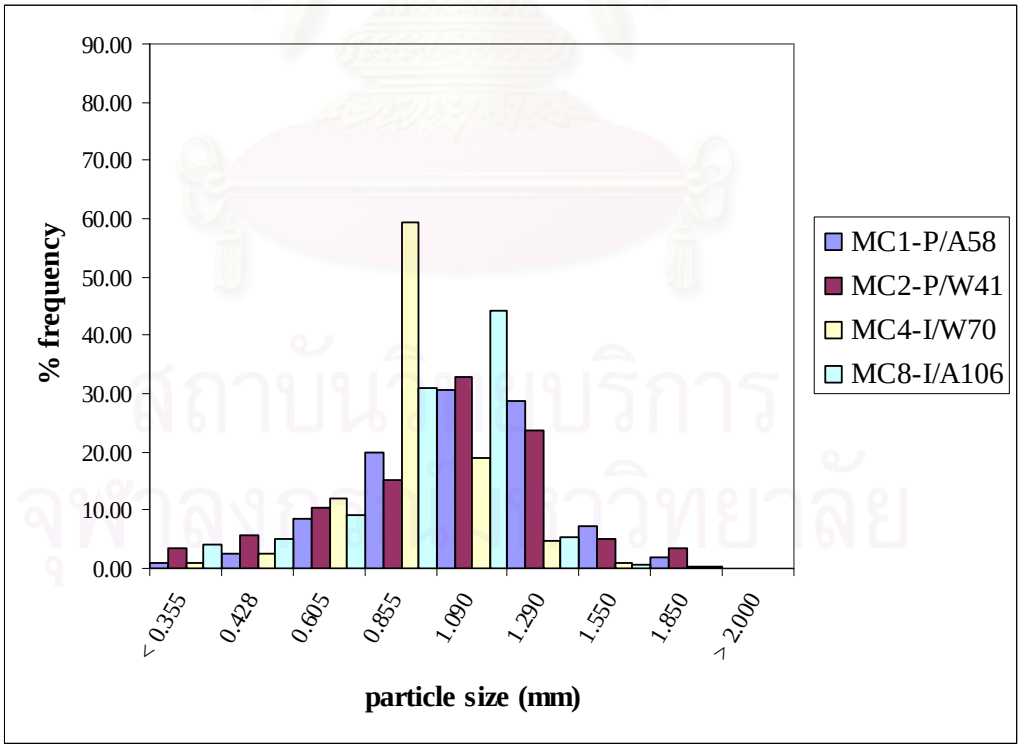


Figure 96. Size distributions of propranolol hydrochloride and ibuprofen pellets prepared by using MC 15 as the formulation aid.

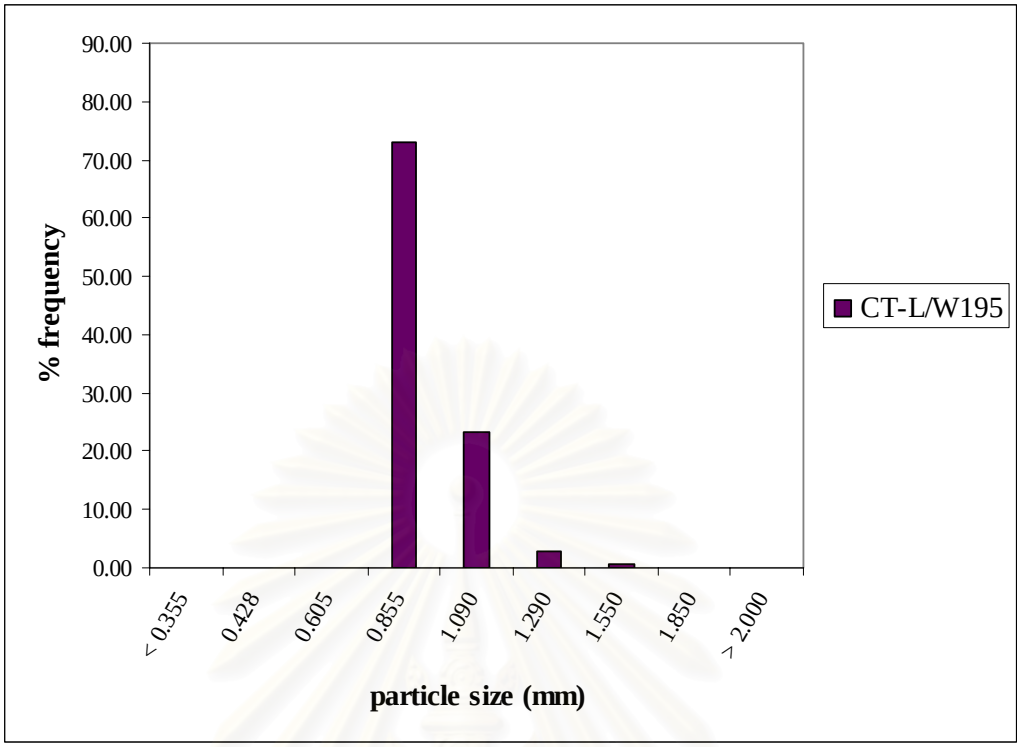


Figure 97. Size distributions of lactose pellets prepared by using MCC as the formulation aid.

4.3 Flowability and angle of repose

Flowability and angle of repose of pellet using NaCMC 1180, MC 15 and HPMC E15 as the formulation aids was presented in Table 15. The angle of repose and flow rate of all formulations were in range of 9.3- 26.4 degree and 8.43-11.58 g/sec, respectively. These results could be classified as good flowability. The minimum value of the angle of repose was 9.31 degrees for HPMC3-L/A67. The angle of repose was a method of indirectly measuring a combination of the following properties that affect to flow property; i.e. shape, size, cohesion, and surface area (Saenz, 2001). For pellets, flowability depended on surface characteristic, sphericity and cohesion. If pellets was smooth surface, round shape and less cohesion, it posed good flowability. It indicated that HPMC3-L/A67 had smooth surface, round shape and less cohesion between particles.

Table 14. Median diameter and interquartile range (IQR) of pellets prepared by using NaCMC 1180, MC 15 or HPMC E15 as the formulation aid and water or ethanol as liquid binder.

Formulation	Median diameter (mm)	IQR (mm)
CMC2-L/W50	1.20	0.12
CMC2-L/W51	1.42	0.16
CMC3-L/W45	0.92	0.22
CMC3-L/W46	0.94	0.16
CMC2-L/A82	1.40	0.16
CMC2-L/A83	0.98	0.14
CMC2-L/A84	1.70	0.18
CMC2-L/A85	2.00	0.24
CMC2-L/A86	1.78	0.26
CMC2-L/A87	1.44	0.14
CMC3-L/A90	0.92	0.20
MC2-L/W45	1.22	0.16
MC3-L/W42	1.24	0.18
MC3-L/W45	2.10	0.30
MC3-L/A62	1.34	0.26
MC3-L/A64	1.45	0.30
MC3-L/A66	1.50	0.20
MC3-L/A68	1.46	0.16
HPMC2-L/A65	1.38	0.74
HPMC2-L/A66	1.20	0.10
HPMC3-L/A63	1.30	0.24
HPMC3-L/A64	1.30	0.24
HPMC3-L/A65	1.46	0.18
HPMC3-L/A66	1.42	0.18
HPMC3-L/A67	0.90	0.22
CT-L/W195	0.78	0.20
MC3-P/A58	1.00	0.34
MC4-P/W41	0.86	0.46
MC4-I/W70	0.72	0.18
MC8-I/A106	0.78	0.20

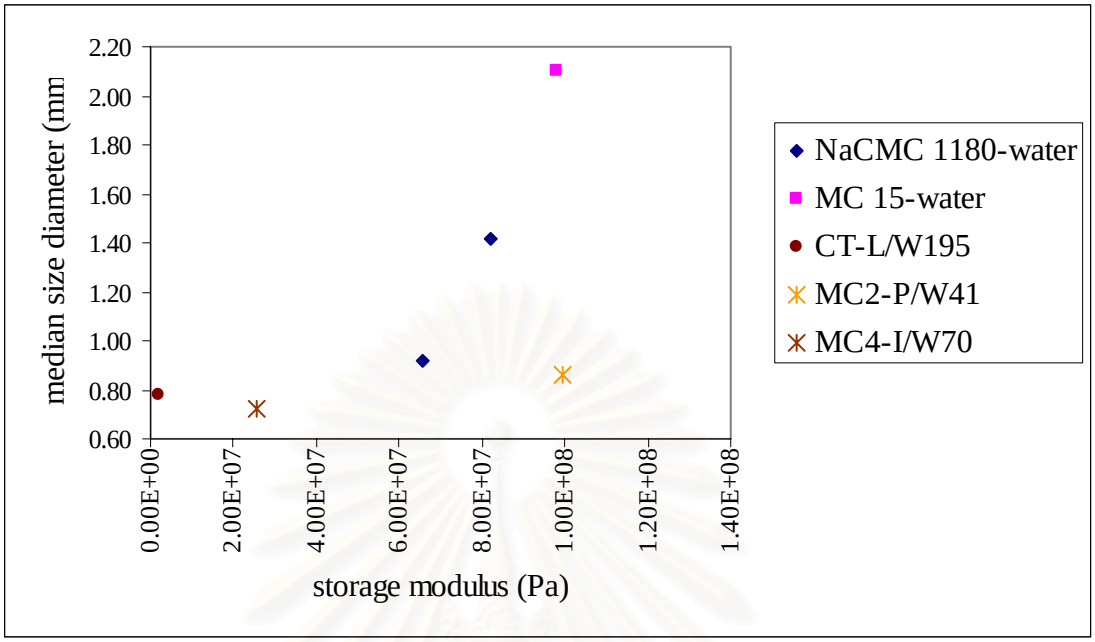


Figure 98. Effect of storage modulus (G′) on median size diameter (mm) of water formulation

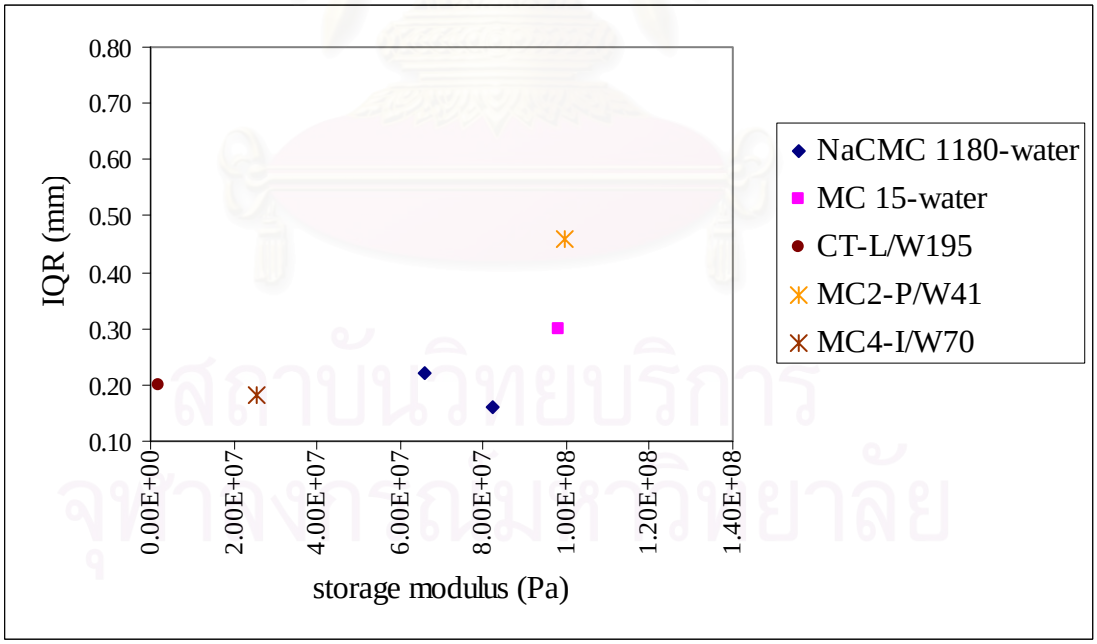


Figure 99. Effect of storage modulus (G′) on IQR (mm) of water formulation

Table 15. Flowability, angle of repose, bulk and tapped densities and percent compressibility, (mean (SD), n=3)

Formulation	Flow rate (g/sec)	Angle of repose (degree)	Bulk density (g/cm^3)	Tapped densnity (g/cm^3)	% Compressibility
CMC2-L/W50	10.64 (0.01)	19.45 (1.35)	0.74 (0.01)	0.76 (0.00)	2.33 (1.26)
CMC2-L/W51	10.01 (0.05)	21.18 (0.56)	0.68 (0.00)	0.76 (0.01)	10.73 (0.98)
CMC3-L/W45	9.69 (0.15)	16.94 (0.68)	0.65 (0.00)	0.73 (0.01)	10.61 (2.02)
CMC3-L/W46	9.75 (0.07)	22.94 (0.22)	0.63 (0.00)	0.71 (0.00)	12.50 (0.00)
CMC2-L/A82	11.13 (0.07)	21.55 (0.51)	0.64 (0.00)	0.72 (0.00)	10.65 (0.56)
CMC2-L/A83	9.83 (0.17)	14.87 (0.11)	0.65 (0.00)	0.79 (0.00)	9.72 (0.61)
CMC2-L/A84	10.28 (0.10)	21.80 (0.07)	0.63 (0.00)	0.70 (0.00)	9.47 (0.09)
CMC2-L/A85	10.02 (0.02)	20.25 (0.19)	0.62 (0.00)	0.69 (0.00)	10.72 (0.69)
CMC2-L/A86	10.69 (0.05)	17.25 (0.15)	0.64 (0.00)	0.71 (0.00)	10.16 (0.83)
CMC2-L/A87	9.86 (0.11)	22.07 (0.12)	0.64 (0.00)	0.72 (0.00)	11.44 (0.63)
CMC3-L/A90	9.54 (0.13)	16.83 (0.33)	0.62 (0.00)	0.69 (0.00)	9.36 (0.03)
MC2-L/W45	11.58 (0.07)	17.06 (0.48)	0.62 (0.00)	0.68 (0.00)	9.12 (0.69)
MC3-L/W42	11.01 (0.15)	18.51 (0.03)	0.61 (0.00)	0.68 (0.00)	10.61 (0.00)
MC3-L/W45	10.93 (0.07)	18.59 (0.17)	0.66 (0.00)	0.72 (0.00)	8.99 (0.82)
MC3-L/A62	12.30 (0.03)	16.41 (0.21)	0.68 (0.00)	0.74 (0.00)	8.47 (0.00)
MC3-L/A64	11.09 (0.09)	18.49 (0.15)	0.67 (0.00)	0.74 (0.00)	10.00(0.00)
MC3-L/A66	12.51 (0.16)	19.00 (0.56)	0.68 (0.00)	0.74 (0.00)	8.93 (0.39)
MC3-L/A68	11.00 (0.01)	19.84 (0.19)	0.68 (0.00)	0.74 (0.00)	8.47 (0.00)
HPMC2-L/A65	9.95 (0.20)	18.53 (0.37)	0.62 (0.00)	0.68 (0.01)	9.00 (0.53)
HPMC2-L/A66	10.22 (0.37)	16.21 (0.74)	0.64 (0.01)	0.70 (0.01)	9.73 (0.24)
HPMC3-L/A63	11.48 (0.09)	16.66 (0.41)	0.68 (0.00)	0.75 (0.00)	9.21 (0.37)
HPMC3-L/A64	10.65 (0.12)	20.84 (0.57)	0.68 (0.01)	0.76 (0.00)	10.67 (0.86)
HPMC3-L/A65	11.00 (0.03)	20.11 (0.50)	0.68 (0.00)	0.74 (0.00)	8.47 (0.00)
HPMC3-L/A66	10.73 (0.24)	18.38 (0.51)	0.67 (0.00)	0.74 (0.00)	9.78 (0.34)
HPMC3-L/A67	8.43 (0.02)	9.31 (1.43)	0.67 (0.00)	0.73 (0.00)	8.33 (0.00)
CT-L/W195	11.43 (0.10)	17.93 (0.18)	0.72 (0.00)	0.78 (0.00)	7.44 (0.36)
MC1-P/W41	7.20 (0.02)	26.47 (0.56)	0.48 (0.00)	0.55 (0.00)	12.10 (0.08)
MC2-P/A58	7.98 (0.03)	24.14 (0.59)	0.54 (0.01)	0.61 (0.01)	12.59 (0.09)
MC4-I/W70	10.02 (0.38)	23.66 (0.57)	0.55 (0.00)	0.61 (0.00)	10.02 (0.38)
MC8-I/A106	10.26 (0.00)	22.82 (0.24)	0.51 (0.00)	0.57 (0.01)	10.26 (0.00)

4.4 Bulk and tapped densities and percent compressibility

The results of bulk and tapped densities and percent compressibility were shown in Table 15. Percent compressibility or Carr's index was calculated by bulk density and tapped density. The borderline between free flowing and non free flowing is about 20% to 21%. Percentage compressibility was an excellent indication of uniformity in size and shape, and moisture content (Saenz, 2001). All formulations which could form pellets, the bulk density was close to tapped density. Thus, percent compressibility was low, 2.33-12.59 %. The minimum and maximum value of percent compressibility was obtained from formulation containing 0.5% w/w NaCMC 1180 and 50 g (16.66%) water, CMC2-L/W50, 2.33 % in case of minimum value and MC2-P/WA58, which was the formulation contain 0.5% w/w MC 15 and 58 g (19.33%) of 50% ethanol, 12.59% for maximum value.

4.5 Apparent densities

Apparent densities of pellets were in the range of 1.41-1.62 g/cm^3 as presented in Table 16. In general, the apparent density of CT-L/W195 of MCC formulation was the lowest, 1.41 g/cm^3, in comparison with that of pellets formed with NaCMC 1180, MC 15 and HPMC E15 as formulation aid. The effect of formulation aid on the apparent density was not clearly observed.

4.6 Friability

The friability is an indicator of pellets strength or hardness, the less friability, the greater hardness (Vervaet et al., 1995). Percent friability was shown in Table 16. All of lactose pellet formulation had the percent friability close to zero, 0.01-0.15%, due extrusion-spheronization process produced spherical, dense and smooth surfaces (Lindner et al., 1994). Furthermore, the percent friability was unclearly related to type of the formulation aid used. It has been reported that MCC formulation produced friable pellets if hydroalcoholic was used as liquid binder (Chatlapalli and Rohera, 1998). In this study, fraiable pellets could be avoided if MCC was removed from the formulation

For propranolol hydrochloride and ibuprofen pellets, the higher value of friability was observed as opposed to the lactose pellets. Percent friability was within range 0.23-0.60%. It might be inferred that these pellets were the agglomerated pellets.

4.7 Sphericity

In this study, degree of sphericity was derived from two parameters; i.e., aspect ratio and roundness, which based two dimensional image of the particle. Image analysis was used to obtain these parameters and results from various formulation were present in Table 17. The values of aspect ratio and roundness were close to 1; this meant more sphericity. In this experiment, aspect ratio 1.099 ± 0.55 and roundness 1.042 ± 0.052 were obtained from MCC. It exhibited that MCC was a practical formulation aid to manufacture spherical granules with high sphericity. The sphericity of MCC pellets increased with an increase in the amount of MCC (Kanbe et al., 2006; Alvarez et al., 2004; Heng and Koo, 2001b). The pellets prepared by using NaCMC 1180, MC 15 and HPMC E15 as the formulation aids were found that CMC3-L/A90 had the greatest aspect ratio, 1.418. For roundness, there is not clearly different.

The aspect ratio and roundness of pellets prepared by using water as liquid binder was in the range of 1.087-1.281 and 1.053-1.128, respectively (Figure 100 and 102). According to Chopra et al. (2002) the threshold value of an aspect ratio was 1.2 or less so that only MC2-L/W45 and MC4-I/W70 were the best sphericity. The results of MC2-L/W45 agreed with the results from roundness. It indicated that MC2-L/W45 was the pellets with the best sphericity. However, the values of instantaneous compliance which could form lactose pellets with NaCMC 1180, MC 15, and HPMC E15 as the formulation aids were in the range of 8.70E-08 1/Pa to 2.20E-07 1/Pa for water and 7.77E-08 to 1.74EE-0.7 1/Pa in case of 50% ethanol.

Table 16. Apparent density, friability and moisture content of pellets, (mean (SD))

Formulation	Apparent density (g/cm^3) (n=5)	Friability (%) (n=3)	Moisture content (% LOD) (n=3)
CMC2-L/W50	1.57 (0.00)	0.01 (0.001)	0.20
CMC2-L/W51	1.55 (0.00)	0.15 (0.001)	0.16
CMC3-L/W45	1.60 (0.00)	0.12 (0.001)	0.25
CMC3-L/W46	1.56 (0.00)	0.11 (0.009)	0.30
CMC2-L/A82	1.52 (0.00)	0.04 (0.001)	0.23
CMC2-L/A83	1.59 (0.00)	0.01 (0.002)	0.23
CMC2-L/A84	1.57 (0.00)	0.10 (0.003)	0.18
CMC2-L/A85	1.56 (0.00)	0.04 (0.002)	0.16
CMC2-L/A86	1.56 (0.00)	0.08 (0.004)	0.29
CMC2-L/A87	1.54 (0.00)	0.00 (0.002)	0.20
CMC3-L/A90	1.53 (0.00)	0.04 (0.001)	0.30
MC2-L/W45	1.54 (0.00)	0.00 (0.001)	0.13
MC3-L/W42	1.55 (0.00)	0.07 (0.012)	0.30
MC3-L/W45	1.52 (0.00)	0.04 (0.001)	0.36
MC3-L/A62	1.56 (0.00)	0.04 (0.001)	0.23
MC3-L/A64	1.62 (0.00)	0.03 (0.007)	0.21
MC3-L/A66	1.61 (0.00)	0.04 (0.013)	0.23
MC3-L/A68	1.51 (0.00)	0.08 (0.005)	0.21
HPMC2-L/A65	1.61 (0.00)	0.09 (0.022)	0.18
HPMC2-L/A66	1.58 (0.00)	0.08 (0.006)	0.24
HPMC3-L/A63	1.60 (0.00)	0.01 (0.001)	0.20
HPMC3-L/A64	1.53 (0.00)	0.01 (0.007)	0.17
HPMC3-L/A65	1.62 (0.00)	0.01 (0.001)	0.15
HPMC3-L/A66	1.56 (0.01)	0.05 (0.006)	0.19
HPMC3-L/A67	1.53 (0.00)	0.07 (0.014)	0.14
CT-L/W195	1.41 (0.00)	0.01 (0.001)	0.42
MC1-P/W41	1.21 (0.00)	0.33 (0.115)	0.26
MC2-P/A58	1.21 (0.00)	0.23 (0.027)	0.15
MC4-I/W70	1.10 (0.00)	0.60 (0.197)	0.11
MC8-I/A106	1.11 (0.00)	0.57 (0.179)	0.40

Table 17 Sphericity and roundness of the pellets

Formulation	Aspect		Roundness	
	mean	(SD)	mean	(SD)
CMC2-L/W50	1.362	(0.275)	1.142	(0.120)
CMC2-L/W51	1.281	(0.184)	1.057	(0.050)
CMC3-L/W45	1.278	(0.250)	1.114	(0.083)
CMC3-L/W46	1.416	(0.275)	1.118	(0.067)
CMC2-L/A82	1.215	(0.184)	1.045	(0.045)
CMC2-L/A83	1.216	(0.157)	1.037	(0.039)
CMC2-L/A84	1.251	(0.134)	1.052	(0.038)
CMC2-L/A85	1.251	(0.157)	1.069	(0.055)
CMC2-L/A86	1.207	(0.126)	1.038	(0.037)
CMC2-L/A87	1.340	(0.191)	1.085	(0.052)
CMC3-L/A90	1.418	(0.251)	1.139	(0.076)
MC2-L/W45	1.087	(0.073)	1.054	(0.053)
MC3-L/W42	1.148	(0.108)	1.061	(0.052)
MC3-L/W45	1.237	(0.191)	1.055	(0.052)
MC3-L/A62	1.093	(0.081)	1.032	(0.051)
MC3-L/A64	1.120	(0.088)	1.067	(0.181)
MC3-L/A66	1.202	(0.102)	1.116	(0.154)
MC3-L/A68	1.296	(0.140)	1.067	(0.041)
HPMC2-L/A65	1.068	(0.046)	1.061	(0.059)
HPMC2-L/A66	1.087	(0.074)	1.079	(0.086)
HPMC3-L/A63	1.206	(0.587)	1.117	0.416)
HPMC3-L/A64	1.274	(0.196)	1.077	(0.057)
HPMC3-L/A65	1.208	(0.116)	1.043	(0.048)
HPMC3-L/A66	1.171	(0.151)	1.048	(0.051)
HPMC3-L/A67	1.169	(0.116)	1.028	(0.270)
CT-L/W195	1.099	(0.55)	1.042	(0.052)
MC1-P/A58	1.233	(0.133)	1.095	(0.067)
MC2-P/W41	1.262	(0.175)	1.128	(0.095)
MC4-I/W70	1.157	(0.105)	1.053	(0.055)
MC8-I/A106	1.216	(0.169)	1.096	(0.064)

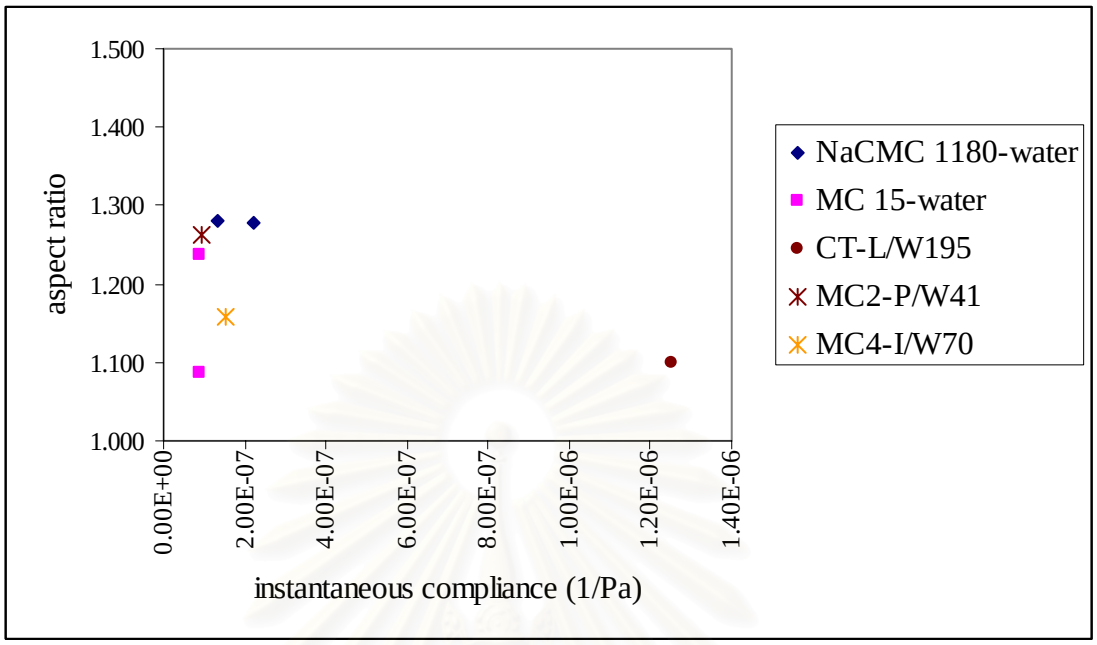


Figure 100. Effect of instantaneous compliance on aspect ratio of the pellets for water formulation.

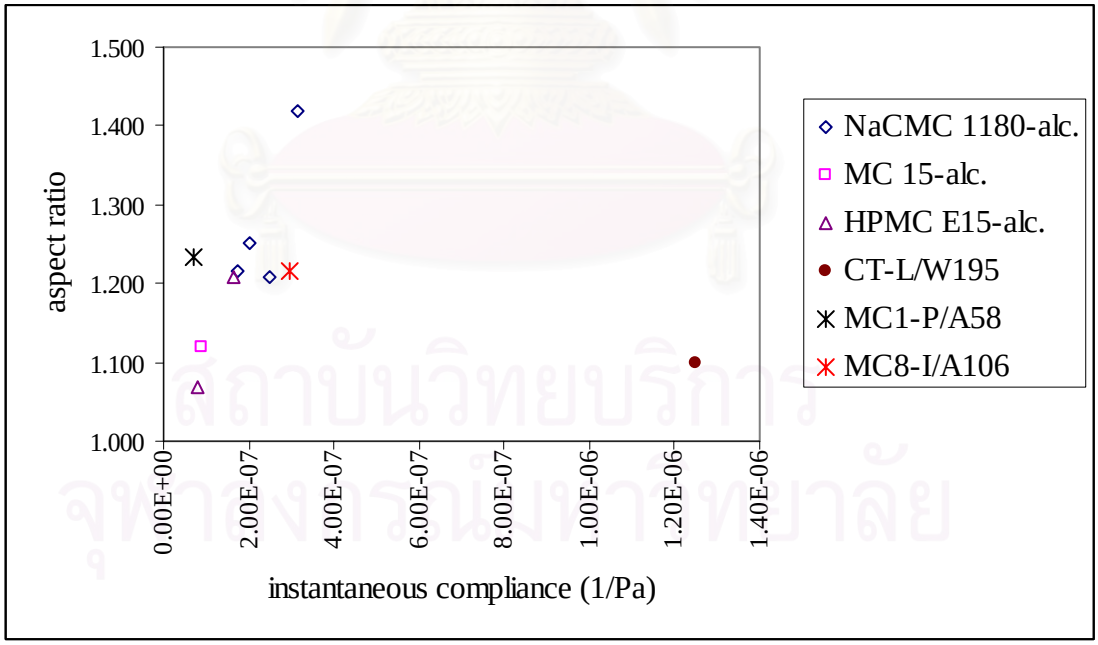


Figure 101. Effect of instantaneous compliance on aspect ratio of the pellets for 50% ethanol formulation.

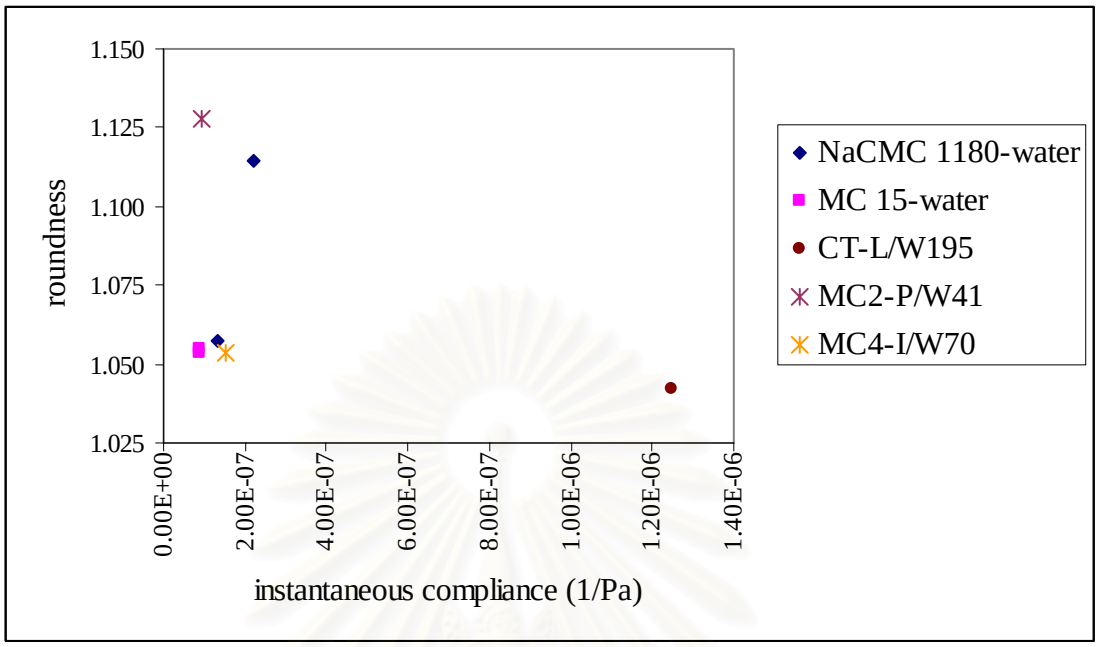


Figure 102. Effect of instantaneous compliance on roundness of the pellets for water formulation.

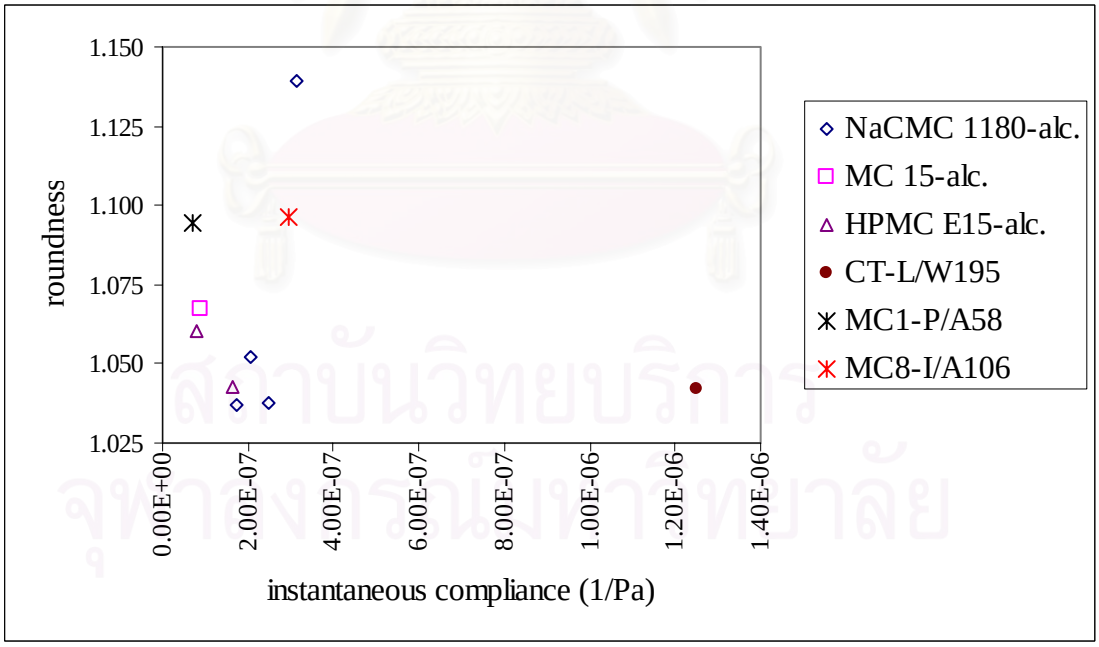


Figure 103. Effect of instantaneous compliance on roundness of the pellets for 50% ethanol formulation.

4.8 Moisture

The moisture contents of pellets are shown in Table 16. The values are in the range of 0.11-0.42%. The maximum value was obtained from CT-L/W195. According to Charoenkitpaiboon (2003), reported that the moisture content of pellet depended on the amount of water used and the drying period. In this study, pellets were dried at same drying period so that, CT-L/W195 which was granulated with the higher water content in formulation, 65% w/w based on dry weight, resulted in maximum moisture content.

4.9 Dissolution

Dissolution of propranolol hydrochloride pellets was shown in Figure 104. It showed that dissolution of the propranolol hydrochloride pellets prepared by using water and 50% ethanol as liquid binder were similar. Dissolution profile exhibited that propranolol hydrochloride was immediately released. It reached to almost 100% within 5 min. O′connor and Schwarts (1985) showed that the dissolution profile of pellets depended on the formulation aid and drug solubility. Their pellets were prepared by using MCC as the formulation aid; the drug release of some drugs was very slow particularly the hydrophobic drug (Pinto et. al., 1992). Propranolol hydrochloride was a water soluble drug and the formulation of propranolol hydrochloride pellets composed with 98-99% w/w drug so that the dissolution profile might depend on the water solubility propranolol hydrochloride.

As the result of dissolution of ibuprofen, dissolution profiles were different between using the water and 50% ethanol formulation (Figure 105). Dissolution profile of ibuprofen indicated that using water as liquid binder, ibuprofen could be released faster in early stage than using 50%ethanol as liquid binder. Similar to propranolol hydrochloride, ibuprofen in the formulation using water and 50% ethanol as liquid binder was 92% and 96% w/w, respectively. Costa et al. (2004) reported that the excipient in formulation could be changed the dissolution profile. Hence, using 50% ethanol as liquid binder might influence the drug release because of MC 15 could not be soluble in ethanol and the MC 15 in 50% ethanol formulation was 8% w/w

higher than water formulation (4% w/w). After 3 hours, it was found that ibuprofen pellets prepared with both water and 50% ethanol as liquid binder remained intact, although the reduction of size was observed.

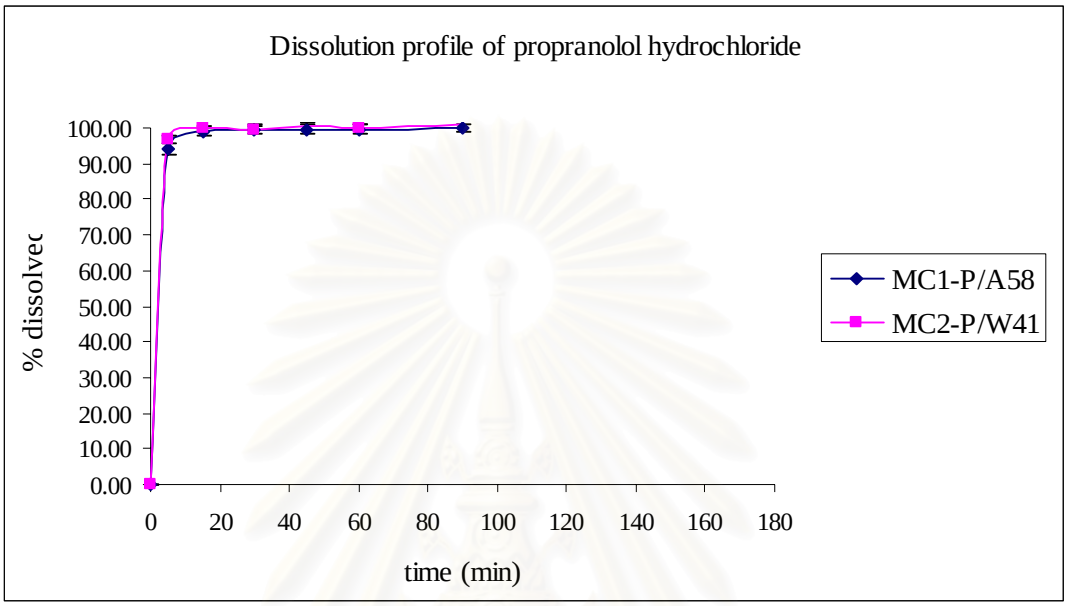


Figure 104. Dissolution profile of propranolol hydrochloride pellets in dilute hydrochloric acid (1:100).

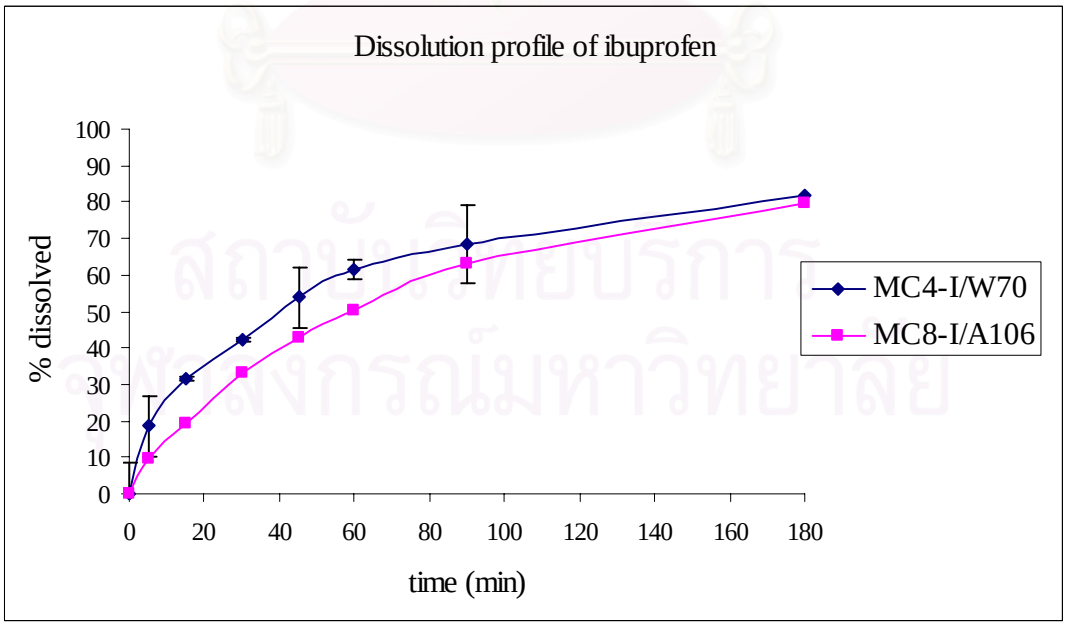


Figure 105. Dissolution profile of ibuprofen pellets in pH 7.2 phosphate buffer.

CHAPTER V

CONCLUSIONS

The pellets containing no MCC could be prepared with 0.5-1% of the formulation aids, i.e. NaCMC 1180, MC15 or HPMC E15 and by using either water and/or 50% ethanol as the liquid binder. When lactose was changed to propranolol hydrochloride or ibuprofen, the higher quantity of the formulation aid, i.e. MC15 were required.

The pellets formulations without MCC were sensitive to liquid content as opposed to pellet formulation containing MCC as the formulation aid.

The rheological properties of wet mass with NaCMC 1180, MC 15 or HPMC E15 granulated with water, all of which could form pellets were significantly different from those with MCC. The relationship between rheological properties of wet mass and pellets formation was not clearly observed. However, there was evidence of optimum rheological properties, in term of instantaneous compliance (J_0), storage modulus (G′), loss modulus (G″) and loss tangent (tan δ) of the wet mass that could form pellets. The value of loss tangent (tan δ) of the wet mass that could form pellets were in the range of 0.07-0.49, either for water or 50% ethanol formulations. Beyond this range, the pellets could not form. The rheological properties could be varied with the formulation variables.

The characteristics of the pellets in terms of size, size distribution, aspect ratio and roundness could not be markedly related to viscoelastic property of the wet mass studied.

The pellet formulations in this study may be applied for the drug which is incompatible with MCC and/or are degraded when exposed to high level of moisture as well as for pellets with high-drug loading.

The evaluation of rheological properties by the controlled stress rheometer may be useful in quality control of the wet mass for pellets preparation by extrusion-spheronization process.

REFERENCES

Agrawal, A. M., Howard, M.. A., and Neau, S. H. Extruded and spheronized beads containing no microcrystalline cellulose: Influence of formulation and process variables. Pharmaceutical Development and Technology 9 (2004): 197-214.

Alvarez, L., Concheiro, A., Gomez-Amoza, J. L., Souto, C., and Pacheco, R. M. Powdered cellulose as excipient for extrusion-spheronization pellets of a cohesive hydrophobic drug. European Journal of Pharmaceutics and Biopharmaceutics 55 (2003): 291-295.

Arslan, E. Rheological characterization of Tahin/Pekmez (sesame paste/concentrated grape juices blends). Master's Thesis. Department of Food Engineering, Middle East Technical University, 2003.

Augsburger, L L. Relevant technical properties of powders[Online]. (n.d.). Available from: http://rxsecure.umaryland.edu.[2006, July 18]

Barnes, H. A., and Bell, D. Controlled-stress rotational rheometry: An historical review. Korea-Australia Rheology Journal 15 (2003): 187-196.

Barry, B. W. Rheology of pharmaceutical and cosmetic semisolids. In H. S. Bean, A. H. Beckett, and J. E. Carless (eds.), Advances in pharmaceutical sciences vol. 4, pp.1-72. New York: Academic Press, 1974.

Basit, A. W., Newton, J. M., and Lacey, L. F. Formulation of ranitidine pellets by extrusion-spheronization with little or no microcrystalline cellulose. Pharmaceutical Development and Technology 4 (1999): 499-505.

Bataille, B., Ligarski, K., Jacob, M., Thomas, C., and Duru, C. Study of the influence of spheronization and drying condition on the physico-chemical properties of neutral spheroids containing Avicel PH101 and lactose. Drug Development and Industrial Pharmacy 19 (1993): 653–671.

Benchard, H., and Neilsen, G. H. Controlled-released multiple-units and single unit dose. Drug Development and Industrial Pharmacy 4 (1978): 53-67.

Bhattacharya, S., Vasudha, N., and Murthy, K. S. K. Rheology of mustard paste: Controlled stress measurement. Journal of Food Engineering 41 (1999): 187-191.

Blair, S. Elementary rheology. London: Academic Press Inc., 1969.

Bolmstedt, U. Viscosity & rheology: Theoretical and practical considerations in liquid food processing[Online]. 2000. Available from: http://www.tetrapak.com[2004, February 9]

Bornhöfta, M., Thommes, M., and Kleinebudde, P. Preliminary assessment of carrageenan as excipient for extrusion/spheronisation. European Journal of Pharmaceutics and Biopharmaceutics 59 (2005): 127–131.

Bourne, M. C. Food texture and viscosity: Concept and measurement. 2nd San Diego: Academic Press, 2002.

Brookfield Engineering Laboratory. Brookfield DV-II+ programmable viscometer operating instruction manual No. M/97-164-D1000[Online]. 2004. Available form: http://www.can-am.net/supplier/brookfield/DVII-D.pdf[2006, Aug 7]

Carter, R. E., ed. Rheology of food, pharmaceutical and biological materials with general rheology. London: Chapman&Hall, 1998.

Cellulosic Specialties. Introduction to rheology[Online]. 2004. Available from: http://www.cs.akzonobel.com[2006, July 21].

Chang, G. S., Koo, J. S., and Song, K. W. Wall slip of vaseline in steady shear rheometry. Korea-Australia Rheology Journal 15 (2003): 55-61.

Charoenkitpaiboon, C. Development of dry coating technique for pellets. Master's Thesis, Department of Manufacturing Pharmacy, Chulalongkorn University, 2003.

Chatchawalsaisin. J., Podczeck, F., and Newton, J. M. The preparation by extrusion/spheronization and the properties of pellets containing drugs, microcrystalline cellulose and glyceryl monostrate. European Journal of Pharmaceutical Sciences 24 (2005): 35-48.

Chatlapalli, R., and Rohera, D. B. Physical characterization of HPMC and HEC and investigation of their use as pelletization aids. International Journal of Pharmaceutics 161 (1998): 179-193.

Chatlapalli, R., and Rohera, D. B. Rheological characterization of diltiazem HCl/cellulose wet masses using a mixer torque rheometer. International Journal of Pharmaceutics 175 (1998): 47-59.

Chopra, R., Newton, J. M., Alderborn, G., and Podczeck, F. Preparation of pellets of different shape and their characterization. Pharmaceutical Development and Technology 6 (2001): 495-503.

Chopra, R., Podczeck, F, Newton, J. M., and Alderborn, G. The influence of pellet shape and film coating on the filling of pellets into hard shell capsules. European Journal of Pharmaceutics and Biopharmaceutics 53 (2002): 327–333.

Conine, J. W., and Hadley, H. R. Preparation of small solid spheres. Drug Cosmetic Industry 106 (1970): 38-41.

Costa, F. O., Pais, A. A. C. C., and Sousa, J. J. Analysis of formulation effects in the dissolution of ibuprofen pellets. International Journal of Pharmaceutics 270 (2004), 9-19.

Dinger, D. R. Rheology for ceramist. United States: Morris Publishing, 2002

Dyer, A. M., Khan, K. A., and Aulton, M. E. Effect of drying method on mechanical and drug release properties of pellets prepares by extrusion-spheronization. Drug Development and Industrial Pharmacy 20 (1994): 3045-3068.

Edmundson, I. C. Particle size analysis. In H. S. Bean (ed.), Advances in pharmaceutical sciences vol. 2, pp.95-179. New York: Academic Press, 1974.

Ek, R., and Newton, J. M. Microcrystalline cellulose as a sponge as an alternative concept to the crystallite gel model for extrusion-spheronization. Pharmaceutical Research 4 (1998): 509-512.

Erkoboni, D. F. Extrusion – spheronization as a granulation technique. In D. M. Parikh (ed.), Drugs and the pharmaceutical sciences vol.81: Handbook of pharmaceutical granulation technology, pp.333-368. New York: Marcel Dekker, 1997.

Fechner, P. M., Wartewig, S., Füting, M., Heilmann, A., Neubert, R. H. H, and Kleinebudde, P. Property of microcrystalline cellulose and powder cellulose after extrusion/spheronization as studied by fourier transform raman spectroscopy and enviromental scanning electron microscopy. AAPS PharmSci 5 (2003): article 31.

Fielden, K. E., and Newton, J. M. In J., Swarbrick, and J. C., Boylan (eds.), Encyclopedia of pharmaceutical technology vol.5, pp.395-442. Marcel Dekker: New York, 1992.

Fielden, K. E., Newton, J. M., and Rowe, R. C. A comparison of the extrusion and spheronization behaviour of wet powder masses processed by a ram extruder and a cylinder extruder. International Journal of Pharmaceutics 81 (1992): 225-233.

Florence, A. T., ed. Materials used in pharmaceutical formulation. vol.6. Oxford : Blackwel Sciencetific, 1984.

Funck, J. A. B., Schwartz, J. B., Reilly, W. J., and Ghali, E. S. Binder effectiveness for beads with high drug levels. Drug Delvelopment and Industrial Pharmacy 17 (1991): 1143-1156.

Fuongfuchat, A. Rheology lab: Application note[Online]. 2002. Available from: http://www.mtec.or.th[2002, June 30]

Gabriele. Chapter 1 rheology[Online]. 2006. Available from: http://etd.adm.unipi.it [2007, April 1]

Gandhi, R., Kaul, C. L., and Panchagnula, R. Extrusion and spheronization in the development of oral controlled-release dosage forms. PSTT 4 (April 1999): 160-170.

Ghebre-Sellassie, I. Pharmaceutical pelletization technology. New York: Marcel Dekker, 1989.

Ghooray, G. A simple viscosity test[Online]. 2002. Available form: http://www.standford.edu[2002, July 8]

Govender, T., and Dangor, C. M. Formulation and preparation of controlled release pellets of salbutamol by the air suspension technique. Journal of Microencapsulation 14 (1997): 445-455.

Graule, T. Rheology[Online]. 2004. Available form: http://www.food.upm.edu[2004, November 2]

Hackley, V. A., and Ferraris, C. F. Guide to rheological nomenclature: Measurements in ceramic particulate systems. Washington, DC: U.S. Government printing office, 2001.

Hashim, D. M. Rheology of foods[Online]. 2006. Available from: http://www.psigate.ac.uk[2006, July 19]

Heng, P. W. S., and Koo, O. M. Y. The influence of microcrystalline cellulose grade on shape and shape distributions of pellets produced by extrusion-spheronization. Chemical & Pharmaceutical Bulletin 49 (2001): 1383-1387.

Heng, P. W. S., and Koo, O. M. Y. A study of the effects of the physical characteristics of microcrystalline cellulose on performance in extrusion spheronization. Pharmaceutical Research 18 (2001): 480-487.

Hoefler, A. C. Sodium carboxymethyl cellulose: Chemistry, functionality, and applications[Online]. 2000. Available from: http://www.herc.com/foodgum [2007, January 19]

Hongprapas, P. Physicochemistry of foods: Colloids, emulsions and gels. Bangkok: CU print, 2000.

Jerwanska, E., Alderborn, G., Newton, J. M., and Nystrom, C. The effect of water content on the porosity and liquid saturation of extruded cylinders. International Journal of Pharmaceutics 121 (1995): 65-71.

Kanbe, H., Hayashi, T., Onuki, Y., and Sonobe, T. Manufacture of fine spherical granules by an extrusion/spheronization method. International Journal of Pharmaceutics (2007).

Kleinebudde, P. Shrinking and swelling properties of pellets containing microcrystalline cellulose: Differentiation between individual particles and their agglomerates. International Journal of Pharmaceutics 111 (1994): 43-50.

Kleinebudde, P. Application of low-substitued hydroxypropyl methylcellulose (L-HPC) in production of pellet using extrusion-spheronization. International Journal of Pharmaceutical Science 96 (1993): 119-128.

Kleinebudde, P. The crystallite-gel model for microcrystalline cellulose in wet-granulation, extrusion and spheronization. Pharmaceutical Research 14 (1997): 804-809.

Kleinebudde, P., Jumaa, M., and El, S. F. Influence of degree of polymerization on behavior of cellulose during homogenization and extrusion/spheronization. AAPS PharmSci 2 (2000): article 21.

Kleinebudde, P., Schröder, M., Schultz, P., Müller, B., Waaler, T., and Nymo, L. Importance of the fraction of microcrystalline cellulose and spheronization speed on the properties of extruded pellets made from binary mixtures. Pharmaceutical Delvelopment and Technology 4 (1999): 397-404.

Kreiba, A. The rheological properties of aqueous polyacrylamide solutions. Master's Thesis, Department of Mechanical Engineering, Concordia University, 2000.

Laba, D., ed. Rheological properties of cosmetics and toiletries. New York: Marcel Dekker, 1993.

Lakes, R. S. Viscoelastic measurement techniques. Review of Scientific Instruments 75 (2004): 797-809.

Lapasin, R., Prici, S., Sirtori, V., and Casati, D. Viscoelastic properties of solder pastes. Journal of Electronic Material 27 (March 1998): 138-148.

Läuger, J., Huck, S., Wollny, K., and Bernzen, M. Real controlled stress and controlled strain experiments with the same rheometer[Online]. (n.d.). Available from: http://www.physica.de[2005, January 14]

Law, M. F., and Deasy, P. B. Use of hydrophilic polymers with microcrystalline cellulose to improve extrusion-spheronization. European Journal of Pharmaceutics and Biopharmaceutics 45 (1998): 57-65.

Lazaridou, A., Duta, D., Papageorgiou, M., Belc, N., and Biliaderis, C. G. Effect of hydrocolloids on dough rheology and bread quality parameters in gluten-free formulations. Journal of food engineering 79 (2007): 1033-1047.

Lewis, R. J., Sr. Hawley's condensed chemical dictionary. 13th ed. New York: John Wiley & Sons, 1997.

Linder, H., and Kleinebudde, P. Use of powdered cellulose for the production of pellets by extrusion/spheronization. Journal of Pharmaceutical and Pharmacology 46 (1994): 2-7.

Luukkonen, P. Rheological properties and the state of water of microcrystalline cellulose and silicified microcrystalline cellulose wet mass. Doctoral dissertation, Pharmacy Technology Division, Department of Pharmacy, Helsinki University, 2001.

Luukkonen, P., Schaefer, T., Hellen, L., Juppo, A. M., and Yliruusi, J. Rheological characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a mixer torque rheometer. International Journal of Pharmaceutics 188 (1999): 181-192.

MacRitchie, K. A., Newton, J. M., and Rowe, R. C. The evaluation of the rheological properties of lactose/microcrystalline cellulose and water mixtures by

controlled stress rheometry and the relationship to the production of spherical pellets by extrusion/spheronization. European Journal of Pharmaceutical Sciences 17 (2002): 43-50.

Marriott, C. Rheology. In M. E. Aulton (ed.), Pharmaceutic: The science of dosage form design, pp.41-58. London: Churchill Livingstone, 2002.

Martindale, W. In E. F. R. James (ed.), Martindale: The extra pharmacopoeia. 31st, pp.50-51. London: Royal Pharmaceutical Society, 1996.

Mezger, T. G. The rheology handbook for users of rotational and oscillatory rheometers. Hannover: Vincentz, 2002.

Millili, G. P., and Schwartz, J. B. The strength of MCC pellets: The effect of granulating with water/ethanol mixtures. Drug Development and Industrial Pharmacy 16 (1990): 1411-1426.

Narongrakdaj, B. Vibro viscometer. LAB. Today 3 (February 2004): 46-48.

Neaman, A., and Singer, A. Rheological properties of aqueous suspension of palygorskite. Soil Science Society of America Journal 64 (2000): 427-436.

Neau, S. H., Chow, M. Y., and Durrani, M. J. Fabrication and characterization of extruded and spheronized beads containing Carbopol 974, NF resin. International Journal of Pharmaceutics 131 (1996): 47-55.

Newton, J. M., Boutel, S., Chatchawalsaisin, J., and Podczeck, F. The preparation of spherical granules by extrusion/spheronization without microcrystalline cellulose. Pharmaceutical Technology Europe (October 2004): 21-27.

O′ Neil, M. J., et al., eds. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 13th ed. New Jersey: Merck & Co, 2001.

O'connor, R. E, and Schwartz, J. B. Spheronization: II. drug release from drug-diluent mixtures. Drug Delvelopment and Industrial Pharmacy 11 (1985): 1837-1857.

O'connor, R. E., and Schwartz, J. B. Drug releases mechanism from microcrystalline cellulose system. Pharmaceutical Research 10 (1993): 356-361.

Obara, S. Low-substituted hydroxypropyl cellulose. United Stated Patent[Online]. (n.d.). Available from: http://www.freepatentsonline.com/6380381.html[2006, May 17]

Parker, M. D., York, P., and Rowe, R. C. Binder-substrate interactions in wet granulation 3: The effect of excipient source variation. International Journal of Pharmaceutics 80 (1992): 179-190.

Pinto, J. F., Buckton, G., and Newton, J. M. The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronisation. International Journal of Pharmaceutics 83 (1992): 187-196.

Pinto, J. F., Lamerio, M. H., and Martins, P. Investigation on the co-extrudability and spheronization properties of wet masses. International Journal of Pharmaceutics 227 (2001): 71-80.

Prieto, S. A., Méndez, J. B., and Espinar, F. J. Starch-dextrin mixtures as base excipients for extrusion-spheronization pellets. European Journal of Pharmaceutics and Biopharmaceutic (2004): 1-11.

R. T. Vanderbilt, Company. Rheology Control Additives[Online]. (n.d.). Available from: http://www.rtvanderbilt.com[2006, Decenber 18]

Ramaker, J. S. Fundamental of the high-shear pelletisation process. Doctoral dissertation, Faculty of Science, University of Groningen, 2001.

Rao, M. A. Rheology of fluid and semisolid foods: Principles and applications. Maryland: Aspen Publishers, 1999.

Raymond, K. E., and Othmer, D. F., eds. Encyclopedia of chemical technology. vol.3. New York: International Encyclopedia, 1954.

Raymond, K. E., and Othmer, D. F., eds. Encyclopedia of chemical technology. vol.13. New York: International Encyclopedia, 1954.

Reynolds, A. D. A new technique for production spherical particles. Manufacture Chemical Aerosol News 41 (1997): 40-43.

Robinson, R. L, and Hollenbec, R. G. Manufacture of spherical acetaminophen pellets: Comparison of rotary processing with multiple-step extrusion and spheronization. Pharmaceutical Tcchnology 15 (1991): 48-56.

Rongrongmuang, S. Effect of process and formulation variables on formulation of diclofenac sodium pellets prepared by melt technique. Master's Thesis, Department of Manufacturing Pharmacy, Chulalongkorn University, 2005.

Rowe, R. C., and Sadeghnejad, G. R. The rheology of microcrystalline cellulose powder/water mixes-measurement using a mixer torque rheometer. International Journal of Pharmaceutical Sciences 38 (1987): 227-229.

Rudraraju, V. S., and Wyandt, C. M. Rheology of microcrystalline cellulose and sodiumcarboxymethyl cellulose hydrogels using a controlled stress rheometer: Part II. International Journal of Pharmaceutics 292 (2005): 63–73.

Saenz, I., Papazoglou, E., and Robert, L. Quantitative evaluation of feeding different physical forms of stabilizers[Online]. 2001. Available from: http://www.e1.greatlakes.com[2007, March 1]

Santos, H., Veiga, F., Pina, M., Podczeck, F., and Sousa, J. Physical properties of chitosan pellets produced by extrusion-spheronization: Influence of formulation variables. International Journal of Pharmaceutics 246 (2002): 153-169.

Sausa, J. J., Sousa, A., Moura, M. J., Podczeck, F., and Newton, J. M. The influence of core materials and film coating on the drug release from coated pellets. International Journal of Pharmaceutics 233 (2002): 111-122.

Schaefer, T., and Mathiesen, C, Melt pelletization in a high shear mixer: VII effect of product temperature. International Journal of Pharmaceutics 134 (1996): 105-117.

Schramm, G. A practical apporach to rheology and rheometry. 2nd Germany: Gebrueder HAAKE GmbH, 2002.

Schröder, M., and Klienebudde, P. Structure of disintegrating pellets with regard to fractal geometry. Pharmaceutical Research 12 (1995): 1694-1700.

Shin-Etsu, Company. Low-substituted hydroxypropyl cellulose[Online]. (n.d.). Available from: http://www.rwunwin.co.uk[2006, April 20]

Sinko, P. J. Martin's physical pharmacy and pharmaceutical science. 5thed. Philadelphia: Lippincott Williams&Wilkins, 2006.

Smolinske, S. C. Handbook of food, drug, and cosmetic excipients. Colorado: Micromedex, 1992.

Stading, M. Basic rheology: Terms and techniques revised[Online]. 2004. Available from: http://www.sik.se[2006, July 1]

Staniforth, J. Particle-size analysis. In M. E. Aulton (ed.), Pharmaceutic: The science of dosage form design, pp.152-165. London: Churchill Livingstone, 2002.

Staniforth, J. Powder flow. In M. E. Aulton (ed.), Pharmaceutic: The science of dosage form design, pp.197-210. London: Churchill Livingstone, 2002.

Steckel, H., and Nogly, M. F. Production of chitosan pellets by extrusion/spheronization. European Journal of Pharmaceutics and Biopharmaceutics 57 (2004): 107–114.

Summer, M. and Aulton, M. Granulation. In M. E. Aulton (ed.), Pharmaceutic: The science of dosage form design, pp.41-58. London: Churchill Livingstone, 2002.

Taylor, C., Pearson, J. P., Draget, K. I., Dettmar, P. W., and Smidrød, O. Rheological characterization of mixed gels of mucin and alginate. Carbohydrate Polymer 59 (2005): 189-195.

The Joint FAO/WHO Expert Committee on Food Additives, JECFA. Hydroxypropyl cellulose: Combined compendium of food additive specifications 2006[Online]. 2006. Available from: http://www.fao.org[2007, February 2]

Tho, I., Sande, S. R., and Kleinebudde, P. Pectinic acid, a novel excipient for production of pellets by extrusion/spheronisation: Preliminary studies. European Journal of Pharmaceutics and Biopharmaceutics 54 (2002): 95-99.

Thommes, M., and Kleinebudde, P. Use of κ-carrageenan as an alternative pelletisation aid to MCC in extrusion/spheronization: I. influence of type and fraction of filler. European Journal of Pharmaceutics and Biopharmaceutics 63 (2006): 59-67.

Tomer, G., and Newton, J. M. A centrifugation technique for the evaluation of the extent of water movement in wet powder masses. International Journal of Pharmaceutics 188 (1999): 31-38.

Tomer, G., and Newton, J. M. Water movement evaluation during extrusion of wet powder masses by collecting extrudate fraction. International Journal of Pharmaceutics 182 (1999): 71-77.

Tomer, G., Patel, H., Podeczeck, F., and Newton, J. M. Measuring the water retention capacities (MRC) of different microcrystalline cellulose grades. European Journal of Pharmaceutical Science 12 (2001): 321-325.

United States Pharmacopeial Convention. The united states pharmacopoeia 24 and the national formulary 19. Maryland: U.S. Pharmacopeia, 2000.

Vervaet, C., Baert, L., and Remmon, J. Extrusion – spheronization: A literature review. International Journal of Pharmaceutics 116 (1995): 131-146.

Wade, A., and Weller, P. J., eds. Handbook of pharmaceutical excipients. 2nd ed. Washington, DC: American Pharmaceutical Association, 1994.

Wallace, J. W. Cellulose derivatives and natural products utilized in pharmaceutics. In J. Swarbrick, and J. C. Boylan (eds.), Encyclopedia of pharmaceutical technology vol.2., pp.319-337. Marcel Dekker: New York, 1934.

Webb, P. A. Volume and density determinations for particle technologists[Online]. 2001. Available from: http://www.particletesting.com[2007, February 20]

Zhejiang Shangyu Haishen Chemical, Company. Hydroxy ethyl cellulose (HEC) [Online]. (n.d.). Available from: http://www.haishenchem.com[2007, March 8]

APPENDICES

Appendix A

PARTICLE SIZE AND SIZE DISTRIBUTION

The particle size and size distribution were determined by a laser light diffractometer equipped with a wet dispersion part (Mastersizer 2000). It is a range of light scattering based particle sizers (Mastersizer particle size analyzer, Insrtument manual). The result from the analysis is volume based particle size. The span and uniformity are described for the distribution of particles. The span gives a description of the width of the distribution, which is independent of median size. The uniformity is a measure of the deviations from the median.

The 50% volume percentile, $d(v,0.5)$, is the median of the volume distribution. The $d(v.0.9)$ and $d(v,0.1)$ are 10% and 90% cut offs for distribution curve. The span of the particle size distribution curve is defined as:

$$Span = \frac{d(v,0.9) - d(v,0.1)}{d(v,0.5)} \qquad \ldots(\text{A-1})$$

The uniformity of the particle size distribution curve is defined as:

$$Uniformity = \frac{\sum Xi\left(d(v,0.5) - di\right)}{d(v,0.5)\sum Xi} \qquad \ldots(\text{A-2})$$

Where di and Xi are the mean diameter and result in size class i, respectively
The Particle size and size distribution of material are shown in Table A-1

Table A-1. Particle size and size distribution of raw materials

Material	d (v,0.1) µm mean (SD)	d (v,0.5) µm mean (SD)	d (v,0.9) µm mean (SD)	D[4,3] µm mean (SD)	Span mean (SD)	Uniformity mean (SD)
Lactose	26.44 (0.31)	79.90 (2.07)	194.94 (4.78)	98.65 (1.64)	2.11 (0.01)	0.67 (0.02)
$CaHPO_4$	2.84 (0.07)	10.99 (0.58)	51.353 (2.84)	21.89 (3.61)	4.41 (0.15)	1.51 (0.26)
NaCMC 1180	26.36 (0.38)	79.98 (1.15)	199.29 (8.75)	112.51 (17.61)	2.16 (0.08)	0.84 (0.20)
MC 15	31.55 (0.36)	88.94 (1.25)	204.98 (5.49)	105.46 (2.21)	1.95 (0.04)	0.60 (0.01)
HEC 4000	70.07 (0.37)	159.06 (1.49)	323.3 (4.90)	179.98 (1.94)	1.59 (0.03)	0.49 (0.01)
HPC-L	17.60 (0.19)	54.50 (0.85)	140.50 (5.77)	71.19 (2.87)	2.26 (0.07)	0.75 (0.03)
HPMC E15	53.15 (0.63)	188.68 (2.60)	407.20 (17.06)	212.26 (5.63)	1.88 (0.07)	0.58 (0.02)
MCC	27.46 (0.39)	91.43 (0.67)	193.89 (1.41)	102.26 (0.73)	1.83(0.00)	0.56 (0.01)
Propranolol	11.78 (0.06)	38.34 (0.64)	130.59 (3.46)	56.99 (1.46)	3.10 (0.04)	0.95 (0.10)
Ibuprofen	75.00 (0.94)	212.12 (2.98)	447.09 (10.48)	237.46 (4.33)	1.75 (0.02)	0.55 (0.06)

Note: - d(v, 0.1), d(v, 0.5) and d(v,0.9) are standards percentile readings from the analysis.

- d(v, 0.1) is the size of particle for which 10% of the sample is below this size.
- d(v, 0.5) is the size of particle at which 50% of the sample is smaller and 50% is larger than this size . This value is known as the median diameter.
- d(v, 0.9) gives a size of particle for which 90% of the sample is below this size.
- D[4.3] is the volume mean diameter.

APPENDIX B

PREPARATION OF PELLETS

1. Formulation

Table B-1. Formulations of lactose pellets using cellulose derivatives – sodium carboxymethylcellulose (NaCMC 1180) as the formulation aid and water as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
CMC1-L/W30	NaCMC1180	0.25	99.75	30 (10.00%)	(-)
CMC1-L/W32				32 (10.66%)	(-)
CMC1-L/W34				34 (11.33%)	(-)
CMC1-L/W35				35 (11.66%)	(-)
CMC1-L/W36				36 (12.00%)	(-)(-)
CMC2-L/W42		0.50	99.50	42 (14.00%)	(-)
CMC2-L/W45				45 (15.00%)	(-)
CMC2-L/W49				49 (16.33%)	(-)
CMC2-L/W50				50 (16.66%)	+
CMC2-L/W51				51 (17.00%)	+
CMC2-L/W52				52 (17.33%)	(-)(-)
CMC3-L/W43		1.00	99.00	43 (14.33%)	(-)
CMC3-L/W44				44 (14.66%)	(-)
CMC3-L/W45				45 (15.00%)	+
CMC3-L/W46				46 (15.33%)	+
CMC3-L/W47				47 (15.66%)	(-)(-)
CMC3-L/W48				48 (16.00%)	(-)(-)
CMC3-L/W49				49 (16.33%)	(-)(-)
CMC3-L/W50				50 (16.66%)	(-)(-)
CMC3-L/W51				51 (17.00%)	(-)(-)
CMC3-L/W52				52 (17.33%)	(-)(-)
CMC3-L/W53				53 (17.66%)	(-)(-)

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
CMC3-L/W62	NaCMC1180	1.00	99.00	62 (20.66%)	(-)(-)
CMC3-L/W65				65 (21.66%)	(-)(-)
CMC4-L/W36		2.00	98.00	36 (12.00%)	(-)
CMC4-L/W38				38 (12.66%)	(-)
CMC4-L/W40				40 (13.33%)	(-)
CMC4-L/W42				42 (14.00%)	(-)(-)
CMC4-L/W43				43 (14.33%)	(-)(-)
CMC4-L/W44				44 (14.66%)	(-)(-)
CMC4-L/W45				45 (15.00%)	(-)(-)
CMC4-L/W46				46 (15.33%)	(-)(-)
CMC4-L/W47				47 (15.66%)	(-)(-)
CMC4-L/W48				48 (16.00%)	(-)(-)
CMC4-L/W49				49 (16.33%)	(-)(-)
CMC4-L/W50				50 (16.66%)	(-)(-)
CMC4-L/W51				51 (17.00%)	(-)(-)
CMC4-L/W52				52 (17.33%)	(-)(-)
CMC4-L/W53				53 (17.66%)	(-)(-)
CMC4-L/W54				54 (18.00%)	(-)(-)
CMC4-L/W55				55 (18.33%)	(-)(-)
CMC4-L/W60				60 (20.00%)	(-)(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-2. Formulations of lactose pellets using cellulose derivatives - methylcellulose (MC 15) as the formulation aid and water as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
MC1-L/W39	MC15	0.25	99.75	39 (13.00%)	(-)
MC1-L/W42				42 (14.00%)	(-)(-)
MC1-L/W45				45 (15.00%)	(-)(-)
MC2-L/W39		0.50	99.50	39 (13.00%)	(-)
MC2-L/W42				42 (14.00%)	(-)
MC2-L/W45				45 (15.00%)	+
MC2-L/W48				48 (16.00%)	(-)(-)
MC2-L/W50				50 (16.66%)	(-)(-)
MC3-L/W39		1.00	99.00	39 (13.00%)	(-)
MC3-L/W42				42 (14.00%)	+
MC3-L/W45				45 (15.00%)	+
MC3-L/W48				48 (16.00%)	(-)(-)
MC4-L/W45		2.00	98.00	45 (15.00%)	(-)
MC4-L/W48				48 (16.00%)	(-)
MC4-L/W50				50 (16.66%)	(-)(-)
MC4-L/W52				52 (17.33%)	(-)(-)
MC4-L/W55				55 (18.33%)	(-)(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-3. Formulations of lactose pellets using cellulose derivatives-hydroxyethylcellulose (HEC 4000) as the formulation aid and water as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	rResults
HEC1-L/W45	HEC4000	0.25	99.75	45 (15.00%)	(-)
HEC1-L/W50				50 (16.66%)	(-)
HEC1-L/W50				55 (18.33%)	(-)
HEC1-L/W60				60 (20.00%)	(-)(-)
HEC2-L/W45		0.50	99.50	45 (15.00%)	(-)
HEC2-L/W50				50 (16.66%)	(-)
HEC2-L/W55				55 (18.33%)	(-)(-)
HEC3-L/W35		1.00	99.00	35 (11.66%)	(-)
HEC3-L/W45				45 (15.00%)	(-)
HEC3-L/W50				50 (16.66%)	(-)
HEC3-L/W55				55 (18.33%)	(-)(-)
HEC3-L/W60				60 (20.00%)	(-)(-)
HEC4-L/W45		2.00	98.00	45 (15.00%)	(-)
HEC4-L/W50				50 (16.66%)	(-)(-)
HEC4-L/W55				55 (16.66%)	(-)(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-4. Formulations of lactose pellets using cellulose derivatives-hydroxypropyl cellulose, low-substituted (HPC-L) as the formulation aid and water as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
HPC1-L/W38	HPC-L	0.25	99.75	38 (12.66%)	(-)
HPC1-L/W40				40 (13.33%)	(-)
HPC1-L/W43				43 (14.33%)	(-)
HPC1-L/W45				45 (15.00%)	(-)
HPC2-L/W40		0.50	99.50	40 (13.33%)	(-)
HPC2-L/W43				43 (14.33%)	(-)
HPC2-L/W45				45 (15.00%)	(-)
HPC2-L/W50				50 (16.66%)	(-)
HPC3-L/W50		1.00	99.00	50 (16.66%)	(-)
HPC3-L/W52				52 (17.33%)	(-)
HPC3-L/W55				55 (18.33%)	(-)
HPC3-L/W58				58 (19.33%)	(-)
HPC3-L/W60				60 (20.00%)	(-)
HPC4-L/W40		2.00	98.00	40 (13.33%)	(-)
HPC4-L/W45				45 (15.00%)	(-)
HPC4-L/W50				50 (16.66%)	(-)
HPC4-L/W53				53 (17.66%)	(-)
HPC4-L/W55				55 (18.33%)	(-)
HPC4-L/W60				60 (20.00%)	(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-5. Formulations of lactose pellets using cellulose derivatives-hydroxypropyl methylcellulose (HPMC E15) as the formulation aid and water as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
HPMC1-L/W30	HPMC E15	0.25	99.75	30 (10.00%)	(-)
HPMC1-L/W35				35 (11.66%)	(-)
HPMC1-L/W38				38 (12.66%)	(-)(-)
HPMC2-L/W35		0.50	99.50	35 (11.66%)	(-)
HPMC2-L/W36				36 (12.00%)	(-)
HPMC2-L/W38				38 (12.66%)	(-)(-)
HPMC3-L/W35		1.00	99.00	35 (11.66%)	(-)
HPMC3-L/W38				38 (12.66%)	(-)
HPMC3-L/W39				39 (13.00%)	(-)
HPMC3-L/W40				40 (13.33%)	(-)
HPMC3-L/W41				41 (13.66%)	(-)(-)
HPMC3-L/W42				42 (14.00%)	(-)(-)
HPMC3-L/W43				43 (14.33%)	(-)(-)
HPMC3-L/W44				44 (14.66%)	(-)(-)
HPMC3-L/W45				45 (15.00%)	(-)(-)
HPMC3-L/W50				50 (16.66%)	(-)(-)
HPMC4-L/W30		2.00	98.00	30 (10.00%)	(-)
HPMC4-L/W34				34 (11.33%)	(-)
HPMC4-L/W35				35 (11.66%)	+
HPMC4-L/W36				36 (12.00%)	(-)(-)
HPMC4-L/W38				38 (12.66%)	(-)(-)
HPMC4-L/W40				40 (13.33%)	(-)(-)
HPMC4-L/W45				45 (15.00%)	(-)(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-6. Formulations of lactose pellets using microcrystalline cellulose PH 101 (Avicel®PH 101(MCC)) as the formulation aid and water as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
CT-L	MCC	50.00	50.00	195 (65.00%)	+

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-7. Formulations of lactose pellets using cellulose derivatives – sodium carboxymethylcellulose (NaCMC 1180) as the formulation aid and 50% ethanol as liquid binder

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
CMC1-L/A60	NaCMC1180	0.25	99.75	60 (20.00%)	(-)
CMC1-L/A65				65 (21.66%)	(-)
CMC1-L/A66				66 (22.00%)	(-)(-)
CMC1-L/A67				67 (22.33%)	(-)(-)
CMC1-L/A68				68 (22.66%)	(-)(-)
CMC1-L/A69				69 (23.00%)	(-)(-)
CMC1-L/A70				70 (23.33%)	(-)(-)
CMC1-L/A84				84 (28.00%)	(-)(-)
CMC2-L/A65		0.50	99.50	65 (21.66%)	(-)
CMC2-L/A70				70 (23.33%)	(-)
CMC2-L/A80				80 (26.66%)	(-)
CMC2-L/A82				82 (27.33%)	+
CMC2-L/A83				83 (27.66%)	+
CMC2-L/A84				84 (28.00%)	+
CMC2-L/A85				85 (28.33%)	+
CMC2-L/A86				86 (28.66%)	+

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
CMC2-L/A87	NaCMC1180	0.50	99.50	87 (29.00%)	+
CMC2-L/A88				88 (29.33%)	(-)(-)
CMC2-L/A90				90 (30.00%)	(-)(-)
CMC3-L/A65		1.00	99.00	65 (21.66%)	(-)
CMC3-L/A70				70 (23.33%)	(-)
CMC3-L/A71				71 (23.66%)	(-)
CMC3-L/A75				75 (25.00%)	(-)
CMC3-L/A80				80 (26.66%)	(-)
CMC3-L/A82				82 (27.33%)	(-)
CMC3-L/A84				84 (28.00%)	(-)
CMC3-L/A85				85 (28.33%)	(-)
CMC3-L/A86				86 (28.66%)	(-)
CMC3-L/A88				88 (29.33%)	(-)
CMC3-L/A90				90 (30.00%)	+
CMC3-L/A92				92 (30.66%)	(-)(-)
CMC3-L/A94				94 (31.33%)	(-)(-)
CMC3-L/A96				96 (32.00%)	(-)(-)
CMC3-L/A98				98 (32.66%)	(-)(-)
CMC3-L/A100				100 (33.33%)	(-)(-)
CMC3-L/A102				102 (34.00%)	(-)(-)
CMC4-L/A100		2.00	98.00	100 (33.33%)	(-)
CMC4-L/A101				101 (33.66%)	(-)
CMC4-L/A102				102 (34.00%)	(-)
CMC4-L/A103				103 (34.33%)	(-)
CMC4-L/A104				104 (34.66%)	(-)
CMC4-L/A105				105 (35.00%)	(-)
CMC4-L/A106				106 (35.33%)	(-)
CMC4-L/A107				107 (35.66%)	(-)
CMC4-L/A108				108 (36.00%)	(-)

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
CMC4-L/A109	NaCMC1180	2.00	98.00	109 (36.33%)	(-)
CMC4-L/A110				110 (36.66%)	(-)
CMC4-L/A111				111 (37.00%)	(-)(-)
CMC4-L/A112				112 (37.33%)	(-)(-)
CMC4-L/A115				115 (38.33%)	(-)(-)
CMC4-L/A123				123 (41.00%)	(-)(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-8. Formulations of lactose pellets using cellulose derivatives -methylcellulose (MC 15) as the formulation aid and 50% ethanol as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
MC1-L/A54	MC15	0.25	99.75	54 (18.00%)	(-)
MC1-L/A56				56 (18.66%)	(-)
MC1-L/A58				58 (19.33%)	(-)(-)
MC2-L/A58		0.50	99.50	58 (19.33%)	(-)
MC2-L/A59				59 (19.66%)	(-)
MC2-L/A62				62 (20.66%)	(-)(-)
MC3-L/A58		1.00	99.00	58 (19.33%)	(-)
MC3-L/A61				61 (20.33%)	(-)
MC3-L/A62				62 (20.66%)	+
MC3-L/A64				64 (21.33%)	+
MC3-L/A66				66 (22.00%)	+
MC3-L/A68				68 (22.66%)	+
MC3-L/A72				72 (24.00%)	(-)(-)

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
MC4-L/A50	MC 15	2.00	98.00	50 (16.66%)	(-)
MC4-L/A54				54 (18.00%)	(-)
MC4-L/A58				58 (19.33%)	(-)
MC4-L/A60				60 (20.00%)	(-)

Table B-9. Formulation of lactose pellets using cellulose derivatives-hydroxyethylcellulose (HEC 4000) as the formulation aids and 50% ethanol as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
HEC1-L/A22	HEC 4000	0.25	99.75	22 (7.33%)	(-)
HEC1-L/A36				36 (12.00%)	(-)
HEC1-L/A42				42 (14.00%)	(-)
HEC2-L/A22		0.50	99.50	22 (7.33%)	(-)
HEC2-L/A36				36 (12.00%)	(-)
HEC2-L/A42				42 (14.00%)	(-)
HEC2-L/A48				48 (16.00%)	(-)
HEC2-L/A56				56 (18.66%)	(-)
HEC3-L/A55		1.00	99.00	56 (18.66%)	(-)
HEC3-L/A60				60 (20.00%)	(-)
HEC3-L/A64				64 (21.33%)	(-)
HEC3-L/A76				76 (25.33%)	(-)
HEC4-L/A74		2.00	98.00	74 (24.66%)	(-)
HEC4-L/A76				76 (25.33%)	(-)
HEC4-L/A77				77 (25.66%)	(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-10. Formulations of lactose pellets using cellulose derivatives-hydroxypropyl cellulose, low-substituted (HPC-L) as the formulation aid and 50% ethanol as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
HPC1-L/A38	HPC-L	0.25	99.75	38 (12.66%)	(-)
HPC1-L/A40				40 (13.33%)	(-)
HPC1-L/A43				43 (14.33%)	(-)
HPC1-L/A45				45 (15.00%)	(-)
HPC2-L/A40		0.50	99.50	40 (13.33%)	(-)
HPC2-L/A43				43 (14.33%)	(-)
HPC2-L/A45				45 (15.00%)	(-)
HPC2-L/A50				50 (16.66%)	(-)
HPC3-L/A50		1.00	99.00	40 (13.33%)	(-)
HPC3-L/A52				50 (16.66%)	(-)
HPC3-L/A55				55 (18.33%)	(-)
HPC3-L/A58				58 (19.33%)	(-)
HPC3-L/A60				60 (20.00%)	(-)
HPC4-L/A40		2.00	98.00	40 (13.33%)	(-)
HPC4-L/A45				45 (15.00%)	(-)
HPC4-L/A50				50 (16.66%)	(-)
HPC4-L/A53				53 (17.66%)	(-)
HPC4-L/A55				55 (18.33%)	(-)
HPC4-L/A60				60 (20.00%)	(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

Table B-11. Formulations of lactose pellets using cellulose derivatives-hydroxypropyl methylcellulose (HPMC E15) as theformulation aid and 50% ethanol as liquid binder.

Code	Polymer	Polymer (%)	Lactose (%)	H_2O g (%*)	Results
HPMC1-L/A57	HPMC E15	0.25	99.75	57 (19.00%)	(-)
HPMC1-L/A60				60 (20.00%)	(-)
HPMC1-L/A62				62 (20.66%)	(-)
HPMC1-L/A65				65 (21.66%)	(-)(-)
HPMC2-L/A62		0.50	99.50	62 (20.66%)	(-)
HPMC2-L/A65				65 (21.66%)	+
HPMC2-L/A66				66 (22.00%)	+
HPMC2-L/A67				67 (22.33%)	(-)(-)
HPMC2-L/A68				68 (22.66%)	(-)(-)
HPMC3-L/A62		1.00	99.00	62 (20.66%)	(-)
HPMC3-L/A63				63 (21.00%)	+
HPMC3-L/A64				64 (21.33%)	+
HPMC3-L/A65				65 (21.66%)	+
HPMC3-L/A66				66 (22.00%)	+
HPMC3-L/A67				67 (22.33%)	+
HPMC3-L/A68				68 (22.66%)	(-)(-)
HPMC3-L/A70				70 (23.33%)	(-)(-)
HPMC3-L/A87				87 (29.00%)	(-)(-)
HPMC4-L/A58		2.00	98.00	58 (19.33%)	(-)
HPMC4-L/A60				60 (20.00%)	(-)
HPMC4-L/A62				62 (20.66%)	(-)(-)
HPMC4-L/A64				64 (21.33%)	(-)(-)
HPMC4-L/A65				65 (21.66%)	(-)(-)
HPMC4-L/A68				68 (22.66%)	(-)(-)
HPMC4-L/A71				71 (23.66%)	(-)(-)

(-), Too dry formulation; (-)(-), Too wet formulation; +, Rounded/spherical granules
* % of liquid binder based on dry weight

2. Percentage yield during extrusion-spheronization process

Table B-12. Percentage yield during extrusion-spheronization process of preparation of pellets, calculated based on total weight of wet mass.

Formulation	% Yield	
	Extrude	Spheronization
CMC2-L/W50	63.46	59.37
CMC2-L/W51	61.76	59.19
CMC3-L/W45	55.18	51.76
CMC3-L/W46	53.15	48.94
CMC2-L/A82	64.40	60.49
CMC2-L/A83	66.34	61.62
CMC2-L/A84	65.92	60.89
CMC2-L/A85	66.81	61.62
CMC2-L/A86	66.95	62.61
CMC2-L/A87	65.47	61.11
CMC3-L/A90	65.07	56.53
MC2-L/W45	66.30	63.48
MC3-L/W42	63.46	58.83
MC3-L/W45	62.56	60.45
MC3-L/A62	59.94	47.78
MC3-L/A64	66.84	63.33
MC3-L/A66	66.01	61.51
MC3-L/A68	65.74	61.40
HPMC2-L/A65	68.80	55.38
HPMC2-L/A66	66.89	60.76
HPMC3-L/A63	66.73	43.98
HPMC3-L/A64	64.09	58.16
HPMC3-L/A65	66.68	61.98
HPMC3-L/A66	69.61	64.50
HPMC3-L/A67	67.28	52.11
CT-L/W195	67.95	64.33
MC1-P/W41	64.52	59.37
MC2-P/A58	43.86	59.19
MC4-I/W70	76.43	51.76
MC8-I/A106	57.31	48.94

APPENDIX C

1. Amplitude sweep

Amplitude sweep test is used to determine the upper boundary of the linear viscoelatic (LVE) range from a stress sweep.

Table C-1. Linear viscoelastic range (LVE) for NaCMC 1180 gel.

Formulation	LVE (mNm)	Formulation	LVE (mNm)
CMC1-G/W30	1.45E-03	CMC3-G/W43	4.85E-01
CMC1-G/W32	3.86E-02	CMC3-G/W46	5.47E-01
CMC1-G/W34	2.11E-03	CMC3-G/W51	3.80E-01
CMC1-G/W35	4.15E-02	CMC3-G/W52	1.74E-02
CMC2-G/W49	9.71E-03	CMC4-G/W40	1.23E-01
CMC2-G/W50	7.05E-02	CMC4-G/W46	2.42E+00
CMC2-G/W51	5.00E-02	CMC4-G/W52	1.74E+00
CMC2-G/W52	6.32E-02	CMC4-G/W55	1.38E+00

Table C-2. Linear viscoelastic range (LVE) for wet mass of lactose, with NaCMC 1180 as the formulation aid.

Formulation	LVE (mNm)	Formulation	LVE (mNm)
CMC2-L/W45	1.89E+00	CMC1-L/A65	1.99E+00
CMC2-L/W50	1.88E+00	CMC1-L/A70	2.56E+00
CMC2-L/W51	1.13E+00	CMC2-L/A70	6.46E+00
CMC2-L/W52	1.16E+00	CMC2-L/A83	1.77E+00
CMC3-L/W43	5.63E+00	CMC2-L/A84	1.52E+00
CMC3-L/W45	9.99E-01	CMC2-L/A86	2.12E+00
CMC3-L/W50	1.05E+01	CMC2-L/A90	1.90E+00
CMC3-L/W52	4.86E+00	CMC3-L/A68	4.24E+00
CMC4-L/W43	2.23E+00	CMC3-L/A90	1.98E+00
CMC4-L/W45	3.46E+00		
CMC4-L/W52	4.16E+00		
CMC4-L/W55	5.84E+00		

Table C-3. Linear viscoelastic range (LVE) for wet mass of lactose, with MC 15 and HPMC E15 as the formulation aid.

Formulation	LVE (mNm)	Formulation	LVE (mNm)
MC2-L/W39	5.60E+00	MC3-L/A58	3.72E-01
MC2-L/W45	4.61E+00	MC3-L/A64	2.70E+00
MC2-L/W50	2.80E+00	MC3-L/A68	3.17E+00
MC3-L/W45	3.30E+00	MC3-L/A72	4.89E-01
		HPMC2-L/A65	1.27E+00
		HPMC3-L/A62	7.42E-01
		HPMC3-L/A65	3.80E+00
		HPMC3-L/A68	1.95E+00

Table C-4. Linear viscoelastic range (LVE) for wet mass of lactose, with MCC as the formulation aid.

Formulation	LVE (mNm)
CT-L/W195	5.35E-01

Table C-5. Linear viscoelastic range (LVE) for wet mass of propranolol hydrochloride or ibuprofen, with MC 15 wet mass as the formulation aid.

Formulation	LVE (mNm)
MC1-P/A58	3.84E-01
MC2-P/W41	2.80E-02
MC4-I/W70	1.21E+00
MC8-I/A106	5.92E-01

2. Creep experiment

Table C-6. Data of creep experiment for NaCMC 1180 gel.

Formulation	Creep phase		Recovery phase				
	J_0 (1/Pa) mean	SD	Je (1/Pa) mean	Jv (1/Pa) mean	Je/J_{max}(%) mean	Jv/J_{max}(%) mean	SD
CMC1-G/W30	1.31E-02	6.12E-04	2.33E-02	2.91E-02	44.88	55.52	3.51E-04
CMC1-G/W32	1.34E-02	7.09E-04	2.27E-02	3.64E-02	38.38	61.62	3.36E-04
CMC1-G/W34	2.19E-02	9.28E-04	4.43E-02	5.52E-02	44.55	55.45	7.63E-04
CMC1-G/W35	1.47E-02	8.76E-04	2.56E-02	4.37E-02	36.94	63.06	3.77E-04
CMC1-G/W36	3.27E-02	1.72E-03	6.41E-02	1.11E-01	36.68	63.32	9.82E-04
CMC2-G/W49	6.38E-03	2.48E-04	1.15E-02	1.42E-02	44.90	55.10	1.95E-04
CMC2-G/W50	5.52E-03	2.51E-04	1.20E-02	1.18E-02	50.38	49.62	1.84E-04
CMC2-G/W51	7.60E-03	2.73E-04	1.21E-02	1.67E-02	42.14	57.86	1.76E-04
CMC2-G/W52	7.95E-03	3.92E-04	1.79E-02	1.92E-02	48.26	51.74	2.93E-04
CMC3-G/W43	7.20E-04	2.32E-05	9.26E-04	1.34E-03	40.88	59.12	1.20E-05
CMC3-G/W46	5.55E-04	1.15E-05	8.00E-04	5.97E-04	57.26	42.74	9.88E-06
CMC3-G/W49	9.24E-04	3.39E-05	1.49E-03	1.97E-03	43.07	56.93	2.17E-05
CMC3-G/W51	9.69E-04	3.69E-05	1.56E-03	2.17E-03	41.74	58.62	2.21E-05
CMC4-G/W40	1.20E-04	3.19E-06	1.48E-04	1.84E-04	44.59	55.41	1.94E-06
CMC4-G/W43	1.86E-04	5.96E-06	2.51E-04	3.82E-04	39.66	60.34	2.96E-06
CMC4-G/W46	1.87E-04	5.33E-06	2.24E-04	2.24E-04	39.09	60.91	2.78E-06
CMC4-G/W52	2.22E-04	5.62E-06	2.38E-04	3.68E-04	39.26	60.74	2.80E-06
CMC4-G/W55	2.44E-04	7.23E-06	3.34E-04	4.15E-04	44.58	55.42	4.02E-06

Note: J_0 = instantaneous compliance

Je = elastic compliance

Jv = viscous compliance

Je/J_{max} = elastic shear of compliance

Jv/J_{max} = viscous shear of compliance

Table C-7. Data of creep experiment for wet mass of lactose, with NaCMC 1180 as the formulation aid.

Formulation	Creep phase		Recovery phase				
	J_0 (1/Pa) mean	SD	Je (1/Pa) mean	Jv (1/Pa) mean	Je/J_{max}(%) mean	Jv/J_{max}(%) mean	SD
CMC2-L/W45	1.78E-07	8.40E-09	3.91E-07	1.09E-06	26.30	73.70	4.90E-09
CMC2-L/W51	1.31E-07	1.12E-08	3.41E-07	1.27E-07	21.22	78.78	4.65E-09
CMC2-L/W52	2.14E-07	1.12E-08	5.64E-07	1.19E-06	32.22	67.78	6.68E-09
CMC2-L/W55	1.41E-07	7.60E-09	4.79E-07	7.90E-07	37.75	62.25	5.79E-09
CMC3-L/W43	1.17E-07	5.64E-09	3.09E-07	6.49E-07	32.27	67.76	3.56E-10
CMC3-L/W45	2.20E-07	1.09E-08	3.55E-07	1.18E-06	23.06	76.94	4.62E-09
CMC3-L/W50	2.48E-07	1.04E-08	4.25E-07	9.96E-07	29.90	70.10	5.32E-09
CMC3-L/W52	1.59E-07	1.01E-08	4.65E-07	9.80E-07	32.16	67.84	5.68E-09
CMC4-L/W43	2.39E-07	4.72E-09	4.41E-07	7.98E-07	35.56	64.44	4.72E-09
CMC4-L/W45	2.79E-07	1.16E-08	4.03E-07	1.07E-06	27.36	72.64	4.70E-09
CMC4-L/W52	1.67E-07	8.77E-09	4.33E-07	9.18E-07	32.08	67.92	5.16E-09
CMC1-L/A65	3.15E-07	1.10E-08	2.53E-07	1.32E-06	16.08	83.92	3.84E-09
CMC1-L/A70	1.93E-07	8.23E-09	3.13E-07	8.48E-07	26.96	73.04	4.15E-09
CMC2-L/A70	1.49E-07	3.75E-09	3.84E-07	8.62E-07	30.83	69.17	4.45E-09
CMC2-L/A83	1.74E-07	7.47E-09	3.00E-07	1.22E-06	19.75	80.25	4.20E-09
CMC2-L/A84	2.04E-07	1.48E-08	4.51E-07	1.71E-06	20.85	79.15	5.48E-09
CMC2-L/A86	2.47E-07	1.08E-08	6.29E-07	1.50E-06	29.57	70.43	6.91E-09
CMC2-L/A90	2.20E-07	9.12E-09	5.16E-07	1.42E-06	26.58	73.42	7.11E-09
CMC2-L/A90	1.64E-07	8.46E-09	5.14E-07	1.41E-06	26.71	73.29	6.67E-09
CMC3-L/A68	9.21E-08	2.88E-09	3.45E-07	5.15E-07	40.14	59.86	4.13E-09
CMC3-L/A90	3.14E-07	5.00E-09	5.28E-07	1.29E-06	29.08	70.92	6.54E-09

Note: J_0 = instantaneous compliance

Je = elastic compliance

Jv = viscous compliance

Je/J_{max} = elastic shear of compliance

Jv/J_{max} = viscous shear of compliance

Table C-8. Data of creep experiment for wet mass of lactose, with MC 15 and HPMC E15 as the formulation aids.

Formulation	Creep phase		Recovery phase				
	J_0 (1/Pa) mean	SD	Je (1/Pa) mean	Jv (1/Pa) mean	Je/J_{max}(%) mean	Jv/J_{max}(%) mean	SD
MC2-L/W39	6.33E-08	2.50E-09	1.23E-07	4.10E-07	23.17	76.83	1.58E-09
MC2-L/W45	8.71E-08	5.44E-09	1.57E-07	6.27E-07	19.97	80.03	2.00E-09
MC2-L/W50	1.21E-07	3.46E-09	1.74E-07	8.77E-07	16.53	83.47	2.56E-09
MC3-L/W45	8.70E-08	5.06E-09	3.01E-07	4.53E-07	39.94	60.06	3.38E-09
MC3-L/W45	1.14E-07	5.91E-09	2.48E-07	7.59E-07	24.62	75.38	3.03E-09
MC3-L/A58	7.90E-08	3.09E-09	1.46E-07	4.51E-07	24.45	75.55	2.02E-09
MC3-L/A64	8.77E-08	4.46E-09	2.48E-07	5.18E-07	32.39	67.61	3.17E-09
MC3-L/A72	1.06E-07	4.13E-09	2.44E-07	6.63E-07	26.88	73.12	3.66E-09
HPMC2-L/A65	7.77E-08	4.40E-09	1.49E-07	6.08E-07	19.64	80.36	2.21E-09
HPMC3-L/A62	1.17E-07	4.02E-09	2.25E-07	6.54E-07	25.58	74.42	3.44E-09
HPMC3-L/A65	1.66E-07	7.43E-09	2.35E-07	8.64E-07	21.36	78.64	3.17E-09
HPMC3-L/A68	8.76E-08	2.39E-09	1.27E-07	5.23E-07	19.57	80.43	2.02E-09

Note: J_0 = instantaneous compliance

Je = elastic compliance

Jv = viscous compliance

Je/J_{max} = elastic shear of compliance

Jv/J_{max} = viscous shear of compliance

Table C-9. Data of creep experiment for wet mass of lactose, with MCC as the formulation aid.

Formulation	Creep phase		Recovery phase				
	J_0 (1/Pa) mean	SD	Je (1/Pa) mean	Jv (1/Pa) mean	Je/J_{max}(%) mean	Jv/J_{max}(%) mean	SD
CT-L/W195	1.25E-06	3.24E-08	2.12E-06	1.97E-06	51.82	48.18	2.76E-08

Note: J_0 = instantaneous compliance
Je = elastic compliance
Jv = viscous compliance
Je/J_{max} = elastic shear of compliance
Jv/J_{max} = viscous shear of compliance

Table C-10. Data of creep experiment for wet mass of propranolol hydrochloride or ibuprofen, with MC 15 as the formulation aid

Formulation	Creep phase		Recovery phase				
	J_0 (1/Pa) mean	SD	Je (1/Pa) mean	Jv (1/Pa) mean	Je/J_{max}(%) mean	Jv/J_{max}(%) mean	SD
MC1-P/A58	7.04E-08	5.40E-09	2.39E-09	7.50E-07	0.32	99.68	1.10E-08
MC2-P/W41	9.43E-08	1.62E-09	1.17E-07	1.77E-07	40.03	59.97	1.94E-09
MC8-I/A106	2.97E-07	3.38E-08	7.01E-07	3.98E-06	14.97	85.03	1.41E-08
MC4-I/W70	1.53E-07	5.82E-09	2.80E-07	8.81E-07	24.08	75.92	4.85E-09

Note: J_0 = instantaneous compliance
Je = elastic compliance
Jv = viscous compliance
Je/J_{max} = elastic shear of compliance
Jv/J_{max} = viscous shear of compliance

3. Oscillation experiment

Table C-11. Data of oscillation experiment for NaCMC 1180 gel.

Formulation	G′ (Pa)		G″ (Pa)		G* (Pa)	
	mean	(SD)	mean	(SD)	mean	(SD)
CMC1-G/W30	1.62E+02	(9.64)	8.28E+01	(4.18)	2.90E+01	(1.63)
CMC1-G/W32	1.74E+02	(5.13)	8.71E+01	(2.93)	3.10E+01	(0.88)
CMC1-G/W34	1.04E+02	(3.41)	5.36E+01	(1.51)	1.86E+01	(0.58)
CMC1-G/W35	1.48E+02	(4.20)	7.48E+01	(2.75)	2.64E+01	(0.76)
CMC1-G/W36	6.76E+01	(2.10)	3.99E+01	(1.34)	1.25E+01	(0.36)
CMC2-G/W49	3.67E+02	(10.90)	1.49E+02	(6.97)	6.30E+01	(1.89)
CMC2-G/W50	3.51E+02	(9.24)	1.47E+02	(6.22)	6.06E+01	(1.67)
CMC2-G/W51	3.12E+02	(8.68)	1.28E+02	(5.10)	5.36E+01	(1.52)
CMC2-G/W52	2.49E+02	(14.53)	1.16E+02	(6.62)	4.37E+01	(2.46)
CMC3-G/W43	3.20E+03	(31.73)	8.60E+02	(8.96)	5.27E+02	(4.85)
CMC3-G/W46	2.86E+03	(23.52)	9.15E+02	(32.87)	4.78E+02	(2.47)
CMC3-G/W49	2.14E+03	(13.33)	6.64E+02	(13.64)	3.56E+02	(2.19)
CMC3-G/W51	2.02E+03	(22.47)	6.51E+02	(17.62)	3.38E+02	(3.12)
CMC4-G/W40	1.58E+04	(66.24)	2.60E+03	(12.74)	2.54E+03	(9.06)
CMC4-G/W43	1.03E+04	(48.80)	1.98E+03	(1.47)	1.66E+03	(6.73)
CMC4-G/W46	1.14E+04	(61.38)	2.17E+03	(4.53)	1.84E+03	(8.68)
CMC4-G/W52	1.01E+04	(53.70)	1.97E+03	(4.44)	1.64E+03	(7.43)
CMC4-G/W55	7.83E+03	(28.10)	1.64E+03	(0.00)	1.27E+03	(5.37)

Note: G′ = storage modulus, G″ = loss modulus, G* = complex modulus

Table C-12. Data of oscillation experiment for wet mass of lactose, with NaCMC 1180 as the formulation aid

Formulation	G′ (Pa)		G″ (Pa)		G* (Pa)	
	mean	(SD)	mean	(SD)	mean	(SD)
CMC1-L/A65	8.24E+07	(4.07E+06)	3.37E+07	(1.09E+06)	1.42E+07	(6.69E+05)
CMC1-L/A70	7.54E+07	(3.31+E06)	3.02E+07	(8.85E+05)	1.29E+07	(5.39E+05)
CMC2-L/A70	5.06E+07	(4.02E+05)	2.28E+07	(2.64E+05)	8.83E+06	(5.06E+04)
CMC2-L/A83	5.39E+07	(1.33E+06)	2.21E+07	(3.49E+05)	9.28E+06	(2.17E+05)
CMC2-L/A84	4.46E+07	(9.51E+05)	1.82E+07	(2.52E+05)	7.66E+06	(1.54E+05)
CMC2-L/A86	5.02E+07	(1.71E+06)	2.09E+07	(4.95E+05)	8.66E+06	(2.81E+05)
CMC2-L/A90	3.61E+07	(1.16E+06)	1.79E+07	(4.86E+05)	6.41E+06	(1.97E+05)
CMC3-L/A86	5.61E+07	(9.66E+05)	2.78E+07	(3.99E+05)	9.97E+06	(1.65E+05)
CMC3-L/A90	5.12E+07	(1.31E+06)	2.19E+07	(3.76E+05)	8.86E+06	(2.13E+05)
CMC2-L/W45	7.60E+07	(3.26E+06)	3.76E+07	(1.21E+06)	1.35E+07	(5.50E+05)
CMC2-L/W45	9.61E+07	(6.57E+06)	3.91E+07	(2.10E+06)	1.65E+07	(1.08E+06)
CMC2-L/W50	9.11E+07	(3.57E+06)	3.52E+07	(9.46E+05)	1.55E+07	(5.78E+05)
CMC2-L/W51	8.21E+07	(2.99E+06)	4.05E+07	(1.53E+06)	1.46E+07	(5.02E+05)
CMC2-L/W52	5.60E+07	(1.69E+06)	3.08E+07	(7.74E+05)	1.02E+07	(2.86E+05)
CMC3-L/W43	7.16E+07	(2.05E+06)	3.82E+07	(6.62E+05)	1.29E+07	(3.31E+05)
CMC3-L/W45	6.57E+07	(2.56E+06)	3.08E+07	(4.04E+06)	1.16E+07	(4.37E+05)
CMC3-L/W50	6.50E+07	(2.56E+06)	3.43E+07	(8.02E+05)	1.17E+07	(4.21E+05)
CMC3-L/W52	7.92E+07	(2.67E+06)	3.99E+07	(7.34E+05)	1.41E+07	(4.30E+05)
CMC4-L/W43	9.02E+07	(2.77E+06)	4.41E+07	(9.33E+05)	1.60E+07	(4.55E+05)
CMC4-L/W45	5.68E+07	(1.38E+06)	3.07E+07	(4.85E+05)	1.03E+07	(2.30E+05)
CMC4-L/W52	5.22E+07	(5.67E+05)	3.02E+07	(3.73E+05)	9.60E+06	(1.05E+05)
CMC4-L/W55	6.43E+07	(1.33E+06)	3.62E+07	(5.18E+05)	1.18E+07	(2.19E+05)

Note: G′ = storage modulus, G″ = loss modulus, G* = complex modulus

Table C-13 Data of oscillation experiment for wet mass of lactose, with MC 15 and HPMC E15 as the formulation aids

Formulation	G′ (Pa)		G″ (Pa)		G* (Pa)	
	mean	(SD)	mean	(SD)	mean	(SD)
MC2-L/W39	9.67E+07	(2.30E+06)	2.37E+07	(2.17E+05)	1.58E+07	(3.56E+05)
MC2-L/W45	1.46E+08	(8.11E+06)	5.85E+07	(1.86E+06)	2.51E+07	(1.29E+06)
MC2-L/W50	1.12E+08	(3.31E+06)	4.85E+07	(1.46E+06)	1.95E+07	(5.33E+05)
MC3-L/W45	9.82E+07	(2.50E+06)	3.71E+07	(7.57E+05)	1.67E+07	(4.14E+05)
MC3-L/A58	1.00E+08	(5.59E+06)	2.97E+07	(6.79E+05)	1.66E+07	(8.82E+05)
MC3-L/A64	8.78E+07	(3.69E+06)	2.76E+07	(8.33E+05)	1.46E+07	(5.94E+05)
MC3-L/A68	8.40E+07	(3.59E+06)	2.97E+07	(1.09E+06)	1.42E+07	(5.96E+05)
MC3-L/A72	7.28E+07	(1.88E+06)	1.87E+07	(2.59E+05)	1.20E+07	(3.00E+05)
HPMC2-L/A65	9.50E+07	(4.63E+06)	2.90E+07	(1.12E+06)	1.58E+07	(7.59E+05)
HPMC3-L/A62	7.20E+07	(2.37E+06)	1.69E+07	(3.23E+05)	1.18E+07	(3.70E+05)
HPMC3-L/A65	8.69E+07	(2.54E+06)	2.80E+07	(5.63E+05)	1.45E+07	(4.10E+05)
HPMC3-L/A68	1.28E+08	(4.83E+06)	4.52E+07	(1.22E+06)	2.17E+07	(7.81E+05)

Note: G′ = storage modulus, G″ = loss modulus, G* = complex modulus

Table C-14. Data of oscillation experiment for wet mass of lactose, with MCC as the formulation aid

Formulation	G′ (Pa)		G″ (Pa)		G* (Pa)	
	mean	(SD)	mean	(SD)	mean	(SD)
CT-L/W195	1.85E+06	(1.17E+04)	2.20E+05	(1.96E+03)	2.96E+05	(1.82E+03)

Note: G′ = storage modulus, G″ = loss modulus, G* = complex modulus

Table C-15. Data of oscillation experiment for wet mass of propranolol hydrochloride or ibuprofen with MC 15 as the formulation aid

Formulation	G′ (Pa)		G″ (Pa)		G* (Pa)	
	mean	(SD)	mean	(SD)	mean	(SD)
MC1-P/A58	1.27E+08	(1.22E+07)	1.33E+07	(2.56E+06)	2.03E+07	(1.92E+06)
MC2-P/W41	9.95E+07	(4.70E+06)	7.38E+06	(1.62E+06)	1.59E+07	(7.34E+05)
MC4-I/W70	2.54E+07	(2.20E+05)	5.93E+06	(7.29E+04)	4.15E+06	(3.41E+04)
MC8-I/A106	2.20E+07	(1.07E+06)	7.16E+06	(2.36E+05)	3.68E+06	(1.71E+05)

Note: G′ = storage modulus, G″ = loss modulus, G* = complex modulus

APPENDIX D

SIEVE ANALYSIS

1. Sieve analysis

Table D-1. Sieve analysis of CMC2-L/W50.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	3.65	2.22	100.00
2.00-1.70	1.850	0.29	0.18	97.78
1.70-1.40	1.550	9.74	5.91	97.61
1.40-1.18	1.290	120.02	72.86	91.69
1.18-1.00	1.090	22.85	13.87	18.83
1.00-0.71	0.855	5.23	3.18	4.96
0.71-0.50	0.605	1.14	0.69	1.78
	< 0.500	1.80	1.09	1.09
	Total	164.72	100.00	

Table D-2. Sieve analysis of CMC2-L/W51.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	8.90	5.60	100.00
2.00-1.70	1.850	7.20	4.53	94.40
1.70-1.40	1.550	118.14	74.31	89.87
1.40-1.18	1.290	18.27	11.49	15.57
1.18-1.00	1.090	3.49	2.20	4.08
1.00-0.71	0.855	2.40	1.51	1.88
0.71-0.50	0.605	0.49	0.31	0.37
	< 0.500	0.10	0.06	0.06
	Total	158.99	100.00	

Table D-3. Sieve analysis of CMC3-L/W45.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	0.66	0.45	100.00
2.00-1.70	1.850	0.16	0.11	99.55
1.70-1.40	1.550	0.51	0.35	99.44
1.40-1.18	1.290	2.56	1.75	99.09
1.18-1.00	1.090	92.30	63.02	97.34
1.00-0.71	0.855	40.00	27.31	34.32
0.71-0.50	0.605	4.54	3.10	7.01
	< 0.500	5.73	3.91	3.91
	Total	146.46	100.00	

Table D-4. Sieve analysis of CMC3-L/W46.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	1.48	0.98	100.00
2.00-1.70	1.850	0.20	0.13	99.02
1.70-1.40	1.550	0.36	0.24	98.89
1.40-1.18	1.290	4.45	2.94	98.65
1.18-1.00	1.090	108.81	71.77	95.72
1.00-0.71	0.855	20.80	13.72	23.94
0.71-0.50	0.605	3.78	2.49	10.22
	< 0.500	11.72	7.73	7.73
	Total	151.60	100.00	

Table D-5. Sieve analysis of CMC2-L/A82.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	20.39	11.48	100.00
2.00-1.70	1.850	4.96	2.79	88.52
1.70-1.40	1.550	134.78	75.87	85.73
1.40-1.18	1.290	11.08	6.24	9.86
1.18-1.00	1.090	1.92	1.08	3.62
1.00-0.71	0.855	0.97	0.55	2.54
0.71-0.50	0.605	0.08	0.05	1.99
	< 0.500	3.46	1.95	1.95
	Total	177.64	100.00	

Table D-6. Sieve analysis of CMC2-L/A83.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	3.03	1.64	100.00
3.35-2.80	3.075	4.66	2.52	98.36
2.80-2.36	2.580	14.83	8.01	95.85
2.36-2.00	2.180	137.05	74.05	87.83
2.00-1.70	1.850	19.26	10.41	13.79
1.70-1.40	1.550	2.37	1.28	3.38
1.40-1.18	1.290	1.14	0.62	2.10
1.18-1.00	1.090	0.93	0.50	1.49
1.00-0.71	0.855	1.03	0.56	0.98
0.71-0.50	0.605	0.27	0.15	0.43
	< 0.500	0.52	0.28	0.28
	Total	185.09	100.00	

Table D-7. Sieve analysis of CMC2-L/A84.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.16	0.09	100.00
3.35-2.80	3.075	0.28	0.15	99.91
2.80-2.36	2.580	1.17	0.63	99.76
2.36-2.00	2.180	19.00	10.29	99.13
2.00-1.70	1.850	149.92	81.18	88.84
1.70-1.40	1.550	4.63	2.51	7.66
1.40-1.18	1.290	1.39	0.75	5.15
1.18-1.00	1.090	1.05	0.57	4.40
1.00-0.71	0.855	1.14	0.62	3.83
0.71-0.50	0.605	0.32	0.17	3.22
	< 0.500	5.62	3.04	3.04
	Total	184.68	100.00	

Table D-8. Sieve analysis of CMC2-L/A85.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	10.05	5.49	100.00
3.35-2.80	3.075	3.99	2.18	94.51
2.80-2.36	2.580	15.07	8.23	92.34
2.36-2.00	2.180	119.95	65.48	84.11
2.00-1.70	1.850	19.24	10.50	18.63
1.70-1.40	1.550	3.97	2.17	8.13
1.40-1.18	1.290	2.26	1.23	5.96
1.18-1.00	1.090	1.78	0.97	4.73
1.00-0.71	0.855	1.80	0.98	3.76
0.71-0.50	0.605	0.41	0.22	2.77
	< 0.500	4.67	2.55	2.55
	Total	183.19	100.00	

Table D-9. Sieve analysis of CMC2-L/A86.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	3.23	1.70	100.00
3.35-2.80	3.075	2.38	1.25	98.30
2.80-2.36	2.580	3.98	2.09	97.05
2.36-2.00	2.180	59.64	31.39	94.95
2.00-1.70	1.850	112.42	59.16	63.57
1.70-1.40	1.550	3.28	1.73	4.40
1.40-1.18	1.290	1.43	0.75	2.68
1.18-1.00	1.090	1.01	0.53	1.93
1.00-0.71	0.855	1.29	0.68	1.39
0.71-0.50	0.605	0.55	0.29	0.72
	< 0.500	0.81	0.43	0.43
	Total	190.02	100.00	

Table D-10. Sieve analysis of CMC2-L/A87.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	2.40	1.30	100.00
2.00-1.70	1.850	16.15	8.73	98.70
1.70-1.40	1.550	158.73	85.80	89.97
1.40-1.18	1.290	2.70	1.46	4.18
1.18-1.00	1.090	1.40	0.76	2.72
1.00-0.71	0.855	1.73	0.94	1.96
0.71-0.50	0.605	0.86	0.46	1.03
	< 0.500	1.04	0.56	0.56
	Total	185.01	100.00	

Table D-11. Sieve analysis of CMC3-L/A90.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	0.11	0.06	100.00
2.00-1.70	1.850	0.12	0.07	99.94
1.70-1.40	1.550	86.19	50.65	99.86
1.40-1.18	1.290	69.29	40.72	49.22
1.18-1.00	1.090	2.58	1.52	8.50
1.00-0.71	0.855	2.12	1.25	6.98
0.71-0.50	0.605	1.50	0.88	5.74
	< 0.500	8.26	4.85	4.85
	Total	170.17	100.00	

Table D-12. Sieve analysis of MC2-L/W42.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	24.05	13.58	100.00
2.00-1.70	1.840	103.53	58.48	86.42
1.70-1.40	1.545	39.70	22.42	27.94
1.40-1.18	1.295	3.15	1.78	5.52
1.18-1.00	1.090	1.88	1.06	3.74
1.00-0.71	0.854	2.44	1.38	2.68
0.71-0.50	0.604	0.65	0.37	1.30
	< 0.500	1.65	0.93	0.93
	Total	177.05	100.00	

Table D-13. Sieve analysis of MC3-L/W42.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	14.81	9.18	100.00
2.00-1.70	1.840	93.89	58.23	90.82
1.70-1.40	1.545	41.27	25.59	32.59
1.40-1.18	1.295	2.26	1.40	7.00
1.18-1.00	1.090	1.01	0.63	5.59
1.00-0.71	0.854	0.89	0.55	4.97
0.71-0.50	0.604	0.14	0.09	4.42
	< 0.500	6.98	4.33	4.33
	Total	161.25	100.00	

Table D-14. Sieve analysis of MC3-L/W45.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.000	100.00
3.35-2.80	3.075	0.00	0.000	100.00
2.80-2.36	2.580	0.00	0.000	100.00
2.36-2.00	2.180	5.98	3.672	100.00
2.00-1.70	1.840	50.36	30.920	96.33
1.70-1.40	1.545	102.14	62.713	65.41
1.40-1.18	1.295	2.36	1.449	2.70
1.18-1.00	1.090	1.10	0.675	1.25
1.00-0.71	0.854	0.84	0.516	0.57
0.71-0.50	0.604	0.06	0.037	0.06
	< 0.500	0.03	0.018	0.02
	Total	162.87	100.00	

Table D-15. Sieve analysis of MC3-L/A62.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	6.75	4.99	100.00
2.00-1.70	1.840	46.44	34.35	95.01
1.70-1.40	1.545	72.61	53.71	60.66
1.40-1.18	1.295	2.61	1.93	6.95
1.18-1.00	1.090	1.09	0.81	5.02
1.00-0.71	0.854	3.22	2.38	4.22
0.71-0.50	0.604	0.72	0.53	1.83
	< 0.500	1.76	1.30	1.30
	Total	135.20	100.00	

Table D-16. Sieve analysis of MC3-L/A64.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.000	100.00
3.35-2.80	3.075	0.00	0.000	100.00
2.80-2.36	2.580	0.00	0.000	100.00
2.36-2.00	2.180	19.28	10.514	100.00
2.00-1.70	1.840	2.20	1.200	89.49
1.70-1.40	1.545	105.48	57.523	88.29
1.40-1.18	1.295	28.96	15.793	30.76
1.18-1.00	1.090	8.59	4.685	14.97
1.00-0.71	0.854	8.86	4.832	10.29
0.71-0.50	0.604	4.46	2.432	5.45
	< 0.500	5.54	3.021	3.02
	Total	183.37	100.00	

Table D-17. Sieve analysis of MC3-L/A66.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.000	100.00
3.35-2.80	3.075	0.00	0.000	100.00
2.80-2.36	2.580	0.00	0.000	100.00
2.36-2.00	2.180	0.49	0.273	100.00
2.00-1.70	1.840	0.56	0.313	99.73
1.70-1.40	1.545	119.31	66.594	99.41
1.40-1.18	1.295	53.63	29.934	32.82
1.18-1.00	1.090	3.21	1.792	2.89
1.00-0.71	0.854	0.64	0.357	1.09
0.71-0.50	0.604	0.12	0.067	0.74
	< 0.500	1.20	0.670	0.67
	Total	179.16	100.00	

Table D-18. Sieve analysis of MC3-L/A68.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.000	100.00
3.35-2.80	3.075	0.00	0.000	100.00
2.80-2.36	2.580	0.00	0.000	100.00
2.36-2.00	2.180	0.25	0.139	100.00
2.00-1.70	1.840	3.13	1.749	99.86
1.70-1.40	1.545	141.95	79.200	98.11
1.40-1.18	1.295	29.31	16.353	18.91
1.18-1.00	1.090	2.07	1.155	2.56
1.00-0.71	0.854	0.90	0.502	1.40
0.71-0.50	0.604	0.17	0.095	0.90
	< 0.500	1.45	0.806	0.81
	Total	179.23	100.00	

Table D-19. Sieve analysis of HPMC2-L/A65.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.000	100.00
2.80-2.36	2.580	0.00	0.000	100.00
2.36-2.00	2.180	10.00	6.238	100.00
2.00-1.70	1.840	47.43	29.585	93.76
1.70-1.40	1.545	53.12	33.134	64.18
1.40-1.18	1.295	7.80	4.865	31.04
1.18-1.00	1.090	5.85	3.649	26.18
1.00-0.71	0.854	5.51	3.437	22.53
0.71-0.50	0.604	2.88	1.796	19.09
	< 0.500	27.73	17.297	17.30
	Total	160.32	100.00	

Table D-20. Sieve analysis of HPMC2-L/A66.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	15.31	8.65	100.00
2.00-1.70	1.840	118.74	67.06	91.35
1.70-1.40	1.545	33.07	18.68	24.30
1.40-1.18	1.295	1.30	0.73	5.62
1.18-1.00	1.090	0.59	0.33	4.89
1.00-0.71	0.854	0.38	0.21	4.55
0.71-0.50	0.604	0.19	0.11	4.34
	< 0.500	7.49	4.23	4.29
	Total	177.07	100.00	

Table D-21. Sieve analysis of HPMC3-L/A63.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	0.93	0.72	100.00
2.00-1.70	1.840	62.87	48.87	99.28
1.70-1.40	1.545	49.63	38.58	50.41
1.40-1.18	1.295	1.92	1.49	11.83
1.18-1.00	1.090	2.32	1.80	10.34
1.00-0.71	0.854	5.90	4.59	8.53
0.71-0.50	0.604	0.69	0.54	3.95
	< 0.500	4.39	3.41	3.41
	Total	128.65	100.00	

Table D-22. Sieve analysis of HPMC3-L/A64.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	1.08	0.60	100.00
2.00-1.70	1.840	80.23	44.54	99.40
1.70-1.40	1.545	86.61	48.08	54.86
1.40-1.18	1.295	2.51	1.39	6.78
1.18-1.00	1.090	2.92	1.62	5.39
1.00-0.71	0.854	4.07	2.26	3.77
0.71-0.50	0.604	2.10	1.17	1.51
	< 0.500	0.62	0.34	0.34
	Total	180.14	100.00	

Table D-23. Sieve analysis of HPMC3-L/A65.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.00	100.00
3.35-2.80	3.075	0.00	0.00	100.00
2.80-2.36	2.580	0.00	0.00	100.00
2.36-2.00	2.180	0.08	0.04	100.00
2.00-1.70	1.840	0.37	0.20	99.96
1.70-1.40	1.545	137.63	73.79	99.76
1.40-1.18	1.295	38.33	20.55	25.97
1.18-1.00	1.090	3.20	1.72	5.42
1.00-0.71	0.854	3.80	2.04	3.70
0.71-0.50	0.604	1.35	0.72	1.67
	< 0.500	1.76	0.94	0.94
	Total	186.52	100.00	

Table D-24. Sieve analysis of HPMC3-L/A66.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.00	0.000	100.00
3.35-2.80	3.075	0.00	0.000	100.00
2.80-2.36	2.580	0.00	0.000	100.00
2.36-2.00	2.180	3.72	1.965	100.00
2.00-1.70	1.840	9.43	4.982	98.03
1.70-1.40	1.545	155.36	82.075	93.05
1.40-1.18	1.295	10.13	5.352	10.98
1.18-1.00	1.090	1.82	0.961	5.63
1.00-0.71	0.854	1.95	1.030	4.66
0.71-0.50	0.604	0.47	0.248	3.63
	< 0.500	6.41	3.386	3.39
	Total	189.29	100.00	

Table D-25. Sieve analysis of HPMC3-L/A67.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	>3.350	0.50	0.325	100.00
3.35-2.80	3.075	0.34	0.221	99.68
2.80-2.36	2.580	61.15	39.703	99.45
2.36-2.00	2.180	78.65	51.065	59.75
2.00-1.70	1.840	3.90	2.532	8.69
1.70-1.40	1.545	1.64	1.065	6.16
1.40-1.18	1.295	0.96	0.623	5.09
1.18-1.00	1.090	1.20	0.779	4.47
1.00-0.71	0.854	3.85	2.500	3.69
0.71-0.50	0.604	0.70	0.454	1.19
	< 0.500	1.13	0.734	0.73
	Total	154.02	100.00	

Table D-26. Sieve analysis of CT-L/W195.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	> 2.000	0.01	0.006	100.00
2.00-1.70	1.840	0.07	0.040	99.99
1.70-1.40	1.545	1.22	0.689	99.95
1.40-1.18	1.295	5.02	2.835	99.27
1.18-1.00	1.090	41.40	23.382	96.43
1.00-0.71	0.854	129.25	72.998	73.05
0.71-0.50	0.604	0.07	0.040	0.05
0.50-0.35	0.428	0.01	0.006	0.01
	< 0.355	0.01	0.006	0.01
	Total	177.06	100.00	

Table D-27. Sieve analysis of MC2-P/W41.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	> 2.000	0.00	0.000	100.00
2.00-1.70	1.840	4.17	3.445	100.00
1.70-1.40	1.545	6.24	5.156	96.55
1.40-1.18	1.295	28.50	23.548	91.40
1.18-1.00	1.090	39.69	32.794	67.85
1.00-0.71	0.854	18.34	15.153	35.06
0.71-0.50	0.604	12.67	10.468	19.90
0.50-0.35	0.428	7.04	5.817	9.44
	< 0.355	4.38	3.619	0.94
	Total	121.03	100.00	

Table D-28. Sieve analysis of MC1-P/A58.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	> 2.000	0.00	0.00	100.00
2.00-1.70	1.850	3.34	1.85	100.00
1.70-1.40	1.550	12.94	7.17	98.15
1.40-1.18	1.290	51.61	28.60	90.98
1.18-1.00	1.090	55.10	30.53	62.38
1.00-0.71	0.855	36.14	20.02	31.85
0.71-0.50	0.605	15.30	8.48	11.83
0.50-0.35	0.428	4.36	2.42	3.35
	< 0.355	1.69	0.94	0.94
	Total	180.48	100.00	

Table D-29. Sieve analysis of MC4-I /W70.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	> 2.000	0.00	0.000	100.00
2.00-1.70	1.840	0.52	0.262	100.00
1.70-1.40	1.545	1.85	0.932	99.74
1.40-1.18	1.295	9.66	4.869	98.81
1.18-1.00	1.090	37.53	18.916	93.94
1.00-0.71	0.854	117.88	59.415	75.02
0.71-0.50	0.604	24.08	12.137	15.60
0.50-0.35	0.428	5.30	2.671	3.47
	< 0.355	1.58	0.796	0.94
	Total	198.40	100.00	

Table D-30. Sieve analysis of MC8-I /A106.

Sieve size (mm)	Arithmetic mean opening (mm)	Retained weight (g)	% Retained	Cumulative % undersize
	> 2.000	0.00	0.000	100.00
2.00-1.70	1.840	0.59	0.399	100.00
1.70-1.40	1.545	0.84	0.569	99.60
1.40-1.18	1.295	8.14	5.512	99.03
1.18-1.00	1.090	65.15	44.113	93.52
1.00-0.71	0.854	45.75	30.977	49.41
0.71-0.50	0.604	13.59	9.202	18.43
0.50-0.35	0.428	7.51	5.085	9.23
	< 0.355	6.12	4.144	0.94
	Total	147.69	100.00	

2. Size and size distribution

Table D-31. Median size diameter and intrquartile range (IQR).

Code	Interquartile			
	Q_1	Q_2	Q_3	IQR
CMC2-L/W50	1.12	1.20	1.24	0.12
CMC2-L/W51	1.34	1.42	1.50	0.16
CMC3-L/W45	0.80	0.92	1.02	0.22
CMC3-L/W46	0.86	0.94	1.02	0.16
CMC2-L/A82	1.34	1.40	1.50	0.16
CMC2-L/A83	0.92	0.98	1.06	0.14
CMC2-L/A84	1.62	1.70	1.80	0.18
CMC2-L/A85	1.88	2.00	2.12	0.24
CMC2-L/A86	1.68	1.78	1.94	0.26
CMC2-L/A87	1.36	1.44	1.50	0.14
CMC3-L/A90	0.80	0.92	1.00	0.20
MC2-L/W45	1.14	1.22	1.30	0.16
MC3-L/W42	1.14	1.24	1.32	0.18
MC3-L/W45	1.98	2.10	2.28	0.30
MC3-L/A62	1.20	1.34	1.46	0.26
MC3-L/A64	1.34	1.45	1.64	0.30
MC3-L/A66	1.40	1.50	1.60	0.20
MC3-L/A68	1.38	1.46	1.54	0.16
HPMC2-L/A65	1.22	1.38	1.96	0.74
HPMC2-L/A66	1.16	1.20	1.26	0.10
HPMC3-L/A63	1.20	1.30	1.44	0.24
HPMC3-L/A64	1.20	1.30	1.44	0.24
HPMC3-L/A65	1.40	1.46	1.58	0.18
HPMC3-L/A66	1.34	1.42	1.52	0.18
HPMC3-L/A67	0.78	0.90	1.00	0.22
CT-L/W195	0.69	0.78	0.89	0.20
MC3-P/A58	0.78	1.00	1.12	0.34
MC4-P/W41	0.68	0.86	1.14	0.46
MC4-I/W70	0.66	0.72	0.84	0.18
MC8-I/A106	0.69	0.78	0.89	0.20

Q_2 = median size diameter
IQR = Q_3-Q_1

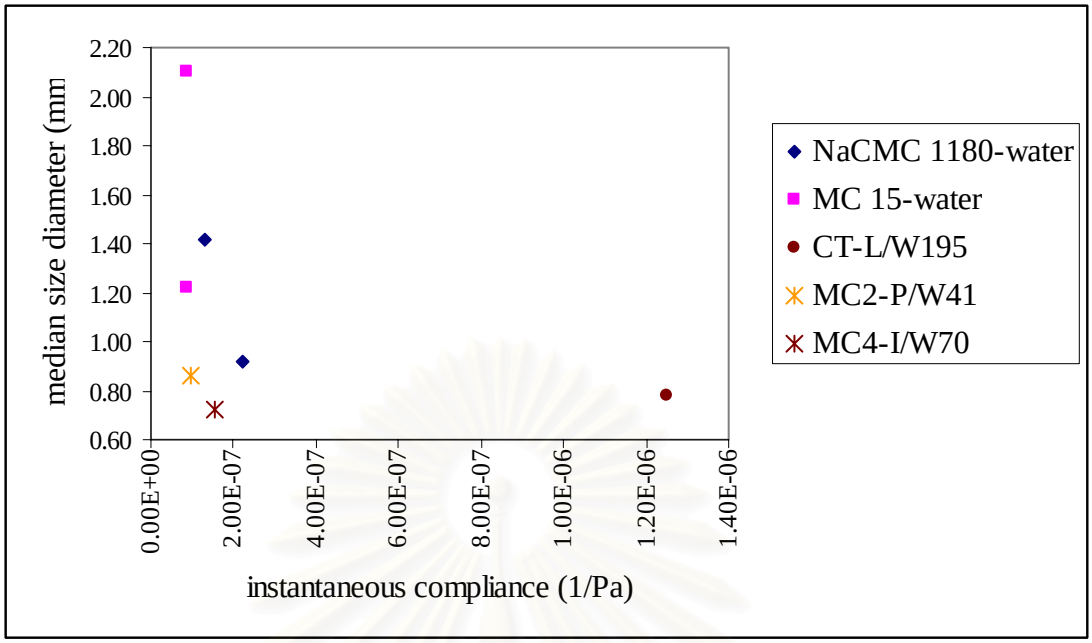


Figure D-1. Effect of instantaneous compliance on median size diameter (mm) of water formulation.

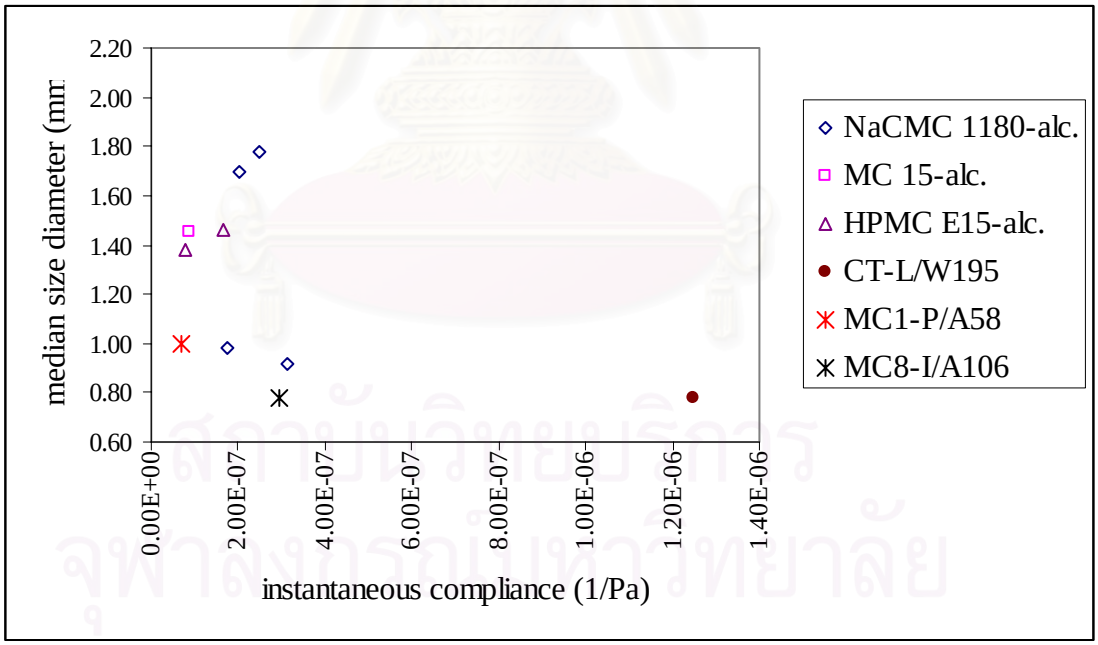


Figure D-2. Effect of instantaneous compliance on median size diameter (mm) of 50% ethanol formulation.

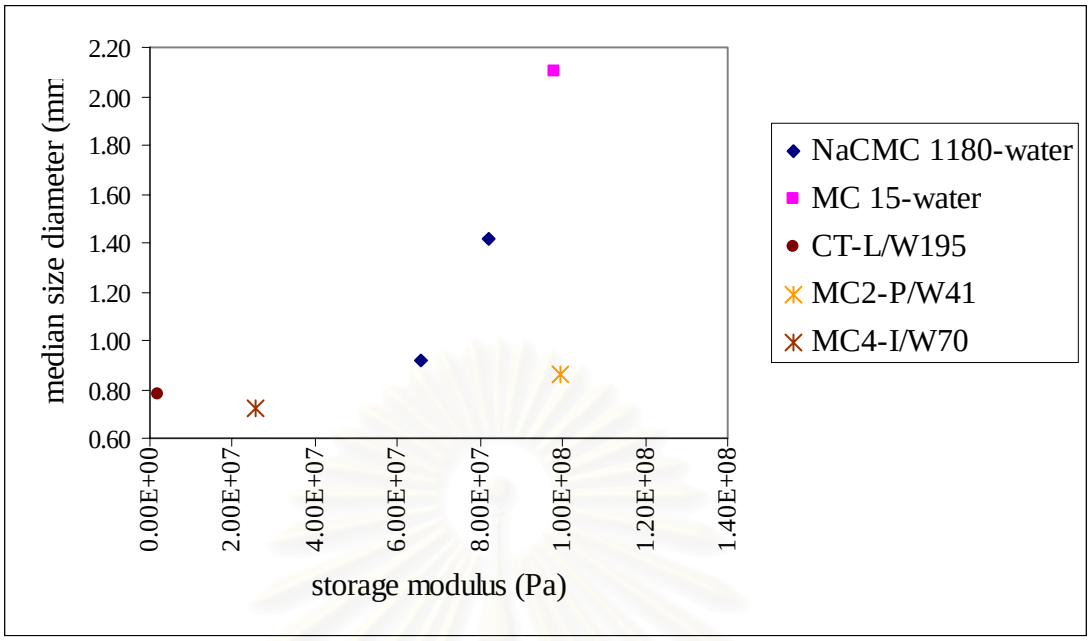


Figure D-3. Effect of storage modulus (G′) on median size diameter (mm) of water formulation.

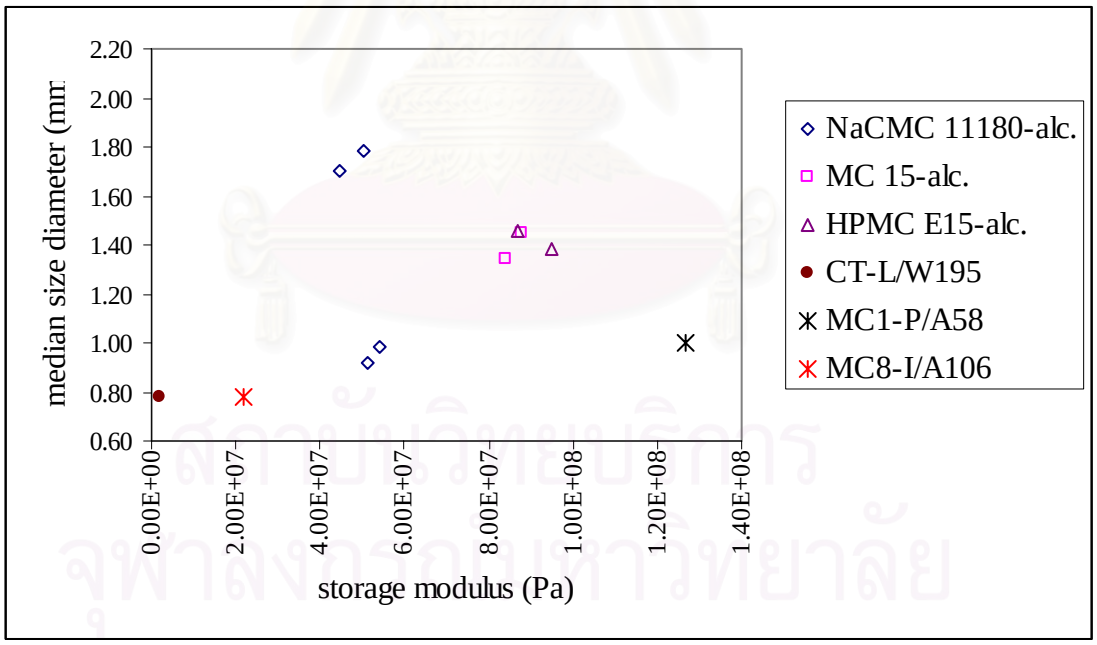


Figure D-4. Effect of storage modulus (G′) on median size diameter (mm) of 50% ethanol formulation.

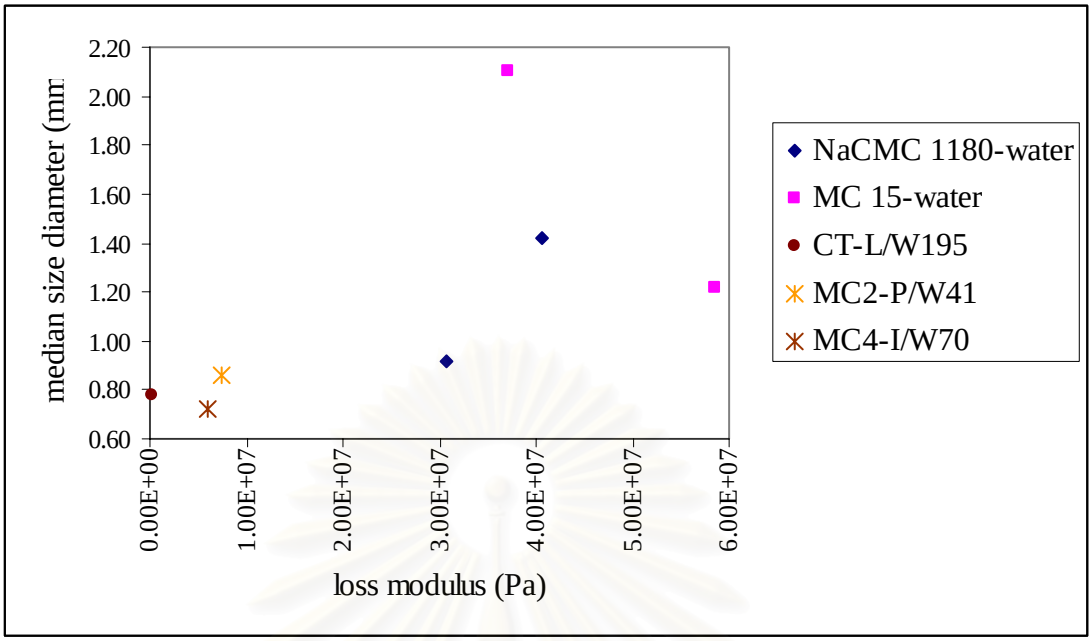


Figure D-5. Effect of loss modulus (G″) on median size diameter (mm) of water formulation.

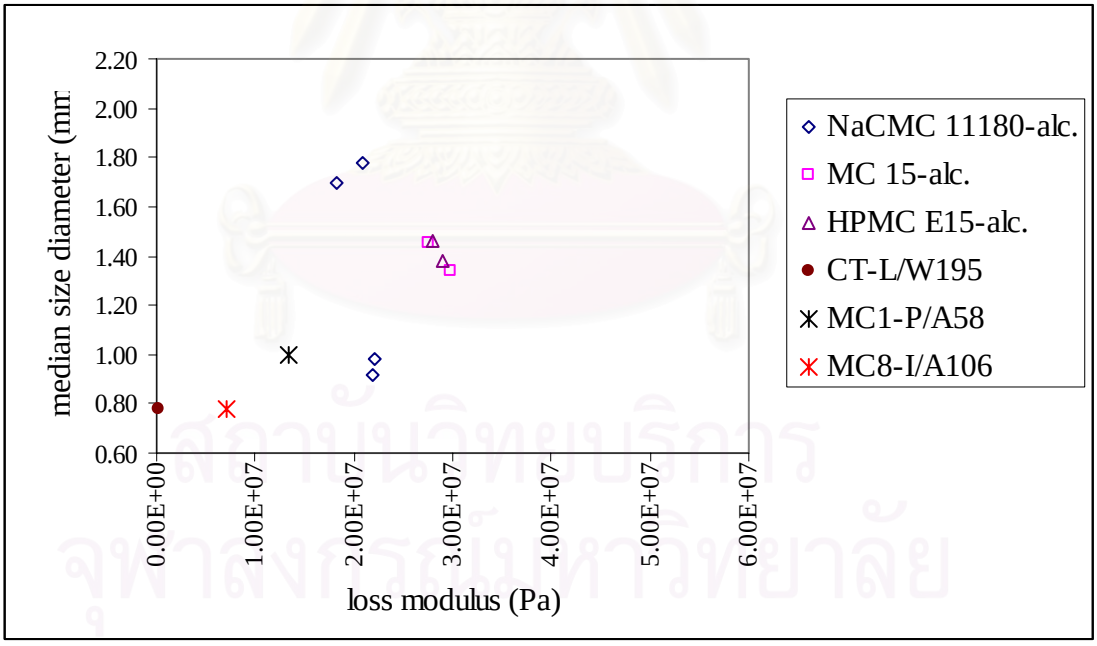


Figure D-6. Effect of loss modulus (G″) on median size diameter (mm) of 50% ethanol formulation.

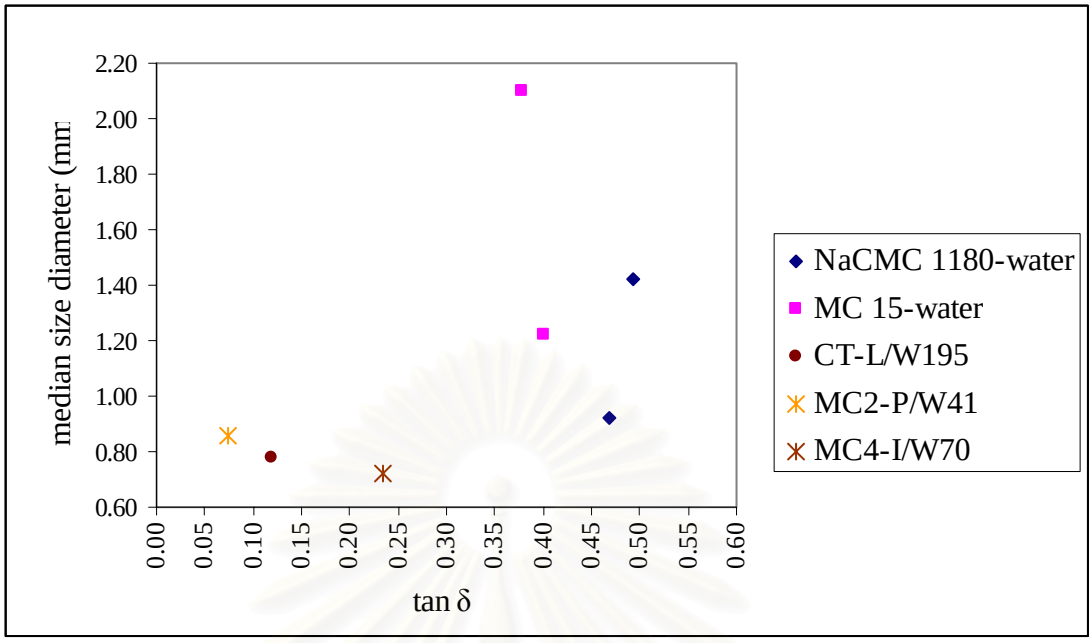


Figure D-7. Effect of tan δ on median size diameter (mm) of water formulation.

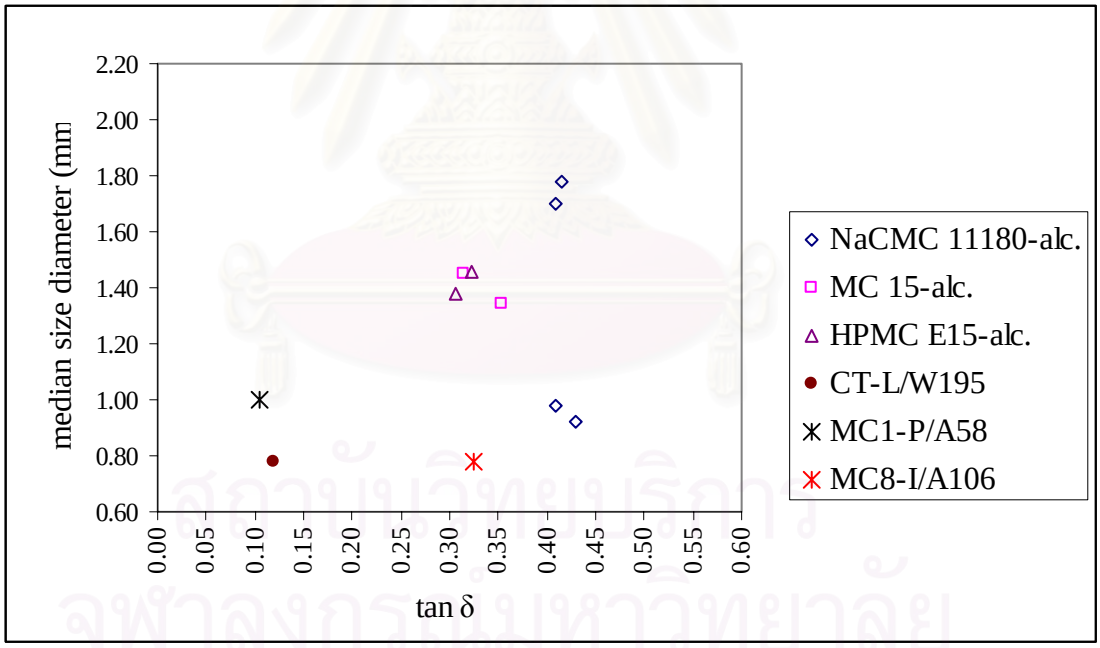


Figure D-8. Effect of tan δ on median size diameter (mm) of 50% ethanol formulation.

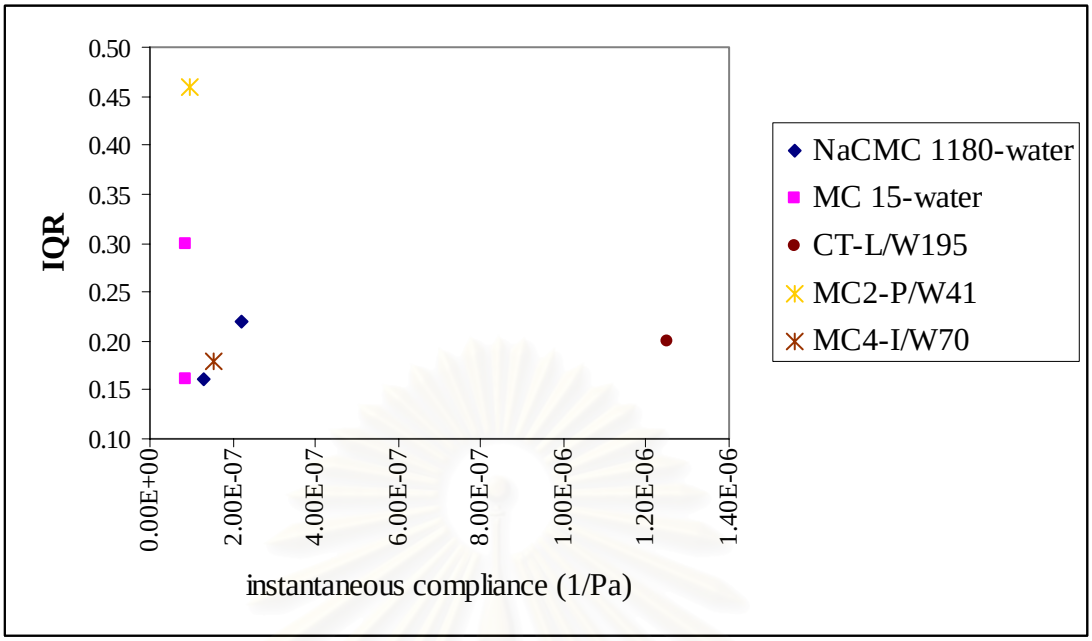


Figure D-9. Effect of instantaneous compliance on IQR of water formulation.

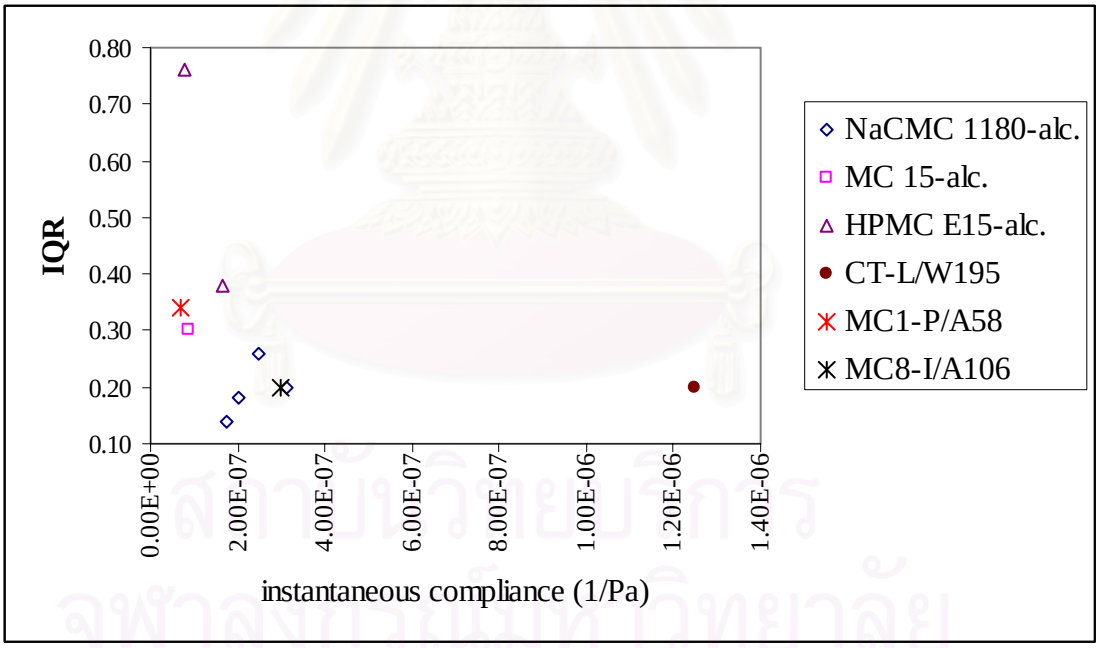


Figure D-10. Effect of instantaneous compliance on IQR of 50% ethanol formulation.

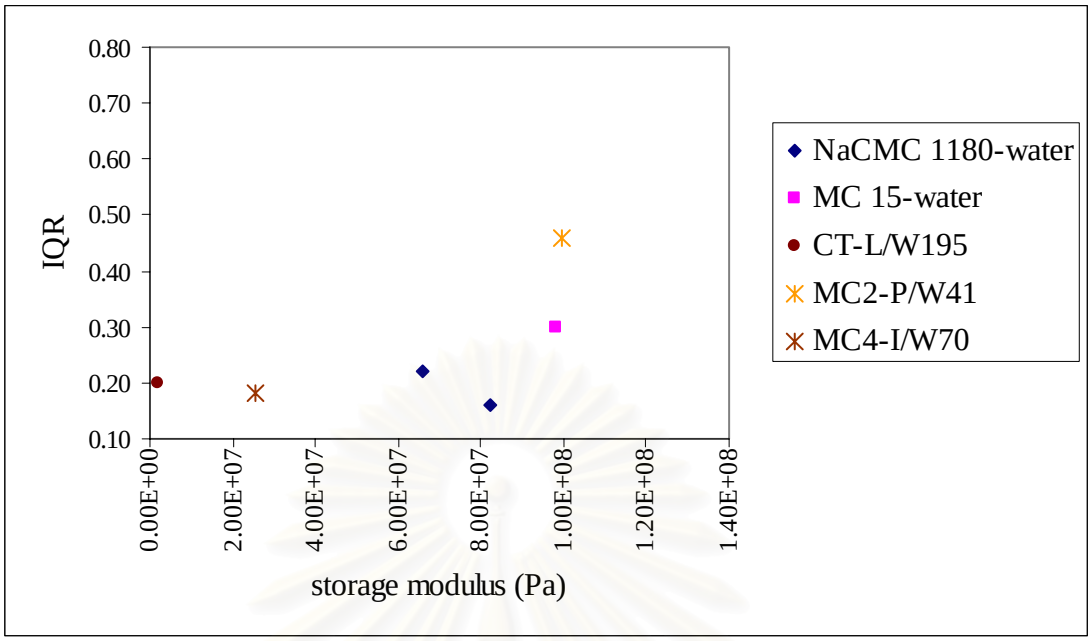


Figure D-11. Effect of storage modulus (G′) on IQR of water formulation.

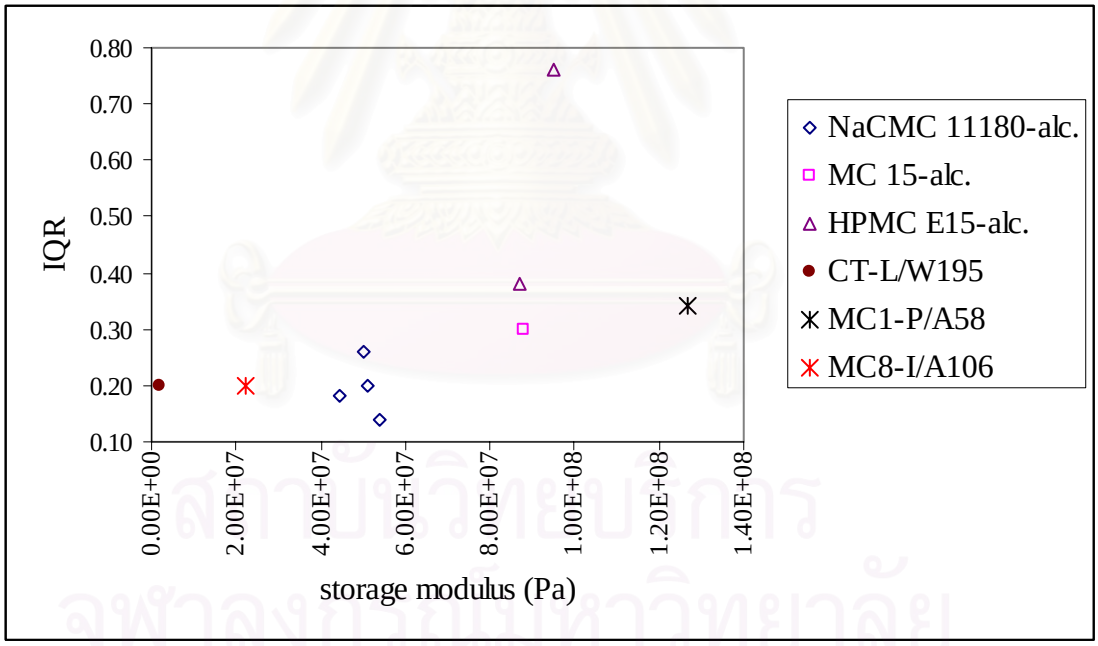


Figure D-12. Effect of storage (G′) modulus on IQR of 50% ethanol formulation.

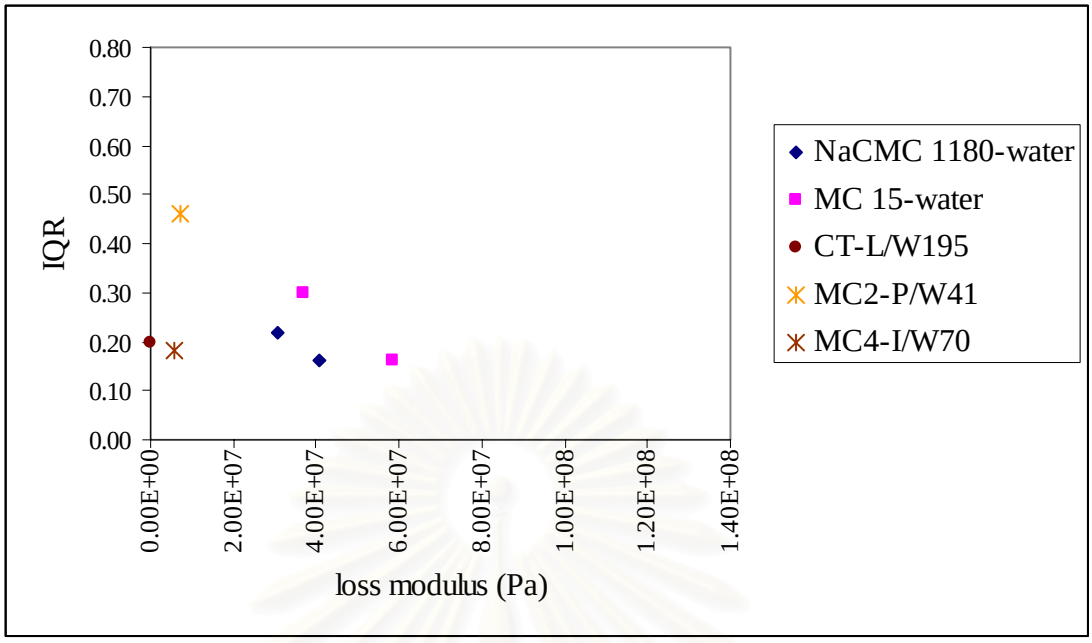


Figure D-13. Effect of loss modulus (G″) on IQR of water formulation.

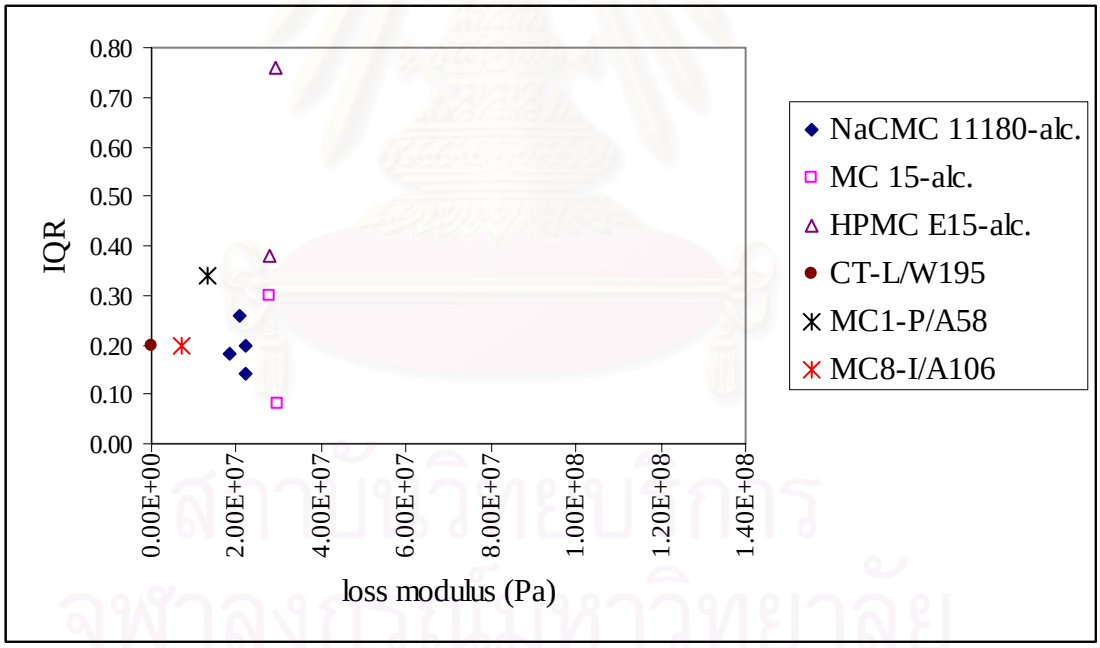


Figure D-14. Effect of loss modulus (G″) on IQR of 50% ethanol formulation.

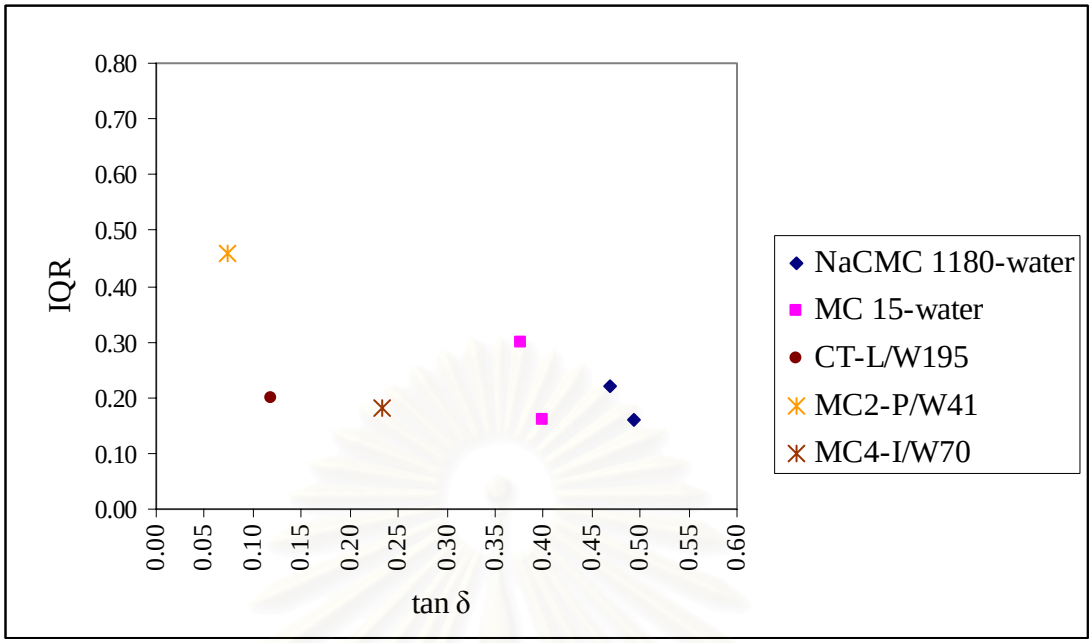


Figure D-15. Effect of tan δ on IQR of water formulation.

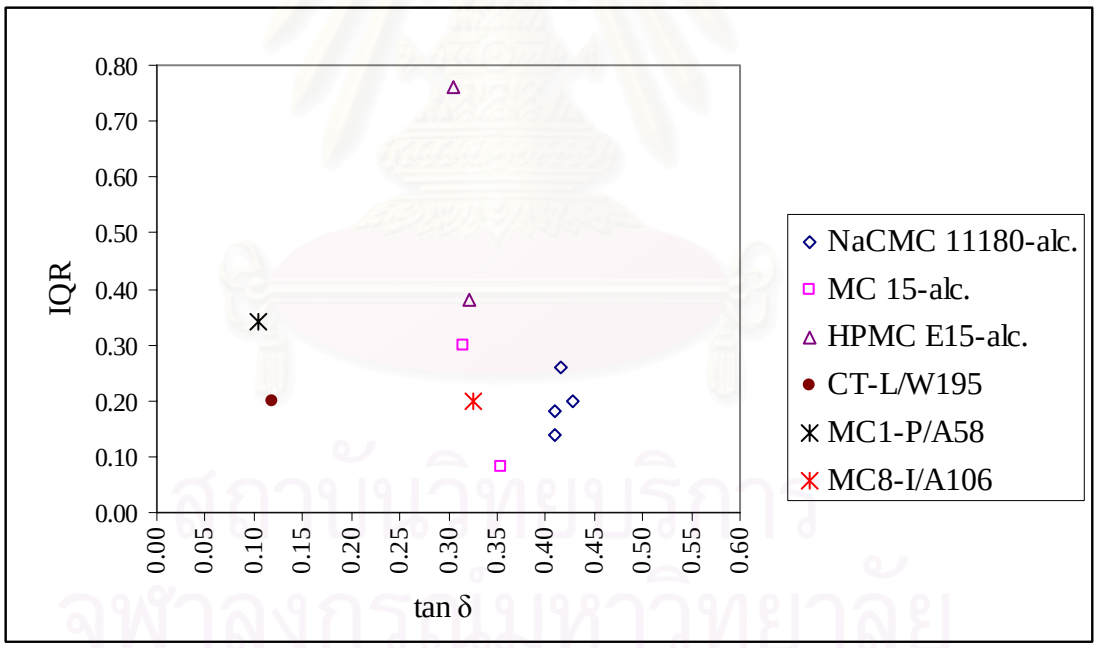


Figure D-16. Effect of tan δ on IQR of 50% ethanol formulation.

APPENDIX E

SPHERICITY

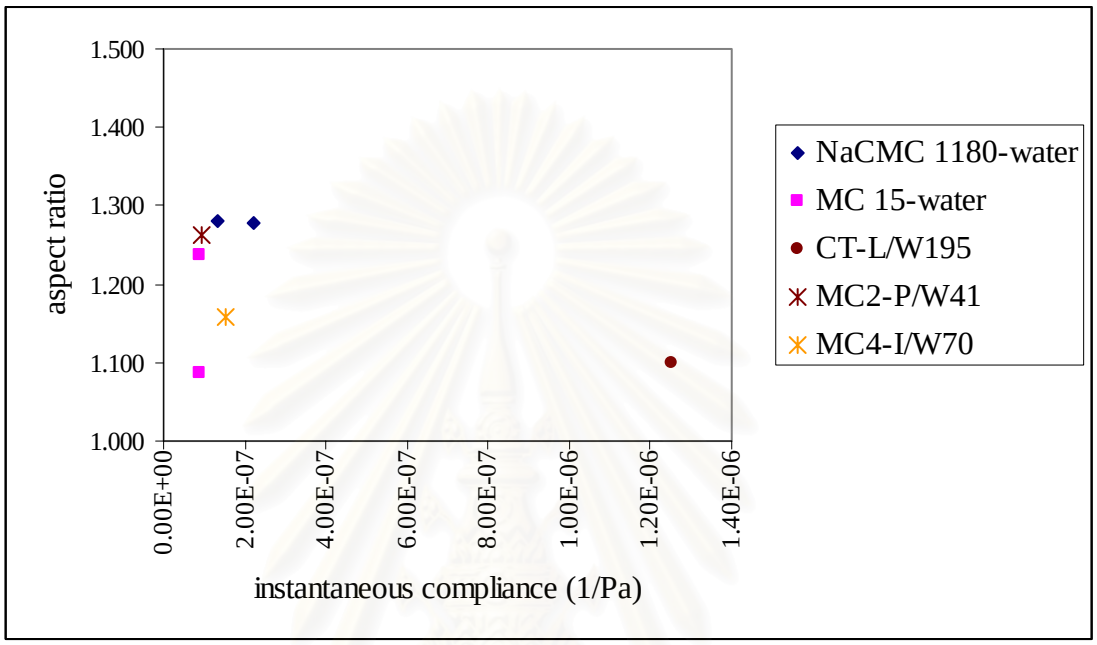


Figure E-1. Effect of instantaneous compliance on aspect ratio of water formulation.

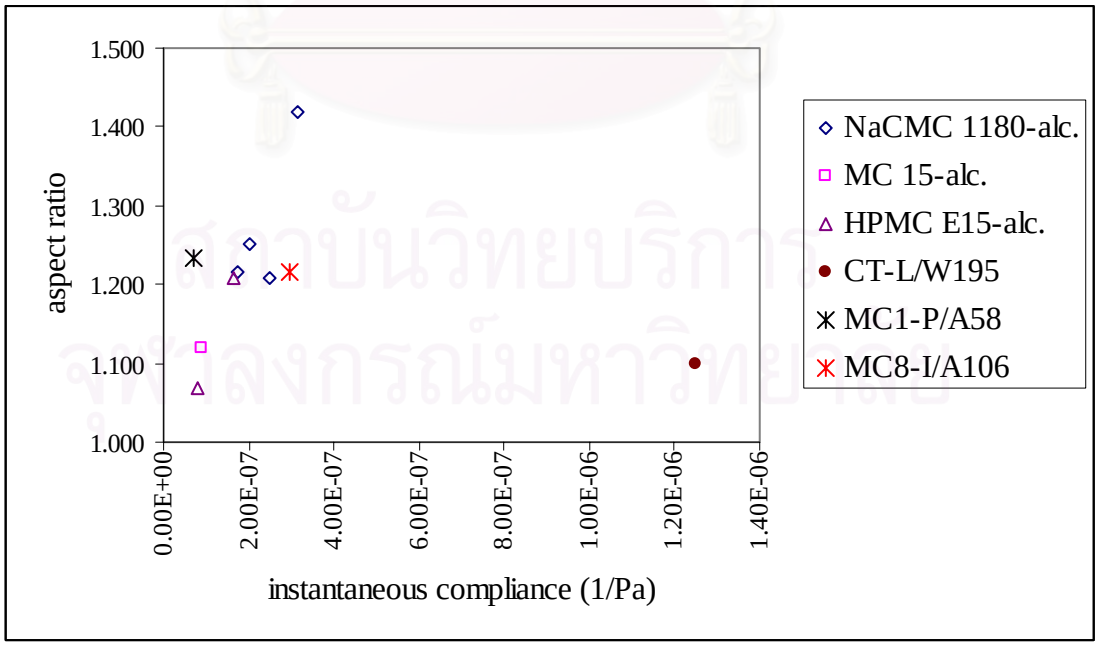


Figure E-2. Effect of instantaneous compliance on aspect ratio of 50% ethanol formulation.

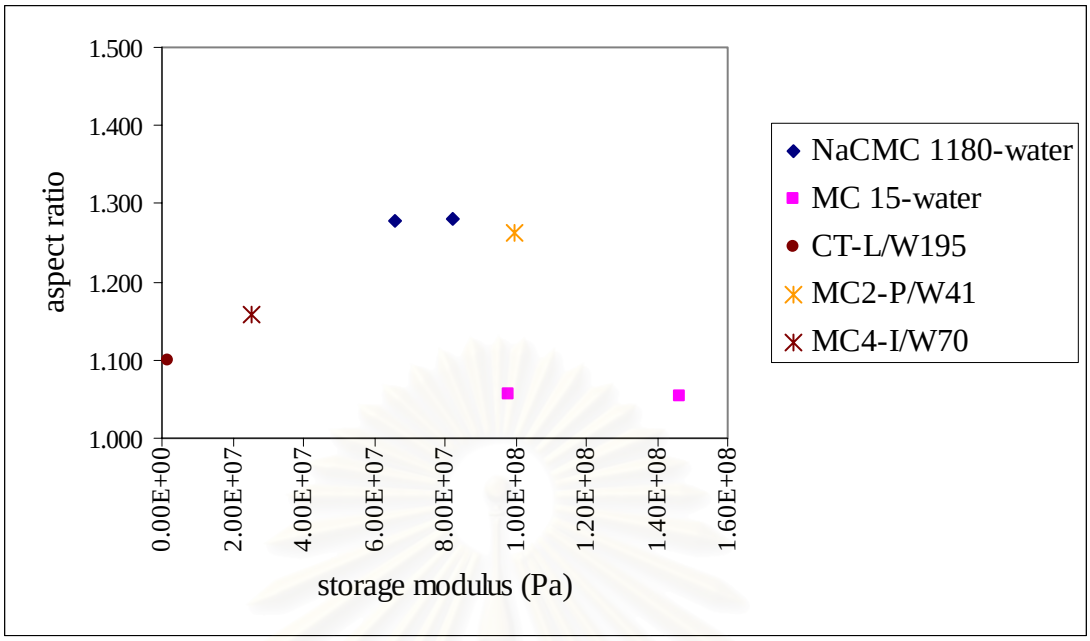


Figure E-3. Effect of storage modulus (G′) on aspect ratio of water formulation.

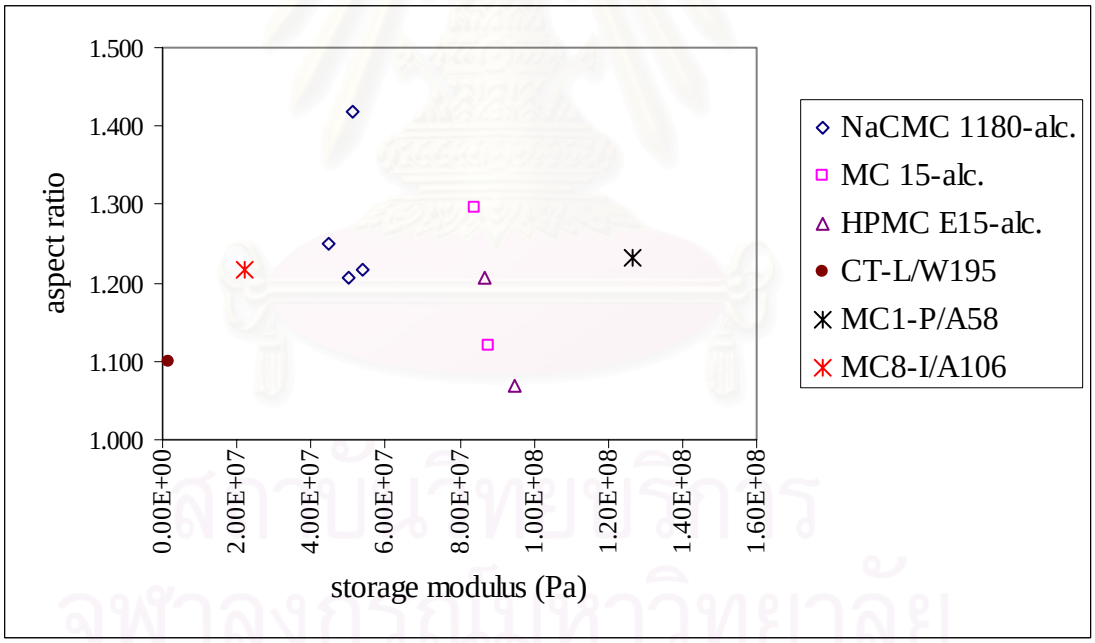


Figure E-4. Effect of storage modulus (G′) on aspect ratio of 50% ethanol formulation.

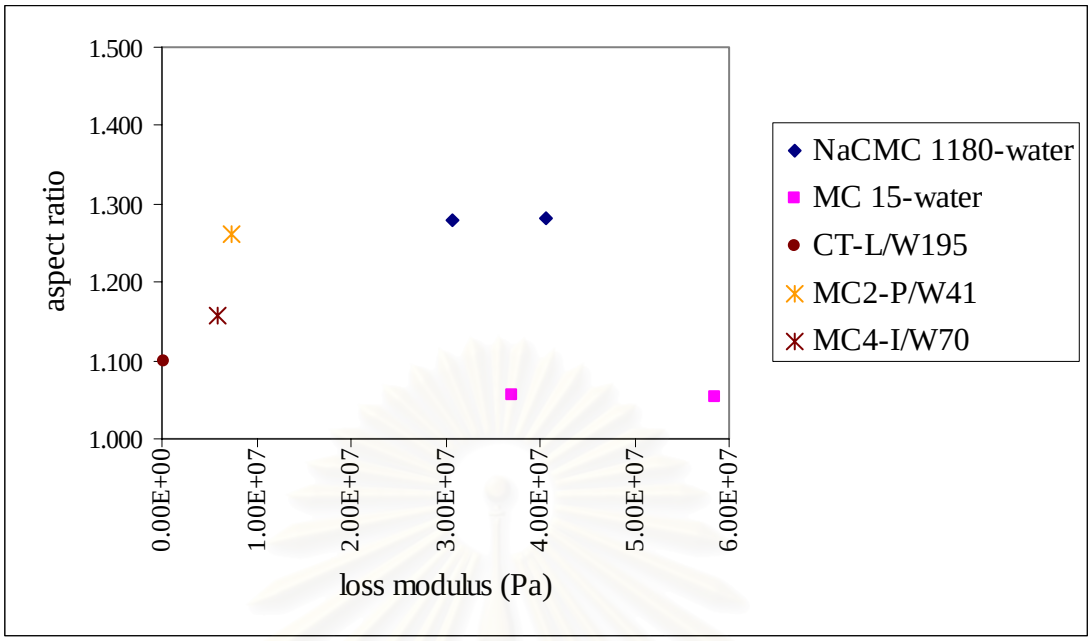


Figure E-5. Effect of loss modulus (G″) on aspect ratio of water formulation.

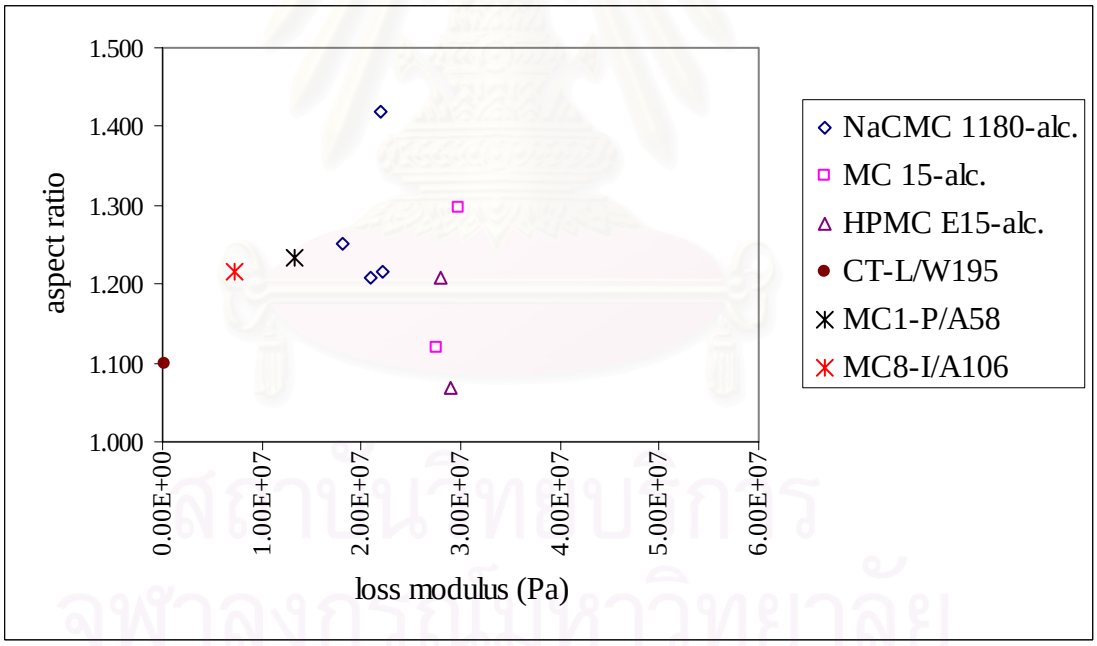


Figure E-6. Effect of loss modulus (G″) on aspect ratio of 50% ethanol formulation.

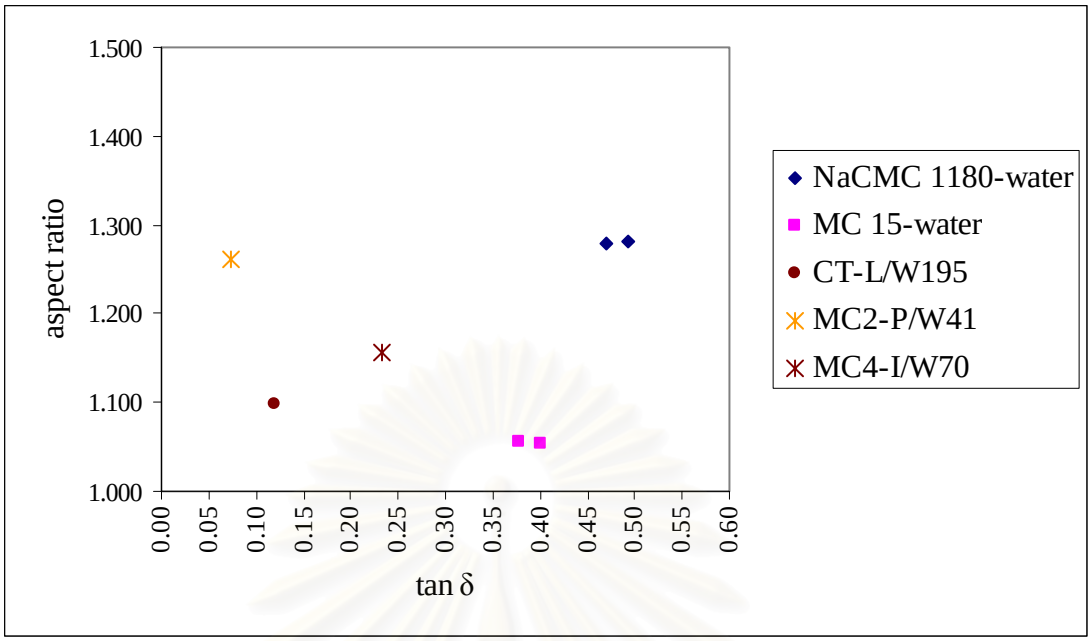


Figure E-7. Effect of tan δ on aspect ratio of water formulation.

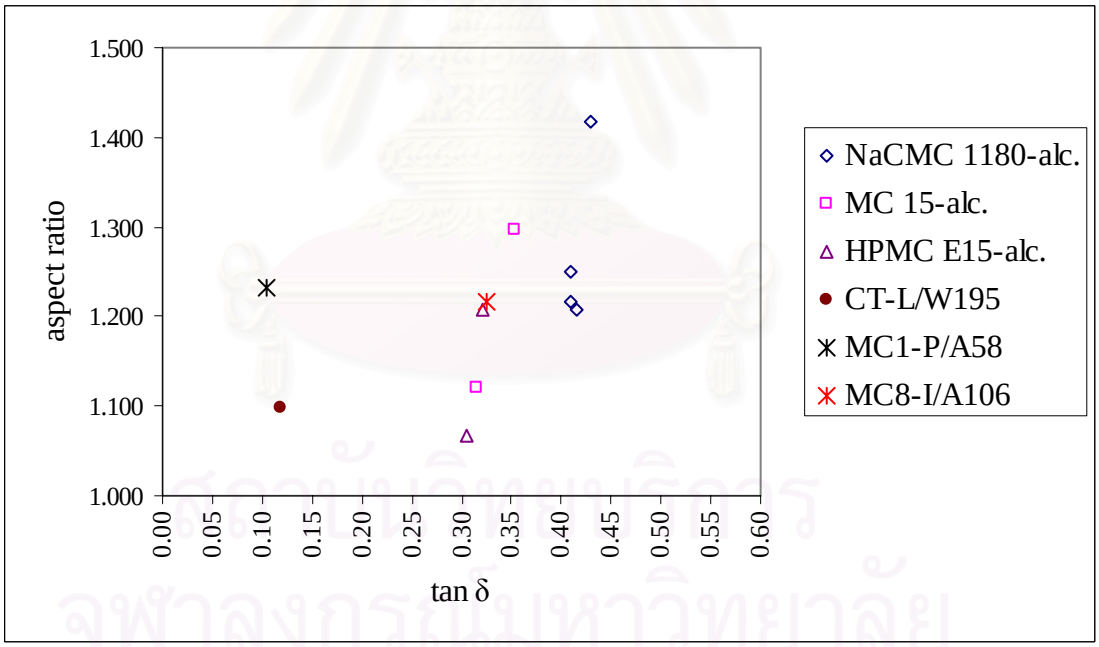


Figure E-8. Effect of tan δ on aspect ratio of 50% ethanol formulation.

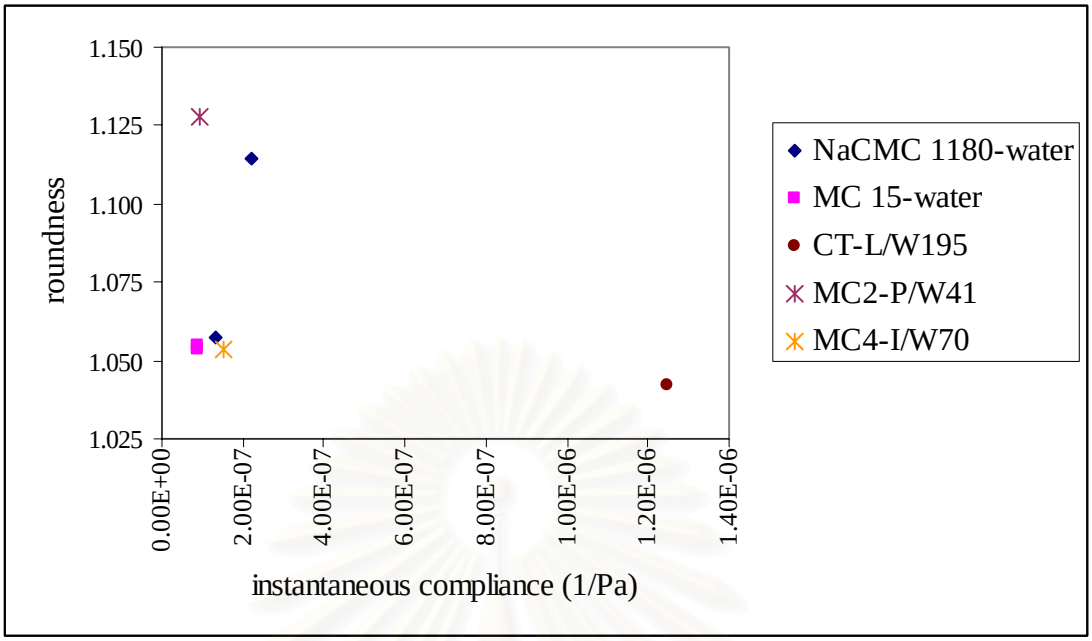


Figure. E-8. Effect of instantaneous compliance on roundness of water formulation.

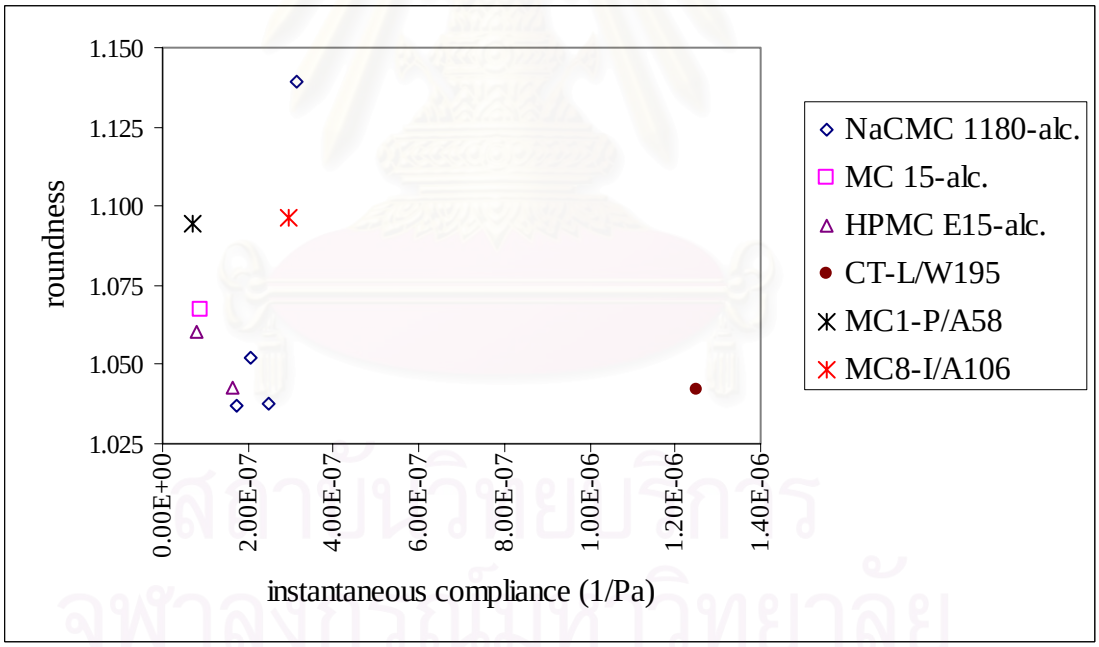


Figure. E-9. Effect of instantaneous compliance on roundness of 50% ethanol formulation.

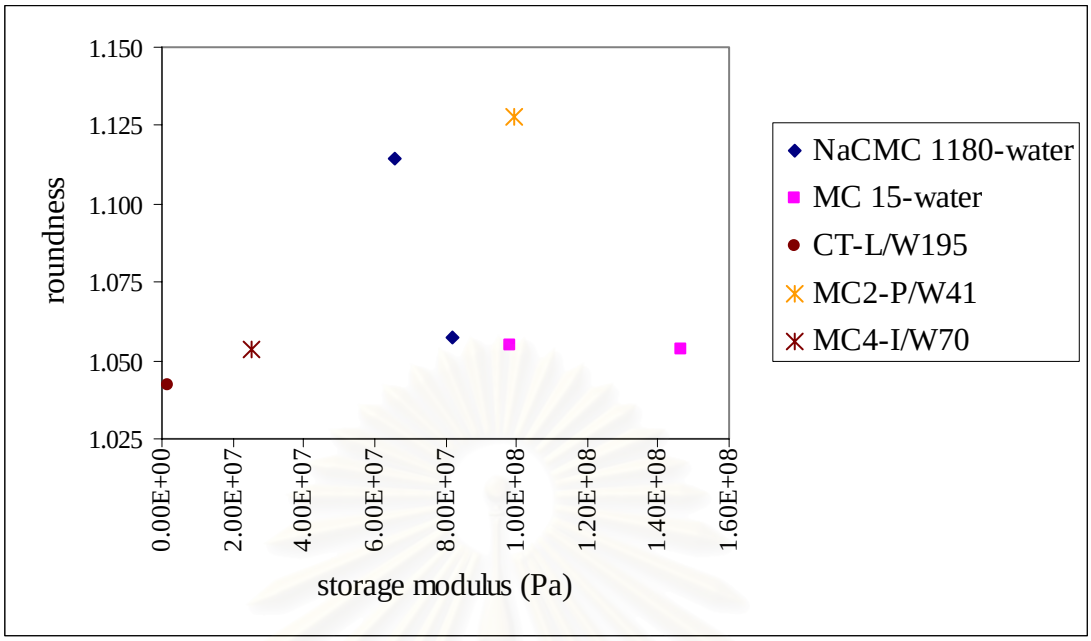


Figure.E-10. Effect of storage modulus (G′) on roundness of water formulation.

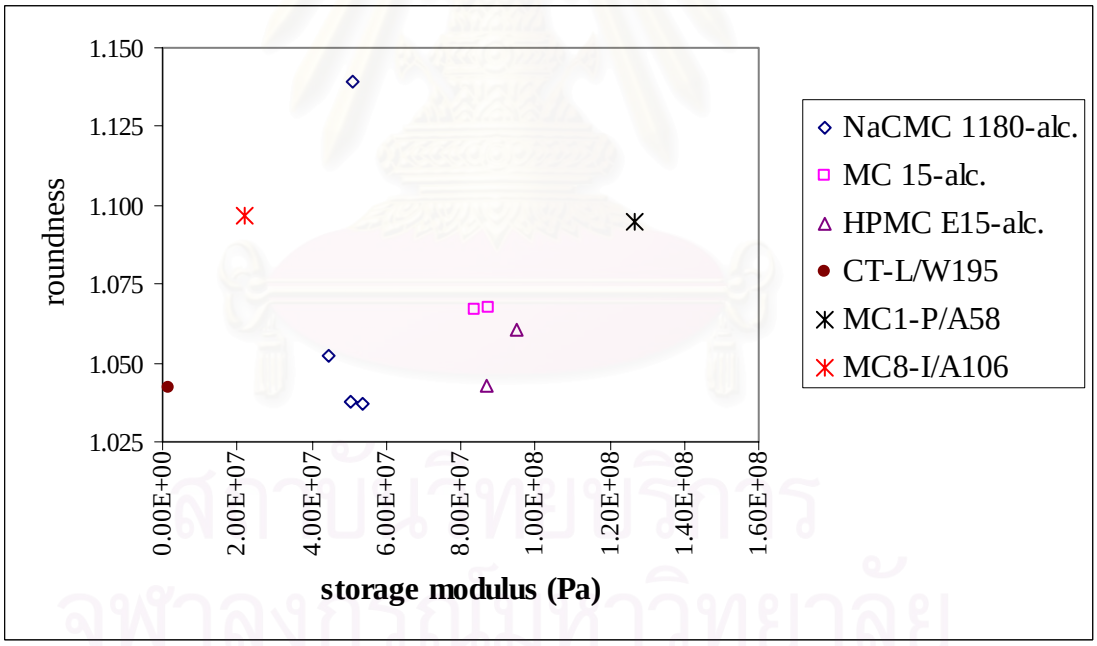


Figure E-11. Effect of storage modulus (G′) on roundness of 50% ethanol formulation.

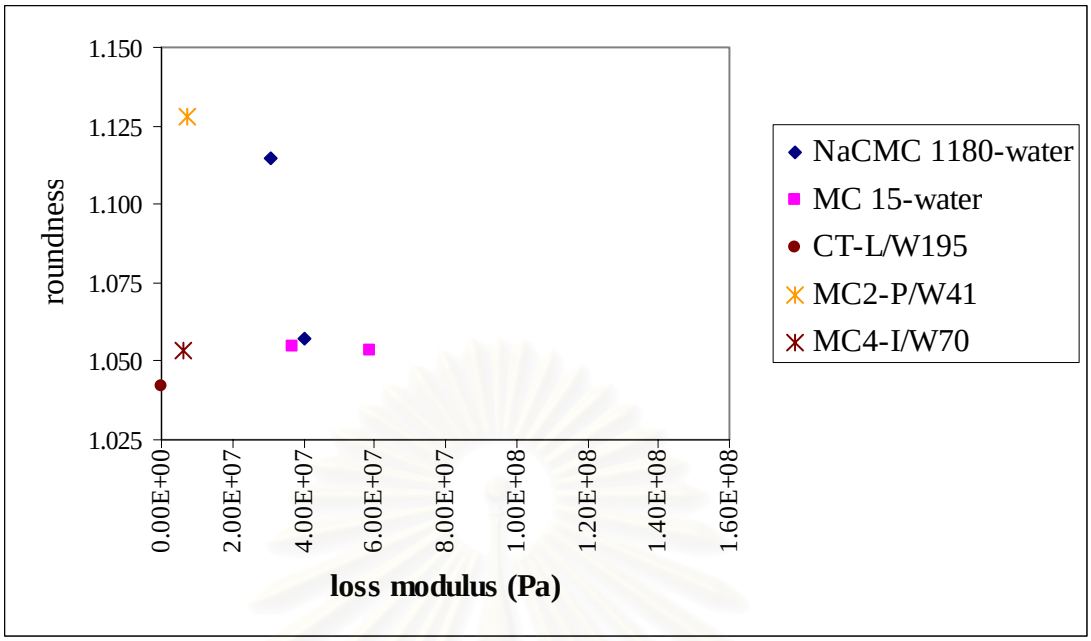


Figure E-12. Effect of loss modulus (G″) on roundness of water formulation.

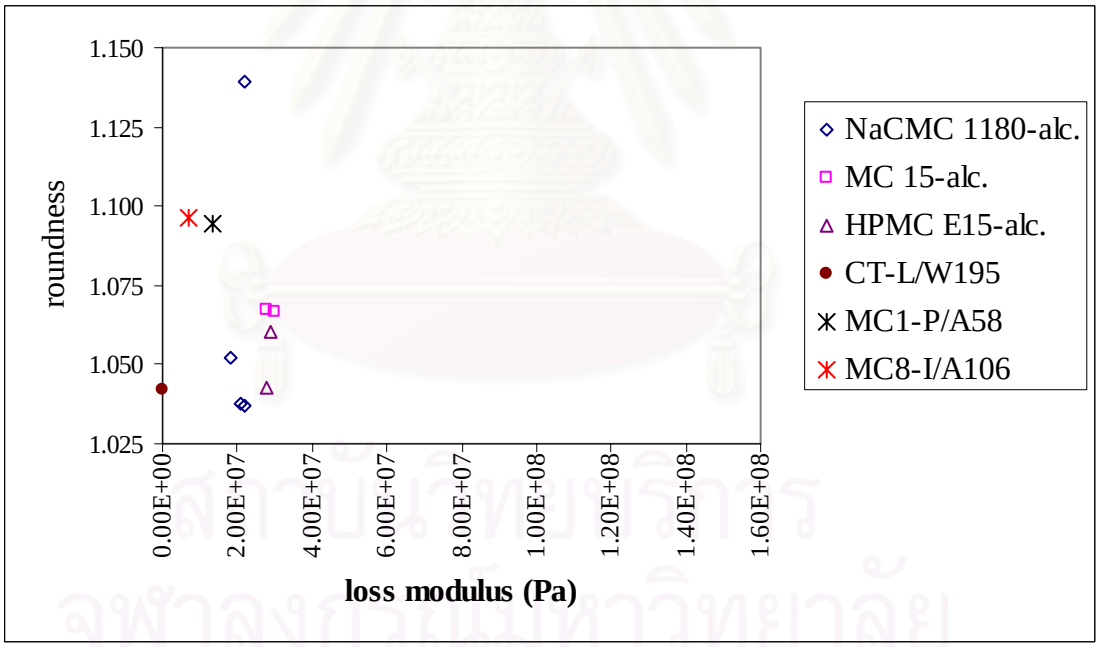


Figure E-13. Effect of loss modulus (G″) on roundness of 50% ethanol formulation.

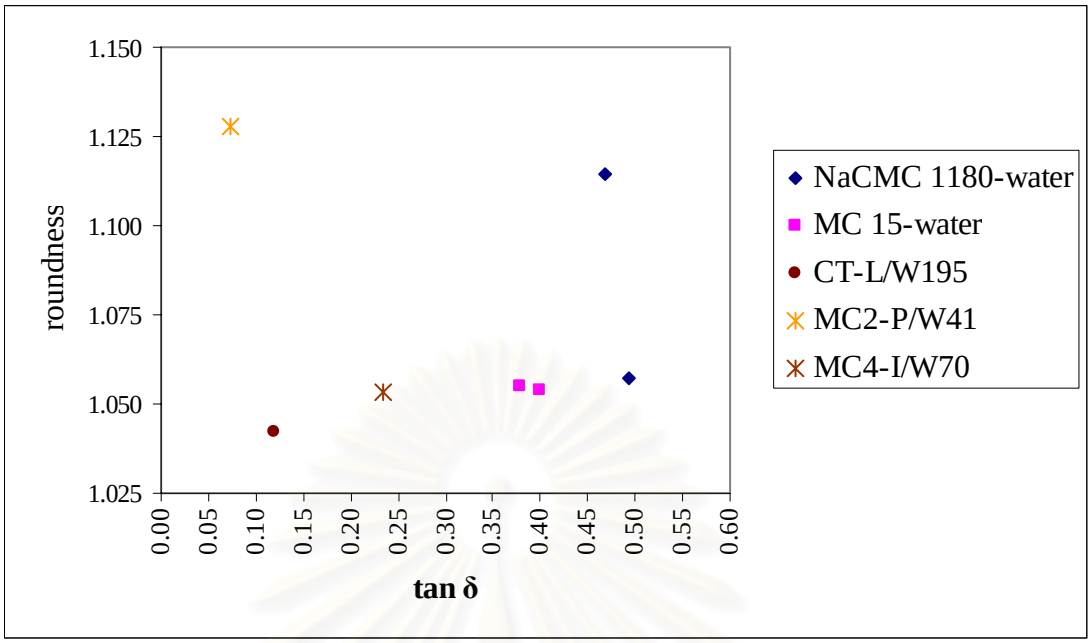


Figure E-14. Effect of tan δ on roundness of water formulation.

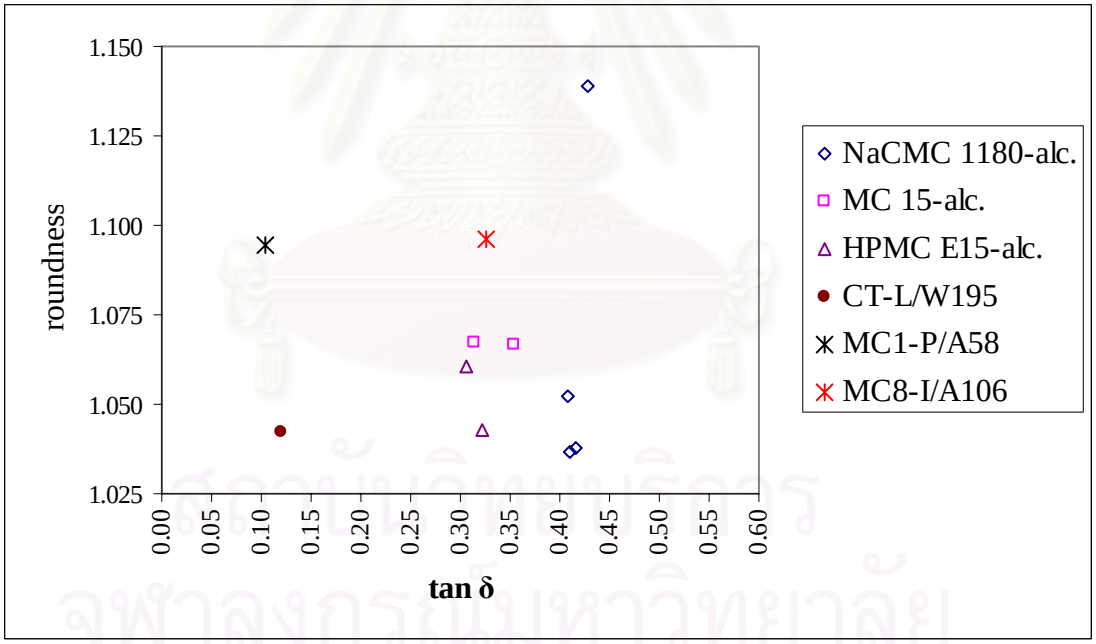


Figure E-15. Effect of tan δ on roundness of 50% ethanol formulation.

APPENDIX F

CALIBRATION CURVE

1. Calibration curve of propranolol hydrochloride for dissolution studies

The concentration (μg/ml) versus absorbance of propranolol hydrochloride in dilute hydrochloric acid at a maximum wavelength of 286 nm are presented in Table F-1. The standard curve of propranolol hydrochloride in these media is illustrated in Figure F-1.

Table F-1. Absorbance of propranolol hydrochloride in dilute hydrochloric acid at the maximum wavelength 286 nm

	Absorbance			
Concentration (μg/ml)	1	2	3	Average
9.94	0.1860	0.1860	0.1861	0.1860
19.89	0.3898	0.3895	0.3896	0.3896
29.83	0.5956	0.5952	0.5951	0.5953
39.78	0.8045	0.8046	0.8047	0.8046
49.72	0.9982	0.9989	0.9986	0.9986

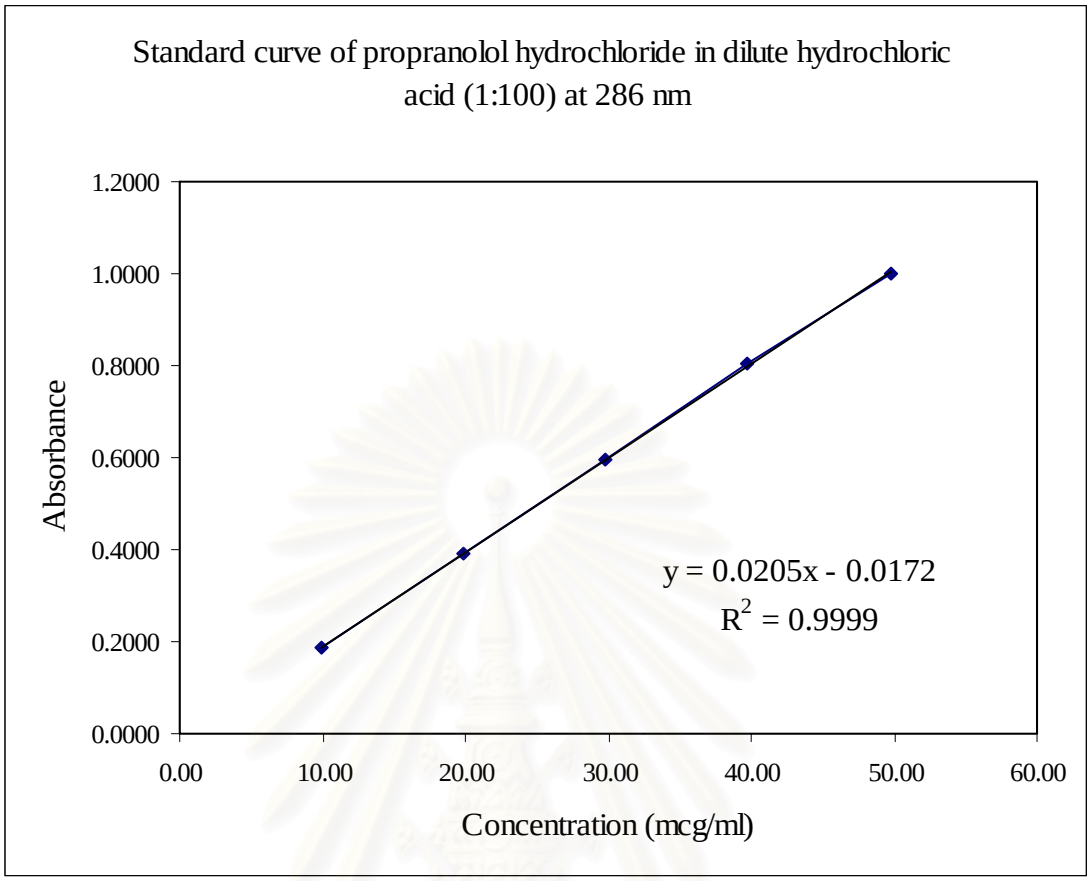


Figure F-1. Standard curve of propranolol hydrochloride in dilute hydrochloric acid (1:100) at 286 nm.

2. Calibration curve of ibuprofen for dissolution studies

The concentration (µg/ml) versus absorbance of ibuprofen in phosphate buffer pH 7.2 at maximum wavelength 269 nm are presented in Table F-2. The standard curve of ibuprofen in these media are illustrated in Figure F-2.

Table F-2. Absorbance of ibuprofen in phosphate buffer pH 7.2 at the maximum wavelength 269 nm

	Absorbance			
Concentration (µg/ml)	1	2	3	Average
10.14	0.0591	0.0590	0.0589	0.0590
20.28	0.0731	0.0729	0.073	0.0730
40.56	0.1067	0.1062	0.1061	0.1063
202.80	0.3469	0.3462	0.3456	0.3462
304.20	0.4995	0.4992	0.4993	0.4993
405.60	0.6488	0.6489	0.6489	0.6489
507.00	0.7901	0.7900	0.7900	0.7900
608.40	0.9479	0.9477	0.9478	0.9478

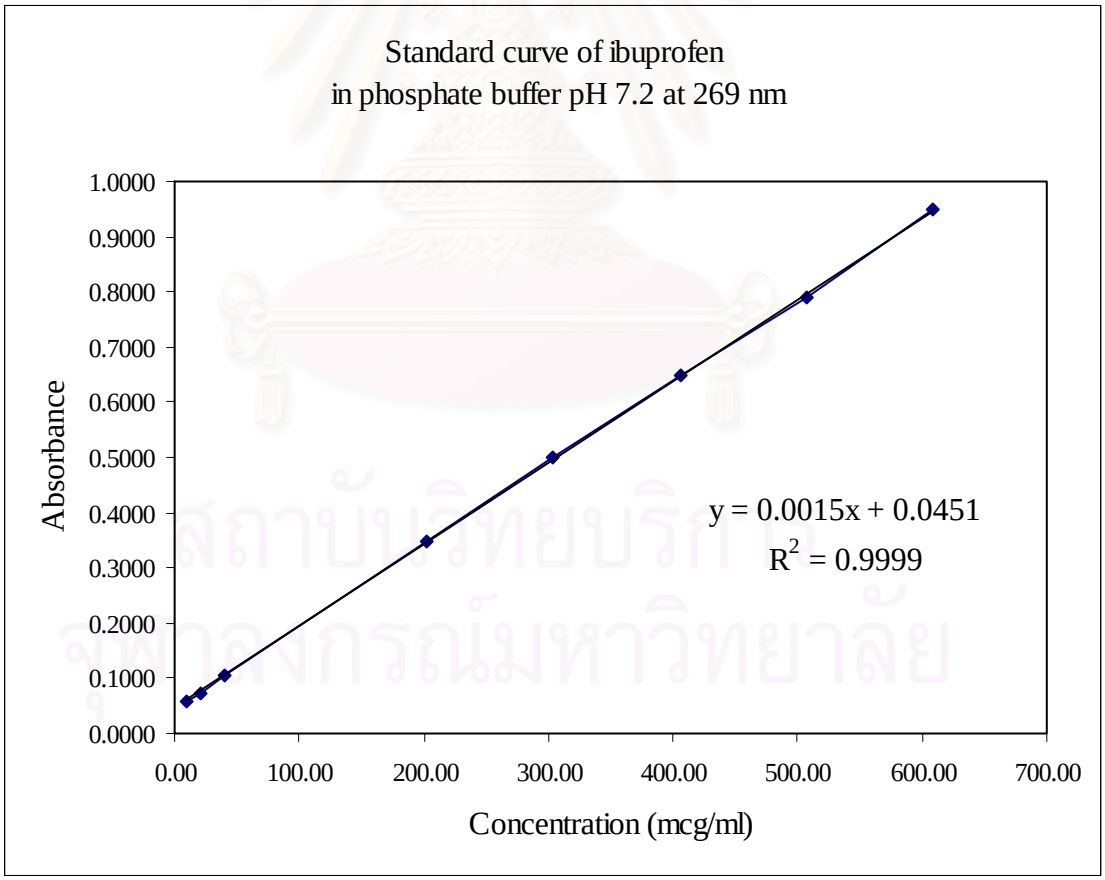


Figure F-2. Standard curve of ibuprofen in phosphate buffer pH 7.2 at maximum wavelength 269 nm.

APPENDIX G

DRUG RELEASE DATA

1. Propranolol hydrochloride

Table G-1. Percentage amount of propranolol hydrochloride release from pellets

Formulation	Time (min)	drug dissolved (mg)					% dissolved				
		1	2	3	mean	SD	1	2	3	mean	SD
MC1-P/A58	5	19.5	20.1	19.4	19.7	0.4	96.0	95.0	95.3	95.4	0.5
	15	20.1	21.1	20.3	20.5	0.6	99.0	99.6	99.5	99.4	0.3
	30	20.5	21.4	20.3	20.7	0.6	100.5	100.7	99.6	100.3	0.6
	45	20.5	21.3	20.3	20.7	0.5	100.8	100.1	99.6	100.1	0.6
	60	20.4	21.2	20.6	20.7	0.4	100.0	99.7	101.2	100.3	0.8
	90	20.6	21.4	20.5	20.8	0.5	101.3	100.7	100.5	100.8	0.4
MC2-P/W41	5	20.3	19.8	19.55	19.9	0.4	97.4	97.2	96.9	97.2	0.2
	15	20.8	20.5	20.1	20.4	0.3	99.9	100.1	100.0	100.0	0.1
	30	20.9	20.3	19.6	20.3	0.7	100.5	99.6	97.4	99.2	1.6
	45	20.9	20.4	20.2	20.5	0.4	100.8	100.2	100.5	100.5	0.3
	60	21.0	20.4	20.3	20.6	0.4	101.0	100.3	100.6	100.6	0.3
	90	21.2	20.6	20.5	20.7	0.4	101.6	101.2	101.6	101.5	0.2

2. Ibuprofen

Table G-2. Percentage amount of ibuprofen release from pellets

Formulation	Time (min)	drug dissolved (mg)					% dissolved				
		1	2	3	mean	SD	1	2	3	mean	SD
MC4-I/W70	5	1.8	4.1	5.3	1.8	4.1	9.1	20.3	26.2	18.5	8.7
	15	5.0	5.9	8.3	5.0	5.9	24.7	28.9	41.0	31.5	8.4
	30	8.7	8.6	8.5	8.7	8.6	42.9	42.0	42.0	42.3	0.5
	45	10.9	10.9	11.0	10.9	10.9	53.6	53.5	54.2	53.8	0.4
	60	11.2	14.4	11.9	11.2	14.4	55.4	70.8	58.7	61.6	8.1
	90	14.5	13.6	13.6	14.5	13.6	71.3	66.7	67.1	68.4	2.5
	180	18.2	14.1	17.4	18.2	14.1	89.4	69.2	86.2	81.6	10.9
MC8-P/A106	5	3.0	1.8	1.5	3.0	1.8	13.4	8.4	6.5	9.4	3.6
	15	5.5	3.7	3.7	5.5	3.7	24.7	17.1	16.5	19.4	4.6
	30	7.4	7.4	7.4	7.4	7.4	33.2	33.6	32.7	33.2	0.5
	45	9.2	9.6	9.6	9.2	9.6	41.5	44.0	42.2	42.5	1.3
	60	11.2	11.0	11.6	11.2	11.0	50.3	50.3	50.9	50.5	0.4
	90	14.1	13.6	14.4	14.1	13.6	63.4	62.2	63.3	63.0	0.7
	180	18.1	17.1	18.1	18.1	17.1	80.9	78.2	79.8	79.6	1.4

VITA

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